# Chapter 4
# Nervous System

## TABLE OF CONTENTS





*High weighting*

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# Nervous System

## 1 Epilepsy and other seizure disorders

The main aim of treatment is to prevent the occurrence of seizures by maintaining an effective dose of one or more antiepileptic drugs. Dosage frequency should be kept as low as possible to encourage adherence, however large doses may require frequent doses to avoid adverse effects associated with high plasma-drug concentration.

Monotherapy with first or second line antiepileptic drug is preferred, as the concurrent use of multiple drugs increases the risk of adverse effects and drug interactions. When changing from one antiepileptic to another, the first drug should be slowly withdrawn.

### 1.1 MHRA/CHM advice

***Switching between different manufacturers' products***
Loss of seizure control and/or worsening of side-effects may be associated with but not excluded to switching between products.

The following guidance has been issued to help minimise risk:

- Antiepileptic drugs have been divided into three risk-based categories to decide whether it is necessary to maintain continuity of supply of a specific manufacturer's product
- If a patient is to be maintained on a specific manufacturer's product this should be prescribed either by specifying a brand name, or by using the generic drug name and name of the manufacturer
- This advice relates only to antiepileptic drug use for treatment of epilepsy; it does not apply to their use in other indications (e.g. mood stabilisation, neuropathic pain);
- Please report on a Yellow Card any suspected adverse reactions to antiepileptic drugs
- If a prescribed product is unavailable, it may be necessary to dispense a product from a different manufacturer to maintain continuity of treatment of that antiepileptic drug

**Risk-based categories of antiepileptic drugs**

1. ***Patient should be maintained on a specific brand***
   Phenytoin, carbamazepine, phenobarbital, primidone
2. ***Supply of a specific brand based on clinical judgment***
   Valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, topiramate
3. ***Unnecessary to supply a specific brand***
   Levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin

***Risk of suicidal thoughts and behaviour***
All antiepileptic drugs are associated with a small increased risk of suicidal thoughts and behaviour. Patients should seek medical advice if the develop symptoms which may occur as early as one week after starting treatment.

### 1.2 Withdrawal

Avoid abrupt withdrawal. Reduction in dosage should be gradual and, in the case of barbiturates, withdrawal of the drug may take months. There is a significant risk of seizure recurrence on drug withdrawal. In patients receiving several antiepileptic drugs, only one drug should be withdrawn at a time.

### 1.3 Driving

Patients with epilepsy may drive a motor vehicle (but not a large goods or passenger carrying vehicle) provided that they have:

- Been seizure-free for one year or,
- Established a 3-year period of asleep attacks without awake attacks

Those affected by drowsiness should not drive or operate machinery. DVLA recommends that patients should not to drive during medication changes or withdrawal of antiepileptic drugs, and for 6 months afterwards.

## 1.4 Pregnancy

There is an increased risk of teratogenicity associated with the use of valproate, phenytoin, primidone, phenobarbital, lamotrigine, and carbamazepine. Valproate is associated with the highest risk of congenital malformations, and long-term developmental disorders. Valproate should not be used during pregnancy, female children, or in women of child-bearing potential unless there is no safer alternative. Specialist monitoring should be instigated when valproate has been taken in pregnancy. Topiramate carries an increased risk of cleft palate if taken in the first trimester of pregnancy.

Women of child-bearing should be given advice about the need for an effective contraception method to avoid unplanned pregnancy. Women who want to become pregnant should be referred to a specialist.

Once an unplanned pregnancy is discovered it is usually too late for changes to be made to the treatment regimen. The likelihood of a woman who is taking antiepileptic drugs having a baby with no malformations is at least 90%, and it is important that women do not stop taking essential treatment because of concern over harm to the fetus. In the case of sodium valproate and valproic acid, an urgent consultation is required to reconsider the benefits and risks of valproate therapy.

To reduce the risk of neural tube defects, folate supplementation is advised before conception and throughout the first trimester. Women who have seizures in the second half of pregnancy should be assessed for eclampsia before any change is made to antiepileptic treatment. Routine injection of vitamin K at birth minimises the risk of neonatal haemorrhage associated with antiepileptics. Withdrawal effects in the new-born may occur with some antiepileptic drugs.

## 1.5 Breastfeeding

Women taking antiepileptic monotherapy should generally be encouraged to breast-feed, otherwise specialist advice should be sought. All infants should be monitored for sedation, feeding difficulties, adequate weight gain, and developmental milestones. Withdrawal effects may occur in infants if a mother suddenly stops breast-feeding.

Infants should also be monitored for adverse effects associated with the antiepileptic drug. Serum-drug concentration monitoring should be undertaken in breast-fed infants if suspected adverse reactions develop; if toxicity develops it may be necessary to introduce formula feeds to limit the infant's drug exposure, or to wean the infant off breast-milk altogether.

## 1.6 Antiepileptic hypersensitivity syndrome

Antiepileptic hypersensitivity syndrome is a rare but potentially fatal syndrome associated with some antiepileptic drugs (carbamazepine, lacosamide, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, primidone, and rufinamide). The symptoms usually start between 1 and 8 weeks of exposure; fever, rash, and lymphadenopathy are most commonly seen. Other systemic signs include liver dysfunction, haematological, renal, and pulmonary abnormalities, vasculitis, and multi-organ failure. If signs or symptoms of hypersensitivity syndrome occur, the drug should be withdrawn immediately, and expert advice should be sought.

## 1.7 Types of Seizures

### 1.7.1 **Focal** (small part of the brain is affected)

1. Simple partial seizures, are where you remain fully conscious throughout
2. Complex partial seizures, are when you lose awareness and can't remember what happened after the seizure has passed

### 1.7.2 **Generalised** (most/all of the brain is affected)

1. Absence seizures, cause the person to lose awareness of their surroundings, usually for up to 15 seconds
2. Myoclonic seizures, cause your arms, legs or upper body to jerk or twitch
3. Clonic seizures, similar twitching to myoclonic jerks, except for longer, normally up to two minutes; loss of consciousness may occur
4. Atonic seizures, cause all your muscles to suddenly relax, injury often results due to a fall
5. Tonic seizures cause all the muscles to suddenly become stiff, injury often results due to a fall
6. Tonic-clonic seizures, have two stages and last a few minutes. Your body will initially become stiff and then your arms and legs will begin twitching

### 1.7.3 Status Epilepticus

Any seizure that lasts longer than 30 minutes, or a series of seizures where the person does not regain

consciousness in between. This is a medical emergency!

## 1.8 Carbamazepine (high risk)

*(inhibits voltage-gated sodium channels, thus preventing repetitive firing of action potentials) Therapeutic range: 4 to 12mg/L (20 to 50 micromol/litre); brand-specific category 1*

### 1.8.1 Warning signs

*(patients advised to report all to doctor immediately)*

- *Toxicity*
  *(incoordination, blurred vision, double vision, drowsiness, nystagmus, ataxia, arrhythmias, nausea & vomiting, diarrhoea, hyponatraemia)*
- *Blood disorders*
  *(fever, sore throat, unexplained bruising or bleeding)*
- *Skin disorders*
  *(mouth ulcers, rash)*
- *Hepatic disorders e.g. hepatitis*
  *(severe GI upset, fatigue, jaundice, dark urine)*
- *Antiepileptic Hypersensitivity Syndrome*
  *(fever, rash, swollen lymph nodes)*

### 1.8.2 Monitoring

- *Plasma concentration*
  *(measured after 2 weeks to ensure within therapeutic range)*
- *Full blood count, renal and hepatic function*
  *(recommended by manufacturers)*

### 1.8.3 Hepatic

*Metabolism impaired in advanced liver disease, dose may need to be increased*

### 1.8.4 Pregnancy and breastfeeding

*During pregnancy, doses should be adjusted on the basis of plasma-concentration monitoring; during breastfeeding, monitor infant for any adverse effects*

### 1.8.5 Drug interactions

- *Increased plasma concentration with acetazolamide, cimetidine, clarithromycin, erythromycin,*
- *Decreased plasma concentration with phenytoin, rifabutin, St. John's Wort*
- *Carbamazepine reduces plasma concentration of antipsychotics, corticosteroids, coumarins, eplerenone, oestrogens, progestogens, simvastatin*
- *Possible increased risk of convulsions when antiepileptics given with orlistat*

## 1.9 Fosphenytoin

(a pro-drug of phenytoin)

**Side effects – Cardiovascular reaction**

IV infusion of fosphenytoin associated with severe cardiovascular reactions including asystole, ventricular fibrillation, and cardiac arrest. Hypotension, bradycardia, and heart block have also been reported. The following are recommended:

- monitor heart rate, blood pressure, and respiratory function for duration of infusion
- observe patient for at least 30 minutes after infusion
- if hypotension occurs, reduce infusion rate or discontinue
- reduce dose or infusion rate in elderly, and in renal or hepatic impairment

## 1.10 Gabapentin

**Safety information**

Levels of propylene glycol, acesulfame K and saccharin sodium may exceed the recommended WHO daily intake limits if high doses of gabapentin oral solution (Rosemont brand) are given to adolescents or adults with low body-weight (39–50 kg).

## 1.11 Lamotragine

### 1.11.1 Blood disorders

Patients and their carers should be alert for symptoms and signs suggestive of bone-marrow failure, such as anaemia, bruising, or infection. Aplastic anaemia, bone-marrow depression, and pancytopenia have been associated rarely with lamotrigine.

### 1.11.2 Skin reactions

Serious skin reactions including Stevens-Johnson syndrome and toxic epidermal necrolysis can develop within the first 8 weeks. Factors associated with increased risk of serious skin reactions include concomitant use of valproate, initial lamotrigine dosing higher than recommended, and more rapid dose escalation than recommended.

Rash is sometimes associated with hypersensitivity syndrome. Consider withdrawal if rash or signs of hypersensitivity syndrome develop.

## 1.12 Phenytoin (high risk)

*(inhibits voltage-gated sodium channels, thus preventing repetitive firing of action potentials) Therapeutic Range: 10 to 20mg/L (or 40 to 80 micromol/litre); brand-specific category 1; Non-linear relationship between dose and plasma drug concentration (dose changes and missed doses)*

### 1.12.1 Dose equivalence and conversion

*Preparations containing phenytoin sodium and phenytoin base are not bioequivalent. 100mg of phenytoin sodium is equivalent in therapeutic effect to 92mg phenytoin base. When switching formulations, the difference in phenytoin content may be clinically significant.*

### 1.12.2 Warning signs

*(patients advised to report all to doctor immediately)*

- *Toxicity*
  *(nystagmus, double vision, slurred speech, ataxia, confusion, and hyperglycaemia)*
- *Skin disorder*
  *(rash, toxic epidermal necrolysis)*
- *Hepatotoxicity*
  *(jaundice, GI pain, dark urine)*
- *Blood disorders*
  *(bleeding, bruising, fever, mouth ulcers, sore throat)*
- *Suicidal thoughts*
- *Low vitamin D levels*
  *(rickets in children, osteomalacia in adults)*

### 1.12.3 Drug interactions

- *Increased plasma concentrations with amiodarone, chloramphenicol, cimetidine, disulfiram, diltiazem, fluconazole, fluoxetine, miconazole, topiramate, trimethoprim, metronidazole, clarithromycin, telithromycin*
- *Reduced plasma concentrations with rifamycins, st Johns Wort, theophylline, itraconazole, ciclosporin*

## 1.13 Sodium Valproate

**Liver toxicity**

Liver dysfunction has occurred in association with valproate usually in first 6 months, and usually involves multiple antiepileptic therapy. Raised liver enzymes during valproate treatment are usually transient but patients should be monitored every 6 months until liver function returns to normal.

Discontinue treatment immediately if abnormally prolonged prothrombin time persists, or signs of toxicity present i.e. persistent vomiting and abdominal pain, anorexia, jaundice, and loss of seizure control.

## 1.14 Topiramate

**Acute myopia with secondary-angle closure glaucoma**

Topiramate has been associated with acute myopia (short-sightedness) with secondary angle-closure glaucoma, typically occurring within 1 month of starting treatment. Fluid build-up resulting in anterior displacement of the lens and iris have also been reported.

If raised intra-ocular pressure occurs:

- seek specialist ophthalmological advice;
- use appropriate measures to reduce intra-ocular pressure;
- stop topiramate as rapidly as feasible

## 1.15 Vigabatrin

**Visual field defects**

The onset of symptoms varies from 1 month to several years after starting. Visual problems usually persist despite discontinuation, and further deterioration cannot be excluded. Visual field testing before treatment and at 6-month intervals is advised. Any new visual symptoms that develop should be reported and reviewed urgently by an ophthalmologist. Gradual withdrawal of vigabatrin should be considered.

## 1.16 Benzodiazepines

**for anaesthesia, e.g. lorazepam and midazolam**

Should only be administered by or under the direct supervision of experienced personnel with adequate training in anaesthesia and airway management.

# 2 Sleep Disorders

The majority if hypnotics and anxiolytics are benzodiazepines, most are sedatives and are associated with a risk of dependence and tolerance. Therefore, they should be reserved only for short courses to alleviate acute conditions.

## 2.1 Hypnotics & anxiolytics

### 2.1.1 Hypnotics

Benzodiazepines, Z-drugs (zaleplon, zolpidem, zopiclone), Chlomethiazole, promethazine, melatonin

### 2.1.2 Anxiolytics

Benzodiazepines, buspirone, meprobamate, barbiturates

## 2.2 Dependence and Withdrawal

Gradual withdrawal minimises effects such as confusion, convulsions, and toxic psychosis.

The benzodiazepine withdrawal syndrome may develop up to 3 weeks after stopping a long acting drug, and days after stopping a short acting one. It is characterised by insomnia, anxiety, loss of body-weight and appetite, tremor, and perspiration.

## 2.3 Barbiturates

Intermediate-acting barbiturates are only recommended for severe intractable insomnia, *in patients already taking barbiturates,* and should be avoided in the elderly. Long-acting have a place only in epilepsy, and short-acting in anaesthesia.

## 2.4 Benzodiazepines

### 2.4.1 Benzodiazepine Indications

1. Benzodiazepines are indicated for the short-term relief (two to four weeks only) of anxiety that is severe or disabling, occurring with or without insomnia
2. The use of benzodiazepines to treat short-term 'mild' anxiety is inappropriate
3. Benzodiazepines should be used to treat insomnia only when it is severe, disabling, or causing the patient extreme distress

### 2.4.2 Types of benzodiazepines

*Short acting (TOLLL)*

Temazepam, Oxazepam, Loprazolam, Lormetazepam, and Lorazepam

*Longer acting*

Nitrazepam, Flurazepam, Diazepam, Alprazolam, Chlordiazepoxide HCl, and Clobazam

### 2.4.3 Side Effects - Overdose

Drowsiness and light-headedness the next day; confusion and ataxia (especially in the elderly); amnesia.

Over dose can cause drowsiness, ataxia, dysarthria, nystagmus, and occasionally respiratory depression, and coma. Activated charcoal can be given within 1 hour of ingesting a significant quantity of benzodiazepine, provided the patient is awake and the airway is protected.

### 2.4.4 Paradoxical effects

Benzodiazepines can also cause a paradoxical increase in hostility and aggression e.g. talkativeness, excitement, and aggressive antisocial acts.

### 2.4.5 Elderly

Benzodiazepines and the Z-drugs (zopiclone, zolpidem, zaleplon) should be avoided in the elderly due to an increased risk of confusion leading to falls and injury.

# 3 Attention deficit hyperactivity disorder

The CNS stimulants methylphenidate and atomoxetine are used for the management of ADHD; dexamfetamine and lisdexamfetamine are an alternative in children who do not respond to these drugs.

## 3.1 Atomoxetine

**Monitoring**

Pulse, blood pressure, psychiatric symptoms, appetite, weight and height should be recorded at initiation of therapy, following each dose adjustment, and at least every 6 months thereafter

Monitor for appearance or worsening of anxiety, depression or tics; history of seizures

**Hepatic disorders**

Rare risk; prompt medical attention should be sought in case of abdominal pain, unexplained nausea, malaise, darkening of the urine, or jaundice

**Suicidal ideation**

Risk of suicidal thoughts and behaviour; report to GP any clinical worsening, suicidal thoughts or behaviour, irritability, agitation, or depression

## 3.2 Dexsamfetamine & Lidexasamfetamine

**Tics and Tourette syndrome**

Discontinue if tics occur; Monitor height and weight as growth restriction may occur during prolonged therapy

# 4 Bipoalr disorder and mania

Treatment usually involves control of acute attacks, and then long-term treatment of disorder for at least two years from the last manic episode, and up to five years if the patient has risk factors for relapse.

Acute benzodiazepine use may be helpful in the initial management of agitation; long-term use not recommended due to risk of dependence. Atypical antipsychotic drugs (normally olanzapine, quetiapine, or risperidone) are useful in acute episodes of mania and hypomania; lithium or valproate are alternatives. Carbamazepine may be used in patients who do not respond to lithium.

## *4.1 Lithium (high risk)*

Narrow therapeutic range: 0.4 to 1 mmol/L (lower end for maintenance and elderly) and 0.8 to 1 mmol/L for acute episodes of mania and relapse patients

### *4.1.1 Warning signs*

(report immediately; requires treatment withdrawal)

- Toxicity – serum concentration over 2 mmol/L (seizures, coma, renal failure, arrhythmias, blood pressure changes, circulatory failure, death)
- Increasing gastrointestinal disturbances (vomiting, diarrhoea)
- Visual disturbances (blurred vision)
- CNS disturbances (drowsiness, unsteadiness, confusion)
- Fine tremor increasing to coarse tremor, muscle weakness
- Signs and symptoms of hypothyroidism (unexplained fatigue, weight gain, hair loss)
- Signs and symptoms of renal dysfunction (polyuria and polydipsia)
- Signs and symptoms of benign intracranial hypertension (persistent headache and visual disturbance)

### *4.1.2 Monitoring*

- Serum lithium concentration – weekly, then every 3 months once dose becomes stable
- Renal function – every 6 months
- Cardiac function – every 6 months
- Thyroid function – every 6 months

### *4.1.3 Driving and skilled tasks*

May impair performance of skilled tasks (e.g. driving, operating machinery)

### *4.1.4 Interactions*

- Increased risk of toxicity with ACE inhibitors, angiotensin-II receptor antagonists, loop diuretics, thiazides and related diuretics, NSAIDs, potassium-sparing diuretics, aldosterone antagonists, metronidazole, SSRIs (and CNS effects), tricyclics
- Increased risk of ventricular arrhythmias with amiodarone
- Risk of neurotoxicity with methyldopa, phenytoin, carbamazepine, diltiazem, verapamil
- Increased risk of extrapyramidal side effects with clozapine, haloperidol, sulpiride, phenothiazines, risperidone, flupentixol, zuclopenthixol

### *4.1.5 Cautions*

Long-term use of lithium has been associated with thyroid disorders and mild cognitive and memory impairment. Long-term treatment should therefore be undertaken only with careful assessment of risk and benefit, and with monitoring of thyroid, cardiac, and renal function every 6 months. Serum lithium concentration should be measured weekly, then every 3 months once dose becomes stable.

### *4.1.6 Dose equivalence and conversion*

Citrate and carbonate salts have different dose equivalence; preparations vary widely in bioavailability, changing the preparation requires the same precautions as initiation of treatment.

### *4.1.7 Other points*

- A lithium treatment pack should be given to patients on initiation of treatment with lithium
- Patient should be kept on the same brand of lithium
- Toxicity is made worse by sodium depletion, therefore keep a constant and adequate salt and water intake (especially if they have an infection or during hot spells)
- Avoid NSAIDs and alcohol
- Do not stop lithium suddenly unless told to by a doctor; risk of relapse

# 5 Antidepressant drugs

The major classes of antidepressant drugs include the tricyclic and related antidepressants (amitriptyline, nortriptyline, doselupin), the selective serotonin re-uptake inhibitors (SSRIs) (citalopram, escitalopram, fluoxetine, sertraline), and the monoamine oxidase inhibitors (MAOIs) (phenlzine).

SSRIs are better tolerated and are safer in overdose than other classes, and should be considered first-line. Tricyclic antidepressants are not effective for treating depression in children. MAOIs have dangerous interactions with some foods and drugs.

## 5.1 St John's wort

Should not be recommended for depression as St John's wort is an enzyme inducer, and it also interacts with many drugs, including antidepressants.

## 5.2 Hyponatraemia and antidepressant therapy

Hyponatraemia (usually in the elderly) risk with all types of antidepressants; more frequently with SSRIs. Hyponatraemia should be considered in all patients who develop drowsiness, confusion, or convulsions while taking an antidepressant.

## 5.3 Suicidal behaviour and antidepressant therapy

Antidepressants have been linked with suicidal thoughts and behaviour in children, young adults, and patients with a history of suicidal behaviour. Patients should be monitored for suicidal behaviour, self-harm, or hostility, particularly at the beginning of treatment or if the dose is changed.

## 5.4 Serotonin syndrome

Serotonin syndrome is an uncommon adverse drug reaction. Symptoms can be life-threatening and fall into 3 main areas:

1. neuromuscular hyperactivity (tremor, hyperreflexia, clonus, myoclonus, rigidity)
2. autonomic dysfunction (tachycardia, blood pressure changes, hyperthermia, diaphoresis, shivering, diarrhoea)
3. altered mental state (agitation, confusion, mania)

## 5.5 Monoamine-oxidase inhibitors

Less common than tricyclics, or SSRIs because of dietary and drug interactions.

**Interactions**

MAOIs inhibit the metabolism of pseudoephedrine present in many cough and decongestant; the hypertensive effect of tyramine (in foods, such as mature cheese, pickled herring, broad bean pods, and Bovril®, Oxo®, Marmite® or any similar meat or yeast extract or fermented soya bean extract) may also be dangerously potentiated. These interactions may cause a dangerous rise in blood pressure. An early warning symptom may be a throbbing headache. Patients should be advised to eat only fresh foods and avoid food that is suspected of being stale or 'going off'. This is especially important with meat, fish, poultry or offal; game should be avoided. Patients should also avoid alcoholic drinks or de-alcoholised (low alcohol) drinks.

Other antidepressants should not be started for 2 weeks after treatment with MAOIs has been stopped. Tricyclics used in conjunction with MAOIs is potentially lethal. SSRIs used with MAOIs increases the risk of serotonergic adverse effects.

**Treatment cessation**

If possible MAOIs should be withdrawn slowly. Withdrawal symptoms include agitation, irritability, ataxia, movement disorders, insomnia, drowsiness, vivid dreams, cognitive impairment, and slowed speech. Occasionally, patients experience hallucinations and paranoid delusions.

The dose should be tapered over at least 4 weeks to avoid these effects.

## 5.6 Selective serotonin re-uptake inhibitors

**Depressive illness in children and adolescents**

The use of citalopram, escitalopram, paroxetine, sertraline, mirtazapine, and venlafaxine is not recommended in individuals under 18. Children and adolescents should be monitored carefully for suicidal behaviour, self-harm or hostility, particularly at the beginning of treatment.

Only fluoxetine has been shown to be effective for use in children and adolescents. However, it is still associated with a small risk of self-harm and suicidal thoughts.

**Cautions**

Epilepsy (avoid if poorly controlled, discontinue if convulsions develop), cardiac disease, diabetes mellitus, susceptibility to angle-closure glaucoma, a history of mania or bleeding disorders (especially gastro-intestinal bleeding), and if used with other drugs that increase the risk of bleeding.

**Overdose**

Symptoms of poisoning include nausea, vomiting, agitation, tremor, nystagmus, drowsiness, and sinus tachycardia; convulsions may occur. Rarely, severe poisoning results in the serotonin syndrome, with marked neuropsychiatric effects, neuromuscular hyperactivity, and autonomic instability; hyperthermia, rhabdomyolysis, renal failure, and coagulopathies may develop.

**Treatment cessation**

Gastro-intestinal disturbances, headache, anxiety, dizziness, paraesthesia, electric shock sensation in the head, neck, and spine, tinnitus, sleep disturbances, fatigue, influenza-like symptoms, and sweating are the most common features of abrupt withdrawal; palpitation and visual disturbances can occur less commonly. The dose should be tapered over at least 4 weeks to avoid these effects.

#### 5.6.1 Paroxetine and venlafaxine

Associated with a higher risk of withdrawal effects.

### 5.7 Tricyclic and related antidepressants

**Cautions**

Use with caution in cardiovascular disease, hyperthyroidism, prostatic hypertrophy, chronic constipation, urinary retention, and glaucoma. Elderly patients are more susceptible to adverse effects.

**Treatment cessation**

Withdrawal symptoms include influenza-like symptoms (chills, myalgia, sweating, headache, nausea), insomnia, vivid dreams, and may occasionally include movement disorders and mania. The dose should be tapered over at least 4 weeks to avoid these effects.

**Children and adolescents**

Studies have shown that tricyclic antidepressants are not effective for treating depression in children.

### 5.8 Agomelatine

**Suicidal behaviour**

Antidepressants have been linked with suicidal thoughts and behaviour in children, young adults, and patients with a history of suicidal behaviour. Patients should be monitored for suicidal behaviour, self-harm, or hostility, particularly at the beginning of treatment or if the dose is changed.

**Hepatotoxicity**

Rare risk of hepatic injury; test liver function before treatment. Patients should be advised on the risk of hepatic side-effects, and advised to seek immediate medical attention if symptoms such as dark urine, light coloured stools, jaundice, bruising, fatigue, abdominal pain, or pruritus develop.

## 6 Psychoses and schizophrenia

Antipsychotic drugs relieve positive psychotic symptoms such as thought disorder, hallucinations, and delusions, and prevent relapse; atypical antipsychotics may be better for negative symptoms such as apathy and social withdrawal.

### 6.1 Doses of antipsychotic drugs above BNF upper limit

Doses in the BNF are licensed doses—any higher dose is therefore unlicensed:

- Consider adjuvant therapy and newer or second-generation antipsychotic drugs such as clozapine
- Bear in mind risk factors, including obesity; particular caution is indicated in older patients, especially those over 70.
- Consider potential for drug interactions
- Carry out ECG to exclude abnormalities such as prolonged QT interval; repeat ECG periodically and reduce dose if prolonged QT interval or other adverse cardiac abnormality develops.
- Increase dose slowly and not more often than once weekly.
- Carry out regular pulse, blood pressure, and temperature checks; ensure that patient maintains adequate fluid intake
- Consider high-dose therapy for a limited period and review regularly; abandon if no improvement after 3 months (return to standard dosage)

## 6.2 Emergency treatment

Emergency IM dose should be lower than the corresponding oral dose (owing to absence of first-pass effect); review dose at least daily.

## 6.3 Prescribing for the elderly

In elderly patients with dementia, antipsychotic drugs are associated with an increased risk of mortality and stroke or transient ischaemic attack. Furthermore, elderly patients are particularly susceptible to postural hypotension and to hyper- and hypothermia in hot or cold weather. It is recommended that:

- Antipsychotic drugs should be avoided in mild to moderate cases
- Initial doses in elderly patients should be reduced (to half the adult dose or less)
- Treatment should be reviewed regularly

Risperidone is the only atypical licensed for patients over 65; should be used for maximum of 6 weeks then reviewed.

## 6.4 Anti-psychotic drugs

### 6.4.1 Typical (fist-generation)

Cause extra-pyramidal side effects (EPSEs) e.g. chlorpromazine, haloperidol, flupentixol, fluphenazine

### 6.4.2 Atypical (second-generation)

Reduced risk of EPSEs, but may occur in high doses; associated more with metabolic side effects e.g. amisulpride, aripiprazole, olanzapine, quetiapine, risperidone

## 6.5 Side effects

### 6.5.1 Extrapyramidal symptoms

- ACUTE Pseduoparkinsonism (tremor or rigidity); can be treated with antimuscarinic e.g. procyclidine
- ACUTE Dystonia (abnormal face and body movements); can be treated with antimuscarinic e.g. procyclidine
- ACUTE akathisia (inner restlessness); either discontinued or treated with different antipsychotic
- CHRONIC tardive dyskinesia (rhythmic, involuntary movements of tongue, face, and jaw); usually develops on long-term therapy; may be irreversible on withdrawing therapy; worth switching patient to atypical antipsychotic

### 6.5.2 Hyperprolactinaemia

Both first- and second-generation, increase prolactin concentration to some extent because dopamine inhibits prolactin release. Common with risperidone and amisulpride; symptoms include sexual dysfunction, reduced bone mineral density, menstrual disturbances, breast enlargement, and galactorrhoea.

### 6.5.3 Sexual dysfunction

Decreased libido, disorders of arousal, and erection / ejaculation problems in men. Common with haloperidol and risperidone.

### 6.5.4 Cardiovascular

Risk of QT-interval prolongation with doses exceeding the recommended maximum; side-effects such as tachycardia, arrhythmias, and hypotension possible. Cases of sudden death have occurred.

### 6.5.5 Hyperglycaemia, weight gain, and diabetes

Particularly with clozapine, olanzapine, quetiapine, and risperidone; regular monitoring necessary

### 6.5.6 Hypotension and interference with temperature regulation

Risk of dangerous falls and hypothermia or hyperthermia in the elderly. Clozapine, chlorpromazine, and quetiapine can cause postural hypotension which may be associated with syncope.

## 6.6 Monitoring

- Full blood count, urea and electrolytes, and liver function tests are required at the start of therapy, and then annually thereafter
- Blood lipids and weight should be measured at baseline, at 3 months and then yearly (patients taking clozapine or olanzapine require more frequent monitoring)
- Fasting blood glucose should be measured at baseline, at 4–6 months, and then yearly (patients taking clozapine or olanzapine require more frequent monitoring)
- Blood pressure monitoring is advised before starting therapy and frequently during dose titration of antipsychotic drugs
- ECG may be required, particularly with cardiovascular risk factors, or if personal history of cardiovascular disease exists
- Monitor prolactin concentration at the start of therapy, at 6 months, and then yearly
- Patients with schizophrenia should have physical health monitoring (including cardiovascular disease risk assessment) at least once per year

### 6.7 Chlorpromazine

**Acute dystonic reaction**

Increased risk of dystonic reactions such as facial and skeletal muscle spasms and oculogyric crisis; especially in young children, and young women.

**Contact sensitisation**

Avoid direct contact with chlorpromazine; tablets should not be crushed and solutions should be handled with care

### 6.8 Pimozide

**ECG monitoring**

ECG recommended before treatment due to risk of sudden unexplained death. Patients should also have an annual ECG, and pimozide should not be given with other antipsychotic drugs, tricyclic antidepressants or other drugs which prolong the QT interval. If the QT interval is prolonged, treatment should be reviewed.

### 6.9 Clozapine

**Agranulocytosis**

Risk of fatal blood disorder; blood counts must be normal before starting treatment. Avoid drugs which exacerbate leukopenia; patients should report immediately symptoms of infection, especially influenza-like illness.

**Myocarditis and cardiomyopathy**

Risk of fatal myocarditis and cardiomyopathy:

- Perform physical examination and take full medical history before starting
- Specialist examination required if cardiac abnormalities or history of heart disease found
- Persistent tachycardia especially in first 2 months should prompt observation for other indicators for myocarditis or cardiomyopathy
- If myocarditis or cardiomyopathy suspected clozapine should be stopped and patient evaluated urgently by cardiologist
- Discontinue permanently in clozapine-induced myocarditis or cardiomyopathy

**Intestinal obstruction**

Risk if constipation, intestinal obstruction, faecal impaction, and fatal paralytic ileus. Clozapine should be used with caution in patients receiving drugs that may cause constipation (e.g. antimuscarinic drugs) or in those with a history of colonic disease or lower abdominal surgery.

**Hypersalivation**

Can be treated with hyoscine hydrobromide; provided that the patient is not at risk from the additive antimuscarinic side-effects of hyoscine and clozapine.

**Monitoring -** see above

### 6.10 Olanzapine

**CNS and respiratory depression**

Increased risk especially in those also receiving a benzodiazepine; blood pressure, pulse and respiratory rate should be monitored for at least 4 hours after intramuscular injection (leave at least one hour between administration of IM olanzapine and parenteral benzodiazepines)

## 7 Parkinson's disease

The progressive degeneration of neurones in the substantia nigra leads to a deficiency of the neurotransmitter dopamine. Drug therapy does not prevent disease progression, but it improves most patients' quality of life.

### 7.1 Dopaminergic drugs

(Levodopa, ropinorole, rotigotine)

**Impulse control disorders**

Patient may experience pathological gambling, binge eating, and hypersexuality. If impulse control disorder develops, the dopamine-receptor agonist or levodopa should be withdrawn or the dose reduced until the symptoms resolve.

**Driving**

***Sudden onset of sleep***

Excessive daytime sleepiness and sudden onset of sleep can occur; exercise caution when driving or operating machinery. Patients should be counselled on improving sleep behaviour.

***Hypotensive reactions***

Hypotensive reactions can occur in some patients; these can be particularly problematic during the first few days of treatment and care should be exercised when driving or operating machinery.

#### 7.1.1 Bromocriptine, Cabergoline, and Pergolide

**Fibrotic reactions (ergot-derived dopamine-receptor agonists)**

Associated with pulmonary, retroperitoneal, and pericardial fibrotic reactions. Conduct ECG before treatment with ergot derivatives; may also be appropriate to measure the erythrocyte sedimentation rate and serum creatinine and to obtain a chest X-ray. Patients should be monitored for dyspnoea, persistent cough, chest pain, cardiac failure, and abdominal pain or tenderness.

#### 7.1.2 Pramipexole

**Dose equivalence and conversion**

Doses and strengths are stated in terms of pramipexole (base); equivalent strengths in terms of pramipexole dihydrochloride monohydrate (salt) are as follows:

- 88 micrograms base ≡ 125 micrograms salt;
- 180 micrograms base ≡ 250 micrograms salt;
- 350 micrograms base ≡ 500 micrograms salt;
- 700 micrograms base ≡ 1 mg salt

# 8 Nausea and Vertigo

Need to identify cause e.g. diabetic ketoacidosis, or digoxin or antiepileptic overdose, to prevent complications.

## 8.1 Pregnancy

Nausea in the first trimester is generally mild and does not require drug therapy. If vomiting is severe, short-term treatment with an antihistamine, such as promethazine, may be required. Prochlorperazine or metoclopramide are alternatives.

## 8.2 Motion sickness

Ideal to prevent motion sickness rather than treat nausea or vomiting. The most effective drug is hyoscine hydrobromide. For children over 10, a transdermal patch provides prolonged activity. If sedative effect is desired, cyclizine or cinnarizine is preferred.

## 8.3 Ménière's disease

Betahistine is licensed for vertigo, tinnitus, and hearing loss associated with the condition.

## 8.4 Domperidone

Domperidone is licensed only for the relief of nausea and vomiting. It has the advantage over metoclopramide and the phenothiazines as it does not readily cross the blood-brain barrier, and is less likely to cause central effects such as sedation and dystonic reactions.

**Risk of cardiac side-effects**

Domperidone is associated with an increased risk of serious cardiac side-effects:

- Domperidone should only be used for the relief of the symptoms of nausea and vomiting
- Domperidone should be used at the lowest effective dose for the shortest possible duration (max. duration should not exceed 1 week)
- Domperidone is contra-indicated for use in conditions where cardiac conduction is, or could be impaired, or where there is underlying cardiac disease, when administered concomitantly with drugs that prolong the QT interval or potent CYP3A4 inhibitors, and in severe hepatic impairment
- The recommended dose in adults and adolescents over 12 years and over 35 kg is 10 mg up to 3 times daily
- The recommended dose in children under 35 kg is 250 micrograms/kg up to 3 times daily
- Oral liquid formulations should be given via an appropriately designed, graduated oral syringe to ensure dose accuracy

## 8.5 Metoclopramide

Metoclopramide is an effective antiemetic; it can induce acute dystonic reactions involving facial and skeletal muscle spasms and oculogyric crises. These effects are more common in young children, and young women. The antimuscarinic procyclidine can reverse such attacks.

**Risk of neurological adverse effects**

The risk of EPSE outweigh the benefits in long-term or high-dose treatment:

- In adults over 18 years, metoclopramide should only be used for prevention of postoperative nausea and vomiting, radiotherapy-induced nausea and vomiting, delayed (but not acute) chemotherapy-induced nausea and vomiting, and symptomatic treatment of nausea and vomiting,
- Metoclopramide should only be prescribed for short-term use (up to 5 days);

- Usual dose is 10 mg, repeated up to 3 times daily; max. daily dose is 500 micrograms/kg
- Intravenous doses should be administered as a slow bolus over at least 3 minutes
- Oral liquid formulations should be given via graduated oral syringe to ensure dose accuracy

# 9 Non-opioid analgesics

**Aspirin**
Indicated for headache, transient musculoskeletal pain, dysmenorrhoea, and pyrexia. However, NSAIDs are preferred as they are better tolerated. Gastric irritation may be a problem; it is minimised by taking the dose after food.

**Paracetamol**
Similar in efficacy to aspirin, but has no demonstrable anti-inflammatory activity; it is less irritant to the stomach and for that reason is now generally preferred to aspirin, particularly in the elderly.

**Nefopam**
May be useful in the relief of persistent pain unresponsive to other non-opioid analgesics; antimuscarinic side-effects may be troublesome.

**NSAIDs**
Useful in chronic and short-term treatment of mild to moderate pain (particularly musculoskeletal pain). However, paracetamol is often preferred, especially in the elderly. COX2 inhibitors may be used in patients at high risk of developing serious GI side-effects.

## 9.1 Ibuprofen doses

**Post-immunisation pyrexia in infants**
Child 2–3 months 50 mg as a single dose repeated once after 6 hours if necessary

**By mouth**
- 1–3 months 5 mg/kg QDS
- 3–6 months 50 mg TDS
- 6 months–1 year 50 mg QDS
- 1–4 years 100 mg TDS
- 4–7 years 150 mg TDS
- 7–10 years 200 mg TDS
- 10–12 years 300 mg TDS
- 12 and over initially 300–400 mg QDS; increased if necessary to max. 600 mg QDS

## 9.2 Paracetamol doses

- Increased risk of toxicity at therapeutic doses in those with a body-weight under 50 kg and those with risk factors for hepatotoxicity.
- not licensed in children < 2 months by mouth

**Post-immunisation pyrexia in infants**
2 – 4 months 60 mg as a single dose repeated once after 4–6 hours if necessary (max 4 doses in 24 hours)

**By mouth**
- 1–3 months 30–60 mg TDS
- 3–6 months 60 mg QDS;
- 6 months–2 years 120 mg QDS
- 2–4 years 180 mg QDS
- 4–6 years 240 mg QDS
- 6–8 years 240–250 mg QDS
- 8–10 years 360–375 mg QDS
- 10–12 years 480–500 mg QDS
- 12–16 years 480–750 mg QDS
- 16 and over 500 mg–1 g QDS

# *10 Opiates (high risk)*

## *10.1 Warning signs*

*(report to GP immediately)*
- *Respiratory depression (difficulty breathing)*
- *Bradycardia / hypotension (feeling faint, dizziness)*
- *Extreme sleepiness*
- *Reduced concentration or confusion (not able to think, walk or talk normally)*
- *Cyanosis (of lips, ears, nose)*
- *Vivid dreams, hallucinations or nightmares*
- *Convulsions*
- *Pinpoint pupils*

## 10.2 Dependence and tolerance

*Psychological behaviours include craving, compulsive use, continued use despite harm. Physical dependence or withdrawal occurs when the drug is stopped suddenly or when the dose is tapered rapidly; sings include sweating, restlessness, tremor, increase in normal pain, diarrhoea, nausea / vomiting, and anxiety. Tolerance can develop during long-term treatment where increasing doses are required to achieve the same therapeutic effect.*

### *10.3 Monitoring*

*Pain and sedation*

### *10.4 Interactions*

- *Enhanced hypotensive and sedative effects when given with alcohol*
- *Tramadol enhances anticoagulant effect of coumarins*
- *Decreased effect of fentanyl, morphine, codeine, methadone and alfentanil when given with rifampicin*
- *Possible CNS excitation or depression (hypertension or hypotension) when opiates given with MAOIs*

### *10.5 Other points*

- *Doses increases should not be more than 50% of previous dose*
- *Treatment should not be stopped suddenly*
- *Dose of opioid for breakthrough pain should be 1/10$^{th}$ to 1/6$^{th}$ of total daily dose*
- *Analgesic ladder*
  1. *Non-opioid: (aspirin, paracetamol, NSAID)*
  2. *Weak opioid (codeine, dihydrocodiene, meptazinol)*
  3. *Strong opioid (morphine, buprenorphine, diamorphine, fentanyl/ils, oxycodone, tapentadol, tramadol)*

### 10.6 Codeine

**Variation in metabolism**

Hepatic codeine metabolism produces morphine. This capacity to metabolise codeine varies between individuals; there is an increased risk of morphine toxicity in patients who are ultra-rapid codeine metabolisers (CYP2D6 ultra-rapid metabolisers), and a reduced therapeutic effect in poor codeine metabolisers

**Contra-indications**

- children younger than 12 years old
- patients of any age known to be CYP2D6 ultra-rapid metabolisers
- breastfeeding mothers
- all children under 18 who undergo surgery of tonsils or adenoids for sleep apnoea
- all children under 18 with respiratory problems

## 10.7 Fentanyl

**Transdermal fentanyl**

*Fever or external heat*

Monitor patients using patches for increased side-effects if fever present (increased absorption possible); avoid exposing application site to external heat, for example a hot bath or sauna (may also increase absorption); due to long duration of action, patients who have had severe side-effects should be monitored for up to 24 hours after patch removal

*Respiratory depression*

Risk of fatal respiratory depression, particularly in opioid naïve patients; manufacturer recommends use only in opioid tolerant patients

*Counselling*

Patches should be removed immediately in case of breathing difficulties, marked drowsiness, confusion, dizziness, or impaired speech, and patients and carers should seek prompt medical attention.

# 11 Neuropathic pain

Occurs as a result of damage to neural tissue, includes phantom limb pain, compression neuropathies, peripheral neuropathies.

Generally managed with a tricyclic antidepressant or with certain antiepileptic drugs e.g. amitriptyline and pregabalin. Nortriptyline may be better tolerated than amitriptyline. Gabapentin is also effective for the treatment of neuropathic pain.

Capsaicin is licensed for neuropathic pain (but the intense burning sensation during initial treatment may limit use).

# 12 Antimigraine drugs

Aspirin, paracetamol or a NSAID is often effective for acute treatment; concomitant antiemetic treatment may be required. If simple analgesics are inadequate, 5HT1-receptor agonists ('triptans') are used. Ergot alkaloids are rarely used, as they are less suitable for prescribing.

### 12.1 Ergotamine

**Peripheral vasospasm**

Stop treatment immediately if numbness or tingling of extremities develops and to contact doctor.

# 13 Substance Dependence

## 13.1 Alcohol dependence

### 13.1.1 Acute alcohol withdrawal

Moderate dependence can generally be treated in a community setting. Without inpatient medical support, withdrawal in severely dependent patients may lead to seizures, delirium tremens, and death. Long-acting benzodiazepines are used to reduce alcohol withdrawal symptoms. Carbamazepine [unlicensed] is sometimes used as an alternative treatment in acute alcohol withdrawal when benzodiazepines are contra-indicated or not tolerated. Patients with clear agitation or hallucinations and those at risk of delirium tremens may be prescribed antipsychotic drugs, such as haloperidol or olanzapine [unlicensed indication].

### 13.1.2 Drugs used in alcohol dependence

*Acamprosate* and *naltrexone* are effective treatments for relapse prevention; *disulfiram* is an alternative in patients in whom acamprosate and naltrexone are not suitable. *Nalmefene* is also licensed for the reduction of alcohol consumption in patients with alcohol dependence who have a high drinking risk.

## 13.2 Nicotine dependence

Nicotine replacement therapy, bupropion, and varenicline are effective aids to smoking cessation. Nicotine replacement therapy with varenicline or bupropion is not recommended.

### 13.2.1 Concomitant medication

Smoking increases the metabolism of drugs such as theophylline, ropinirole, and some antipsychotics, by stimulating the hepatic enzyme CYP1A2. When smoking is discontinued, the dose of these drugs may need to be reduced.

### 13.2.2 Varenicline

**MHRA/CHM advice - Suicidal behaviour and varenicline**

Patients should be advised to discontinue treatment and seek prompt medical advice if they develop agitation, depressed mood, or suicidal thoughts. Patients with a history of psychiatric illness should be monitored closely while taking varenicline.

## 13.3 Opioid dependence

Untreated heroin dependence shows early withdrawal symptoms within 8 hours, symptoms subside substantially after 5 days. Methadone or buprenorphine withdrawal occurs later, with longer-lasting symptoms.

### 13.3.1 Opioid substitution therapy

Methadone and buprenorphine are used as substitution therapy in opioid dependence. Patients who miss 3 days or more of their regular prescribed dose of opioid maintenance therapy are at risk of overdose because of loss of tolerance. Consider reducing the dose in these patients.

Buprenorphine is an opioid-receptor partial agonist, it is preferred by some patients because it is less sedating than methadone. Methadone, a long-acting opioid agonist, is usually administered in a single daily dose as methadone oral solution 1 mg/mL.

### 13.3.2 Pregnancy and breastfeeding

Acute withdrawal of opioids should be avoided in pregnancy because it can cause foetal death. Treatment of opioid dependence should be continued during pregnancy [buprenorphine is not licensed for use in pregnancy].

Withdrawal of methadone or buprenorphine should only be undertaken gradually during the second trimester. During the first trimester, there is an increased risk of spontaneous miscarriage, and during the third trimester as maternal withdrawal is associated with foetal distress, stillbirth, and the risk of neonatal mortality. The neonate should also be monitored for respiratory depression and signs of withdrawal.

The dose of methadone should be kept as low as possible in breast-feeding mothers. Neonates and infants should be monitored for should be monitored for drowsiness, adequate weight gain, and developmental milestones. Adverse effects in breast-fed babies should be reported urgently.

## 13.3.3 Methadone

Methadone Linctus is licensed for analgesia in severe pain, and cough in terminal disease. NOTE: Methadone oral solution strength is 1 mg/mL, Methadone Linctus strength is 2mg/5mL.

### 13.3.4 QT-interval prolongation

Patients with the following risk factors for QT-interval prolongation should be carefully monitored while taking methadone: heart or liver disease, electrolyte abnormalities, or concomitant treatment with drugs that can prolong QT interval; patients requiring more than 100 mg daily should also be monitored.

### 13.3.5 Side effects

Methadone, even in low doses is a special hazard for children; non-dependent adults are also at risk of toxicity; dependent adults are at risk if tolerance is incorrectly assessed during induction.

Methadone overdose requires pro-longed monitoring due to the long-acting nature of the opioid.