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Anticonvulsants used for generalised seizures

Other relevant separate articles include Status Epilepticus Management, Epilepsy in Adults, Epilepsy in Children and Young People and Epilepsy in Elderly People.

What are generalised seizures?

Generalised seizures are characterised by widespread involvement of bilateral cortical and subcortical regions at the outset and are usually accompanied by impairment of consciousness: [1]

The World Health Organization (WHO) International Classification of Diseases (ICD-11) describes the different types of generalised seizures as follows: [2]

- **Generalised tonic-clonic seizure**: a seizure characterised by an abrupt onset with loss of consciousness and bilateral tonic extension of the trunk and limbs (tonic phase) followed by synchronous muscle jerking (clonic phase). Usually followed by a postictal phase, lasting for several minutes up to hours, characterised by initial mydriasis, body relaxation, hypotonia, and sleep.
- **Absence seizures, typical**: seizures characterised by sudden onset, interruption of ongoing activities, blank stare, possibly brief upward gaze deviation, unresponsiveness, duration from few seconds to half a minute, and rapid recovery. An EEG would show generalised epileptiform discharges during the event.
- **Absence seizures, atypical**: absence seizures with changes in tone more pronounced than in typical absences or with non-abrupt onset and/or cessation, often associated with slow, irregular, generalised spike-wave activity.

- **Generalised myoclonic seizure**: seizure characterised by sudden, rapid brief (<100 msec) involuntary muscle jerks that may involve just one muscle or the entire trunk musculature and are associated with an ictal EEG discharge. Can occur bilaterally, unilaterally, synchronously or asynchronously.
- **Generalised tonic seizure**: a seizure characterised by sustained increase in muscle contraction lasting a few seconds to minutes.
- **Generalised atonic seizure**: seizure characterised by sudden loss or diminution of muscle tone without apparent preceding myoclonic or tonic event lasting 1-2 seconds, involving head, trunk, jaw, or limb muscles.

About two in three adults with new-onset epilepsy will achieve lasting generalised seizure remission on or off antiepileptic drugs (AEDs), although around half will experience mild to moderately severe adverse effects.[3]

Antiepileptic drugs for generalised seizures[1] [4] [5]

General information about prescribing for epilepsy

- Carefully adjust the dose, starting with low doses and increasing gradually until seizures are controlled or there are significant adverse effects.
- Dosage frequency should be kept as low as possible to encourage adherence.
- Changing from one antiepileptic drug to another should be cautious; slowly withdraw the first drug only when the new regimen has been established. Antiepileptic drugs should be withdrawn under specialist supervision.
- Reduction in dosage should be gradual. Avoid abrupt withdrawal as this can precipitate severe rebound seizures.
- Combination therapy with two or more antiepileptic drugs may be necessary, but the concurrent use of antiepileptic drugs increases the risk of adverse effects and drug interactions. Therefore a single antiepileptic drug should be prescribed wherever possible.

- Even in patients who have been seizure-free for several years, there is a significant risk of seizure recurrence on drug withdrawal. If taking several antiepileptic drugs, only one drug should be withdrawn at a time.

Switching between different manufacturers' products

Antiepileptic drugs have been divided into three risk-based categories to help decide whether it is necessary to maintain continuity of supply of a specific manufacturer's product:

- Category 1: carbamazepine, phenobarbital, phenytoin, primidone - patients should be maintained on a specific manufacturer’s product.
- Category 2: clobazam, clonazepam, eslicarbazepine acetate, lamotrigine, oxcarbazepine, perampanel, rufinamide, topiramate, valproate, zonisamide - the need for continued supply of a particular manufacturer's product should be based on clinical judgement and consultation with the patient and/or carer, taking into account factors such as seizure frequency, treatment history, and potential implications to the patient of having a breakthrough seizure. Non-clinical factors as for Category 3 drugs should also be considered.
- Category 3: brivaracetam, ethosuximide, gabapentin, lacosamide, levetiracetam, pregabalin, tiagabine, vigabatrin:
    - Usually unnecessary to ensure that patients are maintained on a specific manufacturer's product as therapeutic equivalence can be assumed; however, other factors are important when considering whether switching is appropriate.
    - Differences between alternative products (eg, product name, packaging, appearance, and taste) may be perceived negatively by patients and/or carers, and may lead to dissatisfaction, anxiety, confusion, dosing errors, and reduced adherence.
    - Difficulties for patients with comorbid autism, mental health problems, or learning disability should also be considered.

Adverse effects

All antiepileptic drugs may be associated with a small increased risk of suicidal thoughts and behaviour. Symptoms may occur as early as one week after starting treatment.

Patients and their carers should be advised to seek medical advice if any mood changes, distressing thoughts, or feelings about suicide or self-harming develop. Patients should be advised not to stop or switch antiepileptic treatment, and to seek advice from a healthcare professional if concerned.

Antiepileptic hypersensitivity syndrome

- Rare but potentially fatal syndrome associated with some antiepileptic drugs (carbamazepine, lacosamide, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, primidone, and rufinamide).
- Rarely cross-sensitivity occurs between some of these antiepileptic drugs. Some other antiepileptics (eslicarbazepine, stiripentol, and zonisamide) have a theoretical risk.
- The symptoms usually start between 1 and 8 weeks of exposure; fever, rash, and lymphadenopathy are most commonly seen.
- Other systemic signs include liver dysfunction, haematological, renal, and pulmonary abnormalities, vasculitis, and multi-organ failure.
- If signs or symptoms of hypersensitivity syndrome occur, the drug should be withdrawn immediately, the patient must not be re-exposed, and expert advice should be sought.

Interactions

Interactions between antiepileptics are complex and may increase toxicity without any increase in antiepileptic effect. Interactions are usually caused by hepatic enzyme induction or inhibition, and are very variable and unpredictable.

Pregnancy and breastfeeding

There is an increased risk of teratogenicity associated with the use of antiepileptic drugs (especially if used during the first trimester and particularly if the patient is taking two or more antiepileptic drugs).

Valproate[6]

See also the article on Epilepsy and Pregnancy, particularly regarding that valproate should never be used for epilepsy in women with childbearing potential, unless there is no other effective treatment available. Valproate is highly teratogenic and evidence supports that use in pregnancy leads to congenital malformations (approximately 10% risk) and neurodevelopmental disorders (approximately 30-40% risk).

Data has also suggested an increased risk of neurodevelopmental disorders in children whose fathers took valproate in the 3 months before conception.

- Valproate must not be started in new patients (male or female) younger than 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment, or there are compelling reasons that the reproductive risks do not apply. For the majority of patients, other effective treatment options are available.
- At their next annual specialist review, women of childbearing potential and girls receiving valproate should be reviewed using the revised valproate Annual Risk Acknowledgement Form. A second specialist signature will be needed if the patient is to continue on valproate, however subsequent annual reviews will only require one specialist
- Male patients who are planning a family within the next year, are advised to discuss treatment options with a healthcare professional.
- Report suspected adverse drug reactions associated with valproate on a Yellow Card.

See also the separate article Epilepsy and Pregnancy for further details.

Although initiating, changing and discontinuing antiepileptic medication is organised in secondary or tertiary care, the following is a brief summary of the recommended treatments for the various types of generalised seizures.

Generalised tonic-clonic (GTC) seizures

- Sodium valproate is the first-line treatment (but see above regarding teratogenicity of valproate.
- For females who are able to have children or if treatment with sodium valproate is unsuccessful, offer lamotrigine or levetiracetam as first-line monotherapy. If monotherapy with either lamotrigine or levetiracetam is unsuccessful, the other of these options should be tried.
- If monotherapy is unsuccessful, adjunctive treatment should be considered:
    - First-line options for adjunctive treatment include clobazam, lamotrigine, levetiracetam, perampanel, sodium valproate (in males, and females unable to have children), or topiramate.
    - Second-line options include brivaracetam, lacosamide, phenobarbital, primidone, or zonisamide.
- Patients who also have absence or myoclonic seizures may have their seizures exacerbated if treated with carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin.

Absence seizures

- Offer ethosuximide as first-line treatment for absence seizures.
- If treatment with ethosuximide is unsuccessful, consider sodium valproate as second-line monotherapy or adjunctive treatment for males, and females unable to have children.
- Sodium valproate should be used as the first choice if there is a high risk of generalised tonic-clonic seizures.
- If treatment with sodium valproate is unsuitable or unsuccessful, lamotrigine or levetiracetam should be considered as third-line monotherapy or adjunctive treatment.
- If treatment with either lamotrigine or levetiracetam is unsuccessful, the other of these options should be considered.
- Patients with absence seizures may have their seizures exacerbated if treated with carbamazepine, gabapentin, oxcarbazepine, phenobarbital, phenytoin, pregabalin, tiagabine, or vigabatrin.

Myoclonic seizures

Myoclonic seizures (myoclonic jerks) occur in a variety of syndromes, and response to treatment varies considerably.

- Offer sodium valproate as first-line treatment for myoclonic seizures in males, and females unable to have children. For females who are able to have children, offer levetiracetam as first-line monotherapy.
- If treatment with sodium valproate is unsuccessful, levetiracetam should be offered as second-line monotherapy or adjunctive treatment.
- If treatment with levetiracetam is unsuccessful, consider monotherapy or adjunctive treatment (for all patients) with brivaracetam, clobazam, clonazepam, lamotrigine, phenobarbital, piracetam, topiramate, or zonisamide.
- In patients with myoclonic seizures, the use of carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin, tiagabine, or vigabatrin is not recommended because they may exacerbate seizures. Lamotrigine may also occasionally exacerbate myoclonic seizures.
- Sodium valproate and levetiracetam are effective in treating the generalised tonic-clonic seizures that coexist with myoclonic seizures in idiopathic generalised epilepsy.

Tonic or atonic seizures

- Atonic or tonic seizures are usually seen in childhood, in specific epilepsy syndromes, or associated with cerebral damage or learning disabilities. They may respond poorly to the traditional drugs.
- Offer sodium valproate as first-line treatment for atonic or tonic seizures in males, and females unable to have children. For females who are able to have children, offer lamotrigine as first-line monotherapy.
- If treatment with sodium valproate is unsuccessful, lamotrigine should be offered as second-line monotherapy or adjunctive treatment.

- If treatment with lamotrigine is unsuccessful, consider monotherapy or adjunctive treatment (for all patients) with clobazam, rufinamide, or topiramate.
- If all other treatments are unsuccessful, consider felbamate as adjunctive treatment under the supervision of a neurologist with expertise in epilepsy.
- Patients with atonic or tonic seizures may have their seizures exacerbated if treated with carbamazepine, gabapentin, oxcarbazepine, pregabalin, tiagabine, or vigabatrin.

Infantile spasms

See the separate West's Syndrome (Infantile Spasms) article.

- Combination therapy with high-dose oral prednisolone and vigabatrin is considered first-line treatment for infantile spasms that are not due to tuberous sclerosis, unless the child is at high risk of steroid-related side-effects.
- Vigabatrin alone can be used as first-line treatment for infantile spasms in children at high risk of steroid-related side-effects.
- Vigabatrin alone is first-line treatment for infantile spasms due to tuberous sclerosis. If vigabatrin is ineffective after one week, high-dose oral prednisolone should be added.
- If first-line treatment for infantile spasms is unsuccessful, further treatment should be discussed with a tertiary paediatric epilepsy specialist. The following are considered as a second-line monotherapy or add-on treatment options for infantile spasms: ketogenic diet, levetiracetam, nitrazepam, sodium valproate, topiramate.

Dravet syndrome (severe myoclonic epilepsy of infancy) [7]

- Sodium valproate should be considered as first-line treatment for all patients with Dravet syndrome, including females, because of the severity of the syndrome and the lack of evidence for other effective first-line options.

- If sodium valproate is started or continued in females who are able to have children, ensure that the potential risks and benefits of treatment are discussed, and that the likelihood of pregnancy is considered and a pregnancy prevention programme put in place, if appropriate.
- If monotherapy with sodium valproate is unsuccessful, consider triple therapy with clobazam and stiripentol as first-line adjunctive therapy.
- If triple therapy with sodium valproate, clobazam, and stiripentol is unsuccessful, cannabidiol with clobazam may be considered as second-line adjunctive treatment in certain patients.
- Fenfluramine may also be considered as adjunctive treatment to other antiepileptic drugs in certain patients.
- Under the supervision of a neurologist with expertise in epilepsy, further adjunctive treatment options include topiramate or levetiracetam. If all other treatments are unsuccessful, potassium bromide may be considered.
- Patients with Dravet syndrome may have their seizures exacerbated if treated with carbamazepine, gabapentin, lacosamide, lamotrigine, oxcarbazepine, phenobarbital, pregabalin, tiagabine, or vigabatrin.

Fenfluramine for treating seizures associated with Dravet syndrome [8]

Fenfluramine is a serotonin-releasing medication that stimulates multiple 5-HT receptor subtypes. This action on serotonin receptors in the brain is thought to contribute to its anti-seizure activity.

The National Institute for Health and Care Excellence (NICE) has issued advice that fenfluramine is now recommended as an add-on to other anti-seizure medicines for treating seizures associated with Dravet syndrome in people aged 2 years and older.

It can only be used if:

- Seizures have not been controlled after trying two or more anti-seizure medicines.

- The frequency of convulsive seizures is checked every six months, and fenfluramine is stopped if it has not fallen by at least 30% compared with the six months before starting treatment.

Clinical evidence shows that patients who are prescribed fenfluramine in addition to medications used for standard care:

- Have a reduction in how long their seizures last.
- Have fewer non-convulsive seizures.
- Have quality-of-life benefits for both themselves and their carers.

Lennox-Gastaut syndrome

See also the separate Lennox-Gastaut Syndrome article.

- Sodium valproate should be considered as first-line treatment for all patients with Lennox-Gastaut syndrome, including females, because of the severity of the syndrome and the lack of evidence for other effective first-line options.
- If sodium valproate is started or continued in females who are able to have children, ensure that the potential risks and benefits of treatment are discussed, and that the likelihood of pregnancy is considered and a pregnancy prevention programme put in place, if appropriate.
- If monotherapy with sodium valproate is unsuccessful, consider lamotrigine as second-line monotherapy or adjunctive treatment.
- Third-line adjunctive treatment options include cannabidiol with clobazam in certain patients, or clobazam, rufinamide, or topiramate.
- Felbamate may be considered as adjunctive therapy under the supervision of a neurologist with expertise in epilepsy when all other treatment options are unsuccessful.
- Patients with Lennox-Gastaut syndrome may have their seizures exacerbated if treated with carbamazepine, gabapentin, lacosamide, lamotrigine, oxcarbazepine, phenobarbital, pregabalin, tiagabine, or vigabatrin.

Self-limited epilepsy with centrotemporal spikes

- Consider lamotrigine or levetiracetam as first-line treatment for self-limited epilepsy with centrotemporal spikes. If either lamotrigine or levetiracetam is unsuccessful, try the other of these options.
- If first-line treatments for self-limited epilepsy with centrotemporal spikes are unsuccessful, consider the following as second-line monotherapy treatment options: carbamazepine, oxcarbazepine or zonisamide.
- If second-line treatments tried are unsuccessful, consider sulthiame as monotherapy or add-on treatment, but only after discussion with a tertiary paediatric neurologist.
- Carbamazepine, oxcarbazepine and lamotrigine may rarely exacerbate seizures or the development of another epilepsy syndrome, or affect cognitive performance, in a small number of children and young people with self-limited epilepsy with centrotemporal spikes.
- If there is concern about the school performance of a child or young person having antiseizure medication, seek guidance from an epilepsy specialist and consider sleep EEG to exclude exacerbation of epileptic activity (electrical status epilepticus during sleep) and neuropsychology assessment to review academic performance.
- If a child or young person having antiseizure medication treatment develops other seizure types, consider a sleep EEG to exclude exacerbation of epileptic activity (developmental epileptic encephalopathy with spike-wave activation in sleep).
- Discuss discontinuing treatment if a child or young person with self-limited epilepsy with centrotemporal spikes is seizure-free for at least 2 years or at age 14 years.

Epilepsy with myoclonic-atonic seizures (Doose's syndrome)

- Discuss the treatment and management of epilepsy with myoclonic-atonic seizures in children with a tertiary paediatric neurologist.
- Consider levetiracetam or sodium valproate as first-line treatments for epilepsy with myoclonic-atonic seizures. If either levetiracetam or sodium valproate is unsuccessful, try the other of these options.

- If sodium valproate is started or continued for epilepsy with myoclonic-atonic seizures in girls or women able to have children (including young girls who are likely to need treatment when they are old enough to have children), discuss the risks and benefits of treatment, including the risks to an unborn child, and take into account the likelihood of pregnancy and put in place a pregnancy prevention programme, if appropriate.
- If first-line treatments are unsuccessful, consider a ketogenic diet as a second-line monotherapy or add-on treatment, under the supervision of a ketogenic diet team.
- If second-line treatment for epilepsy with myoclonic-atonic seizures is unsuccessful, consider the following as third-line monotherapy or add-on treatment options: clobazam, ethosuximide, topiramate or zonisamide.
- Do not use any of the following medications because they may exacerbate seizures in people with epilepsy with myoclonic-atonic seizures:
  carbamazepine, gabapentin, oxcarbazepine, phenytoin, pregabalin or vigabatrin.
- Consider discontinuing antiseizure medication treatment in children with epilepsy with myoclonic-atonic seizures who are seizure-free for two years.

Other epilepsy syndromes

Refer to a tertiary paediatric epilepsy specialist all children and young people with continuous spike and wave during slow sleep, Landau-Kleffner syndrome or myoclonic-astatic epilepsy.

Generalised seizures drug treatment[1] [4]

- AED therapy should only be started once the diagnosis of epilepsy is confirmed, except in exceptional circumstances. AED therapy should be initiated by a specialist.

- Treatment with AED therapy is generally recommended after a second epileptic seizure. AED therapy should be considered and discussed after a first unprovoked seizure if:

    - There is a neurological deficit.
    - The EEG shows unequivocal epileptic activity.
    - The patient considers the risk of having a further seizure unacceptable.
    - Brain imaging shows a structural abnormality.

- The dose of each medication should be titrated slowly to the maximally tolerated dose or the maximum level as recommended in the British National Formulary. The effect may be monitored by patient-recorded seizure frequency.
- Formulations of AEDs are not interchangeable and generic substitution should not be routinely made. Routine switching between different manufacturers of AEDs should be avoided.

Continuation of generalised seizure drug treatment[1] [4]

- Maintain a high level of vigilance for adverse effects of treatment.
- Be aware that treatment with AEDs is associated with a small risk of suicidal thoughts and behaviour, possibly as early as one week after starting treatment.
- Continuing AED therapy should be planned by a specialist but part of an agreed treatment plan and the needs of the child, young person or adult and their family and/or carers as appropriate should be taken into account.
- If management is straightforward, continuing AED therapy can be prescribed in primary care if local circumstances and/or licensing allow.

- Adherence to generalised seizure treatment can be optimised with the following:
    - Educating children, young people and adults and their families and/or carers in the understanding of their condition and the rationale of treatment.
    - Reducing the stigma associated with the condition.
    - Using simple medication regimens.
    - Positive relationships between healthcare professionals, the child, young person or adult with epilepsy and their family and/or carers.
- Regular blood test monitoring is not recommended as routine, and should be done only if clinically indicated. Indications for monitoring of AED blood levels are:
    - Detection of non-adherence to the prescribed medication.
    - Suspected toxicity.
    - Adjustment of phenytoin dose.
    - Management of pharmacokinetic interactions (eg, changes in bioavailability, changes in elimination, and co-medication with interacting drugs).
    - Specific clinical conditions - eg, status epilepticus, organ failure and certain situations in pregnancy.
- Examples of blood tests include:
    - Before surgery - clotting studies in those on sodium valproate.
    - FBC, electrolytes, liver enzymes, vitamin D levels and other tests of bone metabolism (eg, serum calcium and alkaline phosphatase) every 2-5 years for adults taking enzyme-inducing drugs.
    - Asymptomatic minor abnormalities in test results are not necessarily an indication for changes in medication.

Management of drug-resistant epilepsy[1] [4]

- Drug-resistant epilepsy has been defined as failure to achieve sustained seizure freedom after trials of two tolerated and appropriate AED schedules (as monotherapies or in combination). The majority of patients with newly diagnosed epilepsy respond well to AEDs. Failure to do so may be due to:
    - An incorrect diagnosis of epilepsy.
    - An inappropriate choice of AED for the epilepsy syndrome.
    - Failure to take the prescribed AED.
    - An underlying cerebral neoplasm, metabolic condition or immune process.
    - Concurrent drug or alcohol misuse.
- Given a correct diagnosis of epilepsy, failure to control generalised seizures completely with the first well-tolerated AED is a predictor of drug-resistant epilepsy. Once two AEDs have failed as monotherapy the chance of seizure freedom with further monotherapy is low.
- Improvement in generalised seizure control may be obtained by combining AEDs. A range of different AEDs appropriate to the epilepsy syndrome should be added as necessary in sequence, increasing the dose of each slowly to obtain the best response. It may be worthwhile trying the addition of a small dose of a third AED but it may be necessary to accept the persistence of some generalised seizures.
- For drug-resistant generalised or unclassified epilepsy: lamotrigine, levetiracetam, ethosuximide, sodium valproate and topiramate may be used in the adjunctive treatment of generalised epilepsy.
- Failure to respond to appropriate AEDs should prompt a review of the diagnosis of epilepsy and adherence to medication. Combination therapy should be considered when treatment with two first-line AEDs has failed or when improved control occurs during the process of phased substitution.

Withdrawal of drug treatment[1] [4]

- The decision to continue or withdraw medication should be taken after a full discussion of the risks and benefits of continuing or withdrawing AED therapy. Withdrawal of AEDs must be managed by, or be under the guidance of, the specialist.
- The risks and benefits of continuing or withdrawing AED therapy should be discussed when the person with epilepsy has been seizure-free for at least two years.
- Withdrawal of AED treatment should be carried out slowly (at least 2-3 months) and one drug should be withdrawn at a time.
- Particular care should be taken when withdrawing benzodiazepines and barbiturates (may take up to six months or longer) because of the possibility of drug-related withdrawal symptoms and/or seizure recurrence.
- There should be an agreed plan that if seizures recur, the last dose reduction is reversed and medical advice is sought.

Further reading

- Epilepsy Action
- Epilepsy Society
- Epilepsy Scotland
- Epilepsy Wales

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