The management of epilepsy in children and adults

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Epilepsy is a disease of the brain characterised by an enduring predisposition to generate epileptic seizures.[1] It is one of the most common neurological illnesses, affecting individuals of any age and ethnicity. In industrialised countries, 3−4% of people will develop epilepsy during their lifetime. The risk is higher in resource-poor countries.[2] Epilepsy has deleterious effects on social, vocational, physical and psychological wellbeing. In the Global Burden of Disease 2010 study, severe epilepsy ranked fourth among 220 health conditions in terms of disability weight.[3]

The diagnosis of epilepsy is made primarily on clinical grounds. Supporting investigations include electroencephalography (EEG) and neuroimaging, primarily magnetic resonance imaging (MRI). According to the 2014 practical definition of epilepsy of the International League Against Epilepsy, epilepsy can be diagnosed:

- after at least two unprovoked seizures > 24 hours apart (the traditional definition);
- after one unprovoked (or reflex) seizure when there is $\geq 60\%$ chance of seizure recurrence (similar to that after two unprovoked seizures) over the next 10 years; or
- when an epilepsy syndrome can be identified.[4]

Epilepsy should be classified according to seizure type, epilepsy type and, when possible, aetiology and epilepsy syndrome. Classification informs selection of the most appropriate therapy. In this review, we describe the new International League Against Epilepsy classification of seizure types and epilepsies, updated to reflect the major advances in our understanding of the biology of seizure disorders.[5,6] We also discuss the management of epilepsy in children and adults, highlighting recent advances. To provide an evidence-based review, we searched PubMed for original and review articles as well as specialist society guidelines up to 31 August 2017. We also identified relevant publications from the reference lists of retrieved articles and our files.

2017 International League Against Epilepsy classification of seizure types

Epileptic seizures are categorised by seizure onset into focal seizures (arising within networks limited to one hemisphere), generalised seizures (arising at some point within, and rapidly engaging, bilaterally distributed networks), and seizures of unknown onset (when there is insufficient information to classify the seizure as focal or generalised) (Box 1).[5]

Focal seizures can be differentiated into focal aware seizures (formerly simple partial seizures) or focal impaired awareness seizures (formerly complex partial seizures), depending on whether awareness is lost at any point through the seizure. Seizures can be further subgrouped according to their first feature, whether that be a motor or non-motor manifestation. Motor features include tonic, atonic, clonic and epileptic spasms. Non-motor features include cognitive, autonomic and emotional

Summary

- The International League Against Epilepsy has recently published a new classification of epileptic seizures and epilepsies to reflect the major scientific advances in our understanding of the epilepsies since the last formal classification 28 years ago. The classification emphasises the importance of aetiology, which allows the optimisation of management.

- Antiepileptic drugs (AEDs) are the main approach to epilepsy treatment and achieve seizure freedom in about two-thirds of patients.

- More than 15 second generation AEDs have been introduced since the 1990s, expanding opportunities to tailor treatment for each patient. However, they have not substantially altered the overall seizure-free outcomes.

- Epilepsy surgery is the most effective treatment for drug-resistant focal epilepsy and should be considered as soon as appropriate trials of two AEDs have failed. The success of epilepsy surgery is influenced by different factors, including epilepsy syndrome, presence and type of epileptogenic lesion, and duration of post-operative follow-up.

- For patients who are not eligible for epilepsy surgery or for whom surgery has failed, trials of alternative AEDs or other non-pharmacological therapies, such as the ketogenic diet and neurostimulation, may improve seizure control.

- Ongoing research into novel antiepileptic agents, improved techniques to optimise epilepsy surgery, and other non-pharmacological therapies fuel hope to reduce the proportion of individuals with uncontrolled seizures. With the plethora of gene discoveries in the epilepsies, "precision therapies" specifically targeting the molecular underpinnings are beginning to emerge and hold great promise for future therapeutic approaches.

features. Focal to bilateral tonic−clonic seizures (formerly secondarily generalised seizures) are tonic−clonic seizures reflecting propagation of focal seizures to both hemispheres.

Generalised seizures are divided into motor (tonic−clonic, clonic, tonic, myoclonic, myoclonic−tonic−clonic, myoclonic−atonic, atonic, and epileptic spasms) and non-motor (absences, further categorised as typical, atypical, myoclonic, and absence with eyelid myoclonia). Seizures of unknown onset can be defined by the presence of motor or non-motor phenomena. An additional "unclassified" group is used when there is insufficient information available for classification.
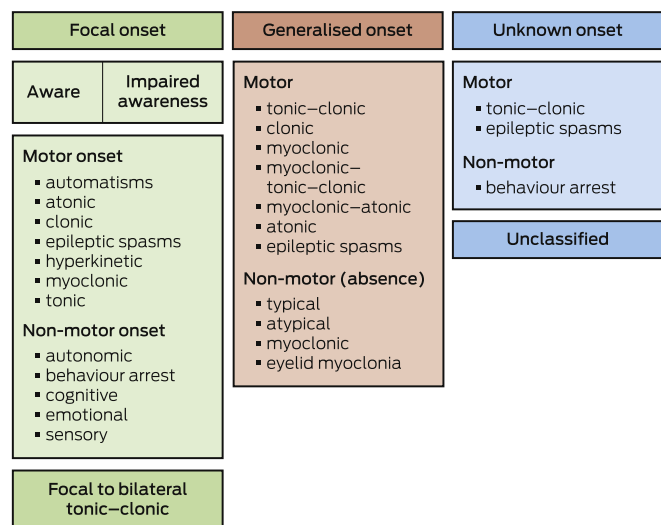
2017 International League Against Epilepsy classification of the epilepsies

The new classification of the epilepsies provides a diagnostic framework at three levels, highlighting the importance of aetiological consideration at all stages (Box 2).[6] It begins with defining the seizure type.[5] The second level is the epilepsy type, which includes focal, generalised, combined focal and generalised, and unknown epilepsy. The third level is diagnosis of the epilepsy

1 The 2017 International League Against Epilepsy classification of seizure types*

Focal onset	Generalised onset	Unknown onset

Focal onset

Aware	Impaired awareness

Motor onset
- automatisms
- atonic
- clonic
- epileptic spasms
- hyperkinetic
- myoclonic
- tonic

Non-motor onset
- autonomic
- behaviour arrest
- cognitive
- emotional
- sensory

Focal to bilateral tonic–clonic

Generalised onset

Motor
- tonic–clonic
- clonic
- myoclonic
- myoclonic–tonic–clonic
- myoclonic–atonic
- atonic
- epileptic spasms

Non-motor (absence)
- typical
- atypical
- myoclonic
- eyelid myoclonia

Unknown onset

Motor
- tonic–clonic
- epileptic spasms

Non-motor
- behaviour arrest

Unclassified

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syndrome whenever possible. Aetiological categories, which have important management implications, include structural, genetic, infectious, metabolic, immune and unknown. The new framework also emphasises the importance of identifying comorbidities, such as learning, psychiatric and behavioural problems, enabling prompt diagnosis and appropriate management.
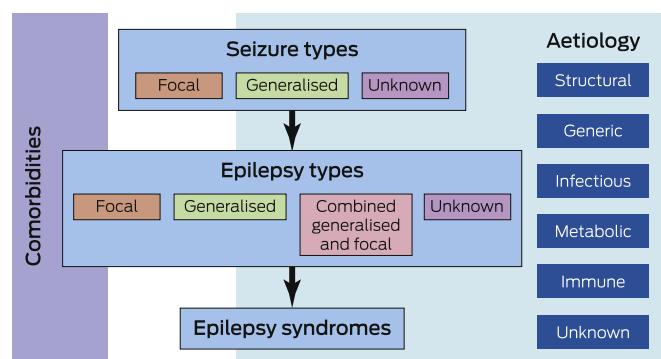
The term "idiopathic generalised epilepsies" refers collectively to four syndromes: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy and generalised tonic–clonic seizures alone (formerly generalised tonic–clonic seizures on awakening). These syndromes can also be termed genetic generalised epilepsies, because there is strong clinical evidence that their aetiology is genetic. However, sociocultural factors in some countries make the genetic designation problematic.

The management of epilepsy

Pharmacological therapy

Antiepileptic drugs (AEDs) are the mainstay of treatment. The term "antiepileptic" reflects conventional terminology, although

2 The 2017 International League Against Epilepsy classification of the epilepsies*

Comorbidities

Seizure types
- Focal
- Generalised
- Unknown

Epilepsy types
- Focal
- Generalised
- Combined generalised and focal
- Unknown

Epilepsy syndromes

Aetiology
- Structural
- Generic
- Infectious
- Metabolic
- Immune
- Unknown

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"antiseizure" would be more accurate because these drugs suppress the symptoms (seizures) not the underlying disease. The goal of AED therapy is to ensure the best possible quality of life by maximising seizure control and minimising drug toxicity.[7,8] About two-thirds of people with epilepsy become seizure-free with AEDs (Box 3), with response varying according to different factors, including epilepsy syndrome, aetiology and pre-treatment seizure frequency.[8]

Newly diagnosed epilepsy. General principles guiding pharmacological therapy are illustrated in Box 4. Because AEDs are continued for at least 2 years, and sometimes for life, the decision to start treatment requires careful appraisal of the risk-to-benefit ratio and the patient's and family's preferences.[8] Treatment is usually indicated when a diagnosis of epilepsy has been made.[4] It may also be justified after a single seizure not meeting the criteria for epilepsy, when the risk of recurrence is deemed to be significant and the risk of injury (eg, frail individuals) or social consequences (eg, loss of employment) with seizure recurrence is high. Conversely, treatment may not be warranted in mild epilepsies (eg, patients with rare, non-disabling focal aware seizures).

Treatment is started with a single AED introduced at a small dose, unless an immediate therapeutic effect is needed; for example, for status epilepticus or frequent seizures. The dose should be gradually increased to the lowest effective maintenance dose to minimise adverse effects.[8,10] About 50% of patients become seizure-free on the first AED, most on low to moderate doses.[11] There is no single AED that is ideal for all patients. Rather, AED selection should be tailored to the patient's characteristics and drug-related factors (Box 5). Although first generation AEDs such as carbamazepine and valproic acid remain valuable first-line therapies, availability of newer AEDs has expanded opportunities to tailor treatment (Box 6). Second generation AEDs are no more efficacious than older agents, but some offer advantages in terms of fewer drug interactions and improved tolerability. The Standard versus New Antiepileptic Drugs (SANAD) study compared the effectiveness of several AEDs in adults and children with newly diagnosed epilepsy.[12,13] For focal epilepsies, carbamazepine, lamotrigine and oxcarbazepine fared better than topiramate and gabapentin.[12] Overall, lamotrigine was slightly better than carbamazepine due to fewer patients discontinuing treatment because of adverse effects. However, it is unclear how many patients were on controlled release carbamazepine, which is better tolerated than immediate release carbamazepine.[14] Other head to head trials in newly diagnosed focal epilepsy have not shown substantial differences in efficacy or tolerability between controlled release carbamazepine and other second generation AEDs; that is, levetiracetam, zonisamide and lacosamide.[14-16]

A separate arm of the SANAD study found valproic acid to be more effective than lamotrigine and topiramate for generalised and unclassified epilepsies.[13] The superiority of valproic acid was more pronounced in the subgroup with genetic generalised epilepsy. However, current guidelines recommend avoiding valproic acid in women of childbearing potential whenever possible, due to higher risks of anatomical teratogenesis, including neural tube defects, and behavioural teratogenesis, namely impaired postnatal cognitive development and autism.[17] The broader management of epilepsy in women of childbearing potential or pregnancy is beyond the scope of this article and the reader is referred to a comprehensive review on the topic.[18]

If seizures persist on the first AED despite up-titration to the maximally tolerated optimal dose, non-compliance should be excluded and the appropriateness of the diagnosis and

3 Efficacy spectrum of currently available antiepileptic drugs (AEDs)*

	AED	Efficacy spectrum	Comments
First generation AEDs	Valproic acid	All seizure types	
	Benzodiazepines	All seizure types	Can precipitate tonic seizures, especially after IV use in LGS
	Phenobarbital	Most seizure types	Not effective against absence seizures
	Primidone	Most seizure types	Not effective against absence seizures
	Carbamazepine	Focal seizures and generalised tonic–clonic seizures	Can precipitate or aggravate absence seizures and myoclonic seizures
	Phenytoin	Focal seizures and generalised tonic–clonic seizures	Can precipitate or aggravate absence seizures and myoclonic seizures
	Ethosuximide	Absence seizures	
Second generation AEDs	Lamotrigine	Most seizure types	Can precipitate or aggravate myoclonic seizures
			Efficacy best documented against focal seizures, generalised tonic–clonic seizures, absence seizures, and drop attacks associated with LGS
	Levetiracetam	Most seizure types	Efficacy against tonic and atonic seizures not documented
			Efficacy best documented against focal seizures, generalised tonic–clonic seizures and myoclonic seizures
	Topiramate	Most seizure types	Efficacy against absence seizures not documented
			Efficacy best documented against focal seizures, generalised tonic–clonic seizures, and drop attacks associated with LGS
	Zonisamide	Most seizure types	Efficacy against most generalised seizure types poorly documented
			Efficacy best documented against focal seizures
	Oxcarbazepine	Focal seizures and generalised tonic–clonic seizures	Can precipitate or aggravate absence seizures and myoclonic seizures
	Perampanel	Focal seizures and generalised tonic–clonic seizures	
	Vigabatrin	Focal seizures and infantile spasm	Shown to be particularly efficacious in the treatment of infantile spasms associated with tuberous sclerosis complex
			Can precipitate or aggravate myoclonic seizures
	Rufinamide[†]	Focal seizures, and drop attacks associated with LGS	
	Felbamate[†]	Focal seizures, and drop attacks associated with LGS	
	Elisacarbazepine acetate[†]	Focal seizures	May precipitate or aggravate absence seizures and myoclonic seizures
	Lacosamide	Focal seizures	
	Pregabalin	Focal seizures	Can precipitate or aggravate myoclonic seizures
	Gabapentin	Focal seizures	Can precipitate or aggravate myoclonic seizures
	Tiagabine	Focal seizures	Can precipitate or aggravate absence seizures and myoclonic seizures
	Brivaracetam	Focal seizures	
	Everolimus[‡]	Seizures associated with tuberous sclerosis complex only	Efficacy best documented against focal seizures associated with tuberous sclerosis complex
	Stiripentol[†]	Seizures associated with Dravet syndrome only	Only indicated for use in combination with clobazam and valproic acid against tonic–clonic seizures associated with Dravet syndrome

IV = intravenous. LGS = Lennox–Gastaut syndrome. * In Australia, some Therapeutic Goods Administration (TGA)-approved AEDs, such as primidone and tiagabine, are almost no longer used in routine clinical practice (except for carefully selected cases) due to their unfavourable adverse effect profile. For the same reason (particularly due to the risk of visual field defects), the use of vigabatrin is restricted to the treatment of infantile spasms. Modified from Perucca,[9] with permission from John Wiley and Sons. † Not approved by the TGA. ‡ Not approved by the TGA for the treatment of seizures or epilepsy. ◆
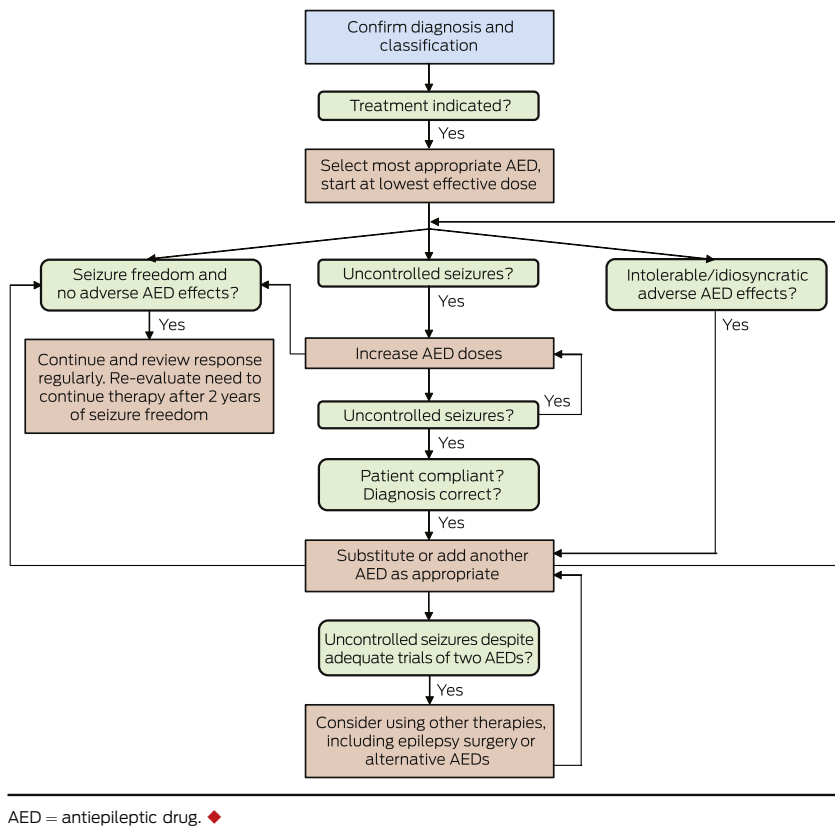
treatment re-appraised (Box 4). If an AED change is indicated, switching to an alternative monotherapy carries about 15% chance of attaining seizure freedom.[11] Polytherapy is usually offered after failure of two or three sequential monotherapies, but might be considered earlier when prognostic factors indicate a difficult to treat form of epilepsy unlikely to respond fully to monotherapy.[7]

Drug-resistant epilepsy. Overall, fewer than 15% of patients who continue to have seizures after two appropriate AED trials become seizure-free with subsequent AEDs.[11] Based on this observation, the International League Against Epilepsy defined drug-resistant epilepsy as "failure of adequate trials of two tolerated, appropriately chosen and used AED schedules (whether as monotherapies or in combination) to achieve sustained seizure-freedom".[19] Drug-resistant epilepsy is associated with excess disability, morbidity and mortality.[19] As soon as a patient has failed two AEDs, the feasibility of epilepsy surgery should be considered[20] (Box 4). For patients who are not surgical candidates, alternative AEDs may be tried. However, the introduction of many second generation AEDs has had minimal impact on the overall clinical outcomes, with seizures remaining uncontrolled in about a third of patients.[11]

Medicinal cannabis has received considerable attention after anecdotal reports of impressive results in severe epilepsies.[21] However, scientifically sound evidence on the effectiveness of cannabinoids in epilepsy was provided only recently. In a

4 General principles in the pharmacological treatment of epilepsy

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                    Confirm diagnosis and
                         classification
                               │
                      Treatment indicated?
                               │ Yes
                  Select most appropriate AED,
                   start at lowest effective dose
                               │
   Seizure freedom and    Uncontrolled seizures?   Intolerable/idiosyncratic
   no adverse AED effects?         │ Yes            adverse AED effects?
          │ Yes                    │                         │ Yes
   Continue and review       Increase AED doses
   response regularly.              │
   Re-evaluate need to      Uncontrolled seizures?  ── Yes ─┐
   continue therapy              │ Yes
   after 2 years of         Patient compliant?
   seizure freedom          Diagnosis correct?
                               │ Yes
                   Substitute or add another
                      AED as appropriate
                               │
                  Uncontrolled seizures despite
                  adequate trials of two AEDs?
                               │ Yes
                  Consider using other therapies,
                  including epilepsy surgery or
                       alternative AEDs
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AED = antiepileptic drug. ◆

randomised, double-blind, add-on, placebo-controlled 14-week trial in Dravet syndrome (a severe infantile onset epilepsy), a 20 mg/kg/day dose of cannabidiol (a non-psychoactive cannabinoid) was associated with a median decrease in monthly frequency of convulsive seizures from 12.4 to 5.9, compared with a decrease from 14.9 to 14.1 for the placebo group ($P = 0.01$).[22] Five per cent of children receiving cannabidiol were seizure-free, versus 0% of those receiving placebo. Most common adverse events in the cannabidiol group included somnolence, fatigue, diarrhoea, vomiting and decreased appetite. Notably, two-thirds of patients were on clobazam.[22] As cannabidiol increases serum clobazam levels by 60% and those of its active metabolite (N-desmethylclobazam) by 500%,[23] this interaction might have contributed to the efficacy and toxicity of cannabidiol. In similarly designed trials reported in conference abstracts, cannabidiol was superior to placebo in reducing drop attacks in patients with Lennox–Gastaut syndrome.[24,25] Overall, more evidence is required before cannabidiol can be considered further for the treatment of most individuals with epilepsy.

In Australia, medicinal cannabis was reclassified by the Therapeutic Goods Administration from "prohibited substance" to "controlled drug" on 1 November 2016, enabling the prescription of unapproved cannabis-based treatments through one of three pathways: Authorised Prescriber Scheme, Special Access Scheme or as part of a clinical trial. However, adoption of the classification changes varies between states and territories, as do specific requirements relating to prescription and possession. More information can be found in the Therapeutic Goods Administration website.[26]

Surgical therapy

Epilepsy surgery involves resection or, less commonly, disconnection or destruction of epileptic tissue, and it is the most effective therapy for selected patients with drug-resistant epilepsy.[20] Eligibility for surgery is determined based on a battery of investigations, including scalp video-EEG monitoring, structural MRI, fluorodeoxyglucose positron emission tomography, ictal and interictal single-photon emission computed tomography, functional MRI, and neuropsychological testing. These studies aim at delineating the "epileptogenic zone" (ie, the minimum amount of cortex which if resected, disconnected or destructed will result in seizure freedom) and defining the risk of post-operative morbidity.[20] Some patients also require intracranial EEG, either as intra-operative electrocorticography or chronic extra-operative recordings, to improve localisation of the epileptogenic zone.[20]

The probability of seizure freedom after epilepsy surgery depends on many factors, including epilepsy type, the results of pre-surgical investigations, underlying pathology, extent of resection, and duration of follow-up.[20] Wiebe and colleagues[27] randomised 80 patients with drug-resistant temporal lobe epilepsy to anterior temporal lobe resection or continued AED therapy. At one year, 23/40 surgically treated patients (58%) were free of disabling seizures versus only 3/40 medically treated patients (8%) ($P < 0.001$). The surgical group reported better subjective wellbeing compared with the medical group. One patient in the medical group died of sudden unexpected death in epilepsy; no deaths occurred in the surgical group. In a decision analysis, anterior temporal lobe resection for a 35-year-old man with drug-resistant temporal lobe epilepsy increased life expectancy by 5 years (95% CI, 2.1–9.2) compared with continued AED therapy.[28] This benefit compares favourably with other medical interventions: eliminating lifelong coronary heart disease mortality in a 35-year-old individual increases life expectancy by 3.1–3.3 years, whereas coronary grafting or β-blocker use after myocardial infarction increases survival by 0.25–1.1 years.[28]

In 2003, the American Academy of Neurology recommended that patients with disabling focal seizures "who have failed appropriate trials of first-line AEDs should be considered for referral to an epilepsy surgery center".[29] Of concern, however, these recommendations have not translated to increased use of epilepsy surgery.[30] Consideration of epilepsy surgery still occurs typically 20 years after epilepsy onset, despite evidence of its effectiveness after failure of two adequate AED trials,[31] and despite data suggesting that longer epilepsy duration adversely affects surgical outcome.[20]

When surgical cure is not feasible, palliative epilepsy surgery, such as corpus callosotomy, may be undertaken in selected patients, with the goal of improving quality of life by decreasing seizure frequency and severity.[20]

Other therapies

Among other non-pharmacological therapies available for patients with drug-resistant epilepsy, vagus nerve stimulation has been found to produce ≥ 50% seizure reduction in half the patients, but fewer than 5% become seizure-free.[32] Transcutaneous stimulation of the vagus or trigeminal nerve are newer techniques,[33] which require validation in well designed studies. Two other

5 Factors to be considered in the selection of an antiepileptic drug

Factors related to the individual	• Age
	• Sex
	• Ethnicity
	• Genetics
	• Lifestyle
	• Socio-economic status (eg, financial constraints)
Disease-related factors	• Epilepsy (ie, seizure type, epilepsy syndrome etc)
	• Aetiology
	• Comorbidities
	• Family history
	• Past medical history
Drug-related factors	• Comedications
	• Previous adverse drug reactions

neuromodulatory therapies that may be applied in patients with drug-resistant epilepsy are deep brain stimulation of the anterior nucleus of the thalamus[34] and responsive cortical stimulation, which delivers electrical stimulation when abnormal electro-corticographic activity is detected via a closed loop implanted device.[35] These treatments can result in seizure reduction, but rarely render patients seizure-free.[34,35]

The ketogenic diet therapies comprise the classical ketogenic diet and the modified Atkins diet. The ketogenic diet is a high-fat, adequate protein, low-carbohydrate diet which is the first-line therapy for glucose transporter type 1 deficiency syndrome and pyruvate dehydrogenase complex deficiency, and a proven effective treatment for drug-resistant childhood epilepsies.[36,37] In a randomised trial, 28/73 children assigned to the diet (38%) had > 50% seizure reduction at 3-month follow-up versus 4/72 controls (6%) ($P < 0.0001$).[37] Five children in the diet group (7%) had > 90% seizure reduction compared with no controls ($P = 0.06$). The classical diet is associated with poor long term compliance, particularly in adults, and more flexible diets such as the modified Atkins diet, in which more carbohydrate is allowed, are associated with improved adherence.[36] The diet holds promise in the treatment of refractory status epilepticus,[38] but early observations need to be substantiated by well designed studies.

Targeted therapies

Pharmacogenomics. Pharmacogenomics is the study of variation in the genes encoding drug-metabolising enzymes, transporters and drug targets, and how these variations influence drug disposition and response.[39] There has been major progress in identifying genomic predictors of idiosyncratic AED reactions. In Han Chinese and other South Asian populations, *HLA-B*1502* is strongly associated with the risk of carbamazepine-induced Stevens–Johnson syndrome and toxic epidermal necrolysis.[40] *HLA-B*1502* screening is highly recommended in high risk individuals before commencing carbamazepine (eg, Chinese, Thai, Indian, Malay, Filipino and Indonesian populations).[41] *HLA-A*3101* is also associated with an increased risk of carbamazepine-induced cutaneous reactions, including maculopapular exanthema, Stevens–Johnsons syndrome, toxic epidermal necrolysis and drug reaction with eosinophilia and systemic symptoms.[42] As opposed to *HLA-B*1502*, *HLA-A*3101* is common in most ethnic groups, including European and Asian populations.[41] However, the predictive value of

*HLA-A*3101* is less than that of *HLA-B*1502*, and the clinical utility of *HLA-A*3101* screening is not clearly established.[41]

Phenytoin is metabolised primarily by the cytochrome P450 (CYP) 2C9 enzyme. In a study from Japan, Malaysia and Taiwan, *CYP2C* variants, particularly *CYP2C9*3*, which causes 93–95% reduction in phenytoin clearance, increased the risk of phenytoin-induced severe cutaneous reactions.[43] Whether these reactions can be prevented through slower phenytoin dose up-titration is unknown.

To date, efforts to identify genomic predictors of AED efficacy have been largely unsuccessful. A genome-wide study concluded that any single common genetic variant is unlikely to explain > 4.4% of the variation in the outcome of newly treated epilepsy.[44]

Precision medicine. Delivering treatments targeting the molecular cause of a disease has been a long sought-after goal in medicine. The advent of next generation sequencing has fuelled renewed hope, especially following successful models developed in oncology. Epilepsy offers a promising opportunity for precision medicine, due to the myriad of gene discoveries, availability of experimental in vitro and in vivo models for drug screening, and the feasibility of conducting small, cost-effective trials of novel agents.[45]

For some genetic epilepsies, precision medicine is already a reality. A prime example is glucose transporter type 1 deficiency syndrome, in which dominant mutations in *SLC2A1* result in impaired brain uptake of glucose.[39] These patients respond to the ketogenic diet, which provides the brain with an alternative energy substrate. Another example is pyridoxine-dependent epilepsy caused by recessive mutations in *ALDH7A1*, which requires prompt treatment with pyridoxine.[39]

Identifying the molecular cause of epilepsy also allows the prevention or minimisation of AED adverse effects. In *SCN1A*-related epilepsies, sodium channel-blocking AEDs, such as carbamazepine, may aggravate seizures.[46] In epilepsies due to *POLG* mutations, avoidance of valproate is recommended due to increased risk of hepatic failure.[47]

Sudden unexpected death in epilepsy

Individuals with epilepsy are at increased risk of premature mortality, with seizure-related causes of death including sudden unexpected death in epilepsy, status epilepticus, falls, drowning, suicide, and motor vehicle accidents.[48] Sudden unexpected death in epilepsy is the main cause of death in several epilepsy populations, and the second principal neurological cause of total years of potential life lost, after stroke.[48] It has been defined as a "sudden, unexpected, witnessed or unwitnessed, nontraumatic 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 toxicologic or anatomic cause for death".[49] In a recent systematic review of Class I studies, the overall incidence of sudden unexpected death in epilepsy was 0.58/1000 patient-years (95% CI, 0.31–1.08), being lower in children than adults.[50] Poorly controlled tonic–clonic seizures are the strongest risk factor for sudden unexpected death in epilepsy, which often follows a tonic–clonic seizure occurring in bed during sleeping hours.[48,50] Other risk factors include male sex, longstanding epilepsy and young age at onset.[48] Patients and their families should be informed about sudden unexpected death in epilepsy and the importance of lifestyle adjustments (eg, optimal AED adherence) to minimise the risk associated with seizure recurrence. There is some evidence that the risk of sudden unexpected death in epilepsy can be reduced with nocturnal supervision and use of safety pillows, whereas the potential value of

6 Antiepileptic drugs (AEDs) most commonly used as first-line therapy in epilepsy

Drug	Maintenance dose*		Number of daily doses	Notable adverse effects	Comments	TGA-approved indication[†]
	Children (mg/kg/day)	Adults (mg/day)				
Carbamazepine	20–30	400–1600	2–3	Drowsiness, dizziness, unsteadiness, ataxia, blurred vision, diplopia, nausea, hyponatraemia, hypersensitivity reactions, decreased bone mineral density, cardiac conduction abnormalities (older patients)	• Advantages: highly efficacious against focal seizures; extensive clinical experience; low teratogenic risk; PBS-approved as first-line therapy • Disadvantages: enzyme inducer; vulnerability to enzyme induction and inhibition; hypersensitivity reactions in high risk populations	Treatment of "complex or simple partial seizures (with or without loss of consciousness) with or without secondary generalisation; generalised tonic-clonic seizures; mixed seizure patterns incorporating the above"
Ethosuximide	20–30	500–1500	2–3	Nausea, abdominal discomfort, vomiting, diarrhoea, drowsiness, hypersensitivity reactions, psychosis	• Advantages: highly efficacious against absence seizures; PBS-approved as first-line therapy • Disadvantages: not effective against generalised tonic–clonic seizures, which can coexist with absence seizures in certain syndromes; vulnerability to enzyme induction and inhibition; unknown teratogenic risk	Treatment of "petit mal epilepsy"
Phenytoin	4–10	200–400	1–2	Nystagmus, dizziness, unsteadiness, ataxia, blurred vision, diplopia, hypersensitivity reactions, hirsutism, gingival hyperplasia, decreased bone mineral density, cerebellar atrophy	• Advantages: highly efficacious against focal seizures; extensive clinical experience; rapid up-titration; availability of parenteral formulation; low teratogenic risk; PBS-approved as first-line therapy • Disadvantages: enzyme inducer; vulnerability to enzyme induction and inhibition; Michaelis–Menten kinetics; cosmetic adverse effects	Treatment of "grand mal and psychomotor seizures"
Valproic acid	15–40	500–2500	2	Tremor, nausea, abdominal discomfort, hyperammonaemia, hepatotoxicity, pancreatitis, thrombocytopenia, weight gain, alopecia, polycystic ovary syndrome, anatomical and behavioural teratogenesis	• Advantages: most effective AED against generalised seizure types; efficacious also against focal seizures; rapid up-titration; efficacious for migraine prophylaxis; mood stabiliser; PBS-approved as first-line therapy • Disadvantages: enzyme inhibitor; vulnerability to enzyme induction and inhibition; weight gain; high risk of anatomical and behavioural teratogenicity (dose-dependent)	Treatment of "primary generalised epilepsy (petit mal absences, various forms of myoclonic epilepsies and tonic-clonic grand mal seizures); partial (focal) epilepsies, either alone or as adjuvant therapy"
Lamotrigine	2–10	100–300	2	Dizziness, ataxia, blurred vision, diplopia, insomnia, hypersensitivity reactions	• Advantages: efficacious against focal and most generalised seizure types; non-enzyme inducer; efficacious in bipolar depression; low teratogenic risk • Disadvantages: slow up-titration; dosing requirements influenced by interactions with enzyme inducers, contraceptives containing oestrogens, and valproic acid; can precipitate or aggravate myoclonic seizures; not PBS-approved as first-line therapy	Treatment of "partial and generalised seizures in adults and children … Initial monotherapy treatment in newly diagnosed paediatric patients is not recommended"

6 Antiepileptic drugs (AEDs) most commonly used as first-line therapy in epilepsy (continued)

Drug	Maintenance dose* Children (mg/kg/day)	Maintenance dose* Adults (mg/day)	Number of daily doses	Notable adverse effects	Comments	TGA-approved indication[†]
Levetiracetam	20–60	1000–3000	2	Drowsiness, fatigue, irritability, aggression, depression, psychosis	• Advantages: efficacious against focal seizures, myoclonic seizures and generalised tonic–clonic seizures; rapid up-titration; non-enzyme inducer; no significant drug interactions; low teratogenic risk • Disadvantages: psychiatric adverse effects; not PBS-approved as first-line therapy	"Monotherapy in the treatment of partial onset seizures, with or without secondary generalisation, in patients from 16 years of age with newly diagnosed epilepsy" Also approved for use in "patients aged 4 years and older, initially as add-on therapy, in the treatment of partial onset seizures with or without secondary generalisation; add-on therapy in the treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy; add-on therapy in the treatment of primary generalised tonic–clonic seizures in adults and children from 4 years of age with idiopathic generalised epilepsy"
Oxcarbazepine	30–50	600–2400	2–3	Drowsiness, dizziness, unsteadiness, ataxia, blurred vision, diplopia, nausea, hyponatraemia, hypersensitivity reactions	• Advantages: efficacy profile similar to carbamazepine, but lower risk of hypersensitivity reactions and lower enzyme induction potential; probably low teratogenic risk (limited evidence) • Disadvantages: reduces serum levels of oral contraceptives; risk of hyponatraemia more common than with carbamazepine; not PBS-approved as first-line therapy	"Use as monotherapy or adjunctive therapy for the treatment of partial seizures and generalised tonic–clonic seizures, in adults and children"
Topiramate	2–10	100–400	2	Cognitive impairment, concentration/attention and word finding difficulties, drowsiness, fatigue, depression, psychosis, paraesthesiae, angle closure glaucoma, oligohydrosis, hyperthermia, anorexia, weight loss, nephrolithiasis	• Advantages: efficacious against focal seizures and most generalised seizure types; low potential for drug interactions; efficacious for migraine prophylaxis • Disadvantages: slow up-titration; cognitive and psychiatric adverse effects; low to moderate risk of anatomical teratogenicity (limited evidence); not PBS-approved as first-line therapy	"Use in adults and children, 2 years and over: as monotherapy in patients with newly diagnosed epilepsy; for conversion to monotherapy in patients with epilepsy; as add-on therapy in partial onset seizures (with or without secondary generalised seizures), primary generalised tonic–clonic seizures or drop attacks associated with Lennox–Gastaut syndrome"

PBS = Pharmaceutical Benefits Scheme. TGA = Therapeutic Goods Administration. * Dose adjustments may be required with concomitant medications. † TGA-approved indications often comprise old seizure classifying terms, which in most cases can be mapped to the new terms in the 2017 International League Against Epilepsy classification. For example, "old seizure term → new seizure term": complex partial → focal impaired awareness; drop attack → (focal/generalised) atonic, (focal/generalised) tonic; petit mal (absence) → absence; partial → focal; primary generalised tonic–clonic → generalised tonic–clonic; psychomotor → focal impaired awareness; secondarily generalised (tonic–clonic) → focal to bilateral tonic–clonic; simple partial → focal aware; (tonic–clonic) grand mal → generalised tonic–clonic, focal to bilateral tonic–clonic, unknown onset tonic–clonic. ◆

seizure-detecting devices for sudden unexpected death in epilepsy prevention requires investigation.[48]

Conclusion

The treatment of epilepsy relies primarily on AED therapy, which fully controls seizures in about two-thirds of patients. Second generation AEDs have expanded opportunities for tailoring treatment, but the burden of drug-resistant epilepsy, with its associated risks of disability, morbidity and mortality, has remained substantially unchanged for several decades. A subset of drug-resistant individuals can be rendered seizure-free by epilepsy surgery, which should be considered as soon as two AEDs have failed. In other individuals, seizure control can be improved by using alternative AEDs or non-pharmacological therapies, but they

rarely result in seizure freedom. Hope to reduce the proportion of patients with uncontrolled seizures rests on future therapeutic advances, including precision therapies targeting underlying molecular mechanisms.

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