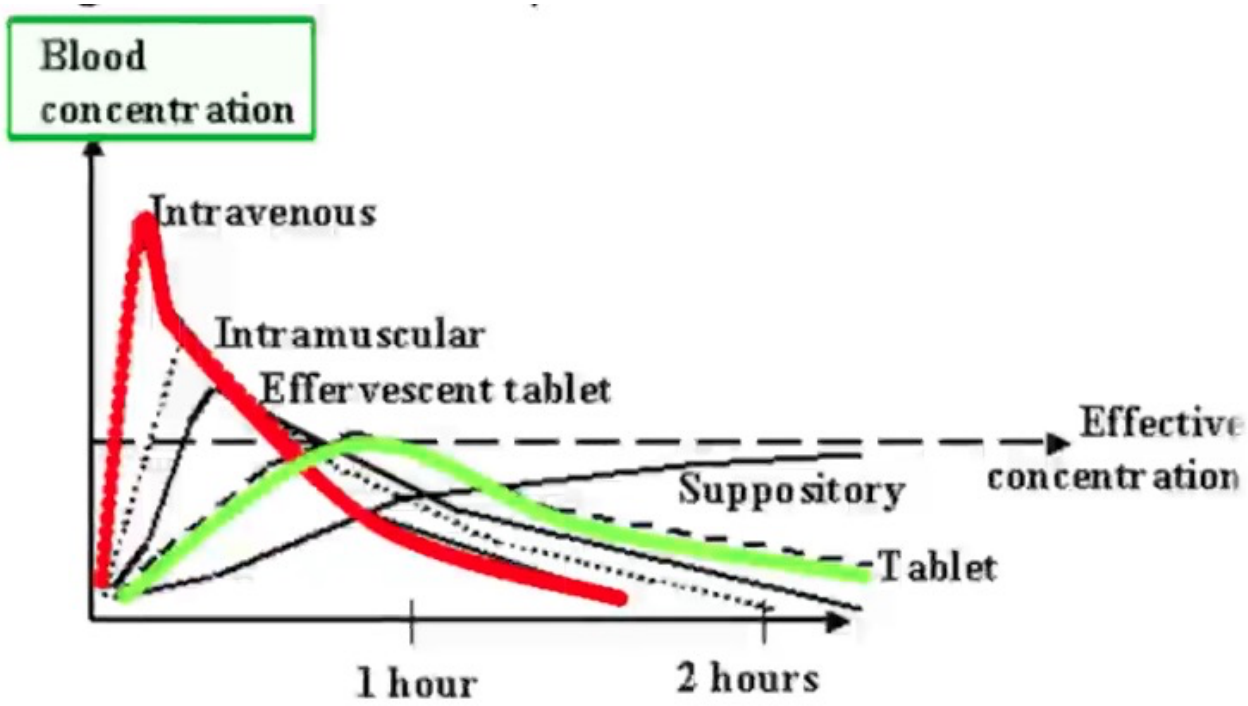
Pharmacology

PHARMACOKINETICS - what the body does to the drug

1. **Absorption**
    - IV has a bioavailability of 1 (or 100%) by definition
    - Area under curve for oral almost always less than for IV.
        - Tablets are normally around 50% bioavailable (versus IV)
    - 

2. **Distribution**
    - Factors that affect distribution -
        - 1. lipid solubility - propofol is very lipid soluble - rapidly distributed into fat, away from circulation - so rapid recovery time
        - 2. protein binding - many drugs bind to albumin
3. **Metabolism**
    1. Phases
        - Phase 1
            - Addition of a ‘polar’ group (usually -OH) by oxidation
            - This is performed by cytochrome enzymes, available in gut, liver etc. CYP450 classic example, in liver
        1. Phase 2
            1. Further addition of other chemical groups to facilitate excretion
    2. Pro-drugs - e.g. codeine —> metabolised into active drug of ‘morphine'
4. **Excretion**

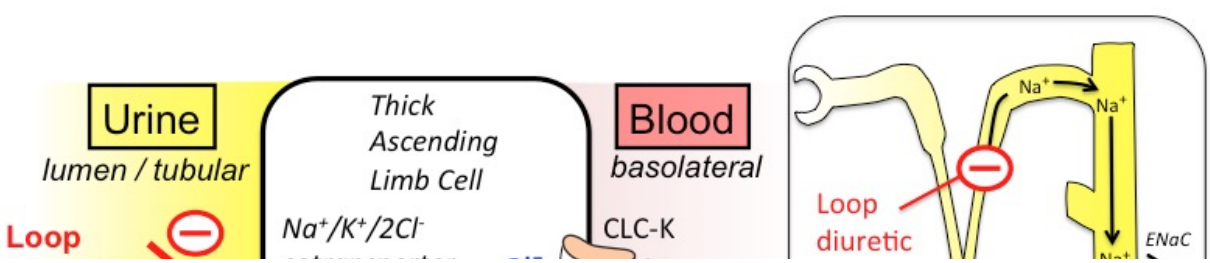
GI

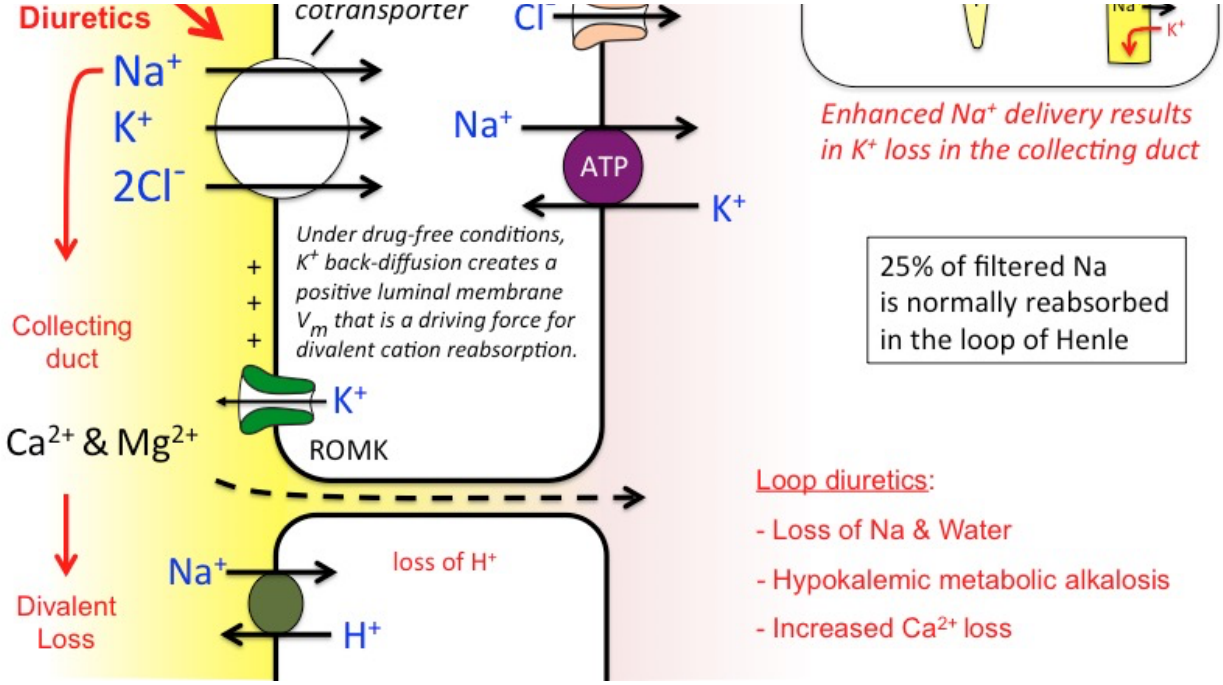
- Gord
  - Alginates (gaviscon) for reflux
  - Antacids
    - Aluminium based - constipating
    - Magnesium based - diarrhoea
  - PPI
    - Inhibit H+/K+ ATPase on gastric parietal cell
    - Triple therapy for H pylori = clarithromycin, amoxicillin + PPI
    - Constipation/diarrhoea, may increase risk of c.diff (because reduce acid as barrier to infection). Especially if + abx
  - H2 blockers = ranitidine
- IBD
  - Steroids
  - Mesalazine (amino-salicylate)
  - Infliximab - anti-TNF
- Laxatives
  - Bulking - fybogel, ispaghula husk
  - Stimulating - senna, bisacodyl
  - Osmotic - lactulose (for hepatic encephalopathy), macrogol, laxido
  - Softener - sodium docusate

CARDIOLOGY

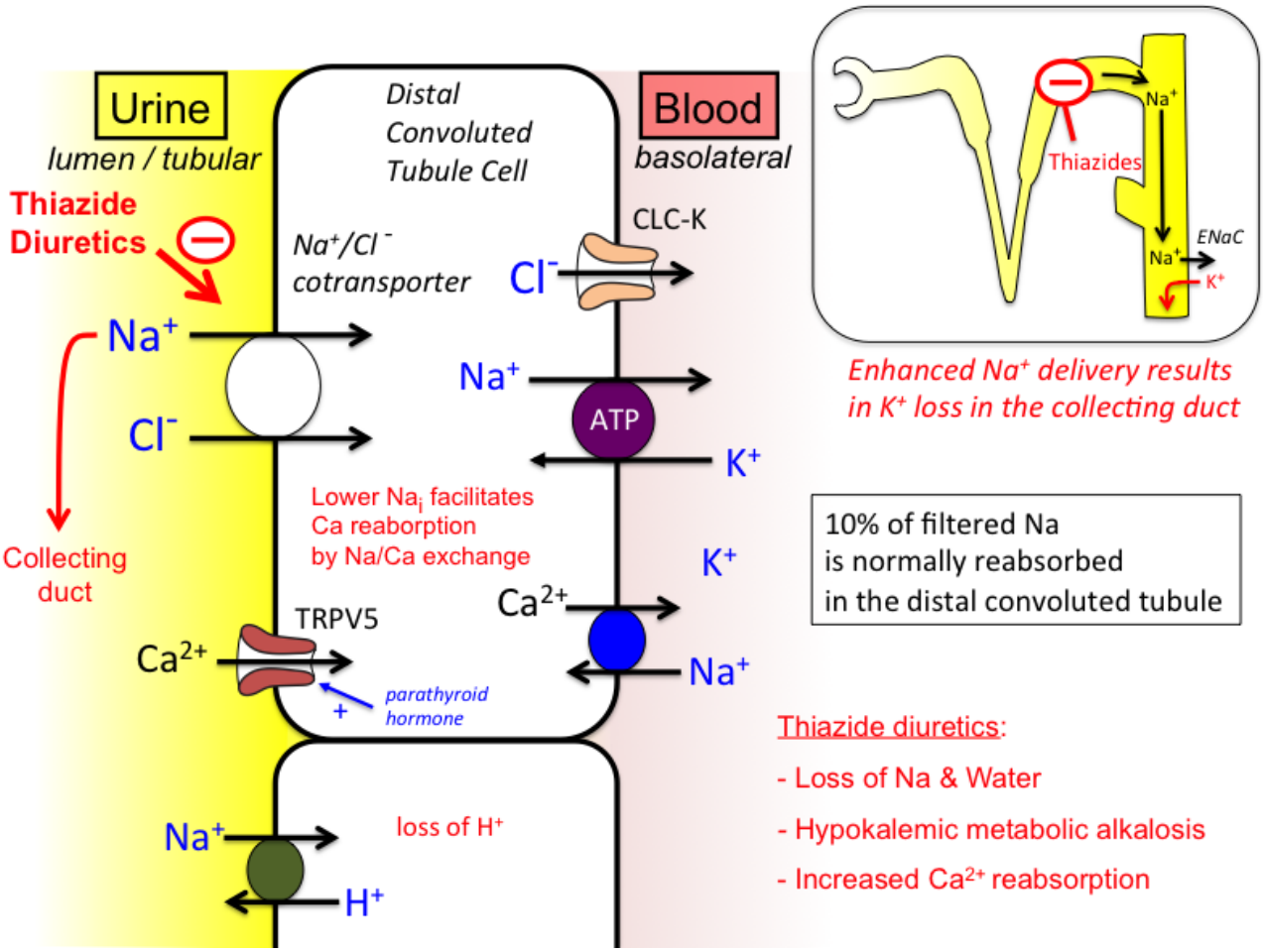
<u>Diuretics</u>

- **Loop (most potent type)**
  - Inhibits Na+/K+/Cl- symporter - ↓ resorption in ascending loop of Henle. Reduces osmotic gradient around loop of henle. ↓H2O resorption.
  - Net ↓ in all main electrolytes - MAINLY ON K though
    - ↓ Na and Cl resorption
    - ↑ Ca2+ excretion, ↑ loss of K and Mg
  - Furosemide, bumetanide (1mg = 40mg furosemide)
  - Milder ↓K risk. *Unlikely to cause ↓ Na*
  -





- **Thiazide (in DCT)**
  - Bendroflumethiazide
  - More ↓K risk, ↑ uric acid, ↑ serum glucose
  - Can precipitate gout attack
  -



- **Osmotic**
  - Mannitol
  - Pulls fluid from cells into tissues —> buys time in ↑ ICP
  - Not for HTN or diuretic effect - just for ICP
- **Carbonic anhydrase inhibitor**

    - Acetazolomide - *used in acute angle glaucoma - not for diuretic action*
    - Inhibits carbonic anhydrase (which turns CO2 + H2O —> H2CO3)
        - Prevents Na+/H+ exchange and bicarb resorption
        - ↓ resorption of these = ↓ water resorption
- **Aldosterone antagonist**
    - Spironolocatone
    - ↓ Na, ↑ K (serum)
- **Potassium sparing**
    - Amiloride

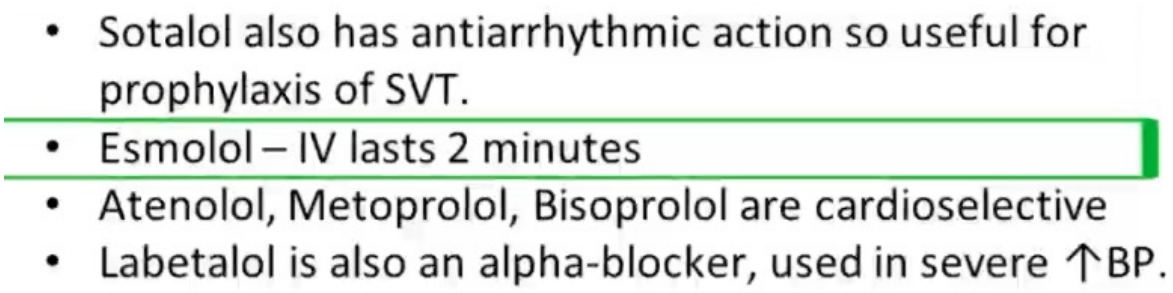
Anti-arrhythmics

- **Adenosine**
    - Transient AV block, up to 10 seconds
    - 6, 12, 12mg
    - CIs
        - Cardiac failure
        - Asthma / COPD (bronchoconstriction)
        - 2nd / 3rd degree AV block
        - Hypotension
        - Long QTc
- **Amiodarone (domestos - as works for most arrhythmias)**
    - Works for supra and ventricular arrhythmias - mainly used in ventricular arrhythmias
    - IV and PO
    - SEs: Thyroid disease, photosensitivity rash, pneumonitis = risks
    - Pharmacology:
        - Blocks K efflux (repolarisation - phase 3) = prolonged refractory period
            - Prevents re-entry mechanisms
        - Also interferes with Na channels, Ca channels, and beta-adrenergic receptors
        - ↓ SA node automaticity, ↓ AV node conduction, ↓ pacemaker automaticity
        - Long half life. NOT negatively inotropic
- **Digoxin**
    - AV nodal slowing agent - to control ventricular response in AF
        - *Less effective slowing response in exercise. Not suitable for younger/fitter patients*
    - +ve inotropic effect
    - Narrow therapeutic index - renal excretion. Accumulates in renal impairment
    - SEs:
        - GI disturbance, visual (yellow vision), CNS disturbance, conduction disorders (reverse tick morphology)
    - Used if B-blocker contraindicated (e.g. asthma) or very poor inotropy e.g. HF with AF
    - SLOW time to onset, around 6 hrs
    - Inotropic effect:

Digoxin directly inhibits membrane Na+/K+ ATPase, which is responsible for Na+/K+ exchange across the myocyte cell membrane. This increases intracellular Na+ and produces a secondary increase in intracellular Ca2+ that increases the force of myocardial contraction. The increase in intracellular Ca2+ occurs because the decreased Na+ gradient across the membrane reduces the extrusion of Ca2+ by the Na+/Ca2+ exchanger that normally occurs during diastole. Digoxin and K+ ions compete for the receptor on the outside of the muscle cell membrane, and so the effects of digoxin may be dangerously increased in hypokalaemia.

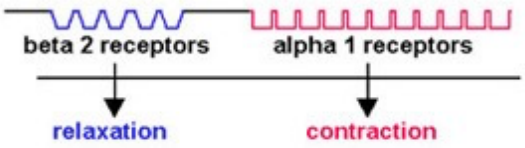
Chronotropic effect:

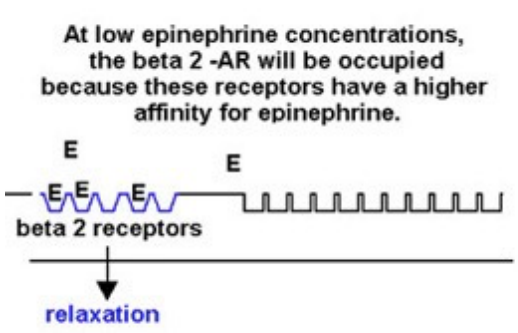
Digoxin stimulates vagal activity , causing the release of ACh, which slows the heart rate, slows atrioventricular conduction and prolongs the refractory period in the AVN and bundle of His. By delaying AV conduction, digoxin increases the degree of block, and slows and strengthens the ventricular beat.

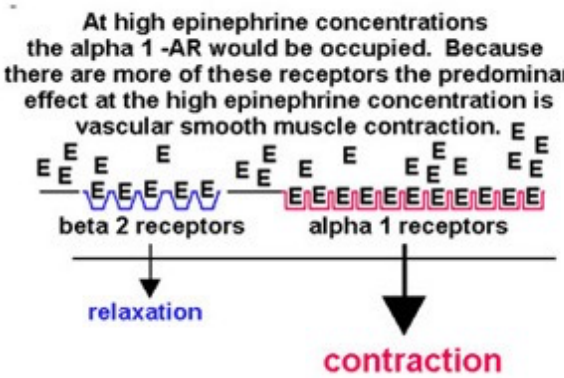
- **Fleicanide**
  - Supraventricular tachycardias, particularly AF
  - Blocks Na channels - slows pacemaker action potential upstroke - so slows electrical impulse conduction and reduces excitability
  - Is *NEGATIVELY* inotropic - avoid in IHD, HF, etc
  - Useful for pill in the pocket paroxysmal AF treatment
- **Betablockers**
  - 

- **Atropine**
  - Reduces vagal slowing
  - Start 500mcg - up to 300mg
- **ACEi**
  - HTN, HF, proteinuria/renal impairment in diabetes
  - SEs: renal impairment, hyperkalaemia (due to reduced aldosterone), hypotension, anaphylactoid reaction, cough
- **AIIRBs**
  - Losartan, candesartan.
  - Same situations as ACEi - similar side effect profile
  - DONT cause cough - 2nd line after ACEi
- **Nitrates**
  - Angina, pulmonary oedema
  - SE: hypotension, headache, flushing
- **Calcium Channel blockers**
  - Verapamil - mainly anti-arrhythmic
    - slows AV conduction. NEGATIVELY inotropic. May precipitate HF in reduced cardiac function
    - Verapamil + beta blocker can —> *complete heart block*
    - Oral = slower action.
  - Nifedipine - mainly anti-hypertension

    - Vasodilator, less cardiac activity. Not for rhythm control
    - Can cause swelling in legs/hands
  - Nimodopine
    - Vasodilation on cerebral vascular smooth muscles
    - Mainly in SAH control - to reduce arterial vasospasm in brain (from blood irritating arteries)

- **Inotropes**
  - Adrenaline
    - LOW doses
      - Beta-1 ARs: ↑ HR and ↑ contractility (inotropy)
      - Preferential beta-2 AR activation: ↓ peripheral vascular resistance
    - HIGH doses:
      - Same as Beta-1 ARs
      - Now has preferential *alpha-1* receptor activity: ↑ peripheral vascular resistance
    - 





    - **Roles in circulation** [edit]

      Epinephrine (adrenaline) reacts with both α- and β-adrenoreceptors, causing vasoconstriction and vasodilation, respectively. Although α receptors are less sensitive to epinephrine, when activated at pharmacologic doses, they override the vasodilation mediated by β-adrenoreceptors because there are more peripheral α_1 receptors than β-adrenoreceptors. The result is that high levels of circulating epinephrine cause vasoconstriction. However, the opposite is true in the coronary arteries, where β_2 response is greater than that of α_1, resulting in overall dilation with increased sympathetic stimulation. At lower levels of circulating epinephrine (physiologic epinephrine secretion), β-adrenoreceptor stimulation dominates since epinephrine has a higher affinity for the β_2 adrenoreceptor than the α_1 adrenoreceptor, producing vasodilation followed by decrease of peripheral vascular resistance.[*citation needed*]

  - Noradrenaline
    - Alpha receptors - vasco constrictor - re-divert blood from peripheries to vital organs
    - Useful in shocked states
  - Dopamine

- Dopamine
  - Inotropic effect. No chronotropic effect, and variable effect on blood vessels
  - Useful in shock unresponsive to fluids
- Dobutamine
  - Inotropic effect + vasodilator
- Anaesthetic-context agents:
  - Ephedrine
    - vasoconstrictor for use after spinal anaesthetic
  - Metaraminol
    - Used to ↑ BP in anaesthesia

	Drugs used in shock	
1	Dopamine	First drug to use. Increases contractility.
2	Noradrenaline	Useful if the patient is vasodilated (eg septic, 'warm' shock) as a vasoconstrictor
3	Adrenaline	Can be added for 'cold' shock because of useful vasodilator function (eg coronaries) in lower doses
4	Dobutamine	Used in cardiogenic shock as a vasodilator to reduce afterload if the patient is not too hypotensive

- **Anticoagulants**
  - Heparin
    - Potentiates activity of antithrombin —> causing inactivation of thrombin
    - Monitor via PTT
    - Protamine reverses
    - Can cause heparin induced thrombocytopaenia (HIT)
      - 30% reduction in platelets, bruising, skin reaction
      - Usually onset 5-10 days after starting
      - Stop heparin and find alternative anti-coagulation
  - LMWH
    - Specific action on inhibiting factor Xa
    - Unable to monitor - but more predictable
  - Fondaparinux
    - Identical to part of LMWH
    - Less risk of bleeding than LMWH
  - Coumarins - *Warfarin*
    - Antagonises vit K (II, VII, IX, X)
    - INR 3.5 for mechanical heart valves
    - INR 2.5 for most other things - PE/DVT/AF/biological heart valves
    - 2-3 days for full effect. Bridge with LMWH or other anti-coagulant
    - PC BRAS - will induce enzymes and reduce warfarin effect

- DOACs
- **Anti-platelets**
  - Aspirin - irreversible cyclooxyrgenase inhibitor
  - Clopidogrel - ADP receptor inhibitor
  - Abciximab - IV. Used in coronary procedures.
  - Dipyridamole - adenosine reuptake inhibitor
- **Fibrinolysis**
  - tPA - alteplase, tenectaplase
    - Activates fibrin-bound plasminogen - break down fibrin
    - 3-4 minute half life - given by continuous IV infusion
    - Reversible by TXA
  - Streptokinase - created by streptococci - breaks down clots
    - Less widely used due to reactions. Form anti-bodies against it so less effect second use
- **Lipid-regulating**
  - Statin
    - HMG CoA reductase inhibitors
    - SEs: muscle cramps/weakness, ↑ diabetes risk, abnormal LFTs

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RESPIRATORY

Acute asthma algorithm:

1. Salbutamol + steroid
2. Ipratropium
3. IV magnesium 1.2-2g over 20 mins

Bronchodilators

- Beta-2 AR agonists -
  - salbutamol, terbutaline
  - Tachycardia and tremor SEs
- Anti-muscarinic
  - Ipratropium bromide
- Aminophylline
  - IV theophylline - 3rd line in severe asthma

Steroids -

- not direct action asthma - promote production of anti-inflammatory proteins
- therefore, IV is not faster than oral. Rate limiting factor is the production of the proteins
  - Prednisalone
  - Hydrocortisone - I
  - Beclomethasone - in asthma prophylaxis - candida as SE

Anti-histamines (H1 blockers - act on mast cells in type I hypersensitivity)

- Cetirizine / loratadine - non sedating
- Chlorphenamine - sedating

CNS

Benzos

> Midazolam has a short duration of action (< 6 hours), lorazepam and temazepam have an intermediate duration of action (12 - 18 hours) and diazepam and chlordiazepoxide have a long duration of action (24 - 48 hours). Shorter-acting compounds may be preferred in patients with hepatic impairment but they carry a greater risk of withdrawal symptoms.

Carbamazapine

- CIs:
  - AV block
  - BM suppression - risk of agranulocytosis
  - History of acute porphoryia

Lithium

- Features of toxicity include:
  - Increasing gastrointestinal disturbances (vomiting, diarrhoea, anorexia)
  - Visual disturbances
  - Polyuria and incontinence
  - Muscle weakness and tremor
  - Tinnitus
  - CNS disturbances (dizziness, confusion and drowsiness increasing to lack of coordination, restlessness, stupor)
  - Abnormal reflexes and myoclonus
  - Hypernatraemia
- Normal levels = 0.4 - 1.0 mmol/l (lower end for elderly)
- Toxicity occurs around ≥1.5 mmol/l

TCA's

- Amitriptyline, nortriptyline
- Overdose: anti-cholinergic (like atropine) - dried mouth, blurred vision, tachycardias, urine retention
  - CNS depressant effect - ↓ consciousness
  - Metabolic acidosis
  - Cardiac conduction problems - heart block, ↑QRS width (sinusoidal), ↑QTc
  - *Note on serotonin syndrome - only cholmipramine and imipramine have risk pf SS*
- Effects normally go when acidosis is treated - hence sodium bicarb as mainstay rx

SSRIs

- Safer in overdose versus TCAs,

- Serotonin syndrome risk - high temp, tachycardias, sweating, diarrhoea, confusion, agitation
- Reduce pre-synaptic serotonin re-uptake to ↑ serotonin amount around synapse

Nausea

- Anti-histamine - cyclizine
  - SAFE in pregnancy
  - Slightly sedating
- Phenothiazines - prochlorperazine (IM or PO ok), Chlorpromazine
  - Can cause parkinsonism features, hypotension, photosensitising rashes - ok in short term rx
- Metoclopramide
  - SAFE in pregnancy
  - Associated with EPSEs - occulogyric crises, dystonia,

Anti-psychotics

- Phenothiazines (typical anti-psychotics) - Chlorpromazine
  - Sedating, hypotension/syncope can be an issue
  - Anticholinergic, extrapyramidal SEs, photosensitivty, neuroleptic malignant syndrome
- Haloperidol
  - Calming effect, less sedating than chlorpromazine
  - Marked EPSEs, but ok short term use
  - ↑ QTc
- Atypical antipsychotics
  - Quetiapine
  - Olanzapine

Newer anti-histamines (cetirizine, loratadine) = less sedating than older (chloramphenamine) because less lipid soluble and so do not cross the BBB

ANTIBIOTICS

Bactericidal antibiotics	Bacteriostatic antibiotics
Penicillins e.g. benzylpenicillin	Macrolides e.g. erythromycin
Cephalosporins e.g. ceftriaxone	Tetracyclines e.g. doxycycline
Vancomycin	Trimethoprim
Metronidazole	Chloramphenicol
Fluoroquinolones e.g. ciprofloxacin	Clindamycin
Co-trimoxazole	Sulfonamides e.g. sulfamethoxazole

Mechanism of action	Examples
	Penicillins

Inhibition of cell wall synthesis	Cephalosporins Vancomycin
Disruption of cell membrane function	Polymyxins Nystatin Amphotericin B
Inhibition of protein synthesis	Macrolides Aminoglycosides Tetracyclines Chloramphenicol
Inhibition of nucleic acid synthesis	Quinolones Trimethoprim 5-nitroimidazoles Rifampicin
Anti-metabolic activity	Sulfonamides Isoniazid

Penicillin V

- Strep viridans, strep pyogenes
- Bactericidal - acts on cell wall
- Low oral bioavailability (60%)

Flucloxacillin

- Unique in penicillins - resistant to beta-lactamases

Amoxicillin

- Some gram -ve cover
  - But often resistance in s. pneumoniae and h. influenzae
- Better oral bioavailability (95%) versus penicillin
- Some SEs, rash in infectious mononucleosis (EBV)

Co-amoxiclav

- Amoxicillin + clavulanic acid
- Broad gram +ve and -ve action
- Beta-lactamase inhibiting effect (which normally breaks down part of penicillin ring)
- Similar range to piptaz - tazobactam = similar to clavulanic acid

Extended spectrum penicillins

- Piperacillin, ticarcillin
- Extended spectrum to Gram +ve, -ve and some anaerobes
- Synergistic effect with aminoglyocsides

Cephalosporins

- Broad spectrum, beta-lactam abx

- RELATED to penicillins, chemically similar - cross-sensitivity with penicillins (10% with true pen allergy will react)
- Strong association with c diff
- 3rd generation - Cefotaxime, ceftriaxone -
    - More activity against gram -ve organisms
    - meningitis, gonorrhoea
    - Crosses BBB
    - Ceftriaxone = longer half life versus cefotaxime

Sulphonamides

- Anti-folate - Can cause a fatal stevens johnson reaction
- Some strep, staph, e. coli, H infl
- Co-trimoxazole

Trimethoprim

- Anti-folate - *predisposes elderly and neonates to folate deficiency*
- *TERATOGENIC risk* - mainly first trimester. If must be used in 1st trimester, co-prescrive folic acid 5mg OD
- E. coli

Macrolides

- MAINLY gram -ve spectrum
- Erythromycin, clarithromycin
- Similar spectrum to penicillins. Clarithromycin slightly broader gm +ve activity
    - Mycoplasma, atypical pneumonias
    - Clarithromycin can be used for soft tissue infections
- Bind to ribosomes, inhibit protein synthesis
- SEs
    - *MOST people get GI SEs* - clarithromycin better tolerated
    - Macrolides inhibit p450 - increases bioavailability of other drugs
    - ↑ QTc, arrhythmias

Clindamycin

- Bind to ribosomes, inhibit protein synthesis
- Good for streptococci, good for soft tissue infections
- Anaerobes, gram +ve
- Strongly associated c diff

Tetracyclines

- Bind to ribosomes, inhibit protein synthesis
- Doxycycline most often used. Loading dose on first day
- SEs: teratogenic, photosensitive, can cause ↑ CSF pressure
- **Contraindicated -** children under 12 yr old and pregnant women

Aminoglycosides

- Protein synthesis inhibition
- Gram -ve, wide spectrum. NOT ABSORBED ORALLY
- Gentamicin, streptomycin
- Synergistic with penicillin
- SEs:
    - Oto and renal toxicity - need to measure levels to check toxicity
    - *CONTRAINDICATED in myasthenia gravis*

Glycopeptides

- Disrupts wall synthesis
- Vancomycin, teicoplenin - NOT ABSORBED ORALLY - but can be taken orally for c. diff (because in gut)
- Gram +ve, c diff

Nitrofurantoin

- Damages bacterial DNA
- Gram -ve, good for e coli
- NOT effective in tissues (doesn't reach high enough concentrations), so NOT FOR PYELONEPHRITIS
    - 25% of oral dose concentrated into urine
    - Just for UTI
- Antagonises quinolones, *can cause pulmonary fibrosis*

Quinolones

- Disrupts DNA
- Ciprofloxacin, ofloxacin
- Very good gram -ve, moderate gram +ve
    - Campylobacter, shigella, salmonella, neisseria, pseudomonas
    - Some effect on gram +ve e.g. strep and e. faecalis
- Good soft tissue penetration, good oral absorption
- SE: *tendon rupture,* QT prolongation, antibiotic associated colitis

Metronidazole

- Inhibition bacterial nucleic acid synthesis
- Anaerobes, protozoa, c. diff, H pylori
- NOT to have alcohol - have a disulfuram-like reaction
- Indications for metronidazole include:
    - Clostridium difficile colitis
    - Helicobacter pylori eradication (with clarithromycin/amoxicillin and PPI)
    - Bacterial vaginosis
    - Pelvic inflammatory disease (with doxycycline and ceftriaxone or ofloxacin)
    - Peritonitis (with cephalosporin or gentamicin)
    - Acute oral infections

- Tetanus
- Rosacea and acne (topical)
- Surgical prophylaxis
- Protozoal infections
    - Amoebic dysentery
    - Giardiasis
    - Trichomoniasis

Chloramphenicol

- Broad-spectrum
- Systemic use - risk of aplastic anaemia - also crosses BBB (can be used in meningitis)
- Therefore only used in eye drops now

Fusidic acid

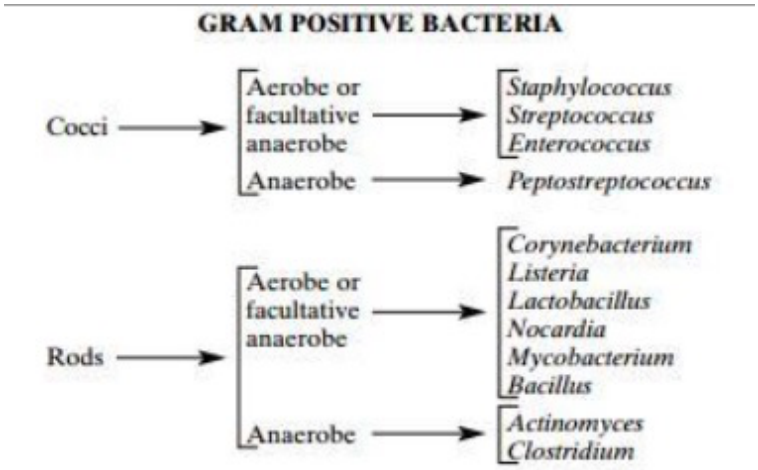
- Cream based abx
- Impetigo, infected superficial skin

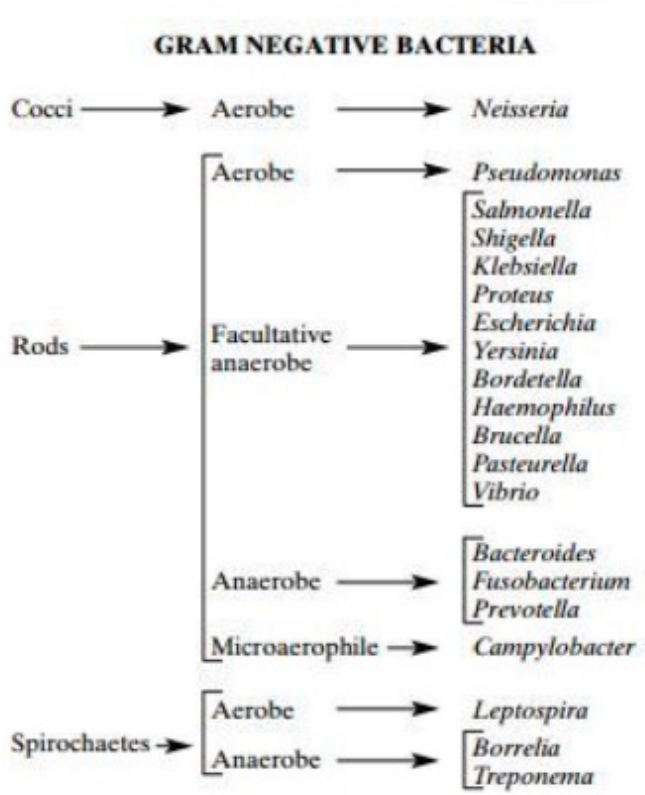
Infections

Nystatin. Local infection of candida. No systemic absorption.

Fluconazole. Systemic treatment of candida and other fungi

Acyclovir. Anti-viral, Herpes simplex and zoster. Higher dose required for zoster. Short half life. Well tolerated





Anti-malarials

- Quinine - falciparum
  - SEs: tinnitus, nausea, vertigo
- Chloroquine - vivax, ovale, and malariae

T2DM

- Sulphonylureas - gliclazide
  - Hypoglycaemia SE - long 1/2 life
  - Stimulates insulin release by pancreas
- Metformin
  - Reduces gluconeogenesis, ↑ glucose utilisation peripherally
  - SEs = lactic acidosis, loose stools
    - *NO hypoglycaemic Res*

NSAIDs

- ↓ COX-1 and COX-2 production (which converts arachidonic acid to prostaglandins)
- COX-2 = more selective for inflammation and pain
  - COX-1 will reduce the gastric lining (by reducing protective function of prostaglandins in this area)
  - COX-2 = naproxen, ibuprofen

- Diclofenac and mefanamic acid (menstrual pain) not selective
- SEs of NSAIDs
    - Cardiac risk (in COX-2), peptic ulceration, fluid retention (and HF), asthma aggravation (in 1%), acute = renal impairment and longer term = interstitial nephritis
    - NSAIDs may counteract cardio-protective benefits of aspirin

Gout

1. Indomethacin preferred choice - IS AN NSAID
2. Colchicine second line - associated with diarrhoea
3. Corticosteroids

ANAESTHESIA

Induction agents

1. Propofol
    - GABA receptor agonist
    - Fast action, short duration
    - Pain on injection, ↓ BP, bradycardia, allergic reaction, LOSS OF AIRWAY
    - Negatively ionotropic
    - Largest ↓ in BP (vasodilation, negative isotropy, ↓ preload) - dose-dependant
2. Thiopental sodium (barbituate)
    1. Smooth induction, rapid recovery because of absorption into tissues rapid
        - *Not used for maintenance of anaesthesia*
    2. Induction in around 30 seconds, slow metabolism - return to consciousness in around 10 minutes
    3. SEs: Extraneous muscular movements, respiratory depression
3. Etomidate
    1. Less commonly used now
    2. Suppressed adrenal function, AVOID in sepsis/trauma/adrenergic states. Usually need steroids alongside if given
    3. Pain on injection common
4. Ketamine
    1. Sympathetic properties - ↑ HR, BP and cardiac output
    2. Duration of action of single dose = 5-10 mins
    3. Slower onset time than other above drugs
    4. ↑ salivation, laryngospasm, and dissociative phenomena - distressing waking/emergence for some adults (mainly older)

	Propofol (1-2.5mg/kg)	Thiopentone (3-7 mg/kg)	Ketamine (1.5-2mg/kg)	Etomidate (0.25-0.3 mg/kg)

BP	↓↓	↓	↑	↔
Cardiac output	↓↓	↓	↑	↔↓
HR	↓↔	↑	↑	↔
SVR	↓	↓	↑	↔↓
ICP	↓	↓	↑	↔
IOP	↓	↓	↑	↔
Metabolism	Liver	Liver	Liver	Liver/Plasma esterases

*IOP = intraoccular pressure

Nitrous oxide

- Usually in 50/50 with O2
- Higher doses - 50-66% can induce deep anaesthesia (unconscious)
- Disinhibited, some useful amnesic effect

<u>Neuromuscular blockade</u>

1. Atracurium
    - ACh receptor blocking mechanism
    - Longer duration - rarely used in EM
2. Suxemethonium
    - Quick onset, short acting - often for intubation
    - SEs - painful muscle fasciculations at onset of action (so give anaesthetic agent prior),
    - AVOID in
        - ↑K+ or risk of ↑K+ (e.g. burns and trauma (crush injuries for example))
            - - Suxemethonium results in transient ↑ K (0.5 to 1.0 mEq/L)
        - FH of malignant neuroleptic syndrome

<u>Local anaesthesia</u>

Penetrate in a lipophilic, non-ionised form. Once in nerve axon, become ions and inhibit Na+ channels to prevent action potentials propagating pain

	Onset (min)	Duration (min)	Max dose (mg/kg)	Max volume (70kg person)
Lidocaine (1% or 2%)	20	3mg/kg	21 mls (1%)	

Lidocaine with adrenaline (1% or 2%)	90	7mg/kg	49 mls (1%)
Bupivicaine (0.25%)	240-480	2.5mg/kg	70 mls (0.25%)
Prilocaine (0.5% or 1%)	20	7mg/kg	42 mls (0.5%)

Prilocaine = IV anaesthesia

- e.g. Colle's fracture, beers block - inject into veins of forearm - BP cuff fully inflated above injection site

Toxicity

Toxic effects after administration of local anaesthetics are a result of excessively high plasma concentrations; severe toxicity usually results from inadvertent intravascular injection or too rapid injection. Following most regional anaesthetic procedures, maximum arterial plasma concentration of anaesthetic develops within about 10 to 25 minutes, so careful surveillance for toxic effects is necessary during the first 30 minutes after injection.

Local anaesthetics depress other excitable tissues producing:

- Central nervous system effects (with increasing toxic doses)
  - Sedation, lightheadedness, anxiety and restlessness
  - Twitching, tremor and visual disturbance
  - Convulsions and coma, with respiratory depression resulting from medullary depression
- Cardiovascular effects
  - Vasodilation (partly by direct action on blood vessels and partly by blocking their sympathetic nerve supply) with hypotension
  - Myocardial depression with bradycardia

Hartmann's solution contains:

- Na^+ 131 mmol/L
- K^+ 5 mmol/L
- HCO_3^- 29 mmol/L
- Cl^- 111 mmol/L
- Ca^{2+} 2 mmol/L

Normal saline (sodium chloride 0.9%) contains:

- Na^+ 150 mmol/L
- Cl^- 150 mmol/L

STATUS EPILEPTICUS

Drug	Child 1 month - 11 years	Child 12 years - 17 years	Adults
IV lorazepam	100 micrograms/kg (max. per dose 4 mg)	4 mg	4 mg
IV diazepam	300 - 400 micrograms/kg (max. per dose 10 mg)	10 mg	10 mg
Rectal diazepam	5 - 10 mg (5 mg in children < 1 years)	10 - 20 mg	10 - 20 mg (10 mg in elderly)
Buccal midazolam	• 1 - 2 months: 300 micrograms/kg (max. per dose 2.5 mg) • 3 - 11 months: 2.5 mg • 1 - 4 years: 5 mg • 5 - 9 years: 7.5 mg • 10 - 11 years: 10 mg	10 mg	10 mg

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HYPOGLYCAEMIA

Management (adults)

- In adults who are conscious, cooperative and can swallow:
  - Give 15 - 20 g quick acting carbohydrate of the patient's choice where possible e.g. 90 – 120 mL of Lucozade or 5 – 7 Dextrosol tablets
  - Repeat capillary blood glucose 10 – 15 minutes later
  - If blood glucose is still < 4.0 mmol/L, repeat step 1 (no more than 3 treatments in total)
  - If blood glucose remains < 4.0 mmol/L after 45 minutes or 3 cycles, consider:
    - 1 mg glucagon IM
    - IV 10% glucose infusion at 100ml/hr
- In adults who are conscious but uncooperative:
  - Give either 1.5 – 2 tubes Glucogel/Dextrogel (may repeat up to 3 times)
  - If this is ineffective give glucagon 1 mg IM (may only give once)
  - If blood glucose level remains less than 4.0 mmol/L after 45 minutes (or 3 cycles), consider IV 10% glucose infusion at 100ml/hr
- In adults who are unconscious:
  - Give either:
    - 1 mg glucagon intramuscularly (if not effective after 10 - 15 minutes, IV glucose should be given)
    - 75 – 80 mL of 20% glucose intravenously over 10 – 15 minutes

- 75 – 80 ml of 20% glucose intravenously over 10 - 15 minutes
- 150 – 160 ml of 10% glucose intravenously over 10 - 15 minutes

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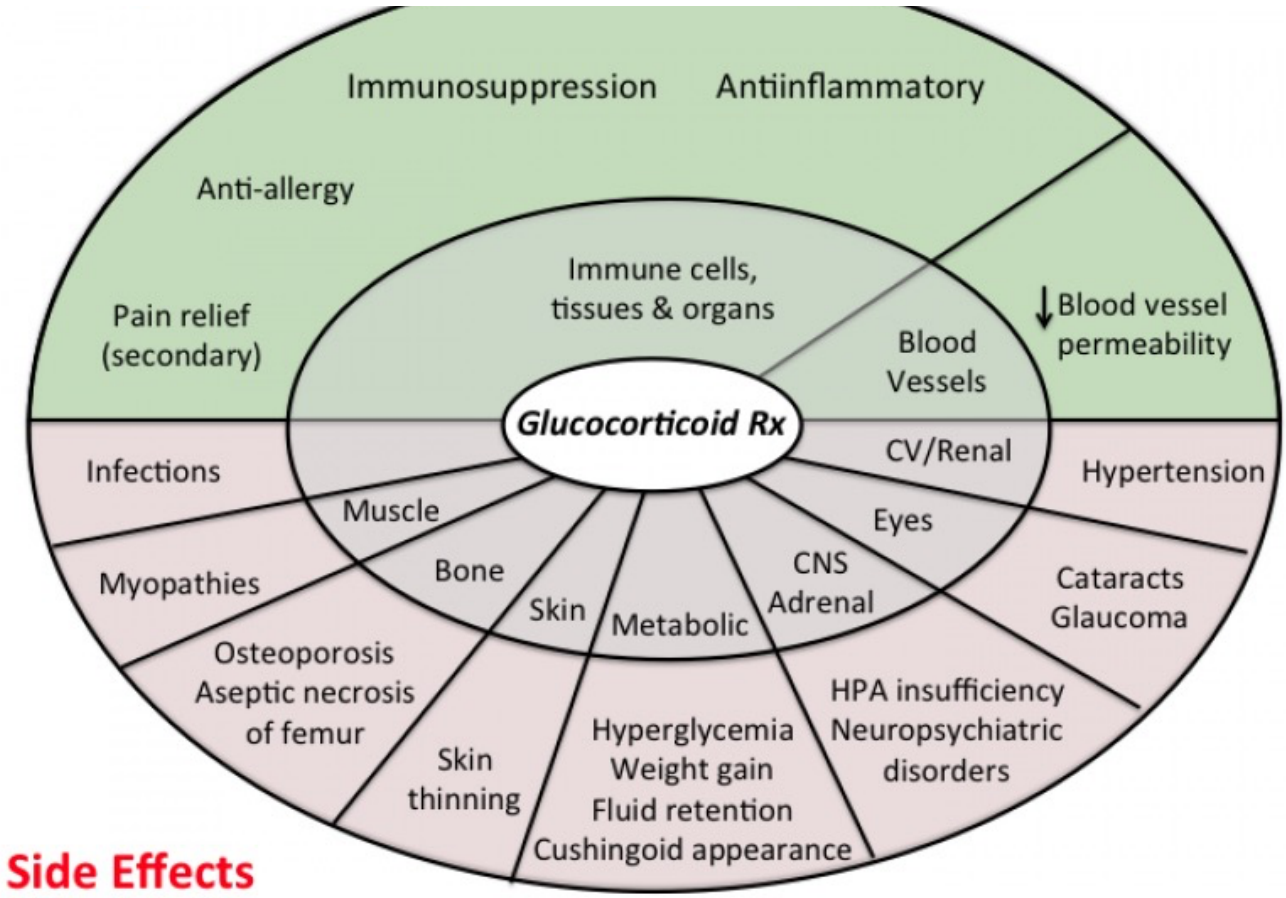
Steroids

Prednisolone 5mg ≡	Betamethasone 750micrograms
	Deflazacort 6mg
	Dexamethasone 750micrograms
	Hydrocortisone 20mg
	Methylprednisolone 4mg
	Prednisone 5mg
	Triamcinolone 4mg

- Hydrocortisone
  - Relatively high mineralocorticoid activity
- Prednisalone / prednisone
  - Predominantly glucocorticoid activity
- Dexamethasone
  - ↑ glucocorticoid, minimal mineralocorticoid
- Fludrocortisone
  - ↑↑ mineralocorticoid activity

Glucocorticoid activity = good for anti-inflammatory response
Mineralocorticoid activity = good for aldosterone like effects, (↑ na, ↓ K, ↑ fluid retention)

Agent	Relative Glucocorticoid Potency	Relative Mineralocorticoid Potency	Duration of Action
Hydrocortisone (Cortisol)	1	1	Short
Prednisolone	4–5	0.25	Short
Methylprednisolone	5–6	0.25	Short
Dexamethasone	18	<0.01	Long
Fludrocortisone	10	125	Short



Drug	Adverse effects
ACE inhibitors e.g. ramipril	If given in 2nd and 3rd trimester can cause hypoperfusion, renal failure and the oligohydramnios sequence.
Aminoglycosides e.g. gentamicin	Ototoxicity Deafness
Aspirin	High doses can cause 1st trimester abortions, delayed onset labour, premature closure of the fetal ductus arteriosus and fetal kernicterus. Low doses (e.g. 75 mg) have no significant associated risk.
Benzodiazepines e.g. diazepam	When given late in pregnancy respiratory depression and a neonatal withdrawal syndrome can occur.
Calcium-channel blockers	If given in 1st trimester can cause phalangeal abnormalities. If given in the 2nd and 3rd trimester can cause fetal growth retardation.
Carbemazepine	Haemorrhagic disease of the newborn Neural tube defects
Chloramphenicol	Grey baby syndrome
Corticosteroids	If given in the 1st trimester may cause orofacial clefts
Danazol	If given in the 1st trimester can cause masculinisation of female fetus's genitals.

Finasteride	Finasteride should not be even handled by a pregnant woman. Crushed or broken tablets can be absorbed through the skin and can affect male sex organ development.
Haloperidol	If given in the 1st trimester may cause limb malformations. If given in the 3rd trimester increased risk of extrapyramidal symptoms in neonate.
Heparin	Maternal bleeding Thrombocytopaenia
Isoniazid	Maternal liver damage. Neuropathy and seizures in the neonate.
Isotretinoin	High risk of teratogenicity (e.g. multiple congenital malformations, spontaneous abortion, and intellectual disability.
Lithium	If given in 1st trimester risk of fetal cardiac malformations. If given in 2nd and 3rd trimesters risk of hypotonia, lethargy, feeding problems, hypothyroidism, goitre and nephrogenic diabetes insipidus in neonate.
Metformin	Risk of neonatal hypoglycaemia.
Methadone	Risk of neonatal opioid withdrawal syndrome.
Methotrexate	Risk of numerous congenital malformations e.g. fetal growth retardation, mandibular hypoplasia, cleft palate, spinal defects, ear defects and club foot.
Misoprostol	Can cause miscarriage.
NSAIDS e.g. ibuprofen	If given in 1st trimester can cause miscarriage, delayed onset labour, premature closure of the fetal ductus arteriosus and fetal kernicterus.
Oestrodial	Increased risk of urogenital abnormalities.
Phenobarbitone	Haemorrhagic disease of the newborn. Some risk of congenital malformation.
Phenytoin	Haemorrhagic disease of the newborn. Risk of congenital malformations e.g. cleft lip, hypospadias and cardiovascular defects.
Sodium valproate	Risk of major congenital malformations e.g. neural tube, cardiac, craniofacial and limb defects.
SSRIs e.g. sertraline, fluoxetine	If given in 3rd trimester is associated with discontinuation syndrome and persistent pulmonary hypertension of the newborn.
Statins e.g. simvastatin, atorvastatin	Cholesterol is required for fetal growth and its reduction by statins may affect fetal development.
Tetracycline	Slowed bone growth, enamel hypoplasia, permanent yellowing of teeth and increased susceptibility to cavities in offspring. Occasionally causes liver failure in pregnant women.
Trimethoprim	If given in 1st trimester increased risk of neural tube defects due to folate antagonism.