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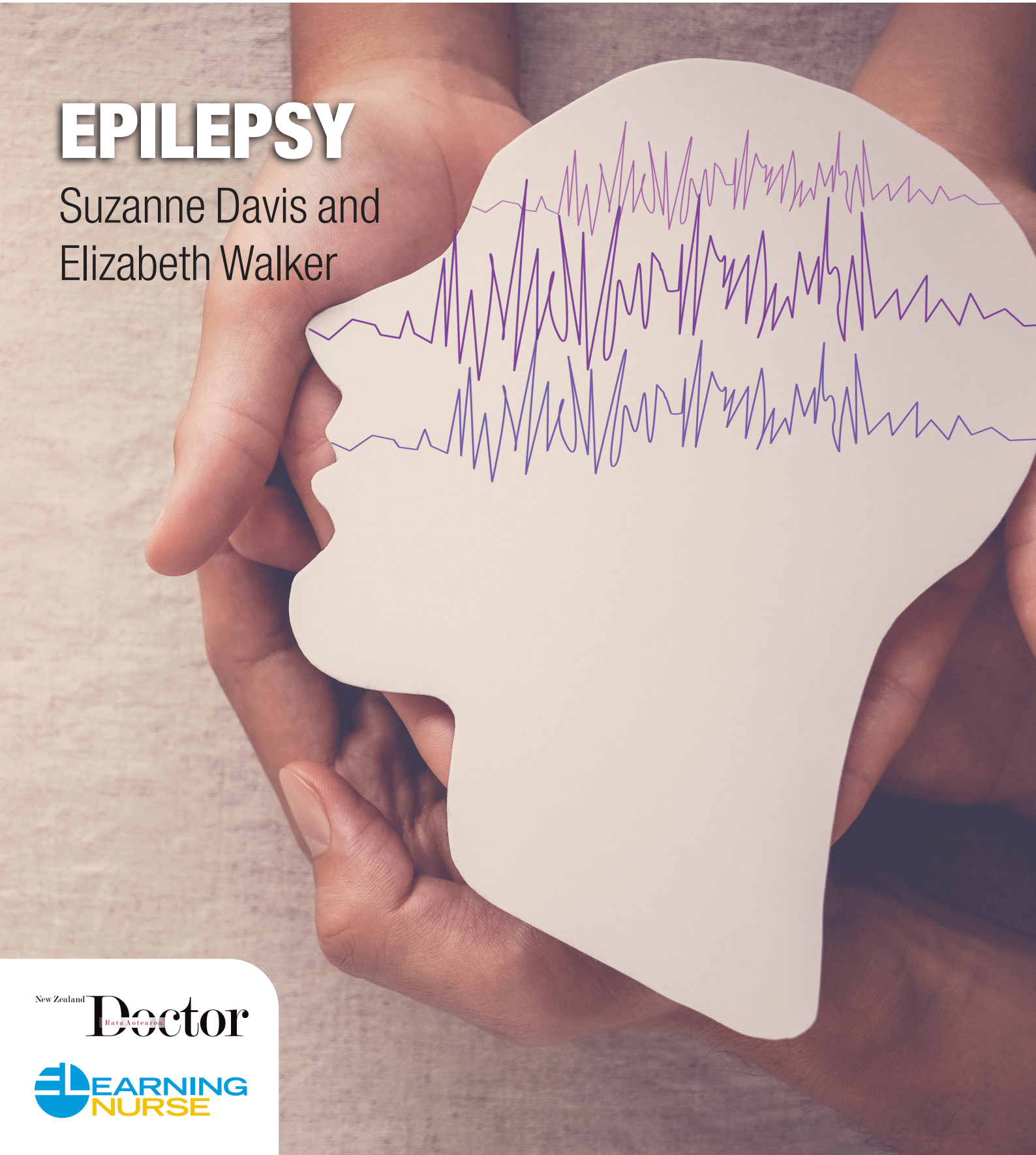

EPILEPSY

Suzanne Davis and Elizabeth Walker

New Zealand Doctor Rata Aotearoa

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How much do you already know?

Try this quiz

1. A seizure is classified as focal based on the signs and symptoms present at the onset of the seizure.
   True/False
2. The drug of first choice for any epilepsy type is carbamazepine.
   True/False
3. Rectal diazepam has a better safety profile compared with buccal midazolam when used as rescue medication for prolonged seizures.
   True/False
4. The risk of neurodevelopmental deficits in a child exposed to an anti-seizure medication in utero is greatest with sodium valproate.
   True/False
5. Topiramate does not interfere with the effectiveness of oral contraceptives.
   True/False

Answers on page 11

Epilepsy

Epilepsy is a common neurological condition encountered in general practice. This article, by Suzanne Davis and Elizabeth Walker, discusses recommendations regarding diagnosis and indications for starting anti-seizure medication. It also reviews self-management and lifestyle issues for people with epilepsy

Learning objectives

- **Discuss the diagnosis and classification of epilepsy syndromes**
- **Identify appropriate anti-seizure medications for different types of epilepsy**
- **Recognise adverse effects of anti-seizure medications**
- **Explain the risks related to epilepsy for women of childbearing age**
- **Discuss the role of primary care in managing patients with epilepsy**

Epilepsy is a group of disorders defined by the occurrence of epileptic seizures, which are events that arise due to abnormal electrical activity in the brain. Epileptic disorders can present at any age but have peaks of onset in infancy/childhood and in older age.

Epileptic seizures can range from brief behavioural arrests to stiffening and/or jerking of the whole body. The International League Against Epilepsy (ILAE; www.ilae.org) defines epilepsy as:

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

For example, a person with tuberous sclerosis who has a single seizure would have a probability of experiencing a second seizure of greater than 60 per cent. A young adult who had a single generalised tonic-clonic seizure, has myoclonic jerks in the mornings, and generalised polyspike discharges with photosensitivity on electroencephalogram (EEG) would have an epilepsy syndrome – juvenile myoclonic epilepsy.

There are multiple causes of epilepsy. In many individuals, it has an underlying genetic cause. This can be due to an abnormality in a single gene or due to the interaction of multiple genes, but it is often not inherited. Epilepsy can also be acquired due to an insult to the brain, such as head injury, hypoxic ischaemic injury (including stroke), infection or immunologically mediated disorders.[1,2]

A 2017 systematic review and meta-analysis of international studies reporting the prevalence and incidence of epilepsy found the pooled point prevalence of active epilepsy in high-income countries to be 5.49 per 1000 people. The pooled estimate for the incidence of epilepsy in high-income countries was 48.86 per 100,000 people.[3]

Applying these international estimates to our New Zealand population suggests that approximately 2400 people are diagnosed with epilepsy each year and approximately 27,000 people in New

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Suzanne Davis is a retired paediatric neurologist and president of the New Zealand League Against Epilepsy

Elizabeth Walker is a neurologist and clinical neurophysiologist at Auckland City Hospital, and honorary senior clinical lecturer at the University of Auckland School of Medicine

Diagnosis involves identifying the type of seizure and type of epilepsy

The first step in the management of epilepsy is to establish the correct diagnosis. Current guidelines require that the diagnosis of an epileptic seizure be made by a specialist – either a paediatrician or neurologist.

Identify the type of epileptic seizure

A new terminology for describing and classifying epileptic seizures was introduced by the ILAE in 2017.[1] It is summarised in Table 1.

An accurate history of events is most important in determining a patient's seizure type. Focal seizures are first defined by the earliest symptom or sign as motor (eg, clonic or atonic) or non-motor (eg, sensory or cognitive). The second step in the definition is determination of altered awareness at any stage in the progression of the seizure event.

For example, in a focal aware motor seizure, the patient is aware and fully oriented to the environment throughout the seizure. In a focal sensory seizure with impaired awareness, the patient experiences a sensory phenomenon, such as an unusual smell, then loses awareness and may have no memory of the event. Note that focal seizures with altered awareness were previously termed "partial complex seizures".

Another important feature of the new classification is the term "focal to bilateral seizure". This term replaces the previous "secondarily generalised seizure".

Often, the onset of an epileptic seizure is not witnessed. In this case, a seizure with bilateral motor signs, such as tonic or tonic-clonic movements, is classified as an "unknown" seizure type as the description of the onset of the event is not available.

Table 1. **Classification of epileptic seizure types**[1]

Focal onset	Generalised onset	Unknown onset
Aware/impaired awareness (optionally included)		
Motor onset • Automatisms • Atonic • Clonic • Epileptic spasms • Hyperkinetic • Myoclonic • Tonic	Motor • Tonic-clonic • Clonic • Tonic • Myoclonic • Myoclonic-tonic-clonic • Myoclonic atonic • Atonic • Epileptic spasms	Motor • Tonic-clonic • Epileptic spasms Non-motor • Behaviour arrest Unclassified
Non-motor onset • Autonomic • Behaviour arrest • Cognitive • Emotional • Sensory	Non-motor (absence) • Typical • Atypical • Myoclonic • Eyelid myoclonia	
Focal to bilateral tonic-clonic		

Identify the type of epilepsy

The next step, after diagnosis of the type of seizure, is diagnosis of the type of epilepsy. Epilepsy syndromes were also reclassified by the ILAE in 2017, into four types: focal, generalised, combined generalised and focal, and unknown.[2] These epilepsy syndromes are defined according to seizure type, age of onset and comorbidities, such as cognitive and behavioural disorders. The EEG and brain imaging findings (discussed later) may also play a role in identification of an epilepsy syndrome.

Confirm the diagnosis

The diagnosis of epilepsy carries significant implications for the patient, particularly with respect to driving, education and employment. It is imperative to be confident in the diagnosis of an epileptic disorder before recommending and commencing treatment with an anti-seizure medication (ASM). The features of some epileptic and non-epileptic events are summarised in Table 2.

An accurate history of events is most important in determining a patient's seizure type

Acute symptomatic seizures

Acute symptomatic seizures have a direct reversible cause and do not indicate that seizures will recur when the immediate cause is removed. Examples include drug exposure (eg, tramadol or alcohol), hypoglycaemia, electrolyte disorders, acute head injury, stroke, cerebral hypoxia, central nervous system infections and autoimmune encephalitis. The seizures may be managed acutely with an ASM, but medication is not necessarily continued after the patient has recovered from the underlying condition.

Febrile seizures

The ILAE defines a febrile seizure as a seizure occurring in childhood after one month of age and associated with a febrile illness not caused by any infection of the central nervous system. It occurs

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Zealand live with epilepsy. Thus, it is likely that most practices have patients in their care who have epilepsy.

A recent report of prolonged seizures in patients presenting to Auckland hospitals from 2015 to 2016 found the age-adjusted incidence of patients with seizures lasting 10 minutes or longer to be 22.22 per 100,000 head of population per year.

The age-adjusted incidence of longer seizures was higher in Māori (29.31/100,000/year) and Pacific patients (26.55/100,000/year) than in those with European (19.13/100,000/year) or Asian/other descent (17.76/100,000/year).[4]

Table 2. **Differential diagnosis of epileptic seizures**

Clinical event	Provoking factors	Discriminating clinical features
Generalised tonic-clonic epileptic seizure	Sleep deprivation, alcohol, drugs	Cry followed by tonic posturing of limbs, then rhythmic jerking of limbs and face Eyes open Duration of 2–3 minutes Postictal drowsiness and confusion for 10–20 minutes
Focal seizure with altered awareness	Stress, sleep deprivation	Stereotyped automatism with unresponsiveness May be tonic posturing of one arm and/or leg Duration of 30–90 seconds Postictal confusion for up to 20 minutes and amnesia for the event
Absence seizure	None, more frequent when tired	Abrupt onset and offset Duration of 10–20 seconds Unresponsive to external stimulation Eyes remain open, face may relax May be fidgeting movements of hands, clonic movements of face Induced by hyperventilation
Non-epileptic blank spell	Often in a school situation in children with learning difficulty	Can be stopped by touch or distraction Occur in specific contexts (eg, in school)
Syncope	Prolonged standing, heat, painful procedure, dehydration	Light-headedness, dimming of vision, sweating, pallor May be tonic stiffening and small jerking movements of one or more limbs Duration of 20–30 seconds Rapid recovery of cognition followed by lethargy
Cardiac arrhythmia	Stress, fright, exercise	May be a prolonged prodrome of dizziness Patient pale and limp May be tonic stiffening and limb jerking with prolonged cerebral hypoxia May be a family history of sudden death at a young age (under age 30)
Sleep attack	Sleep deprivation, history of snoring and daytime sleepiness	Often unobserved brief blackout Eyes closed Rapid recovery with no confusion
Breath-holding attack	Fright, minor injury, frustration (common from age 6 months to 3 years)	Provoking event always present Initial cry Loss of responsiveness Tonic posturing followed by small jerking movements of limbs Rapid recovery
Panic attack, hyperventilation	Stressful social situation, anxiety	Anxiety Dizziness, breathlessness, paraesthesia
Psychogenic non-epileptic event	Stressful social situation	May be prolonged motionless collapse with eyes closed Side-to-side thrashing, alternating limb movements Rapid recovery of cognition
Focal dystonia	Voluntary movement, pain	Focal dystonic posturing of one or more limbs of limited duration Often occurs with movement after a period of rest No altered awareness
Transient global amnesia	Physical exertion	Amnesia lasting several hours, during which the patient is alert and can perform tasks but cannot form new memories
Migraine	Sleep deprivation	Visual hallucinations are monochromatic or dichromatic and begin centrally Duration typically longer than 3 minutes Rarely move to the opposite field No tonic eye deviation Headache and vomiting are common
Focal unimpaired awareness sensory seizure with visual symptoms		Visual hallucinations are multicoloured and often begin peripherally May move to the opposite visual field There is commonly eye deviation Headache is common, vomiting is rare

without previous neonatal seizures or previous unprovoked seizures and does not meet the criteria for other symptomatic seizures.

A simple febrile seizure is a generalised tonic-clonic seizure under 10 minutes in duration with no recurrence within 24 hours or within the same febrile illness. A complex febrile seizure may have some focal features, be longer than 10 minutes in duration, and two or more may occur within 24 hours or within the same febrile illness.

Hospital admission should be considered after the first febrile seizure if the child is under 18 months of age, has a complex febrile seizure, has no identified focus of infection, or where there is high parental or carer anxiety.

The risk of recurrence after a febrile seizure is 30–40 per cent and is higher in infants under 12 months (50 per cent) than in children over three years (20 per cent). There is a low but increased risk of epilepsy after a febrile seizure (3 per cent overall). The risk is higher (up to 10 per cent) if there is abnormal neurological examination, a family history of epilepsy in a first-degree relative, and after a complex febrile seizure.

Regular or intermittent ASM is not recommended for febrile seizures. Infants and children should be referred to a paediatrician if they have more than three discrete febrile seizure events, if they are younger than six months or older than six years, if the seizures last longer than 30 minutes or they have focal features.

Investigate the cause

The first step in the identification of the cause of an epileptic disorder is the accurate definition of the type of seizure(s) based on a detailed history. This includes review of video recordings of typical events if these are available.

As so many people carry smart phones, video recording of seizure events is now commonplace. People who witness recurrent seizures should be encouraged to record the events on their phones. It is important to remember that in most videos, only the second half or end of an event is recorded.

Family history

Genetic causes of epilepsy may or may not be associated with inheritability, and the family history may be non-contributary. On the other hand, many genetic epilepsies (eg, childhood absence epilepsy and juvenile myoclonic epilepsy) are associated with an increased incidence of epileptic seizures in other family members.

MRI is the investigation of choice for identifying structural changes in the brain that may cause seizures

Electroencephalogram

The EEG is often helpful in determining whether an epileptic disorder is focal or generalised; some EEG findings will point to a specific epilepsy syndrome. In New Zealand, an EEG is recommended after the first epileptic seizure and is ordered by the specialist who carries out the initial diagnostic evaluation.

The EEG cannot be used to identify a seizure event as epileptic because abnormalities defined as epileptiform can be present in people who do not have epilepsy, especially in children. On the other hand, many people with epilepsy will have a normal EEG.

In New Zealand, a routine EEG is often performed after sleep deprivation to increase the likelihood of finding diagnostic abnormalities. The inclusion of a period of natural sleep in the EEG recording also increases the diagnostic yield.

Brain imaging

MRI is the technique of choice in investigation of an epileptic disorder. It is recommended for any patient under the age of two presenting with an epileptic seizure, following a focal epileptic seizure, in the presence of focal neurological signs, and in patients with specific comorbidities, such as cognitive and behavioural disorders.

CT imaging is not sufficient to investigate the cause of an epileptic disorder. A CT scan is indicated when acute focal pathology (eg, trauma, haemorrhage or stroke) is suspected in the setting of an acute presentation of an epileptic seizure and an MRI is not immediately available.

Brain imaging is not necessary when a definite diagnosis of a generalised genetic epilepsy, such as childhood absence epilepsy or juvenile myoclonic epilepsy, is made.

CASE STUDY 1

A timely second opinion

Presentation and history

Susan is a 52-year-old woman who consults her GP about a recent probable seizure and her disallowed driving. She has no past history of seizures. Susan recently had herpes ophthalmicus complicated by acute glaucoma, for which she received aggressive therapy, including timolol maleate ophthalmic solution. She has hypertension treated with a diuretic.

Recent seizure event

On the day of the event, Susan went with her husband to a movie. She had been feeling a little unwell before leaving home. When she was watching the movie, she began to feel nauseated and sweaty. Her husband describes her as moaning, then becoming rigid with her right arm elevated for about one minute. She then slumped and her head dropped onto his shoulder. She was incontinent of urine.

The ambulance was called. Susan recalls walking in the aisle to the ambulance, and her husband says she did not appear confused. Her blood pressure, recorded at the scene, was 60/80mmHg.

In the emergency department, Susan's head CT scan was normal. Routine blood tests, including electrolytes, were also normal. A diagnosis of seizure was made, and she was instructed not to drive for 12 months.

Referral

The driving restriction is significant as Susan is a sales representative. Her GP decides to refer her to a neurologist for an opinion.

Diagnosis

The neurologist makes a confident diagnosis of a convulsive syncope based on the preceding symptoms of nausea and sweating, the low blood pressure on initial assessment and relatively rapid recovery without confusion. The event was more severe than a typical syncope as Susan was wedged upright in her seat. Urine incontinence can occur in the context of prolonged cerebral hypoxia.

Predisposing factors were the beta-blocker used for glaucoma and the diuretic for hypertension. Syncope is confirmed by a cardiologist and the diuretic is stopped. Susan is able to return to driving after two months.

Type of epileptic seizure and epileptic syndrome guides treatment

In general, treatment is considered when there is evidence of recurrent seizures and is usually initiated after a second epileptic seizure. In some epileptic disorders, depending on the identification of the cause of the epilepsy, treatment is indicated after the first seizure when the probability of subsequent recurrent seizures is greater than 60 per cent.

Recurrence risk after the first epileptic seizure varies, with the highest risk (up to 90 per cent) in people with epileptic discharges in the EEG and focal neurological deficits. In people with a normal EEG and no identifiable cause for the epilepsy, the recurrence risk is lower (13–40 per cent). Overall, the risk of a second seizure is 30–40 per cent and is greatest in the first 12 months, falling to less than 10 per cent after two years.

In New Zealand, it is recommended that an evaluation be made by a specialist after the first suspected epileptic seizure. Current recommendations state that this should occur within three weeks of the initial presentation. Many DHBs have established first-seizure clinics or have made other arrangements for patients to be seen in a timely fashion after the first seizure.

It is expected that the specialist completes a diagnostic evaluation and orders an EEG if a probable epileptic seizure is identified. A decision regarding brain imaging and a choice of first-line ASM is then made. In many circumstances, the patient will present to their GP with a subsequent seizure, and the ASM can be commenced as recommended by the specialist.

Patients are encouraged to practice self-management, including good compliance with the medication regimen, if education regarding the justification for treatment and expectations about possible adverse effects is available from the onset of treatment. There is excellent information regarding epilepsy and its treatment available online that should be provided to the patient and family as appropriate (see the patient information resources listed at the end of this article).

In most circumstances, this protocol of delaying treatment until a diagnostic assessment has been completed is safe and effective. There is evidence that the timing of onset of treatment does not alter the long-term prognosis for seizure control. Factors that predict outcome include the response to the appropriately selected first-line medication and the number of seizures occurring in the first six months from presentation.

People who witness recurrent seizures should be encouraged to record the events on their phones

Which medication to choose?

Treatment should include the most effective medication for achieving complete seizure control with the least adverse effects. An inappropriately chosen medication may be ineffective and produce adverse effects that are more disabling than the seizures themselves. The choice of treatment should be guided by seizure and epilepsy type (Table 3).

Focal epilepsies

Carbamazepine, lamotrigine and levetiracetam have been shown to be equally effective as first-line therapy for focal seizures, with lamotrigine having a better adverse effects profile. Levetiracetam has the advantage of a more rapid titration than carbamazepine or lamotrigine, but it has the disadvantage of causing unacceptable psychiatric side effects of behavioural agitation, depression and anxiety in approximately 10 per cent of patients.

Generalised epilepsies

Sodium valproate has been shown to be the most effective medication for first-line therapy in genetic generalised epilepsies, such as juvenile myoclonic epilepsy. However, as sodium valproate is associated with the highest risk of foetal malformations and neurodevelopmental disorders in children exposed in utero, it is not indicated as first-line therapy for generalised epilepsies in women of childbearing age. Levetiracetam or lamotrigine are the most appropriate first-line therapies for these patients.

Rescue medications

Buccal midazolam

Patients who have experienced prolonged seizures of greater than five minutes should be prescribed midazolam, taken by the buccal or nasal route. Midazolam is available in New Zealand in plastic ampoules (15mg/5ml).

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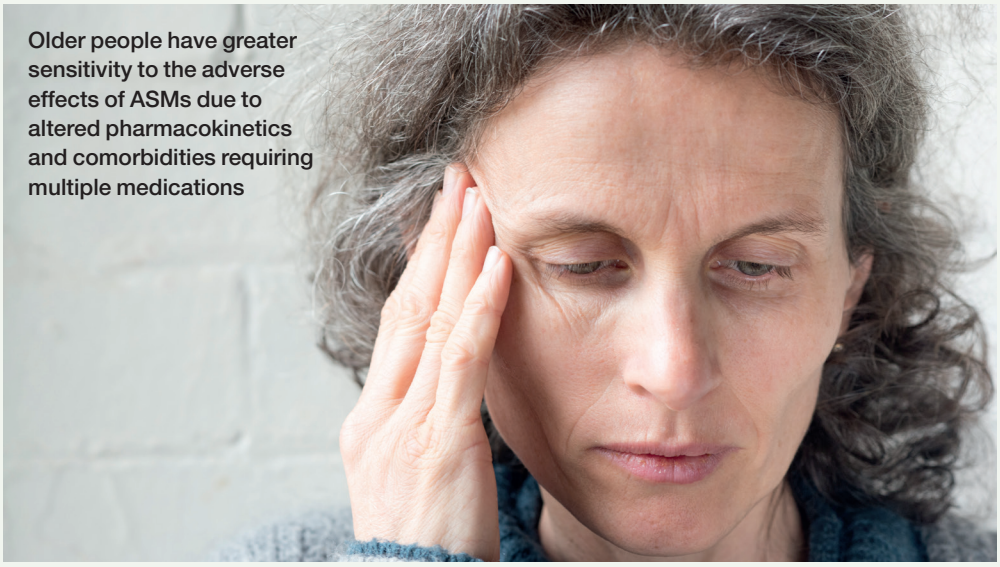
Table 3. **Anti-seizure medications for epilepsy type**

Seizure type	First-line ASM	Alternative ASMs
Generalised epilepsy with tonic-clonic seizures	Sodium valproate, except for women of childbearing age	Lamotrigine, levetiracetam
Childhood absence epilepsy	Ethosuximide	Sodium valproate, lamotrigine, levetiracetam
Focal epilepsy, including focal to bilateral seizures	Lamotrigine	Carbamazepine, levetiracetam, sodium valproate
Myoclonic epilepsy	Sodium valproate	Clobazam
Epilepsy with seizures of undetermined type	Sodium valproate, except for women of childbearing age	Lamotrigine, levetiracetam

Consider potential adverse effects, especially in women of childbearing age



Older people have greater sensitivity to the adverse effects of ASMs due to altered pharmacokinetics and comorbidities requiring multiple medications

It should be assumed that every patient taking ASMs may experience some side effects, mostly by causing sedation or mood changes. This should be taken into consideration when a decision is made to treat the disorder, and good patient self-management requires an understanding of how side effects can be managed.

Many side effects are dose related, predictable and can be minimised by a gradual escalation in the dose. Carbamazepine is a typical example of a medication that should be commenced at a low dose (100–200mg/day in an adult) and increased in increments of 100–200mg over the course of two weeks as it increases its own metabolism over this time period. Older people are more susceptible to medication side effects due to altered pharmacokinetics.

Adverse effects and monitoring

Rare idiosyncratic medication reactions mostly occur in the first few weeks of treatment, and they can be severe. Rash is the most common and occurs most often with carbamazepine and lamotrigine. The incidence of rash is reduced by slow introduction of the medication. A rash occurring between two weeks and two months of medication introduction is an indication to discontinue the medication immediately. Most rashes will resolve over days when the medication is discontinued. Life-threatening ASM hypersensitivity with multi-organ failure occurs rarely – in up to 4.5 per 10,000 people exposed.

Mild blood dyscrasias (eg, leucopenia with carbamazepine and thrombocytopenia with sodium valproate) are common and no intervention is needed. Severe blood dyscrasias are rare, occurring in up to six per 10,000 people exposed. Routine monitoring of blood count is not recommended as there is no evidence that this reduces the risk.

Hyponatraemia is common in people taking carbamazepine, especially in children, older people and those with restricted dietary salt intake. Monitoring of electrolytes and liver function should depend on clinical symptoms and is not recommended as routine in asymptomatic people taking ASMs. Enzyme induction is common with carbamazepine and phenytoin, resulting inelevation of enzymes, such

Continued from page 7

Training is necessary for caregivers and family who will administer the midazolam.

Rectal diazepam

Diazepam administered rectally has been used in the past as a rescue medication. It has been shown to be less effective than buccal midazolam in stopping prolonged seizures and has a higher incidence of respiratory depression.

Oral clobazam

Clobazam can be administered orally after a seizure when the person habitually experiences seizures in clusters over several hours, especially if there has been a provocation, such as sleep deprivation. Clobazam can also be taken as a single daily dose on several consecutive days during a seizure cluster (eg, perimenstrually in women who experience catamenial seizures).

Medication-resistant epilepsy

Approximately 60 per cent of people with newly diagnosed epilepsy become seizure free on first-line medication. If seizures recur, it may be because the diagnosis of epilepsy was incorrect, an inappropriate medication was chosen for the epilepsy syndrome or the person is not compliant with the medication regimen.

In some cases, other medications, drugs or alcohol may cause further seizures or there may be an undetected epileptogenic cerebral lesion, such as a tumour.

Failure of a first-line medication to control seizures may be an indication to repeat the EEG to confirm the epilepsy syndrome, and to review or repeat brain imaging with MRI.

A second-line medication is indicated when first-line medication has clearly failed. However, up to 30 per cent of patients will have medication-resistant epilepsy, which is defined as a failure of two tolerated and appropriately chosen and used ASM schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom.

Some people with medication-resistant epilepsy have a developmental and epileptic encephalopathy, with cognitive and behavioural disorders in addition to epilepsy. Any person who has failed two appropriately chosen and tolerated ASMs should be referred to a specialist – paediatrician or neurologist – for diagnostic re-evaluation and consideration of non-medical treatment, such as diet or epilepsy surgery.

It is important to advise all girls and women of the issues related to epilepsy and pregnancy when ASMs are first prescribed

as gamma-glutamyl transferase. This is not an indication to change or cease therapy.

Long-term treatment with ASMs may reduce bone density, especially in people with limited mobility. There are no current guidelines regarding routine monitoring of bone density, but prophylactic vitamin D should be considered for people at highest risk.

Psychiatric comorbidity

Depression is the most common psychiatric comorbidity in people with epilepsy – it occurs in up to 45 per cent of patients at some stage. All ASMs are associated with behavioural side effects, and some (particularly levetiracetam and topiramate) have a higher incidence of significant psychiatric adverse effects, including depression.

Women of childbearing age

Women of childbearing age should be fully informed of the risks to the foetus with any of the medications prescribed, as well as the risks to both herself and her foetus from uncontrolled seizures during pregnancy. As about half of pregnancies are unplanned, it is important to advise all girls and women of the issues related to epilepsy and pregnancy when ASMs are first prescribed.

Women are advised to use two forms of contraception when taking ASMs and should be assessed and managed by a neurologist before planning a pregnancy. Daily folic acid at a dose of 5mg per day is recommended in all women of childbearing age with epilepsy.

Educational resources about the use of ASMs in pregnancy are available for both prescribers and patients (see the lists at the end of this article), including two booklets prepared by ACC (go to: acc.co.nz/treatmentsafety).

Hormonal contraception

Enzyme-inducing ASMs (eg, carbamazepine and topiramate) reduce the contraceptive effect of oral contraceptives. There is evidence that lamotrigine induces the metabolism of the progestin levonorgestrel. If an oral contraceptive is used with an enzyme-inducing ASM, a higher oestrogen formulation is recommended (eg, 50µg). Even at the higher dose, contraception cannot be guaranteed, and additional protection is needed.

Progesterone-only oral contraceptives are likely to be ineffective when enzyme-inducing ASMs are taken. On the other hand, depot medroxyprogesterone acetate injections appear to be effective but need to be given more frequently. Use of additional forms of contraception, such as intrauterine devices, is recommended.

It is also important to be aware that lamotrigine levels are reduced by oral contraceptives. Women taking lamotrigine for epilepsy need to have levels monitored when oral contraceptives are commenced, and signs of toxicity should be monitored when oral contraceptives are discontinued.

Anti-seizure medication during pregnancy

Uncontrolled generalised tonic-clonic seizures expose both the pregnant mother and foetus to significant risk for morbidity and mortality. For some women, pregnancy exposes them to a higher risk for seizures. Lamotrigine levels are significantly reduced during the second trimester of pregnancy, requiring close monitoring of the dose and blood levels. Another frequent cause of breakthrough seizures during pregnancy is self-manipulation of the medication dose.

ASM exposure to the foetus is known to increase the risk of major foetal malformations and, in some cases, also increase the risk of later developing neurodevelopmental disorders, including autistic spectrum disorder. For some ASMs, such as sodium valproate, the risk to the foetus is dose related:

- Sodium valproate at doses greater than 1500mg/day exposes the foetus to the highest risk for foetal malformations, such as spina bifida, cleft palate and heart defects – 24 per cent risk of babies are affected, compared with 2–3 per cent of babies unexposed to ASMs and 4–7 per cent of babies exposed to any ASM.
- Sodium valproate at doses greater than 800mg/day are associated with an increased risk for childhood developmental delays, and autistic spectrum disorder occurs in 4–15 per cent of children exposed in utero compared with 2–7 per cent of children unexposed to ASMs. Children exposed to sodium valproate in utero are eight times more likely to need extra help in school than other children.

Carbamazepine, lamotrigine and levetiracetam are associated with a significantly lower risk to the foetus. Monotherapy is recommended during pregnancy, and there is substantial evidence that polytherapy with sodium valproate is associated with higher risks.

It is recommended that women with epilepsy who plan a pregnancy are referred for specialist evaluation one year, but no less than six months, before discontinuing contraception so gradual transition to a more appropriate medication regimen can occur.

CASE STUDY 2

Day and night seizures

Presentation and assessment

Jen is a 20-year-old woman who visits her GP for advice. For the last two to three years, she has had spells when she blanks out and loses track of conversations. She also has muscle twitches in her hands in the mornings. She awoke on the morning before this visit with a sore mouth and found she had bitten her tongue during her sleep. Her muscles also felt sore.

Jen appears normal except for bruising on one side of her tongue. Her bitten tongue and sore muscles suggest she had a convulsion during her sleep. As she lives alone, there is no witness to the event. Her GP assumes that the history indicates both focal seizures and a generalised seizure. Jen is prescribed carbamazepine 200mg twice daily.

Referral and diagnosis

Jen returns four weeks later as she is concerned that her hand twitching has increased. Her GP refers her for a neurological assessment.

The neurologist orders an EEG, which shows a generalised spike wave discharge when Jen is asleep. She also has a photoconvulsive response to flashing lights. The neurologist makes a diagnosis of a genetic generalised epilepsy (juvenile myoclonic epilepsy) based on the history of daytime myoclonic and absence seizures, the nocturnal generalised seizure and the EEG findings. Brain imaging is not recommended.

Management

In juvenile myoclonic epilepsy, carbamazepine is likely to exacerbate the myoclonic seizures. Although sodium valproate is the medication of choice, it has the potential for teratogenic and neurodevelopmental effects on an exposed foetus. The neurologist recommends that Jen starts on levetiracetam. Jen is advised to stop driving because of her daytime absence seizures.

Stopping anti-seizure medication

The timing of a decision to discontinue ASMs will depend on the specific epilepsy syndrome as this will determine the prognosis for seizure freedom when off medication. Some epilepsies may require long-term ASM therapy. When a person with epilepsy has been seizure free on medication for two or more years, it is customary to begin a discussion regarding discontinuation of medication.

The balance between adverse effects of continued medication and the risk of further seizures should be discussed. It is reasonable to refer the patient to a specialist for this discussion.

Most ASMs can be tapered over two months. However, several ASMs, such as phenobarbital and clonazepam, will require a longer period of dose reduction (up to six months). The patient must cease driving during the taper and for three months afterwards.

Enhancing the roles of primary care and patient self-management

Climbing to places about one metre or more off the ground should be avoided

The GP and practice nurses play an important role in supporting self-management in people with epilepsy. This includes actions that enhance adherence to a medication regimen and liaising between patients and community, educational or other health services, particularly for patients with cognitive, psychiatric and multiple comorbidities.

A person taking medication for epilepsy should have a review of their management at least annually, even if seizure free, but especially if seizures are recurring. Even as few as one seizure per year can cause major disruption to social, educational and employment opportunities, and will prevent the person from legally driving a vehicle.

The annual review will determine medication compliance and assess any barriers to full compliance, confirm appropriate contraception by two methods and discuss any plans for pregnancy in women of childbearing age, assess any adverse effects of medications and determine if there are any important medication interactions.

At the review, the patient's management of risks in their everyday life should be discussed. In addition, the review should note any barriers to participation in education or employment and reinforce knowledge of the regulations regarding driving. The patient should be given information about the services of Epilepsy New Zealand if they are not already participating.

A person with epilepsy who continues to have seizures, even as infrequently as once per year, and is compliant with the recommended medication regimen should be referred to a paediatrician or neurologist.

Minimising risk of injury

People with epilepsy should be aware of the risks they might be exposed to during a seizure. Preventable injuries and deaths during seizures are not uncommon. Drowning is the most common cause of death caused by a seizure. Risk of drowning can be minimised by advising the patient to shower rather than take a bath, and to swim with one-on-one supervision from a responsible adult who is aware of their epilepsy. Bicycle riding, especially around traffic, and climbing to places about one metre or more off the ground should be avoided.

Driving after a seizure

Seizures are a rare cause of traffic accidents, but the regulations regarding driving are clearly laid out by the NZ Transport Agency. The regulations should be brought to the attention of any patient who is driving, or intends to drive, after the first seizure.

For Class 1 licences, a single seizure means a person will need to stop driving for 12 months. In exceptional circumstances, the 12-month stand-down period may be reduced if there is a clearly identified, non-recurring cause. This can be reviewed in consultation with a neurologist.

A person taking medication for epilepsy should have a review of their management at least annually

When a person with epilepsy is treated with an ASM, they are required to be free of a seizure for 12 months before they are permitted to drive. There is also a stand-down period from driving if the medication is changed or discontinued.

There is an exception for people who have only nocturnal seizures – they may drive if they have a stable pattern of seizures at night and are free of awake seizures for 12 months.

For other classes of licence and endorsements, a person with a seizure or seizure disorder is considered permanently unfit to drive.

Sudden unexpected death in epilepsy

People with epilepsy have a small but real risk of death. It is important that patients and their caregivers are educated regarding this risk at the time of diagnosis.

Sudden unexpected death in epilepsy is defined as sudden, unexpected, witnessed or unwitnessed, non-traumatic and non-drowning death in patients with epilepsy, with or without evidence for a seizure and excluding documented status epilepticus, in which post-mortem examination does not reveal a structural or toxicological cause of death.

SUDEP is reported to be the cause of 2–18 per cent of all deaths in people with epilepsy. The overall incidence is one in 4500 patient-years in children and one in 1000 patient-years in adults.

The cause of SUDEP is unknown but is theorised to be due to respiratory suppression followed by cardiac arrest in the postictal period of a tonic-clonic seizure.

The main risk factor for SUDEP is the presence of tonic-clonic seizures – one or two tonic-clonic seizures per year increases the risk fivefold, while more than three per year results in a 15-fold increased risk compared with those who are seizure free. Other risk factors include age (highest risk in the 18–25 age group), uncontrolled epilepsy, nocturnal seizures and intellectual disability.

Community services for people with epilepsy

Epilepsy New Zealand is an organisation that has a nationwide focus and employs support workers (also known as field staff and educators) across 12 field offices. These field offices deliver services through paid staff and volunteers. Programmes provided by Epilepsy New Zealand include advocacy, awareness, research, information and education, and support services.

People with epilepsy can engage with Epilepsy New Zealand casually by attending a seminar or contacting an epilepsy educator. People may also be more actively involved by joining as a member. It is recommended that all patients are provided with information regarding community support services at the time of diagnosis of their epilepsy. ■

References

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2. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. *Epilepsia*. 2017;58(4):512–21.
3. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. *Neurology* 2017;88(3):296–303.
4. Bergin PS, Brockington A, Jayabal J, et al. Status epilepticus in Auckland, New Zealand: Incidence, etiology, and outcomes. *Epilepsia* 2019;60(8):1552–64.

Quiz answers

1. True **2.** False **3.** False **4.** True **4.** False

Patient information

Health Navigator
Search for "epilepsy" at healthnavigator.org.nz

Epilepsy New Zealand
epilepsy.org.nz

My Medicines
mymedicines.nz

Valproate risk in pregnancy
sanofi.com.au/valproate

ACC
Medicines for epilepsy, mental health, and pain can harm your unborn baby: Talk to your doctor about the risks to you and your baby, and how to balance them. May 2020 – available at acc.co.nz/treatmentsafety

Useful resources

New Zealand Formulary
nzf.org.nz

New Zealand Formulary for Children
nzfchildren.org.nz

Regional HealthPathways
https://bit.ly/2YRBtTA

International League Against Epilepsy
ilae.org

EpilepsyDiagnosis.org
epilepsydiagnosis.org

Paediatric Neurology Clinical Network
Epilepsy Guidelines and Pathways for Children and Young People. June 2017. https://bit.ly/2ZA5TsD

National Institute for Health and Care Excellence
Epilepsies: diagnosis and management. February 2020. nice.org.uk/guidance/cg137

ACC
Benefits and risks of taking anti-seizure medicines for epilepsy, mental health, or pain: Information for healthcare professionals to discuss with anyone who could get pregnant. May 2020 – available at acc.co.nz/treatmentsafety

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Benefits and risks of anti-seizure medicines in pregnancy

In some cases, anti-seizure/mood stabilising medicines may result in Fetal Anti-Convulsant Syndrome (FACS) in babies exposed in utero. Sodium valproate is the medicine known to have the highest risk.

Information resources about the benefits and risks of these medicines can be ordered for free at **www.acc.co.nz/treatmentsafety.** Two booklets are available, one for health professionals and one for people taking the medicines, as well as a flyer suitable for waiting rooms.

Please make sure anyone taking these medicines who could get pregnant has a copy of the patient information booklet, and understands the benefits and risks.

The resources were developed by medical experts and consumers, and endorsed by ACC, the Health Quality and Safety Commission, the Ministry of Health, and Foetal Anti-Convulsant Syndrome New Zealand.