

Third edition

Notes & Notes

For MRCP part 1 & 11

By

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Pharmacology

**Updated
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Basic pharmacology

Pharmacokinetics: metabolism

Drug metabolism

- phase I: oxidation, reduction, hydrolysis
- phase II: conjugation
- Drug metabolism usually involves two types of biochemical reactions - phase I and phase II reactions.
- The majority of phase I and phase II reactions take place in the liver
- **Phase I reactions:** oxidation, reduction, hydrolysis.
 - ⇒ Mainly performed by the P450 enzymes but some drugs are metabolised by specific enzymes, for example alcohol dehydrogenase and xanthine oxidase.
 - ⇒ Products of phase I reactions are typically more active and potentially toxic
- **Phase II reactions:** conjugation.
 - ⇒ Products are typically inactive and excreted in urine or bile.
 - ⇒ Glucuronyl, acetyl, methyl, sulphate and other groups are typically involved

In the elderly population, phase I reactions will usually become impaired before phase II reactions.

Drug absorption

- Diffusion.
 - ⇒ **Most drug absorption** in the gastrointestinal tract occurs **by diffusion**.
 - ⇒ For diffusion to occur:
 - the drug must be dissolved so that individual drug molecules come into contact with the gut epithelium,
 - **the drug must be lipid soluble so that it can cross the cell membrane.**
 - ☞ Because the cell membrane is lipoid, lipid-soluble drugs diffuse most rapidly.
 - ☞ **Drugs that are not ionized are lipid soluble and most likely to be well absorbed from the gastrointestinal tract.**
 - 📖 The ionized form has low lipid solubility (but high water solubility—ie, hydrophilic) and high electrical resistance and thus cannot penetrate cell membranes easily.
 - Theoretically, **weakly acidic drugs (eg, aspirin)** are more readily absorbed from an **acid medium (stomach)** than are weakly basic drugs (eg, quinidine). However, whether a drug is acidic or basic, most absorption occurs in the small intestine because the surface area is larger and membranes are more permeable

Lipid soluble drug vs lipid insoluble drug

lipid soluble drug	lipid insoluble drug
have good gastrointestinal absorption	have poor gastrointestinal absorption
can be given orally	may need to be given parenterally
will be widely distributed in the body (large volume of distribution)	has limited distribution (may not cross blood-brain barrier or placenta and less likely to be stored in fat tissue)
usually requires metabolism before elimination (to decrease lipid solubility)	may be eliminated without metabolism
often have a long plasma half-life (prolonged by 'reservoir' of drug in tissues and by requirement for metabolism).	often have a short plasma half-life as elimination does not require metabolism.

MRCPUK-part-1-Sep 2017: What is the mechanism that make salmeterol acts as a LABA?
 → Its long duration results from its **high lipid solubility**

Lipophilic, Hydrophilic and Amphiphilic

	Chemical nature	Clinical significance	Example
Lipophilic	<ul style="list-style-type: none"> Predominantly nonpolar compounds 	<ul style="list-style-type: none"> can easily diffuse across the lipid bilayer of the cell membrane. <ul style="list-style-type: none"> can be administered topically can across the blood-brain barrier Metabolised in the liver and then excreted through the bile duct 	<ul style="list-style-type: none"> Scopolamine (hyoscine) <ul style="list-style-type: none"> Tertiary amine Used to treat motion sickness
Hydrophilic	<ul style="list-style-type: none"> Predominantly polar compounds 	<ul style="list-style-type: none"> can only cross the lipid bilayer via facilitated transport Smaller hydrophilic molecules can diffuse along a concentration gradient through pores in the membrane eliminated by the kidneys 	<ul style="list-style-type: none"> Butylscopolamine (hyoscine butylbromide) <ul style="list-style-type: none"> Quaternary amine Used as an antispasmodic to treat GI colic
Amphiphilic	<ul style="list-style-type: none"> Both lipophilic and hydrophilic 		Local anesthetics, e.g., lidocaine

Drug metabolism in patients with advanced liver disease

- Plasma proteins fall in liver disease and may negatively affect drug **distribution**
- Both intrahepatic and extrahepatic cholestasis may affect the **metabolism** of drugs that are actively secreted into bile, eg ciprofloxacin
- Conjugation reactions are affected to a lesser extent by advanced liver disease and only occur in very late stage disease**

Pharmacokinetics in chronic renal failure

- Renal failure disturbs virtually every kinetic parameter including:
 - gastric absorption
 - hepatic metabolism of some drugs
 - protein binding
 - volume of distribution

- The bioavailability of an intravenously administered drug is 100% and does not change in renal failure

What is the reason for phenytoin toxicity in patient with chronic renal failure?

→ Decreased protein binding of phenytoin

- In CRF, drugs lose some of their affinity for protein binding → ↑ availability of free drug at any given dose → toxicity
- Because laboratory assays for **phenytoin** usually measure total drug concentration, this give a false re-assurance (**drug level may be within therapeutic range**)
- In CRF dose reduction of phenytoin is therefore required
- Other drugs may cause same problem → **sodium valporate** and **warfarin**

First-pass metabolism

- This is a phenomenon where the concentration of a drug is greatly reduced before it reaches the systemic circulation due to hepatic metabolism.
⇒ As a consequence much larger doses are need orally than if given by other routes.
- This effect is seen in many drugs, including:**

- | | |
|---|---|
| ⇒ Aspirin
⇒ isosorbide dinitrate
⇒ glyceryl trinitrate
⇒ lignocaine
⇒ propranolol | ⇒ verapamil
⇒ isoprenaline
⇒ testosterone
⇒ hydrocortisone
⇒ morphine |
|---|---|

- Drugs with high first-pass metabolism should be used with caution in liver disease,** since poor hepatic function may lead to their accumulation because of increased bioavailability

What is the reason for a different dose of sublingual glyceryl trinitrate (GTN) and oral isosorbide mononitrate?

⇒ **First-pass metabolism**

Drug kinetics (first order + zero order kinetics)

- In drugs which have saturation kinetics → initially Small doses of the drug lead to a linear increase in serum drug concentration (follow a linear line) → **first order kinetics**
- Then their metabolism slows down leading to a plateau of the line, for example due to enzyme depletion. Small doses in the drug then lead to large increases in plasma concentration → **zero order kinetics**.
- Types of drug kinetics**
 - ⇒ **Zero order kinetics:**
 - The rate of metabolism and/or elimination remains constant and is independent of the plasma concentration of a drug at steady state (C_p decreases linearly over time)
 - Zero-order is a capacity-limited elimination.
 - Examples include**
 - ethanol
 - phenytoin
 - aspirin (at high concentrations)
 - heparin
 - ⇒ **First order kinetics:**
 - The rate of metabolism and/or elimination is directly proportional to the plasma concentration of the drug (C_p decreases exponentially over time)
 - First-order is a flow-dependent elimination.
 - Applies to most drugs

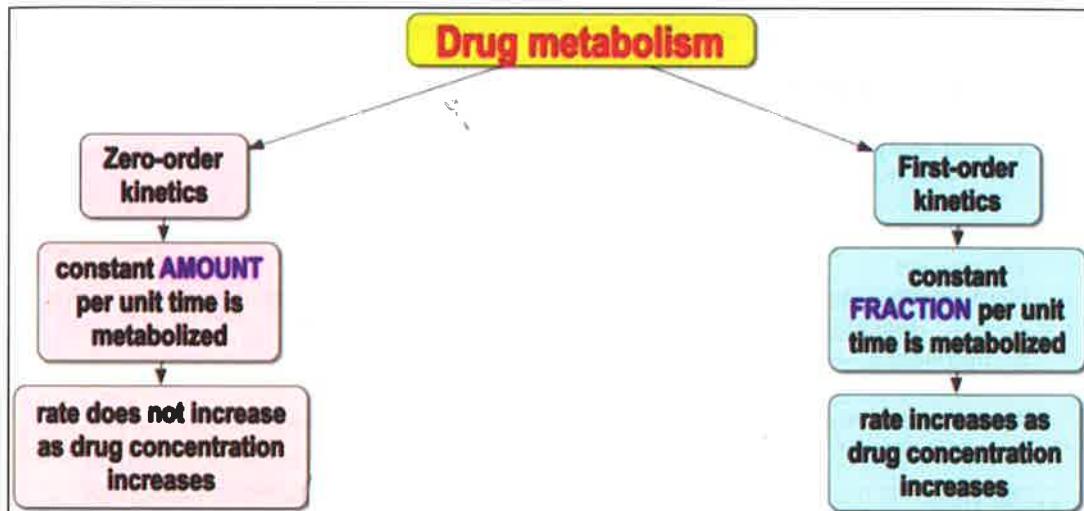
Zero-order kinetics

Zero-order (saturation) kinetics

- phenytoin
- alcohol
- Zero-order kinetics describes: metabolic pathways becoming saturated resulting in **constant amount of drug being eliminated per unit time** (metabolism which is independent of the concentration of the reactant).
- This explains why people may fail a breathalyser test in the morning if they have been drinking the night before
- Drugs following zero order kinetics continue to be metabolised at a steady rate, independent of the concentration of the substrate.
- **The plot of metabolism against time is linear.**

Drugs exhibiting zero-order kinetics

- Phenytoin
- Salicylates (e.g. high-dose aspirin)
- Heparin
- Ethanol



FIRST ORDER & ZERO ORDER KINETICS

Plasma Drug Concentration

First order

Time

Plasma Drug Concentration

Zero order

Time

- Constant fraction of drug eliminated per unit time
- Rate of drug elimination proportional to drug plasma concentration
- Constant amount of drug eliminated per unit time
- Rate of drug elimination independent of drug plasma concentration

Acetylator status

- 50% of the UK population are deficient in hepatic N-acetyltransferase
- Greater than 60% of Japanese are recognised to be fast acetylators
- Approximately 50% of black and Caucasian people are 'slow acetylators' and the rest are 'rapid acetylators'.
- The majority of Eskimos and Orientals are 'rapid acetylators'.
- **Slow acetylation** → ↑drug concentrations → ↑toxicity from drugs adverse effects.
- **Fast acetylation:**
 - ⇒ ↓↓response to the drug effect
 - ⇒ ↑↑ blood levels of the toxic metabolite

Drugs affected by acetylator status (slow acetylators → increased unwanted effects)

1. isoniazid
 - ⇒ **Slow acetylation** → ↑↑ drug concentrations → (peripheral neuropathy and toxic hepatitis)
2. hydralazine → drug-induced lupus
3. dapsone → haemolysis and neuropathy but not fibrosis
4. **sulfasalazine** → **haemolysis**
5. procainamide

Half-life

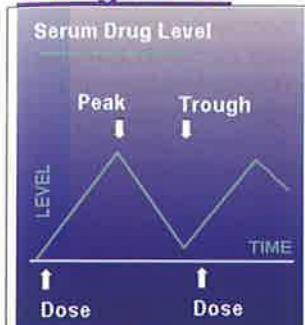
↑↑ lipid solubility → ↑↑ tissue binding of the drug → ↓↓ renal and hepatic clearance rate
 → ↑↑ half life

- The half-life is the time taken for the concentration of a drug to reduce by 50%
- Plasma half-life is the most important pharmacokinetic factor in determining the appropriate timing between doses
- The half-lives are related to:
 1. lipid solubility (amiodarone, fluoxetine and diazepam are very lipid-soluble)
 2. the rate of drug clearance

- **Steady state:** Drug concentration stays constant because the rate of drug elimination equals the rate of drug administration
- It takes 1 half-life to reach 50% of the steady-state level, 2 half-lives to reach 25%, 3 half-lives to reach 12.5%, and 4 half-lives to reach 6.25%.
- Complete steady-state attainment takes 4–5 half-lives for drugs infused at a constant rate; 90% of steady-state level is reached after 3.3 half-lives
- **Amiodarone the longest half-life = 25 days**, fluoxetine 53 h; diazepam 43 h; gentamicin 2-3 h; and bumetanide 0.8 h

After 4 half-lives, more than 90% of the drug is eliminated

Trough level



- The **lowest concentration** reached by a drug **before the next dose** is administered, often used in therapeutic drug monitoring.
- **Half-life** is the major determinant of trough concentration.
- A peak is the highest level of a medication in the blood, while a trough level indicates the lowest concentration.

Affinity & efficacy

Drug affinity

- a measure of the tendency of a drug to bind to its receptor

Drug efficacy

- the maximum degree to which a drug activates receptors after binding and triggers a cell response

Potency

- The potency of a drug is measured as the concentration required to produce a pharmacological response of a specified intensity.
- Not related to efficacy (drugs with a high potency can have a low efficacy) but dependent on affinity

Therapeutic index

- a measurement of the safety of a drug
- The greater the therapeutic index, the safer the drug
- Drugs with a narrow therapeutic index require monitoring (e.g., lithium, theophylline, warfarin, digoxin, and antiepileptic drugs).

Dosage intervals

Loading dose

Why is a loading dose used in amiodarone? Because Amiodarone is widely bound in body tissues

- **Definition:** the amount of an initial dose of a certain drug needed to reach a target plasma concentration
- **Formula: loading dose = $(C_p \times V_d) / F$**
 - ⇒ C_p = target peak plasma concentration at steady state (mg/L or units/L)
 - ⇒ V_d = volume of distribution (L/kg)
 - ⇒ F = bioavailability
- **In patients with renal and/or liver dysfunction, loading dose (which does not depend on drug clearance) and time to steady-state are usually unaffected.**
- Tissue-binding sites must be 'filled up' by a loading dose before a therapeutic plasma concentration can be achieved.
- Metabolism/elimination/clearance rates and plasma half-life determine the time taken to achieve a steady-state plasma concentration and the level of that steady-state concentration when a steady dosing regimen is established.
- **The loading dose is mainly dependent on the volume of distribution of a drug but in patient with moderate renal failure it depends on renal clearance.**
- Volume of distribution becomes important particularly when body weight is 40 kg or less.
- **What is the main factor that determines the choice of loading dose of digoxin in patient with high creatinine?**
 - Renal clearance
 - Digoxin is cleared by the kidneys, so the maintenance dose would require adjustment in renal failure.
 - **In digoxin both the initial loading dose and the maintenance dose must be reduced in patients with underlying renal disease.**
- Most useful for drugs which have a long half-life such as:
 - ⇒ Amiodarone
 - ⇒ Digoxin
 - ⇒ Teicoplanin
 - antibiotic → inhibit bacterial cell wall synthesis.
 - spectrum of activity similar to vancomycin → against Gram-positive bacteria including *Staphylococci* and *Clostridium* spp. Oral teicoplanin is effective in the treatment of pseudomembranous colitis
 - ⇒ Voriconazole
 - ⇒ Procainamide
 - ⇒ Fulvestrant (selective estrogen receptor degrader (SERD). used to treat hormone receptor (HR)-positive metastatic breast cancer)

Renal or liver conditions lower the maintenance dose without affecting the loading dose.

The main factor influencing the time to steady-state is Half-life ($t_{1/2}$), not dose or administration frequency.

Maintenance dose

- **Definition:** The amount of a certain drug needed to achieve a steady target plasma concentration.
- **Formula:** maintenance dose = $(C_p \times Cl \times \tau) / F$
 - ⇒ C_p = target plasma concentration at steady state (mg/L)
 - ⇒ Cl = clearance (L/h)
 - ⇒ τ = dosing interval (hours)
 - ⇒ F = bioavailability
- In patients with renal and/or liver dysfunction, maintenance dose is decreased (because of impaired drug clearance) and time to steady-state is unchanged (time to steady state depends on $t_{1/2}$).

Loading dose vs maintenance dose:

- **Loading doses** usually do not need to be adjusted in patients with chronic kidney disease, but **maintenance doses** should be adjusted by: dose reduction, lengthening the dosing interval, or both.
- in renal or liver disease, dosage of the same drug when given as **maintenance dose** is decreased and when it is given as **loading dose** is usually unchanged.

Clinical trial: phases

Clinical trials are commonly classified into 4 phases;

Phase	Goal	Notes
I	Determines pharmacokinetics and pharmacodynamics and side-effects prior to larger studies	Conducted on healthy volunteers
II	Assess efficacy + dosage	Involves small number of patients affected by particular disease May be subdivided into: <ul style="list-style-type: none"> • IIa - assesses optimal dosing • IIb - assesses efficacy
III	Assess effectiveness	Typically involves 100-1000's of people, often as part of a randomised controlled trial, comparing new treatment with established treatments
IV	Postmarketing surveillance	Monitors for long-term effectiveness and side-effects

How many patients would need to be recruited to detect one adverse event?

- Roughly speaking, to detect one adverse event in a clinical trial you would need to enrol **three times** as many patients as the expected event frequency
- **So if the frequency expected was 1 in 10 000, then you would need to recruit 30 000 patients**

Prodrugs

Definition

- A drug that, on administration, must undergo chemical conversion by metabolic processes before becoming an active pharmacological agent; (a precursor of a drug).

Prodrug	Active form	Note
Levodopa	Dopamine	converted by dopa decarboxylase to dopamine in the brain (in the striatum).
Enalapril	Enalaprilat	
S-methyldopa	Alpha methylnorepinephrine	It is converted to α -methylnorepinephrine by dopamine beta-hydroxylase → activation of α_2 adrenergic receptors in the brainstem → ↓ sympathetic output → ↓ BP.
Loratadine	desloratadine	non-sedating antihistamine
Terfenadine	fexofenadine	<ul style="list-style-type: none"> non-sedating antihistamine Terfenadine, withdrawn from the market because of serious side effect. fexofenadine, is safe, does not carry the same risks as the parent compound.
salicin	salicylic acid	salicin is a β -D-glucopyranoside that is cleaved by esterases to release salicylic acid.
codeine and morphine	(morphine-glucuronides)	codeine and morphine is enzymatically activated to form sugar derivatives (morphine-glucuronides) that are more active than the parent compound
Mercaptopurine	Methymercaptopurine ribonucleotide	
Fluouracil	Fluororidine monophosphate	
Cyclophosphamide	Aldophosphamide, Phosphormamide mustard	
Sulfasalazine	5-Aminosalicylic acid	
Becampicillin	Ampicillin	
Prednisone	Prednisolone	
Proguanil	Proguanil triazine	Antimalarial is an inhibitor of dihydrofolate reductase
Hydrazide MAO inhibitors	Hydrazine derivatives	
Dipivefrine	Epinephrine	used to treat open-angle glaucoma

P450 enzyme system

3 "O" antibiotics inhibitOrs → isOniazid , ciprOfloxacin , erythrOMycin

1 "C " antibiotic induCer → rifampiCine

Induction usually requires prolonged exposure to the inducing drug, as opposed to P450 inhibitors, where effects are often seen rapidly

Inhibitors of the P450 system include

Isoniazid inhibits the P450 system

- antibiotics: ciprofloxacin, erythromycin
- isoniazid
- cimetidine, omeprazole
- **amiodarone**
- allopurinol
- imidazoles: ketoconazole, fluconazole
- SSRIs: fluoxetine, sertraline
- sulphonamides
- Disulfiram
- ritonavir
- **sodium valproate**
- acute alcohol intake
- quinupristin

Inducers of the P450 system include:

- antiepileptics: phenytoin, carbamazepine
- barbiturates: phenobarbitone
- rifampicin
- St John's Wort
- chronic alcohol intake
- griseofulvin
- smoking (affects CYP1A2, reason why smokers require more aminophylline)

Carbamazepine is an inducer of the P450 system. This in turn increases the metabolism of carbamazepine itself - auto- induction

P450 drug interactions: more detail

the most important and common reason for drug interactions is the P450 **CYP3A4 system**.
The table below shows the main enzyme systems that are affected by common drugs.

P450 system	Substrates	Inhibitors	Inducers
CYP3A4	Macrolides Antiretrovirals Calcium channel blockers simvastatin	Macrolides Protease inhibitors (including ritonavir) Imidazoles grapefruit juice	Carbamazepine Phenytoin Phenobarbitone Rifampicin St John's Wort
CYP2D6	Tricyclic antidepressants Antipsychotics	SSRIs Ritonavir	
CYP2C9	Warfarin Sulfonylureas	Imidazoles Amiodarone Sodium valproate	Rifampicin
CYP1A2	Theophylline	Ciprofloxacin	Smoking Omeprazole
CYP2E1	Alcohol		Chronic alcohol Isoniazid

Interestingly, **codeine** and **dihydrocodeine** are metabolised by cytochrome **P450 2D6** to morphine, which provides the analgesic effect; therefore, those patients who are CYP-2D6 poor metabolisers will have a reduced analgesic effect with codeine or Dihydrocodeine

CYP-2C8	CYP-2C18/19	CYP-2D6
Omeprazole	Diazepam	Tricyclic antidepressants
Diazepam	Tricyclic antidepressants	β -blockers
Barbiturates	Omeprazole	Dihydrocodeine
	Proguanil	Ecstasy (MDMA)
		Selective serotonin reuptake inhibitors

Drug interactions with cytochrome P450

- Drug interactions with the cytochrome P450 system are only clinically significant for drugs that have a narrow therapeutic index (ie small changes in plasma concentrations lead to the drug concentration being either sub-therapeutic or toxic)
- Examples of these drugs include:
 - ⇒ **Ciclosporin**
 - ⇒ warfarin
 - ⇒ theophylline and
 - ⇒ phenytoin
- Lithium has a narrow therapeutic index owing to changes in absorption and excretion and does not interact with cytochrome P450

Drugs required therapeutic monitoring

Antiepileptics <ul style="list-style-type: none"> • Carbamazepine • Phenobarbital • Phenytoin • Valproic Acid 	Antiarrhythmics <ul style="list-style-type: none"> • Digitoxin • Digoxin • Lidocaine • NAPA • Procainamide 	Antibiotics <ul style="list-style-type: none"> • Gentamicin • Tobramycin • Vancomycin
Immunosuppressants <ul style="list-style-type: none"> • Cyclosporine • Mycophenolic Acid • Sirolimus • Tacrolimus 	Antimanics <ul style="list-style-type: none"> • Lithium 	Bronchodilators <ul style="list-style-type: none"> • Theophylline

Drug induced manifestations

Drug causes gingival hyperplasia

Gingival hyperplasia: phenytoin, ciclosporin, calcium channel blockers and AML

Drug causes of gingival hyperplasia

- phenytoin
- Ciclosporin
- **calcium channel blockers** (especially nifedipine)

Other causes of gingival hyperplasia include

- acute myeloid leukaemia (myelomonocytic and monocytic types)

Drugs causing photosensitivity

- thiazides
- tetracyclines, sulphonamides, ciprofloxacin
- amiodarone
- NSAIDs e.g. piroxicam
- psoralens
- sulphonylureas

Drugs causing specific skin reactions

- **Psoriatic-type reactions are most commonly caused by beta-blockers**
- Antibiotics may cause lupus-type reactions, erythema multiforme, Stevens–Johnson syndrome and erythroderma
- Warfarin is associated with alopecia, as are cytotoxic agents and antithyroid agents
- Phenytoin may cause both acne and gingival hyperplasia

Drug affects folic acid metabolism

Drugs which inhibit dihydrofolate reductase are:

- Methotrexate
- **Pyrimethamine**, and
- Trimethoprim.

Drugs which interfere with absorption/storage of folate are:

- Phenytoin
- Primidone, and
- Oral contraceptives.

Drug causes SIADH

most commonly causes SIADH	Other causes
<ul style="list-style-type: none"> • Thiazide diuretics • Vincristine • Vinblastine • Cyclophosphamide 	<ul style="list-style-type: none"> • Chlorpropamide • Carbamazepine • Phenothiazines • Tricyclic antidepressants • Clofibrate • Oxytocin • Vasopressin • Morphine • Barbiturates • Nicotine

Drug causes of urticaria

The following drugs commonly cause urticaria:

- **aspirin**
- penicillins
- NSAIDs
- opiates

Drugs induced galactorrhoea

Drug causes of raised prolactin

- **metoclopramide**, Domperidone
 - ⇒ Domperidone is a dopamine antagonist producing large rises in prolactin concentrations.
- phenothiazines
- haloperidol
- Cimetidine produces hyperprolactinaemia **only** when given intravenously (IV).
- very rare: SSRIs, opioids

Drugs associated with gynaecomastia

- **Spironolactone** (the most common), causes gynaecomastia by several mechanisms.
 - ⇒ block androgen production by inhibiting enzymes in the testosterone synthetic pathway,
 - ⇒ block receptor binding of **testosterone** and dihydrotestosterone.
 - ⇒ **increases free oestrogen levels** by displace oestradiol from sex hormone binding globulin (SHBG)

Other causes

- | | |
|---|--|
| <ul style="list-style-type: none"> inhibitors of testosterone synthesis: <ul style="list-style-type: none"> ⇒ ketoconazole ⇒ metronidazole ⇒ cimetidine, Omeprazole ⇒ etomidate, and ⇒ cisplatin. Oestrogens: <ul style="list-style-type: none"> ⇒ Digoxin → direct action at oestrogen receptors. LHRH analogues Finasteride. | <ul style="list-style-type: none"> marijuana heroin isoniazid Ciclosporin calcium-channel blockers ACE inhibitors tricyclic antidepressants busulphan diazepam |
|---|--|

Drug-induced impaired glucose tolerance

- Drugs which are known to cause impaired glucose tolerance include:
 - ⇒ thiazides, furosemide (less common)
 - ⇒ steroids
 - ⇒ tacrolimus, ciclosporin
 - ⇒ interferon-alpha
 - ⇒ nicotinic acid
 - ⇒ atypical antipsychotics e.g. olanzapine
- Beta-blockers an glycemic status:
 - ⇒ beta -2-adrenergic antagonism → inhibition of hepatic gluconeogenesis
 - **unselective beta-blockade associated with hypoglycemia** (e.g. **propranolol** rather than the use of beta-1 selective blockers e.g. atenolol, metoprolol).
 - **selective beta-1 blockers** would not lead to hypoglycaemia - however "...in patients with abnormal energy requirements or metabolism, administration of beta 1-selective-adrenergic antagonists may be associated with hypoglycaemia
 - ⇒ Beta-blockers cause a slight impairment of glucose tolerance.
 - ⇒ They should also be used with caution in diabetics as they can interfere with the metabolic and autonomic responses to hypoglycaemia

Drug-induced lupus erythematosus

The most commonly associated drugs

- procainamide
- hydralazine 2,
- anti-TNF alpha agents,
- statins
- isoniazid
- minocycline.**

Drug-induced Pancytopenia

Trimethoprim may cause pancytopenia

Drug causes of Pancytopenia

- cytotoxics
- antibiotics: **trimethoprim**, chloramphenicol
- anti-rheumatoid: gold, penicillamine
- carbimazole (causes both agranulocytosis and pancytopenia)
- anti-epileptics: carbamazepine
- sulphonylureas: tolbutamide
- Although both **azathioprine** and **mesalazine** cause pancytopenia, it is **more commonly seen in patients undergoing azathioprine therapy.**

Drug-induced thrombocytopenia

Drug-induced thrombocytopenia (probable immune mediated)

- quinine
- abciximab
- NSAIDS
- diuretics: furosemide
- antibiotics: penicillins, sulphonamides, rifampicin
- anticonvulsants: carbamazepine, valproate
- heparin

Sulfa drugs

- Hypersensitivity reactions to sulfa medications are common and are usually limited to pruritic rashes.
- An acronym for remembering sulfa drugs is Popular FACTSSS:
 - ⇒ Probencid,
 - ⇒ **Furosemide**,
 - ⇒ Acetazolamide,
 - ⇒ Celecoxib,
 - ⇒ Thiazides,
 - ⇒ Sulfonamide antibiotics,
 - ⇒ Sulfasalazine,
 - ⇒ Sulfonylureas.
- **Furosemide**
 - ⇒ Most loop diuretic, such as furosemide are sulfa-containing drugs,
 - ⇒ sulfa-containing drugs can cause interstitial nephritis.
 - **Interstitial is the site of furosemide toxicity.**
 - For these patients, **ethacrynic acid** can be used instead, because it does not contain a sulfa group.

Disulfiram

Action

- Alcohol antagonist drug used to treat chronic alcoholism
- Ethanol is metabolized by two enzymes:
 - Alcohol dehydrogenase, which is located in the cytosol, converts ethanol to acetaldehyde.
 - Aldehyde dehydrogenase, which is located in the mitochondria**, converts acetaldehyde to acetyl CoA. Both enzymes require NAD⁺ for function.
- Disulfiram is an inhibitor of aldehyde dehydrogenase** and causes accumulation of acetaldehyde, leading to severe nausea and vomiting if alcohol is consumed.

Disulfiram reaction

- The elevations in serum acetaldehyde levels cause the **symptoms of disulfiram reaction** which include:
 - flushing,
 - headache,
 - nausea, vomiting
 - sweating
 - blurred vision,
 - dyspnea,
 - palpitations, hypotension, chest pain and syncope.
- avoid all alcohol-containing products (e.g., cough and cold syrups, mouthwash, or foods containing alcohol) while taking this medication.
- Disulfiram typically causes an acute hepatitis like syndrome 2 to 12 weeks after starting the medication** that can be severe and lead to acute liver failure or need for liver transplantation.

Disulfiram → inhibitor of Aldehyde dehydrogenase, which is located in the mitochondria

Fomepizole → inhibitor of Alcohol dehydrogenase, which is located in the cytosol

The target of disulfiram is located in which cellular compartments?

⇒ Mitochondria

Drug-induced ethanol intolerance (disulfiram-like reaction)

- As in the case with disulfiram, the underlying mechanism is believed to be the accumulation of acetaldehyde in the blood, due to inhibition of the hepatic aldehyde dehydrogenases.
- drugs which can produce DISULFIRAM like reaction when taken with Alcohol:
 - chloramphenicol,
 - furazolidone,
 - nitroimidazole antibiotics, including metronidazole**, and
 - quinacrine,
 - First-generation sulfonylureas, e.g. tolbutamide and chlorpropamide
 - cephalosporins, including cefoperazone, céfamandole and cefotetan
 - antifungal eg: Griseofulvin
 - Procarbazine

Drug-induced long QT

Commonly medications that cause QT prolongation		
class	Examples	
Antiarrhythmic	<ul style="list-style-type: none"> • Amiodarone • Disopyramide • Ibutilide 	<ul style="list-style-type: none"> • Procainamide • Quinidine • Sotalol
antipsychotics	<ul style="list-style-type: none"> • Chlorpromazine • Clozapine • Haloperidol 	<ul style="list-style-type: none"> • Quetiapine • Risperidone • Thioridazine
antibiotics	<ul style="list-style-type: none"> • Azithromycin • Clarithromycin • Erythromycin • Ciprofloxacin • Levofloxacin 	<ul style="list-style-type: none"> • Ofloxacin • Trimethoprim – sulpha • Ketoconazole • Fluconazole • Itraconazole
Antidepressants	<ul style="list-style-type: none"> • Amitriptyline • Citalopram • Desipramine • Doxepin • fluoxetine 	<ul style="list-style-type: none"> • Imipramine • Nortriptyline • Paroxetine • Sertraline • venlafaxine
Antiemetics	<ul style="list-style-type: none"> • Ondansetron 	<ul style="list-style-type: none"> • prochlorperazine

Drugs causing ocular problems

Visual disturbance	cataract	Corneal opacities	Optic neuritis	Retinopathy	Blue tinge in vision	Yellow-green tinge
Drug	steroids	Amiodarone Indomethacin	Ethambutol Amiodarone Metronidazole	Chloroquine, quinine	Sildenafil	Digoxin

Visual changes secondary to drugs

- blue vision: Viagra ('the blue pill')
- yellow-green vision: digoxin

Sildenafil can cause both blue discolouration and non-arteritic anterior ischaemic neuropathy

Drug induced photosensitivity

Rash on the forearms and face is typical of a photosensitivity rash

- Thiazides
- Tetracyclines, sulphonamides, ciprofloxacin
- Amiodarone
- NSAIDs e.g. Piroxicam
- Psoralens
- Sulphonylureas

Mnemonic: **FAST-N** (Fluoroquinolones eg: cipro. **A**miodarone. **S**ulfo. **T**etracyclines. **N**SAIDs)

Drug induced ototoxicity

- Causes
 - ⇒ Aminoglycosides
 - Streptomycin → irreversible cochlear and vestibular dysfunction
 - ⇒ Platinum-based antineoplastic agents,
 - ⇒ Salicylates
 - ⇒ Quinine
 - ⇒ Loop diuretics.
- Ototoxicity is typically associated with bilateral high-frequency sensorineural hearing loss and tinnitus.
- The time of onset is unpredictable:
 - ⇒ marked hearing loss can occur even after a single dose.
 - ⇒ may occur several weeks or months after completion of antibiotic or antineoplastic therapy.
- Usually irreversible with most agents.

Drug induced seizures

- Drugs that cause seizures as a drug reaction include:
 - ⇒ Isoniazid (vitamin B6 deficiency)
 - ⇒ Bupropion,
 - ⇒ Imipenem/cilastatin
 - ⇒ Tramadol
 - ⇒ Enflurane

Isoniazid, Bupropion, Imipenem/cilastatin, Tramadol, Enflurane.

With seizures, I BITE my tongue.

Drug causes erythema multiforme, and the Stevens-Johnson syndrome subtype.

- **Allopurinol** → (the Most commonly associated)
- Recent drugs - nevirapine, lamotrigine, sertraline, pantoprazole, tramadol
- Antibiotics - sulphonamides, co-trimoxazole, penicillin, cephalosporins, fluoroquinolones, vancomycin
- NSAIDs - piroxicam, fenbufen, ibuprofen, ketoprofen, naproxen, tenoxicam, diclofenac, sulindac

- Anti-TB - rifampicin, ethambutol, isoniazid, pyrazinamide
- Anticonvulsants - barbiturates, carbamazepine, phenytoin, valproate, lamotrigine
- Antifungals - fluconazole, nystatin, griseofulvin
- Antidepressants - lamotrigine, sertraline.
- **Sulfasalazine**

Drugs which act on serotonin receptors

- Below is a summary of drugs which are known to act via modulation of the serotonin (5-HT) system.
- It should be noted that 5-HT receptor agonists are used in the acute treatment of migraine whilst 5-HT receptor antagonists are used in prophylaxis.

Agonists

- sumatriptan is a 5-HT1D receptor agonist which is used in the acute treatment of migraine
- ergotamine is a partial agonist of 5-HT1 receptors

Antagonists

- pizotifen is a 5-HT2 receptor antagonist used in the prophylaxis of migraine attacks.
- Methysergide is another antagonist of the 5-HT2 receptor but is rarely used due to the risk of retroperitoneal fibrosis
- **ciproheptadine is a 5-HT2 receptor antagonist which is used to control diarrhoea in patients with carcinoid syndrome**
- ondansetron is a 5-HT3 receptor antagonist and is used as an antiemetic

5HT-2 receptor inhibition

- 5HT-2 receptor inhibition also reduces platelet aggregation
- one example is sarpogrelate developed in North East Asia primarily as an alternative to aspirin because of its association with a lower risk of haemorrhage.

Drugs that can be cleared with Hemodialysis - mnemonic: **BLAST**

<ul style="list-style-type: none"> • Barbiturate • Lithium • Alcohol (inc methanol, ethylene glycol) • Salicylates • Theophyllines (charcoal hemoperfusion is preferable) 	<p>Drugs which cannot be cleared with HD include</p> <ul style="list-style-type: none"> • Tricyclics • Benzodiazepines (diazepam, midazolam, alprazolam) • Dextropropoxyphene (co-proxamol) • Digoxin, β-blockers
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Cardiovascular drugs

Prescribing in patients with heart failure

The following medications may **exacerbate heart failure**:

- **thiazolidinediones:** pioglitazone is contraindicated as it causes fluid retention
⇒ pioglitazone is now the only thiazolidinedione on the market
- **verapamil:** negative inotropic effect
- **NSAIDs & glucocorticoids:** should be used with caution as they cause fluid retention
⇒ low-dose aspirin is an exception - many patients will have coexistent cardiovascular

disease and the benefits of taking aspirin easily outweigh the risks

- **Class I antiarrhythmics; flecainide** (negative inotropic and proarrhythmic effect)
- **Celecoxib** (rofecoxib has been withdrawn) acts by inhibiting prostaglandin synthesis via inhibition of cyclo-oxygenase-2 (COX-2). It causes fluid retention and can worsen an already pre-existing heart failure. The CSM reminds prescribers that **celecoxib is contraindicated** in:
 - ⇒ patients with severe congestive heart failure,
 - ⇒ active peptic ulceration
 - ⇒ or gastrointestinal bleeding.

Antiarrhythmics: Vaughan Williams classification

The Vaughan Williams classification of antiarrhythmics is still widely used although it should be noted that a number of common drugs are not included in the classification e.g. adenosine, atropine, digoxin and magnesium

AP = action potential

Class	Examples	Mechanism of action
Ia	Quinidine Procainamide Disopyramide	1. Block sodium channels 2. Increases AP duration Notes: <ul style="list-style-type: none"> • Quinidine toxicity causes cinchonism (headache, tinnitus, thrombocytopaenia) • Procainamide may cause drug-induced lupus • Disopyramide toxicity → Urinary retention
Ib	Lidocaine Mexiletine Tocainide	1. Block sodium channels 2. Decreases AP duration
Ic	Flecainide Encainide Propafenone	1. Block sodium channels 2. No effect on AP duration
II	Propranolol Atenolol Bisoprolol Metoprolol	Beta-adrenoceptor antagonists
III	Amiodarone Sotalol Ibutilide Bretylium	Block potassium channels
IV	Verapamil Diltiazem	Calcium channel blockers

Antiarrhythmic agents

- Calcium-channel blockers act mainly on (SA) (AV) nodes (direct membrane effect), as these structures are almost exclusively depolarised by the slow calcium channels
- **Flecainide** binds to the sodium channel and decreases the speed of depolarisation (in other words, decreases conduction velocity) (**Slows the upstroke of the action potential**)
- **Atenolol** decreases sympathetic tone
- **Amiodarone** and **sotalol** increase the action-potential duration and therefore the refractory periods
 - ⇒ they have little effect on conduction velocity
 - ⇒ **Sotalol have a high risk of producing torsades de pointe**
- **Class V agents (digitalis agents)** affect SA and AV nodes by increasing vagal tone

Atropine**Action**

- Atropine is an antagonist of the muscarinic acetylcholine receptor

Uses

- Treatment of organophosphate poisoning
- Bradycardia , heart block

Physiological effects

- Tachycardia
- Mydriasis
- ↓ Secretions of exocrine glands
- ↓ Tone and motility of smooth muscles (i.e., ↓ urgency in cystitis)
- ↓ Cholinergic overactivity in CNS

MRCPUK-part-1-january 2018 exam: Which physiological effect would be expected following administration of atropine? **Tachycardia + mydriasis**

Adenosine

Adenosine

- dipyridamole enhances effect
- aminophylline reduces effect

Mechanism of action

- causes transient heart block in the AV node
- agonist of the A1 receptor which inhibits adenylyl cyclase thus reducing cAMP and causing hyperpolarization by increasing outward potassium flux
- Acts on specific adenosine cell surface receptors (A1 and A2)
- Stress testing: A2A adenosine receptor agonist;
 - ⇒ activation of the A2A adenosine receptor produces coronary vasodilation and increases coronary blood flow
- ↑ coronary vasodilatation (**Adenosine is an important mediator of metabolic vasodilatation**)
- Increasing O₂ demands are met by → adenosine production → vasodilatation → increased blood supply.
- Adenosine effect on renal
 - ⇒ In the renal vasculature, in contrast, adenosine can produce vasoconstriction
 - ⇒ However, the vasoconstriction elicited by an intravenous infusion of adenosine is

- only short lasting, being replaced within 1-2 min by vasodilatation.
- ⇒ It appears that the steady-state response to the increase of plasma adenosine levels is global renal vasorelaxation that is the result of A2A receptor activation
- ⇒ Adenosine lowers glomerular filtration rate (GFR) by constricting afferent arterioles, especially in superficial nephrons. In contrast, it leads to vasodilation in deep cortex and medulla.
- ↓↓ sinus node automaticity and AVN conduction.
- adenosine has a very short half-life of about 8-10 seconds
- Inactivated by adenosine deaminase.

Adverse effects

- transient facial **flushing** (18%) (most common)
- bronchospasm
 - ⇒ Dyspnea (12%)
 - ⇒ It should be avoided in asthmatics
- choking sensation, where patients often clutch their chest
- chest pain
- can enhance conduction down accessory pathways, resulting in increased ventricular rate (e.g. WPW syndrome)

Interaction

- The effects of adenosine are enhanced by dipyridamole (anti-platelet agent)
 - ⇒ Adenosine transported out of the cell to the extracellular space by specific bi-directional nucleoside transporters. **Inhibitors of these transporters**, such as dipyridamole, increase the extracellular concentrations of adenosine and are useful clinically to treat certain cardiovascular complications.
- Adenosine effects blocked by theophyllines.
- **Unlike verapamil it may be used following β-blockade**

Adenosine is a coronary vasodilator (which is why we use it in cardiac stress testing) and a bronchoconstrictor (action opposed by theophylline).

Flecainide

Action

- Flecainide is a Vaughan Williams class 1c antiarrhythmic.
- It slows conduction of the action potential by acting as a potent **sodium channel blocker**.
 - ⇒ **Slows the upstroke of the action potential**
 - ⇒ does not alter the overall length of the action-potential duration.
- This may be reflected by widening of the QRS complex and prolongation of the PR interval

Indications

- atrial fibrillation
- SVT associated with accessory pathway e.g. Wolf-Parkinson-White syndrome

Contraindications

- post myocardial infarction → increase mortality

Adverse effects

- | | |
|--|--|
| <ul style="list-style-type: none"> • negatively inotropic • bradycardia • proarrhythmic | <ul style="list-style-type: none"> • oral paraesthesia • visual disturbances |
|--|--|

Amiodarone

Amiodarone - MOA: blocks potassium channels

- Amiodarone is a **class III antiarrhythmic agent**
- used in the treatment of atrial, nodal and ventricular tachycardias.
- metabolized in the liver via cytochrome **P450 3A4**.

Action

- The main mechanism of action is by blocking potassium channels which inhibits repolarisation and hence prolongs the action potential.
 - ⇒ Amiodarone **prolongs the refractory period** of the cardiac conducting system.
 - ⇒ Its antiarrhythmic effects are due mostly to the **inhibition of the rapid component of the delayed potassium rectifier IKr channel** (as with sotalol) but also have an effect on the slow component.
- Amiodarone also has other actions such as blocking sodium channels (a class I effect)

Several factors limit the use of amiodarone:

- long half-life (20-100 days)
 - ⇒ Because of its long half-life there is a potential for drug interactions to occur for several weeks after amiodarone has been stopped.
- should ideally be given into central veins (causes thrombophlebitis)
- has proarrhythmic effects due to lengthening of the QT interval
- interacts with drugs commonly used concurrently e.g. Decreases metabolism of warfarin
- numerous long-term adverse effects.

Monitoring of patients taking amiodarone

- TFT, LFT, U&E, CXR prior to treatment
- TFT, LFT every 6 months
 - ⇒ and for up to 12months after discontinuation of amiodarone
 - ⇒ An **increase of up to 40% above the baseline T4 is a normal effect of amiodarone**. This occurs approximately 2 months after initiation of therapy & **does not require discontinuation**.

Administration

- 300 mg of amiodarone made up to 20 ml with 5% dextrose given as an intravenous bolus is the drug of choice in treating refractory ventricular fibrillation or pulseless ventricular tachycardia (100 mg of lidocaine may be given intravenously when amiodarone is unavailable).

Adverse effects

corneal deposits is the most common side effect

hypothyroidism occur more frequently than hyperthyroidism

- **Thyroid dysfunction:** both hypothyroidism and hyperthyroidism
 - ⇒ Amiodarone blocks the peripheral conversion of thyroxine (T4) to triiodothyronine (T3) → **hypo** (occurs in up to 20% of patients taking amiodarone)
 - ⇒ It is also a potential source of large amounts of inorganic iodine → **hyper** (occurs in 3% of patients in iodine-deficient areas, but in 20% in areas where iodine is sufficient).
- **Corneal deposits**
 - ⇒ **present in most patients**,
 - almost universal in patients taking amiodarone therapy (at least **90%**).

- ⇒ rarely interfere with vision, becomes manifest by the presence of night-time visual glare, noticed while driving.
- ⇒ usually reversible on withdrawal of drug
- **Photosensitivity**
 - ⇒ Skin deposits result in photodermatitis and a greyish-blue discoloration on sun-exposed areas ('slate-grey' appearance (Skin sensitivity))
 - ⇒ can be prevented by using a sun block
- **Pulmonary fibrosis/pneumonitis** (5-7%).
- Liver cirrhosis/hepatitis
- Peripheral neuropathy, myopathy
- Prolonged QT interval
- Thrombophlebitis and injection site reactions
- Bradycardia
- **Persistent slate-grey skin discolouration (ceruloderma)**



- ⇒ more common in males than females.
- ⇒ the pigmentation consists of brownish-yellow deposits of amiodarone, iron and others (not including melanin or hemosiderin)
- ⇒ On biopsy of these lesions, which cell type is laden with pigment?
 - histiocytes of the dermis
- ⇒ appears in sun-exposed areas and is thought to be activated by an UVA-related hypersensitivity response.
 - Sun exposure is not recommended for patients on amiodarone.
- ⇒ Treatment
 - discontinuation of the drug
 - if not disappeared after discontinuation → laser-based therapy.
- Neutropenia
- Nightmares, sleep disturbance

Important drug interactions of amiodarone

- Decreased metabolism of warfarin, therefore increased INR
 - ⇒ Decrease warfarin dose by 33- 50% and monitor the INR weekly
- Increased digoxin levels
 - ⇒ the dose of digoxin should be halved when patients are started on amiodarone.
- There is an increased risk of ventricular arrhythmias when amiodarone is given with tricyclics, hence concomitant use should be avoided.

For amiodarone and the thyroid gland (See Endocrinology chapter)

Dobutamine & Dopamine

	Dobutamine	Dopamine
Action	<ul style="list-style-type: none"> Direct Sympathomimetics (β_1 receptor agonist) $\beta_1 > \beta_2$, agonist positive inotropic effect >> chronotropic effects 	<ul style="list-style-type: none"> $D_1 = D_2 > \beta > \alpha$ Chronotropic effects at lower doses (β effect) Vasoconstriction at high doses (α effect)
Indications	<ul style="list-style-type: none"> Cardiogenic shock Acute heart failure Cardiac stress testing 	<ul style="list-style-type: none"> Heart failure Cardiogenic shock Unstable bradycardia

Adrenaline

Adrenaline induced ischaemia - phentolamine

Recommend Adult Life Support (ALS) adrenaline doses

- anaphylaxis: 0.5ml 1:1,000 IM
- cardiac arrest: 10ml 1:10,000 IV or 1ml of 1:1000 IV

Adrenaline is a sympathomimetic amine with **both alpha and beta** adrenergic stimulating properties.

The β - effect will cause significant **tachycardia**

Indications

- anaphylaxis
- cardiac arrest

Recommend Adult Life Support (ALS) adrenaline doses

- anaphylaxis: 0.5ml 1:1,000 IM**
- cardiac arrest: 10ml 1:10,000 IV or 1ml of 1:1000 IV

Management of accidental injection

- local infiltration of phentolamine**
- An alternative possibility is locally applied GTN paste

Anaphylaxis

- Where there is a history of a typical allergic reaction, current United Kingdom resuscitation guidelines **suggest adrenaline if there is:**
 - Stridor
 - Wheeze
 - Respiratory distress, or
 - Clinical evidence of shock.
- Adrenalin is **used for its alpha-agonist effects** that include increased peripheral vascular resistance and reversed peripheral vasodilatation, systemic hypotension, and vascular permeability.

- **Beta-agonist effects** include bronchodilatation, chronotropic cardiac activity, and positive inotropic effects.
- IM administration is preferred because of a superior safety profile with respect to cardiac adverse events compared with the IV route, although 1:10000 adrenalin IV may be used in a life-threatening situation.
- **The intramuscular (IM) route for adrenaline is the route of choice** for most healthcare providers.
- Adult **EpiPen** which allergy sufferers can carry with them contains 0.3 mg or 0.15 mg adrenaline in a 1:1000 dilution for intramuscular (IM) injection.

Antiplatelets

Overview of antiplatelet agents

Overview of antiplatelet agents			
Group	Agents	Indications	Adverse effects
Irreversible cyclooxygenase inhibitors	Acetylsalicylic acid (aspirin)	<ul style="list-style-type: none"> • Acute coronary syndrome • Ischemic stroke • Primary and secondary prevention of cardiovascular disease 	<ul style="list-style-type: none"> • Reye syndrome • Aspirin exacerbated respiratory disease • GI upset • Salicylate toxicity • Affects the kidneys in a dose-dependent manner <ul style="list-style-type: none"> ⇒ Low doses → uric acid retention ⇒ High doses → uric acid excretion
P2Y12 receptor antagonists (ADP receptor inhibitors)	<ul style="list-style-type: none"> • Clopidogrel • Prasugrel • Ticagrelor • Ticlopidine • Cangrelor 	<ul style="list-style-type: none"> • Dual antiplatelet therapy (with acetylsalicylic acid) in ACS • Alternative to aspirin 	<ul style="list-style-type: none"> • Allergic reactions • Haemorrhage • GI upset
Glycoprotein IIb/IIIa inhibitors	<ul style="list-style-type: none"> • Abciximab • Eptifibatide • Tirofiban 	<ul style="list-style-type: none"> • High-risk patients with unstable angina/NSTEMI before undergoing PCI 	<ul style="list-style-type: none"> • Acute thrombocytopenia • Haemorrhage

Summary of latest guidance

The table below summarises the most recent guidelines regarding antiplatelets:

Diagnosis	1st line	2nd line
NSTEMI	Aspirin (lifelong) & clopidogrel (12 months)	If aspirin contraindicated, clopidogrel (lifelong)
STEMI	Aspirin (lifelong) & clopidogrel (1m if no/bare stent, 12 m if drug-eluting stent)	If aspirin contraindicated, clopidogrel (lifelong)
TIA*	Clopidogrel (lifelong)	Aspirin (lifelong) & dipyridamole (lifelong)
Ischaemic stroke	Clopidogrel (lifelong)	Aspirin (lifelong) & dipyridamole (lifelong)
Peripheral arterial disease	Clopidogrel (lifelong)	Aspirin (lifelong)

*the guidelines for TIA are based on the 2012 Royal College of Physicians National clinical guideline for stroke. These guidelines corrected the anomaly where patients who've had a stroke were given clopidogrel, but those who'd suffered a TIA were given aspirin + dipyridamole.

Peri-Operative Management of Anticoagulation and Antiplatelet Therapy

(British society for Haematology guidelines 2016)

- **Warfarin and other vitamin K antagonists**

- ⇒ Emergency surgery in patients on warfarin
 - If surgery can wait for 6–8 h then 5 mg of intravenous **phytomenadione** can restore coagulation factors;
 - if this is not possible, anticoagulation can be reversed with 25–50 u/kg of four-factor **prothrombin complex concentrate**
- ⇒ **Consider bridging with treatment dose heparin in:**
 - 1) Patients with a VTE **within previous 3 months**.
 - 2) Very high risk patients such as patients with a previous VTE whilst on therapeutic anticoagulation who now have a target INR of 3·5.
 - 3) Patients with a previous stroke/TIA **in last 3 months**.
 - 4) Patients with a previous stroke/TIA and three or more of the following risk factors:
 - ❖ Congestive cardiac failure
 - ❖ Hypertension (>140/90 mmHg or on medication)
 - ❖ Age >75 years
 - ❖ Diabetes mellitus
 - 5) mechanical heart valve (MHV) patients other than those with a bileaflet aortic valve and no other risk factors

- ⇒ the post-operative bridging (i.e. full dose anticoagulation) should not start until **at least 48 h after high bleeding risk surgery** although thromboprophylaxis should be given if indicated.
- ⇒ Warfarin should be stopped for **5 days before an elective procedure** if anticoagulation needs to be discontinued

- **Antiplatelet therapy**

- ⇒ aspirin monotherapy (for secondary prevention of cardiovascular disease) can be continued for most invasive non-cardiac procedures
- ⇒ Aspirin can be continued both before and after coronary artery bypass surgery

The lifespan of a platelet is 7–10 days. If aspirin is held prior to surgery, it should be discontinued one week in advance.

Acetylsalicylic acid (ASA, aspirin)

Aspirin is a common cause of urticaria

Overview

- **Aspirin works by blocking the action of both cyclooxygenase-1 and 2.**
- Cyclooxygenase is responsible for prostaglandin, prostacyclin and thromboxane synthesis.
- Cyclo-oxygenase is an enzyme that converts arachidonic acid to thromboxane A2 (TXA2), a strong platelet agonist
- Because the platelet has no protein synthetic apparatus the effects of aspirin are irreversible and last for the life of the platelet (8-10 days)
- ↑ bleeding time (PT and PTT unchanged)
- The blocking of thromboxane A2 formation in platelets reduces the ability of platelets to aggregate which has lead to the widespread use of low-dose aspirin in cardiovascular disease.
- Until recent guidelines changed all patients with established cardiovascular disease took aspirin if there was no contraindication. Following the 2010 technology appraisal of clopidogrel this is no longer the case.

Mechanism of action

- ASA covalently attaches an acetyl group to COX.
- **Irreversible COX-1 inhibition** → inhibition of thromboxane (TXA2) synthesis in platelets → inhibition of platelet aggregation (antithrombotic effect)
- Onset of antiplatelet action: within minutes
- Duration of antiplatelet action: 7–10 days
- Irreversible COX-1 and COX-2 inhibition → inhibition of prostacyclin and prostaglandin synthesis → antipyretic, anti-inflammatory, and analgesic effect

Effects

- Low dose (below 300 mg/day): inhibition of platelet aggregation
- Intermediate dose (300-2400 mg/day): antipyretic and analgesic effect
- High dose (2400-4000 mg/day): anti-inflammatory effect

What do the *current* guidelines recommend?

- first-line for patients with ischaemic heart disease
- Current NICE guidelines advise that **people with acute upper gastrointestinal bleeding who take aspirin for secondary prevention of vascular events and in whom haemostasis has been achieved continue on low dose aspirin.**
- the U.S. Preventive Services Task Force (USPSTF), recommended that, for some people, aspirin can be used to help reduce their risk of cardiovascular disease **and colorectal cancer.**

Potentiates

- oral hypoglycaemics
- warfarin
- steroids

Reye syndrome

- **Definition:** a rare type of hepatic encephalopathy that is associated **with aspirin use** for viral illness in children < 19 years
- **Aetiology:** aspirin use in individuals < 19 years of age with a febrile illness
- **Pathophysiology**
 - ⇒ accumulation of salicylate metabolites in the liver → mitochondrial injury and reversible inhibition of enzymes required for fatty acid oxidation; acute encephalopathy
 - ⇒ Hyperammonemia → cerebral edema → ↑ ICP
- **Features**
 - ⇒ Preceding viral infection (e.g., influenza, varicella or viral gastroenteritis)
 - ⇒ Acute encephalopathy
 - ⇒ Severe vomiting
 - ⇒ coma
 - ⇒ Liver failure
 - ⇒ Fatty degeneration
 - ⇒ Hepatomegaly
- **Diagnostics:** clinical diagnosis; further testing to rule out other causes (diagnosis of exclusion)
 - ⇒ ↑ AST and ALT
 - ⇒ Hyperammonemia
 - ⇒ Hypoglycemia
 - ⇒ Liver biopsy: microvesicular hepatic steatosis
- **Prevention**
 - ⇒ Aspirin should be avoided in individuals < 19 years of age
 - ⇒ Exception: children with Kawasaki disease
- **Prognosis** → Mortality rate: ~ 20%

In hypersensitive patients aspirin can cause:

- Angioedema
- Bronchospasm, and
- Urticaria (skin rashes).

ASA can be continued normally if patient is going for dental procedure

Avoid aspirin in children < 16 years as risk of Reye's syndrome

Aspirin is not considered to be safe in breast-feeding due to the risk of causing Reye's syndrome in the baby.

Salicylate overdose

The mixed respiratory alkalosis and metabolic acidosis in a sweaty, confused patient point towards salicylate overdose.

The development of pulmonary edema suggests severe poisoning and is an indication for hemodialysis.

Tinnitus is characteristic and salicylate toxicity may produce deafness.

Overview

- A key concept for the exam is to understand that salicylate overdose leads to a **mixed respiratory alkalosis and metabolic acidosis**.
 - ⇒ Early stimulation of the respiratory centre leads to a respiratory alkalosis
 - ⇒ later the direct acid effects of salicylates (combined with acute renal failure) may lead to an acidosis.
- The metabolic acidosis can increase the transfer of salicylates across the blood-brain barrier, thereby increasing CNS toxicity

Features

- **Early features:**
 - ⇒ hyperventilation (centrally stimulates respiration) → respiratory alkalosis
 - the most prominent feature of the early period after aspirin overdose
 - ⇒ tinnitus: typically occurs at plasma salicylate concentrations above 400-500 mg/l
 - ⇒ vertigo
 - ⇒ lethargy
 - ⇒ **sweating, pyrexia**
 - salicylates cause the uncoupling of oxidative phosphorylation leading to decreased adenosine triphosphate production, increased oxygen consumption and increased carbon dioxide and heat production
 - ⇒ peripheral vasodilatation and bounding pulse
 - ⇒ nausea/vomiting → dehydration
- **Later features:**
 - ⇒ metabolic acidosis
 - by **uncoupling oxidative phosphorylation**, leading to a build-up of organic acids in the blood.
 - ⇒ hyperglycaemia and hypoglycaemia
 - Hypoglycaemia is commonly seen in children but not in adults
 - ⇒ seizures
 - ⇒ coma
 - Although decreased consciousness is seen in aspirin overdose, it is seen late, and is associated with severe metabolic acidosis and hypokalaemia.
 - **Early presentation with coma will suggest that another drug has been taken in addition to aspirin.**

Treatment

- No specific antidote
- The management is supportive, with measures to prevent further absorption from the gastrointestinal tract and enhance excretion.
- General (ABC, charcoal) **Multi-dose activated charcoal may be indicated**

- ⇒ activated charcoal should be repeated as bezoars may form, resulting in delayed absorption of salicylate. This **should continue until salicylate levels have peaked.**
- **Urinary alkalinization**
 - ⇒ alkalinisation of the urine should be considered in patients with a plasma level > 300 mg/L.
 - ⇒ **urine and serum alkalinization through intravenous sodium bicarbonate**
(1.25% or 8.4%)
 - ⇒ By alkalinizing the urine, charged salicylic acid will become protein bound and secreted through the proximal tubule, which minimizes the diffusion of uncharged salicylate back into the renal epithelium.
 - The ionisation of a weak acid, such as salicylic acid, is increased in an alkaline environment.
 - The administration of an intravenous infusion of sodium bicarbonate aiming for a urinary pH of 7.5-8 will increase the excretion of the acid 10-fold.
 - ⇒ Alkalization of the serum further promotes diffusion of salicylate out of the brain.
- Haemodialysis
 - ⇒ **Indications for haemodialysis in salicylate overdose**
 - serum concentration > 700mg/L
 - metabolic acidosis resistant to treatment
 - acute renal failure
 - **pulmonary oedema**
 - neurological impairment (coma, hallucinations or seizures)

Clopidogrel

Most (PPIs) ↓ Clopidogrel effect but lansoprazole is OK

- Clopidogrel is an antiplatelet agent used in the management of cardiovascular disease.
- Clopidogrel belongs to a class of drugs known as thienopyridines which have a similar mechanism of action. Other examples include:
 - ⇒ prasugrel
 - ⇒ ticagrelor
 - ⇒ ticlopidine

Mechanism (**Inhibition of the platelet ADP receptor**)

- antagonist of the P2Y₁₂ adenosine diphosphate (ADP) receptor, inhibiting the activation of platelets

Indications

- clopidogrel is used in addition to aspirin in patients with an acute coronary syndrome. The dose is 300 mg.
- NICE now recommend clopidogrel first-line following an ischaemic stroke and for peripheral arterial disease.
- Recent Royal College of Physician (RCP) guidelines support the use of clopidogrel in TIAs. However the older NICE guidelines still recommend aspirin + dipyridamole

Interactions

- concurrent use of proton pump inhibitors (PPIs) may make clopidogrel less effective (MHRA July 2009)
- this advice was updated by the MHRA in April 2010, evidence seems inconsistent but omeprazole and esomeprazole still cause for concern. **Other PPIs such as lansoprazole should be OK**

Clopidogrel

- action → antagonist of the **P2Y12 adenosine diphosphate (ADP) receptor**, inhibiting the activation of platelets
- other members of the same class (thienopyridines):
 - ⇒ prasugrel
 - ⇒ ticagrelor
 - ⇒ ticlopidine
- Indications → 1st line for : ACS , an ischaemic stroke , TIA and peripheral arterial disease.
- Interaction → most (PPIs) ↓ Clopidogrel effect but Lansoprazole is OK

Prasugrel

- a third-generation thienopyridine antiplatelet agent
- ADP receptor inhibitors
- advantages compared with clopidogrel
 - ⇒ faster onset of action,
 - ⇒ greater potency in the inhibition of adenosine-induced platelet aggregation,
 - ⇒ more consistent antiplatelet response
- **Prasugrel is contra-indicated in patients with prior transient ischaemic attack or stroke.**
 - ⇒ In the TRITON-TIMI 38 trial, patients in this group had a higher rate of stroke when taking Prasugrel compared with those taking Clopidogrel.

IIb/IIIa inhibitors (eg: Abciximab)

- Other members of this drug group
 - ⇒ abciximab
 - ⇒ eptifibatide
 - ⇒ tirofiban
- Action
 - ⇒ monoclonal antibody **antagonizes IIb/IIIa glycoprotein receptor** on activated platelets
- prevents platelet aggregation
- Abciximab is a humanised monoclonal antibody

Phosphodiesterase III (PDE) inhibitors (dipyridamole & cilostazol)

Dipyridamole is a non-specific phosphodiesterase inhibitor and decreases cellular uptake of adenosine

Dipyridamole may provoke bronchospasm. Avoid in asthmatics.

Mechanism of action

- inhibits phosphodiesterase → increase platelet cAMP (due to decreased breakdown of cAMP) → reduce intracellular calcium levels → inhibition of platelet aggregation.
- direct arterial vasodilation
 - ⇒ inhibits cellular uptake of adenosine → more available to act on coronary vessels → vasodilation
- inhibition of thromboxane synthase

Indications

- Dipyridamole is an antiplatelet mainly used in combination with aspirin after an ischaemic stroke or transient ischaemic attack
- **Cilostazol** is currently licensed for the **management of patients with intermittent claudication without rest pain and with no signs of tissue necrosis**.
 - ⇒ It is a first-line medication for the treatment of claudication caused by peripheral artery disease (PAD).
 - ⇒ Trials show an improvement in time to initial pain on walking and maximal walking distance when compared to placebo.
 - ⇒ **metabolised by cytochrome P450 3A4.**

Contraindications

- known bleeding tendencies (e.g. active peptic ulcer disease, previous haemorrhagic stroke in the last 6 months).
- Asthmatics (may provoke bronchospasm)

Angiotensin-converting enzyme (ACE) inhibitors

Mechanism of action

- Inhibit the conversion angiotensin I to angiotensin II

Indications

- hypertension
 - ⇒ first-line treatment in younger patients with hypertension and are also extensively used to treat
 - ⇒ less effective in treating hypertensive Afro-Caribbean patients.
- diabetic nephropathy
- heart failure.
- secondary prevention of IHD.

Side-effects

- Cough:
 - ⇒ occurs in around 15% of patients
 - ⇒ **may occur up to a year after starting treatment.**
 - ⇒ Thought to be **due to increased bradykinin levels**
 - ⇒ The enzyme ACE is also responsible for the metabolism of bradykinin in mast cells and ACEi leads to its bradykinin accumulation
 - ⇒ This phenomenon is not seen in subjects taking angiotensin receptor blockers such as losartan.
- Angioedema:
 - ⇒ may occur up to a year after starting treatment
 - ⇒ ACE inhibitors are the most common cause of **drug-induced angioedema**

(swelling of his lips and tongue)

- Hyperkalaemia
- ACEi → **dilate the efferent arteriole** of the glomerulus, → ↓GFR → ↑ creatinine and BUN.
- 1st-dose hypotension: more common in patients taking diuretics

Cautions and contraindications

- Pregnancy and breastfeeding – avoid (ACEi & ARB → renal dysgenesis in the fetus)
Exposure to ACE inhibitors in the first trimester → showed a significant increase in major (in particular, cardiovascular) congenital malformation.
- Renovascular disease - significant renal impairment may occur in patients who have undiagnosed bilateral renal artery stenosis
- Aortic stenosis - may result in hypotension
- Patients receiving high-dose diuretic therapy (more than 80 mg of furosemide a day) - significantly increases the risk of hypotension
- Hereditary of idiopathic angioedema
- The co-administration of a **potassium-sparing diuretic** and an ACE inhibitor, may result in profound **hyperkalaemia**. Thus patients on both these drugs should have their potassium monitored closely.

Monitoring

- Urea and electrolytes should be checked before treatment is initiated and after increasing dose
 - ⇒ Monitoring of renal function and potassium is important after commencement of an ACE inhibitor.
 - **The optimum period to check this is one to two weeks after commencing the medication.**
- A rise in the creatinine and potassium may be expected after starting ACE inhibitors.
 - ⇒ **Acceptable increases are an increase in serum creatinine, up to 50% from baseline or up to 265µmol/l (whichever is smaller) and an increase in potassium up to 5.5 mmol/l.**
 - ⇒ NICE guidelines state that when initiating ACE inhibitor therapy a **25% reduction in the eGFR or 30% increase in the serum creatinine is tolerable and should not lead to changes in dosing.**
 - ⇒ ACE inhibitors should also be stopped or dose adjusted if there is a rise in the serum potassium level to greater than 6 mmol/l.
 - ⇒ Other causes of a deterioration in renal function should be excluded first before stopping the ACE inhibitor.
 - **e.g:** patient taking trimethoprim
 - ❖ This drug **competes with creatinine for excretion in the nephron** → ↑ serum creatinine.
 - ❖ **the appropriate option would be to re-check the blood tests in one to two weeks once trimethoprim has been discontinued to see whether the level of renal dysfunction is sustained or improves.**

Usage of ACEi & ARB as combination (NICE January 2015)

- **Do not combine an ACE inhibitor with an ARB to treat hypertension.**
- no significant benefits of ACEi & ARB combination were seen in people who did not have heart failure and there was an increased risk of hyperkalaemia, hypotension, and impaired renal function.
- The NICE guideline on **chronic heart failure** recommends that, after seeking specialist advice, the addition of an ARB licensed for heart failure is an option that could be considered for people who remain symptomatic despite optimal therapy with an ACE

inhibitor and a beta-blocker

- ⇒ Candesartan and valsartan are the only ARBs licensed as add-on therapy to ACE inhibitors in this situation.
- ⇒ Other options are adding an aldosterone antagonist licensed for heart failure or hydralazine in combination with nitrate.

direct renin inhibitors

- **Aliskiren** (branded as Rasilez) → **Direct renin inhibitor**
- **Action:** by inhibiting renin blocks the conversion of angiotensinogen to angiotensin I
- **indication:** only current role would seem to be in patients who are intolerant of more established antihypertensive drugs
- no trials have looked at mortality data yet. Trials have only investigated fall in blood pressure. Initial trials suggest aliskiren reduces blood pressure to a similar extent as angiotensin converting enzyme (ACE) inhibitors or angiotensin-II receptor antagonists
- **adverse effects** were uncommon in trials although diarrhoea was occasionally seen

Other notes

- Enalapril is a prodrug for enalaprilat, the active agent
- **irbesartan : the dose response is linear, as such dose can be titrated more easily from a base of 75 mg to a maximum of 300 mg.**

Adrenoceptor antagonists

Doxazosin is an α-1 adrenoceptor antagonist used in the treatment of hypertension and benign prostatic hypertrophy

Alpha antagonists

- alpha-1: doxazosin
⇒ cause → **orthostatic hypotension**
- alpha-1a: tamsulosin - acts mainly on urogenital tract
- alpha-2: yohimbine
- non-selective: phenoxybenzamine (previously used in peripheral arterial disease)
Phenoxybenzamine → presurgical management of hypertension in phaeochromocytoma.

Beta antagonists

- beta-1: atenolol
- non-selective: propranolol

Carvedilol and labetalol are mixed alpha and beta antagonists

Beta-blockers

3 Generations of beta-blockers

	Properties	Drugs
1 st Generation	Non-selective No vasodilatation	Propranolol, Timolol, Pindolol, Nadolol, Sotalol
2 nd Generation	β1-selective without vasodilation β1selective with vasodilation	Atenolol, Bisoprolol, Metoprolol Nebivolol, Acebutolol
3 rd Generation	Non-selective with vasodilation	Carvedilol, Bucindolol

Indications

- angina
- post-myocardial infarction
- Heart failure: there is now strong evidence that certain beta-blockers improve both symptoms and mortality. Especially Bisoprolol
- arrhythmias: beta-blockers have now replaced digoxin as the rate-control drug of choice in atrial fibrillation
- hypertension: the role of beta-blockers has diminished in recent years due to a lack of evidence in terms of reducing stroke and myocardial infarction.
- thyrotoxicosis
- migraine prophylaxis
- anxiety

Beta-blocker in heart failure

- NICE recommends β blockers in all HF patients.
- In chronic obstructive pulmonary disease (COPD) patients with HF, cardioselective β blockers appear safer at **lower doses** than higher doses or non-selective β blockers.
- Bisoprolol 5 mgs is too high an initial starting dose, a low dose can always be titrated up later, if tolerated. (**starting dose → Bisoprolol 1.25 mg od**)
- Carvedilol though effective treatment for heart failure is not selective and therefore carries a greater risk of causing bronchospasm.
- Atenolol though cardioselective has no clinical evidence for prognostic benefit in heart failure.
- The patient should be closely monitored for deterioration in lung function post-administration.

Examples

- **Atenolol**
 - ⇒ Atenolol is a water soluble beta-blocker,
 - ⇒ taken once daily
 - ⇒ not associated with drowsiness/sleep disturbance like the lipid-soluble beta-blockers.
- **Propranolol**
 - ⇒ one of the first beta-blockers to be developed.
 - ⇒ Lipid soluble therefore crosses the blood-brain barrier
- **Nebivolol**
 - ⇒ has a vasodilatory action in addition to β-blocking effects
 - ⇒ associated with a lower incidence of erectile dysfunction compared with other β-blocking agents
- **Bisoprolol → the most cardio-selective beta-blocker**
- **Metoprolol**
 - ⇒ **The most lipid-soluble and therefore has the largest volume of distribution**
 - ⇒ ↑lipid solubility → greater penetration across the blood-brain barrier (and also into other tissues), and therefore a greater incidence of **night terrors**
 - ⇒ Maximal gastrointestinal absorption of drugs occurs when there is intermediate lipid and water solubility, so that drugs with **greater lipid solubility, although allowing greater tissue penetration, may be more poorly absorbed**
 - ⇒ Metoprolol though **selective** is **shorter acting**.
- **Oxprenolol** → has an intrinsic sympathomimetic properties.

Carvedilol	Bisoprolol
Not β_1 - selective	Highly β_1 - selective
Vasodilatation due to α_1 - blockade	No α_1 - blocking activity
Lipids effects Positive lipid effect $\rightarrow \uparrow\uparrow$ HDL & $\downarrow\downarrow$ LDL Negative lipid effect $\rightarrow \uparrow\uparrow$ cholesterol , TG, VLDL	Lipid profile almost not affected
Oral bioavailability of digoxin increased	No interaction with other CV drugs known
Sensitive to liver enzyme induction	Not sensitive to liver enzyme induction
Extensive metabolism in the liver (CYP2D6)(dose adjustment in liver impairment)	No dose adjustment required

Side-effects

- bronchospasm
- cold peripheries
- β -Blockers cause a rise in peripheral vascular resistance due to the unopposed α -adrenoceptor effects (vasoconstriction)
- Fatigue
 - ⇒ fatigue is a frequent side effect
 - ⇒ typically is felt two hours and beyond after taking the drug.
- sleep disturbances, including nightmares
- β -blockers associated with increased dreams/possible night terrors

Contraindications

- uncontrolled heart failure
- asthma
- sick sinus syndrome
- concurrent verapamil use: may precipitate severe bradycardia
- There is a theoretical risk of **intrauterine growth retardation** with the use of atenolol in pregnancy although the studies which showed this effect were done **with very large doses of atenolol**.

Beta-blocker overdose

Beta-blocker overdose management: atropine + glucagon

Features

- bradycardia
- hypotension
- heart failure
- syncope

Management

- if bradycardic then atropine
- **in resistant cases glucagon may be used**
- Glucagon acts by bypassing the blocked β -receptor, thus activating adenyl cyclase \rightarrow formation of cyclic AMP from ATP. Cyclic AMP in turn exerts a direct stimulant action on the heart.
- **The action of glucagon, essential for reversing the effect of beta-blocker overdose \rightarrow Promotes the formation of cyclic AMP.**
 - ⇒ Doses of glucagon used are much higher than those conventionally used for reversing hypoglycaemia in diabetes, with a bolus of 3-10 mg being required, then 2-5 mg/hr by infusion.
- Haemodialysis is not effective in beta-blocker overdose

Calcium channel blockers

Calcium channel blockers - side-effects: headache, flushing, ankle oedema

- Voltage-gated calcium channels are present in:
 1. myocardial cells,
 2. cells of the conduction system and
 3. cells of the vascular smooth muscle.
 - (they have no effect on veins).
- The various types of calcium channel blockers have varying effects on these three areas and it is therefore important to differentiate their uses and actions.

Examples	Indications & notes	Side-effects and cautions
Verapamil	<ul style="list-style-type: none"> • Angina, hypertension, arrhythmias • Highly negatively inotropic • Should not be given with beta-blockers as may cause heart block 	<ul style="list-style-type: none"> • Heart failure, • constipation, • hypotension, • bradycardia, flushing
Diltiazem	<ul style="list-style-type: none"> • Angina, hypertension • Less negatively inotropic than verapamil but caution should still be exercised when patients have heart failure or are taking beta-blockers 	<ul style="list-style-type: none"> • Hypotension, • bradycardia, • heart failure, • ankle swelling
Nifedipine, amlodipine, felodipine (dihydropyridines)	<ul style="list-style-type: none"> • Hypertension, angina, Raynaud's • Affects the peripheral vascular smooth muscle more than the myocardium and therefore do not result in worsening of heart failure 	<ul style="list-style-type: none"> • Flushing, • headache, • ankle swelling

- What is the conventional cardiac micro-anatomical structure targeted by calcium-channel blockers?

⇒ L-type calcium channels

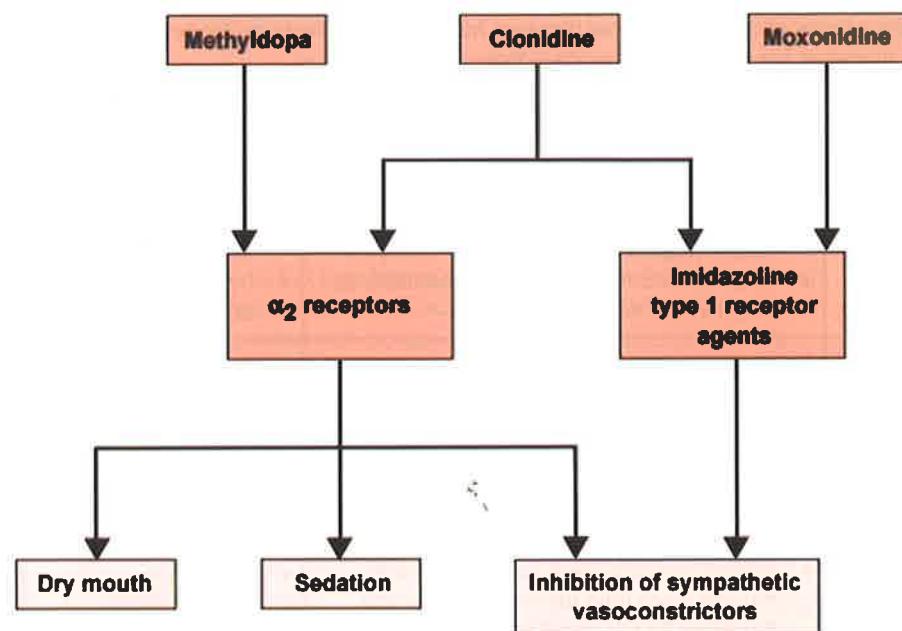
- all conventional calcium-channel blockers work on L-type calcium channels
- The L-type channels are found on a tubular network of invaginations of sarcolemma of muscle fibres called T (transverse) tubules.
- T tubules contain 2 main types of calcium channels:
 - ❖ L-type calcium channels (where calcium channel blocker do interact)
 - ❖ T (transient) type calcium channels (conventional calcium channel blockers have no effect here).

Centrally acting antihypertensives

Methyldopa → not utilised in a patient with abnormal LFTs

Examples of centrally acting antihypertensives include:

- methyldopa: used in the management of hypertension during pregnancy
- moxonidine: used in the management of essential hypertension when conventional antihypertensives have failed to control blood pressure
- clonidine: the antihypertensive effect is mediated through stimulating alpha-2 adrenoceptors in the vasomotor centre



Bosentan

- Bosentan is a competitive antagonist of **both endothelin-A (ET_A) and endothelin-B (ET_B) receptors**, leading to falls in both pulmonary and systemic vascular resistances without an increase in heart rate
- effective in patients with pulmonary arterial hypertension
- It is excreted in bile following metabolism by the cytochrome P450 enzymes and this is a potential source of interaction with drugs metabolised by the same isoenzyme
- **Common unwanted effects** include
 - ⇒ flushing
 - ⇒ **hypotension**
 - ⇒ dyspepsia
 - ⇒ fatigue
 - ⇒ Haemoglobin concentrations can **fall** by up to 1 g/dl during bosentan treatment
 - ⇒ Hepatotoxicity:
 - The most serious unwanted effect is dose-dependent hepatotoxicity, and it is therefore contraindicated in patients with moderate to severe liver disease
 - Generally, hepatotoxicity occurs within the first 3-4 months of treatment
 - ⇒ teratogenic and therefore contraindicated in pregnancy

Nitroglycerin

- Nitroglycerin products are both venous capacitance dilators and coronary and systemic artery dilators
- Administration of nitroglycerin results in:
 - ⇒ **dilation of systemic veins**
 - ⇒ decreased myocardial wall tension
 - ⇒ decreased oxygen demand
 - ⇒ vasodilation of large and medium-sized coronary arteries
 - ⇒ increased coronary blood flow to the subendocardium
 - ⇒ reduced afterload
 - ⇒ reduced preload
 - ⇒ increased ventricular compliance
- **Nitrates may cause → haemolytic anaemia**

Nicorandil

Action

- **acts through the opening of potassium channels .**
- Nicorandil is an activator of ATP-dependent potassium channels
- Effect → relaxation of smooth muscle in veins → venodilatation → ↓ ventricular filling pressures + dilatation of the coronary arterioles
- It relaxes vascular smooth muscle through membrane hyperpolarisation via increased transmembrane potassium conductance and, like nitrates, through an increase in intracellular cyclic guanosine monophosphate (GMP).

Indication

- **now second-line treatment for angina**
- Use nicorandil for treatment of stable angina only in patients whose angina is inadequately controlled by first line anti-anginal therapies, or who have a contraindication or intolerance to first line anti-anginal therapies such as beta-blockers or calcium antagonists

Side effects

- Headache
 - ⇒ **The most common** unwanted effect (- 35% of patients),
 - ⇒ appears to be dose-dependent
 - ⇒ resolves with continued treatment
- **Ulcerations**
 - ⇒ oral ulceration, flushing and gastrointestinal disturbances
 - ⇒ **(ulceration of the upper and lower gastrointestinal tract and may present with life threatening bleeding)**
 - ⇒ Nicorandil can cause serious skin, mucosal, and eye ulceration, including gastrointestinal ulcers which may progress to perforation, haemorrhage, fistula, or abscess

Contraindication

- **Use with phosphodiesterase inhibitors such as sildenafil is contraindicated since they can potentiate the hypotensive effects of nicorandil**

Digoxin and digoxin toxicity

The half-life of digoxin is around 36-48 hours. This results in a delay before steady plasma levels are seen, it may take a week to start its action

Digoxin - inhibits the Na^+/K^+ ATPase pump

- Digoxin is a cardiac glycoside now mainly used for rate control in the management of atrial fibrillation.
- As it has positive inotropic properties it is sometimes used for improving symptoms (but not mortality) in patients with heart failure.
- **digoxin is highly water-soluble**
- Digoxin has a high volume of distribution and long half-life (36-48 h), which means that loading doses are required to allow the drug to reach a steady-state concentration more quickly.
 - ⇒ If initiated on a maintenance dose (without loading), it will take several days to reach a steady state.
- Digoxin is almost exclusively renally cleared; as a result, renal impairment will significantly alter the half-life of this medication.

Mechanism of action

- decreases conduction through the atrioventricular node which slows the ventricular rate in atrial fibrillation and flutter
- Increases the force of cardiac muscle contraction due to inhibition of the Na^+/K^+ ATPase pump which is located in the sarcolemmal membrane.
- Also stimulates vagus nerve

What is the pharmacokinetic reason that drives the practice of loading with digoxin?

→ Volume of distribution.

- The volume of distribution for Digoxin is very large (510 litres). This means that administered doses are rapidly distributed to body tissues.
- The initial distribution lasts for some 6-8hrs, which drives the typical loading regimen for Digoxin of two larger doses (500mcg) some 6-12hrs apart.
- Without loading Digoxin typically takes a few days to reach therapeutic effect.

Digoxin can worsen hyperkalaemia

- Translocation of potassium from the cells into the extracellular space can occur from digoxin overdose due to its dose-dependent Na-K-ATPase pump inhibition.

Drug Interactions Associated with Digoxin

Drug	Effect*	Mechanism
Quinidine	Increase	Decreases renal clearance of digoxin
Verapamil, diltiazem	Increase	Decreases renal clearance of digoxin
Cholestyramine, colestipol	Decrease	Binds digoxin in gastrointestinal tract; interferes with enterohepatic circulation
Spironolactone	Increase	Inhibits tubular secretion of digoxin
Thiazides, furosemide	Increase	Diuretic-induced hypokalemia and/or bumetanide hypomagnesemia potentiates digitalis action

*Increase indicates enhances digitalis effect; decreases diminishes digitalis effect.

Digoxin toxicity

- Plasma concentration alone does not determine whether a patient has developed digoxin toxicity.
- The BNF advises that the likelihood of toxicity increases progressively from 1.5 to 3 mcg/l.
 - Samples taken after 6 h will be more accurate in estimating the body's digoxin
- the mechanism of action leading to tachy-arrhythmias in digoxin toxicity → Inhibition of the sodium pump**

Features

- generally unwell, lethargy, anorexia,
 - **The earliest features** of digitalis toxicity include: Nausea, vomiting, anorexia.
- cholinergic effects : nausea, vomiting, diarrhea
- confusion,
- yellow-green** vision
- arrhythmias (e.g. AV block, bradycardia)
 - **(Digoxin toxicity can result in any abnormal cardiac rhythm except type-II second-degree atrioventricular (AV) block)**

Precipitating factors

- classically: hypokalaemia**
 - (hyperkalaemia may also worsen digoxin toxicity, although this is very small print)
- increasing age
- renal failure
- myocardial ischaemia
- hypomagnesaemia,
- hypercalcaemia,**
- hypernatraemia,**
- acidosis
- hypoalbuminaemia
- hypothermia
- hypothyroidism
- amyloidosis

- drugs: amiodarone, quinidine, **verapamil**, diltiazem, spironolactone (competes for secretion in distal convoluted tubule therefore reduce excretion), ciclosporin. Also drugs which cause hypokalaemia e.g. thiazides and **loop diuretics**
 - **Bumetanide is a loop diuretic and may cause hypokalaemia as a side effect.**
The potassium loss caused by bumetanide increases the toxicity of digoxin.

Management

Antidote "KLAM"

- slowly normalize K⁺
- Lidocaine
- digoxin Antibodies (anti-dig Fab fragments)
- Mg²⁺

Phenytoin may be used as an alternative to lidocaine (both are class IB agents) if immune therapy is unsuccessful or unavailable in the treatment of tachyarrhythmias secondary to digoxin toxicity.

- Treatment of digoxin toxicity should be guided by the patient's signs and symptoms and the specific toxic effects and not necessarily by digoxin levels alone.
- Activated charcoal if presented within 1 h of an overdose
 - The first-line treatment for acute ingestion is repeated dosing of activated charcoal to reduce absorption and interrupt enterohepatic circulation.
- Binding resins (eg, cholestyramine)
 - may bind enterohepatically-recycled digoxin.
 - may be more appropriately used for treatment of chronic toxicity in patients with renal insufficiency.
- correct arrhythmias
- severe sinus bradycardia (hemodynamically unstable bradyarrhythmic patients) → Atropine
- ventricular tachycardia → responds best to digoxin immune therapy, but phenytoin and lidocaine are useful if immune therapy is ineffective or unavailable.
 - These drugs depress the enhanced ventricular automaticity without significantly slowing AV conduction
- Magnesium sulfate, 2 g IV over 5 minutes, has been shown to terminate dysrhythmias in digoxin-toxic patients with and without overt cardiac disease.
 - Magnesium is contraindicated in the setting of bradycardia or AV block and should be used cautiously in patients with renal failure.
- Premature ventricular contractions (PVCs), bigeminy, or trigeminy may require only observation unless the patient is hemodynamically unstable, in which case lidocaine may be effective.
- Digibind
 - **Its brand name of Digoxin immune fab or Digoxin-specific antibody** is an antidote for overdose of digoxin
 - Action: bind to the digoxin → unable to bind to its action sites
 - is an immunoglobulin fragment that binds with digoxin.
 - first-line treatment for significant dysrhythmias from digitalis toxicity
 - ⇒ Indications for digoxin-specific antibodies include:
 - Hemodynamically unstable arrhythmia
 - ❖ **Tachyarrhythmias** with hypotension
 - ❖ bradycardia with hypotension that do not respond to atropine

- treatment.
- End organ damage
- digoxin level > 4ng/ml if chronic ingestion
- digoxin level > 10 ng/ml if acute ingestion (taken 6 h after the last dose)
- **Hyperkalaemia** (if not respond to insulin-dextrose infusions): potassium > 5 mEq/L and symptomatic
- **SE → Serum sickness**
- If digoxin-specific antibodies not available → lidocaine or phenytoin
- Digoxin toxicity related ventricular tachycardia:
 - **Phenytoin and lidocaine are useful for ventricular tachycardia if immune therapy is ineffective or unavailable**
 - Phenytoin is thought to suppress the pro-arrhythmic properties of digoxin without diminishing its inotropic effects.
 - **lidocaine is useful for chemical cardioversion of digoxin toxicity related ventricular tachycardia.** This is because it can reduce ventricular automaticity without significantly slowing AV conduction.
 - Calcium channel blockers are contraindicated because they may increase digoxin levels.
 - Amiodarone is shown to increase digoxin levels and as such can worsen the risk of rhythm disturbance further.
 - VT in digoxin toxicity is resistant to electrical cardioversion, which may actually precipitate VF and asystole.
 - Bretylium is contraindicated in the treatment of digoxin induced arrhythmias as it can actually precipitate ventricular tachycardia.
 - Quinidine worsens AV and SA conductivity and reduces digoxin tissue binding and is therefore also contraindicated.
- conventional dialysis is ineffective
- monitor potassium
 - ⇒ Electrolytes
 - In **acute toxicity, hyperkalemia** is common
 - ❖ Although calcium is often used to ameliorate cardiac toxicity from hyperkalemia, it is not recommended in patients with digoxin toxicity because it can delay after-depolarization and may precipitate ventricular tachycardia or fibrillation. This is based on the fact that intracellular calcium levels are already high in this setting.
 - ❖ potassium level > 5 mEq/L → digoxin Fab fragments
 - **Chronic toxicity** is often accompanied by **hypokalemia** and hypomagnesemia
 - ❖ Concomitant hypomagnesemia may result in refractory hypokalemia
 - Correction of electrolyte imbalances may reverse dysrhythmias.

Which measurement would be most useful when monitoring patient for digoxin efficacy?

→ **Pulse rate**

- Measuring drug plasma concentration will tell you whether digoxin is at therapeutic concentrations in the blood, but not whether it is having a therapeutic effect.

Diuretics

Class	Compound	Action	Side effects
Loop Diuretics	Furosemide Bumetanide ethacrynic acid	inhibit NKCC2 in the thick ascending loop of Henle	Deafness
Thiazides	hydrochlorothiazide, indapamide	inhibit NaCl co-transporter in early distal tubule	hyponatraemia, hypokalaemia, hypercalcaemia
K+ sparing agents	spironolactone	Aldosterone receptor antagonist	Hyperkalemia
	amiloride, triamterene	inhibit Na channel in late distal tubule	Hyperkalemia
Osmotic Diuretics	mannitol	Inhibit water reabsorption throughout the tubules, but mostly in the proximal tubule	Pulmonary edema

Loop diuretics

Action

- Furosemide and bumetanide are loop diuretics that act by inhibiting the Na-K-Cl cotransporter (NKCC) in the thick ascending limb of the loop of Henle, reducing the absorption of NaCl.
- There are two variants of NKCC; **loop diuretics act on NKCC2**, which is more prevalent in the kidneys.

Indications

- heart failure: both acute (usually intravenously) and chronic (usually orally)
- resistant hypertension, particularly in patients with renal impairment

Adverse effects

- | | |
|---|--|
| <ul style="list-style-type: none"> hypotension hyponatraemia hypokalaemia hypochloraemic alkalosis ototoxicity | <ul style="list-style-type: none"> hypocalcaemia renal impairment (from dehydration + direct toxic effect) hyperglycaemia (less common than with thiazides) gout |
|---|--|
- Loop diuretics induces ototoxicity by affecting Na+/K+/2Cl- cotransporters present in the inner ear.**
 - Explanation of respond to i.v furosemide but not oral in heart failure → Increased bioavailability**
 - ⇒ In right heart failure → The patient has a lot of gut oedema which would → reduce the absorption of oral furosemide. Intravenous furosemide would have a much better bioavailability and thus therapeutic effect.
 - ⇒ Protein binding of drugs may be reduced in elderly patients, this may be due to malnutrition.
 - Explanation of not responding to furosemide in chronic kidney disease (CKD) → Tubular secretion of furosemide is reduced in CKD**
 - ⇒ Organic acids accumulate in renal failure and compete for tubular secretion with furosemide. This competition can be overcome by using a larger dose of the drug.

A 76-year-old lady taking perindopril 2 mg, bisoprolol 1.25 mg and had recently had her dose of furosemide increased from 40 mg to 80 mg. C/O dizziness, particularly when standing upright after being seated. There were no clinical signs of cardiac failure. Serum urea: 13.3 mmol/L. **Serum creatinine: 221 µmol/L.** What is the next step in her management?

→ Stop the furosemide temporarily and restart at a lower dose within a few days

- This lady is developing postural hypotension after the recent increase in furosemide dose.
- She has moderate renal impairment.
- Stopping either her beta-blocker or **ACE inhibitor** is not the best option for treatment at this stage.

Which loop diuretic is known to cause sulfa-drug allergy?

→ Furosemide

Which loop diuretic is used for diuresis in patients allergic to sulfa drugs?

→ Ethacrynic Acid

Bendroflumethiazide

Bendroflumethiazide - site of action = proximal part of the distal convoluted tubules

the target of action of thiazide diuretics → NaCl co-transporter

the target of action of loop diuretics → NKCC2

- Bendroflumethiazide (bendrofluazide) is a thiazide diuretic which works by inhibiting sodium absorption at the beginning of the distal convoluted tubule (DCT).
- **The NaCl co-transporter:**
 - ⇒ the target of thiazide diuretics
 - ⇒ it contributes to the reabsorption of about 10% of the filtered load of sodium.
 - ⇒ Mutations causing loss of function of the NaCl co-transporter cause Gitelman's syndrome, the commonest monogenic cause of hypokalaemia in adults.
- Potassium is lost as a result of more sodium reaching the collecting ducts.
- Bendroflumethiazide has a role in the treatment of mild heart failure although loop diuretics are better for reducing overload.
- The main use of bendroflumethiazide was in the management of hypertension but recent NICE guidelines now recommend other thiazide-like diuretics such as indapamide and chlortalidone.

Bendroflumethiazide - mechanism of Hypokalemia:

- ↑ sodium reaching the collecting ducts
- Activation of the renin-angiotensin-aldosterone

Common adverse effects	Rare adverse effects
<ul style="list-style-type: none"> • dehydration • postural hypotension • hyponatraemia, hypokalaemia, Hypomagnesaemia, hypercalcaemia • gout • impaired glucose tolerance • impotence 	<ul style="list-style-type: none"> • thrombocytopaenia • agranulocytosis • photosensitivity rash • pancreatitis • hypochloraemic alkalosis

Amiloride

- The potassium-sparing diuretic **amiloride** → inhibits sodium channels in the distal segment of the distal convoluted tubule
- **Amiloride** → inhibits the action of aldosterone on the distal convoluted tubule producing potassium reabsorption.
- In treating a patient with congestive heart failure who develops hypokalaemia, the best choice is to add a small dose of amiloride to his furosemide therapy

Triamterene

- Triamterene, a potassium sparing diuretic similar to amiloride.
- occasionally prescribed with thiazide or loop diuretics, to prevent hypokalaemia.
- It inhibits the movement of sodium through channels towards the end of the distal tubule and collecting ducts, preventing the passage of sodium from the urinary space into the tubular cells. This action causes hyperpolarisation of the apical plasma membrane, preventing the secretion of potassium into the collecting ducts.
- **Hyperkalaemia is common (>5%)**, and is unaffected by concurrent potassium depleting diuretics.
- In mild hyperkalaemia, (eg: K = 5.9 mmol/l) with no evidence of cardiac toxicity. The management involves stopping the triamterene, and repeating the U&E in one week.

Spironolactone

- Spironolactone is an aldosterone antagonist
- acts in the cortical **distal convoluted tubule** and collecting duct.

Indications

- ascites: patients with cirrhosis develop a secondary hyperaldosteronism. Relatively large doses such as 100 or 200mg are often used
- hypertension: used in some patients as a NICE 'step 4' treatment
- heart failure (see RALES study below)
- nephrotic syndrome
- Conn's syndrome
- **Spironolactone** is a diuretic with **anti-androgen effects**. This makes it a useful agent in the treatment of hormonal acne and hirsutism.
 - ⇒ It blocks the androgen receptor and 5α-reductase enzyme that is responsible for the synthesis of dihydrotestosterone (DHT) and **can be used to treat hirsutism.**

Adverse effects

- **hyperkalaemia**
- gynaecomastia
 - ⇒ Spironolactone and **eprelenone** are both aldosterone receptor antagonists that have shown survival benefit in patients with NYHA III/IV systolic heart failure.

- ⇒ Eplerenone has a lower antiandrogenic effect compared to spironolactone and may, therefore, be preferable if patient develops erectile dysfunction and bilateral gynecomastia.

RALES

- NYHA III + IV, patients already taking ACE inhibitor
- low dose spironolactone reduces all-cause mortality

Eplerenone

Indications

- Eplerenone is a **spironolactone-like agent** indicated as an add-on to standard therapy after a myocardial infarction, and heart failure

Side-effects

- **Common side-effects:** **hyperkalaemia**, dizziness, hypotension, diarrhoea, nausea and prerenal renal dysfunction
- **Uncommon side-effects :** eosinophilia, dehydration, hypercholesterolemia and hypertriglyceridaemia

Cautions

- The drug is metabolised via the CYP3A4 system, so that inducers or inhibitors of the 3A4 enzyme subtype may precipitate drug interactions

Diuretic abuse

- Diuretic abuse is not uncommon amongst athletes and jockeys as a means of weight loss.
- **The patient has a hypokalaemic alkalosis, and urine potassium excretion is high despite the hypokalaemia.**

Respiratory drugs

Theophylline

- Theophylline, like caffeine, is one of the naturally occurring methylxanthines.
- The main use of theophyllines in clinical medicine is as a bronchodilator in the management of asthma and COPD

Action

- The exact mechanism of action has yet to be discovered.
- One theory suggests theophyllines may be a non-specific **inhibitor of phosphodiesterase** resulting in an increase in cAMP.
- **antagonism of adenosine** and prostaglandin inhibition
 - **It blocks the adenosine receptor**
 - Blockade of the receptors by theophylline results in:
 - relaxation of smooth muscles, especially bronchial muscles
 - constriction of cerebral blood vessels
 - stimulation of the cardiac pacemaker
 - stimulation of gastric secretions
- Theophylline also releases calcium ions from the sarcoplasmic reticulum in skeletal and cardiac muscle, thus enhancing their contractility, including diaphragmatic contractility
- plasma theophylline concentration of between 10 and 20 mg/l is required for satisfactory bronchodilatation.

Side effect

- **At therapeutic doses, the side-effect of Aminophylline → Jitteriness**

- adverse effects can occur within the range 10-20 mg/l and both the frequency
- severity increase at concentrations above 20 mg/l**

Factors increasing the plasma theophylline concentration:

- heart failure
- cirrhosis
- viral infections
- increased age (the elderly)
- Diet:
 - Obesity
 - High carbohydrate intake
 - High methylxanthine intake (for example, tea, coffee)
- drugs that **inhibit** its metabolism
 - Commonly prescribed drugs that can increase serum theophylline levels include:
 - clarithromycin, **erythromycin**
 - ciprofloxacin**,
 - cimetidine,
 - oral contraceptives
 - allopurinol.
 - Fluvoxamine
 - Consideration should be given to reducing theophylline dose when these drugs are prescribed.
- cessation of enzyme-inducing drugs.

Factors decreasing the plasma theophylline concentration: (increasing theophylline clearance):

- Diet:
 - Low carbohydrate
 - High protein intake
- Social:
 - chronic alcoholism without cirrhosis
 - smoking**
 - Smoking cessation → sudden increase in theophylline level**
 - Regular tobacco use up-regulates hepatic enzyme activity; cessation will be associated with a decrease of hepatic enzyme activity, such that theophylline concentrations may increase.
- Drugs: drugs that **induce** liver metabolism: eg:
 - Rifampicin
 - Carbamazepine.

Theophylline poisoning

- Theophylline has a narrow therapeutic window and needs close monitoring of its serum level to avoid toxicity**
- Symptoms of toxicity may be delayed following the ingestion of sustained-release preparations for up to 48 h
- Theophylline toxicity occurs with concomitant use of clarithromycin **due to inhibition of cytochrome P450 (CYP1A2 and CYP3A4) by clarithromycin.**
- Features of mild to moderate theophylline toxicity include nausea, vomiting, epigastric, tremor, tachycardia, restlessness and hallucinations. Severe toxicity can cause convulsions, arrhythmias and metabolic acidosis.
- Studies have shown an approximate 20% increase in both peak and trough theophylline levels with concomitant use of clarithromycin and it is recommended that theophylline levels should be monitored prior, during and on cessation of clarithromycin and dosage

adjustment of theophylline made accordingly.

- **Features**

- mild to moderate theophylline toxicity
 - nausea, vomiting, epigastric,
 - tremor,
 - tachycardia,
 - restlessness and
 - hallucinations.
- Severe toxicity:
 - convulsions,
 - arrhythmias
 - metabolic acidosis, **hypokalaemia** and hyperglycaemia

- **Management**

- activated charcoal
- charcoal haemoperfusion is preferable to haemodialysis

In cases of severe theophylline toxicity, charcoal haemoperfusion can be used

Antimuscarinic agent

- Muscarinic antagonists (antimuscarinic agents) are a group of anticholinergic drugs that competitively inhibit postganglionic muscarinic receptors.
- Which organ systems are most affected by an antimuscarinic agent **depends on** the specific characteristics of the agent, particularly **its lipophilicity**.
 - Lipophilic agents (i.e., atropine or benztropine) are able to cross the blood-brain barrier and therefore affect the central nervous system (CNS) in addition to other organ systems.
 - Less lipophilic agents (i.e., ipratropium or butylscopolamine) are administered if the CNS does not need to be targeted, specifically for respiratory (e.g., asthma), gastrointestinal (e.g., irritable bowel syndrome), or genitourinary applications (e.g., urinary incontinence).

Action

- Muscarinic antagonists (the majority of anticholinergic drugs) inhibit the effect of acetylcholine on muscarinic receptors,

Effects of muscarinic antagonists

Muscarinic receptors	Organ/Tissue	Effects
M1, M4, M5	Central nervous system	<ul style="list-style-type: none"> Influences neurologic function (e.g., cognitive impairment)
M2	Heart	<ul style="list-style-type: none"> ↑ Heart rate Increases AV-node conduction → arrhythmias
M3	Smooth muscle	<ul style="list-style-type: none"> Gastrointestinal tract <ul style="list-style-type: none"> ↓ Intestinal peristalsis , ↓ Salivary and gastric secretions Urinary tract <ul style="list-style-type: none"> ↓ Bladder contraction (decreases detrusor muscle tone, increases the internal urethral sphincter tone) Airway <ul style="list-style-type: none"> Bronchodilation ↓ Bronchial secretions Eye <ul style="list-style-type: none"> Mydriasis → narrowing of the iridocorneal angle Impaired accommodation Blood vessels: minimal effect on vascular tone and blood pressure
	Exocrine glands	<ul style="list-style-type: none"> ↓ Secretions (sweat)

Antimuscarinic side effects

"Blind as a bat (mydriasis), mad as a hatter (delirium), red as a beet (flushing), hot as a hare (hyperthermia), dry as a bone (decreased secretions and dry skin), the bowel and bladder lose their tone (urinary retention and paralytic ileus), and the heart runs alone (tachycardia)."

	Side effect	Contraindications
Impaired secretion by exocrine glands	<ul style="list-style-type: none"> Dry mouth and sore throat ↓ Respiratory tract secretions Hyperthermia und warm, dry skin 	<ul style="list-style-type: none"> Acute asthma Respiratory distress
Cardiovascular system	<ul style="list-style-type: none"> Tachycardia 	<ul style="list-style-type: none"> Tachyarrhythmias Heart failure Myocardial infarction Hyperthyroidism
Decreased smooth muscle tone	<ul style="list-style-type: none"> Gastroesophageal reflux Obstipation or ileus Impaired micturition/urinary retention Vasodilatation and flush 	<ul style="list-style-type: none"> Hiatal hernia associated with reflux esophagitis Ulcerative colitis Paralytic ileus Obstructive disease of the gastrointestinal tract (e.g., achalasia, pyloric stenosis or duodenal stenosis) Obstructive uropathy (e.g., benign prostatic hyperplasia, urinary retention)
Eye	<ul style="list-style-type: none"> Mydriasis and photophobia Blurred vision 	<ul style="list-style-type: none"> Narrow-angle glaucoma
CNS	<ul style="list-style-type: none"> Excitement, agitation, and hallucinations with the use of lipophilic parasympatholytics (e.g., atropine), especially in elderly patients Confusion, disorientation Coma, seizure, and rarely death 	<ul style="list-style-type: none"> Myasthenia gravis

Lipophilic antimuscarinic (good oral bioavailability and CNS penetration) (Tertiary amines)

Drug	Effect	Indication
• Atropine	<ul style="list-style-type: none"> ↑ Heart rate ↓ Secretions of exocrine glands ↓ Tone and motility of smooth muscles ↓ Cholinergic overactivity in CNS Mydriasis and cycloplegia 	<ul style="list-style-type: none"> First drug of choice in unstable (symptomatic) sinus bradycardia (IV) Premedication: prior to intubation to decrease salivary, respiratory, and gastric secretions Ophthalmology: uveitis Antidote for anticholinesterase poisoning Scorpion stings
• Scopolamine(hyoscine)	<ul style="list-style-type: none"> ↓ Vestibular disturbances (antiemetic) 	• Motion sickness
• Homatropine • Tropicamide	<ul style="list-style-type: none"> Mydriasis Impair accommodation 	<ul style="list-style-type: none"> Ophthalmology <ul style="list-style-type: none"> Therapeutic use: in patients with uveitis Diagnostic use: pupillary dilation to allow ocular fundus examination and cycloplegia to allow refractory testing
• Benztropine • Biperiden • Trihexyphenidyl	<ul style="list-style-type: none"> ↓ Cholinergic overactivity in CNS 	<ul style="list-style-type: none"> Antiparkinsonian effect (Parkinson disease) ↓ Extrapyramidal symptoms (EPS) caused by antipsychotics
• Oxybutynin • Tolterodine • Solifenacin • Dicyclomine	<ul style="list-style-type: none"> ↓ Tone and motility of smooth muscle cells 	<ul style="list-style-type: none"> Oxybutynin, tolterodine, and solifenacin: overactive bladder incontinence Dicyclomine: irritable bowel syndrome
• Darifenacin	<ul style="list-style-type: none"> ↑ Sphincter tone 	<ul style="list-style-type: none"> Urinary urgency, urge incontinence, urinary frequency, and/or nocturia(symptoms resulting from, e.g., overactive bladder)

Hydrophilic (poor oral bioavailability and CNS penetration) (Quaternary amines)

Drug	Effect	Indication
<ul style="list-style-type: none"> Glycopyrrrolate 	<ul style="list-style-type: none"> Decreases secretions of exocrine glands 	<ul style="list-style-type: none"> Peptic ulcer disease treatment
<ul style="list-style-type: none"> Ipratropium bromide Tiotropium bromide 	<ul style="list-style-type: none"> Bronchodilation 	<ul style="list-style-type: none"> COPD and bronchial asthma Ipratropium bromide: <ul style="list-style-type: none"> COPD grade I and higher Acute management of refractory asthma Tiotropium bromide: <ul style="list-style-type: none"> Longer duration of action Long-term treatment of COPD (grade II and above)

Anticholinergic syndrome (overdose)

- Etiology
 - Belladonna poisoning
 - Jimson weed/Angel's trumpet (*Datura stramonium*) poisoning
 - Medications
 - Anticholinergic agents (e.g., atropine, benztropine, trihexyphenidyl)
 - Drugs with anticholinergic properties
 - Tricyclic antidepressives (predominantly doxepin, amitriptyline, imipramine, and trimipramine)
 - Antipsychotics (e.g., clozapine, quetiapine)
 - First-generation antihistamines (e.g., promethazine, dimenhydrinate)
- Clinical features
 - Dry mouth, warm, flushed skin, thirst, tachycardia, arrhythmias, mydriasis, confusion, and agitation
 - Possibly anticholinergic delirium: Excessive use of tricyclic antidepressants (or other medications with significant anticholinergic effects) can cause life-threatening delirium, hallucinations, and psychomotor symptoms.
- Treatment: antidote for purely anticholinergic poisoning (e.g. atropine): physostigmine**

One mnemonic used to remember the symptoms of anticholinergic toxicity is:

Hot as a hare: increased body temperature
Blind as a bat: mydriasis (dilated pupils)
Dry as a bone: dry mouth, dry eyes, decreased sweat
Red as a beet: flushed face
Mad as a hatter: delirium

Tiotropium

Indications

- Tiotropium is a specific long-acting **antimuscarinic** agent indicated as maintenance therapy for patients with (COPD)

Cautions

- Caution is advised in patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction

Side-effects

- Dry mouth
- Paradoxical bronchospasm
- Rarer side-effects include tachycardia, blurred vision, urinary retention and constipation

Doxapram

Indications

- Doxapram is a centrally acting respiratory stimulant, used in patients with severe respiratory disease who are deemed unsuitable for admission to the Intensive Therapy Unit
- Intravenous doxapram only used if the patient is not suitable for either intubation or non-invasive ventilation.
- The main purpose in using doxapram is to allow time for recovery from an acute respiratory event
- The usual dosing regimen is 1-4 mg/min given as an intravenous infusion

Contraindications

- heart disease,
- epilepsy, cerebral oedema, stroke,
- status asthmaticus,
- hypertension, **hyperthyroidism** and phaeochromocytoma

Side-effects

- hypertension,
- exacerbation of apparent dyspnoea,
- agitation,
- confusion,
- sweating,
- cough,
- headache,
- dizziness,
- nausea, vomiting
- urinary retention

Sodium cromoglicate

- Sodium cromoglicate principally acts by reducing the degranulation of mast cells triggered by the interaction of antigen and IgE
- The **inhibitory effect on mast cells** appears to be cell-type specific, since cromoglicate has little inhibitory effect on mediator release from human basophils
- More recent research has also shown that cromoglicate may act on eosinophils to reduce their inflammatory response to inhaled allergens, but this is not the most probable mechanism of action of sodium cromoglicate **in the prophylaxis of asthma**

Magnesium treatment in asthma

- Intravenous magnesium (1.2 - 2 g given over 20 minutes) is now indicated in the management of severe life threatening acute asthma attacks

Its principal actions are to:

- inhibit acetylcholine release at the neuromuscular junction

- relax bronchial smooth muscle
- stabilise mast cells

Unwanted effects are uncommon following single-dose therapy, although a slight decrease in blood pressure can be noticed and flushing can occur

Symptoms of hypermagnesaemia include:

- | | |
|---|--|
| <ul style="list-style-type: none"> ▪ nausea ▪ diarrhoea ▪ flushing ▪ hypertension | <ul style="list-style-type: none"> ▪ confusion ▪ coma ▪ loss of tendon reflexes |
|---|--|

CNS & Psychiatric drugs

Anti-convulsants

Remarkable side effects of anti-epileptic drugs are:

- SIADH and rash (carbamazepine)
- Liver toxicity (sodium valproate)
- Severe rash (lamotrigine)
- Retinal damage (vigabatrin)
- Aplastic anaemia (felbamate).
- **Topiramate**
 - ⇒ anticonvulsant ,most frequently prescribed for the prevention of migraines
 - ⇒ **Side effects:**
 - Renal stones
 - ❖ topiramate causes systemic metabolic acidosis, lowers urinary citrate excretion, and increases urinary pH. These changes increase the propensity to form **calcium phosphate stones**.
 - weight loss (weight gain with sodium valproate),
 - impaired taste sensation,
 - cognitive dysfunction
 - depression.
 - Tingling in extremities.
- **Felbamate**
 - ⇒ Because of its **potentially fatal toxic effects** (especially **aplastic anemia** and hepatic failure), the use of felbamate should be restricted to patients with severe partial epilepsy or Lennox-Gastaut syndrome who do not respond to other medications.
- **Lamotrigine**
 - ⇒ Lamotrigine has a black box warning because of its association with Stevens-Johnson syndrome.
 - **the risk of tevens-Johnson syndrome increases if it is co-administered with valproate .**
 - When co-administered with valproate, the dosage of lamotrigine should be half that required in the absence of valproate and should be very slowly escalated.

Epilepsy medication in pregnancy

- There is an increased risk of neural tube defects associated with anti-convulsants during pregnancy.
- However, the risks associated with treatment are outweighed by the benefits in preventing seizures, so the drug should be continued.
- The risks may be minimised through use of folate supplements.
- **If a patient is planning on pregnancy, then registry studies suggest that lamotrigine would be the best choice**
- **Percentage of Congenital malformations associated with Anti-epileptics**
 - ⇒ Valproate → 6% (neural tube defects in the fetus)
 - **Valproate should be avoided in pregnancy if possible**
 - NICE guidance suggests that **phenytoin** should be avoided in women of child-bearing age because of the risk of congenital malformations.
 - ⇒ Topiramate → 4.3%
 - ⇒ Phenytoin → 3.5% (fetal hydantoin syndrome with facial dysmorphism)
 - ⇒ Carbamazepine → 2.5%
 - ⇒ General population → 1.5%
 - ⇒ Primidone and phenobarbital → withdrawal symptoms in the newborn

Breast feeding is acceptable with nearly all anti-epileptic drugs

Contraception in epilepsy

- Phenytoin induces liver enzymes, thereby increasing oestrogen breakdown and reducing the effectiveness of oestrogen-containing contraceptives
- Where the combined contraceptive pill is used in conjunction with phenytoin, the contraceptive should contain high dose oestrogen: 50 mg ethinylestradiol or more
- **Lamotrigine** is a suitable first-line treatment for partial epilepsy, and **does not alter oestrogen metabolism**
- **Lamotrigine** is the most appropriate choice in women of child-bearing age because:
 - ⇒ low risk of congenital malformations.
 - ⇒ it does not affect the effectiveness of the oral contraceptive pill
- Women taking **lamotrigine** monotherapy and **oestrogen-containing contraceptives** should be informed of the potential **increase in seizures due to a fall in the levels of lamotrigine**.
- Whilst **Carbamazepine** is a potent enzyme inducer and therefore **can't be used in combination with the pill**

Antiepileptic and weight (medical-masterclass.com 2017 part 2)

- **Two antiepileptic medications have been found to induce weight loss;** topiramate and zonisamide.
- Valproate, vigabatrin, gabapentin, carbamazepine, and pregabalin **induce weight gain**.
- Levetiracetam, lamotrigine, and phenytoin are **weight neutral**.

Sodium valproate

Indications

- management of epilepsy and is first line therapy for generalised seizures.
- acute mania

Action

- blockage of voltage-gated sodium channels
- increasing GABA activity (by inhibits GABA transaminase).

Adverse effects

- | | |
|--|---|
| <ul style="list-style-type: none"> gastrointestinal: nausea increased appetite and weight gain alopecia: regrowth may be curly
(note that phenytoin → hirsutism while valporate → alopecia) ataxia tremor | <ul style="list-style-type: none"> hepatitis pancreatitis thrombocytopaenia teratogenic hyponatraemia polycystic ovarian (PCOS) syndrome strong inhibitor of CYP450s. |
|--|---|

Which enzyme does Valproic Acid inhibit?

GABA Transaminase

What ion channel does valproic acid block?

voltage-gated sodium channels

Sodium valproate can lead to severe hepatic toxicity. more commonly if the patient has a metabolic or degenerative disorder, organic brain disease or severe seizures associated with mental retardation. Usually this reaction occurs within the first three months of therapy.

Phenytoin

Indications

- management of seizures.
- used as an antidote for Digitalis-induced arrhythmias.

Action

- blockage of voltage gated Na⁺ channels.
- refractory period of voltage-gated Na⁺ channels **decreasing the sodium influx into neurons** which in turn decreases excitability

Side effects

- Acute**
 - initially: dizziness, diplopia, nystagmus, slurred speech, ataxia
 - later: confusion, seizures
- Chronic**
 - common: **gingival hyperplasia** (secondary to increased expression of platelet derived growth factor, PDGF), **hirsutism**, coarsening of facial features, drowsiness
 - megaloblastic anaemia** (secondary to **altered folate metabolism**)

- peripheral neuropathy
- enhanced vitamin D metabolism causing osteomalacia
- lymphadenopathy
- dyskinesia
- **Idiosyncratic**
 - fever
 - rashes, including severe reactions such as toxic epidermal necrolysis
 - hepatitis
 - Dupuytren's contracture (although not listed in the BNF)
 - aplastic anaemia
 - **drug-induced lupus**
 - Hypocalcaemia
 - Pseudolymphoma or, rarely, malignant lymphoma and mycosis-fungoides-like lesions.
- **Teratogenic**
 - associated with cleft palate and congenital heart disease

Interaction

- Phenytoin would speed up metabolism of ethinyloestradiol making the pill less effective.
 - **strong inducer of CYP450 enzymes.**
- **Cimetidine increases the efficacy of phenytoin by reducing its hepatic metabolism**
- Sucralfate may decrease the pharmacological effects of phenytoin when administered concurrently
- **Effect on other anti-epileptic:**
 - ⇒ Phenytoin usually lowers the serum concentration of carbamazepine, clonazepam, topiramate and sodium valproate,
 - ⇒ **elevates the serum level of phenobarbitone.**
 - ⇒ Phenytoin does not appear to influence the serum concentration of levetiracetam.

In renal failure

Renal failure → ↓ drug affinity for protein binding → ↑ free drug → toxicity (drug level may be within the therapeutic range)

- In patients with renal failure, dose reduction of phenytoin is therefore required.
- Other drugs where this may be a problem include sodium valproate and warfarin.

There is no oral preparation of fosphenytoin; it is used in status epilepticus only.

Phenytoin toxicity typically gives rise to a cerebellar-like syndrome. Nystagmus is present even in mild toxicity.

Carbamazepine

Carbamazepine is chemically similar to the tricyclic antidepressant drugs.

Indications:

- most commonly used in the treatment of epilepsy, particularly partial seizures, where carbamazepine remains a first-line medication.
- Other uses include
 - neuropathic pain (e.g. trigeminal neuralgia, diabetic neuropathy)
 - bipolar disorder

Mechanism of action

- binds to sodium channels increases their refractory period

Adverse effects

- P450 enzyme inducer
 - **Auto-induction of carbamazepine metabolism → need to increase the dose to achieve a therapeutic plasma concentration.**
 - In patients on carbamazepine who develop Hashimoto's thyroiditis the dose of thyroxine should be increased to maintain therapeutic levels
- dizziness and ataxia
- drowsiness
- headache
- nystagmus
- visual disturbances (especially diplopia)
 - **The most common dose-related adverse effects of carbamazepine are diplopia and ataxia**
- **Steven-Johnson syndrome**
 - **HLA-B*1502 in individuals of Han Chinese and Thai origin** has been shown to be strongly associated with the risk of developing Stevens-Johnson syndrome (SJS) when treated with carbamazepine.
 - The prevalence of the HLA-B*1502 carrier is about 10% in Han Chinese and Thai populations.
 - Whenever possible, these individuals should be screened for this allele before starting treatment with carbamazepine
- leucopenia and agranulocytosis
- syndrome of inappropriate ADH secretion
- Carbamazepine is nephrotoxic and may cause **proteinuria**.

Carbamazepine overdose presents with:

- | | |
|--|--|
| <ul style="list-style-type: none"> • Drowsiness • Slurred speech • Ataxia • Hallucinations • Nausea • Vomiting | <ul style="list-style-type: none"> • Tremor • Blurred vision • Seizures • Oliguria, and • Bullous skin lesions. |
|--|--|

Contraindications:

- atrioventricular (AV) conduction abnormalities
- porphyria
- history of bone marrow depression

Vigabatrin

Vigabatrin → Visual field defects

Action

- Inhibition of GABA Transaminase, thereby increasing GABA levels

Indication:

- Vigabatrin should be used only in combination with other anti-epileptic drugs for patients with resistant partial epilepsy when all other appropriate drug combinations have proved inadequate or have not been tolerated.
- **Vigabatrin** is the drug of choice for infantile spasms, is not generally used outside the situation of infantile spasms

Adverse effects:

- reduced peripheral vision
 - ⇒ 40% of patients develop visual field defects, which may be irreversible
 - ⇒ The pattern of the field defect is typically a bilateral, absolute concentric constriction of the visual field, the severity of which varies from mild to severe.
 - ⇒ Vigabatrin-associated field defects are typically nasal more so than temporal,
 - ⇒ **visual fields should be checked** before the start of treatment and **every 6 months**
- aggression
- alopecia
- retinal atrophy

Topiramate

a patient with epilepsy and hepatic impairment → Topiramate

Action

- ⇒ blocks voltage-gated Na⁺ channels
- ⇒ ↑ GABA action

advantages

- ⇒ Topiramate is one of the few antiepileptic drugs (also including gabapentin) with almost exclusively renal metabolism
- ⇒ It would be less likely to cause worsening of hepatic function

adverse effects of topiramate include

- renal stones
- weight loss
- and neuropsychiatric side-effects

Gabapentin

MOA of Gabapentin and Pregabalin?

- Inhibits voltage gated Ca channels as a GABA analog

used for add-on therapy in partial or generalised seizures.

- does not induce cytochrome P450 unlike other anticonvulsants such as phenytoin and phenobarbitone.

Requires dose adjustment in renal disease

Levetiracetam (Keppra)

- Action
 - unknown.
- it does not affect hepatic enzymes, but dose reduction is required in renal failure.
- Usage:
 - Is an adjunctive treatment for partial seizures with or without secondary generalisation.
- Advantages:
 - The drug appears to be well tolerated with few side effects.
 - has least interactions and is **safe with warfarin**.

Procyclidine

- Action
 - antimuscarinic
- Indication
 - used to treat the Parkinsonian side effects of neuroleptics;
- Signs of **procyclidine overdose** include:
 - Agitation
 - Confusion
 - Sleeplessness lasting up to 24 hours or more
 - Pupils are dilated and unreactive to light.
 - Visual and auditory hallucinations and tachycardia have also been reported.

Barbiturates

- Examples
 - phenobarbital, pentobarbital, thiopental, and secobarbital
- Mechanism
 - increases GABA_A action by ↑ duration of Cl⁻ channel opening resulting in ↓ neuron firing
 - barbitDURATE
- Clinical use
 - CNS depressant for anxiety and seizures
 - induction of anesthesia (thiopental)
- kinetics
 - induction of P450
 - tolerance/dependence
- Phenobarbitone suppress the central nervous system causing:
 - Hypoventilation (and therefore a respiratory acidosis)
 - Hypotension, and
 - Hypothermia.

Anticholinergic syndrome

Common causes	Signs and symptoms	Management
<ul style="list-style-type: none"> • tricyclic antidepressants • atropine • H-1-antihistamines 	<ul style="list-style-type: none"> • hot, dry skin • hypertension • tachycardia • urinary retention • dilated pupils (mydriasis) • Agitated delirium can also occur 	supportive
<ul style="list-style-type: none"> • Although physostigmine, a reversible inhibitor of acetylcholinesterase, is effective in treating symptoms, there is a significant risk of cardiac toxicity (bradycardia, AV conduction defects and asystole). • Treatment therefore consists of withdrawal of the precipitating drug and supportive care. 		

Serotonin syndrome

Causes

- monoamine oxidase inhibitors
- SSRIs
- ecstasy
- amphetamines
- The serotonin syndrome occurs primarily because of interactions between monoamine-oxidase inhibitors (MAOI) and drugs that enhance serotonin function (eg selective serotonin-reuptake inhibitors (SSRIs))

Features

- neuromuscular excitation (e.g. hyperreflexia, myoclonus, Tremor, rigidity)
- autonomic nervous system excitation (e.g. hyperthermia)
- altered mental state
- sweating
- tachycardia

Management (Cyproheptadine may be useful in treatment)

- stopping the precipitating drugs
- instituting generalised cooling measures and diazepam to reduce agitation
- Studies have suggested that drugs possessing serotonin-antagonist activity (eg **cyproheptadine**, methysergide) may provide some benefit in the management of patients with the serotonin syndrome

Oculogyric crisis

An oculogyric crisis is a dystonic reaction to certain drugs or medical conditions

Features

- restlessness, agitation
- involuntary upward deviation of the eyes

Causes

- phenothiazines
- haloperidol
 - Usually a consequence of **typical neuroleptic drugs** such as haloperidol or chlorpromazine, but is **unusual with newer agents** such as olanzapine or clozapine.
- metoclopramide
- postencephalitic Parkinson's disease

The condition is often precipitated by re-introduction of the agent.

Management

- procyclidine (usually IV or IM)
- Benz tropine

St John's Wort

Overview

- shown to be as effective as tricyclic antidepressants in the treatment of mild-moderate depression
- mechanism: thought to be similar to SSRIs (although noradrenaline uptake inhibition has also been demonstrated)
- NICE advise 'may be of benefit in mild or moderate depression, but its use should not be prescribed or advised because of uncertainty about appropriate doses, variation in the nature of preparations, and potential serious interactions with other drugs'

Adverse effects

- profile in trials similar to placebo
- can cause serotonin syndrome
- **inducer of P450 system**, therefore decreased levels of drugs such as warfarin, ciclosporin. The effectiveness of the combined oral contraceptive pill may also be reduced.

Dopamine receptor agonists

Overview

- e.g. bromocriptine, cabergoline, ropinirole, apomorphine
- ergot-derived dopamine receptor agonists (bromocriptine, cabergoline, pergolide*) have been associated with pulmonary, retroperitoneal and cardiac **fibrosis**.
 - ⇒ The Committee on Safety of Medicines advice that an ESR, creatinine and chest x-ray should be obtained prior to treatment and patients should be closely monitored
 - ⇒ *pergolide was withdrawn from the US market in March 2007 due to concern regarding increased incidence of valvular dysfunction

Action

- L-DOPA is a precursor of dopamine. Dopamine itself does not cross the blood-brain barrier and so is no effective as a drug.
- Levodopa exerts its therapeutic action after being converted by dopa decarboxylase to dopamine in the brain (in the striatum).
- It is also converted to dopamine in the periphery, causing nausea and vomiting through action at the area postrema, which lies outside the blood-brain barrier in the brain stem.

Indications

- Parkinson's disease
 - ⇒ Currently treatment is delayed until the onset of disabling symptoms
 - ⇒ If the patient is elderly, L-dopa is sometimes used as an initial treatment
- prolactinoma/ galactorrhoea
- cyclical breast disease
- acromegaly

Adverse effects

- nausea/vomiting
- postural hypotension
- hallucinations
- daytime somnolence

Bromocriptine

Action

- Bromocriptine is an ergotamine dopamine agonist that leads to activate central and peripheral D2 receptors

Indications

- used to inhibit prolactin release from the anterior pituitary
- preferred in women who are looking to get pregnant** (less teratogenicity than cabergoline).

Side effects

- Common:** nausea, nasal congestion, constipation,
- Uncommon:** dizziness (orthostatic hypotension)
- Rare**
 - ⇒ **Tinnitus**
 - ⇒ Excessive sleepiness (it is seen more commonly with modern agents such as ropinirole).
 - ⇒ Pulmonary fibrosis
 - ⇒ Vasospasm in the peripheral circulation: Higher doses may cause cold-induced peripheral digital vasospasm (**Raynaud's phenomenon**).
 - ⇒ Hallucinations and psychosis : exacerbation or unmasking of depression and psychosis (only at very high doses)

Dopa-decarboxylase inhibitors

- Reduce the extracerebral complications of L-dopa therapy.** These include nausea, vomiting, postural hypotension and cardiac arrhythmias.
- When given in combination with dopamine agonists dyskinetic movements are more likely.
- Carbidopa is an inhibitor of dopa decarboxylase that does not cross the blood-brain barrier, so it reduces peripheral, but not central, metabolism of levodopa to dopamine, thereby reducing the unwanted side effect but not the therapeutic action.
- Benserazide is another peripheral dopa decarboxylase inhibitor that is commonly used in combination with levodopa (as co-beneldopa (Madopar)).

Amitriptyline (tricyclic antidepressants)

Adverse effects

Antimuscarinic effects: relatively common and occur before an antidepressant effect is obtained.

<ul style="list-style-type: none"> Dry mouth Constipation → paralytic ileus Urinary retention 	<ul style="list-style-type: none"> Blurred vision and disturbances in accommodation Increased intraocular pressure, and Hyperthermia.
<ul style="list-style-type: none"> Tolerance is often achieved if treatment is continued. adverse effects may be less troublesome if treatment is begun with small doses and then increased gradually, although this may delay the clinical response. 	

Neurological adverse effects:

- | | |
|--|--|
| <ul style="list-style-type: none"> • Drowsiness • Headache • Peripheral neuropathy • Tremor • Ataxia • Epileptiform seizures • Tinnitus | <ul style="list-style-type: none"> • extrapyramidal symptoms including speech difficulties (dysarthria). Confusion, hallucinations, or delirium may occur, particularly in the elderly, and mania or hypomania, and behavioural disturbances (particularly in children) have been reported. |
|--|--|

Gastrointestinal complaints include:

- Sour or metallic taste
- Stomatitis, and
- Gastric irritation with nausea and vomiting.
- rarely, cholestatic jaundice

cardiovascular

- Orthostatic hypotension and tachycardia can occur in patients without a history of cardiovascular disease, and may be particularly troublesome in the elderly.

blood disorders:

- Eosinophilia
- Bone marrow depression
- Thrombocytopenia
- Leucopenia, and
- Agranulocytosis.

Endocrine effects

- testicular enlargement
- gynaecomastia and breast enlargement, and galactorrhoea.
- Sexual dysfunction.
- Changes in blood sugar concentrations
- hyponatraemia associated with inappropriate secretion of antidiuretic hormone.
- increased appetite with weight gain (or occasionally anorexia with weight loss).
- Sweating may be a problem.

Others

- Hypersensitivity reactions, such as urticaria and angioedema, and photosensitisation have been reported

Tricyclic overdose

Tricyclic overdose - give IV bicarbonate

- Overdose of tricyclic antidepressants is a common presentation to emergency departments. Amitriptyline and dosulepin (dothiepin) are particularly dangerous in overdose.
- Other tricyclic antidepressants includes **imipramine**
- Early features relate to anticholinergic properties: dry mouth, dilated pupils, agitation, sinus tachycardia, blurred vision.

Features of severe poisoning include:

- Hypertension
 - results from the blockade of norepinephrine reuptake
 - is an early and transient finding.
 - Catecholamines are eventually depleted and in most patients hypertension is mild and self-limiting and is best left untreated.
- Orthostasis and hypotension
 - are the result of direct myocardial depression, catecholamine depletion, alpha-adrenergic blockade, and arrhythmias.
 - The combination of decreased contractility and vasodilation produce decreased preload and can result in severe and refractory hypotension.
- Arrhythmias
 - secondary to blockage or slowing of fast sodium channels (causing a quinidine-like effect)
 - the most serious consequence of TCA overdose.
 - Mild overdoses** produce **sinus tachycardia**, mostly as a result of **anticholinergic effects**.
 - More severe overdoses** result in **prolonged QRS and QTc intervals**, followed by a **prolonged PR interval**, and, finally, **ventricular arrhythmias**, including **ventricular tachycardia** and **ventricular fibrillation**.
- seizures
- metabolic acidosis
- coma

ECG changes include: (**ECG is the most appropriate initial action**)

- sinus tachycardia
- widening of QRS
- prolongation of QT interval

Widening of QRS > 100ms is associated with an increased risk of seizures whilst QRS > 160ms is associated with ventricular arrhythmias

Management

- Check U&Es, looking specifically for hypokalaemia, and ABG looking for acidosis. Hypokalaemia should be corrected. ECG should be done to assess the QRS interval.
- Gastric lavage should only be considered if it is within one hour a potentially fatal overdose. 50 g of charcoal can be given if it is within one hour of ingestion.
- 50 ml of 8.4% sodium bicarbonate should be given if the pH is less than 7.1, QRS interval is more than 0.16 s, or there are cardiac arrhythmias or hypotension.

- Indication for sodium bicarbonate in tricyclic poisoning includes wide QRS complex.
- Intravenous sodium bicarbonate is the standard initial therapy for patients who develop cardiotoxicity (usually a QRS > 100ms or a ventricular arrhythmia) as a result of tricyclic antidepressant (TCA) overdose.
 - Mechanism of Sodium bicarbonate action:
 - ❖ alkalinisation of blood to a pH of 7.45-7.55 uncouples TCA from myocardial sodium channels;
 - ❖ also, additional sodium increases extracellular sodium concentration, thereby improving the gradient across the channel.
 - Intravenous magnesium sulphate can be used as a second-line agent in refractory arrhythmias.
 - IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity
- arrhythmias: class 1a (e.g. Quinidine) and class 1c antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias
- intravenous lipid emulsion is increasingly used to bind free drug and reduce toxicity
- dialysis is ineffective in removing tricyclics
- Patients who display signs of toxicity should be monitored for a minimum of 12 hours.

Tricyclic Withdrawal symptoms rare and include:

- cholinergic effects such as: abdominal cramps, diarrhoea, vomiting and dehydration
- extrapyramidal symptoms such as: anxiety, psychosis, delirium and mania

Monoamine oxidase (MAO) inhibitors

Overview

- serotonin and noradrenaline are metabolised by monoamine oxidase in the presynaptic cell

Non-selective monoamine oxidase inhibitors

- e.g. tranylcypromine, phenelzine
- used in the treatment of atypical depression (e.g. hyperphagia) and other psychiatric disorder
- not used frequently due to side-effects
- Abrupt withdrawal of phenelzine leads to panic, shaking, sweats and nausea

Adverse effects of non-selective monoamine oxidase inhibitors

- hypertensive reactions with tyramine containing foods e.g. cheese, pickled herring, Bovril, Oxo, Marmite, broad beans
- anticholinergic effects

Selective serotonin reuptake inhibitors (SSRIs)

Selective serotonin reuptake inhibitors (SSRIs) are considered first-line treatment for the majority of patients with depression.

- citalopram and fluoxetine are currently the preferred SSRIs
- **sertraline is useful post myocardial infarction** as there is more evidence for its safe use in this situation than other antidepressants
- SSRIs should be used with caution in children and adolescents. Fluoxetine is the drug of choice when an antidepressant is indicated

Adverse effects

- gastrointestinal symptoms are the most common side-effect

- there is an increased risk of gastrointestinal bleeding in patients taking SSRIs. A proton pump inhibitor should be prescribed if a patient is also taking a NSAID
- patients should be counselled to be vigilant (حذق) for increased anxiety and agitation after starting a SSRI
- fluoxetine and paroxetine have a higher propensity for drug interactions
- The Committee on Safety of Medicines (CSM) have reported that **hyponatraemia is associated with all types of antidepressants**; however it has been reported **more frequently with selective serotonin reuptake inhibitors (SSRIs)** than with other antidepressants.
- Hyponatraemia should be considered in all patients who develop drowsiness, confusion or convulsions whilst taking an antidepressant.

Citalopram and the QT interval

- citalopram and escitalopram are associated with dose-dependent QT interval prolongation and should not be used in those with:
 - congenital long QT syndrome;
 - known pre-existing QT interval prolongation;
 - or in combination with other medicines that prolong the QT interval
- the maximum daily dose is now 40 mg for adults; 20 mg for patients older than 65 years; and 20 mg for those with hepatic impairment

Interactions

- NSAIDs: NICE guidelines advise 'do not normally offer SSRIs', but if given co-prescribe a proton pump inhibitor
- warfarin / heparin: NICE guidelines recommend avoiding SSRIs and considering mirtazapine**
- aspirin: see above
- triptans: avoid SSRIs
- monoamine oxidase inhibitor (MAOI) → serotonin syndrome

follow up

- Following the initiation of antidepressant therapy patients should normally be reviewed by a doctor after 2 weeks.
- For patients under the age of 30 years or at increased risk of suicide they should be reviewed after 1 week.
- If a patient makes a good response to antidepressant therapy they should continue on treatment for at least 6 months after remission as this reduces the risk of relapse.

Discontinuation symptoms

- When stopping a SSRI the dose should be gradually reduced over a 4 week period (**this is not necessary with fluoxetine**).
- Paroxetine has a higher incidence of discontinuation symptoms**
 - Withdrawal of paroxetine can lead to deterioration in mood and cognition and orofacial dystonias
- Symptoms:

<ul style="list-style-type: none"> increased mood change restlessness difficulty sleeping unsteadiness 	<ul style="list-style-type: none"> sweating gastrointestinal symptoms: pain, cramping, diarrhoea, vomiting paraesthesia
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Lithium

Lithium: fine tremor in chronic treatment, coarse tremor in acute toxicity

- Lithium is mood stabilising drug used most commonly prophylactically in bipolar disorder but also as an adjunct in refractory depression.
- It has a very narrow therapeutic range (0.4-1.0 mmol/L) and a long plasma half-life being excreted primarily by the kidneys.

Mechanism of action - not fully understood, two theories:

- interferes with inositol triphosphate formation
- interferes with cAMP formation

Adverse effects

Chronic lithium use is recognised to reduce both cAMP- and non-cAMP-related upregulation of aquaporin-2 gene expression. The role of aquaporin-2 is to drive reuptake of water from the urine, and the number of aquaporin-2 channels is increased in response to vasopressin. Blockade of the upregulation of aquaporin-2 gene expression reduces the effect of vasopressin causing nephrogenic diabetes insipidus.

- nausea/vomiting, diarrhoea
- fine tremor
- polyuria (secondary to nephrogenic diabetes insipidus)
- thyroid enlargement, may lead to hypothyroidism
- ECG: T wave flattening/inversion
- weight gain
- **Hypercalcaemia** and primary hyperparathyroidism.
 - ⇒ It has been suggested that lithium → alters the sensitivity of the parathyroid cells to calcium → hyperplasia.
 - ⇒ Other studies have however failed to confirm an excess of parathyroid hyperplasia in this population, suggesting instead that lithium selectively stimulates growth of parathyroid adenomas in susceptible patients, who are best treated therefore with adenoma excision rather than total parathyroidectomy.

Pregnancy

- **Exposure to lithium in utero is associated with Ebstein's anomaly.**
- **Lithium is contraindicated during the first trimester and when breast-feeding.**
- In the first trimester lithium can cause atrialisation of the right ventricle.
- During the second and third trimesters lithium can be used, but dose requirements are increased.
- Immediately after delivery lithium dose requirements return to normal abruptly. Lithium levels can rise dangerously if a high dose is continued.
- Long-term treatment with lithium can produce frank **hypothyroidism**
 - Lithium is concentrated by the thyroid and inhibits thyroidal iodine uptake. It also inhibits iodothyrosine coupling, alters thyroglobulin structure, and inhibits thyroid hormone secretion.
 - The best management in this case would be to **discontinue the lithium** therapy and replace it with another agent (after consulting the patient's psychiatrist) – carbamazepine, sodium valproate or lamotrigine could all be alternative agents for mood stabilisation. Lamotrigine is the preferred option, assuming pregnancy is

desired.

- Lithium is excreted in breast milk and if the infant becomes dehydrated, then toxic lithium levels develop rapidly.

Monitoring of patients on lithium therapy

- NICE and the National Patient Safety Agency (NPSA) recommends:
 - lithium blood level should 'normally' be checked every 3 months. Levels should be taken 12 hours post-dose
 - thyroid and renal function should be checked before starting treatment and then every 6 months
 - patients should be issued with an information booklet, alert card and record book
 - monitor serum lithium levels 1 week after treatment starts and every dose change, and then every 3 months.

Lithium monitoring (NICE 2017):

thyroid and renal function	serum lithium levels	ECG
before treatment	1 week after treatment starts	For people at high risk of cardiovascular disease
every 6 months	every dose change every 3 months	

Sodium valproate is the second line therapy for bipolar disorder in patients who don't tolerate lithium or where it's contraindicated.

Interaction:

- Acetazolamide leads to decreased lithium concentration**
 - Osmotic diuretics and carbonic anhydrase inhibitors such as acetazolamide lead to decreased lithium concentration because of increased excretion
- Calcium channel blockers combined with lithium may cause a syndrome of ataxia, confusion and sleepiness, which is reversible on stopping the drug.
- ACE inhibitors lead to increased lithium concentration because of decreased excretion.
- thiazide diuretics increased lithium reabsorption and may cause lithium intoxication.
- Methyldopa also leads to increased risk of neurotoxicity.

Lithium toxicity

Toxicity may be precipitated by dehydration, renal failure, diuretics (Especially bendroflumethiazide) or ACE inhibitors and ARBs

- Lithium has a very narrow therapeutic range (0.4-1.0 mmol/L)
- long plasma half-life (20 h)
- excreted primarily by the kidneys.
- Lithium toxicity generally occurs following concentrations > 1.5 mmol/L.
- Toxicity may be precipitated by dehydration, electrolyte imbalance, renal failure, , and drugs

Drugs that may precipitate lithium toxicity include:

- diuretics (especially bendroflumethiazide),
- ACE inhibitors & ARB
- NSAIDs
- Metronidazole
- Tetracycline

- Phenytoin
- Ciclosporin
- Methyldopa

Features of toxicity

- **coarse tremor** (a fine tremor is seen in therapeutic levels)
- hyperreflexia
- acute confusion
- **dysarthria**
- **ataxia**
- seizure
- coma

Mild to moderate toxicity (levels less than 2 mmol/L)	severe toxicity (levels more than 2 mmol/L)
<ul style="list-style-type: none"> • anorexia • vomiting • ataxia • dysarthria • blurring of vision • coarse tremor • diarrhoea • drowsiness, and • muscle weakness. 	<ul style="list-style-type: none"> • circulatory failure • coma • convulsions • hyper-reflexia • oliguria • psychosis, and • death (in severe cases).

Management

- The management of lithium toxicity is largely supportive.
- The first step is to establish renal function and correct serum electrolytes.
- Which investigation will help you in the immediate setting?
 - ⇒ Serum electrolytes and renal function
 - Renal function will determine the patient's ability to excrete lithium.
 - Lithium levels should be taken but may be of limited value in the acute setting (rapid result may not be available; levels not always reliable especially with sustained release preparations).
- mild-moderate toxicity may respond to volume resuscitation with normal saline.
 - In case of significant hypernatraemia, 5% dextrose is an initial option for fluid replacement
- haemodialysis may be needed in severe toxicity
 - indication of Haemodialysis:
 - if serum lithium levels > 4 mmol/l or
 - serum lithium levels > 2.5 mmol/l with signs of significant lithium toxicity (e.g. seizures, depressed mental status) or inability to excrete lithium (e.g. renal disease, decompensated heart failure).
- sodium bicarbonate is sometimes used but there is limited evidence to support this.
 - By increasing the alkalinity of the urine, it promotes lithium excretion
- Activated charcoal does not bind lithium effectively and is therefore ineffective except where co-ingestion of other poisons is suspected.
- Whole bowel irrigation should be considered in adults who have ingested a slow release preparation of lithium of greater than 4 g.

Prognosis

- 10% of patients who survive severe lithium toxicity will be left with a neurological deficit.

Therapeutic drug monitoring

Lithium

- range = 0.4 - 1.0 mmol/l
- take 12 hrs post-dose

Digoxin

- at least 6 hrs post-dose

Ciclosporin

- trough levels immediately before dose

Phenytoin

- trough levels immediately before dose

Baclofen

- gamma-aminobutyric acid-B receptor agonist
- The primary site of action is the spinal cord by depressing monosynaptic and polysynaptic transmission.
- It can hyperpolarise cells by increasing K⁺ conductance and inhibit Ca²⁺ channels in others.
- Avoid abrupt **withdrawal** as it can cause serious side-effects including:
 - ⇒ Autonomic dysreflexia.
 - ⇒ **hallucinations**

Baclofen toxicity

- Onset of toxicity is rapid and its effect can last up to 35-40 hours post ingestion.
- Features include:
 - Drowsiness
 - Coma
 - Respiratory depression
 - CO₂ retention is likely to be due to central nervous system depression and reduction in diaphragmatic contraction secondary to baclofen toxicity.
 - Hyporeflexia
 - Hypotonia
 - Hypothermia, and
 - Hypotension.
 - Bradycardia with first degree heart block and prolongation of Q-T interval can occur.
- Treatment is usually supportive and often requires intensive care.
 - **Intubation and mechanical ventilation**
- Patients with a high risk of aspiration pneumonia (↓ Glasgow coma scale (GCS)) are a contraindication to non-invasive ventilation.

Endocrinology drugs

For all diabetic drugs → See endocrinology

Lipid-lowering agents

See endocrinology (Hyperlipidaemia: management)

Octreotide

Octreotide → Stimulation of the somatostatin (SMS) receptor

Overview

- long-acting analogue of somatostatin
- somatostatin is released from D cells of pancreas and inhibits the release of growth hormone, glucagon and insulin

Uses

- acute treatment of variceal haemorrhage
- acromegaly
- gastrinomas
- carcinoid syndrome
- prevent complications following pancreatic surgery
- VIPomas
- refractory diarrhoea

Adverse effects

- gallstones (secondary to biliary stasis)

Orlistat → Reduces fat absorption from the intestine

- Orlistat promotes weight loss and improves co-morbidities in obese patients
- Orlistat operates by preventing the absorption of fat molecules in the intestinal tract
- Approximately 30% of fat that would otherwise have been absorbed passes straight through the bowel and is excreted in the faeces
- As a result it can cause 'fatty stools', urgency and increased frequency of defaecation often with anal leakage or oily spotting
- these effects encourage people taking the drug to limit fat intake
- Orlistat itself is not absorbed, except in very small quantities and thus its side-effects are restricted to the gastrointestinal tract
- Patients taking orlistat may require concomitant vitamin supplements because of malabsorption of fat-soluble vitamins such as vitamins A, D, K and E
- Orlistat is shown to be clinically efficacious in reducing a person's weight over a period of a year
- Study results also showed significant improvement in reducing fasting glucose, total cholesterol, LDL-cholesterol and blood pressure

Obs & Gyna drugs

Prescribing in pregnant patients

Very few drugs are known to be completely safe in pregnancy. The list below largely comprises of those known to be harmful.

Drugs	Antibiotics
<ul style="list-style-type: none"> ACE inhibitors, ARBs Statins Warfarin Sulfonylureas Retinoids (including topical) Cytotoxic agents 	<ul style="list-style-type: none"> Tetracyclines Aminoglycosides Sulphonamides Trimethoprim Quinolones: the BNF advises to avoid due to arthropathy in some animal studies

- The majority of antiepileptics including valproate, carbamazepine and phenytoin are known to be potentially harmful. The decision to stop such treatments however is difficult as uncontrolled epilepsy is also a risk.
- Verapamil is relatively safe in pregnancy** and has been widely used to treat maternal and fetal supraventricular tachycardias.
- Amiodarone is associated with fetal hypothyroidism,
- lisinopril with oligohydramnios,
- lithium with Ebstein's anomaly,
- and warfarin with facial / CNS abnormalities.

Combined oral contraceptive pills

Mechanisms of action

- Estrogen**
 - ⇒ Hypothalamus: ↓ release of GnRH
 - ⇒ Pituitary: ↓ LH → inhibits ovulation, ↓ FSH → prevents ovarian folliculogenesis
- Progestin** → **thickens the cervical mucus, preventing the entry of sperm.**

Advantages

- Treatment of menopausal symptoms such as hot flashes.
- Other beneficial effects of MHT include the decreased risk of colon cancer, diabetes mellitus type 2, and all-cause mortality for women ages 50-59 years.

Emergency contraception (after unprotected sexual intercourse)

- Most effective when taken within 3 days of intercourse
 - ⇒ **The rate of pregnancy is ≤ 3.0% if emergency contraception is taken within 72 hours.**
- Typically administered as a single dose or as two doses over one day
- Significantly less effective in patients who are obese or overweight
- Action of emergency contraception:** ↓ tubal motility and ciliary activity thereby preventing sperm from reaching the oocyte in the ampulla of the tube.
- Example:** levonorgestrel

Side effects

- Irregular periods (unscheduled bleeding): **is the most common adverse effect**
- **Breast tenderness**
- Headaches
- ↑ incidence of functional ovarian cysts, hepatic adenomas
- ↑relative risk of venous and arterial thrombotic events.
- Erythema nodosum

Transdermal administration of estradiol is associated with a lower risk of stroke and venous thromboembolism than oral administration of estradiol and is unlikely to increase the risk of stroke and venous thrombosis above that of non-users.

Contraindications

- People >35 years old who smoke tobacco (risk of cardiovascular events)
- Migraine (especially with aura)
- Breast cancer
- Liver disease.
- breast feeding < 6 weeks post-partum
- Uncontrolled hypertension
- History of thromboembolic disease (stroke or ischaemic heart disease)

Progestogen only pills (POPs)

- **Examples:** Norethindrone, drospirenone, and desogestrel
- **Mechanism of contraception:**
 - ⇒ Norethindrone → thickening cervical mucus thereby preventing sperm penetration; ovulation is not consistently suppressed.
 - ⇒ Drospirenone and desogestrel → suppression of ovulation.
- **Advantages**
 - ⇒ can be used whilst breast-feeding
 - ⇒ can be used in situations where the combined oral contraceptive pill is contraindicated (most women with medical comorbidities).
- Failure rate = over 7 % (women choosing POPs are often subfertile as a result of breastfeeding or older reproductive age)
- Hepatic enzyme-inducers (e.g. anticonvulsants phenytoin, carbamazepine, topiramate, and barbiturates and the antituberculosis drug rifampin) → ↓ efficacy of POPs.

Studies have shown that women taking estrogen- progestin combination OCPs before menopause have an increased risk of cervical carcinoma but a decreased risk of endometrial and ovarian carcinoma.

An entirely normal 16-year-old girl is very tall and would like to stop growing. What is the most appropriate treatment for her?

- **Oral contraceptive pill**
 - The oral contraceptive pill used in this context would be associated with **fusion of long-bone growth plates, and subsequent cessation of longitudinal growth.**
 - Although ideally she should be encouraged not to receive medical intervention at all, in this situation use of the OCP represents the lowest-risk option.

What is the action of emergency contraception in preventing conception following unprotected sexual intercourse?

- ⇒ Decreasing tubal motility and ciliary activity thereby preventing sperm from reaching the oocyte in the ampulla of the tube.

The rate of pregnancy is ≤ 3.0% if emergency contraception is taken within 72 hours after unprotected sexual intercourse. The earlier it is taken, the lower the likelihood of pregnancy!

Breakthrough bleeding is most commonly associated with low-dose combined oral contraceptive pills, especially those containing 20 micrograms ethinylestradiol.

Breast feeding: contraindications

Breast feeding is acceptable with nearly all anti-epileptic drugs

The major breastfeeding contraindications tested in exams relate to drugs (see below). Other contraindications of note include:

- galactosaemia
- viral infections - this is controversial with respect to HIV in the developing world. This is because there is such an increased infant mortality and morbidity associated with bottle feeding that some doctors think the benefits outweigh the risk of HIV transmission

SAFE	DANGEROUS
<ul style="list-style-type: none"> • Antibiotics: penicillins, cephalosporins, trimethoprim • Endocrine: glucocorticoids (avoid high doses), levothyroxine* • Epilepsy: sodium valproate, carbamazepine • Asthma: salbutamol, theophyllines • Psychiatric drugs: tricyclic antidepressants, antipsychotics** • Hypertension: β-blockers, hydralazine, methyldopa • Anticoagulants: warfarin, heparin • Digoxin 	<ul style="list-style-type: none"> • Antibiotics: ciprofloxacin, tetracycline, chloramphenicol, sulphonamides • Psychiatric drugs: lithium, benzodiazepines, clozapine • Aspirin • Carbimazole • Sulphonylureas • Cytotoxic drugs • Amiodarone • vitamin A derivatives.

*the BNF advises that the amount is too small to affect neonatal hypothyroidism screening

**clozapine should be avoided

Drug causes teratogenesis

Some common drugs and their potential teratogenic effect are given below:

drug	teratogenic effect
Androgens	cardiac deformities
Alcohol	fetal alcohol syndrome
Carbamazepine	microcephaly
Diethylstilbestrol	vaginal carcinoma
Lithium	cretinism
Phenobarbital	cleft palate
Sodium valproate	neural tube defects
Thalidomide	phocomelia
Warfarin	chondrodysplasia punctata

Unwanted drug effects in pregnancy

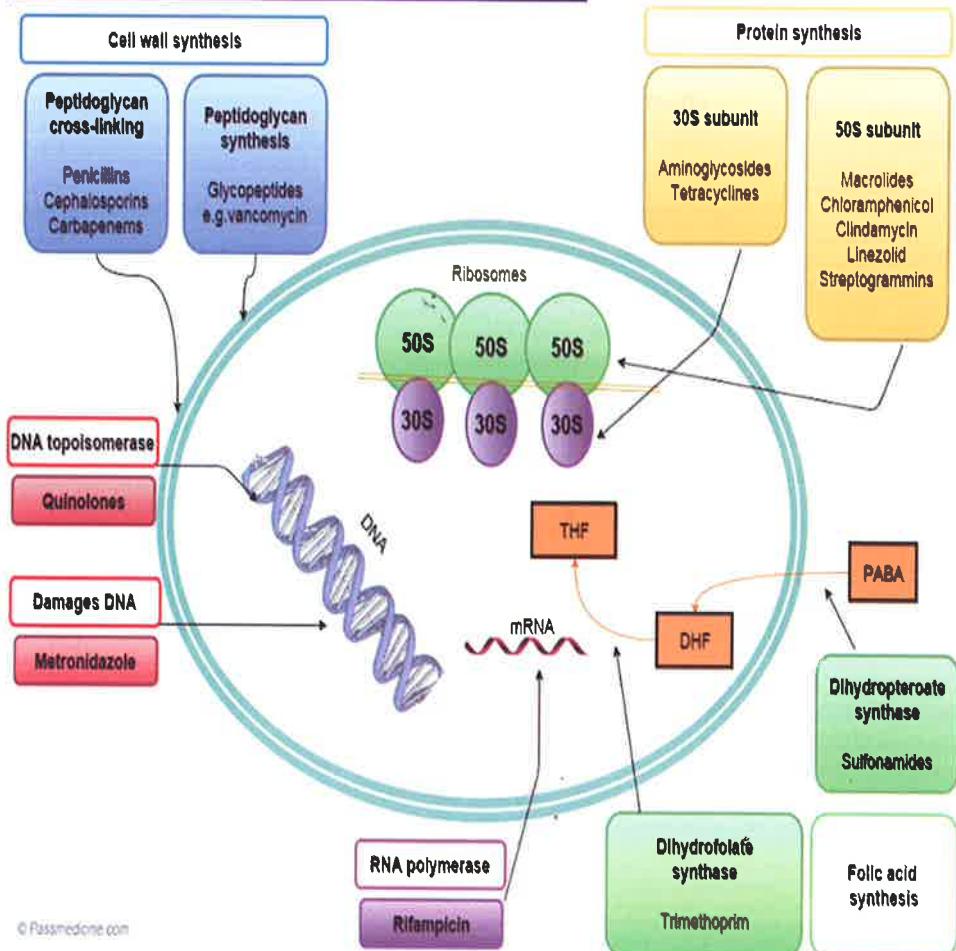
drug	effects in pregnancy
ACE inhibitors	oligohydramnios, impaired renal function
Aspirin	kernicterus
β-Blockers	hypoglycaemia, intrauterine growth retardation, fetal bradycardia
Carbimazole	neonatal goitre
NSAIDs	close ductus arteriosus
Sulphonamides	kernicterus
Thiazide diuretics:	neonatal thrombocytopenia

Antimicrobial

Antibiotics: bactericidal vs. bacteriostatic

Bactericidal antibiotics	Bacteriostatic antibiotics
<ul style="list-style-type: none"> • penicillins • cephalosporins • aminoglycosides • nitrofurantoin • metronidazole • quinolones • rifampicin • isoniazid 	<ul style="list-style-type: none"> • chloramphenicol • macrolides • tetracyclines • sulphonamides • trimethoprim

Antibiotics: mechanisms of action



The lists below summarise the site of action of the commonly used antibiotics

Inhibit cell wall formation	Inhibit protein synthesis (by acting on ribosome)	Inhibit DNA synthesis	Inhibit RNA synthesis
peptidoglycan cross-linking <ul style="list-style-type: none"> • β-lactams <ul style="list-style-type: none"> > Penicillins > Cephalosporins • carbopenems 	50S subunit <ol style="list-style-type: none"> 1. chloramphenicol 2. macrolides (e.g. erythromycin) 3. fusidic acid 4. (Quin/Dalfo)pristin 5. Linezolid 30S subunit <ol style="list-style-type: none"> 1. aminoglycosides (cause misreading of mRNA) 2. tetracyclines 	<ul style="list-style-type: none"> • quinolones (e.g. ciprofloxacin) Damages DNA <ol style="list-style-type: none"> 1. metronidazole Inhibits folic acid formation <ol style="list-style-type: none"> 1. sulphonamides 2. trimethoprim 	• Rifampicin
peptidoglycan synthesis <ul style="list-style-type: none"> • glycopeptides <ul style="list-style-type: none"> > Vancomycin > teicoplanin • Isoniazid <p>(Those organisms lacking a cell wall are resistant to these drugs eg. Chlamydia's)</p>			

Antibiotics: anaerobic activity

antibiotics have anti-anaerobic activity	antibiotics do not have anti-anaerobic activity
<ul style="list-style-type: none"> • penicillins • cephalosporins (except ceftazidime) • erythromycin • metronidazole • tetracycline 	<ul style="list-style-type: none"> • gentamicin • ciprofloxacin • ceftazidime

Skin rash with antibiotics

- Ampicillin and amoxicillin can cause skin rashes that are **not allergic** in nature
- Erythromycin, benzylpenicillin, cefuroxime and cefadroxil all produce a diffuse, papular, non-purpuric rash that may be **intensely pruritic**
- A maculopapular rash is also seen when tonsillitis/pharyngitis is related to EBV infection

Cephalosporins

- Cephalosporins are safe in penicillin allergy if it is only a rash.
- Only ceftazidime and cefepime will cover Pseudomonas

Co-trimoxazole

The sulfamethoxazole in co-trimoxazole causes haemolysis in G6PD, not the trimethoprim

Indications

- now only indicated for oral prophylaxis against Pneumocystis pneumonia, toxoplasmosis and nocardiosis
- It should only be considered in the treatment of chronic bronchitis or urinary tract infection where there is no other alternative

Side-effects

- nausea, vomiting,

- allergy : rash (including Stephens-Johnson syndrome), toxic epidermal necrolysis and photosensitivity
- Blood disorders: **neutropenia**, thrombocytopenia and, rarely, agranulocytosis

Cautions/contraindications

- used with caution (or avoided) in renal or hepatic impairment

Aminoglycosides

Action

- bactericidal antibiotics that bind to the **30S** ribosome and inhibit bacterial protein synthesis.
- active **only** against aerobic gram-negative bacilli and cocci.
➤ **ineffective against anaerobic bacteria** as they require O₂ to enter bacterial cells.

Indications

- endocarditis in combination with penicillin (gentamycin)
- added to a beta-lactam antibiotic when serious *Pseudomonas aeruginosa* (cystic fibrosis)
- tuberculosis (streptomycin)

Side effects

- Nephrotoxicity
 - The reversible acute tubular necrosis after aminoglycoside reflects a concurrent impairment in the concentrating ability, and most patients are non-oliguric.
 - Irreversible tubulointerstitial damage, however, is uncommon after discontinuing aminoglycoside.
 - We expect a diagnosis of **acute renal failure beginning more than five days after the initiation of gentamicin;**
 - **Aminoglycoside nephrotoxicity correlates with → Frequency of aminoglycoside dosing**
- Ototoxicity:
 - Streptomycin, tobramycin, and gentamycin are primarily **vestibulotoxic**
 - Kanamycin, amikacin, neomycin, and dihydrostreptomycin are preferentially **cochleotoxic**.
 - Cochlear toxicity that results in hearing loss usually begins in the high frequencies and is secondary to irreversible destruction of outer hair cells in the organ of Corti, predominantly at the basal turn of the cochlea
 - What is the explanation of progression of hearing loss or onset of hearing loss after cessation of aminoglycoside treatment?
 - Aminoglycosides are cleared more slowly from inner ear fluids than from serum
 - monitor the patient for cochleotoxic and vestibulotoxic effects **up to 6 months after cessation of aminoglycoside** treatment is important.
 - What is the initial manifestation of early hearing loss?
 - increase in the threshold of highest frequencies (>4000 Hz).
 - what is the main teratogenic effect of aminoglycosides.
 - CN VIII toxicity

- **Transient myaesthetic syndrome**
 - Aminoglycosides may impair neuromuscular transmission and should not be given to patients with myasthenia gravis;
 - large doses given during surgery have been responsible for a transient myaesthetic syndrome in patients with normal neuromuscular function.
- **What is the mechanism of resistance of Aminoglycosides?**
 - Bacterial transferase enzymes;
 - they inactivate the drug by acetylation, phosphorylation or adenylation
- **Why is the gentamycin trough level likely to be too high in patients with chronic renal failure?**
 - **Prolongation of the half-life**
 - The usual half-life of gentamicin is between 2 and 3 h, although this can be considerably prolonged in patients with renal failure.

Administration

- **There are two commonly used regimens** for dosing gentamicin. Both require the patient's body weight to ensure accurate dosing. For patients who are over their ideal body weight, this value rather than the patient's actual weight should be used. Ideal body weight can be calculated using age, sex and height on a number of online applications.
- 1. The most commonly used dosing regimen in the UK is the **once daily regime**, which is thought to be associated with reduced toxicity whilst being effective against gram-negative infections.
 - It is not recommended for patients with a creatinine clearance of less than 60 ml/min.
 - The dose used is 7 mg/kg IV every 24 hours.
 - Levels should be monitored for patients on this regimen for 3 days or more, with a level taken 6-14 hours following the third dose. A nomogram is then used to determine whether the interval between doses should be altered.
- 2. Patients with creatinine clearance of less than 60 ml/min are usually given a reduced dose of gentamicin with a multiple-daily dosing regimen. This may also be recommended by microbiologists for the treatment of serious gram-negative infections such as Pseudomonas. Dosing is dependent on creatinine clearance:
 - >60 ml/min: 1.5-1.7 mg/kg IV every 8 hours
 - 40-60 ml/min: 1.2-1.5 mg/kg IV every 12 hours
 - 20-40 ml/min: 1.2-1.5 mg/kg IV every 12-24 hours
 - <20 ml/min: 2 mg/kg loading dose then discuss with microbiology and pharmacy
- On this regimen monitoring is typically initiated after the 3rd or 4th dose, which allows a steady-state to be reached. Peak levels should be taken 30 minutes following the end of the infusion, and a trough level taken before the next dose. The desired trough level is less than 2 micrograms/ml, with a peak level of 5-8 micrograms/ml.

Administering gentamicin in conjunction with loop diuretics →↑ risk of exacerbating renal and ototoxicity

- **Aminoglycosides Ototoxicity:**

➤ mechanism:

- **cochlear dysfunction** (e.g., tinnitus, hearing impairment) by damaging cochlear cells, and/or
- **vestibulopathy** (e.g., nausea, vomiting, dizziness, vertigo, oscillopsia, ataxia) by damaging hair cells of the inner ear.
 - ❖ **nystagmus** may be present as an early sign.
 - ❖ The vestibular dysfunction of gentamicin toxicity is typically bilateral; accordingly, there is no imbalance between right-sided and left-sided input to the central nervous system, so patients do not typically experience vertigo.
 - ❖ However, patients can experience oscillopsia and an abnormal head thrust test in both horizontal directions.
 - ⇒ Oscillopsia is a visual disturbance in which stationary objects appear to oscillate.
 - ➡ occur only when the head is moving.
 - ➡ Quick movements of the head are associated with transient visual blurring.
 - ➡ This can cause difficulties with seeing signs while driving or recognizing people's faces while walking.
 - ⇒ Head thrust test (Head impulse test)
 - ➡ a physical examination maneuver to test for vestibular neuritis.
 - ➡ While the patient fixates on a target, the examiner administers brisk, horizontal head rotations to the side.
 - ➡ Considered positive if the patient is unable to maintain visual fixation, in which case the patient requires corrective saccades (quick eye movements) to re-fixate back to the target).

Macrolides

- Erythromycin was the first macrolide used clinically. Newer examples include clarithromycin and azithromycin.
- They are used against intracellular pathogens, including Mycoplasma and Legionella, and can also be used as alternatives in case of penicillin allergy.

Action

- Macrolides act by inhibiting bacterial protein synthesis by blocking translocation.
- Macrolides are **bacteriostatic** agents that **inhibit protein synthesis by binding to the 50S subunit of the bacterial ribosome**. If used in high doses, they may be bactericidal.
- If pushed to give an answer they are bacteriostatic in nature, but in reality this depends on the dose and type of organism being treated.
 - **bacteriostatic at low doses and bactericidal at high doses**

Macrolides (erythromycin, azithromycin and clarithromycin), **aminoglycosides** and **chloramphenicol** → bind to bacterial ribosomes and disrupt protein synthesis

- Clarithromycin is a macrolide antibiotic with good gram positive cover and that of atypical

organisms. Its mechanism of action is via reversible inhibition of 50s ribosome subunit.

Mechanism of resistance

- post-transcriptional methylation of the 23S bacterial ribosomal RNA

Adverse effects

- gastrointestinal side-effects are common. Nausea is less common with clarithromycin than erythromycin
- cholestatic jaundice: risk may be reduced if erythromycin stearate is used
- P450 inhibitor (see below)

Common interactions

- statins should be stopped whilst taking a course of macrolides. Macrolides inhibit the cytochrome P450 isoenzyme CYP3A4 that metabolises statins. Taking macrolides concurrently with statins significantly increases the risk of myopathy and rhabdomyolysis.
- Clarithromycin enhances anticoagulant effect of coumarins. This is because warfarin is metabolised by the same CYP3A isozyme as clarithromycin. Clarithromycin, known to inhibit CYP3A, and a drug primarily metabolised by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug.
- Clarithromycin is a potent inhibitor of CYP3A4, and as such may interfere significantly with metabolism of a number of medications, including **theophylline**, **simvastatin**, and **cyclosporine** as the most important drug interactions.
- The effect of **warfarin** and **digoxin** may also be potentiated by clarithromycin.

Erythromycin

- Was the 1st macrolide used clinically. Newer examples include clarithromycin and azithromycin.
- Erythromycin may potentially interact with **amiodarone**, **warfarin** and **simvastatin**
- Erythromycin would inhibit the metabolism of theophylline.**
- Macrolides act by inhibiting bacterial protein synthesis.
- If pushed to give an answer they are bacteriostatic in nature, but in reality this depends on the dose and type of organism being treated.

Erythromycin is used in gastroparesis as it has prokinetic properties, Promotes gastric emptying

Used in diabetic gastropathy,

Adverse effects of erythromycin

- GI side-effects are common
- Cholestatic jaundice: risk may be ↓ if erythromycin stearate is used
- P450 inhibitor
- associated with prolonged QT interval and torsades de pointes,

Quinolones

Ciprofloxacin - tendinopathy

Quinolones are a group of antibiotics which work by inhibiting DNA synthesis and are bactericidal in nature.

Examples include:

- ciprofloxacin
- levofloxacin

Mechanism of action

- inhibit topoisomerase II (DNA gyrase) and topoisomerase IV

Mechanism of resistance

- mutations to DNA gyrase, efflux pumps which reduce intracellular quinolone concentration

Adverse effects

- lower seizure threshold in patients with epilepsy**
- tendon damage (including rupture) - the risk is increased in patients also taking steroids
 - Rupture has been reported in the achilles, shoulder and hand.
 - This may occur due to disruption of the extracellular matrix and depletion of collagen which is observed in animal models.
- cartilage damage has been demonstrated in animal models and for this reason quinolones are generally avoided (but not necessarily contraindicated) in children

Interaction & contraindication

- It should not be used with **drugs that prolong the QT interval** (eg erythromycin, tricyclic antidepressants) since there is an increased risk of cardiac arrhythmias
- Contraindicated in left heart failure with reduced ejection fraction
- It should not be given at the same time as bivalent or trivalent cations (eg aluminium, iron) as these reduce absorption. **Antacids** → reduce quinolones absorption leading to therapeutic failure.
- Quinolone absorption is markedly reduced with **antacids** containing aluminium, magnesium and/or calcium and therapeutic failure may result. Other metallic **ion-containing drugs**, such as sucralfate, **iron salts**, and zinc salts, can also reduce absorption.
- The affinity of quinolones for the gamma-aminobutyric acid (GABA) receptor may induce CNS adverse effects; these effects are enhanced by some nonsteroidal anti-inflammatory drugs (NSAIDs).

Co-amoxiclav

- Because of cholestatic jaundice, prescription of co-amoxiclav is not recommended for longer than 14 days.**
- If patient developed cholestatic jaundice → the co-amoxiclav should be withdrawn, and the combination avoided in future.**

Probenecid

- Drugs can be excreted into the proximal convoluted tubule of the nephron by cation or anion transporters:
 - cation transporters: basic drugs, eg quinine, pethidine, morphine
 - anion transporters: acidic drugs, eg penicillins, bendroflumethiazide, furosemide, cephalosporins
- The anion transporters are inhibited by probenecid, which can lead to increased plasma concentrations of acidic drugs
- probenecid used clinically to increase the plasma half-life and therefore the therapeutic duration of the drug
- For example, in the management of gonorrhoea infection, probenecid may be combined with oral penicillin to **increase the half-life of the penicillin**

Sulfonamides

Antibacterial sulfonamides act as competitive inhibitors of the enzyme dihydropteroate synthetase (DHPS), an enzyme involved in folate synthesis.

Other uses

- The sulfonamide chemical moiety is also present in other medications that are not antimicrobials, including thiazide diuretics (including hydrochlorothiazide, metolazone, and

indapamide, among others), loop diuretics (including furosemide, bumetanide and torsemide) sulfonylureas (including glipizide, glyburide, among others), some COX-2 inhibitors (e. g. celecoxib) and acetazolamide.

- Sulfasalazine, in addition to its use as an antibiotic, is also utilized in the treatment of inflammatory bowel disease.
- Co-trimoxazole:** sulfonamide antibiotic combination of trimethoprim and sulfamethoxazole, in the ratio of 1 to 5, used in the treatment of a variety of bacterial infections. The name co-trimoxazole is the British Approved Name, and has been marketed worldwide under many trade names including Septra, Bactrim, and various generic preparations. Sources differ as to whether co-trimoxazole usually is bactericidal or bacteriostatic

Vancomycin

Spectrum of the drug – MEC

- M** – MRSA
- E** – Enterococcus
- C** - *C. difficile*

Side effects – RON

- R** - Red man syndrome
- O** – Ototoxicity
- N** - Nephrotoxicity

Action

- glycopeptide antibiotic
- Bactericidal
 - inhibits formation of peptidoglycan in bacterial cell walls, but a step earlier in the process compared to β -lactams
 - binds D-alanine-D-alanine moieties of the peptides

Resistance

- D-alanine-D-alanine mutates to D-alanine-D-lactate, conferring resistance

Indications

- IV administration for serious, multidrug resistant Gram-positive infections
 - including methicillin-resistant *Staphylococcus aureus* infections (MRSA)
 - including Enterococcus
 - including multidrug resistant Staph epidermidis
- Given orally for *C. difficile* → not systemically absorbed when given orally
 - when antibiotic-associated colitis fails to respond to metronidazole therapy or is severe and potentially life-threatening;
- prophylaxis,
 - for endocarditis following certain procedures in patients at high risk for endocarditis;
 - for major surgical procedures involving the implantation of prosthetic materials or devices, e.g., cardiac and vascular procedures and total hip placement,

Side effects

- Red man syndrome
 - non-immunological reaction, related to the rate of infusion (infuse drug too fast → release of histamine → red rash)
 - If a patient experiences an infusion related reaction to vancomycin:
 - 1. Cease infusion
 - 2. Administer antihistamine (cetirizine 10mg PO)
 - 3. If newly hypotensive consider adrenaline

- 4. recommencement of vancomycin at a slower rate of infusion (doubling the time to infuse the solution, or changing to a continuous infusion).
- **Ototoxicity**
 - more likely in patients with high plasma concentrations, renal impairment or pre-existing hearing loss.
 - may progress after drug withdrawal,
 - may be irreversible.
 - Hearing loss may be preceded by tinnitus, which must be regarded as a sign to stop treatment.
- Nephrotoxicity
- Thrombophlebitis

Dosage

- loading dose: 25mg / kg (actual body weight)
- Maintenance dose: 15 mg/kg per dose (actual body weight)
 - (15mg/kg 12-hourly if GFR \geq 40mL/min, (maximum 2 grams per dose)
- When to start maintenance dose:
 - According to GFR level:
 - if GFR \geq 40mL/min : 12 hours after loading dose
 - if GFR = 20-39 mL/min : 24 hours after loading dose
 - If GFR < 20mL/min : check trough level 24 hours after loading dose; wait for trough result prior to re-dosing.

➢ Maintenance dose determination

GFR (mL/min)*		GFR >90	GFR 60-90	GFR 40-59	GFR 20-39	GFR <20
Maintenance dose		1.5g 12-hourly	1g 12-hourly	750mg 12-hourly	1g 24-hourly	1g every 2 to 7 days
Dosage Adjustment (intermittent infusions)	Trough level < 10mg/L	Convert to 1g 6-hourly	Convert to 1.5g 12-hourly	Convert to 1g 12-hourly	Convert to 750mg 12-hourly†	Monitor 48 hourly* Re-dose when trough <20mg/L
	Trough level 10 – 14.9 mg/L	Convert to 1.25g 8-hourly	Convert to 1.25g 12-hourly			
	Trough level 15 – 20mg/L	IN TARGET RANGE - no change required. Repeat trough levels twice weekly if vancomycin levels and renal function are stable. If not, more frequent monitoring is suggested*				
	Trough level 21 – 25mg/L	Convert to 1.25g 12-hourly	Convert to 750mg 12-hourly	Convert to 500mg 12-hourly	Convert to 750mg 24-hourly	Monitor 48- hourly* Re-dose when trough <20mg/L
	Trough level 26 – 30mg/L	Convert to 1g 12-hourly				
	Trough level > 30mg/L	Hold dose for 24 hours. Re-check level and recommence at reduced dose when level < 20mg/L. Review renal function				

Monitoring

- **Vancomycin → requires plasma level monitoring** (after three or four doses if the renal function is normal, or earlier if renal impairment is present)
- the best determinant of vancomycin efficacy is the AUC/MIC
- A 24-hour AUC/MIC of 400 or more is the target for clinical success
- AUC/MIC means: ratio of **Area Under the Curve** (plasma concentration vs time) to **Minimum**

Inhibitory Concentration (Units are mg.hr/Litre)

- For practical reasons, a trough (pre-dose) plasma concentration is used as a surrogate measure of efficacy.
- Trough level means: a serum vancomycin level taken at the end of the dosing interval, approximately one hour prior to next dose
- The important level to measure here is the **trough level** as opposed to the **peak level** with gentamicin.
- the target vancomycin trough level for the treatment of (MRSA) bacteraemia is 15 to 20 µg/ml to achieve an AUC/MIC of 400
- The trough level toxic threshold (30 mg/l).
 - If trough level > 30 mg/l → Omit dose and restart when level <15 mg/l**
 - dose omission is required to reduce the risk of significant complications (including ototoxicity and nephrotoxicity).
 - The BNF recommends trough levels of 15-20 mg/l for endocarditis.

Intravenous administration

- Doses of 1g should be administered over at least 60 minutes. For higher doses the duration of infusion should be extended by 30 minutes for each additional 500mg. This is recommended to reduce the risk of red man syndrome.
- The usual dilution is 5mg/mL; for fluid-restricted patients, concentrations of up to 10mg/mL may be used

Vancomycin Infusion Rate	
Dose	Minimum Infusion Duration*
≤ 1 g	60 min
1.1 - 1.5 g	90 min
1.6 - 2.0 g	120 min
> 2 g	Infuse at approx. 1 g per hour

Which molecular change is responsible for vancomycin resistance?

→ **D-alanine D-alanine to D-alanine D-lactate**

- Vancomycin resistance is involves its Binding sites the D-Ala-D-Ala.
- terminal D-Ala is replaced by D-Lactate(D-Lac).

Linezolid

- is a type of oxazolidinones antibiotic class

Action

- inhibits bacterial protein synthesis** by binding at the **50S subunit of the bacterial ribosome**
 - linezolid occupies the A site of the 50S ribosomal subunit, inducing a conformational change that **prevents tRNA from entering the site** and ultimately **forcing tRNA to separate from the ribosome**
 - work on the first step of protein synthesis, **initiation**, unlike most other protein synthesis inhibitors, which inhibit **elongation**
- bacteriostatic

Spectrum, highly active against **Gram positive** organisms including:

- MRSA (Methicillin-resistant *Staphylococcus aureus*)
- VRE (Vancomycin-resistant enterococcus)
- GISA (Glycopeptide Intermediate *Staphylococcus aureus*)

Advantages

- **high bioavailability** (close to 100%) when given by mouth:
 - the entire dose reaches the bloodstream, as if it had been given intravenously.

Adverse effects

- Bone marrow suppression (especially **thrombocytopenia**)
 - (reversible on stopping)
- Peripheral neuropathy
- GI upset
- **Serotonin syndrome**

Contraindications

- Concurrent use with monoamine oxidase inhibitors (**MAOIs**) and selective serotonin reuptake inhibitors (**SSRIs**)
- tyramine **diet**

Carbapenems

- **Carbapenems** are antibiotics used for multidrug-resistant (MDR) bacteria.
- members
 - imipenem (+ cilastatin)
 - normal kidneys break down imipenem with a dihydropeptidase
 - cilastatin, a selective dihydropeptidase inhibitor, is always given with imipenem
 - inhibits renal dihydropeptidase I, thereby decreasing inactivation of drug in renal tubules
 - cilastatin not needed for meropenem
 - meropenem
- Their use is primarily in people who are hospitalized.
- Like the penicillins and cephalosporins, they are members of the **beta lactam** class of antibiotics, which kill bacteria by binding to penicillin-binding proteins and inhibiting cell wall synthesis.
- Side effect
 - Gastrointestinal distress, skin rash and **seizures** are three common complications of carbapenem administration when there are high plasma levels.
 - 5-10% of patients with penicillin allergy are also allergic to carbapenems

Meropenem

- Which Carbapanem antibiotic has less CNS toxicity? → **Meropenem**
- Meropenem is a carbapanem antibiotic that does not need to be coadministered with Cilastatin.

Trimethoprim

- Trimethoprim is an antibiotic, mainly used in the management of urinary tract infections.
- **It is combined with sulfamethoxazole for synergistic reasons**

Mechanism of action

- interferes with DNA synthesis by inhibiting dihydrofolate reductase

Adverse effects

- myelosuppression
- **transient rise in creatinine:** trimethoprim competitively inhibits the tubular secretion of creatinine resulting in a temporary increase which reverses upon stopping the drug
 - ⇒ Trimethoprim interferes with tubular handling of creatinine and thereby leads to an increase in serum creatinine, without impairment of GFR.
- Megaloblastic anaemia may occur owing to folate deficiency

Quinupristin & dalfopristin antibiotics

Overview

- injectable streptogrammin antibiotic Only administered via a central line.
- combination of group A and group B streptogrammin respectively.
- inhibits bacterial protein synthesis by blocking tRNA complexes binding to the ribosome

Spectrum

- most Gram-positive bacteria
- **Particularly useful against multi-resistant *Strep. pneumoniae* and *Staph. aureus*.**
- exception: *Enterococcus faecalis**

Adverse effects

- thrombophlebitis (give via a central line)
- arthralgia
- P450 inhibitor

*not to be confused with *Enterococcus faecium*, which is sensitive to Quinupristin & dalfopristin

Tuberculosis: drug side-effects and mechanism of action

Drug	Most common side effects
Rifampicin	Orange bodily fluids, rash, hepatotoxicity, drug interactions
Isoniazid	Peripheral neuropathy, psychosis, hepatotoxicity
Pyrazinamide	Arthralgia, gout, hepatotoxicity, nausea
Ethambutol	Optic neuritis, rash

Rifampicin

- mechanism of action: inhibits bacterial DNA dependent RNA polymerase preventing transcription of DNA into mRNA
- potent liver enzyme inducer
- hepatitis,
- orange secretions
Patients on rifampicin should be warned that their urine, tears and other secretions will develop a bright orange-red colour
- flu-like symptoms
- **acute interstitial nephritis (pt may present with acute renal failure after 1 month of starting rifampicin)**

Interaction

- **Interact with oral contraceptive induces → failure of the oral contraceptive treatment**
- Rifampicin is a potent hepatic enzyme inducer that increases the metabolism of many drugs, including all the steroid hormones
- Barrier contraceptives must be used during treatment with rifampicin and for 4-8 weeks after a course of rifampicin is completed

Isoniazid

Isoniazid inhibits the P450 system

Isoniazid causes peripheral neuropathy

- mechanism of action: inhibits mycolic acid synthesis
- peripheral neuropathy:
 - Occurs in less than 1%
 - **Those with N-acetyltransferase type-2 gene defect → resulting in abnormal isoniazid metabolism → predisposed to neuropathy**
 - Prevented with 10 mg pyridoxine (Vitamin B6)
- hepatitis, raised transaminases in 10-20%
 - **Isoniazid-induced hepatitis** occurs in ~1% of individuals and is much commoner in people more than 35-years-old (risk of hepatitis is less than 0.3% in patients under 20 years; 2-3% risk in individuals over 50 years).
- agranulocytosis
- liver enzyme inhibitor
- isoniazid inhibits the conversion of tryptophan to niacin → nicotinic acid (niacin) deficiency
→ Pellagra (the 3 D's - dermatitis, diarrhoea and dementia)
- systemic lupus erythematosus (SLE)-like syndrome.
- **Isoniazid toxicity**
 - **Isoniazid toxicity should be suspected in any patient with intractable seizures and profound metabolic acidosis with an elevated anion gap.**
 - Intravenous pyridoxine (vitamin B6) is the treatment of choice.
 - The acidosis may need to be corrected with bicarbonate.

Pyrazinamide

- mechanism of action: converted by pyrazinamidase into pyrazinoic acid which in turn inhibits fatty acid synthase (FAS) I
- hyperuricaemia causing gout
- arthralgia, myalgia
- hepatitis

Ethambutol

- mechanism of action: inhibits the enzyme arabinosyl transferase which polymerizes arabinose into arabinan
- optic neuritis: check visual acuity before and during treatment
- dose needs adjusting in patients with renal impairment

The main adverse effects of ethambutol are:

- loss of visual acuity
- restriction of visual fields
- colour blindness
- retrobulbar neuritis
- arthralgia.

Uncommonly it may be associated with

- hyperuricaemia, and with interstitial nephritis. This is thought to occur less frequently than with rifampicin.

Antiviral agents

Drug	Mechanism of action	Indication s	Adverse effects/toxicit y
Aciclovir	Guanosine analog, phosphorylated by thymidine kinase which in turn <u>inhibits the viral DNA polymerase</u>	HSV, VZV	Crystalline nephropathy
Ganciclovir	Guanosine analog, phosphorylated by thymidine kinase which in turn <u>inhibits the viral DNA polymerase</u>	CMV	Myelosuppression/n/agranulocytosis
Ribavirin	Guanosine analog which inhibits inosine monophosphate (IMP) dehydrogenase, <u>interferes with the capping of viral mRNA</u>	Chronic hepatitis C, RSV	Haemolytic anaemia
Amantadine	Inhibits uncoating (M2 protein) of virus in cell. Also releases dopamine from nerve endings	Influenza, Parkinson's disease	Confusion, ataxia, slurred speech
Oseltamivir	Inhibits neuraminidase	Influenza	
Foscarnet	Pyrophosphate analog which inhibits viral DNA polymerase	CMV, HSV if not responding to aciclovir	Nephrotoxicity, hypocalcaemia, hypomagnesaemia, seizures
Interferon-α	Human glycoproteins which <u>Inhibit synthesis of mRNA</u>	Chronic hepatitis B & C, hairy cell leukaemia	Flu-like symptoms, anorexia, myelosuppression
Cidofovir	Acyclic nucleoside phosphonate, and is therefore independent of phosphorylation by viral enzymes (compare and contrast with aciclovir/ganciclovir)	CMV retinitis in HIV	Nephrotoxicity

Which step is required for acyclovir activation?

→ Conversion to monophosphate form by viral thymidine kinase

HIV: anti-retrovirals

Highly active anti-retroviral therapy (HAART) involves a combination of at least three drugs, typically two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). This combination both decreases viral replication but also reduces the risk of viral resistance emerging.

Anti-retroviral agent used in HIV	About
Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI)	Examples: zalcitabine, zidovudine (AZT), didanosine, lamivudine, stavudine,
Protease inhibitors (PI)	<ul style="list-style-type: none"> Inhibits a protease needed to make virus able to survive outside the cell Examples: indinavir, nelfinavir, ritonavir, saquinavir
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	examples: nevirapine, efavirenz

Nucleoside analogue reverse transcriptase inhibitors (NRTI)

- examples: zidovudine (AZT), didanosine, lamivudine, stavudine, zalcitabine
- general NRTI side-effects: peripheral neuropathy
- zidovudine: anaemia, myopathy, black nails
- didanosine: pancreatitis

Non-nucleoside reverse transcriptase inhibitors (NNRTI)

- examples: nevirapine, efavirenz
- side-effects: P450 enzyme interaction (nevirapine induces), rashes

Protease inhibitors (PI)

- Protease inhibitors are multi-pathway **inhibitors of rivaroxaban clearance and elimination.**
- examples: indinavir, nelfinavir, ritonavir, saquinavir
- side-effects: diabetes, **hyperlipidaemia**, buffalo hump, central obesity, P450 enzyme inhibition
- indinavir: renal stones, asymptomatic hyperbilirubinaemia
- ritonavir: a potent inhibitor of the P450 system

HIV: anti-retrovirals - P450 interaction

- nevirapine (NNRTI): induces P450**
- protease inhibitors: inhibits P450**

Abnormalities of serum lipid levels are likely to be multifactorial in patients with HIV disease, but appear much commoner in patients taking protease inhibitors.

Isolated hypertriglyceridaemia can occur in HIV disease in the absence of protease inhibitors, but extremely high serum triglycerides have been documented in some patients treated with these drugs.

Oseltamivir (Tamiflu)

- Oseltamivir (**Tamiflu**) like its predecessor zanamivir (Relenza) functions as an antiviral through inhibition of the enzyme neuraminidase, thus slowing viral replication down rather than directly killing the virus particle.
- This slowing down of replication is important in permitting time for the body's own immune system to deal with the virus.
- Unlike inhaled zanamivir, oseltamivir is administered orally.
- **Oseltamivir → It is of value in prophylaxis against influenza**
- However, viral replication is rapid and to be effective the drug must be given as early as possible after the development of symptoms of flu and preferably within 48 hours.

Anti-fungal

- **Nystatin** is poorly absorbed through mucous membranes and is thus useful in oral, vaginal and enteric candidiasis
- **Terbinafine** is used to treat superficial mycoses such as dermatophyte infections
- **Fluconazole** is useful in candidiasis and central nervous system infections with Cryptococcus neoformans and is usually commenced after initial treatment with amphotericin and flucytosine
- **Itraconazole** is the agent of choice for non-life threatening blastomycosis and histoplasmosis it is also moderately effective against invasive aspergillosis
- **Amphotericin B → treatment of Aspergilloma**
 - The drug may exert either fungicidal or fungistatic activity, depending on its concentration at the site of infection and sensitivity of the organism
 - increases the permeability of the fungal cell wall by binding to ergosterol and forming micropores
 - side effect → nephrotoxicity associated with **hypokalaemia** and hypomagnesaemia
 - **To decrease toxicity, newer lipid-bound preparations are now available**

Griseofulvin

- Is not active against *Candida albicans*. It is active against trichophytons (tinea) and other dermatophytes.
- It is metabolised in the liver (note also it's an enzyme inducer). Only 0.1-0.2% excreted in urine.
- Treatment with griseofulvin is often needed for a long period, sometimes years, depending on the rate of nail growth.
- **It is associated with drug-induced Stevens-Johnson syndrome**

Diethylcarbamazine

Indication:

- Treatment of individual patients with certain filarial diseases.
- These diseases include: lymphatic filariasis caused by infection with Wuchereria bancrofti, Brugia malayi, or Brugia timori; (ELEPHANTIASIS) tropical pulmonary eosinophilia, and loiasis.

Overdose of antimalarial medications

Chloroquine

Symptoms

- Nausea
- Headaches
- Visual disturbances
- Cardiac arrhythmias
- Convulsions
- Coma

Treatment

- Activated charcoal should be given to patients who present within 1 h
- The initial **hypokalaemia that occurs appears to be cardio-protective** and should not be corrected for at least 8 h after the ingestion
- In patients with **severe toxicity, high-dose (2 mg/kg) diazepam and adrenaline (0.25 pg/kg per min)** have been shown to reduce mortality

Quinine toxicity (cinchonism)

Classical hallmarks of cinchonism are tinnitus, visual blurring, flushed, dry skin and abdominal pain.

- **Indications of Quinine:**
 - antimalarial
 - prophylactic agent against leg cramps,
- **The effect of Quinine toxicity**, (known as cinchonism), may be fatal:
 - In the short term:
 - cardiac arrhythmia (common) (ventricular tachyarrhythmias or fibrillation)
 - ❖ due to blockade of sodium and potassium channels prolonging QRS and QT intervals respectively
 - flash pulmonary oedema
 - Hypoglycaemia (common)
 - ❖ quinine stimulates pancreatic insulin secretion
 - Visual complications, including **blindness**, can occur and **may be permanent**
 - in the long term
 - renal failure
- **Differential diagnosis (Quinin vs Aspirin)**
 - Clinically, quinine toxicity is difficult to distinguish from aspirin poisoning and so measurement of serum salicylate levels is important when this clinical picture is seen.
 - Central nervous symptoms such as tinnitus, deafness and visual defects which may occur with aspirin are usually transient whereas quinine leaves permanent neural damage, if the patient survives.
 - In terms of management however, whereas aspirin can be cleared from overdose victims by haemofiltration, quinine cannot be extracted easily by extracorporeal methods.
- **Management**
 - Supportive
 - fluids, inotropes and bicarbonate as needed
 - positive pressure ventilation for pulmonary oedema.

➤ Avoid

- Lidocaine (lignocaine) should not be used in the management of cardiac arrhythmias as this can increase the risk of seizures
- Urine acidification is not recommended as whilst it increases quinine elimination, it also increases the risk of cardiotoxicity

Immunosuppressants

Ciclosporin (Cyclosporine)

Ciclosporin + tacrolimus - MOA: inhibit calcineurin thus decreasing IL-2

Ciclosporin side-effects: everything is increased - fluid, BP, K⁺, hair, gums, glucose

Mode of action

- It acts by **binding to cyclophilin** forming a complex which → **inhibits calcineurin**, (a phosphatase that activates various transcription factors in T cells) → **reducing IL-2 release** → decreases clonal proliferation of T cells → immunosuppression

Indications

- following organ transplantation
- rheumatoid arthritis
- psoriasis (has a direct effect on keratinocytes as well as modulating T cell function)
- ulcerative colitis
- pure red cell aplasia
- **atopic dermatitis (AD)** (T lymphocytes are involved in the pathophysiology of AD and increased production of cytokines particularly IL-4)

Adverse effects (note how everything is increased - fluid, BP, K⁺, hair, gums, glucose)

- Nephrotoxicity
 - **Chronic interstitial nephritis is a major side-effect of ciclosporin**
 - **Fluconazole inhibits the metabolism of ciclosporin which increases the risk of ciclosporin nephrotoxicity.**
- hepatotoxicity
- fluid retention
- **hypertension**
- hyperkalaemia
- hypertrichosis
- gingival hyperplasia
- impaired glucose tolerance
- hyperlipidaemia
- increased susceptibility to severe infection

- **Tremor**
 - cause **coarse tremor**.
 - In the **first** instance the **dose should be reduced**.
 - Usually the neurological side effects of cyclosporin are **dose dependent**.
- **increased risk for Squamous cell carcinoma**
 - Cutaneous squamous cell carcinoma (SCC) is the second most common human cancer
 - transplant-associated SCC (TSCC), which occurs in immune-suppressed solid organ transplant recipients (OTRs) may be considerably more aggressive than SCC in immune competent patients, with metastatic rates as high as 8%
 - IL-22 receptor is most highly expressed in TSCC and is induced by cyclosporine A.
 - Treatment with anti-IL-22 antibody decreases SCC tumor number and tumor burden.

Note:

- Interestingly for an immunosuppressant, ciclosporin is noted by the BNF to be '**virtually non-myelotoxic**'.

Cyclosporine A immunosuppression drives catastrophic squamous cell carcinoma through IL-22 (September 2016)

Monitoring

- These patients are seen monthly to have their blood pressure, urea, and electrolytes checked.
- **indications for stopping cyclosporine treatment:**
 - Difficult to control hypertension
 - **increase in creatinine by more than 30% from baseline**

Tacrolimus

Mode of action

- similar to the action of ciclosporin

Tacrolimus vs Ciclosporin:

- It has a very similar action to ciclosporin (**inhibits calcineurin, reducing IL-2 release**)
- The action of tacrolimus differs from ciclosporin in that it **binds to a protein called FKBP rather than cyclophilin**
- Tacrolimus is more potent than ciclosporin and hence the incidence of organ rejection is less.
- However, nephrotoxicity and impaired glucose tolerance is more common

Indications

- immunosuppressant to prevent transplant rejection.
- Other T-cell mediated diseases
 - Eczema (as ointment)
 - Severe refractory uveitis after bone marrow transplant
 - Vitiligo

Monitoring

- Tacrolimus levels can be affected by concomitant use of other drugs and changes in gut absorption, and so **need to be monitored carefully**.

Many side effects of tacrolimus are similar to cyclosporine A, but tacrolimus does not cause gingival hyperplasia or hirsutism

Sirolimus

Overview

- A macrolide compound
- Also known as rapamycin

Mode of action

- binding with intracellular FKBP-12 protein → inhibition of mTORC1 → ↓ cytokine-induced T-cell proliferation → immunosuppression
- Sirolimus binds to the immunophilin FK binding protein 12 (FKBP12), and the drug-immunophilin complex acts on the Target of Rapamycin (rapamycin being the original name of sirolimus) to interrupt stimulation of cell proliferation via the interleukin-2 receptor.
- **What is the target of action of sirolimus?**
⇒ FK binding protein 12 (FKBP12)

Indications

- treatment of acute rejection.

Adverse Effects

- **Pancytopenia**
- **Hyperlipidemia**
- Peripheral edema
- Insulin resistance
➤ Inhibition of mTORC2 → diabetes-like symptoms

Azathioprine

Azathioprine → check thiopurine methyltransferase deficiency (TPMT) before treatment

- Azathioprine is metabolised to the active compound mercaptopurine, a purine analogue that inhibits purine synthesis → **Impaired DNA synthesis**
- A thiopurine methyltransferase (TPMT) test may be needed to look for individuals prone to azathioprine toxicity.
 - ⇒ The enzyme activity of thiopurine methyltransferase (TPMT) is under the control of a genetic polymorphism.
 - ⇒ **90 % of the population have normal or high (TPMT) enzyme activity.** 10 % have intermediate levels
 - ⇒ One in 300 people have no functional enzyme activity.
 - ⇒ Several groups of patients have developed azathioprine induced myelosuppression linked to TPMT deficiency.

Adverse effects include

- bone marrow depression → Pancytopenia
⇒ **It suppresses lymphocyte numbers and function**
- nausea/vomiting
- pancreatitis
- Hepatotoxicity
- 100-fold increased risk of skin cancers and lymphomas.

Monitoring

- (BNF) suggest monitoring CBC, LFTs and U&E every 3 months once patients are established and stable on azathioprine treatment.

interaction

- Azathioprine and 6-MP are metabolized by xanthine oxidase. Therefore, allopurinol—a xanthine oxidase inhibitor—increases the risk of azathioprine and 6-MP toxicity.
- A significant interaction may occur with allopurinol and hence lower doses of azathioprine should be used.
 - ⇒ Allopurinol acts by inhibition of xanthine oxidase and thus inhibits the metabolism of 6-mercaptopurine, an active metabolite of azathioprine.
 - ⇒ The prodrug azathioprine is metabolised to its active compound 6-mercaptopurine (6-MP). 6-MP undergoes catabolic oxidation to 6-thiouric acid by xanthine oxidase.
 - ⇒ Allopurinol has a peak onset of action of one to two weeks and works by inhibiting xanthine oxidase.
 - ⇒ Co-administration of (Azathioprine + Allopurinol) → accumulation of 6-MP (6-MP toxicity) → ↑ risk of myelosuppression (aplastic anaemia)
 - ⇒ if concomitant use is to occur, a **dose reduction in azathioprine by 25%** is advised with regular blood count monitoring.

Usage in pregnancy

- **Azathioprine can be used in pregnancy without significant risk to the fetus**

Methotrexate

Action

- Methotrexate is an **antimetabolite** which **inhibits dihydrofolate reductase**, an enzyme essential for the synthesis of purines and pyrimidines
 - ⇒ Methotrexate inhibits dihydrofolate reductase, thereby inhibiting the production of tetrahydrofolate required for thymidine and purine synthesis.
 - ⇒ inhibits purine and pyrimidine synthesis **by competing for the active site** of dihydrofolate reductase (**by competitive inhibition**).
 - ⇒ It is cytotoxic **during the S-phase of the cell cycle**, and has a greater toxic effect on rapidly dividing cells.
 - ⇒ **Take 6 -12 weeks to achieve full affect**

Indications

- rheumatoid arthritis
- psoriasis (Methotrexate would be the only correct treatment for someone with **erythrodermic psoriasis**)
- acute lymphoblastic leukaemia

Adverse effects

- mucositis
- myelosuppression
- **Macrocytosis is seen as a consequence of long term methotrexate therapy.**
- pneumonitis
- pulmonary fibrosis
- liver cirrhosis
- ⇒ **What is the toxicity of Methotrexate (MTX) at the liver?**
 - * **Macrovesicular fatty change**

Pregnancy

- women should avoid pregnancy for at least 3 months after treatment has stopped
- the BNF also advises that men using methotrexate need to use effective contraception for at least 3 months after treatment

Prescribing methotrexate

- methotrexate is taken weekly, rather than daily

- FBC, U&E and LFTs need to be regularly monitored.
 - ⇒ The Committee on Safety of Medicines recommend '**FBC and renal and LFTs before starting treatment and repeated weekly until therapy stabilised, thereafter patients should be monitored every 2-3 months'**
- **Folic acid 5mg once weekly should be co-prescribed**, taken more than 24 hours after methotrexate dose
- the starting dose of methotrexate is 7.5 mg once weekly, can be increased by 2.5 mg every 6 weeks, to a maximum of 20 mg weekly (Ref: oxford handbook of practical drug therapy)
- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg)
- do not prescribe with aspirin or NSAIDs → ↓ methotrexate excretion → ↑ toxicity
- avoid prescribing anti-folate antibiotics trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia
- In the circumstances of infection one should consider temporarily stopping methotrexate as it is an immunosuppressant.

Interaction

- OAT-1 inhibitors
 - Methotrexate is a substrate for the OAT-1 renal transporter and levels of methotrexate are therefore affected by decreased renal function.
 - OAT-1 inhibitors include drugs such as **probenecid**, and therefore should not be used in conjunction with methotrexate.
- **Omeprazole**
 - **Omeprazole is also known to affect clearance of methotrexate**; this interaction is not thought to be via OAT-1, but is **thought to be related to inhibition of breast cancer resistance protein**, which is responsible for methotrexate transport.

Monitoring

- Clinicians are recommended to check **FBC fortnightly until 6 weeks** after the last dose increase.
 - Provided it is **stable**, it can be checked **monthly** thereafter until the dose and disease is stable for one year.
 - Thereafter, monitoring is guided by clinical judgement. If white cell count is less than 3.5, neutrophils less than 2 or platelets less than 150, methotrexate should be withheld pending discussion with the specialist team.
 - An MCV greater than 105 fL warrants checking B12, folate and TSH and treating any abnormality. If these are normal, discuss with the specialist team.
- **Liver function tests** should be checked **three monthly**. If there is an unexplained decrease in albumin, or AST/ALT twice the upper limit of normal, the specialist team should be informed.
- **Urea, creatinine and electrolytes** should be checked **six monthly**. If the estimated glomerular filtration rate falls below 50 mL/minute, methotrexate should be withheld until the result has been discussed with the specialist team.

Drug	MOA
Mycophenolate mofetil	inhibits inosine monophosphate dehydrogenase
Azathioprine	metabolised to the active compound mercaptopurine a purine analogue that inhibits DNA synthesis. purine synthesis inhibitor
Methotrexate	antimetabolite which inhibits dihydrofolate reductase

Methotrexate overdose

Methotrexate overdose → Folinic acid

- Methotrexate is a folic acid antagonist which can result in multi-organ failure in overdose.
- medication errors with respect to rheumatoid arthritis are not uncommon.
 - Patients occasionally find it difficult to understand that they must take their medication weekly as opposed to daily.
- **Calcium folinate is a potent antagonist for the effects of methotrexate** on the haematopoetic system, given by IV infusion at doses up to 75mg in the first 12hrs. This can then be followed by doses of 6-12mg every 4hrs.
- **Folinic acid is the antidote** and should be given intravenously as soon as possible, regardless of the liver function tests.
- Blood transfusion may also be required in exceptional circumstances.
- Where massive overdose of methotrexate has occurred, hydration and urinary alkalinisation may be an option.
- Standard dialysis is ineffective in removing methotrexate, although intermittent high flux dialysis may be of value.

Mycophenolate mofetil

Mode of action

- inhibits inosine monophosphate dehydrogenase, which is needed for purine synthesis as T and B cells are particularly dependent on this pathway it can reduce proliferation of immune cells
- A growing number of studies have demonstrated the efficacy of mycophenolate in SLE, especially in the context of lupus nephritis.
- Mycophenolate is an anti-purine drug that selectively depletes B and T lymphocytes (preferentially targeting activated cells). The result of this mode of action is that **neutropenia is rare**, which would be advantageous in (SLE) patients complicated by an autoimmune neutropenia.
 - **the most appropriate agent for (SLE) which complicated by an autoimmune neutropenia**
- adverse effects
 - Pancytopenia
 - Hypertension
 - Hyperglycemia

Hydroxychloroquine

- Hydroxychloroquine ocular toxicity includes:
 - Keratopathy
 - Ciliary body involvement
 - Lens opacities (Lenticular deposits)
 - Retinopathy.
 - Retinopathy is the major concern; the others are more common but benign.
 - The incidence of true hydroxychloroquine retinopathy is exceedingly low.
 - Risk factors include:
 - ❖ Daily dosage of hydroxychloroquine
 - ❖ Cumulative dosage
 - ❖ Duration of treatment
 - ❖ Coexisting renal or liver disease

- ❖ Patient age, and
- ❖ Concomitant retinal disease.
- Patients usually complain of difficulty in reading, decreased vision, missing central vision, glare, blurred vision, light flashes, and metamorphopsia.
- They can also be asymptomatic.
- Most patients with advanced retinopathy have a bull's eye (also known as target, as in darts) fundoscopic appearance. All patients have field defects including paracentral, peri-central, and central and peripheral field loss.
- Regular screening may be necessary to detect reversible premacularopathy.
- Cessation of the drug is the only effective management of the toxicity.

Sulfasalazine

Side effects

- hypersensitivity,
- myelosuppression,
- macrocytosis, and
- azoospermia in males.

sulfasalazine toxicity

- There are numerous signs of sulfasalazine toxicity.
- **Rash and oral ulceration** should be asked about and, if severe, the drug should be withheld until specialist advice has been sought.
- Nausea, dizziness and headache can be common and sometimes necessitate dose reduction.
- If patients present with abnormal bruising or sore throat an urgent CBC should be done, and sulfasalazine withheld until results are available.

Monitoring

- **CBC**
 - CBC should be monitored monthly for the first 3 months.
 - Sulphasalazine should be withheld until discussion with the specialist team if:
 - The white cell count is less than 3.5
 - Neutrophils is less than 2, or
 - Platelets are less than 150.
 - If (MCV) > 105 fl, vitamin B12, folate and TSH should be checked and treated if found to be abnormal. If these are all normal it should be discussed with the specialist team.
 - If counts remain normal within the first 3 months, CBC can be checked 3 monthly.
- **Liver function tests (LFTs)**
 - should also be checked monthly for the first 3 months.
 - If either AST or ALT are **more than twice the upper limit of normal**, sulfasalazine should be withheld until discussion with the specialist team.
 - If the LFTs remain normal for the first 3 months, monitoring can be decreased to 3 monthly.

- If, following the first year, the dose has not been increased and blood results have been stable, the frequency of monitoring can be reduced to every six months for the second year of treatment. Thereafter monitoring is not required, although CBC and LFTs should be checked one month after any dose increase.

Leflunomide

- an immunosuppressive disease-modifying antirheumatic drug (DMARD), used in active moderate-to-severe rheumatoid arthritis and psoriatic arthritis.
- It is a **pyrimidine synthesis inhibitor**.
- achieves its effects by **inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH)**, which plays a key role in the *de novo* synthesis of uridine monophosphate (rUMP), which is required for the synthesis of DNA and RNA. Hence, leflunomide inhibits the reproduction of rapidly dividing cells, especially lymphocytes.

Side effects

- Hepatotoxicity (occurring in 15-20% of cases)
 - most hepatic events occur within the first 6 months of use.
- signs of leflunomide toxicity should be monitored. If the patient develops a **rash or itch** dose reduction should be considered, with or without the addition of antihistamines. If severe, leflunomide should be stopped and washout considered.
- **Hair loss, headaches and gastrointestinal upset** may also warrant dose reduction or washout.
- **A blood pressure of greater than 140/90 mmHg** should be treated as per NICE guidelines. If it remains elevated, stop leflunomide and consider washout.
- Weight should be monitored, and a **weight loss** of greater than 10% should be identified. If no other cause can be found, consider dose reduction or washout.
- If there is increasing shortness of breath, **pneumonitis** should be considered and leflunomide should be stopped.
- Leflunomide **reduces sperm count**.

Monitoring

- **LFT**
 - (LFTs) should be checked monthly for 6 months and, if stable, 2 monthly thereafter.
 - If AST or ALT is between 2 and 3 times the upper limit of normal, and the leflunomide dose is more than 10 mg daily, the dose should be reduced to 10 mg and LFTs rechecked weekly until normalised. If the ALT and AST are returning to normal, the patient should be left on 10 mg per day. If the LFTs remain elevated, leflunomide should be stopped and discussed with the specialist team.
 - If the AST or ALT is more than 3 times the upper limit of normal, the LFTs should be rechecked within 72 hours. If they remain more than 3 times the reference range, leflunomide should be stopped and washout considered (cholestyramine and activated charcoal).
 - It is important to note that the half-life of leflunomide is usually 2 weeks (mean 14) therefore if a rapid response is required, washout should be considered.

- CBC**

- (CBC) should be checked monthly for six months and, if stable, two monthly thereafter.
- White cell count less than 3.5, neutrophils less than 2 or platelets less than 150 should be discussed with the specialist team, and leflunomide withheld until this has taken place.

Poisoning & Toxicology

Overdose and poisoning: management

The table below outlines the main management for common overdoses:

Toxin	Treatment
Paracetamol	Management <ul style="list-style-type: none"> activated charcoal if ingested < 1 hour ago N-acetylcysteine (NAC) liver transplantation
Salicylate	Management <ul style="list-style-type: none"> urinary alkalinization is now rarely used - it is contraindicated in cerebral and pulmonary oedema with most units now proceeding straight to haemodialysis in cases of severe poisoning haemodialysis
Opioid/opiates	Naloxone
Benzodiazepines	Flumazenil
Tricyclic antidepressants	Management <ul style="list-style-type: none"> IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias dialysis is ineffective in removing tricyclics
Lithium	Management <ul style="list-style-type: none"> mild-moderate toxicity may respond to volume resuscitation with normal saline

Toxin	Treatment
	<ul style="list-style-type: none"> haemodialysis may be needed in severe toxicity sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion
Warfarin	Vitamin K, prothrombin complex
Heparin	Protamine sulphate
Beta-blockers	<p>Management</p> <ul style="list-style-type: none"> if bradycardic then atropine in resistant cases glucagon may be used
Ethylene glycol	<p>Management has changed in recent times</p> <ul style="list-style-type: none"> ethanol has been used for many years works by competing with ethylene glycol for the enzyme alcohol dehydrogenase this limits the formation of toxic metabolites (e.g. Glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning fomepizole, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol haemodialysis also has a role in refractory cases
Methanol poisoning	<p>Management</p> <ul style="list-style-type: none"> fomepizole or ethanol haemodialysis
Organophosphate insecticides	<p>Management</p> <ul style="list-style-type: none"> atropine the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit
Digoxin	Digoxin-specific antibody fragments
Iron	Desferrioxamine, a chelating agent
Lead	Dimercaprol, calcium edetate
Carbon monoxide	<p>Management</p> <ul style="list-style-type: none"> 100% oxygen hyperbaric oxygen
Cyanide	Hydroxocobalamin; also combination of amyl nitrite, sodium nitrite, and sodium thiosulfate
Sarin (organophosphorus)	Pralidoxime → reactivates acetyl cholinesterase enzyme. It should be used in the first few hours.

Drug poisoning: Hypersalivation

Hypersalivation is seen with:

- Parasympathomimetic agents
- Insecticides
- Arsenic
- Strychnine
- Chlormethiazole, and
- Clozapine.

Other poisoning signs

Acneiform rash around the buccal cavity → Solvent abuse

Nasal septum perforation (and hypertension) → Cocaine abuse

Drug poisoning: Altered serum glucose in unknown overdose

Alteration in serum glucose concentration, in addition to other clinical signs and symptoms, can be helpful in diagnosing the ingestion of an unknown drug:

Drugs induce hyperglycaemia	Drugs induce hypoglycaemia
<ul style="list-style-type: none"> • Corticosteroids, • thiazide diuretics, • theophylline, • iron (during the initial period after overdose), • caffeine and • B2-agonists 	<ul style="list-style-type: none"> • insulin, sulphonylureas, • Salicylates • sodium valproate, • propranolol, • iron (later if hepatic failure ensues)

Drugs cleared by alkalization of the urine

The clearance of which drug would be increased by alkalization of the urine?

- Weak acids are ionized in an alkaline environment, and this lessens their tubular absorption.
- Alkalization of urine, achieved by IV infusion of sodium bicarbonate, can thereby be used to increase the urinary elimination of:
 1. barbiturates,
 2. salicylates and
 3. **isoniazid**.

Measurement of drug concentrations

- Measurement of drug concentrations is clinically important for relatively few compounds.
- Drug concentrations are particularly important for those compounds where the concentration is predictive of serious toxicity in an otherwise asymptomatic patient.

Compounds where measurement of drug concentration is clinically indicated:

- **Paracetamol**
- **Theophylline**
 - Theophylline concentrations predict the risk of seizures and cardiac toxicity in both acute and chronic toxicity
 - Patients who have ingested more than 10 mg kg^{-1} of theophylline should receive repeated doses of activated charcoal.
- **Digoxin**
- **Iron**

- **Lithium**
- **Salicylate**
- **Ethylene glycol**
 - An ethylene glycol concentration of $>50 \text{ mg dl}^{-1}$ is a possible indication for haemodialysis and a definite indication for 4-methylpyrazole (4MP) or ethanol infusion
- **Methanol**
 - A methanol level of greater than 50 mg dl^{-1} is a possible indication for haemodialysis and a definite indication for 4MP or ethanol infusion.
 - haemodialysis usually considered at methanol concentrations **above 20 mmol/l** (approximately 90 mg/dl).
- **Ethanol**
- **Anticonvulsants**
 - Measurement of anticonvulsant concentrations will confirm ingestion but do not substantially influence treatment in overdose, which is supportive care.
- **Paraquat**
 - non-selective contact herbicide
 - paraquat concentrations are useful for confirming ingestion and defining prognosis but do not influence treatment, which is predominantly supportive care

Drug toxicity in renal failure

- A wide range of drug-handling processes occur in the kidney:
 - ⇒ Filtration
 - ⇒ tubular secretion
 - ⇒ active and passive tubular reabsorption
- The overall renal clearance of drugs declines in parallel with falls in the glomerular filtration rate and creatinine clearance

Norpethidine

- In patients with renal impairment pethidine is metabolised to norpethidine, but at this stage metabolism stops and **norpethidine accumulates** rather than being excreted through the kidneys
- **Norpethidine is toxic and is associated with a risk of seizures**

Morphine

- A similar accumulation of morphine 6-glucuronide occurs after morphine administration in patients with renal impairment, which **may lead to narcosis**
- **fluid overloaded + pin point pupils in a patient taking morphine with renal impairment → the most likely cause of his symptoms → Renal failure leading to accumulation of morphine** (not overdose) (masterclass 2017 part 2)
 - ⇒ Patients with relapsed ovarian cancer may develop an obstructive nephropathy due to pelvic recurrence. If they are on morphine they may get accumulation of this drug and signs of opiate toxicity superimposed on the signs of renal failure.

Other drugs

- Other drugs where physiologically active metabolites accumulate leading to toxicity in renal failure include:
 - ⇒ nitroprusside (active metabolite thiocyanate)
 - ⇒ allopurinol (accumulation of oxypurinol leads to rash and allergy)

Characteristic smells of toxins/poisons

Certain toxins/poisons have characteristic smells that can assist in the identification of substances taken. Below is a list of well-recognised smells/odours and the poisons/toxins for which they are characteristic.

- Garlic: Arsenic, selenium
- Bitter almonds: Cyanide
- **Rotten eggs: Hydrogen sulphide, mercaptans**
- Wintergreen: Methyl salicylate
- Mothballs: Naphthalene

Arsenic toxicity

The combination of mixed sensorimotor polyneuropathy in the presence of possible exposure to pesticides in a farmer would suggest a diagnosis of chronic arsenic poisoning.

- Arsenic is a heavy metal which is a natural component of the earth's crust.
- exists in organic or inorganic . It is highly toxic in its inorganic form.
⇒ organic arsenics found in fish and seafood are non-toxic
- Arsenic exposure is usually occupational or environmental
- **routes of exposure include:**
 - ⇒ Groundwater most often becomes contaminated naturally
 - Arsenic contamination of groundwater is widespread
 - most common in Bangladesh, West Bengal and India
 - ⇒ **Occupational exposures:** toxic waste sites and traditional medicines.
- Features
 - ⇒ Acute
 - GI (nausea, vomiting, hemorrhagic gastroenteritis, garlic breath)
 - CNS (coma, seizures)
 - ⇒ Chronic
 - Skin changes: dermatitis, hyperkeratosis & hyperpigmentation
 - ❖ **The first symptoms of long-term exposure**
 - ❖ **the most common effect of chronic exposure**
 - ❖ Keratoses on the palms and soles are characteristic.
 - ❖ occur after a minimum exposure of approximately five years
 - ❖ may be a precursor to skin cancer.
 - **Mees lines: leukonychia striata (transverse white lines on the finger nails)**
 - Abdominal pain
 - Sensory-motor **Peripheral neuropathy**
 - Diabetes
 - Cancers (lung, bladder, skin).
- Arsenic can interfere with the mechanism of hemoglobin synthesis and the ribosomes may **form dot-like precipitates, called basophilic stippling, at the periphery of RBCs.**
- Basophilic stippling is also found in:
 - ⇒ thrombotic thrombocytopenic purpura, in hemoglobin H disease (rarely)
 - ⇒ megaloblastic anemia.
 - It indicates a RBC cell line maturation defect in the bone marrow.
- The hematological effects of arsenic toxicity include:
 - ⇒ Anemia
 - ⇒ Pancytopenia

- ⇒ Hemolysis in some cases
- Management
 - ⇒ Acute exposure → Chelation:
 - Consider chelation therapy in patients who are symptomatic and/or have urine concentration >200 mcg/L.
 - ❖ DMPS is the chelation agent of choice.
 - ❖ DMSA is an alternative (oral preparation only, so unsuitable if the patient is vomiting).
 - ⇒ Chronic exposure
 - arsenic-free drinking water, to reduce the risk of further disease
 - It is recommended that all patients with skin lesions be given multivitamins.

Drugs altered pupil size

Many drugs can cause changes in pupil size as detailed below:

- **Dilated pupils (mydriasis):**
 - sympathomimetic drugs, eg cocaine, dopamine, amphetamines
 - anticholinergic drugs, eg antihistamines, atropine, tricyclic antidepressants
- **Constricted pupils (miosis):**
 - sympatholytic drugs, eg opiates, phenothiazines, clonidine, sodium valproate
 - cholinergic drugs, eg organophosphates, pilocarpine

Charcoal

- reduce drug absorption from the gastrointestinal tract, and interrupting enterohepatic recirculation.
- **Which factor would be most strongly influence your decision to administer or avoid oral activated charcoal?**
 - **Absence of bowel sounds**
 - It is generally safe, but should be administered only in patients who are able to protect their airway. The absence of bowel sounds may indicate a paralytic ileus, which is surprisingly common after overdose, and which is associated with an increased risk of charcoal aspiration and pneumonitis.
- Iron, lithium and other cations are not adsorbed by charcoal; alcohols including ethanol, methanol and ethylene glycol are not adsorbed either.
- Activated charcoal is capable of adsorbing around 10% of its own weight, so administration of charcoal 50 g might be expected to adsorb around 5 g of drug.
- should normally be administered within 1 hour of drug overdose, but may be effective when administered after a longer interval, particularly after modified-release preparations.

Multi-dose activated charcoal

When Activated charcoal can be repeatedly given to increase elimination of the poison?

⇒ **When the drug circulates through the enterohepatic circulation**

- Multi-dose activated charcoal means giving 50 g of activated charcoal every 3-4 h
- It is useful in patients who have taken significant amounts of salicylates, and should be continued until plasma salicylate concentrations have peaked
- It is also useful in the management of patients who have taken drugs with significant enterohepatic circulation (carbamazepine, phenobarbital, theophylline and quinine) and sustained-/modified-release preparations
- It is contraindicated in patients with signs of bowel obstruction,

Methanol poisoning

Overview

- Methanol, like ethanol, is metabolised by **alcohol dehydrogenase** to form **formaldehyde**. **Formaldehyde** is then further metabolised by **aldehyde dehydrogenase** to **formic acid**.
- Formate formation leads to:
 - severe **metabolic acidosis**, and
 - crystals forming within the eye can lead to so called '**snow field cataract formation**'.

Feature

- **Early signs** (are due to methanol) include:
 - ⇒ Nausea and vomiting
 - ⇒ Headache,
 - ⇒ Confusion.
- **later signs** (are due to its metabolite, formic acid)
 - ⇒ high gap metabolic acidosis
 - Anion gap = $(\text{Na} + \text{K}) - (\text{Cl} + \text{HCO}_3)$; normal range 7-17 mmol/L.
 - Although elevated, the lactate level does not account for the anion gap.
 - ⇒ visual problems, retinal injury, including blindness (methanol-associated visual loss)
 - accumulation of formic acid → a form of optic neuropathy

Differential diagnosis

- The differential diagnosis of this form of a **high anion gap metabolic acidosis** is (**SLUMPED**) (salicylates, lactic acidosis, uremia, methanol/ethylene glycol, paraldehyde, ethanol, and diabetic ketoacidosis).

Similarities between Methanol and ethylene glycol intoxication

- Both are causes a very similar biochemical and clinical picture.
- Both require the enzyme alcohol dehydrogenase for metabolism.
- Both are treated with fomepizole or ethanol, which inhibit alcohol dehydrogenase
- Both can present with metabolic acidosis, hyperpnea and tachypnea, coma, seizures, and hypotension.
- The fruity smell suggests ketosis.

Differences between Methanol and ethylene glycol intoxication

- From history
 - ⇒ Methanol is pure distilled alcohol, more likely to be consumed by those with a history of alcohol abuse.
 - ⇒ Ethylene glycol is antifreeze, usually consumed by those with suicidal intent or history of deliberate self-harm.
- From examination
 - ⇒ **eye signs (macular oedema and poor pupillary responses) → methanol**
 - In exams, cases involving methanol toxicity often involve patients not meeting your gaze or asking for the lights to be switched on, as well as the more traditional visual acuity results.
 - Methanol leads to the formation of **formate**, which causes retinal damage with optic disc hypemia and edema, blindness, and basal ganglia infarcts.
 - ⇒ Ethylene glycol causes the formation of calcium oxalate crystals, leading to renal

failure and hypocalcemia (\rightarrow tetany)

- * Oxalate crystals are a specific sign of ethylene glycol toxicity.

► **formate** is the toxic metabolite of methanol

► **oxalic acid** is the toxic metabolite of ethylene glycol

Management

- fomepizole or ethanol \rightarrow Inhibition of methanol metabolism by alcohol dehydrogenase **is the treatment of choice**.
 - \Rightarrow 1st line \rightarrow fomepizole which is an inhibitor of alcohol dehydrogenase.
 - \Rightarrow 2nd line \rightarrow If fomepizole is not available, then ethanol is recommended.
- sodium bicarbonate if necessary to correct severe acidaemia (pH < 7.20)
- Haemodialysis

Treatment is aimed at:

1. Eliminating formic acid (alkaline diuresis or **haemodialysis**).
2. Correcting acidosis with IV bicarbonate.
3. Preventing metabolism of methanol to formic acid by administering IV ethanol.

Ethylene glycol toxicity

Ethylene glycol toxicity management - fomepizole. Also ethanol / haemodialysis

- Ethylene glycol is a type of alcohol used as a coolant or antifreeze

Features of toxicity are divided into 3 stages:

- Stage 1: symptoms similar to alcohol intoxication: confusion, slurred speech, dizziness
- Stage 2: metabolic acidosis with high anion gap and high osmolar gap. Also tachycardia, hypertension
- Stage 3: acute renal failure
 - \Rightarrow renal, respiratory and cardiac failure.
 - \Rightarrow Multi-organ failure is thought to occur at least in part due to widespread deposition of calcium oxalate crystals around 12 h after the initial insult.

Management

- treatment is often given based on clinical suspicion due to a delay in obtaining ethylene glycol levels in most centres.
- **fomepizole**, an inhibitor of alcohol dehydrogenase, is now used **first-line** in preference to ethanol
 - \Rightarrow prevents metabolism of ethylene glycol to oxalic acid, responsible for the acidosis and renal failure
 - \Rightarrow Because of the potential formation of calcium oxalate, calcium levels should also be assessed.
- **ethanol** has been used for many years
 - \Rightarrow works by competing with ethylene glycol for the enzyme alcohol dehydrogenase
 - \Rightarrow this limits the formation of toxic metabolites (e.g. glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning
- **IV fluids with bicarbonate** to correct the metabolic acidosis in severe lactic acidosis.
- **Calcium gluconate for hypocalcemia**,

- **haemodialysis** also has a role in refractory cases

Fomepizole - used in ethylene glycol and methanol poisoning - competitive inhibitor of alcohol dehydrogenase

Isopropyl alcohol (Isopropanol) intoxication

Acidosis + eye signs → methanol poisoning

Acidosis without eye signs → ethylene glycol poisoning

Ketosis without acidosis → isopropyl alcohol poisoning

Overview

- It is a clear colorless liquid with a BITTER TASTE and **fruity odor**.
- commonly used as a rubbing alcohol and as a solvent in hair-care products, skin lotions and home aerosols.
- Also found in products including cleaners, disinfectants, antifreezes, cosmetics, solvents, inks, and pharmaceuticals.
- Inexpensive and can be a substitute for ethanol.
- the second most common alcohol intoxication next to ethanol.
- It is twice as potent as ethanol as a central nervous system depressant but without an early elation phase.

Feature:

- Severe isopropanol poisoning results in CNS and respiratory depression and circulatory collapse.
- GIT and CNS symptoms are predominating,
- **alcohol**, benzodiazepines, **isopropyl alcohol**, lithium, and organophosphates may all lead to **miosis** (constriction of the pupil)
- Large ingestions can result in coma.
- The most common metabolic effects are an increased osmol (osmolal) gap, ketonemia, and ketonuria
- **metabolic acidosis - unlike in other alcohols intoxication - is not present**, this is because isopropyl alcohol is metabolized by alcohol dehydrogenase to acetone, (a ketone is not an acid).
 - ⇒ therefore, ketone appear in breath and in urine.
- Isopropyl alcohol intoxication can be remembered as "**ketosis without acidosis**".
- Another unique finding is "**pseudo renal failure**" or **ISOLATED false elevation of creatinine with a normal BUN**.

Diagnosis:

- An osmol gap, ketonemia, and/or ketonuria **without metabolic acidosis**, along with a fruity or sweet odor on the breath and CNS depression support the diagnosis.
- Although ethylene glycol, methanol, and ethanol ingestions result in anion gap **and** osmolar gap, **isopropyl alcohol results in only an osmolar gap**.
 - ⇒ Osmolar gap = Osmolality – Osmolarity
 - Osmolality is **measured** in laboratory by osmometers
 - Osmolarity is **calculated** = $(2 \times [\text{Na}^+]) + [\text{glucose}] + [\text{urea}]$
 - normal = < 10

- the units of osmolality are mOsm/kg of solute
- the units of osmolarity are mOsm/L

Treatment:

- supportive care (is the mainstay of management) → Patients usually make a full recovery
- hemodialysis → elimination of isopropanol and acetone → only in severe life-threatening poisonings.

Ecstasy poisoning

- Ecstasy is an amphetamine derivative (MDMA, 3,4-Methylene-Dioxy-Meth-Amphetamine) use became popular in the 1990's during the emergence of dance music culture
- is a semi-synthetic hallucinogen used as a recreational drug.

Clinical features

- neurological: agitation, anxiety, confusion, ataxia
- cardiovascular: tachycardia, hypertension
- **hyponatraemia**
- Hyperventilation
- **hyperthermia**
- rhabdomyolysis

Management → supportive (no specific antidote)

- Cold intravenous fluids if the core temperature is over 39 °C
- dantrolene may be used for hyperthermia if simple measures fail
- and/or paralysis and ventilation
- Treatment of associated hyperthermia

Opioid misuse

Acute confusion and visual hallucinations are common symptoms of opioid toxicity and pin point pupils and myoclonas are common signs.

- Opioids are substances which bind to opioid receptors. This includes both naturally occurring opiates such as morphine and synthetic opioids such as buprenorphine and methadone.

Features of opioid misuse

- rhinorrhoea
- needle track marks
- pinpoint pupils
- drowsiness
- watering eyes
- yawning
- symptoms of neurotoxicity (for example, hallucinations, **myoclonus** and delirium)
- respiratory depression

Complications of opioid misuse

- viral infection secondary to sharing needles: HIV, hepatitis B & C
- bacterial infection secondary to injection: infective endocarditis, septic arthritis, septicaemia, necrotising fasciitis
- venous thromboembolism
- overdose may lead to respiratory depression and death
- psychological problems: craving
- social problems: crime, prostitution, homelessness

Emergency management of opioid overdose

- IV or IM **naloxone**: has a rapid onset and relatively short duration of action
- intravenous naloxone (0.4 mg), repeated up to a total dose of 2 mg depending on clinical response.
- **The half-life of naloxone is shorter than that of opioids**, hence if the patient wakes up it can be anticipated that he will 're-narcose'. A naloxone infusion may be necessary.

Harm reduction interventions may include

- needle exchange
- offering testing for HIV, hepatitis B & C

Management of opioid dependence

- patients may be offered maintenance therapy or detoxification
- NICE recommend methadone or buprenorphine as the first-line treatment in opioid detoxification
- compliance is monitored using urinalysis
- detoxification should normally last up to 4 weeks in an inpatient/residential setting and up to 12 weeks in the community
- **Naltrexone can be used to help prevent relapse in the treatment of Opioids dependency**
 - ⇒ Naltrexone is a long-acting opioid antagonist.
 - ⇒ It can be used as an adjunct to psychosocial treatments to prevent relapse in detoxified patients who were formerly dependent on opioids.
 - ⇒ Naltrexone should only be initiated in specialist clinics.
 - ⇒ Patients should have remained opioid-free for at least 7–10 days before naltrexone is started.
 - ⇒ Naltrexone has also been shown to be useful for relapse prevention in those who misuse alcohol.

Dihydrocodeine

- Dihydrocodeine is an opiate analgesic and when taken in overdose has a number of toxic effects.
- It acts as a respiratory depressant leading to reduced respiratory rate.
- **It can cause bradycardia and hypotension in large doses.**
- Pupillary constriction is a diagnostic feature in opiate overdose.
- It is also a central nervous system depressant and therefore causes coma in overdose.

Pain relief

- Titrating the dose of morphine needed for analgesia should be done with rapidly acting formulations of morphine, and once adequate analgesia is obtained sustained-release morphine can then be substituted (at the same total daily dose)

Analgesia in opiate users (eg: on methadone)

- Discontinuation of methadone may result in symptoms of acute opiate withdrawal and this is not recommended
- **Continuation of methadone and consideration of analgesics with a different mode of action (ie non-steriodals such as parenteral diclofenac) is recommended**

Opioid withdrawal

- The symptoms and signs of opioid withdrawal include dysphoric mood, yawning, insomnia, nausea, vomiting, diarrhoea, muscle aches, lacrimation / rhinorrhoea, pupillary dilatation, piloerection, sweating and fever.
- Initially give 10 mg of methadone syrup and wait about 60 min to determine its effect. Continue administering in 10 mg doses until symptoms are under control. It is rare to exceed a total dose of 40 mg over 24 hours.

Morphine

Side-effects including:

- Nausea, vomiting
 - ⇒ Nausea affects up to two-thirds of patients starting morphine but in the majority of these it is self-limiting to within 1 week.
 - ⇒ **Haloperidol is the first-line drug for opioid-induced nausea**, kidney disease and hypercalcaemia
- **constipation**
- drowsiness, confusion
- others, including: bronchospasm, angioedema, urinary retention, ureteric or biliary spasm, dry mouth, **sweating**, rash, facial flushing, vertigo, tachycardia, bradycardia, palpitations, orthostatic hypotension, hypothermia, restlessness, mood change, hallucinations, seizures (adults and children) and miosis, headache and allergic reactions (including anaphylaxis) and decreased libido or potency
- **pruritus** in some patients, secondary to intradermal histamine release.
 - ⇒ changing to an alternative opioid such as oxycodone, which is less likely to cause itching, may be more appropriate
- raised intracranial pressure
- Muscle rigidity may occur with high doses
- biliary sphincter constriction → Elevated liver enzymes
- Large doses can lead to respiratory depression, circulatory failure and coma

Morphine vs pethidine

- **Morphine acts for four to five hours while pethidine works for two to three hours.**
 - ⇒ This means that pethidine would have to be given at more frequent intervals to produce the same analgesic effects as morphine.

Pethidine

- Meperidine (Pethidine) is a full opioid agonist at μ receptors.
 - ⇒ the only opioid that acts as an **antimuscarinic**
- **Pethidine is contraindicated in most cases of sickle cell pain.** It is metabolized into a cerebral irritant that can lead to clonus, seizures, or altered mental status.
- Pethidine is preferred to morphine in the **preoperative management** of biliary colic and in the management of acute diverticulitis.
 - ⇒ Pethidine is comparable to morphine in its sedative and tranquillizing effects, **but the analgesia and respiratory depression it produces are of shorter duration**, and it **induces less smooth muscle spasm**.
- It is largely metabolized in the liver and the end-products are excreted in the urine.
- Contraindications
 - Bronchial asthma, emphysema or heart failure secondary to chronic lung disease.
 - Increased intracranial pressure, head injury or brain tumour.
 - Severe hepatic impairment, adrenocortical insufficiency, hypothyroidism.
 - Convulsive disorders, acute alcoholism, delirium tremens.
 - Use of monoamine oxidase inhibitors within the previous 14 days.

Buprenorphine

Action

- **partial** opiate agonist at mu and kappa opioid receptors.
 - meaning that by occupying the receptor, it doesn't achieve the effects of full agonism, and thus has less addictive potential versus other opiates.
 - Due to the fact that buprenorphine is a partial agonist, at higher doses it displays "functional antagonism", meaning that by occupying the receptor it blunts the effects of other full opiate agonists.
- It also has a long half-life of up to 32hrs.
 - This means that it can be utilised in cases of addiction to short-acting opiates such as diamorphine because it reduces the highs, and thus addictive potential, associated with these agents.

Interaction

- Since **buprenorphine is a partial agonist at opioid receptors, it will antagonise the action of a full agonist such as morphine**
- therefore it is appropriate to substitute morphine for buprenorphine, but not to add the two together

MRCPUK- part-1- jan- 2017: What is the mode of action of buprenorphine?

- ➔ **Partial mu opioid receptor agonist**

Cocaine

- Cocaine is an alkaloid derived from the coca plant.
- cocaine toxicity becoming a much more frequent clinical problem.

Mechanism of action

- cocaine blocks the uptake of dopamine, noradrenaline and serotonin

The use of cocaine is associated with a wide variety of adverse effects:

Cardiovascular effects

- myocardial infarction
 - ⇒ cocaine-induced MI is thought to be related to coronary artery spasm
 - ⇒ It is probably caused by stimulation of the α -adrenergic receptors in smooth muscle cells. In addition, cocaine increases endothelin-1 (a vasoconstrictor) and decreases nitric oxide (vasodilator).
- both tachycardia and bradycardia may occur
- hypertension
 - ⇒ (Blockage of noradrenaline (norepinephrine) re-uptake leads to →tachycardia, & ↑BP)
- QRS widening and QT prolongation
- aortic dissection

Neurological effects

- seizures
- mydriasis
- hypertonia
- hyperreflexia
- haemorrhagic stroke
- **cocaine-induced spinal cord infarct:**
 - ⇒ **The constellation of quadriplegia, spinothalamic sensory loss with sparing of posterior columns and sphincter dysfunction is most suggestive of an anterior spinal cord syndrome.**
 - The areflexia may reflect spinal cord shock.

- With a C3/4 spinal cord lesion, it is not surprising that the patient has respiratory difficulties.
- detection of cocaine in the urine suggesting he was using it

Psychiatric effects

- agitation (inhibition of dopamine re-uptake → psychomotor agitation)
- psychosis
- hallucinations (serotonin re-uptake blockade leads to → hallucinations)

Others

- hyperthermia which may lead to rhabdomyolysis and renal failure
- **metabolic acidosis**
- rhabdomyolysis

Management of cocaine toxicity

- in general benzodiazepines are generally first-line for most cocaine related problems
 - ⇒ **Agitation, seizures and hypertension are best treated with benzodiazepines (such as midazolam) initially.**
 - ⇒ Diazepam is useful for the treatment of anxiety and may precipitate a small reduction in blood pressure, **but will not treat coronary artery vasospasm.**
 - ⇒ Calcium channel blockers (such as nifedipine) can be used as a **second line treatment for hypertension** if benzodiazepines are ineffective.
- chest pain:
 - ⇒ benzodiazepines + **glyceryl trinitrate.**
 - Other option include calcium antagonists,
 - ⇒ If myocardial infarction develops then primary percutaneous coronary intervention
- hypertension:
 - ⇒ benzodiazepines + sodium nitroprusside
- Beta blockers should be avoided in cocaine associated myocardial ischaemia or infarction as they can potentiate coronary vasoconstriction.
 - ⇒ Beta blockers are contraindicated as they can cause unopposed alpha activity and worsen hypertension.
- **Intubation and ventilation** will lower blood pressure and improve the ischaemia
 - ⇒ **the most appropriate next intervention if diazepam fail to control the acute symptoms (eg: seizure)**
 - Whilst IV sodium valproate and IV phenytoin may be effective in terminating the recurrent seizures, these options would cost precious time with respect to controlling blood pressure and pyrexia

MRCPUK-Part-1-January 2016 exam: A 23-year-old man found 'collapsed' in the bathroom at a house party. Then C/O severe abdominal pain + blood in his stool. What is the single most likely cause of his abdominal pain? **Ischaemic colitis** (Ischaemic colitis is a recognised phenomenon following cocaine ingestion and should be considered if patients develop abdominal pain or rectal bleeding)

Heroin withdrawal

- The following are all signs of heroin withdrawal:
 - rhinorrhoea
 - diarrhoea
 - nausea and vomiting
 - lacrimation
 - irritability and restlessness, which are cardinal features

Heroin substitutes in medical management of withdrawal

- Both buprenorphine and methadone may be considered for use as heroin replacements
- Buprenorphine may be associated with less risk in overdose, but NICE recommends that unless circumstances dictate otherwise, **methadone should be the first-choice therapy**
- Co-abuse of alcohol and benzodiazepines may drive preferential use of buprenorphine, as these agents increase the risk of significant CNS depression

Benzodiazepine overdose

Benzodiazepine overdose is best managed supportively and with airway protection and ventilation if needed. Flumazenil should be avoided unless for reversal of anaesthesia

Overview

- toxicity with sedative drugs is the second most common agent - after analgesic agents- in some parts of the United Kingdom.
- Benzodiazepine overdose is very rarely life-threatening unless associated with the co-ingestion of alcohol or other respiratory depressants

Features

- **CNS depression:** lethargy, somnolence, hyporeflexia
- Ataxia
- Slurred speech
- Mild hypotension
- Respiratory depression

Treatment

- **Supportive therapy**
 - **GCS ≤ 8: endotracheal intubation**
 - Hypotension: fluid resuscitation
- **Antidote:** flumazenil
 - **Routine use of flumazenil for benzodiazepine overdose is not recommended**
 - A general rule of thumb is that a benzodiazepine toxicity syndrome should never be reversed with the antidote drug flumazenil unless it was you who gave the benzodiazepine.
 - ❖ Most cases of benzodiazepine overdose occur in patients who are on chronic benzodiazepine therapy for psychiatric illness, anxiety or seizures.
 - ❖ Rapid reversal of benzodiazepines with flumazenil can precipitate withdrawal symptoms and seizures in patients with benzodiazepine dependence.
 - ❖ If a seizure is precipitated by flumazenil the treatment is to give further benzodiazepines.
 - Indications
 - Severe respiratory depression
 - Overdose in benzodiazepine-naïve patients (e.g., accidental ingestion in children, periprocedural oversedation with benzodiazepines)
 - reversal of anaesthesia.

Cathinone toxicity

- NRG-1 is a synthetic cathinone drug which is increasingly used recreationally.
- Pharmacologically it is a derivative of phenylpropanone which is a naturally occurring psychotropic in khat (*Catha edulis*).
- Synthetic cathinones became increasingly popular in the last ten years as an alternative to ecstasy since they were cheaper, easier to produce and initially were unrestricted. As legislation changes, chemical substitutions are made to molecular moieties to create similar drugs to avoid restrictions.
- All exert their effect by increasing synaptic concentrations of noradrenaline, dopamine and serotonin, giving users the sensation of euphoria, detachment and wellbeing as well as upregulation of the sympathetic system.

- Toxicity is often seen due to lack of regulation of constituents and active ingredients

Features

- Tachycardia and hypertension may be seen due to the sympathomimetic effects of the drug and in some cases myocardial ischaemia can be seen.
- In the majority of cases of toxicity, however, similar to ecstasy toxicity, **hyponatraemia** and **serotonin syndrome** are seen. Hyponatraemia occurs as a consequence of significant water intake to reduce body temperature. Serum sodium levels may be markedly low and patients may present seizing.
- Serotonin syndrome** is due to massive flooding of synapses with liberated serotonin and causes agitation, confusion, muscle hyperactivity with fasciculations, hypertonia and clonus.
- Creatine kinase and white cell counts are often raised and body temperature may be extremely high.

Treatment

- If there is evidence of neurological compromise with an accompanying hyponatraemia, rapid correction of sodium is recommended with infusion of 3% saline solution at a maximum rate of 1ml/kg/hour.
- 0.9% saline solution is not recommended in patients with hyponatraemia and agitation due to the risk of worsening the hyponatraemia.

Cannabinoids

- Cannabinoids are derived from the resin of cannabis sativa,
- 9-tetrahydrocannabinol (9-THC) is its most important pharmacologically active constituent.
- Oral bioavailability of THC, whether given in the pure form or as THC in marijuana, is low and extremely variable, ranging between 5% and 20%, with effects occurring 0.5-3 hours later.
- Bioavailability of THC in a marijuana cigarette or pipe also rarely exceeds 10-20%.
- Naloxone and other opioid receptor antagonists block the analgesic actions of cannabinoids.
- Synthetic cannabinoids reduce arachidonic acid-induced inflammation by inhibiting eicosanoid production.

Cyanide poisoning

cyanide mechanism of action → Inhibition of enzyme Cytochrome oxidase C

- Cyanide may be used in:
 - insecticides,
 - photograph development and
 - production of certain metals.
- Acute cyanide toxicity may occur secondary to burning plastics in the house fire.**
- Toxicity results from reversible inhibition of cellular oxidising enzymes
- Cyanide ions inhibit mitochondrial cytochrome oxidase**, preventing aerobic respiration, which is an essential part of the mitochondrial electron transfer chain (ETC). It therefore interferes with the basic process of cellular respiration, preventing the formation of ATP and causing rapid cell death.

Presentation (classical features: brick-red skin, smell of bitter almonds)

- manifests in normal oxygen saturations, a high pO₂ and flushing (or 'brick red' skin) brought on by the excess oxygenation of venous blood. (It is important to note that the blood gas sample given is venous rather than arterial)
- acute: hypoxia, hypotension, headache, confusion
 - increased anion gap, consistent with high lactate (generated by anaerobic respiration due to the inability to use available oxygen).

- very high lactate and high venous pO₂ fit better with cyanide toxicity.
- chronic: ataxia, peripheral neuropathy, dermatitis

Management

- supportive measures: 100% oxygen
- definitive: **hydroxocobalamin** (intravenously), also combination of **amyl nitrite** (inhaled), sodium nitrite (intravenously), and sodium thiosulfate (intravenously)
- The recommended treatment for moderate cyanide toxicity in the UK is one of three options:
 1. Hydroxocobalamin,
 - has the best side-effect profile and speed of onset compared with other treatments
 2. dicobalt edetate,
 - only given when the patient is tending to lose or has lost consciousness.
 - ❖ When the patient is fully conscious, it is unlikely that the extent of poisoning warrants the use of Dicobalt Edeate Injection.
 - Dangerous if given without confirmed cyanide poisoning
 - Other antidotes such as hydroxocobalamin or sodium thiosulphate are preferred.
 3. sodium thiosulfate

Hydroxocobalamin

- also known as **vitamin B12a** and hydroxocobalamin,
- is an injectable form of **vitamin B 12**
- indications
 - vitamin B 12 deficiency
 - cyanide poisoning,
 - Leber's optic atrophy,
 - toxic amblyopia (Nutritional optic neuropathy)
 - a condition where a **toxic** reaction in the optic nerve results in visual loss.
 - Various poisonous substances may cause the condition as well as nutritional factors.
 - **Tobacco amblyopia** is a form of **toxic amblyopia** caused by tobacco containing **cyanide**.

Sarin gas

- **Sarin gas** and related agents cause inhibition of the enzyme acetylcholinesterase, causing levels of acetylcholine to build up in the nervous system causing prolonged sustained contraction of the diaphragm. This hinders and eventually paralyses normal breathing.
- Sarin has muscarinic and nicotinic effects.
 - ⇒ Muscarinic effects:
 - Paralysis
 - Fasciculations
 - Hyperglycaemia, and
 - Ketosis.
 - ⇒ Nicotinic effects:
 - Hypotension
 - Meiosis
 - Dyspnoea, and
 - GI disturbance.

Arsenic

- Arsenic causes inhibition of the enzyme pyruvate dehydrogenase which is necessary for the conversion of pyruvate to acetyl CoA. This also interferes with the basic process of cellular respiration, as pyruvate formed during glycolysis cannot be changed to acetyl CoA to enter the Kreb's cycle.
- Arsenic and mustards → cause mutational damage to DNA → ↑ risks of skin and haematological malignancy in the longer term.
- Arsenic can also accelerate atherosclerosis.

Acid poisoning

Pathology

- Acids cause injury by coagulative necrosis

Presentation

- Acid effects are mainly topical, with corrosive burns to the mouth, oropharynx and stomach
- They are less likely than alkalis to cause significant localised damage to the oesophagus
- Aspiration can lead to inflammation and a chemical pneumonitis

Management

- Neutralisation of acids is not appropriate, since this can generate increased heat and so exacerbate any injury sustained
- Gastric lavage is contraindicated due to the increased risk of oesophageal perforation
- Management consists of **supportive care and early endoscopy**
- Early surgical intervention is required to prevent mediastinitis, from which there is a high mortality, in those patients with signs or symptoms of perforation
- **Hydrofluoric acid** causes significant hypocalcaemia as it binds calcium,
 - even small amounts (topically or ingested) can produce significant hypocalcaemia and be rapidly fatal
 - in cases of significant topical exposure, patients should be monitored for signs of systemic hypocalcaemia
 - patient treated with intravenous calcium supplementation if required .
 - Calcium gluconate applied both topically and injected around the burn may be required
 - **Systemic fluorosis may occur as a complication**

Alkali poisoning

- Alkalies cause saponification (liquefactive necrosis) of tissue
- Neutralisation of alkalies is not appropriate, as this can generate increased heat and so exacerbate any injury sustained
- Assuming survival, fluorosis may lead to further problems later on

Radiosensitiser drugs

Radiosensitiser drugs → radiation toxicity

- | | |
|--|---|
| <ul style="list-style-type: none"> • dactinomycin, • metronidazole • 5-fluorouracil • gemcitabine • cisplatin | <ul style="list-style-type: none"> • hydroxyurea • paclitaxel • mitomycin C • topotecan |
|--|---|

Radioprotector

- Amifostine is a radioprotector

Management of body packers

- The management of body packers and body stuffers is relatively straightforward
- Abdominal radiographs may show **some** packages in the gastrointestinal tract - they appear as air halos trapped within the packages, **but not all packages** may contain trapped air
- In patients with no signs of drug-associated toxicity, whole-bowel irrigation with polyethylene glycol will clear the gastrointestinal tract of all the swallowed packages
- Endoscopy may also be useful in removing packages that are still in the stomach, but packages should be carefully removed to prevent damage and drug release
- Gastric lavage may increase the risk of package rupture
- Laxatives may also help the packages to pass naturally, but paraffin-based laxatives should not be used since they increase the risk of package rupture
- Surgical intervention to remove all the remaining packages may be necessary in patients who start to develop signs of drug toxicity, since the strength and amount of drug in each package is unknown

Heavy metal poisoning

Causes

- lead: most common**
- mercury
- manganese
- cadmium
- thallium

Lead poisoning

- Along with acute intermittent porphyria, lead poisoning should be considered in questions giving a combination of **abdominal pain and neurological signs**
- Lead can also be absorbed through the skin and by inhalation.

Aetiology: ingestion of:

- lead-containing compounds, deliberate (pica) or inadvertent
 - > Patients with learning disabilities may be prone to lead poisoning due to pica.
- contaminated water from old lead water pipes
- occupation, such as a painter have a lead exposure while stripping the walls in old houses.
- certain traditional remedies such as ayurvedic medicines

Features

- abdominal pain
- nausea
- constipation
- peripheral neuropathy (mainly motor) due to demyelination
- fatigue
- blue lines on gum margin (only 20% of adult patients, very rare in children)
- may be associated with **anterior** uveitis or iritis

Laboratory tests

- Whole blood lead levels:
 - > $<10 \mu\text{g}/\text{dL}$ - normal.
 - > $>10 \mu\text{g}/\text{dL}$ - may cause impaired cognitive development in children.
 - > $>45 \mu\text{g}/\text{dL}$ - GI symptoms in adults and children.
 - > $>70 \mu\text{g}/\text{dL}$ - high risk of acute CNS symptoms.

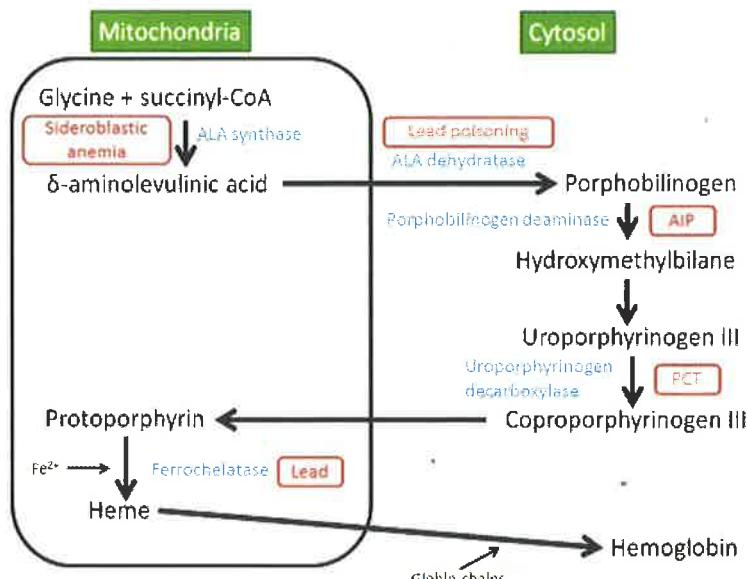
➤ >100 µg/dL - may be life-threatening.

Investigations

- Abdominal radiographs are essential to see if there is any unabsorbed lead present, which can be removed by whole-bowel irrigation
- The blood lead level is usually used for diagnosis. **Levels greater than 10 mcg/dl are considered significant**
- full blood count:
 - microcytic anaemia.
 - Blood film shows red cell abnormalities including:
 - ❖ **basophilic stippling**
 - ➡ This occurs due to accumulation of (RNA) in the RBCs due to inhibition of pyrimidine 5 nucleotidase by lead.
 - ❖ clover-leaf morphology
- raised serum and urine levels of delta aminolaevulinic acid may be seen making it sometimes difficult to differentiate from acute intermittent porphyria
- urinary coproporphyrin is also increased (urinary porphobilinogen and uroporphyrin levels are normal to slightly increased)

Management - various chelating agents are currently used:

- dimercaptosuccinic acid (DMSA)
 - **the most appropriate intervention**
 - The recommended dose is 10 mg/kg three times per day for five days, followed by 10 mg/kg twice per day for two weeks.
- EDTA
 - This is used IV or IM, which makes administration less convenient than DMSA.
 - It is considered for patients with symptoms of severe acute lead poisoning.
- Dimercaprol
- Penicillamine
- succimer



Mercury poisoning

Features

- paraesthesia
- visual field defects
- ataxia
- dysarthria
- hearing loss
- irritability
- renal tubular acidosis
- Chronic poisoning from the inhalation of mercury vapour results in a classic **triad** of tremor, neuropsychiatric disturbance and gingivostomatitis

Cadmium (Cd) poisoning

- **Workers in zinc factories are at risk of cadmium (Cd) poisoning.**

Feature

- Bone pain, osteopenia
- Renal failure.
 - The Cd-protein complex is mainly taken up by proximal tubular cells. This may give rise to a **tubular proteinuria**
 - may also cause a Fanconi syndrome-like presentation, with **amino aciduria** and **phosphaturia**.
 - Prolonged renal tubular toxicity may cause glomerular damage.
 - Another renal effect of prolonged Cd exposure is **calcium phosphate stones**.

Thallium poisoning

Features

- painful polyneuropathy
- mood change
- alopecia

Treatment is chelation therapy with oral Prussian Blue.

Iron overdose

- Undissolved iron tablets are radio-opaque

Presentation

- Early features of iron overdose are due to the direct corrosive effects of iron and include vomiting, diarrhoea and gastrointestinal bleeding
- Typically, there is then a latent phase of up to 24 h when the patient is asymptomatic
- This is then followed by widespread organ failure
- **Initial hyperglycaemia can occur following significant ingestion of iron**, but hypoglycaemia can be seen later in cases of severe poisoning with associated hepatic failure
- In patients who recover, there may be long-term GI strictures and possible gastrointestinal obstruction due to the initial corrosive effects of iron

Treatment

- Iron is a metal and therefore will not be adsorbed by activated charcoal
- Patients with serum iron concentrations over 90 mmol/l, as well as those with signs of severe toxicity, require chelation therapy with desferrioxamine

LSD intoxication

Lysergic acid diethylamide (LSD)

- No medicinal use.
- Recreationally used as a hallucinogen and for its ability to alter human perception and mood.

Pharmacodynamics:

- LSD is primarily a non-selective 5-HT agonist.
- LSD may exert its hallucinogenic effect by interacting with 5-HT_{2A} receptors as a partial agonist and modulating the NMDA receptor-mediated sensory, perceptual, affective and cognitive processes.
- LSD mimics 5-HT at 5-HT_{1A} receptors, producing a marked slowing of the firing rate of serotonergic neurons.

Features

- hallucinations
- heightened sense of awareness
- synaesthesia
- palinopsia

New recreational drugs

Drug types	Street names
Gamma-hydroxybutyric acid (GHB) and gamma-butyrolactone (GBL)	G, Geebs or Liquid Ecstasy
Synthetic agonists of the CB ₁ receptor	Spice
Methoxetamine (derivative of ketamine)	Mexxy
Benzylpiperazine	Exodus, Legal X, Legal E
Nitrous oxide	Hippie crack

Paracetamol overdose

Overview

- it is the most common agent of intentional self-harm
- it is the most common cause of acute liver failure
- As little as 10–15 g (20–30 tablets) in an adult or 150 mg/kg of paracetamol taken within 24 h may cause severe hepatocellular necrosis and, less frequently, renal tubular necrosis.

Pathophysiology

- ➔ Paracetamol is conjugated to glucuronic acid and sulphate under normal conditions.
- ➔ In overdose these processes become saturated and the drug is then converted into a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI).
- ➔ (NAPQI) inactivated by glutathione, rapidly preventing any harm.
- ➔ If the glutathione supply is depleted then a toxic metabolite is formed.

After ingestion of a therapeutic dose:

- The liver normally conjugates paracetamol with glucuronic acid/sulphate.
- and the resulting non-toxic metabolites are excreted in the urine.
- About 4% of a therapeutic dose is metabolised by the cytochromes P450, mainly CYP2E1,

- to a potentially toxic intermediate metabolite N-acetyl-p-benzoquinone imine (NAPQI).
- NAPQI combines with intracellular glutathione to become a non-toxic mercapturate derivative with urinary excretion.

after ingestion of an overdose:

- the conjugation system becomes saturated leading to oxidation by P450 mixed function oxidases*.
- the normally minor CYP2E1 pathway becomes important.
- This produces a **toxic metabolite (N-acetyl-B-benzoquinone imine)**
 - *this explains why there is a lower threshold for treating patients who take P450 inducing medications e.g. phenytoin or rifampicin
- Normally glutathione acts as a defence mechanism by conjugating with the toxin forming the non-toxic mercapturic acid.
- If glutathione stores run-out, the toxin leads to cell death of hepatocytes and renal tubules

Paracetamol overdose: risk factors

The following groups of patients are at an increased **risk of developing hepatotoxicity** following a paracetamol overdose:

- patients taking liver enzyme-inducing drugs (rifampicin, phenytoin, carbamazepine, chronic alcohol excess, St John's Wort)
- malnourished patients (e.g. anorexia or bulimia, cystic fibrosis, hepatitis C, alcoholism, HIV
 - ⇒ ↓ glutathione stores
- patients who have not eaten for a few days
- Human immunodeficiency virus (HIV) positive patients.

Investigations

- Paracetamol level: take paracetamol level
 - four hours post-ingestion**, or
 - as soon as the patient arrives if:
 - Time of overdose is greater than four hours.
 - Staggered overdose (in staggered overdoses, the level is not interpretable except to confirm ingestion).

Management

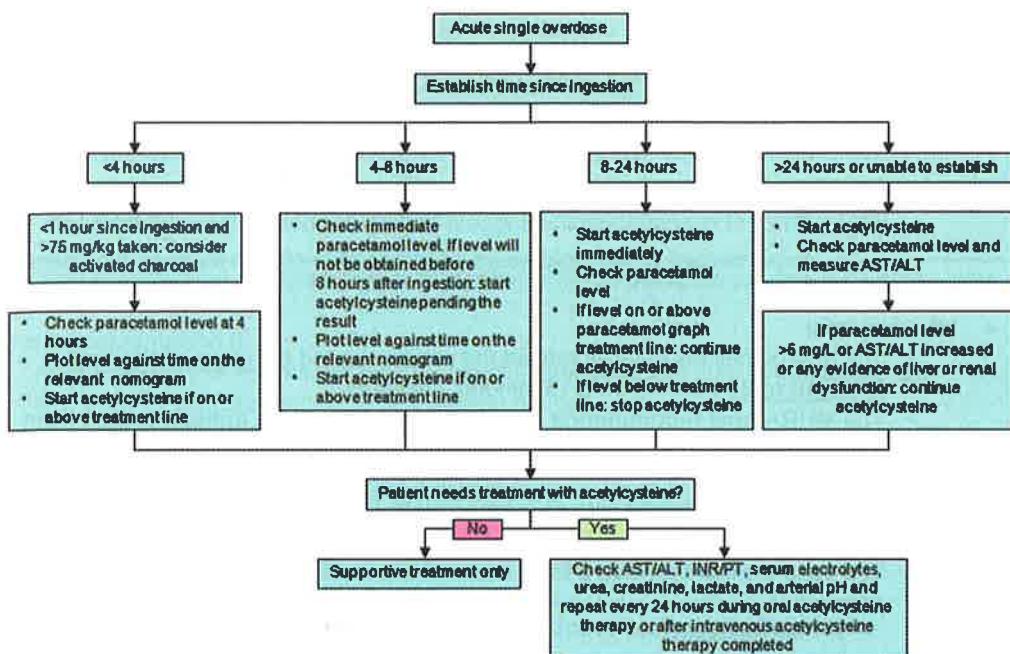
The essentials of management are:

- Check paracetamol level **four hours after ingestion**, check levels against the Rumack-Matthew nomogram.
- Gastric lavage if large dose ingested (more than 7.5 g) and/or presenting within eight hours of ingestion; consider oral charcoal.
- Give N-acetylcysteine or methionine.
- Hourly BMs monitored.
- Check INR 12 hourly.

If patient present with ingestion of non-significant amount (<150mg/kg) and timing of ingestion is known (1- 4 hrs) → **No immediate action**

- A single dose of activated charcoal (50g for adults) can be given **up to 1 hour after ingestion**
- Acetylcysteine should be **started immediately** or empirically **when**:
 - ⇒ if a significant amount has been taken (>150mg/kg).

- ⇒ Serum paracetamol level: 100 mg/L at 4 hours and 15 mg/L at 15 hours after ingestion
 - ⇒ patients who present late (8-24 hours)
 - ⇒ Serum paracetamol level is not available within an 8-hour time window
 - ⇒ If there is any doubt about the timing of the ingestion (including a staggered overdose over one hour or more).
 - ⇒ Patients are unconscious or have a suspected overdose.
- Hepatotoxicity is unlikely if it is >24 hours since last ingestion of paracetamol and all the following apply:
 1. Patient is asymptomatic.
 2. Paracetamol concentration is <5 mg/L.
 3. INR is 1.3 or less.
 4. ALT is less than 2 times upper limit of normal.
 - ⇒ If all of the above criteria are fulfilled then acetylcysteine may be stopped, and the patient discharged with the advice to return if he or she becomes symptomatic (vomiting, abdominal pain).
 - **Repeated supratherapeutic ingestion**
 - ⇒ Patients who have ingested <75 mg/kg in a period of 24 hours are very unlikely to develop hepatotoxicity.
 - ⇒ Those who have ingested 75 mg, or less/kg/24 hours of paracetamol require no treatment.
 - ⇒ Those who have ingested 75-150 mg/kg/24 hours should be considered for acetylcysteine (based on amount ingested, timing, and other relevant features)
 - ⇒ Those who have ingested >150 mg/kg/24 hours are treated with acetylcysteine.



Prescribing N-acetyl cysteine (NAC)

- Action:
 - ⇒ it is a precursor of glutathione and hence can increase hepatic glutathione production
- Route and administration:
 - Acetylcysteine is the treatment of choice and is given intravenously (in the US and some other places it is still occasionally given orally).
 - Although the oral route is simpler, it frequently causes nausea and vomiting and is unpleasant. Additionally, the standard oral regimen is 72 hours in duration compared with 21 hours intravenously,
 - ⇒ Acetylcysteine should be administered by intravenous infusion **preferably using Glucose 5%** as the infusion fluid. Sodium Chloride 0.9% solution may be used if Glucose 5% is not suitable.
- Indications:
 - N-Acetylcysteine is recommended in all cases where the paracetamol overdose exceeds 150 mg/kg body weight
 - All patients with a plasma paracetamol level $\geq 100 \text{ mg/L}$ at 4 hours or $\geq 15 \text{ mg/L}$ at 15 hours after ingestion should receive acetylcysteine regardless of risk factors for hepatotoxicity.
 - The paracetamol level is not used to guide treatment in the setting of a **staggered overdose**, and N-acetylcysteine should be given without delay to reduce the risk of liver failure.
 - **In the case of staggered overdose or unclear timing of overdose, acetylcysteine should be given.**

- When to be started:
 - ⇒ **N-acetylcysteine is most effective when administered within 8 h of ingestion**
 - ⇒ If acetylcysteine is started within 8 hours of the ingestion, hepatotoxicity is extremely unlikely.
 - ⇒ The urgency of treatment is underlined by the fact that the **incidence of hepatotoxicity is worse if treatment is delayed.**
 - Trials of N-acetylcysteine suggest that the incidence of hepatotoxicity is 1% in those treated within eight hours as opposed to 46% in those treated after 16 hours.
- Infusion rate:
 - The new guidelines have increased the recommended **duration of the first infusion to 60 minutes** from 15 minutes previously.
 - The MHRA now recommends **extending the time of the initial infusion from 15 minutes to 60 minutes** in order to reduce the incidence of adverse reactions.
- Doses:
 - ⇒ The full course of treatment with acetylcysteine comprises of 3 consecutive intravenous infusions.
 - ⇒ The patient should receive a **total dose of 300 mg/kg body weight over a 21-hour period.**
 1. First infusion
 - ❖ Add the appropriate volume of acetylcysteine injection to **200 mL of infusion fluid** and infuse **over 1 hour.**
 2. Second infusion
 - ❖ Add the appropriate volume of acetylcysteine injection to **500 mL of infusion** fluid and infuse **over the next 4 hours.**
 3. Third infusion
 - ❖ Add the appropriate volume of acetylcysteine injection to **1 litre** of infusion fluid and infuse over the next 16 hours.
- Reactions to NAC
 - Features:
 - (eg: patient became flushed and hypotensive)
 - Mechanism:
 - Reactions to NAC are well recognized and are not related to hypersensitivity.
 - The majority of dose-related adverse reactions occur within the first hour of the initial infusion of acetylcysteine.
 - Any 'hypersensitivity-like' reactions are more likely to be anaphylactoid in nature (i.e. not immunologically mediated) and therefore may not occur on repeated exposure.
 - Management:
 - NAC can almost always be safely restarted, and total dose safely administered after symptomatic treatment.
 - **Even if a patient has a history of a previous reaction to intravenous acetylcysteine, the benefits outweigh the risks and patient should receive treatment.**
 - **IV chlorpheniramine and restart NAC infusion once symptoms resolved**
 - **What is the most appropriate next step after iv antihistamine?**
 - ⇒ **Re-start the N-acetylcysteine infusion at half rate**
 - Oral methionine may be an alternative but is definitely **second line.**
 - ❖ Patients often have an associated history of alcohol intake and episodes

of vomiting, which can affect the pharmacokinetics of oral medications.

Paracetamol overdose during pregnancy

- resulting toxic metabolites can cross the placenta and lead to hepatocellular necrosis of maternal and fetal liver cells.
- NAC can bind the toxic metabolites in the mother and fetal circulation as it crosses the placenta.
- NAC appears to be safe during pregnancy and therefore should be administered.

King's College Hospital criteria for liver transplantation in paracetamol-induced acute liver failure

List for transplantation if:

- Arterial pH <7.3 or arterial lactate >3.0 mmol/L after adequate fluid resuscitation; **OR**
- If all three of the following occur in a 24-hour period:
 - ⇒ Creatinine >300 µmol/L.
 - ⇒ PT >100 seconds (INR >6.5).
 - ⇒ Grade III/IV encephalopathy.

Strongly consider transplantation if:

- Arterial lactate >3.5 mmol/L after early fluid resuscitation.

The criteria for transfer to a specialist liver unit are: (poor prognostic factors)

- Encephalopathy
- **INR:** >2.0 at < 48 hours, or > 3.5 at < 72 hours
 - ⇒ synthetic function (as determined by INR or PT) is the best indicator.
- Serum creatinine: >200 µmol/L
- **Blood pH: <7.3**
- Systolic BP: <80 mmHg.

Monitoring and endpoints for treatment

Hepatotoxicity

- In patients being treated with acetylcysteine for liver toxicity the acetylcysteine should be continued until the INR is 1.3 or less **OR** INR is falling towards normal on two consecutive blood tests, and less than 3.0.
- Blood tests (urea and electrolytes, creatinine, INR, and ALT) should be re-checked every 8 to 16 hours to assess the progress of the hepatic injury. There is no clinical benefit in continuing treatment with acetylcysteine for a rise in ALT if the INR has normalised.

Time-sensitive treatment issues

- 8-hour window
 - ⇒ the need for acetylcysteine treatment should be based on a serum paracetamol concentration determined within this 8-hour window.
 - ⇒ acetylcysteine within 8 hours of an acute ingestion → prevent hepatic injury in nearly all patients
 - ⇒ Empiric acetylcysteine therapy should be initiated for patients who:
 - ❖ present later than 8 hours after ingestion;
 - ❖ when serum paracetamol concentrations cannot be determined within 8hours;

❖ or if the exact timing of the ingestion is uncertain.

adverse effects

- oral acetylcysteine → nausea and vomiting,
- intravenous acetylcysteine → anaphylactoid reaction (e.g., nausea, flushing, vomiting, rash, urticaria, pruritus, angio-oedema, dyspnoea, wheezing, bronchospasm, tachycardia, and hypotension),
- Previous anaphylactoid reaction to acetylcysteine is not a contraindication to receiving acetylcysteine.
 - ⇒ Patients with a previous anaphylactoid reaction should be given an H1 and an H2 antagonist.
 - ⇒ Patients with previous bronchospasm reaction to acetylcysteine can be given nebulised salbutamol.
 - ⇒ Patients considered at risk of anaphylactoid reactions (e.g., those with atopy, bronchospasm, asthma, or a previous reaction) should be administered prophylactic medication such as antihistamines to reduce adverse reactions.
- **Methionine is used as an oral antidote for paracetamol poisoning in those who cannot tolerate N-acetylcysteine**

Paracetamol and smoking

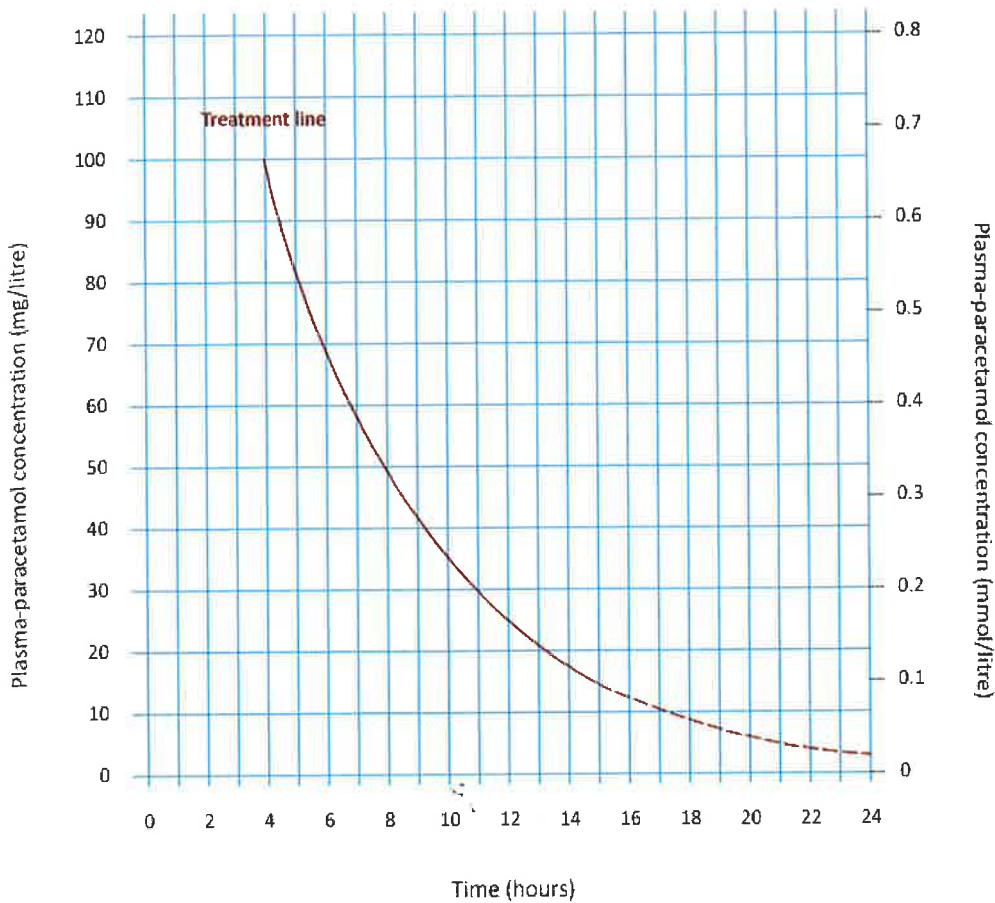
- Enzyme induction with cigarette smoking does affect paracetamol metabolism. Its importance however, is in toxicity.
- Smokers would be classified as in a high risk for paracetamol overdose and are assessed using a different time - paracetamol level curve.

Complications

- Untreated paracetamol poisoning may cause varying degrees of liver injury over the 2 to 4 days following ingestion, including fulminant hepatic failure.
 - ⇒ **Hepatotoxicity is extremely rare in patients treated with acetylcysteine within 8 hours of an acute paracetamol overdose.**
- **Lactic acidosis is recognised complication**
- **Hypoglycaemia is seen when paracetamol toxicity leads to significant impairment of hepatic synthetic function**
 - ⇒ Severe hypoglycaemia affects 40% of patients with fulminant liver failure, which exacerbates encephalopathy.
- Paracetamol nephrotoxicity
 - can develop later than liver toxicity
 - The mechanism of kidney injury is similar to that of the liver,
 - there is little evidence that N-acetyl cysteine confers any renal protection.
 - usually the renal function returns to baseline after a few weeks.
 - Haemodialysis may be required to support the patient during the acute episode.

Prognosis

- **The prognosis is poor in those with**
 - Blood PH less than 7.0
 - Prolonged prothrombin time (more than 100s) and
 - Serum creatinine more than 300 µM.
 - Mortality is greater if the patient is more than 40 years of age.



paracetamol overdose treatment nomogram

Adult Dosage Table (Royal College of Emergency Medicine Guidance. <http://www.rcem.ac.uk>)

Regimen	First Infusion	Second Infusion	Third Infusion
Infusion fluid	200 mLs 5% glucose or sodium chloride 0.9%	500 mLs 5% glucose or sodium chloride 0.9%	1000 mLs 5% glucose or sodium chloride 0.9%
Duration of infusion	1 hour	4 hours	16 hours
Drug dose	150 mg/kg acetylcysteine	50 mg/kg acetylcysteine	100 mg/kg acetylcysteine

Although hepatotoxic in high doses even in fairly advanced chronic liver disease paracetamol can be used safely as long as doses do not exceed 2-3 g per day. The main exception to this is alcoholic liver disease where the patient continues to drink, in this setting induction of enzymes and depletion of glutathione increases the chances of hepatotoxicity.

Paraquat poisoning

Properties of Paraquat

- Paraquat is a very toxic compound
- As little as 2 g is potentially fatal (10 ml of a concentrated 20% solution)

Presentation

- Initial signs of toxicity are due to its corrosive effects on the gastrointestinal tract and oropharynx

Pathology

- Paraquat is rapidly absorbed and is sequestered in the lungs, where it reacts with oxygen to form hydrogen peroxide and superoxide anions
- Hydrogen peroxide and superoxide anions are responsible for cell death, which leads to an acute alveolitis

Prognosis

- Death tends to occur within hours to days in patients who have ingested more than 6 g of Paraquat
- Death tends to occur within days in those who have ingested 3-6 g of Paraquat
- Illness following ingestion of 1.5-3 g Paraquat follows a much more protracted course and delayed pulmonary
- fibrosis can lead to death up to 6 weeks after ingestion

Management

- supportive care
- activated charcoal to reduce absorption
- **oxygen supplementation can increase pulmonary toxicity**, by increasing the rate of hydrogen peroxide and superoxide anion production

- Measurement of plasma paraquat concentration can help in assessing prognosis and can aid treatment
- Plasma concentration measurements are also useful in the management of poisoning with paracetamol, salicylates, lithium, iron, methanol, ethylene glycol and theophylline

Organophosphate insecticide poisoning

Organophosphate is an anticholinesterase, thus prolonging the effects of acetylcholine.

One of the effects of organophosphate poisoning is inhibition of acetylcholinesterase

Organophosphates are rapidly absorbed through the gastrointestinal and respiratory tracts and the skin

Mechanism

- The principal action of organophosphates is inhibition of acetylcholinesterases
- This results in the accumulation of acetylcholine at muscarinic receptors, nicotinic receptors and in the central nervous system

Features can be predicted by the accumulation of acetylcholine (mnemonic = SLUD)

Hypersalivation and miosis are the specific clues to acetylcholine overactivity.

- Salivation
- Lacrimation
- Urination
- Defecation/diarrhoea
- cardiovascular: hypotension, bradycardia
- also: small pupils, muscle fasciculation

Presentation

The presentation relates to the sites of accumulation of acetylcholine

- Accumulation at muscarinic receptors leads to:
 - miosis
 - hypersalivation
 - sweating
 - diarrhoea
 - excessive bronchial secretions
- Accumulation at nicotinic receptors leads to:
 - muscle fasciculations
 - tremor
- Accumulation in the central nervous system leads to:
 - anxiety
 - loss of memory
 - headache
 - coma
- Organophosphate-induced neuropathy starts to develop 2 weeks after exposure
 - Initial presentation of neuropathy is a flaccid paralysis
 - Later, hypertonia, hyperreflexia and a spastic paralysis occur

Management

- atropine
- the role of pralidoxime(an activator of cholinesterase) is still unclear - meta-analyses to date have failed to show any clear benefit

Carbon Monoxide (CO) Poisoning



In carbon monoxide poisoning, the patient's oxygen saturation is usually normal. This is because carboxyhemoglobin is read by the pulse oximeter as a normal saturated hemoglobin molecule.

Risk factors

- A hypoxic poisoning syndrome seen in patients who have been exposed to automobile exhaust, smoke inhalation, barbecues, or old appliances **in poorly ventilated locations**.

Pathophysiology

- **CO binds with high affinity to haemoglobin, forming carboxyhaemoglobin.** CO also binds myoglobin and mitochondrial cytochrome oxidase.

Features

- Presents with hypoxemia, cherry-red skin (rare), confusion, and headaches. Coma or seizures occur in severe cases.
- Chronic low-level exposure may cause flu-like symptoms with generalized myalgias, nausea, and headaches. Ask about symptoms in others living in the same house.
- Suspect smoke inhalation in the presence of singed nose hairs, facial burns, hoarseness, wheezing, or carbonaceous sputum.
- CO poisoning causes tissue hypoxia, anaerobic metabolism and lactic acidosis.

Diagnosis

- Check an ABG and serum carboxyhemoglobin level (normal is < 5% in nonsmokers and < 10% in smokers).
- Check an ECG in the elderly and in patients with a history of cardiac disease.

Treatment

- 100% O₂
- after which transfer to a centre with **hyperbaric oxygen** should be considered.
- Patients with airway burns or smoke inhalation may require early intubation, since upper airway edema can rapidly lead to complete obstruction.

Antiemetic

Antiemetics

- **Aprepitant** → is a neurokinin receptor blocker used in the prevention of chemotherapy induced nausea.
- **Hyosine** → antiemetics functions as a cholinergic muscarinic antagonist
 - ⇒ It acts as a competitive antagonist at muscarinic acetylcholine receptors; it is thus classified as an anticholinergic or as an antimuscarinic drug.
- **Metoclopramide** is a dopamine receptor antagonist that **can induce parkinsonism**. It can also worsen control in patients with idiopathic Parkinson's disease to its antagonistic effect on dopamine receptors.
- **Domperidone** is also a dopamine antagonist but acts peripherally.
 - ⇒ **Best drug for nausea and vomiting associated with Parkinson treatment.**
 - ⇒ Drugs such as apomorphine and bromocriptine cause vomiting through peripheral stimulation of the chemoreceptor trigger zone. Worsening of Parkinson's disease may result from the use of dopamine antagonists; however, **domperidone is much less likely to cross the blood-brain barrier and is therefore the preferred agent in this case.**
- **Haloperidol: the main site of action for haloperidol with regards anti-emetic effects --> Chemoreceptor trigger zone**
 - ⇒ Haloperidol is an anti-dopaminergic agent licensed for and used mainly as an anti-psychotic agent
 - ⇒ It does result in more extrapyramidal side-effects than phenothiazine-type agents, but is associated with less hypotension
- **Phenothiazines** (e.g. promethazine) and domperidone are also used as anti-emetic agents and act at the chemoreceptor trigger zone
- **Cyclizine** is an anticholinergic antihistamine acting through the vomiting centre.

Group	Drug	Antagonized receptor	Mechanism	Specific features	Side effects
Dopamine receptor antagonists/ prokinetic agents	Prochlorperazine	D ₂	<ul style="list-style-type: none"> Antiemetic effect at the area postrema 	<ul style="list-style-type: none"> Antipsychotic agent Used in severe hyperemesis gravidarum 	<ul style="list-style-type: none"> Depression Fatigue Diarrhea Hyperprolactinemia Overdose leads to reversible extrapyramidal syndrome (e.g., dystonia, parkinsonism, tardive dyskinesia, and akathisia) and neuroleptic malignant syndrome Antidote: biperiden (anticholinergic agent) Do not combine metoclopramide with antipsychotics because of the increased risk of dyskinesias! Domperidone may cause cardiac arrhythmias.
	Domperidone		<ul style="list-style-type: none"> Antiemetic effect at the area postrema Prokinetic effect 	<ul style="list-style-type: none"> Prokinetic effect: to treat diabetic and post-surgery gastroparesis (delayed gastric emptying) 	
	Metoclopramide		<ul style="list-style-type: none"> Antiemetic effect in the CNS and at the area postrema Prokinetic effect : ↑ gastric contractions, duodenal and jejunal motility, resting tone of the lower esophageal sphincter and decreased pylorus sphincter activity allow food to pass quickly 	<ul style="list-style-type: none"> Used in severe hyperemesis gravidarum 	
Serotonin receptor antagonists	Ondansetron (Zofran®)	5-HT ₃	<ul style="list-style-type: none"> Central- acting antiemetic effect Peripheral inhibition of the intestinal tract's vagal nerve signals 	<ul style="list-style-type: none"> Chemotherapy and radiation-induced-vomiting and postoperative nausea and vomiting (PONV) 	<ul style="list-style-type: none"> *Headaches *Constipation or diarrhea *QT interval prolongation(torsades de pointes) *Increase in liver enzymes *Serotonin syndrome
Anticholinergic Agents	Scopolamine	M ₂	<ul style="list-style-type: none"> Antiemetic effect at the area postrema Peripheral inhibition of the intestinal tract's vagal nerve signals 	<ul style="list-style-type: none"> Especially effective against motion sickness or vestibular-induced nausea and vomiting 	<ul style="list-style-type: none"> Anticholinergic side effects: dry mouth, mydriasis, tachycardia, urinary retention Antidote: physostigmine(cholinesterase inhibitor)
Antihistamines	Meclizine, dimenhydrinate, diphenhydramine, doxylamine, promethazine	H ₁	<ul style="list-style-type: none"> Antiemetic effect in the CNS 	<ul style="list-style-type: none"> Strong sedative Used in hyperemesis gravidarum (also see "Drugs of choice in pregnancy" (antiemetics)) 	<ul style="list-style-type: none"> drowsiness and confusion Anticholinergic side effects: dry mouth, dilated pupils, blurred vision, reduced bowel sounds, and urinary retention) → antidote: physostigmine

5-HT3 antagonists

- 5-HT3 antagonists are antiemetics used mainly in the management of chemotherapy related nausea.
- They mainly **act in the chemoreceptor trigger zone area of the medulla oblongata.**

Examples

- Ondansetron
 - ⇒ **Ondansetron → is a selective 5-HT3 (5-hydroxytryptamine 3A receptor) antagonist both centrally and peripherally and as such is a potent antiemetic.**
 - Ondansetron is the first line drug for chemotherapy related nausea and vomiting.
 - Its effects are on both **peripheral** and **central nerves**.
 - ❖ One part is to reduce the activity of the vagus nerve, which is a nerve that activates the vomiting center in the medulla oblongata,
 - ❖ the other is a blockage of serotonin receptors in the chemoreceptor trigger zone.
 - ⇒ Common side effects of ondansetron are headache, drowsiness, and dizziness.

- **granisetron**

Adverse effects

- constipation is common

Metoclopramide

Action

- D2 receptor antagonist

Indications

- mainly used in the management of nausea.
- gastro-oesophageal reflux disease
- prokinetic action is useful in gastroparesis secondary to diabetic neuropathy
- often combined with analgesics for the treatment of migraine (migraine attacks result in gastroparesis, slowing the absorption of analgesics)

Adverse effects

- extrapyramidal effects: oculogyric crisis. This is particularly a problem in children and young adults , especially girls , usually subsides within 24 hours following cessation of treatment and can be **treated with procyclidine 5-10 mg i.m. (antimuscarinic).**
- hyperprolactinaemia
- tardive dyskinesia

Acute dystonic-dyskinetic reactions

- Risk factors
 - ⇒ mostly occur in children and young adults
 - ⇒ about 70% of cases are female.
 - ⇒ It occurs more commonly when excess of the recommended dose of metoclopramide is administered.
- Time frame
 - ⇒ The effects usually occur within 72 hours but have been reported to occur within 30 minutes of starting treatment.
- Features
 - ⇒ oculogyric crisis
 - ⇒ opisthotonus
 - ⇒ torticollis
 - ⇒ trismus,
 - ⇒ tetanus-like reactions.

- ⇒ A blue discolouration of the tongue has also been described.
- Treatment
 - ⇒ generally self-limiting,
 - ⇒ the reaction can be reversed by an anticholinergic such as **benztropine** or **procyclidine** or an antihistamine such as diphenhydramine.

MRCPUK-part-2-march-218: A 21-year female presented with acute spasm of her neck after metoclopramide injection. What is the most appropriate intervention?

→ **Procyclidine**

Other drugs

Antihistamines

- Antihistamines (H_1 inhibitors) are of value in the treatment of allergic rhinitis and urticaria.
- Sedation and headaches are the most common adverse effects of antihistamines
- First generation antihistamines (chlorpheniramine and diphenhydramine) are more sedating than the newer agents.

Sedating antihistamines

- **Cyproheptadine**
- Chlorpheniramine
 - ⇒ As well as being sedating these antihistamines have some antimuscarinic properties (e.g. urinary retention, dry mouth).

Non-sedating antihistamines

- loratadine
- cetirizine
- **Desloratadine**
 - is a long-acting H_1 -receptor antagonist
 - has poor penetration into the central nervous system
 - does not interact with antibiotics or other co-administered medications
- Of the non-sedating antihistamines there is some evidence that cetirizine may cause more drowsiness than other drugs in the class.
- Of the newer antihistamines, cetirizine and levocetirizine are more sedating than loratadine and desloratadine, and possibly more sedating than fexofenadine.

Other notes

- **Terfenadine (a pro-drug) has been associated with cardiac arrhythmias (torsades de pointes) especially in individuals with prolonged QT intervals.**
 - **Fexofenadine** is the active metabolite of terfenadine and does not appear to have the same arrhythmogenic effects as terfenadine.
 - second-generation antihistamine
 - has fewer sedative and anticholinergic side effects.
 - in patients with allergy + history of narrow-angle glaucoma → **Fexofenadine**
 - ❖ first-generation antihistamines (eg: Chlorpheniramine) have anticholinergic side effects that can cause mydriasis and trigger an acute attack in patients with a history of narrow-angle glaucoma,
- Cetirizine, desloratadine and fexofenadine are prescribed for allergic rhinitis (hay fever) and

- all three are equally effective
- cetirizine and fexofenadine interact with erythromycin and other macrolides
- Chlorphenamine maleate and terfenadine cause drowsiness and also interact with erythromycin

Human and animal bite

- Co-amoxiclav** is recommended as first-line treatment for all cat or human bites and other complicated animal bites.
- In patients who are penicillin allergic, doxycycline plus metronidazole is a typical first choice regimen.
- Only 15 - 20% of dog bites become infected, and providing the wound is appropriately cleaned and not considered at risk (for example, crush or deep wounds) then antibiotic prophylaxis may not be required.

Botox → Paralysis of frontalis → eyebrows are drooping (eyebrow ptosis).

- Botox (onabotulinumtoxinA) is an injectable neuro-toxin used for the treatment of chronic migraines, limb spasticity, axillary hyperhidrosis, cervical dystonia, strabismus, and blepharospasm.
- Botox is a neurotoxin derived from the bacteria, *Clostridium botulinum*. It blocks neuromuscular transmission inhibition of acetylcholine release at the presynaptic membrane. The end result is that the muscle contraction is inhibited.
- The action of Botox is not permanent because collateral axonal sprouting establishes new neuromuscular junctions, restoring muscle function.
- Frontalis is a quadrilateral muscle found on the forehead that elevates the eyebrows; hence paralysis of this muscle can lead to eyebrow ptosis.

D-Penicillamine

- used to reduce the body copper in Wilson's disease & as a chelating agent in lead poisoning
- D-Penicillamine** is associated with → **pancytopenia and tubulointerstitial nephritis**

Isotretinoin

Isotretinoin adverse effects

- teratogenicity - females MUST be taking contraception
- low mood
- dry eyes and lips
- raised triglycerides
- hair thinning
- nose bleeds
- Isotretinoin is an oral retinoid used in the treatment of severe acne.
- Two-thirds of patients have a long term remission or cure following a course of oral isotretinoin

Adverse effects

- Teratogenicity:** ♀s **MUST** be using two forms of contraception (e.g. COCP and condoms).
 - Women must have a negative pregnancy test before treatment
 - and be on effective contraception **for at least a month before the course begins**, during the course **and for a month after it finishes**

- Congenital **deafness**, **CNS** and **heart** defects may occur in children exposed to isotretinoin in utero
- Dry skin, eyes and lips: the most common side-effect of isotretinoin
- Low mood, depression
- Raised triglycerides
- Hair thinning
- Nose bleeds (caused by dryness of the nasal mucosa)
- Benign intracranial hypertension: isotretinoin treatment should not be combined with tetracyclines for this reason

Cinnarizine

- Cinnarizine is thought to be particularly **useful for the treatment of motion sickness** as it has a dual action:
 - it acts as a depressant of the vestibular system
 - it dampens down smooth muscle contraction in the gut

Ergotamine

- Ergotamine is an old drug and a member of the family of ergot alkaloids.
- It is licensed as a treatment and prophylaxis for migraines but has been largely superseded by newer agents despite its efficacy, cost and relatively benign side effect profile.
- A derivative of the drug, ergometrine, is used in obstetrics to reduce the incidence of post partum haemorrhage.
- Ergotamine, like all ergot alkaloids, is a potent vasoconstrictor which is partly how it exerts its clinical effects, however in overdosage it can cause significant peripheral vasoconstriction causing critical ischaemia and gangrene. Coronary vasoconstriction may occur, with or without flow limiting lesions causing cardiac ischaemia which may be manifest as chest pain, arrhythmia or even sudden death.
- Contraindications to the use of ergotamine are flow limiting coronary lesions or peripheral vascular disease.
- Additionally, ergotamine has a complex series of effects on central nervous neurotransmitter systems including serotonergic, dopaminergic and noradrenergic systems which can cause excitement, confusion, paranoia, visual **and** auditory hallucinations and delusions in overdose.
- It is also a metabolic precursor to the highly hallucinogenic chemical lysergic acid diethylamide (LSD) which inactivates 5-HT2A receptors in the brain.
- At normal doses, side effects of ergotamine are relatively minor and unlikely to cause significant clinical signs in the absence of underlying pathology. However, metabolism of ergot alkaloids is predominantly by the hepatic enzyme CYP3A4 which is almost totally inhibited by macrolide antibiotics. Co-administration of ergotamine and clarithromycin may be expected to produce a rapid picture of ergotism with confusion, psychosis, muscle cramps, seizures, peripheral and coronary vasospasm, severe headache and gastrointestinal symptoms of bowel ischaemia, cramps, diarrhoea and GI haemorrhage. Myocardial infarction, renal infarction, stroke and critical limb ischaemia may occur if not treated.
- Interestingly, ergot alkaloid derivatives are naturally produced by the fungus *Claviceps purpurea* which may infect crops.
- Historically, significant outbreaks of ergotism have been seen due to ingestion of crops contaminated with ergot and there is some historical evidence that claims of witchcraft are ascribable to the psychosis of ergot poisoning.

Finasteride

Finasteride treatment of BPH may take 6 months before results are seen

- Finasteride is an inhibitor of 5 alpha-reductase.
- **5- α -Reductase converts testosterone to dihydrotestosterone (DHT)**
- DHT is much more active than testosterone and binds more avidly to cytoplasmic receptors
- DHT stimulates prostate growth and may be responsible for benign prostatic hyperplasia in the elderly

Indications

- benign prostatic hyperplasia
- male-pattern baldness

Adverse effects

- impotence
- decrease libido
- ejaculation disorders
- gynaecomastia and breast tenderness

Finasteride causes decreased levels of serum prostate specific antigen

Acetazolamide

Action

- **carbonic anhydrase inhibitor**, hence causing the accumulation of carbonic acid
- Inhibits **proximal tubule bicarbonate reabsorption** in a similar fashion to type-2 renal tubular acidosis (RTA) → associated with metabolic acidosis
- By excreting bicarbonate, the blood becomes acidic, causing compensatory hyperventilation with deep respiration (Kussmaul respiration), increasing levels of oxygen and decreasing levels of carbon dioxide in the blood. Hence used in treatment of high altitude sickness.

Indications

- intracranial hypertension
 - post-haemorrhagic hydrocephalus (often with furosemide)
 - primary idiopathic pseudotumour cerebri (benign intracranial hypertension)
- reducing intraocular pressure
- **prevent acute mountain sickness**
- preventative agent for contrast nephropathy

Side effects

- metabolic acidosis, due to bicarbonate loss in the proximal and distal tubules through inhibition of reabsorption
 - **hyperchloraemic, normal anion gap metabolic acidosis**
- Hypokalaemia
- **Acute interstitial nephritis (AIN)**
- Agranulocytosis and thrombocytopenia
- hyponatremia,
- hyperglycemia, hypoglycemia, glycosuria,
- **crystalluria** (and hematuria), and polyuria.
- **peripheral paresthesiae**

carbonic anhydrase works to control the equilibrium between carbon dioxide and carbonic acid in order to maintain proper blood pH. Through which mechanism does **carbonic anhydrase** exert its influence on reaction kinetics?

→ **Lowers the activation energy**

- Enzymes like **carbonic anhydrase** lower the energy of activation that is needed to initiate a reaction.
 - ❖ Inhibition of carbonic anhydrase prevents the conversion of carbon dioxide (CO_2) and water (H_2O) to carbonic acid (H_2O_3) thus affecting the blood pH.

Bicarbonate therapy

- Can increase extracellular pH only if the carbon dioxide (CO_2) produced can be removed by adequate ventilation.
- Indeed, if hypercapnia occurs then as CO_2 crosses cell membranes easily, intracellular pH may decrease even further with further deterioration of cellular function.
- Bicarbonate has a negative inotropic effect,
- reducing cerebral blood flow;
- It shifts the oxygen dissociation curve to the left, inhibiting oxygen release to tissues.
- **Exacerbates intracellular acidosis in cardiorespiratory arrest**

Bisphosphonates

Bisphosphonates inhibit osteoclasts

Bisphosphonates are analogues of pyrophosphate, a molecule which decreases demineralisation in bone. They **inhibit osteoclasts** by reducing recruitment and promoting apoptosis.

The mechanism of action of bisphosphonates involves the inhibition of farnesyl diphosphate synthase within osteoclasts. In doing this they interfere with geranylgeranylation (attachment of the lipid to regulatory proteins), which causes osteoclast inactivation. This leads to reduced bone turnover, increased bone mass and improved mineralisation.

Clinical uses

- prevention and treatment of osteoporosis
 - Bisphosphonates licensed for the prevention and treatment of osteoporosis **include** alendronate, risedronate and ibandronate.
- hypercalcaemia
- Paget's disease
- pain from bone metastases
 - The bisphosphonates zoledronate and pamidronate are used for the treatment of metastatic bone disease and short term management of hypercalcaemia.

Adverse effects

Bisphosphonates can cause a variety of oesophageal problems

- oesophageal reactions: oesophagitis, oesophageal ulcers (especially alendronate)
 - **osteonecrosis of the jaw:**
 - This is a consequence of potent anti-resorptive action of the nitrogen containing bisphosphonates.
 - Most cases have been associated with **zoledronic acid** and pamidronate given intravenously for metastatic bone disease.
 - The reported incidence in patients with malignancy treated with these drugs is between 1.3-4.0%.
 - Dental disease is a recognised predisposing factor.
 - The lesions usually heal with minimal surgical debridement, chlorhexidine mouthwashes, antibiotics and analgesia.
 - **Bisphosphonate infusions can lead to hypocalcaemia** although it is more common when using larger doses in malignancy induced hypercalcaemia as oppose to the smaller dose used in osteoporosis.
 - increased risk of atypical stress fractures of the proximal femoral shaft in patients taking alendronate
- The BNF suggests the following counselling for patients taking oral bisphosphonates
- 'Tablets should be swallowed whole with plenty of water while sitting or standing; to be given on an empty stomach at least 30 minutes before breakfast (or another oral medication); patient should stand or sit upright for at least 30 minutes after taking tablet'

Botulinum toxin

As well as the well publicised cosmetic uses of Botulinum toxin ('Botox') there are also a number of licensed indications:

- blepharospasm
- hemifacial spasm
- focal spasticity including cerebral palsy patients, hand and wrist disability associated with stroke
- spasmodic torticollis
- severe hyperhidrosis of the axillae
- achalasia

Immunoglobulins: Therapeutics

The Department of Health issued guidelines on the use of intravenous immunoglobulins in May 2008

Uses

- Primary and secondary immunodeficiency
- Idiopathic thrombocytopenic purpura (ITP)
- Myasthenia gravis
- Guillain-Barre syndrome
- Kawasaki disease
- Toxic epidermal necrolysis (TEN)
- Pneumonitis induced by CMV following transplantation
- Low serum IgG levels following hematopoietic stem cell transplant for malignancy
- Dermatomyositis
- Chronic inflammatory demyelinating polyradiculopathy

Basics

- Formed from large pool of donors (e.g. 5,000)
- IgG molecules with a subclass distribution similar to that of normal blood
- Half-life of 3 weeks

Malignant hyperthermia (MH)

Overview

- condition often seen following administration of anaesthetic agents
- characterised by increased temperature and muscle rigidity during anaesthesia, which results from abnormal skeletal muscle contraction and increased metabolism.
- caused by excessive release of Ca^{2+} from the sarcoplasmic reticulum of skeletal muscle
- associated with defects in a gene on chromosome 19 encoding the ryanodine receptor, which controls Ca^{2+} release from the sarcoplasmic reticulum
- neuroleptic malignant syndrome may have a similar aetiology

Causative agents

- halothane (volatile anaesthetic agents)
- suxamethonium
- other drugs: antipsychotics (neuroleptic malignant syndrome)

Investigations

- Serum creatine kinase(CK) elevation and myoglobinuria are suggestive but not diagnostic of MH,(both known to increase after giving suxamethonium to normal patients)
- Contracture tests with halothane and caffeine are the investigations of choice.
- **Muscle biopsies may appear histologically normal.**

Management

- dantrolene - prevents Ca^{2+} release from the sarcoplasmic reticulum
 - ⇒ Intravenous dantrolene (up to 10 mg/kg) is the only available specific treatment
 - ⇒ Care must be taken when administering as the solution has a pH of 9-10.

Prognosis

- The prognosis of malignant hyperpyrexia is good when the appropriate treatment is instigated early, mortality being less than 5% (prior to dantrolene the mortality was 80%).

Intravenous fluid therapy

Composition of electrolytes in commonly used crystalloids

Content	Plasma	Sodium chloride 0.9%*	Sodium chloride 0.18%/4% glucose(a)	0.45% NaCl/4% glucose(a)	5% glucose(a)	Hartmann's	Lactated Ringer's (USP)	Ringer's acetate
Na^+ (mmol/l)	135-145	154	31	77	0	131	130	130
Cl^- (mmol/l)	95-105	154	31	77	0	111	109	112
$[\text{Na}^+]:[\text{Cl}^-]$ ratio	1.28 : 1.45 : 1	1:1	1:1	1:1	-	1.18:1	1.19:1	1.16:1
K^+ (mmol/l)	3.5-5.3	*	*	*	*	5	4	5
HCO_3^- / Bicarbonate	24-32	0	0	0	0	29 (lactate)	28 (lactate)	27 (acetate)
Ca^{2+} (mmol/l)	2.2-2.6	0	0	0	0	2	1.4	1
Mg^{2+} (mmol/l)	0.8-1.2	0	0	0	0	0	0	1
Glucose (mmol/l)	3.5-5.5	0	222(40 g)	222 (40g)	278(50 g)	0	0	0
pH	7.35-7.45	4.5-7.0	4.5		3.5-5.5	5.0-7.0	6.7.5	6.8
Osmolarity (mOsm/l)	275-295	308	284		278	278	273	276

Intravenous fluid therapy in adults in hospital (NICE guidelines 2013)

- Indicators for urgent fluid resuscitation:
 - systolic blood pressure is less than 100 mmHg
 - heart rate is more than 90 beats per minute
 - capillary refill time is more than 2 seconds or peripheries are cold to touch
 - respiratory rate is more than 20 breaths per minute
 - National Early Warning Score (NEWS) is 5 or more
 - passive leg raising suggests fluid responsiveness
- Resuscitation
- If patients need IV fluid resuscitation, use crystalloids that contain sodium in the range 130–154 mmol/l, with a bolus of 500 ml over less than 15 minutes.
- Consider human albumin solution 4–5% for fluid resuscitation only in patients with severe sepsis.
- Routine maintenance
 - ➔ If patients need IV fluids for routine maintenance alone, restrict the initial prescription to:
 - 25–30 ml/kg/day of water **and**
 - approximately 1 mmol/kg/day of potassium, sodium and chloride **and**
 - approximately 50–100 g/day of glucose to limit starvation ketosis. (This quantity will not address patients' nutritional needs)
 - (patients rarely need more than a total of 3 litres of fluid per day)
 - ➔ Consider prescribing less fluid (for example, 20–25 ml/kg/day fluid) for patients who:
 - are older or frail
 - have renal impairment or cardiac failure
 - are malnourished and at risk of refeeding syndrome
 - ➔ When prescribing for routine maintenance alone, consider using 25–30 ml/kg/day sodium chloride 0.18% in 4% glucose with 27 mmol/l potassium on day 1.
 - ➔ Prescribing more than 2.5 litres per day increases the risk of hyponatraemia. **These are initial prescriptions and further prescriptions should be guided by monitoring.**
 - ➔ Consider delivering IV fluids for routine maintenance during daytime hours to promote sleep and wellbeing.

British Consensus Guidelines on Intravenous Fluid Therapy (2011)

Recommendation

- Because of the risk of inducing **hyperchloraemic acidosis** in routine practice, when crystalloid resuscitation or replacement is indicated, balanced salt solutions e.g. **Ringer's lactate/acetate or Hartmann's solution should replace 0.9% saline**, except in cases of hypochloraemia e.g. from vomiting or gastric drainage.
- Hypochloraemia is an indication for the use of 0.9% saline, with sufficient additions of potassium and care not to produce sodium overload.
- Losses from diarrhoea/ileostomy/small bowel fistula/ileus/obstruction should be replaced volume for volume with Hartmann's or Ringer-Lactate/acetate type solutions.
- "Saline depletion," for example due to excessive diuretic exposure, is best managed with a balanced electrolyte solution such as Hartmann's.

Daily requirement

- The typical daily requirement is:
 - ⇒ 1.5 ml/kg/hr fluid - for a 80kg man around 2-3 litres/day
 - ⇒ 70-150mmol sodium
 - ⇒ 40-70mmol potassium
- This is why the typical regime prescribed for patients is:

- ⇒ 1 litre 5% dextrose with 20mmol potassium over 8 hours
- ⇒ 1 litre 0.9% normal saline with 20mmol potassium over 8 hours

The table below shows the electrolyte concentrations (in millimoles/litre) of plasma and the most commonly used fluids:

	Na ⁺	Cl ⁻	K ⁺	HCO ₃ ⁻	Ca ²⁺
Plasma	135-145	98-105	3.5-5	22-28	2.3-2.6
0.9% normal saline	150	150	-	-	-
5% dextrose	-	-	-	-	-
Hartmann's solution	131	111	5	29	2

Normal saline has a pH of 5 and may produce a mild metabolic acidosis with significant infusions.

Which fluid would be the most appropriate to replace the fluid being lost in a patient with a paralytic ileus draining 2 litres of fluid a day through a nasogastric tube?

→ 0.9% sodium chloride with potassium according to electrolytes

- it is essential to supply sufficient chloride ions to replace the chloride being lost in the gastric fluid (gastric juice is essentially dilute hydrochloric acid).

Lactulose

- Lactulose MOA → Osmotic laxative
- Causes hypomagnesaemia associated with diarrhoea
- Is not absorbed
- Does not affect the absorption of spironolactone and
- May be used in diabetics.
- It reduces proliferation of ammonia producing bacteria

It is used in patients with cirrhosis/hepatic encephalopathy to limit the proliferation of ammonia-forming gut organisms and increase the clearance of protein load in the gut.

- lactulose broken down by colonic bacteria → production of lactic acid and other organic acids → contents of the gut become more acidic (↓ PH) → ↓↓ absorption of ammonia

→ ↑ ammonia in the gut → ↑↑ water drawn into the lower bowel

Laxative abuse

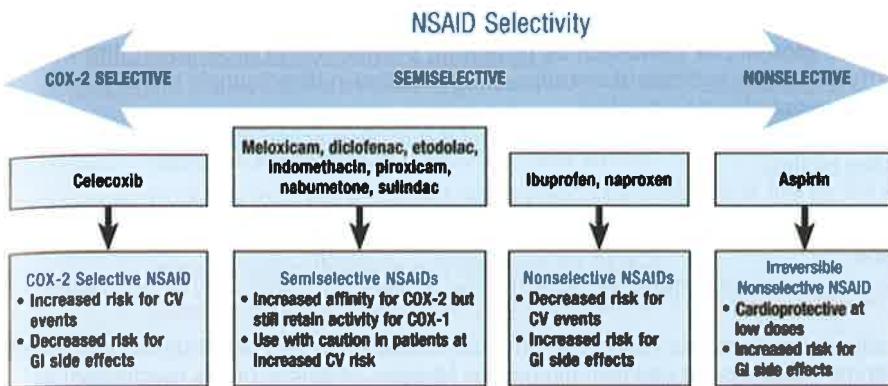
Features

- most commonly seen in young female patients complaining of chronic diarrhoea.
 - ⇒ The diarrhoea is frequently high volume
- underweight girl with calluses on her knuckles may point towards induced vomiting and a diagnosis of bulimia, which would fit with possible laxative abuse.
- Hypokalaemia
 - Due to increased GI potassium loss
 - symptoms of fatigue which are consistent with hypokalaemia.
 - GI loss leads to renal conservation of potassium, a urinary concentration of potassium of less than 1 mmol/l being highly suggestive of laxative abuse.

Bismuth

- subsalicylate is a colloidal substance frequently included in over-the-counter treatments for gastrointestinal discomfort.
- It has anti-secretory, anti-inflammatory, and antibacterial properties.
- It may be included in multidrug regimens against *H. pylori*.
- Its most unique side-effect is the appearance of black stool or a black tongue, both secondary to the drug's interaction with sulfur.

Non-steroidal anti-inflammatory drugs (NSAID)



Non-steroidal anti-inflammatory drugs (Nice 2015)

- If an NSAID is needed, use ibuprofen (1200 mg a day or less) or naproxen (1000 mg a day or less).
- Naproxen (1000 mg a day or less) and low-dose ibuprofen (1200 mg a day or less) are considered to have the most favourable thrombotic cardiovascular safety profiles of all NSAIDs.
- Co-prescribe gastroprotective treatment (a proton pump inhibitor) with NSAIDs
- In October 2012, a European Medicines Agency (EMA) review on the cardiovascular safety of NSAIDs confirmed that diclofenac is associated with cardiovascular risks that are higher than ibuprofen and naproxen, and similar to the COX-2 inhibitors.
- etoricoxib should not be prescribed to people whose blood pressure is persistently above 140/90 mmHg
- the arterial thrombotic risk with diclofenac is similar to that of COX-2 inhibitors.
- diclofenac is now contraindicated in patients with established:
 - ischaemic heart disease
 - peripheral arterial disease
 - cerebrovascular disease
 - congestive heart failure (New York Heart Association [NYHA] classification II–IV)

Indometacin → is an inhibitor of both prostaglandin synthase and lipoxygenase enzymes

Side effects

- Current evidence suggests that naproxen, a nonselective NSAID, is associated with the lowest risk of cardiovascular events. Therefore, naproxen is the NSAID of choice in patients with high cardiovascular risk.
- **Optic neuritis is described as being rarely associated with diclofenac therapy.**

- A range of other CNS side effects has also been noted on the summary of product characteristics, these include headache, dizziness, vertigo and in rare circumstances drowsiness.
- **gastrointestinal bleeding occurs due to depletion of mucosal prostaglandin E (PGE) levels**
- Endoscopic evidence of peptic ulceration is found in 20% of NSAID users even in the absence of symptoms
- The relative risk of causing GI bleeds differs with different preparations:
 - ibuprofen has a low risk
 - piroxicam and azapropazone have the highest risk
- While all NSAIDs may contribute to anaemia, usually via gastrointestinal bleeding, **mefenamic acid is particularly associated with immune haemolytic anaemia.**
- NSAIDs **reduce glomerular perfusion by inhibiting production of prostaglandins** which dilate the afferent arteriole of the glomerulus. The reduction in blood supply to the kidney results in impairment of kidney function.
- NSAIDs can also cause an interstitial nephritis but this is often accompanied by a nephrotic syndrome-like picture.

Non-steroidal anti-inflammatory drugs are contraindicated in chronic liver disease for a variety of reasons:

- their gastrointestinal side effects increase the risk of bleeding, particularly in those with varices.
- Additionally, due to systemic vasodilatation renal circulation is very dependent upon prostaglandin production to maintain glomerular filtration. Inhibition of this mechanism by non-steroids, in addition to their other nephrotoxic effects, means that their use in patients with chronic liver disease, especially where there is pre-existing renal impairment, can precipitate renal failure.

Overdose with (NSAIDs)

Presentation and aetiology

- GIT upset (epigastric tenderness, nausea, vomiting and diarrhea)
These effects are mainly due to the inhibition of cyclo-oxygenase
- **convulsions** (10-20%) → **more common in mefenamic acid over dose**

Large overdoses can present with:

- acidosis
- renal impairment
- gastrointestinal haemorrhage
- CNS effects (drowsiness, coma, cerebellar signs)

Management

- Activated charcoal in patients presenting within the first hour
- Supportive care
- Oral H2-histamine blockers and proton-pump inhibitors may reduce the symptoms of gastrointestinal toxicity

Celecoxib (COX)-2 inhibitor

Celecoxib is an NSAID that is **safe** to use in patients with gastritis or **gastric ulcers** as it does not affect COX1 action at the stomach.

Cox-2 inhibitors have a much lower risk of gastrointestinal bleed and high risk of cardiovascular events, they should not be prescribed to those with cardiovascular disease, or in those with high risk of cardiovascular disease.

Action

- Celecoxib is a **selective cyclo-oxygenase(COX)-2 inhibitor**
 - differing from the other non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen which affects both COX-1 and COX-2.
 - COX-1 is involved in platelet aggregation and inhibition of this by the NSAIDs produces its beneficial cardiovascular effects.
 - **platelet aggregation is not affected by COX-2.**
 - **Celecoxib has a lower level of anti-platelet activity than naproxen**

Advantages

- Naproxen and celecoxib have been shown to be as effective at reducing inflammation.
- **One of the benefits of celecoxib is its reduced incidence of upper gastrointestinal side effects.**

Side effects

- As with the non-specific NSAIDS, **hepatotoxicity** may occur with the COX-2 specific inhibitors resulting in cholestatic, hepatocellular or mixed liver injury. Rates seem to be comparable between the traditional NSAIDs and the COX-2 selective inhibitors.
- The **cardiovascular effects** of the COX-2 inhibitors remains under study, and care should be taken before prescribing them to patients with a past medical history of significant cardiovascular disease.
- Rofecoxib (Vioxx) has been withdrawn due to its increased cardiovascular events compared with naproxen.
- **What is the mechanism of celecoxib-induced deterioration in renal function?**
 - ❖ **inhibition of afferent arteriole vasodilatation**

Interaction

- **Co-administration of diuretics** and COX-2 inhibitors should be avoided if possible, as COX-2 inhibitors may reduce the antihypertensive and diuretic effects of diuretics. This may be due to impaired prostaglandin synthesis, which results in salt-and water retention. In addition, COX-2 inhibitors have nephrotoxic effects which can be exacerbated by diuretics.

Aminosalicylate drugs

- 5-aminosalicylic acid (5-ASA) is released in the colon and is not absorbed. It acts locally as an anti-inflammatory. The mechanism of action is not fully understood but 5-ASA may inhibit prostaglandin synthesis
- The safety of the 5-aminosalicylic acid (5-ASA) drugs in pregnancy is best supported by the data on Salazopyrin which have been available for the longest.

Sulphasalazine

- a combination of sulphapyridine (a sulphonamide) and 5-ASA
- many side-effects are due to the sulphapyridine moiety: rashes, oligospermia, headache, Heinz body anaemia, megaloblastic anaemia
- other side-effects are common to 5-ASA drugs (see mesalazine)

Mesalazine

- a delayed release form of 5-ASA
- sulphapyridine side-effects seen in patients taking sulphasalazine are avoided
- side-effects: GI upset, headache, agranulocytosis, pancreatitis, interstitial nephritis
 - pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine

Olsalazine

- two molecules of 5-ASA linked by a diazo bond, which is broken by colonic bacteria

Anti-TNF therapy (NICE January 2016)

TNF- α inhibitors may reactivate TB

Drugs

- adalimumab, Golimumab, infliximab, certolizumab, tocilizumab
- etanercept,

Action

- tumour necrosis factor alpha (TNF- α) inhibitors

Indications

- Refractory Crohn's disease,
- rheumatoid arthritis: for adults who have both the following characteristics:
 - **Active rheumatoid arthritis** as measured by **disease activity score (DAS28)** greater than 5.1 confirmed on at least two occasions, 1 month apart.
 - Have undergone **trials of two disease-modifying anti-rheumatic drugs (DMARDs)**, including methotrexate (unless contraindicated).
 - A trial of a DMARD is defined as being normally of 6 months, with 2 months at standard dose, unless significant toxicity has limited the dose or duration of treatment.
 - ❖ Use of the TNF- α inhibitors for rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.
- **Follow up**
 - Continue treatment only if there is a moderate response measured using **European League Against Rheumatism (EULAR)** criteria **at 6 months after starting therapy**.
 - monitored 6-monthly
 - ❖ withdraw treatment if a moderate EULAR response is not maintained.

- **Plaque psoriasis**

- Adalimumab is recommended for adults with **plaque psoriasis** only if:
 - **condition is severe** and
 - **not improved with other treatments** such as ciclosporin, methotrexate and PUVA (psoralen and long-wave ultraviolet radiation), or they have had side effects with these in the past or there is a medical reason why they should not be given these treatments.

- Follow up

- Adalimumab treatment should be continued beyond **16 weeks** only if the psoriasis has clearly improved within this time.

- **ankylosing spondylitis**

- NICE states that adalimumab, etanercept and golimumab may be used for ankylosing spondylitis (AS) **only if:**
 - treatment with two or more NSAIDs for four weeks at the highest possible dose has not controlled the symptoms
 - confirms that **condition has not improved** by 2 methods:
 - 1) level of **pain is assessed twice** (using a simple scale to fill in) 12 weeks apart and confirms that condition has **not improved**
 - 2) **Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)** is tested twice, 12 weeks apart, and confirms that **condition has not improved**

► BASDAI is a set of measures to evaluate condition, by asking a number of questions about symptoms

Side effects

- Reactions
 - Injection site reactions
 - Cutaneous reactions, including psoriasis
 - Infusion reactions
 - Infusion reactions with infliximab are classified as one of two types:
 - ❖ Acute reactions : occur within 24 hours.
 - ❖ Delayed reactions: develop between 1 and 14 days
- Neutropenia
- Infections
 - **risk of reactivation of tuberculosis or new infection**
 - including miliary TB and some unusual extra-pulmonary TB
 - **If patient had previous active TB, the optimal TB screening test in this situation→ Interferon gamma release assay**
- Demyelinating disease → exacerbation of neurologic disorders associated with demyelination, such as multiple sclerosis.
- Heart failure
 - Given the evidence to date, patients with symptomatic HF should be treated with strategies other than TNF-alpha inhibitors.
 - In a patient who develops HF while on a TNF-alpha inhibitor, a drug-induced cause should be suspected.
- Malignancy
- Induction of autoimmunity

Usage

- Prior to initiating a TNF-alpha inhibitor, all patients **should be screened for:**
 - **tuberculosis,**
 - hepatitis B, and
 - hepatitis C.
- All forms of anti-TNF therapy are given by injection.
 - **Etanercept** is given as **subcutaneous** injection twice per week.
 - **Infliximab** is given as an **infusion (intravenous)**.
 - requires intravenous infusion in a hospital setting.
 - It is given 2-4 weekly initially and then on a 6-8 weekly basis and as per protocol.
 - Infliximab monotherapy induces the production of **anti-infliximab antibodies**, which may reduce its effectiveness. **Adding methotrexate to infliximab therapy may prevent this response.**
 - **Adalimumab** is given as (**subcutaneous injection**) on alternate weeks (every second week).
- **Unlike methotrexate,**
 - there is little problem with nausea.
 - Nor is there the same concern for effects on blood cells and the liver which means less blood tests are required.
- TNF- α inhibitors should normally be used in combination with methotrexate.
 - If methotrexate is intolerant, adalimumab and etanercept may be given as monotherapy.

Monoclonal antibodies

Rituximab - monoclonal antibody against CD20

Cetuximab - monoclonal antibody against the epidermal growth factor receptor

Trastuzumab (Herceptin) - monoclonal antibody that acts on the HER2/neu receptor

Overview

- manufactured by a technique called somatic cell hybridization.
- This involves the fusion of myeloma cells with spleen cells from a mouse that has been immunized with the desired antigen. The resulting fused cells are termed a hybridoma and act as a 'factory' for producing monoclonal antibodies.
- The main limitation to this is that mouse antibodies are immunogenic leading to the formation of human anti-mouse antibodies (HAMAs). This problem is overcome by combining the variable region from the mouse body with the constant region from a human antibody.

Some monoclonal antibodies in clinical use include:

monoclonal antibodies	Action	Indication
Digibind	Digoxin-binding antibody	for treatment of overdoses (increases clearance).
Abciximab	Glycoprotein IIb, IIIa receptor	for unstable angina.
Pexelizumab	Anti-C5 (complement) - anti-inflammatory	reduces myocardial infarction and death following coronary artery bypass graft (CABG) and angioplasty.
Rituximab	Anti-CD20	non-Hodgkin's lymphoma
Infliximab	anti-TNF	rheumatoid arthritis and Crohn's
Cetuximab	anti-epidermal growth factor receptor	metastatic colorectal cancer and head and neck cancer
Trastuzumab	anti-HER2, anti EGF receptor	metastatic breast cancer
Alemtuzumab	anti-CD52	chronic lymphocytic leukemia
Abciximab	anti-glycoprotein IIb/IIIa receptor	undergoing PCI, prevention of ischemic events in patients
OKT3	anti-CD3	prevent organ rejection
Tocilizumab	directed against IL-6 receptor	treatment of moderate-to-severe RA in patients with an inadequate response to DMARDs and/or anti-TNF
Nivolumab	PD-1 (programmed cell death) inhibitor (PD-1 receptors are found on the surface of T cells.)	carcinoma of the lung Nivolumab in combination with ipilimumab used in metastatic melanoma and lymphoma.

Monoclonal Antibodies in Rheumatoid Arthritis

Monoclonal Antibodies Directed Against TNF- α	Antibodies Against B Cells	Antibodies That Interfere With IL-6 Function	Antibodies That Interfere With IL-1 Function
Infliximab Adalimumab Golimumab Certolizumab	Rituximab	Tocilizumab	Anakinra

Monoclonal antibodies are also used for:

- medical imaging when combined with a radioisotope
- identification of cell surface markers in biopsied tissue
- diagnosis of viral infections

Side effects

- Nivolumab** (PD-1 inhibitor) and **ipilimumab** (CTLA-4 inhibitor) are checkpoint inhibitors which are **used in the treatment of metastatic melanoma**. Effects on the endocrine system are being increasingly reported with prolonged therapy (hypophysitis and **hypothyroidism**) and therefore it is important to assess patients carefully who present with symptoms of hypothyroidism whilst on these drugs.

Abatacept

- What is the mechanism of action of abatacept?**
 - Chimeric protein that inhibits T-lymphocyte activation
 - CTLA4 homologue**
 - Abatacept is a cytotoxic lymphocyte antigen 4 (CTLA 4) homologue –
- Indication
 - licensed for RA treatment.

Proton pump inhibitors

- The proton pump is only contained in the tubo-vesicles of the parietal cell → **secrete acid**.
- Proton-pump inhibitors (e.g omeprazole) **binds to gastric K⁺/H⁺-ATPase proton pump irreversibly**
- However, as the half-life of the pump is 24-36 hours, the duration of the effect of proton-pump inhibitors is limited by the degradation of these pumps.

Sildenafil

Viagra? - contraindicated by nitrates and nicorandil

Action

- Sildenafil is a phosphodiesterase type V inhibitor (**PDE-5 inhibitors**) used in the treatment of impotence.
- It **increases** intracavernosal cGMP levels, thereby **competitively inhibiting the PDE-5 enzyme**, and **allowing nitric oxide-induced vasodilation**.
 - it **blocks cGMP phosphodiesterase**, which is normally responsible for the breakdown of cGMP. Sildenafil therefore leads to increased levels of cGMP, which has vasodilatory effects to relax smooth muscle.

Contraindications

- patients taking nitrates and related drugs such as nicorandil
- hypotension
- recent stroke or myocardial infarction (NICE recommend waiting 6 months)
- non-arteritic anterior ischaemic optic neuropathy

Side-effects

- visual disturbances e.g. blue discolouration, non-arteritic anterior ischaemic neuropathy
Sildenafil is a PDE-5 inhibitor, but at high doses it also **inhibits PDE-6, which leads to blue discolouration of vision**. This can often be managed by reducing the dose of Sildenafil.
- nasal congestion
- flushing
- gastrointestinal side-effects
- headache

Anaesthetic drugs

halothane hepatitis (medical-masterclass.com 2017 mrcp part 2)

- There are many causes of **post-operative jaundice**, but **the fact that the surgery was uncomplicated, the time course, the presence of joint / muscle pains and an eosinophilia, all suggest halothane hepatitis as the most likely diagnosis.** This is thought to result as a hypersensitivity reaction. Treatment is supportive.

Effects on the liver

• Halothane

- ⇒ Halothane undergoes ~25% metabolism by oxidative phosphorylation via hepatic cytochrome P450 systems.
- ⇒ The major metabolite is trifluoroacetic acid (TFA), which is protein-bound and this TFA–protein complex can induce a T-cell-mediated immune response resulting in hepatitis ranging from mild transaminitis to fulminant hepatic necrosis and possibly death.
- ⇒ the risk of fatal hepatic necrosis → one in 10 000 anaesthetics.
- ⇒ Adult females are more commonly affected.
- ⇒ Repeated exposure increases the risk of hepatitis.

• Halothane and hepatitis

- Halothane can cause a mild liver dysfunction in approximately 30% of patients, due to the binding of reactive halothane metabolites to hepatocytes
- Halothane oxidation by cytochrome P450 enzymes leads to the synthesis of trifluoroacetyl chloride, which covalently binds to hepatic molecules and causes an immune reaction **Fulminant hepatitis results from the reactive metabolite, trifluoroacetyl chloride**
- Further exposure to halothane anaesthesia may lead to a fulminant hepatitis, where the mortality is approximately 90%.
- Halothane induced hepatitis typically occurs five to seven days after exposure

- Less commonly hepatitis has been described after exposure to **enflurane > isoflurane > desflurane.**
- **Sevoflurane** is not metabolized to antigenic TFA–protein complexes.

Inhaled anaesthetic-like agent

- If patient was markedly comatose on arrival but **quickly regains consciousness**. This suggests a short acting (probably) inhaled anaesthetic-like agent → e.g **Inhaled solvent glue**.
- The inhaled solvents, due to their lipophilicity, are rapidly absorbed through the lungs and then quickly distributed to the brain and other organs. The effects therefore appear within minutes of inhalation.
- Typical substances that are inhaled include toluene, aromatic hydrocarbons and butane.

Pseudocholinesterase deficiency

Overview

- Pseudocholinesterase is a glycoprotein enzyme, produced by the liver.
- It specifically hydrolyzes exogenous choline esters.
- most common in European; rare in Asians.
- Pseudocholinesterase deficiency results in delayed metabolism of the following:
 1. **Succinylcholine**. depolarizing neuromuscular blocking agent (the most clinically important drug)
 - **Suxamethonium** is a depolarising neuromuscular blocking agent,

metabolised by plasma pseudocholinesterases.

- Approximately 1 in 2500 individuals have deficiency of this enzyme, **resulting in prolonged neuromuscular blockade if they are given suxamethonium.**
- 2. mivacurium.
- 3. procaine.
- 4. cocaine.
- After an intravenous dose of succinylcholine in individuals with normal plasma levels of normally functioning pseudocholinesterase enzyme:
 - ⇒ hydrolysis and inactivation of 90-95% of i.v succinylcholine occurs before it reaches the neuromuscular junction.
 - ⇒ The remaining 5-10% of the dose acts as an acetylcholine receptor agonist at the neuromuscular junction, causing prolonged depolarization of the postsynaptic junction of the motor-end plate.
 - ⇒ This depolarization initially triggers fasciculation of skeletal muscle.
 - ⇒ As a result of prolonged depolarization, endogenous acetylcholine released from the presynaptic membrane of the motor neuron does not produce any additional change in membrane potential after binding to its receptor on the myocyte.
 - ⇒ Flaccid paralysis of skeletal muscles develops within 1 minute.
- In normal subjects, skeletal muscle function returns to normal approximately 5 minutes after a single bolus injection of succinylcholine as it passively diffuses away from the neuromuscular junction.
- Pseudocholinesterase deficiency can result in higher levels of intact succinylcholine molecules reaching receptors in the neuromuscular junction, causing the duration of paralytic effect to continue for as long as 8 hours.
- This condition is recognized clinically when paralysis of the respiratory and other skeletal muscles fails to spontaneously resolve after succinylcholine is administered as an adjunctive paralytic agent during anesthesia procedures.

Diagnosis:

- by plasma assays of pseudocholinesterase enzyme activity.

Management

- prolonged ventilation until the action of the drug wears off.
- Relatives of affected patients should be screened.

Prognosis

- exposed to succinylcholine → excellent when close monitoring and respiratory support measures.
- exposed to cocaine, sudden cardiac death can occur.

Succinyl choline

- **Depolarizing Skeletal muscle relaxants**
- Also called suxamethonium
- Analogue of acetyl choline, **acts on nicotinic Nm receptors**
- Only depolarizing skeletal muscle relaxant
- Fastest onset of action, Shortest duration of action
- can stimulate autonomic ganglia
- **Side effect and contraindications (CI)**
 - ⇒ **Cause hyperkalemia** in patients with nerve and muscular disorders so **CI in:**
 - nerve disorders (Paraplegia, hemiplegia, GBS) and
 - muscular disorders(muscular dystrophy, Myasthenia, crush injury, **burns**, rhabdomyolysis)
 - ⇒ **Increases all pressures** so **CI in:**

- glaucoma,
 - head injury,
 - increase BP,
 - nausea and vomiting due to intragastric pressure.
- ⇒ Trigger **malignant hyperthermia** when used with halothane

Local spinal anesthetics

Hypotension and **bradycardia** following spinal anesthesia suggest neurogenic shock.

- Local spinal anesthetics, can interrupt the transmission of nerve impulses in spinal sympathetic pathways, causing a **loss of sympathetic vascular tone** that ultimately results in neurogenic shock.
- Neurogenic shock is a type of distributive shock characterized by:
 - ⇒ generalized vasodilation (causing **diaphoresis** and **flushed skin**).
 - ⇒ This vasodilation leads to decreased preload and subsequently reduced cardiac output, which results in **hypotension** and **bradycardia**.
 - ⇒ Consequently, cerebral perfusion is impaired, leading to a **loss of consciousness**.

Fentanyl

- Large, rapidly given doses of specific opioids such as fentanyl, sufentanil, remifentanil, and alfentanil are associated with systemic skeletal muscle rigidity.
 - ⇒ Of most concern to the anesthesiologist is **chest wall rigidity** (which impairs mask and bag ventilation) and **rigidity of the jaw muscles** which can prevent the insertion of an advanced airway.

Ketamine

- Ketamine is commonly used as a recreational drug.

adverse effects include:

- stimulation, **euphoria**, depersonalisation, floating feeling
- synaesthesia (a sensory stimulus in one modality is perceived as a sensation in another), eg: being **able to 'smell sounds'**
- delirium,
- vivid dreams
- hallucinations.

Topoisomerase inhibitors

Overview

- Topoisomerase I and II are enzymes that control the changes in DNA structure during the normal cell cycle.
- Topoisomerase inhibition leads to apoptosis and cell death.
- Used in:
 - ⇒ chemotherapy treatments.
 - ⇒ as antibacterial agents :Quinolones (including nalidixic acid and ciprofloxacin)

Topoisomerase I inhibitors

- Agent:
 - ⇒ Irinotecan: used mainly for Colorectal cancer
 - ⇒ Topotecan: used mainly for Ovarian cancer and Small-cell lung cancer

- **Mechanism of action:** Inhibition of topoisomerase I → ↓ DNA unwinding → ↓ DNA replication and DNA degradation (because of ssDNA breaks)
- **Side effects :** Myelosuppression and GI symptoms (e.g., diarrhea)

Topoisomerase II inhibitors

- **Agent:** Etoposide
- **Indications:** used for Solid tumors, Testicular cancer, Small-cell lung cancer, Leukemias, Lymphomas
- **Mechanism of action:** Inhibition of topoisomerase II → ↑ DNA degradation (dsDNA breaks) and ↓ DNA replication (**cell cycle arrest in S and G2 phase**)
- **Side effects:** Myelosuppression, Alopecia

By what mechanism does topoisomerase catalyse DNA replication?

⌚ **Helix torsion release**

📖 Topoisomerase releases torsion in the DNA helix during replication. It accomplishes this by **cutting the DNA helix at specific points to allow it to unravel and then ligates the ends together again**. This **allows large proteins such as DNA polymerase to replicate DNA along the sequence**.