[X] Close

Approach to managing acute seizures and status epilepticus

Approach to managing acute seizures and status epilepticus

Most seizures are brief and end within 1 to 3 minutes without drug treatment. Acute symptomatic seizures are caused by a transient systemic or central nervous system insult. Epilepsy is a disorder characterised by a tendency to experience recurrent seizures.

Most seizures are brief and do not require drug treatment.

Status epilepticus refers to continuous seizure activity or repeated seizures without full recovery of consciousness between attacks. The minimum duration of continuous seizure activity required for the diagnosis of status epilepticus is traditionally agreed to be 30 minutes. However, drug treatment for a seizure should start after 5 minutes of continuous seizure activity.

Status epilepticus may be convulsive or nonconvulsive. The seizures of convulsive status epilepticus are usually tonic-clonic but may be tonic and, after treatment, may become clinically subtle. Nonconvulsive status epilepticus may be generalised (absence status epilepticus) or focal (partial) (impaired awareness [complex partial] or aware [simple partial] status epilepticus).

The treatment of nonconvulsive status epilepticus is less urgent and the risks of therapy, particularly respiratory depression, must be weighed against the risks of continuing nonconvulsive seizures.

The goals of managing status epilepticus are to:

- resuscitate the patient
- stop the seizures
- diagnose the cause of the seizures and treat it when possible
- find and treat complications of the seizures.

Factors that influence management include:

- type of seizure and its setting
- patient's age
- history of seizures and drugs taken for them (including concordance with therapy)
- treatment already administered for this episode.

Acute symptomatic seizures

Acute symptomatic seizures

Acute symptomatic seizures are caused by a transient systemic or central nervous system insult (see examples of causes). For seizures caused by a known toxin or drug, see specific treatment in the Toxicology and toxinology guideline. If alcohol withdrawal cannot be excluded as the cause of a seizure, give intravenous thiamine (see advice for Wernicke encephalopathy).

Resolution of the cause usually stops the seizure. Seizures will recur if the cause recurs (eg during benzodiazepine withdrawal) or if the acute illness has caused permanent brain injury (eg gliosis caused by herpes encephalitis). Acute symptomatic seizures may take the form of status epilepticus—if the seizure continues after 5 minutes, treat as for status epilepticus.

If the cause of an acute symptomatic seizure has been corrected and it is unlikely that the patient will have recurrent seizures (eg when the seizure was caused by hyponatraemia), continued antiepileptic drug therapy is not needed. However, sometimes continued antiepileptic therapy is needed to prevent recurrent seizures when the cause is not immediately reversible (eg bacterial meningitis, eclampsia). In these patients, consider withdrawal of antiepileptic therapy when a minimum of 3 months has elapsed without further seizure activity.
Figure 7.1 Some causes of acute symptomatic seizures

- metabolic disorders
  - hypoglycaemia
  - hyponatraemia
  - hypocalcaemia
  - kidney failure
- intoxication with some drugs or poisons
- drug or alcohol withdrawal
- stroke (ischaemic or haemorrhagic)
- brain trauma (including neurosurgery)
- intracranial infection
  - meningitis (nonviral)
  - encephalitis
  - cerebral abscess
- autoimmune encephalitis
- hypertensive encephalopathy
- severe cerebral hypoxia (eg cardiac arrest)
- eclampsia

Acute management of seizures

Acute management of seizures

Give supportive care

Give supportive care

Most seizures are brief (1 to 3 minutes) and do not require drug treatment.

Most seizures are brief and do not require drug treatment.

Give supportive care to all patients. Position the patient on the left side, protect the airway and maintain oxygenation.

If the patient is in an emergency department or similar setting, connect monitoring equipment and check the blood glucose concentration. Obtain intravenous access if possible. Send blood samples to pathology for a full biochemical panel, full blood count, and antiepileptic drug concentration (if readily available, to check concordance with therapy). Venous blood gas measurements give a fast indication of the patient's acid-base status, ventilation and concentrations of sodium, glucose and haemoglobin. If alcohol withdrawal cannot be excluded, give intravenous thiamine (see advice for Wernicke encephalopathy).

If the seizure stops, see advice on immediate follow-up after a seizure.

Treat status epilepticus

Treat status epilepticus
Step 1. Give a benzodiazepine

Start drug treatment:

- after 5 minutes of continuous seizure activity, or

- when the patient has repeated seizures without full recovery of consciousness between attacks.

Manage status epilepticus as a medical emergency. Most patients need to be intubated.

For seizures in children, in addition to the advice that follows, see febrile seizures, infantile spasms and neonatal seizures.

If intravenous access is available quickly, use:

1 midazolam 10 mg (child: 0.15 to 0.2 mg/kg up to 10 mg) intravenously, over at least 2 minutes *status epilepticus*

OR

2 diazepam 10 mg (child: 0.1 to 0.25 mg/kg up to 10 mg) intravenously, over at least 2 minutes *status epilepticus*

OR

3 clonazepam 1 mg (child: 0.25 to 0.5 mg) intravenously, over at least 2 minutes. *status epilepticus*

If intravenous access cannot be obtained quickly, use:

1 midazolam, adult over 40 kg, 10 mg; adult under 40 kg, 5 mg (child: 0.15 to 0.2 mg/kg up to 10 mg) intramuscularly

OR

2 midazolam 5 to 10 mg (child: 0.2 to 0.3 mg/kg up to 10 mg) buccally or intranasally [Note 1].

Note 1: Midazolam solution for injection (hydrochloride salt) can be given buccally or intranasally and may be provided under expert advice to parents and carers who have been trained in its use. Fact sheets that explain the method are available (eg from the Royal Children's Hospital Melbourne).

Step 2. Give an antiepileptic drug

If the seizure stops promptly and the cause has been identified and reversed (see acute symptomatic seizures), further treatment is not needed. In all other patients, prevent further acute seizures by starting treatment with an antiepileptic drug—the benzodiazepines recommended in Step 1 have a short anticonvulsant effect.

If the patient usually takes an antiepileptic drug(s) for epilepsy, the choice of drug in this step depends on several clinical variables—seek expert advice.

In adults, levetiracetam and sodium valproate are the preferred antiepileptic drugs to prevent further acute seizures after benzodiazepine administration (see Step 1). In a randomised controlled trial, levetiracetam, sodium valproate and phenytoin were found to be equally efficacious at the doses recommended below [Note 2]; however, phenytoin is not preferred because of its adverse effect profile (eg arrhythmia, infusion problems, hypotension) and requirement for a slow infusion rate.

For **adults**, if intravenous access is available [Note 3], use:

1levetiracetam 60 mg/kg up to 4500 mg intravenously, over 5 minutes *status epilepticus*

OR

1 sodium valproate 40 mg/kg up to 3000 mg intravenously, over 5 to 10 minutes *status epilepticus*

OR

2 phenytoin sodium 20 mg/kg intravenously, no faster than 50 mg/minute (25 mg/minute in elderly patients and those with comorbidities). Monitor blood pressure and electrocardiogram (if monitor available) [Note 4]

[Note 5]. *status epilepticus*

In adults, lacosamide can be used to treat status epilepticus, but supporting evidence is limited. Phenobarbital (phenobarbitone) can also be used in adults, though ideally it should be given in an intensive care setting due to the risk of respiratory depression when given after a benzodiazepine.

In children, levetiracetam, phenytoin and sodium valproate are the preferred antiepileptic drugs to prevent further acute seizures after benzodiazepine administration (see Step 1) and have been found to be equally efficacious in clinical trials [Note 2] [Note 6] [Note 7]. Despite phenytoin's adverse effect profile (eg arrhythmias, infusion problems, hypotension) and requirement for a slow infusion rate, phenytoin is still a preferred antiepileptic drug in children because of extensive experience with its use and because sodium valproate is associated with a risk of hepatotoxicity in children younger than 3 years. Phenobarbital (phenobarbitone) can also be used in children, but it is not preferred because of the risk of respiratory depression when given after a benzodiazepine; ideally phenobarbital should be given in an intensive care setting.

For **children**, if intravenous access is available [Note 3], use:

1levetiracetam 40 mg/kg up to 3000 mg intravenously, over 5 minutes

OR

1 phenytoin sodium 20 mg/kg intravenously, no faster than 25 mg/minute. Monitor blood pressure and electrocardiogram (if monitor available) [Note 4] [Note 5]

OR

1 sodium valproate (child 3 years and older) 40 mg/kg intravenously, over 5 to 10 minutes [Note 8]

OR

2 phenobarbital (phenobarbitone) 20 mg/kg up to 1000 mg intravenously, no faster than 1 mg/kg/minute (maximum 60 mg/minute). *status epilepticus (child)*

When the visible signs of seizure have stopped, perform an electroencephalogram (EEG) in all patients who have not fully regained consciousness, to exclude nonconvulsive status epilepticus.

If the seizure stops after giving an antiepileptic drug, see advice on immediate follow-up after a seizure.

Note 2: Chamberlain JM, Kapur J, Shinnar S, Elm J, Holsti M, Babcock L, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. Lancet 2020;395(10231):1217-24. https://www.ncbi.nlm.nih.gov/pubmed/32203691

Note 3: When intravenous access is unobtainable, these drugs can be given intraosseously.

Note 4: Use phenytoin with caution when status epilepticus is due to overdose with a cardiotoxic drug (eg a tricyclic antidepressant). Specific antidotes or treatments may be indicated in certain cases (eg pyridoxine for isoniazid poisoning). Seek expert toxicology advice. To treat seizures caused by a drug overdose, see specific pharmacological therapies in the Toxicology and toxinology guideline.

Note 5: Administer phenytoin undiluted in a syringe driver, if available. If a syringe driver is not available, dilute the phenytoin sodium in sodium chloride 0.9% to 5 mg/mL. The diluted solution must be used within 1 hour to avoid precipitation. After injection, flush the needle or catheter with sodium chloride 0.9% to avoid local venous irritation. Phenytoin is incompatible with other infusion fluids, due to the risk of precipitation.

Note 6: Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze J, Donath S, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. Lancet 2019;393(10186):2135-45. https://www.ncbi.nlm.nih.gov/pubmed/31005386

Note 7: Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet 2019;393(10186):2125-34. https://www.ncbi.nlm.nih.gov/pubmed/31005385

Note 8: Sodium valproate should be avoided in children younger than 3 years of age because of an increased risk of hepatotoxicity in this age group.

Step 3. Transfer to intensive care unit and seek expert advice

If the seizure continues, transfer the patient to the intensive care unit and seek expert advice. Continuous EEG monitoring should be used, if available.

Deciding when to escalate therapy to an anaesthetic drug with artificial ventilation depends on several clinical factors and the skill set of available personnel. Ongoing seizures with airway or respiratory compromise should prompt early escalation, to minimise the risk of injury to the central nervous system.

As a general guide, an infusion of a general anaesthetic (eg thiopentone, propofol) should be started in patients who are still having seizures after 15 minutes, despite treatment with a benzodiazepine and an antiepileptic drug. Evidence to guide the choice of drug is lacking. When patients are ventilated, avoid long-acting neuromuscular blocking drugs if possible, because these can mask ongoing seizures.

Complications of seizures

Complications of seizures

Check for complications of seizures and treat if needed. Complications include:

- aspiration
- trauma (eg posterior shoulder dislocation).

When seizures are prolonged, complications include:

- central nervous system injury
- noncardiogenic pulmonary oedema
- rhabdomyolysis, acidosis and kidney failure
- hyperthermia.

Seizures caused by eclampsia

Seizures caused by eclampsia

Urgent obstetric and intensive care unit consultation is mandatory for patients with eclampsia. For eclamptic seizures, the drug of choice is magnesium sulfate [Note 9].

Note 9: For information on treating eclampsia with magnesium sulfate, see The Royal Women's Hospital clinical guideline 'Magnesium sulphate - management of hypertensive disorders of pregnancy'

Immediate follow-up after a seizure

Immediate follow-up after a seizure

Immediate management of patients who have had a seizure depends on the patient's history and whether an acute treatable cause can be identified.

If the patient has no history of previous seizures, take a detailed history from the patient and witnesses to classify the seizure and explore causes. If not already done, check the blood glucose concentration and send blood for a full biochemical panel and blood count. Consider performing a urine drug screen. Perform computed tomography. Perform a lumbar puncture if intracranial infection is suspected. If an acute treatable cause is suspected, see acute symptomatic seizures. If an acute treatable cause is not found, suspect epilepsy.

If the patient has a history of previous seizures but is not being treated with an antiepileptic drug, investigate as above unless the results of previous investigations are known. Antiepileptic drug therapy is usually required (see advice).

If the patient has a history of previous seizures and is being treated with an antiepileptic drug, explore common seizure triggers (eg sleep deprivation, febrile illness, nonconcordance with therapy). Measure the plasma concentration of antiepileptic drug(s) if this is readily available.

References

Key references: Treat status epilepticus

- Alldredge BK, Gelb AM, Isaacs SM, Corry MD, Allen F, Ulrich S, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med 2001;345(9):631–7. https://www.ncbi.nlm.nih.gov/pubmed/11547716
- Al-Mufti F, Claassen J. Neurocritical care: status epilepticus review. Crit Care Clin 2014;30(4):751–64. https://www.ncbi.nlm.nih.gov/pubmed/25257739
- Betjemann JP. Current trends in treatment of status epilepticus and refractory status epilepticus. Semin Neurol 2015;35(6):621–8. https://www.ncbi.nlm.nih.gov/pubmed/26595862
- Chamberlain JM, Kapur J, Shinnar S, Elm J, Holsti M, Babcock L, et al. Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial. Lancet 2020;395(10231):1217-24. https://www.ncbi.nlm.nih.gov/pubmed/32203691
- Dalziel SR, Borland ML, Furyk J, Bonisch M, Neutze J, Donath S, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. Lancet 2019;393(10186):2135-45. https://www.ncbi.nlm.nih.gov/pubmed/31005386
- Falco-Walter JJ, Bleck T. Treatment of established status epilepticus. J Clin Med 2016;5(5). https://www.ncbi.nlm.nih.gov/pubmed/27120626
- Glauser T, Shinnar S, Gloss D, Alldredge B, Arya R, Bainbridge J, et al. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr 2016;16(1):48–61. https://www.ncbi.nlm.nih.gov/pubmed/26900382
- Grover EH, Nazzal Y, Hirsch LJ. Treatment of convulsive status epilepticus. Curr Treat Options Neurol 2016;18(3):11. https://www.ncbi.nlm.nih.gov/pubmed/26920416
- Haller JT, Bonnin S, Radosevich J. Rapid administration of undiluted intravenous levetiracetam. Epilepsia 2021;62(8):1865–70. https://www.ncbi.nlm.nih.gov/pubmed/34164804
- Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. Epilepsia 1999;40(1):120–2. https://www.ncbi.nlm.nih.gov/pubmed/9924914
- Lyttle MD, Rainford NEA, Gamble C, Messahel S, Humphreys A, Hickey H, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet 2019;393(10186):2125-34. https://www.ncbi.nlm.nih.gov/pubmed/31005385
- Navarro V, Dagron C, Elie C, Lamhaut L, Demeret S, Urien S, et al. Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial. Lancet Neurol 2016;15(1):47–55. https://www.ncbi.nlm.nih.gov/pubmed/26627366

- Prasad M, Krishnan PR, Sequeira R, Al-Roomi K. Anticonvulsant therapy for status epilepticus. Cochrane Database Syst Rev 2014;(9):CD003723. https://www.ncbi.nlm.nih.gov/pubmed/25207925
- Riviello JJ Jr., Claassen J, LaRoche SM, Sperling MR, Alldredge B, Bleck TP, et al. Treatment of status epilepticus: an international survey of experts. Neurocrit Care 2013;18(2):193–200. https://www.ncbi.nlm.nih.gov/pubmed/23097138
- Rossetti AO, Lowenstein DH. Management of refractory status epilepticus in adults: still more questions than answers. Lancet Neurol 2011;10(10):922–30. https://www.ncbi.nlm.nih.gov/pubmed/21939901
- Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. Brain 2011;134(Pt 10):2802–18. https://www.ncbi.nlm.nih.gov/pubmed/21914716
- Silbergleit R, Durkalski V, Lowenstein D, Conwit R, Pancioli A, Palesch Y, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med 2012;366(7):591–600. https://www.ncbi.nlm.nih.gov/pubmed/22335736
- Treiman DM. Electroclinical features of status epilepticus. J Clin Neurophysiol 1995;12(4):343–62. https://www.ncbi.nlm.nih.gov/pubmed/7560022
- Treiman DM, Meyers PD, Walton NY, Collins JF, Colling C, Rowan AJ, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med 1998;339(12):792–8. https://www.ncbi.nlm.nih.gov/pubmed/9738086
- Trinka E, Hofler J, Leitinger M, Rohracher A, Kalss G, Brigo F. Pharmacologic treatment of status epilepticus. Expert Opin Pharmacother 2016;17(4):513–34. https://www.ncbi.nlm.nih.gov/pubmed/26629986
- Wheless JW, Clarke D, Hovinga CA, Ellis M, Durmeier M, McGregor A, et al. Rapid infusion of a loading dose of intravenous levetiracetam with minimal dilution: a safety study. J Child Neurol 2009;24(8):946–51. https://www.ncbi.nlm.nih.gov/pubmed/19264738
- Yasiry Z, Shorvon SD. The relative effectiveness of five antiepileptic drugs in treatment of benzodiazepine-resistant convulsive status epilepticus: a meta-analysis of published studies. Seizure 2014;23(3):167–74. https://www.ncbi.nlm.nih.gov/pubmed/24433665

Key references: Immediate follow-up after a seizure

- Berg AT, Shinnar S. The risk of seizure recurrence following a first unprovoked seizure: a quantitative review. Neurology 1991;41(7):965–72. https://www.ncbi.nlm.nih.gov/pubmed/2067659
- Gavvala JR, Schuele SU. New-onset seizure in adults and adolescents: a review. JAMA 2016;316(24):2657–68. https://www.ncbi.nlm.nih.gov/pubmed/28027373
- Kramer U, Zelnik N, Lerman-Sagie T, Shahar E. Benign childhood epilepsy with centrotemporal spikes: clinical characteristics and identification of patients at risk for multiple seizures. J Child Neurol 2002;17(1):17–9. https://www.ncbi.nlm.nih.gov/pubmed/11913563

Published November 2017 (Amended May 2022)

[X] Close

Overview of Parkinson disease

Overview of Parkinson disease

Parkinsonism is a syndrome diagnosed by bradykinesia plus one of the following features:

- muscular rigidity
- 4 to 6 Hz rest tremor
- postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction.

Parkinsonism has many causes, but sporadic idiopathic Parkinson disease is the most common. While clinical criteria help distinguish Parkinson disease from other causes, autopsy studies show that diagnostic accuracy is only around 80%. Features that support a diagnosis of Parkinson disease include unilateral rest tremor, excellent response to levodopa, a progressing disorder and persistent asymmetry. Certain clinical features (see Figure 7.7) should prompt a review of the diagnosis. If the diagnosis is in doubt, refer for expert advice.

Figure 7.7 Features that suggest a diagnosis other than Parkinson disease

early dementia

early falls

early severe autonomic dysfunction

other neurological signs (eg upper motor neurone signs, abnormal eye movements, cerebellar signs)

onset of symptoms coinciding with dopamine antagonist treatment (eg antipsychotic drugs, metoclopramide)

no response to large doses of levodopa (if malabsorption is excluded)

history of repeated strokes with stepwise progression of parkinsonian features

Nonmotor complications of Parkinson disease are major causes of disability, even in the early stages of the disease. These complications include fatigue, neuropsychiatric symptoms (eg depression, anxiety, psychosis), sleep disturbance, autonomic symptoms (eg orthostatic hypotension, bladder dysfunction, constipation, sexual dysfunction), pain and other sensory symptoms, and dysphagia. Dementia is common in late disease, with a prevalence of 20 to 40%. See advice on orthostatic hypotension, neuropsychiatric symptoms, bladder dysfunction, dementia and sialorrhoea.

Many genes associated with Parkinson disease have been identified, but genetic mutations account for only 1 to 2% of sporadic cases. No therapy directed at specific gene mutations is available at the time of writing.

Parkinson disease has no cure, so the principles of treatment are to:

- keep the patient functioning as long as possible with the minimum amount of medication
- choose each patient's therapy according to their disease stage and main symptoms.

Levodopa and dopamine agonists are the main drugs used to improve motor function in Parkinson disease. Parkinson disease does not need pharmacotherapy when it does not cause functional impairment. Deciding when to start therapy and the type of therapy varies for each patient, based on a range of factors (eg age, occupation, activity level, economic status, patient preference, cognitive state).

As Parkinson disease progresses, most patients need levodopa. A consistent response to levodopa is diminished with prolonged use, leading to motor complications. Nonmotor complications also become worse in advancing Parkinson disease. Autonomic dysfunction is not usually as severe as in multiple system atrophy (one of the differential diagnoses of Parkinson disease).

When the disease progresses, discuss advance care planning with the patient. Some patients will need palliative care.

Nonpharmacological intervention is essential at all stages of Parkinson disease, and many disciplines (eg physiotherapy, speech therapy, occupational therapy, dietetics) are involved. Studies suggest that various physical therapies (including active music therapy, treadmill training, balance training and 'cued' exercise training [using visual and auditory cues to treat freezing]) can improve function in patients with Parkinson disease. Although the functional improvement is small and not sustained, physical therapy actively involves patients in their disease.

Treating Parkinson disease

Treating Parkinson disease

Overview of drug therapy for Parkinson disease

Overview of drug therapy for Parkinson disease

The main drugs used to improve motor function in patients with Parkinson disease are levodopa and dopamine agonists. Evidence is lacking for a drug or nutritional supplement (eg vitamin E, vitamin C, ubidecarenone [coenzyme Q10]) that significantly delays the progression of Parkinson disease.

Of all the antiparkinson drugs, levodopa has the greatest benefit with the least adverse effects, especially in patients who are elderly (older than 70 years) or have cognitive decline. However, long-term complications (ie motor fluctuations and drug-induced dyskinesia) are more likely with higher levodopa doses (more than 600 mg daily) than with dopamine agonists. Therefore, use lower levodopa doses in early disease.

Dopamine agonists may be used as monotherapy in early Parkinson disease in certain circumstances, with caution. Warn patients about behavioural adverse effects—these include pathological shopping, eating, hoarding, gambling, sexual preoccupation, medication abuse and punding (incessantly doing and undoing a project [eg fixing an engine, organising a wardrobe]). Do not use dopamine agonists in patients with a history of impulse control disorders (including problem gambling). The behaviours can also occur in patients taking levodopa, but are less common. The ergot-derived dopamine agonist, cabergoline, should not be used, because it increases the risk of cardiac valve damage.

When tremor is the main symptom, if the response to levodopa is inadequate, refer for expert advice—amantadine or anticholinergic drugs can be useful alternatives or adjuncts. The monoamine oxidase type B inhibitors, selegiline and rasagiline, have a mild effect on the symptoms of Parkinson disease.

If a patient needs to change from one route of antiparkinson therapy to another (eg changing from levodopa to a rotigotine patch before surgery), see advice.

Treating early Parkinson disease

Treating early Parkinson disease

The preferred first-line therapy for Parkinson disease is levodopa. Dopamine agonists may be used as first-line therapy in exceptional circumstances (eg rotigotine for a patient who can't swallow, pramipexole for a patient who strongly prefers once-daily dosing).

With all antiparkinson drugs, start at a low dose and increase gradually over days or weeks—this reduces the risk of adverse effects and improves concordance with therapy. A clear response can take 2 to 3 weeks.

Use:

1 levodopa+benserazide 50+12.5 mg orally, 3 times daily, increasing to 100+25 mg 3 times daily over 1 to 2 weeks *Parkinson disease* _

OR

1 levodopa+carbidopa 50+12.5 mg orally, 3 times daily, increasing to 100+25 mg 3 times daily over 1 to 2 weeks *Parkinson disease* _

OR

2 pramipexole 0.125 mg orally, 3 times daily, slowly titrating to effect, to a maximum of 1.5 mg 3 times daily *Parkinson disease* _

OR

2 pramipexole modified-release 0.375 mg orally, once daily, slowly titrating to effect, to a maximum of 4.5 mg once daily

OR

2 rotigotine 2 mg transdermally, once daily applied for 24 hours, increasing by 2 mg every week until an effective dose is reached, to a maximum of 8 mg once daily. *Parkinson disease* _

All antiparkinson drugs can cause nausea, but tolerance to this adverse effect usually develops rapidly. Taking doses with food can help. Avoid metoclopramide, prochlorperazine and other centrally acting dopamine-blocking antiemetics, because they often make parkinsonism worse.
Avoid metoclopramide and prochlorperazine in patients with Parkinson disease.

When nausea is a problem, treat with a short course of domperidone. Use:

domperidone 10 mg orally, 3 times daily for up to 7 days, then stop [Note 1]. *nausea due to antiparkinson drug* _

Note 1: Evidence shows an increased risk of serious cardiac adverse effects (ventricular arrhythmias, sudden cardiac death) from domperidone at doses over 30 mg daily and in patients older than 60 years. For more information, see the Therapeutic Goods Administration (TGA) Medicines Safety Update.

Managing motor complications as Parkinson disease progresses

Managing motor complications as Parkinson disease progresses

Most patients with Parkinson disease on levodopa therapy eventually develop motor complications. These include:

- different patterns of motor fluctuations (eg predictable and unpredictable ‘wearing off’ of effect, intermittent ‘dose failures’, delayed or poor effect of individual doses)
- drug-induced chorea (also known as dyskinesia) or dystonia.

Patients with Parkinson disease who are especially at risk of motor complications:

- are younger at onset
- have more severe disease
- are on a higher levodopa dosage
- have had the disease longer.

Smaller, more frequent, evenly spaced doses of levodopa are often needed to manage motor complications. High-protein meals may interfere with levodopa absorption, so modifying the diet and avoiding dosing at

mealtimes (eg giving drugs 1 hour before meals) can be helpful. Adherence to regular dosing times is important, as variations from the patient's usual schedule can lead to deterioration in function.

Refer for expert advice to manage motor complications of advancing Parkinson disease. Combination therapy is often needed, and adjusting drug therapy is complex.

To manage ‘wearing off’ of therapy, an expert may choose to:

- combine levodopa and a dopamine agonist
- use modified-release levodopa
- give smaller, more frequent doses of levodopa
- adjust dietary protein
- switch dopamine agonists
- use a catechol-O-methyl transferase (COMT) inhibitor (ie entacapone)
- use rasagiline or selegiline.

To manage dyskinesia, an expert may choose to:

- decrease the levodopa dose
- add amantadine
- add a dopamine agonist or increase its dose
- switch dopamine agonists.

Treating advanced Parkinson disease

Treating advanced Parkinson disease

Advanced therapies (ie surgery and pump-delivered dopaminergic therapy) for Parkinson disease are provided in specialised movement disorders units.

Increasingly, surgery is used to treat Parkinson disease—high-frequency deep brain stimulation is preferred. Surgery is most successful in patients with severe motor fluctuations and dyskinesias. However, surgery does not alleviate cognitive deficits, nonmotor complications and some motor effects (especially postural instability, falls, dysarthria and on-period gait freezing).

Surgery is contraindicated when the patient has:

- a major psychiatric illness
- cognitive impairment
- a major medical illness
- a cardiac pacemaker that is not compatible with magnetic resonance imaging (deep brain stimulation is not possible)
- levodopa-resistant parkinsonism, except when tremor is the main symptom.

Advanced age is a relative contraindication for surgery.

Continuous dopaminergic therapy via portable, programmable pumps is available for older patients or when surgery is unsuitable. Levodopa+carbidopa intestinal gel is administered continuously through a permanent tube, directly into the duodenum or upper jejunum. Apomorphine is delivered subcutaneously. For both drugs, adjusting infusion rates and giving bolus doses helps smooth out motor fluctuations and dyskinesias.

Orthostatic hypotension in Parkinson disease

Orthostatic hypotension in Parkinson disease

Orthostatic hypotension is common in Parkinson disease and can have serious results (eg falls, injuries).

Review the patient's antiparkinson drugs and other drugs (eg antihypertensive drugs).

Advise patients to:

- avoid extreme heat, alcohol, large meals, straining and standing up rapidly
- increase sodium and water intake
- eat smaller, more frequent meals
- take regular exercise in the horizontal position (eg swimming)
- wear compression stockings
- sleep with the head of the bed raised.

If pharmacological treatment is needed, use:

fludrocortisone 0.1 mg orally, daily, increasing to 0.2 mg daily if needed. *orthostatic hypotension (Parkinson disease)*

In resistant cases, seek expert advice—pyridostigmine, midodrine, ephedrine [Note 2] and octreotide may be useful.

Note 2: Ephedrine as an oral preparation is not registered for use in Australia but is available via the Special Access Scheme.

Neuropsychiatric symptoms in Parkinson disease

Neuropsychiatric symptoms in Parkinson disease

Depression and anxiety are common in Parkinson disease, and are treated with standard pharmacotherapy (see advice: depression; anxiety).

Psychosis is common in Parkinson disease, especially in patients who are elderly, have cognitive disturbance or are taking anticholinergic drugs. Review antiparkinson treatment and possibly reduce levodopa dose or withdraw anticholinergic drugs and dopamine agonists.

If psychosis continues, low doses of second-generation antipsychotic drugs can be helpful. Clozapine is the most effective, and may improve motor function, but can have significant adverse effects and needs regular blood monitoring. Open-label studies have suggested low-dose quetiapine is beneficial, and it is often used empirically, but randomised controlled trials have not confirmed its efficacy.

Avoid using other second-generation antipsychotic drugs (eg olanzapine, risperidone, aripiprazole) because they are not as effective and can aggravate parkinsonism at higher doses. Avoid using first-generation antipsychotic drugs (eg chlorpromazine, haloperidol) as these often make parkinsonism worse.

Bladder dysfunction in Parkinson disease

Bladder dysfunction in Parkinson disease

Bladder dysfunction is common in Parkinson disease, especially in its late stages. Detrusor overactivity is most common, leading to urinary frequency and urgency, and sometimes to urge incontinence. Obstructive symptoms (eg hesitancy, weak urinary stream) also occur. Exclude prostatism in males.

In mild bladder dysfunction, restricting fluid intake in the evening may be sufficient treatment. Dopaminergic therapy does not usually relieve urinary symptoms. If additional treatment is needed, follow the advice for multiple sclerosis (botulinum toxin type A and sacral neuromodulation are less common therapies for patients with Parkinson disease).

Dementia in Parkinson disease

Dementia in Parkinson disease

Cognitive impairment is common in Parkinson disease, and its prevalence increases with time. Severe dementia is a major cause of disability and mortality in Parkinson disease. The pattern of cognitive impairment is executive dysfunction and impaired visuospatial function, with fewer memory deficits. Language function is preserved.

A systematic review [Note 3] of the effect of acetylcholinesterase inhibitors on dementia in Parkinson disease showed mild to moderate benefits. Donepezil and rivastigmine are used most often as they have fewer adverse effects (eg gastrointestinal disturbance, tremors). However, in studies of rivastigmine almost 20% of patients stopped taking the drug because of adverse effects, including worsening tremor. Donepezil and rivastigmine can also improve neuropsychiatric symptoms (eg hallucinations).

As the benefits of an acetylcholinesterase inhibitor are modest, a trial of 2 to 3 months is suggested. Regularly review the patient's response, and stop treatment if they have serious adverse effects or if no benefit is seen (measured by bedside testing or carers' observations). Taper the dose slowly if stopping treatment, to avoid sudden cognitive and behavioural deterioration.

Use:

1 donepezil 5 mg orally, once daily at night for 4 weeks. If tolerated, increase to 10 mg at night. Review after 2 to 3 months *dementia (Parkinson disease)*

OR

1 rivastigmine 4.6 mg transdermally, once daily applied for 24 hours. If tolerated, after 4 weeks increase to 9.5 mg daily. If needed, after at least 4 more weeks, increase to 13.3 mg daily. Review after 2 to 3 months [Note 4] *dementia (Parkinson disease)*

OR

2 rivastigmine 1.5 mg orally, twice daily. If needed, every 4 weeks increase dose by 1.5 mg twice daily as tolerated, to a maximum of 6 mg twice daily. Review after 2 to 3 months.

Note 3: Rolinski M, Fox C, Maidment I, McShane R. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. Cochrane Database Syst Rev 2012;(3):CD006504. [URL]

Note 4: Available patch sizes of rivastigmine are 4.6 mg/24 hours (9 mg patch), 9.5 mg/24 hours (18 mg patch) and 13.3 mg/24 hours (27 mg patch).

Sialorrhoea in Parkinson disease

Sialorrhoea in Parkinson disease

When a patient has sialorrhoea as a complication of Parkinson disease, refer for expert advice. First-line treatment is botulinum toxin type A injections in the salivary glands.

Managing a patient with Parkinson disease who is nil-by-mouth

Managing a patient with Parkinson disease who is nil-by-mouth

It is good practice for patients with Parkinson disease to take antiparkinson therapy regularly and avoid missing doses. However, expert opinion is that a patient with good control can miss two or three doses of oral antiparkinson therapy if necessary. Patients who will miss more than two or three doses of oral therapy (eg

after abdominal surgery, after a stroke) should be changed to a nonoral route. For example, rotigotine patches can be applied the night before surgery and used until the patient can resume oral therapy.

Patients with fragile disease control (eg they need to take levodopa every 2 to 3 hours) who need to be nil-by-mouth should have their antiparkinson therapy changed to a nonoral route. Caution is advised—these patients are more likely to have problems when converting from oral therapy, and the consequences can be grave (eg losing control of symptoms, dopaminergic withdrawal syndrome).
Seek expert advice if possible before changing the route of antiparkinson therapy, particularly for patients with fragile disease control.

Seek expert advice if possible before changing the route of antiparkinson therapy, particularly for patients with fragile disease control.

One approach to switching from oral to transdermal antiparkinson therapy is described here. It is based on the concept of levodopa equivalent doses (LEDs). An LED is the dose of antiparkinson drug that produces the same symptom control as 100 mg immediate-release levodopa combined with a dopa-decarboxylase inhibitor. The conversion factors in Table 7.6 are from a systematic review of studies reporting LEDs [Note 5]—these are only a guide, as comprehensive dose equivalence studies are lacking.

Convert the patient's total daily doses of levodopa and/or pramipexole to LEDs by multiplying each drug's dose by the conversion factor in Table 7.6. Add the results to get the patient's total daily dose expressed as LEDs. Then divide the total daily LED by the conversion factor for rotigotine, which is 30, and round down to the nearest patch strength—this is the target dose.

Variability in patient response to rotigotine patches means there is a risk of adverse effects, even when the target patch strength has been calculated. Unless the patient has fragile disease control, consider starting rotigotine at a lower patch strength than the target dose, then titrate as tolerated to the effective dose.

Closely monitor patients who have been converted to rotigotine patches in case further dose adjustment is necessary.

Table 7.6 Converting doses of oral antiparkinson drugs to rotigotine patches

[NB1]

Printable table

Step 1. Calculate total daily levodopa equivalent dose (LED) [NB2]

Antiparkinson drug [NB3]	**Total daily dose (mg)**	**Conversion factor [NB4]**	**LED (mg)**
levodopa+benserazide/carbidopa		x 1	
modified-release levodopa+benserazide/carbidopa		x 0.75	
pramipexole		x 100	
modified-release pramipexole		x 100	
		Total daily LED [NB5] =	

Step 2. Convert total daily LED to target rotigotine dose

$$\frac{\text{Total daily LED (mg)}}{30} = \text{..... mg rotigotine/24 hours}$$

Round down to the nearest rotigotine patch / combination of patches—this is the target dose [NB6]

Maximum daily dose of rotigotine is 16 mg/24 hours

NB1: Seek expert advice if possible before changing the route of antiparkinson therapy, particularly for patients with fragile disease control.

NB2: A levodopa equivalent dose (LED) is the dose of drug that produces the same symptom control as 100 mg immediate-release levodopa combined with a dopa-decarboxylase inhibitor.

NB3: Seek expert advice if the patient is taking an antiparkinson drug that is not listed (eg amantadine, entacapone, rasagiline, ropinirole, selegiline).

NB4: Conversion factors are only a guide, as comprehensive dose equivalence studies are lacking.

NB5: If total daily LED is more than 480 mg, seek expert advice. The patient may need apomorphine subcutaneously or levodopa+carbidopa intestinal gel.

NB6: Unless the patient has fragile disease control, consider starting rotigotine at a lower patch strength than the target dose, then titrate as tolerated to the effective dose.

Note 5: Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25(15):2649-53. [URL]

Key references: Overview of Parkinson disease

Key references: Overview of Parkinson disease

- Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55(3):181–4. https://www.ncbi.nlm.nih.gov/pubmed/1564476

Key references: Orthostatic hypotension in Parkinson disease

Key references: Orthostatic hypotension in Parkinson disease

- Sanchez-Ferro A, Benito-Leon J, Gomez-Esteban JC. The management of orthostatic hypotension in Parkinson's disease. Front Neurol 2013;4:64. https://www.ncbi.nlm.nih.gov/pubmed/23772219

Key references: Neuropsychiatric symptoms in Parkinson disease

Key references: Neuropsychiatric symptoms in Parkinson disease

- Chang A, Fox SH. Psychosis in Parkinson's disease: epidemiology, pathophysiology, and management. Drugs 2016;76(11):1093–118. https://www.ncbi.nlm.nih.gov/pubmed/27312429

Key references: Bladder dysfunction in Parkinson disease

Key references: Bladder dysfunction in Parkinson disease

- Mirabegron for overactive bladderAust Prescr 2014;37:64–71. http://dx.doi.org/10.18773/austprescr.2014.031

Key references: Dementia in Parkinson disease

Key references: Dementia in Parkinson disease

- Rolinski M, Fox C, Maidment I, McShane R. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. Cochrane Database Syst Rev 2012;(3):CD006504. https://www.ncbi.nlm.nih.gov/pubmed/22419314

Key references: Managing a patient with Parkinson disease who is nil-by-mouth

Key references: Managing a patient with Parkinson disease who is nil-by-mouth

- Brennan KA, Genever RW. Managing Parkinson's disease during surgery. BMJ 2010;341:c5718. https://www.ncbi.nlm.nih.gov/pubmed/21041319
- Tomlinson CL, Stowe R, Patel S, Rick C, Gray R, Clarke CE. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. Mov Disord 2010;25(15):2649–53. https://www.ncbi.nlm.nih.gov/pubmed/21069833
- Wullner U, Kassubek J, Odin P, Schwarz M, Naumann M, Hack HJ, et al. Transdermal rotigotine for the perioperative management of Parkinson's disease. J Neural Transm (Vienna) 2010;117(7):855–9. https://www.ncbi.nlm.nih.gov/pubmed/20535621

Published November 2017 (Amended March 2018)

[X] Close

Essential tremor

Essential tremor

In general, the only sign of essential tremor is postural or kinetic tremor in the frequency of 4 to 12 Hz (usually at the lower end of the range in older patients). When essential tremor is severe, some patients also have rest tremor and mild abnormalities of muscle tone and gait. A family history of essential tremor and temporary benefit after drinking alcohol are common.

Essential tremor can be confused with Parkinson disease or other tremors, and the conditions can overlap. Conditions related to essential tremor (eg task-specific tremors, isolated tremor, orthostatic tremor) are not common, and need expert diagnosis and treatment.

Exclude drug- or toxin-induced tremor or systemic illness (eg hyperthyroidism) before starting treatment for essential tremor.

Mild essential tremor does not need treatment.

Propranolol and primidone suppress essential tremor, but primidone is less well tolerated (especially by elderly patients). It is reasonable to start treatment with propranolol, depending on the patient's age and other medical conditions. Use:

1 propranolol 10 mg orally, twice daily. Increase dose slowly over several weeks up to a maximum of 160 mg daily in 2 or 3 divided doses *tremor, essential* _

OR

2 primidone 62.5 mg orally, at night. If needed, increase dose slowly over several weeks up to 250 mg at night. *tremor, essential* _

If initial therapy is not effective, refer the patient for expert advice. Occasionally, the patient needs propranolol and primidone combined. Some evidence shows that atenolol and sotalol are also effective. A benzodiazepine, gabapentin or topiramate may also be considered. In severe cases of essential tremor, if drug therapy is not effective, the expert may refer the patient to a specialised movement disorders unit for botulinum toxin injections or deep brain stimulation.

Key references: Essential tremor

Key references: Essential tremor

- Fasano A, Deuschl G. Therapeutic advances in tremor. Mov Disord 2015;30(11):1557–65. https://www.ncbi.nlm.nih.gov/pubmed/26293405
- Hassan A, Ahlskog JE, Matsumoto JY, Milber JM, Bower JH, Wilkinson JR. Orthostatic tremor: clinical, electrophysiologic, and treatment findings in 184 patients. Neurology 2016;86(5):458–64. https://www.ncbi.nlm.nih.gov/pubmed/26747880
- Ondo WG, Jankovic J, Connor GS, Pahwa R, Elble R, Stacy MA, et al. Topiramate in essential tremor: a double-blind, placebo-controlled trial. Neurology 2006;66(5):672–7. https://www.ncbi.nlm.nih.gov/pubmed/16436648
- Schneider SA, Deuschl G. The treatment of tremor. Neurotherapeutics 2014;11(1):128–38. https://www.ncbi.nlm.nih.gov/pubmed/24142589
- Zesiewicz TA, Elble RJ, Louis ED, Gronseth GS, Ondo WG, Dewey RB Jr., et al. Evidence-based guideline update: treatment of essential tremor: report of the Quality Standards subcommittee of the

American Academy of Neurology. Neurology 2011;77(19):1752–5.
https://www.ncbi.nlm.nih.gov/pubmed/22013182

Published November 2017

[X] Close

Sydenham chorea

Sydenham chorea

Sydenham chorea is an autoimmune movement and neuropsychiatric disorder that is triggered by *Streptococcus pyogenes* (group A streptococcus) infection. Only treat Sydenham chorea when it is sufficiently disabling to interfere with normal daily activities. Antiepileptic drugs are effective, but a response may not be seen for 1 to 2 weeks after starting therapy. Use:

1 carbamazepine (preferably modified-release) 5 to 10 mg/kg (adult and child) orally, twice daily (up to 1200 mg daily) until 2 to 4 weeks after the chorea subsides [Note 1] *Sydenham chorea*

OR

1 sodium valproate 7.5 to 12.5 mg/kg (adult and child) orally, twice daily (up to 2500 mg daily) until 2 to 4 weeks after the chorea subsides. Avoid in females of childbearing potential (see teratogenic and neurodevelopmental effects of antiepileptic drugs). *Sydenham chorea*

Limited evidence suggests that immunosuppression with a corticosteroid or intravenous immunoglobulin can improve the extent or speed of recovery. Consider this therapy in patients with moderate to severe chorea. Continue antiepileptic drugs until immunotherapy takes effect.

All patients with Sydenham chorea must have long-term antibiotic prophylaxis against *Streptococcus pyogenes* infection.

Children whose antipsychotic drugs are withdrawn suddenly can develop generalised choreiform movements that resemble Sydenham chorea. Treat this ‘withdrawal emergent syndrome’ by restarting the antipsychotic drug and slowly tapering the dosage.

Note 1: Pharmacogenetic studies are identifying an increasing number of genes that confer a predisposition to cutaneous drug reactions. Testing for the HLA-B*1502 allele in patients of Asian origin (other than Japanese) is advised before starting therapy with carbamazepine.

Key references: Sydenham chorea

Key references: Sydenham chorea

- Genel F, Arslanoglu S, Uran N, Saylan B. Sydenham's chorea: clinical findings and comparison of the efficacies of sodium valproate and carbamazepine regimens. Brain Dev 2002;24(2):73–6. https://www.ncbi.nlm.nih.gov/pubmed/11891095
- Mohammad SS, Nosadini M, Grattan-Smith P, Dale RC. Intravenous immunoglobulin in acute Sydenham's chorea: A systematic review. J Paediatr Child Health 2015;51(12):1235–8. https://www.ncbi.nlm.nih.gov/pubmed/26633611
- Paz JA, Silva CA, Marques-Dias MJ. Randomized double-blind study with prednisone in Sydenham's chorea. Pediatr Neurol 2006;34(4):264–9. https://www.ncbi.nlm.nih.gov/pubmed/16638499
- Walker KG, Wilmshurst JM. An update on the treatment of Sydenham's chorea: the evidence for established and evolving interventions. Ther Adv Neurol Disord 2010;3(5):301–9. https://www.ncbi.nlm.nih.gov/pubmed/21179620

Published November 2017

Focal dystonias

Focal dystonias

Focal dystonias are the most common type of dystonia and include blepharospasm, cervical dystonia (spasmodic torticollis), spasmodic dysphonia and occupational dystonias (eg writer's cramp). In general, focal dystonias occur in adults and generalised dystonia occurs in children.

Refer patients with significant focal dystonias for expert advice. First-line treatment is usually botulinum toxin type A injections. If this is not effective in cervical dystonia, another option is surgery (deep brain stimulation). Both treatments should only be given in specialised movement disorders units.

Focal hand dystonia often responds poorly to botulinum toxin type A injections—patients may find it helpful to switch to the other hand or alter the way they perform tasks (eg use a fatter pen).

Generalised dystonia

Generalised dystonia

When a patient presents with generalised dystonia, the first step is to find out whether the dystonia responds to a trial of levodopa. Levodopa-responsive dystonia is rare. It often presents with predominant leg dystonia with diurnal variation, and is more likely in children, adolescents and young adults. Consider levodopa-responsive dystonia in any child with a spastic diplegia. Diagnostic gene testing is available.

Refer all children with generalised dystonia for expert advice. If the child does have levodopa-responsive dystonia, low doses of levodopa may be adequate.

In adults with generalised dystonia, to test for levodopa responsiveness, use:

1 levodopa+benserazide 50+12.5 mg orally, 3 times daily, increasing to 100+25 mg 3 times daily over 1 to 2 weeks *dystonia, levodopa response test*

OR

1 levodopa+carbidopa 50+12.5 mg orally, 3 times daily, increasing to 100+25 mg 3 times daily over 1 to 2 weeks. *dystonia, levodopa response test*

If the adult responds to levodopa, therapy is lifelong.

In a small proportion of patients (usually children), generalised dystonia is caused by a specific condition that can be treated. Investigate for Wilson disease, mitochondrial encephalomyopathies, lysosomal storage disorders (eg Niemann-Pick disease type C) and neuroacanthocytosis.

Pure dystonia with focal onset in childhood that becomes generalised over years is usually due to a deletion in the DYT1 gene.

If no cause for generalised dystonia is found, refer the patient for expert advice. First-line treatment for symptoms is an anticholinergic drug. Trihexyphenidyl (benzhexol) is effective—occasionally a child may need a dose as high as 60 mg daily, if tolerated. Pallidal deep brain stimulation is effective, especially in primary generalised dystonia, and clinical improvement is most evident after at least 6 months.

Key references: Dystonia

Key references: Dystonia

- Lubarr N, Bressman S. Treatment of generalized dystonia. Curr Treat Options Neurol 2011;13(3):274–89. https://www.ncbi.nlm.nih.gov/pubmed/21455718

Published November 2017 (Amended March 2021)

[X] Close

Tics

Tics

Tics are common and can be an isolated movement disorder or part of Tourette syndrome.

Tics often don't need treatment. If the tics become socially disabling, drug therapy can be tried, but the response varies. In children, psychological support and behaviour management (eg habit-reversal training, Comprehensive Behavioural Intervention for Tics) can be effective, and should be considered before starting drug therapy.

If drug therapy is considered appropriate, for an adult, use:

clonidine 25 micrograms orally, twice daily for 2 weeks, then 50 to 75 micrograms twice daily. *tics* _

For a child 5 years or older, use:

clonidine 1 microgram/kg (up to 50 micrograms) orally, daily. If needed, increase dose gradually to a maximum of 4 micrograms/kg (up to 300 micrograms) daily in 2 or 3 divided doses.

If drug therapy is not effective, and the tics are severe, refer for expert advice.

Key references: Tics

Key references: Tics

- Koy A, Lin JP, Sanger TD, Marks WA, Mink JW, Timmermann L. Advances in management of movement disorders in children. Lancet Neurol 2016;15(7):719–35. https://www.ncbi.nlm.nih.gov/pubmed/27302239

Published November 2017

[X] Close

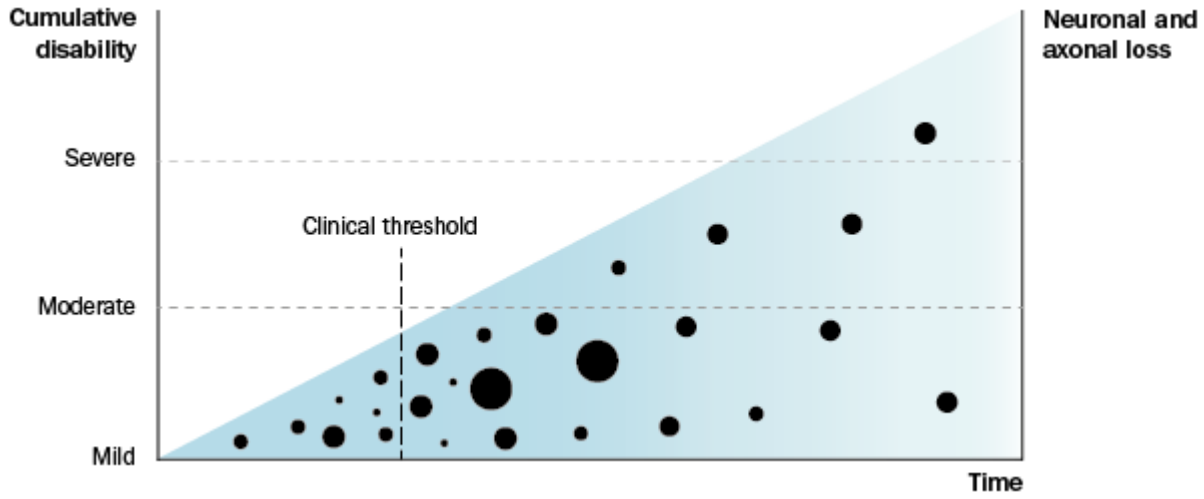
Overview of multiple sclerosis

Overview of multiple sclerosis

Multiple sclerosis (MS) is an inflammatory disease of the central nervous system. Earlier in the course of MS, discrete demyelinating lesions cause axonal and neuronal damage. Later, diffuse inflammatory processes and neurodegeneration exacerbate central nervous system dysfunction. The result is progressive disability (see Figure 7.8). The emphasis in treating MS is on:

- introducing immunotherapy early, to slow or minimise disability
- using corticosteroids for acute inflammatory clinical events (relapses)
- easing symptoms caused by neurological damage (eg pain).

Figure 7.8 Course of multiple sclerosis



Background shading represents general inflammation of the central nervous system, which decreases over time (as degenerative processes increase).

Black circles represent discrete inflammatory events that cause brain, spine or optic nerve lesions and present as clinical attacks or appear as lesions on magnetic resonance imaging.

Trajectory is different for each patient.

The risk of MS in the general population is 0.1%. The first-degree relatives of a patient diagnosed with MS have a 3 to 4% risk.

Discrete inflammatory events cause brain, spine or optic nerve lesions and present as clinical attacks or appear as lesions on magnetic resonance imaging (MRI) (some lesions are too small for resolution by MRI). These events cause acute damage, are associated with adaptive immune infiltrations (so can be treated) and diminish over time. Generalised inflammation (eg microglial activation) continues even after the discrete inflammatory events diminish, and over time is accompanied by increasing neurodegeneration.

The contribution of inflammation and neurodegeneration varies among patients. Relapsing-remitting MS has an early inflammatory course with secondary degenerative changes (secondary progression). Primary progressive MS can be associated with greater degenerative change earlier in the clinical presentation.

Multiple sclerosis is relatively rare in childhood and adolescence—the disease starts before the age of 16 years in 2 to 5% of patients, and the course in children seems to be slower than in adults. More than 90% of

children with MS have relapsing-remitting disease; primary progressive MS is rare. Refer a child with MS for expert care.

Patients with clinical disease activity mainly present with symptoms that are subacute, consistent and often progressive, lasting several days and referable to one part of the central nervous system. Any MS symptom can occur as part of a relapse, but symptoms that are chronic, transient or relatively isolated are less likely to be due to acute inflammation. Although the mainstay of MS treatment is immunotherapy to prevent damage, over time, symptomatic therapies are needed.

Diagnosing multiple sclerosis

Diagnosing multiple sclerosis

Certain symptoms strongly suggest multiple sclerosis (see left-hand column of Table 7.7) and should prompt magnetic resonance imaging (MRI) directed at the site of suspected inflammation. For example, Lhermitte phenomenon [Note 1] in a young person is likely to be due to a demyelinating lesion in the posterior cervical spinal cord. On the other hand, many MS symptoms (see right-hand column of Table 7.7) are less specific and do not localise a lesion in the central nervous system (CNS), making diagnosis harder. Refer patients with suspected MS for expert advice, to confirm the diagnosis and start therapy.

Table 7.7 Multiple sclerosis symptoms

[NB1] [NB2]

More specific symptoms of multiple sclerosis that often reflect disease activity [NB3]	Less specific symptoms of multiple sclerosis [NB4]
acute painful loss of vision in one eye (optic neuritis)	pain
limb weakness and numbness that can occur with or without bladder/bowel dysfunction, sometimes with acute pain (transverse myelitis)	spasticity
ataxia, facial numbness or diplopia (brainstem syndrome)	fatigue
first episode of trigeminal neuralgia (rare)	cognitive dysfunction
hemiplegia (hemisphere syndromes; rare)	psychiatric symptoms
new onset of Lhermitte phenomenon [NB5]	urinary symptoms
tonic spasms (rare, more likely to be neuromyelitis optica)	sexual dysfunction
	recurrence of Lhermitte phenomenon [NB5]

NB1: The course of multiple sclerosis varies among patients, but the prognosis may be poorer in patients with:

- cortical lesions and/or brain atrophy and their consequences (seizures, cognitive dysfunction)
- long tract signs or evidence on magnetic resonance imaging of brainstem and spinal lesions.

NB2: Symptoms that are rare in multiple sclerosis and should prompt consideration of different diagnoses include dysphasia, new headaches, hemiplegia, movement disorders and seizures.

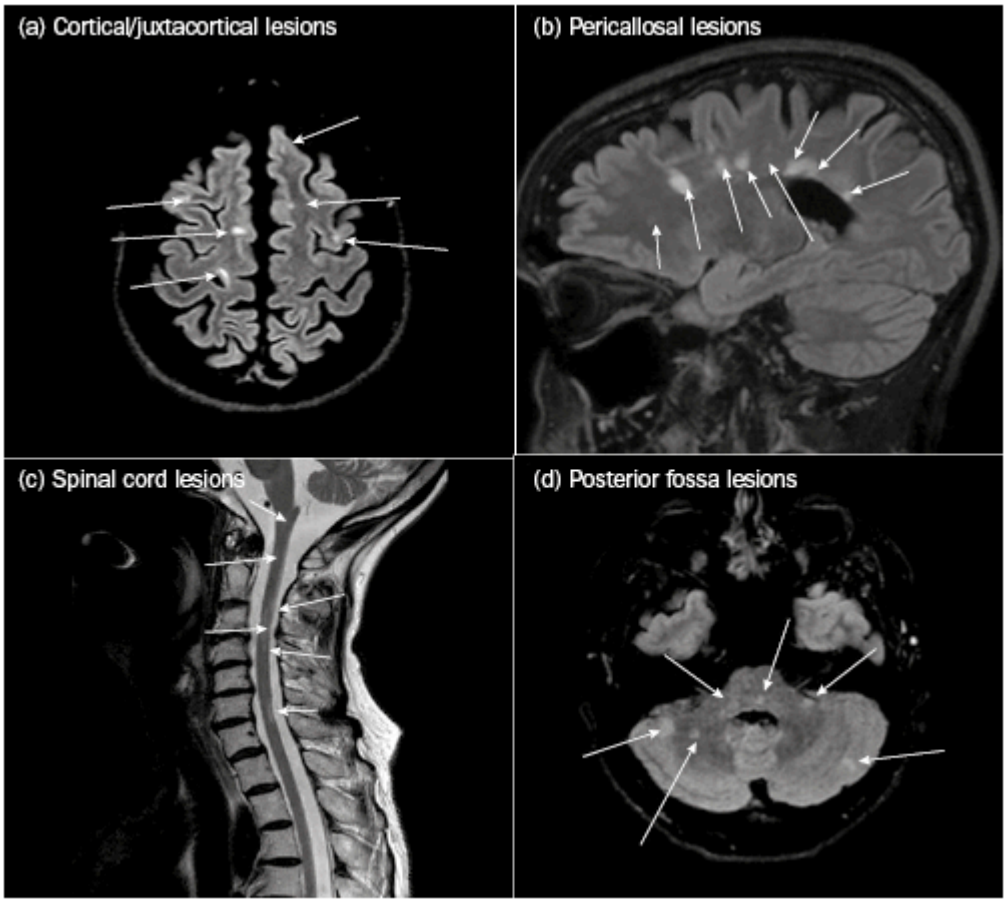
NB3: Likely to need corticosteroid treatment

NB4: Likely to need symptomatic treatment

NB5: The Lhermitte phenomenon is sudden transient electric-like shocks that spread down the body when the patient flexes the head forward.

The diagnosis of MS is based on the presence of typical lesions throughout the CNS, shown clinically and on MRI (see Figure 7.9), with new lesions occurring over time. Using accepted criteria, MS can be diagnosed after a single clinical event if the MRI shows lesions of different ages.

Figure 7.9 Typical demyelinating lesions in multiple sclerosis



Axial brain, sagittal brain, sagittal spine and axial cerebellar sections from fluid attenuated inversion recovery (FLAIR) magnetic resonance imaging.

(a) Typical cortical lesions have a curvilinear, juxtacortical distribution involving U-fibres.

(b) Pericallosal / periventricular lesions abut the ependymal surface and radiate linearly towards the brain surface.

(c) Spinal cord lesions are short segment (fewer than three vertebral spaces), usually involve part of the spinal cord and can traverse grey and white matter.

(d) Posterior fossa lesions are ovoid or circular and involve the cerebellum, pons, medulla and midbrain.

Other tests that can be useful when diagnosing MS are:

- cerebrospinal fluid (CSF) analysis—this shows the typical inflammatory process (oligoclonal bands in the CSF without matching bands in the serum)
- evoked potential measurement—this shows electrophysiological evidence of a demyelinating lesion in the spinal cord (somatosensory evoked potential [SSEP]), optic nerve (visual evoked potential [VEP]) or (rarely) the brainstem (brainstem auditory evoked response [BAER]).

Some patients have a single demyelinating event without evidence of changes over time (ie no new clinical events and/or new lesions on MRI)—this is called a clinically isolated syndrome (CIS), and patients must be monitored in case MS develops. If the initial MRI shows two or more white matter lesions, the patient has about an 80% risk of developing MS—if the MRI is normal, the risk falls to about 11%.

Before confirming a diagnosis of MS, the expert excludes other neuroinflammatory diseases (eg acute disseminated encephalomyelitis, neuromyelitis optica [NMO] spectrum disorders, sarcoidosis, systemic lupus

erythematosus).

If the patient has a progressive presentation, as well as excluding the differential diagnoses above, the expert needs to consider other conditions that mimic MS (eg vitamin B_{12} deficiency, spinal cord masses and fistulas, genetic syndromes [eg hereditary spastic paraparesis]).

Patients with NMO spectrum disorders (neuromyelitis optica [Devic disease] and myelin oligodendrocyte glycoprotein [MOG] NMO spectrum disorders) can present with:

- symptoms of optic neuritis that is more often bilateral or sequential than in MS
- transverse myelitis, usually with long cord lesions
- intractable hiccups or vomiting, due to a brainstem lesion.

A simple blood test (aquaporin-4 antibodies for NMO spectrum disorders, or MOG antibodies for MOG NMO spectrum disorders) diagnoses these conditions, which are treated differently from MS—patients with NMO spectrum disorders may deteriorate if given MS drug therapy. For treatment, refer for expert advice.

Note 1: The Lhermitte phenomenon is sudden transient electric-like shocks that spread down the body when the patient flexes the head forward.

Overview of therapy for multiple sclerosis

Overview of therapy for multiple sclerosis

Relapsing forms of multiple sclerosis (MS) are treated with preventive immunotherapy (see Table 7.8), aimed at reducing inflammatory disease activity. At the time of writing, primary and secondary progressive MS do not have preventive therapies, but research is ongoing. Acute inflammatory activity that occurs despite immunotherapy is treated with corticosteroids—in atypical cases or fulminant presentations, plasma exchange may be added.

Most patients with relapsing-remitting MS start treatment with immunotherapy. However, rare and fulminant forms may need more potent treatment, including autologous stem cell transplant.

Available immunotherapies for multiple sclerosis

Available immunotherapies for multiple sclerosis

Immunotherapy is indicated for patients with relapsing forms of multiple sclerosis and active disease. When starting immunotherapy, the expert chooses the drug after considering the relative harms and benefits to the patient and having an informed discussion with them. Historically, the approach has been to start therapy with the safest drugs, before scaling up to more potent drugs that have higher risk. However, when using this approach, careful monitoring is needed to ensure that the disease does not progress and cause damage. Increasingly, the approach to therapy is to give highly effective treatment early, so the patient achieves a target called NEDA (no evidence of disease activity)—with NEDA, the patient is stable clinically, and has no relapses and no new lesions on magnetic resonance imaging.

Patients at high risk of disability start early on more potent but higher risk therapies—these are alemtuzumab, natalizumab and ocrelizumab, which are monoclonal antibody drugs given intravenously. Drugs given orally (eg dimethyl fumarate, fingolimod, teriflunomide) have moderate potency. The older drugs, interferons (subcutaneous or intramuscular) and glatiramer acetate (subcutaneous), work well in some patients. However, the effect of these older drugs is less predictable, and relapses are more common than with monoclonal antibody and oral drugs. Immunotherapies available for MS (other than ocrelizumab) are shown in Table 7.8, with reported efficacy and the most serious adverse effects.

Precautions before starting immunomodulatory therapy (eg pretreatment screening and vaccination), and during therapy, are described in the Product Information for each drug. For guidance on when to give antimicrobial prophylaxis for patients taking immunotherapy, see Assessing the need for antimicrobial

prophylaxis in immunocompromised adults without HIV infection. For further information, consult local protocols or seek expert advice.

Table 7.8 Immunotherapy drugs for multiple sclerosis

[NB1]

- monoclonal antibody drugs
  - alemtuzumab
  - natalizumab
- oral drugs
  - dimethyl fumarate
  - fingolimod
  - teriflunamide
- interferons
  - interferon beta 1a
    - intramuscular
    - subcutaneous
  - interferon beta 1b
- glatiramer acetate

alemtuzumab [NB4]	
route	intravenous
efficacy [NB2]: relapses (ARR RRR)	67%
efficacy [NB2]: disability (3m SDP RRR)	52%
efficacy [NB2]: new Gad lesions on MRI (RRR)	94%
serious adverse effects [NB3]	anti-GBM kidney disease (rare) thyroid autoimmunity immune thrombocytopenic purpura haemolytic anaemia listeriosis (rare; avoid soft cheeses or unpasteurised food for the first 6 months after infusion)
natalizumab [NB4]	
route	intravenous
efficacy [NB2]: relapses (ARR RRR)	68%
efficacy [NB2]: disability (3m SDP RRR)	54%
efficacy [NB2]: new Gad lesions on MRI (RRR)	92%
serious adverse effects [NB3]	progressive multifocal leukoencephalopathy (rare) [NB5]
dimethyl fumarate [NB4]	
route	oral
efficacy [NB2]: relapses (ARR RRR)	53%
efficacy [NB2]: disability (3m SDP RRR)	38%
efficacy [NB2]: new Gad lesions on MRI (RRR)	90%

serious adverse effects [NB3]	progressive multifocal leukoencephalopathy (very rare) [NB5]
fingolimod [NB4]	
route	oral
efficacy [NB2]: relapses (ARR RRR)	55%
efficacy [NB2]: disability (3m SDP RRR)	30%
efficacy [NB2]: new Gad lesions on MRI (RRR)	82%
	cardiac arrhythmia
	cryptococcal meningitis (very rare)
serious adverse effects [NB3]	macular oedema
	progressive multifocal leukoencephalopathy (very rare) [NB5]
	shingles
teriflunomide [NB4]	
route	oral
efficacy [NB2]: relapses (ARR RRR)	32%
efficacy [NB2]: disability (3m SDP RRR)	30%
efficacy [NB2]: new Gad lesions on MRI (RRR)	80%
	Stevens-Johnson syndrome (very rare)
serious adverse effects [NB3]	hepatitis [NB3]
	peripheral neuropathy
interferon beta 1a (intramuscular) [NB4]	
route	intramuscular
efficacy [NB2]: relapses (ARR RRR)	18%
efficacy [NB2]: disability (3m SDP RRR)	37%
efficacy [NB2]: new Gad lesions on MRI (RRR)	52%
serious adverse effects [NB3]	hepatitis [NB3]
interferon beta 1a (subcutaneous) [NB4]	
route	subcutaneous
efficacy [NB2]: relapses (ARR RRR)	32%
efficacy [NB2]: disability (3m SDP RRR)	29% [NB6]
efficacy [NB2]: new Gad lesions on MRI (RRR)	88%
serious adverse effects [NB3]	hepatitis [NB3]
interferon beta 1b [NB4]	
route	subcutaneous

efficacy [NB2]: relapses (ARR RRR)	34%
efficacy [NB2]: disability (3m SDP RRR)	25% [NB6]
efficacy [NB2]: new Gad lesions on MRI (RRR)	43%
serious adverse effects [NB3]	hepatitis [NB3]
glatiramer acetate [NB4]	
route	subcutaneous
efficacy [NB2]: relapses (ARR RRR)	29%
efficacy [NB2]: disability (3m SDP RRR)	12% [NB6]
efficacy [NB2]: new Gad lesions on MRI (RRR)	33%
serious adverse effects [NB3]	–

3m SDP RRR = 3 months sustained disability progression relative risk reduction; ARR RRR = annualised relapse rate relative risk reduction; Gad = gadolinium enhancing; GBM = glomerular basement membrane; MRI = magnetic resonance imaging; RRR = relative risk reduction

NB1: This table is based on the reference cited below, which lists efficacy of drugs that were available in Australia at the time; since its publication, ocrelizumab has become available.

NB2: 'Efficacy' is 2-year efficacy for treating relapsing-remitting multiple sclerosis. Efficacy figures for the drugs are not directly comparable, because trial populations vary.

NB3: Less serious adverse effects of immunotherapy drugs for multiple sclerosis include:

- raised concentrations of liver enzymes in patients using oral drugs or interferons. If the liver enzyme concentration is less than 3 times the upper limit of the normal range, monitor the patient. If higher than this, refer for expert advice
- lymphopenia. This is expected with alemtuzumab or fingolimod therapy, but if it occurs with dimethyl fumarate or teriflunomide, refer for expert advice.

NB4: Precautions before starting treatment and during treatment are described in the Product Information for each drug. When appropriate, follow local protocols.

NB5: Progressive multifocal leukoencephalopathy is a chronic, progressive and often severe brain infection, caused by the John Cunningham virus (JCV). It can be life-threatening. Symptoms include progressive cognitive decline, visual changes, ataxia and seizures.

NB6: Not significant compared with placebo

Adapted with permission from 'Table 1. Comparison of 2 year efficacy for treatment of RRMS from pivotal trials/Cochrane reviews' in Broadley SA, Barnett MH, Boggild M, Brew BJ, Butzkueven H, Heard R, et al. Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: an Australian and New Zealand perspective. Part 2: New and emerging therapies and their efficacy. MS Neurology Group of the Australian and New Zealand Association of Neurologists. J Clin Neurosci 2014;21(11):1847-56. [URL]

Acute relapses of multiple sclerosis

Acute relapses of multiple sclerosis

Mild relapses (eg tingling in the extremities) can occur in multiple sclerosis (MS). If the patient has no signs of disability (eg no objective neurological signs, no increase in urinary symptoms or bowel dysfunction),

reassure the patient and monitor to ensure resolution. Refer for expert advice if unsure whether the relapse is mild.

Moderate to severe acute relapses of MS usually have objective neurological signs, and are treated with corticosteroids. Therapy hastens recovery from the relapse and improves clinical outcomes in the short term, and may also prevent neuronal loss and improve outcomes in the longer term. A minority of relapses cause permanent disability, so it is important to recognise and treat relapses.

When a patient with MS presents with symptoms that suggest a relapse, the clinician needs to determine whether these are due to:

- an inflammatory lesion of the central nervous system (CNS), and corticosteroid therapy is justified
- other conditions that mimic a relapse, and corticosteroid therapy is inappropriate.

Diagnosing a relapse in patients with significant disability can be difficult—refer for expert advice if unsure.

A typical relapse develops over hours to days and has consistent, and often progressive, symptoms that can be localised to part of the CNS. See examples of symptoms specific for MS in the left-hand column of Table 7.7.

Any MS symptom can occur as part of a relapse. However, transient symptoms which last for minutes to hours and then resolve, are less likely to be due to a relapse—these are often associated with fatigue, sleep deprivation, stress or increased body temperature (eg during exercise). Also, chronic symptoms are less likely to be due to a relapse. Longstanding symptoms can be exacerbated by fever, illness and metabolic disturbance.

If the symptoms are short-lived (eg Lhermitte phenomenon recurs) but an acute inflammatory lesion is a concern, magnetic resonance imaging with gadolinium contrast is useful.

Treatment for moderate to severe relapses of MS is high-dose corticosteroids—intravenous therapy is preferred. Oral formulations [Note 2] have slightly more adverse effects (eg insomnia) but are convenient when intravenous therapy is not available (eg in rural settings). Intravenous formulations can be given as a day-patient, but severe relapses warrant admission for multidisciplinary care. For moderate to severe relapses of MS in a child, seek expert advice. For moderate to severe relapses in an adult, an appropriate dosage is:

methylprednisolone sodium succinate 1 g intravenously, over 1 hour, once daily for 3 days. *multiple sclerosis, acute relapse (adult)*

If the patient with a moderate to severe relapse of MS deteriorates despite corticosteroid treatment, refer for expert advice.

Note 2: Methylprednisolone sodium succinate vials can be reconstituted with water and taken orally, mixed in orange juice. Methylprednisolone 100 mg tablets are not registered for use in Australia but are available via the Special Access Scheme.

Spasticity due to multiple sclerosis

Spasticity due to multiple sclerosis

Spasticity is common in multiple sclerosis (MS), due to corticospinal tract damage. Appropriate management can reduce pain, improve mobility and prevent contractures. Start therapy at low doses, to prevent flaccidity (with a paradoxical decrease in mobility) and adverse effects. Use:

baclofen 5 mg orally, 3 times daily, initially. Increase daily dose by 10 to 15 mg every 3 days to optimum response. Usual optimum dose is 10 to 25 mg 3 times daily (maximum daily dose 100 mg in 3 divided doses). Review after 6 to 8 weeks. If stopping therapy, reduce dose slowly over 2 weeks, to avoid withdrawal syndrome. *spasticity (multiple sclerosis)*

A benzodiazepine may be added at night to help spasms. Clonazepam is better tolerated than diazepam. Add:

1 clonazepam 0.5 mg orally, once daily at night. If needed, increase up to 2 mg at night *spasticity (multiple sclerosis)* _

OR

2 diazepam 2.5 mg orally, once daily at night. If needed, increase up to 5 mg at night. *spasticity (multiple sclerosis)* _

If this treatment does not reduce spasticity, refer for expert advice. Gabapentin can be useful when the patient also has neuropathic pain and spasms.

Medicinal cannabis (nabiximols and other cannabis products) has been used overseas to treat spasticity in MS.

Diminished mobility due to multiple sclerosis

Diminished mobility due to multiple sclerosis

Fampridine (4-aminopyridine in a long-acting form) has been shown to improve walking in patients with multiple sclerosis, and can have a modest effect on cognitive function. It increases the conduction speed in demyelinated nerves. Fampridine is prescribed by an expert, who reviews the patient after 8 weeks to see if the drug has been effective. The usual dose is:

fampridine modified-release 10 mg orally, twice daily, approximately 12 hours apart. *diminished mobility (multiple sclerosis)*

Pain due to multiple sclerosis

Pain due to multiple sclerosis

Pain due to multiple sclerosis (MS) can affect different parts of the body and has various causes. The conditions that are most common and difficult to treat are:

- trigeminal neuralgia, due to a lesion of the trigeminal tract in the pons
- neuropathic pain in the lower limbs or thorax, due to spinal cord lesions.

Trigeminal neuralgia presents, and is treated, as for other causes of the condition (see advice), except that microvascular decompression is not appropriate therapy.

Neuropathic pain in MS can be due to spinal cord lesions or other causes. It is treated as for other causes of neuropathic pain (see advice).

Pain on eye movement, with impaired vision or changes in colour vision, is usually due to optic neuritis. For acute changes, refer immediately for expert advice, as the patient may have had an acute relapse and need a corticosteroid.

Pain in MS can also be due to other complications (eg spasticity, contractures)—diagnose and treat appropriately. Tonic spasms are rare in MS, common in neuromyelitis optica, and often painful (see paroxysmal symptoms).

Paroxysmal symptoms due to multiple sclerosis

Paroxysmal symptoms due to multiple sclerosis

Paroxysmal symptoms (eg dystonic posturing, tonic spasms) in patients with multiple sclerosis usually respond to carbamazepine. Use:

carbamazepine modified-release 100 mg orally, once or twice daily; increase as tolerated and according to response every 7 days to a maximum of 600 mg twice daily [Note 3]. *paroxysmal symptoms (multiple sclerosis)* _

Carbamazepine can aggravate fatigue and ataxia.

Often the patient can sense when the paroxysms have stopped. If so, long-term carbamazepine therapy may not be needed—an appropriate strategy is to slowly wean the drug (eg by reducing the daily dose by 100 mg per week).

Note 3: Pharmacogenetic studies are identifying an increasing number of genes that confer a predisposition to cutaneous drug reactions. Testing for the HLA-B*1502 allele in patients of Asian origin (other than Japanese) is advised before starting therapy with carbamazepine.

Fatigue due to multiple sclerosis

Fatigue due to multiple sclerosis

Up to 75% of patients with multiple sclerosis (MS) have fatigue—the causes are complex and management is difficult.

Seek contributing factors (eg nocturia, pain or spasms, mood disorders or anxiety, sleep disorders [restless legs syndrome is more common in people with MS]). Exclude hypothyroidism, anaemia and concomitant conditions (eg infection).

Drugs have low efficacy for fatigue in MS, but amantadine and modafinil are sometimes used.

Chronic or relapsing fatigue may reflect disease activity—refer the patient for expert advice. In some patients, immunotherapy can improve fatigue by reducing inflammation in the brain.

Bladder symptoms due to multiple sclerosis

Bladder symptoms due to multiple sclerosis

Urgency (due to detrusor overactivity) is the most common bladder symptom in patients with multiple sclerosis (MS). However, always consider the possibility of infection or residual urine (readily measured with ultrasound). If the problem is not urgency, or if the residual urine volume is more than 100 mL, refer the patient for expert advice and urodynamic testing. Possible expert treatments include intradetrusor injections of botulinum toxin type A and sacral neuromodulation.

Relatively mild symptoms (ie urinary urgency and frequency) usually respond to taking an anticholinergic drug and emptying the bladder frequently. Use:

1 oxybutynin 2.5 to 5 mg orally, 2 or 3 times daily *urinary urgency (multiple sclerosis)* _

OR

1 oxybutynin 3.9 mg transdermally, twice weekly _

OR

2 darifenacin modified-release 7.5 to 15 mg orally, daily *urinary urgency (multiple sclerosis)*

OR

2 solifenacin 5 to 10 mg orally, daily *urinary urgency (multiple sclerosis)*

OR

2 tolterodine 1 to 2 mg orally, twice daily. *urinary urgency (multiple sclerosis)*

Anticholinergic drugs can exacerbate cognitive dysfunction. Newer drugs (eg mirabegron) may have fewer cognitive adverse effects—refer for expert advice.

If the patient has high residual urine volumes, and has sufficient dexterity, the expert may teach them to perform clean intermittent self-catheterisation. If not, a permanent indwelling suprapubic or urethral catheter must be considered.

Bowel symptoms due to multiple sclerosis

Bowel symptoms due to multiple sclerosis

The most common bowel problem in patients with multiple sclerosis (MS) is constipation. Patients can also have faecal urgency and incontinence. Constipation is managed as for all patients (see functional constipation). Causes of constipation that can be overlooked in patients with MS include:

- drugs taken to control bladder symptoms or spasticity
- fluid intake reduction to manage bladder symptoms.

Psychiatric symptoms due to multiple sclerosis

Psychiatric symptoms due to multiple sclerosis

Depression is common in patients with multiple sclerosis (MS), mania is rare and psychosis is extremely rare. Causes of depression in patients with MS include:

- a reaction to the diagnosis, its physical effects and its effects on relationships, employment and social life
- an adverse effect of drugs taken for MS
- an attack of demyelination.

Behavioural disorders can occur due to frontal lobe demyelination.

The full range of psychotropic drugs can be used to treat psychiatric symptoms in patients with MS (see advice in the Psychotropic guideline).

Sexual difficulties due to multiple sclerosis

Sexual difficulties due to multiple sclerosis

Sexual difficulties in patients with multiple sclerosis (MS) can be due to spinal plaques, psychological factors, relationship difficulties, fatigue or medication. Often multiple factors are involved. Specialist counselling can be helpful. Sildenafil can be effective in treating erectile dysfunction in male patients with MS (see advice).

General health advice in multiple sclerosis

General health advice in multiple sclerosis

No single diet has been shown in controlled trials to alter the course of multiple sclerosis (MS), but diet has been shown to improve body mass index and lipid profile, and possibly fatigue. Patients with MS often follow specific diets that are not supported by evidence. Encourage patients to eat a healthy, varied low-fat diet, to improve their general health.

A low serum vitamin D concentration has been associated with increased relapse frequency and magnetic resonance imaging activity in early MS. Check vitamin D at diagnosis and supplement if the serum 25-hydroxyvitamin D is lower than 50 nmol/L (see advice). It is uncertain whether supraphysiological doses of vitamin D are beneficial.

Smoking has been shown to increase the risk of developing MS, and to increase disease progression in patients with MS. Strongly advise patients with MS to stop smoking.

Encourage patients to increase exercise and moderate their alcohol intake—these changes were associated with lower disability in self-reported observational studies of MS [Note 4].

Note 4: Jelinek GA, De Livera AM, Marck CH, Brown CR, Neate SL, Taylor KL, et al. Associations of lifestyle, medication, and socio-demographic factors with disability in people with multiple sclerosis: an international cross-sectional study. PLoS One 2016;11(8):e0161701. [URL]

Women's health advice in multiple sclerosis

Women's health advice in multiple sclerosis

Contraception and hormone replacement therapy

Contraception and hormone replacement therapy

The use of oral contraceptives or other hormone preparations, including hormone replacement therapy, is not contraindicated in multiple sclerosis (MS).

Pregnancy

Pregnancy

The risk of MS relapse is decreased in pregnancy, but this is balanced by an increased risk of relapse in the first 3 months after delivery. Pregnancy does not alter the prognosis of MS. Ideally, pregnancies should be planned with expert advice from a neurologist and an obstetrician.

Disease activity during pregnancy is sufficiently infrequent that in most cases immunotherapy can be stopped before attempting conception. However, if treatment is withdrawn too early, relapses may develop. When (or whether) to stop therapy is an expert decision that is different for each patient, and based on several factors (eg teratogenicity of the drugs, potential for rebound disease activity, severity of MS). Teriflunomide has a long half-life and is category X [Note 5] —before the patient attempts conception, the drug needs to be washed out with charcoal or colestyramine. Fingolimod is category D [Note 6], so therapy must be stopped before the patient attempts conception.

Disease activity can be treated with corticosteroids during pregnancy, but seek expert advice if this is not sufficient and ongoing treatment is required.

Pregnancy and labour are managed as for females without MS (ie with the usual procedures [including epidural anaesthesia, if indicated] and drugs).

Note 5: The Australian Therapeutic Goods Administration Prescribing medicines in pregnancy database defines category X as 'Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is a possibility of pregnancy'.

Note 6: The Australian Therapeutic Goods Administration Prescribing medicines in pregnancy database defines category D as 'Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details'.

Post partum

Post partum

In patients with moderate to severe MS, restart immunotherapy 2 weeks post partum, to minimise the risk of relapse. Immediately restarting immunotherapy (eg the day after giving birth) is not advised, in case the patient has a postpartum infection or wound infection (eg after a Caesarean section).

Evidence for the safety of breastfeeding during immunotherapy is lacking—seek expert advice.

In patients with mild MS, breastfeeding may be possible—seek expert advice.

Immunisation advice in multiple sclerosis

Immunisation advice in multiple sclerosis

There is no evidence that vaccinations increase the risk of relapse in multiple sclerosis (MS).

Inactivated influenza vaccine can be given to patients with MS.

Difficulties arise when a patient with MS needs a live vaccine (eg measles, mumps, rubella, varicella, zoster, yellow fever, Japanese encephalitis, Bacille Calmette-Guérin [BCG], oral typhoid), as these can be dangerous with certain immunotherapies. A problem is unlikely with interferons and glatiramer acetate, but drugs that suppress lymphocytes may allow live virus to disseminate. Avoid live vaccines in patients taking dimethyl fumarate, fingolimod, natalizumab, ocrelizumab and teriflunomide [Note 7]. Vaccination in patients taking alemtuzumab is complex—refer for expert advice.

Note 7: Precautions before starting treatment and during treatment are described in the Product Information for each drug. When appropriate, follow local protocols.

Key references: Overview of multiple sclerosis

Key references: Overview of multiple sclerosis

- Sadovnick AD, Macleod PM. The familial nature of multiple sclerosis: empiric recurrence risks for first, second-, and third-degree relatives of patients. Neurology 1981;31(8):1039–41. https://www.ncbi.nlm.nih.gov/pubmed/7196517

Key references: Diagnosing multiple sclerosis

Key references: Diagnosing multiple sclerosis

- Marignier R, Calvo A, Vukusic S. Neuromyelitis optica and neuromyelitis optica spectrum disorders. Curr Opin Neurol 2017;30(3):208–15. https://www.ncbi.nlm.nih.gov/pubmed/28306572

- O'Riordan JI, Thompson AJ, Kingsley DP, MacManus DG, Kendall BE, Rudge P, et al. The prognostic value of brain MRI in clinically isolated syndromes of the CNS. A 10-year follow-up. Brain 1998;121 (Pt 3):495–503. https://www.ncbi.nlm.nih.gov/pubmed/9549525
- Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69(2):292–302. https://www.ncbi.nlm.nih.gov/pubmed/21387374

Key references: Overview of therapy for multiple sclerosis

Key references: Overview of therapy for multiple sclerosis

- Muraro PA, Pasquini M, Atkins HL, Bowen JD, Farge D, Fassas A, et al. Long-term outcomes after autologous hematopoietic stem cell transplantation for multiple sclerosis. JAMA Neurol 2017;74(4):459–69. https://www.ncbi.nlm.nih.gov/pubmed/28241268

Key references: Available immunotherapies for multiple sclerosis

Key references: Available immunotherapies for multiple sclerosis

- Broadley SA, Barnett MH, Boggild M, Brew BJ, Butzkueven H, Heard R, et al. Therapeutic approaches to disease modifying therapy for multiple sclerosis in adults: an Australian and New Zealand perspective. Part 2: New and emerging therapies and their efficacy. MS Neurology Group of the Australian and New Zealand Association of Neurologists. J Clin Neurosci 2014;21(11):1847–56. https://www.ncbi.nlm.nih.gov/pubmed/24986155
- Hauser SL, Bar-Or A, Comi G, Giovannoni G, Hartung HP, Hemmer B, et al. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. N Engl J Med 2017;376(3):221–34. https://www.ncbi.nlm.nih.gov/pubmed/28002679

Key references: Acute relapses of multiple sclerosis

Key references: Acute relapses of multiple sclerosis

- Page E, Veillard D, Laplaud DA, Hamonic S, Wardi R, Lebrun C, et al. Oral versus intravenous high-dose methylprednisolone for treatment of relapses in patients with multiple sclerosis (COPOUSEP): a randomised, controlled, double-blind, non-inferiority trial. Lancet 2015;386(9997):974–81. https://www.ncbi.nlm.nih.gov/pubmed/26135706
- Yamasaki R, Matsushita T, Fukazawa T, Yokoyama K, Fujihara K, Ogino M, et al. Efficacy of intravenous methylprednisolone pulse therapy in patients with multiple sclerosis and neuromyelitis optica. Mult Scler 2015;22(10):1337–48. https://www.ncbi.nlm.nih.gov/pubmed/26564994

Key references: Spasticity due to multiple sclerosis

Key references: Spasticity due to multiple sclerosis

- Mueller ME, Gruenthal M, Olson WL, Olson WH. Gabapentin for relief of upper motor neuron symptoms in multiple sclerosis. Arch Phys Med Rehabil 1997;78(5):521–4. https://www.ncbi.nlm.nih.gov/pubmed/9161373
- Murnion B. Medicinal cannabis. Aust Prescr 2015;38(6):212–5. https://www.ncbi.nlm.nih.gov/pubmed/26843715
- Shakespeare DT, Boggild M, Young C. Anti-spasticity agents for multiple sclerosis. Cochrane Database Syst Rev 2003;(4):CD001332. https://www.ncbi.nlm.nih.gov/pubmed/14583932
- Thompson AJ, Toosy AT, Ciccarelli O. Pharmacological management of symptoms in multiple sclerosis: current approaches and future directions. Lancet Neurol 2010;9(12):1182–99. https://www.ncbi.nlm.nih.gov/pubmed/21087742

Key references: Diminished mobility due to multiple sclerosis

Key references: Diminished mobility due to multiple sclerosis

- Goodman AD, Brown TR, Krupp LB, Schapiro RT, Schwid SR, Cohen R, et al. Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial. Lancet 2009;373(9665):732–8. https://www.ncbi.nlm.nih.gov/pubmed/19249634
- Jensen H, Ravnborg M, Mamoei S, Dalgas U, Stenager E. Changes in cognition, arm function and lower body function after slow-release Fampridine treatment. Mult Scler 2014;20(14):1872–80. https://www.ncbi.nlm.nih.gov/pubmed/24852920

Key references: Fatigue due to multiple sclerosis

Key references: Fatigue due to multiple sclerosis

- Manconi M, Fabbrini M, Bonanni E, Filippi M, Rocca M, Murri L, et al. High prevalence of restless legs syndrome in multiple sclerosis. Eur J Neurol 2007;14(5):534–9. https://www.ncbi.nlm.nih.gov/pubmed/17437613
- Penner IK, Sivertsdotter EC, Celius EG, Fuchs S, Schreiber K, Berko S, et al. Improvement in fatigue during natalizumab treatment is linked to improvement in depression and day-time sleepiness. Front Neurol 2015;6:18. https://www.ncbi.nlm.nih.gov/pubmed/25755648

Key references: Bladder symptoms due to multiple sclerosis

Key references: Bladder symptoms due to multiple sclerosis

- Kalsi V, Gonzales G, Popat R, Apostolidis A, Elneil S, Dasgupta P, et al. Botulinum injections for the treatment of bladder symptoms of multiple sclerosis. Ann Neurol 2007;62(5):452–7. https://www.ncbi.nlm.nih.gov/pubmed/17890635
- Phe V, Chartier-Kastler E, Panicker JN. Management of neurogenic bladder in patients with multiple sclerosis. Nat Rev Urol 2016;13(5):275–88. https://www.ncbi.nlm.nih.gov/pubmed/27030526

Key references: General health advice in multiple sclerosis

Key references: General health advice in multiple sclerosis

- Farinotti M, Vacchi L, Simi S, Pietrantonj C, Brait L, Filippini G. Dietary interventions for multiple sclerosis. Cochrane Database Syst Rev 2012;(12):CD004192. https://www.ncbi.nlm.nih.gov/pubmed/23235605
- Hernan MA, Jick SS, Logroscino G, Olek MJ, Ascherio A, Jick H. Cigarette smoking and the progression of multiple sclerosis. Brain 2005;128(Pt 6):1461–5. https://www.ncbi.nlm.nih.gov/pubmed/15758034
- Jelinek GA, Livera AM, Marck CH, Brown CR, Neate SL, Taylor KL, et al. Associations of lifestyle, medication, and socio-demographic factors with disability in people with multiple sclerosis: an international cross-sectional study. PLoS One 2016;11(8):e0161701. https://www.ncbi.nlm.nih.gov/pubmed/27560626
- Loken-Amsrud KI, Holmoy T, Bakke SJ, Beiske AG, Bjerve KS, Bjornara BT, et al. Vitamin D and disease activity in multiple sclerosis before and during interferon-beta treatment. Neurology 2012;79(3):267–73. https://www.ncbi.nlm.nih.gov/pubmed/22700809
- Riemann-Lorenz K, Eilers M, Geldern G, Schulz KH, Kopke S, Heesen C. Dietary interventions in multiple sclerosis: development and pilot-testing of an evidence based patient education program. PLoS One 2016;11(10):e0165246. https://www.ncbi.nlm.nih.gov/pubmed/27764237
- Yadav V, Marracci G, Kim E, Spain R, Cameron M, Overs S, et al. Low-fat, plant-based diet in multiple sclerosis: A randomized controlled trial. Mult Scler Relat Disord 2016;9:80–90. https://www.ncbi.nlm.nih.gov/pubmed/27645350

Key references: Women's health advice in multiple sclerosis

Key references: Women's health advice in multiple sclerosis

- Alroughani R, Altintas A, Jumah M, Sahraian M, Alsharoqi I, AlTahan A, et al. Pregnancy and the use of disease-modifying therapies in patients with multiple sclerosis: benefits versus risks. Mult Scler Int 2016;2016:1034912. https://www.ncbi.nlm.nih.gov/pubmed/28078140
- Bove R, White CC, Fitzgerald KC, Chitnis T, Chibnik L, Ascherio A, et al. Hormone therapy use and physical quality of life in postmenopausal women with multiple sclerosis. Neurology 2016;87(14):1457–63. https://www.ncbi.nlm.nih.gov/pubmed/27605175
- Houtchens MK, Zapata LB, Curtis KM, Whiteman MK. Contraception for women with multiple sclerosis: Guidance for healthcare providers. Mult Scler 2017;23(6):757–64. https://www.ncbi.nlm.nih.gov/pubmed/28338393
- Thone J, Thiel S, Gold R, Hellwig K. Treatment of multiple sclerosis during pregnancy - safety considerations. Expert Opin Drug Saf 2017;16(5):523–34. https://www.ncbi.nlm.nih.gov/pubmed/28333552

Key references: Immunisation advice in multiple sclerosis

Key references: Immunisation advice in multiple sclerosis

- Mailand MT, Frederiksen JL. Vaccines and multiple sclerosis: a systematic review. J Neurol 2017;264(6):1035–50. https://www.ncbi.nlm.nih.gov/pubmed/27604618

Published November 2017 (Amended December 2019)

[X] Close

Diagnosing muscle diseases

Diagnosing muscle diseases

Diseases of muscle include acquired myopathies (eg immune-mediated myopathies) and inherited disorders (eg muscular dystrophies, congenital myopathies, metabolic myopathies, mitochondrial myopathies, channelopathies).

Acquired myopathies usually present as subacute onset of nonselective symmetrical weakness in the proximal (shoulder and hip girdle) muscles. Dysphagia can occur, especially in immune-mediated myopathies. In contrast to acquired myopathies, inherited muscle disorders often have a specific pattern of chronic, slowly progressive muscle weakness—the pattern may suggest a particular genetic cause.

Perform a complete physical examination that includes testing muscle strength and function, to identify the pattern and severity of muscle weakness. A standard scoring system for muscle strength is outlined in Table 7.9. A complete neurological examination and a complete systemic examination (including skin and joints) are also essential.

Table 7.9 The standard Medical Research Council scoring system for muscle strength

Muscle strength	Score
no contraction	0
contracts, but no movement	1
full range of movement (with gravity eliminated)	2
full range of movement (with gravity)	3
some resistance	4 [NB1]
normal power	5 [NB1]

NB1: Gradations exist between scores 4 and 5.

Myopathies may be associated with a raised serum creatine kinase (CK) concentration, as well as raised alanine aminotransferase (ALT), aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) concentrations. A blood screen for autoantibodies (eg myositis antibodies) or endocrine abnormalities can help identify the cause of an acquired myopathy.

Further testing is best ordered and performed by experts, and could include electromyography, magnetic resonance imaging (MRI), muscle biopsy and genetic testing. Electromyography can confirm that the cause of the weakness is primarily muscle in origin, and exclude neurogenic causes or neuromuscular junction disorders. Electromyography and MRI can help guide the site for a muscle biopsy, and also show the pattern of muscle involvement. Often a muscle biopsy is needed to establish the diagnosis. The biopsy result needs to be correlated with the clinical picture. Genetic testing is best requested by experts, because they can provide genetic counselling and interpret complex results.

See additional advice on diagnosing immune-mediated myopathies.

Published November 2017

[X] Close

Classifying and diagnosing immune-mediated myopathies

Classifying and diagnosing immune-mediated myopathies

See also the overview of diagnosing muscle diseases.

Immune-mediated myopathies include dermatomyositis, polymyositis, overlap myositis, necrotising autoimmune myopathy (NAM) and inclusion body myositis (IBM). See Figure 7.10 for a detailed classification. See advice on adult and juvenile dermatomyositis.

Figure 7.10 Classifying immune-mediated myopathies

- dermatomyositis
  - adult, with or without malignancy
  - juvenile
- polymyositis
- overlap myositis
  - myositis associated with other connective tissue disorders (eg systemic lupus erythematosus, mixed connective tissue disease, Sjögren syndrome, rheumatoid arthritis)
  - antisynthetase syndrome (fever, arthralgia, Raynaud syndrome, interstitial lung disease and mechanic's hands; associated with the anti–tRNA synthetase antibodies, especially anti–Jo-1 antibodies)
- necrotising autoimmune myopathy (NAM)
  - HMGCR positive (statin-associated and statin-naïve)
  - SRP-positive
  - associated with
    - malignancy
    - connective tissue disorders
    - viral infection (eg HIV, hepatitis C)
- inclusion body myositis (IBM)
- rarer causes
  - eosinophilic myositis/myofasciitis
  - infection-related myositis
  - granulomatous myositis, including sarcoid-associated myositis

HMGCR = 3-hydroxy-3-methyl-glutaryl-CoA reductase; SRP = signal recognition particle

The clinical suspicion of an immune-mediated myopathy is triggered by the tempo of disease, pattern of muscle weakness and associated features (eg Raynaud syndrome, arthritis and pulmonary fibrosis in overlap myositis). Typically it presents as subacute onset of proximal (shoulder and hip girdle) muscle weakness that progresses over weeks. The bulbar muscles can be involved, as well as respiratory and/or cardiac muscle.

Inclusion body myositis is distinct in clinical presentation and pathology from the other immune-mediated myopathies. Although rare, IBM is the most common acquired muscle disease in adults older than 40 years. Consider IBM when an older patient presents with new muscle weakness. Inclusion body myositis has a specific pattern of wasting and weakness of the long finger flexors and the quadriceps. Patients often present with symptoms attributable to proximal lower limb weakness (eg falls, difficulty going up or down stairs or rising from low chairs).

Usually the creatine kinase (CK) concentration is raised, in association with other enzymes that include lactate dehydrogenase (LDH), aspartate aminotransferase (AST) and alanine aminotransferase (ALT). However, in IBM the creatine kinase concentration can be normal or raised (usually not more than 12 times

the upper limit of normal). Awareness of antibodies in identifying disease subtypes is increasing [Note 1]. Electromyography shows myopathic potentials, abnormal spontaneous activity and fibrillation potentials. Magnetic resonance imaging can show oedema in affected muscles, and may help target a muscle biopsy.

The diagnosis is confirmed by muscle biopsy, which is more sensitive if performed before starting immunosuppression. Clinicopathological correlation is important (eg in IBM, up to one-third of biopsies are missing one or more of IBM's usual cardinal features). Ideally start treatment after biopsy results are known.

Managing immune-mediated myopathies requires expert advice, and patients usually need lifelong treatment and monitoring. Exercise is an important aspect of treating patients with immune-mediated myopathy. It is safe, and improves muscle strength and patient function and health-related quality of life. However, no evidence-based advice on the optimal exercise regimen is available. A neurophysiotherapist can help guide the program.

Note 1: Needham M, Mastaglia FL. Sporadic inclusion body myositis: A review of recent clinical advances and current approaches to diagnosis and treatment. Clin Neurophysiol 2016;127(3):1764-73. [URL]

Managing immune-mediated myopathies other than inclusion body myositis

Managing immune-mediated myopathies other than inclusion body myositis

The approach to treating all forms of immune-mediated myopathy (other than inclusion body myositis) is the same. First-line therapy is a corticosteroid, usually oral prednis(ol)one. High-dose corticosteroids are usually given at the same time as a corticosteroid-sparing drug (eg azathioprine, methotrexate, mycophenolate).

In severe cases, before starting an oral corticosteroid, patients may be given pulse parenteral corticosteroid therapy. Intravenous immunoglobulin (IVIg) may also be given at the same time as the parenteral corticosteroid. The usual dose of intravenous corticosteroid is:

1 methylprednisolone sodium succinate 1 g intravenously, over 1 hour, once daily for 3 days *immune-mediated myopathy (other than inclusion body myositis)*

OR

1 methylprednisolone sodium succinate 0.5 g intravenously, over 1 hour, once daily for 5 days.

The usual doses of oral prednis(ol)one and corticosteroid-sparing drugs are:

prednis(ol)one 1 mg/kg (up to 75 mg) orally, daily in the morning for 6 weeks, then reduce daily dose by 5 mg every 2 weeks to 25 mg daily, then reduce further according to response and tolerability. Reduce dose faster, with expert supervision, if patient responds rapidly or has adverse effects [Note 2] *immune-mediated myopathy (other than inclusion body myositis)*

PLUS

1 azathioprine 1.5 to 2.5 mg/kg orally, daily [Note 3] *immune-mediated myopathy (other than inclusion body myositis)*

OR

1 methotrexate 10 to 25 mg subcutaneously, intramuscularly or orally, on one specified day per week [Note 2] *immune-mediated myopathy (other than inclusion body myositis)*

PLUS

folic acid 5 to 10 mg orally, weekly (preferably not on the same day as methotrexate) *immune-mediated myopathy (other than inclusion body myositis)*

OR

1 mycophenolate mofetil 500 mg orally, twice daily (maximum 1500 mg twice daily) [Note 2] *immune-mediated myopathy (other than inclusion body myositis)*

OR

1 mycophenolate sodium 360 mg orally, twice daily (maximum 1080 mg twice daily) [Note 2]. *immune-mediated myopathy (other than inclusion body myositis)*

When myositis does not respond to therapy or is not adequately controlled, review the diagnosis. Exclude other disorders that can have an inflammatory biopsy (eg a dysferlinopathy or other form of muscular dystrophy) before changing the therapy (eg switching drugs, combining immunosuppressive drugs, adding IVIg or rituximab).

In severe cases of polymyositis, dermatomyositis and NAM, IVIg has been reported to be effective. Intravenous immunoglobulin is also an option for treating women who are pregnant or of childbearing age, or treating patients with severe adverse reactions to immunosuppressive drugs.

Note 2: Consider precautions and monitoring requirements when prescribing immunomodulatory drugs—consult local protocols or seek expert advice.

Note 3: Consider precautions (eg measuring thiopurine methyltransferase [TPMT] before starting therapy) and monitoring requirements when prescribing azathioprine—consult local protocols or seek expert advice. Azathioprine therapy does not reach maximum effect for at least 6 months.

Managing inclusion body myositis

Managing inclusion body myositis

For most patients with inclusion body myositis (IBM), care is supportive (eg physiotherapy, structured exercise programs, mobility aids).

In severe dysphagia, a gastrostomy may be considered. A trial of intravenous immunoglobulin may have short-term benefit, but rarely maintains swallowing long term. Refer for expert advice.

At the time of writing, evidence for immunosuppressive therapy for IBM is lacking. However, in rare cases (eg younger patients with more aggressive disease and severe inflammation on biopsy, or patients with another autoimmune disorder), an expert may choose to trial this therapy.

Key references: Managing immune-mediated myopathies other than inclusion body myositis

Key references: Managing immune-mediated myopathies other than inclusion body myositis

- Lundberg IE, Vencovsky J, Alexanderson H. Therapy of myositis: biological and physical. Curr Opin Rheumatol 2014;26(6):704–11. https://www.ncbi.nlm.nih.gov/pubmed/25198241

Key references: Managing inclusion body myositis

Key references: Managing inclusion body myositis

- Needham M, Mastaglia FL. Immunotherapies for immune-mediated myopathies: a current perspective. Neurotherapeutics 2016;13(1):132–46. https://www.ncbi.nlm.nih.gov/pubmed/26586486
- Needham M, Mastaglia FL. Sporadic inclusion body myositis: A review of recent clinical advances and current approaches to diagnosis and treatment. Clin Neurophysiol 2016;127(3):1764–73. https://www.ncbi.nlm.nih.gov/pubmed/26778717

Published November 2017

[X] Close

Diagnosing myasthenia gravis

Diagnosing myasthenia gravis

Myasthenia gravis is an autoimmune disorder, with antibodies to the postsynaptic acetylcholine receptor (Ach-R) or (less commonly) the muscle-specific tyrosine kinase (MuSK). Using tests available at the time of writing, antibodies are not detected in some patients. Myasthenia gravis presents most often in females aged 10 to 30 years and males aged 50 to 70 years. To confirm a diagnosis of myasthenia gravis, muscle fatigability must be shown, typically in the ocular, facial, bulbar or limb muscles. Ptosis may improve after applying ice to the eyelid. Myasthenia gravis does not cause sensory loss, sphincter disturbance or loss of reflexes—if these are present, consider an alternative diagnosis and refer for expert advice.

Many patients with ocular symptoms only (ocular myasthenia) are at risk of developing generalised disease within 2 years of onset. This is more likely in patients who have anti–Ach-R antibodies. Observational studies suggest that corticosteroids may reduce progression to generalised myasthenia gravis, or else mask the symptoms of generalised disease—the potential benefit needs to be weighed against the harms of immunosuppression.

When myasthenia gravis is suspected, investigations that can help confirm the diagnosis include:

- blood tests for Ach-R antibodies—these are positive in about 85% of patients. If the result is negative, consider testing for MuSK antibodies, especially if the patient has bulbar symptoms
- neurophysiological tests—appropriate findings are a decremental response on repetitive stimulation or positive single-fibre electromyography.

Perform thyroid function tests and measure vitamin B_{12} concentration in all patients, because patients with myasthenia gravis are at higher risk of other autoimmune disorders. Also perform a computed tomography scan of the chest, to check for a thymoma.

If the patient has ocular signs only and serology is negative, consider magnetic resonance imaging of the brain to exclude a structural abnormality.

When the investigations above are equivocal or negative but myasthenia gravis is still suspected, refer for expert advice and consideration of an edrophonium (Tensilon) test—this test should be performed under expert care in a hospital setting with resuscitation facilities.

Many drugs can make myasthenia gravis worse (see advice).

Approach to treating myasthenia gravis

Approach to treating myasthenia gravis

Do not start treating myasthenia gravis until the diagnosis is confirmed, except in a medical emergency. Management depends on the degree of disability and the muscles involved. Always assess breathing and swallowing. When the patient has isolated ocular symptoms, or only mild to moderate limb or bulbar weakness, they can be managed as an outpatient. If the patient has significant bulbar symptoms, rapidly progressing muscle weakness, or significant respiratory involvement, inpatient management is recommended. Forced vital capacity can help guide admission to intensive care.

Thymectomy is recommended for patients with a thymoma. A 2016 randomised controlled trial supports thymectomy in nonthymomatous anti–Ach-R positive myasthenia gravis patients (younger than 65 years),

even when they only have mild generalised myasthenia [Note 1].

Note 1: Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, et al. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med 2016;375(6):511-22. [URL]

Acetylcholinesterase inhibitors for symptoms of myasthenia gravis

Acetylcholinesterase inhibitors for symptoms of myasthenia gravis

To treat the symptoms of muscle-specific tyrosine kinase (MuSK)–negative mild generalised myasthenia gravis or ocular myasthenia, first-line therapy is the acetylcholinesterase inhibitor, pyridostigmine. (In MuSK-positive myasthenia gravis, acetylcholinesterase inhibitors are less effective and often have adverse effects.) Start therapy at a lower dose in smaller people. Use:

pyridostigmine 30 mg orally, 3 times daily. Increase dose every 4 to 7 days according to response and tolerability (maximum dose 120 mg orally, 2 to 6 times daily). Review after 4 to 6 weeks. If response to pyridostigmine is incomplete, consider immunosuppression. *myasthenia gravis*

Time the doses for when the patient is most fatigued (eg 30 to 45 minutes before meals when the patient has bulbar weakness). Use the lowest effective dose to achieve symptom control. If muscarinic adverse effects (eg diarrhoea, abdominal pain, cramps, exacerbation of glaucoma) occur, adding an anticholinergic drug (eg propantheline) may help.

Use larger doses of pyridostigmine (more than 540 mg daily) with caution, because of the:

- risk of increasing tolerance to the drug due to receptor downregulation
- greater risk of adverse effects
- possibility that a cholinergic crisis is misinterpreted as the myasthenia deteriorating.

Sustained-release pyridostigmine can be useful overnight. However, avoid this preparation during the day because its release varies and absorption is delayed. If considered appropriate, substitute sustained-release pyridostigmine for the final daily dose of the immediate-release preparation. Use:

pyridostigmine sustained-release 180 mg orally, once daily at night.

In an intensive care setting, a parenteral cholinesterase inhibitor (eg neostigmine) can be used instead of oral pyridostigmine—neostigmine 500 micrograms intravenously is approximately equal to pyridostigmine 60 mg orally.

Immunosuppression for myasthenia gravis

Immunosuppression for myasthenia gravis

Immunosuppression is needed if myasthenia gravis is moderate to severe or if the response to pyridostigmine is incomplete (ie patient is symptomatic despite an adequate trial of pyridostigmine).

As the patient goes into remission on immunosuppression, pyridostigmine should no longer be needed. Stopping pyridostigmine avoids wrongly interpreting its adverse effects (eg muscle twitching or cramping) as disease activity. Pyridostigmine should be withdrawn over a few weeks, to ensure that myasthenia gravis is in remission.

An uncommon effect of starting a high corticosteroid dose is that symptoms can get worse in the first 3 to 7 days, but this is transient. Start therapy as an inpatient or slowly work up to the high dose as an outpatient (as in the drug recommendations below). Lower corticosteroid dosages are usual in ocular myasthenia. Start a corticosteroid-sparing drug at the same time as the corticosteroid. Use:

prednis(ol)one 5 mg orally, daily in the morning. Increase daily dose by 5 mg every 3 days to a maximum of 1 mg/kg (up to 75 mg) daily. After 4 to 6 weeks, reduce daily dose by 5 mg every 2 weeks to 25 mg daily,

then reduce further according to response and tolerability [Note 2] *myasthenia gravis*

PLUS

1 azathioprine 1.5 to 2.5 mg/kg orally, daily [Note 3] *myasthenia gravis*

OR

1 mycophenolate mofetil 500 mg orally, twice daily (maximum 1500 mg twice daily) [Note 2] *myasthenia gravis*

OR

1 mycophenolate sodium 360 mg orally, twice daily (maximum 1080 mg twice daily) [Note 2]. *myasthenia gravis*

An alternative corticosteroid-sparing drug is methotrexate [Note 2].

In a myasthenic crisis or before an operation, IVIg or plasma exchange may be used. Randomised controlled trial evidence is insufficient to justify ongoing IVIg for chronic myasthenia, but it may be used in rare cases (eg pregnancy, severe treatment-resistant disease, intolerance to other treatments).

For refractory myasthenia (anti–Ach-R positive and anti-MuSK positive), case series show positive responses to rituximab [Note 4] [Note 5], and a small randomised controlled trial showed a positive response to cyclophosphamide [Note 6].

For MuSK-associated myasthenia gravis, cohort evidence supports plasma exchange (thought to be more effective than IVIg) and rituximab (which can induce remission or allow corticosteroid doses to be reduced) [Note 7].

Note 2: Consider precautions and monitoring requirements when prescribing immunomodulatory drugs—consult local protocols or seek expert advice.

Note 3: Consider precautions (eg measuring thiopurine methyltransferase [TPMT] before starting therapy) and monitoring requirements when prescribing azathioprine—consult local protocols or seek expert advice. Azathioprine therapy does not reach maximum effect for at least 6 months.

Note 4: Benveniste O, Hilton-Jones D. The role of rituximab in the treatment of myasthenia gravis. European Neurological Review 2010;5(2):95-100. [URL]

Note 5: Nowak RJ, Dicapua DB, Zebardast N, Goldstein JM. Response of patients with refractory myasthenia gravis to rituximab: a retrospective study. Ther Adv Neurol Disord 2011;4(5):259-66. [URL]

Note 6: De Feo LG, Schottlender J, Martelli NA, Molfino NA. Use of intravenous pulsed cyclophosphamide in severe, generalized myasthenia gravis. Muscle Nerve 2002;26(1):31-6. [URL]

Note 7: El-Salem K, Yassin A, Al-Hayk K, Yahya S, Al-Shorafat D, Dahbour SS. Treatment of MuSK-associated myasthenia gravis. Curr Treat Options Neurol 2014;16(4):283. [URL]

Drugs to avoid or use with caution in myasthenia gravis

Drugs to avoid or use with caution in myasthenia gravis

Certain drugs (see Table 7.10) must be avoided or used with caution in patients with myasthenia gravis, because they can make the symptoms worse. Monitor the patient whenever they start a new drug, especially

when the drug has adverse effects of weakness or fatigue. Closely monitor myasthenia gravis patients for hypothyroidism, hyperthyroidism and electrolyte imbalances (eg hypermagnesaemia, hypokalaemia), as these conditions can exacerbate myasthenic symptoms. Some drugs have been reported to cause myasthenia gravis (eg case reports implicating ipilimumab, as monotherapy or with nivolumab).
Table 7.10 Drugs to avoid or use with caution in myasthenia gravis

[NB1]

Printable table

Avoid	
D-penicillamine	
botulinum toxin type A	–
interferon alfa	
Use with caution	
neuromuscular blocking drugs:	Intravenous lidocaine and large doses of other local anaesthetics (even given subcutaneously) can potentiate the effect of neuromuscular blocking drugs. However, in general, local anaesthesia is safe in myasthenia gravis
nondepolarising	Avoid if possible, or use with extreme caution (cause highly variable potentiation of neuromuscular blockade) Avoid long-acting agents (eg pancuronium) Reduce doses, according to disease severity and concurrent use of anticholinesterase inhibitors Closely monitor neuromuscular function and consider a test dose
depolarising	Avoid if possible, due to variable response A loss of acetylcholine receptors in myasthenia gravis may confer a degree of resistance to depolarising drugs In contrast, cholinesterase inhibitors and vancomycin may potentiate the action of suxamethonium
halogenated inhalation anaesthetics	Myasthenic patients may be more sensitive to the relaxant effect of inhaled anaesthetics. Monitor neuromuscular function closely
antibiotics:	
aminoglycosides	Use an alternative drug when possible. Tobramycin is probably the least toxic
fluoroquinolones	Use an alternative drug when possible
macrolides	Use an alternative drug when possible
quinine	Use an alternative drug when possible
iodinated radiographic contrast media	Use noncontrast imaging when possible and discuss with radiologist

NB1: Case reports suggest several other drugs (eg beta blockers [including eye drops], verapamil, statins, lincosamide antibiotics) exacerbate myasthenia gravis symptoms. Rather than avoiding these drugs completely, consider their harms versus benefits before deciding whether to use them.

Key references: General topic references

Key references: General topic references

- Benatar M, Kaminski H. Medical and surgical treatment for ocular myasthenia. Cochrane Database Syst Rev 2012;(12):CD005081. https://www.ncbi.nlm.nih.gov/pubmed/23235620

- Benveniste O, Hilton-Jones D. The role of rituximab in the treatment of myasthenia gravis. European Neurological Review 2010;5(2):95–100. http://doi.org/10.17925/ENR.2010.05.02.95
- Cea G, Benatar M, Verdugo RJ, Salinas RA. Thymectomy for non-thymomatous myasthenia gravis. Cochrane Database Syst Rev 2013;(10):CD008111. https://www.ncbi.nlm.nih.gov/pubmed/24122674
- De Feo LG, Schottlender J, Martelli NA, Molfino NA. Use of intravenous pulsed cyclophosphamide in severe, generalized myasthenia gravis. Muscle Nerve 2002;26(1):31–6. https://www.ncbi.nlm.nih.gov/pubmed/12115946
- El-Salem K, Yassin A, Al-Hayk K, Yahya S, Al-Shorafat D, Dahbour SS. Treatment of MuSK-associated myasthenia gravis. Curr Treat Options Neurol 2014;16(4):283. https://www.ncbi.nlm.nih.gov/pubmed/24504626
- Gajdos P, Chevret S, Toyka KV. Intravenous immunoglobulin for myasthenia gravis. Cochrane Database Syst Rev 2012;(12):CD002277. https://www.ncbi.nlm.nih.gov/pubmed/23235588
- Gilhus NE. Myasthenia gravis. N Engl J Med 2016;375(26):2570–81. https://www.ncbi.nlm.nih.gov/pubmed/28029925
- Mehndiratta MM, Pandey S, Kuntzer T. Acetylcholinesterase inhibitor treatment for myasthenia gravis. Cochrane Database Syst Rev 2014;(10):CD006986. https://www.ncbi.nlm.nih.gov/pubmed/25310725
- Nowak RJ, Dicapua DB, Zebardast N, Goldstein JM. Response of patients with refractory myasthenia gravis to rituximab: a retrospective study. Ther Adv Neurol Disord 2011;4(5):259–66. https://www.ncbi.nlm.nih.gov/pubmed/22010039
- Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton-Jones D. Myasthenia gravis: Association of British Neurologists' management guidelines. Pract Neurol 2015;15(3):199–206. https://www.ncbi.nlm.nih.gov/pubmed/25977271
- UK Medicines Information (UKMi). How do you convert an oral pyridostigmine or neostigmine dose to a parenteral neostigmine dose? [Q&A 248.4]. [London: NHS Specialist Pharmacy Service; 2015.
- Wolfe GI, Kaminski HJ, Aban IB, Minisman G, Kuo HC, Marx A, et al. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med 2016;375(6):511–22. https://www.ncbi.nlm.nih.gov/pubmed/27509100

Key references: Drugs to avoid or to use with caution in myasthenia gravis

Key references: Drugs to avoid or to use with caution in myasthenia gravis

- Abel M, Eisenkraft JB. Anesthetic implications of myasthenia gravis. Mt Sinai J Med 2002;69(1-2):31–7. https://www.ncbi.nlm.nih.gov/pubmed/11832968
- Aspen Pharmacare Australia. Tracrium injection (atracurium besylate) [product information]. eMIMS; 2013.
- Barrons RW. Drug-induced neuromuscular blockade and myasthenia gravis. Pharmacotherapy 1997;17(6):1220–32. https://www.ncbi.nlm.nih.gov/pubmed/9399604
- Blichfeldt-Lauridsen L, Hansen BD. Anesthesia and myasthenia gravis. Acta Anaesthesiol Scand 2012;56(1):17–22. https://www.ncbi.nlm.nih.gov/pubmed/22091897
- Bonanni L, Vestra M, Presotto F. Can we say that modern radiologic contrast agents are safe in myasthenia gravis? Muscle Nerve 2015;51(5):782–3. https://www.ncbi.nlm.nih.gov/pubmed/25656739
- Dalakas MC. Treating myasthenia on consensus guide: Helpful and challenging but still unfinished business. Neurology 2016;87(4):350–1. https://www.ncbi.nlm.nih.gov/pubmed/27358340
- Howard JF, editor. Myasthenia gravis: a manual for the health care provider. St. Paul, MN: Myasthenia Gravis Foundation of America; 2009. http://myasthenia.org/HealthProfessionals/EducationalMaterials.aspx
- Johnson DB, Saranga-Perry V, Lavin PJ, Burnette WB, Clark SW, Uskavitch DR, et al. Myasthenia gravis induced by ipilimumab in patients with metastatic melanoma. J Clin Oncol 2015;33(33):e122–4. https://www.ncbi.nlm.nih.gov/pubmed/24778401
- Jones SC, Sorbello A, Boucher RM. Fluoroquinolone-associated myasthenia gravis exacerbation: evaluation of postmarketing reports from the US FDA adverse event reporting system and a literature review. Drug Saf 2011;34(10):839–47. https://www.ncbi.nlm.nih.gov/pubmed/21879778
- Liao B, Shroff S, Kamiya-Matsuoka C, Tummala S. Atypical neurological complications of ipilimumab therapy in patients with metastatic melanoma. Neuro Oncol 2014;16(4):589–93. https://www.ncbi.nlm.nih.gov/pubmed/24482447
- Loochtan AI, Nickolich MS, Hobson-Webb LD. Myasthenia gravis associated with ipilimumab and nivolumab in the treatment of small cell lung cancer. Muscle Nerve 2015;52(2):307–8.

https://www.ncbi.nlm.nih.gov/pubmed/25759003
- Mehrizi M, Fontem RF, Gearhart TR, Pascuzzi RM. Medications and myasthenia gravis (A reference for health care professionals). St. Paul, MN: Myasthenia Gravis Foundation of America; 2012. http://myasthenia.org/HealthProfessionals/EducationalMaterials.aspx
- Mehrizi M, Pascuzzi RM. Complications of radiologic contrast in patients with myasthenia gravis. Muscle Nerve 2014;50(3):443–4. https://www.ncbi.nlm.nih.gov/pubmed/24677227
- Merck Sharp & Dohme (Australia). Norcuron (vecuronium bromide) [product information]. eMIMS; 2014.
- Naidoo J, Page DB, Li BT, Connell LC, Schindler K, Lacouture ME, et al. Toxicities of the anti-PD-1 and anti-PD-L1 immune checkpoint antibodies. Ann Oncol 2015;26(12):2375–91. https://www.ncbi.nlm.nih.gov/pubmed/26371282
- Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, et al. International consensus guidance for management of myasthenia gravis: Executive summary. Neurology 2016;87(4):419–25. https://www.ncbi.nlm.nih.gov/pubmed/27358333
- Somashekar DK, Davenport MS, Cohan RH, Dillman JR, Ellis JH. Effect of intravenous low-osmolality iodinated contrast media on patients with myasthenia gravis. Radiology 2013;267(3):727–34. https://www.ncbi.nlm.nih.gov/pubmed/23360741

Published November 2017

[X] Close

Epilepsy classification

Epilepsy classification

Epilepsy is a disorder characterised by a tendency to experience recurrent seizures. The International League Against Epilepsy's [Note 1] definition is 'a disease of the brain defined by:

- at least two unprovoked (or reflex) seizures occurring more than 24 hours apart
- one unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after two unprovoked seizures, occurring over the next 10 years
- diagnosis of an epilepsy syndrome.'

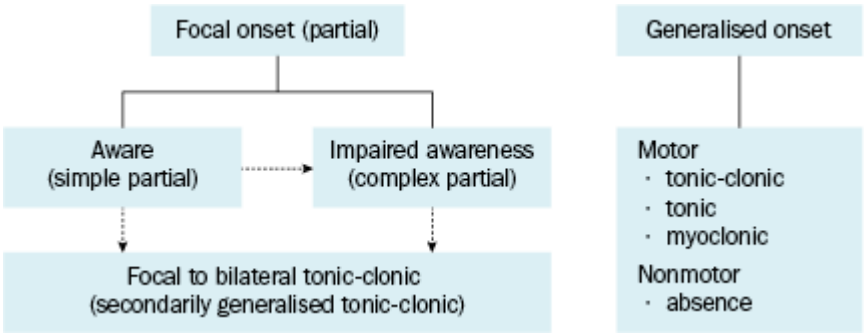
Epilepsy can be the primary problem or a symptom of another brain disorder (eg brain tumour, injury, stroke). About half the patients who have a seizure for the first time do not have another, and do not have epilepsy.

Epilepsy consists of many syndromes or diseases [Note 2], defined by seizure type and associated features (eg age of onset, timing of seizures, seizure precipitation, clinical course, response to treatment). Epileptic seizures are best considered a symptom of an epileptic disorder. Focal (partial) seizures start in one cerebral hemisphere. Generalised seizures start in, and rapidly engage, networks that are bilaterally distributed. Generalised seizures usually appear to start in both hemispheres simultaneously.

A revised classification of seizure types was published in 2017 by the International League Against Epilepsy. See Figure 7.2 for seizure types and Figure 7.3 for syndrome classification.

Figure 7.2 Classification of seizure types

[NB1] [NB2]



NB1: Adapted with permission from Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia 2017; 58(4):531-542. Wiley Periodicals, Inc. © 2017 International League Against Epilepsy [URL]

NB2: Dotted lines with arrows show that a seizure can start as one type, then evolve to another type as it propagates through the brain. Terms in parentheses are older terms.

Figure 7.3 Epileptic syndrome classification

[NB1]

Generalised epilepsies

- idiopathic (genetic) [NB2] generalised

    - childhood absence epilepsy
    - juvenile absence epilepsy
    - juvenile myoclonic epilepsy
    - epilepsy with tonic-clonic seizures on awakening
- symptomatic (structural, metabolic, immune, infectious [NB2]) generalised
    - Lennox-Gastaut syndrome

Focal (partial [NB2]) epilepsies

- self-limited (eg benign childhood epilepsy with centrotemporal spikes)
- symptomatic (eg mesial temporal lobe epilepsy)

Epilepsies that can be focal (partial [NB2]) or generalised

- neonatal seizures
- West syndrome (infantile spasms)

Special syndromes

- febrile seizures
- isolated seizure or status epilepticus
- metabolic and toxin-induced seizures

NB1: Based on the International League Against Epilepsy 1989 classification of epileptic syndromes

NB2: Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(4):512-21 [URL]

Note 1: Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55(4):475-82. [URL]

Note 2: Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(4):512-21. [URL]

Epilepsy diagnosis

Epilepsy diagnosis

When a diagnosis of epilepsy is suspected, usual practice is to refer the patient to an expert to confirm the diagnosis and consider long-term therapy.

Epilepsy is a clinical diagnosis that relies primarily on a description of the seizures. An eyewitness account or video can exclude other causes of loss of consciousness (eg syncope). Electroencephalography (EEG) can support the diagnosis, but a normal EEG does not exclude a diagnosis of epilepsy, nor does an abnormal EEG necessarily confirm the diagnosis. Brain imaging, especially magnetic resonance imaging (MRI), is often useful in revealing the cause, but cannot confirm the diagnosis, which remains clinical.

Diagnose the seizure type (see Figure 7.2) because this influences the choice of drug. When possible, diagnose the epilepsy syndrome (see Figure 7.3) because this can also influence the choice of drug, and can inform prognosis and guide investigation. See also acute symptomatic seizures.

Deciding when to treat epilepsy

Deciding when to treat epilepsy

Seizures are more likely to recur in patients with focal (partial) seizures, epileptiform abnormalities on EEG, abnormal neurological examination or a lesion on neuroimaging. In these situations, consider starting treatment after the first seizure.

When deciding whether to treat with drugs, the severity of the seizure and the patient's circumstances (eg employment, hobbies, driving) and preferences are considered.

Prophylactic use of antiepileptic drugs in situations associated with a high risk of epilepsy (eg traumatic brain injury, brain tumours or brain surgery) is not recommended.

See specific advice on treating:

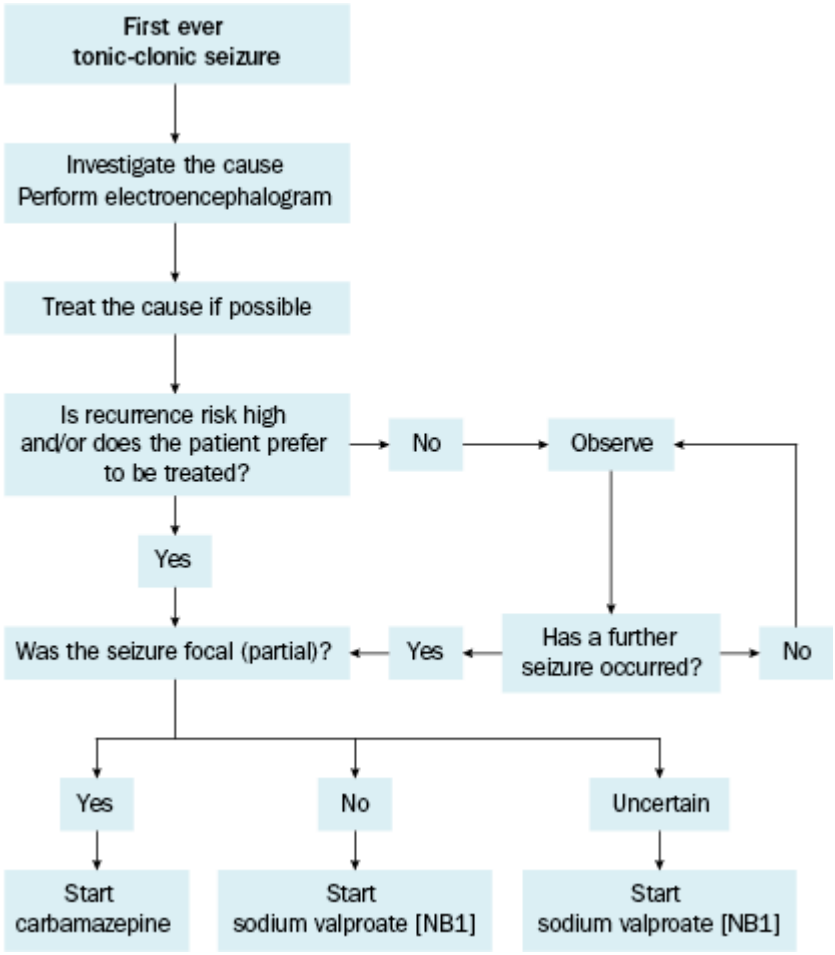
- childhood and juvenile absence epilepsies
- juvenile myoclonic epilepsy
- Lennox-Gastaut syndrome and other symptomatic generalised epilepsies
- focal (partial) epilepsies
- tonic-clonic seizures where generalised or focal (partial) onset is unclear
- West syndrome (infantile spasms)
- neonatal seizures
- febrile seizures
- benign childhood epilepsy with centrotemporal spikes.

Choosing an antiepileptic drug

Choosing an antiepileptic drug

The aim of drug therapy for epilepsy is to completely suppress seizures without adverse effects. This is not always possible and a compromise may be needed. A general approach to the initial management of tonic-clonic seizures is summarised in Figure 7.4.

Figure 7.4 Initial management of tonic-clonic seizures



NB1: If possible, avoid sodium valproate in females of childbearing potential. If sodium valproate is the drug of choice, ensure reliable contraception (see advice).

Many factors are considered when choosing the most appropriate drug for the patient. Based on efficacy, the first-line drug for focal (partial) epilepsy is carbamazepine, and for generalised epilepsy is sodium valproate. Factors that influence the choice of drug are listed in Figure 7.5.

It is essential to discuss plans for pregnancy with female patients of childbearing age. If possible, avoid sodium valproate in these patients. If sodium valproate is the drug of choice, ensure reliable contraception. Before starting valproate therapy, discuss the harms (see pregnancy in patients with epilepsy) and benefits.

Figure 7.5 Factors affecting choice of antiepileptic drug

Factors to consider when choosing an antiepileptic drug include:

- efficacy in treating the syndrome
- certainty of syndrome diagnosis—if uncertain, consider drugs that are effective in focal (partial) and generalised epilepsies (eg sodium valproate, levetiracetam, lamotrigine, topiramate)
- pregnancy—if possible, avoid starting sodium valproate in females of childbearing potential (see pregnancy in patients with epilepsy)
- adverse effects
    - body weight changes (eg sodium valproate and pregabalin can cause weight gain; topiramate can cause weight loss)
    - impaired cognition (eg phenobarbital [phenobarbitone] and topiramate are more likely to cause sedation or cognitive impairment, which may be overlooked if the patient already has cognitive impairment; benzodiazepines and phenytoin are more likely to cause sedation in children)
    - cosmetic changes (eg phenytoin can cause hirsutism, gingival hyperplasia and coarser facial features; sodium valproate can cause hair loss)

    - hypersensitivity (eg patients of Asian origin [other than Japanese] are at higher risk of serious skin reactions caused by carbamazepine and phenytoin)
- age (eg sodium valproate hepatotoxicity is more likely in infants)
- cost
- ease of use
- need for measuring serum drug concentration
- pharmacokinetics
- drug interactions (eg with contraceptives or warfarin)
- time to achieve therapeutic dose (eg phenytoin can be started at therapeutic doses; lamotrigine, perampanel and topiramate need to be started slowly)
- preparations available (eg intravenous, paediatric, liquid, scored)

There is anecdotal evidence that cannabis-derived products may be beneficial in several epilepsy syndromes. A single randomised controlled trial [Note 3] showed modest efficacy in Dravet syndrome. It is premature to recommend the use of medicinal cannabis in other epilepsy syndromes before the results of properly conducted clinical trials are known.

There is little evidence that switching between originator and generic brands or between generic brands of antiepileptic drugs is harmful.

Note 3: Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017;376(21):2011-20. [URL]

Titrating and withdrawing antiepileptic drugs

Titrating and withdrawing antiepileptic drugs

Starting antiepileptic drug therapy

Starting antiepileptic drug therapy

Most antiepileptic drugs are started at a low dose, which is slowly increased to the initial target. This is especially important for lamotrigine, to reduce the risk of serious adverse skin reactions. An exception is phenytoin, which can be started at the initial target dose or even with a loading dose.

Antiepileptic therapy should start with a single drug. The initial target is the dose likely to be effective, based on the drug's effective dose range (or, for phenytoin, serum concentration). If seizures continue, the dose is increased until seizures stop or the maximum dose is reached. The maximum dose depends on the patient and the drug, and is decided in one of three ways—it is the dose that:

- is slightly less than the dose that has produced dose-related toxicity
- if exceeded, is likely to produce dose-related toxicity or is unlikely to achieve further efficacy
- results in a serum concentration near the upper limit of the target range (for phenytoin).

Adding a second antiepileptic drug

Adding a second antiepileptic drug

If seizures are not controlled by the first antiepileptic drug, a second drug is added. The dose of the second drug is adjusted as for the first. If combined therapy is effective, the first drug may be gradually withdrawn (see advice) to find out if monotherapy with the second drug is effective. However, many patients prefer to continue combination therapy rather than risk the seizures returning. If combination therapy is not effective, one of the drugs is withdrawn gradually and replaced by a third drug (see also uncontrolled epilepsy).

Withdrawing an antiepileptic drug

Withdrawing an antiepileptic drug

Withdrawal of an antiepileptic drug should be gradual. Six weeks is usually sufficient, but up to 6 months may be preferred for a barbiturate or clonazepam. When withdrawing all antiepileptic drug therapy, see advice.

Driving is not permitted when the dose of an antiepileptic drug is being reduced, unless it is being reduced due to dose-related adverse effects and the dose reduction is unlikely to result in a seizure. Driving must not resume until 3 months after completing the dose reduction or withdrawal [Note 4].

Note 4: National standards of fitness to drive are available from the Austroads website. See Section 6.2 Seizures and epilepsy.

Stopping antiepileptic drug therapy

Stopping antiepileptic drug therapy

When a patient with epilepsy has not had a seizure for a long time, the only way to find out if drug therapy is still needed is to withdraw it. The decision to stop therapy must consider the patient's views. As the patient must stop driving during dose reduction and for 3 months after the last dose, many patients choose to continue therapy indefinitely.

Do not try to withdraw antiepileptic drugs until at least 2 years after the last seizure. When therapy is withdrawn after at least 2 seizure-free years, the risk of seizures recurring is about 50%. Factors that predict a high risk include:

- symptomatic (structural, metabolic, immune, infectious) epilepsy
- neurological abnormalities on examination
- a history of seizures that are difficult to control
- epileptiform abnormalities on EEG
- abnormalities on magnetic resonance imaging or computed tomography
- recurrence after past attempts to withdraw all antiepileptic therapy.

Usually the dose of antiepileptic drug is reduced over several months, but barbiturates and benzodiazepines (especially clonazepam) are reduced more slowly. If seizures recur, the patient should start therapy again on the previous effective dose—they can resume driving 1 month after this (see the national standards of fitness to drive [Note 5]).

Juvenile myoclonic epilepsy has such a high recurrence rate that it is best not to withdraw therapy, at least not until many years without seizures of any type (including jerks).

Note 5: National standards of fitness to drive are available from the Austroads website. See Section 6.2 Seizures and epilepsy.

Avoiding adverse effects of antiepileptic drugs

Avoiding adverse effects of antiepileptic drugs

For a full list of adverse effects caused by antiepileptic drugs, refer to a drug formulary.

Serious adverse reactions to antiepileptic drugs (eg hepatic failure with sodium valproate, agranulocytosis with carbamazepine) usually occur suddenly. Blood tests before starting treatment may be useful for comparison later, but there is no evidence that routine haematological and biochemical monitoring reduces the risk of adverse reactions.

Serious skin reactions to antiepileptic drugs include Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) and drug reaction with eosinophilia and systemic symptoms (DRESS). Pharmacogenetic

studies are identifying an increasing number of genes that confer a predisposition to cutaneous drug reactions. Testing for the HLA-B*1502 allele in patients of Asian origin (other than Japanese) is advised before starting therapy with carbamazepine. Some evidence suggests an increased risk of SJS/TEN in patients with the HLA-B*1502 allele when taking phenytoin or lamotrigine, but the risk appears to be lower than when taking carbamazepine [Note 6]. When selecting subsequent antiepileptic drug therapy, be aware of the potential for cross-reactivity for skin adverse effects (eg carbamazepine and phenytoin).

Monitor serum 25(OH)D (vitamin D) concentration in patients on long-term antiepileptic drug therapy, especially those taking enzyme-inducing drugs or with risk factors for osteoporosis. See advice on vitamin D deficiency and osteoporosis.

See also teratogenic and neurodevelopmental effects of antiepileptic drugs.

Note 6: Amstutz U, Shear NH, Rieder MJ, Hwang S, Fung V, Nakamura H, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia 2014;55(4):496-506. [URL]

When to measure serum concentrations of antiepileptic drugs

When to measure serum concentrations of antiepileptic drugs

For many antiepileptic drugs, the correlation between serum concentration and efficacy or toxicity is poor. Consequently, efficacy of drug treatment is judged by clinical response rather than by target drug serum concentration.

Drug efficacy for epilepsy is measured by clinical response to the antiepileptic drug rather than its serum concentration.

The serum concentration of an antiepileptic drug may be used to:

- document concordance with therapy
- help diagnose that symptoms or signs are due to toxicity
- guide the dosage of phenytoin
- adjust the dosage of lamotrigine in pregnancy (see advice).

When the dose is changed, wait at least 5 half-lives of the drug before rechecking the serum concentration, to ensure it has reached the new steady state.

Phenytoin monitoring and dose adjustment are complicated by the drug's nonlinear pharmacokinetics. A small change in the dose can cause a large change in the steady-state serum concentration. If the serum concentration is 30 micromol/L or less (7 mg/L or less), the daily dose of phenytoin in adults can be increased by 100 mg. If the serum concentration is higher than 30 micromol/L, the daily dose should not be increased by more than 50 mg. In patients with hypoalbuminaemia (eg in kidney disease, malnutrition, advanced chronic liver disease), a greater proportion of the phenytoin is free (because of lower protein binding) for the same total concentration.

Advice for patients with epilepsy

Advice for patients with epilepsy

Ask the patient to keep a seizure diary. As some people are unaware of their seizures, their carers may need to do this.

Warn patients that abruptly stopping antiepileptic drugs can provoke status epilepticus.

Warn patients that abruptly stopping antiepileptic drugs can provoke status epilepticus.

Advise patients that seizures can be provoked by sleep deprivation, excessive alcohol intake, illegal stimulants and psychological stress. Some drugs provoke seizures. Advise patients with epilepsy to check with a healthcare professional before taking nonprescribed medicines (eg over-the-counter, alternative or complementary medicines). Healthcare professionals must consult an appropriate text on drug interactions when prescribing for patients taking antiepileptic drugs.

Counsel patients to avoid situations in which a seizure may be especially dangerous (eg unsupervised swimming or bathing, climbing, operating machinery).

Advise drivers with epilepsy that they:

- have a legal obligation to report the condition to the driver licensing authority in their state or territory
- should not drive until deemed fit by the licensing authority.

In South Australia and the Northern Territory, it is mandatory for doctors to report drivers with epilepsy to the licensing authority. National standards of fitness to drive are available [Note 7].

Patients with an established pattern of prolonged or repetitive seizures need a management plan for their carers.

See advice on contraception and pregnancy for females with epilepsy.

Sudden unexpected death in epilepsy (SUDEP) typically affects 1 in 4500 children with epilepsy in 1 year, and 1 in 1000 adults with epilepsy in 1 year [Note 8]. Freedom from seizures, especially from generalised tonic-clonic seizures, is strongly associated with lower risk of SUDEP.

Note 7: National standards of fitness to drive are available from the Austroads website. See Section 6.2 Seizures and epilepsy.

Note 8: Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, et al. Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2017;88(17):1674-80. [URL]

Contraception in patients with epilepsy

Contraception in patients with epilepsy

Many drugs used to treat epilepsy reduce the efficacy of hormonal contraception by inducing hepatic enzymes. The enzyme-inducing antiepileptic drugs are carbamazepine, oxcarbazepine, perampanel (at doses of more than 8 mg daily), phenobarbital (phenobarbitone), phenytoin, primidone, rufinamide and topiramate (at any dose). For advice on improving the reliability of contraception for female patients taking these drugs, see Drugs that affect hormonal contraceptives.

Lamotrigine may reduce the efficacy of combined oral contraceptives (COCs) and the contraceptive vaginal ring; see Drugs that affect hormonal contraceptives. In addition, the metabolism of lamotrigine may be increased by COCs; see Drugs affected by hormonal contraceptives.

Antiepileptic drugs that do not affect hormonal contraception include brivaracetam, gabapentin, lacosamide, levetiracetam, sodium valproate, tiagabine and zonisamide.

Pregnancy in patients with epilepsy

Pregnancy in patients with epilepsy

Planning for pregnancy

Planning for pregnancy

Refer females with epilepsy who are planning conception to an expert.

Babies born to mothers taking antiepileptic drugs have a 4 to 6% risk of major congenital malformations, which is about twice the risk for babies born to mothers without epilepsy.

All antiepileptic drugs may be teratogenic and none is the 'drug of choice' in pregnancy (see teratogenic effects of antiepileptic drugs). The priority is to avoid seizures, which can seriously affect the patient and unborn child. The risks of antiepileptic drug therapy to the fetus, and the risks of suboptimally treated epilepsy to the mother and fetus, should be considered and discussed with the patient. When planning a pregnancy, make changes to the treatment regimen (eg attempting to withdraw antiepileptic drugs) well before conception. Most teratogenic effects occur before the pregnancy is confirmed, but neurodevelopmental effects probably depend on fetal drug exposure throughout the pregnancy.

Principles for treating epilepsy in females planning a pregnancy follow.

- Only continue treatment if needed to prevent seizures.
- Use monotherapy if possible.
- Minimise the dose of antiepileptic drug. In practice, the minimal effective dose can only be established by lowering the dose sufficiently to cause a seizure. If a dose is particularly high, it may be possible at least to reduce it. If the dose is reduced, driving is not permitted during the reduction and for 3 months after [Note 9].
- Avoid sodium valproate unless other drugs are unlikely to prevent seizures (eg in patients with juvenile myoclonic epilepsy). If sodium valproate is essential, use 600 mg or less daily if possible.

Offer prenatal screening (alpha-fetoprotein measurement and ultrasound examination) to females taking antiepileptic drugs. Although unproven, folic acid may reduce the risk of neural tube defects in infants of females taking antiepileptic drugs. Use:

folic acid 5 mg orally, once daily for at least 3 months before and after conception. *neural tube defects (epilepsy and conception)*

Vitamin K supplementation has been recommended to reduce the risk of haemorrhage in neonates whose mothers take enzyme-inducing antiepileptic drugs. However, there is no evidence to support its routine use.

Note 9: National standards of fitness to drive are available from the Austroads website. See Section 6.2 Seizures and epilepsy.

Antiepileptic drug dose adjustment and monitoring during pregnancy

Antiepileptic drug dose adjustment and monitoring during pregnancy

Serum concentrations of some antiepileptic drugs fall during pregnancy. The dose of lamotrigine may need to be increased. Before conception, or as early as possible in pregnancy, measure the serum concentration of lamotrigine to establish a baseline. Measure the serum lamotrigine concentration at least every 2 months during pregnancy and adjust the dose so the serum concentration stays near the baseline value. After childbirth, maternal lamotrigine kinetics return to normal in 2 to 3 weeks.

Phenytoin and carbamazepine serum concentrations can also fall during pregnancy, and baseline and serial measurements may be used to adjust the dosage. Although levetiracetam serum concentration may fall significantly, measurement is not widely available.

Teratogenic and neurodevelopmental effects of antiepileptic drugs

Teratogenic and neurodevelopmental effects of antiepileptic drugs

Sodium valproate increases the risk of spina bifida up to ten-fold (0.2 to 2%) and is associated with other serious malformations. Evidence also shows that children of mothers taking sodium valproate during pregnancy have lower intelligence and greater risk of learning difficulties than those exposed to other antiepileptic drugs. These effects are dose-related—at daily doses less than 600 to 800 mg, sodium valproate's teratogenicity and effect on cognition are similar to other antiepileptic drugs. However, a controlled cohort study [Note 10] showed that even at doses less than 800 mg daily, maternal valproate therapy was associated with an increased need for educational intervention. During pregnancy, avoid doses of sodium valproate more than 600 mg daily if possible.

Valproate is often the only drug that controls genetic (idiopathic) generalised epilepsies, including juvenile myoclonic epilepsy. Because low doses are usually sufficient, valproate therapy can continue in a female with genetic (idiopathic) generalised epilepsy planning a pregnancy, without increasing the risk of teratogenicity and neurodevelopmental adverse effects to an unacceptable level. The harms and benefits of valproate and its alternatives must be discussed with the patient. Juvenile myoclonic epilepsy is a long-lasting condition—withdrawal of sodium valproate in anticipation of pregnancy can be hazardous, because seizures are likely to recur.

Phenytoin increases the risk of congenital abnormalities.

Lamotrigine and carbamazepine are associated with a slight and dose-related increased risk of congenital abnormalities.

Topiramate may increase the risk of congenital malformations.

Many newer antiepileptic drugs have not been taken as monotherapy in enough pregnancies to establish teratogenic risk. The limited data available for levetiracetam suggest it has a low risk of teratogenicity.

Note 10: Baker GA, Bromley RL, Briggs M, Cheyne CP, Cohen MJ, Garcia-Finana M, et al. IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. Neurology 2015;84(4):382-90. [URL]

Uncontrolled epilepsy

Uncontrolled epilepsy

Approximately one-third of patients with epilepsy do not achieve complete seizure control. Reasons include:

- poor concordance with antiepileptic drug therapy or lifestyle advice
- wrong diagnosis of epilepsy (eg psychogenic nonepileptic events, convulsive syncope)
- wrong diagnosis of epilepsy syndrome (focal seizures mistaken for generalised seizures, or vice versa)
- suboptimal choice or use of antiepileptic drug
- drug-resistant epilepsy.

If the patient does not respond to first-line therapy, refer to an expert. Treatment may include a trial of two or three more antiepileptic drugs, individually or in combination. If these drugs fail to control seizures completely, the patient should be referred to a specialist epilepsy centre for further evaluation.

Of patients who have video-electroencephalogram monitoring in a specialist epilepsy centre:

- up to 30% are diagnosed with psychogenic nonepileptic seizures (pseudoseizures)
- more than 50% have the diagnosis of epilepsy or the type of epilepsy syndrome changed.

Patients referred to an epilepsy centre who have drug-resistant epilepsy may be considered for surgery. If surgery is not suitable, a vagus nerve stimulator may be implanted.

For a child with refractory epilepsy, a ketogenic diet should be considered, under the guidance of a specialist dietitian.

Habitually prolonged or repetitive seizures

Habitually prolonged or repetitive seizures

A management plan is advised for patients with an established pattern of:

- recurrent prolonged convulsive seizures (lasting 5 minutes or more)
- serial seizures (three or more seizures in an hour).

In some cases, the plan may include advice for carers or relatives to give a benzodiazepine, to end the seizure or cluster of seizures. Drug choices include:

1 clobazam 20 to 30 mg (child 0.25 mg/kg) orally *epilepsy, habitually prolonged or repetitive seizures*

OR (if the patient cannot safely swallow)

1 midazolam 5 to 10 mg (child: 0.2 to 0.3 mg/kg up to 10 mg) buccally or intranasally [Note 11]. *epilepsy, habitually prolonged or repetitive seizures*

The management plan should clearly state when urgent assessment at the nearest emergency department is needed.

Note 11: Midazolam solution for injection (hydrochloride salt) can be given buccally or intranasally and may be provided under expert advice to parents and carers who have been trained in its use. Fact sheets that explain the method are available (eg from the Royal Children's Hospital Melbourne).

Childhood and juvenile absence epilepsies

Childhood and juvenile absence epilepsies

Childhood and juvenile absence epilepsies are genetic (idiopathic) generalised epilepsies.

The usual age of onset for childhood absence epilepsy (formerly known as petit mal epilepsy) is 4 to 9 years, and for juvenile absence epilepsy is 10 to 15 years. Ethosuximide and sodium valproate are equally effective, but ethosuximide is better tolerated and therefore is the drug of first choice. Unlike sodium valproate, ethosuximide does not protect against associated generalised tonic-clonic seizures—these occur later in about 25% of patients, especially those with juvenile absence epilepsy. Lamotrigine is not as effective as ethosuximide and sodium valproate. Absence epilepsy can be aggravated by carbamazepine, oxcarbazepine and phenytoin.

If possible, avoid sodium valproate in girls of childbearing potential. If the drug is needed, have an informed discussion with the patient and parents about its harms (see pregnancy in patients with epilepsy) and benefits before starting therapy. Ensure that the girl has reliable contraception.

Use:

1 ethosuximide 5 mg/kg (up to 250 mg) orally, twice daily for 4 to 7 days, then increase to 10 mg/kg twice daily; usual maintenance dose 10 to 20 mg/kg (up to 750 mg) twice daily *epilepsy, childhood and juvenile absence*

OR

2 sodium valproate , child older than 2 years, 5 mg/kg orally, twice daily for 5 days, then increase to 10 mg/kg twice daily; usual maintenance dose 10 to 20 mg/kg (up to 1250 mg) twice daily. *epilepsy, childhood*

and juvenile absence

Continue treatment until the electroencephalogram (EEG) stops showing 3 per second spike-wave activity and seizures have not occurred for 2 years. If an epileptiform abnormality persists in the EEG, this does not necessarily contraindicate stopping treatment. See advice on stopping treatment.

Juvenile myoclonic epilepsy

Juvenile myoclonic epilepsy

Despite its name, juvenile myoclonic epilepsy is probably the most common form of genetic (idiopathic) generalised epilepsy in adults. Onset is usually in late adolescence. Typically, the patient presents with a single tonic-clonic seizure and often has a history of myoclonic jerks (especially when waking in the morning, and after sleep deprivation). Childhood or juvenile absence epilepsy may precede juvenile myoclonic epilepsy. Occasionally, patients present with myoclonus without tonic-clonic seizures.

Myoclonic and generalised tonic-clonic seizures usually respond to sodium valproate. To prevent seizures, the patient may need to avoid sleep deprivation and excessive alcohol intake. Other antiepileptic drugs are not as effective as sodium valproate, and some (eg carbamazepine, oxcarbazepine, phenytoin) can aggravate juvenile myoclonic epilepsy. Long-term treatment is usually needed, even when seizures are fully controlled, because the epileptic disorder lasts for many years.

If possible, avoid sodium valproate in young females of childbearing potential who do not have reliable contraception. Levetiracetam and lamotrigine are alternative drugs. If sodium valproate is needed, have an informed discussion with the patient (and parents of younger patients) about its harms (see pregnancy in patients with epilepsy) and benefits before starting therapy.

For sodium valproate monotherapy in females of childbearing potential who do not have reliable contraception, use:

sodium valproate 400 mg orally, once daily for 1 week, then increase to a maximum of 600 mg daily, given as 200 mg in the morning and 400 mg at night. *epilepsy, juvenile myoclonic*

For adult females who have reliable contraception or cannot have children, or for adult males, use:

sodium valproate 500 mg orally, once daily for 1 week, then increase to initial target dose of 500 mg twice daily. If needed, increase to a maximum of 1500 mg twice daily.

If the maximum dose of sodium valproate is not effective or adverse effects are intolerable, refer for expert advice—other antiepileptic drugs (eg levetiracetam, lamotrigine) may need to be added or substituted.

Lennox-Gastaut syndrome and other symptomatic generalised epilepsies

Lennox-Gastaut syndrome and other symptomatic generalised epilepsies

Symptomatic (structural, metabolic, immune, infectious) generalised epilepsies occur in patients with generalised or multifocal brain disorders that also usually cause intellectual disability. Typically, these epilepsies start in childhood and persist in adult life. The seizures are often difficult to control.

Lennox-Gastaut syndrome is a symptomatic generalised epilepsy that is characterised by:

- significant intellectual disability
- slow spike-wave pattern on electroencephalogram
- multiple seizure types (including tonic [especially nocturnal], myoclonic, atypical absence and tonic-clonic seizures).

First-line therapy for symptomatic generalised epilepsy is sodium valproate monotherapy.

For a child, use:

sodium valproate , child older than 2 years, 5 mg/kg orally, twice daily for 5 days, then increase to 10 mg/kg twice daily; usual maintenance dose is 10 to 20 mg/kg twice daily; maximum 2500 mg daily. *epilepsy, Lennox-Gastaut syndrome*

For females of childbearing potential who do not have reliable contraception, consider the relative harms and benefits of sodium valproate therapy, and the probability of pregnancy. If appropriate, use:

sodium valproate 400 mg orally, once daily for 1 week, then increase to initial target dose of 600 mg daily, taken as 200 mg in the morning and 400 mg at night. If needed, increase up to 1500 mg twice daily, but see teratogenic and neurodevelopmental effects. *epilepsy, symptomatic generalised*

For adult females who have reliable contraception or cannot have children, or for adult males, use:

sodium valproate 500 mg orally, once daily for 1 week, then increase to initial target dose of 500 mg twice daily. If needed, increase up to 1500 mg twice daily.

If the maximum dose of sodium valproate is not effective or adverse effects are intolerable, refer for expert advice—other antiepileptic drugs may need to be added or substituted. Second-line therapy is combination therapy with lamotrigine and sodium valproate. Sodium valproate inhibits lamotrigine clearance—reduce the rate of introduction and target dose of lamotrigine to lower the risk of serious skin reactions and dose-related toxicity. Other useful drugs include clobazam and topiramate.

Focal (partial) epilepsies

Focal (partial) epilepsies

In focal (partial) epilepsies, the patient may be aware (simple partial seizures) during the seizures, or have impaired awareness (complex partial seizures). Focal (partial) seizures can evolve to bilateral (secondarily generalised) tonic-clonic seizures. The most common form of structural focal (partial) epilepsy is mesial temporal lobe epilepsy due to hippocampal sclerosis—other causes include tumours and head injuries, and in children, congenital brain anomalies and perinatal brain injury.

Carbamazepine is generally considered the drug of choice for focal (partial) epilepsies.

For children, use:

carbamazepine (preferably modified-release) 2.5 mg/kg orally, twice daily for 5 days, then increase to initial target dose of 5 mg/kg twice daily. If needed, increase up to 10 mg/kg twice daily [Note 12]. *epilepsy, focal (partial)*

For adults, use:

carbamazepine modified-release 100 mg orally, at night for 1 to 2 weeks, then every week increase the daily dose by 100 to 200 mg to initial target dose of 200 mg twice daily. If needed, increase up to 600 mg twice daily [Note 12].

The earliest sign of dose-related toxicity is usually diplopia, starting 30 to 60 minutes after the morning dose. Serum carbamazepine concentration is of limited use for determining the dose.

If carbamazepine does not fully control focal (partial) seizures or is not tolerated, refer for expert advice. A range of drugs can be used second-line (see Figure 7.6) and none is preferred—choice is based on the factors listed in Figure 7.5.

Figure 7.6 Second-line drugs used for focal (partial) epilepsy

Adults: clobazam, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenytoin, pregabalin, sodium valproate [NB1], tiagabine, topiramate, zonisamide

Children: clobazam, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital (phenobarbitone), phenytoin, sodium valproate [NB1], tiagabine, topiramate, zonisamide

NB1: Avoid sodium valproate in females of childbearing potential (see teratogenic and neurodevelopmental effects of antiepileptic drugs).

If the patient's seizures are not controlled after trying two or three second-line drugs, the patient should be referred to a specialist epilepsy centre.

Patients with focal (partial) epilepsy who do not respond to antiepileptic drugs may be suitable for surgery—the most common procedure is anterior temporal lobectomy for temporal lobe epilepsy associated with hippocampal sclerosis or another temporal lobe lesion. Sometimes surgery is effective even when no structural lesion is found. After surgery, up to 80% of patients achieve long-term seizure control.

Note 12: Pharmacogenetic studies are identifying an increasing number of genes that confer a predisposition to cutaneous drug reactions. Testing for the HLA-B*1502 allele in patients of Asian origin (other than Japanese) is advised before starting therapy with carbamazepine.

Tonic-clonic seizures where generalised or focal (partial) onset is unclear

Tonic-clonic seizures where generalised or focal (partial) onset is unclear

In some patients with tonic-clonic seizures, it is not clear from clinical, electroencephalogram or neuroimaging data whether the seizures are generalised or focal (partial) in onset. Use a ‘broad-spectrum’ antiepileptic drug effective against both types of seizure (eg sodium valproate, levetiracetam, lamotrigine, topiramate, clobazam). Carbamazepine and phenytoin are less likely to be effective, and may even aggravate the epilepsy, if the seizures are of generalised onset.

For children, as first-line therapy, use:

sodium valproate , child older than 2 years, 5 mg/kg orally, twice daily for 5 days, then increase to 10 mg/kg twice daily; usual maintenance dose 10 to 20 mg/kg twice daily; maximum 2500 mg daily. *epilepsy, tonic-clonic seizures of unclear onset* _

For females of childbearing potential who do not have reliable contraception, as first-line therapy, use:

levetiracetam 250 mg orally, twice daily for 1 week, then increase to initial target dose of 500 mg twice daily. If needed, increase by 500 mg daily up to 1500 mg twice daily. *epilepsy, tonic-clonic seizures of unclear onset* _

For adult females who have reliable contraception or cannot have children, or adult males, as first-line therapy, use:

sodium valproate 500 mg orally, once daily for 1 week, then increase to initial target dose of 500 mg twice daily. If needed, increase up to 1500 mg twice daily.

If seizures persist, or if sodium valproate is not tolerated or indicated, refer the patient to an expert. Drugs that may be added or substituted include levetiracetam, lamotrigine, topiramate and clobazam.

If the patient's seizures are not controlled after trying two or three drug options, the patient should be referred to a specialist epilepsy centre.

West syndrome (infantile spasms)

West syndrome (infantile spasms)

The usual age of onset of West syndrome (infantile spasms) is 4 to 12 months. The spasms are sudden brief contractions of the head, neck and trunk, usually in flexion but sometimes in extension. Characteristically, the spasms occur in runs lasting several minutes. Hypsarrhythmia is typical on electroencephalogram but is not essential to diagnosis. When spasms occur, use:

1 prednis(ol)one 10 mg orally, 4 times daily for 2 weeks (or increase to 20 mg orally 3 times daily after the first week if spasms continue), then taper dose over 2 to 3 weeks and stop *West syndrome (infantile spasms)*

OR

1 tetracosactide (tetracosactrin) (depot) 0.5 mg intramuscularly, on alternate days for 2 weeks (or increase to 0.75 mg on alternate days after the first week if spasms continue), then stop *West syndrome (infantile spasms)*

OR

2 vigabatrin 50 mg/kg orally, twice daily (or increase to 75 mg/kg twice daily after 4 days if spasms continue) for 3 months, then taper over 1 month and stop *West syndrome (infantile spasms)*

OR

3 clonazepam 0.005 to 0.015 mg/kg orally, twice daily. Increase dose gradually to 0.05 to 0.1 mg/kg twice daily. After 3 months, taper over 3 months and stop *West syndrome (infantile spasms)*

OR

3 nitrazepam 0.3 to 1 mg/kg orally, daily for 3 months, then taper over 3 months and stop. *West syndrome (infantile spasms)*

Results of studies comparing the effectiveness of these drugs are inconsistent, and no drug has been proved superior. Prednisolone controls spasms better than vigabatrin initially but not at 12 to 14 months of age. In infantile spasms with no identified cause, a 2010 trial showed that better initial spasm control with prednisolone or tetracosactide (tetracosactrin), compared with vigabatrin, led to an improved developmental outcome after 4 years [Note 13]. A trial published in 2017 showed that initial treatment combining vigabatrin with either prednisolone or tetracosactide (tetracosactrin) had a better outcome after 4 weeks than prednisolone or tetracosactide (tetracosactrin) alone [Note 14].

Vigabatrin commonly causes permanent visual field defects that are usually asymptomatic and may not be detected by confrontation testing. Perform formal visual field testing before starting therapy and at intervals during therapy. When visual field testing is not possible (eg in a young child or a person with a developmental disability), use ocular coherence tomography (OCT) to detect early retinal changes caused by vigabatrin.

Sodium valproate can also be used but the risk of liver toxicity is higher in young children. Rare cases of infantile spasms that respond to pyridoxine have been reported.

Note 13: Darke K, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Lux AL, et al. Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multi-centre randomised trial. Arch Dis Child 2010;95(5):382-6. [URL]

Note 14: O'Callaghan FJ, Edwards SW, Alber FD, Hancock E, Johnson AL, Kennedy CR, et al. Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial. Lancet Neurol 2017;16(1):33-42. [URL]

Neonatal seizures

Neonatal seizures

Neonatal seizures need highly specialised care. The priority is to stop the seizures quickly.

When possible, identify and treat the cause of the neonatal seizure. The most common causes are hypoxic-ischaemic encephalopathy, intracranial haemorrhage and perinatal ischaemic strokes. Treatable causes include meningitis, hypoglycaemia, hypocalcaemia, electrolyte disturbances and metabolic conditions. Some neonatal seizures are familial and benign, so ask about the family history.

As first-line treatment for controlling seizures, use:

phenobarbital (phenobarbitone) 15 to 20 mg/kg intramuscularly or intravenously, followed by phenobarbital 3 to 5 mg/kg intravenously or orally, daily. After 3 days, stop therapy if the baby has normal neurological examination, electroencephalogram and magnetic resonance imaging and has not had more seizures. *neonatal seizures* _

If a cause is not apparent, consider the rare syndrome of pyridoxine-dependent seizures, and give pyridoxine under expert advice. A typical regimen is:

pyridoxine 50 to 100 mg intramuscularly or intravenously, as a single dose. If seizures do not stop, repeat the dose every 5 to 15 minutes to a maximum total dose of 500 mg. *neonatal seizures*

If the baby responds favourably to pyridoxine, treatment must continue for life. Use:

pyridoxine 50 to 100 mg orally, daily indefinitely.

During an acute febrile illness, the pyridoxine dose should be doubled for several days to prevent an exacerbation of seizures.

Febrile seizures

Febrile seizures

A febrile convulsion is a seizure that usually occurs from 3 months to 6 years of age—it is associated with fever (more than 38°C) without concurrent acute intracranial disease, metabolic disturbance or central nervous system infection. Reducing the child's temperature (eg with paracetamol or ibuprofen) does not stop febrile seizures or prevent subsequent febrile seizures.

Most febrile seizures are brief and end within 1 to 3 minutes without drug treatment. Give supportive care. If the seizure lasts more than 5 minutes, use:

1 midazolam 0.2 to 0.3 mg/kg (up to 10 mg) buccally or intranasally. Repeat once 10 minutes later if seizure continues [Note 15] *febrile seizures* _

OR

1 midazolam 0.15 to 0.2 mg/kg (up to 10 mg) intramuscularly. Repeat once 10 minutes later if seizure continues.

If the seizure continues 10 minutes after the second dose of midazolam, treat with an antiepileptic drug as in Step 2 for status epilepticus.

Most children do not need antiepileptic drug treatment to prevent recurrent febrile seizures. If needed, phenobarbital (phenobarbitone) or sodium valproate, but not phenytoin or carbamazepine, may be used.

Note 15: Midazolam solution for injection (hydrochloride salt) can be given buccally or intranasally and may be provided under expert advice to parents and carers who have been trained in its use. Fact sheets that explain the method are available (eg from the Royal Children's Hospital Melbourne).

Benign childhood epilepsy with centrotemporal spikes

Benign childhood epilepsy with centrotemporal spikes

Benign childhood epilepsy with centrotemporal spikes typically starts in mid-childhood. Seizures usually occur during sleep and begin in the face or mouth, producing a typical glugging sound. Speech arrest is common. The focal (partial) seizure may become generalised. The electroencephalogram is typical, showing epileptiform discharges in the centrotemporal region. The prognosis is excellent and most children are seizure-free by early adolescence.

Carbamazepine, sodium valproate and sulthiame are the drugs of choice. Seizures in benign childhood epilepsy with centrotemporal spikes usually occur during sleep and at low frequency, so treatment is not always indicated (consider the harms of generalised tonic-clonic seizures and the rare occurrence of sudden unexpected death in epilepsy).

When treatment is appropriate, use:

1 carbamazepine (preferably modified-release) 2.5 mg/kg orally, twice daily for 5 days, then increase to initial target dose of 5 mg/kg twice daily. If needed, increase up to 15 mg/kg twice daily [Note 16] *epilepsy, benign childhood with centrotemporal spikes* _

OR

1 sodium valproate , child older than 2 years, 5 mg/kg orally, twice daily for 5 days, then increase to 10 mg/kg twice daily; usual maintenance dose 10 to 20 mg/kg twice daily; maximum 2500 mg daily. Avoid in females of childbearing potential (see teratogenic and neurodevelopmental effects of antiepileptic drugs) *epilepsy, benign childhood with centrotemporal spikes* _

OR

1 sulthiame 2 mg/kg orally, 3 times daily. If needed, increase up to 5 mg/kg 3 times daily. *epilepsy, benign childhood with centrotemporal spikes* _

Note 16: Pharmacogenetic studies are identifying an increasing number of genes that confer a predisposition to cutaneous drug reactions. Testing for the HLA-B*1502 allele in patients of Asian origin (other than Japanese) is advised before starting therapy with carbamazepine.

References

Key references: Epilepsy classification

- Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification

and Terminology, 2005-2009. Epilepsia 2010;51(4):676–85. https://www.ncbi.nlm.nih.gov/pubmed/20196795
- Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia 2014;55(4):475–82. https://www.ncbi.nlm.nih.gov/pubmed/24730690
- Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 operational classification of seizure types. Epilepsia 2017;58(4):531–42. https://www.ncbi.nlm.nih.gov/pubmed/28276064
- Lawn N, Chan J, Lee J, Dunne J. Is the first seizure epilepsy--and when? Epilepsia 2015;56(9):1425–31. https://www.ncbi.nlm.nih.gov/pubmed/26222507
- Scheffer IE, Berkovic S, Capovilla G, Connolly MB, French J, Guilhoto L, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia 2017;58(4):512–21. https://www.ncbi.nlm.nih.gov/pubmed/28276062

Key references: Choosing an antiepileptic drug

- Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. N Engl J Med 2017;376(21):2011–20. https://www.ncbi.nlm.nih.gov/pubmed/28538134

Key references: Titrating and withdrawing antiepileptic drugs

- Beghi E, Gatti G, Tonini C, Ben-Menachem E, Chadwick DW, Nikanorova M, et al. Adjunctive therapy versus alternative monotherapy in patients with partial epilepsy failing on a single drug: a multicentre, randomised, pragmatic controlled trial. Epilepsy Res 2003;57(1):1–13. https://www.ncbi.nlm.nih.gov/pubmed/14706729
- Chadwick D, Taylor J, Johnson T. Outcomes after seizure recurrence in people with well-controlled epilepsy and the factors that influence it. The MRC Antiepileptic Drug Withdrawal Group. Epilepsia 1996;37(11):1043–50. https://www.ncbi.nlm.nih.gov/pubmed/8917053
- Lamberink HJ, Otte WM, Geerts AT, Pavlovic M, Ramos-Lizana J, Marson AG, et al. Individualised prediction model of seizure recurrence and long-term outcomes after withdrawal of antiepileptic drugs in seizure-free patients: a systematic review and individual participant data meta-analysis. Lancet Neurol 2017;16(7):523–31. https://www.ncbi.nlm.nih.gov/pubmed/28483337

Key references: Avoiding adverse effects of antiepileptic drugs

- Amstutz U, Shear NH, Rieder MJ, Hwang S, Fung V, Nakamura H, et al. Recommendations for HLA-B*15:02 and HLA-A*31:01 genetic testing to reduce the risk of carbamazepine-induced hypersensitivity reactions. Epilepsia 2014;55(4):496–506. https://www.ncbi.nlm.nih.gov/pubmed/24597466
- Zaccara G, Franciotta D, Perucca E. Idiosyncratic adverse reactions to antiepileptic drugs. Epilepsia 2007;48(7):1223–44. https://www.ncbi.nlm.nih.gov/pubmed/17386054

Key references: When to measure serum concentrations of antiepileptic drugs

- Patsalos PN, Berry DJ, Bourgeois BF, Cloyd JC, Glauser TA, Johannessen SI, et al. Antiepileptic drugs - best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008;49(7):1239–76. https://www.ncbi.nlm.nih.gov/pubmed/18397299

Key references: Advice for patients with epilepsy

- Alper K, Schwartz KA, Kolts RL, Khan A. Seizure incidence in psychopharmacological clinical trials: an analysis of Food and Drug Administration (FDA) summary basis of approval reports. Biol Psychiatry 2007;62(4):345–54. https://www.ncbi.nlm.nih.gov/pubmed/17223086
- Harden C, Tomson T, Gloss D, Buchhalter J, Cross JH, Donner E, et al. Practice guideline summary: Sudden unexpected death in epilepsy incidence rates and risk factors: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2017;88(17):1674–80. https://www.ncbi.nlm.nih.gov/pubmed/28438841

- Somerville ER, Black AB, Dunne JW. Driving to distraction—certification of fitness to drive with epilepsy. Med J Aust 2010;192(6):342–4. https://www.ncbi.nlm.nih.gov/pubmed/20230353

Key references: Contraception in patients with epilepsy

- Reddy DS. Clinical pharmacokinetic interactions between antiepileptic drugs and hormonal contraceptives. Expert Rev Clin Pharmacol 2010;3(2):183–92. https://www.ncbi.nlm.nih.gov/pubmed/20369030

Key references: Pregnancy in patients with epilepsy

- Baker GA, Bromley RL, Briggs M, Cheyne CP, Cohen MJ, Garcia-Finana M, et al. IQ at 6 years after in utero exposure to antiepileptic drugs: a controlled cohort study. Neurology 2015;84(4):382–90. https://www.ncbi.nlm.nih.gov/pubmed/25540307
- Chaudhry SA, Jong G, Koren G. The fetal safety of levetiracetam: a systematic review. Reprod Toxicol 2014;46:40–5. https://www.ncbi.nlm.nih.gov/pubmed/24602560
- Eadie M, Vajda FJE. Topiramate [chapter 9 - Particular antiepileptic drugs and foetal malformations]. In: Antiepileptic drugs and pregnancy - a guide for prescribers. Cham: ADIS; 2016. p. 164–6.
- Harden CL, Pennell PB, Koppel BS, Hovinga CA, Gidal B, Meador KJ, et al. Practice parameter update: management issues for women with epilepsy--focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology 2009;73(2):142–9. https://www.ncbi.nlm.nih.gov/pubmed/19398680
- Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, et al. Cognitive function at 3 years of age after fetal exposure to antiepileptic drugs. N Engl J Med 2009;360(16):1597–605. https://www.ncbi.nlm.nih.gov/pubmed/19369666
- Somerville ER, Cook MJ, O'Brien TJ. Pregnancy treatment guidelines: throwing the baby out with the bath water. Epilepsia 2009;50(9):2172. https://www.ncbi.nlm.nih.gov/pubmed/19706065
- Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Perucca E, et al. Dose-dependent teratogenicity of valproate in mono- and polytherapy: an observational study. Neurology 2015;85(10):866–72. https://www.ncbi.nlm.nih.gov/pubmed/26085607
- Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, et al. Dose-dependent risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry. Lancet Neurol 2011;10(7):609–17. https://www.ncbi.nlm.nih.gov/pubmed/21652013
- Tomson T, Marson A, Boon P, Canevini MP, Covanis A, Gaily E, et al. Valproate in the treatment of epilepsy in girls and women of childbearing potential. Epilepsia 2015;56(7):1006–19. https://www.ncbi.nlm.nih.gov/pubmed/25851171
- Vajda FJ, Eadie MJ. Maternal valproate dosage and foetal malformations. Acta Neurol Scand 2005;112(3):137–43. https://www.ncbi.nlm.nih.gov/pubmed/16097954

Key references: Uncontrolled epilepsy

- Callaghan BC, Anand K, Hesdorffer D, Hauser WA, French JA. Likelihood of seizure remission in an adult population with refractory epilepsy. Ann Neurol 2007;62(4):382–9. https://www.ncbi.nlm.nih.gov/pubmed/17880009
- Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. Epilepsia 2009;50(2):304–17. https://www.ncbi.nlm.nih.gov/pubmed/18823325
- Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser W, Mathern G, et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51(6):1069–77. https://www.ncbi.nlm.nih.gov/pubmed/19889013
- Neal EG, Zupec-Kania B, Pfeifer HH. Carnitine, nutritional supplementation and discontinuation of ketogenic diet therapies. Epilepsy Res 2012;100(3):267–71. https://www.ncbi.nlm.nih.gov/pubmed/22704584
- Shorvon S, Luciano AL. Prognosis of chronic and newly diagnosed epilepsy: revisiting temporal aspects. Curr Opin Neurol 2007;20(2):208–12. https://www.ncbi.nlm.nih.gov/pubmed/17351493

Key references: Childhood and juvenile absence epilepsies

- Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy: initial monotherapy outcomes at 12 months. Epilepsia 2013;54(1):141–55. https://www.ncbi.nlm.nih.gov/pubmed/23167925
- Glauser TA, Cnaan A, Shinnar S, Hirtz DG, Dlugos D, Masur D, et al. Ethosuximide, valproic acid, and lamotrigine in childhood absence epilepsy. N Engl J Med 2010;362(9):790–9. https://www.ncbi.nlm.nih.gov/pubmed/20200383
- Shinnar S, Cnaan A, Hu F, Clark P, Dlugos D, Hirtz DG, et al. Long-term outcomes of generalized tonic-clonic seizures in a childhood absence epilepsy trial. Neurology 2015;85(13):1108–14. https://www.ncbi.nlm.nih.gov/pubmed/26311751
- Wirrell EC. Natural history of absence epilepsy in children. Can J Neurol Sci 2003;30(3):184–8. https://www.ncbi.nlm.nih.gov/pubmed/12945939

Key references: Juvenile myoclonic epilepsy

- Camfield CS, Camfield PR. Juvenile myoclonic epilepsy 25 years after seizure onset: a population-based study. Neurology 2009;73(13):1041–5. https://www.ncbi.nlm.nih.gov/pubmed/19786695
- Genton P, Gelisse P, Thomas P, Dravet C. Do carbamazepine and phenytoin aggravate juvenile myoclonic epilepsy? Neurology 2000;55(8):1106–9. https://www.ncbi.nlm.nih.gov/pubmed/11071486
- Marson AG, Al-Kharusi AM, Alwaidh M, Appleton R, Baker GA, Chadwick DW, et al. The SANAD study of effectiveness of valproate, lamotrigine, or topiramate for generalised and unclassifiable epilepsy: an unblinded randomised controlled trial. Lancet 2007;369(9566):1016–26. https://www.ncbi.nlm.nih.gov/pubmed/17382828
- Noachtar S, Andermann E, Meyvisch P, Andermann F, Gough WB, Schiemann-Delgado J, et al. Levetiracetam for the treatment of idiopathic generalized epilepsy with myoclonic seizures. Neurology 2008;70(8):607–16. https://www.ncbi.nlm.nih.gov/pubmed/18285535
- Tomson T, Marson A, Boon P, Canevini MP, Covanis A, Gaily E, et al. Valproate in the treatment of epilepsy in girls and women of childbearing potential. Epilepsia 2015;56(7):1006–19. https://www.ncbi.nlm.nih.gov/pubmed/25851171

Key references: Lennox-Gastaut syndrome and other symptomatic generalised epilepsies

- Arzimanoglou A, French J, Blume WT, Cross JH, Ernst JP, Feucht M, et al. Lennox-Gastaut syndrome: a consensus approach on diagnosis, assessment, management, and trial methodology. Lancet Neurol 2009;8(1):82–93. https://www.ncbi.nlm.nih.gov/pubmed/19081517
- Glauser TA, Levisohn PM, Ritter F, Sachdeo RC. Topiramate in Lennox-Gastaut syndrome: open-label treatment of patients completing a randomized controlled trial. Topiramate YL Study Group. Epilepsia 2000;41 Suppl 1:S86–90. https://www.ncbi.nlm.nih.gov/pubmed/10768308
- Sachdeo RC, Glauser TA, Ritter F, Reife R, Lim P, Pledger G. A double-blind, randomized trial of topiramate in Lennox-Gastaut syndrome. Topiramate YL Study Group. Neurology 1999;52(9):1882–7. https://www.ncbi.nlm.nih.gov/pubmed/10371538
- Tomson T, Marson A, Boon P, Canevini MP, Covanis A, Gaily E, et al. Valproate in the treatment of epilepsy in girls and women of childbearing potential. Epilepsia 2015;56(7):1006–19. https://www.ncbi.nlm.nih.gov/pubmed/25851171

Key references: Tonic-clonic seizures where generalised or focal (partial) onset is unclear

- Somerville ER. Some treatments cause seizure aggravation in idiopathic epilepsies (especially absence epilepsy). Epilepsia 2009;50 Suppl 8:31–6. https://www.ncbi.nlm.nih.gov/pubmed/19702731
- Tomson T, Marson A, Boon P, Canevini MP, Covanis A, Gaily E, et al. Valproate in the treatment of epilepsy in girls and women of childbearing potential. Epilepsia 2015;56(7):1006–19. https://www.ncbi.nlm.nih.gov/pubmed/25851171

Key references: West syndrome (infantile spasms)

- Darke K, Edwards SW, Hancock E, Johnson AL, Kennedy CR, Lux AL, et al. Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for

infantile spasms: a multi-centre randomised trial. Arch Dis Child 2010;95(5):382–6. https://www.ncbi.nlm.nih.gov/pubmed/20457702
- O'Callaghan FJ, Edwards SW, Alber FD, Hancock E, Johnson AL, Kennedy CR, et al. Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial. Lancet Neurol 2017;16(1):33–42. https://www.ncbi.nlm.nih.gov/pubmed/27838190
- The International Collaborative Infantile Spasms Study (ICISS)Protocol for a randomised trial in the medicinal treatment of infantile spasms. Bath, UK: ICISS; 2006. http://www.bath.ac.uk/health/research/iciss/index2.php

Key references: Neonatal seizures

- Slaughter LA, Patel AD, Slaughter JL. Pharmacological treatment of neonatal seizures: a systematic review. J Child Neurol 2013;28(3):351–64. https://www.ncbi.nlm.nih.gov/pubmed/23318696

Key references: Benign childhood epilepsy with centrotemporal spikes

- Tan HJ, Singh J, Gupta R, Goede C. Comparison of antiepileptic drugs, no treatment, or placebo for children with benign epilepsy with centro temporal spikes. Cochrane Database Syst Rev 2014; (9):CD006779. https://www.ncbi.nlm.nih.gov/pubmed/25190506

Published November 2017 (Amended June 2023)

[X] Close

Idiopathic facial nerve (Bell) palsy

Idiopathic facial nerve (Bell) palsy

Idiopathic facial nerve (Bell) palsy is the most common cranial neuropathy. The cause is uncertain, but the palsy might be related to a virus infection. Consider the differential diagnosis of facial nerve palsy, as many other conditions (eg diabetes, hypertension, parotid tumours, tick bites, trauma) can affect the facial nerve—the treatment is different from that for idiopathic facial nerve (Bell) palsy. If vesicles are seen in the ipsilateral ear, varicella zoster virus infection of the facial nerve (Ramsay-Hunt syndrome) is the probable cause—treat with prednis(ol)one as below, plus an antiviral drug. If the palsy has atypical features (eg bilateral involvement) or recovery is prolonged, refer for magnetic resonance imaging and expert review to exclude other diagnoses.

Many patients with idiopathic facial nerve (Bell) palsy return to normal with no residual weakness. If a lower motor neurone facial palsy is mild and incomplete, the outlook for recovery is so good that treatment may not be needed. If the paralysis is complete or nearly complete, or the sense of taste is lost on the anterior two-thirds of the tongue on the affected side, the prognosis for complete recovery is still good but less certain. Advise patients that facial nerve recovery can take several weeks or months. Depending on the severity of facial nerve involvement, some weakness may persist.

When the patient has had symptoms of idiopathic facial nerve (Bell) palsy for less than 72 hours, evidence supports starting treatment with a corticosteroid [Note 1]. Use:

prednis(ol)one 1 mg/kg (up to 75 mg) orally, once daily in the morning for 5 days. *idiopathic facial nerve (Bell) palsy*

A 2015 systematic review concluded that low-quality evidence showed a benefit from combining a corticosteroid with an antiviral drug, compared with the corticosteroid alone [Note 2].

If eye closure is impaired, cover the eye on the affected side in windy or dusty surroundings and instil artificial tears liberally. Ophthalmological review is often helpful if the facial nerve palsy is severe.

After recovery from facial nerve palsy, aberrant regeneration of the facial nerve can have adverse effects (eg co-contraction of facial muscles [synkinesis], involuntary tearing of the eye on the affected side when eating [crocodile tears], gustatory sweating).

Note 1: Madhok VB, Gagyor I, Daly F, Somasundara D, Sullivan M, Gammie F, et al. Corticosteroids for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev 2016;(7):CD001942. [URL]

Note 2: Gagyor I, Madhok VB, Daly F, Somasundara D, Sullivan M, Gammie F, et al. Antiviral treatment for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev 2015;(11):CD001869. [URL]

Key references: Idiopathic facial nerve (Bell) palsy

Key references: Idiopathic facial nerve (Bell) palsy

- Gagyor I, Madhok VB, Daly F, Somasundara D, Sullivan M, Gammie F, et al. Antiviral treatment for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev 2015;(11):CD001869. https://www.ncbi.nlm.nih.gov/pubmed/26559436

- Madhok VB, Gagyor I, Daly F, Somasundara D, Sullivan M, Gammie F, et al. Corticosteroids for Bell's palsy (idiopathic facial paralysis). Cochrane Database Syst Rev 2016;(7):CD001942. https://www.ncbi.nlm.nih.gov/pubmed/27428352

Published November 2017

[X] Close

Acute inflammatory polyradiculoneuropathy (Guillain-Barré syndrome)

Acute inflammatory polyradiculoneuropathy (Guillain-Barré syndrome)

Acute inflammatory polyradiculoneuropathy (Guillain-Barré syndrome) typically presents as widespread weakness and sensory disturbance (often without sensory signs) that progresses rapidly. It usually starts peripherally, with impaired or lost tendon reflexes. Clinical presentations vary, and include the Miller Fisher variant (external ophthalmoplegia, ataxia, areflexia) and an uncommon bulbar presentation. Autonomic instability can occur (eg blood pressure variation, cardiac arrhythmia, urinary retention). Some cases are triggered by infection (eg with *Campylobacter* enteritis, *Mycoplasma pneumoniae*, Epstein-Barr virus, cytomegalovirus).

Tests to confirm the diagnosis include a cerebrospinal fluid examination—typically, the protein concentration is raised and the cellular response is absent or minimal. Early in the illness the only finding in nerve conduction studies may be the absence of F-waves, but later in the illness nerve conduction slows. Magnetic resonance imaging can exclude other causes and may show enhancement of nerve roots.

Manage patients in hospital. Monitor the vital capacity every 4 hours—if it falls to less than 20 mL/kg or declines rapidly, transfer the patient to an intensive care unit.

Intravenous immunoglobulin (IVIg) and plasma exchange are proven therapies of similar efficacy [Note 1]. However, plasma exchange:

- is not available at all sites
- needs good intravenous access
- has effects on fluids and blood pressure that may not be tolerated by older patients.

If acute inflammatory polyradiculoneuropathy is moderate to severe and onset was less than 2 weeks ago, use:

1 intravenous immunoglobulin (IVIg) 0.4 g/kg intravenously, daily for 5 days *acute inflammatory polyradiculoneuropathy (Guillain-Barre syndrome)*

OR

1 intravenous immunoglobulin (IVIg) 1 g/kg intravenously, daily for 2 days

OR

1 plasma exchange (discuss regimen with local haematologist).

Prophylaxis for deep vein thrombosis is suggested for these patients, as the risk is increased by immobility and IVIg therapy.

Note 1: Hughes RA, Swan AV, van Doorn PA. Intravenous immunoglobulin for Guillain-Barre syndrome. Cochrane Database Syst Rev 2014;(9):CD002063. [URL]

Key references: Acute inflammatory polyradiculoneuropathy (Guillain-Barré syndrome)

Key references: Acute inflammatory polyradiculoneuropathy (Guillain-Barré syndrome)

- Alkan O, Yildirim T, Tokmak N, Tan M. Spinal MRI findings of guillain-barre syndrome. J Radiol Case Rep 2009;3(3):25–8. https://www.ncbi.nlm.nih.gov/pubmed/22470650
- Hughes RA, Swan AV, Doorn PA. Intravenous immunoglobulin for Guillain-Barre syndrome. Cochrane Database Syst Rev 2014;(9):CD002063. https://www.ncbi.nlm.nih.gov/pubmed/25238327

Published November 2017

[X] Close

Motor neurone disease

Motor neurone disease

Motor neurone disease (the most common form of which is amyotrophic lateral sclerosis) is a progressive neurodegenerative disorder of the upper and lower motor neurones. It presents with limb, bulbar and/or respiratory muscle weakness. The disease is fatal, usually within 3 to 4 years of onset. A small percentage of patients survive much longer—often these patients have pure upper (primary lateral sclerosis) or pure lower (progressive muscular atrophy) motor neurone variants of the disease.

Multidisciplinary care improves quality of life and survival in patients with motor neurone disease, and is an effective way to manage symptoms (eg limb weakness; difficulty walking, speaking, breathing and swallowing). Other management options include noninvasive ventilation, which can improve survival and quality of life, and a gastrostomy tube.

Motor neurone disease has no cure. Riluzole slows the disease modestly (ie improves survival by 3 to 6 months). The usual dosage is:

riluzole 50 mg orally, twice daily. *motor neurone disease* _

Hepatic disturbance and neutropenia are uncommon adverse effects.

Symptoms of motor neurone disease that often need treating are muscle cramps, spasticity, sialorrhoea, musculoskeletal pain and emotional lability. There is no high-quality evidence on which to base choice of therapy, and the following advice is based on expert opinion.

Muscle cramps are common, and may respond to baclofen, gabapentin, carbamazepine or magnesium.

Spasticity can be treated with stretching and drug therapy (eg baclofen, dantrolene). Be aware when treating spasticity that some patients with limb weakness rely on the spasticity to maintain mobility.

Sialorrhoea usually occurs when patients have significant bulbar weakness and lose the ability to swallow their saliva. This can be distressing for the patient and family. First-line therapy is oral drugs that have anticholinergic effects (eg propantheline, amitriptyline, atropine [drops applied sublingually]). For example, use:

propantheline 15 mg orally, 1 to 3 times daily. Review efficacy after 2 weeks. *sialorrhoea (motor neurone disease)* _

Try one oral anticholinergic drug for 2 weeks, and if it is not effective, consider subcutaneous glycopyrronium (glycopyrrolate). Use:

glycopyrronium (glycopyrrolate) 20 to 30 micrograms subcutaneously, twice daily. Increase dose slowly to avoid thick sticky secretions (maximum dose 100 micrograms subcutaneously, 3 times daily). *sialorrhoea (motor neurone disease)*

Subcutaneous glycopyrronium (glycopyrrolate) is usually so effective that third-line treatment (eg botulinum toxin type A injection into the salivary glands) is not needed.

Mild to moderate musculoskeletal pain can be treated with paracetamol, nonsteroidal anti-inflammatory drugs, physiotherapy and corticosteroid injections in local joints. When pain is severe, consider transdermal buprenorphine or oral oxycodone.

Emotional lability may be treated with an antidepressant. Psychological support can help the patient and their family.

Another aspect of managing patients with motor neurone disease is to discuss advanced health care directives. See also advice on managing the disease in patients receiving palliative care.

Key references: Motor neurone disease

Key references: Motor neurone disease

- Dharmadasa T, Henderson RD, Talman PS, Macdonell RA, Mathers S, Schultz DW, et al. Motor neurone disease: progress and challenges. Med J Aust 2017;206(8):357–62. https://www.ncbi.nlm.nih.gov/pubmed/28446118
- Ng L, Khan F, Young CA, Galea M. Symptomatic treatments for amyotrophic lateral sclerosis/motor neuron disease. Cochrane Database Syst Rev 2017;(1):CD011776. https://www.ncbi.nlm.nih.gov/pubmed/28072907

Published November 2017 (Amended March 2021)

[X] Close

Acute brachial neuritis

Acute brachial neuritis

Acute brachial neuritis (neuralgic amyotrophy, Parsonage-Turner syndrome) is an uncommon painful plexopathy that is probably caused by an immune-mediated neuritis. It usually presents as acute severe pain (often at night) in the shoulder and upper arm on one side. Acute brachial neuritis can follow an upper respiratory tract infection, vaccination or local trauma. Within 1 to 4 days the patient may have a patch of numbness and weakness in some muscles, especially around the shoulder girdle. Severe pain persists for days or weeks, and affected muscles can waste.

In the acute stage, diagnosis is largely based on clinical presentation, but imaging (including high-resolution ultrasound or magnetic resonance imaging) can be useful. Magnetic resonance imaging has been reported to show T2 hyperintensity in affected nerves and oedema in affected muscles, and helps exclude nerve root compression.

Motor recovery can take months and may not be complete.

Treatment for acute brachial neuritis is mainly supportive, and includes physiotherapy. Corticosteroids can help relieve pain and improve time to recovery, but it is not known whether they improve the extent of motor recovery. Use:

prednis(ol)one 1 mg/kg (up to 75 mg) orally, daily in the morning for 3 to 5 days. *acute brachial neuritis* _

To treat neuropathic pain, see advice.

Key references: Acute brachial neuritis

Key references: Acute brachial neuritis

- Lieba-Samal D, Jengojan S, Kasprian G, Wober C, Bodner G. Neuroimaging of classic neuralgic amyotrophy. Muscle Nerve 2016;54(6):1079–85. https://www.ncbi.nlm.nih.gov/pubmed/27074430
- Naito KS, Fukushima K, Suzuki S, Kuwahara M, Morita H, Kusunoki S, et al. Intravenous immunoglobulin (IVIg) with methylprednisolone pulse therapy for motor impairment of neuralgic amyotrophy: clinical observations in 10 cases. Intern Med 2012;51(12):1493–500. https://www.ncbi.nlm.nih.gov/pubmed/22728480
- van Alfen N, Malessy MJ. Diagnosis of brachial and lumbosacral plexus lesions. Handb Clin Neurol 2013;115:293–310. https://www.ncbi.nlm.nih.gov/pubmed/23931788
- van Alfen N, Engelen BG, Hughes RA. Treatment for idiopathic and hereditary neuralgic amyotrophy (brachial neuritis). Cochrane Database Syst Rev 2009;(3):CD006976. https://www.ncbi.nlm.nih.gov/pubmed/19588414
- van Eijk JJ, Alfen N, Berrevoets M, Wilt GJ, Pillen S, Engelen BG. Evaluation of prednisolone treatment in the acute phase of neuralgic amyotrophy: an observational study. J Neurol Neurosurg Psychiatry 2009;80(10):1120–4. https://www.ncbi.nlm.nih.gov/pubmed/19321467

Published November 2017

[X] Close

General information about restless legs syndrome and periodic limb movements of sleep/wakefulness

General information about restless legs syndrome and periodic limb movements of sleep/wakefulness

Restless legs syndrome and periodic limb movements of sleep/wakefulness often coexist, and are common causes of insomnia and excessive daytime sleepiness.

Periodic limb movements are repetitive flexion of the legs (and occasionally the arms) and dorsiflexion and fanning of the toes—these movements can occur during sleep or when awake. Periodic limb movements occur in 80% of patients with restless legs syndrome. However, periodic limb movements can be normal (eg in elderly people) and are not specific for restless legs syndrome.

Restless legs syndrome is diagnosed using clinical criteria, and a sleep study is not usually needed. The condition can be idiopathic or secondary—causes include iron deficiency, pregnancy and end-stage kidney disease. Some drugs (eg antidepressants, antihistamines) can exacerbate the condition.

Typically, patients complain of limb (usually leg) discomfort at rest, followed by an urge to move the affected part. Often patients cannot describe their symptoms, but may describe the sensation as creeping, crawling, itching, burning, searing, tugging, pulling, drawing, aching, hot and cold, electric current–like, restless or painful. Symptoms affect both arms and legs in about 50% of patients; symptoms confined to the arms are uncommon. Sometimes only one side of the body is affected.

Usually, symptoms occur when the patient has been lying quietly, and last for a few minutes or an hour. Symptoms can also occur when the patient is sitting quietly, but this is rare. When the patient is more mentally rested and physically quiet, the symptoms are more intense. The syndrome is worse from the evening to the early hours of the morning, whether or not the patient is asleep. This circadian pattern can be lost in severe cases. Shift work, medication and sleep disorders may modify the pattern.

Voluntary movement (not necessarily of the affected limb) gives prompt relief, but the effect is temporary. Characteristically, to get relief the patient moves about in their bed or chair, gets up and paces about, or stretches or rubs the limbs. Sometimes, placing the limbs on a cold or hot surface gives the same relief as movement.

Treatment for restless legs syndrome and periodic limb movements of sleep/wakefulness

Treatment for restless legs syndrome and periodic limb movements of sleep/wakefulness

Most cases of restless legs syndrome and periodic limb movements are mild and don't need treatment. Mild, infrequent symptoms may respond to lifestyle changes alone, mainly physical exercise and good sleep practices. Exclude iron deficiency, as it can cause and aggravate restless legs syndrome. Replace iron so the serum ferritin concentration is at least 50 micrograms/L.

If lifestyle changes are not sufficient, drug therapy may be needed. Start treatment at a low dose and titrate gradually to minimise adverse effects. When using a dopaminergic drug to treat restless legs syndrome and periodic leg movements, the maximum dose is lower than in Parkinson disease. Behavioural adverse effects (eg pathological gambling, hypersexuality) due to dopamine agonists can occur, even at these lower doses. Common adverse effects of all dopaminergic drugs are nausea and orthostatic hypotension.

If limb movements at sleep onset are mild and infrequent, use:

1 levodopa+benserazide 100+25 to 200+50 mg orally, before bedtime when needed *restless legs syndrome or periodic limb movements of sleep/wakefulness* _

OR

1 levodopa+carbidopa 100+25 to 200+50 mg orally, before bedtime when needed. *restless legs syndrome or periodic limb movements of sleep/wakefulness* _

More severe symptoms are treated with a calcium channel alpha 2 delta ligand or a dopamine agonist. For therapy with an alpha 2 delta ligand, use:

1 gabapentin 100 to 300 mg orally, once daily at night. Gradually increase dose every 3 to 7 days as tolerated and according to response, up to 2400 mg daily. If the daily dose is more than 1200 mg, give one-third in the evening and two-thirds at bedtime *restless legs syndrome or periodic limb movements of sleep/wakefulness* _

OR

1 pregabalin 75 mg orally, once daily at night. If needed, gradually increase dose every 3 to 7 days as tolerated and according to response, up to 450 mg daily. *restless legs syndrome or periodic limb movements of sleep/wakefulness* _

For therapy with a dopamine agonist, use:

1 pramipexole 0.125 mg orally, once daily 2 to 3 hours before bedtime. If needed, after 4 to 7 days increase dose to 0.25 mg at night, then increase daily dose by 0.25 mg every 4 to 7 days as tolerated and according to response, up to 0.75 mg daily *restless legs syndrome or periodic limb movements of sleep/wakefulness* _

OR

1 ropinirole 0.25 mg orally, once daily 1 to 3 hours before bedtime. If initial dose is tolerated, after 2 days increase dose to 0.5 mg once daily for 5 days, then increase daily dose by 0.5 mg every 7 days according to response, up to 4 mg daily (usual daily dose is 2 mg) *restless legs syndrome or periodic limb movements of sleep/wakefulness*

OR

1 rotigotine 1 mg transdermally, once daily applied for 24 hours. If needed, increase dose as tolerated and according to response, up to 3 mg daily [Note 1]. *restless legs syndrome or periodic limb movements of sleep/wakefulness* _

If therapy is not effective, refer for expert advice.

Augmentation is when the symptoms of restless legs and periodic limb movements of sleep/wakefulness get worse after treatment—the symptoms may shift to an earlier time in the day, have greater intensity and involve new limb areas. Augmentation is mainly a problem with dopaminergic drugs, particularly levodopa, and may occur as early as 3 to 4 weeks after starting treatment.

Risk factors for augmentation are taking more than 200 mg levodopa daily, and taking levodopa early in the day.

Strategies to reduce or stop augmentation include having a drug holiday, stopping the drug or using an alternative drug.

Rebound restless leg symptoms occur when drug treatment has worn off, similar to ‘wearing off’ in Parkinson disease. These symptoms often occur late at night or early in the morning, and are treated by using long-acting preparations (eg transdermal rotigotine) or divided levodopa doses.

Refer patients with augmentation or rebound to an expert.

Note 1: At the time of writing, rotigotine 1 mg and 3 mg transdermal patches are not registered for use in Australia but are available via the Special Access Scheme. Patches cannot be cut.

Key references: Restless legs syndrome and periodic limb movements of sleep/wakefulness

Key references: Restless legs syndrome and periodic limb movements of sleep/wakefulness

- Aurora RN, Kristo DA, Bista SR, Rowley JA, Zak RS, Casey KR, et al. Update to the AASM Clinical Practice Guideline: "The treatment of restless legs syndrome and periodic limb movement disorder in adults-an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses". Sleep 2012;35(8):1037. https://www.ncbi.nlm.nih.gov/pubmed/22851800
- Aurora RN, Kristo DA, Bista SR, Rowley JA, Zak RS, Casey KR, et al. The treatment of restless legs syndrome and periodic limb movement disorder in adults--an update for 2012: practice parameters with an evidence-based systematic review and meta-analyses: an American Academy of Sleep Medicine Clinical Practice Guideline. Sleep 2012;35(8):1039–62. https://www.ncbi.nlm.nih.gov/pubmed/22851801
- Garcia-Borreguero D, Cano-Pumarega I. New concepts in the management of restless legs syndrome. BMJ 2017;356:j104. https://www.ncbi.nlm.nih.gov/pubmed/28242627
- Garcia-Borreguero D, Kohnen R, Silber MH, Winkelman JW, Earley CJ, Hogl B, et al. The long-term treatment of restless legs syndrome/Willis-Ekbom disease: evidence-based guidelines and clinical consensus best practice guidance: a report from the International Restless Legs Syndrome Study Group. Sleep Med 2013;14(7):675–84. https://www.ncbi.nlm.nih.gov/pubmed/23859128
- Garcia-Borreguero D, Silber MH, Winkelman JW, Hogl B, Bainbridge J, Buchfuhrer M, et al. Guidelines for the first-line treatment of restless legs syndrome/Willis-Ekbom disease, prevention and treatment of dopaminergic augmentation: a combined task force of the IRLSSG, EURLSSG, and the RLS-foundation. Sleep Med 2016;21:1–11. https://www.ncbi.nlm.nih.gov/pubmed/27448465
- Garcia-Borreguero D, Stillman P, Benes H, Buschmann H, Chaudhuri KR, Rodriguez VM, et al. Algorithms for the diagnosis and treatment of restless legs syndrome in primary care. BMC Neurol 2011;11:28. https://www.ncbi.nlm.nih.gov/pubmed/21352569
- Hornyak M, Scholz H, Kohnen R, Bengel J, Kassubek J, Trenkwalder C. What treatment works best for restless legs syndrome? Meta-analyses of dopaminergic and non-dopaminergic medications. Sleep Med Rev 2014;18(2):153–64. https://www.ncbi.nlm.nih.gov/pubmed/23746768
- Scholz H, Trenkwalder C, Kohnen R, Riemann D, Kriston L, Hornyak M. Dopamine agonists for restless legs syndrome. Cochrane Database Syst Rev 2011;(3):CD006009. https://www.ncbi.nlm.nih.gov/pubmed/21412893
- Scholz H, Trenkwalder C, Kohnen R, Riemann D, Kriston L, Hornyak M. Levodopa for restless legs syndrome. Cochrane Database Syst Rev 2011;(2):CD005504. https://www.ncbi.nlm.nih.gov/pubmed/21328278
- Wijemanne S, Jankovic J. Restless legs syndrome: clinical presentation diagnosis and treatment. Sleep Med 2015;16(6):678–90. https://www.ncbi.nlm.nih.gov/pubmed/25979181
- Wilt TJ, MacDonald R, Ouellette J, Khawaja IS, Rutks I, Butler M, et al. Pharmacologic therapy for primary restless legs syndrome: a systematic review and meta-analysis. JAMA Intern Med 2013;173(7):496–505. https://www.ncbi.nlm.nih.gov/pubmed/23460396
- Winkelman JW, Armstrong MJ, Allen RP, Chaudhuri KR, Ondo W, Trenkwalder C, et al. Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology 2016;87(24):2585–93. https://www.ncbi.nlm.nih.gov/pubmed/27856776
- Yeh P, Walters AS, Tsuang JW. Restless legs syndrome: a comprehensive overview on its epidemiology, risk factors, and treatment. Sleep Breath 2012;16(4):987–1007. https://www.ncbi.nlm.nih.gov/pubmed/22038683

Published November 2017

[X] Close

Classification of stroke

Classification of stroke

Stroke is a heterogeneous condition, but can be divided into broad pathogenic subgroups (see Table 7.11). About 85% of strokes are ischaemic, and 10% are haemorrhagic. Subarachnoid haemorrhage is traditionally included as a cause of stroke, and makes up the remaining 5%. However, it has distinct clinical features and is managed differently (see advice).

Table 7.11 Types of stroke and approximate incidence in Australia

Stroke subgroup	Incidence (%)
Ischaemic stroke	
large vessel disease (artery-to-artery embolism)	30
cardioembolic (heart-to-artery embolism)	20
small vessel disease (lacunar infarcts)	15
uncertain type	15
rare (eg dissection, venous infarction, vasculopathies)	5
Haemorrhagic stroke (eg primary intracerebral haemorrhage [eg amyloid angiopathy, hypertensive])	10
Subarachnoid haemorrhage	5

Presentation of acute stroke and transient ischaemic attack

Presentation of acute stroke and transient ischaemic attack An acute stroke or a transient ischaemic attack is a medical emergency.

Patients with stroke or transient ischaemic attack (TIA) present in two ways—either the symptoms are ongoing, or the symptoms have resolved.

If the symptoms are ongoing, suspect acute stroke. Patients will have a focal neurological deficit (eg hemiparesis, language dysfunction, vision loss and/or brainstem signs) that has come on abruptly. The patient must be evaluated in hospital urgently, because the timing of treatment is critical. Send the patient by ambulance to an emergency department.

In contrast, suspect TIA in a patient whose symptoms have resolved by the time they present. Most TIAs are brief—more than 90% last less than 1 hour. The patient will report a transient episode of neurological dysfunction (eg language dysfunction, vision loss, hemiparesis).

Subarachnoid haemorrhage (SAH) presents as acute onset of severe headache or sudden loss of consciousness (see advice on assessment and treatment). Focal neurological symptoms and signs are uncommon. A patient with suspected SAH must be assessed urgently in hospital.

Initial assessment of acute stroke and transient ischaemic attack

Initial assessment of acute stroke and transient ischaemic attack

Clinical assessment is the cornerstone of diagnosing acute stroke and transient ischaemic attack (TIA). Urgently refer the patient to hospital for rapid expert clinical assessment (including prognosis), immediate treatment and an early start to secondary prevention.

About 30% of patients with suspected stroke have a 'stroke mimic' (eg tumour, subdural haematoma, migraine, hypoglycaemia, postictal paralysis, cerebral abscess)—this must be identified by clinical assessment, brain imaging and other tests.

Urgent brain imaging is central to assessing suspected stroke/TIA and identifying stroke mimics. Computed tomography (CT) scanning can identify intracerebral haemorrhage, and often detects early signs of ischaemia. Magnetic resonance imaging (MRI; especially diffusion-weighted imaging) is more sensitive for detecting ischaemia, so is most helpful in TIA and posterior circulation events. Computed tomography angiography can show occluded intracranial vessels. Computed tomography or magnetic resonance perfusion studies show potentially salvageable brain tissue.

The first step in clinical assessment is to confirm the diagnosis of stroke by ruling out mimics and determining whether the patient has an intracerebral haemorrhage or ischaemic stroke. If ischaemic, the next step is to decide whether the patient is suitable for reperfusion therapy. As reperfusion is time-critical, establishing the time of onset of the stroke (or the last time when the patient was seen to be well) is essential. Imaging the brain to look for occluded vessels or perfusion abnormalities can indicate that endovascular thrombectomy is required. Decisions on reperfusion therapy need expert involvement, and must consider patient factors (eg severity of stroke, preferences for treatment).

The final step in initial assessment is to determine the cause of the stroke. Most ischaemic strokes are due to atherosclerosis (see also a description of rarer causes). Use clinical features and brain imaging to determine the area of brain affected (eg anterior or posterior circulation, cortical or subcortical). This can suggest the cause and guide further investigation. For example, subcortical syndromes (eg lacunar stroke) are often due to small vessel disease, while cortical syndromes should prompt a search for cardiogenic emboli or carotid stenosis.

All patients with a confirmed diagnosis of stroke should be admitted for care in a dedicated stroke unit. Organised care in a multidisciplinary stroke unit reduces mortality and dependency, increases the likelihood of discharge to home, and does not increase the length of hospital stay. These benefits are independent of age, gender, and type or severity of stroke.

Transient ischaemic attack

Transient ischaemic attack

Traditionally, when magnetic resonance imaging (MRI) was less readily available, the definition of transient ischaemic attack (TIA) was based on time (ie an episode of focal neurological dysfunction, with an abrupt onset, that lasted less than 24 hours and had a vascular cause). Often, after an apparent TIA, the patient has signs of brain infarction on MRI even though their symptoms resolve. As a consequence, the definition of TIA has become less strictly based on time, with greater emphasis on whether the patient has had an infarct. An episode is considered to be a:

- mild stroke if brain infarction is identified
- TIA if symptoms resolve completely within 24 hours and there is no brain infarction.

The risk of a stroke after a TIA is about 10% at 2 weeks, and half these events occur within 48 hours. This emphasises the need for rapid clinical assessment and investigations (see advice).

Factors associated with an increased risk of subsequent stroke include age older than 60 years, raised blood pressure (more than 140/90 mmHg), motor or speech symptoms, symptoms that last longer than 1 hour, and diabetes. At greatest risk are patients with established infarction on brain imaging, atrial fibrillation or a high-grade symptomatic carotid stenosis.

The causes and management of TIA are similar to acute ischaemic stroke. All patients with a TIA should start taking aspirin (see drug advice) and follow other secondary prevention measures.

Immediate treatment for acute ischaemic stroke

Immediate treatment for acute ischaemic stroke

Intravenous thrombolysis

Intravenous thrombolysis

Intravenous alteplase (recombinant tissue plasminogen activator) is effective when given within 4.5 hours of onset of symptoms of acute ischaemic stroke. Earlier treatment has better outcomes, so when alteplase is indicated [Note 1], it should start as soon as possible after stroke onset. The main adverse effect of alteplase is bleeding, including symptomatic intracranial haemorrhage.

If the patient has raised blood pressure, this should be treated before starting thrombolysis. Local hospital protocols should be followed to reduce the blood pressure to 185/110 mmHg or lower—possible drugs include glyceryl trinitrate and labetalol. Thrombolysis should not be started if the blood pressure can't be lowered to this level.

Intravenous alteplase should be given in a setting with expert staff. Blood pressure and neurological status should be monitored for 24 hours after alteplase infusion. If blood pressure exceeds 185/110 mmHg, it should be treated promptly, aiming to maintain it below this level. Aspirin should be withheld for 24 hours, to minimise the risk of haemorrhage.

Note 1: For advice on when alteplase is indicated, see Chapter 3 Acute medical and surgical management (Section 8: Reperfusion therapy) in: Stroke Foundation. Clinical guidelines for stroke management 2017 [online]. Melbourne Australia: Stroke Foundation; 2017.

Endovascular thrombectomy

Endovascular thrombectomy

When stroke is due to occlusion of a large vessel (ie distal internal carotid artery, proximal middle cerebral artery [M1 segment], basilar artery—ususally detected by computed tomography angiography), endovascular thrombectomy is highly effective when performed within 6 hours of symptom onset. Eligible patients are usually a subset of those in whom intravenous alteplase is indicated, and both treatments can be given to the same patient. However, endovascular thrombectomy is appropriate when intravenous alteplase is contraindicated (eg the patient is taking an anticoagulant) or when patients present too late for alteplase therapy (between 4.5 and 6 hours after onset of stroke symptoms).

Endovascular thrombectomy may also be highly effective in patients who present 6 to 24 hours after onset of stroke symptoms, including those who wake up with symptoms. To be eligible, patients must have an occluded large vessel (as defined above) and salvageable brain tissue (as detected by computed tomography or magnetic resonance perfusion imaging).

Only a few specialised centres provide neurointerventional therapy, but most Australian states have (or are moving to) a system-wide, organised approach to providing this service—seek local expert advice.

Antiplatelet therapy for acute ischaemic stroke

Antiplatelet therapy for acute ischaemic stroke

Aspirin has a modest benefit when given within 48 hours of acute ischaemic stroke, and is routinely used. Do not give aspirin until brain imaging excludes intracranial haemorrhage. If the patient has received alteplase,

withhold aspirin for 24 hours and do not start until follow-up imaging excludes haemorrhage.
Do not give aspirin until brain imaging excludes intracranial haemorrhage.

If brain imaging has excluded intracranial haemorrhage, and within 48 hours of onset of ischaemic stroke, use:

aspirin 300 mg orally or via nasogastric tube or rectally, on the first day. Reduce dose to 100 mg daily on the second day and continue daily therapy indefinitely [Note 2]. *stroke, acute (adult)* _

It is reasonable to use another standard antiplatelet drug (eg clopidogrel) in patients who are allergic to aspirin, but no evidence supports their use in acute ischaemic stroke.

Note 2: Aspirin suppositories are available from some hospitals.

Neurosurgery for acute ischaemic stroke

Neurosurgery for acute ischaemic stroke

Because of the effects of cerebral oedema, an extensive hemispheric infarction is fatal in over 80% of patients. In a few highly selected patients (ie aged 18 to 60 years with extensive infarcts), hemicraniectomy saves lives and reduces disability. Hemicraniectomy should be considered within 48 hours of stroke onset for these patients—the decision should involve stroke specialists and neurosurgeons from specialised stroke units.

Oedema surrounding large cerebellar infarcts is also associated with high mortality. Ventricular drainage (to relieve acute hydrocephalus) and posterior fossa decompression are treatments of choice for large space-occupying cerebellar infarcts.

General measures for acute ischaemic stroke

General measures for acute ischaemic stroke

Assess a patient's ability to swallow before giving oral drugs—the gag reflex is not a useful measure. If the patient has difficulty swallowing, maintain them nil-by-mouth and refer to a speech pathologist for assessment. Dysphagia often improves rapidly, but for the first few days fluids and drugs can be given parenterally. Before deciding to insert a nasogastric tube, the harms and benefits must be assessed, taking into account the patient's prognosis.

Blood pressure is often raised after an acute ischaemic stroke, but usually reduces spontaneously. In general, avoid lowering blood pressure in the acute phase of ischaemic stroke (first 48 hours); exceptions can include patients with malignant hypertension or hypertensive encephalopathy, or patients receiving alteplase. Cautious use of blood pressure–lowering drugs (preferably oral) is recommended for patients with markedly raised blood pressure (systolic blood pressure greater than 220 mmHg, diastolic blood pressure greater than 110 mmHg)—the aim is to reduce the blood pressure by about 20%. Standard drugs can be used (see advice on urgent reduction of blood pressure).

Give supplemental oxygen to patients who are hypoxic—routine use of oxygen is not supported. Lower fever with paracetamol.

Hyperglycaemia is associated with a worse outcome after stroke, so avoid intravenous fluids containing glucose. About 20% of patients admitted with acute stroke have unrecognised diabetes. Monitor the blood glucose concentration and maintain euglycaemia, but avoid aggressive management of blood glucose.

Early mobilisation, adequate hydration and antiplatelet therapy can help prevent deep vein thrombosis in patients with ischaemic stroke. If a patient is immobilised by the ischaemic stroke, give low molecular weight heparin (eg enoxaparin, dalteparin) in doses used for prophylaxis (see advice), or apply an intermittent pneumatic compression device.

Secondary prevention of ischaemic stroke and transient ischaemic attack

Secondary prevention of ischaemic stroke and transient ischaemic attack

Importance of secondary prevention of stroke or transient ischaemic attack

Importance of secondary prevention of stroke or transient ischaemic attack

The management of patients with ischaemic stroke or transient ischaemic attack (TIA) includes detailed investigations to determine the cause—tailor secondary prevention in each patient to the stroke pathogenesis. The risk of a further stroke is approximately 2 to 4% per year, although it can be higher in some subgroups (eg patients with atrial fibrillation). Start secondary prevention while the patient is in hospital.

Stroke patients are at high risk of a cardiovascular event (especially ischaemic heart disease)—monitor closely for symptoms of myocardial ischaemia.

Lifestyle and general health measures as secondary prevention of stroke or transient ischaemic attack

Lifestyle and general health measures as secondary prevention of stroke or transient ischaemic attack

After stroke or TIA, screen all patients for diabetes. Assess patients for obesity. Advise the patient to eat healthily [Note 3] and not to have more than two standard drinks of alcohol daily. Encourage physical activity. Advise patients who smoke to stop, and help them to do so [Note 4]. See also behavioural risk factor modification.

Note 3: For advice on healthy eating, see the Australian Dietary Guidelines.

Note 4: To help a patient stop smoking, one resource is available on the Royal Australian College of General Practitioners website.

Antiplatelet therapy as secondary prevention of stroke or transient ischaemic attack

Antiplatelet therapy as secondary prevention of stroke or transient ischaemic attack

Aspirin reduces the risk of subsequent stroke by approximately 13% and of all vascular events by 20%. Low-dose aspirin is recommended, as doses above 300 mg daily have more adverse effects.

The combination of dipyridamole and aspirin is marginally more effective than aspirin alone, but has more adverse effects. It should be considered in patients who have recurrent cerebral ischaemic events despite aspirin therapy. The most common adverse effect of dipyridamole+aspirin is headache, and starting treatment with smaller doses may avoid it. One regimen is to continue once-daily aspirin in the morning and take dipyridamole+aspirin at night for the first week, then stop the aspirin and take dipyridamole+aspirin twice daily.

Clopidogrel is modestly more effective than aspirin in preventing serious vascular outcomes (ie stroke, myocardial infarction, vascular death). However, the absolute risk reduction is small and the drug costs more. Therefore, clopidogrel is mainly used as an alternative for patients who can't tolerate aspirin or have had recurrent cerebral ischaemic events while taking aspirin.

For initial antiplatelet therapy, use:

1 aspirin 100 mg orally, once daily *stroke, secondary prevention (adult)*

OR

1 clopidogrel 75 mg orally, once daily *stroke, secondary prevention (adult)*

OR

1 dipyridamole modified-release+aspirin 200+25 mg orally, twice daily. *stroke, secondary prevention (adult)*

Dipyridamole alone can be used in patients who don't tolerate aspirin and clopidogrel—its efficacy is about the same as aspirin, but evidence supporting its use is limited.

A study of clopidogrel plus aspirin as short-term therapy [Note 5] showed benefit, when started straight after minor ischaemic stroke or TIA and continued for up to 90 days. More randomised controlled trial evidence is needed before changing clinical practice.

The combination of clopidogrel plus aspirin for long-term secondary prevention after stroke or TIA has no benefit, because a reduction in ischaemic events is offset by an increase in serious bleeding. It may be continued, with care, in patients already taking the combination for clear cardiac indications (eg post–coronary artery stenting).

Note 5: Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 2013;369(1):11-19. [URL]

Oral anticoagulants as secondary prevention of stroke or transient ischaemic attack

Oral anticoagulants as secondary prevention of stroke or transient ischaemic attack

The recurrent stroke risk in patients with atrial fibrillation is approximately 15% per year. Atrial fibrillation becomes more prevalent with age, and is a major cause of severe stroke. The evidence is strong that anticoagulation is better than antiplatelet therapy for long-term secondary prevention of ischaemic stroke in patients with atrial fibrillation—it reduces the incidence of further events by at least 66% per year. See advice on using anticoagulants in patients with atrial fibrillation.

Atrial fibrillation is the most common source of cardiogenic embolism, but other sources should be considered—these include mural thrombus after a myocardial infarct, thrombi associated with cardiomyopathy and prosthetic cardiac valves, and rare causes (eg nonbacterial thrombotic [marantic] endocarditis). If identified, these non–atrial fibrillation sources of cardiogenic embolism should be treated with warfarin—evidence is lacking or insufficient to support using a direct-acting oral anticoagulant (DOAC).

In patients without atrial fibrillation or another source of cardiogenic embolism, the use of warfarin is not recommended. It causes harm due to major bleeding complications. Trials were underway at the time of writing to compare dabigatran with aspirin in patients with embolic stroke of unknown source.

The best time to start anticoagulation after stroke is not known. The Stroke Foundation guidelines [Note 6] recommend starting anticoagulation immediately after a TIA or minor stroke, after 5 days for a moderate stroke, and after 10 days for a severe stroke. If anticoagulation is delayed, an antiplatelet drug should be used in the interim but stopped when anticoagulation is effective.

If a patient has an ischaemic stroke while already taking an anticoagulant, consult the original prescriber if possible. Common causes of stroke in patients taking an anticoagulant are poor international normalised ratio (INR) control in patients taking warfarin, or incorrect dose of a DOAC.

Note 6: Chapter 4 Secondary prevention (Section 9: Anticoagulant therapy) in: Stroke Foundation. Clinical guidelines for stroke management 2017 [online]. Melbourne Australia: Stroke Foundation; 2017.

Blood pressure lowering as secondary prevention of stroke or transient ischaemic attack

Blood pressure lowering as secondary prevention of stroke or transient ischaemic attack

Raised blood pressure is the main reversible risk factor for first and recurrent stroke. Lowering blood pressure reduces the risk of recurrent strokes and cardiovascular events by about 30% per year. Even patients with initial blood pressure in the normal range benefit.

In all patients, after the acute phase of stroke or TIA, start treatment to lower blood pressure (see drug advice). Aim for a systolic blood pressure of 120 to 130 mmHg.

Lowering cholesterol as secondary prevention of stroke or transient ischaemic attack

Lowering cholesterol as secondary prevention of stroke or transient ischaemic attack

Lowering cholesterol with a statin reduces the risk of further ischaemic stroke, at the expense of a slight increase in the risk of further haemorrhagic stroke. Statin therapy has a greater effect on subsequent coronary events.

Consider starting a statin in all patients whose stroke or TIA is presumed to be due to atherosclerotic disease, regardless of the initial cholesterol concentration (see drug advice).

Managing carotid stenosis as secondary prevention of stroke or transient ischaemic attack

Managing carotid stenosis as secondary prevention of stroke or transient ischaemic attack

All patients with ischaemic stroke or TIA in the territory of the carotid circulation should be screened promptly for a carotid stenosis, which is presumed to be the source of atheroembolism. If the only stenosis seen is in the vessel supplying the unaffected hemisphere (asymptomatic carotid stenosis), see advice—management is different.

If a carotid stenosis in the vessel supplying the affected hemisphere is found on ultrasound, confirm this with a second, independent imaging test (eg computed tomography angiography, magnetic resonance angiography, digital subtraction angiography) if possible.

If the patient with recent mild stroke or TIA has a high-grade ipsilateral carotid stenosis (more than or equal to 70%), refer for urgent carotid endarterectomy. The benefit of surgery is greatest within 2 weeks of a TIA or mild stroke, as this is when the risk of recurrent stroke is greatest. Benefit is marginal for patients with 50 to 69% symptomatic stenosis or when surgery is delayed beyond 3 months.

Percutaneous transluminal cerebrovascular angioplasty and stenting is less effective than carotid endarterectomy. It may be considered in certain circumstances, usually when technical challenges increase the risk of surgery (eg previous neck radiotherapy, high carotid bifurcation, medical comorbidities).

After endarterectomy, all patients need intensive secondary prevention therapy (ie an antiplatelet drug, blood pressure lowering, cholesterol lowering, lifestyle measures [including stopping smoking]).

Rarer causes of ischaemic stroke

Rarer causes of ischaemic stroke

Consider uncommon causes of stroke in young patients without traditional vascular risk factors. Refer to a stroke physician. No cause is identified in about 40% of young patients with ischaemic stroke, despite extensive investigation.

Rarer causes of ischaemic stroke are listed below.

- **Bacterial endocarditis**. Consider this in patients with a stroke, signs of infection (eg fever, night sweats) and cardiac murmur (this may be absent). See management. Anticoagulants are contraindicated.

- **Cerebral venous thrombosis**. This has several clinical manifestations. Acutely, it can present as a stroke, often with seizures and a haemorrhagic infarct on computed tomography (CT). Diagnosis is by CT or magnetic resonance venography. Usually the patient is given heparin as an anticoagulant during the acute phase of the stroke, even if they have a cerebral haemorrhage. After the acute phase the patient is given warfarin for 6 months, or longer if they have a clotting disorder. Expert management by a stroke physician and haematologist is recommended.
- **Carotid or vertebrobasilar arterial dissection**. This can be spontaneous or due to neck trauma (even minor). It can present with neck pain, headache, Horner syndrome, or ischaemic stroke due to thromboembolism. Neuroimaging confirms the diagnosis. Recurrence is rare, and evidence shows no superiority of anticoagulation over antiplatelet therapy as secondary prevention.
- **Patent foramen ovale**. This is a common finding in young patients with stroke, but management is controversial. Seek expert advice.

Ischaemic stroke in children

Ischaemic stroke in children

Stroke in children is uncommon. Atherosclerosis is not a cause, unlike in adults. However, localised forms of vasculitis and other forms of cerebral vasculopathy, congenital heart disease, arterial dissection and metabolic diseases are common causes. Always consider stroke mimics (eg Todd paresis, migraine).

Ischaemic stroke most commonly presents in children as acute hemiparesis, due to involvement of the carotid distribution. Vertebrobasilar stroke is unusual—look for a dissection of the vertebrobasilar arteries when it occurs. Neurological signs in childhood stroke can be subtle.

On presentation, start neuroprotective measures (ie normalise blood pressure, fluid volume, blood glucose concentration, body temperature and blood gases; control seizures). Perform urgent brain imaging (preferably magnetic resonance imaging, otherwise computed tomography) within 1 hour of arrival at hospital, and preferably within 4 hours of onset of symptoms.

The harms and benefits of thrombolytic therapy in children have not been fully assessed—at the time of writing, thrombolytic therapy should only be given in paediatric stroke centres. The efficacy of thrombectomy has not been fully assessed in young children. It is recommended that a tertiary paediatric centre be contacted for urgent neurological advice.

Perform imaging of the cervical and proximal intracranial arterial vasculature in all children with arterial ischaemic stroke, ideally within 24 hours of presentation. Also perform transthoracic echocardiography in this time frame.

Investigate all children with ischaemic stroke for a prothrombotic tendency (eg protein C or protein S deficiency, activated protein C resistance, increased lipoprotein (a), factor V Leiden, prothrombin gene mutation, antithrombin III, antiphospholipid antibodies). Measure serum homocysteine and urine homocystine concentrations. Exclude sickle cell disease. Measure the blood lactate concentration (raised in mitochondrial disease).

In acute arterial ischaemic stroke in a child, after brain imaging has excluded intracranial haemorrhage, and within 48 hours of onset, give aspirin. Use:

aspirin 5 mg/kg (up to 300 mg) orally, daily. *stroke, acute (child)* _

Anticoagulation with unfractionated heparin or low molecular weight heparin is used as an alternative to aspirin in some centres.

Although secondary prevention of ischaemic stroke with aspirin is established in adults, good evidence for its efficacy is not available in children. Nevertheless, aspirin is widely used for childhood ischaemic stroke. For secondary prevention, use:

aspirin 1 mg/kg (up to 75 mg) orally, daily. *stroke, secondary prevention (child)* _

To prevent recurrent cardiogenic embolism, seek expert advice.

Intracerebral haemorrhage

Intracerebral haemorrhage

Manage patients with an intracerebral haemorrhage in hospital.

Some patients with an intracerebral haemorrhage have a bleeding tendency, usually due to drugs such as anticoagulants. As growth of the haematoma is associated with a worse outcome, reverse the bleeding diathesis if possible. If the patient has coagulation factor deficiency or severe thrombocytopenia, give factor replacement therapy or platelets. If the patient is on warfarin therapy, reverse this urgently with a combination of prothrombin complex concentrate, fresh frozen plasma and vitamin K—seek advice from a haematologist. Also seek advice from a haematologist if the patient is taking a direct-acting oral anticoagulant (DOAC).

Urgently lower the blood pressure in acute intracerebral haemorrhage, to reduce haematoma expansion—see advice. It is safe to aim to lower systolic blood pressure to about 140 mmHg.

If a patient is immobilised by the intracerebral haemorrhage, use an intermittent pneumatic compression device as prophylaxis for deep vein thrombosis. Common practice is to start low molecular weight heparin (eg enoxaparin, dalteparin) 48 hours after the haemorrhage—see dosing information.

Surgical evacuation of the haematoma can be considered, but is an expert decision that must take into account patient comorbidity and preferences. In general, large supratentorial haematomas have a high risk of death or major disability and should not be evacuated. In contrast, decompression of cerebellar haematomas may have benefit. Seek local advice from stroke specialists and neurosurgeons.

Raised blood pressure is the main risk factor for recurring intracerebral haemorrhage. Aggressively manage blood pressure in all patients after intracerebral haemorrhage, aiming to reduce the systolic blood pressure to 120 mmHg or lower (as tolerated)—see treatment advice. Treatment continues lifelong.

Using antiplatelet and anticoagulant drugs after haemorrhagic stroke is controversial. Seek expert advice.

Subarachnoid haemorrhage

Subarachnoid haemorrhage

About 75% of patients with subarachnoid haemorrhage present with acute severe headache, and the rest present with loss of consciousness. The mortality is high, and many patients die before reaching hospital.

About 20% of patients with subarachnoid haemorrhage have a sudden headache several weeks before the acute event. This is thought to be due to a sentinel bleed, which is a minor subarachnoid bleed before the main rupture. It is a warning sign that must be investigated. If diagnosed at this early stage, the aneurysm can be treated while the patient is still clinically well.

Patients with suspected subarachnoid haemorrhage need urgent evaluation in hospital. If subarachnoid blood is seen on a computed tomography (CT) scan, this is diagnostic. However, a normal CT scan does not exclude subarachnoid haemorrhage. If the CT scan is normal but the index of suspicion is high, perform a lumbar puncture, or arrange urgent magnetic resonance imaging to look for blood products in the cerebrospinal fluid space.

In hospital, patients are managed by a neurosurgeon, in close collaboration with an interventional neuroradiologist, and occasionally with a neurologist. Most subarachnoid haemorrhages are due to a ruptured intracranial aneurysm, and management is to treat the aneurysm (surgically or endovascularly) and identify and treat the consequences of the bleed. Delayed cerebral ischaemia is the main complication.

Recovery after an ischaemic or haemorrhagic stroke

Recovery after an ischaemic or haemorrhagic stroke

Mood disturbance and depression

Mood disturbance and depression

Psychological problems are common in stroke patients and often do not manifest until the patient is at home. Low mood and depression occur in 25 to 40% of patients. The risk of psychological problems is higher in patients with previous depression, social isolation and more severe stroke (especially when language is affected). Treating psychological problems can help functional recovery (see advice on treating depression).

Anxiety is also common, especially in relation to the course of recovery. The patient and carer/s may not know that recovery can take months. Also they may be unduly pessimistic about the risk of the stroke recurring or of death. Discuss this with the patient and carer.

After a stroke, about 15% of patients are emotionally labile. Signs include weeping (or less commonly, laughing) uncontrollably, out of proportion to the event being discussed and to the patient's inner feelings of sadness (or mirth). Emotional lability usually resolves in a few weeks, but consider treatment with an antidepressant if it persists (see drug advice)—the patient often responds in a few days, faster than in depression.

Fatigue is common after stroke. The extent of the fatigue does not seem to correlate with stroke severity, and it can be reported by patients who have fully recovered physically. Fatigue has no effective treatment. Reassure the patient that fatigue is normal and usually resolves after several months.

Driving after stroke or transient ischaemic attack

Driving after stroke or transient ischaemic attack

All patients are unfit to drive after a stroke or TIA.

After a stroke, a private vehicle driver cannot drive for at least 4 weeks, and a commercial vehicle driver cannot drive for at least 3 months—this applies even if the patient has no detectable neurological deficit. Before starting to drive again, the patient must be assessed for residual impairments that could affect the functions needed to drive safely [Note 7].

Particular concerns are sensory and/or visual inattention (neglect) and hemianopia. Refer patients with significant neurological, cognitive or perceptual impairment (especially inattention) for a driving assessment, supervised by an occupational therapist. Refer patients with hemianopia for assessment by an ophthalmologist.

After a TIA, it is advised that private drivers do not drive for 2 weeks and commercial drivers do not drive for 4 weeks [Note 7].

Note 7: National standards of fitness to drive are available from the Austroads website. For advice on driving after a stroke or a transient ischaemic attack, see Section 6.3 Other neurological and neurodevelopmental conditions. A checklist for assessing fitness to drive after a stroke is in Box 3.

Key references: Initial assessment of acute stroke and transient ischaemic attack

Key references: Initial assessment of acute stroke and transient ischaemic attack

- Jauch EC, Saver JL, Adams HP Jr., Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from

the American Heart Association/American Stroke Association. Stroke 2013;44(3):870–947. https://www.ncbi.nlm.nih.gov/pubmed/23370205

Key references: Transient ischaemic attack

Key references: Transient ischaemic attack

- Jauch EC, Saver JL, Adams HP Jr., Bruno A, Connors JJ, Demaerschalk BM, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2013;44(3):870–947. https://www.ncbi.nlm.nih.gov/pubmed/23370205
- Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45(7):2160–236. https://www.ncbi.nlm.nih.gov/pubmed/24788967

Key references: Immediate treatment for acute ischaemic stroke

Key references: Immediate treatment for acute ischaemic stroke

- Clots Trials Collaboration, Dennis M, Sandercock P, Reid J, Graham C, Forbes J, et al. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. Lancet 2013;382(9891):516–24. https://www.ncbi.nlm.nih.gov/pubmed/23727163
- Goyal M, Menon BK, Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet 2016;387(10029):1723–31. https://www.ncbi.nlm.nih.gov/pubmed/26898852
- Stroke Foundation. Clinical guidelines for stroke management 2017 [online]. Melbourne Australia: Stroke Foundation; 2017 [accessed October 2018]..https://informme.org.au/Guidelines/Clinical-Guidelines-for-Stroke-Management-2017

Key references: Secondary prevention of ischaemic stroke and transient ischaemic attack

Key references: Secondary prevention of ischaemic stroke and transient ischaemic attack

- Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2014;45(7):2160–236. https://www.ncbi.nlm.nih.gov/pubmed/24788967
- Sandercock PA, Gibson LM, Liu M. Anticoagulants for preventing recurrence following presumed non-cardioembolic ischaemic stroke or transient ischaemic attack. Cochrane Database Syst Rev 2009; (2):CD000248. https://www.ncbi.nlm.nih.gov/pubmed/19370555
- .Stroke Foundation. Clinical guidelines for stroke management 2017 [online]. Melbourne Australia: Stroke Foundation; 2017. .https://informme.org.au/Guidelines/Clinical-Guidelines-for-Stroke-Management-2017
- Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med 2013;369(1):11–9. https://www.ncbi.nlm.nih.gov/pubmed/23803136

Key references: Ischaemic stroke in children

Key references: Ischaemic stroke in children

- Mackay MT, Monagle P, Babl FE. Brain attacks and stroke in children. J Paediatr Child Health 2016;52(2):158–63. https://www.ncbi.nlm.nih.gov/pubmed/27062619

- Rivkin MJ, Bernard TJ, Dowling MM, Amlie-Lefond C. Guidelines for urgent management of stroke in children. Pediatr Neurol 2016;56:8–17. https://www.ncbi.nlm.nih.gov/pubmed/26969237
- Royal College of Paediatrics and Child Health (RCPCH), Stroke AssociationStroke in childhood - clinical guideline for diagnosis, management and rehabilitation. London: RCPCH; 2017. http://www.rcpch.ac.uk/stroke-guideline#fullclinicalguideline

Key references: Intracerebral haemorrhage

Key references: Intracerebral haemorrhage

- Hemphill JC, Greenberg SM, Anderson CS, Becker K, Bendok BR, Cushman M, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2015;46(7):2032–60. https://www.ncbi.nlm.nih.gov/pubmed/26022637

Published November 2017 (Amended June 2023)

[X] Close

Dizziness and vertigo diagnosis

Dizziness and vertigo diagnosis

Dizziness is a broad term used by patients to describe a range of sensations that include vertigo, gait ataxia and presyncope. Vertigo is an illusion of motion and is usually rotatory (ie a spinning sensation), but sometimes linear (ie a sense of falling or pitching). Autonomic symptoms (eg nausea, retching, vomiting, pallor, sweating) often accompany vertigo.

Vertigo is often due to pathology of one of the inner ear balance organs, causing hypofunction (eg vestibular neuritis) or hyperfunction (eg benign paroxysmal positional vertigo). Peripheral features suggest inner ear pathology (see Table 7.12 for the clinical features that differentiate peripheral from central causes of vertigo). Acoustic neuromas and acute middle ear infections rarely cause vertigo. Central causes of vertigo (ie neurological disorders that affect vestibular pathways in the brain stem, cerebellum and cortex) other than vestibular migraine are uncommon. However, suspect a central cause (eg multiple sclerosis, vertebrobasilar ischaemia, tumour) if the patient has other neurological or central features.

Table 7.12 Clinical features differentiating peripheral and central causes of vertigo

[NB1]

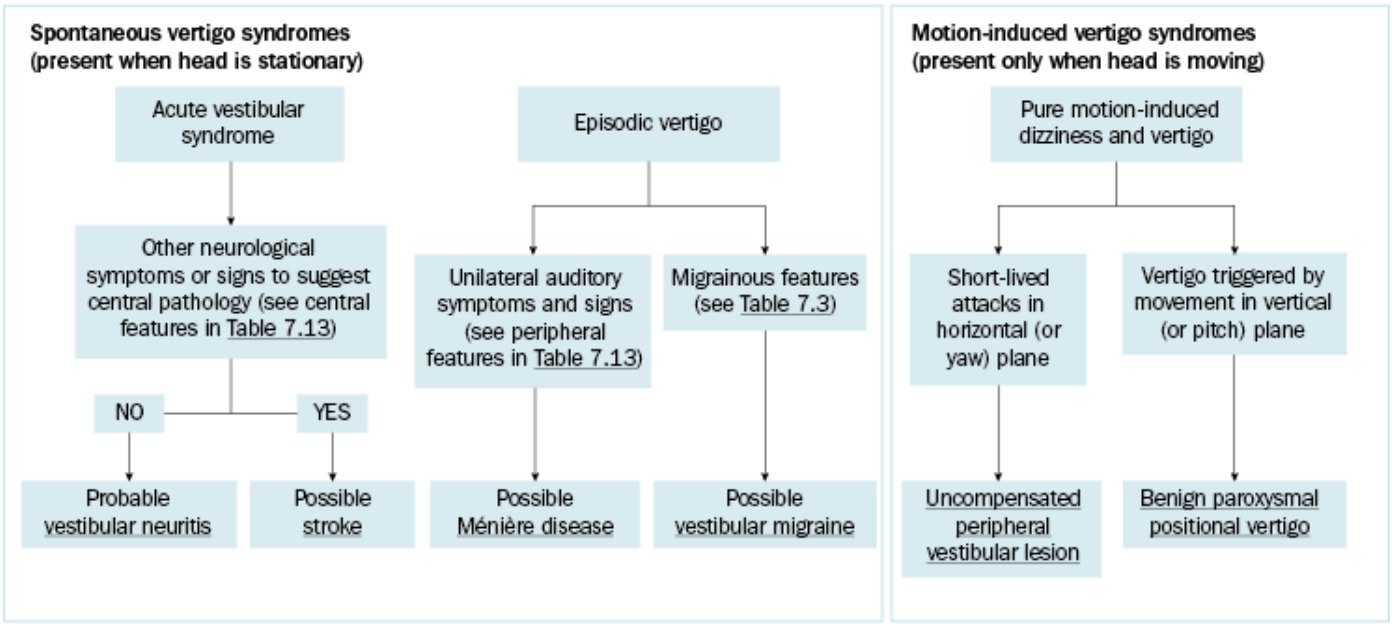
Peripheral features	Central features
	gait ataxia out of proportion to extent of vertigo
	visual field loss
hearing loss	diplopia
tinnitus	hemisensory loss
aural fullness	limb weakness and ataxia
positive head impulse test	slurred speech (dysarthria)
	difficulty swallowing (dysphagia)
	eye movement abnormalities (direction-changing nystagmus, skew deviation)

NB1: For advice on bedside assessment of vertigo (including eye movement abnormalities and the head impulse test), see Welgampola MS, Bradshaw AP, Lechner C, Halmagyi GM. Bedside assessment of acute dizziness and vertigo. Neurol Clin 2015;33(3):551-64, vii. [URL]

Vertigo is classified according to clinical syndromes, and may be spontaneous (present when the head is stationary) or motion-induced (present only when the head is moving)—spontaneous forms of vertigo are also worse with head movement. Further differential diagnosis is based on duration, periodicity and associated features (see summary in Figure 7.11). Episodic spontaneous vertigo attacks are usually due to Ménière disease or vestibular migraine. In unexplained episodic vertigo, especially without the auditory symptoms that suggest another cause (eg Ménière disease), an empirical trial of migraine prophylaxis may be considered.

Figure 7.11 Differential diagnosis of vertigo

[NB1]



NB1: For more advice on bedside assessment of vertigo, see Welgampola MS, Bradshaw AP, Lechner C, Halmagyi GM. Bedside assessment of acute dizziness and vertigo. Neurol Clin 2015;33(3):551-64, vii. [URL]

Vertigo caused by acute unilateral loss of vestibular function (eg vestibular neuritis) is mostly self-limiting—it improves over hours to days due to central vestibular compensation, even when peripheral vestibular function has not recovered. Some patients still have motion-induced dizziness after the acute vertigo resolves, due to incomplete compensation (see uncompensated peripheral vestibular lesion).

Dizziness can also be due to drugs, postural hypotension and other medical disorders. It can be a somatic symptom in primary psychiatric disorders (eg panic disorder, agoraphobia). Chronic intractable dizziness can occur in persistent postural-perceptual dizziness.

Key references: Dizziness and vertigo diagnosis

Key references: Dizziness and vertigo diagnosis

- Welgampola MS, Bradshaw AP, Lechner C, Halmagyi GM. Bedside assessment of acute dizziness and vertigo. Neurol Clin 2015;33(3):551–64, vii. https://www.ncbi.nlm.nih.gov/pubmed/26231271

Published November 2017

[X] Close

Assessing new-onset headache

Assessing new-onset headache

A new-onset headache may result from a primary headache syndrome or be secondary to other pathology. When assessing the patient, first consider whether they have any 'red flags' that suggest they need urgent evaluation (eg neuroimaging, lumbar puncture, urgent expert/emergency department review; see Table 7.1).

Table 7.1 Warning features in a patient with new-onset headache

Symptoms and signs associated with new-onset headache that suggest urgent evaluation is needed	Possible diagnosis
sudden onset	subarachnoid haemorrhage, pituitary apoplexy, haemorrhage into mass lesion, arterial dissection, reversible cerebral vasoconstriction syndrome
first ever headache with focal neurological signs, confusion or drowsiness	stroke, venous sinus thrombosis, reversible cerebral vasoconstriction syndrome, meningitis/encephalitis
patient older than 50 years	giant cell arteritis, mass lesion, stroke
onset after head trauma	subdural/epidural haemorrhage
frequency/severity increases over weeks to months	mass lesion, subdural haemorrhage, analgesic rebound
new onset in patient who has HIV or cancer, or is immunosuppressed	meningitis, abscess, metastasis
signs of systemic illness (eg fever, rash, neck flexion stiffness)	systemic infection, meningitis, encephalitis, vasculitis
papilloedema	mass lesion, idiopathic intracranial hypertension, venous sinus thrombosis
positional headache (eg worse when lying down) and cough headache (especially if prolonged)	space-occupying or posterior fossa lesion, Chiari malformation

Classifying headache and facial pain

Classifying headache and facial pain

Headache has many types, and analysing the phenotype allows accurate diagnosis and guides appropriate therapy. A headache diary is useful to determine the frequency and precipitants of the headache and the frequency of analgesic use.

The International Classification of Headache Disorders, 3rd edition (beta version) [Note 1] is a detailed classification of headaches—it separates them into three parts, which are:

- primary headaches (migraine, tension-type headache, trigeminal autonomic cephalgias, other primary headache disorders)
- secondary headaches (due to structural causes [eg space-occupying lesion, subarachnoid haemorrhage, venous sinus thrombosis] or disease [eg giant cell arteritis, meningitis, systemic infection])
- painful cranial neuropathies (eg trigeminal neuralgia) and other facial pains and headaches.

Table 7.2 gives an overview of some key types of headache and is not intended to cover every type. The purpose of the table is to help diagnose the type of headache, which then directs investigation and management. The companion table, Table 7.3, expands on the clinical features of the trigeminal autonomic cephalgias. The main types of facial pain (including trigeminal neuralgia) are listed in Table 7.4. For warning signs and symptoms of dangerous secondary headaches, see Table 7.1.

Table 7.2 Classifying headaches

[NB1]

Printable PDF

Headache type	Headache characteristics
Primary headaches	
	Recurrent attacks that last 4 to 72 hours. Typically one-sided (not side-locked [NB2], can be bilateral), pulsating, moderate to severe intensity, aggravated by routine physical activity, associated with nausea and/or photophobia, phonophobia or osmophobia.
migraine	Can occur with or without aura. Migraine can present primarily as neck pain or mid-facial pain rather than headache. The associated features listed above are important in making the diagnosis. See treatment.
	Migraine that is preceded by aura (ie reversible focal neurological symptoms that usually develop over 5 to 20 minutes and last for less than 60 minutes).
migraine with aura	Aura symptoms can affect vision, senses, speech and/or language, motor function, brainstem and retina. Exclude transient ischaemic attack.
	Typical aura of migraine that is not accompanied, or followed, by a headache of any sort. Most common form is scintillating scotoma.
aura without headache (acephalgic migraine)	Can occur at times in a patient who usually has a headache after aura. Is the predominant form of migraine in a few patients. Differential diagnosis must exclude aura mimics, especially transient ischaemic attack. See advice on differential diagnosis and treatment.
	Lasts from 30 minutes to 7 days. Usually bilateral, feels like pressure or tightness in head. Mild to moderate intensity (rarely severe enough to prevent walking or climbing stairs).
tension-type headache	Not associated with nausea, may be associated with photophobia or phonophobia. Does not fit diagnostic criteria for other headache types better than criteria for tension-type headache. See treatment.
trigeminal autonomic cephalgias (see subtypes) (trigeminal neuralgia is a different condition)	Unilateral and side-locked [NB2] (usually follow distribution of first division of trigeminal nerve) with unilateral autonomic features (eg tearing, conjunctival injection/irritation, ptosis, nasal stuffiness/rhinorrhoea, fullness of the ear, tinnitus, facial flushing or sweating). Possible photophobia or phonophobia (usually unilateral). Patient often agitated and restless.

Headache type	Headache characteristics
	See treatment for cluster headache, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, and hemicrania continua and paroxysmal hemicrania.
reversible cerebral vasoconstriction syndrome (RCVS)	Thunderclap, recurring over 1 to 2 weeks. May be triggered by exertion, Valsalva manoeuvre, sexual activity or strong emotion. Can also be triggered post partum or by serotonergic and sympathomimetic drugs. Can be associated with fluctuating neurological deficits and seizures. Angiography shows 'string and bead' appearance, but may be normal in first week. Changes on MRI are mainly posterior and may include oedema, infarction, subarachnoid haemorrhage or intracranial haemorrhage.
new daily persistent headache	Persistent and daily since onset (usually patient remembers starting date), present for more than 3 months. No other characteristic features (may be like a migraine or like a tension-type headache). Can resolve spontaneously over several months or become chronic. Treat as for main phenotype.
primary headache associated with sexual activity (benign sex headache)	More frequent in males than females. Usually benign, although thunderclap headache at orgasm can (rarely) be associated with subarachnoid haemorrhage or infarction. May occur before (usually milder) or at (usually more abrupt and severe) orgasm. Often resolves spontaneously over a few months. Consider reversible cerebral vasoconstriction syndrome. Exclude space-occupying lesion or aneurysm. See treatment.
primary exercise headache (benign exertional headache)	Only occurs after strenuous physical activity, especially in hot weather or at high altitude. Lasts less than 48 hours. Exclude space-occupying lesion, aneurysm, carotid stenosis, posterior fossa mass lesion or Chiari malformation. May be an unusual presentation of angina. See treatment.
primary stabbing headache (also known as 'ice-pick headache' or 'jabs and jolts')	Transient and localised stabs of pain in the head. Occur spontaneously in the absence of organic disease in underlying structures or cranial nerves. Each stab lasts a few seconds. Stabs recur irregularly. Mainly extratrigeminal, but can change site. No associated autonomic features. Can occur with a migraine and often ease when migraine is treated. Isolated cases are so brief and infrequent that treatment is not warranted. Persistent cases may respond to indometacin.
primary cough headache (benign cough headache)	Provoked by cough or Valsalva manoeuvre, can last seconds to 2 hours. Exclude space-occupying lesion or aneurysm, posterior fossa pathology, Chiari malformation and cerebrospinal fluid obstruction.
hypnic headache	Typical patient is older (more than 50 years) and woken early (1 to 3 am) by bilateral headache, often with nausea. Headache usually lasts 30 to 60 minutes (up to 4 hours). Can often be prevented by 1 to 2 cups of coffee before bed. Lithium, melatonin and indometacin may also be used. [NB3]
Secondary headaches	
low cerebrospinal fluid (CSF) pressure headache	Generally worse in evening and improved by lying flat. May be associated with 'coat-hanger' pain across the shoulders or pulsatile tinnitus. Intracranial pressure less than 6 cmH20. May be spontaneous or follow trauma or dural puncture. See treatment.
increased cerebrospinal fluid (CSF) pressure headache	Associated with raised intracranial pressure (more than 25 cmH20, measured by lumbar puncture manometry in the lateral decubitus position). Typically worse in the morning and when lying down, improved by upright posture. Aggravated by cough, straining and Valsalva manoeuvre. May be associated with transient visual obscuration, pulsatile tinnitus and papilloedema. Exclude a space-occupying lesion, venous sinus thrombosis or obstruction, and use of drugs such as tetracyclines and vitamin A analogues (eg isotretinoin, acitretin). Consider idiopathic intracranial

Headache type	Headache characteristics
	hypertension (see treatment), especially if recent weight gain. Visual field loss and permanent damage can follow initial transient visual problems.
	Usually accompanied by neck pain and is unilateral (side-locked [NB2]) with radiations from posterior to anterior.
cervicogenic headache	Due to disorder of cervical spine (eg bone, disc, soft tissue). Neck has reduced range of movement. Headache is provoked by neck manoeuvres or digital pressure on affected structures.
	High cervical or greater occipital nerve block may relieve symptoms.
drug-induced headache	Follows intake of drugs (eg alcohol, marijuana, cocaine, monosodium glutamate, nitrates, ciclosporin, phosphodiesterase inhibitors, carbon monoxide, exogenous hormones).
headache induced by metabolic/other medical condition	Patient has a medical condition associated with the headache (eg obstructive sleep apnoea, hypoxia, arterial hypertension, phaeochromocytoma, epilepsy, hypoglycaemia, hypercapnia, haemodialysis).

CSF = cerebrospinal fluid

NB1: Classification based on: Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders 3rd edition (Beta version) [website]. London: International Headache Society; 2013. This table is not intended to cover every type of headache.

NB2: A side-locked headache always affects the same side of the head (ie does not change sides between attacks, and does not change sides during an attack).

NB3: Hypnic headache may be confused with exploding head syndrome (a parasomnia), in which a patient wakes from sleep shortly after onset with sense of a loud bang (painless) in the head. May respond to 1 to 2 cups of coffee before bed.

Trigeminal autonomic cephalgias are a group of headaches that are strictly unilateral and have autonomic features (see further description in Table 7.2 and key features of subtypes in Table 7.3). Trigeminal autonomic cephalgias are distinct from trigeminal neuralgia—the latter does not have prominent autonomic features, and its pain is often evoked by contact or use of the affected region (see Table 7.4).

Table 7.3 Clinical features of trigeminal autonomic cephalgias

[NB1] [NB2] [NB3]

- cluster headache
- paroxysmal hemicrania
- short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
- hemicrania continua

cluster headache	
sex distribution	males more than females
pain	stabbing, boring
frequency of attacks	0.5 to 8 daily
duration of attack	15 to 180 minutes
cutaneous trigger	no
alcohol trigger	yes
indomethacin effect [NB4]	–
paroxysmal hemicrania	
sex distribution	females and males equal
pain	throbbing, stabbing, boring

frequency of attacks	1 to 40 daily
duration of attack	2 to 30 minutes
cutaneous trigger	no
alcohol trigger	no
indomethacin effect [NB4]	absolute response to therapeutic trial
short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)	
sex distribution	females and males approximately equal
pain	burning, stabbing, sharp
frequency of attacks	3 to 200 daily
duration of attack	5 to 240 seconds
cutaneous trigger	yes
alcohol trigger	no
indomethacin effect [NB4]	–
hemicrania continua	
sex distribution	females more than males
pain	may vary in intensity
frequency of attacks	persist for more than 3 months
duration of attack	–
cutaneous trigger	no
alcohol trigger	no
indomethacin effect [NB4]	absolute response to therapeutic trial

NB1: For trigeminal neuralgia, see Table 7.4.

NB2: Strictly unilateral, 'side-locked' headaches (always affect the same side of the head [ie do not change sides between attacks, and do not change sides during an attack]) that typically affect the first division of the trigeminal nerve (see additional clinical features in Table 7.2).

NB3: See treatment for cluster headache, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing, and paroxysmal hemicrania and hemicrania continua.

NB4: A 100% response to a therapeutic trial of indomethacin is one of the diagnostic criteria for paroxysmal hemicrania and hemicrania continua. See indomethacin dosage.

Table 7.4 Facial pain types

Facial pain type	Pain characteristics
rhinosinusitis (acute or chronic)	Frontal, maxillary or periorbital pressure or throbbing pain. Sinuses tender to palpate. Patient may have a sense of blockage and a nasal or postnasal discharge. Pain worse when bending forward.
trigeminal neuralgia	Recurrent, unilateral, shock-like pain in one or more divisions of the trigeminal nerve (especially V2 and V3). Can be triggered by simple stimuli (eg touch [eating, brushing teeth, speaking, shaving] or exposure to cold winds). Attacks last seconds to minutes, and are typically followed by a brief refractory period. May be associated with moderate persistent background pain. Often affects people (mainly women) aged 40 to 70 years. See advice on imaging and treatment. May be associated with neurovascular compression or multiple sclerosis plaque.
glossopharyngeal neuralgia	Severe, transient, unilateral stabbing pain in the distribution of the ninth cranial nerve (eg ear, base of tongue, tonsillar fossa, below the angle of the jaw). Provoked by swallowing (particularly cold liquids), talking, coughing, chewing or yawning. Onset usually after 60 years of age. Two percent of patients lose consciousness in association with pain paroxysm, probably due to cardiac arrhythmia. See advice on treatment.

Facial pain type	Pain characteristics
greater occipital neuralgia	Shooting or stabbing pain over the occipital region (over the territory of the greater and lesser occipital nerve), typically unilateral. Pain may radiate to the ipsilateral fronto-orbital region. Pressure over the site of the nerve often evokes the pain. May be allodynia or dysaesthesia over the posterior scalp. See advice on treatment.
postherpetic trigeminal neuropathy	Unilateral head or facial pain that persists or recurs for at least 3 months in the distribution of one or more branches of the trigeminal nerve. Variable sensory changes and a history of acute varicella zoster virus reactivation in the affected region.
facial pain:	–
eye and facial pain/headache	Localised to the orbit or associated with eye signs (see causes).
dental pain	Usually localised to the dental area or face, can rarely cause more generalised headache. May be due to infection or traumatic irritation around a tooth. See advice on treatment.
temporomandibular joint (TMJ) dysfunction	Pain associated with pathology of TMJ or chewing muscles. Aggravated by active and passive jaw movements or pressure over affected structures. See advice on treatment.
atypical (persistent idiopathic) facial pain	Persistent poorly localised facial and/or oral pain that recurs daily for more than 2 hours over more than 3 months. Pain is dull, aching or nagging (can have sharp exacerbations), and does not follow the distribution of a peripheral nerve. May start after insignificant trauma or minor surgery, but persists after healing. No clinical neurological deficit or dental pathology. Distribution can increase over time. See advice on treatment.

Note 1: Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders 3rd edition (Beta version) [website]. London: International Headache Society; 2013.

References

Key references: Headache and facial pain classification and diagnosis

- Headache Classification Committee of the International Headache Society. The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33(9):629–808. https://www.ncbi.nlm.nih.gov/pubmed/23771276
- Hutton E, Stark R. Unusual primary headaches: keys to an accurate diagnosis. MedicineToday 2013;14(10):38–44. http://medicinetoday.com.au/2013/october/feature-article/unusual-primary-headaches-keys-accurate-diagnosis

Published November 2017 (Amended March 2021)

[X] Close

Symptomatic treatment of acute vertigo

Symptomatic treatment of acute vertigo

Only use symptomatic treatment for acute vertigo for a short time, while nausea is a problem (usually up to 48 hours). To treat the symptoms of acute vertigo due to vestibular neuritis or other vestibular disorders (eg Ménière disease, vestibular migraine), first-line therapy is prochlorperazine or promethazine.

If the patient has nausea but is not vomiting, use:

1 prochlorperazine 5 to 10 mg orally, 6- to 8-hourly for up to 2 days *vertigo, acute*

OR

1 promethazine 25 to 50 mg orally, 8- to 12-hourly for up to 2 days (maximum daily dose 100 mg). *vertigo, acute*

If the patient has nausea but is not vomiting, and prochlorperazine or promethazine is not effective or tolerated, use:

1 diazepam 5 mg orally, 3 times daily for up to 2 days *vertigo, acute*

OR

1 ondansetron 4 to 8 mg orally, 2 to 3 times daily for up to 2 days [Note 1]. *vertigo, acute*

If the patient is vomiting, use:

1 prochlorperazine 12.5 mg intramuscularly, immediately, followed in 6 hours by 5 to 10 mg orally, as a single dose if needed

OR

1 promethazine 10 to 25 mg intramuscularly or by slow intravenous infusion, then 10 to 25 mg orally or intramuscularly or by slow intravenous infusion, 8- to 12-hourly

OR

2 ondansetron 4 to 8 mg intramuscularly or by slow intravenous injection, 8- to 12-hourly.

Do not use prolonged treatment for the symptoms of vertigo, because of the risk of neurological adverse effects.

Do not continue symptomatic treatment of chronic dizziness or vertigo with these drugs long term, because of the risk of tardive dyskinesia, drug-induced parkinsonism or dependence.

Note 1: Ondansetron is available orally as tablets to swallow, or disintegrating tablets or wafers to dissolve on the tongue.

Published November 2017

[X] Close

Vestibular neuritis

Vestibular neuritis

Vestibular neuritis (vestibular neuronitis) is an acute vestibular syndrome that is a common cause of severe spontaneous vertigo (see Figure 7.11 for the differential diagnosis of vertigo). Evidence suggests that many cases are due to herpes simplex type 1 reactivation. Diagnosis is based on:

- a history of acute or subacute onset of severe rotatory vertigo, nausea and postural imbalance, without hearing loss
- the finding of a unidirectional mixed horizontal and torsional nystagmus and a positive head impulse test, without other neurological signs.

Vertigo due to vestibular neuritis is usually self-limiting, improving over hours to days, even without recovery of function in the affected ear. However, clinical recovery is incomplete in up to 30% of cases (see uncompensated peripheral vestibular lesion). If the patient has nausea or vomiting, treat as described. A corticosteroid may hasten clinical recovery, but the effect on long-term outcomes is not clear. In severe cases, use:

prednis(ol)one 1 mg/kg (up to 75 mg) orally, daily in the morning for 5 days, then taper dose over 15 days and stop. *vestibular neuritis, severe* _

Adding antiviral therapy has no benefit.

Key references: Vestibular neuritis

Key references: Vestibular neuritis

- Okinaka Y, Sekitani T, Okazaki H, Miura M, Tahara T. Progress of caloric response of vestibular neuronitis. Acta Otolaryngol Suppl 1993;503:18–22. https://www.ncbi.nlm.nih.gov/pubmed/8470487

Published November 2017

[X] Close

Stroke and vertigo

Stroke and vertigo

Stroke that involves the vertebrobasilar circulation can cause spontaneous vertigo (see Figure 7.11 for the differential diagnosis of vertigo). It is an important differential diagnosis in acute vestibular syndrome, particularly in patients with vascular risk factors. Refer the patient to hospital for immediate neurological assessment when they have:

- a history of other neurological symptoms besides vertigo
- features on clinical examination that suggest a central cause for the vertigo (see Table 7.12).

Neurological findings may not be obvious in small strokes involving the vertebrobasilar circulation—the HINTS+ clinical assessment is more accurate than early magnetic resonance imaging. HINTS+ is an acronym for 'Head Impulse, Nystagmus, Test of Skew plus hearing loss'. See Table 7.13 for the HINTS+ test results that are helpful when trying to differentiate stroke from peripheral causes of vertigo. Computed tomography scans are not sensitive for diagnosing posterior circulation stroke.

Table 7.13 HINTS+ test results for differentiating peripheral and central causes of vertigo

[NB1] [NB2]

Test	Peripheral cause of vertigo	Central cause of vertigo
head impulse	+	–
nystagmus type	unidirectional	direction-changing
test of skew (ie skew deviation)	–	+
new hearing loss [NB3]	–	+

NB1: HINTS+ is an acronym for 'Head Impulse, Nystagmus, Test of Skew plus hearing loss'. For further information, see Newman-Toker DE, Kerber KA, Hsieh YH, Pula JH, Omron R, Saber Tehrani AS, et al. HINTS outperforms ABCD2 to screen for stroke in acute continuous vertigo and dizziness. Acad Emerg Med 2013;20(10):986-96 [URL]

NB2: Each test is not 100% specific for a peripheral or central cause.

NB3: Hearing loss is a common feature of peripheral disorders in patients with episodic vertigo. However, sudden hearing loss in acute vestibular syndrome can be a sign of an anterior inferior cerebellar infarct, due to involvement of the internal auditory artery. Hearing loss is not typical of vestibular neuritis.

Key references: Stroke and vertigo

Key references: Stroke and vertigo

- Newman-Toker DE, Kerber KA, Hsieh YH, Pula JH, Omron R, Tehrani AS, et al. HINTS outperforms ABCD2 to screen for stroke in acute continuous vertigo and dizziness. Acad Emerg Med 2013;20(10):986–96. https://www.ncbi.nlm.nih.gov/pubmed/24127701

Published November 2017

[X] Close

Ménière disease

Ménière disease

Ménière disease (idiopathic endolymphatic hydrops) causes episodic spontaneous vertigo (see Figure 7.11 for the differential diagnosis of vertigo). It is an inner ear condition characterised by a distended endolymph compartment. Vertigo is accompanied by tinnitus, aural fullness and progressive or fluctuating hearing loss. The cause is not known, but theories include abnormal endolymph drainage and immune dysfunction. Endolymphatic hydrops can also be secondary to otosclerosis, trauma and long-term sensorineural hearing loss.

Symptomatic treatment for an acute attack is often needed.

Conclusive evidence that pharmacological treatment for Ménière disease reduces the frequency and severity of attacks is lacking (apart from intratympanic therapy, which is expert care). Betahistine has been widely used, but a randomised controlled trial in 2016 failed to show a benefit [Note 1].

One aim of treatment is to lower endolymphatic pressure by reducing the sodium and water content of the endolymph. This may control the vertigo, but the tinnitus and hearing loss are generally less responsive. Advise the patient to restrict salt intake to no more than 3 g daily and to avoid caffeine. For prophylaxis, a thiazide diuretic may be tried as monotherapy or in combination with a potassium-sparing diuretic (eg amiloride, triamterene). Use:

1 hydrochlorothiazide 25 mg orally, once daily. Increase if needed up to 50 mg daily *Meniere disease*

OR

1 hydrochlorothiazide+amiloride 50+5 mg orally, once daily *Meniere disease*

OR

1 hydrochlorothiazide+triamterene 25+50 mg orally, once daily. Increase if needed up to 50+100 mg daily. *Meniere disease*

Refer for expert advice when diuretic therapy is ineffective. Intratympanic injections of gentamicin or a corticosteroid are often effective, but occasionally surgery (eg endolymphatic sac decompression, vestibular nerve section) is needed to control symptoms.

Note 1: Adrion C, Fischer CS, Wagner J, Gurkov R, Mansmann U, Strupp M, et al. Efficacy and safety of betahistine treatment in patients with Meniere's disease: primary results of a long term, multicentre, double blind, randomised, placebo controlled, dose defining trial (BEMED trial). BMJ 2016;352:h6816. [URL]

Key references: Ménière disease

Key references: Ménière disease

- Adrion C, Fischer CS, Wagner J, Gurkov R, Mansmann U, Strupp M, et al. Efficacy and safety of betahistine treatment in patients with Meniere's disease: primary results of a long term, multicentre, double blind, randomised, placebo controlled, dose defining trial (BEMED trial). BMJ 2016;352:h6816. https://www.ncbi.nlm.nih.gov/pubmed/26797774

- Syed MI, Ilan O, Nassar J, Rutka JA. Intratympanic therapy in Meniere's syndrome or disease: up to date evidence for clinical practice. Clin Otolaryngol 2015;40(6):682–90. https://www.ncbi.nlm.nih.gov/pubmed/25916787

Published November 2017

[X] Close

Diagnosing benign paroxysmal positional vertigo

Diagnosing benign paroxysmal positional vertigo

Benign paroxysmal positional vertigo (BPPV) is due to crystalline deposits (otoconia) that are displaced from the utricle and lodge in the posterior semicircular canal. These deposits cause excessive deflection of the sensory organ (cupula) when the head moves in certain directions. Most often BPPV has no obvious trigger, but it can be a complication of head trauma or other conditions that damage the labyrinth (eg vestibular neuritis, Ménière disease). Suspect BPPV when vertigo is triggered by head movement in the vertical (or pitch) plane (eg head extension, lying down) or when rolling over in bed (see Figure 7.11 for the differential diagnosis of vertigo). The diagnosis is confirmed when a Hallpike manoeuvre induces positional nystagmus.

Uncommon variants of BPPV affect the horizontal and anterior canals (causing prominent horizontal and downbeating nystagmus, respectively). Refer for expert advice, as these atypical forms of positional nystagmus can also be due to neurological disorders (eg cerebellar disease).

Hallpike manoeuvre

Hallpike manoeuvre

To perform the Hallpike manoeuvre, follow steps 1 to 4 of the Epley manoeuvre (see Figure 7.13). Tell the patient to keep their eyes open—a mixed torsional (upper pole of the eye beating towards the ground) and upbeating nystagmus is typical of a positive test, but may not start for a few seconds. The nystagmus fades and resolves over 30 seconds. Sometimes the nystagmus may recur when the patient sits up, but reverses direction. If the test is negative, repeat it with the head turned to the other side. The symptomatic ear is the lower ear on the side of the positive Hallpike manoeuvre.

If the patient has difficulty bending their neck back (due to stiffness or kyphosis), perform the Hallpike manoeuvre with the patient lying on their side (use steps 1 to 3 of the Semont manoeuvre in Figure 7.14).

Treating benign paroxysmal positional vertigo

Treating benign paroxysmal positional vertigo

Drugs may relieve the nausea and vomiting associated with benign paroxysmal positional vertigo (BPPV) (see symptomatic treatment of acute vertigo), but do little for the vertigo. The vertigo is treated with particle repositioning manoeuvres (Epley manoeuvre, Semont manoeuvre) or exercise therapy (Brandt-Daroff exercises). These treatments displace the otoconia from the posterior semicircular canal into the utricular cavity. The Epley and Semont manoeuvres are equally effective. However, the Semont manoeuvre is usually easier to perform on patients with limited neck movement or a prominent cervical kyphosis.

If the original nystagmus is reproduced in the final head position of the manoeuvre, this usually means the treatment has been effective. If the nystagmus reverses direction in the final head position, this means that the otoconia may have fallen back into the posterior canal. If one particle repositioning manoeuvre (ie Epley or Semont) is not effective at the first visit, then at the next visit repeat it or try the other manoeuvre.

Avoid performing another Hallpike manoeuvre within 15 minutes of a particle repositioning manoeuvre (sometimes done to assess the response to treatment)—this is because of the risk of displacing the otoconia into the horizontal canal, causing horizontal canal BPPV. If the particle repositioning manoeuvre appears to be a success, the repeat Hallpike manoeuvre can be deferred to the next visit.

Clinicians who are not familiar with the Epley and Semont manoeuvres can prescribe the Brandt-Daroff exercises (performed at home). Alternatively, they can refer the patient to a physiotherapist with expertise in vestibular rehabilitation therapy.

Symptoms recur in 20 to 30% of cases. If so, teach the patient to perform the Epley or Semont manoeuvre at home, or advise them to continue the Brandt-Daroff exercises (the manoeuvres and exercises can be printed as patient handouts). Refer refractory cases for expert assessment.

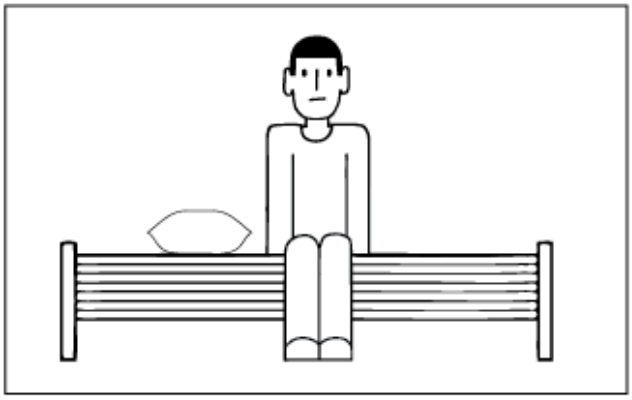
Epley manoeuvre

Epley manoeuvre

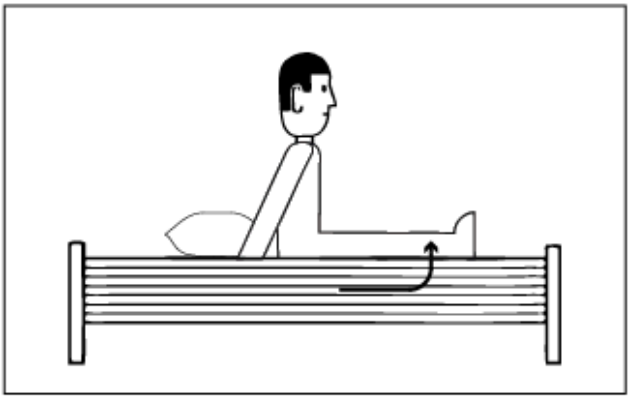
See printable instructions for using the Epley manoeuvre to treat right-sided and left sided benign paroxysmal positional vertigo (BPPV). Also see printable instructions for patients with right-sided or left-sided BPPV to perform the manoeuvre at home.

Figure 7.13 Epley manoeuvre for treating right-sided benign paroxysmal positional vertigo (BPPV)

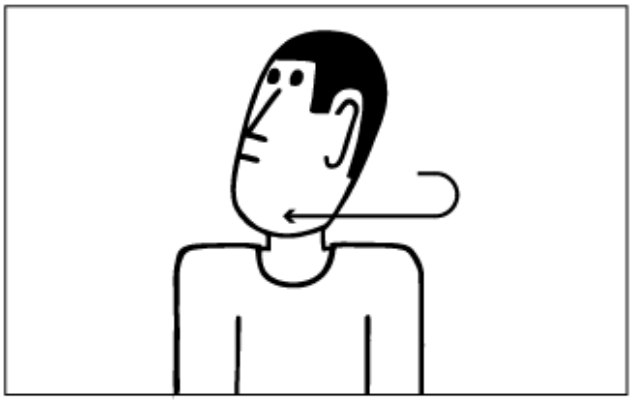
[NB1] [NB2]



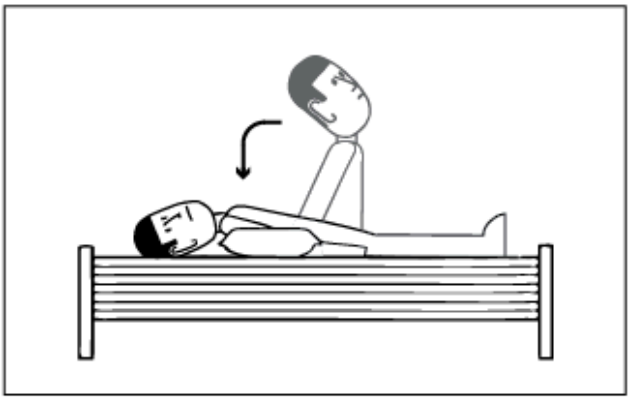
1. Put a pillow a quarter of the way down the examination couch. Ask patient to sit in the middle of the couch.



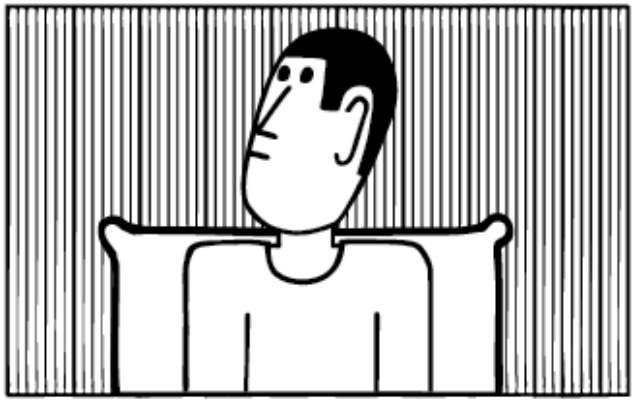
2. Swing patient's legs onto the couch so they are straight out in front.



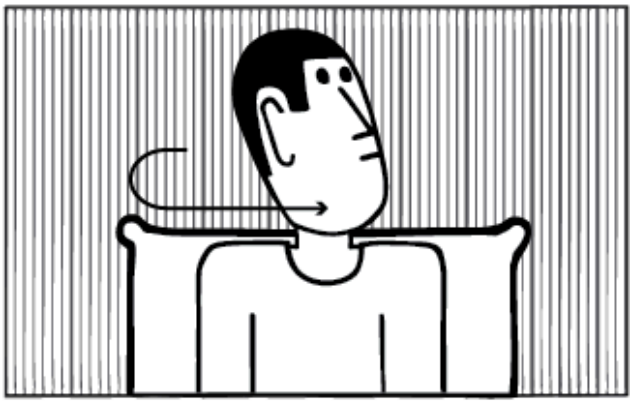
3. Ask patient to look up and tip the head back slightly, then turn the head 45 degrees to the right.



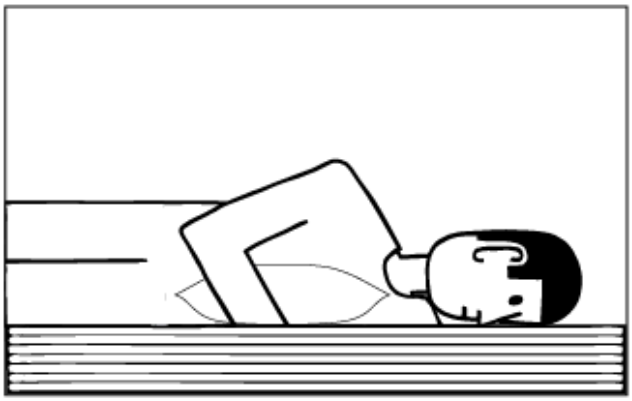
4. Keep head in this position and lie patient down with head over top edge of pillow—pillow is at shoulder level and head is about 30 degrees below the horizontal.



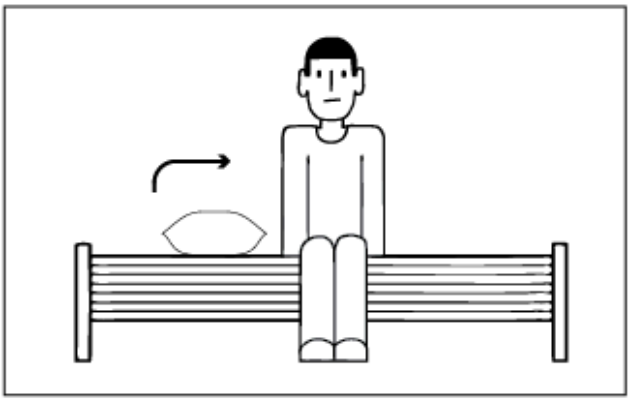
5. Wait in this position for 1 minute.



6. Turn head 90 degrees to left.
Wait in this position for 1 minute.



7. Turn head a further 90 degrees to left, while telling patient to roll onto left side. Wait in this position for 1 minute.



8. Sit patient up slowly. Tell patient not to lie down flat again until bedtime. Warn them that they may have mild nausea or dizziness or feel unsteady for several hours after a successful treatment.

NB1: To treat left-sided BPPV, perform the manoeuvre in the opposite direction.

NB2: Steps 1 to 4 are the same as a Hallpike manoeuvre.

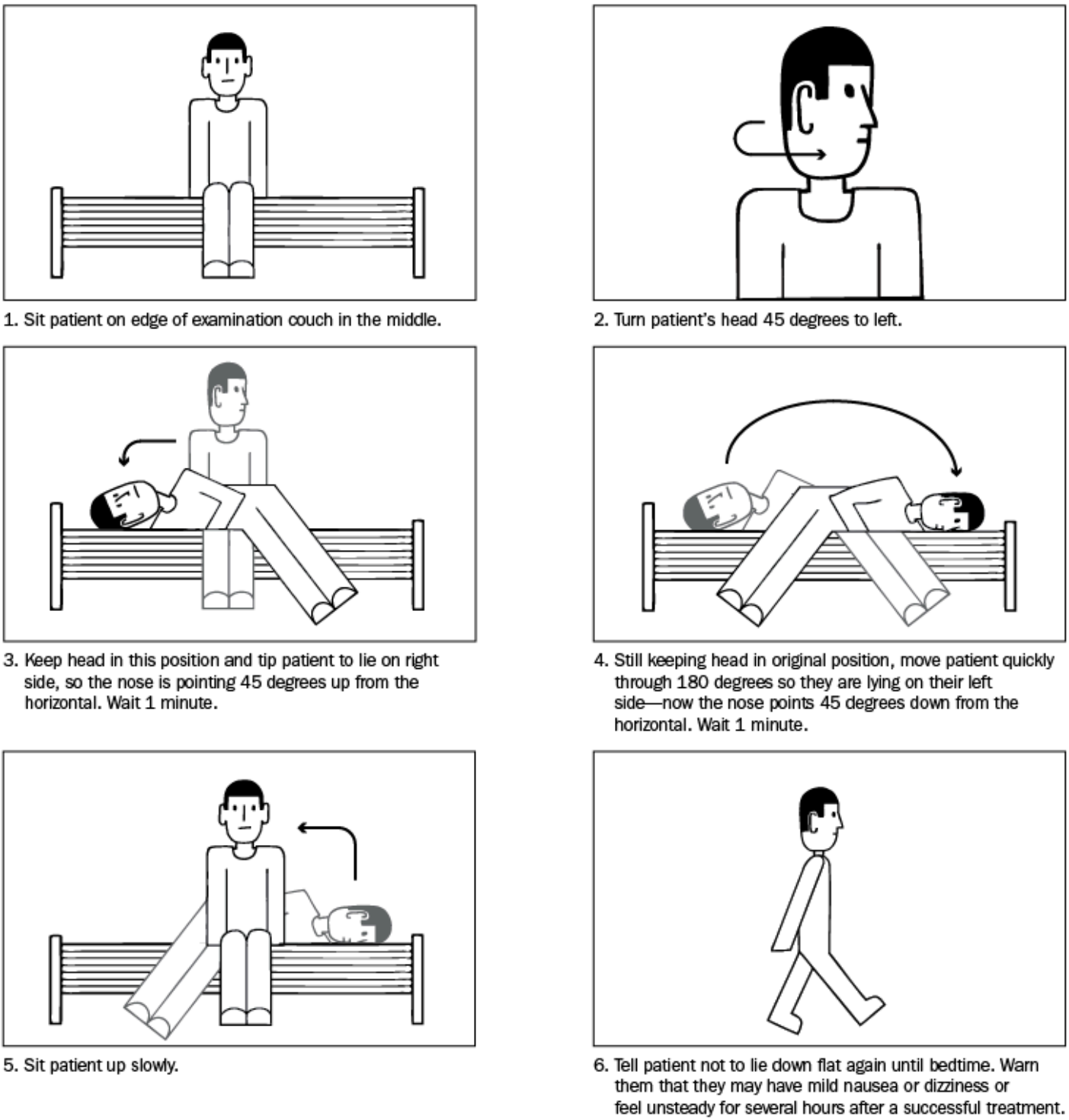
Semont manoeuvre

Semont manoeuvre

See printable instructions for using the Semont manoeuvre to treat right-sided and left-sided benign paroxysmal positional vertigo (BPPV). Also see printable instructions for patients with right-sided or left-sided BPPV to perform the manoeuvre at home.

Figure 7.14 Semont manoeuvre for treating right-sided benign paroxysmal positional vertigo (BPPV)

[NB1]



NB1: To treat left-sided BPPV, perform the manoeuvre in the opposite direction.

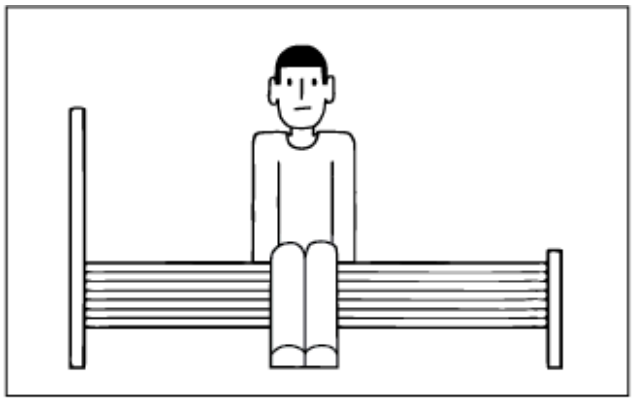
Brandt-Daroff exercises

Brandt-Daroff exercises

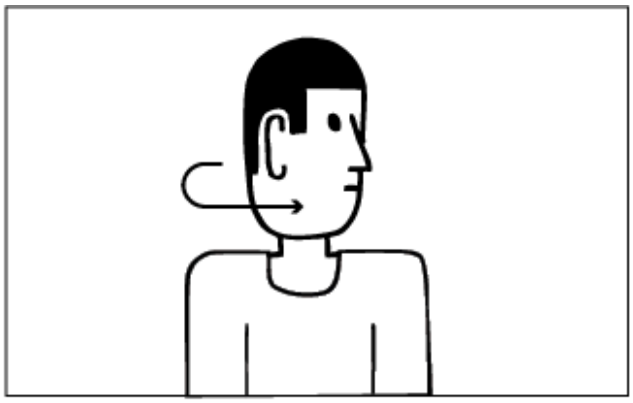
The Brandt-Daroff exercises can be printed as a patient handout.

Figure 7.15 Brandt-Daroff exercises for treating benign paroxysmal positional vertigo (BPPV)

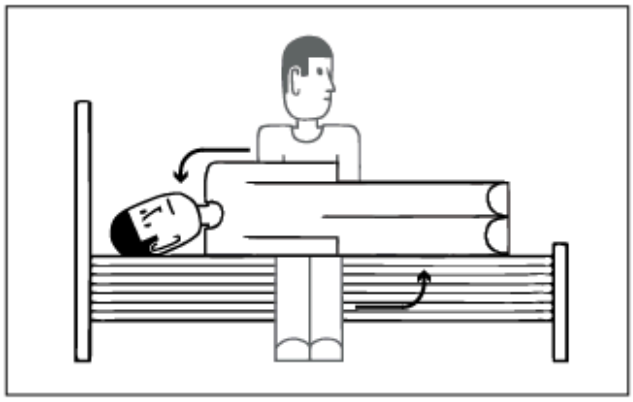
Benign paroxysmal positional vertigo (BPPV) is caused by crystals collecting in one of the fluid-filled balance canals of the inner ear. These exercises are designed to flush the crystals out of the canal—if you do them regularly, the dizziness usually goes away after a few days. The exercises need to make you feel dizzy if they're going to work. If you were prescribed drugs for nausea, do not use them for more than 2 days.



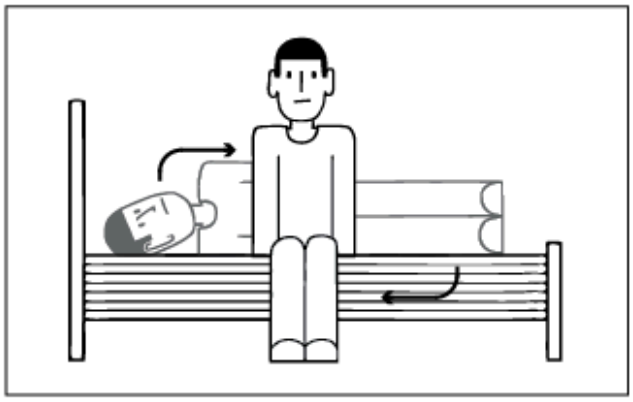
1. Take the pillows off the bed.
   Sit on the edge of the bed, in the middle.



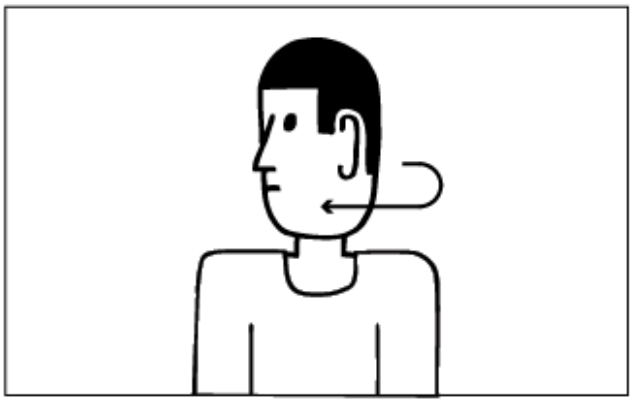
2. Turn your head 45 degrees to the left.



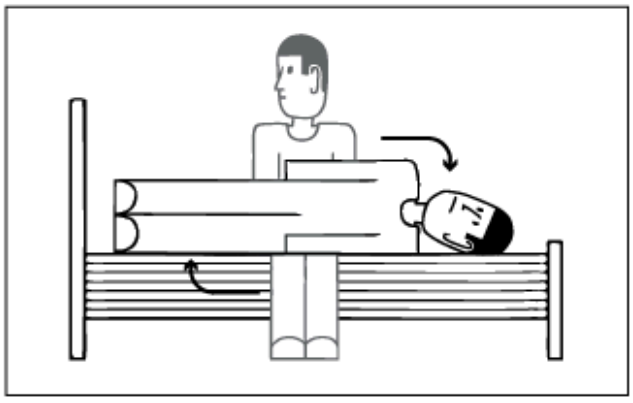
3. Keeping your head in this position, lie down quickly on your right side so the back of your head is resting on the bed. If you're dizzy, wait for this to go away. If you're not dizzy, wait 20 to 30 seconds.



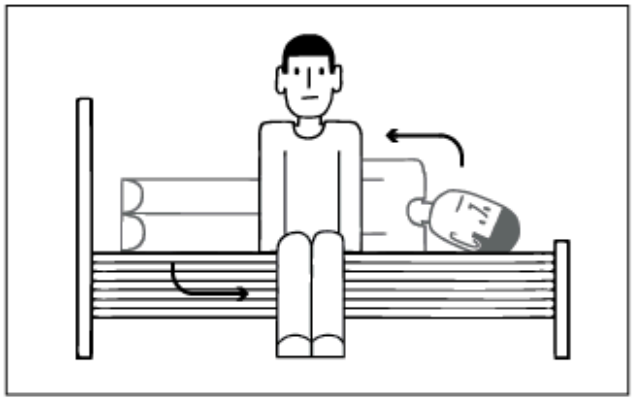
4. Sit up straight. If you're dizzy, wait for this to go away. If you're not dizzy, wait 20 to 30 seconds.



5. Turn your head 45 degrees to the right.



6. Keeping your head in this position, lie down quickly on your left side so the back of your head is resting on the bed. If you're dizzy, wait for this to go away. If you're not dizzy, wait 20 to 30 seconds.



7. Sit up straight. If you're dizzy, wait for this to go away. If you're not dizzy, wait 20 to 30 seconds.

Repeat the exercises for 10 minutes. Do the exercises at least 5 times on each side. If you can, do the exercises 3 times a day (in the morning, early afternoon and at night).

Key references: Benign paroxysmal positional vertigo

Key references: Benign paroxysmal positional vertigo

- Foster CA, Zaccaro K, Strong D. Canal conversion and reentry: a risk of Dix-Hallpike during canalith repositioning procedures. Otol Neurotol 2012;33(2):199–203. https://www.ncbi.nlm.nih.gov/pubmed/22143303

Published November 2017

[X] Close

Motion sickness

Motion sickness

Motion sickness is an autonomic syndrome similar to that which accompanies vertigo, the difference being that motion is the trigger. The vestibular system has many cholinergic and histaminergic receptors, so anticholinergic and antihistamine drugs are first choice for prophylaxis of motion sickness. These drugs are effective in most patients, but can be sedating and impair performance. Hyoscine is less sedating than an antihistamine but is more likely to have anticholinergic adverse effects. Motion sickness is more common in patients with vestibular migraine, and migraine prophylaxis is often effective in these patients.

It is best to take an anticholinergic or antihistamine drug before travel, as these drugs are more effective at preventing motion sickness than treating it.

For an adult, use:

1 cyclizine 50 mg orally, 1 to 2 hours before travel. Repeat 6- to 8-hourly if needed, up to 150 mg in 24 hours *motion sickness*

OR

1 dimenhydrinate+hyoscine hydrobromide+caffeine tablets 50+0.2+20 mg, 1 to 2 tablets orally, 30 minutes before travel. Repeat 4- to 6-hourly if needed, up to 4 tablets in 24 hours *motion sickness*

OR

1 hyoscine hydrobromide 300 to 600 micrograms orally, 30 minutes before travel. Repeat 4- to 6-hourly if needed, up to 1200 micrograms in 24 hours *motion sickness*

OR

1 promethazine 25 mg orally, 1 to 2 hours before travel. Repeat 6- to 8-hourly if needed, up to 100 mg in 24 hours. *motion sickness*

For a child, use:

1 dimenhydrinate+hyoscine hydrobromide+caffeine tablets 50+0.2+20 mg (child 4 to 7 years: quarter to half tablet; 8 to 13 years: half to 1 tablet) orally, 30 minutes before travel. Repeat 6- to 8-hourly if needed, up to 3 doses in 24 hours. Do not use in children younger than 4 years

OR

1 hyoscine hydrobromide (child 2 to 7 years: 75 micrograms; 8 to 12 years: 150 to 300 micrograms) orally, 30 minutes before travel. Repeat 6-hourly if needed (child 2 to 7 years: up to 300 micrograms in 24 hours; 8 to 12 years: up to 600 micrograms in 24 hours). Do not use in children younger than 2 years

OR

1 promethazine (child 2 to 5 years: 5 mg; 6 to 12 years: 10 mg) orally, 1 to 2 hours before travel. Repeat 6- to 8-hourly if needed, up to 3 doses in 24 hours. Do not use in children younger than 2 years.

Key references: Motion sickness

Key references: Motion sickness

- Brand JJ, Colquhoun WP, Gould AH, Perry WL. (—)-Hyoscine and cyclizine as motion sickness remedies. Br J Pharmacol Chemother 1967;30(3):463–9. https://www.ncbi.nlm.nih.gov/pubmed/4860708
- Murdin L, Golding J, Bronstein A. Managing motion sickness. BMJ 2011;343:d7430. https://www.ncbi.nlm.nih.gov/pubmed/22138695

Published November 2017

[X] Close

Approach to treatment for migraine

Approach to treatment for migraine

Regular habits, lifestyle measures, physiotherapy and complementary therapies can help patients who have migraines (see advice).

Start treatment for migraine at the onset of symptoms. Acute treatment does not appear to reduce aura symptoms. Nonpharmacological measures can give some relief.

The main drug groups for acute treatment for migraine are nonopioid analgesics and triptans. Try a nonopioid analgesic first. Choice of drug depends on efficacy, tolerability and other factors (eg nausea). Naproxen and naratriptan may be slower to take effect, but have a longer duration of action, which may be helpful in rebound headaches. Avoid opioid analgesics, as they should only be used when other drugs are not tolerated or are contraindicated—if needed, refer for expert advice.

Limit nonopioid analgesic use to less than 15 days per month, and limit triptan use (or drugs that contain opioid analgesics) to less than 10 days per month. If used more often, the patient is at risk of medication overuse headache.

If a patient needs treatment for acute migraine on more than 2 to 4 days per month, consider migraine prophylaxis.

Beneficial habits, physiotherapy and complementary therapies for migraine

Beneficial habits, physiotherapy and complementary therapies for migraine

Based on extensive clinical experience, expert opinion is that nondrug therapy is a key component of migraine management.

People with migraine need to keep regular habits, as change can trigger attacks. Anecdotally, beneficial habits include:

- regular sleep schedules (see advice on good sleep practices)
- minimal variation in blood glucose concentrations (eg eating regular meals, avoiding excess simple carbohydrates)
- adequate hydration (eg drinking 1.5 to 2 litres water daily)
- limited caffeinated beverages (1 to 2 cups daily)
- regular exercise (aiming for 30 to 40 minutes, 3 to 4 times a week; walking is a good option, as exercise that involves jumping or running often provokes migraine in people who have them regularly)
- good workplace ergonomics (especially when using a computer) and regular short breaks (to stretch and to rest eyes)
- regular use of a relaxation technique (eg meditation, mindfulness, yoga, breathing techniques, progressive muscular relaxation), especially if stress is a trigger (biofeedback and cognitive behavioural therapy may help)
- avoidance of patient's known triggers (eg alcohol, monosodium glutamate, citrus fruit, chocolate, preserved meats, perfume).

This list can be printed as a patient information sheet.

If a patient has postural problems and neck muscle tightness or limited range of motion, refer to a physiotherapist.

Although supporting evidence is not strong, a three-month trial of magnesium, riboflavin or ubidecarenone (coenzyme Q10) may be tried, because the risk of harm is low. If a supplement is considered appropriate, in an adult, try:

1 magnesium (elemental) 400 to 650 mg orally, once daily for 3 months, then review *migraine (adult)*

OR

1 riboflavin 200 mg orally, twice daily for 3 months, then review [Note 1] *migraine (adult)*

OR

1 ubidecarenone 150 to 300 mg orally, once daily for 3 months, then review. *migraine (adult)*

These supplements can be tried in combination.

A 2016 systematic review [Note 2] supports a trial of acupuncture in some patients.

Note 1: Use a single ingredient product that only contains riboflavin. Do not use a multivitamin or vitamin B complex tablet.

Note 2: Linde K, Allais G, Brinkhaus B, Fei Y, Mehring M, Vertosick EA, et al. Acupuncture for the prevention of episodic migraine. Cochrane Database Syst Rev 2016;(6):CD001218. [URL]

Acute nonpharmacological treatment for migraine

Acute nonpharmacological treatment for migraine

Nonpharmacological treatment that can help migraine includes:

- cold packs over the forehead or back of the skull (targeting the supraorbital and greater occipital nerves)
- hot packs over the neck and shoulders (targeting the innervation of the scalp)
- neck stretches and self-mobilisation
- rest in a quiet dark room.

Acute treatment for migraine with nonopioid analgesics and antiemetics

Acute treatment for migraine with nonopioid analgesics and antiemetics

See separate advice for a child.

As initial treatment for acute migraine, try a nonopioid analgesic. In adults, use:

1 aspirin soluble 900 to 1000 mg orally. Wait 4 to 6 hours before repeating dose if needed (maximum dose 4 g in 24 hours) *migraine (adult)*

OR

1 ibuprofen 400 to 600 mg orally. Wait 4 to 6 hours before repeating dose if needed (maximum dose 2.4 g in 24 hours) *migraine (adult)*

OR

2 diclofenac potassium 50 mg orally. Wait 4 to 6 hours before repeating dose if needed (maximum dose 200 mg in 24 hours) [Note 3] *migraine (adult)*

OR

2 naproxen 500 to 750 mg orally. Wait 4 to 6 hours before repeating dose if needed (maximum dose 1250 mg in 24 hours) *migraine (adult)*

OR

2 paracetamol soluble 1 g orally. Wait 4 to 6 hours before repeating dose if needed (maximum dose 4 g in 24 hours). *migraine (adult)*

When the response to a nonopioid analgesic is suboptimal, consider adding an antiemetic (especially metoclopramide)—the antiemetic can improve treatment response by increasing drug absorption. In general, trial one nonopioid analgesic for a couple of migraine attacks. If this is not effective, change to a different nonopioid analgesic (eg from aspirin to ibuprofen) or a triptan.

Limit nonopioid analgesic use to less than 15 days per month. If used more often, the patient is at risk of medication overuse headache.

Avoid opioid analgesics, as they should only be used when other drugs are not tolerated or are contraindicated—if needed, refer for expert advice.

If the patient has nausea, give an oral antiemetic with the acute migraine treatment. Use:

1 metoclopramide 10 mg orally. If nausea persists, give up to 2 more doses (maximum daily dose 30 mg) *nausea due to migraine (adult)*

OR

2 domperidone 10 to 20 mg orally. If nausea persists, give up to 2 more doses (maximum daily dose 30 mg) [Note 4] *nausea due to migraine (adult)*

OR

2 ondansetron 4 to 8 mg orally. If nausea persists, give up to 2 more doses (maximum daily dose 16 mg) [Note 5] *nausea due to migraine (adult)*

OR

2 prochlorperazine 5 to 10 mg orally. If nausea persists, give up to 2 more doses (maximum daily dose 30 mg). *nausea due to migraine (adult)*

If a patient needs treatment for acute migraine on more than 2 to 4 days per month, consider migraine prophylaxis.

Note 3: If the patient has nausea, diclofenac is available as a rectal preparation.

Note 4: Evidence shows an increased risk of serious cardiac adverse effects (ventricular arrhythmias, sudden cardiac death) from domperidone at doses over 30 mg daily and in patients older than 60 years. For more information, see the Therapeutic Goods Administration (TGA) Medicines Safety Update.

Note 5: Ondansetron is available orally as tablets to swallow, or disintegrating tablets or wafers to dissolve on the tongue.

Acute treatment for migraine with a triptan

Acute treatment for migraine with a triptan

See separate advice for a child.

When a nonopioid analgesic (with or without an antiemetic) does not relieve the patient's migraine, prescribe a triptan for them to take the next time they have a migraine.

Choice of triptan depends on several factors, and is usually refined after the patient uses a triptan for the first time. If a patient has adverse effects from the first triptan, try naratriptan or eletriptan (at the lower dose of 40 mg)—sometimes these are better tolerated, but may also have a milder acute effect. If rebound headache after effective triptan treatment is a problem, naratriptan may be preferred because of its slower onset and offset. If the patient has severe early nausea, a tablet that dissolves on the tongue (eg rizatriptan) or a nonoral preparation (eg nasal or injectable sumatriptan) may be helpful.

Do not give ergotamines for 24 hours before or after a triptan.

Some patients respond better to a combination of a triptan and a nonopioid analgesic (eg aspirin, ibuprofen, naproxen).

In adults, use:

1 eletriptan 40 to 80 mg orally. If symptoms recur, wait at least 2 hours before repeating the dose (maximum dose 160 mg in 24 hours) *migraine (adult)*

OR

1 naratriptan 2.5 mg orally. If symptoms recur, wait at least 4 hours before repeating the dose (maximum dose 5 mg in 24 hours) *migraine (adult)*

OR

1 rizatriptan 10 mg orally. If symptoms recur, wait at least 2 hours before repeating the dose (maximum dose 30 mg in 24 hours) *migraine (adult)*

OR

1 sumatriptan 20 mg intranasally. If symptoms recur, wait at least 2 hours before repeating the dose (maximum dose 40 mg in 24 hours) *migraine (adult)*

OR

1 sumatriptan 50 to 100 mg orally. If symptoms recur, wait at least 2 hours before repeating the dose (maximum dose 300 mg in 24 hours)

OR

1 zolmitriptan 2.5 mg orally. If symptoms recur, wait at least 2 hours before repeating the dose (maximum dose 10 mg in 24 hours). If 2.5 mg tolerated but not effective in previous migraine, give 5 mg at onset of next migraine *migraine (adult)*

OR

2 sumatriptan 6 mg subcutaneously. If symptoms recur, wait at least 1 hour before repeating the dose (maximum dose 12 mg in 24 hours).

If there is no response to the first dose of triptan, do not give a second dose for the same migraine attack. The triptan can still be tried in future attacks.

Limit triptan use to less than 10 days per month. If used more often, the patient is at risk of medication overuse headache.

Patients taking a selective serotonin reuptake inhibitor (SSRI) or a serotonin and noradrenaline reuptake inhibitor (SNRI) can be prescribed a triptan. However, they must be counselled about the symptoms of serotonin toxicity (agitation, confusion, rapid heart rate, dilated pupils, muscle twitching or rigidity, sweating, diarrhoea, headache, shivering), despite its rarity.

If a patient needs treatment for acute migraine on more than 2 to 4 days per month, consider migraine prophylaxis.

Acute treatment for migraine during pregnancy

Acute treatment for migraine during pregnancy

Headache in pregnancy can be due to a range of conditions besides migraine. Differential diagnoses include pre-eclampsia, posterior reversible encephalopathy syndrome/reversible cerebral vasoconstriction syndrome, HELLP (haemolysis, elevated liver enzymes, low platelet count) syndrome, venous sinus thrombosis and pituitary apoplexy.

Migraine can get worse or improve in the first trimester, but usually improves later in pregnancy. In a quarter of females with migraine, headaches do not change in pregnancy. When managing migraine in pregnancy, it is important to ensure optimal concordance with the beneficial habits for people with migraine, to minimise the need for drugs.

During pregnancy, paracetamol is the preferred nonopioid analgesic. Avoid aspirin and NSAIDs in the first trimester and after 30 weeks. Use:

paracetamol soluble 1 g orally, wait 4 to 6 hours before repeating dose if needed (maximum dose 4 g in 24 hours). *migraine (pregnant female)*

If the patient does not respond to paracetamol, sparing use of codeine is an option [Note 6].

If the patient has nausea, metoclopramide is considered safe. In severe migraine, occasional use of sumatriptan is generally considered safe, but few data are available on other triptans.

For severe, refractory migraine, treatment options for a pregnant female include intravenous rehydration and a short course of intravenous magnesium sulfate or oral prednis(ol)one. If a corticosteroid is chosen, use:

prednis(ol)one 50 mg orally, once daily for 2 days, then stop. *migraine, refractory (pregnant female)*

Note 6: Codeine should not be used in breastfeeding women, patients known to be ultrarapid metabolisers, in children younger than 12 years, and in children 12 to 18 years who have recently had a tonsillectomy and/or adenoidectomy for obstructive sleep apnoea. For more information, see the TGA Medicines Safety Update.

Intractable migraine (status migrainosus)

Intractable migraine (status migrainosus)

Intractable migraine (status migrainosis) is defined as a migraine attack that persists for more than 72 hours. However, patients may present earlier than this because their usual drug/s for an acute attack have not been effective—other treatment (usually parenteral) may be needed to relieve the headache, and is usually provided in a hospital setting.

Rehydrate the patient and give a parenteral antiemetic if needed.

When acute migraine does not respond to first-line oral treatment and is severe, use:

1 sumatriptan 6 mg subcutaneously (only if a triptan has not been given in the last 2 hours and a parenteral triptan has not been tried) *migraine, intractable (status migrainosus)*

OR

2 ketorolac 30 mg by slow deep injection intramuscularly (only if an oral NSAID has not been given in the last 4 to 6 hours). *migraine, intractable (status migrainosus)*

If a parenteral triptan or NSAID is contraindicated or the migraine does not respond, and the patient is in hospital, the next step is chlorpromazine. Perform an electrocardiogram to exclude a prolonged QTc interval. Check the serum potassium and magnesium concentrations (see advice). If the patient is at risk of a high or low serum potassium concentration or a low serum magnesium concentration, wait for the blood test results before giving the first dose of chlorpromazine.

To avoid hypotension, pretreat with a fluid bolus (eg sodium chloride 0.9% 500 mL). Monitor blood pressure and fluid status every 30 minutes during treatment with chlorpromazine, and repeat the fluid bolus if needed. Use:

chlorpromazine 12.5 mg in sodium chloride 0.9% 100 mL intravenously over 30 minutes. If needed, repeat infusion twice, 30 minutes after preceding infusion ends (total chlorpromazine dose 37.5 mg). *migraine, intractable (status migrainosus)*

Chlorpromazine can cause an acute dystonic reaction. If so, treat with:

benzatropine 1 to 2 mg intravenously, as a single dose. *acute dystonia, due to chlorpromazine for intractable migraine*

Although chlorpromazine is more effective, a corticosteroid is an alternative. Use:

dexamethasone 12 to 20 mg intravenously. Repeat after 12 hours if needed. *migraine, intractable (status migrainosus)*

If the patient has not had a triptan in the preceding 24 hours, another option for treating intractable migraine is dihydroergotamine. Do not give a triptan for 24 hours after dihydroergotamine therapy.
Do not give a triptan for 24 hours before or after dihydroergotamine therapy.

Lidocaine is the last option, but should only be administered in a monitored inpatient setting.

While not supported by strong evidence, intravenous magnesium sulfate may be helpful, especially if the serum magnesium concentration is low (normal adult range is 0.8 to 1.0 mmol/L; see infusion advice).

Prophylaxis for migraine

Prophylaxis for migraine

Approach to prophylaxis for migraine and drugs used

Approach to prophylaxis for migraine and drugs used

See separate advice for a child. See also advice on beneficial habits, physiotherapy and complementary therapies.

Several drugs are available if a patient needs prophylaxis for frequent (more than 2 in a month) migraine. There are no direct comparisons of prophylactic drugs, nor can an individual's response to a particular drug be guaranteed. Therefore, the choice of prophylactic drug depends on the:

- adverse effects of each drug
- patient's comorbidities (see Table 7.5) and other drugs they are taking.

Table 7.5 Examples of how patient comorbidity can guide choice of drug for migraine prophylaxis

Comorbidity	Drugs to consider for migraine prophylaxis	Drugs to avoid for migraine prophylaxis
insomnia	TCA, pregabalin, gabapentin	–
anxiety, postural orthostatic tachycardia syndrome	propranolol	–
obesity, diabetes	candesartan, topiramate	sodium valproate [NB1], pizotifen
fibromyalgia	TCA, pregabalin	–
neck muscular tension, bruxism	TCA	–
asthma	–	beta blockers
history of renal calculi	–	topiramate
current or past history of depression	SNRI, SSRI, TCA	be cautious using topiramate, beta blockers, flunarizine
untreated or inadequately treated menopause symptoms (hot flushes)	propranolol, gabapentin, SSRI	–

SNRI = serotonin and noradrenaline reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

NB1: Avoid sodium valproate in females of childbearing potential (see teratogenic and neurodevelopmental effects of antiepileptic drugs).

Trial a prophylactic drug for migraine for at least 8 to 12 weeks to assess its efficacy. As first-line drugs in adults, use:

1 amitriptyline 10 mg orally, once daily at night. Increase daily dose by 10 mg at intervals of at least 1 week (maximum daily dose 75 mg). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy [Note 7] *migraine, prophylaxis (adult)*

OR

1 candesartan 4 mg orally, once daily. Increase daily dose by 4 mg at intervals of at least 1 week (maximum daily dose 32 mg). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy [Note 7] *migraine, prophylaxis (adult)*

OR

1 nortriptyline 10 mg orally, once daily at night. Increase daily dose by 10 mg at intervals of at least 1 week (maximum daily dose 75 mg). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy [Note 7] *migraine, prophylaxis (adult)*

OR

1 pizotifen 0.5 mg orally, once daily at night. Increase daily dose by 0.5 mg at intervals of at least 1 week (maximum daily dose 1.5 to 3 mg). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy *migraine, prophylaxis (adult)*

OR

1 propranolol 20 mg orally, once daily at night. Increase daily dose by 20 mg at intervals of at least 1 week (maximum daily dose 160 mg in 2 or 3 divided doses). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy *migraine, prophylaxis (adult)*

OR

1 sodium valproate 200 mg orally, once daily at night. Increase daily dose by 200 mg at intervals of at least 1 week (maximum dose 500 mg twice daily). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy [Note 7] [Note 8] *migraine, prophylaxis (adult)*

OR

1 topiramate 25 mg orally, once daily at night. Increase daily dose by 25 mg at intervals of at least 1 week (maximum dose 100 mg twice daily). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy *migraine, prophylaxis (adult)*

OR

1 verapamil sustained-release 90 mg orally, once daily. Increase daily dose slowly over 3 weeks (maximum daily dose 240 mg). Continue at maximum tolerated dose for 8 to 12 weeks to assess efficacy [Note 7]. *migraine, prophylaxis (adult)*

Other drugs (eg gabapentin, pregabalin, venlafaxine) have less evidence to support their use in migraine prophylaxis.

If the first drug is not effective after a reasonable trial (ie maximum tolerated dose for at least 8 to 12 weeks), try another from the list of first-line drugs above.

If several drugs are given a reasonable trial and are not effective, refer for expert advice. Strict Pharmaceutical Benefits Scheme criteria apply [Note 9] before a patient is eligible for botulinum toxin type A injections in the head and neck as treatment for migraine. Other drugs that may be tried by an expert include metoprolol, atenolol, carbamazepine, clonidine, cyproheptadine, duloxetine and flunarizine [Note 10]. An external trigeminal nerve stimulation device (Cefaly) is another option for migraine prophylaxis.

Note 7: At the time of writing, this drug is not approved by the Australian Therapeutic Goods Administration (TGA) for migraine prophylaxis. See the TGA website for current information.

Note 8: Avoid sodium valproate in females of childbearing potential (see teratogenic and neurodevelopmental effects of antiepileptic drugs).

Note 9: See the Pharmaceutical Benefits Scheme website for criteria for botulinum toxin type A injections for migraine.

Note 10: Flunarizine is not registered for use in Australia but is available via the Special Access Scheme.

Prophylaxis for migraine during pregnancy

Prophylaxis for migraine during pregnancy

Ideally, a woman with frequent or severe migraine should be referred to a neurologist for expert advice before pregnancy, to optimise management and plan the approach to therapy during pregnancy.

When managing migraine in pregnancy, the first step is to ensure optimal concordance with the beneficial habits that improve migraine control.

Avoid using preventive drugs during pregnancy if possible. If a preventive drug is needed, a beta blocker or a tricyclic antidepressant is considered safest. Use preventive drugs at the lowest effective dose. If treatment can be delayed until after the first trimester, the risk of teratogenicity is less. Beta blockers can be associated with intrauterine growth retardation, and should be weaned before labour to prevent fetal bradycardia or impaired uterine contraction. Data about the safety of tricyclic antidepressants in pregnancy are conflicting. However, adverse fetal outcomes do not appear to be increased significantly overall. Consider the harms and benefits for each patient.

Supplements such as riboflavin and ubidecarenone (coenzyme Q10) are probably safe for migraine prophylaxis in pregnancy, but have not been studied as much as drugs routinely used for migraine prophylaxis. Oral magnesium has been considered safe, but in 2013 a possible link was noted between high-dose intravenous magnesium sulfate and fetal hypocalcaemia and bone abnormalities. Further studies of

long-term oral magnesium therapy are needed. Short-term (less than 5 days) magnesium infusions are still considered safe for acute management.

See also acute treatment for migraine during pregnancy.

Prophylaxis for menstrual migraine

Prophylaxis for menstrual migraine

Some women only, or mainly, have migraine around the time of menses (typically from a few days before until 3 days after menses begin). If the menstrual cycle is regular, short-term migraine prophylaxis can be helpful.

As short-term prophylaxis, possible drugs include:

1 ibuprofen 400 mg orally, 3 times daily for 5 to 7 days, starting 2 to 3 days before menses are due *migraine, menstrual, prophylaxis* _

OR

1 naproxen modified-release 750 mg to 1 g orally, once daily for 5 to 7 days, starting 2 to 3 days before menses are due *migraine, menstrual, prophylaxis* _

OR

1 naratriptan 1.25 to 2.5 mg orally, twice daily for 5 to 7 days, starting 2 to 3 days before menses are due. *migraine, menstrual, prophylaxis* _

If the woman is already taking a drug as prophylaxis for migraine, another option is to increase the dose of that drug for a week, starting 2 to 3 days before menses are due. Continuous cycling of the combined oral contraceptive or a perimenstrual estrogen supplement can also be considered.

Migraine in children

Migraine in children

As for adults, when managing migraine in children, ensure optimal concordance with the beneficial habits that improve migraine control.

Migraines can be short-lived in children and resolve with 2 to 3 hours of sleep. If drug therapy is needed, often ibuprofen or paracetamol is sufficient. Use:

1 ibuprofen 5 to 10 mg/kg (up to 400 mg) orally. Wait 4 to 6 hours before repeating dose if needed (maximum dose 30 mg/kg [up to 2400 mg] in 24 hours) *migraine (child)* _

OR

2 paracetamol 15 mg/kg (up to 1000 mg) orally. Wait 4 to 6 hours before repeating dose if needed (maximum dose 60 mg/kg [up to 4000 mg] in 24 hours). *migraine (child)* _

Avoid aspirin in children under 16 years because it has a rare association with Reye syndrome.

When nausea accompanying the migraine is a problem, expert opinion is that ondansetron is preferred therapy. Use:

1 ondansetron 0.1 to 0.15 mg/kg (up to 8 mg) orally *nausea due to migraine (child)* _

OR

1 ondansetron 0.1 to 0.15 mg/kg (up to 4 mg) intravenously.

Use metoclopramide and prochlorperazine for nausea with caution, as these drugs can cause restlessness, dystonia and sedation.

Triptans can be used in children older than 6 years if analgesics are ineffective. Use:

1 sumatriptan 10 to 20 mg intranasally. If symptoms recur, wait at least 2 hours before repeating the dose (no more than 2 doses in 24 hours) *migraine (child older than 6 years)*

OR

2 rizatriptan (child 20 to 39 kg: 5 mg; child 40 kg or more: 10 mg) orally (disintegrating tablet placed on tongue to dissolve). If symptoms recur, wait at least 2 hours before repeating the dose (no more than 2 doses in 24 hours) [Note 11]. *migraine (child older than 6 years)*

Monitor triptan use to prevent dose escalation and medication overuse headache.

Behavioural therapy (eg cognitive behavioural therapy, relaxation, hypnotherapy) is effective prophylaxis and may be the treatment of choice for children with frequent migraine.

Most drugs used for migraine prophylaxis have not been evaluated in children or adolescents. Evidence for the effectiveness of topiramate as prophylaxis for childhood migraine is conflicting. As topiramate has behavioural adverse effects, it should only be used with expert advice. Some evidence suggests that propranolol and flunarizine may be effective [Note 12]. Pizotifen, clonidine and amitriptyline are ineffective. There is insufficient or conflicting evidence to support using cyproheptadine, levetiracetam, sodium valproate or riboflavin.

Poor quality evidence supports complementary therapy (eg magnesium, acupuncture) as preventive treatment.

Note 11: Break rizatriptan 10 mg orally disintegrating tablet in half to give 5 mg dose to a child 20 to 40 kg.

Note 12: Flunarizine is not registered for use in Australia but is available via the Special Access Scheme.

When to refer a migraine patient to an expert

When to refer a migraine patient to an expert

Refer patients with migraine to an expert when:

- neurological symptoms are prolonged
- the usual headache pattern deteriorates suddenly
- they need acute treatment (analgesics or triptans) for more than 8 to 10 days per month and do not respond to prophylaxis in the usual dose range
- they often need emergency department or hospital treatment or have to take days off work due to migraine
- they have isolated aura without headache
- the diagnosis is uncertain.

Send patients with thunderclap headache (even if they routinely have migraines) for urgent assessment in an emergency department.

Aura without headache (acephalgic migraine)

Aura without headache (acephalgic migraine)

In aura without headache (acephalgic migraine), the typical aura of migraine is not accompanied or followed by a headache of any sort (see description in Table 7.2).

The differential diagnosis must exclude aura mimics, especially transient ischaemic attack or epilepsy. Concerning signs include a first episode of aura after the age of 40 years, exclusively negative symptoms (eg hemianopia) or prolonged aura (more than 60 minutes). The presence of other migraine features (eg photophobia, phonophobia, nausea) may support the diagnosis, but maintain a high index of suspicion for other diagnoses. Refer for expert advice.

Acute treatment of isolated aura is not usually helpful, because the attacks are so brief. Consider migraine prophylaxis for frequent attacks.

References

Key references: Approach to treatment for migraine

- Aurora SK, Barrodale PM, McDonald SA, Jakubowski M, Burstein R. Revisiting the efficacy of sumatriptan therapy during the aura phase of migraine. Headache 2009;49(7):1001–4. https://www.ncbi.nlm.nih.gov/pubmed/19438735
- Becker WJ. Acute migraine treatment. Continuum (Minneap Minn) 2015;21(4):953–72. https://www.ncbi.nlm.nih.gov/pubmed/26252584
- Becker WJ. Acute migraine treatment in adults. Headache 2015;55(6):778–93. https://www.ncbi.nlm.nih.gov/pubmed/25877672

Key references: Beneficial habits, physiotherapy and complementary therapies for migraine

- Linde K, Allais G, Brinkhaus B, Fei Y, Mehring M, Vertosick EA, et al. Acupuncture for the prevention of episodic migraine. Cochrane Database Syst Rev 2016;(6):CD001218. https://www.ncbi.nlm.nih.gov/pubmed/27351677
- Schiapparelli P, Allais G, Gabellari I, Rolando S, Terzi MG, Benedetto C. Non-pharmacological approach to migraine prophylaxis: part II. Neurol Sci 2010;31 Suppl 1:S137–9. https://www.ncbi.nlm.nih.gov/pubmed/20464605
- Tepper SJ. Nutraceutical and other modalities for the treatment of headache. Continuum (Minneap Minn) 2015;21(4 Headache):1018–31. https://www.ncbi.nlm.nih.gov/pubmed/26252588

Key references: Acute treatment for migraine with nonopioid analgesics and antiemetics

- Ellis GL, Delaney J, DeHart DA, Owens A. The efficacy of metoclopramide in the treatment of migraine headache. Ann Emerg Med 1993;22(2):191–5. https://www.ncbi.nlm.nih.gov/pubmed/8427430
- Schulman EA, Dermott KF. Sumatriptan plus metoclopramide in triptan-nonresponsive migraineurs. Headache 2003;43(7):729–33. https://www.ncbi.nlm.nih.gov/pubmed/12890127

Key references: Acute treatment for migraine with a triptan

- Aurora SK, Barrodale PM, McDonald SA, Jakubowski M, Burstein R. Revisiting the efficacy of sumatriptan therapy during the aura phase of migraine. Headache 2009;49(7):1001–4. https://www.ncbi.nlm.nih.gov/pubmed/19438735
- Becker WJ. Acute migraine treatment. Continuum (Minneap Minn) 2015;21(4):953–72. https://www.ncbi.nlm.nih.gov/pubmed/26252584
- Becker WJ. Acute migraine treatment in adults. Headache 2015;55(6):778–93. https://www.ncbi.nlm.nih.gov/pubmed/25877672

Key references: Acute treatment for migraine during pregnancy

- Becker WJ. Acute migraine treatment. Continuum (Minneap Minn) 2015;21(4):953–72. https://www.ncbi.nlm.nih.gov/pubmed/26252584
- Ephross SA, Sinclair SM. Final results from the 16-year sumatriptan, naratriptan, and treximet pregnancy registry. Headache 2014;54(7):1158–72. https://www.ncbi.nlm.nih.gov/pubmed/24805878
- Hutchinson S, Marmura MJ, Calhoun A, Lucas S, Silberstein S, Peterlin BL. Use of common migraine treatments in breast-feeding women: a summary of recommendations. Headache 2013;53(4):614–27. https://www.ncbi.nlm.nih.gov/pubmed/23465038
- Hutton E, Stark R. Episodic migraine in women. MedicineToday 2013;14(2):42–8. http://medicinetoday.com.au/2013/february/feature-article/episodic-migraine-women
- Kennedy D. Analgesics and pain relief in pregnancy and breastfeeding. Aust Prescr 2011;34:8–10. https://www.nps.org.au/australian-prescriber/articles/analgesics-and-pain-relief-in-pregnancy-and-breastfeeding
- Kvisvik EV, Stovner LJ, Helde G, Bovim G, Linde M. Headache and migraine during pregnancy and puerperium: the MIGRA-study. J Headache Pain 2011;12(4):443–51. https://www.ncbi.nlm.nih.gov/pubmed/21442333

Key references: Intractable migraine (status migrainosus)

- Bell R, Montoya D, Shuaib A, Lee MA. A comparative trial of three agents in the treatment of acute migraine headache. Ann Emerg Med 1990;19(10):1079–82. https://www.ncbi.nlm.nih.gov/pubmed/2221511
- Rozen TD. Emergency department and inpatient management of status migrainosus and intractable headache. Continuum (Minneap Minn) 2015;21(4 Headache):1004–17. https://www.ncbi.nlm.nih.gov/pubmed/26252587

Key references: Approach to prophylaxis for migraine and drugs used

- Silberstein SD. Preventive migraine treatment. Continuum (Minneap Minn) 2015;21(4 Headache):973–89. https://www.ncbi.nlm.nih.gov/pubmed/26252585
- Simpson DM, Hallett M, Ashman EJ, Comella CL, Green MW, Gronseth GS, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016;86(19):1818–26. https://www.ncbi.nlm.nih.gov/pubmed/27164716
- Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. JAMA 2003;289(1):65–9. https://www.ncbi.nlm.nih.gov/pubmed/12503978

Key references: Prophylaxis for migraine during pregnancy

- Wells RE, Turner DP, Lee M, Bishop L, Strauss L. Managing migraine during pregnancy and lactation. Curr Neurol Neurosci Rep 2016;16(4):40. https://www.ncbi.nlm.nih.gov/pubmed/27002079

Key references: Prophylaxis for menstrual migraine

- MacGregor EA. Migraine management during menstruation and menopause. Continuum (Minneap Minn) 2015;21(4 Headache):990–1003. https://www.ncbi.nlm.nih.gov/pubmed/26252586

Key references: Migraine in children

- El-Chammas K, Keyes J, Thompson N, Vijayakumar J, Becher D, Jackson JL. Pharmacologic treatment of pediatric headaches: a meta-analysis. JAMA Pediatr 2013;167(3):250–8. https://www.ncbi.nlm.nih.gov/pubmed/23358935
- Lewis D, Winner P, Saper J, Ness S, Polverejan E, Wang S, et al. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. Pediatrics 2009;123(3):924–34. https://www.ncbi.nlm.nih.gov/pubmed/19255022

- Ng QX, Venkatanarayanan N, Kumar L. A systematic review and meta-analysis of the efficacy of cognitive behavioral therapy for the management of pediatric migraine. Headache 2017;57(3):349–62. https://www.ncbi.nlm.nih.gov/pubmed/28028812
- O'Brien HL, Kabbouche MA, Kacperski J, Hershey AD. Treatment of pediatric migraine. Curr Treat Options Neurol 2015;17(1):326. https://www.ncbi.nlm.nih.gov/pubmed/25617222
- Orr SL. Diet and nutraceutical interventions for headache management: A review of the evidence. Cephalalgia 2016;36(12):1112–33. https://www.ncbi.nlm.nih.gov/pubmed/26069242
- Powers SW, Coffey CS, Chamberlin LA, Ecklund DJ, Klingner EA, Yankey JW, et al. Trial of amitriptyline, topiramate, and placebo for pediatric migraine. N Engl J Med 2017;376(2):115–24. https://www.ncbi.nlm.nih.gov/pubmed/27788026
- Richer L, Billinghurst L, Linsdell MA, Russell K, Vandermeer B, Crumley ET, et al. Drugs for the acute treatment of migraine in children and adolescents. Cochrane Database Syst Rev 2016; (4):CD005220. https://www.ncbi.nlm.nih.gov/pubmed/27091010
- Winner P, Pearlman EM, Linder SL, Jordan DM, Fisher AC, Hulihan J, et al. Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. Headache 2005;45(10):1304–12. https://www.ncbi.nlm.nih.gov/pubmed/16324162

Published November 2017 (Amended January 2019)

[X] Close

Medication overuse headache

Medication overuse headache

Medication overuse can cause a rebound headache as the dose wears off, and limit the efficacy of migraine prophylaxis. It can also cause a secondary headache disorder that is superimposed on the primary headache. Patients with migraine and tension-type headache are more susceptible to medication overuse headache than patients with cluster headache. Opioid analgesics (including codeine), triptans and ergots (ie ergotamine, dihydroergotamine) are more potent than nonopioid analgesics in inducing medication overuse headache. Patients taking opioid analgesics, triptans or ergots for more than 10 days per month are at risk. Nonopioid analgesics (eg paracetamol, NSAIDs) can induce medication overuse headache when taken for more than 15 days per month.

Appropriate management includes counselling the patient on the risks associated with taking analgesics too often. If headaches need treatment more than 4 days per month, consider starting a preventive drug. If the patient's use of headache drugs is escalating, re-evaluate the diagnosis and then consider a preventive drug. The patient may need expert referral to manage psychological problems that contribute to medication overuse, to overcome fear of analgesic withdrawal, and to manage psychiatric comorbidities (eg anxiety). Start a preventive drug before withdrawing analgesic medication from patients with medication overuse headache—if they are already on a preventive drug, review therapy and change if needed.

Strategies for analgesic medication withdrawal include:

- a graded reduction in dose and frequency
- bridging therapy.

An NSAID or a short course of prednis(ol)one can be used as bridging therapy while withdrawing an opioid analgesic or triptan. Use:

1 naproxen modified-release 750 mg orally, once daily for 5 days in the first week, then 3 to 4 days per week for 2 weeks, then stop *headache, medication overuse*

OR

2 prednis(ol)one 50 mg orally, once daily for 3 days. Decrease dose gradually over 7 to 10 days, then stop. *headache, medication overuse*

After bridging therapy, restart the patient's usual acute medication with restrictions on frequency (less than 10 days a month for triptans or opioid analgesics, less than 15 days a month for nonopioid analgesics). If it is unlikely that the patient will restrict use of a triptan, prescribe an NSAID instead.

In severe refractory cases, refer for expert management in hospital. Possible therapy includes lidocaine or ketamine infusion.

References

Key references: Medication overuse headache

- Lipton RB. Risk factors for and management of medication-overuse headache. Continuum (Minneap Minn) 2015;21(4 Headache):1118–31. https://www.ncbi.nlm.nih.gov/pubmed/26252595

Published November 2017

[X] Close

Tension-type headache

Tension-type headache

For a description of tension-type headache, see Table 7.2. Advise patients to follow the same lifestyle measures as for migraine. Manage stress and depression appropriately, and refer to an expert if needed. In more frequent tension-type headache, nonpharmacological therapies (eg cognitive behavioural therapy, relaxation training) may be effective. Acupuncture may be effective, but at least six sessions are needed. Physiotherapy (incorporating a neck muscle stretching and endurance program) and general aerobic exercise can help.

For infrequent tension-type headache, nonopioid analgesics are appropriate. A lower dose of aspirin than used for migraine can be effective. Use:

1 aspirin soluble 600 to 900 mg orally. Wait 4 to 6 hours before repeating dose if needed (maximum dose 2 g in 24 hours) *headache, tension*

OR

1 diclofenac potassium 50 mg orally. Wait 4 to 6 hours before repeating dose if needed (maximum dose 150 mg in 24 hours) [Note 1] *headache, tension*

OR

1 ibuprofen 400 mg orally. Wait 4 to 6 hours before repeating dose if needed (maximum dose 2.4 g in 24 hours) *headache, tension*

OR

1 naproxen 500 to 750 mg orally. Wait 4 to 6 hours before repeating dose if needed (maximum dose 1250 mg in 24 hours) *headache, tension*

OR

1 paracetamol soluble 1 g orally. Wait 4 to 6 hours before repeating dose if needed (maximum dose 4 g in 24 hours). *headache, tension*

The efficacy of nonopioid analgesics may decline with increasing headache frequency—if so, try adding a preventive drug (eg a tricyclic antidepressant). For more frequent tension-type headache, use:

1 amitriptyline 10 mg orally, once daily at night. Increase dose by 10 mg every 7 days to a maximum of 75 mg once daily at night, for 8 weeks, then review *headache, tension, prophylaxis*

OR

1 nortriptyline 10 mg orally, once daily at night. Increase dose by 10 mg every 7 days to a maximum of 75 mg once daily at night, for 8 weeks, then review. *headache, tension, prophylaxis*

If these drugs are effective, continue therapy for 6 months and then consider a trial of withdrawing therapy.

If no response to a preventive drug after 8 to 12 weeks, switch to another preventive drug or refer for expert advice. As an alternative preventive drug, use:

1 mirtazapine 15 to 30 mg orally, once daily at night, for 8 to 12 weeks, then review *headache, tension, prophylaxis*

OR

1 venlafaxine modified-release 75 mg orally, in the morning after food. Increase dose according to tolerability and patient response to 150 mg daily. Review after 8 to 12 weeks. *headache, tension, prophylaxis*

Note 1: If the patient has nausea, diclofenac is available as a rectal preparation.

References

Key references: Tension-type headache

- Bendtsen L, Evers S, Linde M, Mitsikostas DD, Sandrini G, Schoenen J, et al. EFNS guideline on the treatment of tension-type headache - report of an EFNS task force. Eur J Neurol 2010;17(11):1318–25. https://www.ncbi.nlm.nih.gov/pubmed/20482606
- Fernandez-de-Las-Penas C, Cuadrado ML. Physical therapy for headaches. Cephalalgia 2016;36(12):1134–42. https://www.ncbi.nlm.nih.gov/pubmed/26660851
- Linde K, Allais G, Brinkhaus B, Fei Y, Mehring M, Shin BC, et al. Acupuncture for the prevention of tension-type headache. Cochrane Database Syst Rev 2016;(4):CD007587. https://www.ncbi.nlm.nih.gov/pubmed/27092807

Published November 2017

[X] Close

Diagnosing cluster headache

Diagnosing cluster headache

For the characteristics of cluster headache, a subtype of trigeminal autonomic cephalgia, see Tables Table 7.2 and Table 7.3.

Cluster headache can be associated with structural lesions in the pituitary gland or surrounding regions, so requesting an MRI with pituitary views is advisable. Cluster headache is known as a 'suicide headache' because the pain is so severe. Urgently refer a patient with suspected cluster headache for expert review, to confirm the diagnosis and optimise treatment—if the patient is having an acute attack, send them to an emergency department. Cluster headache can be treated acutely and preventively. Bridging strategies may be needed to control the headaches while starting a preventive drug.

Acute treatment for cluster headache

Acute treatment for cluster headache

A subcutaneous triptan is the most effective treatment for cluster headache. Some patients respond to intranasal sumatriptan or oral rizatriptan or zolmitriptan. Use:

1 sumatriptan 6 mg subcutaneously *headache, cluster*

OR

2 sumatriptan 20 mg intranasally

OR

3 rizatriptan 10 mg orally *headache, cluster*

OR

4 zolmitriptan 2.5 mg orally. *headache, cluster*

Patients with cluster headache can also get relief from using high flow oxygen. In an emergency, consider using oxygen as well as subcutaneous treatment with a triptan.

For high flow oxygen, use:

oxygen 100% 15 L/minute by inhalation via a tight-fitting nonrebreathing mask, for 15 to 20 minutes, then stop. *headache, cluster*

If effective, oxygen can be used at home. However, to get an appropriate cylinder and regulator, the patient needs a letter of authorisation from the treating physician to a medical gas supplier.

For severe refractory cluster headache, indometacin or dihydroergotamine (if the patient has not had a triptan in the preceding 24 hours) can be used.

Do not give a triptan for 24 hours after dihydroergotamine therapy.

Do not give a triptan for 24 hours before or after dihydroergotamine therapy.

A greater occipital nerve block, as used for bridging treatment, can be used as acute treatment in some patients (see advice).

Bridging treatment for cluster headache

Bridging treatment for cluster headache

Bridging treatment may be needed to control the cluster headache while starting a preventive drug and waiting for it to reach an effective dose. Options include a short course of oral prednis(ol)one. Use:

prednis(ol)one 50 mg orally, once daily for 5 days, then reduce daily dose by 12.5 mg every 3 days, then stop. *headache, cluster, bridging treatment*

Another option as bridging treatment is a greater occipital nerve block (eg using methylprednisolone acetate and bupivacaine 0.5%). This can provide relief for up to 3 months in patients with cluster headache. If effective, the nerve block may be used as sole therapy in patients whose typical bouts of cluster headaches last 1 to 3 months. Lidocaine 2% can be used instead of bupivacaine in the nerve block and may be preferred in pregnant patients.

Naratriptan can also be used as a bridging drug. Use:

naratriptan 2.5 mg orally, twice daily for 1 week. *headache, cluster, bridging treatment*

Preventive treatment for cluster headache

Preventive treatment for cluster headache

Preventive treatments may be used continuously for chronic cluster headache or intermittently for episodic cluster headache. In predictable episodic cluster headache it is prudent to build up to a therapeutic dose in the 2 to 6 weeks before the expected onset of headaches. Continue treatment at the effective dose during the bout of cluster headache, then taper the dose the month after the cluster headache is predicted to have resolved.

First-line drugs for preventing cluster headache include verapamil, topiramate, sodium valproate [Note 1], gabapentin and melatonin (high dose). Drug doses in cluster headache may need to be titrated faster than in acute migraine. Attaining a therapeutic dose swiftly must be balanced with the adverse effects (especially sedation), which may be more pronounced with rapid titration.

Of these first-line drugs, verapamil has fewer adverse effects and so is recommended as the first drug to try. Verapamil can cause heart block, especially at the doses needed to treat cluster headache. Heart block may not appear until 10 days after starting, or increasing the dose of, verapamil. Before starting verapamil, perform an electrocardiograph (ECG) to exclude heart block, marked bradycardia and prolonged PR interval. Always repeat the ECG before increasing the dose of verapamil.

Anecdotally, immediate-release verapamil is more effective in cluster headache than the sustained-release preparation. Use:

verapamil immediate-release 80 mg orally, 3 times daily for 2 weeks; then 120 mg 3 times daily for 2 weeks; then 160 mg 3 times daily. Repeat ECG before each dose increase; do not increase dose unless ECG is normal. *headache, cluster, prophylaxis*

Higher doses (up to 720 mg daily) of verapamil may be used with expert advice.

Lithium is effective for cluster headache, but is not first-line due to its toxicity (the serum concentration of the drug and the patient's thyroid and kidney function must be monitored).

Neuromodulation (eg occipital nerve stimulator, deep brain stimulation with a posterior inferior hypothalamic target) [Note 2] may be considered in refractory cases—refer for expert advice.

Note 1: Avoid sodium valproate in females of childbearing potential (see teratogenic and neurodevelopmental effects of antiepileptic drugs).

Note 2: Sphenopalatine stimulation can be effective, but the technique was not available in Australia at the time of writing.

References

Key references: Cluster headache

- Becker WJ. Cluster headache: conventional pharmacological management. Headache 2013;53(7):1191–6. https://www.ncbi.nlm.nih.gov/pubmed/23773141
- Goadsby PJ, Cittadini E, Cohen AS. Trigeminal autonomic cephalalgias: paroxysmal hemicrania, SUNCT/SUNA, and hemicrania continua. Semin Neurol 2010;30(2):186–91. https://www.ncbi.nlm.nih.gov/pubmed/20352588
- Koppen H, Stolwijk J, Wilms EB, Driel V, Ferrari MD, Haan J. Cardiac monitoring of high-dose verapamil in cluster headache: An international Delphi study. Cephalalgia 2016;36(14):1385–8. https://www.ncbi.nlm.nih.gov/pubmed/26868817
- Newman LC. Trigeminal autonomic cephalalgias. Continuum (Minneap Minn) 2015;21(4 Headache):1041–57. https://www.ncbi.nlm.nih.gov/pubmed/26252590

Published November 2017

[X] Close

Trigeminal neuralgia and other cranial neuralgias

Trigeminal neuralgia and other cranial neuralgias

Neuropathic facial pain can arise from the trigeminal, glossopharyngeal or greater occipital nerves—trigeminal neuralgia is most common.

Trigeminal neuralgia is recurrent, unilateral, shock-like pain in one or more divisions of the trigeminal nerve (see description in Table 7.4). It can be due to demyelination or neurovascular compression. Request imaging to exclude a structural cause, especially in the presence of sensory loss, which suggests trigeminal neuropathy. Request specific views of the trigeminal nerve and ganglion.

Drugs are first-line therapy for trigeminal neuralgia. There is stronger evidence for carbamazepine, but oxcarbazepine may be better tolerated. Use:

1 carbamazepine modified-release 100 mg orally, twice daily. If needed, gradually increase dose as tolerated and according to response every 7 days up to 400 mg twice daily [Note 1]

OR

2 oxcarbazepine 300 mg orally, twice daily. If needed, gradually increase dose after 7 days up to 600 mg twice daily *trigeminal neuralgia*

OR

3 baclofen 5 mg orally, twice daily. If needed, gradually increase dose every 4 days up to 10 to 20 mg 3 times daily *trigeminal neuralgia*

OR

3 gabapentin 300 mg orally, once daily at night. If needed, gradually increase dose every 3 to 7 days up to 600 to 1200 mg 3 times daily *trigeminal neuralgia*

OR

3 lamotrigine 25 mg orally, once daily on alternate days for 14 days, then 25 mg once daily for 14 days, then 25 mg twice daily for 14 days. If needed, increase daily dose by 25 mg every 14 days up to 100 mg twice daily *trigeminal neuralgia*

OR

3 phenytoin 300 mg orally, once daily *trigeminal neuralgia*

OR

3 pregabalin 75 mg orally, once daily at night. If needed, gradually increase dose every 3 to 7 days up to 150 to 300 mg twice daily. *trigeminal neuralgia*

If the patient does not respond to an adequate dose of drug or does not tolerate it, or if the drug loses efficacy or the diagnosis is in doubt, refer to an expert. If drug therapy is not effective, patients may be considered for surgery (eg microvascular decompression of the trigeminal nerve, percutaneous rhizotomy, stereotactic radiotherapy [‘gamma knife’ therapy]).

Glossopharyngeal neuralgia is a rare facial pain syndrome characterised by paroxysmal pain in the throat, tonsillar fossa, base of tongue and ear (see description in Table 7.4). Exclude a structural cause (eg oropharyngeal malignancy, peritonsillar infection, vascular compression). Treat with drugs as for trigeminal neuralgia (see above).

Greater occipital neuralgia is characterised by shooting or stabbing pain (typically unilateral) over the occipital region (see description in Table 7.4). Initial treatment is a greater occipital nerve block. If effective, the nerve block can be repeated every 3 months (more frequent use risks local atrophy of skin and subcutaneous tissue). If a nerve block is not effective, drug therapy is an option. Use:

1 gabapentin 300 mg orally, once daily at night. If needed, gradually increase dose every 3 to 7 days up to 600 to 1200 mg 3 times daily *occipital neuralgia*

OR

1 pregabalin 75 mg orally, once daily at night. If needed, gradually increase dose every 3 to 7 days up to 150 to 300 mg twice daily. *occipital neuralgia*

Refer for expert advice if the diagnosis of greater occipital neuralgia is in doubt, a structural cause is identified or the patient does not respond to, or tolerate, the therapy.

Note 1: Pharmacogenetic studies are identifying an increasing number of genes that confer a predisposition to cutaneous drug reactions. Testing for the HLA-B*1502 allele in patients of Asian origin (other than Japanese) is advised before starting therapy with carbamazepine.

Key references: Trigeminal neuralgia and other cranial neuralgias

Key references: Trigeminal neuralgia and other cranial neuralgias

- Cheshire WP Jr., Cranial neuralgias. Continuum (Minneap Minn) 2015;21(4 Headache):1072–85. https://www.ncbi.nlm.nih.gov/pubmed/26252592
- Zakrzewska JM, Patsalos PN. Oxcarbazepine: a new drug in the management of intractable trigeminal neuralgia. J Neurol Neurosurg Psychiatry 1989;52(4):472–6. https://www.ncbi.nlm.nih.gov/pubmed/2738589

Published November 2017

[X] Close

General information on idiopathic hypersomnolence and narcolepsy

General information on idiopathic hypersomnolence and narcolepsy

Idiopathic hypersomnolence and narcolepsy are disorders of sleep–wake regulation that usually appear between adolescence and the age of 30 years. They are characterised by chronic daytime sleepiness, which may lead to sudden uncontrollable sleep attacks. Idiopathic hypersomnolence is more common than narcolepsy. Narcolepsy is associated with disturbed sleep at night and abnormal manifestations of rapid eye movement sleep–like behaviour during waking. Symptoms include cataplexy (sudden loss of muscle tone, usually associated with strong emotion), muscle paralysis on falling asleep or waking (sleep paralysis) and vivid hallucinations (often visual) on falling asleep (hypnagogic) or waking (hypnopompic).

Idiopathic hypersomnolence and narcolepsy are diagnosed on the basis of:

- clinical history
- absence of other sleep disorders (particularly obstructive sleep apnoea) on overnight sleep study
- objective evidence of excessive daytime sleepiness, using a multiple sleep latency test or maintenance of wakefulness test.

Advise patients with severe sleepiness to avoid dangerous activities at home and at work. They should not operate a motor vehicle until sleepiness is adequately managed and they satisfy the Australian standards of fitness to drive [Note 1].

Patients with severe sleepiness must avoid dangerous activities at home and at work.Patients with severe sleepiness must not drive a motor vehicle until sleepiness is adequately managed.

Note 1: National standards of fitness to drive are available from the Austroads website. See Section 8 Sleep disorders.

Treatment for idiopathic hypersomnolence and narcolepsy

Treatment for idiopathic hypersomnolence and narcolepsy

Treatment for excessive sleepiness is mainly symptomatic, and is normally started by an expert after confirming the diagnosis. Scheduled naps can help, but seldom suffice as primary therapy. Advise the patient to follow good sleep practices.

Modafinil is first-line drug therapy for increasing alertness. Other drugs that may be prescribed by an expert are dexamfetamine and methylphenidate. No studies directly compare modafinil with dexamphetamine and methylphenidate as treatment for sleepiness, but modafinil has fewer adverse effects. In Australia, legal requirements limit who can prescribe these drugs—check state guidelines as these vary. Use:

1 modafinil 200 mg orally, once daily in the morning, or modafinil 100 mg orally, twice daily, in the morning and at midday (maximum daily dose 400 mg) *idiopathic hypersomnolence or narcolepsy*

OR

2 armodafinil 150 to 250 mg orally, once daily in the morning. *idiopathic hypersomnolence or narcolepsy*

Some patients may need higher doses under expert supervision, with the dose being titrated gradually until tests of daytime alertness (eg maintenance of wakefulness test) are normal.

If a patient with narcolepsy has cataplexy, sleep paralysis and hypnagogic hallucinations, the expert may prescribe a tricyclic antidepressant or a selective serotonin reuptake inhibitor.

Key references: Idiopathic hypersomnolence and narcolepsy

Key references: Idiopathic hypersomnolence and narcolepsy

- Billiard M, Sonka K. Idiopathic hypersomnia. Sleep Med Rev 2016;29:23–33. https://www.ncbi.nlm.nih.gov/pubmed/26599679
- Thorpy MJ, Dauvilliers Y. Clinical and practical considerations in the pharmacologic management of narcolepsy. Sleep Med 2015;16(1):9–18. https://www.ncbi.nlm.nih.gov/pubmed/25458251

Published November 2017