TABULATED PHARMACOLOGY

PREFACE

These notes are made according to the katzung tables given at the end of each chapter. While going through the katzung tables, I felt there was more to add, and hence, had to annotate onto them using different sources, and it was a meticulous task. Hence, with this idea in mind, I tried to synchronize additional information from multiple sources, and here you have TABULATED PHARMA in your hands.I have tried my best to SHORTLIST and encorporate everything in the tables, important from an exam point of view, with certain significant points present at the start of every topic, making them an effective tool for revision. I hope these notes are beneficial to you.

Happy studying!

TOPICS COVERED

- CHEMOTHERAPY
- ENDOCRINOLOGY
- CVS PHARMACOLOGY
- ANS PHARMACOLOGY
- CNS PHARMACOLOGY

RESOURCES USED:

- Mini Katzung
- Kaplan
- Lipponcott(for ANS & CVS)
- Professor's slides(made from different books, primarily big katzung)
- Contains important points from both NUMS & UHS pastpapers

DEDICATED TO MY PARENTS

RANDOM FACTS ABOUT DRUGS

DRUGS CAUSING HYPOKALEMIA:

*thiazide and loop direutics

*insulin

*steroids

DRUGS CAUSING HYPERKALEMIA:

*ACEi

*ARBs

*K+ sparing direutics

DRUGS CAUSING HYPERTENSION:

*acetaminophen

*alcohol

*cocaine

*alpha agonist

DRUGS CAUSING DISULFIRAM LIKE ACTION:

*metronidazole

*griseofulvin

*cefamandole & cefoperazone

*chlorpropamide(a sulfonyl urea)

DRUGS CAUSING HEMOLYSIS IN G6PD DEFECIENCY:

*anti-malarial(primaquine, chloroquine, quinine, dapsone)

*anti-bacterials(sulfamethoxazole, cotrimoxazole)

*aspirin(high dose)

*quinidine

DRUGS CAUSING NEPHROTOXICITY:

*ACEi

*acetazolamide

*aminoglycosides

*aspirin

*amphotericin B

*cyclosporine

*furosemide

*gold salts, lithium

*methicillin

*NSAIDS

*sulfonamides

*tetracyclines

*thiazides

DRUGS CAUSING QT PROLONGATION:

*anti-arrhythmics(group 1A & group 3)

*erythromycin

*mefloquine

*pentamidine

*thioridazine

*TCA

*ziprasidone

DRUGS CAUSING PHOTOSENSITIVITY:

*tetracyclines

*fluoroquinolones

*sulfonamides

*pyrazinamidases

ANTIBIOTICS CONTRAINDICATED IN PREGNANCY:

*streptomycin

*tetracyclines

*TMP-SMZ

*floroquinolones

*aminoglycosides

*pyrazinamidases

*voriconazole

DRUGS INHIBITING CYP 450:

*amiodarone

*chloramphenicol

*HIV protease inhibitors

*clarithromycin, erythromycin, isoniazid

*MAOI

*secobarbital

*acute ethanol

*ketoconazole

*furanocoumarins(grape fruit juice)

DRUGS INDUCING CYP 450:

*carbamazepine

*phenobarbital

*phenytoin

*rifampin

*chronic alcohol

SUICIDE INHIBITORS:

*ethinyl estradiol

*norethindrone

*spironolactone

*secobarbital

*allopurinol

*propylthiouracil

DOSE DEPENDANT EFFECTS OF ASPIRIN:

***<300mg/dl: reduces platelet aggregation**

***300-2400mg/dl: anti-pyretic and analgesic effect**

***2400-4000mg/dl: anti-inflammatory effect**

DOSE DEPENDANT EFFECTS OF ATROPINE:

***0.5-2mg/dl: slight brady cardia, dryness of mouth, impairement of sweating**

***5mg:rapid HR, dilated pupil, blurring of vision**

***5-10mg:halluciantions, coma, delirium**

DOSE DEPENDANT EFFECTS OF DOPAMINE:

***2-5ug/kg/min: acts on D1 receptor>causes vasodilation or renal vessels>maintains GFR**

***5-10ug/kg/min: acts on B1 receptors>inc HR and CO**

***>10ug/kg/min: acts on alpha-1 recepyors>causes inc in TPR through vasoconstriction**

CHEMOTHERAPY

ANTIBACTERIALS

ALL IMPORTANT POINTS RELATED TO ANTI-BACTERIAL GIVEN AT START

MECHANISM OF RESISTANCE IN CELL WALL SYNTHESIS INHIBITORS:

1.inactivation by lactamases(staph aureus, H,influenza, E.coli

2.modification of target PBP(MRSA, PRSP, enterocoli, Neisseria)

3.impaired penetration to target PBP(e coli)

4.presence of efflux pump(p.aeroginosa)

5.replacement of D-Ala with D-lactate in VRE

MECHANISM OF RESISTANCE IN TETRACYCLINES:

1.efflux pump

2.formation of ribosomal proteins which interfere with tetracycline binding

MECHANISM OF RESISTANCE IN MACROLIDES:

1. decreased affinity of receptor resulting from methylation of adenine in 23S subunit of 50S subunit(methyl transferase)

2. presence of efflux pump

3.inability to take up antibody(gram negative)

4.enterobacter: formation of drug metabolizing esterases

5.partial cross resistance with other drugs binding to same 50S subunit(streptogramins and clindamycin)

MECHANISM OF RESISTANCE IN CHLORAMPHENICOL:

1.plasma mediated

2.formation of acetyl transferases that inactivate drugs

MECHANISM OF RESISTANCE IN AMINOGLYCOSIDES:

1.decreased influx(streptococci and enterococci)

2.formation of group transferase that acetylate the amine residue and cause transfer of phosphoryl and adenylyl groups to oxygen atoms of hydroxyl group on aminoglycosides(streptomycin is transferase resistant)

3.changes in ribosomal binding site(streptomycin)

MECHANISM OF RESISTANCE IN SULFONAMIDES:

1.plasma mediated resistance

2.decreased intracellular accumulationof drug

3.increased production of PABA by bacteria

4.decrease in sensitivity of dihydropteroate synthase to sulfonamides

5.TRIMETHOPRIM: decreased affinity of dihydropteroate synthase for drug

MECHANISM OF RESISTANCE IN QUINOLONES:

*resistance emerged for 2nd generation(campylobacter jejuni, gonococci, MRSA, pseudomonas serratia)

1.decreased intracelleular accumulation of the drug vua production of efflux pump(TB,staph aureus, streptococcus pneumonia) /changes in porin structure(gram – bacteria)

2.changes in sensitivity of target enzymes via point mutations in antibiotic binding regions

3.mutation in gyrA gene that encodes DNA gyrase(gonococci)

SPECTRUM NOT COVERED BY CEPHALOSPORINS:

1.listeria monocytes(give ampicillin/ gentamicin)

2.atypicals(chlamydia and mycoplasma)>(tetracyclines and macrolides)

3.MRSA(vancomycin, ceftriaxone)

4.enterococci(same drugs as listeria)

PERSON RESISTANT TO PENICILLIN:

A)GRAM POSITIVE INFECTION: give macrolides(azithromycin)

B)GRAM NEGATIVE INFECTION: give aztreonam

BETA-LACTAMASES CAN BE OF TWO KINDS:

A)PLASMA ENCODED: gonococci, streptococci, e.coli, H.influenza

B)CHROMOSOMAL ENCODED: enterobacter, pseudomonas, serratia

ANTI-BIOTICS DEPICT TWO TYPES OF KILLING:

A)CONCENTRATION-DEPENDANT: aminoglycosides, quinolones

B)TIME DEPENDANT: cephalosporin, penicillin

BACTERIOSTATIC DRUGS: inhibit bacterial cell growth

*macrolides

*tetracyclines

*sulfonamides

*chloramphenicol

*oxazolidinones(linezolid)

*lincosamides(clindamycin)

BACTERICIDAL DRUGS: kill bacterial cell

*beta lactam

*aminoglycosides

*quinolones

*vancomycin

*metronidazole

*rifampicin

CELL WALL SYNTHESIS INHIBITOR:

*beta lactam drugs(penicillin, cephalosporin, carbapenem, aztreonam)

*non-beta lactam drugs(cycloserine+fosfomycin+bacitracin+vancomycin)

PROTEIN SYNTHESIS INHIBITORS:

*binding to 30S ribosomal subunit: aminoglycosides, tetracyclines, tigecyclines

*binding to 50S ribosomal subunit: clindamycin, macrolides, linezolid, streptogramins, chloramphenicol

*__aminoglycosides__: prevent formation of initiation complex

*__tetracyclines__: prevents binding of charged amino acid tRNA to acceptor site of the ribosomal-mRNA complex(interfers with amino acid incorporation)

*__macrolides, telithromycin, clindamycin__: prevents translocation of peptidly tRNA from acceptor to donor site

*__chloramphenicol:__ inhibits transpeptidation by blocking binding of aminoacyl moiety of charged tRNA molecule to acceptor site on ribosomal-messenger complex

NUCLEIC ACID SYNTHESIS INHIBITORS:

*sulfonamides: inhibits dihydropteroate synthase

*quinolones: inhibits DNA gyrase

DIFFERENCE BTW ERYTHROMYCIN & AZITHROMYCIN:

BOTH GIVEN EMPTY STOMACH! CLARTHORMYCIN CAN BE GIVEN WITH FOOD

ERTHROMYCIN	AZITHROMYCIN
Inhibits CYP 450, inc plasma levels of anti-coagulants, carbamazepine, cisapride, digoxin, theopylline	Doesn't inhibit CYP450
Half-life:2-6hrs	Half-life: 2-4 days
Biliary elimination	Urinary elimination
Long course of Rx	Short course of Rx
Drug interaction with digoxin	No drug reaction with digoxin
Less compliance with GIT distress	More patient compliance
Increased resistance *cholestatic jaundice and QT prolongation common	More resistance
SPECTRUM DIFFERENCE:	SPECTRUM DIFFERENCE:

*atypicals: chlamydia, mycoplasma, legionella *g+ cocci *g-cocci *campylobacter, MAC, toxoplasma gondi, bordetella pertussis	*SAME AS ERTHROMYCIN *SOME MORE: *more activity for *H.infleunza, Moraxella, Neisseria *chlamydia trachomatis(long half-life single dose effective) *CAP(4 days Rx)

DOC FOR H.PYLORI:

*BMT regime(bismuth, metronidazole, tetracyclines)

*clarithromycin, amoxicillin, PPI

DOC FOR SALMONELLA:

*ceftriaxone

*BACK-UP DRUGS: ampicillin, chloramphenicol, clotrimoxazole, fluoroquinolones

IN MRSA>give vancomycin>IN VRSA>dive daptomycin/tigecycline/linezolid

IN CAP(community acquired pneumonia)

*doxycycline (DOC)

*azithromycin

*levofloxacin

NAME OF DRUG	MECHANISM OF ACTION	PHARMACOKINETICS	DRUG INTERACTION	CLINICAL USES	TOXICITIES
CELL WALL SYNTHESIS INHIBITORS					
PENICILLIN	*bactericidal *binding to PBP> inhibition of transpeptidation> prevents formation of cell wall>bacteria unable to withstand osmotic changes>autolysis of bacteria *activation of autolytic enzymes	*vary in resistance to gastric acid *excreted unchanged in urine via GfR and tubular secretion ***biiiary clearance for nafcillin and oxacillin** *benzathine penicillin G detected in serum upto 14days(repository form)	*inhibitors of beta lactamase> clavulanic acid used.	PENICLLIN G: * drug of choice for **syphilis(benzathine penicillin G)** *oropharyngeal infection(penicillin V) * common streptococci, meningococci, gram positive bacilli, spirochetes. METHICILLIN: *staph aureus AMPICILLIN/AMOXICILLIN: *listeria, ecoli, proteus, H.infleunza, Moraxellah catarrhalis ***enterococci and listeria:ampicillin in synergism with aminoglycosides** PIPERACILLIN/ TICARCILLIN: *pseudomonas, enterobacter, klebsiella *used in combo with tazobactam and clavulanic acid to enhance activity	1.Allergy: urticarial, pruritus, **joint swelling**, **fever, hemolytic anemia**, nephritis, **anaphylaxis** 2.Methicillin: interstitial nephritis 3.Naficillin: neutropenia 4.Ampicillin: maculopapular skin rash 5. GIT infection: nausea, vomiting>direct irritation and superinfection(pseudomembranous colitis) 6.jarish-hexihmer reaction in Rx of syphilis
CEPHALOSPORIN	Similar to penicillin *gram negative coverage increases moving down(contrast to flouroquinolones, as their gram positive spectrum increases on going down)	*major elimination by renal excretion by active tubular secretion ***cefoperazone and ceftriaxone excreted in bile(**hence for a neonate with meningitis give cefotaxime not ceftriaxone as this is eliminated by bile and liver isn't properly developed) & (ceftriaxone can be given in renal failure) ***1st and 2nd generation donot enter CSF even when meninges are inflamed!**		1ST GENERATION: CEFAZOLIN(oral)&CEPHALEXIN(IV): *staphylococci, streptopneumonia *E.coli, Klebsiella proteus * **no activity against g-cocci,** enterococci, MRSA ***surgical prophylaxis** 2NDGENERATION:CEFACLOR, CEFUROXIME, CEFPRZIL: ***extended g-spectrum** ***anaerobes bacteroides fragillis**(cefotetan, cefoxitin) ***sinus, ear and resp infection** by H.influenza, M.catarrhalis(cefaclor,cefuroxime, cefamandole) 3RD GENERATION: CEFOPERAZONE, CEFTAZIDIME, CEFOTAXIME: *providencia, serratia, Neisseria, H.infleunza	***Allergy:** skin rashes to anaphylactic shock *** Other adverse effects**: *pain at IM injection *phlebitis at IV administration *nephrotoxitcity when administrated with aminoglycosides ***cefotetan, cefoperazone:** hypoprothrombinemia, disulfiram like reactions

		***3rd generation enter CSF(except cefoperazone & cefixime)**		*__PRSP__:ceftriaxone, cefotaxime *__pseudomonas__: cefoperazone, ceftazidime *__gonorrhea__:ceftriaxone and cefixime *__acute otitis media__:ceftriaxone *__neonatal meningitis__: cefotaxime 4TH GENERATION: *cefipime: resistant to beta lactamaseproducing strains of gram negative organisms like: enterobacter, Haemophilus, Neisseria * **combines the g+activity of 1st generation with g-activity of 3rd**. 5TH GENERATION; *ceftaroline: MRSA	
AZTREONAM	*monobactam *inhibitor of cell wall synthesis *binding to specific penicillin binding protein PBP3 *synergistic to aminoglycosides	*administered IV *eliminated via renal tubular secretion *halflife prolonged with renal failure		Aerobic g-rods:klebsiella, pseudomonas, serratia *may give pateints who are allergic to penicillin and cephalosporin	*GIT upset, superinfection, vertigo, headache ***no allergenicity with beta lactams**
CARBAPENEM(imipenem-cilastin, doripenem, meropenem,ertapenem)	*chemically different from penicillin, but retain the beta-lactam ring structure *inhibits transpeptidation	*given IV *cilastatin (1)inhibits renal metabolism of imipenem, by enzyme dihydropeptidase >hence prevents formation of nephrotoxic metabolite(2)prevents entry into renal tubular cell by OAT(organic anion transferase) *renal elimination	Synergistic with beta lactam and quinolone antibiotics	*broad spectrum,PRSP(but not MRSA) *Carbapenem: enterobacter, citrobacter, serratia *effective against g+cocci**, g-rods, anarerobes** *except ertapenem, carbapenem effective against **P.aeruginosa**, acinetobacter *important in hospital empiric use(for life-threatening emergencies)	*imipenem-cilastin: GIT distress, skin rash**,at high dose**:CNS toxicity(confusion, seizure, encephalopathy) *partial cross-allergenicity with penicillins *ertapenem(IM causes pain and irritation) 1.phlebitis IM

VANCOMYCIN	*bactericidal glycoprotein *binds to D-Ala D-Ala of nascent peptidoglycan side chain and inhibits transglycosylation (and indirectly transpeptidation) *this action prevents elongation of peptidoglycan chain and intefers with cross-linking	*IV penetration and eliminated unchanged in urine(modification in renal dysfunction) *used orally for Rx of enterocolitis *D-ala changed by D-lactate in VRE and VRSA		1.MRSA 2.PRSP(in combo with third generation cephalosporin) 3.Clostridium difficile(used orally, as not absorbed from GIT)	2.nephrotoxity and ototoxicity alongside aminoglycosides 3.rapid infusion causes red man syndrome due to massive release of histamines: flushing, pruritis, erythematous rash on upper torso(how to prevent? Decrease rate of infusion)
FOSFOMYCIN	*__Antimetabolite inhibitor__ of cytosolic enolpyruvate transferase>prevents formation of Nacetyl muramic acid>essential precursor of peptidoglycan	*excreted via kidney *drug less effective than a 7day course of flouroquinolones		*synergistic with beta-lactams and quinolone for ceratin antibiotics	Diarrhea
BACITRACIN	*late stage in cell wall synthesis inhibitor **in g+ organism**				Nephrotoxic
CYCLOSERINE	*__Antimetabolite__ that blocks incorporation of D-Ala into pentapeptide side chains			*Rx used only for tuberculosis resistant to 1st line drug(2nd line ATT)	Neurotoxic(tremors, serizure and psychosis)
DAPTOMYCIN	*novel cyclic lipopeptide *inserts into cytoplasmic membrane causing potassium leak and cell death	Eliminated via kidney			Creatinine kinase needs to be monitored as it leads to muscle myopathy

PROTEIN SYNTHESIS INHIBITOR TETRACYCLINES A)SHORT ACTING:6-8hrs *chlortetracyclines *oxytetracyclines *tetracycliens *clomocyclines B)INTERMEDIATE ACTING: 10-14hrs *methacycline *demeoclocyclin *lymecycline C)LONG ACTING:16-18hrs *doxycycline *minocycline	*bacteriostatic *binds to 30S ribosomal subunit *prevents binding of aminoaacid-charged tRNA to acceptor site of the ribosomal-mRNA complex *interfers with oxidative phosphorylation *tigecycline broadest spectrum(g+,g-, anaerobes)	***oral absorption is variable** ***impaired by foods and multivalent cation, dairy product, anatcids, alkaline pH** *wide tissue distribution(cross placental barrier) *excreted in breast milk *minocycline reaches high concentration in saliva and CSF(meningocarrier state) *undergo extrahepatic cycling *all tetracyclines excreted in urine, except doxycycline secreted in feces and **tigecycline excreted in bile** also tigecycline has long half-life, IV administration, and is broad spectrum		1.<u>Primary uses:</u> ***mycoplasma pneumonia** ***chlamydia, ricketssiae**, vibrios, and some spirochetes *doxycycline an alternative to macrolides in CAP 2.<u>Secondary uses:</u> *syphilis *treatment of respiratory infection *prophylaxis against chronic bronchitis *treatment of leptospirosis *treatment of acne 3.<u>Selective uses:</u> *tetracycline: Rx of GIT ulcer *doxycycline: lyme disease *minocycline: meningocarrier state *doxycycline: prevention of malaria and in treatment of amebiasis *demeclocycline: SIADH *tigecycline:SSTI, VRE,MRSA, gram- and anaerobes 4.<u>Other uses:</u> *lymphogranulum venereum *granuloma inguinale *atypical pneumonia *cholera, brucellosis, plague *relapsing fever, lyme disease, ricketssial infection	1.<u>GIT disturbance:</u> *mild nausea and vomiting *life threatening enterocolitis *superinfection leading to candidiasis and superinfection with S.aureus and C.diificile(Rx with vancomycin 650mg+metronidazole 200-450mg TDS) 2.<u>Bony structure and teeth:</u> *tooth enamel dysplasia *irregularities in bone growth *cr own deformation *discoloration of teeth(contraindicated in pregnancy) 3.<u>Hepatic toxicity:</u> *impaired liver function leading to hepatic necrosis *oxytetracyclines and tetracycline least heptotoxixities 4.<u>Renal toxicity</u>: *renal tubular acidosis *fanconi syndrome *may aggravate azotemia in patient 5.<u>photosensitivity:</u> Demeclocycline enhance sensitivity to UV light(others: sulfoanmides and quinolines) 6.<u>vestibular toxicity:</u> *dose dependant reported with doxycycline and minocycline 7.<u>Others:</u> Pseudomotor cerebri, thrombophlebitis, disturbance of bone marrow, thrombocytopenic purpura

MACROLIDES	*bacteriostatic but bactericidal at high conc *binds reversibly to 50S ribosomal subunit *inhibits elongation of protein by blocking the translocation of aminoacid-tRNA complex *clarithromycin favoured as given once daily, higher spectrum, better acid stability, lower GIT irritation	Erthromycin: *inactivated by gastric acid(enteric coated tablet), hence given empty stomach' *excreted in active form in bile *half-life:2 hrs Clarithromycin: *given once daily(absorbed easily from GIT) *rapid first pass metabolism to 14hydroxyclarithromycin *hepatic meta and urinary excretion of intact drug Azithromycin: *achieves high conc in tissues and macrophages than in plasma *PPB low *eliminated by urinary excretion *halflife:2-4 days	*erthromycin inhibits several forms of cytochrome P450: increase plasma of anticoagulant, carbamazepine, digoxin and theophyllline(not azithromycin as macrolide ring slightly differs)	Erythromycin *activity against: *gram + cocci(not MRSA) *atypicals:(chlamydia, ycoplasma, ureaplasma) *legionella *campylobacter *MAC * cornynebacterium, bordetella pertussis, g+cocci, and **beta-lactamase producing strains of staphylococci(but not MRSA**) *rheumatic fever, dental prophylaxis Clarithromycin: *same spectrum as erthromyin, used for the Rx against MAC, and H.pylori Azithromycin: *similar as erythromycin *effective in gonorrhea and in syphilis *H. influenza, Moraxella catarrhalis, Neisseria *single dose: C.trachomatis(also doxycycline for 7 days used too) *4day Rx: CA pneumonia	GIT:anorexia, nausea, vomiting(erthyomycin stimulation of motilin receptors), diarrhea Liver toxicity:**acute cholestatis hepatitis**(increased risk in pregnant patients taking erythromycin estolate) Hypersensitivity:fever, eosinophilia, skin eruptions Cardiac: **QT prolongation** MENTION ITS DRUG INTERACTIONS
TELITHROMYCIN	*ketolide *similar to macrolides(inhibit transpeptidtion) *some macrolide resistant strains are susceptible to ketolides(tighter ribosomal binding and poor substrate for bacterial efflux)	*given orally once daily *eliminated in bile and urine	* inhibitor of CYP3A4 drug-metabolizing enzyme	*CAP resistant to azithromycin *strept pyogenes *strept pneumonia, H.infleunza,H.pylori, N.gonorhea *respiratory infection, pharynxgitis, chronic bronchitis	*hepatic dysfunction *QT prolongation *inhibitor of CYP3A4 MENTION ITS DRUG INTERACTION
CLINDAMYCIN (lincosamide)	*50S ribosomal subunit *similar to macrolides *bacteriostatic) *not for gram-, due to poor penetration of	***penetrates into abscess(pharyngitis) and phagocytic cells** *hepatic metabolism *eliminated by urinary and biliary	*potent inhibitor of CYP3A4 and increases levels of astemizole, cisapride, cyclosporine, diazepam, NNRT, warfarin	*Rx for **anaerobic infection** by bacteroides *back up against **g+cocci,** active against CA of MRSA ***prophlaxis of endocarditis in valvular disease patients allergic to penicillin** ***pneumocystitis**	*GIT irriation * skin rashes, neutropenia, hepatic dysfunction *superinfection by C.difficile pseudomembranous enterocollitis(clindamycin decreases bacteroides/normal flora)

	drug through outer membrane	excretion		**jirovecci**(clindamycin+primaquin alternative to co-trimaxole) *combo with pyrimethamine for **AIDS related toxoplasmosis** PAST PAST(pneumonic) P peritonitis A acne S staph aureus infection T toxoplasma P prophylaxis of endocarditis A aspiration pneumonia S T toxoplasma	MENTION DRUG INTERACTIONS
STREPTOGRAMINS	*bactericidal *binds to 50S ribosomal subunit, constricting the exit channel thru which nascent polypeptide are extruded) *tRNA synthetase synthetic activity is inhibited leading to a decrease in free tRNA within the cell	*administered IV *quinupristin-dalfopristin *PAE	*revesible inhibitor of CYP enzymes, increases half-life of phenytoin, tolbutamide, warfarin	*PRSP *VRSA *E.faecium(not E.faecalis)	*IV:pain *arthralgia myalgia syndrome MENTION DRUG INTERACTIONS
CHLORAMPHENICOL	*binds to 50S ribosomal subunit *inhibits transpeptidation by blocking the binding of aminoacyl moiety of the charged tRNA molecule to the acceptor site on ribosomal mRNA complex	*oral +IV *widely distributed *crosses placental and BBB *enterohepatic cycling *small portion excretd in urine unchanged *inactivated by glucuronosyltransferase		*__H.influenza, N.meningitides, Bacteroides__ are highly susceptible *backup drug for salmonella *Rx of meningococcal and pneumococcal meningitis in beta-lactam sensitive patient *used for **ricketssial disease**(endemic typhus, rocky mountain spotted fever, Q fever)	1.<u>GIT disturbance</u>: *direct infection *super infection 2.<u>Bone marrow</u> *dose dependant and reversible decrease in circulating RBC *aplastic anemia irreversible and fatal 3.<u>Gray baby syndrome</u>: *neonates lack glucorosyltransferase *dec RBC, cyanosis, CVS collapse
OXAZOLIDINONES(linezolid)	*binds to a unique site on 23S ribosomal	*oral +IV *liver meta *half-life: 4-6hrs		*penicillin resisant g+cocci(MRSA, PRSP, VRE) *__L.monocytes,__	*thrombocytopenia(bone amrrow suppression) *neutropenia

	RNA *inhibits formation of initiation complex in bacterial system(prevents formation of N-formylmethionyl tRNA-ribosome-mRNA ternary complex			**corynebacterium**	*SSRI(serotonin syndrome) *dose related neuropathy
AMINOGLYCOSIDES	*bactericidal *binds tightly to 30S ribosomal subunit ***penetration requires oxygen** dependant active transport 1.blocks formation of initiation complex 2.misleading of mRNA leading to incorporation of wrong aminoacid 3.prevent translocation of ribosomes 4.cause premature termination of translation *also mention how aminoglycosides diffuse thru porin channel and enter protoplasmic space ***PAE(aminoglycosides, quinolones, streptogramins)& conc-dependant killing**	*highly polar cations(never given orally) *given IV or IM *limited tissue penetration, donot cross BBB *excreted via GFR(with normal renal function, elimination half-life is 2-3hrs) *high conc: renal cortex,endolymph &perilymph		*gentamicin, tobramycin, amikacin: *aerobic g-infections(e.coli, enterobacter, klebsiella, proteus, providencia) *H.influenza, M.catarrhalis, shigella **SELECTIVE USES** 1.<u>Streptomycin:</u> *Rx of MDR-TB, IM *plague, tularemia, brucellosis *with penicillin for enterococcal endocarditis 2.<u>Gentamycin:</u> *most commonly used for aerobia g- *sepsis, pneumonia *endocarditis in combo with penicillin G *local application in wound *ocular infection 3.<u>Amikacin</u> *broad spectrum Ig *g-bacteria:serratia, proteus, pseudomonas, enterobcater 4.<u>Neomycin&Kanamycin:</u> *g+/- bacteria *restricted **to oral/topical use** due to their toxic potential *infected surface, joint and pleural cavity *abd surgery 5.<u>Spectinomycin:</u> *aminocyclitol drug *back-up drug administered IM for treatment of gonorrhea *pain at IM site **INCOMBO WITH PENICILLIN** *pseudomonas *listeria *enterococcal	1.<u>Ototoxicity:</u> *hence contraindicated in pregnancy(alomg with: fluoroquinolones, sulfonamides, tetracyclines) *increased by use of loop direutics *cochlear: amikacin, kanamycin *vestibular:gentamicin, streptomycin *both:tobramycin 2.<u>Nephrotoxixity:</u> *acute tubular necrosis *most common in elderly patients and those receiving cephalosporin, vancomycin, and amphotericin B *gentamicin and tobramycin most nephrotoxic *FANCONI SYNDROME: outdated tetracyclines and amnioglycosides 3.<u>Neuromuscular blockade</u>: *curare-like blockade *respiratory paralysis *Rx: calcium and neostigmine 4.<u>Skin reaction:</u> *neomycin most likely to cause *follicular dermatitis *angioedema

NUCLEIC ACID SYNTHESIS INHIBITOR					
SULFONAMIDES	*bacteriostatic *inhibitors of folic acid synthesis *competitive inhibitors of dihydropteroate synthase- prevents conversion of PABA to dihydrofolic acid	*weakly acidic compounds *modest tissue penetration, hepatic meta, excretion of intact drug and hepatically acetylated metabolites in urine *high PPB ***solubility decreased in acidic urine** *SULFSALAZINE METABOLISM BY COLONIC BACTERIA YIELDS: A)5-ASA(mesalamine) >ulcerative colitis B)SP>RA	*compete with methotrexate and warfarin for plasma protein ***displace bilirubin from plasma protein, with risk of kernicterus in neonates if used in 3rd month**	*active against g+/- organism, chylamydia, nocardia 1.simple UTI: oral, triple sulfa, sulfisosaxole 2.ocular infection: topical sulfacetamide 3.burn infection:mafenide,silver sulfadiazine 4.ulcerative colitis, rheumatoid arthritis: oral sulfasalazine 5.toxoplasmosis:oral sulfadiazine pus pyrimethamine plus folinic acid	1.Hypersensitivity: *skin rashes, fever *cross allergnicity with individual sulfonamide, oral hypoglycemic, thiazides *exfoliative dermatitis *polyarteritis nodosa ***stevens johnsons syndrome** *2.GIT disturbance: *nausea, vomiting, diarrhea 3.Hematotoxicity: *granulocytopenia *thrombocytopenia *aplastic anemia ***acute hemolysis in G6PD deficiency** 4.Nephrotoxicity: *may precipitate in acidic urine(being weak base), causing: *crystalluria, hematuria MENTION DRUG INTERACTIONS
TRIMETHOPRIM	*analogue of folic acid *selective inhibitor of dihydrofolate reductase *cotrimoxazole(trimethoprim and sulfomethaxozole) TMP-SMZ	***weak base**, concentrates in acidic urine *reaches high in prostatic and vaginal fluids *large amount excreted in urine *given orally, half-life:10hrs		TMP-SMZ: *effective orally for **UTI** ***DOC in nocardia** ***2nd DOC in salmonella** ***gram +(CA MRSA, streptococcus)** ***gram-(e.coli, salmonella, shigella)** *resp, ear and sinus infections by Haemophilus influenza, Moraxella catarrhalis *used in immunocomprised for Aeromonas hydrophila, drug of choice for **pneumocystis pneumonia** *backup drug for cholera,typhoid fever, shigellosis,MRSA, listeria monocytes	1.hypersensitivity 2.SJS syndrome, **bone marrow suppression**, hyperkalemia 3.UTI: crystaluria, hematuria 4hematologic effects: *megaloblastic anemia *leukopenia *granulocytopenia *ameliorated by supplementary folinic acid *AIDS patient with TMP-SMZ: fevr, rashes, leukopenia, diarrhea

FLUOROQUINOLONES *1st generation: norfloxacin *2nd generation: ciprofloxacin, ofloxacin *3rd generartion: levofloxacin, gemifloxacin, moxifloxacin	*interfere with bacterial DNA synthesis ***inhibits topoisomerase 2(DNA gyrase) in g-organism**>blocks relxation of supercoiled DNA catalyzed by DNA gyrase, required for normal transcription and duplication ***inhibits topo 4 in g+organism**>interfers with separation of replicated chromosomal DNA *PAE	*good oral F, penetrate most tissues *calcium ions and antacids limit their absorption *norfloxacin doesn't achieve adequate levels to be used in systemic infections *elimination by fluoroquinolones(blocked by probenecid) *morfloxacin eliminated by hepatic metabolism and biliary excretion *half life:3-8hrs		***1st gen**:UTI+gram –(but not pseudomonas) ***2nd gen**:g-(gonococci)/g+(MRSA)/atypical pneumonia(mycoplasma, chlamydia) ***3rdgen/respiratory flouroquinolones**: used for strept pneumonia, enterococci, MRSA(more gram + spectrum) ***4th gen**: anaerobic coverage as well OTHER FUNCTIONS: *used for urogenital and GIT infection caused by g- aerobic organisms:E.coli, klebsiella, C.jejuni, enterobacter, P.aeruginosa ***fluoroquinolones used for pseudomonal infectioncomplicated with cystic fibrosis in children** *for resp, skin and soft tissue infection ***cipro & ofloxacin:** gonorrhea(single dose), chlamydia trachomatis(7day) *levofloxacin: CA pneumonia, chalmydia, mycoplasma,legionella' ***gemi&moxi**: g+/g-/atypical pneumonia/anaerobic organism 1.**ciprofloxacin:** *SSTI, atypical pneumonia, shigella, SALMONELLA,campylobacter,gonococci(UTI), used in TB ***prophylaxis in anthrax** ***prophylaxis in neutropenic pateints** ***chalmydia, gonorrhea, CAP, TB** 2. **levofloxacin:** *chronic bronchitis, pneumonia, intra abd infection 3.**moxifloxacin:** Chronic bronchitis, bacterial conjunctivitis, sinusitis	***GIT distress** *skinrashes, headache, dizziness, insomnia, abnormal LFT ***photosensitivity**(tetracyclines, sulfonamides, fluroroquinolones), neurotoxicity ***tendinitis & tendon rupture**(retard growth in cartilage, hence contre-indicated in pregnancy) ***cartlage damaged anthropathy in children** *opportunistic infections by C.albicans, streptococci *increases plasma levels of theophyllines *graapfloxacin:serioud cardiotoxicity *QT PROLONGATION SEEN IN: *ciprofloxacin *moxifloxacin *gemifloxacin *levofloxacin

ANTIFUNGALS

THERAPEUTIC CLASSIFICATION:

A)DRUGS FOR DEEP SYSTEMIC INFECTIONS:

***amphotericin B**

***flucytosine**

***azoles**

***echinocandins**

***nystatin**

B)DRUGS FOR SUPERFICIAL INFECTIONS:

1)SYSTEMIC (griseofulvin, terbinafine and azoles/not posi and vori conazole)

2)TOPICAL(nystatin and azoles)

FUNGISTATIC DRUGS:

***flucytosine**

***griseofulvin**

***echinocandins(against aspergillus)**

***azoles**

FUNGICIDAL DRUGS:

***polyenes**

***echinocandins for candida**

***terbinafine**

NAME	MECHANSIM	PHARMACOKINETICS	RESISTANCE	THERAPEUTIC USES	ADVERSE EFFECTS
AMPHOTERICIN B .	***fungicidal** due to its effects on permeability and transport of fungal membranes ***amphipathic** properties *binds to ergosterol>**cause formation of artificial pores**>leakage of cellular cell and causes death of cells *exhibits concentration dependant killing	*polyene antibiotic related to nystatin ***poorly absorbed from GIT(only given orally when there is fungal infection of GIT and since its not absorbed it stays in lumen)** *adm IV, as a nonlipid colloidal suspension, lipid complex, or a liposomal complex *intrathecal adm:fungal meningitidis *widely distributed to all tissues except CNS *eliminated via hepatic meta, half-life:2 weeks *small fraction eliminated by urine, hence dose modification only in renal failure *amphoteric: soluble in both acidic and basic environment	*reduction in ergosterol biosynthesis *synthesis of alternate sterols, or modification of target sterols that lessen the ability of amphotericin B to interact with the fungal membrane *structural change in membrane sterols	*used for **initial induction** regimes and treatment of **systemic mucoses** *widest antifungal spectrum, drug of choice for all life threatening fungal infection ***candida esophagitis** *meningitis caused by coccidioides *aspergillosis *blastomycoses ***Cryptococcus** *histoplasmosis ***mucormycosis** *local application**: mycotic corneal ulcers and keratitis** *****nystatin: too toxic for systemic use>used topically for localized infections(candidiasis)	1.**Infusion related:** *fever, chills, muscle spasms, vomiting, headache, hypotension *premed with anti-pyretics, anti-histamines, steroids,meperidine 2.**Cumultative** * nephrotoxicty(dose limiting>amphotericin B being lipid soluble crosses human cell membrane>forms pores in renal tubular cells>causes nephrotoxic effects *lipid formations less nephrotoxic&volume expansion with IV normal saline before drug administration decreases dose dependant effect *renal toxicity manifests as renal tubular acidosis, severe muscle K+ and Mg2+ wasting , GFR dec MECHANISM: IV drug infusion of amphotericin B>vasodilation to prevent hypertension>hypotension in body occurs>GFR dec and urine production dec>H+excretion

					dec>retention of H+ inside tubules>(1) RTA occurs (2) compensatory loss of K+ and Mg2+ from cells *anemia due to erythropoietin deficiency 3.Neurotoxicity: *intrathecal adm causes seizures and neurological damage
5-FLUOROCYTOSINE	*accumulate in the fungal cells by action of **membrane permease** *converted by **cytosine deaminase** to 5FU >converted to 5 FdUMP>inhibitor of thymidylate synthase enzyme>decreased formation of TMP to dUMP > decreased DNA methylation leads to impaired DNA synthesis	*5-FC(flucytosine) is a pyrimidine metabolite converted to anti -cancer drug 5-Fluorouracil(5-FU) *penetrates into CNS as well *eliminated intact in urine, dose modification in renal damage!	*resistance develops in flucytosine used alone *low levelsof deaminase and permease *synergism with amphotericin or azole reduces resistance	*anti-fungal spectrum narrow(3Cs!) *used in combo with amphotericin B, and azole ***cyptococcus neoformans** ***chromoblastomycosis caused by molds** ***systemic candida infection** *all candida species except C.krusei	*reversible bone marrow depression *alopecia *liver dysfunction
AZOLES IMIDAZOLE: *ketoconazole *clotriconazole *micoconazole TRIAZOLES: *itraconazole *fluconazole *posaconazole *voriconazole	*fungicidal>decreases ergosterol **synthesis by inhibition of fungal CYP 450** enzyme(prevent 14alpha-demethylation of **lanosterol**) *reduces **fungal membrane ergosterol conc** results in damaged, leaky	*oral F is variable(normal gastric acidity is required) *absorption of ketoconazole decreased by antacid *absorption of itraconazole increased by food *fluconazole, posaconazole,isavuconazole, voriconazole:readily	1.mutation in ERG11, gene encoding for 14-sterol demethylase 2.increased azole efflux by both ATP binding cassette and other facilitator transporter family 3.increased	1.**Topical infection**(ketoconazole, miconazole,clotrimazole) *ring worm(tineacapitis, corporis) *onychomycosis *oral candidiasis(thrush) 2.**Disseminated systemic infections**(itraconazole, voriconazole, posaconazole) *invasive aspergillosis *cryptococcus *candidiasis	*GIT side effects *Rash & SJ syndrome *severe hepatotoxicity in some instances requiring discontinuation of drug *hypokalemia *hyperTAG ***enzyme inhibitors**: *ketoconazole notorious inhibitor of CYP450, increases levels of cyclosporine,oral hypoglycemic, phenytoin, warfarin

	membranes and **decreased permeability**	absorbed via oral route *only fluconazole can enter CNS(used in meningeal infection) *liver meta responsible for elimination of ketoconazole, itraconazole, posaconazole, voriconazole(except fluconazole>urine!) *inducers of drug meta enzymes(rifampin) decreases itraconazole	production of C14-sterol demethylase *seen in long term prophylaxis and immunocompris ed and neurtropoenic patients	3.Individual uses: ***ketoconazole**:Co-DOC for paracoccidiodes and back up for blastomyces and histoplasma *oral uses for:chronic muco-cutaneous candidiasis&dermatophytes ***itraconazole**: **drug of choice** against systemic infections caused Blastomyces, Sporothrix and for subcutaneous chromoblastomycosis ***alternative drug** against infection caused by aspergillus, coccidiodes, Cryptococcus, histoplasma ***esophageal candidiasis useful for strains resistant to fluconazoles** *used extensively against dermtophytes, esp onychomycosis ***voriconazole**: wider spectrum than itraconazole**, co-drug** of choice for treatment of invasive aspergillosis ***alternative drug** in candidemia, **and in AIDS patient with candida esophagitis and stomatitis** ***posaconazole**:**broadest spectrum triazole,** *against most species of candida and aspergillus ***only azole active against Rhizopus**(agent for mucormycosis) ***prophylaxis of fungal infections** during cancer chemotherapy *1st DOC for angio invasive aspergilosis(voriconazoles, amphotericin B also used, but are Co-DOC)	*inhibition of CYP 450, interfers with the synthesis of adrenal and gonadal steroids leading to gynecomastia, menstrual irregularities , and infertility ***ketoconazole:hypokalemia,gynecomastia** *voriconazole: immediate but transient visual disturbances *posaconazole inhibitor of CYP3A4, increasing levels of cyclosporine and tacrolimus
FLUCONAZOLE	Like azoles	*oral and i/v		1.**drug of choice** oropharnygeal candidiasis	*nausea, vomiting,

		*complete absorption *bioavailability unaltered by food/gastric acidity *elimination:half-life:25-30hrs *renal excretion accounts for >90% elimination** *11% protein binding *diffuse readily in all body fluids including CSF!		and esophageal infections:fluconazole 200mg on first day, then 100mg daily for atleast 2 weeks 2.uncomplicated vaginal candidiasis:a single dose of 150mg 3.**drug of choice** and **secondary prophylaxis** against cyptococcal meningitis:400mg daily for 8 weeks 4.**alternative drug** to amphotericin B in cryptococcus neoformans & candidemia 4.coccidiodal meningitis(good penetration into CSF)	diarrhea, headache, abd pain
ECHINOCANDINS (novel:caspofungin Older:anidulafungin, micafungin)	***fungicidal** action, **inhibits synthesis of B-glucan(1-3)**, a component of fungal cell wall	*only I/V(distributed widely to tissues) *eliminated via hepatic metabolism(monitor LFTs) *half-life of caspofungin:9-12hrs *half-life of micafungin slightly longer *half-life of anidulafungin:24-48hrs		*aspergillus ***caspofungin** used for systemic and disseminated muco-cutaneous candidainfection**(patients unresponsive to amphotericin B**) & mucor mycosis ***anidulafungin**: used for esophageal and invasive candidiasis ***micafungin**: use for mucocutaneous candidiasis and for **prophylaxi**s of candida infection in bone marrow transplant patient	*well tolerated *infusion related: ***caspofungin:** headache, GIT distress, fever, rash,flushing ***micafungin:** causes histamine release and elevates blood levels of immunosuppressant drugs: cyclosporine and sirolimus
GRISEOFULVIN	*insoluble fungistatic drug *distributed to stratum corneum>interacts with polymerized microtubules>disrupts mitotic	*orally active drug(absorption unaided by high fat food) *drug distributed to stratum corneum, binds to keratin *biliary excretion is responsible for	*resistance due to decrease influx by enegy dependant mechanism	*mycotic disease of skin, hair and nails due to :microsporum, trichophyton, epidermophyton *efficacy best for tinea capitis	*headache, mental confusion, GIT irritation, photosensitivity *decreases the F of warfarin *di-sulfiram like reaction *contraindicated in

	spindles>arrests fungal growth *inhibits synthesis and polymerization of nucleic acid	elimination *ultramicrosize formulation better absorbed and aided by high food content			porphyria!!!
TERBINAFINE	***fungicidal** ***inhibition of fungal squalene epoxidase** *blocks ergosterol biosynthesis ***inc intra-cellular conc of squalene** also impairs ergosterol biosynthesis	*not absorbed from GIT tract, skin or vagina *supplied in prep intended for cutaneous, vaginal, oral administration in forms of creams, ointments, suppositerties		*nail onychomycosis(more effective than griseofulvin) *tinea capitis	*GIT upsets, rash, headache, taste disturbance *doesn't inhibits CYP 450
NYSTATIN	*similar to amphotericin B			*useful for candidiasis(topical) *eradicate GIT fungi	

ANTIHELMINTHS

AGAINST NEMATODES: albendazole, mebendazole, diethylcarbamazepine, ivermectin, pyrantel pamoate

AGAINST TREMATODES: bithionol, oxamniquine, praziquantel, metrifonate

AGAINST CESTODES: albendazole, mebendazole, praziquantel, niclosamide

***albendazole: ascaris, ankylostoma, trichuris, cutaneous larva migrans**

***mebendazole: ascaris, ankylostoma, enterobiuc, trichinella**

***pyrantel pamoate: ascaris, ankylostoma, enterobius**

***ivermectin: strongyloides, onchocerca volvulus**

***diethylcarbamazepine: wucheria and bruglia**

***praziquantel: schistoma haematobium, schistosoma mansoni, schistosoma japonicum,paragonimus westermani, fascialopsis buksi**

NAME	MECHANISM	PHARMACOKINETICS	CONTRAINDICATIONS	THERAPEUTIC USES	TOXICITIES
ALBENDAZOLE	*inhibition of microtubule assembly, by binding to beta tubulin>immobilization>death of parasites *larvicidal:ascariasis,cysterserosis,hookworm, hydatid disease *ovicidal:ascariasis, acylostomiasis, trichuriasis	*erratic oral absorption *increased with fatty meal *rapid 1st pass metabolism *half-life:8-12hrs *highly protein bound *excreted in urine	*hypersensitivity *pregnancy *children<2 years *cirrhosis	*wide anti-helminth spectrum of action ***primary drug: ascariasis, ancyclostoma duodenale, enterobius vermicularis** *alternative drug: **threadworm infections**, filariasis, both visceral and **cutaneous larva migrans** *also used in **hyatid disease**, and active against pork tapeworm in larval stage(**cysticercosis)**	*1-3days: GIT distress, headache,lassitude, insomnia *long-term: reversible leukopenia, alopecia, elevation of liver enzymes, fetal toxicity, urticarial *bone marrow suppression
DIETHYLCARBAMAZEPINE	*immobilize microfilariae by unknown mechanism *increases their susceptibiltity to host defense	*rapid oral absorption *halflife (acidic urine): 2-3hrs *halflife (alkaline urine): 10hrs		*severe filarial infections caused by **Wuchereria, Bruglia malayi** *eye worm disease Loa Loa	*headache, fever,malaise, anorexia ****mazzoti reaction**: (also seen with ivermectin)reactions to proteins released by dying filarial; fever, rash, ocular damage, lymphangitis,esosinophilia

					*in onchocerciasis: hypotension, respiratory distress, prostration, pyrexia
IVERMECTIN	***intensifies GABA mediated neurotransmissio m** ***leads to immobilization of parasites** ***facilitating the removal of RES** *selective toxicity just for nematodes, as ivermectin doesn't cross BBB	*rapid absorption *volume of distribution: 50L	*pregnancy *drugs that increase GABA mediated transmission: barbiturates, benzodiazipines , valproic acid	***drug of choice for onchocerciasis** ***strongyloidiasis**, ascariasis, trichomoniasis, scabies ***cutaneous larva migrans**	*single oral dose for treatment to dying worms**(mazzotti reaction)** results in fever, headache, dizziness, prurities, tachycardia, pain in joints and lymph nodes *these reduced with anti-histamines,NSAIDS
MEBENDAZOLE	***selectively inhibits microtubule synthesis and glucose uptake** in nematodes	*poor absorption: increased with fatty meal *70% PPB *tablet chewed before swallowing	*cirrhosis *children<2 years *pregnancy	***primary drug for ascariasis, enterobius, trichuriasis** *also used in visceral larva migrans *hyatid disease	*limited to GIT irriration *high dose: granulocytopenia, alopecia *plasma levels decreased by carbamazepine, phenytoin *increased by cimetidine
PIPERAZINE	*paralyzes Ascaris by blocking acetylcholine at myoneural junction *paralyzed round worms expelled by normal peristalsis	*poor absorption *excreted in feces	*pregnancy *hepatic/renal disease *seizure disease	*alternative drugs for ascariasis	*mild GIT irritation

PYRANTEL PAMOATE	***stimulates nicotinic receptor at NMJ of nematodes** ***contraction of muscles occur** ***followed by depolarization induced(spastic) paralysis** *no action on flukes or tapeworm	*oral and dermal application *rapidly absorbed from gut *excreted in urine	*hepatic dysfunction	*wide activity againt nematodes *killing adult worms in the colon but not intestine ***drug of choice for ancylostoma and ascaris!** ***alternative drug for enterobius vermicularis**	*minor *GIT distress, headache, weakness, abdominal cramps
THIABENDAZOLE	*structural congener of mebendazole *similar action on microtubule(inhibits microtubule synthesis)	*rapidly absorbed *PPB: 80% *rapidly metabolized to inactive mono and poly hydroxylated products *half-life:0.8-1.5hrs *60-80% excreted via kidney *15-35%excreted via bile	*pregnancy *hepatic and renal disease	*alternative drug for **strongyloidiasis(to ivermectin) a nd trichinosis(to mebendazole**) *anti-inflammatory and immunorestorative action in host	*common: GIT irritation, headache, dizziness, leukopenia, hematuria, intra hepatic cholestasis *reaction caused by drying parasites: fevr, chills, lymphadenopathy, *irreversible liver failure, fatal steven Johnson syndrome
TREMATODES					
PRAZIQUANTEL	***increases membrane permeability to calcium>marked contraction initially>paralysis of trematode and cestode>followed by vacuolization and parasite death**	*orally effective *eliminated in urine	*pregnancy *ocular cysticerosis *causes dizziness so avoided in driving	*tapeworm infections *trematodes/cestode(doc) ***neurocysticercosis(alternative to albendazole**), not ocular cysticercosis! *hyatid disease(adjunct) ***drug of choice in schistosomiasis, clonorchiasis, paragonimiasis** *active against immature and adult schistosomal forms ***alternate to niclosamide to cestode infection**	*common: headache, dizziness, drowsiness, malaise *less frequent: GIT irritation, skin rash, fever, arthralgia, myalgia, urticaria *liver enzymes elevation, eosinophila *may exacerbate inflammation around dying parasites: headache, meningismus *more serious:arachnoiditis, hyperthermia, intracranial hypertension *intracranial

					hypertension and seizure in treatment of neurocysticercosis(corticosteroids reduce severity)
BETHIONOL	*mechanism unknown			***co-drug of choice(with triclabendazole) for treatmrnt of fascioliasis(sheep liver fluke**) ***alternative agent in paragonimiasis**	*nausea, vomiting, diarrhea, abd cramps, dizziness, headache, skin rash *less frequent: pyrexia, tinnitus, proteinuria, leukopenia
METRIFONATE	***organophosphate prodrug** converted in body to cholinesterase inhibitor **dichlorvos**>active meta against schistosoma haematobium(cause of bilharziasis)		*contraindicated in pregnancy	***low cost effective against Schistosoma haematobium**	*due to excess cholinergic stimulation
OXAMNIQUINE	*paralysis of worms		*seizures *pregnancy	*effective solely in Scistosoma mansoni infection(intestinal bilharzizsis) *acts on male immature forms and adult schistosomal forms	*dizziness**(no driving for 24hrs)** *headache, irritation, pruritis *eosinophilia, urticarial, pulmonary infiltrate
CESTODES NICLOSAMIDE	*acts by **uncoupling oxidative phosphorylation** *or **by activating ATPase** ***rapidly kills worms, not ova**		*ethanol consumption avoided for 24hrs	*alternative drug to praziquantel for infections caused **by beef, pork and fish tapeworm** *scoleces and cestodes segments are killed, not ova	*toxic effects mild, include GIT distress, headache, rash, fever(due to systemic absorption of antigen from disintegrating parasite)

ANTIMALARIALS

1.TISSUE SCHIZONTICIDE: primaquine

2. BLOOD SCIZONTICIDE: chloroquine, artemisins, quinine,mefloquine,pyrimethamine,lumefantrine,artemsins

3.GAMETOCIDE: choloquine and quinine for vivax and primaquine for falciparum

IMP DRUG COMBINATIONS:

1.coartem: artemether+lumefantrine (treatment of uncomplicated malarial infection which is choloquine resistant….1st line drug)

2.malarone: atovaquone+proguanil (prophylaxis of chloroquine resistant malaria and mefloquine resistant malaria)

3.fansidar: sulfadoxine+pyrimethamine(Rx of choloquine resistant malaria)

DRUGS SAFE IN PREGNANCY:	DRUGS CONTRAINDICATED IN PREGNANCY:
1)CHOLOQUINE	1)QUININE
2)ARTEMISINS COMPOUND	2)PRIMAQUINE
3)MEFLOQUINE	3)HALOFANTRINE
4)FANSIDAR&MALARONE	

CHEMOPROPHYLAXIS OF MALARIA/TRAVELERS MALARIA:

*__CHOLOQUINE SENSITIVE__: CHOLOQUINE(500mg weekly)

*__CHOLOQUINE RESISTANT__:

1.MEFLOQUINE(250mg weekly)

2)MALARONE(1tab daily,25mg atovaquone&100mg proguanil)

3.AMODIAQUINE

4.DOXYCYCLINE(MDR)

*__FOR RADICAL CURE OF P.VIVAX AND P.OVALE__: PRIMAQUINE

TREATMENT OF MALARIA: (ACUTE INFECTIONS)

*CHOLOQUINE

*IF RESISTANT TO CHOLOQUINE: ARTEMETHER(COARTEM)

*QUININE:CHOLOQUINE RESISTANT INFECTIONS WHO CAN TOLERATE ORAL Rx TO QUININE

*QUINIDINE:SEVERE/COMPLICATED MALARIAL INFECTIONS

*MEFLOQUINE(ACUTE ATTACK AND UNCOMPLICATED MALARIAL INFECTIONS)

*FANSIDAR

CHEMICAL CLASSIFICATION(asked in proff)

*4-aminoquinolones;choloquine and amodiaquine

*4-quinolone methanol:mefloquine

*8-aminoquinolone:primaquine

*quinine containing enchona alkaloids:quinine&quinidine

*sulfonamides:sulfapyrimethamine&sulfadoxine

*tetracyclines:doxycycline

NAME	MECHANISM OF ACTION	PHARMACOKINETICS	CONTRAINDICATIONS	THERAPEUTIC USES	TOXICITIES
CHLOROQUINE	*accumulates in food vacoule of organism(role of pH gradient)>**prevents polymerization of heme to hemozoin**>intacellular accumulation of heme toxic to parasite *resistance due to **mutation in pfcrt**, and **increased efflux mechanism** ***verapamil** restore chloroquine concentration ability	*completely absorbed from GIT *large Vd:100-1000l/kg(loading dose) *excreted in urine *has affinity for melanin *concentrates in liver, spleen, kidney,lungs	*psoariasis *porphyria *myopathy *retinal damage	1.**drug of choice for non-falciparum and sensitive falciparum malaria and for chemoprophylaxis(500mg/weekly)** 2.**erythrocytic** for all four species, gametocidal for vivax, ovale, malaria 3.**amebic liver abscess** 4.**RA, SLE, sarcoidosis** 5.also is **anti-I nflammatory, antipyretic, anti cohistamine, local anaesthetic, local irritant , muscle relaxant**	***low dose:** GIT irritation, skin rash, headache ***high dose**: skin lesions, peripheral neuropathies, myocardial depression, retinal damage, auditory impairment, toxic psychosis *drug interactions: anti-diarhea calcium and magnesium containing antacids SAFE IN PREGNANCY

QUININE	*__complexes with dsDNA__>prevents strand separation>results in block of DNA replication and transcription to RNA	*rapidly absorbed orally *excreted via kidney *quinidine has shorter half-life than quinine	*cinchonism *hypersensitivity/hemolysis *cardiac abnormality	1.__IV for severe complicated falciparum malaria(quinidine dextro rotatory form of quinine__) 2.__oral__ for uncomplicated __3.given in children in combination with clindamycin/doxycycline to shorten the duration of therapy and limit toxicity__ 3.not given prophylactically to delay emergence of resistance 4.__cerebral malaria__ __5.babesiosis__	1.CINCHONISM; Tinnitus, vertigo, headache, hyperthermia, blurred vision 2.hypoglycemia 3.oxytoxic(when delivered in 3rd trimester) 4.thrombophlebitis 5.atropine like effects 6.hemolysis in G6PD deficiency 7.black water fever-hemoglobinuria and hematuria
MEFLOQUINE	*synthetic 4-quinolne derivative(chemically related to quinolone) *__blood schizonticide__	*can be only given orally *severe GIT irritation on IV use *well absorbed, highly protein bound *extensively distributed	*epilepsy *psychiatric disorder *cardiac conduction defect *not administered with quinine(QT prolongation)	*__first drug in prophlaxis__ against chloroquine resistant malaria(once weekly) *__alternative to quinine__ in acute and uncomplicated attacks of P.falciparum *__mefloquine+artesunate=WHO uncomplicated malaria__	*common: GIT distress, skin rash, headache, dizziness *high: cardiac conduction defects, psychiatric disorder, seizures
PRIMAQUINE	*synthetic 8 aminoquinilone *__forms quinolone-quinone complex>electron transferring redox compound>acts as cellular oxidants__ *tissye schizonticide	*well absorbed orally	*pregnancy *G6PD deficiency	1.__chemoprophylaxis against all four species__, active against hepatic stage of vivax and ovale 2.__radical cure and terminal prophylaxis of vivax and ovale(daily__) 3.chemoprophylaxis (once weekly) 4.__gametocidal(single dose against falciparum__)	*nausea, vomiting, headache *leukopenia, agranulocytosis *methhemoglobinemia *G6PD deficiency

				5.alternative for primary prevention	
ANTIFOLATES	*__sulfonamides(dapsone and sulfadoxine inhibit dihydropteroate synthase__ *proguanil bioactivated to cycloguanil *__pyrimethamine and cycloguanil acts as selective inhibitors of dihydrofolate reductase__ *__pyrimethamine and sulfadoxine act synergistically__ through a sequential blockade of folate acid synthase	*absorbed orally *excreted in urine *proguanil has shorter half-life(12-16hr)	*caution in liver and renal damage	*blood schizonticide act mainly against plasmodium falciparum *__pyrimethamine+sulfadoxine: fansidar__: treatment of chloroquine resistant forms *__proguanil+atovaquone:malarone__:daily for chemoprophylaxis for both chloroquine and mefloquine resistant stains Hence: 1. Chemoprophylaxis 2. intermittent preventative therapy: *fansidar *single dose in 2nd and 3rd trimester *monthly dose in children with routine schedule immunization 3.Chloroquine resistant falciparum: uncomplicated falciparum 4.__toxoplasmosis__: fansidar(1st line treatment) 5. __pneumocystitis jiroveci__(other drugs include TMP-SMX, clindamycin, primaquine, atovaquone)	*GIT distress, hemolysis, kidney interaction *sulfonamides PPB binding and hence displace drugs *pyrimethamine : folic acid deficiency *fansidar: erythema multiform, steven Johnson __syndrome__,toxic epidermal necrolysis *agranulocytosis *in Rx of pneumocyctiti jiroveci(nausea, vomiting, fever, rash, keukopenia, thrombocytopenia)
ARTEMISINS(artesunate, artemether, dihydroartemisinin)	*__metabolized in food vacuole of organism>forming toxic free radical__ *__blood scizonticide__ against MDR falciparum *not used alone due to their short half-life	*short half-lfe(1-3hrs)		*__1st choice__ for chloroquine resistant malaria *against quinine-resistant malaria	*nausea, __vomiting__, diarrhea, hemolysis, neutropenia
DOXYCYCLINE	*a __tetracycline antibiotic__			*used in combo with quinine in children *__chemopropylaxis in travelers to geographical areas with MDR__ falciparum	

AMODIAQUINE	*closely related to chloroquine	*low toxicity, higher efficacy		***chloroquine resistant strains of P.falciparum** *amodiaquine+artesunate: falciparum malaria resstant to other drugs ***amodiaquine+sulfadoxine: 3-4 times weekly prophylaxis**	*agranulocytosis *aplastic anemia *hepatotoxicity
ATOVAQUONE	*hydroxynapthoquine *atovaquone(25mg)+proguanil(100mg)=malaron ***disrupts mitochondrial ETC**	*half-life:2-3 days *orally administered, increased with fatty foods		*Rx of pneumocystitis jiroveci *both chemoprophylaxis and treatment of falciparum malaria	*abdominal pain *GIT effects
HALOFANTRINE			* pregnancy *QT prolongation	*erthrocytic of all 4 species ***not used for prophylaxis** ***lumefantrine: minimal drug with cardiotoxicity** ***lumefantrine used in combo with artemether:coartem**	*embryotoxiciy *QT prolongation

ANTI-AMEBIASIS

THERAPEUTIC CLASSIFICATION:

1.**DRUGS EFFECTIVE AGAINST LUMINAL INFECTIONS**:

*Amide: diloxanide furoate(1st line)

*8-hydroxy derivative: iodoquinol(resistant to diloxanide), diiodohydroxyquin

*antibiotics: paramomycin, tetracyclines

2.**TISSUE AMEBICIDES:**

*4-aminoquinolone derivative: choloquine(for extraintestinal amebiasis)

*nitroimidazoles: metronidazole, tinidazole

*alkaloids:emetine(resistant to metronidazole), dihydoremetine

3.**BOTH:**

*metronidazole, tinidazole, emetine, dehydroemetine

CHEMICAL CLASSIFICATION:

*NITROIMIDAZOLE DERIVATIVES: metronidazole, tinidazole, benzidazole, nimorazole

*DICHLOROACETAMIDE DERIVATIVES: diloxanide furoate, etofamide

*4-AMINOQUINOLINE:chloroquine

*ALKALOIDS/IPECACAUCAUNHA: emetine/dehydroemetine

*ANTIBIOTICS: tetracyclines, paramomycin

*8-HYDROXYQUINOLONE DERIVATIVES: iodoquinol, broxyquinoline

DRUG REGIMES:

***ASYMPTOMATIC INFECTIONS**: diloxanide furoate

***MILD TO MODERATE INFECTIONS**: metronidazole & plus luminal agent

***SEVERE INTESTINAL INFECTIONS**: metronidazole/tinidazole + luminal agent

* **INFECTIONS: HEPATIC ABSCESS/ EXTRAINTESTINAL**: metronidazole/tinidazole+ luminal agent

NAME	MECHANISM OF ACTION	PHARMACOKINETICS	THERAPEUTIC USES	ADVERSE EFFECTS
TISSUE AMEBCIDES				
METRONIDAZOLE	***undergoes a reduction bioactivation of its nitro group>forms highly active nitroradical>by ferridoxin present in the anaerobic parasite>forms reactice cytotoxic products>DNA fragmentation** *in anaerobic infections *ferridoxin low redox potential electron transport proteins responsible for metabolic electron removal reactions	***effective orally** *widely distributed to tissues ***readily absorbed from GIT** *PPC 13hrs *PPB 10-20% *half-life of metronidazole:6-8hrs(duration of Rx longer) *half-half of tinidazole:12-14hr(twice daily) ***excreted in urine**	*drug of choice in severe **intestinal wall disease** and in **hepatic abscess**, and in **extraintestinal amebic liver disease** *drugs used with luminal amebicides ***drug of choice for** : 1.amebiasis(intestinal and hepatic) 2.giardiais 3.trichomoniasis 4.blantidiasis 5.H pylori infections(combo therapy) 6.pseudomembrane enterocolitis 7.bacteroides fragilis endocarditis 8.acne 9.brain and lung infections 10.crohns disease with perianal involvement 11.gingivitis 12.hepatic encephalopathy *tinidazole in metronidazole resistant strains of	***gastrointestinal irritation**(taken with meals): Dry mouth, nausea, vomiting, metallic taste, cong &furring of tongue, glossitis, pancreatitis, stomatitis *headache, paresthesia,dark coloration of urine ***neurotoxic effects**: Insomnia, weakness, dizziness, parestheia, seiures, ataxia, encephalopathy *allergic reactions, dysuria, cystitis, carcinogenic in rodents, mutagenic in bacteria ***MORE SERIOUS:** neutron penia, dizziness, ataxia *tinidazole less toxic ***DRUG INTERACTION**: *disulfiram like action with ethanol *potentiation of coumarin anticoagulants *phenytoin & phenobarbitone increase elimination *cimetidine decreases plasma clearance *lithium toxicity

			trichomoniasis & giardiasis equal efficacy	CONTRAINDICATION: PREGNANCY & LACTATION
EMETINES	*emetine &dihydroemetine>**inhibit protein synthesis by blocking movemet of ribosome along mRNA**	*sub cutanoues *IM	*back-up drug for severe **intestinal/hepatic liver amebiasis** together with luminal agent **in hospitalized patient** *RESTRICTED TO SEVERE AMEBIASIS WHEN METRONIDAZOLE CANNOT BE USED	*GIT distress *muscle weakness ***CVS dysfunction(arthymias and congestive cardiac failure)**
CHLOROUINE		*given orally , concentrates in liver	*hepatic liver abscess *given with metronidazole to ensure complete eradication of trophozoies in liver	
LUMINAL AMEBICIDES				
DILOXANIDE FUROATE	*converted in gut to diloxanide freebase forms>active amebicide		*SOLE agent for Rx of asymptomatice amebiasis *mild intestinal disease	*mild *GITsymptoms
IODOQUINOL	*halogenated hydroxyquinolone	*orally active *take with meals	*alternative to diloxanide for mild to severe intestinal infections	*mild GIT upset *IODINE TOXICITY: thyroid enlargement and skin rash *peripheral neuropathy *visual dysfunction

PARAMOMYCIN	*aminoglycoside antibiotic		*superior to diloxanide in asymptomatic infections *efficacy against **cryptosporodiasis in AIDS patient** ***lesihmaniasis**	*systemic absorption in renal insufficiency leads to headache, dizziness, rash, **arthralgia**
NITROXANIDE			*various protozoa(E. hitolytica) and helminthes *GIT infection caused by **giardia** and **cytptosporidium hominis** *metronidazole resistant protozoa	

ANTI-MYCOBACTERIAL

FIRST GENERATION DRUGS:

*high anti-Tb effect

*acceptable degree of toxicity

*used routinely

1.ISONIAZID

2.RIFAMPIN

3.ETHAMBUTOL

4.PYRIZINAMIDE

5.STREPTOMYCIN

SECOND GENERATION DRUGS:

*low anti-Tb effect

*high degree of toxicity

*used in special circumstance only

1. PARAAMINOSALICYIC ACID

2.ETHIONAMIDE

3.AMIKACIN

4.OFLOXACIN/CIPROFLOXACIN

5.CYCLOSERINE

6.RIFABUTIN

7.CLARITHROMYCIN/AZITHROMYCIN

DIFFICULTY TO Rx MYCO-TB:

1.antibiotic active against rapidly growing bacteria(tb: slowly growing)

2.mycobacteria gets dormant, completely resistant to drugs

3.lipid rich cell wall resistant to drugs

4.bacteria located intracellularly, and gets difficult for drug to penetrate into cell

5.developement of resistance'

6.caseation & fibrosis block supplying necrotic area

RATIONALE BEHIND COMBO THERAPY:

1.to prevent emergence of resistance

2. drugs like isoniazid & rifampin act synergistically while pyrazinamide act during inflam phase

3.reduce the duration of Rx

4.to act simultaneously on all subtypes of myco tb

STANDARD REGIMES:

***<4% INH resistance:**

INH, rifampin, pyrazinamide (2 months)

INH, rifampin (4 months)

***>4%INH resistance:**

Rifampin+pyrizamide+ethambutol/streptomycin

***MDR (to both INH & rifampin):**

-3 drugs for 18 months

-12 months after culture becomes +

ALTERNATIVE REGIMES:

*INH & rifampin (9 months)

*INH & ethambutol (18 months)

DRUGS FOR LEPROSY:

*DAPSONE(sulfones)
*clinical use: for Rx of leprosy, used in combination with rifampin

*TOXICITY: GIT distress, skin rash, METHMOGLOBINEMIA & HEMOLYSIS IN G6PD DEFECIENCY

DRUGS FOR MAC: cause of diiseminated infection in AIDS

*PROPHYLAXIS: macrolide(clarithromycin/azithromycin) & rifabutin

*Rx: macrolide+ rifabutin+ ethambutol

NAME	MECHANISM OF ACTION	PHARMACOKINETICS	RESISTANCE	THERAPEUCTIC USES	ADVERSE EFFECTS
1ST LINE					

DRUGS					
ISONIAZID	*structural congener of pyridoxine 1.prodrug…requires bioactivation(by catalase peroxidase encoded by catG gene)inhibits acyl carrier protein reducatse and beta ketoacyl ACP synthase>inhibition of synthesis of mycolic acid 2.inhibits glycolysis 3. inhibits nucleic acid synthesis and stress response *bactericidal against actively growing tubercle bacilli, less effective against dormant organism *25-30mg of pyridoxine(vitB6) given as isoniazid inhibits pyridoxine phosphokinase *given to prevent peripheral neuropathy (muscle twitching)	*well absorbed orally *penetrates cells to act upon intracellular bacteria *therapeutic CNS levels when meninges are inflammed *metabolism by acetylation: *slow acetylators:3-4hrs *fast acetylators:60-90min *dose:5mg/kg(upto 300mg)PO daily	*high level resistance associated with **mutation in katG** gene>encodes for catalase-peroxidase>involved in bioactivation of of INH *low level resistance>occurs via **deletion in inhA** gene>encodes for target enzyme, an acyl carrier protein(fatty acid synthase)	1.single most important drug for tuberculosis *component of drug regimes 2.treatment of latent infection, including skin test converters, including close contact with active patients, INH sole drug	*SLE like syndrome *hepatotoxic, may cause abnormal LFTs, jaundice, hepatitis(hepatotoxicity rar in children) *G6PD hemolytic anemia *peripheral neuropathy(peripheral neuritis, restlessness, muscl twitching)>>>>increased ris with DM, malnutrition, anemia (pneumonic-SHAP) *inhibits metabolism of dru like carbamazepine, phenytoin, warfarin, stavudine, didanosine(henc you must reduce dose)
RIFAMPIN	*derivative of rifamycin *bactericidal against myco tb *inhibits DNA dependant RNA polymerase(encoded by rpo gene)>inhibits bacterial RNA synthesis>no transcription nor translation of proteins>no growth and multiplication of bacteria>bactericidal effect of bacteria ALSO *effective against g+, g-bacteria,S.aureus,H.influenza, Ecoli,pseudomonas,proteus, legionella	*given orally *distributed to CNS *undergoes enterohepatic metabolism>partially metabolized in liver *both free drug and metabolites are orange colored, eliminated in feces	*resistance occurs via changes in drug sensitivity of polymerase *mutation in rpo gene>defective beta-subunit of RNA polymerase>decreased Binding of rifampin to RNA polymerase>decreased drug sensitivity and action	1.primary drug for use in active TB in combination(optional drug in LTBI) 2.sole drug in INH-resistant and INH-intolerant patient 3.in leprosy given monthly delays the emergence of resistance 4.in combo with vancomycin for use in MRSA and PRSP 5.meningococcal and staphylococci carrier states OTHER RIFAMYCIN: 1.RIFABUTIN *less likely to cause drug interactions *preferred over rifampin in **TB co-**	*colors sweat, urine and tears orange(harmless though contact lens staind permanently) *light chain proteinuria(nephrotoxic) *skin rash, thrombocytopenia, nephriti liver dysfunction *flu like syndrome and anemia with intermittent doses *enhances elimination of anti-convulsants, contraceptives, steroids, cyclosporine, ketoconazole, warfarin(hence never given rifampin to female taking or contraceptives) REMEMBER THREE SYNDROMES: 1.Respiratory syndrome

				infected with HIV receiving HAART 2.RIFAPENTINE: *more potent *kinetics for once daily dosing *for LTBI 3.RIFAXIMIN: *not absorbed from GIT *for **travelers diarrhea**	(breathlessness, shock, collapse) 2.cutaneous syndrome 3.flu like syndrome
ETHAMBUTOL	*bacteriostatic but at larger conc bactericidal 1.inhibit arabinosyltransferase(encoded by embCAB operon)>involved in synthesis of arabinogalactan and lipoarabinomannan synthesis>a component of mycobacterium cell wall 2.disrupts formation of cell wall 3. active against actively dividing bacilli	*well absorbed orally *distributed to most tissues, including CNS *eliminated unchanged in urine(dose reduction in renal impairment) *clearance:75% in urine(adjust dose in kidney disease) *dose:15-25mg/kg PO daily	*resistance in emb gene	*component of many drug regimes against active TB *atypical mycobacteria>MAC	1.dose dependant visual disturbances: *decreased visual acuity *red-green color blindness *optic neuritis *retinal damage 2.headache and confusion 3.hyperuricemia and hypothyroidism 4.peripheral neuritis *NEVER ADMINSTER LESS THAN 6YEARS
PYRAZINAMIDE	*mech unknown *requires metabolic activation to pyrizanoic acid by pyrazinamidases(encoded by pncA gene) *inhibits mycolic acid synthesis *mainly static, cidal at high concentrations(concentration and susceptibility dependant) *ACTIVE DURING INFLAMMATORY STATES *ALSO AN STERILISING AGENT:TO REDUCE LEVELS OF MYCOBACTERIUM TB IN CNS	*well absorbed orally *penetrates body tissues including CNS(inflamed meninges) *plasma half-life increased in hepatic/renal failure	*mutation in gene encoding for bioactivation of pyrazinamidase *increased expression of efflux pumps *develops quickly if used as monotherapy	*short course treatment regimes	*nongouty polyarthralgia(hyperuricemi hence administer allopurinc on initiation) ***porphyria**, contraindicated in pregnancy, photosensitivity *myalgia, maculopapular rash *hepatic dysfunction, GIT irritation

STREPTOMYCIN	*binds to 30S ribosomal subunit(S12) *inhibits protein synthesis *doesn't enter cells, intracellular organism escape	*rapid absorption after IM injection *poor distribution into cells, CSF, respiratory secretion	*ribosomal protein mutation *develops gradually over course of therapy *as monotherapy 80 %at 4 months	*life-threatening tuberculosis *meningitis *military dissemination *severe organ tuberculosisl	*injection site pain *nephrotoxic(SM least nephrotoxic, doesn't concentrate in renal cortex) *ototoxicity(with vancomycin, cisplatin)
ETHIONAMIDE	1.structural analogue of INH, inhibits mycolic acid synthesis, inhibits cell wall synthesis 2.liver converts to ethionamide S-oxide(active moiety) 3.static and cidal(concentration and TB susceptibility dependant)	*absorption rapid/complete *wide distribution. Therapeutic CSF levels with inflamed meninges *extensive metabolism(active sulphoxide metabolite) *half-life:2hrs *take with food to reduce GIT intolerance	* possible cross resitance with INH		*severe GIT irritation(abd pain, anorexia, metallic tast *adverse neurological reaction on therapeutic dose(dizziness, drowsiness, paresthesia) ***hypothyroidism** *drug interactions: Stavudine, didanosine, (increases risk of peripheral neuropathy), cycloserine(increases risk of seizures in patients)
PARA-AMINOSALICYLIC ACID	*similar to sulfonamides, impairs folate biosynthesis *bacteriostatic(activity only against M.tb)		*resistance develops slowly		*GIT: anorexia, abdominal pain, peptic ulceration, *hypersensitivity(fever, abdominal pain, sore throat *leukopenia, agranulocytos eosinophilia, thrombocytopenia, hemolyt anemia *drug interactions: probenecid decrease renal excretion
CYCLOSERINE	*inhibits cell wall synthesis *structural analogue of D-alaine(involved in cell wall synthesis)	*rapid absorption *wide distribution, CSF levels			*neuropsychiatric toxicities(vertigo, nervousness, tremor, irritability)

		*renal clearance: 65% unchanged in urine)			*EtOH increases seizure ris contraindicated in serizures

ANTI-CANCER

(mention both the acute and chronic toxicities!!, for almost drug acute is nausea, vomiting and diarrhea unless stated otherwise)

GENERAL TOXIXICTIES OF ALL DRUGS:

1.myelosuppression(dose limiting)

2.nausea and vomiting

3.teratogenesis&gonadal atrophy

4.lymphocytopenia:pneumocystitis jirovec

5.hyper uricemia

6.alopecia

7.carcinogenicity

SPECIFIC TOXICITIES OF ANTI-CANCER DRUGS:

*HEPATOTOXICITY: 6-mercaptopurine, busulfan, cyclophosphamide

*NEPHROTOXICITY: cyclophosphamide, methotrexate, cisplatin

*PULMONARY: busulfan, bleomycin, procarbamazine, amiodarone(anti-arythmic drug)

*NEUROTOXICITY: cisplatin, oxaliplatin, vincristine

*CARDIOTOXICITY: daunorubicin, doxorubicin

*PANCREATITIS: L-asparaginase

*IMMUNOSPPRESSION: cyclophosphamide, methotrexate

NAME	MECHANISM OF ACTION	PHARMCOKINETICS	RESISTANCE	THERAPEUTIC USES	ADVERSE EFFECTS
ALKYLATING AGENTS **1.nitrogen mustards(**chlorambucil,cyclophosphamide, mechlorethamine) **2.nitrosurea**(carbmustine, lomustine) 3.**alkyl sulfonates**(busulfan) 4**.platinum analogues**(cisplatin,carboplatin,	*alkylating agents are **CCNS** drugs *form **reactive molecular species>that alkylate nucleophilic groups on DNA especially the N-7 position of guanine**>leads to cross linking of bases>abnormal base pairing>and DNA strand breakage>DNA unable to replicate and cell		***increased DNA repair** *decreased drug permeability(membrane transport decreaseded) ***production of trapping agents like thiols**> **drug bound by glutathione (GSH) via GSH-S-**		

oxaliplatin) 5.decarbazine,	reproduction inhibited		**transferase** or m etallothioneins in cytoplasm a nd is inactivat ed		
CYCLOPHOSPHAMIDE		*hepatic CYP 450 mediated biotransformation required for activation *breakdown product:acrolein		***chronic lymphocytic leukemia** ***non-hodgkins lymphoma** ***breast and ovarian cancers** *neuroblastoma *potent **immunosuppressant(ma nagent** of rheumatoid arthritis and autoimmune nephritis)	*GIT distress, **myelosuppression** ***hemorrhagic cystitis**(treated with vigorous hydration and mesna and N-acetyl cysteine) ***cardiac dysfunction** ***pulmonary toxicity** ***syndrome of inappropriate ADH secretion**
MECHLORETHAMINE	*converts in body to reactive cytotoxic product			*hodgkins and non-hodgkins lym(BEST USE)	*GIT distress *myelosuppression, **alopecia, sterility** ***marked vesicant action**
PLATINUM ANALOGUES(CISPLATIN, CARBOPLATIN, OXALIPLATIN)	*ginds to guanine in DNA and RNA> interaction stabilized by H-bonds>unwinding and shortening of DNA			*cisplatin: **testicular cancer(1st lline) cancers of bladder, lung and ovary(SOLID TUMORS)** *Carboplatin:second line drug for ovarian cancer ***oxaliplatin**: advanced colon cancer	**CISPLATIN**: *GIT distress *mild hepatotoxicity *neurotoxic(periph eral neuritis, acoustic nerve damage) *nephrotoxic *renal damage(reduced by use of mannitol) **CARBOPLATIN:** *less nephrotoxic and less likely to cause toxicity OXALIPLATIN: Dose limiting

					neurotoxicity
PROCARBAZINE		*active orally ***penetrates into most tissues including CSF** *eliminated via hepatic metabolism		*hodgkins and non-hodgkins lymphoma *brain tumors(penetration into CSF)	***myelosuppressant** *GIT irritation CNS dysfunction, peripheral neuropathy, skin reactions *inhibits many enzymes, including MAO *disulfiram like reactions with ethanol ***leukemogenic**
MUSTINE	***reactive agent that forms hydrogen peroxide that generates free radicals that cause DNA strand excision(like anthracyclines)**	*injected IV *disappears from blood, activity last for only a few minutes		*hodgkins disease and lymphomas	
NITROSUREA(carbmustine, lomustine, semustine)		*highly lipophilic *reach **CSF about 30%concentration**		*due to excellent CNS penetration, carbmustine and lomustine to treat **brain tumors(along with procarbazine)**	
PHENLYLALANINE NITROGEN MUSTARD				*multiple meloma(plasma cell myeloma) *breast and ovarian cancer **(solid tumor**)	
BUSULFAN(myleran)				*administered orally to treat **chronic granulocytic leukemia** and other	***adrenal insufficiency** ***pulmonary**

				granulocytic leukemia	**fibrosis** ***skin pigmentation**
THIOTEPA		*Converted rapidly by liver mixed function oxidase to active metabolites triethylenephosphoramide(TEPA)		***active in bladder cancer**	
ANTIMETABOLITES **1.anatgonists of folic acid**: methrotrexate 2**.purine antagonist**:mercaptopurine, thioguanine 3.**pyrimidine antagonist:** fluouracil, cytarabine, gemicitabone	\				
METHOTREXATE	*actively transported into mammalian cell ***inhibits dihydrofolate**	*oral and IV: good tissue administration to all tissues except CNS *excretion solely	*decreased drug accumulation *changes in drug	*effective in **choriocarcinoma, acute leukemia, non-hodgkins**	***myelosuppression(** leukopenia, bone marrow aplasia,

	reductase>leads to decrease in synthesis of thymidylate, purine nucleotides, amino acids> interfers with nucleic acid and protein metabolism *formation of **polyglutamate derivatives** of methotrexate important for cytotoxic actions	dependant on renal function ***adequate hydration to prevent crystallization in renal tubules**	sensitivity\activity of DHF *decreased formation of polyglutamates	**and primary CNS lymphoma(meningeal metastases…prophylaxis)** ***solid tumor like breast,head and ncek, bladder cancer** ***lower doses for: rheumatoid artheritis, psoriasis, ectopic pregnancy**	thrombocytopenia) *renal toxicity>ppt of 7-OH metabolite of MTX…crystaluria..hydration *GIT mucositis *administration of folinic acid(leucovorin rescue) *long term use:hepatotoxicity& pulmonary infiltrate and fibrosis
MERCAPTOPURINE& THIOGUANINE	*ourine animetabolites ***converted by HGPRTase** to active toxic compounds which inhibit purine metabolism	*low oral F(1st pass meta) *meta of 6-MP by xanthine oxidase inhibitor allopurinol and febuxostat	*decreased activity of HGPRTase *increased activity of alkaline phosphatases which inactivate toxic nucleotides	*Rx **remission of acute myelogenous leukemia**(along with MTX) *chronic myelocytic leukemia	***bone marrow suppression**(dose limiting) ***hepatic dysfunction!**(cholestasis, jaundice, necrosis)
FLUOROURACIL	*analogue of thymine, methyl group replaced by fluorine atom ***5-FdUMP & 5-FdUTP** *converted in cells to 5-FdUMP>**inhibits thymidylate synthase**>leads to thymineless death *incorporation of **5-FdUMP** in DNA>inhibits DNA synthesis and function *incorporation into RNA interfers with RNA processing and function	*IV *distributed to CSF(along with procarbazine, carbmustine)	*decreased activation of 5-FU *increased thymidylate synthase *reduced drug sensitivity of this enzyme	***SOLID TUMORS** *bladder,breast, colon, head and neck,liver and ovarian cancer ***topical use**: keratosis, superficial basal cell carcinoma	***GIT distress, myelosuppression** ***alopecia** ***hepatotoxicity** *myelosuppression more problematic after bolus injection, mucosal damage with continuous infusion

CYTARABINE	*cytarabine arabinose *pyrimidine antimetabolite ***activated by kinases to AraCTP>inhibitor of DNA polymerases** *MOST SPECIFIC FOR S PHASE	*eliminated via metabolism	*dereased uptake *decreased conversion to AraCTP Hhh	*combination therapy ***combo with daunorubicin/thioguanine for Rx of acute non lypmhocytic leukemia**	*hepatotoxicity
GEMICITABINE	*deoxycytidine analoue ***converted to active diphosphate and triphosphate nucleotide form** ***gemicitabine diphosphate>inhibits ribonucleotide reductase>diminish pool of deoxyribonucleoside triphosphatases required for DNA synthesis** *incorporated into DNA causing chain termination	*via metabolism		*pancreatic cancer *Rx of non-small cell lung cancer *bladder cancer *non-hodgkins lymphoma	*myelosuppression(**neutropenia**) *pulmonary toxicity
ANTITUMOR ANTIBIOTICS: *Adriamycin(anthracycline derivative) *mitomycin D *bleomycin *actinomycin D			Hhhhhhhhhhhh		

ANTHRACYCLINES *doxorubicin *daunorubicin *idarubicin *epirubicin' *mitoxantrone ***agents impart red tings to urine**	*CCNS drugs *DNA intercalating agent ***oxygen free radicals** ***intercalate btw DNA base pairs** ***inhibits topoisomerase 2**(along with camptothecins) *block synthesis of RNA and DNA(S PHASE) and **cause DNA strand excision** *membrane disruption also occurs	***doxorubicin & duanorubicin must be given IV!** *metabolized in urine *Products excreted in urine *Adriamycin & daunorubicin: tetracyclines having daunosamine		***doxorubicin**: hodgkins and hodgkins lymphoma, myeloma, sarcoma, breast, lung,ovarian, **thyroid cancer** ***daunorubicin**: acute leukemia ***idarubicin**: newer anthracyclin>acute myelogenous ***epirubicin**: breast cancer&**gastroesophageal cancer** ***mitaxantrone**:acute myeloid leukemia, non hodgkins lymphoma, breast cancer, gastroesophageal cancer ***adraimycin**:leukemia, lymphoma, **solid tumors**	*__ACUTE__:nausea, arythmia *__CHRONIC__: *bone marrow suppression, alopecia *CARDIOTOXICITY(initial electrographic abnormality, resulting in cardiomyopathy) *__dexrazone__: protects against dose dependant cardiotoxicity(inhibitor of iron mediated free radical generation) *liposomal complex of doxorubicin less cardiotoxic
BLEOMYCIN	*mixture of **glycopeptides>generate free radicals causes DNA strand breaks** *CCS *during G2 phase *major damage!: **iron catalyzed free radical formation and DNA strand breakage**	*must be given IV!! *inactivated by tissue peptidases		***drug regimes for hodgkins lymphoma and testicular carcinoma** ***Rx of lymphomas and squamous cell carcinoma**	***PULMONARY FIBROSIS** & PNEUMONITIS ***hypersensitivity**: rash, fever, anaphylaxis ***mucocutaneous**: alopecia, blister,hyperkeratosis
MITOMYCIN	*CCNS ***metabolized** by liver enzymes to form **alkylating agent that cross link DNA>strand breakage>inhibition of DNA synthesis**	*given IV *eliminated via hepatic metabolism		***hypoxic cancer** *combo therapy: **adenocarcinomas of cervix**, stomach,pancreas, lungs ***SALVAGE therapy:BREAST CANCER**	*myelosppression *toxic to heart, liver, lung, kidney

ACTINOMYCIN D HORMONE ANTICANCER AGENTS *Glucocorticoids: Rx of lymphocytic leukemia & lymphomas *Estrogen antagonsits: Rx of breast cancer *Androgen antagonist:Rx of prostatic cancer *Progesterone antagonists:endometrial carcinoma	*intercalates DNA>prevents DNA transcription and mRNA synthesis	*given IV		*Rx of **trophoblastic(gestational** tumors *Rx of **pediatric tumors**, Wilms tumor & ewings sarcoma	
ESTROGENS	*__inhibits__ the effect of **endogenous androgens and androgen dependant metastatic prostatic carcinoma** *diethylstilbestrol drug of choice				*cardiac and cerebrovascular complicattions & **carcinoma of male breast a**re main complications

PROGENSTINS					*__endometrial carcinoma__ *__metastatic hormone-dependant breast cancer__
ANDROGENS	*Fluoxymesterone			*danazol: hematology in aplastice anemia and congenital anemia *to Rx breast cancer	
ANTIESTROGEN	TAMOXIFEN *__selective estrogen receptor modulator__(prevents binding of estrogen to receptors of estrogen sensitive cancer cells in breast tissues)			<u>TAMOXIFEN</u>: *estrogen receptor positive breast carcinoma *__drug of choice in__ post-menopausal __women/recovering from metastatic breast cancer__ *adjuctive therapy to oophorectomay to leuprolide or goserelin in premenopausal women in __estrogen positive breast carcinoma__ <u>TOREMIFENE:</u> *newer agent used in advanced breast cancer *<u>FLUTAMIDE:</u> *androgen receptor antagonist used in prostatic carcinoma	<u>TAMOXIFEN:</u> *increases the risk of endometrial hyperplasia *nausea, vomiting, hot flushes, vaginal bleeding, venous thrombosis <u>FLUTAMIDE:</u> *gynecomastia, hot flushes, hepatic dysfunction
GONADOTROPIN RELEASING HOTMONE ANALOGUES (leuprolide,goserelin)	*inhibit release of pituitary hormone(LH&FSH)			*prostatic carcinoma: leuprolide, goserelin, nafarelin	*leuprolide__:bone pain__, gynecomastia, hematuria, __impotence__, __testicular atrophy__

AROMATASE INHIBITOR(aminoglutethimide, anastrazole)	*inhibits aromatase>enzyme responsible for the conversion of androstenedione to estrone(estrogenic hormone)			*advanced breast cancer	*naus ea, diarrhea, hot flushes,bone&back pain, dyspnea, **peripheral edema**
CORTICOSTEROIDS	***role in chemotherapy:** 1.prevention of allergic response 2.emesis control 3.relief of intracranial hypertension 4.spinal cord compression in neurological complications 5.pain relief			*prednisone in combo therapy for leukemia and lymphoma *non hodgkins and Hodgkins disease	*growth inhibition *osteoporosis *muscle wasting *salt retention *reduced wound healing *psychosis
<u>NATURAL ANTI-CANCER DRUGS:</u> ***VINCA ALKALOIDS**(vinblastine,vincristine,vinorelbine) ***PODOPHYLOTOXINS:** etoposide,teniposide ***CAMPTOTHECINS:** Topotecan, irinotecan ***TAXANES**: Paclitaxel, docetaxel					
VINCA ALKALOIDS(vincristine, vinblastine,vinorelbine)	*CCS *act during M phase ***prevent assembly of tubulin dimers into microtubules**>block formation of mitotic spindle	***must be given IV** *penetrate most tissue except CSF *cleared via biliary excretion	*increased efflux of drugs from anti-cancer cells via membrane dependant transporter	*VINCRISTINE *:**acute leukemia, hodgkins and non-hodgkins lymphomas,wilms tumor, neuroblastoma**	*<u>VINBLASTINE&VINORELBINE</u>: GIT distress, alopecia, bone marrow suppression

				*<u>VINBLASTINE:</u> *lymphomas,neuroblastoma,testicular carcinoma, **Kaposi sarcoma** <u>*VINORELBINE</u> *:**non-small cell lung cancer, breast cancer**	*<u>VINCRISTINE</u>: less serious myelosuppression ***areflexia** ***paralytic ileus** ***peripjeral neuritis** ***inappropriate ADH secretion**
PODOPHYLLOTOXIN: etoposide, teniposide	***inhibit topoisomerase 2>induce DNA strand breakage** *effective during late S and early G2 phase	***well absorbed orally!!** *etoposide:eliminated via kidney>dose reducation in renal impairment		*combo therapy ***lymphoma, lung cancer, germ cell cancer, gastric cancer**	ACUTE: nausea, vomiting CHRONIC: **alopecia, myelosuppression**
CAMPTOTHECINS: Topotecan, irinotecans	*inhibit topoisomerase 2>prevents relaxation of supercoils>DNA damage	*irinotecan: **prodrug converted by liver to active metabolite SN-38** *topotecan:eliminated renally *irinotecan:**bile and feces** ***GENETIC VARIATION** AFFECTS IRINOTECAN METABOLISM> excessive toxicity in individuals with variants of UGT1A>results in low glucoronidation activity		<u>*topotecan:</u> ***SECOND LINE for ovarian cancer and small cell lung cancer** <u>*irinotecan:</u> ***metastatic colorectal cancer**	*ACUTE: nausea, vomiting, diarrhea *CHRONIC: myelosuppression
TOPOISOMERASE INHIBITOR: paclitaxel, docetaxel	*prevent microtubule **disassembly** into tubulin *interfere with mitotic spindle	*given IV		***SOLID TUMORS:** *breast, ovarian, lung, gastroesophageal, prostate, bladder, head and neck	PACLITAXEL: *neutropenia, thrombocytopenia, peripheral neuropathy, hypersensitivity DOCETAXEL: *neurotoxicity and bone marrow

					depression

ANTI-VIRALS

NAME	MECHANISM OF ACTION	PHARMACOKINETICS	MECHANISM OF RESISTANCE	THERPEUTIC USES	ADVERSE EFFECTS

ANTI HERPES DRUGS					
1.ACYCLOVIR(ACYCLOGUANOSNE)-guanine analogue	*guanosine analogue active against HSV/VZV *activated initially by thymidylate kinase>forms acyclovir triphosphate>interfere with viral synthesis in two ways: 1.competitive inhibitor with dGTP for DNA polymerase>inhibition of viral DNA synthesis 2.incorportaion into viral DNA>premature termination of chain	*administered oral/topical/IV *oral>short half-lifr>multiple dosing>only 20% of oral absorbed *renally excreted(tubular secretion) *crosses BBB and levels in CSF are 50% of plasma levels	1.lack thymidylate kinase 2.alteration in viral DNA polymersase *cross resistance to famiclovir, ganciclovir,valaclovir	*oral uses: 1.treatment of mucocutaneous and genital herpes lesion 2.prophylaxis in AIDS and immunocomprised *IV: severe herpes disease> including encephalitis and neonatal HSV infection *HSV/VZV/ genital herpes/herpes proctitis/orolabial herpes/encephalitis	***oral:** GIT distress and headache ***IV:** delirium, tremors, seizures, hypotension, neurotoxicity,thrombophlebitis, crystalline nephropathy ***topical**:burning
2.VALACLOVIR	*L-valyl ester of acyclovir *converted to acyclovir by hepatic meta when ingested *5times better bio-availability and longer duration of action			*HSV1/HSV2/VZV/EBV *HBV	
3.FAMICLOVIR	*prodrug of peniciclovir>undergoes activation by viral thymidine kinase>triphosphate form inhibits DNA polymerase *doesn't cause chain termination	*well tolerated orally *similar to acyclovir		*same as valaclovir	nausea, diarrhea, headache
4.DOCOSANOL	*aliphatic alcohol *prevents fusion of HSV envelope and plasma membrane>prevents viral entry and			*used topically shortens healing time	*same as valaclovir

	subsequent replication				
5.TRIFLURIDINE(thymine analogue)	*fluorinated pyrimidine *inhibits viral DNA synthesis same as acyclovir *incorporates into viral and cellular DNA			*topical:HSV1/HSV2 for recurrent epithelial keratitis, keratoconjuctivitis *acyclovir resistant HSV infection	
ANTI CYTOMEGALOVIRUS					
1.GANCICLOVER(guanosine analogue)	*acyclic guanosine analogue *requires triphosphorylation for activation *monophosphorylation catalyzed by phosphotransferase in CMV and thymidine kinase in HSV cells *100 times more potent than acyclovir	*given IV and penetrates into tissues, including eye and CNS *undergoes renal elimination in proportion to creatinine clearnance *oral F less than 5% *valangiclover:has high oral bioavailability	*CMV:mutation in gene encoding for activating viral phosphotransferase *HSV: thymidine kinase deficient HSV	*CMV *HSV1/2.VZV,EBV *prophylaxis in CMV retinitis, colitis, esophagitis, pneumonitis *IV: induction/maintenance if CMV retinitis *oral: CMV prophylaxis *intraocular implant: CMV retinitis treatment	*systemic effects: **leukopenia, thrombocytopenia, myositis, hepatic dysfunction, seizures** *may cause severe **neutropenia when used with zidovudine** and other myelosuppressive agents *nausea, anorexia, vomiting
2.CIDOFOVIR	*phosphonate ***activated exclusively by host cell kinases** *active diphosphate inhibits DNA polymerase of HSV/CMV/HPV/adenovirus *active against acyclovir and ganciclover strains	*given IV *undergoes renal elimination	*mutation in DNA polymerase gene	*CMV retinitis *mucocutaneous HSV infection *genital warts	***nephrotoxicity major dose-limiting** effect of cidfovir additive with other nephrotoxic drugs including amphotericin B and aminoglycosides ***fanconi syndrome** ***myelosuppression**
3.FOSCARNET	*phosphonoformate derivative *doesn't require phosphorylation for	*given IV *penetratres well into tissues *undergoes renal elimination in	*resistance due to mutation in DNA polymerase gene	*alternative for prophylaxis and treatment for CMV infection(retinitis) ***activity against ganciclover**	***neprotoxicty** ***disturbance in electrolyte balance(hypocalcemia, phosphitemia,**

	anti viral activity *inhibits viral **DNA and RNA polymerase and HIV reverse transcriptase**	proporption to creatinine clearance		**resistant strains** ***suppress resistant herpetic infections in AIDS** *HSV/VZV,CMV,EBV,HHV-6,HBV,HIV	**magnesemia)** ***genitourinary ulceration** ***CNS effects:headache, hallucinations, serizures**
ANTI-HEPATITIS B DRUGS					
1.INTERFERON ALPHA	*cytokine ***acts thru janus kinase receptors>phosphorykate STATS >increases formation of anti viral proteins** ***selective action of IFN alpha due to activation of a host cell ribonuclease that preferentially degrades viral mRNA** ***also inhibits viral penetration**, uncoating and translation ***also promotes formation of natural killer cells that** destroy virus infected cells and inhibit viral penetration, uncoating,virion assembly and release	***absorption from IM and subcutaneous low** ***elimination due to proteolytic hydrolysis in kidney** *conventional forms administered daily/ 3 times a week ***pegylated interferon alpha**>conjugated to polyethylene glycol admininstered once a week>increased half-life and steady drug concentrations>less frequent dosing>**for treatment of chronic hepatitis C with ribavirin**		*used in **chronic HBV** as monotherapy or in combinations *when use with **ribavirin progression of acute HCV** to chronic HCV reduced ***pegyllated with ribavirin:chronic HCV** *Kaposi sarcoma *papillomatosis *topically for genital warts	*GIT irritation ***flu like syndrome** ***neutropenia** *profound fatigue *myelosupprssion ***pneumonitis** ***cardiotoxicity** *severe depression ***un-mask auto immune disease(autoimmune thyroiditis**)
2.ADEFOVIR (nucleotide inhibitor)	*adefovir depoxil prodrug of adefovir *competitively inhibit HBV DNA	*good oral F, unaffected by foods ***dose reductions required in renal dysfunction**		*suppresses HBV replication *improves liver histology and fibrosis ***activity against lamivudine**	*nephrotoxicity dose limiting, lactic acidosis

	polymerase>resulting in chain termination after incorporation into viral DNA			**resistant strains of HBV**	
3.ENTECAVIR	*inihibits HBV DNA polymerase	*effective orally *renal elimination via tubular secretion		*same as lamivudine	*headache, dizzinesss, fatigue ,lactic acidosis, upper abd pain
4.LAMIVUDINE	*NRTI *inhibitor of reverse transcriptase	*longer intracellular half-life in HBV infected cells than in HIV infected cells		*suppresses HBV infection	*headache, myalgia, malaise
5.RIBAVIRIN(guanosine analogue)	*precise mechanism unknown *inhibits guanosine triphosphate formation>1.prevents capping of viral mRNA and 2. can block RNA dependant RNA polymerase 3.inhibits replication of DNA and RNA virus ***activity against influenza A&B** ***parainfuenza, RSV, paramyxovirus, HCV, HIV**	*effective orally(avoid antacids) *available in IV and aerosol *eliminated by kidney		***used with IFN-aplha, in chronic HCV in compensated liver disease** *early IV administration decreases mortality in viral hemorrhagic fever ***used for RSV in immunocomprised children**	***dose dependant hemolytic anemia** *may cause **conjuctival and bronchial irritation** *human teratogen ***contraindicated in pregnancy**
ANTI HEPATITIS C DRUGS					
1.NS5A**(daclatasvir, elbasvir, ledipasvir, ombitasvir, velpatasvir)**	*non-structural 5A nucleoside polymerase inhibitor	***daclatasvir** taken orally with/without food *no adjustment for hepatic and renal impairment *well tolerated *primarily metabolized through CYP3A metabolism, not given with inducers and inhibitors		*used with combo with **sofosbuvir** for treatment of HCV genotypes 1,2 and 3	*headache and fatigue

2.NS5B RNA polymerase inhibitor (nucleoside analogue: sofosbuvir Non nucleoside analogue:dasabuvir)	*__NS5B RNA dependant RNA polymerase involved in post translational modification__ necessary for replication of HCV *__nucleoside/nonnucleoside analogue target catalytic site of NS5B>activated within hepatocyte through phosphorylation to nucleoside triphosphate>competes with nucleotides for chain termination__ *non nucleoside analogue(dasabuvir) allosteric inhibitor of NS5B				
3.NS3/4A PROTEASE INHIBITOR	*__inhibitor of NS3/4A serine protease>enzyme involved in post-translational processing__ and replication of HCV *grazopevir: potent pan genotypic protease inhibitor>reversibly binding to HCV NS3/4A protease	*grazoprevir: __eliminated by oxidative metabolism, primarily via CYP3A__ __*eliminated via feces__ *elbasvir/grazoprevir>not administered in moderate/severe hepatic impairment			*elbasvir/grazepevir: fatigue, headache, nausea

ANTI-INFLUENZA DRUGS					
1.AMANTADINE/RIMANTADINE	*__tricyclic amines__ *__exhibits and early onset in replication of influenza A__(not influenza B) *__blocks M2 proton ion channel>prevents uncoating of viral envelope>hence prevents viral synthesis__	*acidification of core activates viral RNA transcriptase	*minimal cross resistance *resistance due to mutation in RNA sequence encoding for structural M2 protein	*prophylactic against influenza A(reduces duration ig given **within 48hrs** after contact)	*__anti-cholinergic effect__ * insomnia, anemia,lightheadedness *GIT irritation, dizziness, slurred speech
2.OSELTAMIVIR/ZANAMIVIR	*inhibitor of **neuraminidase** *__neuraminidase cleave salicylic aci residues from viral proteins and surface of infected cells>promote viroin release and prevent clumping of newly released proteins__ *neuraminidase inhibitor impede viral spread	*prodrug used orally *zanamivir: can be administered nasally		*decrease duration of symptoms and more effective if used within 24hrs of onset *taken prophylactically decreases incidence of infleunza	*oseltamivir: GIT symptoms *zanamivir**: cough and throat discomfort, induced bronchospasm in asthma, COPD**

ANTI-HIV DRUGS

<u>NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR</u>

MOA:

*prodrugs>converted to active form via hostcell kinases

1.competitively inhibits binding of natural nucleotides to deoxyribonucleotide triphosphate(Dntp) binding site of reverse transcriptase

2.chain termination via their insertion into growing DNA chain

3. because NRTI lack a 3-hydroxyl group on ribose ring, attachment of next nucleotide is impossible

DRUGS:

1.ABACAVIR:

*guanosine analogue*good oral F and intracellular halflife of 12-24hrs*hypersensitivity reaction*SAFE IN PREGNANCY

2.DIDANOSINE(adenosine analogue)
*oral bioavailability reduced by food and chelating agents*drug eliminated via kidney*dose modification in renal impairment*pancreatitis in alcoholics and in hypertriglyceridemia*peripheral neuropathy, diarrhea, hepatic dysfunction, hyperuricemia, CNS effects

3.EMTRICITABINE:

*good oral F*renal elimination with long half-life permits once daily dosing*contraindicated in pregnancy due to propylene glycol in oral solution*asthenia, hyperpigmentation

4.LAMIVUDINE(cytosine analogue)
*HAART regime for AIDS*also for HBV*progressive ascending muscular paralysis*SAFE IN PREGNANCY

5.STAVUDINE (thymine analogue)
*dose adjustment in renal insufficiency*peripheral neuropathy*lactic acidosis with steatosis

6.TENOFOVIR:
*also effective against HBV*Fanconi syndrome*acute renal failure

7.ZALCITABINE:'(cytosine analogue)

*high oral F*dose adjustment in renal insufficiency and nephrotoxic dryg*peripheral neuropathy

8.ZIDOVUDINE:

*also called azidothymidine*active orally and distributed to most tissues*elimination involves hepatic metabolism to glucuronides and renal excretion*myelosupression(anemia, thrombocytopenia, leukopenia)*drugs increasing plasma levels of zidovudine include azole antifungal and protease inhibitor

AUTONOMIC NERVOUS SYSTEM

PARASYMPATHOMIMETICS

RECEPTORS:

M1.M3.M5 = Gq

M2.M4 = Gi

Nm. Nn= Na/K ATPase channel

M1: nerve endings, salivary glands, parietal cells

M2: heart

M3: smooth muscle, glands, epithelium

M4 + M5: CNS

Nm: skeletal muscle end plate

Nn: nicotinic ganglia

*MUST KNOW ACETYLCHOLINE AND CARBACHOL ACT ON BOTH M & N RECEPTORS!

CONTRA-INDICATIONS: (SEQ)

1.ASTHMA

2.GERD(M1 stimulate HCL secretion)

3.CARDIOGENIC SHOCK(M2 negative dromotrophic effect)

4.DIARRHEA

5.HEART FAILURE(MI)

6.URINARY INCONTINENCE

MECHANISM OF ACTION OF

A)DIRECT ACTING:

*mimic the function of acetylcholine binding on muscuranic receptors

B)INDIRECT ACTING:

*acetylcholinesterase inhibitors

***carbamates and organophosphate inhibitors** bind to acetyl-cholinesterase undergo hydrolysis>**alcohol** portion of molecule is released and **acidic portion(carbamate/phosphate ion**) is released slowly from binding site, preventing binding of acetylcholine to binding site>these drugs amplify acetylcholine>increases the concentration half-life and actions of Act

*edrophonium released over 5-15min

*carbamates 2-8hrs

*organophosphate inhibitors 7-30days

ACETYLCHOLINESTERASE:

A)at esteratic site:

***by hydrogen and electrostatic bond:edrophonium**

***by covalent carbamylated enzyme bond:neostigmine/physostigmine**

***by covalent bonding:organophosphate inhibitors**

B)at anionic site:

***only acetylcholine binds**

USE OF MUSCURANIC AGONIST IN EYE:

GLAUCOMA: Administration of M-agonist(pilocarpine)>contraction of sphincter pupil and ciliary muscle>resulting in miosis and accommodation>iris is pulled away from angle of anterior chamber>trabecular meshwork at base of ciliary is opened>flow of aqueous humor into canal of schlem is increased

Hence,

*spinchter muscle(miosis)

*ciliary muscle(contraction>accommodation)

EFFECT OF MUSCURANIC AGONISTS ON HEART:

*SAN: decrease in HR(negative chronotrophy)

*ATRIA: decrease in contractile force(negative inotropy), decrease in refractory period

*AVN: decrease in conduction velocity(negative dromotrphy), increase in refractory period

*VENTRICLES: small decrease in contractile force

REVERSAL OF CHOLINERGIC POISONING: (SEQ)

***CAUSE OF DEATH: RESPIRATORY FAILURE**

***due to CNS depression**

***paralysis of intercostal and diaphragm**

***bronchospasm and increased secretion**

HENCE:

1.REMOVE FROM SOURCE

2. ABC

3.INITIAL: INJECT ATROPINE 2-4mg IM/IV>repeated every 3-10min until mydiasis of pupils, tachycardia and dry mouth develop

4.LATER:inject pralidoxime 1g dissolved in 100ml of saline, administered IV over 2min repeat dose if muscle weakness appears>pralidoxime conatins an oxime group> binds to anionic site of enzyme>displaces the phosphate group of organophosphate>affinity for phosphorous group exceeds enzymes affinity for phosphorous>regenerate AChE before aging of alkylated enzyme occur(REMEMBER PRALIDOXIME IS USED TO TREAT ORAGNIPHOSPHOROUS TOXICITY, AND NOT CARBAMATE TOXICITY, AS IT BINDS TO PHOSPHOROUS GROUP ONLY!)

***OTHER SUPPORTIVE MEASURE:artificial respiration, tracheostomy, inject diazepam, Rx shock**

GENERAL TOXICITIES OF: (SEQ)

A)MUSCURANIC AGONISTS:

*excessive CNS stimulation: miosis, spasm of accommodation(uncommon with pilocarpine & choline esters)

*GIT related symptoms: excessive GIT motility, increased secretion, decreased tone of spinchters

*Respiratory symptoms: bronchoconstriction, increased secretion

*Genitourinary: detrusor muscle contraction, and relaxation of trigone

*increased sweating, lacrimation, salivation

*transient bradycardia followed by reflex tachycardia

*vasodilation(indirect mechanism mediated by release of NO)

Pneumonic:DUMBBELSS

B)NICOTINIC:

***CNS**: stimulation followed by depression

***ganglionic stimulation and block**(confusion, ataxia, generalized convulsion, coma, central respiratory paralysis, HYPERTENSION,NAUSEA, TACHYARDIA, VOMITING, DIARRHEA)

***neuromuscular end plate depolarization** leading to fatigueability, weakness, fasciculations and respiratory muscle paralysis

*nicotine in small doses causes addiction (vaping)

C)ORGANOPHOSPHATE:

*acute: DUMBBELSS

*chronic: peripheral neuropathy causing muscle weakness and sensory loss

SOME IMP MCQ POINT:
1.edrophonium: used to differentiate btw cholinergic and myasthenic crises

2.chronic Rx of myasthenia gravis: pyridostigmine

3.atropine reversal: physostigmine

4.competitive neuro-muscular blockade: neostigmine

THERAPEUTIC CLASSIFICATION OF PARASYMPATHOMIMETICS: (SEQ)

A)EYE

*glaucoma:pilocarpine,carbochol, ectothiophate,physostigmine

B)GIT & GUT:

*postoperative paralytic ileus; bethanicol,carbachol,neostigmine

*congenital megacolon:bethanicol

*gastric atony:neostigmine

*xerostomia and sjogren syndrome:pilocarpine

*atonic and neurogenic bladder: physostigmine, neostigmine,carbalcohol,bethanichol

C)CNS

*myasthenia gravis:edrophonium, chronic Rx(pyridostigmine)

*smoking cessation:varenicline,succinylcholine,nicotine

*Alzheimer:donepezil,rivatigmine,galantamine,tacrine

D)MISCELLANEOUS:

*raynauds disease: carbachol

*reversal of atropine poisoning:physostigmine

*competitive neuromuscular blockade:edrophonium

REMEMBER, INDIRECTLY AGONISTS HAVE A MORE DIVERSE ACTION THAN DIRECTLY ACTING!

DIFFERENCE BTW NEOSTIGMINE & PHYSOSTIGMINE(SEQ):

Neostigmine is preferred over physostigmine in Rx of myasthesnia gravis as:

1.quaternary amine, so lacks CNS action and sideeffects while physotsigmine being tertiary can cause CNS activation

2.neostigmine also has direct effect on Nm receptors, but physostigmine lacks such actions.

CLINICAL USES OF NEOSTIGMINE: SEQ

*myasthenia gravis

*post-operative ileus and urinary retention

*paraoxysmal SVT

*overdosage of muscle relaxants intoxication(tubocurarine)

PHYSOSTIGMINE	NEOSTOGMINE
Natural	Synthetic
Tertiary amine	Quaternary amine
Good oral absorption	Poor oral absorption
Crosses BBB, CNS effects	Doesn't cross BBB, no CNS effects
Glaucoma	Myasthenia gravis
Used in atropine poisoning	Used in curare poisoning

NAME	MECHANISM OF ACTION	THERAPEUTIC USES	ADVERSE EFFECTS
DIRECT ACTING MUSCURANIC AGONIST			
ACETYLCHOLINE	*quaternary amine(cannot penetrate CNS 1**.Decrease in HR&CO**: 2**.Decrease in BP:**activates M3 receptors and causes release of NO from arginine>NO stimulates SMC to stimulate protein kinase G>leading to hyperpolarization and smooth muscle relaxation via phosphodiesterase inhibitors 3**.Other actions**: *overall parasympathomimetic actions *increased salivary secretion, increased gastric acid secretion, increased motility, increased bronchoconstriction, increased urinary expulsion	*lacks therapeutic uses due to its multiplicity of actions & inactivated by cholinesterase	Pneumonic:DUMBBELSS
BETHANECHOL	*lacks nicotinic action, **has strong muscuranic actions(increases IP3 and dag)** ***stimulates muscuranic action, increases intestinal motility and tone *stimulates detrusor muscle of bladder, spinchters muscle are relaxes *hence major action on smooth muscle of bladder and GIT	1.stimulate **Atonic bladder**, particularly in postpartum and postoperative **non-obstructive** urinary retention 2.**neurogenic atony** **3.congenital megacolon** **4.paralytic ileus**	*generalized cholinergic stimulation(cyclospasm, diarrhea,urinary urgency, reflex tachycardia, sweating) *atropine sulfate to overcome CVS and bronchoconstrictor responses
CARBACHOL	***both muscuranic and nicotinic action!** *ester of carbamic acid, poor substrate of AChE ***effects on CVS and GIT**(ganglionic stimulating effects :first stimulates then depresses these system) ***causes release of epinephrine from adrenal medulla!** ***causes miosis and spasm of accommodation**	***glaucoma**(lowers intraocular pressure) *intraocular use also provides miosis for surgery ***systemic urinary retention** ***paralytic ileus** ***raynauds disease**	*adverse effects on eye, CVS, GIT

PILOCARPINE **INDIRECTLY ACTING MUSCURANIC AGONISTS**	*tertiary amine'(can penetrate CNS) ***muscuranic effects only** ***may also activate EPSP via M receptor in ganglia** *effects of eye *miosis, contraction of ciliary muscle, spasm of accommodation *potent stimulators of sweat, urine, tears	***drug of choice for emergency open and close angle **glaucoma**>opens the trabecular network around canal of schlemm>decrease in IOP *promotes salivation **in xerostomia**>due to irradiation ***sjogren syndrome**>dry mouth and lack of tears	*blurred vision *blindness *browache *profuse sweating(diaphoresis) *salivation(these effects similar to effects Inocybe's muscuranic effects *also vasoconstriction due to ganglionic effects
EDROPHONIUM(alcohol)	*prototype short acting AChE inhibitor *binds reversibly to esteratic site of AChE prevents hydrolysis *quaternary amine, alcohol *used iV	***rapid reversal of non depolarizing neuromuscular blockade** ***in diagnosis of myasthenia gravis** ***to differentiate btw myasthenia and cholinergic crises**	*increased parasympathetic effects:**nausea, vomiting, diarrhea,urinary urgency**
PHYSOSTIGMINE(carbamate)	***tertiary amine, enters CNS!!** *stimulates **muscuranic and nicotinic receptors of ANS** ***also stimulates nicotinic receptors of NMJ** *muscuranic stimulation:contraction of GIT muscles, miosis,bradycardia, hypotension *nicotinic stimulation: skeletal muscle twitching, fasciculaions, skeletal muscle paralysis *30min to 2hrs(longer than neostigmine)	1.atony of bladder and intestine 2.acute glaucoma 3.**anti-cholinergic poisoning(reverses effects of atropine**) 4.Alzheimer disease 5.reverses CNS and cardiac effects of TCA	*CNS stimulant>sconvusions *bradycardia *skeletal paralysis *fall in CO
NEOSTIGMINE	***polar quaternary compound** *absorbed poorly from GIT ***doesn't enter CNS** *effects on skeleral muscle greater than physostigmine	***antidote for competitive neuromuscular blockade** *manage symptoms of myasthenia gravis (quaternary hence cannot cross BBB)! *atonic bladder *tubocurarine paralytic reversal	*generalized cholinergic stimulation *doesn't cause CNS side effects *contraindicated in intestinal/urinary obstruction

ECTOTHIOPHATE	*long acting acetylcholinesterase inhibitor *binds to active site of AChE, enzyme permanently inactivated *generalized cholinergic stimulation *intense miosis	*open angle glaucoma	
PYRIDOSTIGMINE	*cholinesterase inhibitor *intermediate actions:3-6hrs	*chronic management of myasthenia gravis	
PARATHION, MALATHION, SARIN	*indirectly acting AChE *lipid soluble	*used as insecticides(malathion & parathion) *for anti-helminths Rx(insecticide and scabicide) *malathion:scabicide too(topical)	
DONEPEZIL,RIVASTIGMINE,GALANTAMINE, TACRINE	*indirect acting AChE *lipid soluble(enters CNS)	*Alzheimer disease	
DIRECTLY ACTING NICOTINIC AGENTS			
NICOTINE	*activates nicotinic receptors *opens sodium-potassium channels in ganglia and neuromuscular plate	*smoking cessation(also as insecticide) *gum or transdermal patch(4-6hrs)	*generalized gangionic stimulation: **hypertension**,tachycardia,nausea,vomiting, diarrhea *major **overdose:convuslions,paralysis,coma**
VARENICLINE	*a partial agonist at N receptors	*smoking cessation	*hypertension,sweating,sensory disturbance,diargea,polyuria,**menstual disturbance**

SUCCINYLCHOLINE	*partial agonist at N receptors *moderately selective for neuromuscular end plate	*muscle relaxation *used IV!	*initial mscle spasms,postoperative pain *prolonged actions in pateints with abnormal butyrlcholinestrase

PARASYMPATHOLYTICS

Cholinergic antagonist are a group of drugs that selectively and competitively inhibit parasympathetic impulse conduction by binding of Act to its receptors

THERAPEUTIC CLASSFICATION OF PARASYMPATHOMYLETICS

A)CNS

***motion sickness and post-operative vomiting**:scopolamine(transdermal patch)

***parkinsonism:**benztropine,biperiden,trihexylphenidyl

*acute dystonia:benztropine

*pre-anaesthesia: scopolamine,glycopyrolate,atropine(asked in SEQ the reason, so anti-muscuranics reduces secretions, and these are necessary for maintenance of patent airways in a patient)

B)EYE

***mydriasis**,**cycloplegia**,prevent accommodation:atropine(>72hrs),homatropine(24hrs),cyclopentolate(2-12hrs),tropicamide(0.5-4hr)>(all well absorbed into conjuctival sac, to prepare for surgery)

C)BRONCHI

*reduce bronchial secretion:IV atropine

*bronchodilation**,asthma,COPD**: ipratropium(less likely to cause arythmias and tachycardia, fewer anti muscuranic effects outside lungs as poorly absorbed), tiotropium(longer duration of action),aclidinium,umeclidinium

D)GUT:

***acid peptic disease**: atropine,methscopolamine,propantheline(non selective M antagonist) & pirenzepine,telenzepine(M3selective)

***reduce cramping and hypermotility in transient diarrhea**: diphenoxylate and loperamide

***anti-spasmodics**:atropine

E)BLADDER:

***urinary incontinence**/nocturnal amesis/neurogenic bladder: oxybutynin(nonselective, available in oral forms and transdermal patch)& darifenacin,solifenacin,tolterodine,fesoterodine(M3selective)

F)OBSOLETE FOR HYPERTENSION:HEXAMETHONIUM

G)SMOKING CESSATION: mecamylamine

H) HYPERTENSIVE EMERGENCIES: trimethaphan(malignant hypertension/produce controlled hypotension)

I)CVS USES:

*vagovagal attacks post MI

*hyperactive carotid sinus reflex

*antibodies against M2

TOXICITIES OF NICOTINIC ANTAGONISTS:

*postural hypotension(major)

*venous pooling

*dry mouth, blurred vision, constipation, sexual disturbance

TOXICITIES OF MUSCURANIC ANTAGONIST>ATROPINE TOXICITY: (SEQ)

1)DRY AS A BONE:

*reduced salivation, lacrimation and sweating

2)HOT AS A PISTOL:

*blockade of thermoregulatory centre>hyperthermia and **atropine fever**(dangerous in children,lethal in infants)

3)RED AS A BEER:

*dilation of cutaneous blood vessels of arms, head,neck and trunk**(atropine flush)**

4)MAD AS A HATTER:

*sedation, amnesia, delirium, hallucinations,convulsions

5)CVS EFFECTS:

*initial bradycardia due to blockade of inhibitory presynaptic M1 receptors on vagus nerve ending

*followed by tachycardia and decreased AV conduction>blockade of postsynaptic M2 receptors on sinus and AVN

6)GUT EFFECTS:

* urinary retention and acute angle glaucoma: severe in elderly

*prostatic hyperplasia

*impairment of erection

(high dose of atropine>dec sweating due to impairment of thermoregulatory centre>dec evaporation>inc body temp>**atropine fever**>vasodilation of cutaneous vessels to eradicate excess heat>flushing of cheek bones>**atropine flush**)

TREATMENT: symptomatic, tachycardia(physostigmine), hyperthermia: cooling blankets

CONTRAINDICATIONS: (SEQ)

*prostatic hyperplasia

*children and infants

*malignant hyperthermia

*pre-existing AVN block

*closed angle glaucoma

REMEMBER COMPETITIVE NEUROMUSCULAR BLOCKER IS TUBOCURARINE & ATRACURIUM

NON-COMPETITIVE NEUROMUSCULAR BLOCKER SUCCIYLCHOLINE & DECAMETHONIUM

DOSE DEPENDANT AFFECTS OF ATROPINE: (SEQ)

*0.5-2mg: slight bradycardia+dryness of mouth+inhibition of sweating

*5.0mg: rapid HR + dilation of pupil+blurring

*>10.0mg: hallucinations, coma, delirium

EFFECTS OF ATROPINE ON HEART: (SEQ)

*initial bradycardia, followed by tachycardia

*bradycardia: due to blockade of M1 receptors located pre-synaptically on inhibitory pre-junctional neurons>permitting increased Act release

*tachycardia: due to blockade of post-synaptic M2 receptors located on heart

MECHANISM OF ACTION & USES OF PRALIDOXIME:

*pralidoxime is the prototype cholinesterase inhibitor

*chemical antagonist

*the oxime group has higher affinity for phosphorus atom in OP, than the affinity for the enzyme active site for phosphorous group

*uses for organophosphate poisoning, not for carbamates poisoining!!

NAME	MECHANISM OF ACTION	PHARMACOKINETICS	CLINICAL APPLICATIONS	TOXICITIES
ANTI-MUSCURANIC NON SELECTIVE				
Atropine	*competitive block at all muscuranic receptors	*lipid soluble *DOA: 2-4 hrs	1.mydriasis and cycloplegia 2.anti-spasmodic 3.anti-secretory 4.antidote for cholinergic poisoning	*all parasympatholytic effects *plus, sedation, delirium, hyperthermia, flushing
Benztropine, trihexyphenidyl, biperidin		*oral and IV	*antiparkinsonism *Rx for acute dystonia caused by first generation anti-psychotics(benztropine)	
Dicyclomine & glycopyrolate			*GIT applications	
Homatropine, cyclopentolate,tropicamide		*atropine DOA: 72 hrs *homatropine: 24hrs *cyclopentolate:2-12 hrs *tropicamide: 0.5-4hrs	*topical opthamoplegic use to produce mydriasis & cycloplegia	

Oxybutynin		*oral *transdermal	*urinary urgency, incontinence(neurogenic bladder)	
Scopolamine	*tertiary amine *effects on CNS too	*trandermal	*motion sickness *post-operative vomiting	
ANTIMUSCURANIC, SELECTIVE				
Darifenacin, fesoterodine, solifenacin, tolterodine	*M3 selective *competitively blocking M3 receptors>intravesical pressure is lowered>bladder capacity isincreased>frequency of contraction is reduced	*oral *DOA: 12-24hrs	*urinary urgency *stress incontinence	
Pienzepine, telenzipine	*significant M1 sensitivity	*oral	*peptic ulcer disease	
ANTIMUSCURANIC FOR BRONCHODILATION				
Aclidinium, ipratropium, tiotropium, umclidinium	*good surface activity in airways	*due to positive charge these drugs don't enter CNS *inhalation *SAMA: ipratropium *LAMA: rest	1.ipratropium: acute management of asthma and COPD 2.tiotropium:chronic management of asthma,COPD 3.aclidinium and umeclidinium used in combo with beta blockers for asthma	*drying of oropharyngeal membrane *less CVS toxicity(comparison to beta agonists)
ANTI-NICOTINIC GANGLION BLOCKERS				
Hexamethonium	*selective blockade of	*oral and IV	*obsolete for HTN	*block of all ANS receptors

Trimethaphan	Nn receptors	*IV only *poorly lipid soluble *short half-life	*malignant hypertension	*postural hypotension! *dry mouth, blurred vision, constipation sexual dysfunction
Mecamylamine		*oral *enters CNS	*smoking cessation	

ADRENERGIC AGONISTS

CLASSIFICATION:

DIRECT ACTING:

A)ALPHA AGONIST:

*non-selective: oxymetaxoline

*alpha-1: midodrine, phenylephrine

*alpha-2: apraclonidine, clonidine, methyl dopa

B)BETA AGONIST:

*non-selective: isoproterenol

*Beta-1 selective: dobutamine

*beta-2 selective:

1.short acting: albuterol/salbutamol, metaproterenol,terbutaline, ritodrine

2.long acting: salmeterol(slow onset), formoterol(fast onset)

3.ultra-long acting:indacaterol, olodaterol,bambuterol,vilanterol

REMEMBER IN Rx OF ASTHMA, BETA-2 SELECTIVE ARE GIVEN DUE TO:

1.longer duration of action

2.economic and feasible

3.used in both acute and chronic disease

4.non-selective cause cardiac arrthymias

C)DOPAMINE AGONIST: dopamine, fenoldepam

D)BOTH: norepinephrine, epinephrine

*nor epinephrine: alpha1, alpha 2, beta 1

INDIRECTLY ACTING

A)REUPTAKE INHIBITORS: amphetamine, tyramine

B)MAO INHIBITORS: parygyline

C) REUPTAKE INHIBITORS: TCA, cocaine

RECEPTOR TYPES AND LOCATION:

ALPHA-1:

*dilator pupilae: contracts

*vascular smooth muscle(skin, mucous membrane): vasoconstriction

*pilomotor smooth muscle: erection

*bladder trigone, prostatic smooth muscle: contraction

*liver: glycogenolysis

ALPHA-2:

*located pre-synaptically on adrenergic and cholinergic nerve terminals: inhibits transmitter release

*platelets: stimulates aggregation

*adipocytes: stimulates lipolysis

*pancreatic beta cells: inhibits insulin release

BETA 1:

*heart: stimulate force and rate

*kidney: stimulates renin release

BETA-2

*smooth muscle of bladder, bronchi, uterus, urinary bladder: relaxation

*vascular smooth muscle to skeletal muscle: vasodilation

*liver: increases glycogenolysis

*pancreas: stimulates insulin release

BETA 3:

Adipocytes:stimulates lipolysis

D-1:

*renal and splanchnic vessels: vasodilation

D-2, D-3:

*nerve terminals in CNS

MECHASNISM OF ACTION:

*alpha 1: Gq

*alpha-2: Gi

*beta1,2, 3: Gs

*D-1: Gs

*D-2: Gi

DOSE DEPENDANT EFFECTS OF DOPAMINE: SEQ

***IV 2.5ug/Kg/min**: acts on D-1 receptors in kidney, vasodilation of renal and splanchnic blood vessels>inc in GFR

***therapeutic dose**: 5-10ug/Kg/min: stimulates B-1 receptors in heart>inc in CO

***high dose> 10ug/kg/min**: activates alpha-1 receptors, causes vasoconstriction> inc in TPR

ADR OF DOPAMINE ADMINISTRATIONS:

*nausea

*vomiting

*tachycardia

*hypertension in high doses

DIFFERENCE BTW CATHECHOLAMINE AND NON-CATECHOLAMINES: SEQ

	CATECHOLAMINES	NONCATECHOLAMINES
1.Structure	Dihydroxyphenyethylamine	Isopropylamine
2.administration	Cannot be given orally(IV)	Orally
3.DOA	Shorter(low F)	Longer(long half-life)
4.meta by COMT & MAO	Readily metabolized	Not metabolized(longer action&better F)
5.CNS activity	Polar, hence cannot cross BBB	CNS activity present
6.mechanism	Acts directly on adrenergic terminals	Acts both directly and indirectly+mixed receptors
7.examples	*epinephrine(given below) *norepinephrine:septic shock *dopamine:IV in acute cardiac failure+CHF *isoproterenol: IV in AV block+bronchodilator	*amphetamine *metaproterenol *albuterol
8.toxicity	less CNS toxicity	More

ORGAN SYSTEM EFFECTS:

A)CNS:

*catecholamine donot enter CNS readily
*non-catecholamines enter CNS: emphetamine, cocaine, mild alertion/reduction of fatigue>progressing to euphoria, anorexia

*rapid dose of amphetamine: tolerance and dependence

*very high dose: aggressiveness, paranoid behaivour

*CLONIDNE: Iv/locally: vaoscontriction into conjuctival ac

*when given chronically, reduce sympathetic outflow(autoreceptors)>dec BPB

B)EYE:
*topical phenylephrine

*nonselective: inc outflow via uveoscleral drainage

*alpha-2: reduce IOP>via dec synthesis of aqueous humor

C)BRONCHI:

*isoproterenol(non-selective)

*albuterol: Beta2 selective

*reversing bronchospasm

D)GIT:

*vessels: alpha-1

*spinchters: alpha 1

*smooth muscle: alpha 1

*ENS: beta 2

E)GUT:
*alpha-1: mediate smooth muscle contration

*beta-2: significant uterine relaxation in pregnant women

F)VASCULAR:

1.aplha-1:

*phenylephrine

*contracts peripheral and visceral smooth muscle>inc TPR

*inc BP>reflex bradycardia

*no change in pulse pressure

2.alpha-2:

*clonidine

*vasoconstriction(IV)

*reduce sympathetic outflow and dec BP(oral)

3.beta agonists:

*beta 2 agonist(albuterol, metaproterenol)

*non-selective(isoproterenol)

*vasodilation of arteriolar vessels in skeletal muscle>dec TPR

4.DOPAMINE:

*vasodilation of renal and splanchnic vessels>Rx of renal failure with shock

D1>B1>A1

5.HEART:

B1>B2

*alpha-1: reflex bradycardia

*beta-1: direct tachycardia

*combining alpha and beta: inc BP with bradycardia, however combination of ganglionic blocker with anti-muscuranic blocker, epinephrine will always cause beta-1 mediated tachycardia

6.METABOLIC EFFECTS:

*alpha-2:inhibits insulin release

*beta1:stimulates renin release

*beta 2: stimulates glycogenolysis and insulin release(hyperkalemia followed by hypokalemia)

*beta 3: stimulates lipolysis

THERAPEUTIC CLASSIFICATION:

A)SHOCK:

*epinephrine: anaphylactic shock(treats hypotension, bronchospasm, angioedema)

*norepinephrine:septic and cardiogenic shock

*phenylepinephrine: neurogenic shock

*cardiogenic shockwith renal shutdown: dopamine

B)CNS:

*amphetamine(phenylisopropylamine): narcolepsy, weight reduction

*methylphenidate: ADHD

C)EYE:

*non-selective alpha agonist: increases drainage of aqueous humor(norepinephrine)

*alpha-2 agonist: decreases production of aqueous humor(apraclonidine, bromidine)

*phenylepinephrine:mydriasis

*phenylepinephrine and tetrahydrozoline: congestion and conjuctival itching caused by allergy and irritation

D)BRONCHI:

*short acting beta-2 agonist: albuterol, metaproterenol, terbutaline: acute attack of asthma

*long acting beta agonist: salmoterol, formoterol, indacaterol, used in combo with corticosteroids and anti-muscarinic agents for prophylaxis of chronic asthma

E)CVS APPLICATIONS:

Inc blood flow:

*used in some types oh acute HF

* beta agonist(inc contractility + reduce afterload)

*norepinephrine: septic and cardiogenic shock

Dec in blood flow/inc in BP

*: alpha-1 agonist:phenylepinephrine+epinephrine

*norepinephrine+phenylepinephrine: temporary maintenance of BP, necessary to maintain perfusion of brain, heart and kidney

*alpha agonist mixed with local anesthetics to prevent loss of anesthetic from tissues

orthostatic hypotension Rx

*oral ephedrine, midodrine

Acute cardiac stimulation:

*epinephrine: cardiac arrest(remember acc to new guidelines, a person with cardiac arrest is Rx first line with atropine)

*isoproterenol: AV block

F)GUT:

*beta agonist: terbutaline and ritodrine: suppress pre-term labor

*long acting symapthomimetics:ephedrine: Rx for urinary incontinence in elderly + children with enuresis

TOXICITY OF CATECHOLAMINES(epinephrine, norepinephrine, isoproterenol, dopamine, dobutamine)

-due to their limited penetration into brain, they have little CNS toxicity

*excessive vasoconstriction

*cardiac arrhythmias

*MI

*hemorrhagic stroke

*pulmonary edema & hemorrhage

TOXICTY OF NON-CATECHOLAMINES(ephrdrine+amphetamine+methylamphetamine)

-mild to moderate to severe toxicity, depending upon symptoms

*moderate: nervousness, anorexia, insomnia

*severe: anxiety, aggressiveness, paranoid behaivour

*alpha-1 agonist: hypertension

*beta-1: sinus tachycardia and arythmias

*beta-2: skeletal muscle tremor

*cocaine: arythmias, infarction, seizures

SOME IMP MCQ STUFF:

***noepinephrine:** alpha1. Alpha-2, beta-1

-alpha-1 effect: TPR inc, BP inc

-beta-1 effect: HR inc, CO inc, pulse pressure same

-results in reflex bradycardia due to vagal stimulation

***epinephrine**:all four receptors(alpha-1+2, beta-1+2)

-low dose: B1, B2: vasodilation, inc HR

-medium dose:B1, B2,alpha-1

-high dose: B1, B2, alpha-1: vasoconstriction

*increases DBP as well

***epinephrine causes significant hyperglycemia due to:**

1.apha-2 effect: inhibits insulin release

2.beta-2 effect: inhibits glycogenolysis

CONTRAINDICATIONS FOR EPINEPHRINE USE:

1.hyperthyroidism

2.diabetes

3.cocaine(longeractions)

4.beta-blocker: unopposed action leads to hypertension

PAST PAPER QUESTIONS

USE OF EPINEPHRINE RATHER THAN NE IN ANAPHYLAXIS

*acts on all adrenergic receptors(even uninnervated), and has a strong cardiostimualtory effect

*acts on all beta receptors with wide distribution(heart, liungs, vessels) compared to NE that has a stng cardiostimulatory effect

1.hypotension: alpha-1 mediated vasoconstriction

2.bronchospasm: beta-2 mediated bronchodilation

3.histamine-related angioedema: epinephrine (an histamine antagonist)

4.suppressionof mediators released from mast cells: epinephrine

*epinephrine when given IV, actsrapidly

HENCE:

***alpha-1 agonist effect:**

*increased vasoconstriction

*increased TPR

*decreased mucosal edema(larynx)

*nasal vasoconstriction

***alpha-2 agonist:**

*lowering of intraocular pressure

***beta-1 agonist:**

*increased ionotrophy

*increases chronotrophy

***beta-2 agonist effect:**

*increased bronchodilation

*increased vasodilation

*decreased release of mediators from basophils & mast cells

***beta-3 agonists:**

*promotion of lipolysis

CARDIOGENIC AND SEPTIC SHOCK: NOREPINEPHRINE

*in both types of shock, heart pumps slowly

*hence we need to reduce the workload on heart, and hence VASOSELECTIVE ACTION!

*BP maintained by VC

NEUROGENIC SHOCK: PHENYLEPINEPHRINE

*excessive vasodilation in this type of shock, hence an alpha-1 selective drug is given to cause vasoconstriction

CARDIOGENIC SHOCK WITH RENAL SHUTDOWN: DOPAMINE

*renal vasoconstriction in this shock

*cardiostimulant and causes VD of renal vessels

DOPAMINE INFUSION:

*since half-life of dopamine is short, so

1.1 min in adult

2.2min in newborn

3.5 min in preterm

USES OF CLONIDINE: (big katzung)

*decreases symphathetic outflow

1.Rx of diabetic diarrhea(due to salt and water retention, by blocking unmasked alpha-2 receptors)

2.diminishing of post-menopausal flush

3.alchohol and opioids withdrawal

4.smoking cessation

5.pre-medication before anesthesia

6.Rx of HTN

7.ADHD

PHARMCOLOGICAL ACTIONS OF EPINEPHRINE:

A)CVS:

*increases rate and force of cardiac conduction

*epinephrine decreases TPR

*SBP is increased and DBP is decreased

B)RESPIRATORY:

*powerful bronchodilation by acting directly on bronchial smooth muscle

*inhibits release of mediators from mast cells

C)HYPERGLYCEMIA:

*increased glycogenolysis(beta-2)

*increased release of glucagon(neta-2 effect)

*decreased release of insulin(alpha-2 effect)

D)LIPOLYSIS:

USES OF EPINEPHRINE: ABCDEG(pneumonic)

* anaphylactic shock

*bronchial asthma

*cardiac arrest

*delay absorption of local anesthesia

*epistaxis, elevated BP

*mydriasis during intraocular surgery(**g**laucoma)

ADVERSE EFFECTS OF EPINEPHRINE:
*anxiety, fear, headache, tension

*hypertension

*arryhthmias

*MI

*pulmonary edema

*stroke

*hyperglycemia

WHY EPINEPHRINE GIVEN ALONG WITH LOCAL ANESTHETICS? SEQ

1.inc duration of action

2. reduce systemic toxicity(VC)

3.promote local hemostasis

NAME	MECHANISM OF ACTION	PHARMCOKINETICS	THERAPEUTIC EFFECTS	ADVERSE EFFECTS
DIRECT ACTING CHOLINOMIMETICS				
Epinephrine	All four receptors	*IV and oral *doesn't enter CNS *duration:short	*anaphylactic shock *asthma *cadiac arrest *open angle glaucoma *adjunct to local anesthesia *hypotension	*hypertension *arthymias(with digoxin) *stroke *MI *pulmonary edema(inc workload as it inc afterload) *hyperglycemia in diabetic patients *anxiety, fear,tremor, headcache
Norepinephrine	Alpha-1, alpha-2,beta-1	*IV only! As it causes ischemic necrosis when given orally	*cardiogenic and septic shock	*vasospasm *tissue necrosis *arrhythmias *excessive BP *(to Rx NE toxicity: phentolamine+nitroglycerin+terbutaline)

Dopamine	D1, B1, B3, alpha 1, alpha2	*IV only	*cardiac shock with renal shutdown: 1.alpha-1 TPR 2.beta-1 CO inc 3.D1 renal perfusion *sometimes used for heart failure *Rx hypotension, bradycardia, heart failure unresponsive to other Rx	*CVS disturbances *arythmias
Isoproterenol	Beta 1, 2 ,3	*oral *IV	*nebulizer in acute asthma *IV in AVN block	
Dobutamine	B1 agonits		*acute HF, to Rx CO without vascular effects	
fenoldepam	D1 agonist		*rapidly acting VD, to Rx hypertension in hospitalized patients	*nausea *vomiting *flushing *headache *dizziness
NONCATECHOLAMINES ALPHA SELECTIVE				
Phenylepinephrine	Alpha1	*oral, IV, topical *DOA:15-60min	*nasal decongestant(topical) *mydiasis *glaucoma *reduce conjuctival itching *neurogenic hypotension(surgical and	*hypertension *reflex tachycardia *stroke *MI

			hospitalzed patients) *paraoxysmal SVT	
Clonidine	*Alpha2>dec SANS outflow(chronically) *IV/topical: cause VC	*oral,IV, topical	*hypertension(not responded to 2-3 drugs) *for glaucoma(reduces AH secretion)	*sedation *rebound HTN *dry mouth, lethargy, xerostomia,constipation
NONCATECHOLAMINE BETA 2 SELECTIVE				
Albuterol, metaproterenol, terbutaline	beta 2 agonist	*inhalation via aerosol *DOA: 2-6 hrs *SHORT ACTING!	*prompt Rx for acute bronchospasm *albuterol DOC, as more beta 2 selective, than metaproterenol	*tachycardia *vascular headache *tremor *hyperglycemia *anorexia, insomnia, restlessness
Salmoterol, formoterol, indacaterol	beta 2 agonist	*slow onset *LONG	*COPD *prophylaxis of asthma with corticosteroids+ anti-muscuranic	*tachycardia, tremor,
INDIRECTLY ACTING PHENYLISOPROPYLAMINES				
Amphetamine, methamphetamine	Displaces stored catecholamines from nerve endings	*oral+IV *DOA: 4-6	*anorexiant *ADHD(methylphenidate) *narcolepsy	*high addiction liability *parainsomnia *aggressiveness, insomnia, hypotension, seizures
Ephedrine	Displacer like amphetamine	*oral *DOA: 4-6hrs	*narcolepsy *idiopathic postural hypotension *enuresis *lower addiction liability than amphetamine	*same

COCAINE	Blocks norepinephrine reuptake and dopamine uptake(DAT & NET)	*IV only *topical, nasal, local injection *DOA; 2 hrs	*local anesthetic with intrinsic hemostatic action	*very high addiction liability *hypertension *arrhythmias *seizures
TYRAMINE	Displaces stored catecholamines	*not a phenylisopropylamine and normally first high-effect, but is absorbed in patients taking MAOI	*not clinical use, but used in fermented foods	*hypertension *arrhythmias *MI

ADRENERGIC ANTAGONIST

CLASSIFICATION

ALPHA BLOCKERS

*ALPHA BLOCKERS NONSELECTIVE:

1.reversible-phenoxybenzamine

2.irreversible-phentolamine

*ALPHA-1 SELECTIVE: prazosin, terazosin, tamsolusin

*ALPHA-2 SELECTIVE: yohimbine, rauwolscine

***BETA BLOCKERS:**

1.NONSELECTIVE: propranolol, timolol, sotalol, pindolol,nadolol

2.BETA-1 SELECTIVE: esmolol, metoprolol, bisprolol, acebutolol, atenolol

3.BETA-2 SELECTIVE:BUTOXAMINE

4. WITH ISA ACTIVITY: pindolol, acebutolol(asthma, less likely to cause bronchospasm, less metabolic derangements>less decrease in HDL)

5.LOCAL ANESTHETIC ACTIVITY: propranolol, labetolol, pindolol, acebutolol-disadvantage as decreased local corneal reflex-leading to corneal ulceration_absent from timolol!>hence given in glaucoma

6.LIPID INSOLUBLE: **atenolol**, bisoprolol, sotalol-less CNS side effects, less sleep disturbance, longer acting

7.SHORTEST ACTING: esmolol

8.LONGEST ACTING: nadolol

9.WITH VASODILATING ACTION: nebivolol

10.BOTH ALPHA AND BETA BLOCK: labetolol+carvedilol>used in HTN patients in which an increases in TPR is undesirable(hence alpha-block)

11.CARDIOSELECTIVE: >cardioselectivity pronounced at low dose(antagonize beta-1 receptors more at 50-100mg/dl)

NAMES OF CARDIO-SELECTIVE BETA-BLOCKERS: seq

pneumonic: MANBABES

Metoprolol

Atenolol

Nebivolol

Bisprolol

Acebutolol

Betaxolol

Esmolol

USES OF BETA BLOCKERS WITH ISA(acebutolol&pindolol)

*useful as they have ISA, beta blockers with partial agonist activity, superior to propranolol in:

1.asthma

2.diabetes

3.HTN with heart block patients

4.HTN with deranged lipid profile

ADVANTAGES OF CARDIOSELECTIVE OVER NON-SELECTIVE:

1.safer in asthmatic

2.safer in diabetes

3.safer in PVD

4.less deleterious effects on lipid profile

5.less likely to impair exercise intolerance

DESENSITIZATION OF ALPHA-BLOCKERS:SEQ

1.sequestration

2.reduced coupling to G protein

3.decreased synthesis of enzyme

SOME IMPORTANT TERMS:

1.**epinehrine reversal**: CONVERSION OF PRESSOR RESPONSE TO EPINEPHRINE(TYPICAL OF LARGE DOSE) TO A DEPRESSOR EFFECT, CAUSED BY ALPHA BLOCKERS, WHICH UNMASK THE BETA-2 DILATING EFFECT

MECHANISM:

*epinephrine in the presence of alpha blockers, leads to a depressor effect due to unmasking of vasodilating action of beta-blockers

*manifestated as orthostatic hypotension

*not seen with phenylepinephrine or norepinephrine as they don't have beta-2 action!

2. intrinsic sympathomimetic activity: partial agonist action by adrenpceptor typical of beta-blockers(pindolol and acebutolol)

ORGAN SYSTEM EFFECTS OF ALPHA-BLOCKERS:

A)CVS: orthostatic hypotension, reflex tachycardia

B) NOSE: nasal stuffiness

C)EYE: miosis

D)GIT: inc GIT motility

E)KIDNEY:hypotension, dec GFR, Na and water retention

F)URINARY BLADDER: tone of smooth muscle of urinary bladder decreases, hence improved urine flow>BPH Rx

G)REPRODUCTION: contraction results in ejaculation>blockade results in impotence

ORGAN SYSTEM EFFECTS OF BETA-BLOCKERS:

A)CVS: dec CO, contractility, dec HR

B)BLOOD VESSELS: peripheral vasoconstriction

C)BRONCHOCONSTRICTION

D)DISTURBANCE IN GLUCOSE METABOLISM(UNMASKS THE EFFECTS OF HYPOGLYCEMIA ON INSULIN INJECTION)

TOXICTY OF ALPHA-BLOCKERS:

*orthostatic hypotension

*reflex tachycardia(less common with alpha-1 blockers)

*angina precipitated via tachycardia

*called as the first dose effect!

*nasal stuffiness

*loss of ejaculation

*nausea and vomiting, swelling and headache

TOXICITY OF BETA-BLOCKERS:

*bradycardia

*hypertension

*AVN block

*exacerbation of asthma

*unmasks the hypoglycemia symptoms from insulin overdosage with beta-blockers>tachycardia, tremors, anxiety

*CNS: sedation, fatigue, sleep alteration

*sexual dysfunction

*fatigue, cold-extremities, headache and nausea

THERAPEUTIC USES OF ALPHA BLOCKERS:

1.pheochromocytoma: nonselective alpha blockers(phenoxybenzamine during preparatory phase and phentolamine during surgery)

2.reversal of tissue ischemia due to epinephrine: phentolamine

3.overdosage of amphetamine, cocaine, tyramine>hypertension>reversed

4.sudden cessation of clonidine therapy> phentolamine

5.erectile dysfunction> phentolamine or yohimbine(local injection)

5.mastocytosis, carcinoid tumor(phenoxybenzamine)

6.BPH

THERAPEUTIC USES OF BETA BLOCKERS:

1.prevents cardiac remodeling

2. acute angle glaucoma> timolol,metoprolol, carterolol(drugs which lack membrane stabilizing activity, as it decreases protective reflexes and increases risk of corneal ulceration)

3. pheochromocytoma(producing epinephrine as well)>labetolol

4.hypertension, arrthythmias, angina>beta-1 selective

5. HEART RELATED: angina, cardiac arrhythmias, CHF, MI

CONTRAINDICATIONS OF NON-SELECTIVE BETA-BLOCKERS:

*asthma

*deranged lipid profile

*diabetes

*acute decompensated HF

*PVD

*raynauds disease

	Phentolamine	phenoxybenzamine
mechanism	Surmountable alpha receptor block	Irreversible alpha blocker
DOA	Shorter(given IV pre-operatively)	Longer
selectivity	For alpha-1	Same for both

NAME	MECHANISM OF ACTION	PHARMACOKINETICS	THERAPEUTIC USES	ADVERSE EFFECTS
NONSELECTIVE ALPHA BLOCKER				
Phentolamine	*competitive pharmacological antagonist at alpha receptors1 and 2	*oral, IV *DOA:2-4hrs(oral) *DOA:20-40min(IV)	*pheochromocytoma(surgical phase) *rebound hypertension caused by clonidine *overdosage of alpha agonist(amphetamine, tyramine) *to Rx dermal necrosis following norepinephrine extravasation	*orthostatic hypotension *reflex tachycardia
Phenoxybenzamine	*irreversible(covalent) binding to alpha-receptors *serotonin receptor blockade *anti-H1 blockade	*short half-life *but longer DOA: 48hrs>binds covalently to its receptor	*pheochromocytome(preparatory phase) *carcinoid tumor *mastocytosis *raynauds phenomenon	*orthostatic hypotension *reflex tachycardia *GIT disturbance *miosis *nasal stuffiness
ALPHA-1 SELECTIVE				
Prazosin	*competitive antagonist at alpha-1 receptor	*oral *DOA: 8hrs	*HTN *BPH	*orthostatic hypotension *reflex tachycardia *1st dose effect
Doxazosin		*longer DOA: 8hrs		
Tamsulosin, silodosin			*BPH	

ALPHA-2 SELECTIVE				
Yohimbine	*competitive antagonism at alpha-2 receptors	*oral *IV	*obsolete used for erectile dysfunction	*tachycardia *GIT disturbance
NONSELECTIBE BETA BLOCKER				
Propranolol	*competitive blockade of all beta-blockers *membrane stabilizing activity	*oral and IV *DOA:4-6hrs *readiy enters CNS	*angina *aythmias(Rx and prophylaxis) *thyrotoxicosis *tremor *stage fright *migraine	*bronchoconstriction *arrhythmias *sexual impairment *metabolic disturbance(dec glycogenolysis+dec glucagon secretion) *CNS effect(depression, dizziness, lethargy, fatigue)
Timolol, betaxolol	*lacks membrane stabilizing effect		*glaucoma	
Pindolol and nadolol	*dec synthesis of AH	*longer DOA	*safer in asthma	*less CNS effect
BETA-1 SELECTIVE				
Atenolol	*competitive block of beta-1 receptor	*oral *DOA:6-9hrs	*HTN with impaired pulmonary function *bisprolol & metoprolol: management of chronic heart failure *angina *arrrythmias	*like propranolol, with less degree og bronchospasm

esmolol		*given IV *short-half life	*given to control BP/HR in surgery patients	
nevibolol	*causes vasodilation			
BETA BLOCKERS WITH ISA				
Acebutolol and pindolol	*acts as partial agonist		*useful in patients with HTN and mild bradycardia(as further decrease less pronounced in these drugs)	
BOTH ALPHA AND BETA BLOCKERS				
Labetolol and carvedilol	*four isomers; 2 bind and block alpha and beta *due to alpha 1 action, produce vasodilation, reducing BP	*IV (emergency!)	*labetolol: -pregnancy induced HTN -hypertensice emergencies(IV) *carvedilol: -stable chronic HF	*like atenolol
BETA -2 SELECTIVE	*competitive block of beta-2 block		*none(research)	*bronchospasm

DRUGS USE IN GLAUCOMA

PUPIL:

A)SYMPATHETIC:DILATES

B)PARASYMPATHETIC: CONSTRICTS

CILIARY BODY:

A)SYMPATHETIC: RESPONSIBLE FOR AQUEOUS HUMOR PRODUCTION

B)PARASYMPATHETIC:RESPONSIBLE FOR CILIARY BODY MOVEMENTS

DRUGS DECREASING SECRETION OF AQUEOUS HUMOR:

1.beta blockers

2.alpha-2 agonist

3.carbonic anhydrase inhibitor

DRUGS INCREASING UVEOSCLERAL OUTFLOW:

1.parasympathomimetics

2.prostaglandins

3.nonselective alpha agents

4.mannitol

DRUGS DECREASING SYNTHESIS OF AQUEOUS HUMOR:

NAME	MECHANISM	METHOD OF ADMINISTRATION	SIDE EFFECTS
BETA BLOCKERS *levobunolol *timolol *carteolol *betaxolol	*acts on ciliary body to dec production	*topical	*CVS(bradycardia, aysytole, syncope) *bronchoconstriction CONTRAINDICATED IN: *elderly *lund disease *CHF *diabetes
ALPHA-2 AGONIST *apraclonidine *brimonidine	1.primary:dec production: *additive to PGA 2.secondary: enhanced uveoscleral outflow *combo with timolol	*topical	*lethargy *fatigue *dry mouth *allergy(more common with apraclonidone) *eyelid swelling *tenderness *itching *follicular reaction
CARBONIC ANHYDRASE INHIBITOR *acetazolamide *dorzolamide *brinzolamide	*blocks CA>reduces production of bicarbonate ions>lower pressure	*oral *topical	*malaise *kidney stones *aplastic anemia *stinging *conjuctival hyperemia *tachyphylaxis *sulfa allergy

DRUGS THAT INCREASES UVEOSCLERAL OUTFLOW:

DRUG	MECHANISM OF ACTION	APPLICATION	TOXICTIES
PROSTAGLANDINS: *latanoprost *bimatoprost *travoprost	*increases uverosleral outflow, by relaxing ciliary body	*topical	*conjuctival hyperemia *iris pigmentation *periorbital darkening *eyelash growth
PARASYMPATHOMIMETICS: *pilocarpine *carbachol *echothiophate *physostigmine	*increases contractile force of cilary body>thus increasing drainage *constrict pupils, pulling iris away from trabecular meshwork	*topical drops	*headache induced myopia *browache *headache *blurred vision

NONSELECTIVE ALPHA AGONIST: *epinephrine *dipivefrin	*produces alterations in ciliary body mediated configuration of outflow apparatus *increases uveoscleral outflow	topical drops	*can precipitate acute attack in patients with narrow isis-corneal angle *CVS arrhythmias *tachycardia

ENDOCRINOLOGY

DRUGS ACTING ON UTERUS

A)OXYTOXIC DRUGS:

1.oxytocin

2.ergot alkaloids(ergometrine, ergonovine)

3.prostaglandin(PGE2+PGF2alpha)

B)TOCOLYTIC DRUGS:

Prevent uterine contraction

Arrest threatened abortion or delay premature labour

1.B-adrenoceptor agonists(ritodrine and terbutaline)

2.Calcium channel blocker

3.prostaglandin inhibitor

NAME	MECHANISM OF ACTION	THERAPEUTIC USES	SIDE EFFECTS
OXYTOCIN	1.hormone secreted by posterior pituatry 2.stimulate both the the frequency and force of contraction particularly of the fundus segment of uterus 3.contraction resemble the physiological contraction of uterus(followed by relaxation) 4.immature uterus resistant to contraction 5.contract uterus only at term 6.sensitivity increases to 8 fold in last 9 weeks, and 30 times early in labor 7.clinically, oxytocin given only when cervix is dilated and soft 8.fetal distress less	1.induction and augmentation in labour(slow IV infusion) 2.uterine inertia 3.incomplete abortion 4.postpartum hemorrhage	1.hypotension 2.uterine rupture 3.fetal distress (ischemia) 4.water intoxication <u>CONTRAINDICATIONS:</u> *hypersensitivity *pre maturity *abnormal fetal position *evidence of fetal distress *cephalopelvic position

	*interaction of endogenous&administered oxytocin with myometrial cell receptor>promotes influx of Ca from ECF and from SR into the cell>increase in calcium contraction>stimulates uterine contraction		*precaution in multiple pregnancy, previous C-section
ERGOT ALKALOIDS(ergometrine,ergonovine)	1.induces tetanic contraction without relaxation(difference from oxytocin!) 2.causes contraction of whole uterus 3.fetal distress more	*PPH(never given in 1st and 2nd trimester)	1.hypertension 2.vasoconstriction of peripheral blood vessels 3.gangrene
PROSTAGLANDIN(PGE2 & PGF2alpha)	1.prostaglandin contract uterus throughout pregnancy 2.given to soften cervix! 3.given during labour phase of 1st trime mother	1.induction of labour 2.induction of abortion(before 32 week) 3.PPH 4.used as vaginal suppository of labour	
<u>TOCOLYTIC DRUGS</u>:			
B AGONIST(ritodrine and terbutaline)	1.selective beta agonists used as uterine relaxants 2.binds to beta receptor>activate AC>increases in cAMP>decreases intracellular calcium level>decreases the sensitivity of actin-myosin contractile unit	*Used for preterm labour *arrest threatented abortion	*tremors *nausea, vomiting *flushing *sweating *hyperglycemia *hypokalemia
CALCIUM CHANNEL BLOCKERS(nifidepine)	*causes relaxation of myometrium by blocking calcium dependant contraction>markedly increases amplitude of spontaneous and oxytocin-induced contraction		*headache, dizziness, hypotension, flushing, tachycardia, ankle edema, constipation

PROSTAGLANDIN INHIBITORS(aspirin, indomethacin, ibuprofen)	*depletion prevents contraction of uterus	*never in last trimester(PDA)	*GIT ulceration, premature closure of patent ductus arteriosus

ADRENOCORTICOSTEROIDS:

Cortisol effects

1.METABOLIC EFFECTS:

*increases in gluconeogenesis

*increases in glycogen synthesis

*decreased uptake and utilization of glucose

*Inc in blood glucose>stimulates insulin release

*both lipolysis & lipogenesis(indirect effect due to insulin) are stimulated

*net increase in fat dep in face, shoulder and back

2.CATABOLIC EFFECTS:

*muscle protein catabolism

*anti-anabolic effect on lymphoid tissue, connective tissue,fat and skin

*catabolic effect on bone>osteoporosis(stimulates osteoclasts activity)

*reduced growth in children

C) IMMUNOSUPPRESSIVE EFFECTS:

*decreased generation of cytokines, IL-1,IL-2,IL-3,IL-4,IL-5,IL-6,IL-8,TNF-gamma

*inhibits cell-mediated immunity

*inhibits peripheral lymphocytes and macropages

*actively lymphotoxic>blood cancer

*used to prevent graft rejections

D)ANTI-INFLAMMATORY:SEQ!

*suppressive effect on mediators of inflammation and inflammatory cytokines(IL-1, IL-6 , TNF)

*stabilizes lysosomal membranes and prevents release of inflammatory cytokines

*dec in mRNA for COX-2

*dec in IL-2 and IL-3

*decrease in PAF(an inflammatory cytokines)

*inc neutrophils in blood(due to dec chemotaxis)
*dec lymphocytes, eosinophils, basophils

E)OTHER EFFECTS:

*required for normal excretion of water

*fetal lung development(betamethasone)

*effects on CNS(inc psychosis)

*stimulate gastric acid secretion and pepsin production>exacerbate ulcer

*negative calcium levels>reduced Ca+ absorption in GIT and increased excretion in urine

CLASSIFICATION OF CORTICOSTEROIDS: SEQ

AGENT	ANTI-INFLAMMATORY ACTIVITY	SALT-RETAINING ACTIVITY	DOSE FOR ANTI-INFLAMMATORY ACTIVITY	USES & ROUTES OF ADMINISTRATION
SHORT ACTING:8-12hrs *hydrocortisone(cortisol)	1	1	20	*DOC in acute adrenal insufficiency *status asthmaticus *oral, IV, topical
*cortisone	0.8	0.8	25	*prodrug converted to hydro-cotisone by liver metabolism
INTERMEDIATE ACTING:12-36hrs *prednisolone	4	0.8	5	*used for allergic, anti-inflammatory, auto-immune disease, and in malignancies *oral, IM, topical
*prednisone	0.8	0.8(synthetic steroids always have less salt-retaining activity)	5	*prodrug, converted to prednisolone
*methylprednisolone	5	0.5	4	*anti-inflammatory, immunosuppressants
*triamcinolone	5	0	4	*more potent, more toxic than prednisolone
LONG ACTING:36-72hrs				

*betamethasone	30	0	0.75	Highly anti-inflammatory&immunosuppressants FETAL LUNG MATURATION
*dexamethasone	30	0	0.75	*cause severe HPA suppression *used in cerebral edema due to neoplasm

ALWAYS REMEMBER THAT DURING ADRENAL SUPPREESSION: SEQ

*when steroids are administered >2weeks

*dosing to be tapered slowly

*stopping the therapy slowly

REASONS:

*adrenal cortex atrophies due to exogenous corticosteroids therapy

*hence, upon abrupt withdrawal, atrophied cortex unable to synthesize steroids>>>leading to withdrawal symptoms: malaise, fever, anorexia, nausea, postural hypotension, electrolyte imbalance

*patients may undergo acute adrenal insufficiency>CVS collapse

SPECIAL PRECAUTIONS WHILE ADMINISTRATING CORTISOL:

*keep dose **as low** as possible

***local application**(aersols for asthma) where possible

***alternate day therapy**(to reduce pituarty suppression, and tapering dose soon after achieving a therapeutic response)

*therapy shouldn't be discontinued abruptly>**tapered slowly**

*prolonged therapy>take X-rays and TB test

*take into consideration diabetes,peptic ulcer, osteroporosis

STEROIDS GIVEN IN ASTHMA:

*SURFACE ACTING:

1.beclomethasone

2.budesonide

3.dexamethasone

4.flunisolide

*ORAL(RARE & CHRONIC USE)

1.prednisone(dose tapering required)

*INTRAVENOUS(STATUS ASTHMATICUS)

*1.prednisolone

2.hydrocortisone

NAME	MECHANISM OF ACTION	PHARMACOKINETICS	THERAPEUTC USES	ADVERSE EFFECTS
GLUCOCORTISONE	CRH by hypothalamus>ACTH by pituatry> acts on zona glomerulosa> secrete cortisol> and bound **to CBG**>binds to specific intracellular receptors bound to **Hsp90**>Hsp90 released as a result of binding>receptor-hormone complex translocates to nucleus>binds to **GRE** on gene and regulates gene transcription>bringing about final hormone response	*Daily secretion:10-20mg ***CBG 95% bound** *short duration of action as compared to synthetic steroids ***1% excreted free in urine as free cortisol(monitoring levels)** *1/3rd metabolized to 17-hydroxysteroids and excreted in urine ***readily absorbed from GIT** *duration of activity higher than pharmacokinetic half-life: alters gene transcription	**ADRENAL DISORDERS**: 1.chronic adrenal cortical insufficiency(addisons disease) 2.acute adrenal insufficiency(associated with shock, infection and trauma) 3.congenital adrenal hyperplasia 4.diagnosis of cushing disease(dexamethasone suppression test) **NON ADRENAL USES:** 1.fetal lung maturation(betamethasone) 2.allergic reactions(rhinitis, dermatitis, urticarial) 3.collagen vascular disease(rheumatoid arthritis, GCA) 4.hematological disorders(leukemia, ITP) 5.pulmonary disease(asthma,sarcoidosis, ARDS) 6.GIT disorders(chemotherapy	*short term <2 weeks is well tolerated *suppression of ACTH: corticol atrophy,malaise, myalgia, shock-like syndrome ***IATROGENIC CUSHING SYNDROME:** *daily dose of 100mg coticosterone or more equivalent amount of syhthetic steroids for longer than two weeks 1.buffalo hump 2.moon face with plethoric cheeks 3.increased abdominal fat 4.thinning of skin 5.thin arms and legs 6.poor wound healing, easy bruising 7.insomina, increased appetite

			induced vomiting) 7.CNS(multiple sclerosis, cerebral edema) 8.organ transplant 9.renal(nephrotic syndrome) 10.hypercalcemia(reduces absorption and increases excretion of calcium) and mountain sickness	**REST:** *weight gain *oteroporosis may lead to vertebral fractures and hip necrosis *hyperglycemia>diabetes *cataracts &glaucoma *psychosis & behaivoural changes *growth retardation *delayed wound healing *myopathy &muscle wasting *fluid and Na+retention *inc gastrointestinal acid release and pepsin release *electrolyte imbalance: (imp) hypernatremia, hypokalemia, metabolic acidosis,hypocalcemia **<u>CONTRAINDICAI ONS</u>:** *peptic ulcer disease *hypertension *congestive heart failure *psychosis *diabetes *oeteoporosis *glaucoma *pregnancy *infection:Tb
SYNTHETIC STEROIDS(prednisolone,dexamethasone,triamcinolone)		MUST SEE DIFFERENCE: *longer half-life *longer duration of action ***reduced salt retaining activity** *better penetration of lipid barrier when used for salt retaining activity	*used for **asthma**, where good surface activity on surface mucous membrane/skin is required ***beclomethasone & budesonide, dexamethasone penetrate airway readiy, a**nd have short half-lives in blood and are used when systemic effects are to avoided	
<u>MINERALOCORTICO STEROIDS</u> AGONIST(fludrocrtisone, aldosterone)	*aldosterone *deoxycorticosterone>precursor	*long duration of action	***adrenal insufficiency**	***hypokalemia** ***hyponatremia**

	of aldosterone ***controlled by RAA(regulates BP &blood volume) and low plasma Na+ and high K+** *aldosterone-little glucocorticoid activity>results in increased Na+ and water retention ***fludrocorticosterone>significant glucocorticoid activity** *MOA similar to glucocorticoids *all mineralocorticoids are strong agonist at Mineralocorticcoids receptor and moderate at glucocorticoids **LEADS TO:** **1.reabsorption of Na from DCT and proximal collecting renal tubules** **2.excretion of K+ and H+ ions**			***metabolic acidosis** ***hypertension**
<u>CORTICOSTEROID ANTAGONISTS:</u> <u>A</u>)RECEPTOR ANTAGONSITS:spironolactone, eplerenone,mifepristone	*mifepristone: competitive inhibitor of glucocorticoid and progesterone receptor *spironolactone:pharmacological antagonist of mineralocoriticoid receptor, weak antagonism of androgen receptor *eplerenone more selective for mineralocorticoid receptor	*mifepristone: oral administration *spironolactone: slow o nset of action + duration:24-48hrs	*mifepristone: medical abortion and rarely cushing syndrome *spironolactone: aldosteronism+hypokalemia due to other direutics+post-myocardialinfarction	*mifepristone: vaginal bleeding+abdominal pain+diarrhea+headache *hyperkalemia *spironolactone: gynecomastia(not epleronone as its more selective!)
B)CORTICOSTEROID ANTAGONIST: *ketoconazole *aminoglutethemide' *metyrapone *etomidate	***ketoconazole**: an anti-fungal drug>inhibits CYP 450 enzyme>enzyme necessary for synthesis of steroids ***aminogluthemide**:blocks conversion of cholesterol to		*a**minoglutethemide**: used in conjunct with other drugs for the Rx of steroid producing adrenocortical cancer	*ketoconazole: hepatic dysfunction+many drug-drug CYP450 interaction

	pregnenolone *__metyrapone__: inhibits inhibits normal production of steroids but not that of cortisol precursors *__etomidate__:inhibits 11 Beta hydroxylase>cushings syndrome		*__metyrapone__:adrenal function *__etomidate__:cushing syndrome	

THYROID AND ANTI-THYROID DRUGS:

EFFECTS OF THYROID HORMONE:

*normal growth of body

*development of skeletal, nervous, reproductive system

*metabolism of fats, carbs, and proteins

*inc BMR

*thermogenic effects

*inc plasma glucose and FFA, reduces cholesterol and TAG

*inc HR and maturation of CNS

*growth and development: brain development, DNA transcription, cretinism, mental alteration, severe morphological alteration

THYROID DRUGS:

1.LEVOTHYROXINE(T4):	2)LIOTHYRONINE(T3)
*inactive form	* active form
*0.02% in unbound form(less systemic toxicity)	*0.2% in bound form
*long half-life	*half-life:1 day

ANTI THYROID DRUGS:

1.**Inhibits hormone synthesis**: PTU(thioamide) & carbimazole(methimazole)

2.**inhibits iodine trapping**(not used now due to aplastic anemia): thiocyanates & percholates

3**: iodine % potassium iodide** lugdiatrizoate & lugol solution(prevents the organification and proteolytic cleavage)

4.**destroy thyroid tissue**: radioactive iodine I131

5.**inhibit peripheral conversion of T4 to T3**: diatrizoate & Iohexol (radiocontrast media) + PTU + others(corticosteroids, amiodarone, beta blockers)

SOME IMPORTANT MISCELLANEOUS POINTS:

THYROID AGENTS

LEVOTHYROXINE:

*dose of T4: 1.6ug/Kg

*INSTRUCTIONS: take first thing in morning, take breakfast after 1hr, AVOID CALCIUM , IRON, ALUMINIUM containing antacids

*retest: 4-6 weeks after initiation of Rx

*Rx: range of TSH: 0.5-2.5ug/Kg.

WHY T4 PREFERRED OVER T3? SEQ

*T3 has shorter half-life(1day compared to 7days)

*shorter duration of action

*more expensive

*more systemic toxicity: 0.2% in unbound form

*difficult to administer and monitor

DIFFERENCE BTW T4 AND T3:

	T3	T4
source	20-25% by gland + 70-75% by peripheral conversion of T4	Solely by gland
Dose	30mg/day	80mg/day
Half-life	1 day	7 days
potency	3-4times more	Less potent
binding	0.2% in unbound	0.02% in unbound

ANTITHYROID DRUGS

*<u>COMPARISON BTW PTU & CARBIMAZOLE</u>: SEQ

PTU advantages:

*high PPB(safe in pregnancy)
dosing*methimazole
*inhibits peripheral conversion of T4 to T3

CARBIMAZOLE advantages:

*5 times more potent*once daily

PTU disadvantages:

*less potent

*multiple dosing

PROPYLTHIOURACIL	CARBIMAZOLE
Less potent	5 times more potent
Highly PPB	Less PPB
Less placenta crossing	High entry
Half-life:1-2hrs	6-10hrs
No active metabolite	Active metabolite-methimazole
Multiple dosing	Single dos
Inhibits T4 to T3 conversion	No T4 to T3 conversion

*Rx of PTU OVER SURGERY/I 131:

ADVANTAGES:

1.no surgical scar

2.no injury to thyroid and parathyroid gland

3.hypothyroidism if induced is reversible

4.can be used in children and young adults

DISADVANTAGES:

1.prolonged Rx

2.relapse high

3.not practical in application

*GENERAL RECOMMENDATIONS WHILE ADMINISTERING RADIOACTIVE IODINE 131:

1.keep distance from pregnant and children

2.dont sit next to patients for more than one hour.

3.avoid close contact

4.sleep alone in a separate room

5.flush toilet twice,wash tub thoroughly

6.follow after every 4-6 weeks

Rx of THYROID STORM:

1.Beta blockers: PROPRANOLOL>160mg/dl ….prevent cardiac abnormality associated with thyrotoxicosis and also prevents peripheral conversion of T4 to T3

2.PTU

3.Iodinated radiocontrast media: (oral diatrizoate and IV iohexol)

4.amiodarone

5. corticosteroids associated with inflammatory version

REMEMBER AMIODARONE CAUSES BOTH HYPOTHYROIDISM AND HYPERTHYROIDISM!

HYPOTHYROIDISM EMERGENCY: MYXEDEMA(give levothyroxine)

HYPERTHYROIDISM EMERGENCY: THYROID STORM(give afore mentioned drugs)

NAME	MECHANISM OF ACTION	PHARMACOKINETICS	CLINICAL USES	TOXICITIES
IODINE DRUGS:				
LEVOTHYROXINE(T4)	*thyroid hormone bound to TBG is taken into cell>binds to intracellular receptors>diffuses into nucleus binds to THRE-TRE(co repressor falls off) and leads o transcription of gene into proteins like Na/K+ATPase pump, specific contractile protein in smooth muscle, heart and enzymes involved in lipid metabolism	*dose:1.6ug/Kg *avoid taking with antacids. Ca, Fe, Al *retest after 4-6 months	1.cretinism 2.adult hypothyroidism 3.myxedema crises(T4: 200-500ug IV, followed by 100ug daily till oral T4 can be stated)	1.headache, insomnia, nervousness, hot flushes 2.irritability, fever, sweating, palpitations 3. weightloss, increased appetite *older patient with CVS disease and *long standing myxendema sensitivee to stimulatory e ffect of T4 in heart
LIOTHYRONINE	*same mechanism of actions	*shorter half-life *shorter duration of action *more potent *T4 converted to T3 in liver ad kidney	*given in low dose to young patients with no cardiac arythmias	*more severe sysemic toxicity: inc weightloss, lnc appetite, menstryal irregularity, decreased fertility
ANTI-THYROID DRUGS:				
THIOAMIDES(PTU, carbimazole/methimaz	1.inhibits peroxidase enzyme:	*delayed onset of action(3-4weeks)	1.used for control of patients for	1.hypothyroidism and goiter due to Rx

ole)	*inhibits oxidation of iodide *prevents organification of tyrosine residues of thyroglobulin 2.prevents coupling of coupling of MIT-DIT to form T3 and T4 3. prevents peripheral conversion of T4 to T3 *methimazole: inhibits peripheral conversion(deiodinase)	*oral admin stration PTU: more frequent dose *Methimazole: once daily	hyperthyroisim (graves disease and toxic nodular goiter) 2.**suppression of thyroid hormone synthesis** until effects of radioactive iodine begins 3.long term Rx for mild to moderate hypothyroidism *PTU USED IN PREGNANCY!	2.decrreased appetite, increased weight gain, decreased fertility, decreased excitability 3.**mild maculopapular rash, joint pain, nausea, GIT disturbances** 4.loss of hair 5.**rare but agranulocytosis** **6.hypoprothombinemia** **7.hepatic dysfunction**!
IODINE SALTS AND IODINE	1.inhibits organification process 2.prvents proteolysis of MIT-DIT-T3-T4 to release T4 3.also decreases size and vascularity of hyperplastic thyroid gland *USUAL FORM OF THIS DRUGG: 1.LUGOLS SOLUTION: (5%iodine and 10%KI)>given 10days prior to surgery to reduce gland size,vascularity and increases firmness of gland 2.saturated solution of KI	*onset of action rapid:2-7days *no long term use:THYROID ESCAPE!	1.used **preoperatively** to reduce **the size** and **vascularity** and **fragility** of hyperplastic thyroid gland 2.used for Rx of thyroid storm 3.prophylaxis of endemic goiter 4.expectorant 5.anti-septic	1.rash, metallic taste. 2.Bleeding disorders 3.anaphylactic shock(RASH, fever, joint pain, swelling of face, lips, wheezing, shortness of breadth)
RADIOACTIVE IODINE 131	*emits gamma and beta rays *gamma rays: traverse tissues *beta:particles utilized to produce destructive effects *accumulate in colloids and penetrates 0.5-2um *thyroid follicle cell>pyknosis>necrosis and fibrosis	*response is slow to develop: 2 weeks at start of response *peaks:3months *MOST COMMON	*single large dose used to Rx thyrotoxicosis(patient must be taking beta blockers before taking I131)	*sore Throat *contraindicated in pregnancy ADV: Outdoor setting, simple, convenient, no surgical scar DISADV: Latent response

IODINATED RADIOCONTRAST MEDIA	1.inhibits peripheral conversion of T4 to T3 2.also suppresses hormone release from thyroid gland	*iohexol:IV *diatrizoate:oral	*used for rapidly developing thyrotoxicosis	
PERCHOLATES AND THIOCYANATES	*inhibits iodine uptake by the thyroid gland by competitive inhibition of transporter			*percholarate:aplastic anemia
BETA BLOCKERS	*inhibits peripheral conversion of T4 to T3		*thyroid storm *adjunct to control tachycardia, hypertension, atrial fibrillation	*asthma *AV blockade *hypotension *bradycardia

GONADAL HORMONES AND INHIBITORS:

*MORINING AFTER PILL: DES

*INFERTILITY PILL: CLOMIPHENE

ESTROGEN:

*steroid hormone produced by the ovaries, and to a some extent also involve the adrenal, the placenta

*ESTRADIOL the principle ovarian estrogen

*other endogenous estrogens are: ESTRIOL & ESTRONE

SPECIFIC AGENTS:

1.NATURAL: estradiol(17-beta estradiol most potent) & conjugated estrogens(means sulfate esters like premarin used in HRT)

2.SYNTHETIC: oral preparations of ethinyl estradiol & mestranol(mestranol is converted in the body to ethinyl estradiol>advantage of syntehtics is that it has increased half-life)

3.NONSTEROIDAL: DES & cholotrianisene

MECHANISM OF ACTION OF ESTROGEN:

*after dissociation from their binding sites on sex-hormone-binding globulin SHBG in plasma>steroid hormones diffuse across cell membrane >binds to specifc nuclear receptor protein>steroid-receptor complex diffuses interacts with nuclear chromatin to initiate hormone-specific RNA synthesis>results in transcription and translation of specific protein involved in esrrogen metabolism

REGULATION OF SECRETION OF ESTROGEN:

*hypothalamic-pituatry ovarian axis

*synthesis by ovarian follicle stimulated by FSH>inc cAMP in the follicular cells>provides negative feedback to the inhibit pituatry secretion of FSH and LH

*Midcycle of LH promotes ovulation

*estrogens remain elevated in luteal phase

PROGESTERONE

*steroid hormone produced by the corpus luteum and adrenal cortex

*during the post-ovulatory phase

*progestins: drugs with progesterone like properties

*SPECIFIC FORMS:

*__synthetic__:medroxyprogesterone has improved oral F

*__OLDER 19-nortestosterone__>more androgenic: L-norgesterol, norethindron

*__NEWER__>less androgenic:norgestimate,desogestrel,etonogestrel(significant as in case of acne where a womon wished to use OCP, we give newer progesterone forms which are less androgenic

*__spironolactone derivative__: drospirenone

*REGULATION OF SECRETION: LH>cAMP

HORMONAL CONTRACEPTIVE THERAPY:SEQ!

MECHANISM OF ACTION:

*combined preparation: estrogen & progesterone causes feedback inhibition of FSH and LH secretion>to inhibit ovulation(progestin only>don't inhibit ovulation, act thru other mechanism)

*progesterone thickens cervical mucous and prevents entry of sperm

*effect on uterine tubes and endometrium to decrease likelihood of fertilization and implantation

DIFFERENT PREPARATION USED: oral, subcutaneous implants, transdermal patches, IUD, vaginal rings, long acting injections

PARENTRAL CONTRACEPTIVES PREPARATIONS!!

A)depot IM injection: medroxyprogesterone

B)weekly patch: ethinyl estradiol

C) vaginal ring: ethinyl estradiol + etonogestrel

D)IUD:L-norgestrel

E)subcutaneous implant: etonogestrel

ORAL CONTRACEPTIVES PREPARATIONS!!

A)MONOPHASIC: taken in constant phase during menstrual cycle

***combo: estrogens and progestins:ethinyl estradiol/mestranol+progestins**

*ex. Yasmin(3mg of drosperinone & 30mg of ethinyl estradiol)

B)BIPHASIC/TRIPHASPHIC/QUADRIPHASIC: closely mimics the hormonal preparations in a menstrual phase, as changes during months

*ortho-Tri-Cyclen

C)**PROGESTIN ONLY PREP:norethindrone& L-norgestrel** (give in women who are smokers, as progestin has an anti-estrogenic effect)

POST-COITAL CONTRACEPTIVES!

*emergency contraceptives

*72hrs after intercourse

*progestin alone(L-norgesterol)

*estrogen alone:ethinyl estradiol

*combo: 0.25mg levonorgestrel and 0.05mg of ethinyl estradiol

ADVERSE EFFECTS OF OCP:

A)THROMBOEMBOLISM: increased risk of DVT, MI, pulmonary embolism

B)BREAST CANCER

C)OTHER TOXICITIES:

*nausea

*vomiting

*skin pigmentation

*headcahe

*depression

*hyperTAG

*hypertension

CONTRAINDICATIONS FOR OCPS!(SEQ)

1.thromboembolic event

2.moderate to severe hypertension

3.hyperlipidemia

4.liver disease

5.malignancy of breast

6.impending surgery

CAUTION FOR OCPS:(SEQ)

1.diabetes

2.obesity

3.smoking(in this case of we use progestin only contraceptives!)

4.undiagnosed vagibal bleeding

5.mentally ill patient

6.migraine

7.mild HTN

SELECTIVE ESTROGEN RECEPTORS MODULATORS!!

GOAL IS TO:

A)produce beneficial effects in some tissues: bone, brain, liver

B)avoid deleterious effects in some tissues: breast and endometrium

ESTROGEN RECEPTOR TYPES:

ER-alpha:

*found in uterus, vagina, breast, kidney(595 aminoacid residues)

ER-beta:

*found in ovaries, lungs and bladder(485 aminoacid residues

EASY SUMMARY FOR ALL GONADAL HORMONES:

ESTROGEN	**PROGESTERONE**	**ANDROGENS**
AGONISTS: *estradiol *estradiol cypionate Rx(primary hypogonadism, OCP, HRT, prevent CAD, treat osteroporosis) **ANTAGONIST:** A)SERMS *tamoxifen(estrogen positive	**AGONIST:** Used for OCP, HRT, assists reproductive techniques, endometriosis and fibrosis A)SYNTHETIC: *medroxy progesterone acetate *megrestrol actetae B)OLDER 19-TESTERONE COMPOUNDS:	AGONIST: *used to Rx primary hypogonadism in males *stimulates RBC production in certain anemia *stimulates weight gain in AIDS patients A)ORAL ANDROGENS: *fluoxyesterone *methyltesterone

breast cancer) *raloxifene(treat and prevent osteoporosis in post-menopausal women) *clomiphene(treat infertility) B) FULL RECEPTOR ANTAGONIST: *fulvestrant(breast cancer resistant to tamoxifen) C)SYNTHESIS INHIBITORS: *AROMATASE INHIBITORSl:anastrazole and exemestane(Rx breast cancer) *CYP 450 INHIBITOR: danzol(Rx endometriosis and fibrocystic disease of ovary) D)GnRH analogue: *leuprolide(Rx of precocious puberty in children and short-term Rx of endometriosis and uterine fibroids) E)GnRH ANTAGONIST: *ganirelix and cetrorelix(used for controlled stimulation of ovaries)	*L norgestrel *nor-ethindrone C)NEWER 19 TESTERONE COMPOUNDS: *nor gestimate *desogestrel *etonogestrel D)SPIRINLACTOEN DERVATIVES: *dorspirenone **ANATGONIST:** *mifepristone(used as abortifacient in early preganancy, antagonist at glucocorticoid and progesterone receptors, luteolytic effect)	B)ESTERS: *testerone cypionate C)ANABOLIC STEROIDS: *androlone ANATGONIST: A)RECEPTOR INHIBITOR *flutamide(Rx prostatic carcinoma) *spironolactone(K+ sparing direutic and Rx hirusitsm in females) B)5 ALPHA REDUCATSE INHIBITOR: *fiansteride(Rx BPH + hairloss in men) C)SYNTHESIIS INHIBITOR: *ketoconazole(Rx steroid responsive metastaic breast cancer) D)GnRH ANALOGUE: *leuprolide(prostatic carcinoma,flutamide added to prevent tumor flare that can result due to increased surge in testerone synthesis) E)GnRH ANATGONIST: *abarelix and dabarelix(advanced prostatic carcinoma)

NAME	EFFECTS	PHARMACOKINETICS	THERAPEUTIC USES	ADVERSE EFFECTS
ESTROGENS	1.normal developemnet of the **secondary sexual characteristics** 2.developement of the **uterus, vagina and uterine tubes** during childhood	*low F in oral administration ***available in topical, IM, transdermal, and vaginal creams** ***long acting (estradiol cypionate)**	1.**oral contraceptives** along with progesterone 2.**Rx hypogonadism** in females 3.**HRT**:results from menopause, premature ovarian failure and surgical removal of uerine tubes>ameliorate hot flushes	***hypogonadism**: premature closure of epiphysealplates and short stature ***HRT**: increases risk of endometrial and breast carcinoma and

	3.required for the initial **proliferation of the endometrium** during menstrual cycle 4**.METABOLIC EFFECTS**: *modifies the serum protein level and reduces bone resorption(osteoclastic activity reduced) *increases the linear bone growth and leads to subsequent closure of the epiphyseal plates *increases HDL and dec LDL *blood clotting facto 2, 2, 9 and 10 are increased and anti-thrombin 3 is reduced	**IM** *conjugated HRT *synthetic: oral contraceptives ***excreted in bile, reabsorbed from intestine**	snd vaginal atrophy 4.**decreases the risk of osteoporosis** and promotes apoptosis of osteoclasts, antagonizes the proosteoclastic effects of PTH 5**.dysmenorhea and abnormal uterine bleeding** 6.**palliative Rx for prostatic carcinoma** to reduce growth of metastases 7.**reduces the CAD** 8.DES can be given to prevent pregnancy>when adminisyered within 24-48hrs after intercourse> known as the MORNING AFTER PILL ***DES:** *morning after pill 1.prevents threatened abortion 2.prevents miscarriage 3.premature labour and related complication sof pregnancy *removed!!due to deleterious effects on fetus and leads to clear cell adenocarcinoma of vagina and uterine tract abnormality(presence of mullerian tracts in upper vagina)	MI ***dose dependant toxicity:** **MODERATE** nausea, breast tenderness **SERIOUS** inc risk of **migraine headache, thromboembolic events(DVT),** gallbladder disease, **hypertriglyceridemia, hypertension** *high ratio of hepatic:peripheral effects.>increases the synthesis of clotting factors(hence minimized in preparation avoiding 1st pass metabolism) *DES! *infertility *ectopic pregnancy *small cell adenocarcinoma of vagina *uterine tract abnormality
PROGESTINS	*produces **a secretory phase** in endometrium ***stimulates breast development** during during puberty and lactation ***maintains pregnancy** by preventing the sloughing off of endometrium ***depressant and a hypnotic effect** ***inc body temperature during post-ovulatory phase!** ***METABOLIC EFFECTS:** 1.DONOT affect plasma protein 2.they affect the carb metabolism>basal insulin increased and decrease blood glucose levels and increases glycogen storage	*largely metabolized in liver ***synthetic are administered orally**	1.oral contraceptives(with estrogens) 2.used in combo with estrogen in HRT to prevent endometrial cancer 3.assisst reproductive methods to promote and maintain pregnancy 4.Rx of dymenorhea 5.Rx of endometriosis(medroxyprogesterone) 6.suppress ovarian cancer	*low systemic toxicity ***increases BP and decreases HDL** ***HRT in postmenopausal**>irreverible decreases in bone density *delayed presumption of ovulation after termination of pregnancy *androgenic effects: *weight gain *hirsutism *acne *tiredness and depression

	3.stimulates the deposition of fat and LPL activity and promotes ketogenesis 4.high doses suppress gonadotrophic secretion>may cause anovulation 5.**androgenic and anti-estrogenic effects**			
HORMONAL CONTRACEPTIVES PILLS	*effects on CVS:inc HR and CO ***skin**:increases pigmentation and acne ***ovary**:decreased follicular developemet ***uterus**: hypertrophic and polyp formation, less bleeding, more glandular atrophy *blood:lipid metabolism		1.combo ocp**: primary hypogonadism** in females 2.combo of hormonal contraceptives and progestins:**Rx acne** ***acne induced hirsutism**(estrogen increases expression of SHBG and reduces concentration of free androgen>causing male-pattern hair growth in females ***dysmenorrhea, endometriosis** 3.reduces **ovarian cyst, ovarian and endometrial cancer, bening disease, pelvic inflammatorydisease, ectopic pregnancy, Fe deficiency anemia, rheumatoid arthritis**	*dose-dependant toxicity: A**)THROMBOEMBOLISM:** *related to estrogenic affects on coagulants affect *increased MI, DVT, pulmonary embolism, B)**BREAST CANCER**: C)**OTHER TOXICITIES**: *low dose combo>significant bleeding ***nausea, vomiting, headchae, skin pigmentation, depression**
ANTI ESTROGENS: A)**SERM**:tamoxifene, raloxifene, clomiphene				
B**)PURE ESTROGEN RECEPTOR** ANTAGONIST:fulvestrant				
C)**SYNTHESIS INHIBITORS**:				

aromatase inhibitor, danazol D)**GNRH AGONIST**: leuprolide SERM				
1.TAMOXIFEN	*agonist:endometrium, venous thrombosis,bone *antagonist:breast		***hormone responsive breast cacer *prevents osteoporosis in post-menopausal women *prevents atherosclerosis by lipid changes	***endometrial hyperplasia** ***hot flushes** *increased **thromboembolic events** *nausea, vomiting, rash, hypercalcemia, menstrual irregularities
2.RALOXIFENE	*SELECTIVE Agonist:bone *antagonist:breast *NO ESTROGENIC EFFECTS ON ENDOMETRIUM		*prevention and Rx of osteoporosis in post menopausal women *lowers LDL	*hot flushes(antagonist effect) *inc venous thrombosis
3.CLOMIPHENE	*partial agonist at estrogen receptors *selectively blocks estrogen receptors in pituatry>hence prevents –ve feedback on LH and FSH secretion		*FERTILITY PILL *increases ovulation via inhibition of negative feedback 1.induces ovulation in amenorrhea and ovulatory dysfunction and PCOS 2.used in men to increase spermatogenesis	*hot flush *constipation *overtimualtion can lead to ovarian cysts
FULVESTRANT	*pure estrogen receptor antagonists		*used to Rx breast cancer resistant to tamoxifen	*headache, hot flushes, injection site pain
ANASTRAZOLE	*nonsteroidal competitive inhibitors of aromatase		*breast cancer	*hot flushes,

	*exemestane:irreversible inhibitor			musculoskeletal changes, joint symptoms, arthralgia, athrosis, ankylosing spondylitis , disk herniation
DANAZOL	*inhibits CYP 450 involved in gonadal steroid synthesis *weak partial agonist at progestins, androgens, and glucocorticoid receptors		*endometriosis *fibrocystic disease of breast	*acne, hepatic dysfunction, hirsutism, acne
LEUPROLIDE	*GNRH analogu *suppresses LH and FSH secretion		*used in Rx of precocious puberty in children *short term <6month for endometriosis and uterine fibroids	*>6months: decreased bone density
MIFEPRISTONE	*steroid antagonist at glucocorticoid and progesterone receptors		*abortifacient in early pregnancy *combo of mifepristone +PGE analogue: complete abortion!	*nausea, vomiting, diarrhea,cramping, sepsis, C.sordelli infection
ANDROGENS				
TESTOSTERONE SYNTHETIC: *oxandrolone *stanozolol	TESTOSTERONE: *synthezied from progesterone & DHEA *plasma bound to SHBG *converted to dihydroteststerone in prostate MOA similar to estrogen(binding to cytosolic receptors)		EFFECTS: *normal developemnet of amle fetus, infants *responsible for puberty changes(growth of penis, larynex, skeleton,facial, pubic hair) *development of secondary sexual characteristics(fertility, libido) *increase muscle size, strength, increases RBC production *excretion of urea nitrogen is reduced>nitrogen balance becomes positive *maintenance of normal bone densilty CLINICAL USES: *replacement therapy in hypogonadism *androgens used to stimulate RBC production(in anemic	*in females>(hirsutism, enlarged clitorius, deepened voice) *pregnant women with a female fetus>virilization of external genitalia *in men>feminization(gynecomastia, testicular shrinkage, infertility,,,,due to feedback inhibition of pituatry and conversion of exogenous androgens to estrogens) *both sexes>cholestatic jaundice, elevation of liver enzymes, HCC

			patients) *used to promote weight gain in patients with wasting syndromes(AIDS) *increases muscle balance(athletic performance)	
ANTI-ANDROGENS RECEPTOR INHIBITOR (flutamide, bicalutamide, nilutamide, spironolactone)	*nonsteroidal competitive antagonist of androgen receptors *used to decrease endogenous androgens in patients with prostatic carcinoma *spironolactone: inhibits androgen receptors		*flutamide: prostatic carcinoma *spironolactone: hirsutism	*rash(apalutamide) *diarrhea(flutamide) *feeling tired *hot flashes *dizziness *nausea *sexual dysfunction(erectile dysfunction) *loss of bone density *galactorrhea and gynecomastia *HEPATOTOXIX(flutamide, less risk with nilutamide & bicalutamide)
5ALPHA-REDUCTASE INHIBITOR: finasteride Dutasteride(long half-life)	*inhibition of conversion of testosterone to DHT *this conversion necessary in prostate and hair follicles		*BPH	*less likely than other anti-androgens to cause impotence, infertility, and loss of libido
GnRH AGONIST	*agonist at GnRH receptor> leading to a		*prostatic carcinoma(GnRH ANTAGONIST	

Leuprolide	decrease in LH production		Flutamide added to prevent tumor flare)	
INHIBITORS OF STEROID SYNTHESIS(ketoconazole)	*inhibits gonadal and sterid synthesis, via inhibition of CYP 450		*steroid responsive prostatic carcinoma(resistant to first line anti-androgens)	*interfers with synthesis of other steroids *many drug-drug interactions due to CYP 450 inhibition

ANTI-DIABETIC DRUGS

MECHANISM OF ACTION OF INSULIN:

*insulin receptor: tyrosine kinase>phosphorylates itself and a variety of intracellular proteins

EFFECTS OF INSULIN:

1)LIVER:

Increases storage of glucose as glycogen as:

*increases insertion of additional GLUT2 glucose transporters molecules in cell plasma membranes

*increased synthesis of PK, phosphofructokinase, glucokinase

*decrease in protein catabolism

*increases VLDL and TAG synthesis

2)SKELETAL MUSCLE:

*also stimulates glycogen synthesis and protein synthesis

*insertion of GLUT 4 transporters into cell membranes

3)ADIPOSE TISSUE:

*facilitates TAG storage by activating LPL

*Increased gluose transporters via GLUT4

PHARMCOKINETIC PROPERTIES OF RAPID INSULIN AND ADVANTAGES OVER REGULAR INSULIN(SEQ)

*lispro, aspart, glulisine

*formed due to modification of amino acid sequences of regular acting

*rapid absorption

*given immediately before meal, compared to regular given 30 -60min before meal

*quicker onset of action(5-15 min compared to regular insulin which produces action in 30-60min

*shorter duration of action(5hrs)

INSULIN DELIVERING SYSTEMS:

*subcutaneous injection

*inhaled insulin

*portable pen sized injectors used to facilitate subcutaneous injection

*continuous subcutaneous insulin infusion devices advantages:
1.prevent need for multiple daily dosing

2.better patient compliance

CAN ORAL ANTI-DIABETIC DRUGS BE USED IN TYPE 1 DM: SEQ

*no, as in DM there is destructiin to the beta cells of islets of Langerhans

*oral anti-diabetic drugs increase sensitivity of insulin receptors

*hence as already there is exhaustion of beta cells, oral anti-diabetic like sulfonyl urea which stimulates beta cells aren't useful in type 1 DM

*hence, given INSULIN PREPARATIONS!

MANAGEMENT IN TYPE 1 DM:

*parentral insulin preparations(a mixture of both short acting and long acting insulin preparations to maintain both basal and postprandial glucose levels)
*pramilinitide to improve control of post prandial hyperglycemia

*careful attention to factors that change insulin requirement: exercise, infections, stress

COMPLICATION IN Rx FOR TYPE 1 DM:

1.hypoglycemia(corrected via giving glucose(Oral/IV) or glucagon(IM)

2.insulin induced immunological reactions(corrected by using recombinant insulin preparation)

3.weight gain(corrected via exercise)

REGIME IN TYPE1 DM:

*mixed regime

*2/3prebreakfast nd 1/3predinner

*8UNPH+4U(alanine/glargine/lispro)+3UNPH+3U(alanine/galrgine/lispro)

MANAGEMENT IN TYPE 2 DM:

*weight reduction, execise, diet

*as type 2 involves both insulin resistance and inadequate insulin production

HENCE, WE COMBINE

*<u>insulin sparing/drugs that augment insulin secretion</u>: metformin, thiazolidinedione, alpha-glucosidase inhibitor

*<u>drugs that increase insulin supplies</u>: insulin secretagogues, insulin

*LONG ACTING DRUGS: sulfonyl urea, metformin, thiazolidinediones, exenatide,sitagliptin>controls both fasting and post prandial glucose levels

*SHORT ACTING: alpha-glucosidase inhibitor, repaglinitide, pramlinitide, rapid acting insulin>controls post-prandial glucose levels

GLUCAGON:

*secreted by alpha cells

*acts thru GPCR on heart, smooth muscle, liver

*given IM/IV

1.glucagon increases HR, force of contraction

2.increases hepatic gluconeogenesis

3.increases hepatic glycogenolysis

CLINICAL USES:

*Rx hypoglycemia

*Rx of severe beta blockers overdose

NAME	MECHANISM OF ACTION	PHARMACOKINETICS	THERAPEUTIC USES	TOXICITIES
INSULINS				
*RAPID ACTING(lispro, aspart, glulisine)	*activates insulin receptor	*rapid onsets(5-15min), IV administration *early peak of activity *shortest DOA(5 hrs) *small alterations in aminoacid sequence that speeds entry into circulation>difference btw all three rapid acting	*injected immediately before a meal to control post prandial hyperglycemia *emergency for DKA	*COMMON FOR ALL INSULIN PREPARATION: **Hypoglycemia**, resulting in: *headache *anxiety *tachycardia *confusion *vertigo *diaphoresis *increased appetite *blurred vision *weakness/fatigue OTHERS: *lipiddystrophy *insulin-induced immunological complication(formation of antibodies)
*SHORT ACTING(regular insulin)		*DOA:12 hrs *IV/SC *onset of action:30-60min	*IV(DKA) *control post-prandial hyperglycemia(injected 1 hr before meal)	
*INTERMEDIATE ACTING(NPH insulin neutral protamine	*other name: insulin isophane	*DOA: 10-12 hrs *onset of action:2-4hrs *NEVER GIVEN		

hagedorn>combination of regular insulin, protamine, zinc)		IV!(contains protamine which is antagonist to heparin and increases thrombus formation at the site of action)		*children<7yrs, elderly, with advanced renal disease prone to complications by hypoglycemia
*LONG ACTING(glargine, detemir, degludec)	*no peak *maintains peakless basal levels	*DOA: >20 hrs *onset of action: 0.5-1hrs		
NONINSULIN NON-DIABETIC DRUGS:				
*INSULIN SECRETAGOGUES 1st generation(less potent,more toxicity, not used now) *tolbutamide *chlorpropamide 2nd generation(more hypoglycemia>more potent) *glyburide *glipizide *glimepiride OTHERS:(fast acting) *repaglinide(meglinitide) *nateglinide(D-phenylalaine derivative)	*binds to and closes ATP sensitive K+channels present on beta cells>lead to depolarization of cell>leads to influx of calcium ions>promotes exocytosis of insulin containing vacuoles	*oral administration	*type 2 DM	*older generation bind to plasma proteins>drugs that compete for PPB lie warfarin increase their toxicity *2nd generation: hypoglycemia *weight gain' *rash *glyburide(renal dysfunction)
DIGUANIDES(METFORMIN)	*MECHANISM OF ACTION: *AMP stimulated PK EFFECTS: *doesn't stimulate insulin secretion, infact reduce sinsulin production(insulin sparing effect) *reduces postprandial fasting blood glucose levels *inhibits renal and hepatic gluconeogenesis *stimulates glucose uptake *glycolysis in peripheral tissues *slows absorption of glucose from GIT *RESTORES FERTIITY IN PCOS!	*oral administration	*type 2 DM *PCOS	*no hypoglycemia or weight gain! *GIT distress *lactic acidosis in: 1.alcholism 2.kidney and liver disease 3.chronic cardiopulmonary dysfunction *Vit-B12 defeciency! *weight loss *monitor RFTs

THIAZOLIDINEDIONES *pioglitazone *rosiglitazone	*activates PPAR-gamma>induces transcription of genes involved in carbs and protein metabolism 1.increases glucose uptake by muscle and adipose tissue 2.inhibit hepatic gluconeogenesis 3.reduce fasting and postprandial hyperglycemia 4.used in monotherapy or in combination with insulin and other anti-diabetic drugs *reduces risk of diabetes in high risk pateints *pioglitazone: lowers TAG and increases HDL	*oral administration		*hypoglycemia(extremely rare) *fluid retention>edema *dilutional anemia *rosiglitazone: MI *troglitazone: hepatotoxicity *female patients increases risk of bone fractures *pioglitazone & troglitazone: induces CYP 450>reduces serum levels of OCP, cyclosporine
EXENATIDE/liraglutide/albiglutide/dulaglutide	*injectable analogue of GLP-1 *used in combo with metformin or a sulfonyl urea *presence of food in stomach stimulates release of GLP-1>augments insulin release from pancreas>retards gastric emptying>inhibits glucagon release>produces a feeling of satiety *GLP-1 family of GPCR> increases Camp>increases intracellular Ca2+ release			*GIT distress *nausea *hypoglycemia(in combo with sulfonyl urea) *acute pancreatitis *weight loss(suppresses appetite)
SITAGLIPTIN/saxagliptin/linagliptin/alogliptin	*inhibitors of DPP(dipeptidyl peptidase-4) *DPP degrades GLP-1>hence increased levels of GLP-1 stimualtes all the afore-mentioned effects *like exenatide, sitagliptin also stimulates insulin release, inhibits glucagon release, has an anorexic			*headache *nasopharyngitis *upper RTI

	effect			
ALPHA-GLUCOSIDASE INHIBITOR(acarbose)	*inhibits apha-glucosidase>this enzyme necessary for conversion of complex starches, oligosaccharides, diasacchrides into monosacchrides *inhibition of enzyme results in slowed absorption of monosacchrides *post prandial hyperglycemia is reduced *monotherapy or in combo with other drugs			*flatulence *diarrhea *abdominal paimn(due to increased fermentation of unabsorbed glucose in small intestine) *hypoglycemia(take sucrose, not glucose!!)
PRAMLINITIDE	*synthetic analogue of amylin *amylin is a 37 aminoacid>produced by beta cells *amylin>contributes to glycemic control and osteogenesis *pramlinitide>suppresses glucagon release *slows gastric emptying *works in CNS to reduce appetite	*SC injection *short duration of action		*hypoglycemia *GIT distress
CANAGLIFLOZIN/danagliflozin/empagliflozin	*inhibits SGLT2>prevents glucose absorption from urine *inhibiton causes glucosuria			*genital infections(vulvovaginal infections) *UTI *osmotic direusis causes intravascular volume depletion>hypotension

AGENTS AFFECTING BONE MINERAL HOMEOSTASIS

ONLY IMP POINTS

REGULATORS OF BONE MINERAL HOMEOSTASIS:

A)HORMONAL:

*PTH

*Vitamin D

*calcitonin

*estrogen

*glucocorticoids

BNON-HORMONAL:

*bisphosphonates(most imp)

*fluoride

*calcimimetics

A)HORMONAL:

DIFFERENCE BTW PTH AND VITAMIN-D:

ORGAN	PTH	ACTIVE VIT-D METABOLITES
INTESTINE	*indirect affect thru increasing vit-D metabolites *increases Ca and P absorption	*increased Ca and P aborption
KIDNEY	*decreased calcium ecretion *increased phsophate excretion	*increased resoprtion of both Ca and phopshates
BONE	*low dose: bone formation(osteoblast) *high dose: increased Ca nd P resorption	*direct effect: increased bone Ca nd P resoprtion *indirect:promotes mineralization by increasing availabilityof Ca and P
NET EFFECT ON SERUM LEVELS	*serum calcium is increased *serum phosphates is decreased	*both increased

FORMS OF VIT-D:

*skin(7-dehydrocholcalciferol)

*diet(D3, cholecalciferol)

*plant(D2, ergocalciferol)

*liver(25-hydroxyvitamin D, calcifediol)

*kidney(1,25 dihydroxyvitamin-D, calcitriol)>synthesis inhibited by phosphates, FGF-23, vit-D metabolites)>direct oral form required in chronic kidney disease, liver disease, hypoparathyroidism

USES OF VIT-D:

*nutritional deficiency

*intestinal osteodystrophy

*hypoparathyroidism

*nephrotic syndrome

*Rx osteoporosis in women and men

*topical: psoriasis

FGF23

*secreted by osteocytes in bone

*inhibits 1,25(OH)2D production

*inhibits P reabsorption in kidney

CALCITONIN:

*secreted by thyroid glands

*causes hypocalcemia and hypophosphatemia

*Rx hyperPTH and pagets dieases

*injection/nasal spray

ESTROGENS:
*raloxifene

*prevents bone loss in postmenopausal women

*inhibits PTH-stimulated bone resorption

GLUCOCORTICOIDS:
*inhibits bone mineral maintenance

*causes osteoporosis

NON-HORMONAL AGENTS:

BISPHOSPHONATES(MOST IMP)

*alendronate

*etidronate

*ibandronate

*pamidronate

*risedronate

*zoledronic acid

MECHANISM OF ACTION:

*anti-resorptive agents(prevents both resorption and formation of bone)

*binds to hydroxyapatite crystal in bone

*directly/indirectly inhibits osteoclasts(inhibits afrnesyl pyrophosphate synthase enzyme>this enzyme plays a role in osteoclast activity)

*inhibits bone mineralization

*pharmacologically active only when on exposed bone surfaces

USES:

*manage hypercalcemia

*pagets disease

*post menopausal osteoporosis(alendronate)

*alendronate(steroid inducing osteoporosis)

*pamidronate(IV>hypercalcemia with pagets disease)

*etidronate(oral)

*REMEMBER ZOLEDRONIC ACID HAS THE HIGHEST ANTI-RESORPTIVE CAPACITY AND ETIDRONATE LOWEST ANTI-RESORPTIVE CAPACITY

DOSINGS OF BISPHOSPHONATES:

*daily(alendronate, risedronate, ibandronate)

*weekly(alendronate, risedroante)
*monthly(ibandronate)

*annual(zoledronate)

TOXICITY:

*bone mineralization defect(etidronate and pamidronate)

*GIT distress>esophageal ulcer(alendronate)

*nephrotoxicity and osteonecrosis of jaw

CONTROL ADR:

*large quantity of water(take 6-8 ounces of plain water daily)

*take risedrone delayed release tablet with atleast 4 ounces of plain water and immediately after breakfast and ibandronate 30-60min before meal

*take upright(don’t recline until after 30min of taking)

*prevents situations which stimulate stress conditions(GERD)

RANK L INHIBITORS:

*denosumab(human monoclonal antibody, prevents action of RANKL)

*inhibits osteoclast activity, inhibits bone resoprtion

*given SC every 6 months

CINACALCET:

*lowers PTH(activates calcium-sensing receptor in parathyroid)

*used for oral Rx of secondary hyperthyroidism in chronic kidney disease

*hypocalcemia & adynamic bone disease

CARDIOVASCULAR SYSTEM

DRUGS USED FOR Rx OF ANGINA PECTORIS

TYPES OF ANGINA:

1)ATHEROSCLEROTIC ANGINA:

*angina of effort/classic angina

*occurs on excercise, emotion or effort

*exercise>cardiac workload increases>obstruction of flow and inadequate blood supply>accumulation of metabolites>like lactic acid and ischemic changes that stimulate cardiac nerve endings

*rest relieves cardiac workload

2)VASOSPASTIC ANGINA:

*rest angina/prinzmetal angina/variant angina

*irreversible spasm of coronaries, at site of atherosclerotic plaque

*spasm may occur during sleep

*Beta blockers contraindicated in this !!!

3)UNSTABLE:

*crescendo angina/acute coronary syndrome

*increased frequency of attack, severity of attacks due to : atherosclerotic plaque/platelet aggregation/vasospasm

*requires hospital attack

DETERMINANTS OF CARDIAC OXYGEN REQUIREMENT:

DIASTOLIC & SYSTOLIC FACTORS AFFECT MYOCARDIAL FIBRE TENSION>ALTERS MYOCARDIAL O2 REQUIREMENT!

A) DIASTOLIC FACTORS : PRELOAD:

*dependant on blood volume & venous tone

*nitates decrease preload

B)SYSTOLIC FACTORS

1.after load >arterial blood pressure(TPR)>Ca channel blockers and nitrate decrease afterload

2.HR: double product: HR into SBP(HR dependant upon beta blockes and nondihydropyrimidine calcium channel blockers

3.Heart force: dependant upon sympathetic force

4.ejection time: inversely related to force of contraction and directly related to impedence to flow

THERAPEUTIC STRATEGY!

1)INC O2 SUPPLY:

*nitrates & Ca channel blockers &

2)DEC O2 REQUIREMENT:

*beta blockers & calcium channel blockers & nitrates

3)INC EFFECIENCY OF O2 UTILIZATION:
*ranolazine & trimetazidine(Pfox inhibitors)

4)DEC SAN NODAL:

*iva bradine

5)MYOCARDIAL REVASCULARIZATION

*__CALCIUM CHANNEL BLOCKER__: effective as prophylaxis against effort-induced and variant angine

*nifedipine: abort angina attacks but prompt release is contraindicated

*__BETA BLOCKERS__: prophylactic therapy of angina, not in acute attacks

IMP THINGS ABOUT NITRATES:

CLASSIFICATION:

1)**ultra short acting**: amyl nitrite DOA:1-5min

2)**short acting**: sublingual

*nitroglycerin(glyceryl trinitrate) DOA:15 min

*isosorbide dinitatre: DOA:20-30min

3)**intermediate acting**: oral

*nitroglycerin DOA:2-4hrs

*isosorbide mono and dinitrate

*pentaerythritol tetranitrate

4)**long acting:transdermal:**

*nitroglycerin DOA:10hrs

ORGAN SYSTEM EFFECTS OF NITRATES!!

1)CARDIOVASCULAR:
*DEC O2 REQUIREMENT: venodilation>dec VR>dec cardiac size>dec EDV<dec Ejection fraction>dec myocardial tension>dec o2 consumption

*INC 02 SUPPLY: vasodilation of coronary artery collaterals

2) OTHER ORGANS:

*relaxes smooth muscles of bronchi, gastrointestinal tract, genitourinary tract

*IV nitroglycerin: reduces platelet aggregation

WHY NITATES SHOULDN'T BE COADMINISTERED WITH PHOSPHODIESTERASE INHIBITORS(SILDENAFIL):

*sildenafil used for erectile dysfunction

*nitrates increase cGMP(via stimulation of GC)

*sildenafil prevents breakdown of cGMP to GMP> hence causes a synergistic relaxation of smooth muscle>dangerous orthostatic hypotension

ROLE OF NITRITES IN Rx of CYANIDE POISONING?

*cyanide ion rapidly complexes **with Fe in cytochrome oxidase**, resulting in block of oxidative phosphorylation and cell death

*fortunately, Fe in methemoglobin has higher affinity for cyanide than Fe in cytochrome oxidase

*hence, NITRITES, convert the ferrous ion in hemoglobin to ferric ion in methemoglobin

METHHEMOGLOBIN PREVENTS INHIBITORY ACTION OF CN ION ON COMPLEX 4 OF ETC!

Therefore, CN poisoning Rx by:

TREATEMENT 1:

1)immediate inhalation of amylnitrite

2)IV adm of sodium nitrite(rapidly increases methemoglobin significantly to remove CN from cytochrome oxidase

3)IV sodium thiosulfate(converts cyanomethemoglobin to thiocyantes and methemoglobin/ regenetaes methemoglobin again)

4)methemoglobin converted to oxyhemoglobin by methylene blue

TREATEMENT 2:

*administer hydroxycobalamin

NITRATES FREE INTERVAL:

*tachyphyaxis develops rapidly and vessels become densitized

*hence provide nitrate free interval

*of 10-12 hrs at night when myocardial 02 demand is least

*variant angina, late afternoon

*patches worn for 12 hrs then removed for 12 hrs

ORGAN SYSTEM EFFECTS OF CALCIUM CHANNEL BLOCKERS:

*acts on smooth muscle of uterus, bronchi, gut and heart

*NONHYDROPYRIMIDINE:

*reduces rate and contractility

*block calcium dependant conduction in AVN(Rx AVN aryhthmias)

*verapamil: greater negative ionotrophic effect, contraindicated in AVN aryhtmias

*diltiazem: slow AVN conduction, coronary artery vasodilation, vasospastic angina

*DIHYDROPYRIMIDINE:

*more vascular effect

*evokes vasodilation> resulting sympathetic reflex results in tachycardia(inc O2 suplly and by dec TPR> dec O2 consumption

*reduces double product

TYPES OF CALCIUM CHANNEL:

1.L type: cardiac muscle, vascular smooth muscle and secretory cells

2.N, P and R: nerve muscle conduction

DOES CCB AFFECT SKELETAL MUSCLE CONTRACTION:
*NO, as contraction in skeletal muscle is mediated via release of Ca+ frpm SER, and CCB affects L-type calcium channels in plasma membranes of cardiac and smooth muscles.

WHY COMBINE NITRATES WITH BETA BLOCKERS:

1.reflex tachycardia caused by nitates reversed by beta blockers

2.increased contractility caused by nitrates reversed by beta blockers(we don't want contractility to increases as it leads to increased oxygen requirement)

3.ventricular remodeling caused by beta blockers reversed by nitrates

4.decreaed coronary blood flow caused by beta blockers reversed by nitrates

NAME	MECHANSIM OF ACTION	PHARMACOKINETICS	THERAPEUTIC USES	TOXICITIES
NITROGLYCRIN	*nitrates release NO by action of mitochondrial ALDH2 *NO stimulates cytoplasmic GC>causes an increase in cGMP>stimulates dephosphorylation of myosin-LC-PO4 to myosin-LC>results in relaxation of smooth muscle *dec VR>dec preload>dec diastolc size>dec 02 requirement *inc arterial vasodilation: inc O2 supply *dec infarct size, dec post MI mortality	*ultrashort acting:amyl nitrate(DOA 1-5min) *short acting:nitroglycerin SL(DOA 15 min, rapid onset 1min) *intermediate oral acting:nitroglycerin and isosorbide dinitrate(DOA 2-4hrs) *long term: transdermal nitroglycerin (DOA 10hrs prophylaxis)	*ultrashort acting:obsolete(recreational use) *short acting: acute coronay syndrome and acute angina pectoris *rest:prophylaxis of angina	1.orthostatic hypotension 2.reflex tachycardia 3.meningeal headache 4.Monday disease(alternating development of tolerance over the work week and loss of tolerance during weekend for vasodilating action and its associated tachycardia, resulting in headache, tachycardia, and dizziness every Monday)
CALCIUM CHANNEL BLOCKERS: A)DIHYDROPYRIMIDINE::nifedipine B)NONDIHYDROPYRIMIDINE: verapamil and diltiazem	NONDIHYDROPYRIMIDINE: *block voltage gated L types Ca channels in smooth muscle and cardiac muscle *reduce intracellular Ca concentrations and muscle contractility *Ca is required for the phosphoactivation of MLCK>which converts myosin-LC to myosin-LC-	NONHYDROPYRIMIDINE: *verapamil: DOA:6-8hrs and given IV *diltiazem:shorter half-life DIHYDROPYRIMIDINE: *nifedipine:oral DOA:6-8hrs *amlodipine:longer acting	NONHDROPYRIMIDINE: *angina(classic and **vasospastic**, nifedipine) *hypertension *AVN arythmias *migraine *preterm labour *stroke *Raynaud phenomenon *supraventricular tachycardia *diltiazem: in variant	**NONDIHYDROPYRIMIDINE**: ***constipation**(verapamil>inhibits P-glycopreotein) *flushing *dizziness ***pretibial edema** *higher doses: cardiac depression, AV blockade**, sinus**

	PO4 *hence reduces contractility of heart, dec HR, dec O2 demand DIHYDROPYRIMIDINE: *vascular effect>cardiac effect *dec TPR>dec afterload>dec 02 demand		angina, reduces coronary artery spasm DIHYDROPYRIMIDINE: *angina *hypertension *amlodipine:variant angina *nifedipine: extended oral release formulations	**nodal depresion and hypotension** *contraindicated in patients with depressed cardiac patient, AVN conduction de fects(verapamil) *gingival hyperplasi: nifedipine *reflex tachycardia **DIHYDROPYRIMIDINE:** *less constipation *less cardiac effects *AVOID SHORT ACTING,PROMPT RELEASE DIHYDROPYRIMIDINES IN MI PATIENT AS THEY INC MORTALITY!
BETA ANTAGONISTS *propranolol *atenolol ***carvedilol**	*Gi receptors *dec cAMP *dec contractility, dec 02 demand 1.dec activation of B1>reduced CO 2.reduced RAA>dec angiotensin, dec aldosterone, dec N and water retention 2.dec CNS outflow	*oral and IV *DOA: 6hrs	*angina(unstable and **classic**) *hypertension *arythmias *migraine *performance anxiety *pindolol with ISA, avoided in angina and MI	*nausea, constipation *palpitation *bradycardia, ankle edema *AV block *contraindicated in sick sinus, PVD, COPD, DM, in severe bradycardia *negative inotrophic effect
RANOLAZINE	*ischemia causes increased sodium which prevents calcium exchange thru Na/Ca exchanger *blocks late Na inward	*oral, DOA:10-12 hrs	*angina(prophylaxis)	*Q T prolongation *inhibits CYP34 and 2D6

	current in myocardium, dec Ca accumulation reduce cardiac workload *results in dec end diastolic pressure and improves diastolic coronary blood flow			
IVABRADINE	*blocks pacemaker Na current in sinoatrial node *reduces HR	*oral *administered twice daily	*heart failure *investigations into angina(prophylaxis)	*excessive bradycardia

DIREUTIC DRUGS

SOME IMP POINTS:

*hyperkalemic metabolic acidosis: K+ sparing direutics

*hyperchloremic metabolic acidosis: carbonic anhydrase inhibitor

*hypokalemic metabolic alkalosis: loop & thiazide direutics

*hypomagnesemia: loop direutics

*hypermagnesemia: thiazide direutucs

*hyperuricemia, hyperlipidemia, hyperglycemia: thiazide direutics

*don’t give thiazide direutics with NSAIDS(as they work when GFR is normal)> as NSAIDS lower prostaglandins synthesis>reducing renal blood flow

*thiazide and loop direutics: marked synergism>severe hypovolemia and CVS collapse

*a person who is severly beaten, administer him with thiazide direutics to prevent renal collapse

*pituatry diabetes inspidus:ADH & desmopressin

*nephrogenIc diabetes inspidus: salt restriction, water restriction, thiazides, loop direutics(all reduce blood volume hence increases, PCT reabsorption)

*thiazide direutics: low-ceeling direutics

*high ceeling direutics: furosemide

*HOW FUROSEMIDE DIREUSIS LEADS TO LESS ABSORPTION OF CALCIUM AND MAGNESIUM?

*dec intracellular K+ in TAL

*de back diffusion of K+

*dec positive potential

*dec reabsorption of Ca and Mg

*SULFONAMIDE CONTAINING DRUGS HAVE CROSS-ALLERGENICITY WITH:

1.carbonic anhydrase inhibitor

2.all loop direutics(except ethacryanic acid)

3.thiazides

4.sulfa antibiotics

5.celecoxib

*DRUGS CAUSING HYPERKALEMIA:

1.K+ sparing direutics

2.ACEI

3.beta blockers

4.direutics

5.aliskiren

NAME	MECHANISM OF ACTION	EFFECTS	PHARMACOKINETICS	THERAPEUTIC USES	ADVERSE EFFECTS
CARBONIC ANHYDRASE INHIBITOR *acetazolamide *dorzolamide *brinzolamide	*inhibits carbonic anhydrase in apical membrane and cytoplasm>HCO3- reabsorption is blocked and Na is excreted with HCO3- *in glaucoma, reduces secretion of aqueous humor and reduce IOP>chronic open angle glaucoma *in metabolic acidosis, increases respiration 1.dec H+ formation in cells 2.dec NA/H+ antiport 3.inc HCO3- and Na in lumen 4.inc direusis	*bicarbonate direusis>metabolic acidosis *excess Na reabsorption from CCT>potassium wasting *secretion of HCO3- by ciliary epithelium and choroid plexus is reduced *metabolic acidosis>hyperventilation >protect against high mountain sickness *phosphate excretion increases in urine	*oral and IV *direusis is self-limiting but in glaucoma and mountain sickness it persists *produces alkaline urine *onsert:30 min	*direusis:only when edema combined with **metabolic alkalosis** *parentrally:severe acute **glaucoma**: acetazolamide *topical:chronic use dorzolamide and brinzolamide(no systemic effects!) ***acute mountain sickness** *epilepsy(dec CSF pressure) *urinary alkalalinizationof urine(cysteine in cystinuria)	*hypokalemia and hypophosphatemia *drowsiness and **paresthesia** ***cross allergenicity** with other sulfonamide derivatives(sulfonylurea, sulfonamide antibiotics) *alkalinization of urine>precipitation of calcium and leads to **renal stones** *alkalinization of urine prevents urine conversion of NH3 to NH4+(secreted in urine in patients with hepatic impairment)>hence these patients develop hepatic encephalopathy and **hyperammonemia** ***hypokalemia** ***hyperchloremia** ***bicarbonuria and acidosis**
LOOP DIREUTICS *furosemide(prototype) *bumetacide and torsemide(sulfonamide derivatives) *ethacrynic acid(phenoxyacetic acid)	*inhibits the 1NA+,2CL-,1K+ transporter *in thick ascending limb *causes powerful direusis and increased Calcium excretion *suitable for emergencies!	***massive NaCl direusis**>if GFR is normal *diluting abilty of nephron is reduced>as loop of henle is the major area for dilution of urine *inhibition of Na/K/2Cl results in loss of lumen positive potential, hence cations like magnesium aren't absorbed>**HYPOMAGNESEMIA** ***hypokalemic metabolic**	*oral *IV *short acting as compared to thiazide *furosemide DOA: 6 hrs	*severe edematous states(**heart failure**, ascite, **acute pulmonary edema**) *used in **hypertension** if response to thiazide direutic is inadequate(as loop direutics are short acting ***refractory edema** *Rx severe **hypercalcemia**(supplemented with IV and oral water and electrolye	***hypokalemic** metabolic alkalosis ***hypovolemia** an CVS complications *hypomagnesemia ***Hypocalcemia** *typical **sulfonamide** rash ***ototoxicity(infused at high dose and fast rate or combo with aminoglycosides)** *efficacy reduced by NSAIDS

		acidosis ***reduce pulmonary vascular pressure>given in pulmonary edema and left ventricular filling pressure, venous capacitance** ***venodilation**: acute venodilation & reduced left ventricular filling pressure via enhanced prostaglandin synthesis		replacement>to prevent hemoconcentration)	*hyperurecemia DRUG INTERACTIONS: *aminoglycosides(enhanced ototoxixty) *lithium(chronic loop administration, dec clearance) *digoxin(inc toxicity due to electrolyte disturbance)
THIAZIDE DIREUTICS *hydrocholorthiazide *other sulfonamides *chlorthalidone(thiazide like properties, lacks characteristics benzothiazine ring of thiazide) *indapamide	*inhibits Na/Cl transporter in luminal side of DCT *causes moderate direusis and reduced excretion of calcium *diazoxide non potent vasodilator of urine(in case of diabtetes inspidus) *dec distal Na+ reabsorption>inc urinary excretion>dec ECF volume>inc proximal Na and H2O reabsorption	1.moderate but sustained **sodium and chloride direusis** *hypokalemic metabolic alkalosis 2.due to reduced intracellular sodium>basolateral activity of Na/Ca pump increases>increased calcium absorption>**HYPERCALCEMIA** *chlorthalidone(longer acting, used in hypertension) ***reduces PVR**	*all active by oral route *duration of action of 6-12 hrs *chlorthiazide(given by IV!) and more potent,longer acting, lower F.	*essential **hypertension**(long duration & moderate intensity useful) ***mild heart failure** *for Rx of chronic renal calcium stones(**renal calciuria/nephrolithiasis)** ***nephrogenic diabetes insipidus(dec GFR and blood volume)**	*ACUTE: marked sodium direusis with **hyponatremia** *CHRONIC: **hypokalemia** ***hypomagesemia and hypotension** ***hyperglycemia(**impaired release of insulin due to hypokalemia) ***hyperuricemia** ***hyperlipidemia(except indapamide)** ***hypercalcemia** ***sulfonamide** allergy *combo with loop direutics: severe hypovolemia & CVS collapse *NEVER GIVEN WITH NSAIDS *DRUG INTERACTIONS: *digoxin(inc toxicity due to electrolyte imbalance) *avoid In diabetes mellitus
K+ SPARING DIREUTICS Spironolactone	*steroid antagonist *reduce aldosterone mediated transcription of ENaC, Na/K ATP ase	*reduce K excretion *increased Na excretion *reduce H excretion	*onset of action: 24-72 hrs *slow onset *oral * eplerenone metabolized	***aldosteronism edema** *prevent cardiac remodellling and reduce mortality with HFrEF(**heart failure**)	***hyperkalemia acidosis** *spironolactone: endocrine

and eplerenone	pump, and K+ channel		by CYP450 3A4	*Rx **potassium wasting** when used with other direutics ***resistant hypertension** ***female hirsutism** *spironolactone-**PCOS** ***primary aldosteronism(crohns disease)** ***secondary aldosteronism(**nephrotic syndrome, heart failure, liver cirrhosis)	disorders(**gynecomastia** and anti-androgenic effects>locks testosterone and aldosterone receptor *epelerone less affinity for steroid receptors
Amiloride and triamterene	*blocks ENaC channel *donot block sodium channel in excitable membrane	*reduces sodium reabsorption and potassium excretion and H+ excretion *cause hyperkalemic metabolic acidosis	*DOA: 12-24 hrs *oral *triamterene less potent than amiloride and lower half-life	*Rx **excessive potassium loss** when used with other direutics *usually in combo with thiazides ***edema with secondary hyperaldosteronism**: hepatic cirrhosis and nephrotic syndrome and CHF *amiloride: **lithium induced nephrogenic diabetes mellitus** ***liddles syndrome**	*hyperkalemia *acidosis *triamterene(megaloblastic anemia)
OSMOTIC DIREUTICS *manitol(prototype drug) *glycerin *isosorbid *urea	*freely filtered at glomerulus, but remain with in tubule as they are poorly reabsorbed ***osmotically** retains water in lumen by reducing absorption of water from PCT, loop of henle, collecting ducts *in periphery, manitol extracts water from cells	*volume of urine is increased *sodium excretion is largely increased *reduces brain volume, and intracranial pressure *osmotically extracts water from eye	*IV!! *short DOA	1.**solute overload in rhabddomyolysis**, hemolysis, tumor lysis syndrome 2.**brain edema with coma** 3.**acute glaucoma** 4.maintain high urine flow when renal blood flow is reduced(**acute toxic ingestion**)	***hyponatremia followed by hypernatremia**(as water is excreted) *pulmonary edema *headache, nausea, vomiting>due to hyponatremia *dehydration *severe hypovolemia *inc ECF volume>complicates HF and pulmonary edema>contra indicated in chronic HF

SGLT2 ANTAGONISTS *dapagliflozin *canagliflozin *empagliflozin *ipragliflozin	*inhibitors of sodium-glucose cotransporters in PCT>reduce reabsorption of glucose >inc its excretion by 30-50% *inc volume of urine		*oral	*diabetes and cardiac failure	*UTI
ADH AGONIST *desmopressin *ADH	*agonist at V1 and V2 receptors>stimulates GS>inc cAMP> hence leads to insertion of aquaporins water channels in collecting tubules>reduce water excretion		*subcutaneous *nasal	*pituatry diabetes inspidus	*hyponatremia *hypertension
ADH ANTAGONIST *conivaptan *tolcaptan *lithium *demeoclocycline	*conivaptan: ADH antagonist at V1 and V2 *tolvaptan: more selective for V2 *demeoclocycline and lithium>inhibit action of ADH distal to generation of cAMP>interfers with insertion of water channels into membranes		*IV	*demeoclocycline: SIADH *hyponatremia *conivaptan & tolvaptam: off label for heart failure with hyponatremia	*infusion site reactions

ANTI-HYPERTENSIVES

DEFINITION: BP>140/90mmHg, monitoring at 3 different times in a day, in 3 different postures for 3 days.

*elevation of DBP is more dangerous

***ESSENTIAL HYPERTENSION**: HTN of unknown etiology

***SECONDARY HYPERTENSION**: HTN due to secondary factors(pheochromocytoma)

***REBOUND HYPERTENSION**: elevated BP above pre-Rx levels, resulting from loss of anti-hypertensive effects

SBO/DBP(mmHg)	CATEGORY
<120/80	Normal
120-130/80-90	preHTN
>140/90	HTN
140-159/90-99	Stage 1
>160/100	Stage 2

MILD TO MODERATE HTN:

1.life style changes

2.alpha 2 agonist:

*clonidine

*methyl dopa

3.thiazide direutics:
*chlorthalidone

*hydrochlorthiazide

MODERATE TO SEVERE HTN:

*hydralazine

CHRONIC HTN IN PREGNANCY: preexisting HTN

*methyl dopa

*labetolol

PRE-ECLAMPSIA: new onset

*hydralazine

*labetolol

MALIGNANT HTN/ HYPERTENSIVE EMERGENCIES

Accelerated blood pressure>rapidly progressing damage to vessels in end-organs>to lower BP from 140-160/90-110mmHg within a few hours

3 VASODILATORS + DIREUTICS+BETA-BLOCKERS

1.nitroprusside(vasodilator)

2.fenoldepam(D1 agonist)
3.diazoxide(K+ channel blocker)

4.furosemide(loop direutic)
5.labetolol(beta blocker)

MONOTHERAPY:

*thiazide direutics

*CCB

*ACEI/ARBS

POLYTHERAPY IS FOR SEVERE HTN:

*HTN with DM: ACEI/ARBS

*HTN with BPH: prazosin

DRUGS FOR ORTHOSTATIC HYPOTENSION

*ephedrine

*milodrine(for chronic orthostatic hypotension)

DRUGS CAUSING ORTHOSTATIC HYPOTENSION

*alpha blockers

*ganglion blockers

PULMONARY HTN:

1.EPOPROSTENOL(PROSTACYCLIN)

*administered via infusion pump

2.BOSENTAN

*endothelin(ET-1) is a powerful vasococnstrictor, through ET-A and ET-B

*besentan is an ET-A receptor antagonist

*sideeffects: those associated with vasodilation(headache, flushing, hypotension)

*CONTRAINDICATED IN PREGNANCY

3.SILDENAFIL

*inhibits PDE(which breaks down cAMP to 5AMP)

*pulmonary artery relaxation'

RATIONALE IN ANTI-HTN:

BP=CO into TPR

CO=HR into SV into BLOOD VOLUME into VENOUS TONE

CO: beta blockers, nondihydropyrimidine calcium channel blockers,

BLOOD VOLUME: direutics, ACEI/ARBS

VENOUS TONE: vasodilators and alpha-1 blockers

ANATOMICAL SITES FOR CONTROLLING BP:

1.heart

2.kidney

3.brain

4.skeletal muscle arteriole

5.post capillary venule

DRUG STRATEGY

*dec TPR

*dec CO

*dec body fluid retention

*BP may be resulting in orthostatic hypotension,compensated via inc sym activity(reflex tachycardia) and edema(inc renin secretion)

REMEMBER MINIMAL COMPENSATORY RESPONSE CAUSED BY BETA BLOCKERS, THIAZIDES, ARBS/ACEI

DOES CCB AFFECT SKELETAL MUSCLES?

*NO

*as contraction in skeletal muscleis mediated by Ca2+ ions released from SER, while CCB affects L-type Ca channels, in smooth and cardiac muscles

WHY LOSARTAN PREFERRED OVER CAPTOPRIL?

*lower incidence of cough

*inhibits kininase 2(which normally prevents degradation of histamine)

CLASSIFICATION OF VASODILATOR:

A)ACCORDING TO SITES OF ACTION:

*arteriolar(CCB, hydralazine, K+channel blockers>diazoxide & minoxidil sulfate, fenodepam)

*venular(nitrates)

B)ACCORDING TO MECHANISM OF ACTION:

1.reduction of calcium influx via L-type calcium channels

*dihydropyrimidine (vessel>heart: nifedipine, verapamil, diltiazem)

*non-dihydropyrimidine(heart>vessels: amlodipine, felodipine, isradipine)

2.release of NO from drug to vacular endothelium:

*nitroprusside

*hydralazine

3.hyperpolarization of vascular smooth muscle through opening of K+channels

*minoxidil sulfate(for HTN)

*diazoxide(closing of K+ channels>causing increased insulin release>insulinoma)

4.activation of dopamine D1 receptors:

*fenoldepam

C) ACCORDING TO MODE OF ADMINISTRATION:

*ORAL> CCB, hydralazine, minoxidil

*PARENTRAL: nitroprusside, diazoxide, fenoldepam

USE OF ANTI-HTN IN COMORBID CONDITIONS:MCQS

INDICATION	DRUG
angina	Beta blockers, CCB
diabetes	ACEI, ARBs
Heart failure	ACEIS, ARB, beta blockers
Post-MI	Beta blockers
BPH	Alpha blockers
dyslipidemia	Alpha, CCB, ACEI/ARB
CKD	ACEI/ARB

NAME	MECHANISM OF ACTION	PHARMACOKINETICS	THERAPEUTIC USES	TOXICITIES
THIAZIDE(chlorthalidone an hydrochlorothiazide **LOOP**(furosemide, tolbutamide, ethacrynic acid)	*inc excretion of salt and water>reduce blood volume>>reduce CO *also with chronic use, reduce TPR>leading to dec BP(due to depletion of Na+ and hence reducing Na/Ca exchange *after 6-8 weeks, CO returns normal, while TPR may decrease		*thiazide: mild to moderate HTN *loop: severe HTN	*thiazide: hypokalemia, hypotension, hyperuricemia, hyperlipidemia, hyperglycemia *loop: hypokalemia, ototoxicity
SYMPATHOPLEGICS: A)baroreceptor sensitizing agent(veratrum alkaloids)	1.increase sensitivity of baroreceptor sensory nerves 2.reduce SANS outflow by increasing vagal tone of heart			
B)centrally acting sympthoplegics *methyldopa *clonidine! *guanabenz *guanfacine	*alpha 2 agonist *enter CNS when given orally *alpha 2 stimulation>**dec sympathetic outflow>**dec TPR>also HR dec ***METHYLDOPA:** *prodrug>converted in brain to methylnorepinephrine>stored in adrenergic nerve vesicles, replacing nor-epinephrine>acts as a false transmitter>acts on pre-synaptic alpha 2	*clonidine(transdermal patch), DOA: 2-3 days *methyldopa(multiple dosing),DOA:12-24 hrs	*mild to moderate HTN(both) *opiate withdrawal diarhea(clonidine) *clonidine doesn't dec GFR>so used in renal disease *HTN in pregnancy(methyl dopa, as protects renal function)	*CNS depressiom(both) *edema(both) *sedation(both) **CLONIDINE**: *rebound HTN *sedation, dry mouth, constipation, hypotension, confusion **METHYLDOPA:** *hematological immunotoxicity

	receptors>sympatholytic			progressing to hemolytic anemia(detected by positive coombs test>agglutination of RBCs, occurring in 10-20% patients undergoing therapy for lomger than 12 months) DRUG INTERACTIONS TCA dec anti hypertensive effects of alpha 2 agonist
C)ganglion blocking agents *hexamethonium *trimethaphan	*competitively block nicotinicreceptors	*oral, IV *no CNS effect *mecamylamine, oral ganglion blocker(enters CNS)	*hexamethonium(obsolete) *trimethaphan(hypertensive emergencies) *BUT, obsolete! Due to vasodilation and orthostatic hypotension	*sympathoplegia: excessive orthostatic hypotension, sexual dysfunction *parasympathoplegia: constipation, urinary retention, blurred vision
D)POST GANGLIONICS SYM NERVE TERMINAL BLOCKERS *reserpine *guanethidine *MAO	*reserpine: blocks VMAT in adrenergic neurons>leads to depletion of norepinephrine, dopamine, serotonin stotage) *guanethidine: blocks release of norepinephrine	*oral acting	*obsolete(used in huntingtons disease)	*r**eserpine**: sedation(severe psychiatric depression),mental depression,parkinsonism *__guanethidine__: pharmacologic sympathectomy(postural hypotension, diarrhea, impaired ejaculation)
E)ADRENOCEPTOR ANTAGONISTS: 1.ALPHA -1 BLOCKERS(prazosin, doxazosin, terazosin) 2.BETA BLOCKERS *nonselective(propranolol)	*dec TPR, hence dec arteriolar and venous return *nonselective not used due to excessive reflex tachycardia *relaxes prostatic smooth muscle tone *Inc HDL, dec LDL	*oral *DOA: 6-8 hrs	*1^{st} and 2^{nd} stage hypertension *BPH:dec urinary frequency and decrease nocturia by decreasing tone of urinary spinchter *GOOD EFFECT ON LIPID PROFILE!	*1^{st} dose syncope: orthostatic hypotension and reflex tachycardia *urinary incontinence

*cardioselective(atenolol, metoprolol, carvedilol) *nebivolol(Vasodilating action)	1.block cardiac B1 receptors>dec Contractility and HR 2.block renal B1 receptor>dec renin, dec Ang 2>dec PVR 3.dec aldosterone>dec SV 4.dec SNS output 5.additional vasodilator(carvedilol, nebivolol)	*labetolo and carvedolol: alpha and beta blockade *oral and IV	*hypertension *carvedilol: Rx of HF, reduves mortality and morbidity *labetolol:HTN in pregnancy	1.CO dec,CVS depression 2.fatigue 3.sexual dysfunction 4.inc LDL and TAG CONTRAINDIACTED in hyper TAG, asthma!
VASODILATORS				
A)CCB *dihydropyrimidien(nifedipine, amlodipine, felodipine, isradipine) *nondihydropyrimidine(verapamil and diltiazem)	*blocks L type calcium channels in heart and blood vessels *results in decreased intracellular calcium ions *causes decreased CO(verapamil and diltiazem) *causes decreased TPR(all CCB) *verapamil also blocks P-glycoprotein transporter	*oral *DOA: 6-24hrs	*hypertension(all drugs) *angina(dihydropyrimidines >evoke vasodilation) *SVT(diltiazem and verapamil>block AV nodal conduction & and dec CO) OTHER USES: *migraine, preterm labor, stroke, raynauds phenomenon	*reflex tachycardia *constipation *pretibial edema *nausea *flushing *dizziness *heart failure, AV blockade, sinus nod arrthymia *gingival hyperplasia
B)RELEASE OF NO: *HYDRALAZINE	*acts on endothelium to release NO *dec TPR through arteriolar vasodilation *causes significant barorecptr homeostatic responses, hence combined with direutics and beta blockers	*oral *DOA:6-8hrs	*pregnancy induced HTN *heart failure in combo with isosorbide dinitrate *DOC for HTN emergency	*SLE! *cyanide toxicity *headache, angina,MI *palpitation *salt and water retention
*NITROPRUSSIDE	*converted to NO by mitochondrial endothelial aldehyde dehydrogenase *NO activates GC	*IV *requires constant infusion	*DOC for hypertensive emergencies *acute cardiac decompensation	*othrostatic hypotension *reflex tachycardia *salt and water

	*converts GTP to cGMP *cGMP causes dephosphorylation of myosin LC *dec TPR through arteriolar and venular dilation			retention *methemoglobinemia
C)HYPERPOLARIZATION OF K+CHANNELS: *MINOXIDIL SULFATE	*opend K+ channels *hyperpolarizes smooth muscles *arteriolar vasodilation *concomitant use with direutics and beta blockers	*oral *topical	*severe HTN *male pattern baldness	*hypertrichosis *hirustism *tachycardia *salt and water retention
*DIAZOXIDE	*K+ channel opener *hyperpolarizes smooth muscle *thiazide like direutics,but lacks anti-direutics properties	*IV for HTN *oral for insulinoma *long duration of action	*insulinoma(hypoglycemia due to insulin secreting tumor>hyperpolarizes beta cells of Langerhans>prevnest release of insulin) *HTN	*hyperglycemia *edema *excessive hypotension *avoided in IHD *salt and water retention
D)FENOLDEPAM	*acts on D1 receptors *arteriolar vasodilation	*short DOA: 10min *IV	*hypertensive emergencies	*excessive hypotenion *tachycardia *angina *salt and water retention *angina
RENIN ANTAGONIST *ALISKIREN	*renin inhibitor>prevents conversion of angiotensinogen to angiotensin *newer drug	*oral *DOA: 12 hrs	*hypertension	*angioedema *renal impairment *metabolized by CYP enzyme

ANGIOTENSIN ANTAGONIST				
A)ACE INHIBITORS *captopril *enalapril *lisinopril *benzapril	*inhibit ACE, kininases 2, peptidyl peptidase 2 enzyme *which converts angiotensin 1 to angiotensin 2 *prevents AT-1 receptor stimulation *prevents angiotensin 2 mediated vasoconstriction>decreases TPR *pevents aldosterone mediated salt and water retention	*oral *half-life:2.2 hrs, large doses provide duration of 12hrs	*hypertension in diabetic renal disease! *congestive heart failure *mild to moderate HTN	*TERATOGENIC(renal damge in fetus) *hyperkalemia *cough(prevents bradykinin breakdown> bradykinin leads to cough) Precipates renal failure with bilateral artety stenosis HOW? (stenosis>increasing renin>increased BP>treatment with ACEI/ARB>blood flow to kidney decreases due to vasodilation>renal shutdown) *skin damage *angioneurotic edema *hypetension
B)ARBs *candesartan 8losartan *irbesartan	*competitively inhibits binding of angiotensin 2 to AT-1 receptor *doesn't interfere with bradykinin degradation	*oral *DOA:6-8hrs	*hypertension *CHF	*hyperkalemia *hypotension *angioedema

ANTI-ARYTHMIC DRUGS

ABNORMAL AUTOMATICITY & ABNORMAL CONDUCTION ARE THE TWO MAJOR MECHANISM OF ARRYHTHMIAS!

TYPES OF ARRYTHMIAS:

1.atrial flutter

2.atrial fibrillation(most common serious arrhythmia>in older patient>may contribute to failing heart)

3.AVN re entry

4.premature ventricular beats

5.ventricular tachycardia

6.ventricular fibrillation

7.torsades de point

DRUG CLASSIFICATION:

A)GROUP 1>SODIUM CHANNEL BLOCKER:

*1A: PROLONG AP> procainamide, quinidine, amiodarone, disopyramide(1-10sec, inc QRS & QT interval)

*1B:SHORTEN AP>lidocaine, phenytoin, mexiletine(<1sec, dec QT interval)

*1C:NO EFFECT ON AP>flecainide(>10sec, markedly inc QRS)

B)GROUP 2>BETA-BLOCKER:

*propranolol

*metoprolol

*esmlol

*sotalol

*amiodarone

C)GROUP 3>K+ CHANNEL BLOCKER: PROLONG AP & REFRACTORY PERIOD

*sotalol

*ibutilide

*dofetilide

*amiodarone’

*dronedarone

D)GROUP 4>L-TYPE CALCIUM CHANNEL BLOCKER:

*verapamil

*diltiazem

*amiodarone

E)GROUP 5>MISCELLANEUS:

*adenosine

*potassium

*magnesium

*ranolazine

*ivabradine

DOC IN DIFFERENT KINDS OF ARRYTHMIAS (MCQS)

*arrhythmias during acute phase of MI: procainamide

*prevent arrhythmias during prophylaxis of MI: propranolol+timolol

*acute ischemic ventricular arrhythmias: lidocaine

*digitalis induced arrhythmias: phenytoin, lidocaine, magnesium ions

*chronic arrhythmias + neuropathic pain: mexilitine

*refractory and intractable arrhythmias: flecainde

*peri-operative and thyroid storm arrhythmias: esmolol+propranolol

*afib arrhythmias: group 3(difetilide)

*broadest spectrum arrythmas: amiodarone

*longest half-life anti-arrthymatic: amiodarone

*converting AVN reentry (nodal tachycardia) into normal sinus rhythm>verampamil

*acute nodal tachycardia:adenosine

*sinus tachycardia & atrial extrasytole: propranolol

*life threatening ventricular arrhythmias:sotalol

*DOC for torsades de point arryhtmias : magnesium ions

*blocking bidirectional block: lidocaine

*SVT: ADENOSINE, VERAPAMIL, DILTIAZEM,ESMOLOL

*VA: LIGNOCAINE, MEXELITINE, BRETYLIUM,PROCAINAMIDE,AMIODARONE

*SVT & VA: AMIODARONE, B-BLOCKERS, DISOPYRAMIDE, PROCAINAMIDE

*AVN BLOCK: ATROPINE, ISOPRENALINE

IMPORTANT POINTS ABOUT DIFFERENT ANTI-ARRYHTMIC DRUGS:

1.NA+ CHANNEL BLOCKERS:

*block OPEN and INACTIVATED(not resting/fully repolarized Na+channel)

*local anesthetic effect(block nerve conduction at higher doses)

*membrane stabilisers

*USE/STATE DEPENDANT ACTION: selectively depress tissue that is frequently depolarizing>ischemic tissue

*HYPERKALEMIA INCREASES TOXICTY OF GROUP 1A DRUGS: <u>Rx of overdose</u>

1.to reverse drug-induced arrhythmias(sodium lactate)

2.to reverse drug-induced hypotension(pressor sympathomimetics

2.BETA-BLOCKERS:

*depress phase 4 of pacemaker cells

*slow sinus & AVN conduction

*dec HR, inc PR

*inc ERP>prolong AP duration by dec AVN conduction

NON PHARMACOLOGICAL MANAGEMENT:

1.external defibrillator

2.implanted defibrillators

3.implanted pacemakers

4.radiofrequency ablation

DRUG	MECHANISM OF ACTION	PHARMACOKINETICS	CLINICAL USES	TOXICITIES
GROUP 1A				
*PROCAINAMIDE	*use and state dependant block of sodium channel *bind to open/inactivated channel *metablolzed to N-acetyl procainamide>blocks K+channel as well(hence PROLONG AP!) *at high doses block AV conduction as well *slowed conduction velocity and pacemaker activity in atria, purkinje fibres,ventricular cells>prolongs AP & RP	*oral and IV *DOA: 2-3hrs	*both atrial and ventricular arrhythmias *arryhtmias during acute phase of MI	*hypotension *SLE(note hydralazine also causes SLE) *TORSADES DE POINT! *don't give below 6 yrs due to SLE
*DISOPROPYRAMIDE	*similar to procainamide *exerts anti-muscuranic effect as well	*longer DOA		*anti-muscuranic effects: precipitation of glaucoma, constipation, dry mouth,

	*better tolerated than quinidine			urinary retention *heart failure
*QUINIDINE	*similar to procainamide *3-hydroxyquinidine nearly as potent as quinidine in blocking saoium channels and prolonging AP	*well absorbed *80& bound to albumin *extensive hepatic oxidative metabolism	*same *maintain sinus rhythm in pateints with atrial flutter & atrial fib *prevent recurrence of vetriculr tachycardia and VF	*CINCHONISM(tinnutis, vertigo, headache) *GIT disturbance *thrombovytopenia *DIGITALIS TOXICITY! *QT PROLONGATION *TORSADES DE POINT DRUG INTERACTIONS: *meta by CYP450 *increases digoxin levels *cardiac depression with beta-blockers *inhibits CYP2D6
GROUP 1B				
*LIDOCAINE	*blocks inactivated sodium channels *local anesthetic *selectively acts on PARTIALLY DEPOLARIZEDand ISCHEMIC TISSUES *acts mainly on **ventricular tissue** and purkinje fibres *doesn't act on atrial muscle as in atria AP are so short that the sodium channel is inactivated only briefly, compared with diastolic recovery time *SHORTEN AP!	*rapid kinetics *action only for 15min *high 1st pass meta *depends on hepatic blood flow *propranolol dec levels of lignocaine *administered IM/IV *never orally! Due to hugh 1st pass meta>metabolites are cardiotoxic *MEXILITINE: ORAL USE!	*post MI ventricular arryhtmias *digitalis induced arryhtmias *MEXILITINE: used in chronic arryhtmias and diabetic neuropathic pain	*local anesthetic toxicity *CNS stimulation *excitation *CVS depressant *MEXILITINE: hypotension, widened QRS, dizziness, nystagmus *TOCAINIDE: pulmonary fibrosis, agranulocytosis
GROUP 1C				
*FLECAINIDE	*selective use and state dependant sodium channel block *slowed conduction activity and pacemaker activity *no effect on AP! *increases QRS duration on ECG!	*Oral *half-life: 20hrs *slow unblocking kinetics	*refractory ventricular *intractable SVT *maintains sinus rhythm in SVT arrhythmias	*PRO-ARYTHMIC EFFECT!

	*blocks K+channels too but no effect on AP & QT interval			
GROUP 2				
*PROPRANOLOL	*block cardiac receptors>dec in cAMP>depress phase4 of depolarization of pacemaker cells>slow sinus rhythm *dec HR & inc PR interval *inc ERP *dec AVN conduction *reduce MI demand *metoprolol(beta 1 selective) *esmolol(beta 1 selective) *sotalol and amiodarone(both group 3 also has group 2 effects)	*oral and IV *DOA: 4-6hrs *esmolol: IV only, 10min DOA	*post MI as prophylaxis against sudden ventricular fibrillation *sudden death Vfib *thyrotoxicosis *esmolol: peri-operative and thyrotoxicosis arthymias+arrthymias associated with anesthesia	*bronchospasm *cardiac depression *hyperglycemia *AVN block *hypotension
GROUP 3				
*AMIODARONE	*IODINE containing long acting drug *MULTIPLE MECHANISM OF ACTION: 1.prolong AP by blocking K+channely 2.blocks inactivated sodium channel 3.beta blocking effects 4.blocks Ca2+channels 5.dec conduction, dec ectopic abnormality DUE TO K+BLOCK: *prolong AP *inc ERP *reduce ability of heart to respond to rapid tachycardia and fibrillation	*oral *slow onset of action *DOA:weeks to months *LD: 0.8-1.2 g daily *MD: 200-400mg daily	*SVT and VT arrhythmias *refractory rrthymias *broad spectrum!	CARDIAC *heart block, QT prolongation, TORSADES IS RARE!! PULMONARY: *pneumonitis leading to pulmonary fibrosis OTHER *thyroid abnormality(since contains iodine) *microdeposit in skin and cornea *GIT disturbance *optic neurtitis
*SOTALOL	*K+block *beta block as well	*oral *DOA: 7 hrs	*ventricular arrthymais *atrial fib	*dose related TORSADES DE POINT *cardiac depression

*IBUTILIDE	*selective K+ block as well *prolongs AP and QT interval	*only IV!	*acute atrial fib	*TORSADES DE POINT
*DOFETILIDE NEWER CLASS 3AGENTS: dronedarone, azimilide, tedisamil, vernakalant	*like ibutilide	*oral *DOA: 7 hrs	*Rx and prophylaxis of atrial fib	*TORSADES DE POINT
GROUP 4				
*VERAPAMIL	*state and use dependant calcium channel block *dec inwards Ca2+ movement>dec contractility and automaticity> and AV conduction *PROLONGS AP! *NOTE WE NEVER GIVE DIHYDROPYRIMIDINE CCB!!!	*oral *IV *DOA: 7hrs *displaces digoxin from PPB>dec renal clearance of digoxin	*AVN arrhythmias in prophylaxis *convert AVN reentry into normal sinus rhythm *AVOIDED IN VENTRICULAR ARRYHTMIAS! *DILTIAZEM: rate control in atrial fib!	*depression of cardiac contractility *dec AVN conduction *constipation *tibial edema
GROUP 5				
ADENOSINE	*acts on GPCR adenosine receptor>activates AcH sensitive potassium channels in SAN, AVN, atrium *shortens AP duration>hyperpolarization of potassium channels>dec automaticity *reduced calcium >inc AVN refractoriness	*IV 8DOA:15sec only!!!!	*acute nodal tachycardia	*flushing *hypotension *chest pain *dyspnea *bronchoconstriction
POTASSIUM ION	*increase in all K+currents *dec automaticity *DEC DIGITALIS	*oral or IV	*Rx digitalis toxicity	*both hypokalemia and hyperkalemia are associated with increased

	TOXICTY(verapamil and quinidine inc toxicity)			arrthymogenesis *severe hyperkalemia causes cardiac arrest
MAGESIUM IONS	*possibly inc in Na/K ATPas epump	*IV	*Rx digitalis toxicity *Rx TORSADES DE POINT ARRTHYMIAS!	*hypermagesemia causes muscle weaknessa and respiratory paralyis

DRUGS USED IN HEART FAILURE

*CLASSIFICATION OF HEART FAILURE:

1)ACC TO EJECTION FRACTION:

*HFrEF/SYSTOLIC HF:

-ejection fraction<40-50%

-inc preload>stretching of heart muscle>**weaker contraction>dec EF>systolic HF**

*HFpEF/DIASTOLIC HF:

-ejection fraction>40-50%

-thickening of ventricular walls>dec in ventricular walls>dec ability of heart muscles to relax>ventricle doesn't fill properly>stroke volume(ejection volume is reduced) but ejection fraction is normal

2)ACC TO TIME COURSE:

*Congestive HF

*Acute HF

3)ACC TO ANATOMY:

*left sided HF:

-ischemic heart disease

-myocarditis

-valvular heart disease

-restrictive pericarditis

*right side HF:

-corpulmonale

-pulmonary HTN

4)ACC TO OUTPUT:

-high output: thyrotoxicosis, anemia

-low output:

HOW DOES HEART TRY TO COMPENSATE?

*via sympathetic discharge: inc force, HR, preload

*via angiotensin 2: inc afterload, causes hypertrophy

CLASSIFICATION OF DRUGS USED IN HF!

1.INOTROPHIC DRUGS:

*cardiac glycosides(digoxin, ouabain)

*sympathomimetics(dobutamine, dopamine)

*phosphodiesterase inhibitors(amrinone)

2.DIREUTICS:

*high ceiling direutics: furosemide

*low ceiling direutics: thiazide

*SGLT2 inhibitors

3.ALDOSTERONE ANTAGONIST:

*spironolactone

4.INHIBITORS OF RAA:

*ACEI: captopril , enalapril

*ARBS: losartan, candesartan

5.VASODILATORS:

*venodilators: glyceryl trinitrate

*arteriodilators: hydralazine

*both: sodium nitrprusside

*NOTE DIREUTICS ARE 1ST LINE FOR BOTH SYSTOLIC AND DIASTOLIC HF!

DRUGS USED IN ACUTE HF:

1.furosemide(1st line)

2.dobutamine and dopamine(beta agonist)

3.milrinone(PDE inhibitor)

4.nitroprusside/nitroglycerin(vasodilator)

DRUGS USED IN CHRONIC HF:

1.MILD HF: thiazide

2.SEVERE:furosemide

3.aldosterone antagonist reduce mortality

4.SGLT-2 inhibitors: in type 2 DM

5.digoxin

6.ACEI & ARBS

7.carvedilol, metaprolol, labetolol(beta anatgonists)

8.hydralazine and isosorbide dinitrate

DIGOXIN!(cardiac, extra cardiac effects, contraindications, drug interaction, Rx of toxicicty discussed here)

NOTE EVERYTHING ABOUT DIGOXIN IS IMP(can come in anyform in seq)

CARDIAC EFFECT:

A)NORMAL HEART:

*increases contractility in normal heart

*HR dec, filling time inc

*ejection fraction inc

B)FAILING HEART:

*MECHANICAL EFFECTS:

1.inc ventricularejection(due to calcium overload)

2.dec end systolic and end diastolic size

3.inc CO>inc renal perfusion>dec activation of RAA>dec afterload,dec preload, dec HR and dec remodeling mediated by angiotensin 2

*ELECTRICAL EFFECTS(also asked as neural effects on digoxin)

A)EARLY PARASYMPATHOMIMETIC EFFECT:

*vagal tone inc>AVN conduction dec>HR dec>AVN refractory period inc

*ECG changes:

1.flattening of T wave

2.shortened QT interval

3.inversion of T wave

4.ST segment depression

B) LATE ARRTHMOGENC EFFECT:

*INC AUTOMATICITY CAUSED BY INC INTRACELLULAR CALCIUM OVERLOAD IS VIMP DETERMINANT FOR DIGITALIS TOXICTY!

*increased intracellular Calcium>delayed afterpolarizations>evokses extrasystoles>tachycardia

*Premature ventricular beats occur as extrasystole(resulting in pulses bigeminus, when PVB coupled to normal heart beat in 1:1 ratio)

EXTRA CARDIAC EFFECTS:

1.blood vessels: direct vasoconstrictor effect

2.kidney: direusis>due to inc renal perfusion>reduces edema

3.GIT: anorexia, diarrhea, nausea, vomiting

4.CNS: disorientation, hallucinations, visual disturbances

DRUG INTERACTIONS OF DIGOXIN:

A)INC TOXICTY:

*quinidine(displaces digoxin from PPB)

*amiodarone

*verapamil

*thiazide and loop direutics

*hypokalemia, hypomagnesemia, hypercalcemia(potassium and digoxin compete for the same binding site on transporter>hence with dec K+ levels>chances for digoxin binding are increased)

B)DEC TOXICITY:

*antacids(dec absorption)

*cholestyramine

*hyperthyroidism(inc renal clearance)

*enzyme inducers(phenytoin, phenobarbital dec metabolism)

CORRECTION OF DIGITALIS TOXICTY:

1.CORRECTION OF MAGNESIUM AND POTASSIUM DEFECIENCY

*mild digoxin toxicity corrected via oral/IV supplementation

*in severe/acute toxicity never given K+

2.ANTI-ARRTHYMIC DRUGS:

*lidocaine

*phenytoin

*magnesium ions

3.DIGOXIN ANTIBODIES:

*Fab fragements;digibind

CONTRAINDICATIONS OF DIGOXIN:

1.hypokalemia

2.hypothyroidism

3.hypomagnesemia

4.hypercalcemia

6.pregnancy

7.myocarditis

8.V fib

9.pulmonary disease

NAME	MECHANISM OF ACTION	PHARMACOKINETICS	CLINICAL USES	TOXICITIES
INOTROPHIC DRUGS DIGOXIN	*cardiac glycosides *inhibits N/K ATPase pump *impairs ability of myocytes to pump Na+ from cardiac cells *increases intracellular sodium levels *alters Na/Ca pumps>less calcium removed from cells *inc Ca2+>stored in SER released *lots of calcium in cells>INC CARDIAC CONTRACTILITY *inc ventricular ejection *dec end systolic and end diastolic size *inc C0 & renal perfusion *dec compensatory reflexes + inotrophy - chronotrophy	*oral *IV DOA:40hrs(hence accumulates in body>dose modifications needed)	1.**chronic** HF 2.nodal arrthymias(reduce AV conduction velocity>inc refractory period 3.paraxysmal SVT(arrthymias due to re-entry phenomenon)	ALL V IMP *arrthymias(due to its late toxic effect>precipitated by inc myocardial calcium level) *nausea *vomiting *confusion *hallucinations *visual/endocrine aberrations ACUTE: cardiac depression>cardiac arrest
SYMPATHOMIMETICS DOBUTAMINE DOPAMINE	*beta-1 selective sympathomimetics	*half-life:2min *IV	*ACUTE HF(not in chronic!)	*arrthymias

	*binds to Gs receptor>inc cAMP>inc force of contraction *CO inc			
PHOSPHODIESTERASE INHIBITORS AMRINONE & MILRINONE	*inhibit PDE *inc levels of cAMP>cause an inc in calcium levels *+ inotrophy		*only ACUTE(never in chornic as it inc mortality)	*thrombocytopenia
DIREUTICS				
FUROSEMIDE	*reduces preload and edema due to powerful direusis *vasodilating action on pulmonary vessels	*oral, IV *DOA:2-4hrs	*acute & chronic HF *acute pulmonary edema *hypercalcemia	*ototoxicty *hypovolemia *hypokalemia
THIAZIDE	*produces direusis		*mild to moderate HF	*Hypokalemia, hyperglycemia, hyperuricemia
SPIRONOLACTONE	*aldosterone antagonist *reduces mortality	*oral *DOA: 24-48hrs	*chronic HF *aldosteronism	*hyperkalemia *gynecomastia
SGLT2 INHIBITORS *empagliflozin *canangliflozin			*used to reduce risk of CVS attack in DM	
ACE inhibitors Captopril Enalapril	*prevents conversion of angiotensin 1 to angiotensin 2 1.reduces salt and water retention 2.reduces vasoconstriction 3.reduces preload and afterload 4.prevens remodeling of heart	*oral short half-life *DOA:12-24hrs	*HF *HTN	*fetal toxicity *hypercalcemia *renal artery stenosis *cough! *1st dose hypotension

ARB Candesartan irbesartan	*prevents binding of angiotension 2 to AT1 receptor			*no cough *rest same as ACEI
BETA ANATGONIST: Carvedilol Labetolol Metaprolol	*block beta-1 receptor *dec cAMP>dec contractility *inc remodeling of heart 1.reduces contractility 2.reduces sympathetic outflow 3.reduces RAA>reduces preload and afterload	*oral	*chronic HF	*arrthymias In case of nonselective beta blockers *asthma *HTN *PVD *AVN block
VASODILATORS				
NITROPRUSSIDE	*powerful vasodilation *reducs preload and afterload *dec ejection fraction	*IV!	*acute HF with severe decompenation	*orthostatic hypotension *reflex tachycardia
HYDRALAZINE	*arteriovasodilator		*CHRONIC HF in African americans	*tavhycardia *headache
NESIRITIDE	*commercial version of ANP	*IV	*ACUTE HF	*nephrotoxic *hypotension
SACUBITRIL	*neprilysin inhibitor *neprilysin>responsible for inactivating natriuretic peptides *inactivates angiotensin 2, bradykinin *hence sacubitril inc levels of ANP & BNP		*prolong life *reduces hospitalization with HF	

ANTI-COAGULANTS

TYPES OF HEPARIN:

*large sulfated polysachride obtained from animal sources

Average MW: 15000-20000

1)UNFRACTIONED HEPARIN:

*given IV

*half-life:1.5hr

***affects thrombin, factor 9 and 10**

2)LMW HEPARIN:

*given SC

*half-life:3-12 hrs

***affects only factor 10**

*MW:2000-6000

3)SYTHETIC:FONDAPARINUX:

*contains the biological active pentasacchride

*given SC, once daily

FEATURES	HEPARIN	LMWH	FONDAPARINUX
*source	Biological	Biological	Synthetic
*MW	15000	5000	1500
*target	Thrombin, factor 9,10a	Mostly factor 10a(selective)	Only 10a
*route	IV	SC	SC
*F	30%	90%	100%
*half-life	Short	Long(6hrs)	Very long(17hrs)

*renal excretion *antidote	No Complete(protamine)	Yes partial	Yes none

WHY FAVOUR LMWH OVER OTHER HEPARIN:

1.greater F

2.longer duration of action than unfractioned heparin(4hrs & half-life: 3-12hrs)

3.doses give less frequently

4.less risk of clotting(HIT), hence not monitored

5.are given SC

6.more selective anti-factor 10 activity

7.renal elimination

ADVANTAGES OF DIRECT THROMBIN IHIBITORS(lepirudin & agratroban) OVER HEPARIN

1.predictable pharmacokinetics>fixed doses

2. no need for routine monitoring

3.doesnt interact with CYP-450

AVANTAGES OF ORAL ANTICOAGULANTS OVER WARFARIN(DABIGATRAN AND RIVAROXABAN)

*equivalent anti-thrombotic efficacy & reduced bleeding tendency

*lack of need for monitoring

*fewer drug interactions

DRUG INTERACTIONS OF WARFARIN: SEQ

*warfarin metabolized by CYP450 enzyme

*enzyme inducers: carbamazepine, phenytoin,rifampin, barbiturates>ALL INCREASE CLEARANCE OF WARFARIN

*enzyme inhibitors: amiodarone, SSRI, cimetidine> REDUCE CLERANCE AND INCREASE TOXICITY

*genetic variability in CYP 450 2C9 and VKOR> affects responses to warfarin

DIFFERENCE BTW HEPARIN & WARFARIN

PROPERTY	HEPARIN	WARFARIN
*structure	Large acidic polysaccharide capsule	Small lipid souble molecule
*route of administration	Parentral	Oral
*site of action	Blood(thrombin and factor 10a)	Liver(2,7,9,10)
*onset of action	Rapid(min)	Slow(days)
*mechanism of action	Activates anti-thrombin 3, which inactivates clotting factors including thrombin and factor 9+10a	Impairs post translational modification of factors 2,7,9 and 10
*monitoring	aPTT for unfractioned heparin, but not LMW heparin	Prothrombin time
*antidote	protamine for unfractioned heparin, but not for	Vitamin K1, plasma, prothrombin complex

*use *use in pregnancy	LMW mostly acute, over days yes	concentrares Chronic, over weeks to months no

NAME	MECHANISM OF ACTION	PHARMACOKINETICS	CLINICAL USES	TOXICITIES	CONTRAINDICATIONS
ANTI-COAGULANTS UNFRACTIONED HEPARIN	*complexes with **anti-thrombin 3** *heparin-antithrombin 3 complex formed *irreversibly inactivates the coagulation factors **thrombin and factor 910a & 9,11,12a)** by proteolysis	*IV	1.venous thrombosis 2.pulmonary embolism 3.MI 4.unstable angina 5.adjuvant to percutaneous coronary intervention PCI, along with glycoprotein 2b/3a inhibitors 6.prophylaxis of post-operative thrombo-embolism of surgery *USED IN PREGNANCY	1.bleeding(monitor with aPTT) 2.protamine is reversal agent 3.heparin induced thrombocytopenia HIT 4.osteoporosis 5.reversible alopecia 6.inhibition of aldosterone like secretion 7.hypersensitivity reaction **PROTAMINE:** *stongly basic, low MW *chemical antagonism *given IV *1mg needed for every 100U of heparin	1.bleeding disorders 2.HIT 3.severe HTN, peptic ulcer 4.subacute bacterial endocarditis, large TB 5.chronic alcoholics 6.renal failure 7.aspirin and other anti-platelets
LMW HEPARIN(endoparinux, dalteparin, tinzaparin)	*selective,binds only factor 10a	*renal elimination		*HIT less common(immune complex mediated reaction)	
SYNTHETIC HEPARIN(fondaparinux)	SIMILAR TO UNFRACTIONED HEPARIN				

DIRECT THROMBIN INHIBITORS (lepirudin, bivalirudin, argatroban, dabigatran>only IV!)					
AGRATROBAN	*binds to active site of thrombin *inhibits both **soluble and thrombin enmeshed in clots**(difference from heparin) *also prevents activation of factors 5,8 and 12 *prevents fibrin formation & platelet aggregation	*bivalirudin & argatroban: IV *dabigatran:oral	*.bivalirudin+aspirin: percutaneous coronary angioplasty *in patiens with **HIT** *dabigatran(oral) prevention of **stroke** and **systemic emboli** in non-valvular atrial fibrillation *__prophylaxis of VTE, following hip replacement__ *reduce risk of developing recurrent VTE	*bleeing, no reversal agents for others *idarucizumab>humanized monoclonal antibody >Fab segment, used to reverse anti-coagulat effects of dabigatran	DABIGATRAN CONTRAINDICATED: *above> 75 yrs *renal failure *dyspepsia *abdominal disease *GIT bleeding
DIRECT FACTOR 10a INHIBITORS (rivaroxaban, apxiban, edoxaban)					
RIVAROXABAN	*binds to active site of factor 10a, and inhibits its enzymatic action *both free factor 10a an enmeshed in clots	*oral administration *fixed dosing' *no routine monitoring(factor 10a test) *rapid onset of action and shorter half-life than warfarin	1.venous thromboembolism 2.pulmonary embolism 3.prevention of stroke in nonvalvular atrial fibrillation&prevention of DVT in hip replacement patients) 4.apxiban: approved for prevention of embolic stroke in patients with non-valvular atrial fibrillation	*bleeding *no reversal agents	

COUMARIN ANTICOAGULANTS					
WARFARIN	*inhibits Vitamin K epoxide reductase VKOR>normally converts vit K epoxide to reduced vit K>required for the gamma carboxylation of thrombin and clotting factors;7, 9 and 10	*oral administration *small lipid soluble molecule *bound to plasma protein(interaction with sulfonamides) *metabolized by CYP450(glucuronidation) *half-life:8-60hrs in plasma ***ANTIDOTE** *vit K *transfusion of fresh/frozen plasma *PT(monitor)	1.DVT & PE 2.MI 3.unstable angina 4.rheumatic heart disease(atrial fibrillation) 5.CVD 6.vascular surgery 7.prosthetic valve disease	*bleeding *EARLY: period of hypercoagulability with subsequent dermal vascular necrosis can occur *bone defect and hemorrhage in developing fetus! *plama protein binding *massive drug interactions(see above)	*pregnancy *bleeding disorders *severe HTN *subacute bacterial endocarditis *aspirin
THROMBOLYTIC DRUGS					
TISSUE PLAMINOGEN ACTIVATORS(alteplase, tenecteplase, reteplase)	*tPA converts plasminogen into plasmin>**selective** for fibrin bound in clot	*IV *alteplase(recombinant) *reteplase(mutated)>faster onset and longer DOA *teneteplase(mutated)>longer half-life *half-life of urokinase:15min	*not given prophylactically! *only in ACUTE EMERGENCY! 1.**PERCUTANEOUS CORONARY ANGIOPLASTY**>Rx for coronary artery thrombosis>within 6hrs can recannalize occluded vessels 2.**ischemic stroke(3hrs**)>alteplase given as bolus,remaining drug injected over 1-3hrs 3**.PE** 4.acute MI>6hrs 5.severe **DVT**	*bleeding>CEREBRAL HEMORRHAGE *allergic reactions(rash, itching, anaphylaxis)witnh streptokinase>HENCE FOLOW PROTOCOL! *hypotension during infusion *additive effects with aspirin *reteplase may cause angioedema(additive with ACEI)	*previous administration of streptokinase *within 10 days of surgery *within 3months of GIT bleed *history of cerebral hemorrhage *severe HTN *history of brain tumor, head injury
STREPTOKINASE UROKINASE	*streptokinase forms a complex with endogenous plasminogen>undergoes conformational activation>rapidly converts plasminogen to plasmin ***doesn't show selectivity for fibrin bound plasminogen**! *urokinase: human enzyme synthesized by kidney				
ANTIPLATELET					

DRUGS *aspirin *glycoprotein 2b/3a inhibitors(abciximab, eptifbatide, tirofiban) *ADP receptor antagonist(clopidogrel, prasugrel, ticagrelor) *PDEI and adenosine uptake inhibitors(dipyramidole, cilostazol)					
ASPIRIN	*inhibit COX enzyme>result in reduced synthesis of TXA2>involved in platelet aggregation	*dose required for anti-thrombotic effect much lower than anti-inflammatory effect *duration of action longer than pharmacokinetic half-life due to irreversible action	*prevention and Rx of arterial thrombosis *prophylaxis of MI, TIAs, ischemic stroke	*GIT distress *nephrotoxicity *hypersensitivity due to increased leukotrienes(asthma *tinnitus *hyperventilation *repiratory alkalosis followed by metabolic acidosis *hyperthermia *coma in overdose	*ulcer *history of bleeding *asthma *pregnancy *hypersensitivity *severe renal + hepatic disease *reyes syndrome
GLYCOPROTEIN 2b/3a INHIBITOR(abciximab, eptifibatide, tirobifan)	*monoclonal antibody *inhibits platelet aggregation by interfering with Gp2b/3a binding to other fibrinogen>prevents platelet aggregation	*IV administration	*used during PCI to prevent restenosis *ACS(unstable angina & non-Q wav acute MI)	*bleeding *thrombocytopenia (chronic use)	
ADP RECEPTOR ANTAGONIST(clopidogrel, ticlopidine, prasugrel,	*prodrug: activated by CYP2C9/CYP2C19 *irreversibly inhibits ADP receptor>prevents	*oral administration *ticlopidine: more toxic	*Prevention of TIA and ischemic stroke in patient who cannot tolerate aspirin	*bleeding *GIT distress *hematologic abnormalities(clopidogrel	

ticagrelor)	ADP receptor mediated aggregation ***ticagrelor:reversible ADP receptor antagonist>doesn't require activation**	*prasugrel:less variable kinetics, activation of CYP3A4	*ACS *prevention of restenosis after PCI	less hematotoxic) *ticlopidine: leukopenia and thrombocytopenia *thrombotic thrombocytopenic purpura TTP>small thrombi+platelet consumption+thromocytopenia	
PDE AND ADENOSINE UPTAKE INHIBITOR(dipyridamole, cilostazol)	*inhibits adenosine uptake by endothelial cells and erythrocytes and thereby increases plasma concentration of adenosine>acts through platelet adenosine A2 receptor to increase cAMP>thus inhibits platelet aggregation *inhibits PDEI *enzyme that degrades cyclic nucleotides(cAMP a platelet aggregation and cGMP a vasodilator)	*oral administration	*combo with warfarin: prevention of TE following cardiac valce replacement *combined with aspirin :for secondary ischemic stroke	*headache *palpitations	*heart failure
DRUGS USED IN BLEEDING DISORDERS					
REVERSAL AGENTS(VIT K/heparin)	*phytonadione *increases vit K>required for synthesis of functional vit K dependant clotting and anti-clotting factors *protamine(unfractioned heparin)	*oral/IV *protamine(cationic form)	*vit K deficiency *reversal of warfarin toxicity	*severe infusion reaction when given IV or IM	
CLOTTING FACTORS					

Factor 8	*key factor in intrinsic pathway	*parentral	*hemophilia A(part from factor 8, plasma, purified human clotting factors are also used)	*infusion reaction *hypersensitivity	
Desmopressin/vasopressin	*V2 antagonist>increases concentration of VWF and factor 8				
ANTI-PLASMIN DRUGS(aminocarpoic acid/tranexamic acid)	*competitively inhibits plasminogen activation	*oral *IV	*excessive fibrinolysis	*thrombosis *hypotension *myopathy *diarrhea	

ANTI-DYSLIPIDEMICS

HYPERLIPOPROTEINEMIA (FREDRICKSON CLASSIFICATION)

TYPE	SYNONYM	PRIMARY FUNCTION
1 (rare)	Primary hyperlipoproteinemia/familial hyperchylomicronema	Chylomicrons
2a	Polygeic or familial hypercholesterolemia	LDL
2b	Combined hyperipidemia	LDL + VLDL
3(rare)	Familial dysbetalipoproteinemia	Chylomicron+IDL
4	Familial hyperlipemia	VLDL
5(rare)	Endogenous hypertriglyceridemia	VLDL+chylomicron

NON PHARMACOLOGICAL MANAGEMENTS:

1.EAT HEALTHY FOODS:

*reduce saturated foods(red meat)

*eliminate transfats

*eat food rich in omega 2 fatty acids(salmon, mackerel)

*increase soluble fibre

2.EXERCISE

3.QUIT SMOKING

4.LOSE WEIGHT

5.AVOID ALCOHOL

PHARMACOLOGICAL MANAGEMENTS:

A)STATINS

B)RESINS(bind bile salts)

C)EZETIMIBE(cholesterol reuptake inhibitors)

D)NIACIN(nicotinic acid)

E)FIBRATES(GEMIFIBROZIL)

F)PCSKP INHIBITORS(ALIROCUMAB, EVOSUMAB)

NAME	MECHANISM OF ACTION	PHARMACOKINETICS	THERAPEUTIC USES	TOXICITIES
STATINS *lovastatin *atorvastatin *rosuvastatin *pitavastatin	*inhibits HMG coA reducatse enzyme *prevents conversion of HMG co A to mevalonate *decreased cholesterol synthesis>decreased intracellular cholesterol>increased expression of LDL receptor>increased LDL receptor mediate dupyake of LDL and VLDL *decreases serum LDL, IDL,VLDL ADDITIONAL ACTIONS: 1.improved endothelial functions 2.plaque stabilization(prevents adhesion of monocytes to endothelium+inhibits smooth muscle cell proliferation+inhibits macrophage secretion of MMP) 3.educed platelet aggregation and reduce s deposition of platelet thrombi 4.reduced vascular inflammation	*high 1st pass effect *high PPB *drug-drug interactions with CYP3A4 *taken orally at bedtime! (as cholesterol synthesisi maximum btw 12am-2am, except atorvastatin>taken anytime due to long half-life)	*MONOTHERAPY: *primary prevention>hyperlipidemia *secondary>prevent ischemic attack *COMBO THERAPY: *mixed dyslipidemia(mix with fibrates and niacin(*type 2 a hyperlipopreotenemia *familial dysbetalipoproetinemia *familial hypercholesterolemia	*hepatotoxicity with increased serum aminotransferases *myopathy with increased CK *GIT upset(dyspepsia, cramps, flatulence) *cataracts *rhaddomyolysis *increased risk of diabetes CONTRAINDICATIONS: *children *pregnancy *breast complications

FIBRATES *gemifibrozil *fenofibrate	*PPAR-alpha agonist *increased LPL>increased clearance and TAG *LIVER:increased FA oxidation *decreases expression of apo C-3>reduces clearance of VLDL *increased apo-A1 AND A3>increased HDL synthesis *can increase LDL in hyperlipidemia		*DOC in severe hyperTAG with increased VLDL *chylomicronemia *damilial combined hyperlipoproteinemia *familial dysbetalipoproteinemia	*GIT symptoms: nausea(most common), vomiying, diarrhea *skin rashes *increased serum aminotransferase *myopathy *rhabdomyolysis *hypokalemia *arrthmias *increased risk of gall stones! DRUG INTERACTIONS: *1.increased risk of myopathy 2.displaces drugs from PPB(oral hypoglycemic & anti-coagulants) CONTRAINDICATIONS: 1.people with impaired renal function 2.pregnant/nurinsg women 3.pre-existing gall bladder disease
NIACIN	*water soluble *at low dose function as vit B3 1.ADIPOSE TISSUE:reduces activity of HSL>reduces FFA release from adipose tissue to liver>decreased TAG synthesis by liver>dec VLDL>dec IDL>inc HDL 2.CAPILLARY:stimulates LPL>increases clearance of chylomicrons and VLDL 3.LIVER:reduces VLDL synthesis 4.niacin only drug to lower Lp(a) a atherogenic lipoprotein 5.also increases secretion of TPA and decreases levels of fibrinogen		*hypercholesterolemia *hyperTAG	*cutanepus flushing (most imp>due to stimulation of PGD2) *dyspepsia *pruritis *dose dependant nausa and vomiting *liver damage(more pronounced with extended release formulations than sustamied release formulation) MORE SEROUS EFFECTS: 1.hepatotoxicity 2.hyperglycemia(due to insulin resistance) 3.hyperuricemia(dec excretion) RARE *ambylopoa and arrhythmia CONTRAINDICATIONS: 1.gout 2.peptic ulcer 3.hepatotoxicity 4.DM

RESINS *cholestyramine *colespitol *colesevelam	*prevents bile salts reabsoprton from small intestine *decreases cholesterol content in hepatocytes by diverting them to form new bile acids thus >compensatory increased expression of LPL>reduces LDL ***can increase TAG in combined hyperlipidemia** *increased VLDL(transient effect) *inc HDL		*primary hypercholesterolemia *can be used to relieve pruritics(in pts with cholestatic jaundice) *used for severe digitalis toxicity	*constipation, heart burn *absorption of: *vit A,D,E,K impaired *thiazides, warfarin, pravastatin impaired *increased bleeding tendency
EZETIMIBE	*prodrug converted to active form by glucoronidation *inhibits transporter NPC1LI>prevents GIT uptake of cholesterol and phytosterols *prevents absorption of dietary cholesterol and cholesterol in bile>reduces hepatic pool of cholesterol>compensatory increases of LPL.increased clearance of LDL		*primary hypercholesterolemia *phytosteromia	*with combo with HMG-coA reductase inhibitors>cause increased hpetaotoxicty *serum levels increased by : fibrates *decreased by cholestyramine

CENTRAL NERVOUS SYSTEM

*SEDATIVE HYPNOTICS

*ALCOHOL

*ANTI-EPILEPTICS

*ANTI-PSYCHOTICS

SEDATIVE HYPNOTICS

*produces dose dependant CNS depressant effects(sedation/relief from anxiety and hypnosis/induction of sleep)

A)BENZODIAZEPINES:

*short acting(half-life:3-8hrs): oxazepam, triazolam

*intermediate acting(half-life:8-20hrs):alprazolam, clonazepam,lorazepam,estazolam

*long acting(half-life:1-3days):flurazepam, diazepam, chlorazepate, chlordiazepoxide

B)BARBITURATES:

*ultra-short acting(half-life:20min+highest lipid soluble):thiopental

*short acting(half-life:2-8hrs):secobarbital, pentobarbital, amobarbital

*long acting(half-life:1-2days): phenobarbital

C)NEWER HYPNOTICS:

*zolpidem, zaleplon, eszopiclone

D)MELATONIN ANAGONIST:

*ramelteon

*tasimelteon

E)5-HT 1A ANTAGONIST:

*buspirone

F)OREXIN ANATGONIST:

*suvorexant

USES OF DIAZEPAM:withdrawal from alcohol, status epilepticus,muscle relaxant, anti-convulsant, anesthesia

DIFFERENCE BTW BARBITUARTES AND BENZODIAEPINES:

FACTOR	BENZODIAZEPINES	BARBITURATES
MECHANISM OF ACTION	*bind to GABA-A receptor, btw alpha-1 and gamma-2 *increases **frequency** of chloride ion influx>membrane hyperpolarization *facilitates inhibitory action of GABA **(potentiates GABA)** *BZ-1: sedation(reduction of anxiety) *BZ-2:hypnosis(induction of sleep)	*binds to a different point on GABA-A receptor, may also block excitatory glutamate receptors>decreasing neuronal activity *increases **duration** of action of chloride channel opening *have **gabamimetic effect** at high doses *inhibit complex 1 of ETC>retains sodium>hydropic change>CNS depression
DEPENDANCE LIABILITY	*less(experience same withdrawal symptoms howver less in intensity)	*more(tolerance, physical dependence, addiction>expeience more withdrawal symptoms: anxiety, hyperreflexia, seizures(MORE COMMON WITH SHORTER ACTING DRUGS!)
HALF-LIFE	*2-4hrs	*4-60hrs
USES	*ANXIETY: alprazolam, clonazepam *SLEEP DISORDERS: estrazolam, flurazepam, triazolam *ANESTHESIA: diazepam, midazolam,lorazeoam	*ANESTHESIA: thiopental *INSOMINA: secobarbital *SEIZURE:primidone(treat seizures, essential tromors along with propranolol) *STATUS EPILEPTICUS :

	*SEIZURES: clonazepam *BIPOLAR DISORDRS: clonazepam *WITHDRAWAL FROM ACOHOL:diazepam, chlordiazepoxide(IV) , FETAL LUNG MATURATION *MUSCLE SPACTICITY: diazepam *STATUS EPILEPTICUS: diazepam, lorazepam *used to treat para-insomnia in children	phenobarbital(first line of drug against children)
CNS EFFECTS	*sedation/paraoxysmal disinhibition/anxiolysis/possibly anti-convulsat and muscle relaxant activity>>>hypnosis>>>flattening of curve as dose increases	*sedation/paraoxysmal disinhibition/anxiolysis>>>hypnosis>>>anesthesia>>>medullary depression>>>coma(respiratory arrest, hypotension, CVS collapse)
METABOLISM	*converted to active metabolites(with longer half-life) *LORAZEPAM & OXAZEPAM>don't form active metabolites!	*extensively metabolized *PHENOBARBITAL(weak acid, isn't metabolized, excreted unchanged in urine) *ENZYME INDUCERS!
TOXICITY	1.<u>psychomotor disturbance</u>: *congnitive impairment *decreased psychomotor dysfunction *unwanted day-time sedation(dose reduced in elderly to prevent risk of falls and fractures) *common with longer acting(diazepam and flurazepam) * anterograde amnesia(common with benzodiazepines) 2.<u>additive CNS depression</u>: *when used with: 1.alcohol 2.anti-histamines 3.anti-psychotics 3.opiod analgesics 4.TCA 3.<u>tolerance develops rapidly</u> 4.overdosage: CVS and respiratory depression(marked	ALL SAME AS BENXODIAZEPINES: SOME ADDITIONAL POINTS: *along with carbamates induce formation of liver metabolizing enzymes>increased drug interactions *may precipitate AIP! *hang-over effect *tremors, anxiety, weakness *nausea, vomiting, diarrhea *medullary depression ACUTE: stupor, coma, resp depression, chyne stroke breathinh CHRONIC: all point written in benzodiazepines toxicity DANGEROUS IN: *elderly(for same reasons) *AIP *liver failure

	with alcohol, barbiturates, carbamates) *ataxia DANGEROUS IN: Elderly, liver pateints, drivers(day time sedation)	
REVERSAL	*flumazenil(competitive antagonist at GABA-A receptor) Note flumazenil administration causes: *agitation *confusion *withdrawal syndrome(hyper-reflexia, tremors, seizures)	*NO ANTAGONIST *symptomatic Rx: -ventilatory support

ORGAN SYSTEM EFFECTS OF BENZODIAZEPINES:SEQ (written in big katzung)

1.slight effect on resp, CVS, GIT

2.inject diazepam: dec BP due to reduction in CO

3.midazolam:dec contractility

4.potentiates effects of alcohol

5.large doses of benzodiazepines before labour(hypothermia, hypotonia, mild resp depression in neonates)

*ZOLPIDEM/ZALEPLON/ESZOPICLONE:

*biphasic release form extends its half-life(zolpidem)

*rapid hepatic metabolism by aldehyde oxidase & CYP450(zaleplon)

*meta by CYP450, half-life of 6hrs(eszopiclone)

*THESE ARENT BENZODIAZEPINES!

*bind to GABA-A receptor>facilitate opening of chloride channels

*selectively bind to alpha-1 subunit od GABA-A receptor

*used when sleep onset is delayed

*short half-life, additive CNS depressant with alcohol, dependence liability

Why prefer these drugs?

-less abuse liability

-less tolerance

-less day time cognition

ATYPICAL SEDATIVE-HYPNOTICS:

***BUSPIRONE**:

-selective anxiolytic

-partial agonist at 5-HT1A receptors

-slow onset of action(1 week)
-used in GAD(less effective for acute cases, like panic disorders)

-short half-life

-interactionwith CYP3A4

-has no muscle relaxant and anti-convulsant activity!

Why favour buspirone?

1.minimal CNS depressant activity

2.tolerance is minimal, less dependance

3.less abuse liability, no rebound insomnia

4.no withdrawal symptoms on discontinuance

RAMELTEON & TASIMELTEON:

*activates MT1 & MT2 receptors in supra chiasmatic nucleus

*decreases latency of sleep onset>with minimal rebound insomnia or withdrawal symptoms

*min abuse liability

*meta by CYP 450(rifampin reduced plasma levels of ramelteon)

*inhibitors of CYP1A2(fluvoxamine) & inhibitors of CYP2C9(fluconazole)>>>inc plasma levels of rameltoen

*ADVERSE EFFECTS: dizziness, fatigue, endocrine changes(dec testerone and inc prolactin)

Tasimelteon: approved for Rx of non 24 hrs sleep wake disorder

ALCOHOLS

DRUGS TO Rx ALCOHOL WITHDRAWAL:

1.thiamine

2.diazepam(only if liver functioning normally>if it isn't administer lorazepam/oxazepam as they are conjugated extra-hepatically)

DRUGS TO Rx ALCOHOL WITHDRAWAL DEPENDANCE:

1.disulfiram

2.naltrexone

3.acamprostate

DRUGS TO Rx ACUTE ETHYLENE OR METHANOL INTOXICATION:

1.ethanol

2.fomepizole

SOME IMPORTANT TERMINOLOGIES!

1)ALCOHOL DEPENDANCE:

*alcohol use disorder, characterized by physical and psychological dependence

2)ALCOHOL WITHDRAWAL SYNDROME:

*insomnia

*tremor

*agitation

*seizures

*autonomic instability

*engendered by a person physically dependant on alcohol

3**)FETAL ALCOHOL SYNDROME:**

*craniofacial dysmorphia

*heart defects

*mental retardation

*due to teratogenic effects of alcohol on fetus

3)WERNICKE-KORSAKOFF SYNDROME:

*ataxia

*confusion

*paralysis of extra-ocular muscles

*associated with chronic alcohol and thiamine deficiency

METHANOL:

*wood alcohol/constituent of acnned heat and windshield cleaners

*INTOXICATION :visual disturbance GIT distress,shortness of breath, loss ofconsciousness

*FORMALDEHYDE& FORMIC ACID: severe acidosis, retinal damage, blindness

*Rx:

1.adminster fomepizole(inhibitor of aldehyde dehydrogenase>adverse effects of fomepizole include headache, nausea, vomiting,allergic reactions

2.ethanol(inhibits oxidation of methanol by alcohol dehydrogenase)

ETHYLENE GLYCOL:

*inhalation/self-administration via anti-freeze

*metabolized by aldehyde dehydrogenase to oxalic acid

*causes acidosis

*nephropathy

*CNS toxicity

NAME	MECHANISM OF ACTION	PHARMACOKINETICS	THERAPEUTIC USES	TOXICITIES
ETHANOL	*facilitates action of GABA at GABA-A receptors *inhibits inability of glutamate to activate NMDA receptor *modifies activities of AC>phospholipase C>and ion channels	*rapidly absorbed *Vd: 0.5-0.7L/Kg ***zero-order kinetics!** ***ALCOHOL DEHYDROGENASE**: -cytosolic NAD dependant enzyme -found in liver and gut -metabolizes low to moderate doses of ethanol -GIT metabolism lower in women(hence women more prone to develop toxicities at low levels) -follows zero-order kinetics due to low levels of NAD+ ***MICROSOMAL ETHANOL-OXIDIZING SYSTEM**: -at ethanol blood levels>100mg/dl -chronic ethanol consumption induces CYP450 synthesis and MEOS>partially responsible for development of tolerance *isoformof CYP450 2E1>converts acetaminophen to hepatotoxic metabolite ***ALDEHYDE DEHYROGENASE**: -mitochondral enzyme -converts aldehyde to acetate ions <u>-INHIBITED BY</u>: 1.disulfiram 2.metronidazole 3.oral hypoglycemic 4.cephalosporins(cefoperazone and ceftriazone) *<u>accumulation of acetaldehyde causes nausea, headache, flushing, hypotension</u>	*antidote in ethylene and methanol toxicity	ACUTE: 1)CNS *sedation, slurred speech, loss of inhibition, impaired judgement and slurred speech *60-80mg/dl: impairment of driving occurs *120-160mg/dl: gross drunkedness *>300mg/dl: loss of consciousness, anesthesia, coma, fatal resp andCVS depression *>500mg/dl: lethal 2.depresses heart 3.vasodilation 4.hypothermia 5.resp failure CHRONIC: 1)tolerance and dependence: *alcohol use disorder *psychological an physical dependence 2)liver: *reversible fatty liver>irreversible hepatitis>cirrhosis>liver failure 3)GIT: *irritation, inflammation *absorption defects *inc risk of pancreatitis 4)neurological: *peripheral neuropathy *Wernicke-korsakoff syndrome *requires prompt administration of thiamineB1 5)endocrine system: *gynecomastia, testicular atrophy *salt retention 6)CVS:

				*hypertension, anemia, dilated cardiomyopathy *binje drinking: arryhtmias *ingestion of ethanol raises HDL 7)fetal alcohol syndrome: *mental retardation *microcephaly 8)neoplasia: INDUCTION OF CYP2E1>RESULTS IN PRODUCTION OF TOXIC METABOLITE FROM ACETAMINOPHEN
DRUGS USED IN ALCOHOL WITHDRAWAL:				
1.DIAZEPAM	*BZ agonist, facilitates GABA mediated activation of GABA-A receptors	*long acting preferred *unless person has liver defect>in which lorazepam is administered	*prevention and Rx of acute alcohol withdrawal syndrome	*psychomotor dysfunction *dependence *additive depression
2.THIAMINES	*vit B1 *required for the synthesis of co-enzyme thiamine pyrophosphate	*IV	*prevent Wernicke korsakoff syndrome(paralysis of extra-ocular muscles, ataxia, confusion)	*none
DRUGS USED IN CHRONIC ALCOHOLISM				
1.NALTREXONE	*non-selective competitive antagonist at opiod receptors *dec effects of endogenous peptides in brain	*oral *parentral formulations	*reduces risk of relapse in alcohol-use disorders	*GIT affects(diarrhea) *liver toxicity *antagonism at opiod receptor
2.ACAMPROSTATE	*NMDA antagonist *GABA-A agonist effect	*oral	*same use	*GIT distress

3.DISULFIRAM	*inhibits aldehyde dehydrogenase *causes aldehyde to accumulate>toxic effects of aldehyde include>nausea, vomiting, headache, flushing, hypotension	*oral	*reduces relapse in a patient with alcohol dependence	*headache *nausea *dizziness *allergy

ANTI-EPILEPTICS:

TYPES OF SEIZURES:

A)FOCAL ONSET:

*simple partial seizures

*complex partial seizures

*grand mal/focal to bilateral tonic-clonic seizures

B)GENERALIZED ONSET:

*generalized tonic-clonic seizures

*generalized absence seizures>petit mal/absence seizures

*myoclonic seizures

*infantile spasms

TONIC-CLONIC GENERALIZED SEIZURES:

*tonic phase(less than 1min)>involves abrupt loss of consciousness, muscle rigidity, respiration arrest

*clonic phase(2-3min)>jerking of body muscle, lip and tongue biting, fecal and urinary incontinence>GRAND MAL

STATUS-EPILEPTICUS:

*series of seizures

*usually tonic-clonic

*without recovery of consciousness, btw attacks and is a life threatening emergency

HOW TO TREAT SEIZURES:

*block repetitive firing

*block synchronization of neuronal discharge

*blocks propagation of seizures

IMP PHARMACOKINETIC PROPERTIES OF ANTI-SEIZURES:

*carbamazepine, oxcarbamzepine, phenobarbital, phenytoin, primidone>>>strong inducers of CYP450 and glucuronyl transferase

*phenytoin, tigabine, valproate, diazepam, parampenal, highyly bound to PPB

*gabapentin, pregabalin, levetiracetem, vigabatrin eliminated in unchanged form

*tigabine, topiramate, zonisamide undergo hepatic metabolism, and renal elimination

*perampanel>long half-life, meta by CYP3A4 and subsequent glucoronidation

TREATMENT OF STATUS EPILEPTICUS:

*STAGE 1(first 30min): give IV lorazepam, buccal midazolam, IV/rectal diazepam

*STAFE-2(30-120min):if still not treated>Rx with IV anti-epileptic(phenytoin, phenobarbital, valproate)

*STAGE-3(>120min):refractory cases: give general anesthesia(propofol, midazolam, thiopental/pentobarbital)

*STAGE-4(after 24hrs):SUPER-REFRACTORY STATUS EPILEPTICUS: which has continued despite Rx for more than 24hrs

MECHANISM OF ACTION:

1.modulation of voltage gated sodium, calcium and potassium channel

2.enhancement of fast GABA mediated synaptic inhibition

3.modification of synaptic release processes

4.dimunition of fast glutamate mediated excitation

MOLECULAR TARGET	DRUGS	MECHANISM
VOLTAGE GATED ION CHANNEL		
SODIUM CHANNEL	Phenytoin, fosphenytoin, carbamazepine, oxcarbazepine, lamotrigine, locosamide	*blocks sodium channels on neurons *prevents repetitive firing and blocks propagation of impulses *rate dependant *all this results in prolongation of inactivated state of Na+channel, and refractory period of neuron
T-TYPE CALCIUM CHANNEL	Ethosuximide, valproic acid, gabapentin, pregabalin	*inhibits these low threshold channels *esp in thalamic neuron that act as pace-maker to generate rhythmic cortical discharge

POTASSIUM CHANNEL	Retigabine	*enhances hyperpolarization of neurons>prevents depolarization of neuronal membrane
GABA INHIBITION GABA-A RECEPTORS	Phenobarbital, primidrone, diazepam, lorazepam, clonazepam	*benzodiazepines: inc frequency of opening of Cl- channels>facilitates inhibitory action of GABA>resulting in hyperpolarization>decreases ability of neurons to transfer signals *barbituartes: inc duration of opening of Cl-channel
GABA-AMINOTRANSFERASE-1 GABA TRANSPORTER(GAT-1 GABA)	Tiagabine	*GAT-1 transporter present in neurons and glial cells>prolongs action of GABA
GABA-TRANSAMINASE	Vigabatrin	*inhibits GABA-T receptor>prevent termination of action of GABA
STRUCTURAL ANALOGUE OF GABA	gabapentin	
FACILITATES INHIBITORY ACTION OF GABA	felbamate, topiramate, valproic acid	
SYNAPTIC RELEASE MACHINERY SV2A	Levetiracetam	*binds SV2A>prevents glutamate release whivh is an excitatory neurotransmitter

IONOTROPHIC GLUTAMATE RECEPTORS AMPA RECEPTOR	 PERAMPANEL, FELBAMATE	 *non-competitive antagonist at glutamate AMPDA receptors

IMPORTANT ANTI-SEIZURE DRUGS!

NAME	PHARMACOKINETICS	MECHANISM OF ACTION	CLINICAL USES	TOXICITIES	DRUG INTERACTIONS
PHENYTOIN	*zero-order kinetics *PPB>98% *phenytoin due to its soluble propylene glycol form causes cardiotoxicity *hence, we prefer fosphenytoin(IV)	*blocks sodium channel 1.blocks inactive voltage sodium channel 2.blocks repetitive firing of action potential 3.promotes stabilization of membranes 4.reduces propagation of impulse in brain *at higher dose: blocks calcium channel *interfers with release of acetylchoine, norepinephrine	1.partial(simple and complex seizures) 2.tonic-clonic seizures 3.status epilepticus 4.arrthymias	*depression of CNS: -seadtion, nystagmus, hallucination, diplopia, ataxia *GIT vomiting LONG TERM USE: 1.coarsening of facial features 2.mild peripheral neuropathy 3.osteomalacia 4.megaloblastic anemia 5.inhibition of ADH release 6.gingival hyperplasia 7.hisrusitsm FETAL HYDANTOIN SYNDROME	*carbamazepine, valproic acid, sulfonamides, compete for binding with PPB *inc levels of phenytoin: phenobarbital, rifampin *declevels of rifampin:cimetidine, isoniazid
CARBAMAZEPINE	*induces liver drug metabolizing>increases metabolism of other anti-convulsants	*blocks sodium channel in inactivated state>characteristic use-dependant blockade 1.reduces propagation of abnormal impulses 2.high frequency repetitive firing in neurons 3.decreases synaptic transmission>inhibits uptake and release of	1.DOC in all partial seizures 2.tonic-clonic seizures 3.trigeminal neuralgia 4.manic depressive patient	*<u>respiratory depression</u> *<u>drowsiness, vertigo, diplopia, blurred vision</u> *<u>serious liver toxicity</u> *hyponatremia and water intoxication ***idiosyncratic blood disorder>aplastic anemia & agranulocytosis** ***CLEFT LIP/PALATE** ***SPINA BIFIDA**	*induces metabolism of: *phenytoin *valproic acid *clonazepam *ethosuximide

		NE 4.post-synaptic action of GABA potential		***MEGALOBLASTIC ANEMIA**	
VALPROC ACID	*hepatic metabolism of valproic acid>hepatotoxicity!	*blocks sodium, calcium channel 1.blocks high frequency repetitive firing of neurons>Na+ channel blockade 2.blockade of NMDA receptor-mediated excitation 3.facilitates glutamic acid decarboxylase(GAD) 4.inhibitory effect on GABA-T 5.inhibits GAT	1.myoclonic seizure 2.atonic seizures 3.generalized absnce seizures 4.focal seizures 5.bipolar disorders 6.migraine prophylaxis!	*drowsiness *nausea *tremor *hair loss *weight gain *hepatotoxicity!!!(in infants less than 2years)	*inhibits metabolism of: *phenobarbital *ethosuximide *lamotrigine *carbamzepine *valproate displaces phenytoin from plasma protein *decreases clearance of lamotrigine
PHENOBARBITAL		*binds to GABA-A receptor *increases duration of opening of chloride channel *elevates seizure potential *blocks excitatory responses by glutamate	1.focal 2.generalized seizures 3.myoclonic seizures 4.refractory status epilepticus		

SPECIFIC TOXICITIES OF DIFFERENT DRUGS!

*ETHOSUXIMIDE: GIT distress, lethargy,headache(remember it has the least withdrawal symptoms!)

*FELBAMATE: aplastic anemia, hepatic failure, hematotoxicity

*LAMOTRIGINE:steven Johnson syndrome, dizziness, ataxia

*RETIGABINE: retinotoxicity

*ZONISAMIDE: dizziness, diarrhea, weight loss

DOC IN DIFFERENT KIND OF SEIZURES:

A)GENERALIZED TONIC-CLONIC & PARTIAL SEIZURES:

*carbamazepine

*lamotrigine

*phenytoin

*valproic acid

*PHENOBARBITAL: DOC in infants

*LAMOTRIGINE, LEVETIRACETEM: DOC in pregnancy

B)FOCAL/PARTIAL SEIZURES:

*DOC: carbamazepine, lamotrigine, phenytoin

*ALTERNATE DRUGS: felbamate, phenobarbital, topiramate, valproic acid

C)ABSENCE SEIZURES:

*DOC: ethosuximide

*valproic acid

*clonazepam

D)MYOCLONIC SEIZURES:

*clonazepam

*lamotrigine

*valproic acid

E)OTHER SEIZURE DISORDER:

-valproic acid: Rx of mania

-carbamazepine & lamotrigine: bipolar disorder

-carbamazepine: trigeminal neuralgia

-gabapentin: post-herpetic neuralgia

-pregabalin: neuropathic pain

ANTI-PSYCHOTICS

PSYCHOSIS IS A VARIETY OF MENTAL DISORDERS CHARACTERIZED BY AN INABILITY TO DISTINGUISH BTW WHAT IS RIGHT/WRONG,. DELUSION AND HALLUCINATION ARE A MAJOR SIGN & SYMPTOMS

A)POSTIVE SYMPTOMS(treated by 1st generation)

*schizophrenia

*hyperactivity

*bizzare ideation

*hallucinations

*delusions

B)NEGATIVE SYMPTOMS(treated by 2nd generation)

*emotional blunting

*social withdrawal

*lack of motivation

CLASSIFICATION:

A)CLASSIC(D2 RECEPTOR AFFINITY DRUGS)

*PHENOTHIAZINES:

-propylamine side chain(chlorpromazine)

-piperidine side chain(thioridazine)

-piperazine(tri-fluoperazine, fluphenazine>EPS are most common with these)

*THIOXANTHENES(thiothixene)

*BUTYROPHENONES(haloperidol)

B)NEWER(5 HT2 RECEPTOR AFFINITY)

*aripiprazole

*clozapine

*olanzapine

*risperidone

C)BIPOLAR DRUGS:

*CLASSIC DRUG: LITHIUM

*NEWER: acute mania(olanzapine, quetiapine, aripiprazole, risperidone)& chronic phase(clonazepam, carbamazepine)

ANTI-PSYCHOTICS Rx:

1.bipolar disorder

2.schizophrenia

DOPAMENERGIC PATHWAYS:

1.**mesolimbic/mesocortical pathway:** midbrain to mesocortical pathway(regulates mentation and mood)

2.nigrostriatal pathway(extrapyrimadal function)

3.tuberoinfundibular pathway(control of prolactin release)

4.medullary peri-ventricular pathway(CTZ)

SPECIFIC POINTS ABOUT DIFFERENT DRUGS:

*ALL HAVE ALPHA AND H1 BLOCK!

*CLOZAPINE: D2 & 5-HT2 antagonist>no affinity for D4 receptor

*OLANZAPINE/QUETIAPINE/RISPERIDONE: affinity for 5-HT2A receptor

*ZIPRASIDONE: antagonist at D2, 5-HT2A, 5-HT1D receptor & agonist at 5-HT1A receptor

*ARIPIPRAZOLE: partal agonist at D2 and 5-HT1A receptor

*HALOPERIDOL: doesn’t block M and H1 receptor

TOXICITIES

1.REVERSIBLE NEUROLOGICAL SYMPTOMS:

*EPS(parkinsonism like effects>>>bradykinesia, rigidity, tremor)

*occurs with HALOPERIDOL and piperazine side chain phenothiazine(fluphenazine & trifluoperazine)

*occurs LESS infrequently with clozapine

*akathisia

*dystonia

*Rx: benztropine & diphenyhydramine

2.TARDIVE DYSKINEISA:

*seen in CHRONIC condition and is irreversible!

*choreoathetoid movement of lips, buccal cavity, muscles of lips

*anti-muscuranic drugs whuch usually ameliorate EPS, inc severity of tardive dyskinesia

*Rx: deutrabenazine, valbenazine

3.AUTONOMIC EFFECTS:
*THIORIDAZONE HAS STRONGEST & alipathic side chains CHLORPROMAZINE

*CLOZAPINE immediate

*anti-M effects: dry mouth, constipation, blurred vision

*alpha-block: orthostatic hypotension. Reflex tachycardia

*NOTE: CLOZAPINE AND ZIPRASIDONE, WHICH ARE ATYPICALS ALSO BLOCK ALPHA RECEPTORS!

4.ENDOCRINE AND METABOLIC EFFECTS:

*hyperprolactinemia

*amenorrhea-galactorrhea

*infertility

*impotence

*elevated prolactin with RISPERIDONE

*weight gain with CLOZAPINE & OLANZAPINE

*aripiprazole and ziprasidone less tendency to cause hyperglycemia or weight gain

5.NEUROLEPTIC MALIGNANT SYNDROME:

*muscle rigidity

*impairment of sweating

*hyperpyrexia

*autonomic instability

*Rx: dantrolene, diazepam, dopamine agonist

6.SEDATION:

*chlorpromazine(phenothiazine)

*FLUPHENAZINE, HALOPERIDOL, APIPIPRAZOLE LEAST SEDATING!

7.MISCELLANOUS:

*thioridazone(retinal deposits and fatal ventricular arrhythmias)

*quetiapine and ziprasidone(prolong QT interval)

*clozapine(agranulocytosis!!)

NAME	MECHANISM OF ACTION	EFFECTS	PHARMACKINETICS	CLNICAL USES	TOXICITIES
PHENOTHIAZINES *chlorpromazine *fluphenazine *thioridazine	*blocks D2 receptors>>>5-HT2 receptors	*blocks alpha, M, H receptors	*oral and IV forms *hepatic metabolism	*schizophrenia(positive symptoms) *bipolar disorder(manic phase) *anti-emetic!!! *pre-op sedation	*thioridazine(anti-M block) *pre-op sedation *tardive dyskinesia *hyperprolactinemia
THIOXANTHENE(THIOTHIXINE)				*schizophrenia	*less risk of tardive dyskinesia
BUTYROPHENONES(HALOPERIDOL)		*some alpha block *less M		*schizophrenia *bipolar disorder(manic phase)	*marked EPS!

		block and sedation		*hungtingtons disease *Tourette syndrome	
SECOND GENERATIONS: *aripiprazole *clozapine *quetiapine *risperisone *ziprasidone	*blocks 5-HT2 >>>>D2 receptors	*alpha block: clozapine, risperidone, ziprasidone		*schizophrenia(negative symptoms) *acute manic phase(aripiprazole and olanzapine) *chronic depressive phase as well *bipolar disorder(quetiapine, lurasidone, olanzapine) *gilles de la Tourette syndrome	*clozapine(agranulocytosis) *clozapine, olanzapine(weight gain, diabetes) *risperidone(hyperprolactinemia) *ziprasidone(QT prolongation)
LITHIUM	1.inhibits neuronal membrane phosphoinositide>depleted levels of IP3 and DAG *2.inhibition of glycogen synthase kinase GSK-3> 3.inhibition of beta-catenin>messenger involved in insulin like GF and BDNF		*absorbed rapidly *plasma levels monitored! *dehydration, Rx with NSAIDS, ACEI, loop direutics>inc levels of lithum in blood *theophylline>dec blood levels	1.bipolar disorder(along with quetiapine, aripiprazole, risperidone, ziprasidone) 2.prevents mood swings	1.tremor 2.sedation 2.ataxia 3.apahsia 4.thyroid enlargement 5.reversible nephrogenic diabetes inspidus 6.acneiform skin eruptions 7.leukocytosis CONGENITAL ABNORMALITY: 1.ebstein anomaly 2.low apgar score 3.hence withheld lithium 24hrs before delivery
OTHER DRUGS USE DFOR BIPOLAR DISORDERS: *carbamazepine *lamotrigine *valproac acid		*ataxia and diplopia(carbamazepine)	*carbamazepine forms active metabolites(phase 1)	1.valproic acid(1^{st} DOC for bipolar disorder) 2.acute phase	*carbamazepine(hematotoxicty and induction of drug

		*nausea, dizziness, headache(lamotrigine) *GIt distress, weight gain, alopecia(valproic acid)	*lamotrigine and valproiac acid forms active metabolite(phase2)		metabolism) *lamotrigine(rash) *valproic acid(inhibition of drig metabolism, weight gain , hepatic dysfunction)

ANTI-DEPRESSANTS:

*CHEESE REACTION:

*MAOI not only blocks MAO of nerve but also of blocks MAO of GIT

*cheese, meat, liver, fish>contains high levels of tyramine

*undegraded tyramine synthesizes large amount of catecholamines:

1.hypertension

2.occipital headache

3.neck stiffness

4.tachycardia

5.HTN, nausea

6.cardiac arrhythmias

*SEROTONIN SYNDROME:

*fluoxetine and MAO interaction

*OTHER DRUG: MAOI, TCA, dextromethorphan, meperidine, St.johns wort

*life threatening syndrome

1.muscle rigidity

2.myoclonus

3.hyperthermia

4.CVS instability

5.seizures

6.headache, drowsiness, dry mouth, postural hypotension