Notes & Notes

For MRCP part 1 & 11

By

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Pharmacology

Contains:

1/ Passmedicine 2015 (white & black fields)
2/ on examination 2015 (green fields)
3/ pastest 2015 (yellow fields)
Preface

‘How do I get started?’ ‘Which books should I read?’ ‘Which are the best Self-assessment questions bank?’ ‘Passmedicine alone? Is it enough?’ or should I add other source? Should I add on-examination or pastest?
These are the usual questions asked by the MRCP candidates. For all these questions, and depending on thorough follow up of a lot of candidates results, feedbacks and comments, rather than my personal experience, and after consultations of a wide range of mrcp experts, I decide to create a very concise notes collected from the most popular three mrcp sources:

- Passmedicine 2015 (in black & white fields)
- Onexamination 2015 (in green fields)
- And pastest 2015 (in yellow fields)

Occasionally, I add a few facts from previous exams, last guidelines and uptodate source.

How to use this "notes & notes"?
I recommend candidates to follow these steps:
- First off all go carefully through this notes 2 times aiming to build a bulky knowledge of mrcp syllabus.
- then start to practice questions from Passmedicine, onexam and pastest, you will find it very easy to answer, and if you face any difficult question you have to open your "notes & notes" and read the topic again before returns to question banks, this is crustily helpful to fix the idea.
- In the last few days before your exam, return to this notes and read it once again. You will find some information written by red or big font, those are the answers of questions, which are tested in above sources and previous exams. I hope this collection will be enough to help you get through mrcp part 1 and give you a good grip before interring part H.

With best wishes

Dr. Yousif Abdallah Hamad
2015
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.

- 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.

The majority of phase I and phase II reactions take place in the liver.

Drug metabolism in patients with advanced liver disease
- Drug processing via mixed function oxidases is affected early in liver disease.
- Conjugation reactions are affected to a lesser extent by advanced liver disease and only occur in very late stage 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.

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.
**Effects of age on drug metabolism**

- All of the following may account for differences in drug metabolism in the elderly:
  - diminished renal function
  - altered proportions of body fat and water
  - **reduced cardiac output**
  - some degree of altered hepatic metabolism
  - disease
  - general debility
  - concomitant medication use

- For these reasons, 'box-ticking' healthy elderly studies are rarely able to detect problems associated with the use of new drugs in the elderly age group.
- Many problems associated with the use of new drugs in the elderly may only be discovered through adverse event reporting during the post-launch period.

**Saturation 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).
- This response is typical of drugs such as **phenytoin** (saturates liver metabolism).

**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

Zero-order kinetics
Questions concerning zero-order kinetics and acetylator status are also common in the exam.

Zero-order kinetics describes metabolism which is independent of the concentration of the reactant. This is due to metabolic pathways becoming saturated resulting in a constant amount of drug being eliminated per unit time. This explains why people may fail a breathalyser test in the morning if they have been drinking the night before.

Drugs exhibiting zero-order kinetics:

- phenytoin
- salicylates (e.g. high-dose aspirin)
- heparin
- ethanol
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.

**Acetylator status**

**Acetylator Status**
50% of the UK population is deficient in hepatic N-acetyltransferase

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Greater than 60% of Japanese are recognised to be fast acetylators

**Slow acetylators** often experience toxicity from drugs such as isoniazid, sulfonamides, procainamide, and hydralazine. Whereas **fast acetylators** may not respond to isoniazid and hydralazine in the management of tuberculosis and hypertension.
Drugs affected by acetylator status (slow acetylators → increased unwanted effects)

- isoniazid → (neuropathy)
- procainamide
- hydralazine → (drug-induced lupus)
- dapsone → (haemolysis and neuropathy but not fibrosis)
- sulfasalazine → (haemolysis)

Half-life

- The half-lives are related to lipid solubility (amiodarone, fluoxetine and diazepam are very lipid-soluble) and the rate of drug clearance
- **Amiodarone the longest half-life = 25 days**, fluoxetine 53 h; diazepam 43 h; gentamicin 2-3 h; and bumetanide 0.8 h
- Clearly, increased lipid solubility results in increased tissue binding of the drug, hence renal or hepatic drug clearance only affects the total pool of drug at a very slow rate (so that the half-life is prolonged)

Which is the most important pharmacokinetic factor in determining the appropriate timing between doses?

⇒ Plasma half life

The half-life is the time taken for the concentration of a drug to reduce by 50%

Affinity & efficacy

- **Affinity** is the measure of the net molecular attraction between a drug (or neurotransmitter or hormone) and its receptor
  - *(the affinity of a drug for its receptor⇒ Potency)*
  - The receptor's affinity for binding a drug determines the concentration of drug required to form a significant number of drug-receptor complexes.
  - Affinity and intrinsic activity are determinants of potency.
- **Efficacy** contributes both to potency and to the maximum effect of the agonist. Efficacy is a measure of the efficiency of the drug-receptor complex in initiating the signal transduction process.
**Bioavailability**
- Bioavailability is expressed as a percentage and is a measure of the proportion of an administered dose that reaches the systemic circulation
- Where a drug is administered intravenously, by definition it has 100% bioavailability
- Bioavailability is affected by both absorption and first-pass metabolism

**Extraction ratio**
- The extraction ratio is a measure of how much drug is extracted from the plasma by the kidney
- It determines the clearance (= renal plasma flow × extraction ratio)
- The extraction ratio is determined by assessing drug concentration on the arterial and venous sides of the renal circulation
- the bioavailability is the proportion of an orally administered drug reaching the circulation

**Drug level and elimination**

**Example:** if the half-life of a drug is 4 h, what percentage of the drug will be eliminated after 20 h?
- The concentration of the drug reduces by 50% over each 4-h period
- After 4 h → 50% remaining
- After 20 h → X % remaining
- X% = (0.5 x 20) / 4 = 2.5 (remaining after 20 h)
- This means that approximately 97% of the drug concentration has been eliminated after 20 h

**Example:** 630 mg of a drug with half-life of 30 min, how much time will it take before the drug level falls below 20 mg?
- 20/630 = approximately 1/32 = 1/2 x 1/2 x 1/2 x 1/2 x 1/2 = 5 half-lives (for less than 20 mg to remain)
- 5 half-lives equals 5 x 30 min = 150 min

**Example:** The half-life of a drug is 4 h, calculate the plasma concentration 12 h after administration of drug that gives a peak initial plasma concentration of 2 mg/dl?
- the half-life here, which is 4 h,
- 12 h is equal to three half-lives
- Therefore, the plasma concentration at 12 h will be 2/(2 x 2 x 2) = 0.25
Bioequivalence
- Bioequivalence means that the two drugs compared have the same pharmacokinetic and pharmacodynamic effects.
- A pharmaceutical company wants to bring generic drug to the market. **What kind of study is needed to obtain approval to market the drug?**
  - Phase-I bioequivalence study. Generic medicines have to be therapeutically equivalent to their branded product.

Clinical trials
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.

The ideal drug pharmacokinetic
In designing a new drug, which of the following compounds, according to its mode of clearance, is most likely to show stable pharmacokinetic properties when tested between patients?

- CYP2D6 shows the greatest genetic variability, and hence there are likely to be significant and unpredictable pharmacokinetic differences between patients in drugs metabolised down this route.
- CYP3A4 is the P450 isoform pathway down which a number of drugs are metabolised, hence there is the potential for significant drug interaction.
- Therefore, the preferred pathway for drug clearance is one-third via the kidneys and two-thirds via P450 isoforms, but not CYP2D6.
- The ideal profile of our candidate drug should be neither an inhibitor nor an inducer of the P450 system.
- To maximise drug absorption, the ideal compound should be small (molecular weight of less than 300 kDa) and have intermediate lipophilicity and hydrophilicity.

Some definitions
- **Competitive antagonists** bind to the site of action for the endogenous receptor ligand and can be displaced, (eg prazosin).
- **Non-competitive antagonists** (eg phenoxybenzamine) cannot be displaced or have their effects diminished by an endogenous receptor ligand.
- **A partial agonist** (eg acebutolol) may exhibit strong receptor-binding activity, but have a limited physiological response.
Adverse drug reactions

- **Type A** (augmented) reactions occur owing to a pharmacological effect of the drug
- they are dose-related and can occur in anyone
- **Type B** (bizarre) reactions are unpredictable and not related to a pharmacological effect of the drug
- **Type C** (continuous) reactions occur because of prolonged drug use (eg analgesic nephropathy or visual-field defects with vigabatrin.)
- **Type D** (delayed) reactions are teratogenic or carcinogenic reactions (eg thalidomide)
- **Type E** (end of use) reactions are withdrawal phenomena identified after a drug is discontinued

Side-effects Classification

- Very common side-effects are said to occur with a frequency of greater than 1 in 10 patients
- Common side-effects: in 1 in 100 to 1 in 10
- Uncommon side-effects: in 1 in 1000 to 1 in 100
- Rare side-effects: in 1 in 10 000 to 1 in 1000
- Very rare side-effects: in less than 1 in 10 000 patients

The Yellow Card recording system of drug adverse effects:

Only 10% of serious adverse drug reactions are identified by Yellow Cards

Dose-response

- The dose-response curve for loop diuretics such as furosemide is steeply rising and prolonged, indicating a large improvement in drug effect across a range of increasing doses
- In contrast, the dose-response curve for thiazide diuretics rapidly reaches a plateau after the use of relatively low doses, indicating that there is no point in increasing doses above 2.5 mg in the case of bendrofluazide for instance
- The dose-response curve reaches a plateau for pioglitazone at above 45 mg (licensed doses 30 mg and 45 mg)
- With respect to losartan, two doses are available, but the dose increment between 50 and 100 mg only results in a relatively modest further drop in blood pressure

Potency

- 'Potency' is a term often used incorrectly to describe dose-response
- Potency is merely the effect of a drug, weight for weight, compared against another

Therapeutic efficacy

- Therapeutic efficacy (eg in a change in mmHg) is a much better measure of dose-response
- Of course, just as dose-response curves are plotted for efficacy, they can also be plotted for toxic effects
- therapeutic index \(\rightarrow\) (the maximum tolerated dose divided by the minimum effective dose)
**P450 enzyme system**

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

**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**

**Inhibitors of the P450 system include**

- antibiotics: ciprofloxacin, erythromycin
- isoniazid **isoniazid inhibits the P450 system**
- cimetidine, omeprazole
- amiodarone
- allopurinol
- imidazoles: ketoconazole, fluconazole
- SSRIs: fluoxetine, sertraline
- **Disulfiram**
- sulphonamides
- ritonavir
- **sodium valproate**
- acute alcohol intake
- quinupristin
**P450 drug interactions: more detail**

Whilst you are expected to know in broad terms what are the main inhibitors and inducers of the P450 system it is unlikely that you will be asked detailed questions about the individual enzyme systems.

It is worthwhile noting that 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. There is clearly a lot of overlap within the various P450 enzymes.

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

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.
### Drug interactions with cytochrome P450

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

### Drug induced manifestations

#### Drug causes gingival hyperplasia
**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)

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**Notes & Notes for mrcp**

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**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**

The drugs **most commonly** implicated in SIADH are:
- Thiazide diuretics
- Vincristine
- Vinblastine
- Cyclophosphamide

**Others include:**
- Chlorpromamide
- 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)**
  
  Spironolactone causes gynaecomastia by several **mechanisms**.
  - It can **block androgen production** by inhibiting enzymes in the testosterone synthetic pathway.
  - and can also **block receptor binding of testosterone** and dihydrotestosterone.
  - In addition, it displaces oestradiol from sex hormone binding globulin (SHBG), which **increases free oestrogen levels**.
- Cimetidine
- ciclosporin,
- omeprazole
- Digoxin → direct action at oestrogen receptors.
- Cimetidine
- LHRH analogues
- Finasteride
- Ramipril has **very rarely** been associated with gynaecomastia
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 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 liver disease

<table>
<thead>
<tr>
<th>Hepatocellular Picture</th>
<th>Cholestasis (+/- Hepatitis)</th>
<th>Liver Cirrhosis</th>
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<tr>
<td>Alcohol</td>
<td>Anabolic steroids, testosterone</td>
<td>Amiodarone</td>
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<tr>
<td>Amiodarone</td>
<td>Antibiotics: flucloxacillin, co-amoxiclav*, erythromycin**, nitrofurantoin</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Anti-tuberculosis: isoniazid, rifampicin, pyrazinamide</td>
<td>Fibrates</td>
<td>Methyldopa</td>
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<tr>
<td>Halothane</td>
<td>Oral contraceptive pill</td>
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<tr>
<td>MAOIs</td>
<td>Phenothiazines: - chlorpromazine, - prochlorperazine</td>
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<tr>
<td>Methyldopa</td>
<td>Statins</td>
<td>Rarely: nifedipine</td>
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<tr>
<td>Paracetamol</td>
<td>Sodium valproate, phenytoin</td>
<td>Sulphonylureas</td>
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<tr>
<td>Sodium valproate, phenytoin</td>
<td>Statins</td>
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<td>Statins</td>
<td>nitrofurantoin</td>
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<td>nitrofurantoin</td>
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</table>

* A four-week delay in symptoms and signs is not unusual.
** Risk may be reduced with erythromycin stearate.
**Prescribing in patients with renal failure**

Questions regarding which drugs to avoid in renal failure are common

**Drugs to avoid in renal failure**

- antibiotics: tetracycline, nitrofurantoin
- NSAIDs
- lithium
- metformin

**Drugs likely to accumulate in chronic kidney disease** - need dose adjustment

- most antibiotics including penicillins, cephalosporins, vancomycin, gentamicin, streptomycin
- digoxin, atenolol
- methotrexate
- sulphonylureas
- furosemide
- opioids

**Drugs relatively safe** - can sometimes use normal dose depending on the degree of chronic kidney disease

- antibiotics: erythromycin, rifampicin
- diazepam
- warfarin

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**Drug-induced lupus erythematosus**

**Pathogenesis**

- The pathogenesis of drug-induced lupus is unclear.
- Factors that influence drug metabolism, such as acetylator status, have been implicated.
- In addition, lupus-inducing drugs have been shown to generate a variety of cytotoxic products on exposure to MPO released from activated neutrophils.

**Causes**
### The most commonly associated drugs

- procainamide
- hydralazine
- anti-TNF alpha agents
- statins
- isoniazid
- minocycline.

- Minocycline associated with the development of long term immunological memory, and therefore exacerbation of symptoms within 12-24 hours of rechallenge.

### Risk factors

- A strongly positive ANA
- HLA-DR4 phenotype (hydralazine-induced disease)
- slow acetylator status
- large total daily doses of precipitating drugs

### Features

Classically, **drug-induced lupus erythematosus is characterised by**

- Systemic disease with a lower incidence of nephritis
- Lack of cutaneous involvement and
- The presence of antihistone antibodies.

### Laboratory features

- Characteristically, the erythrocyte sedimentation rate (ESR) and C reactive protein (CRP) are both markedly elevated,
- the ANA is strongly positive
- and there is a hypergammaglobulinaemia.
- Anti-dsDNA antibodies are usually negative;
- antihistone antibodies are positive in 95% of drug-induced lupus (but also 50-80% of idiopathic SLE3).
There are several features which distinguish drug-induced lupus from idiopathic SLE:

- Males and females are equally affected in drug-induced lupus, whereas idiopathic SLE affects females nine times more frequently.
- **Caucasians are affected by drug-induced lupus more commonly than Afro-Caribbeans**, whereas the inverse is true of idiopathic SLE.
- In addition, the age of onset is typically older in drug-induced lupus, but this depends on the age at drug exposure.
- Fever, arthralgia, serositis and ANA occur at least as frequently in drug-induced lupus as idiopathic SLE.
- Haematological, renal and central nervous system (CNS) involvement, and double-stranded DNA autoantibodies are rare.

**Treatment**

- Typically, no further treatment is required after **Withdrawal of the precipitating drug**.
- However, there are situations where corticosteroids or disease modifying antirheumatic drugs (DMARDs) are required to aid resolution.
- The time taken for symptoms to resolve after stopping minocycline is highly variable, from a few days to two years.

**Prognosis**

- **Spontaneous recovery usually occurs promptly**

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**Drug-induced pancytopenia**

Drug causes of pancytopenia

- cytotoxics
- antibiotics: trimethoprim, chloramphenicol
- anti-rheumatoid: gold, penicillamine
- carbimazole*
- anti-epileptics: carbamazepine
- sulphonylureas: tolbutamide

*Although both azathioprine and mesalazine cause pancytopenia, it is more commonly seen in patients undergoing azathioprine therapy.

*causes both agranulocytosis and pancytopenia
**Drug-induced long QT**
Drugs well-recognized to cause *torsades de pointes*

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
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<td>Amiodarone (Cordarone)</td>
<td>Procainamide (Pronestyl)</td>
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<td>Disopyramide (Norpace)</td>
<td>Quinidine (Quinaglute)</td>
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<td>Dofetilide (Tikosyn)</td>
<td>Sotalol (Betapace)</td>
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<td>Ibutilide (Corvert)</td>
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<td>Antipsychotics</td>
<td>Chlorpromazine (Thorazine)</td>
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<td>Clozapine (Clozaril)</td>
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<td>Ciprofloxacin (Cipro)</td>
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<td>Antidepressants</td>
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<td>Fluoxetine (Prozac)</td>
<td>Venlafaxine (Effexor)</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>Ondansetron (Zofran)</td>
<td>Prochlorperazine (Compazine)</td>
</tr>
</tbody>
</table>

**Drug-induced thrombocytopenia**
Drug-induced thrombocytopenia (probable immune mediated)

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

### Drugs causing ocular problems

<table>
<thead>
<tr>
<th>Visual disturbance</th>
<th>cataract</th>
<th>Corneal opacities</th>
<th>Optic neuritis</th>
<th>Retinopathy</th>
<th>Blue tinge in vision</th>
<th>Yellow-green tinge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
<td>steroids</td>
<td>Amiodarone</td>
<td>Ethambutol</td>
<td>Chloroquine, quinine</td>
<td>Sildenafil</td>
<td>Digoxin</td>
</tr>
<tr>
<td></td>
<td>Amiodarone</td>
<td>Indomethacin</td>
<td>Amiodarone Metronidazole</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

### 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
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
- cyproheptadine 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

Drugs that can be cleared with Hemodialysis - mnemonic: B L A S T

<table>
<thead>
<tr>
<th>Barbiturate</th>
<th>Drugs which cannot be cleared with HD include</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>• Tricyclics</td>
</tr>
<tr>
<td>Alcohol (inc methanol, ethylene glycol)</td>
<td>• Benzodiazepines (diazepam, midazolam, alprazolam)</td>
</tr>
<tr>
<td>Salicylates</td>
<td>• Dextropropoxyphene (co-proxamol)</td>
</tr>
<tr>
<td>Theophyllines (charcoal hemoperfusion is preferable)</td>
<td>• Digoxin, β-blockers</td>
</tr>
</tbody>
</table>
Drug fever

- 'Drug fever' as an isolated phenomenon can occur with
  - Penicillins,
  - phenytoin,
  - hydralazine
  - and quinidine

- Such fevers are usually of low grade and the patient is generally not very ill
- The fever subsides within a few days of stopping the drug

Cardiovascular drugs

Prescribing in patients with heart failure
The following medications may exacerbate heart failure:

- thiazolidinediones*: pioglitazone is contraindicated as it causes fluid retention
- verapamil: negative inotropic effect
- NSAIDs**/glucocorticoids: should be used with caution as they cause fluid retention
- class I antiarrhythmics; flecainide (negative inotropic and proarrythmic 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

*pioglitazone is now the only thiazolidinedione on the market

**low-dose aspirin is an exception - many patients will have coexistent cardiovascular disease and the benefits of taking aspirin easily outweigh the risks
**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

<table>
<thead>
<tr>
<th>Class</th>
<th>Examples</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ia</td>
<td>Quinidine, Procainamide, Disopyramide</td>
<td>Block sodium channels&lt;br&gt;Increases AP duration&lt;br&gt;Notes:&lt;br&gt;Quinidine toxicity causes cinchonism (headache, tinnitus, thrombocytopaenia)&lt;br&gt;Procainamide may cause drug-induced lupus</td>
</tr>
<tr>
<td>Ib</td>
<td>Lidocaine, Mexiletine, Tocainide</td>
<td>Block sodium channels&lt;br&gt;Decreases AP duration</td>
</tr>
<tr>
<td>Ic</td>
<td>Flecaainide, Encainide, Propafenone</td>
<td>Block sodium channels&lt;br&gt;No effect on AP duration</td>
</tr>
<tr>
<td>II</td>
<td>Propranolol, Atenolol, Bisoprolol, Metoprolol</td>
<td>Beta-adrenoceptor antagonists</td>
</tr>
<tr>
<td>III</td>
<td>Amiodarone, Sotalol, Ibutilide, Bretylum</td>
<td>Block potassium channels</td>
</tr>
<tr>
<td>IV</td>
<td>Verapamil, Diltiazem</td>
<td>Calcium channel blockers</td>
</tr>
</tbody>
</table>
**Adenosine**

**Mechanism of action**

- causes transient heart block in the AV node
- agonist of the A1 receptor which inhibits adenyl cyclase thus reducing cAMP and causing hyperpolarization by increasing outward potassium flux
- adenosine has a very short half-life of about 8-10 seconds

**Adverse effects**

- transient facial flushing and a choking sensation, where patients often clutch their chest
- chest pain
- bronchospasm
- can enhance conduction down accessory pathways, resulting in increased ventricular rate (e.g. WPW syndrome)

---

**Flecainide**

Flecainide is a Vaughan Williams class 1c antiarrhythmic. It slows conduction of the action potential by acting as a potent sodium channel blocker. This may be reflected by widening of the QRS complex and prolongation of the PR interval

The Cardiac Arrhythmia Suppression Trial (CAST, 1989) investigated the use of agents to treat asymptomatic or mildly symptomatic premature ventricular complexes (PVCs) post myocardial infarction. The hypothesis was that this would reduce deaths from ventricular arrhythmias. Flecainide was actually shown to increase mortality post myocardial infarction and is therefore contraindicated in this situation

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

Adverse effects

• negatively inotropic
• bradycardia
• proarrhythmic
• oral paraesthesia
• visual disturbances

**Amiodarone:**

*Amiodarone - MOA: blocks potassium channels*

is a class III antiarrhythmic agent used in the treatment of both atrial and ventricular tachycardias. The main mechanism of action is by blocking potassium channels which inhibits repolarisation and hence prolongs the action potential. Amiodarone also has other actions such as blocking sodium channels (a class I-a effect)

The **use of amiodarone is limited** by a number of factors

- Long half-life (20-100 days)
- 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. ↓ metabolism of warfarin = P450 inhibtor
- Numerous long-term adverse effects (see below)

**Monitoring** of patients taking amiodarone

- TFT, LFT, U&E, CXR prior to treatment. **U&E to check hypokalemia**
- TFT, LFT every 6 months

**Indications**
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).

**Amiodarone: adverse effects**

Amiodarone is associated with a wide variety of adverse effects.

- thyroid dysfunction: both hypothyroidism and hyperthyroidism
  - Amiodarone blocks the peripheral conversion of thyroxine (T4) to triiodothyronine (T3) ➔ hypo
  - It is also a potential source of large amounts of inorganic iodine ➔ hyper

- **Corneal deposits**: present in most patients, rarely interfere with vision, becomes manifest by the presence of night-time visual glare, noticed while driving, usually reversible on withdrawal of drug
  - pulmonary fibrosis/pneumonitis
  - liver cirrhosis/hepatitis
  - peripheral neuropathy, myopathy
  - photosensitivity
  - 'slate-grey' appearance: Skin sensitivity ➔ can be prevented by using a sun block

**Skin deposits result in photodermatitis and a greyish-blue discoloration on sun-exposed areas**

- prolonged QT interval
- thrombophlebitis and injection site reactions
- bradycardia

**Important drug interactions of amiodarone include:**

- decreased metabolism of warfarin, therefore increased INR
- increased digoxin levels

---

**Amiodarone and the thyroid gland**

Around 1 in 6 patients taking amiodarone develop thyroid dysfunction

**Amiodarone-induced hypothyroidism**
The pathophysiology of amiodarone-induced hypothyroidism (AIH) is thought to be due to the high iodine content of amiodarone causing a Wolff-Chaikoff effect*.

Amiodarone may be continued if this is desirable.

(Normal T4, low ↓ T3, high ↑ TSH) ➔ These results are typical of amiodarone-induced hypothyroidism which inhibits the peripheral conversion of T4 to T3.

Amiodarone-induced thyrotoxicosis

Amiodarone-induced thyrotoxicosis (AIT) may be divided into two types:

Differentiating between the two forms of Amiodarone-Induced Thyrotoxicosis (AIT)

<table>
<thead>
<tr>
<th></th>
<th>AIT type 1</th>
<th>AIT type 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epidemiology</td>
<td>Most often seen in iodine-deficient areas.</td>
<td>most common in Europe and North America</td>
</tr>
<tr>
<td>Pathophysiology</td>
<td>Amiodarone contains ↑ iodine --&gt; ↑ thyroid hormone synthesis</td>
<td>Amiodarone-related destructive thyroiditis</td>
</tr>
<tr>
<td>history</td>
<td>Occurs in patients with underlying thyroid pathology, such as a nodular goitre or Graves disease.</td>
<td>Occurs in patients without underlying thyroid disease.</td>
</tr>
<tr>
<td>Goitre</td>
<td>Present</td>
<td>Absent</td>
</tr>
<tr>
<td>Color Doppler</td>
<td>↑ Blood flow</td>
<td>↓ Blood flow</td>
</tr>
<tr>
<td>iodine-131 uptake scan</td>
<td>normal or high</td>
<td>minimal or none</td>
</tr>
<tr>
<td>IL-6 levels</td>
<td>highest</td>
<td>-</td>
</tr>
<tr>
<td>Management</td>
<td>Carbimazole or potassium perchlorate</td>
<td>Corticosteroids ± Antithyroid</td>
</tr>
</tbody>
</table>

Unlike in AIH, amiodarone should be stopped if possible in patients who develop AIT.

The presence of markedly elevated serum IL-6 concentrations and low thyroidal radioiodine uptake (RAIU) values in patients with AIT without underlying thyroid disease suggests the presence of amiodarone-induced thyroiditis as the etiology of thyrotoxicosis.

Treatment of AIT

- Mild amiodarone-induced hyperthyroidism can resolve spontaneously on stopping amiodarone. However, the majority of cases require treatment.
- Type 1 is usually treated with a thionamide, but potassium perchlorate and lithium carbonate can be used.
Type 2 cases are treated with glucocorticoids, usually prednisolone, which are weaned over 2-3 months.

*an autoregulatory phenomenon where thyroxine formation is inhibited due to high levels of circulating iodide

---

**Aspirin**

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

- 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).
- 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*.
- Two recent trials (the Aspirin for Asymptomatic Atherosclerosis and the Antithrombotic Trialists Collaboration) have cast doubt on the use of aspirin in primary prevention of cardiovascular disease. Guidelines have not yet changed to reflect this.
- However the Medicines and Healthcare products Regulatory Agency (MHRA) issued a drug safety update in January 2010 reminding prescribers that aspirin is not licensed for primary prevention.

**What do the current guidelines recommend?**

- first-line for patients with ischaemic heart disease

**Potentiates**

- oral hypoglycaemics
- warfarin
- steroids

**In hypersensitive patients aspirin can cause:**

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

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 whilst later the direct acid effects of salicylates (combined with acute renal failure) may lead to an acidosis. In children metabolic acidosis tends to predominate. The metabolic acidosis can increase the transfer of salicylates across the blood-brain barrier, thereby increasing CNS toxicity.

Features

- hyperventilation (centrally stimulates respiration)
- tinnitus: typically occurs at plasma salicylate concentrations above 400-500 mg/l
- lethargy
- sweating, pyrexia*
- nausea/vomiting
- hyperglycaemia and hypoglycaemia: Hypoglycaemia is commonly seen in children but not in adults
- seizures
- coma

Aspirin overdose

- Aspirin - early features:
  - vomiting
  - dehydration
  - hyperventilation
  - tinnitus
  - vertigo
  - sweating
  - slight pyrexia
  - respiratory alkalosis, due to direct stimulation of the central respiratory centres
- Aspirin - later features:
  - metabolic acidosis
  - hyper- or hypoglycaemia may occur
Treatment

- general (ABC, charcoal) **Multi-dose activated charcoal may be indicated**
- urinary alkalinization
- haemodialysis

Indications for haemodialysis in salicylate overdose

- serum concentration > 700mg/L
- metabolic acidosis resistant to treatment
- acute renal failure
- pulmonary oedema
- seizures
- coma

*salicylates cause the uncoupling of oxidative phosphorylation leading to decreased adenosine triphosphate production, increased oxygen consumption and increased carbon dioxide and heat production

**Other antiplatelet agents**

**Dipyridamole**
Dipyridamole is an antiplatelet mainly used in combination with aspirin after an ischaemic stroke or transient ischaemic attack.

**Mechanism of action**

- inhibits phosphodiesterase, elevating platelet cAMP levels which in turn reduce intracellular calcium levels
- other actions include reducing cellular uptake of adenosine and inhibition of thromboxane synthase

- **Dipyridamole is a weak antiplatelet agent that acts by increasing the cellular concentration of cyclic adenosine monophosphate (cAMP)**
- **It inhibits the phosphodiesterase enzyme**, which converts cAMP to inactive 5’ AMP
- Elevated levels of cAMP and cyclic guanosine monophosphate (cGMP) inhibit activation and aggregation of platelets
Clopido
grel \textbf{(Inhibition of the platelet ADP receptor)}

- The antiplatelet effect of clopidogrel, like ticlopidine, results from antagonism of a platelet ADP receptor, P2T, resulting in inhibition of platelet activation.
- P2Y12 is an adenosine diphosphate (ADP) dependent receptor involved in platelet aggregation which is inhibited by clopidogrel.
- This antagonism is non-competitive, irreversible and results in 50-70% inhibition of fibrinogen binding.
- Regardless of the mechanism of activation, the final common pathway for platelet aggregation is the cross-linking of platelets through fibrinogen.

\textbf{Abciximab}

- Abciximab is a humanised monoclonal antibody.
- It is a selective GPIIb-IIIa receptor antagonist.

\textbf{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.

*NICE now recommend clopidogrel first-line following an ischaemic stroke and for peripheral arterial disease. For TIAs the situation is more complex. Recent Royal College of Physician (RCP) guidelines support the use of clopidogrel in TIAs. However the older NICE guidelines still recommend aspirin + dipyridamole - a position the RCP state is 'illogical'.

\textbf{Adrenaline}

\textbf{Adrenaline induced ischemia - phentolamine}

Adrenaline is a sympathomimetic amine with both alpha and beta adrenergic stimulating properties. The $\beta$-effect will cause significant tachycardia.

\textbf{Indications}

- anaphylaxis
- cardiac arrest

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.

**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**

- 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.

**Angiotensin-converting enzyme (ACE) inhibitors**

ACEi are now the established first-line treatment in younger patients with hypertension and are also extensively used to treat heart failure.
They are known to be less effective in treating hypertensive Afro-Caribbean patients. ACE inhibitors are also used to treat diabetic nephropathy and have a role in secondary prevention of IHD.

**Mechanism of action:**

- Inhibit the conversion angiotensin I to angiotensin II

**Side-effects:**

- Cough: occurs in around 15% of patients and may occur up to a year after starting treatment.
- Thought to be due to increased bradykinin levels
- Angioedema: may occur up to a year after starting treatment
- Hyperkalaemia
- 1st-dose hypotension: more common in patients taking diuretics

**Mechanism responsible for ACE-induced cough**

- The enzyme ACE is also responsible for the metabolism of bradykinin in mast cells.
- The accumulation of this substance is responsible for the cough found in up to 30% of subjects taking ACE-inhibitors.
- This phenomenon is not seen in subjects taking angiotensin receptor blockers such as losartan.

**Interaction:**

- 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.

**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
Monitoring

- Urea and electrolytes should be checked before treatment is initiated and after increasing dose.
- 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.

Other notes

**Enalapril is a prodrug for enalaprat, the active agent**

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**Adrenoceptor antagonists**

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

**Alpha antagonists**

- alpha-1: doxazosin
- 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.

**α-Selective antagonists (doxazocin)** cause → orthostatic hypotension

**Beta antagonists**

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

**Carvedilol and labetalol are mixed alpha and beta antagonists**

**Beta-blockers**

Beta-blockers are an important class of drug used mainly in the management of cardiovascular disorders.
3 Generations of beta-blockers

<table>
<thead>
<tr>
<th>Properties</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st Generation</td>
<td>Propanolol, Timolol, Pindolol, Nadolol, Sotalol</td>
</tr>
<tr>
<td>Non-selective</td>
<td></td>
</tr>
<tr>
<td>No vasodilatation</td>
<td></td>
</tr>
<tr>
<td>2nd Generation</td>
<td>Atenolol, Bisoprolol, Metoprolol</td>
</tr>
<tr>
<td>β1-selective without</td>
<td></td>
</tr>
<tr>
<td>vasodilatation</td>
<td>Nebivolol, Acebutolol</td>
</tr>
<tr>
<td>β1-selective with</td>
<td></td>
</tr>
<tr>
<td>vasodilatation</td>
<td></td>
</tr>
<tr>
<td>3rd Generation</td>
<td>Carvedilol, Bucindolol</td>
</tr>
<tr>
<td>Non-selective with</td>
<td></td>
</tr>
<tr>
<td>vasodilatation</td>
<td></td>
</tr>
</tbody>
</table>

Indications

- angina
- post-myocardial infarction
- heart failure: beta-blockers were previously avoided in heart failure but 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 (refs in DTB article).
- 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 and is not associated with drowsiness/sleep disturbance like the lipid-soluble beta-blockers.
  - Atenolol is a cardioselective β-receptor antagonist, but still has some (32-antagonism and is therefore contraindicated in asthma.

- **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 and may be associated with a lower incidence of erectile dysfunction compared with other β-blocking agents

- **Bisoprolol: the most cardio-selective beta-blocker**

- **Metoprolol: is the most lipid-soluble and therefore has the largest volume of distribution**
  - the increased lipid solubility is associated with 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.

<table>
<thead>
<tr>
<th>Carvedilol</th>
<th>Bisoprolol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not β1- selective</td>
<td>Highly β1- selective</td>
</tr>
<tr>
<td>Vasodilatation due to α-1- blockade</td>
<td>No α-1- blocking activity</td>
</tr>
<tr>
<td>Lipids effects</td>
<td>Lipid profile almost not affected</td>
</tr>
<tr>
<td>Positive lipid effect → ↑↑HDL &amp; ↓↓LDL</td>
<td></td>
</tr>
<tr>
<td>Negative lipid effect → ↑↑ cholesterol, TG, VLDL</td>
<td></td>
</tr>
<tr>
<td>Oral bioavailability of digoxin increased</td>
<td>No interaction with other CV drugs known</td>
</tr>
<tr>
<td>Sensitive to liver enzyme induction</td>
<td>Not sensitive to liver enzyme induction</td>
</tr>
<tr>
<td>Extensive metabolism in the liver (CYP2D6)(dose adjustment in liver impairment)</td>
<td>No dose adjustment required</td>
</tr>
</tbody>
</table>

**Side-effects**

- bronchospasm
- cold peripheries
β-Blockers cause a rise in peripheral vascular resistance due to the unopposed α-adrenoceptor effects (vasoconstriction)

- Fatigue => 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

β-blocker overdose management: atropine + glucagon

Features

- bradycardia
- hypotension
- heart failure
- syncope

Management

- if bradycardic then atropine
- in resistant cases glucagon may be used

- 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 are primarily used in the management of cardiovascular disease. Voltage-gated calcium channels are present in myocardial cells, cells of the conduction system and those of the vascular smooth muscle. 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.

<table>
<thead>
<tr>
<th>Examples</th>
<th>Indications &amp; notes</th>
<th>Side-effects and cautions</th>
</tr>
</thead>
</table>
| Verapamil | Angina, hypertension, arrhythmias  
Highly negatively inotropic  
Should not be given with beta-blockers as may cause heart block | Heart failure, constipation, hypotension, bradycardia, flushing |
| Diltiazem | Angina, hypertension  
Less negatively inotropic than verapamil but caution should still be exercised when patients have heart failure or are taking beta-blockers | Hypotension, bradycardia, heart failure, ankle swelling |
| Nifedipine, amlodipine, felodipine (dihydropyridines) | Hypertension, angina, Raynaud's  
Affects the peripheral vascular smooth muscle more than the myocardium and therefore do not result in worsening of heart failure | Flushing, headache, ankle swelling |
**Bosentan**

- Bosentan is a competitive antagonist of **both** endothelin-A (ETa) and endothelin-B (ETb) receptors, leading to falls in both pulmonary and systemic vascular resistances without an increase in heart rate.
- Effective in patients with pulmonary arterial hypertension.
- **Common unwanted effects** include:
  - flushing,
  - hypotension,
  - dyspepsia,
  - and fatigue.
  - Haemoglobin concentrations can fall by up to 1 g/dl during bosentan treatment.
  - 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**

- Nicorandil is an activator of ATP-dependent potassium channels.
- Its effects are to cause venodilatation, due to the relaxation of smooth muscle in veins, leading to reduced ventricular filling pressures and dilatation of the coronary arterioles.
- **Side effects**
  - The most common unwanted effect is headache (~35% of patients), which appears to be dose-dependent and resolves with continued treatment.
  - Other unwanted effects include oral ulceration, flushing and gastrointestinal disturbances.
- 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 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**

**Mechanism of action**

- decreases conduction through the atroventricular 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

Digoxin follows first order kinetics and has a half life of 1.6 days in a patient with normal renal function.

Sixty five per cent of the drug absorbed remains in the system after one day.

Subsequent doses gradually accumulate until a steady state is achieved after four to five days.

**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.
**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.

**the mechanism of action leading to tachy-arrhythmias in digoxin toxicity → Inhibition of the sodium pump**

**Features**

- generally unwell, lethargy, nausea & vomiting, anorexia, confusion, yellow-green vision
- arrhythmias (e.g. AV block, bradycardia)

**Precipitating factors**

- classically: hypokalaemia*
- increasing age
- renal failure
- myocardial ischaemia
- hypomagnesaemia, hypercalcaemia, hypernatraemia, acidosis
- hypoalbuminaemia
- hypothermia
- hypothyroidism
- 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

**Management**

- Activated charcoal if presented within 1 h of an overdose
- Digibind
- correct arrhythmias
- monitor potassium

**Digoxin-specific antibodies (SE → Serum sickness)**

- Indications for digoxin-specific antibodies include:
  - **Hyperkalaemia** (if not respond to insulin-dextrose infusions)
  - **Tachyarrhythmias** with hypotension and bradycardia with hypotension that do not respond to atropine treatment. If digoxin-specific antibodies not available → Amiodarone or phenytoin
*hyperkalaemia may also worsen digoxin toxicity, although this is very small print

---

**Diuretics**

- 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.
- 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.
- Most diuretics act by inhibiting sodium reabsorption in the renal tubules.
- The loop diuretics **furosemide and bumetanide** inhibit Na+/K+/Cl- co-transport in the ascending limb of Henle’s loop.
- The **thiazide** diuretics inhibit Na+/Cl- co-transport in the proximal segment of the distal convoluted tubule.

---

**Loop diuretics**

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**

- hypotension
- hyponatraemia
- hypokalaemia
- hypochloraeemic alkalosis
- ototoxicity
- hypocalcaemia
- renal impairment (from dehydration + direct toxic effect)
- hyperglycaemia (less common than with thiazides)
- gout
Explanation of response 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. In this case scenario, however, furosemide is poorly absorbed from the gut.

- Intravenous furosemide would have a more pronounced effect on the loop of Henle due to increased bioavailability of the drug when given intravenously due to poor absorption secondary to gut oedema.

Bendroflumethiazide

- Bendroflumethiazide (bendrofluazide) is a thiazide diuretic which works by inhibiting sodium absorption at the beginning of the distal convoluted tubule (DCT).
- 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.

Common adverse effects

Bendroflumethiazide - mechanism of Hypokalemia:

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

- dehydration
- postural hypotension
- hyponatraemia, hypokalaemia, hypercalcaemia
- gout
- impaired glucose tolerance
- impotence
Rare adverse effects

- thrombocytopenia
- agranulocytosis
- photosensitivity rash
- pancreatitis

Other notes

- Thiazide diuretics may be associated with hypochloraemic alkalosis
- Hypokalaemia intensifies the effect of digitalis on cardiac muscle and treatment with digitalis or its glycosides may have to be temporarily suspended.
- Patients with cirrhosis of the liver are particularly at risk from hypokalaemia.
- Hypomagnesaemia has also occurred.

Aliskiren → Direct renin inhibitor

- Represents the first new class of drug available in over a decade for the treatment of hypertension.
- Aliskiren binds to the active site of the renin molecule, blocking angiotensinogen cleavage, thus, preventing the formation of angiotensin I.
- Clinical studies have demonstrated at least equivalent blood pressure lowering efficacy compared with existing drugs with a favourable side effect profile.

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
Methyldopa ➔ not utilised in a patient with abnormal LFTs.

Nicorandil ➔ acts through the opening of potassium channels

Nicorandil is a potent potassium channel activator. 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).

Proto-oncogene stimulation

- β-Agonists and angiotensin II ➔ augment proto-oncogene expression, ➔ stimulate protein synthesis and induce the synthesis of fetal forms of actin and myosin, ➔ leading to hypertrophy of smooth muscle
- Thyroxine acts directly via nuclear receptors to regulate myosin heavy-chain gene transcription

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.
- Other proposed mechanisms include 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
In most individuals a plasma theophylline concentration of between 10 and 20 mg/l is required for satisfactory bronchodilatation.

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

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

**Factors increasing the plasma theophylline concentration:**
- heart failure
- cirrhosis
- viral infections
- increased age (the elderly)
- drugs that inhibit its metabolism (eg *erythromycin*)

**Factors decreasing the plasma theophylline concentration:**
- smoking
- chronic alcoholism without cirrhosis
- drugs that induce liver metabolism

**Theophylline poisoning**

*Theophylline has a narrow therapeutic window and needs close monitoring of its serum level to avoid toxicity*

**Features**
- acidosis, hypokalaemia and hyperglycaemia
- vomiting
- tachycardia, arrhythmias
- seizures

Symptoms of toxicity may be delayed following the ingestion of sustained-release preparations for up to 48 h.

**Management**
- activated charcoal
- charcoal haemoperfusion is preferable to haemodialysis

---

**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 and dosing**
- 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
- 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
Salmeterol → may cause paradoxical bronchospasm

**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:**

- nausea
- diarrhoea
- flushing
- hypertension
- confusion
- coma
- loss of tendon reflexes

**Smoking cessation**

NICE released guidance in 2008 on the management of smoking cessation. General points include:

- patients should be offered nicotine replacement therapy (NRT), varenicline or bupropion - NICE state that clinicians should not favour one medication over another
- NRT, varenicline or bupropion should normally be prescribed as part of a commitment to stop smoking on or before a particular date (target stop date)
- prescription of NRT, varenicline or bupropion should be sufficient to last only until 2 weeks after the target stop date. Normally, this will be after 2 weeks of NRT therapy, and 3-4 weeks for varenicline and bupropion, to allow for the different methods of administration and mode of action. Further prescriptions should be given only to people who have demonstrated that their quit attempt is continuing
- if unsuccessful using NRT, varenicline or bupropion, do not offer a repeat prescription within 6 months unless special circumstances have intervened
- do not offer NRT, varenicline or bupropion in any combination
### Nicotine replacement therapy

- adverse effects include nausea & vomiting, headaches and flu-like symptoms
- NICE recommend offering a combination of nicotine patches and another form of NRT (such as gum, inhalator, lozenge or nasal spray) to people who show a high level of dependence on nicotine or who have found single forms of NRT inadequate in the past

<table>
<thead>
<tr>
<th>NRT</th>
<th>Varenicline</th>
<th>Bupropion</th>
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<tbody>
<tr>
<td>Nicotine replacement therapy</td>
<td>Nicotinic receptor partial agonist</td>
<td>Norepinephrine and dopamine reuptake inhibitor, and nicotinic antagonist</td>
</tr>
<tr>
<td>• Adverse effects include nausea &amp; vomiting, headaches and flu-like symptoms</td>
<td>• Should be started 1 week before the patient’s target date to stop</td>
<td>• Should be started 1 to 2 weeks before target date.</td>
</tr>
<tr>
<td>• Nice recommend offering a combination of nicotine patches and another form of NRT (such as gum, inhalator, lozenge or nasal spray) to people who show a high level of dependence on nicotine or who have found single forms of NRT inadequate in the past</td>
<td>• The recommended course of is 12 weeks (but patients should be monitored regularly and treatment only continued if not smoking)</td>
<td>• Small risk of seizures (1:1,000)</td>
</tr>
<tr>
<td></td>
<td>• Has been shown in studies to be more effective than bupropion</td>
<td>• Bupropion should not be prescribed to individuals with epilepsy or other conditions that lower the seizure threshold, such as alcohol or benzodiazepine withdrawal, anorexia nervosa, bulimia, or active brain tumors. It should be avoided in individuals who are also taking MAOIs. When switching from MAOIs to bupropion, it is important to include a washout period of 2 weeks. Also, pregnancy and breastfeeding are contraindications</td>
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<tr>
<td></td>
<td>• Nausea is the most common adverse effect. Other include headache, insomnia, abnormal dreams</td>
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<td></td>
<td>• Varenicline should be used with caution in patients with a history of depression or self-harm.</td>
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<td></td>
<td>• Contraindicated in pregnancy and breastfeeding</td>
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**Notes & Notes for mrcp**

Dr. Yousif Abdallah Hamad
Varenicline

- a nicotinic receptor partial agonist
- should be started 1 week before the patients target date to stop
- the recommended course of treatment is 12 weeks (but patients should be monitored regularly and treatment only continued if not smoking)
- has been shown in studies to be more effective than bupropion
- nausea is the most common adverse effect. Other common problems include headache, insomnia, abnormal dreams
- varenicline should be used with caution in patients with a history of depression or self-harm. There are ongoing studies looking at the risk of suicidal behaviour in patients taking varenicline
- contraindicated in pregnancy and breast feeding

Bupropion

- a norepinephrine and dopamine reuptake inhibitor, and nicotinic antagonist
- should be started 1 to 2 weeks before the patients target date to stop
- small risk of seizures (1 in 1,000)
- Contraindicated in epilepsy, pregnancy and breast feeding. Having an eating disorder is a relative contraindication. **Bupropion: contraindicated in epilepsy**

Pregnant women

NICE recommended in 2010 that all pregnant women should be tested for smoking using carbon monoxide detectors, partly because 'some women find it difficult to say that they smoke because the pressure not to smoke during pregnancy is so intense.'. All women who smoke, or have stopped smoking within the last 2 weeks, or those with a CO reading of 7 ppm or above should be referred to NHS Stop Smoking Services.

Interventions

- the first-line interventions in pregnancy should be cognitive behaviour therapy, motivational interviewing or structured self-help and support from NHS Stop Smoking Services
- the evidence for the use of NRT in pregnancy is mixed but it is often used if the above measures failure. There is no evidence that it affects the child's birthweight. Pregnant women should remove the patches before going to bed
- as mentioned above, varenicline and bupropion are contraindicated
**CNS & Psychiatric drugs**

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**Anti-convulsants**

**Remarkable side effects of other anti-epileptic drugs are:**

- SIADH and rash (carbamazepine)
- Liver toxicity (sodium valproate)
- Severe rash (lamotrigine)
- Retinal damage (vigabatrin)
- Aplastic anaemia (felbamate)

**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.
- Ethosuximide is a suitable treatment for absence and myoclonic attacks in children, not for partial epilepsy in adults.
- If a patient is planning on pregnancy then registry studies suggest that lamotrigine would be the best choice.

- Sodium valproate → neural tube defects in the fetus
- Phenytin → fetal hydantoin syndrome with facial dysmorphism
- Primidone and phenobarbital → withdrawal symptoms in the newborn

**Percentage of Congenital malformations associated with Antiepileptics**

- Valproate → 6%
  - **Valproate should be avoided in pregnancy if possible**
- Topiramate → 4.3%
- Phenytoin → 3.5%
- Carbamazepine → 2.5%
- General population → 1.5%
NICE guidance suggests that **phenytoin** should be avoided in women of child-bearing age because of the risk of congenital malformations. This leaves **lamotrigine** as the most appropriate choice:

- it does not affect the effectiveness of the oral contraceptive pill
- have a significantly **lower risk** of major and minor malformations compared with sodium valproate

**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
- Whilst **Carbamazepine** is a first line option under NICE guidance, it is a potent enzyme inducer and therefore certainly can’t be used in combination with the pill

---

**Sodium valproate**

Sodium valproate is used in the management of epilepsy and is first line therapy for generalised seizures. It works by increasing GABA activity.

**Adverse effects**

- gastrointestinal: nausea
- increased appetite and weight gain
- alopecia: regrowth may be curly (note that phenytoin → hirsutism while valporate → alopecia)
- ataxia
- tremor
- hepatitis
- pancreatitis
- thrombocytopenia
- teratogenic
- hyponatraemia
- Sodium valproate has been associated with the development of polycystic ovarian (PCOS) syndrome
**Phenytoin**
Phenytoin is used to in the management of seizures.

**Mechanism of action**

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

Phenytoin is associated with a large number of adverse effects. These may be divided into acute, chronic, idiosyncratic and teratogenic

**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*
- 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.
- Cimetidine increases the efficacy of phenytoin by reducing its hepatic metabolism
- Sucralfate may decrease the pharmacological effects of phenytoin when administered concurrently

In renal failure

Renal failure $\rightarrow \downarrow$ drug affinity for protein binding $\rightarrow \uparrow$ free drug $\rightarrow$ toxicity (drug level may be within the therapeutic range)

- Renal failure, a state in which drugs that are usually highly protein bound, such as phenytoin, lose some of their affinity for protein binding. This results in increased availability of free drug at any given dose, which then increases the risk of toxicity.
- Because laboratory assays for phenytoin usually measure total drug concentration, this gives a degree of false reassurance.
- 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.

*although not listed in the BNF

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

Carbamazepine

Carbamazepine is chemically similar to the tricyclic antidepressant drugs. It is 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
- leucopenia and agranulocytosis
- syndrome of inappropriate ADH secretion

**Carbamazine overdose presents with:**

- Drowsiness
- Slurred speech
- Ataxia
- Hallucinations
- Nausea
- Vomiting
- Tremor
- Blurred vision
- Seizures
- Oliguria, and
- Bullous skin lesions.

Valproate in combination with carbamazepine has been shown to reduce endogenous T4 concentrations, but not in isolation.

**Contraindications of carbamazepine include:**
- atrioventricular (AV) conduction abnormalities
- porphyria
- a history of bone marrow depression

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**Vigabatrin**

**Key points**

- 40% of patients develop visual field defects, which may be irreversible
- visual fields should be checked every 6 months
- Vigabatrin is the drug of choice for infantile spasms
- is not generally used outside the situation of infantile spasms
- **Adverse effects include:**
  - aggression
  - alopecia
  - retinal atrophy
  - reduced peripheral vision

---

**Gabapentin**

- does not induce cytochrome P450 unlike other anticonvulsants such as phenytoin and phenobarbitone.
- Gabapentin is no use in petit mal and is used for add-on therapy in partial or generalised seizures.
- Requires dose adjustment in renal disease

**Other anti-convulsants:**

- Vigabatrin may cause Visual field defects, which may be irreversible.

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**Levetiracetam (Keppra)**

- Is an adjunctive treatment for partial seizures with or without secondary generalisation.
- Its mechanism of action is unknown.
- It is rapidly absorbed orally, it does not affect hepatic enzymes but dose reduction is required in renal failure.
- The drug appears to be well tolerated with few side effects.

---

**The anticholinergic syndrome**

**Aetiology**
The anticholinergic syndrome is most commonly caused by:
- tricyclic antidepressants
- atropine
- H-1-antihistamines

**Signs and symptoms**
Common symptoms include:
- hot, dry skin
- hypertension
- tachycardia
- dilated pupils
Agitated delirium can also occur

**Management** → supportive

---

**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)**
- Benztropine

Dopamine receptor agonists

Indications

- Parkinson's disease
- prolactinoma/galactorrhoea
- cyclical breast disease
- acromegaly

Currently accepted practice in the management of patients with Parkinson's disease is to delay treatment until the onset of disabling symptoms and then to introduce a dopamine receptor agonist. If the patient is elderly, L-dopa is sometimes used as an initial treatment.

Overview

- e.g. bromocriptine, ropinirole, cabergoline, 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.

**Adverse effects**

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

*pergolide was withdrawn from the US market in March 2007 due to concern regarding increased incidence of valvular dysfunction

---

**Dopa-decarboxylase inhibitors**

- Prevent the systemic metabolism of levodopa which leads to higher (CNS) levels. The effect itself is not enhanced, only the concentration of available levodopa.
- **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.

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**Antidepressants**

- 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.

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**Tricyclic overdose**

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

Features of severe poisoning include:

- arrhythmias
- 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 $>100$ ms is associated with an increased risk of seizures whilst QRS $>160$ ms 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.
  - IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity
- arrhythmias: class 1a (e.g. Quinidine) and class lc 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

Amitriptyline

Many adverse effects of amitriptyline and similar tricyclic antidepressants are caused by their antimuscarinic actions.

**Antimuscarinic effects** are relatively common and occur before an antidepressant effect is obtained. They include:

- Dry mouth
- Constipation occasionally leading to paralytic ileus
- **Urinary retention**
- Blurred vision and disturbances in accommodation
- Increased intraocular pressure, and
- Hyperthermia.

Tolerance is often achieved if treatment is continued and 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** include:

- Drowsiness
- Headache
- Peripheral neuropathy
- Tremor
- Ataxia
- Epileptiform seizures
- Tinnitus, and
- Occasional 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.

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

Hypersensitivity reactions, such as urticaria and angioedema, and photosensitisation have been reported and, rarely, cholestatic jaundice and **blood disorders, including:**

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

**Endocrine effects** include testicular enlargement, gynaecomastia and breast enlargement, and galactorrhoea. Sexual dysfunction may also occur.

Changes in blood sugar concentrations may also occur, and, very occasionally, hyponatraemia associated with inappropriate secretion of antidiuretic hormone.

Other adverse effects that have been reported are increased appetite with weight gain (or occasionally anorexia with weight loss). Sweating may be a problem.

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**Monoamine oxidase 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

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

- citalopram (although see below re: QT interval) 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 for increased anxiety and agitation after starting a SSRI
- fluoxetine and paroxetine have a higher propensity for drug interactions

Citalopram and the QT interval

- the Medicines and Healthcare products Regulatory Agency (MHRA) released a warning on the use of citalopram in 2011
- it advised that 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

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.

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.

Discontinuation symptoms

Withdrawal of paroxetine can lead to deterioration in mood and cognition and orofacial dystonias

- increased mood change
- restlessness
- difficulty sleeping
- unsteadiness
- sweating
- gastrointestinal symptoms: pain, cramping, diarrhoea, vomiting
- paraesthesia

Lithium

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

- nausea/vomiting, diarrhoea
- fine tremor
- polyuria (secondary to nephrogenic diabetes insipidus)
- thyroid enlargement, may lead to hypothyroidism
- ECG: T wave flattening/inversion
- weight gain

Pregnancy

**Exposure to lithium in utero is associated with Ebstein's anomaly.**

Monitoring of patients on lithium therapy

- inadequate monitoring of patients taking lithium is common - NICE and the National Patient Safety Agency (NPSA) have issued guidance to try and address this. As a result it is often an exam hot topic
- 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 every 6 months
- patients should be issued with an information booklet, alert card and record book

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

**Lithium toxicity**

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

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. Lithium toxicity generally occurs following concentrations > 1.5 mmol/L.
Toxicity may be precipitated by dehydration, electrolyte imbalance, renal failure, and drugs.

**Half-life and drug level:**

**Example:** On admission the lithium level was 2.4 mmol/l; *After what period of time post admission is the lithium level likely to be approaching 0?*

- The half-life of lithium is around 20 h
- The level would be 1.2 mmol/l after 20 h, 0.6 mmol/l after 40 h, 0.3 mmol/l after 60 h and 0.15 mmol/l after 80 h

Drugs that may precipitate lithium toxicity include:

- diuretics (especially bendroflumethiazide),
- ACE inhibitors & ARB
- NSAIDs
- Metronidazole
- Tetracycline
- Phenytoin, and
- Ciclosporin
- Methyldopa

**Features of toxicity**

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

Tricyclic overdose may present with seizures but it does not typically cause a tremor.

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

**At levels of 1-2 mmol/L lithium toxicity** *Mild to moderate toxicity (levels less than 2 mmol/L)* results in:

- anorexia
- vomiting
- ataxia
- dysarthria
- blurring of vision
- coarse tremor
- diarrhoea
- drowsiness, and
- muscle weakness.

**Higher levels, result in severe toxicity (levels more than 2 mmol/L) which is characterised by:**

- circulatory failure
- coma
- convulsions
- hyper-reflexia
- oliguria
- psychosis, and
- death (in severe cases).

**Management**

- 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
- 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.**

**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
Ciclosporin

- trough levels immediately before dose

Digoxin

- at least 6 hrs post-dose

Phenytoin

- trough levels immediately before dose

---

**Antipsychotic**

Side effects

Antipsychotic medications, in particular the typical antipsychotics and risperidone, are known to elevate prolactin levels. This is due to their ability to block dopamine D2 receptors. By doing so they block dopamine's action on the pituitary. This reduces inhibition of prolactin secretion, thereby causing hyperprolactinaemia.

Symptoms of this include:

- amenorrhea
- galactorrhoea
- infertility
- loss of libido, and
- erectile dysfunction.

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**Atypical antipsychotics**

Atypical antipsychotics should now be used first-line in patients with schizophrenia, according to 2005 NICE guidelines. The main advantage of the atypical agents is a significant reduction in extra-
pyramidal side-effects.

**Adverse effects of atypical antipsychotics**

- weight gain
- clozapine is associated with agranulocytosis (see below)

The Medicines and Healthcare products Regulatory Agency has issued specific warnings when antipsychotics are used in elderly patients:

- increased risk of stroke (especially olanzapine and risperidone)
- increased risk of venous thromboembolism

**Examples of atypical antipsychotics**

- clozapine
- olanzapine
- risperidone
- quetiapine
- amisulpride

Clozapine, one of the first atypical agents to be developed, carries a significant risk of agranulocytosis and full blood count monitoring is therefore essential during treatment. For this reason clozapine should only be used in patients resistant to other antipsychotic medication.

**Adverse effects of clozapine**

- agranulocytosis (1%), neutropaenia (3%)
- reduced seizure threshold - can induce seizures in up to 3% of patients

---

**Clozapine** (antipsychotic agent)

- **Clozapine is associated with agranulocytosis** and granulocytopenia in approximately 1-2% of patients, which can result in fatal sepsis.
- **monitoring of all patients on this treatment is recommended**
- A white cell count with differential is checked **prior to treatment**
- then **weekly** for the first 18 weeks
- then **two weekly** from week 18 to 52
- and then **four weekly** after one year of clozapine with stable blood results.
- They are then checked for **four weeks after discontinuation of treatment**.

- Olanzapine has been associated with agranulocytosis in the form of case reports in the literature. However, unlike clozapine, this link is not well established.

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### Risperidone

- Risperidone is a novel antipsychotic belonging to the benzisoxazole derivative class
- **It is a high-affinity D2 and 5-HT-2 receptor antagonist**
- To a lesser extent, risperidone is also an antagonist at α2-adrenergic receptors, H1-histaminergic and α2-adrenergic receptors
- Common adverse effects include:
  - insomnia
  - agitation
  - anxiety
  - headache
  - Risperidone may also lead to impaired glucose tolerance, although the incidence of abnormalities in glucose metabolism is less than that seen with other antipsychotics

---

### Baclofen

- 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

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### Benzodiazepines

**Benzodiazepines antidote is flumazenil**
Benzodiazepines (lorazepam, diazepam, chlordiazepoxide) enhance the effect of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA).

**Indications**

- Sedation
- Hypnotic
- Anxiolytic
- Anticonvulsant
- Muscle relaxant

Patients commonly develop a tolerance and dependence to benzodiazepines and care should therefore be exercised on prescribing these drugs. The Committee on Safety of Medicines advises that benzodiazepines are only prescribed for a short period of time (2-4 weeks).

The BNF gives advice on how to withdraw a benzodiazepine. The dose should be withdrawn in steps of about 1/8 (range 1/10 to 1/4) of the daily dose every fortnight. A suggested protocol for patients experiencing difficulty is given:

- Switch patients to the equivalent dose of diazepam
- Reduce dose of diazepam every 2-3 weeks in steps of 2 or 2.5 mg
- Time needed for withdrawal can vary from 1 month to 1 year or more

If patients withdraw too quickly from benzodiazepines they may experience benzodiazepine withdrawal syndrome, a condition very similar to alcohol withdrawal syndrome. This may occur up to 3 weeks after stopping a long-acting drug. Features include:

- Insomnia
- Irritability
- Anxiety
- Tremor
- Loss of appetite
- Tinnitus
- Perspiration
- Perceptual disturbances
- Seizures

**Flumazenil**

- Flumazenil, a benzodiazepine antagonist, is used to reverse the central sedative effects of benzodiazepines after anaesthetic and similar procedures.
- Flumazenil has a shorter half-life than that of diazepam and midazolam and there is a risk that patients may become re-sedated - in which case a repeat dose of flumazenil should be given.

**Donepezil**

Donepezil is a cholinesterase inhibitor, and as such potentiates the actions of cholinergic neurones.

**Side-effects**

- GIT: nausea, vomiting or diarrhoea
- Cardiac: **bradycardia** and, rarely, AV block
- Bladder outflow obstruction
- Rarely associated with hepatitis

**Indication**

- Donepezil is usually prescribed in conjunction with continued cognitive assessment, with many specialists reassessing their patients Mini-Mental State Scores after 4-6 weeks of treatment.

**Other notes**

- Other cholinesterase inhibitors include rivastigmine and galantamine
- Memantine, an N-methyl-D-aspartate (NMDA)-receptor antagonist affects the transmission of glutamate; it is licensed for use in moderate to severe Alzheimer's disease.

**Anticholinergic drugs such as benzhexol remain the treatment of choice in parkinsonian tremor.**

**Memantine**

- Previous treatment options for Alzheimer's disease (AD) have employed cholinesterase inhibitors (eg tacrine, donepezil), but evidence shows that excessive activation of the
NMDA (N-methyl-D-aspartate) receptor may play a role in the pathogenesis of AD.

- **Memantine** is a novel NMDA-receptor antagonist. It has numerous **drug interactions**:  
  - Other NMDA-receptor antagonists (eg ketamine, amantadine): increased risk of psychosis  
  - Dopamine agonists, L-dopa and anticholinergics: enhanced effects  
  - Antispasmodics (eg baclofen): enhanced effects, as memantine has some antispasmodic effects  
  - Drugs excreted by cationic transporters in the kidney (eg quinine, cimetidine, ranitidine): reduced excretion, therefore higher plasma concentrations

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**Haloperidol** ➔ **contra-indicated in Lewy body dementia.**

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**Endocrinology drugs**

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**Insulin**

- It acts via a similar mechanism to cell surface receptors.
- Insulin binding to its receptor results in receptor autophosphorylation on tyrosine residues and the tyrosine phosphorylation of insulin receptor substrates (IRS-1, IRS-2 and IRS-3) by the insulin receptor tyrosine kinase.
- It is synthesised in the beta cells of the islets of Lagerhans.
- It causes an increased glucose-protein transport on the endoplasmic reticulum.

**Insulin glargine**

- in which situations does insulin glargine have the clearest advantage over isophane?
  - In patients with type-1 diabetes who have significant nocturnal hypoglycaemia on isophane

- NICE only recommends use of insulin glargine in patients - with type-2 diabetes - who have significant hypoglycaemia on isophane insulin

**Enzymes and insulin**

- **Insulin inhibits Pyruvate carboxylase**, an enzyme involved in gluconeogenesis
- Insulin stimulate glycogen synthetase ➔ increases glycogenesis in the liver and muscle
Insulin activates the hexose monophosphate (HMP) shunt by inducing the synthesis of glucose 6-phosphate dehydrogenase.

Both acetyl-CoA carboxylase and ATP citrate lyase are stimulated to increase the synthesis of fatty acids.

**Sulfonylureas**

Sulfonylureas are oral hypoglycaemic drugs used in the management of type 2 diabetes mellitus. They work by increasing pancreatic insulin secretion and hence are only effective if functional B-cells are present. On a molecular level they bind to an ATP-dependent K⁺(KₐTP) channel on the cell membrane of pancreatic beta cells. **Glibenclamide** blocks potassium channels.

**Common adverse effects**

- hypoglycaemic episodes (more common with long acting preparations such as chlorpropamide)
- weight gain

**Rarer adverse effects**

- syndrome of inappropriate ADH secretion
- bone marrow suppression
- liver damage (cholestatic)
- photosensitivity
- peripheral neuropathy

Sulfonylureas should be avoided in breast feeding and pregnancy.

**Interaction**

As a result of drug interaction hypoglycaemia may be potentiated when a sulfonylurea is used concurrently with agents such as:

- Long-acting sulfonamides
- Tuberculostatics
- Phenylbutazone
- Clofibrate
- Monoamine oxidase (MAO) inhibitors
- Coumarin derivatives
- Salicylates
- Probenecid
- Propranolol
- Cimetidine
- Disopyramide, and
- Angiotensin converting enzyme inhibitors.

Fluconazole has a low level of plasma protein binding and it is excreted by the kidney. However, it is also a potent inhibitor of CYP2C8 and CYP2C9 and can thus interact with gliclazide and other sulphonylureas (for example, glimepiride, glibenclamide, tolbutamide and glipizide).

Gliclazide is a sulphonylurea drug with an intermediate half life of around 11 hours. It is extensively metabolised within the liver by CYP2C9. Within the circulation, gliclazide is highly bound to plasma proteins, about 94%. Renal clearance accounts for only 4% of total drug clearance.

Therefore gliclazide action can be potentiated predominantly by two mechanisms:

- Displacement of the drug from plasma proteins to give more free (unbound) drug - some agents such as aspirin can do this, and
- Interference with the hepatic metabolism of the drug (e.g. fluconazole)

Metformin

- Metformin is indicated in patients who are overweight or obese, whose blood glucose is inadequately controlled with lifestyle interventions. It can also be first-line in patients who are not overweight.
- Gradual increases in the dose of metformin reduces the risk of side effects, and modified release preparations reduce the risk further.
- The dose should be reviewed if the creatinine excess 130 mmol/L or the eGFR is below 45, and stopped with a creatinine over 150 mmol/L or eGFR below 30.

Action of metformin in polycystic ovary syndrome ➔ increasing peripheral glucose uptake
Lowering serum insulin concentrations with metformin ameliorates hyperandrogenism by reduction of ovarian enzyme activity that results in ovarian androgen production.

Clinical studies have shown that metformin reduces insulin resistance and have demonstrated a fall in serum androgens, luteinising hormone and weight.

The reduced insulin resistance is associated with reduced insulin drive to the insulin sensitive ovary in polycystic ovarian syndrome and hence reduces androgen production.

### Adverse effects

- **vitamin B\(_{12}\) deficiency**
  - Long-term treatment with metformin increases the risk of vitamin B\(_{12}\) deficiency.
  - The possibility of metformin-associated B\(_{12}\) deficiency should be considered in patients on metformin who suffer cognitive impairment, peripheral neuropathy, subacute combined degeneration of the cord or anaemia.
  - Regular measurement of vitamin B\(_{12}\) concentrations during long term metformin treatment should be strongly considered.

### Drug interactions

- Alcohol intake → increases the risk of lactic acidosis in diabetic patients on metformin.

### Pioglitazone

- Pioglitazone, a **PPAR gamma agonist**, is an insulin sensitiser. It upregulates genes for enzymes which deal with the metabolism of free fatty acids.
  - lead to increased peripheral insulin sensitivity, and improve glucose uptake.
  - reduces HbA1c by between 1 and 1.3%.
  - raises HDL cholesterol by around 10%, and had modest effects on blood pressure and triglycerides.
- The main cytochrome P450 enzyme pathway responsible for pioglitazone metabolism is **CYP2C8**

- **Side effects**
  - **fluid retention** in 10% of patients, by means of an action on the collecting ducts of the kidney so promoting sodium and water retention. Is contraindicated in cardiac failure,
  - **reduction in bone mineral density**.

- Metformin also boosts insulin sensitivity, but pioglitazone has more effect on peripheral insulin resistance.
**Thiazolidinediones**
Thiazolidinediones are a new class of agents used in the treatment of type 2 diabetes mellitus. They are agonists to the PPAR-gamma receptor and reduce peripheral insulin resistance. Rosiglitazone was withdrawn in 2010 following concerns about the cardiovascular side-effect profile.

The PPAR-gamma receptor is an intracellular nuclear receptor. Its natural ligands are free fatty acids and it is thought to control adipocyte differentiation and function.

Adverse effects

- weight gain
- liver impairment: monitor LFTs
- fluid retention - therefore contraindicated in heart failure. The risk of fluid retention is increased if the patient also takes insulin
- recent studies have indicated an increased risk of fractures
- bladder cancer: recent studies have showed an increased risk of bladder cancer in patients taking pioglitazone (hazard ratio 2.64)

NICE guidance on thiazolidinediones

- only continue if there is a reduction of > 0.5 percentage points in HbA1c in 6 months

---

**Meglitinides (nateglinide and repaglinide)** → increase postprandial insulin release specifically

**Acarbose**
- has a modest effect on the absorption of sugars from the gut.
- inhibits intestinal α-glucosidase, which therefore delays the digestion and absorption of starch and sucrose
- main side effect → gastrointestinal disturbance → cause flatulence

**Carbimazole**
Carbimazole is used in the management of thyrotoxicosis. It is typically given in high doses for 6 weeks until the patient becomes euthyroid before being reduced.
Mechanism of action

- The active metabolite of carbimazole, methimazole, reduces the synthesis of new thyroid hormones by inhibiting the iodination of tyrosine
- Blocks thyroid peroxidase from coupling and iodinating the tyrosine residues on thyroglobulin (Inhibition of the iodination of tyrosine) → reducing thyroid hormone production
- It also has an immunosuppressive action leading to a reduction in serum thyroid-stimulating hormone (TSH) receptor antibody (TRAb) concentrations
- There is a subjective improvement within 10-14 days of starting carbimazole but euthyroid levels are reached only after 3-4 weeks, since the synthesis rather than the release of hormones is affected
- In contrast propylthiouracil as well as this central mechanism of action also has a peripheral action by inhibiting 5’-deiodinase which reduces peripheral conversion of T4 to T3

Adverse effects

- Agranulocytosis
- Crosses the placenta, but may be used in low doses during pregnancy (also Propylthiouracil does cross the placenta, although thyroxine does not)
- Neonatal hypothyroidism will occur in approximately 10% of babies, because carbimazole crosses the placenta and switches off the fetal thyroid axis. The goitre that occurs is transient and will disappear following delivery

Propylthiouracil (PTU) VS carbimazole

- Propylthiouracil (PTU) and carbimazole are derivatives of thiourea
- Both inhibit the organification of iodine at the thyroid gland as their major mechanism of action
- PTU, but not carbimazole, is an inhibitor of thyroxine to tri-iodothyronine, giving it a modest therapeutic advantage over the latter agent because it reduces the proportion of active thyroid hormone as well as reducing the total amount of T4
- Carbimazole is approximately 15 times as potent as PTU

Cautions

- Both PTU and carbimazole are excreted in very small quantities in breast milk, so breast feeding is not advised with either

Side-effects

- Thiourea derivatives have several side-effects including a maculopapular rash, hepatocellular damage and vasculitis
- The most serious side-effect of both agents is agranulocytosis, although it is more common to see a fall in, rather than total absence of, white cells
Hyperlipidaemia: mechanism of action and adverse effects

The following table compares the side-effects of drugs used in hyperlipidaemia:

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<thead>
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<th>Drugs</th>
<th>Mechanism of action</th>
<th>Adverse effects</th>
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</thead>
<tbody>
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<td>Statins</td>
<td>HMG CoA reductase inhibitors</td>
<td>Myositis, deranged LFTs</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Decreases cholesterol absorption in the small intestine</td>
<td>Headache</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Decreases hepatic VLDL secretion</td>
<td>Flushing, myositis</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Agonist of PPAR-alpha therefore increases lipoprotein lipase expression</td>
<td>Myositis, pruritus, cholestasis</td>
</tr>
<tr>
<td>Cholestyramine</td>
<td>Decreases bile acid reabsorption in the small intestine, upregulating the amount of cholesterol that is converted to bile acid</td>
<td>GI side-effects</td>
</tr>
</tbody>
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Statins

Statins inhibit HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis

<table>
<thead>
<tr>
<th>P450 inhibitors</th>
<th>Nicotinic acid</th>
<th>CK and myopathy</th>
<th>HDL levels</th>
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</table>

Statins inhibit the action of HMG-CoA reductase, the rate-limiting enzyme in hepatic cholesterol synthesis (→ Decreases hepatic cholesterol synthesis)

Adverse effects

- myopathy: includes myalgia, myositis, rhabdomyolysis and asymptomatic raised creatine kinase. Risks factors for myopathy include advanced age, female sex, low body mass index and presence of multisystem disease such as diabetes mellitus. Myopathy is more common in
lipophilic statins (simvastatin, atorvastatin) than relatively hydrophilic statins (rosuvastatin, pravastatin, fluvastatin)

- liver impairment: the 2014 NICE guidelines recommend checking LFTs at baseline, 3 months and 12 months. Treatment should be discontinued if serum transaminase concentrations rise to and persist at 3 times the upper limit of the reference range
- there is some evidence that statins may increase the risk of intracerebral haemorrhage in patients who've previously had a stroke. This effect is not seen in primary prevention. For this reason the Royal College of Physicians recommend avoiding statins in patients with a history of intracerebral haemorrhage

Who should receive a statin?

- all people with established cardiovascular disease (stroke, TIA, ischaemic heart disease, peripheral arterial disease)
- following the 2014 update, NICE recommend anyone with a 10-year cardiovascular risk >= 10%
- patients with type 2 diabetes mellitus should now be assessed using QRISK2 like other patients are, to determine whether they should be started on statins

Statins should be taken at night as this is when the majority of cholesterol synthesis takes place. This is especially true for simvastatin which has a shorter half-life than other statins

Current guidelines for lipid lowering*

<table>
<thead>
<tr>
<th></th>
<th>Total cholesterol (mmol/l)</th>
<th>LDL cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joint British Societies</td>
<td>&lt; 4.0</td>
<td>&lt; 2.0</td>
</tr>
<tr>
<td>National Service Framework for CHD</td>
<td>&lt; 5.0</td>
<td>&lt; 3.0</td>
</tr>
<tr>
<td>SIGN 2007</td>
<td>&lt; 5.0</td>
<td>&lt; 3.0</td>
</tr>
</tbody>
</table>
### Drugs and Adverse Effects

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins (HMG CoA reductase inhibitors)</td>
<td>Myositis, deranged LFTs</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>Headache</td>
</tr>
<tr>
<td>Nicotinic acid</td>
<td>Flushing, myositis</td>
</tr>
<tr>
<td>Fibrates</td>
<td>Myositis, pruritus, cholestasis</td>
</tr>
<tr>
<td>Anion-exchange resins</td>
<td>GI side-effects</td>
</tr>
</tbody>
</table>

### Interaction:

Statin-associated myopathy occurs in up to 5% of those treated with statins and may be exacerbated by the co-prescription of other drugs such as:

- calcium channel blockers
- macrolide antibiotics
- fibrates
- Amiodarone
- grapefruit juice. **Grapefruit juice significantly increases serum concentrations of some statins.** This is achieved by reducing the CYP3A4-mediated first-pass metabolism in the small intestine. Concomitant use of atorvastatin and large amounts of grapefruit juice should be avoided, or the dose of atorvastatin should be reduced accordingly. CYP3A4 is a member of the cytochrome P450 system.
- **Bergamottin is a constituent of grapefruit juice and is metabolised by the cytochrome p450 3A4 pathway.**

- Myopathy or rhabdomyolysis can quite easily be precipitated by the addition of these agents.

**Ezetimibe** → reduces the absorption of cholesterol through the gut.

Although its exact mechanism of action is unclear, it probably downregulates proteins in the brush border of enterocytes to reduce lipid absorption. Unlike bile acid sequestrants, ezetimibe is systemically absorbed.

Ezetimibe is a useful medication for patients who are:

- Intolerant of statins
- Failing targets on statins alone
- Have a history of serious adverse events with statin use.
When used as a monotherapy at a dose of 10 mg daily, ezetimibe reduces LDL cholesterol by around 20%. Increasing the dose further generally does not improve efficacy.

When used in conjunction with statins much greater LDL cholesterol reductions are seen.

*Current NICE guidelines do not recommend a target cholesterol in primary prevention

**OMACOR (omega-3-acid ethyl esters) → Increases peroxisomal beta-oxidation of fatty acids**

- Omacor reduces triglycerides by different, independent effects in the liver.
- The synthesis of triglycerides is inhibited through reduced production of triglycerides in the liver, as EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis.
- EPA and DHA also inhibit esterification of other fatty acids.
- Omacor increases peroxisomal beta-oxidation of fatty acids in the liver.

**Ezetimibe → localises at the brush border of the small intestine, where it inhibits the absorption of cholesterol from the diet.**

**Nicotinic acid**

Nicotinic acid is used in the treatment of patients with hyperlipidaemia, although its use is limited by side-effects. As well as lowering cholesterol and triglyceride concentrations it also raises HDL levels.

Adverse effects

- flushing
- impaired glucose tolerance
- myositis

**Nicotinic acid → may increase blood glucose → ↑ HA1c in diabetics**

A number of postulated mechanisms have been suggested for this. Since nicotinic acid inhibits triglyceride synthesis, it may be that the increased availability of free fatty acids stimulates hepatic...
glucose output by increasing gluconeogenesis or replacing glucose as the primary energy source. Higher levels of fatty acids may also block glucose uptake by skeletal muscle. Direct effects on beta-cell function have also been postulated.

**Peroxisome proliferator-activated receptor (PPAR) classes**

- **The fibrate class of drugs are PPAR-α agonists**, their predominant action is in reducing serum triglyceride levels and increasing HDL-cholesterol.
- **PPAR-γ agonists** (the glitazones) act predominantly by reducing free fatty acid levels, therefore improving insulin resistance and hence blood glucose levels.
- **PPAR-δ agonists**, which have positive effects on HDL-cholesterol, inflammation and blood pressure, are currently under clinical development.

---

**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
- 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

---

**Oncology drugs**

**Cytotoxic agents**
The tables below summarises the mechanism of action and major adverse effects of commonly used cytotoxic agents.

**Alkylating agents**

<table>
<thead>
<tr>
<th>Cytotoxic</th>
<th>Mechanism of action</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Alkylating agent - causes cross-linking in DNA</td>
<td>Haemorrhagic cystitis, myelosuppression, transitional cell carcinoma</td>
</tr>
</tbody>
</table>

**Cyclophosphamide**
- Cyclophosphamide is inactive unless metabolised by the liver to 4-hydroxyl cyclophosphamide, which decomposes into alkylation species as well as to chloroacetaldehyde and acrolein
- Acrolein causes chemical cystitis and therefore excellent hydration must be maintained during therapy with cyclophosphamide
## Cytotoxic antibiotics

<table>
<thead>
<tr>
<th>Cytotoxic</th>
<th>Mechanism of action</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleomycin</td>
<td>Degrades preformed DNA</td>
<td>Lung fibrosis</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>Stabilizes DNA-topoisomerase II complex inhibits DNA &amp; RNA synthesis</td>
<td>Cardiomyopathy</td>
</tr>
</tbody>
</table>

## Antimetabolites

<table>
<thead>
<tr>
<th>Cytotoxic</th>
<th>Mechanism of action</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate</td>
<td>Inhibits dihydrofolate reductase and thymidylate synthesis</td>
<td>Myelosuppression, mucositis, liver fibrosis, lung fibrosis</td>
</tr>
<tr>
<td>Fluorouracil (5-FU)</td>
<td>Pyrimidine analogue inducing cell cycle arrest and apoptosis by blocking thymidylate synthase (works during S phase)</td>
<td>Myelosuppression, mucositis, dermatitis</td>
</tr>
<tr>
<td>6-mercaptopurine</td>
<td>Purine analogue that is activated by HGPRTase, decreasing purine synthesis</td>
<td>Myelosuppression</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Pyrimidine antagonist. Interferes with DNA synthesis specifically at the S-phase of the cell cycle and inhibits DNA polymerase</td>
<td>Myelosuppression, ataxia</td>
</tr>
</tbody>
</table>
Acts on microtubules

<table>
<thead>
<tr>
<th>Cytotoxic</th>
<th>Mechanism of action</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vincristine, vinblastine</td>
<td>Inhibits formation of microtubules</td>
<td>Vincristine: Peripheral neuropathy (reversible), paralytic ileus, Vinblastine: myelosuppression</td>
</tr>
<tr>
<td>Docetaxel</td>
<td>Prevents microtubule depolymerisation &amp; disassembly, decreasing free tubulin. <strong>has a further action in blocking bcl-2</strong></td>
<td>Neutropaenia</td>
</tr>
</tbody>
</table>

Other cytotoxic drugs

<table>
<thead>
<tr>
<th>Cytotoxic</th>
<th>Mechanism of action</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>Causes cross-linking in DNA</td>
<td>Ototoxicity, peripheral neuropathy, hypomagnesaemia</td>
</tr>
<tr>
<td>Hydroxyurea (hydroxycarbamide)</td>
<td>Inhibits ribonucleotide reductase, decreasing DNA synthesis</td>
<td>Myelosuppression</td>
</tr>
</tbody>
</table>

---

**Cisplatin**

**Mechanism of action** → Causes crosslinking in DNA → makes it impossible for rapidly dividing cells to duplicate their DNA for mitosis.

**Typical side effects of cisplatin include:**

- Marrow toxicity
- **Ototoxicity**
- Peripheral neuropathy
- Nephrotoxicity
- Alopecia, and
Changes in taste.

Although optic neuritis is described it is not a typical side effect.

**Trastuzumab**
- Trastuzumab, is used in the treatment of HER2-receptor-positive metastatic breast cancer
- associated with cardiomyopathy in 2% to 7% of users
- The risk of cardiomyopathy is increased when the drug is given in combination with anthracycline
- Studies have shown that activation of Erb-b2 (also known as HER-2), the receptor blocked by trastuzumab (Herceptin), is important in preventing the development of cardiomyopathy

**Erlotinib**
- Erlotinib specifically targets the epidermal growth factor receptor (EGFR) tyrosine kinase (which is required for the conformational change) and binds in a reversible fashion to the adenosine triphosphate binding site.
- For the signal to be transmitted, two members of the EGFR family need to come together to form a homodimer. These then use the molecule of adenosine triphosphate (ATP) to autophosphorylate each other, which causes a conformational change in their intracellular structure, exposing a further binding site for binding proteins that cause a signal cascade to the nucleus. By inhibiting the ATP, autophosphorylation is not possible and the signal is stopped.
- A key issue with EGFR-directed treatments is that after a period of 8-12 months, the cancer cells become resistant to the treatment. This most commonly occurs due to a mutation in the ATP binding pocket of the EGFR kinase domain. This prevents the binding of erlotinib (Tarceva).

**Imatinib**
- **Signal transduction inhibitor**
- Imatinib is a tyrosine kinase inhibitor which is fairly specific for the bcr/abl protein. It blocks the active site, which has a number of downstream effects. The result is reduced cell proliferation, reduced cell motility, decreased adhesion and increased apoptosis.
NICE recommend that imatinib should be used to treat people in the accelerated or blast crisis phase of CML. It is also indicated in the treatment of gastrointestinal stromal tumours.

---

**Tamoxifen**

Tamoxifen is a selective estrogen receptor modulator (SERM) which acts as an oestrogen receptor antagonist and partial agonist. It is used in the management of oestrogen receptor positive breast cancer

**Adverse effects**

- menstrual disturbance: vaginal bleeding, amenorrhoea
- hot flushes
- venous thromboembolism

*Particularly during and immediately after major surgery or periods of immobility*

- endometrial cancer

Tamoxifen is typically used for 5 years following removal of the tumour.

Raloxifene is a pure oestrogen receptor antagonist, and carries a lower risk of endometrial cancer

---

### UK licensed monoclonal antibodies

<table>
<thead>
<tr>
<th>Name</th>
<th>Type of antibody</th>
<th>Target</th>
<th>Licensed indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infliximab</td>
<td>Human–mouse chimaera IgG1</td>
<td>TNF-α</td>
<td>Refractory Crohn's, Crohn's fistulas, refractory rheumatoid arthritis</td>
</tr>
<tr>
<td>Palivizumab</td>
<td>Humanised IgG1</td>
<td>F protein on RSV</td>
<td>Prophylaxis, RSV in premature infants or brochopulmonary dysplasia</td>
</tr>
<tr>
<td>Abciximab</td>
<td>Human–mouse chimaera</td>
<td>Platelet glycoprotein Ilb/Ilia</td>
<td>High risk coronary intervention</td>
</tr>
<tr>
<td>Rituximab</td>
<td>Human–mouse chimaera IgG1</td>
<td>CD20</td>
<td>Refractory low grade or follicular B cell lymphoma</td>
</tr>
<tr>
<td>Basiliximab</td>
<td>Human–mouse chimaera IgG1K</td>
<td>IL-2 receptor α chain</td>
<td>Prophylaxis of acute rejection in allogeneic renal transplantation</td>
</tr>
<tr>
<td>Daclizumab</td>
<td>Humanised IgG1</td>
<td>IL-2 receptor α</td>
<td>As Basiliximab</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Humanised IgG1</td>
<td>HER 2 growth receptor</td>
<td>Relapsed HER2 (high) breast malignancy</td>
</tr>
</tbody>
</table>

IL-2, interleukin 2; TNF-α, tumour necrosis factor α; RSV, respiratory syncitial virus.
**Rituximab**

- **Rituximab binds to CD20**, an antigen located on pre-B and mature B-lymphocytes
- The receptor is thought to mediate B-cell lysis and apoptosis
- After rituximab therapy, levels of B-lymphocytes appear suppressed for around 6 months, with levels slowly increasing after this time
- As well as for rheumatoid arthritis, rituximab is **also used for the treatment of non-Hodgkin's lymphoma**
- Infusion reactions associated with cytokine release occur in up to 15% of patients receiving rituximab, and the medicine is administered in a specialist centre for this reason

**Nice guidelines of RA → Rituximab in combination with methotrexate** is recommended as an option for treatment of rheumatoid arthritis who have had an inadequate response to or intolerance of other disease-modifying anti-rheumatic drugs (DMARDs), including treatment with at least one tumour necrosis factor α (TNF-α) inhibitor therapy.

Treatment with rituximab plus methotrexate should be continued only if:
- There is an adequate response following initiation of therapy.
- An adequate response is defined as an improvement in disease activity score (DAS28) of 1.2 points or more.
- Repeat courses of treatment with rituximab plus methotrexate should be given no more frequently than every 6 months.

---

**Alpha interferon** at 2 million U/m² subcutaneously three times a week for 12-18 months can be used to salvage relapsed or refractory hairy cell leukemia.

---

**Capecitabine versus 5-fluorouracil (5-FU)**

- **Advantages of capecitabine versus 5-fluorouracil (5-FU) → Can be orally administered**
  - The major difference between capecitabine and 5-FU is that capecitabine is an oral prodrug of 5-FU. The final step in metabolism to 5-FU is thymidine phosphorylase, higher activity of thymidine phosphorylase occurring in tumour tissues.
  - Evidence suggests that efficacy of capecitabine versus 5-FU is broadly similar.
**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. Some countries have developed a grading system.

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Antibiotics</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ACE inhibitors, ARBs</td>
<td>• Tetracyclines</td>
</tr>
<tr>
<td>• Statins</td>
<td>• Aminoglycosides</td>
</tr>
<tr>
<td>• Warfarin</td>
<td>• Sulphonamides</td>
</tr>
<tr>
<td>• Sulfonylureas</td>
<td>• Trimethoprim</td>
</tr>
<tr>
<td>• Retinoids (including topical)</td>
<td>• Quinolones: the BNF advises to avoid due to arthropathy in some animal studies</td>
</tr>
<tr>
<td>• Cytotoxic agents</td>
<td></td>
</tr>
</tbody>
</table>

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.

**Combined oral contraceptive pill: contraindications**

The decision of whether to start a women on the combined oral contraceptive pill is now guided by the UK Medical Eligibility Criteria (UKMEC). This scale categorises the potential cautions and contraindications according to a four point scale, as detailed below:

- UKMEC 1: a condition for which there is no restriction for the use of the contraceptive method
- UKMEC 2: advantages generally outweigh the disadvantages
- UKMEC 3: disadvantages generally outweigh the advantages
- UKMEC 4: represents an unacceptable health risk

**Examples of UKMEC 3 conditions include**

- more than 35 years old and smoking less than 15 cigarettes/day
- BMI > 35 kg/m^2
- migraine without aura and more than 35 years old
- family history of thromboembolic disease in first degree relatives < 45 years
- controlled hypertension
- immobility e.g. wheel chair use
- breast feeding 6 weeks - 6 months postpartum

**Examples of UKMEC 4 conditions include**

- more than 35 years old and smoking more than 15 cigarettes/day
- migraine with aura
- history of thromboembolic disease or thrombogenic mutation
- history of stroke or ischaemic heart disease
- breast feeding < 6 weeks post-partum
- uncontrolled hypertension
- breast cancer
- major surgery with prolonged immobilisation

Diabetes mellitus diagnosed > 20 years ago is classified as UKMEC 3 or 4 depending on severity

**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
<table>
<thead>
<tr>
<th>SAFE</th>
<th>DANGEROUS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Antibiotics: penicillins, cephalosporins, trimethoprim</td>
<td>• Antibiotics: ciprofloxacin, tetracycline, chloramphenicol, sulphonamides</td>
</tr>
<tr>
<td>• Endocrine: glucocorticoids (avoid high doses), levothyroxine*</td>
<td>• Psychiatric drugs: lithium, benzodiazepines, clozapine</td>
</tr>
<tr>
<td>• Epilepsy: sodium valproate, carbamazepine</td>
<td>• Aspirin</td>
</tr>
<tr>
<td>• Asthma: salbutamol, theophyllines</td>
<td>• Carbimazole</td>
</tr>
<tr>
<td>• Psychiatric drugs: tricyclic antidepressants, antipsychotics**</td>
<td>• Sulphonylureas</td>
</tr>
<tr>
<td>• Hypertension: β-blockers, hydralazine, methyldopa</td>
<td>• Cytotoxic drugs</td>
</tr>
<tr>
<td>• Anticoagulants: warfarin, heparin</td>
<td>• Amiodarone</td>
</tr>
<tr>
<td>• Digoxin</td>
<td></td>
</tr>
</tbody>
</table>

*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:

<table>
<thead>
<tr>
<th>drug</th>
<th>teratogenic effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Androgens</td>
<td>cardiac deformities</td>
</tr>
<tr>
<td>Alcohol</td>
<td>fetal alcohol syndrome</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>microcephaly</td>
</tr>
<tr>
<td>Diethylstilbestrol</td>
<td>vaginal carcinoma</td>
</tr>
<tr>
<td>Lithium</td>
<td>cretinism</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>cleft palate</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>neural tube defects</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>phocomelia</td>
</tr>
<tr>
<td>Warfarin</td>
<td>chondrodysplasia punctata</td>
</tr>
</tbody>
</table>
Unwanted drug effects in pregnancy

<table>
<thead>
<tr>
<th>drug</th>
<th>effects in pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors</td>
<td>oligohydramnios, impaired renal function</td>
</tr>
<tr>
<td>Aspirin</td>
<td>kernicterus</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>hypoglycaemia, intrauterine growth retardation, fetal</td>
</tr>
<tr>
<td></td>
<td>bradycardia</td>
</tr>
<tr>
<td>Carbimazole</td>
<td>neonatal goitre</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>close ductus arteriosus</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>kernicterus</td>
</tr>
<tr>
<td>Thiazide diuretics:</td>
<td>neonatal thrombocytopenia</td>
</tr>
</tbody>
</table>

Hormone replacement therapy: indications

HRT: unopposed oestrogen increases risk of endometrial cancer

Hormone replacement therapy (HRT) involves the use of a small dose of oestrogen, combined with a progestogen (in women with a uterus), to help alleviate menopausal symptoms.

The indications for HRT have changed significantly over the past ten years as the long-term risks became apparent, primarily as a result of the Women's Health Initiative (WHI) study.

Indications

- **vasomotor symptoms such as flushing, insomnia and headaches**
- Premature menopause: should be continued until the age of 50 years. Most important reason is preventing the development of osteoporosis

The main indication is the control of vasomotor symptoms. The other indications such as reversal of vaginal atrophy should be treated with other agents as first-line therapies

Other benefits include a reduced incidence of colorectal cancer
Combined OCP:
↑ Risk of breast cancer
↑ Risk of DVT
↓ Risk of endometrial ca.

Hormone replacement therapy and effects on bone mass
- Reduction in total-body bone mass **begins in women in their late twenties**
  This loss is accelerated at the menopause
- Both trabecular bone loss at the level of the vertebrae and cortical bone loss at the radius are prevented by oestrogen therapy
- The risk of osteoporotic fractures is reduced, but not eliminated, by oestrogen therapy
- If the uterus has been removed in a patient, there is no need for additional progesterone therapy
- **The effect of oestrogens on bone loss may be reduced after 10 years of oestrogen therapy**

Hormonal related drugs

Adverse effects

Bromocriptine
- Bromocriptine is a dopamine agonist used to inhibit prolactin release from the anterior pituitary
- **Adverse effects** include:
  - nausea
  - headache
  - light-headedness
  - orthostatic hypotension
  - fatigue
  - Higher doses may cause cold-induced peripheral digital vasospasm (Raynaud's phenomenon).

Clomiphene citrate
- Clomifene citrate may cause:
  - visual disturbances
  - ovarian hyperstimulation
  - hot flushes
  - headache
  - weight gain
  - depression
Human chorionic gonadotrophin
- Reported adverse effects of human chorionic gonadotrophin include:
  - headache
  - depression
  - oedema

Human menopausal gonadotrophin
- Human menopausal gonadotrophin can cause:
  - ovarian hyperstimulation
  - uncomplicated ovarian enlargement in 20% of cases, which usually resolves spontaneously
  - a more serious complication, the hyperstimulation syndrome, which occurs in 0.5-4% of patients, and is characterised by gross ovarian enlargement, ascites, hydrothorax, hypovolaemia and shock

Buserelin
- Buserelin is a gonadotrophin-releasing hormone (GnRH) agonist and may cause:
  - hot flushes
  - decreased libido
  - vaginal dryness

**Raloxifene** (selective oestrogen receptor modulator)
- Raloxifene is the first of the so-called selective oestrogen receptor modulators.
- There are fundamentally two types of oestrogen receptor, alpha and beta, distributed at locations such as breast, uterus, bone and in the vasculature.
- Raloxifene acts as an oestrogen agonist at some sites, for example, bone to increase mineralisation, but acts as an antagonist at other sites, for example, uterus/breast (preventing endometrial/breast hyperplasia).
Antibiotics: bactericidal vs. bacteriostatic

Bactericidal antibiotics

- penicillins
- cephalosporins
- aminoglycosides
- nitrofurantoin
- metronidazole
- quinolones
- rifampicin
- isoniazid

Bacteriostatic antibiotics

- chloramphenicol
- macrolides
- tetracyclines
- sulphonamides
- trimethoprim
**Antibiotics: mechanisms of action**
The lists below summarise the site of action of the commonly used antibiotics

<table>
<thead>
<tr>
<th>Inhibit cell wall formation</th>
<th>Inhibit protein synthesis</th>
<th>Inhibit DNA synthesis</th>
<th>Inhibit RNA synthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• β-lactams</td>
<td>• aminoglycosides</td>
<td>• quinolones</td>
<td>• Rifampicin</td>
</tr>
<tr>
<td>- Penicillins</td>
<td>(cause misreading of mRNA)</td>
<td>(e.g. ciprofloxacin)</td>
<td></td>
</tr>
<tr>
<td>- Cephalosporins</td>
<td>• chloramphenicol</td>
<td>• metronidazole</td>
<td></td>
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<tr>
<td>• Isoniazid</td>
<td>• macrolides</td>
<td>• sulphonamides</td>
<td></td>
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<tr>
<td>• Glycopeptides</td>
<td>(e.g. erythromycin)</td>
<td>• trimethoprim</td>
<td></td>
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<tr>
<td>- Vancomycin</td>
<td>• tetracyclines</td>
<td></td>
<td></td>
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<tr>
<td>- Teicoplanin</td>
<td>• fusidic acid</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Quin/Dalfo)pristin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Those organisms lacking a cell wall are resistant to these drugs e.g. Chlamydia's)</td>
<td>• Linezolid</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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

**Co-trimoxazole**

**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

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**Aminoglycosides**

- Aminoglycosides, such as gentamicin, have limited tissue distribution and are renally cleared.
- High plasma concentrations can cause oto and nephrotoxicity, and dosing therefore needs to be carefully planned and monitored.
- **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 \( \rightarrow \) ↑↑ risk of exacerbating renal and ototoxicity

**Macrolides**

Erythromycin was the first macrolide used clinically. Newer examples include clarithromycin and azithromycin.

Macrolides act by inhibiting bacterial protein synthesis by blocking translocation. 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.

**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**

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 topoisomeras 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

- **Ototoxicity** is associated with vancomycin, and is more likely in patients with high plasma concentrations, renal impairment or pre-existing hearing loss. It may progress after drug withdrawal, and may be irreversible.
- Hearing loss may be preceded by tinnitus, which must be regarded as a sign to stop treatment.
- The important level to measure here is the trough level as opposed to the peak level with gentamicin.
- **Vancomycin → requires plasma level monitoring** (after three or four doses if the renal function is normal, or earlier if renal impairment is present).

Linezolid

is a type of oxazolidinone antibiotic which has been introduced in recent years. It inhibits bacterial protein synthesis by stopping formation of the 70s initiation complex and is bacteriostatic nature.

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

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

**Adverse effects**

- Thrombocytopenia (reversible on stopping)

Monoamine oxidase inhibitor: avoid tyramine
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
- Megaloblastic anaemia may occur owing to folate deficiency

Quinupristin & dalfopristin antibiotics

Overview

- injectable streptogrammin antibiotic
- 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

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

- 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%
- agranulocytosis
- liver enzyme inhibitor
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

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

<table>
<thead>
<tr>
<th>Anti-retroviral agent used in HIV</th>
<th>About</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI)</td>
<td>Examples: zalcitabine, zidovudine (AZT), didanosine, lamivudine, stavudine,</td>
</tr>
</tbody>
</table>
| Protease inhibitors (PI) | • 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)

- 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.

**HIV lipodystrophy** *(Antiretroviral insulin-resistance syndrome)*

**Aetiology**
- Long-term use of combination antiretroviral therapy including protease inhibitor regimens is associated with a re-distribution of body fat in some patients

**Presentation**
- HIV lipodystrophy follows an insulin-resistance pattern, with:
  - loss of fat on the face,
  - increasing abdominal fat
  - deposition of subcutaneous fat on the back
  - low high-density lipoprotein (HDL) cholesterol
  - high triglyceride levels,
  - hypertension
  - impaired glucose tolerance or frank type-2 diabetes

**Treatment**
- there is some evidence that the insulin sensitisers (glitazones) may be effective in some patients

---

**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 hypokalemia 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)
- Quinine is a remarkably toxic drug; something which is not so readily acknowledged. It is used as an antimalarial drug and also as a prophylactic agent against leg cramps, although both uses are increasingly falling from vogue due to the availability of better, safer agents.
- Quinine toxicity, known as cinchonism, may be fatal, usually by cardiac arrhythmia or flash pulmonary oedema in the short term, although incipient renal failure may be fatal more long-term.
- Cardiac arrhythmia is a common finding in cinchonism due to blockade of sodium and potassium channels prolonging QRS and QT intervals respectively and these rhythms may degenerate into ventricular tachyarrhythmias or fibrillation causing death.
- Hypoglycaemia is also a common finding in cinchonism since quinine stimulates pancreatic insulin secretion and this should be corrected rapidly if present.
- Flash pulmonary oedema may develop causing hypoxia and necessitating positive pressure ventilation.
- Classical hallmarks of cinchonism are tinnitus, visual blurring, flushed and dry skin and abdominal pain.
- Other visual complications, including blindness, can occur and may be permanent
- 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.
- In terms of management however, whereas aspirin can be cleared from overdose victims by haemofiltration, quinine cannot be extracted easily by extracorporeal methods.
- 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.
- Management of quinine poisoning is largely supportive with fluids, inotropes and bicarbonate as needed as well as positive pressure ventilation for pulmonary oedema.
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**

**Corticosteroids**

Corticosteroids are amongst the most commonly prescribed therapies in clinical practice. They are used both systemically (oral or intravenous) or locally (skin creams, inhalers, eye drops, intra-articular). They augment and in some cases replace the natural glucocorticoid and mineralocorticoid activity of endogenous steroids.

The relative glucocorticoid and mineralocorticoid activity of commonly used steroids is shown below:

<table>
<thead>
<tr>
<th>Minimal glucocorticoid activity, very high mineralocorticoid activity</th>
<th>Glucocorticoid activity, high mineralocorticoid activity</th>
<th>Predominant glucocorticoid activity, low mineralocorticoid activity</th>
<th>Very high glucocorticoid activity, minimal mineralocorticoid activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fludrocortisone</td>
<td>Hydrocortisone</td>
<td>Prednisolone</td>
<td>Dexamethasone Betamethasone</td>
</tr>
</tbody>
</table>

**Side-effects**

The side-effects of corticosteroids are numerous and represent the single greatest limitation on their usage. Side-effects are more common with systemic and prolonged therapy.

**Glucocorticoid side-effects**

- endocrine: impaired glucose regulation, increased appetite/weight gain, hirsutism, hyperlipidaemia
- Cushing’s syndrome: moon face, buffalo hump, striae
- musculoskeletal: osteoporosis, proximal myopathy, avascular necrosis of the femoral head
- immunosuppression: increased susceptibility to severe infection, reactivation of tuberculosis
- psychiatric: insomnia, mania, depression, psychosis
- gastrointestinal: peptic ulceration, acute pancreatitis
- ophthalmic: glaucoma, cataracts
- suppression of growth in children
- intracranial hypertension

**Mineralocorticoid side-effects**

- fluid retention
- hypertension

**Selected points on the use of corticosteroids:**

- patients on long-term steroids should have their doses doubled during intercurrent illness
- the BNF suggests gradual withdrawal of systemic corticosteroids if patients have: received more than 40mg prednisolone daily for more than one week, received more than 3 weeks treatment or recently received repeated courses

**Anabolic steroids**

- Anabolic steroids can be taken orally (eg stanozolol) or may have to be injected because of their high first-pass metabolism (eg testosterone enantate)
- Among their many unwanted effects, they increase the risk of cardiovascular disease:
  - blood pressure is elevated
  - blood lipid profiles change, with increased LDL-cholesterol and decreased HDL-cholesterol
  - haematocrit is increased, leading to a prothrombotic tendency, although there is a protective decrease in plasma fibrinogen concentrations with prolonged use

**Low dose steroids in sepsis**

More recent randomised controlled trials have suggested that there is a benefit in sepsis when lower physiological doses of steroids are given.

(Low dose i.v hydrocortisone ➔ improve outcome in sepsis)

**Steroid doses**

*Equivalence*

- 1mg prednisolone = 4mg hydrocortisone
- 1mg dexamethasone = 7mg prednisolone
- Dexamethasone is roughly 30 times more potent than hydrocortisone.
**Ciclosporin**

**Cyclosporin + tacrolimus - MOA: inhibit calcineurin thus decreasing IL-2**

Ciclosporin is an immunosuppressant, which decreases clonal proliferation of T cells by reducing IL-2 release. It acts by binding to cyclophilin forming a complex which inhibits calcineurin, a phosphotase that activates various transcription factors in T cells.

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

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

- Nephrotoxicity - **Chronic interstitial nephritis is a major side-effect of ciclosporin**
- hepatotoxicity
- fluid retention
- hypertension
- hyperkalaemia
- hypertrichosis
- gingival hyperplasia
- **Tremor**

(Cyclosporin is well known to cause **coarse tremor**. In the first instance the dose should be reduced. Usually the neurological side effects of cyclosporin are **dose dependent**.)

- impaired glucose tolerance
- hyperlipidaemia
- increased susceptibility to severe infection

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

**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)

These patients are seen monthly to have their blood pressure, urea, and electrolytes checked.

---

**Tacrolimus**

Tacrolimus is a macrolide used as an immunosuppressant to prevent transplant rejection. It has a very similar action to ciclosporin:

**Action of ciclosporin**

- decreases clonal proliferation of T cells by reducing IL-2 release
- binds to cyclophilin forming a complex which inhibits calcineurin, a phosphotase that activates various transcription factors in T cells

The action of tacrolimus differs 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.

---

**Azathioprine**

- Azathioprine is metabolised to the active compound mercaptopurine, a purine analogue that inhibits purine synthesis.
- **It suppresses lymphocyte numbers and function**

A thiopurine methyltransferase (TPMT) test may be needed to look for individuals prone to azathioprine toxicity.

**Adverse effects include**

- bone marrow depression
- nausea/vomiting
- pancreatitis
A significant interaction may occur with allopurinol and hence lower doses of azathioprine should be used.

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

---

**Methotrexate**

Methotrexate is an antimetabolite which inhibits dihydrofolate reductase, an enzyme essential for the synthesis of purines and pyrimidines

**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

**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 a drug with a high potential for patient harm. It is therefore important that you are familiar with guidelines relating to its use
- 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 weekly (source: BNF).
- only one strength of methotrexate tablet should be prescribed (usually 2.5 mg).
- avoid prescribing trimethoprim or cotrimoxazole concurrently - increases risk of marrow aplasia.

**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.

<table>
<thead>
<tr>
<th>Drug</th>
<th>MOA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycophenolate mofetil</td>
<td>inhibits inosine monophosphate dehydrogenase</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>metabolised to the active compound mercaptopurine a purine analogue that inhibits DNA synthesis. <strong>purine synthesis inhibitor</strong></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>antimetabolite which inhibits dihydrofolate reductase</td>
</tr>
</tbody>
</table>

**Methotrexate overdose**

- Methotrexate is a folic acid antagonist which can result in multi-organ failure in overdose.

---

*Notes & Notes for mrcp* Dr.Yousif Abdallah Hamad
- **Folinic acid is the antidote** and should be given intravenously as soon as possible, regardless of the liver function tests.

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### Poisoning & Toxicology

#### 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:

- **Hyperglycaemia**,
  - Corticosteroids,
  - thiazide diuretics,
  - theophylline,
  - iron (during the initial period after overdose),
  - caffeine and
  - B2-agonists

- **Hypoglycaemia**,
  - insulin, sulphonylureas,
  - salicylates,
- sodium valproate,
- propranolol,
- iron (later if hepatic failure ensues)

**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

**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

**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

---

**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.

---

**Carbon monoxide poisoning**

Confusion, pyrexia and pink mucosae are typical features of carbon monoxide poisoning

Carbon monoxide has high affinity for haemoglobin and myoglobin resulting in a left-shift of the oxygen dissociation curve and tissue hypoxia.

**Epidemiology**

- Carbon monoxide is the **commonest** cause of poisoning-associated death in the United Kingdom
- There are approximately 50 per year deaths from accidental carbon monoxide poisoning in the UK.
- Patients with pre-existing vascular disease are at an increased risk of morbidity and mortality from carbon monoxide poisoning

Questions may hint at badly maintained housing e.g. student houses

**Features of carbon monoxide toxicity**

- headache: 90% of cases
- nausea and vomiting: 50%
- vertigo: 50%
- confusion: 30%
- subjective weakness: 20%
- severe toxicity: 'pink' skin and mucosae, hyperpyrexia, arrhythmias, extrapyramidal features, coma, death
  - Cerebellar signs are the most reliable indicator of significant neurological toxicity
Typical carboxyhaemoglobin levels

- < 3% non-smokers
- < 10% smokers
- 10 - 30% symptomatic: headache, vomiting
- > 30% severe toxicity

Management

- 100% oxygen (Give high-flow oxygen (12 l/min) via a tight-fitting mask without a re-breathing circuit)
- hyperbaric oxygen

Indications for hyperbaric oxygen*

- loss of consciousness at any point
- neurological signs other than headache
- carboxyhaemoglobin concentrations over 40% at any time
- myocardial ischaemia or arrhythmia
- pregnancy

*as stated in the 2008 Department of Health publication 'Recognising Carbon Monoxide Poisoning'

Alcohol - problem drinking: management

Nutritional support

- SIGN recommends alcoholic patients should receive oral thiamine if their 'diet may be deficient'

Drugs used

- benzodiazepines for acute withdrawal
- Disulfiram: promotes abstinence - alcohol intake causes severe reaction due to inhibition of acetaldehyde dehydrogenase. Patients should be aware that even small amounts of alcohol
(e.g. In perfumes, foods, mouthwashes) can produce severe symptoms. Contraindications include ischaemic heart disease and psychosis

- **acamprosate**: reduces craving, known to be a weak antagonist of NMDA receptors, improves abstinence in placebo controlled trials
  - is derived from taurine
  - increases the γ-aminobutyric acid (GABA) level, which inhibits CNS activity
  - has relatively few side-effects

- **Naltrexone**: reduces the pleasure that alcohol brings and craving when it is withdrawn, and can halve the relapse rates; however, it is associated with a number of **adverse effects**, including:
  - nausea, vomiting, anxiety, nervousness, insomnia, lethargy, arthralgia, increased sweating and lacrimation, diarrhoea or constipation, increased thirst and liver and kidney dysfunction
  - particularly the GI symptoms recognised with naltrexone may discourage use in a patient with a previous history of IBS

---

**Alcohol withdrawal**

**Alcohol withdrawal is the most common cause of paranoid psychosis with visual hallucination**

**Mechanism**

- chronic alcohol consumption enhances GABA mediated inhibition in the CNS (similar to benzodiazepines) and inhibits NMDA-type glutamate receptors
- alcohol withdrawal is thought to be lead to the opposite (decreased inhibitory GABA and increased NMDA glutamate transmission)

**Alcohol withdrawal reflects the damping of neurotransmission through type A gamma-aminobutyric pathways, and enhanced neurotransmission through N-methyl-D-aspartate pathways.**

**Symptoms typically present about 8 hours after a significant fall in blood alcohol levels. The peak is on day two, and by day five the symptoms are significantly better. Minor withdrawal symptoms appear 6-12 hours after cessation of alcohol and include**

- **Insomnia**
Features

- symptoms start at 6-12 hours
  
  **Alcoholic hallucinosis** can appear 12-24 hours after stopping alcohol and includes visual, auditory and tactile hallucinations.

- peak incidence of seizures at 36 hours
  
  **Withdrawal seizures** can appear 24-48 hours after cessation and are generalised tonic-clonic seizures.

- peak incidence of delirium tremens is at 72 hours
  
  **Alcohol withdrawal delirium** (‘delerium tremens’) can appear 48-72 hours after cessation.

Management

- Benzodiazepines ➔ the first line of treatment for withdrawal.
- Thiamine is also indicated in chronic alcoholism but is not as immediately important as diazepam. Oral chlordiazepoxide is the best prophylactic measure against withdrawal seizures
- carbamazepine also effective in treatment of alcohol withdrawal at a starting dose of 800 mg per 24 hours
- phenytoin is said not to be as effective in the treatment of alcohol withdrawal seizures. best avoided because of the risk of causing hypotension.
Methanol poisoning
Methanol poisoning causes both the effects associated with alcohol (intoxication, nausea etc) and also specific visual problems, including blindness. These effects are thought to be secondary to the accumulation of formic acid. The actual pathophysiology of methanol-associated visual loss is not fully understood but it is thought to be caused by a form of optic neuropathy.

Management

- fomepizole or ethanol
- haemodialysis

Methanol poisoning
- 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 a severe metabolic acidosis, and crystals forming within the eye can lead to so called ‘snow field’ cataract formation.
- Inhibition of metabolism of methanol by alcohol dehydrogenase with either ethanol or fomepizole is the treatment of choice.

Ethylene glycol toxicity
Ethylene glycol toxicity management - fomepizole. Also ethanol / hemodialysis

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
Management has changed in recent times

- 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 first-line in preference to ethanol. → prevents metabolism of ethylene glycol to oxalic acid, responsible for the acidosis and renal failure
- In severe lactic acidosis patient needs initial correction and in this case the most appropriate treatment would be IV fluids with bicarbonate to correct the metabolic acidosis.
- haemodialysis also has a role in refractory cases

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

Clinical features

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

Management
supportive

Treatment of associated hyperthermia

- 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
**Opioid misuse**

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

**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

**Harm reduction interventions may include**

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

**Management of opioid dependence**
patients are usually managed by specialist drug dependence clinics although some GPs with a specialist interest offer similar services
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

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

- 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
- 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-steroidals such as parenteral diclofenac) is recommended
**Morphine**

**Side-effects including:**
- Nausea, vomiting
- **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
- raised intracranial pressure occurs in some patients
- Muscle rigidity may occur with high doses
- Elevated liver enzymes may occur owing to biliary sphincter constriction
- Large doses can lead to respiratory depression, circulatory failure and coma

**Cocaine**

Cocaine is an alkaloid derived from the coca plant. It is widely used as a recreational stimulant. The price of cocaine has fallen sharply in the past decade resulting in cocaine toxicity becoming a much more frequent clinical problem. This increase has made cocaine a favourite topic of question writers.

**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
- both tachycardia and bradycardia may occur
- hypertension

(Blocking of noradrenaline (norepinephrine) re-uptake leads to tachycardia, & ↑↑BP)

- QRS widening and QT prolongation
- aortic dissection
Neurological effects

- seizures
- mydriasis
- hypertonia
- hyperreflexia
- haemorrhagic stroke

Psychiatric effects

- agitation (inhibition of dopamine re-uptake $\rightarrow$ psychomotor agitation)
- psychosis
- hallucinations (serotonin re-uptake blockade leads to $\rightarrow$ 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
- chest pain: benzodiazepines + glyceryl trinitrate. If myocardial infarction develops then primary percutaneous coronary intervention
- hypertension: benzodiazepines + sodium nitroprusside
- the use of beta-blockers in cocaine-induced cardiovascular problems is a controversial issue. The American Heart Association issued a statement in 2008 warning against the use of beta-blockers (due to the risk of unopposed alpha-mediated coronary vasospasm) but many cardiologists since have questioned whether this is valid. If a reasonable alternative is given in an exam it is probably wise to choose it
- 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
• **Intubation and ventilation** will lower blood pressure and improve the ischaemia.

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### Heroin withdrawal

- The following are all signs of heroin withdrawal:
  - rhinorrhea
  - 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.

### 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 psychotrope 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.

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**Cyanide poisoning**

Cyanide may be used in insecticides, photograph development and the production of certain metals. Toxicity results from reversible inhibition of cellular oxidising enzymes.

**Presentation**

- 'classical' features: brick-red skin, smell of bitter almonds
- acute: hypoxia, hypotension, headache, confusion
- 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)

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**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

- Alkalis cause saponification (liquefactive necrosis) of tissue
- Neutralisation of alkalis 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

Including:

- dactinomycin,
- metronidazole
- 5-fluorouracil
- gemcitabine
- cisplatin
- hydroxyurea
- paclitaxel
- mitomycin C
- topotecan

**Other notes**

- 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

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**Heavy metal poisoning**

**Causes**

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

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**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 strictures 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 pmol/l, as well as those with signs of severe toxicity, require chelation therapy with desferrioxamine
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

Lead poisoning is due to the ingestion of:

- lead-containing compounds, deliberate (pica) or inadvertent
- contaminated water from old lead water pipes
- 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 μg/dL - normal.
  - >10 μg/dL - may cause impaired cognitive development in children.
  - >45 μg/dL - GI symptoms in adults and children.
  - >70 μg/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** and 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)
• D-penicillamine
• EDTA
• dimercaprol

---

- containing foods
**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-HT2A receptors as a partial agonist and modulating the NMDA receptor-mediated sensory, perceptual, affective and cognitive processes. LSD mimics 5-HT at 5-HT1A receptors, producing a marked slowing of the firing rate of serotonergic neurons.

**Features**

- hallucinations
- heightened sense of awareness
- synaesthesia
- palinopsia

---

**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
**New recreational drugs**

<table>
<thead>
<tr>
<th>Drug types</th>
<th>Street names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma-hydroxybutyric acid (GHB) and gamma-butyrolactone (GBL)</td>
<td>G, Geebs or Liquid Ecstasy</td>
</tr>
<tr>
<td>Synthetic agonists of the CB1 receptor</td>
<td>Spice</td>
</tr>
<tr>
<td>Methoxetamine (derivative of ketamine)</td>
<td>Mexxy</td>
</tr>
<tr>
<td>Benzylpiperazine</td>
<td>Exodus, Legal X, Legal E</td>
</tr>
<tr>
<td>Nitrous oxide</td>
<td>Hippie crack</td>
</tr>
</tbody>
</table>

**Paracetamol overdose: metabolic pathways**

- Paracetamol is conjugated to glucuronic acid and sulphate under normal conditions.
- In overdose these processes become saturated and the drug is then conjugated with glutathione.
- If the glutathione supply is depleted then a toxic metabolite is formed.

The liver normally conjugates paracetamol with glucuronic acid/sulphate. During an overdose the conjugation system becomes saturated leading to oxidation by P450 mixed function oxidases*. This produces a toxic metabolite (N-acetyl-B-benzoquinone imine).

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 forms covalent bonds with cell proteins, denaturing them and leading to cell death. This occurs not only in hepatocytes but also in the renal tubules.
management

- A serum paracetamol level should be drawn as soon as possible, but at least 4 hours after ingestion. At the same time, blood should be taken for AST/ALT, electrolytes and urea, serum creatinine, arterial pH and lactate, and prothrombin time/INR.
- For a single acute ingestion of paracetamol, the serum paracetamol level should be checked 4 hours after ingestion.
- If a hepatotoxic dose (>75mg/kg) has been ingested within the past hour, gastric decontamination with activated charcoal should be considered.
- Patients presenting between 4 and 8 hours after ingestion should have paracetamol levels measured, and acetylcysteine should be begun if the level is on or above the treatment line.
- Acetylcysteine should be started immediately or empirically when:

  - Patients present 8 hours or more after ingestion
  - Serum paracetamol level is not available within an 8-hour time window
  - There is uncertainty as to the timing of the overdose
  - 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 suprathereapeutic 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.
Hypoglycaemia is seen when paracetamol toxicity leads to significant impairment of hepatic synthetic function.
Prescribing N-acetyl cysteine
- 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, the N-acetyl derivative of the naturally occurring amino acid l-cysteine, is a mucolytic agent and sulphydryl donor acting as an antidote for paracetamol overdosage.**
- N-acetylcysteine is used in the management of paracetamol overdose as it is a precursor of glutathione and hence can increase hepatic glutathione production

**N-acetylcysteine is most effective when administered within 8 h of ingestion**

- N-Acetylcysteine is recommended in all cases where the paracetamol overdose exceeds 150 mg/kg body weight
• All patients with a plasma paracetamol level $\geq 100$ mg/L at 4 hours or $\geq 15$ 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.
• If acetylcysteine is started within 8 hours of the ingestion, hepatotoxicity is extremely unlikely.
• The majority of dose-related adverse reactions occur within the first hour of the initial infusion of acetylcysteine.
• 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.
• Even if a patient has a history of a previous reaction to intravenous acetylcysteine, the benefits outweigh the risks and patient should receive treatment.
• 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.

Monitoring and endpoints for treatment

Intravenous acetylcysteine

• Serum AST or ALT, prothrombin time (or INR), electrolytes, urea, creatinine, arterial pH, and lactate should be repeated at the end of intravenous therapy.
• If INR is 1.3 or less AND ALT is less than 2 times the upper limit of normal then no further treatment with acetylcysteine is required. The patient can be discharged safely, with advice to return to hospital if vomiting or abdominal pain occurs.
• If ALT has more than doubled since the admission measurement OR ALT is 2 times the upper limit of normal or more OR INR $>1.3$ (in the absence of any other cause: e.g., warfarin) then further treatment with acetylcysteine should be given. Acetylcysteine should be given at the dose and infusion rate as used in the third treatment bag. The above blood tests should be repeated in a further 8 to 16 hours.

Oral acetylcysteine

• Serum paracetamol, serum AST or ALT, prothrombin time (or INR), electrolytes, urea, creatinine, arterial pH, and lactate should be checked 12 hours after commencing the oral regime. If the paracetamol level is undetectable and the serum AST/ALT is falling,
Acetylcysteine treatment can be stopped. Otherwise, paracetamol levels and serum AST or ALT should then be checked every 24 hours subsequently until the criteria are met to stop acetylcysteine (undetectable paracetamol level and falling ALT/AST).

**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**

- Hepatic injury can be prevented in nearly all patients treated with acetylcysteine within 8 hours of an acute ingestion, regardless of the magnitude of the paracetamol overdose.
- Ideally, the need for acetylcysteine treatment should be based on a serum paracetamol concentration determined within this 8-hour window.
- Empiric acetylcysteine therapy should be initiated for patients who present later than 8 hours after ingestion;
  - when serum paracetamol concentrations cannot be determined within 8 hours;
  - or if the exact timing of the ingestion is uncertain.
- Early treatment is important, as deaths are highly unlikely in patients treated prior to 16 hours following an acute overdose.
- Acetylcysteine also has some therapeutic effect for patients who present 10 to 24 hours after ingestion, although its efficacy diminishes as the time to treatment increases.
- Intravenous acetylcysteine may be of benefit when rendered as late as 36 to 80 hours in patients presenting with fulminant hepatic failure, coagulopathy, and encephalopathy.
Fulminant liver failure

Patients presenting with or progressing to fulminant hepatic failure should be treated with:

- Continuous intravenous acetylcysteine
- referral for liver transplantation.

Referral for liver transplant is indicated if:

- Arterial lactate concentration >3.5 mmol/L after fluid resuscitation OR
- Arterial pH <7.3, and lactate >3.0 mmol/L after fluid resuscitation OR
- PT/INR >100 seconds/6.0 seconds AND encephalopathy grade 3 or more AND creatinine >300 micromol/L (3.3 mg/dL) within 24 hours AND a normal arterial pH.

Treatment adverse effects

- oral acetylcysteine \(\rightarrow\) nausea and vomiting.
- intravenous acetylcysteine \(\rightarrow\) anaphylactoid reaction (e.g., nausea, flushing, vomiting, rash, urticaria, pruritus, angio-oedema, dyspnoea, wheezing, bronchospasm, tachycardia, and hypotension), anaphylaxis, and death.
- If vomiting occurs within 1 hour of oral acetylcysteine, an anti-emetic (e.g., ondansetron) is administered and oral acetylcysteine re-administered. Vomiting that occurs during intravenous acetylcysteine will not affect the efficacy of treatment, but it can be treated with an anti-emetic as for the oral route.
- Previous anaphylactoid reaction to acetylcysteine is not a contraindication to receiving acetylcysteine if the patient requires treatment.

- 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**

*this explains why there is a lower threshold for treating patients who take P450 inducing medications e.g. phenytoin or rifampicin

**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
  \[ \rightarrow \text{glutathione stores} \]
- patients who have not eaten for a few days
- Human immunodeficiency virus (HIV) positive patients.

It is true that tobacco smoking induces CYP1A2 (one of the P450 enzymes). However, it is not currently included in the list of high-risk situations.

**Complications**

- **Lactic acidosis is recognised complication**
- Severe hypoglycaemia affects 40% of patients with fulminant liver failure, which exacerbates encephalopathy.

**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 uM.
- Mortality is greater if the patient is more than 40 years of age.
Efficacy of Paracetamol in migraine

**Migraine → decrease gastric emptying → decrease Paracetamol effects**

- "When salicylate absorption from effervescent aspirin tablets was studied during migraine, the rate of absorption was found to be reduced relative to that found in non-migrainous volunteers and in the same patients when headache-free. There is evidence that this reduced rate of absorption is caused by gastrointestinal stasis and reduced rate of gastric emptying. Patients in whom aspirin absorption was delayed were more likely to take longer to respond and to require additional treatment."

- **Metoclopramide may be useful in accelerating gastric emptying.**

- The same has also been shown with paracetamol absorption

---

**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
**Thallium poisoning**

Features

- painful polyneuropathy
- mood change
- alopecia

Treatment is chelation therapy with oral Prussian Blue.

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**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

Overdose and poisoning: management
The table below outlines the main management for common overdoses:

<table>
<thead>
<tr>
<th>Toxin</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Paracetamol</strong></td>
<td>Management</td>
</tr>
<tr>
<td></td>
<td>- activated charcoal if ingested &lt; 1 hour ago</td>
</tr>
<tr>
<td></td>
<td>- N-acetylcysteine (NAC)</td>
</tr>
<tr>
<td></td>
<td>- liver transplantation</td>
</tr>
<tr>
<td><strong>Salicylate</strong></td>
<td>Management</td>
</tr>
<tr>
<td></td>
<td>- 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</td>
</tr>
<tr>
<td></td>
<td>- haemodialysis</td>
</tr>
<tr>
<td><strong>Opioid/opiates</strong></td>
<td>Naloxone</td>
</tr>
<tr>
<td><strong>Benzodiazepines</strong></td>
<td>Flumazenil</td>
</tr>
<tr>
<td>Toxin</td>
<td>Treatment</td>
</tr>
<tr>
<td>----------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Tricyclic antidepressants</strong></td>
<td>Management</td>
</tr>
<tr>
<td></td>
<td>- IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity</td>
</tr>
<tr>
<td></td>
<td>- arrhythmias: class Ia (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</td>
</tr>
<tr>
<td></td>
<td>- dialysis is ineffective in removing tricyclics</td>
</tr>
<tr>
<td><strong>Lithium</strong></td>
<td>Management</td>
</tr>
<tr>
<td></td>
<td>- mild-moderate toxicity may respond to volume resuscitation with normal saline</td>
</tr>
<tr>
<td></td>
<td>- haemodialysis may be needed in severe toxicity</td>
</tr>
<tr>
<td></td>
<td>- sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion</td>
</tr>
<tr>
<td><strong>Warfarin</strong></td>
<td>Vitamin K, prothrombin complex</td>
</tr>
<tr>
<td><strong>Heparin</strong></td>
<td>Protamine sulphate</td>
</tr>
<tr>
<td><strong>Beta-blockers</strong></td>
<td>Management</td>
</tr>
<tr>
<td></td>
<td>- if bradycardic then atropine</td>
</tr>
<tr>
<td></td>
<td>- in resistant cases glucagon may be used</td>
</tr>
<tr>
<td><strong>Ethylene glycol</strong></td>
<td>Management has changed in recent times</td>
</tr>
<tr>
<td></td>
<td>- ethanol has been used for many years</td>
</tr>
<tr>
<td></td>
<td>- works by competing with ethylene glycol for the enzyme alcohol dehydrogenase</td>
</tr>
<tr>
<td></td>
<td>- this limits the formation of toxic metabolites (e.g. Glycoaldehyde and glycolic acid) which are responsible for the haemodynamic/metabolic features of poisoning</td>
</tr>
<tr>
<td>Toxin</td>
<td>Treatment</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Toxin</td>
<td><strong>fomepizole</strong>, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol</td>
</tr>
<tr>
<td></td>
<td>haemodialysis also has a role in refractory cases</td>
</tr>
<tr>
<td>Methanol poisoning</td>
<td>Management</td>
</tr>
<tr>
<td></td>
<td>fomepizole or ethanol</td>
</tr>
<tr>
<td></td>
<td>haemodialysis</td>
</tr>
<tr>
<td>Organophosphate insecticides</td>
<td>Management</td>
</tr>
<tr>
<td></td>
<td>atropine</td>
</tr>
<tr>
<td></td>
<td>the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Digoxin-specific antibody fragments</td>
</tr>
<tr>
<td>Iron</td>
<td>Desferrioxamine, a chelating agent</td>
</tr>
<tr>
<td>anaesthetic muscle relaxants</td>
<td>Neostigmine</td>
</tr>
<tr>
<td>Lead</td>
<td>Dimercaprol, calcium edetate</td>
</tr>
<tr>
<td>Carbon monoxide</td>
<td>Management</td>
</tr>
<tr>
<td></td>
<td>100% oxygen</td>
</tr>
<tr>
<td></td>
<td>hyperbaric oxygen</td>
</tr>
<tr>
<td>Cyanide</td>
<td>Hydroxocobalamin; also combination of amyl nitrite, sodium nitrite, and sodium thiosulfate</td>
</tr>
<tr>
<td>Sarin (is an organophosphorus)</td>
<td>Pralidoxime ➔ reactivates acetyl cholinesterase enzyme. It should be used in the first few hours.</td>
</tr>
</tbody>
</table>
Anticoagulants

**Heparin**

can be given as either unfractionated, intravenous heparin, or low molecular weight heparin (LMWH), given subcutaneously. Heparins generally act by activating antithrombin III. Unfractionated heparin forms a complex which inhibits thrombin, factors Xa, IXa, XIa and XIIa. LMWH however only ↑ the action of antithrombin III on factor Xa

The table below shows the differences between standard heparin and LMWH:

<table>
<thead>
<tr>
<th></th>
<th><strong>Standard Heparin</strong></th>
<th><strong>(LMWH)</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>administration</strong></td>
<td>Intravenous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td><strong>Action duration</strong></td>
<td>short</td>
<td>long</td>
</tr>
<tr>
<td><strong>Mechanism of action</strong></td>
<td>Activates antithrombin III.</td>
<td>Activates antithrombin III.</td>
</tr>
<tr>
<td></td>
<td>Forms a complex that inhibits thrombin,</td>
<td>Forms a complex that inhibits</td>
</tr>
<tr>
<td></td>
<td>factors Xa, IXa, XIa and XIIa</td>
<td>factor Xa</td>
</tr>
<tr>
<td><strong>Side-effects</strong></td>
<td>Bleeding</td>
<td>Bleeding</td>
</tr>
<tr>
<td></td>
<td>HIT</td>
<td>Lower risk of HIT and</td>
</tr>
<tr>
<td></td>
<td>Osteoporosis</td>
<td>osteoporosis</td>
</tr>
<tr>
<td><strong>Monitoring</strong></td>
<td>Activated partial thromboplastin time (APTT)</td>
<td>Anti-Factor Xa (although</td>
</tr>
<tr>
<td></td>
<td></td>
<td>routine monitoring is not</td>
</tr>
<tr>
<td></td>
<td></td>
<td>required)</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Useful in situations where there is a ↑ risk</td>
<td>Now standard in the management</td>
</tr>
<tr>
<td></td>
<td>of bleeding as anticoagulation can be</td>
<td>of venous thromboembolism</td>
</tr>
<tr>
<td></td>
<td>terminated rapidly</td>
<td>treatment and prophylaxis and</td>
</tr>
<tr>
<td></td>
<td></td>
<td>acute coronary syndromes</td>
</tr>
</tbody>
</table>
Heparin-induced thrombocytopenia (HIT)

- Immune mediated - antibodies form which cause the activation of platelets
- Usually does not develop until after 5-10 days of treatment
- Despite being associated with low platelets HIT is actually a prothrombotic condition
- Features include a greater than 50% reduction in platelets, thrombosis and skin allergy
- Treatment options include alternative anticoagulants such as lepirudin and danaparoid

Both unfractionated and low-molecular weight heparin can cause hyperkalaemia. This is thought to be caused by inhibition of aldosterone secretion.

Heparin overdose may be reversed by protamine sulphate, although this only partially reverses the effect of LMWH.

Heparin resistance

- Heparin resistance is seen in up to 22% of patients undergoing cardiopulmonary bypass surgery.
- Several mechanisms resulting in heparin resistance have been identified, including:
  - antithrombin deficiency,
  - increased heparin clearance,
  - elevated heparin-binding proteins,
  - and elevated factor VIII and fibrinogen levels.

- For cardiopulmonary bypass in particular, rapid neutralisation of thrombin is required. In order for heparin to be successful in this, it requires antithrombin III which is an alpha2-globulin. It is therefore thought that antithrombin III deficiency is the underlying problem which is seen in patients resistant to heparin during cardiopulmonary bypass.
## Warfarin: management of high INR

**Warfarin - clotting factors affected mnemonic - 1972 (10, 9, 7, 2)**

| P450 inhibitors ↑ INR | INR also ↑ by ABX that kill intestinal flora by ↓ Vit K absorption |

### Dentistry in warfarinised patients - check INR 72 hours before procedure, proceed if INR < 4.0

If patient has unstable INR then it should be checked 24H prior to procedure

The following is based on the BNF guidelines, which in turn take into account the British Committee for Standards in Haematology (BCSH) guidelines. A 2005 update of the BCSH guidelines emphasised the preference of prothrombin complex concentrate over FFP in major bleeding.

<table>
<thead>
<tr>
<th>Situation</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major bleeding</strong></td>
<td>Stop warfarin</td>
</tr>
<tr>
<td></td>
<td>Give intravenous vitamin K 5mg</td>
</tr>
<tr>
<td></td>
<td>Prothrombin complex concentrate - if not available then FFP*</td>
</tr>
<tr>
<td><strong>INR &gt; 8.0</strong></td>
<td>Stop warfarin</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>Give intravenous vitamin K 1-3mg</td>
</tr>
<tr>
<td></td>
<td>Repeat dose of vitamin K if INR still too high after 24 hours</td>
</tr>
<tr>
<td></td>
<td>Restart warfarin when INR &lt; 5.0</td>
</tr>
<tr>
<td><strong>INR &gt; 8.0</strong></td>
<td>Stop warfarin</td>
</tr>
<tr>
<td>No bleeding</td>
<td>Give vitamin K 1-5mg by mouth, using the intravenous preparation orally</td>
</tr>
<tr>
<td></td>
<td>Repeat dose of vitamin K if INR still too high after 24 hours</td>
</tr>
<tr>
<td></td>
<td>Restart when INR &lt; 5.0</td>
</tr>
<tr>
<td><strong>INR 5.0-8.0</strong></td>
<td>Stop warfarin</td>
</tr>
<tr>
<td>Minor bleeding</td>
<td>Give intravenous vitamin K 1-3mg</td>
</tr>
<tr>
<td></td>
<td>Restart when INR &lt; 5.0</td>
</tr>
<tr>
<td><strong>INR 5.0-8.0</strong></td>
<td>Withhold 1 or 2 doses of warfarin</td>
</tr>
<tr>
<td>No bleeding</td>
<td>Reduce subsequent maintenance dose</td>
</tr>
</tbody>
</table>
Warfarin

- Warfarin competitively inhibits carboxylation of vitamin-K-dependent factors
- Vitamin-K-dependent factors include:
  - factor II
  - factor VII
  - factor IX
  - factor X ('reverse the year 1972')
  - protein C ( warfarin → reduces protein C levels in the blood)
- The half-life of warfarin is approximately 44 h

Warfarin action → Inhibition of vitamin K epoxide reductase

Warfarin inhibits epoxide reductase (specifically the VKORC1 subunit), thereby diminishing available vitamin K and vitamin K hydroquinone in the tissues which inhibits the carboxylation activity of the glutamyl carboxylase.

Warfarin is generally avoided in pregnancy.

- In the first trimester it is associated with an increased risk of miscarriage, and teratogenic side effects which include chondrodysplasia patellae, asplenia and diaphragmatic herniae.
- In the second and third trimester it is associated with retroplacental and intracerebral foetal haemorrhage, as well as foetal microcephaly, optic atrophy and developmental delay.

Interaction

- Lipid-lowering agents
  - Simvastatin, rosuvastatin and fibrate → potentiate the anticoagulant effects of warfarin
  - Cholestyramine (a cholesterol-binding resin) is known to reduce the anticoagulant action of warfarin
  - Atorvastatin and pravastatin are least likely to interfere with warfarin
- Cranberry juice → (↑ warfarin effect → ↑ INR). The cause is thought to be bioflavonoids contained in the cranberry juice, which block cytochrome-P450-related warfarin metabolism (CYP2C9)
- Paracetamol given in repeated doses may lead to an enhanced response to warfarin and therefore an increased INR
- Commonly used drugs that may lead to an increased INR include cephalosporins, azathioprine, cimetidine, metronidazole and testosterone derivatives
- Diazepam is a p450 enzyme inducer and is therefore likely to reduce INR

*as FFP can take time to defrost prothrombin complex concentrate should be considered in cases of intracranial haemorrhage
Antiemetic:

- **Aprepitant**: is a neurokinin receptor blocker used in the prevention of chemotherapy induced nausea.

- **Ondansteron**: is a selective 5-HT3 (5-hydroxytryptamine 3A receptor) antagonist both centrally and peripherally and as such is a potent antiemetic. Its effects are thought to be 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.

- **Hyoscine**: 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.

- **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.
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
- granisetron

Adverse effects

- constipation is common

Metoclopramide

Indications
Metoclopramide is a D2 receptor antagonist mainly used in the management of nausea. Other uses include:

- 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
- hyperprolactinaemia
- tardive dyskinesia
Allopurinol inhibits xanthine oxidase

Allopurinol is used in the prevention of gout. It works by inhibiting xanthine oxidase. Allopurinol is an isomer of hypoxanthine and as such is a purine analogue. It acts by inhibiting xanthine oxidase thereby blocking the oxidation of hypoxanthine and xanthine. This reduces the production of uric acid.

In addition, the build up of hypoxanthine and xanthine results in their conversion to adenosine and guanosine. This causes feedback inhibition of amidophosphoribosyl transferase, which is the rate-limiting enzyme of purine biosynthesis. Allopurinol therefore reduces both purine breakdown and synthesis.

Initiating allopurinol prophylaxis - see indications below

- allopurinol should not be started until 2 weeks after an acute attack has settled
- initial dose of 100 mg od, with the dose titrated every few weeks to aim for a serum uric acid of < 300 μmol/l
- NSAID or colchicine cover should be used when starting allopurinol

Indications for allopurinol*

- recurrent attacks - the British Society for Rheumatology recommend 'In uncomplicated gout uric acid lowering drug therapy should be started if a second attack, or further attacks occur within 1 year'
- tophi
- renal disease
- uric acid renal stones
- prophylaxis if on cytotoxics or diuretics

*patients with Lesch-Nyhan syndrome often take allopurinol for life
**Interactions**

**Azathioprine**

- metabolised to active compound 6-mercaptopurine
- xanthine oxidase is responsible for the oxidation of 6-mercaptopurine to 6-thiouric acid
- allopurinol can therefore lead to high levels of 6-mercaptopurine
- a much reduced dose (e.g. 25%) must therefore be used if the combination cannot be avoided

**Cyclophosphamide**

- allopurinol reduces renal clearance, therefore may cause marrow toxicity

**Warfarin**

- Allopurinol can interact with warfarin to enhance the anticoagulant effect of warfarin.

**Antihistamines**

Antihistamines (H₁ inhibitors) are of value in the treatment of allergic rhinitis and urticaria.

**Examples of sedating antihistamines**

- chlorpheniramine

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

**Examples of non-sedating antihistamines**

- loratidine
- 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.

**Other notes**

- 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.

---

**Cholestyramine**

Cholestyramine is an anion exchange resin and will interfere with the absorption of fat-soluble vitamins. Thus vitamin D absorption will be reduced making treatment with this drug less effective when given with cholestyramine.

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**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.

---

**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 nephritis

**Isotretinoin**

- 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**: **♀es 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 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**

- Acetazolamide is an inhibitor of carbonic anhydrase
- Inhibits proximal tubule bicarbonate reabsorption in a similar fashion to type-2 renal tubular acidosis (RTA) --> associated with metabolic acidosis

**Indications**

- It is used in post-haemorrhagic hydrocephalus (often with furosemide) and for reducing intraocular pressure
- It is used as a potential preventative agent for contrast nephropathy

**Side effects**

- metabolic acidosis, due to bicarbonate loss in the proximal and distal tubules through inhibition of reabsorption
- **Acute interstitial nephritis (AIN)**
- Agranulocytosis and thrombocytopenia
- hypokalaemia

---

**Acute intermittent porphyria: drugs**

- Acute intermittent porphyria (AIP) is an autosomal dominant condition caused by a defect in porphobilinogen deaminase, an enzyme involved in the biosynthesis of haem. It characteristically presents with abdominal and neuropsychiatric symptoms in 20-40 year olds. AIP is more common in females (5:1)

<table>
<thead>
<tr>
<th>Drugs which may precipitate attack</th>
<th>Safe Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Alcohol</td>
<td>• Paracetamol</td>
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<tr>
<td>• Barbiturates</td>
<td>• Aspirin</td>
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<tr>
<td>• Benzodiazepines</td>
<td>• Ibuprofen</td>
</tr>
<tr>
<td>• Tricyclic antidepressants</td>
<td>• Codeine</td>
</tr>
<tr>
<td>• Halothane</td>
<td>• Morphine</td>
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<tr>
<td>• Oral contraceptive pill</td>
<td>• Chlorpromazine</td>
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<tr>
<td>• Sulphonamides</td>
<td>• β-blockers</td>
</tr>
<tr>
<td>• Cephalosporins</td>
<td>• Penicillin</td>
</tr>
<tr>
<td>• Erythromycin</td>
<td>• Metformin</td>
</tr>
<tr>
<td>• Isoniazid</td>
<td></td>
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<tr>
<td>• Anabolic steroids</td>
<td></td>
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<tr>
<td>• Sulphonylureas</td>
<td></td>
</tr>
<tr>
<td>• Theophylline</td>
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<tr>
<td>• Antihistamines</td>
<td></td>
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<tr>
<td>• MAOIs</td>
<td></td>
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<tr>
<td>• Nifedipine</td>
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<td>• Verapamil</td>
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<td>• Amiodarone</td>
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<tr>
<td>• Simvastatin.</td>
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<tr>
<td>• Diuretics</td>
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<td>• Captopril</td>
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<td>• Diuretics</td>
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<td>• Ibuprofen</td>
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<td>• Codeine</td>
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<td>• Morphine</td>
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<td>• Chlorpromazine</td>
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<tr>
<td>• β-blockers</td>
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<tr>
<td>• Penicillin</td>
<td></td>
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<tr>
<td>• Metformin</td>
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</tbody>
</table>

*ibuprofen is safe for use in acute intermittent porphyria, but diclofenac should be avoided.*

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**Bicarbonate therapy**

- Can increase extracellular pH only if the carbon dioxide (CO₂) 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 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 (alendronate) can cause a variety of esophageal 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.

• 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

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.

**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%.

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**Intravenous fluid therapy**

**Intravenous fluid therapy in adults in hospital**

NICE guidelines 2013

**Indicators that a patient may need urgent fluid resuscitation include:**

- 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[1].

**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.
### Composition of electrolytes in commonly used crystalloids

<table>
<thead>
<tr>
<th>Content</th>
<th>Plasma</th>
<th>Sodium chloride 0.9%*</th>
<th>Sodium chloride 0.18%/4% glucose(a)</th>
<th>0.45% NaCl/4% glucose(a)</th>
<th>5% glucose(a)</th>
<th>Hartmann’s</th>
<th>Lactated Ringer’s (USP)</th>
<th>Ringer’s acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na⁺ (mmol/l)</td>
<td>135-145</td>
<td>154</td>
<td>31</td>
<td>77</td>
<td>0</td>
<td>131</td>
<td>130</td>
<td>130</td>
</tr>
<tr>
<td>Cl⁻ (mmol/l)</td>
<td>95-105</td>
<td>154</td>
<td>31</td>
<td>77</td>
<td>0</td>
<td>111</td>
<td>109</td>
<td>112</td>
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<tr>
<td>[Na⁺]:[Cl⁻] ratio</td>
<td>1.28-1.45:1</td>
<td>1:1</td>
<td>1:1</td>
<td>1:1</td>
<td>-</td>
<td>1.18:1</td>
<td>1.19:1</td>
<td>1.16:1</td>
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<tr>
<td>K⁺ (mmol/l)</td>
<td>3.5-5.3</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>5</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>HCO₃⁻ / Bicarbonate</td>
<td>24-32</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>29 (lactate)</td>
<td>28 (lactate)</td>
<td>27 (acetate)</td>
</tr>
<tr>
<td>Ca²⁺ (mmol/l)</td>
<td>2.2-2.6</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>1.4</td>
<td>1</td>
</tr>
<tr>
<td>Mg²⁺ (mmol/l)</td>
<td>0.8-1.2</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>3.5-5.5</td>
<td>0</td>
<td>222(40 g)</td>
<td>222 (40g)</td>
<td>278(50 g)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>pH</td>
<td>7.35-7.45</td>
<td>4.5</td>
<td>4.5</td>
<td>3.5-5.5</td>
<td>5.0-7.0</td>
<td>6-7.5</td>
<td>6-8</td>
<td></td>
</tr>
<tr>
<td>Osmolarity (mOsm/l)</td>
<td>275-295</td>
<td>308</td>
<td>284</td>
<td>278</td>
<td>278</td>
<td>273</td>
<td>276</td>
<td></td>
</tr>
</tbody>
</table>

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**Lactulose**

Lactulose, an osmotic laxative,

- Causes hypomagnesaemia associated with diarrhoea
- Is not absorbed
- Does not affect the absorption of spironolactone and
- May be used in diabetics.

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.
Malignant hyperthermia (MH)

Overview

- condition often seen following administration of anaesthetic agents
- characterised by hyperpyrexia and muscle rigidity
- cause by excessive release of Ca2+ from the sarcoplasmic reticulum of skeletal muscle
- associated with defects in a gene on chromosome 19 encoding the ryanodine receptor, which controls Ca2+ 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 Ca2+ 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%).

Medication overuse headache

is one of the most common causes of chronic daily headache. It may affect up to 1 in 50 people

Features

- Present for 15 days or more per month
- Developed or worsened whilst taking regular symptomatic medication
- Patients using opioids and triptans are at most risk
- May be psychiatric co-morbidity

Management

- Simple analgesics and triptans should be withdrawn abruptly (may initially worsen headaches)
- Opioid analgesics should be gradually withdrawn

Non-steroidal anti-inflammatory drugs (NSAID)

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

Side effects

- 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

**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 overdose

**Large overdoses can present with:**
- an 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 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. However **platelet aggregation is not affected by COX-2.**
- 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.**
- 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.
- 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.
Rofecoxib (Vioxx) has been withdrawn due to its increased cardiovascular events compared with naproxen. 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.

**Aminosalicylates**

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.

**Sulphasalazine**

- A combination of sulphapyridine (a sulphonamide) and 5-ASA
- Many side-effects are due to the sulphapyridine moiety: rashes, oligospermia, headache, Heinz body anemia
- 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
- Mesalazine is still however associated with side-effects such as GI upset, diarrhea, headache, agranulocytosis, pancreatitis*, interstitial nephritis

**Olsalazine**

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

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.

*pancreatitis is 7 times more common in patients taking mesalazine than sulfasalazine
Anti-TNF therapy

Indications

Nice \( \rightarrow \) The tumour necrosis factor alpha (TNF-\( \alpha \)) inhibitors adalimumab, etanercept and infliximab are recommended as options for the treatment of adults who have both of 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.

- **Golimumab** is an anti-TNF therapy used in the treatment of rheumatoid arthritis.
- **SE \( \rightarrow \)** risk of reactivation of tuberculosis or new infection
- **If patient had previous active TB, the optimal TB screening test in this situation\( \rightarrow \)** interferon gamma release assay

Side effects

The tumor necrosis factor (TNF)-alpha inhibitors have multiple potential adverse events, which include:

- Injection site reactions
- Infusion reactions
- Neutropenia
- Infections
- Demyelinating disease \( \rightarrow \) 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.

- Cutaneous reactions, including psoriasis
- Malignancy
- Induction of autoimmunity

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

Important notes
- 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). It is given 2-4 weekly initially and then on a 6-8 weekly basis and as per protocol.
- 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.
- **Nice →** Use of the TNF-α inhibitors for the treatment of severe, active and progressive rheumatoid arthritis in adults not previously treated with methotrexate or other DMARDs is not recommended.
- In RA nice recommend →**Treatment with TNF-α inhibitors should be continued only if there is an adequate response at 6 months following initiation of therapy. An adequate response is defined as an improvement in DAS28 of 1.2 points or more. Then monitored 6-monthly with assessment of DAS28.**
- TNF-α inhibitors should normally be used in combination with methotrexate. If methotrexate is intolerant, adalimumab and etanercept may be given as monotherapy.

**Adalimumab:** (Nice guidelines)

Adalimumab is recommended as a possible treatment for adults with **plaque psoriasis** only if:

- their condition is severe **and**
- their condition has 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.

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

**Anti – TNF in ankylosing spondylitis**

NICE states that adalimumab, etanercept and golimumab may be used for ankylosing spondylitis (AS) only if:

- **level of pain is assessed twice** (using a simple scale to fill in) 12 weeks apart and confirms that condition has not improved
- **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
- **treatment with two or more NSAIDs** for four weeks at the highest possible dose has not controlled the symptoms
Infliximab

- Infliximab is a monoclonal antibody which is currently licensed in the UK for Crohn's disease and, in combination with methotrexate for the treatment of rheumatoid arthritis in patients with active disease when the response to disease-modifying drugs, including methotrexate, has been inadequate.
- Infliximab monotherapy induces the production of anti-infliximab antibodies, which may reduce its effectiveness. Adding methotrexate to infliximab therapy may prevent this response.

Palliative care prescribing: agitation and confusion

Underlying causes of confusion need to be looked for and treated as appropriate, for example hypercalcaemia, infection, urinary retention and medication. If specific treatments fail then the following may be tried:

- first choice: haloperidol
- other options: chlorpromazine, levomepromazine

In the terminal phase of the illness then agitation or restlessness is best treated with midazolam

Palliative care prescribing: hiccups

Management of hiccups

- chlorpromazine is licensed for the treatment of intractable hiccups
- haloperidol, gabapentin are also used
- dexamethasone is also used, particularly if there are hepatic lesions

Palliative Care Prescribing

SIGN issued guidance on the control of pain in adults with cancer in 2008

Selected points
• The breakthrough dose of morphine is one-sixth the daily dose of morphine
• All patients who receive opioids should be prescribed a laxative
• Opioids should be used with caution in patients with chronic kidney disease. Alfentanil, buprenorphine and fentanyl are preferred
• metastatic bone pain may respond to NSAIDs, bisphosphonates or radiotherapy

Concerning diamorphine elixir for the relief of pain in terminal patients:

• Constipation is a characteristic sequel to treatment
• Hallucinations also tend to occur.
• An aperient should always be added to the treatment regime.
• Addiction is not a problem.
• An intramuscular injection is three times more effective than the same oral dose.

Combination therapies antagonism

Partial opioid agonists (for example, buprenorphine), when used in association with morphine, may produce a reduction in the analgesic effect due to partial antagonism. This is an aspect of pain management that needs to be considered when using combination therapies.

Conversion between opioids

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<tr>
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The BNF states that oral morphine sulphate 80-90mg over 24 hours is approximately equivalent to one '25 mcg/hour' patch, therefore product literature should be consulted

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Management of hiccups in palliative care
• Chlorpromazine is licensed for the treatment of intractable hiccups
• Haloperidol, gabapentin and baclofen are also used

In the terminal phase of the illness (Care of the Dying pathway) then agitation or restlessness is best treated with midazolam S/C injection.

**Proton pump inhibitors**

Proton pump inhibitors (PPI) are a group of drugs which profoundly reduce acid secretion in the stomach. They irreversibly blocking the hydrogen/potassium adenosine triphosphatase enzyme system (the H+/K⁺ ATPase) of the gastric parietal cell.

Examples include omeprazole and lansoprazole

**Sildenafil**

Sildenafil is a phosphodiesterase type V inhibitor (PDE-5 inhibitors) used in the treatment of impotence.

**Contraindications**

**Viagra - contraindicated by nitrates and nicorandil**

• 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 discoloration of vision.** This can often be managed by reducing the dose of Sildenafil.
• nasal congestion
• flushing
• gastrointestinal side-effects
• headache