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Drug therapy for epilepsy

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Antiepileptic drug therapy is obviously important in the management of epilepsy. A clear history of at least two seizures is required before initiating antiepileptic treatment. One should aim to control the epilepsy with a single antiepileptic drug. In some children two antiepileptic drugs are required. Clinicians need to be aware of both the common and severe side effects associated with these drugs.

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Introduction

Epilepsy is thought to affect almost 1% of school age children[1]. It is important to remember that epilepsy is a transient condition in many children and that approximately one third of patients who develop epilepsy in childhood will remit spontaneously within a number of years.

Diagnosis

The diagnosis of epileptic seizures is almost entirely dependent on the history. The examination will often be normal, and the results of any investigations can only be interpreted with reference to the history. A detailed description is required of events occurring before, during and after a suspected epileptic seizure. The accurate account of any eyewitness is essential and will be the only history available when young children present with seizures. Video-recordings of suspected seizures may be helpful and should be encouraged whenever there is any continuing doubt or confusion from the history. If the diagnosis remains uncertain then it is appropriate to await further episodes, because a delay in making a diagnosis of epilepsy is unlikely to be harmful.

Classification of seizures

Seizures are currently classified into either generalised or focal (also called partial) seizures. The whole brain (or at least the whole of the cerebral cortex) is involved in generalised seizures, whereas focal seizures only affect part of the brain, and often only one part of one lobe of the brain. Generalised seizures are broadly classified into 'absence', 'myoclonic', 'atonic', 'tonic', 'clonic' and 'tonic-clonic'. Focal or partial seizures are classified as 'simple', in which consciousness is retained, or 'complex', in which consciousness is impaired or lost. Simple partial seizures with sensory, autonomic or psychic symptoms may be easily overlooked in younger children unable to describe such symptoms. Focal or partial seizures may become secondarily generalised, resulting in a tonic-clonic convulsion. The symptoms of a simple partial seizure prior to secondary generalisation constitute the epileptic aura. A recent diagnostic scheme proposal has been submitted to the International League Against Epilepsy (ILAE)[2]. It encompasses five levels: seizure description, seizure type, epilepsy syndrome, aetiology and associated physical and/or learning impairments.

Epilepsy syndromes

Epilepsy syndromes are determined by seizure type(s), age of onset, EEG findings (interictal and ictal), and associated features, including neurodevelopmental findings and family history.

Epilepsy syndromes are important in the management of epilepsy in terms of:

- predicting prognosis (seizure-control and seizure-remission)
- selecting anti-epileptic treatment
- defining the likelihood of identifying an underlying aetiology

The classification of epilepsies and epilepsy syndromes is divided, according to the anatomical origin of seizures, into those where the origin of the seizures is focal or partial and those that are generalised. A further subdivision is made aetiologically into symptomatic, in which the cause of the epilepsy is known; cryptogenic, in which there is a likely, but unidentified cause; and idiopathic, in which there is no underlying cause apart from perhaps a genetic predisposition. A cause is usually found in two thirds of infants with epilepsy. In contrast, a cause is found in only one third of school age children.

The fifth level of the diagnostic classification proposed by the ILAE is to include any associated physical or cognitive (educational) impairment[2]. The association of epilepsy with physical or cognitive impairments is often termed 'epilepsy plus'. The often (and usually severe) physical, learning and behavioural difficulties that accompany these epilepsy syndromes typically cause more problems than the epilepsy, not just for the individual but for their family and community as well as placing excessive demands on social, educational and public health resources.

Prognosis

Whether seizures respond to treatment and whether the epilepsy will spontaneously remit is determined by the specific epilepsy syndrome, underlying aetiology and almost certainly (and as yet unidentified), genetic factors[3]. There is no evidence that the use of antiepileptic drugs influences the natural history of the vast majority of the epilepsies and epilepsy syndromes; the drugs simply suppress the seizures whilst the epilepsy is active within the child's brain. It is possible that in some of the rare, early onset, infantile epileptic encephalopathies[4], early and aggressive treatment may improve developmental and cognitive outcome although further data are required to confirm or refute these limited findings.

Drug treatment

There are a number of decisions that must be taken regarding the use of antiepileptic drugs:

- when to start a drug?
- which drug and in what dose?
- when to change the drug?
- when to add a second drug (and which one)?
- when to seek a specialist opinion?
- when to stop the drug?

Starting drug therapy

Most clinicians would not recommend starting treatment after a single generalised tonic-clonic seizure, but would after a cluster of seizures or two seizures within a period of six months. Similarly, a child with severe physical and learning difficulties with infrequent myoclonic or brief focal seizures may not require an antiepileptic drug in contrast to a child attending a normal school who experiences frequent generalised tonic-clonic seizures on waking. There are two main reasons why clinicians, and sometimes parents, are keen to start medication after one or only two seizures. Firstly, there has been the theoretical concern that one seizure may lead to a second, a second to a third and eventually to a state of chronic epilepsy that may then be more difficult to treat. This process is termed 'kindling', where one seizure, which may be clinically or only electroencephalographically evident, 'begets another seizure' and so on; the evidence for this is derived from animal data and has not been convincingly demonstrated in humans. Recent data[5] would suggest that this is most unlikely, providing the number of tonic-clonic seizures is 10 or less[6]. Secondly, is the concern that there may be an increased incidence and risk of injuries with further seizures and therefore early treatment may reduce this risk. Recent evidence has suggested that both hypotheses are unlikely[5-7].

Once drug therapy is started, the objective is to use this as monotherapy and to achieve (complete) seizure control without unacceptable side-effects and using the most appropriate formulation that can be taken by the child[8].

Choosing the drug and dose

The specific epilepsy syndrome or seizure type and safety profile of the drug determines the choice of antiepileptic drug. The preparation of drug available is an additional factor when deciding the choice of drug – particularly in infants and young children. In the UK, cost is not currently regarded as an important factor in the choice of the antiepileptic drug, despite the fact that there may be at least a six or even 10-fold difference in cost between an 'older' (e.g. carbamazepine or sodium valproate) and 'newer' drug (e.g. lamotrigine or topiramate). Whichever drug is chosen is introduced gradually to avoid any dose-related side-effects, and increased slowly to its target maintenance dose based on the child's body weight and recommended guidelines. The dose of this drug should be increased to the maximally tolerated level before either adding a second drug (if the first drug has had a partial effect) or substituting another drug (if the first drug was completely ineffective).

The currently recommended first-line drugs in treating the majority of childhood epilepsies are sodium valproate (VPA) for generalised epilepsies and syndromes and carbamazepine (CBZ) for generalised and partial (focal) seizures/epilepsy syndromes. A randomised clinical trial showed that VPA and CBZ were equally effective in both primary generalised tonic-clonic seizures and focal seizures, with or without secondary generalisation[9].

Ethosuximide may be effective for typical absences but does not suppress tonic-clonic seizures, which may develop in 10–20% of children with childhood or juvenile-onset typical absence epilepsy. Ethosuximide may occasionally be helpful in treating myoclonic seizures. Carbamazepine exacerbates myoclonic and typical absence seizures and should therefore be avoided in juvenile myoclonic epilepsy, childhood and juvenile-onset absence epilepsy and the progressive myoclonic epilepsies.

Phenytoin and phenobarbitone must no longer be used as first-line maintenance drugs because of side effects, particularly on behaviour, cognitive performance and bone mineralisation and, with phenytoin, the cosmetic side-effects of gingival hyperplasia and the development of facial and limb hair. These drugs should be considered for oral therapy only when other drugs have failed, and where seizure control is the over-riding, if not the only, priority.

Infantile spasms

Neither VPA nor CBZ are drugs of first choice in West's syndrome, which is characterised by infantile spasms. In Europe, vigabatrin is usually the preferred drug, whereas in the USA, adrenocorticotrophic hormone (ACTH) is generally regarded as the drug of choice[10]. In Japan the drug of choice is pyridoxine (vitamin B6), for which it is reported that up to 10-15% of infants will respond. This does not imply that these infants have pyridoxine dependency, but simply that pyridoxine may occasionally be effective in treating some cases of infantile spasms. The mechanism of action of ACTH (in reducing spasms and normalising the EEG in West syndrome) is unclear. It has to be given by intramuscular injection (which is painful), and is frequently associated with severe, and even fatal, side-effects. Prednisolone or hydrocortisone have fewer and less serious side-effects than ACTH/ tetracosactrin. Vigabatrin is likely to suppress spasms in approximately 60% of patients, and prednisolone or ACTH in 65–70% of patients, depending on the cause. Vigabatrin is particularly effective in treating infantile spasms caused by tuberous sclerosis. If spasms show no reduction after 10 days of the maximum dose of vigabatrin (120 mg/kg/day), then it is very unlikely that this drug will be effective and it should be withdrawn and replaced with another drug (e.g. pyridoxine, nitrazepam, prednisolone, levetiracetam or topiramate), depending on the specific clinical situation (*these specific drugs reflecting the author's clinical experience*). A systematic review of the treatment of infantile spasms gave inconclusive results[11].

Changing drug therapy

If unacceptable side effects develop or if control has been sub-optimal with the first drug then the child will require either a different drug or an additional drug ('polytherapy'). Where the first drug has been ineffective it would be appropriate to replace this drug with an alternative; where the first drug has been partly effective it would seem appropriate to add a second drug and to consider withdrawing the first drug if seizure, freedom is subsequently achieved, to maintain monotherapy. The choice of the second drug is based on the same criteria as for the first drug: namely, seizure type or epilepsy syndrome and safety profile. A single drug (monotherapy) will achieve total seizure control in only 65–70% of children. Two drugs in combination will result in further significant (even complete) control in an additional 5–10% of children. Three drugs rarely (if ever) result in

Table 1 Mechanisms of action and indications for antiepileptic drugs

Drug	Mechanism	Indications
Acetazolamide	Inhibits brain carbonic anhydrase activity	Focal (often in conjunction with carbamazepine)
Benzodiazepines (clobazam, clonazepam, diazepam, nitrazepam)	Allosteric enhancement of GABAA-receptor mediated chloride channels	Generalised (myoclonic and absence); focal (clobazam); infantile spasms (nitrazepam)
Carbamazepine (and oxcarbazepine)	Limits or inhibits repetitive firing of voltage-gated sodium channels	Focal and primary or secondary generalised tonic-clonic (but exacerbates myoclonic and absence seizures)
Ethosuximide	Inhibits low-threshold T-type voltage-gated calcium channels in the thalamus; possible enhancement of non-GABA mediation neuronal inhibition	Generalised (absence and occasionally, myoclonic); no effect on tonic-clonic and focal seizures
Gabapentin	Binds to a novel calcium channel receptor	Focal and secondarily generalised tonic-clonic; no effect on absence and myoclonic seizures
Lamotrigine	Inhibits voltage-gated sodium channels; reduces release of excitatory amino-acids (specifically glutamate)	Generalised (all types; not very effective for myoclonic seizures) and focal
Levetiracetam	Unknown; antiepileptogenic rather than anticonvulsant effect; no obvious effect on the GABA (inhibitory system), benzodiazepine or glutamate/aspartate (excitatory system) amino acid receptors	Generalised (all types) and focal (limited paediatric data)
Phenobarbitone (and primidone)	Enhances GABA-mediated inhibition	Generalised (tonic-clonic, tonic, myoclonic, absence); focal
Phenytoin	Inhibits sustained repetitive firing of voltage-gated sodium channels	Generalised (tonic-clonic; clonic); focal; (exacerbates myoclonic seizures)
Sodium valproate	Uncertain; possible inhibition of voltage-gated sodium channels; possible enhancement of GABA-mediated inhibition by inhibiting GABA transaminase; as yet unidentified novel action (effect on T-type calcium channels)	Generalised (absence, myoclonic, tonic-clonic, atonic, tonic, photosensitive); focal (sometimes)
Stiripentol	Unknown	Myoclonic; absence (limited data)
Sulthiame	Uncertain; possible carbonic anhydrase inhibitor	Focal; myoclonic seizures (for both, often as adjunctive therapy with other drugs)
Tiagabine	Inhibits the neuronal and pre-synaptic glial uptake of GABA after its release from post-synaptic GABA receptors (the drug therefore enhances GABA-mediated inhibition)	Focal and secondary generalised tonic-clonic
Topiramate	Multiple mechanisms; blocks voltage-activated sodium channels; stimulates GABAA-receptor mediated chloride currents; blocks glutamate receptors; weak carbonic anhydrase inhibitor (this latter mechanism is unlikely to exert any significant anticonvulsant/antiepileptic effect)	Generalised (tonic-clonic; tonic, atonic); focal; *possibly* infantile spasms
Vigabatrin	Enzyme-activated suicidal inhibitor of GABA-aminotransaminase therefore increasing GABA-mediated inhibition	Infantile spasms (one of the drugs of first choice); focal with or without secondary generalised tonic-clonic seizures; (exacerbates myoclonic and absence seizures)
Zonisamide	Multiple; blocks voltage-dependent sodium channels; inhibits voltage-dependent T-type calcium channels; facilitates dopaminergic and serotoninergic transmission	Generalised (tonic-clonic, myoclonic, absence); focal; *possibly* infantile spasms (limited paediatric data)

any additional control, and frequently cause more side effects and should therefore be avoided in most situations.

Mechanism of action

Most of the proposed mechanisms of action of the antiepileptic drugs are either speculative or unknown. Many of the older drugs were, almost accidentally, found to have antiepileptic or anticonvulsant actions, including phenobarbitone, phenytoin, carbamazepine and sodium valproate. Table 1 summarises the currently available oral antiepileptic drugs and their proposed or believed mechanisms of action and the main seizure type(s) for which they are used; some or all of these mechanisms may need to be revised pending the results of further neuropharmacological and neurophysiological research[12, 13].

Stopping treatment

Most clinicians would consider withdrawing drug therapy once the patient has been seizure free for two, or at most, three years. The risks and benefits of drug withdrawal and implications of seizure recurrence are different for children and teenagers/young adults and this must be discussed with both the child and parents[14]. There is no evidence that repeating an EEG prior to drug withdrawal is informative and therefore of any clinical benefit in deciding whether anticonvulsant therapy should be stopped. Anticonvulsant withdrawal should be undertaken at a convenient time in term of the child's education and social circumstances and each drug should be withdrawn gradually over two months to prevent withdrawal seizures. This may be a problem with the benzodiazepines but possibly

Table 2 Toxicity of antiepileptic drugs

Drug	Side effects
Acetazolamide	Malaise and fatigue; paraesthesiae of limbs and face; metabolic acidosis; leucopenia
Benzodiazepines	Drowsiness and sedation; irritability; tolerance; excessive salivation (clonazepam and nitrazepam)
Carbamazepine (and oxcarbazepine)	Nausea, dizziness and diplopia; allergic rash; hyponatraemia; agranulocytosis; teratogenic
Ethosuximide	Nausea and diarrhoea; drowsiness; chronic headache; leucopenia
Felbamate	Nausea and anorexia; insomnia; severe and potentially fatal aplastic anaemia and hepatitis
Gabapentin	Behavioural changes (aggression); sedation (high dose)
Lamotrigine	Allergic and dose-related rash (particularly when used simultaneously with sodium valproate); tremor and headache (when used in conjunction with sodium valproate)
Levetiracetam	Drowsiness and dizziness; behavioural changes (aggression)
Phenobarbitone (and primidone)	Drowsiness and irritability; cognitive slowing; allergic rash; osteomalacia/osteopenia; tolerance; teratogenic
Phenytoin	Allergic rash; cosmetic effects (gingival hypertrophy and facial hair often developing after 3-6 months of use); mild cognitive slowing and involuntary movements (chorea, athetosis); osteomalcia/osteopenia; leukopenia and pancytopenia; teratogenic
Sodium valproate	Drowsiness; increased appetite and weight gain; tremor; alopecia; menstrual irregularities; mild cognitive slowing and behavioural changes; hepatitis and pancreatitis; teratogenic (neural tube defects and 'fetal valproate syndrome')
Stiripentol	Drowsiness; behavioural changes (hyperactivity and aggression)
Sulthiame	Somnolence; respiratory changes (hyperpnoea and dyspnoea); paraesthesiae of limbs; psychosis
Tiagabine	Dizziness, somnolence and fatigue; complex partial status epilepticus in some patients
Topiramate	Sedation; anorexia (may be severe leading to weight loss); impaired concentration; impaired short-term memory and word-finding difficulties; behavioural changes (either aggression or withdrawal and depression); renal calculi; teratogenic
Vigabatrin	Sedation and hypotonia (high dose); behavioural changes (irritability); bilateral visual field constriction
Zonisamide	Somnolence, confusion and ataxia; anorexia; renal calculi

not phenobarbitone[15], and is more of a theoretical concern with the newer antiepileptic drugs.

Toxicity

Adverse side effects may be acute and idiosyncratic (allergic), dose-related or chronic, developing after many years of use. Most are mild and may be acceptable to the child and the family. Side effects may, however, be serious and even life-threatening[16]. Cognitive and behavioural side effects are frequently of most concern to parents of children with epilepsy and may be difficult to recognise in children who have 'epilepsy plus' and particularly those with learning difficulties. These children also usually have the more severe or malignant epilepsy syndromes that often require the use of two antiepileptic drugs to achieve 'acceptable' seizure control. In these children a therapeutic compromise has to be reached where the priority is to control the major seizures whilst accepting more minor seizures and without producing excessive sedation or loss of function. Clearly, in many situations, this therapeutic compromise may be difficult to achieve and may be repeatedly influenced by the fluctuating and non-static natural history of epilepsy, particularly in the first decade of life.

The use of multiple antiepileptic drugs (polytherapy) increases both the risk and incidence of side effects and this again emphasises the point that no more than two antiepileptic drugs should be used simultaneously. Adverse side effects have been linked with the premature deaths of both paediatric and adult patients with epilepsy[16]. Although side effects tend to be identified in clinical trials of new drugs, some may not be recognised for some time and after years of routine clinical use. Felbamate and vigabatrin, two of the 'newer' generation of drugs illustrate this problem. Within months of the pivotal clinical trials of felbamate being completed (and published), it became clear that the drug caused severe, including fatal aplastic anaemia and hepatitis, with the drug being withdrawn from the UK and many European countries.

Approximately 10 years after vigabatrin was first prescribed, a characteristic visual field defect (symmetrical, bilateral constriction) was reported which appears to be specific to the use of this drug and may occur in up to 40% of adults. In most cases the defect is asymptomatic and detected only on detailed visual field perimetry. The precise incidence of this defect in children is not known but is thought to be lower, possibly 25%. Current evidence suggests that early visual field constriction may be seen after a minimum of six months' exposure to the drug but far more typically after at least two years of continued use and usually in high doses. Long-term follow-up data will clarify whether the visual field deficit is likely to be permanent and irreversible.

Some children and specific paediatric populations are recognised to be at an increased risk of developing individual and usually serious side effects. Specific examples include:

- sodium valproate and hepatotoxicity: *children under three years of age with a severe epilepsy with multiple seizure types (including myoclonic seizures) with an onset under 12 months of age,*

global developmental delay and receiving at least one other antiepileptic drug (it is possible that the children in this high-risk group have an underlying metabolic defect of fatty acid oxidation)

- lamotrigine and rash: *an idiosyncratic but also dose-related rash (including Stevens-Johnson syndrome) developed in 25–30% of patients in early clinical trials with the drug; a lower starting dose and more gradual dose increase has reduced the incidence to a consistent level of 3–5%*

Table 2 outlines the more common side effects of the antiepileptic drugs; many are well-recognised whilst others are emerging, due to the relatively short periods they have been available.

Conclusion

The management of epilepsy extends far beyond the prescription of antiepileptic medication. It is obviously important to correctly identify the seizure type, epilepsy syndrome and cause of the epilepsy, and to prescribe the most appropriate antiepileptic drug to obtain optimal control of seizures without unacceptable side effects. However, for many patients and their families, social, educational and psychological features far outweigh the problem of controlling seizures. This always requires an inter-disciplinary team approach within a specialist epilepsy clinic that can bring together experience and advice from many sources, including nursing, psychology and social work. Finally, each family should be informed about the existence of all relevant and national voluntary organisations that are frequently able to provide an invaluable support and educative role, as well as contributing to epilepsy research.

The mechanisms underlying the actions of antiepileptic drugs are heterogeneous and complex. This is also true of the responsiveness (and resistance) that children show to the antiepileptic drugs and the development of serious side effects, issues that almost certainly reflect the influence of pharmacogenetic factors.

Despite the advent of the new antiepileptic drugs, there remain a significant number (up to 25%) of children with persistent and refractory seizures. The majority, but not all, of these children will have 'epilepsy plus'. Polytherapy is commonly undertaken in these children but rarely results in seizure-freedom and is frequently accompanied by adverse effects on learning, behaviour and day-to-day functioning. Consequently, the option of no medication is reasonable and appropriate in this population, although there is the theoretical risk of a marked deterioration in seizure control and convulsive (tonic-clonic) status epilepticus. As with all management decisions and irrespective of the drug on intervention, this must be discussed openly and honestly with the child's family – and, where appropriate, the children themselves.

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