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Chapter 13

Notes & Notes for MRCP
By Dr. Yousif Abdallah Hamad Chapter 13

Pharmacology

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

Leflunomide
• an immunosuppressive disease-modifying antirheumatic drug (DMARD), used in active moderate-to-severe rheumatoid arthritis and psoriatic arthritis. • It is a pyrimidine synthesis inhibitor.
• achieves its effects by inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase (DHODH), which plays a key role in the de novo synthesis of uridine monophosphate (rUMP), which is required for the synthesis of DNA and RNA. Hence, leflunomide inhibits the reproduction of rapidly dividing cells, especially lymphocytes.
Side effects • Hepatotoxicity (occurring in 15-20% of cases) most hepatic events occur within the first 6 months of use. • signs of leflunomide toxicity should be monitored. If the patient develops a rash or itch dose reduction should be considered, with or without the addition of antihistamines. If severe, leflunomide should be stopped and washout considered.
• Hair loss, headaches and gastrointestinal upset may also warrant dose reduction or washout.
• A blood pressure of greater than 140/90 mmHg should be treated as per NICE guidelines. If it remains elevated, stop leflunomide and consider washout.
• Weight should be monitored, and a weight loss of greater than 10% should be identified. If no other cause can be found, consider dose reduction or washout.
• If there is increasing shortness of breath, pneumonitis should be considered and leflunomide should be stopped.
• Leflunomide reduces sperm count. Monitoring
• LFT (LFTs) should be checked monthly for 6 months and, if stable, 2 monthly thereafter.
 If AST or ALT is between 2 and 3 times the upper limit of normal, and the leflunomide dose is more than 10 mg daily, the dose should be reduced to 10 mg and LFTs rechecked weekly until normalised. If the ALT and AST are returning to normal, the patient should be left on 10 mg per day. It the LFTs remain elevated, leflunomide should be stopped and discussed with the specialist team.

 If the AST or ALT is more than 3 times the upper limit of normal, the LFTs should be rechecked within 72 hours. If they remain more than 3 times the reference range, leflunomide should be stopped and washout considered (cholestyramine and activated charcoal).
 It is important to note that the half-life of leflunomide is usually 2 weeks (mean 14) therefore if a rapid response is required, washout should be considered.

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

Poisoning &Toxicology

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

Toxin Treatment Paracetamol Management • activated charcoal if ingested < 1 hour ago • N-acetylcysteine (NAC) • liver transplantation Salicylate Management • urinary alkalinization is now rarely used - it is contraindicated in cerebral and pulmonary oedema with most units now proceeding straight to haemodialysis in cases of severe poisoning • haemodialysis Opioid/opiates Naloxone Benzodiazepines Flumazenil Tricyclic antidepressants Management

• IV bicarbonate may reduce the risk of seizures and arrhythmias in severe toxicity • arrhythmias: class 1a (e.g. Quinidine) and class Ic antiarrhythmics (e.g. Flecainide) are contraindicated as they prolong depolarisation. Class III drugs such as amiodarone should also be avoided as they prolong the QT interval. Response to lignocaine is variable and it should be emphasized that correction of acidosis is the first line in management of tricyclic induced arrhythmias • dialysis is ineffective in removing tricyclics Lithium Management

• mild-moderate toxicity may respond to volume resuscitation with normal saline

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Pharmacology Toxin Treatment • haemodialysis may be needed in severe toxicity • sodium bicarbonate is sometimes used but there is limited evidence to support this. By increasing the alkalinity of the urine it promotes lithium excretion Warfarin Vitamin K, prothrombin complex Heparin Protamine sulphate Beta-blockers Management • if bradycardic then atropine • in resistant cases glucagon may be used Ethylene glycol 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 used first-line in preference to ethanol • haemodialysis also has a role in refractory cases Methanol poisoning Management • fomepizole or ethanol • haemodialysis Organophosphate insecticides Management • atropine • the role of pralidoxime is still unclear - meta-analyses to date have failed to show any clear benefit Digoxin Digoxin-specific antibody fragments Iron Desferrioxamine, a chelating agent Lead Dimercaprol, calcium edetate Carbon monoxide Management • 100% oxygen • hyperbaric oxygen Cyanide Hydroxocobalamin; also combination of amyl nitrite, sodium nitrite, and sodium thiosulfate Sarin (organophosphorus) Pralidoxime reactivates acetyl cholinesterase enzyme. It should be used in the first few hours.

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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

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Drug poisoning: Altered serum glucose in unknown overdose

Alteration in serum glucose concentration, in addition to other clinical signs and symptoms, can be helpful in diagnosing the ingestion of an unknown drug: Drugs induce hyperglycaemia Drug induce hypoglycaemia • Corticosteroids, • thiazide diuretics,
• theophylline,
• iron (during the initial period after overdose),
• caffeine and
• B2-agonists • insulin, sulphonylureas, • Salicylates
• sodium valproate, • propranolol, • iron (later if hepatic failure ensues)

Drugs cleared by alkalization of the urine
The clearance of which drug would be increased by alkalization of the urine? • Weak acids are ionized in an alkaline environment, and this lessens their tubular absorption.
• Alkalization of urine, achieved by IV infusion of sodium bicarbonate, can thereby be used to increase the urinary elimination of:

1. barbiturates,
2. salicylates and
3. isoniazid.

Measurement of drug concentrations
• Measurement of drug concentrations is clinically important for relatively few compounds.
• Drug concentrations are particularly important for those compounds where the concentration is predictive of serious toxicity in an otherwise asymptomatic patient. Compounds where measurement of drug concentration is clinically indicated: • Paracetamol • Theophylline

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

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

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Drug toxicity in renal failure • A wide range of drug-handling processes occur in the kidney: Filtration tubular secretion active and passive tubular reabsorption • The overall renal clearance of drugs declines in parallel with falls in the glomerular filtration rate and creatinine clearance Norpethidine • In patients with renal impairment pethidine is metabolised to norpethidine, but at this stage metabolism stops and norpethidine accumulates rather than being excreted through the kidneys • Norpethidine is toxic and is associated with a risk of seizures Morphine • A similar accumulation of morphine 6-glucuronide occurs after morphine administration in patients with renal impairment, which may lead to narcosis • fluid overloaded + pin point pupils in a patient taking morphine with renal impairment the most likely cause of his symptoms Renal failure leading to accumulation of morphine (not overdose) (masterclass 2017 part 2)
 Patients with relapsed ovarian cancer may develop an obstructive nephropathy due to pelvic recurrence. If they are on morphine they may get accumulation of this drug and signs of opiate toxicity superimposed on the signs of renal failure. Other drugs • Other drugs where physiologically active metabolites accumulate leading to toxicity in renal failure include: nitroprusside (active metabolite thiocyanate) allopurinol (accumulation of oxypurinol leads to rash and allergy)

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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

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Arsenic toxicity

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

• Arsenic is a heavy metal which is a natural component of the earth's crust.

• exists in organic or inorganic . It is highly toxic in its inorganic form. organic arsenics found in fish and seafood are non-toxic • Arsenic exposure is usually occupational or environmental

• routes of exposure include: Groundwater most often becomes contaminated naturally Arsenic contamination of groundwater is widespread

 most common in Bangladesh, West Bengal and india Occupational exposures: toxic waste sites and traditional medicines. • Features Acute GI (nausea, vomiting, hemorragic gastroenteritis, garlic breath) CNS (coma, seizures) Chronic Skin changes: dermatitis, hyperkeratosis & hyperpigmentation The first symptoms of long-term exposure the most common effect of chronic exposure Keratoses on the palms and soles are characteristic.

 occur after a minimum exposure of approximately five years

 may be a precursor to skin cancer. Mees lines: leukonychia striata (transverse white lines on the finger nails) Abdominal pain Sensory-motor Peripheral neuropathy Diabetes Cancers (lung, bladder, skin). • Arsenic can interfere with the mechanism of hemoglobin synthesis and the ribosomes may form dot-like precipitates, called basophilic stippling, at the periphery of RBCs. • Basophilic stippling is also found in: thrombotic thrombocytopenic purpura, in hemoglobin H disease (rarely) megaloblastic anemia.

 It indicates a RBC cell line maturation defect in the bone marrow. • The hematological effects of arsenic toxicity include: Anemia Pancytopenia

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 Hemolysis in some cases • Management Acute exposure Chelation: Consider chelation therapy in patients who are symptomatic and/or have urine concentration >200 mcg/L. DMPS is the chelation agent of choice.

 DMSA is an alternative (oral preparation only, so unsuitable if the patient is vomiting). Chronic exposure arsenic-free drinking water, to reduce the risk of further disease

 It is recommended that all patients with skin lesions be given multivitamins.

Drugs altered pupil size

Many drugs can cause changes in pupil size as detailed below: • Dilated pupils (mydriasis): sympathomimetic drugs, eg cocaine, dopamine, amphetamines anticholinergic drugs, eg antihistamines, atropine, tricyclic antidepressants • Constricted pupils (miosis): sympatholytic drugs, eg opiates, phenothiazines, clonidine, sodium valproate cholinergic drugs, eg organophosphates, pilocarpine

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

Multi-dose activated charcoal

When Activated charcoal can be repeatedly given to increase elimination of the poison? When the drug circulates through the enterohepatic circulation

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

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Methanol poisoning Overview • Methanol, like ethanol, is metabolised by alcohol dehydrogenase to form formaldehyde. Formaldehyde is then further metabolised by aldehyde dehydrogenase to formic acid. • Formate formation leads to: severe metabolic acidosis, and
 crystals forming within the eye can lead to so called 'snow field' cataract formation. Feature • Early signs (are due to methanol) include: Nausea and vomiting Headache,
 Confusion. • later signs (are due to its metabolite, formic acid)
 high gap metabolic acidosis Anion gap = (Na + K) - (Cl + HCO3); normal range 7-17 mmol/L.
 Although elevated, the lactate level does not account for the anion gap.
 visual problems, retinal injury, including blindness (methanol-associated visual loss) accumulation of formic acid a form of optic neuropathy Differential diagnosis • The differential diagnosis of this form of a high anion gap metabolic acidosis is (SLUMPED) (salicylates, lactic acidosis, uremia, methanol/ethylene glycol, paraldehyde, ethanol, and diabetic ketoacidosis). Similarities between Methanol and ethylene glycol intoxication • Both are causes a very similar biochemical and clinical picture. • Both require the enzyme alcohol dehydrogenase for metabolism. • Both are treated with fomepizole or ethanol, which inhibit alcohol dehydrogenase • Both can present with metabolic acidosis, hyperpnea and tachypnea, coma, seizures, and hypotension.

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

Pharmacology failure and hypocalcemia (tetany) Oxalate crystals are a specific sign of ethylene glycol toxicity.

formate is the toxic metabolite of methanol
oxalic acid is the toxic metabolite of ethylene glycol

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

Treatment is aimed at:

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

Ethylene glycol toxicity

• Ethylene glycol 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 renal, respiratory and cardiac failure. Multi-organ failure is thought to occur at least in part due to widespread deposition of calcium oxalate crystals around 12 h after the initial insult. Management
• treatment is often given based on clinical suspicion due to a delay in obtaining ethylene glycol levels in most centres. • fomepizole, an inhibitor of alcohol dehydrogenase, is now used first-line in preference to ethanol prevents metabolism of ethylene glycol to oxalic acid, responsible for the acidosis and renal failure Because of the potential formation of calcium oxalate, calcium levels

should also be assessed.
• 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 • IV fluids with bicarbonate to correct the metabolic acidosis in severe lactic acidosis. • Calcium gluconate for hypocalcemia,

• haemodialysis also has a role in refractory cases

Isopropyl alcohol (Isopropanol) intoxication

Acidosis + eye signs methanol poisoning
Acidosis without eye signs ethylene glycol poisoning
Ketosis without acidosis isopropyl alcohol poisoning

Overview • It is a clear colorless liquid with a BITTER TASTE and fruity odor. • commonly used as a rubbing alcohol and as a solvent in hair-care products, skin lotions and home aerosols.
• Also found in products including cleaners, disinfectants, antifreezes, cosmetics, solvents, inks, and pharmaceuticals. • Inexpensive and can be a substitute for ethanol. • the second most common alcohol intoxication next to ethanol. • It is twice as potent as ethanol as a central nervous system depressant but without an early elation phase. Feature: • Severe isopropanol poisoning results in CNS and respiratory depression and circulatory collapse.
• GIT and CNS symptoms are predominating,
• alcohol, benzodiazepines, isopropyl alcohol, lithium, and organophosphates may all lead to miosis (constriction of the pupil) • Large ingestions can result in coma.
• The most common metabolic effects are an increased osmol (osmolal) gap, ketonemia, and ketonuria
• metabolic acidosis - unlike in other alcohols intoxication - is not present, this is because isopropyl alcohol is metabolized by alcohol dehydrogenase to acetone, (a ketone is not an acid).
 therefore, ketone appear in breath and in urine. • Isopropyl alcohol intoxication can be remembered as "ketosis without acidosis".
• Another unique finding is "pseudo renal failure" or ISOLATED false elevation of creatinine with a normal BUN. Diagnosis: • An osmol gap, ketonemia, and/or ketonuria without metabolic acidosis, along with a fruity or sweet odor on the breath and CNS depression support the diagnosis.
• Although ethylene glycol, methanol, and ethanol ingestions result in anion gap and osmolar gap, isopropyl alcohol results in only an osmolar gap. Osmolar gap = Osmolality – Osmolarity Osmolality is measured in laboratory by osmometers
 Osmolarity is calculated = (2 x [Na+]) + [glucose] + [urea] normal = < 10

Pharmacology

 the units of osmolality are mOsm/kg of solute the units of osmolarity are mOsm/L Treatment: • supportive care (is the mainstay of management) Patients usually make a full recovery • hemodialysis elimination of isopropanol and acetone only in severe life-threatening poisonings.

Ecstasy poisoning • Ecstasy is an amphetamine derivative (MDMA, 3,4-Methylene-Dioxy-Meth-Amphetamine) use became popular in the 1990's during the emergence of dance music culture • is a semi-synthetic hallucinogen used as a recreational drug. Clinical features • neurological: agitation, anxiety, confusion, ataxia • cardiovascular: tachycardia, hypertension • hyponatraemia • Hyperventilation • hyperthermia • rhabdomyolysis Management supportive (no specific antidote) • Cold intravenous fluids if the core temperature is over 39 °C • dantrolene may be used for hyperthermia if simple measures fail
• and/or paralysis and ventilation
• Treatment of associated hyperthermia

Opioid misuse Acute confusion and visual hallucinations are common symptoms of opioid toxicity and pin point pupils and myoclonas are common signs.
• Opioids are substances which bind to opioid receptors. This includes both naturally occurring opiates such as morphine and synthetic opioids such as buprenorphine and methadone. Features of opioid misuse • rhinorrhoea • needle track marks • pinpoint pupils • drowsiness • watering eyes • yawning • symptoms of neurotoxicity (for example, hallucinations, myoclonus and delirium) • respiratory depression Complications of opioid misuse • viral infection secondary to sharing needles: HIV, hepatitis B & C • bacterial infection secondary to injection: infective endocarditis, septic arthritis, septicaemia, necrotising fasciitis • venous thromboembolism • overdose may lead to respiratory depression and death • psychological problems: craving • social problems: crime, prostitution, homelessness Emergency management of opioid overdose

• IV or IM naloxone: has a rapid onset and relatively short duration of action • intravenous naloxone (0.4 mg), repeated up to a total dose of 2 mg depending on clinical response. • The half-life of naloxone is shorter than that of opioids, hence if the patient wakes up it can be anticipated that he will 're-narcose'. A naloxone infusion may be necessary. Harm reduction interventions may include • needle exchange • offering testing for HIV, hepatitis B & C Management of opioid dependence • patients may be offered maintenance therapy or detoxification • NICE recommend methadone or buprenorphine as the first-line treatment in opioid detoxification • compliance is monitored using urinalysis • detoxification should normally last up to 4 weeks in an inpatient/residential setting and up to 12 weeks in the community • Naltrexone can be used to help prevent relapse in the treatment of Opioids dependency Naltrexone is a long-acting opioid antagonist. It can be used as an adjunct to psychosocial treatments to prevent relapse in detoxified patients who were formerly dependent on opioids. Naltrexone should only be initiated in specialist clinics. Patients should have remained opioid-free for at least 7–10 days before naltrexone is started. Naltrexone has also been shown to be useful for relapse prevention in those who misuse alcohol. Dihydrocodeine • Dihydrocodeine is an opiate analgesic and when taken

in overdose has a number of toxic effects. • It acts as a respiratory depressant leading to reduced respiratory rate. • It can cause bradycardia and hypotension in large doses. • Pupillary constriction is a diagnostic feature in opiate overdose. • It is also a central nervous system depressant and therefore causes coma in overdose. Pain relief • Titrating the dose of morphine needed for analgesia should be done with rapidly acting formulations of morphine, and once adequate analgesia is obtained sustained-release morphine can then be substituted (at the same total daily dose) Analgesia in opiate users (eg: on methadone) • Discontinuation of methadone may result in symptoms of acute opiate withdrawal and this is not recommended • Continuation of methadone and consideration of analgesics with a different mode of action (ie non-steroidals such as parenteral diclofenac) is recommended Opioid withdrawal • The symptoms and signs of opioid withdrawal include dysphoric mood, yawning, insomnia, nausea, vomiting, diarrhoea, muscle aches, lacrimation / rhinorrhoea, pupillary dilatation, piloerection, sweating and fever. • Initially give 10 mg of methadone syrup and wait about 60 min to determine its effect. Continue administering in 10 mg doses until symptoms are under control. It is rare to exceed a total dose of 40 mg over 24 hours.

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

Pethidine
• Meperidine (Pethidine) is a full opioid agonist at mu receptors. the only opioid that acts as an antimuscarinic • Pethidine is contraindicated in most cases of sickle cell pain. It is metabolized into a cerebral irritant that can lead to clonus, seizures, or altered mental status.
• Pethidine is preferred to morphine in the preoperative management of biliary colic and in the management of acute diverticulitis. Pethidine is comparable to morphine in its sedative and

tranquillizing effects, but the analgesia and respiratory depression it produces are of shorter duration, and it induces less smooth muscle spasm. • It is largely metabolized in the liver and the end-products are excreted in the urine. • Contraindications Bronchial asthma, emphysema or heart failure secondary to chronic lung disease. Increased intracranial pressure, head injury or brain tumour. Severe hepatic impairment, adrenocortical insufficiency, hypothyroidism. Convulsive disorders, acute alcoholism, delirium tremens. Use of monoamine oxidase inhibitors within the previous 14 days.

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

MRCPUK- part-1- jan- 2017: What is the mode of action of buprenorphine? Partial mu opioid receptor agonist

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Cocaine • Cocaine is an alkaloid derived from the coca plant. • cocaine toxicity becoming a much more frequent clinical problem.
Mechanism of action • cocaine blocks the uptake of dopamine, noradrenaline and serotonin

The use of cocaine is associated with a wide variety of adverse effects: Cardiovascular effects • myocardial infarction cocaine-induced MI is thought to be related to coronary artery spasm It is probably caused by stimulation of the α-adrenergic receptors in smooth muscle cells. In addition, cocaine increases endothelin-1 (a vasoconstrictor) and decreases nitric oxide (vasodilator). • both tachycardia and bradycardia may occur • hypertension (Blockage of noradrenaline (norepinephrine) re-uptake leads to tachycardia, & ↑↑BP) • QRS widening and QT prolongation • aortic dissection Neurological effects • seizures • mydriasis • hypertonia • hyperreflexia • haemorrhagic stroke • cocaine-induced spinal cord infarct: The constellation of quadriparesis, spinothalamic sensory loss with sparing of posterior columns and sphincter dysfunction is most suggestive of an anterior spinal cord syndrome. The areflexia may reflect spinal cord shock.

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Pharmacology With a C3/4 spinal cord lesion, it is not surprising that the patient has respiratory difficulties. detection of cocaine in the urine suggesting he was using it Psychiatric effects • agitation (inhibition of dopamine re-uptake psychomotor agitation)
• psychosis • hallucinations (serotonin re-uptake blockade leads to hallucinations)
Others • hyperthermia which may lead to rhabdomyolysis and renal failure • metabolic acidosis • rhabdomyolysis Management of cocaine toxicity • in general benzodiazipines are generally first-line for most cocaine related problems Agitation, seizures and hypertension are best treated with benzodiazepines (such as midazolam) initially.
 Diazepam is useful for the treatment of anxiety and may precipitate a small reduction in blood pressure, but will not treat coronary artery vasospasm. Calcium channel blockers (such as nifedipine) can be used as a second line treatment for hypertension if benzodiazepines are ineffective. • chest pain:
 benzodiazipines + glyceryl trinitrate.
 Other option include calcium antagonists,
 If myocardial infarction develops then primary percutaneous coronary intervention • hypertension:
 benzodiazipines + sodium nitroprusside • Beta blockers should be avoided in cocaine associated myocardial ischaemia or infarction as they can potentiate coronary vasoconstriction.
 Beta blockers are contraindicated as they can cause unopposed alpha activity and worsen hypertension. • Intubation and ventilation will lower blood pressure and improve the ischaemia the most appropriate next intervention if diazepam fail to control the acute symptoms (eg: seizure)
 Whilst IV sodium valproate and IV phenytoin may be effective in terminating the recurrent seizures, these options would cost precious time with respect to controlling blood pressure and pyrexia MRCPUK-Part-1-January 2016 exam: A 23-year-old man found 'collapsed' in the bathroom at a house party. Then C/O severe abdominal pain + blood in his stool. What is the single most likely cause of his abdominal pain? Ischaemic colitis (Ischaemic colitis is a recognised phenomenon following cocaine ingestion and should be considered if patients develop abdominal pain or rectal bleeding)

Heroin withdrawal • The following are all signs of heroin withdrawal: rhinorrhoea diarrhoea nausea and vomiting lacrimation irritability and restlessness, which are cardinal features Heroin substitutes in medical management of withdrawal
• Both buprenorphine and methadone may be considered for use as heroin replacements • Buprenorphine may be associated with less risk in overdose, but NICE recommends that unless circumstances dictate otherwise, methadone should be the first-choice therapy • Co-abuse of alcohol and benzodiazepines may drive preferential use of buprenorphine, as these agents increase the risk of significant CNS depression

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Benzodiazepine overdose

Overview • toxicity with sedative drugs is the second most common agent - after analgesic agents- in some parts of the United Kingdom.

• Benzodiazepine overdose is very rarely life-threatening unless associated with the coingestion of alcohol or other respiratory depressants Features • CNS depression: lethargy, somnolence, hyporeflexia • Ataxia • Slurred speech • Mild hypotension • Respiratory depression Treatment • Supportive therapy GCS ≤ 8: endotracheal intubation Hypotension: fluid resuscitation • Antidote: flumazenil Routine use of flumazenil for benzodiazepine overdose is not recommended A general rule of thumb is that a benzodiazepine toxicity syndrome should never be reversed with the antidote drug flumazenil unless it was you who gave the benzodiazepine.
 Most cases of benzodiazepine overdose occur in patients who are on chronic benzodiazepine therapy for psychiatric illness, anxiety or seizures.
 Rapid reversal of benzodiazepines with flumazenil can precipitate withdrawal symptoms and seizures in patients with benzodiazepine dependence. If a seizure is precipitated by flumazenil the treatment is to give further benzodiazepines. Indications Severe respiratory depression Overdose in benzodiazepine-naive patients (e.g., accidental ingestion in children, periprocedural oversedation with benzodiazepines) reversal of anaesthesia.

Cathinone toxicity • NRG-1 is a synthetic cathinone drug which is increasingly used recreationally.
• Pharmacologically it is a derivative of phenylpropanone which is a naturally occurring 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.
Benzodiazepine overdose is best managed supportively and with airway protection and ventilation if needed. Flumazenil should be avoided unless for reversal of anaesthesia

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• Toxicity is often seen due to lack of regulation of constituents and active ingredients Features • Tachycardia and hypertension may be seen due to the sympathomimetic effects of the drug and in some cases myocardial ischaemia can be seen.
• In the majority of cases of toxicity, however, similar to ecstasy toxicity, hyponatraemia and serotonin syndrome are seen. Hyponatraemia occurs as a consequence of significant water intake to reduce body temperature. Serum sodium levels may be markedly low and patients may present seizing. • Serotonin syndrome is due to massive flooding of synapses with liberated serotonin and causes agitation, confusion, muscle hyperactivity with fasciculations, hypertonia and clonus.
• Creatine kinase and white cell counts are often raised and body temperature may be extremely high. Treatment • If there is evidence of neurological compromise with an accompanying hyponatraemia, rapid correction of sodium is recommended with infusion of 3% saline solution at a maximum rate of 1ml/kg/hour.
• 0.9% saline solution is not recommended in patients with hyponatraemia and agitation due to the

risk of worsening the hyponatraemia.

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

Cyanide poisoning cyanide mechanism of action Inhibition of enzyme cytochrome oxidase c
• Cyanide may be used in: insecticides,
 photograph development and
 production of certain metals.
• Acute cyanide toxicity may occur secondary to burning plastics in the house fire.
• Toxicity results from reversible inhibition of cellular oxidising enzymes • Cyanide ions inhibit mitochondrial cytochrome oxidase, preventing aerobic respiration, which is an essential part of the mitochondrial electron transfer chain (ETC). It therefore interferes with the basic process of cellular respiration, preventing the formation of ATP and causing rapid cell death. Presentation (classical features: brick-red skin, smell of bitter almonds) • manifests in normal oxygen saturations, a high pO2 and flushing (or 'brick red' skin) brought on by the excess oxygenation of venous blood. (it is important to note that the blood gas sample given is venous rather than arterial) • acute: hypoxia, hypotension, headache, confusion increased anion gap, consistent with high lactate (generated by anaerobic respiration due to the inability to use available oxygen).

 very high lactate and high venous pO2 fit better with cyanide toxicity. • chronic: ataxia, peripheral neuropathy, dermatitis Management • supportive measures: 100% oxygen • definitive: hydroxocobalamin (intravenously), also combination of amyl nitrite (inhaled), sodium nitrite (intravenously), and sodium thiosulfate (intravenously) • The recommended treatment for moderate cyanide toxicity in the UK is one of three options:

1. Hydroxocobalamin,
   - has the best side-effect profile and speed of onset compared with other treatments
2. dicobalt edetate,
   - only given when the patient is tending to lose or has lost consciousness.
   - When the patient is fully conscious, it is unlikely that the extent of poisoning warrants the use of Dicobalt Edetate Injection. Dangerous if given without confirmed cyanide poisoning Other antidotes such as hydroxocobalamin or sodium thiosulphate are preferred.
3. sodium thiosulfate

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

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

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

Acid poisoning Pathology • Acids cause injury by coagulative necrosis Presentation • Acid effects are mainly topical, with corrosive burns to the mouth, oropharynx and stomach • They are less likely than alkalis to cause significant localised damage to the oesophagus • Aspiration can lead to inflammation and a chemical pneumonitis Management • Neutralisation of acids is not appropriate, since this can generate increased heat and so exacerbate any injury sustained • Gastric lavage is contraindicated due to the increased risk of oesophageal perforation • Management consists of supportive care and early endoscopy • Early surgical intervention is required to prevent mediastinitis, from which there is a high mortality, in those patients with signs or symptoms of perforation • Hydrofluoric acid causes significant hypocalcaemia as it binds calcium, even small amounts (topically or ingested) can produce significant hypocalcaemia and be rapidly fatal in cases of significant topical exposure, patients should be monitored for signs of systemic hypocalcaemia
 patient treated with intravenous calcium supplementation if required . Calcium gluconate applied both topically and injected around the burn may be required Systemic fluorosis may occur as a complication

Alkali poisoning • 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

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Radiosensitiser drugs Radiosensitiser drugs radiation toxicity
• dactinomycin, • metronidazole • 5-fluorouracil • gemcitabine • cisplatin • hydroxyurea • paclitaxel • mitomycin C • topotecan

Radioprotector
• Amifostine is a radioprotector

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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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Lead poisoning • Along with acute intermittent porphyria, lead poisoning should be considered in questions giving a combination of abdominal pain and neurological signs • Lead can also be absorbed through the skin and by inhalation. Aetiology: ingestion of: • lead-containing compounds, deliberate (pica) or inadvertent Patients with learning disabilities may be prone to lead poisoning due to pica. • contaminated water from old lead water pipes • occupation, such as a painter have a lead exposure while stripping the walls in old houses. • certain traditional remedies such as ayurvedic medicines Features • abdominal pain • nausea • constipation
• peripheral neuropathy (mainly motor) due to demyelination • fatigue • blue lines on gum margin (only 20% of adult patients, very rare in children) • may be associated with anterior uveitis or iritis Laboratory tests • Whole blood lead levels: <10 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 This occurs due to accumulation of (RNA) in the RBCs due to inhibition of pyrimidine 5 nucleotidase by lead. clover-leaf morphology • raised serum and urine levels of delta aminolaevulinic acid may be seen making it sometimes difficult to differentiate from acute intermittent porphyria • urinary coproporphyrin is also increased (urinary porphobilinogen and uroporphyrin levels are normal to slightly increased) Management - various chelating agents are currently used: • dimercaptosuccinic acid (DMSA) the most appropriate intervention The recommended dose is 10 mg/kg three times per day for five days, followed by 10 mg/kg twice per day for two weeks. • EDTA This is used IV or IM, which makes administration less convenient than DMSA. It is considered for patients with symptoms of severe acute lead poisoning. • Dimercaprol • Penicillamine • succimer

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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

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Cadmium (Cd) poisoning • Workers in zinc factories are at risk of cadmium (Cd) poisoning. Feature • Bone pain, osteopenia • Renal failure.
 The Cd-protein complex is mainly taken up by proximal tubular cells. This may give rise to a tubular proteinuria may also cause a Fanconi syndrome-like presentation, with amino aciduria and phosphaturia.
 Prolonged renal tubular toxicity may cause glomerular damage. Another renal effect of prolonged Cd exposure is calcium phosphate stones.

Thallium poisoning Features • painful polyneuropathy • mood change • alopecia Treatment is chelation therapy with oral Prussian Blue.

Iron overdose • Undissolved iron tablets are radio-opaque Presentation • Early features of iron overdose are due to the direct corrosive effects of iron and include vomiting, diarrhoea and gastrointestinal bleeding • Typically, there is then a latent phase of up to 24 h when the patient is asymptomatic • This is then followed by widespread organ failure • Initial hyperglycaemia can

occur following significant ingestion of iron, but hypoglycaemia can be seen later in cases of severe poisoning with associated hepatic failure • In patients who recover, there may be long-term GI strictures and possible gastrointestinal obstruction due to the initial corrosive effects of iron Treatment • Iron is a metal and therefore will not be adsorbed by activated charcoal • Patients with serum iron concentrations over 90 mmol/l, as well as those with signs of severe toxicity, require chelation therapy with desferrioxamine

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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

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New recreational drugs Drug types Street names Gamma-hydroxybutyric acid (GHB) and gammabutyrolactone (GBL) G, Geebs or Liquid Ecstasy Synthetic agonists of the CB1 receptor Spice Methoxetamine (derivative of ketamine) Mexxy Benzylpiperazine Exodus, Legal X, Legal E Nitrous oxide Hippie crack

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Paracetamol overdose
Overview • it is the most common agent of intentional self-harm • it is the most common cause of acute liver failure
• As little as 10–15 g (20–30 tablets) in an adult or 150 mg/kg of paracetamol taken within 24 h may cause severe hepatocellular necrosis and, less frequently, renal tubular necrosis.
Pathophysiology
 Paracetamol is conjugated to glucuronic acid and sulphate under normal conditions. In overdose these processes become saturated and the drug is then results in a toxic metabolite, N-acetyl-p-benzoquinone imine (NAPQI) (NAPQI) inactivated by glutathione, rapidly preventing any harm. If the glutathione supply is depleted then a toxic metabolite is formed. After ingestion of a therapeutic dose: • The liver normally conjugates paracetamol with glucuronic acid/sulphate.
• and the resulting non-toxic metabolites are excreted in the urine.
• About 4% of a therapeutic dose is metabolised by the cytochromes P450, mainly CYP2E1,

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

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

Paracetamol overdose: risk factors The following groups of patients are at an increased risk of developing hepatotoxicity following a paracetamol overdose: • patients taking liver enzyme-inducing drugs (rifampicin, phenytoin, carbamazepine, chronic alcohol excess, St John's Wort) • malnourished patients (e.g. anorexia or bulimia, cystic fibrosis, hepatitis C, alcoholism, HIV ↓ glutathione stores • patients who have not eaten for a few days • Human immunodeficiency virus (HIV) positive patients.

Investigations • Paracetamol level: take paracetamol level

1. four hours post-ingestion, or
2. as soon as the patient arrives if: Time of overdose is greater than four hours. Staggered overdose (in staggered overdoses, the level is not interpretable except to confirm ingestion). Management The essentials of management are:
3. Check paracetamol level four hours after ingestion, check levels against the RumackMatthew nomogram.
4. Gastric lavage if large dose ingested (more than 7.5 g) and/or presenting within eight hours of ingestion; consider oral charcoal.
5. Give N-acetylcysteine or methionine.
6. Hourly BMs monitored.
7. Check INR 12 hourly.

if patient present with ingestion of non-significant amount (<150mg/kg) and timing of ingestion is known (1- 4 hrs) No immediate action
• A single dose of activated charcoal (50g for adults) can be given up to 1 hour after ingestion • Acetylcysteine should be started immediately or empirically when: if a significant amount has been taken (>150mg/kg).

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Pharmacology Serum paracetamol level: 100 mg/L at 4 hours and 15 mg/L at 15 hours after ingestion patients who present late (8-24 hours) Serum paracetamol level is not available

within an 8-hour time window If there is any doubt about the timing of the ingestion (including a staggered overdose over one hour or more). Patients are unconscious or have a suspected overdose. • Hepatotoxicity is unlikely if it is >24 hours since last ingestion of paracetamol and all the following apply:

1. Patient is asymptomatic.
2. Paracetamol concentration is <5 mg/L.
3. INR is 1.3 or less.
4. ALT is less than 2 times upper limit of normal. If all of the above criteria are fulfilled then acetylcysteine may be stopped, and the patient discharged with the advice to return if he or she becomes symptomatic (vomiting, abdominal pain). • Repeated supratherapeutic ingestion Patients who have ingested <75 mg/kg in a period of 24 hours are very unlikely to develop hepatotoxicity. Those who have ingested 75 mg, or less/kg/24 hours of paracetamol require no treatment. Those who have ingested 75-150 mg/kg/24 hours should be considered for acetylcysteine (based on amount ingested, timing, and other relevant features) Those who have ingested >150 mg/kg/24 hours are treated with acetylcysteine.