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Epilepsy in adults

Background

Epilepsy is a common disorder and most adult patients will be managed primarily by general practitioners. Despite new developments in the classification and treatment of epilepsy, basic principles of diagnosis and treatment remain valid, such as the importance of an accurate, detailed history and adjusting antiepileptic drug (AED) doses on the basis of seizure control and adverse effects rather than blood test results.

Objective

This article addresses current issues in the diagnosis and management of epilepsy, including initial evaluation and use of AEDs.

Discussion

Older AEDs are still prescribed commonly; newer AEDs have similar efficacy and improved tolerability. Human leukocyte-associated antigen (HLA) testing is recommended before commencing Asian patients on carbamazepine to minimise the risk of Stevens-Johnson syndrome (SJS). Referral to an epilepsy specialist is recommended if seizures are not controlled after trialling two AEDs. Important issues pertaining to reproductive and bone health are complex and poorly understood.

Keywords

epilepsy; diagnosis; diagnosis, differential; drug therapy

CPD

Classification of epileptic seizures and epilepsy syndromes

Older epilepsy nomenclature imbued terms such as 'symptomatic' and 'complex' with non-intuitive meanings not seen elsewhere in medical parlance.[1] A revised classification replaced those terms with more meaningful and accurate terms, although the older terminology remains in common clinical usage.[2]

Patients most commonly seek medical attention for generalised tonic-clonic seizures (GTCS; grand mal seizures). In the initial phase of stiffening, consciousness is lost for a few seconds, causing falls, often with a forced scream (ictal cry). All-limb jerking then occurs, lasting for up to 2 minutes. Cyanosis, tongue-biting and urinary incontinence are common during these seizures. Post-ictal stertor, confusion and amnesia typically persist for several minutes.

Generalised absence seizures (petit mal seizures) are frequent (>daily), brief (<30 seconds) episodes of behavioural arrest without prominent motor features and with immediate recovery of alertness when the seizure ends. They occur in some forms of genetic generalised epilepsies (primary/idiopathic generalised epilepsies) with onset in childhood or adolescence.

Myoclonic seizures are single jerks of muscles, usually generalised, occurring during wakefulness, but otherwise similar to hypnic jerks. Specific inquiry is necessary as most patients do not recognise these as seizures.

Focal seizures are confined to one cerebral hemisphere, but may evolve to become bilateral convulsive seizures (secondary generalisation). Clinical features are myriad, spanning motor, somatosensory, autonomic, visual, auditory and experiential/psychic disturbances. In the individual patient, seizures show a high degree of stereotypy. Focal seizures without and with impairment of consciousness (simple or complex partial seizures, respectively), are often (mis)labelled by patients and doctors as petit mal seizures as distinct from grand mal seizures. Typically, focal seizures with impairment of consciousness are less frequent and more prolonged than absence seizures, and post-ictal recovery of full alertness is delayed.

Confusion between different seizure types, or between seizures and other episodes such as syncope,[3] (*Table 1*) is minimised with careful history-taking and documentation, preferably assisted by eyewitness account and/or video recording (eg. using a smartphone). Additional

Table 1. Differential diagnosis of epileptic seizures

Syncope
Psychogenic non-epileptic seizures
Migraine
Transient ischaemic attack
Paroxsymal dyskinesia
Parasomnia

history identifies provoking factors[4] (*Table 2*) and previous, possibly unrecognised, seizures.

After a first unprovoked epileptic seizure, the risk of another seizure is approximately 40%.[5] A diagnosis of epilepsy implies demonstrated tendency for recurrent unprovoked seizures,[6] thus justifying long-term use of antiepileptic drugs (AEDs). The diagnosis is often made after two unprovoked seizures (>24 hours apart) or after one seizure if EEG or neuroimaging findings indicate a genetic or structural basis for a seizure tendency.

Epilepsy remains a clinical diagnosis. Normal EEG and neuroimaging do not exclude the diagnosis; rather, abnormal findings assist in classifying the epilepsy syndrome. In structural/metabolic epilepsies, seizures are due to a structural brain lesion or metabolic disturbance; the remaining epilepsies are proven or presumed to have a genetic basis and are hence termed genetic epilepsies.[2]

Juvenile myoclonic epilepsy is a common, under-recognised genetic generalised epilepsy syndrome in which myoclonic seizures, GTCS and sometimes absence seizures commence around adolescence.[7] Typically, excellent seizure control is achieved with low doses of some medications (eg. valproate, levetiracetam). Some other AEDs may control GTCS in this condition but can potentiate absence or myoclonic seizures. Most patients require lifelong treatment.[8]

Antiepileptic drugs

Older medications, especially carbamazepine, phenytoin and valproate, remain in common use in Australia as first-line therapy, largely because of Pharmaceutical Benefits Scheme (PBS) restrictions on newer agents. Newer medications have similar efficacy but lower incidence of adverse effects and less potential for pharmacokinetic interactions with other medications, compared with the older AEDs. All antiepileptic medications have dose-dependent, neurotoxic adverse effects, such as somnolence, cognitive impairment and ataxia, although the dose at which these emerge varies markedly between individuals. These adverse effects resolve rapidly on discontinuation.

Table 3 lists, in chronological order of development, AEDs approved for use in Australia prior to 2010 and still prescribed commonly in adults. Four AEDs have been registered more recently.

- Lacosamide enhances inactivation of voltage-gated sodium channels. Common adverse effects, including dizziness and ataxia, are enhanced by concomitant use of other sodium channel blockers, such as carbamazepine and phenytoin. PBS prescription requires treatment initiation by a neurologist.

Table 2. Causes of provoked epileptic seizures

Acute neurological insult
- Stroke
- Trauma
- Infection
- Inflammation

Biochemical derangement
- Hypo-/hyperglycaemia
- Hypo-/hypernatraemia
- Hypomagnesaemia
- Hypo-/hypercalcaemia

Alcohol (and other drugs) intoxication or withdrawal
Pregnancy (eclampsia)

- Zonisamide has effects on voltage-gated sodium and calcium channels and inhibits carbonic anhydrase. It has a long half-life (>60 hours) and is thus suitable for once daily administration. Anorexia and reduced serum bicarbonate are common; nephrolithiasis is a less common adverse effect.
- Retigabine activates voltage-gated potassium channels. A particular adverse effect is blue-grey skin discolouration and retinal pigmentation. Although registration was approved by the Therapeutic Goods Administration, it is not yet marketed in Australia.
- Clobazam has less sedative and cognitive adverse effects than other benzodiazepines.[9] Registered as an anxiolytic in 1984, it has long been used off-label for epilepsy and is now registered for adjunctive treatment of paediatric epilepsy. It can be a useful 'circuit-breaker' for patients with seizure clusters, catamenial seizures, or for long-haul flights.

Stevens-Johnson syndrome (SJS)

This is a severe cutaneous adverse reaction seen with carbamazepine, phenytoin, phenobarbitone, primidone, zonisamide, lamotrigine and oxcarbazepine, occurring within the first 8 weeks of drug exposure.[10] Initiation of lamotrigine treatment should comprise gradual dose escalation over several weeks in accordance with the product information. The safest approach is to discontinue antiepileptic medication if any rash develops within 8 weeks of commencement, and thence to avoid other causative AEDs.

In patients of Han Chinese and South-East Asian ethnicity, the presence of HLA-B*1502 allele predicts a higher risk of SJS, whereas the absence of HLA-B*1502 is protective. HLA testing is recommended before such patients commence carbamazepine, and could be considered in patients commencing other causative agents.[11] In patients of Japanese and European background, there is an association between carbamazepine SJS and HLA-A*3101, but routine screening is not recommended.[12]

Therapeutic drug monitoring (TDM)

An appropriate dose of AED is that which controls seizures without causing significant adverse effects. Hence, from a purist perspective,

Table 3. Characteristics of AEDs approved for use in Australia prior to 2010

Medication	Typical dose	Adverse effects of note	Other notes
Phenytoin*	200–400 mg od	Hirsutism, acne, coarse facies Gum hypertrophy Rash/SJS	Non-linear pharmacokinetics (steady-state serum concentration not proportional to dose)
Clonazepam	0.5–2 mg bd	Sedation Ataxia	Tolerance (reduced efficacy) may develop with long-term use
Carbamazepine*	200–600 mg bd	Hyponatraemia Rash/SJS	Available in standard-release and controlled-release formulations Autoinduction of metabolism
Valproate	400–1000 mg bd	Weight gain Tremor Alopecia	Use with caution in women of childbearing age Also used as mood stabiliser
Lamotrigine	50–200 mg bd	Rash/SJS (risk reduced with slow titration to target dose over ~8 weeks; refer to Product Information, Dosage and Administration)	Lower dose requirement (approximately half) if also taking valproate Also used as mood stabiliser
Gabapentin	300–800 mg tds	Weight gain	100% renal excretion
Topiramate*	50–200 mg bd	Anorexia, weight loss Word-finding difficulty Nephrolithiasis Oligohidrosis Metabolic acidosis Depression	Also PBS approved for migraine
Oxcarbazepine*	300–900 mg bd	Hyponatraemia (more frequently than with carbamazepine)	Oxcarbazepine:carbamazepine dose equivalence approximately 1.5:1
Levetiracetam	500–1500 mg bd	Agitation Depression	Largely renally excreted
Pregabalin	75–300 mg bd	Weight gain	Not PBS approved for epilepsy 100% renal excretion

Phenobarbitone, primidone, acetazolamide, sulthiame, vigabatrin, tiagabine and ethosuximide are not often prescribed in adults. Typical doses are an approximate guide only. PBS = Pharmaceutical Benefits Scheme; SJS = Stevens-Johnson syndrome. *enzyme-inducing AEDs (although topiramate and oxcarbazepine are weaker enzyme inducers).

To whom it may concern:

David has been my patient since 1 January 2010 and I reviewed him in my clinic this afternoon. He has a diagnosis of focal epilepsy related to right middle cerebral artery infarct in September 2008.

He has been seizure-free since 1 July 2010 on a stable dose of antiepileptic medication. Neurological examination demonstrates left-sided hyper-reflexia but is otherwise normal, with no weakness, haemianopia or inattention. EEG performed 31 March 2009 was normal and MRI brain performed 5 October 2008 showed expected findings of the aforementioned infarct.

I trust this information is sufficient for you to determine his fitness to drive.

Figure 1. A sample letter to the DLA regarding fitness to drive

optimal dosing does not require TDM. Standard assays report total drug levels rather than the more clinically relevant free fraction, and this is subject to variable plasma-protein-binding, especially for valproate.[13] TDM may be useful in selected cases when patient adherence is questioned or when altered pharmacokinetics is expected, (eg. due to pregnancy, drug–drug interactions (including polytherapy) or hepatic or renal impairment). In Australia, TDM is readily available for carbamazepine, phenytoin, phenobarbitone, valproate and lamotrigine.

Pharmacoresistant epilepsy

While AEDs are the mainstay of epilepsy treatment, up to 40% of patients will continue to have seizures.[14] Pharmacoresistance is defined as failure to achieve seizure control with adequate doses of two appropriate AEDs.[15] Referral to a comprehensive epilepsy service is useful for:

- diagnostic clarification to distinguish between epilepsy and non-epileptic seizures
- further pharmacotherapy, including rational polytherapy and access to AEDs through clinical trials

- non-pharmacological treatment, including vagal nerve stimulation[16] and resective epilepsy surgery.[17]

Driving

National standards governing medical fitness to drive were revised in March 2012. In most cases, patients with epilepsy on AEDs and patients after first epileptic seizure will be judged fit to return to driving after being seizure-free for 6 months.[18]

Expectations of patients and driver licensing authorities (DLAs) that treating doctors should adjudicate on fitness to drive undermine the doctor–patient relationship, discourage reporting of seizures, encourage doctor-shopping and expose the practitioner to legal risk.[19] The author's preference is to provide a concise medical report allowing the DLA to make the decision (*Figure 1*).

Reproductive health issues

Enzyme-inducing AEDs (*Table 3*) reduce the efficacy of the combined oral contraceptive pill by increasing clearance of oestrogen and progestogen components. A common, albeit illogical, strategy is to prescribe a high-dose (50 µg) oestrogen formulation; ovulation is likely to occur if the progestogen dose is unchanged. More plausible strategies include doubling the dose; using active pills continuously rather than 21 days on, 7 days off; alternative contraceptive methods; or changing AEDs. Efficacy of etonogestrel subcutaneous implant is also compromised by enzyme-inducing AEDs, but depot medroxyprogesterone acetate and levonorgestrel-releasing intrauterine system remain effective.[20]

The risk of congenital malformations in AED-exposed pregnancies is about 6%, compared with about 3% in non-exposed pregnancies. No specific agent has been shown to be higher risk, with the exception of valproate if the daily dose exceeds 1100 mg.[21] The time frame for organogenesis suggests that the first trimester is most important for exposure. Although not proven to mitigate risk, preconceptional folate supplementation is recommended. There is an association between lower intelligence and valproate exposure in utero; this is likely to be dose-dependent and related to exposure in all trimesters.[22] It has been posited that autism and behavioural disorders are more common in children with in utero exposure to AEDs, but evidence for this is lacking.

AED dose requirements are increased during pregnancy after the first trimester, particularly for lamotrigine and levetiracetam;[23,24] TDM can be extremely useful. Failure to anticipate these changes can lead to gestational deterioration in seizure control. Generally, AED penetration into breast milk is not clinically significant.[25]

Bone health

Increasing evidence is emerging suggesting that long-term use of AEDs is associated with low bone mineral density (BMD).[26] Increased fracture risk in patients with epilepsy is not entirely attributable to reduced BMD and both seizure- and non-seizure-related falls are likely contributors.[27] General preventive measures include optimising physical exercise and dietary calcium intake, correcting vitamin D deficiency and smoking cessation. Unfortunately, there are no evidence-based guidelines for how early and often to perform bone mineral densitometry (which for many patients would be unsubsidised), nor whether AEDs should be altered or anti-resorptive therapy commenced.

Key points

- Diagnosis of seizures and epilepsy is based on accurate history.
- AED treatment is usually reserved until after two seizures have occurred.
- HLA testing should be performed in Asian patients before commencing carbamazepine treatment.
- AED dosing should be adjusted on clinical grounds; TDM is useful in selected patients.
- Specialist referral is recommended after failure of two AEDs.

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