

Drug treatment of paediatric epilepsy

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Basic principles

Once the diagnosis of epilepsy and the epilepsy syndrome have been established (see also Chapter 23), there are a number of decisions which must be taken regarding the use of antiepileptic drugs (AEDs) (Table 1). Only the first four points in Table 1 will be discussed in this chapter.

The decision to treat a child with a drug depends upon the individual (frequency of seizures, epilepsy syndrome and neurological findings) and also the wishes of the parents/carers. It remains unclear when drug treatment should begin¹⁻³, and numerous attempts have been made to accurately predict the risk of epilepsy developing (i.e. recurrent, spontaneous seizures) after the first unprovoked seizure³. Nevertheless, the decision to treat – and when to treat – remains an individual one. Most clinicians would not recommend starting treatment after a single, brief generalised tonic-clonic seizure, but would after a cluster of seizures or, possibly, after an episode of unprovoked status epilepticus. Similarly a child with severe physical and learning difficulties who develops infrequent myoclonic or generalised atypical absence or focal seizures may not necessarily require an AED. The recently published ILAE working definition of epilepsy takes these considerations into account⁴.

Table 1. Decisions regarding AEDs in children.

When to start a drug

Which drug and in what dose

When to change the drug

When (and how) to add a second drug (and which one)

When to seek a specialist opinion (paediatric neurologist)

When to stop the drug(s)

When to consider alternative therapies, including surgery

However, a child with normal intelligence who experiences frequent absence and generalised tonic-clonic seizures on waking may require treatment. Once a drug is started the objective is to achieve complete seizure control using a single drug, without causing side effects, and to use the most appropriate formulation to ensure that the child can actually take and absorb the medication.

The identification of the syndrome or seizure type provides information on the prognosis of the epilepsy and choice of AED. However, when prescribing for infants and young children the selection of the most appropriate AED must take into account the safety profile of that drug (i.e. the risk of and type of side effects) and also the available formulation of the drug.

This is particularly relevant in paediatric epilepsy where there is still a relative lack of knowledge and understanding about possible long-term effects of AEDs on growth and development, as well as concern about the short-term effects on behaviour, intellectual function and patterns of sleep. Although the newer AEDs appear to have a more acceptable safety profile, this optimism should remain somewhat guarded in view of the lack of any long-term data. Justification for this caution is derived from experience with felbamate where aplastic anaemia and hepatitis became manifest only a few years after its introduction in the early 1990s, and also with vigabatrin, where a characteristic bilateral visual field constriction was identified only ten years after introduction.

Once the most appropriate AED has been selected, this should be used alone (monotherapy) and in the lowest dose that controls the seizures without producing unacceptable side effects. This should be possible in approximately 70% of children. In children under the age of 12 years, dosages are usually based on bodyweight (mg/kg) rather than numbers of tablets/capsules (Table 2); this is clearly important in view of the wide age range of children treated and their different metabolic rates. For example, neonates, infants and children under the age of two frequently require relatively higher doses than older children and adolescents because of a higher rate of drug clearance.

When initial seizure control is suboptimal, or the AED has an obvious dose-response relationship, the dosage should be increased gradually until either seizure control is achieved or unacceptable side effects develop. If side effects occur before control is reached, the child will require either a different AED (substitute drug) or an additional AED (polytherapy). The choice of this second AED will depend upon the same criteria used to select the first but also on the likelihood of any potential interaction between the two drugs. How the change in AED therapy is effected depends on the child and the experience and beliefs of the clinician. If there has been some initial seizure control with the first AED it would be reasonable to add the next most appropriate AED, without withdrawing the first. If complete seizure control is then achieved, attempts to withdraw the first drug could be undertaken after a seizure-free period of between two and three months. If the initial AED has been wholly ineffective, it would seem logical to simultaneously replace the first drug with the second, thus maintaining monotherapy.

Polytherapy ('polypharmacy')

In some children, polytherapy with two AEDs is justified as this may result in additional (even complete) seizure control in another 10% of children. However, the problems of polytherapy include: pharmacodynamic interactions potentially reducing the effectiveness of each drug, difficulty in interpreting the effect of each drug, cumulative toxicity, and increased risk of

Table 2. Paediatric maintenance dosages of antiepileptic drugs.

Drug	Usual total daily dosage (mg/kg/day)	Doses/day
Acetazolamide	10–20	2
Carbamazepine	10–20	2/3 ¹
Clobazam	0.5–1.5	2
Clonazepam	0.1–0.3	2/3
Eslicarbazepine	15–30	2
Ethosuximide	15–35	2 (3)
Gabapentin	30–45	3
Lacosamide	2–8	2
Lamotrigine	(a) 2–5 ² (b) 4–10	2
Levetiracetam	30–50	2
Nitrazepam	0.5–1	2/3
Oxcarbazepine	20–30	2
Perampanel	8–10 (possibly 12) mg/day total	1
Phenobarbitone	4–8	2
Phenytoin	4–8 ³	2 (1)
Rufinamide	25–35 ⁴	2
Sodium valproate	20–40	2 ⁵
Stiripentol	25–35	2 (possibly 3)
Tiagabine	0.5–1.0	2/3
Topiramate	4–8 ⁶	2
Vigabatrin	50–100 ⁷	2
Zonisamide	4–5	2 (possibly 3)

1. The sustained release preparation (Tegretol Retard) may be given once or twice a day, depending on the timing of the seizures
2. Dose (a) is used when sodium valproate is being taken concurrently with lamotrigine; dose (b) is used with lamotrigine monotherapy or with drugs other than valproate
3. Dose varies considerably depending on age; neonates frequently require total daily doses in excess of 10–15 mg/kg
4. When used with sodium valproate the total daily dose is usually 20–25 mg/kg in children with a body weight of <30 kg; titration to the maintenance dose also takes slightly longer
5. The sustained release preparation (Epilim Chrono) is usually given once a day
6. The starting dose should be 0.5 mg/kg/day
7. When treating partial seizures, the usual maintenance dose is usually 30–50 mg/kg/day. When treating infantile spasms, the usual dose is 80–100 mg/kg/day although lower doses may be effective; the maximum dose is 120–150 mg/kg/day

idiosyncratic (allergic) toxic interactions. The decision regarding which additional AED to use is again dependent upon the seizure type/epilepsy syndrome and drug safety profile. Some authors term this 'rational polytherapy'. This 'rationalisation' may be determined theoretically by the drug's known (or postulated) mechanisms of action, or practically by following clinicians' experience of using certain drug combinations. Consideration must also be given to whether the two AEDs act synergistically or antagonistically, in terms of both effectiveness and safety. Examples of rational combinations are shown in Table 3 (in part this reflects the authors' personal practice). The simultaneous use of three (or more) AEDs rarely, if ever, proves to be more effective than two drugs and will almost certainly result in increased side effects and, by causing drowsiness and disturbing a normal sleep pattern, may paradoxically exacerbate seizure control. Therefore there needs to be an extremely good reason for using more than two drugs concurrently.

Also, it is unlikely that polytherapy with three AEDs will produce any additional, significant and sustained control; however, polytherapy using three or more drugs will almost certainly be associated with an increased risk and frequency of side effects, as well as toxicity due to drug interactions. The only situation where three drugs are acceptable is during substitution, i.e. one drug being introduced as another is withdrawn. Unfortunately, it is usually far easier to initiate polytherapy than to terminate it.

It is tempting but perhaps rather naive to expect that any of the new AEDs, with recognised and even 'designed' mechanisms of action, will necessarily offer a more rational or scientific basis for using specific drug combinations in every patient.

Drugs available

The older and most commonly used medications in the treatment of childhood epilepsy are sodium valproate and carbamazepine. Phenytoin and phenobarbitone, previously drugs of first choice for most seizure types before the advent of carbamazepine and sodium valproate, are no longer considered to be first, second or third-line drugs because of their relatively unsatisfactory long-term safety profile. However, in certain situations they may still be effective, but only when other drugs have 'failed' and where seizure control is the major – if not only – priority. Further, they remain the first-line treatment in the acute management of neonatal seizures in view of their parenteral availability and safety profile. The benzodiazepines⁵ are also effective AEDs, particularly for generalised, but also for focal seizures and some epilepsy syndromes. Their use may be restricted by acute toxicity, and the development of tolerance or tachyphylaxis. For these reasons, benzodiazepines are rarely, if ever, the initial AED, other than for infants and children with myoclonic seizures as the only seizure type, when low-dose clonazepam or clobazam may be used as monotherapy. Nitrazepam may be effective in suppressing infantile spasms, and particularly when these have arisen as a consequence of neonatal hypoxic-ischaemic encephalopathy. Clobazam is also often very effective as an add-on treatment for treating partial seizures (with or without secondary generalised tonic-clonic seizures), atypical absences, electrical status epilepticus of slow-wave sleep (ECESS) and catamenial seizures. Ethosuximide has traditionally been used for childhood absence epilepsy, but can also be effective where spike-wave activity is prominent, such as atypical absence of Lennox-Gastaut syndrome or continuous spike-wave of slow sleep.

Numerous AEDs are licensed for use in the UK as 'add-on' (adjunctive) or as monotherapy in a range of seizure types and epilepsy syndromes – vigabatrin, lamotrigine, gabapentin, topiramate, tiagabine, oxcarbazepine, levetiracetam, pregabalin, zonisamide, rufinamide, lacosamide, eslicarbazepine and, most recently, perampanel. Lamotrigine has a monotherapy

Table 3. Drugs of first and second choice in the treatment of various seizure types and epilepsy syndromes, and drugs to avoid in view of risk of exacerbation of seizures. (Adapted from NICE¹²) CBZ carbamazepine; CLB clobazam; CLN clonazepam; ESM ethosuximide; GBP gabapentin; LEV levetiracetam; LTG lamotrigine; OXC oxcarbazepine; PHT phenytoin; VPA sodium valproate; TGB tiagabine; TPM topiramate; VGB vigabatrin

Seizure type/syndrome	First line	Adjunctive AEDs	Do not offer (may worsen seizures)
Focal seizures	CBZ, LTG, OXC, TPM, VPA	CLB, GBP, LEV, PHT, TGB	
Generalised seizures			
Absence	ESM, LTG, VPA	ESM, LTG, VPA	CBZ, GBP, OXC, PHT, PGB, TGB, VGB
GTC	CBZ, LTG, OXC VPA,	CLB, LTG, LEV, VPA, TPM	(if absence or myoclonic seizures) CBZ, GBP, OXC, PHT, PGB, TGB, VGB
Myoclonic	LEV, VPA, TPM	LEV, LTG, VPA	CBZ, GBP, OXC, PHT, PGB, TGB, VGB
Tonic or atonic	VPA	LTG	CBZ, GBP, OXC, PHT, PGB, TGB, VGB
Childhood absence epilepsy or other absence syndromes	ESM, LTG, VPA	ESM, LTG, VPA	CBZ, GBP, OXC, PHT, PGB, TGB, VGB
Juvenile absence epilepsy or other absence epilepsy syndromes	ESM, LTG, VPA	ESM, LTG, VPA	CBZ, GBP, OXC, PHT, PGB, TGB, VGB
Juvenile myoclonic epilepsy	LTG, LEV, VPA, TPM	LTG, LEV, VPA, TPM	CBZ, GBP, OXC, PHT, PGB, TGB, VGB
Genetic generalised epilepsy	LTG, VPA, TPM	LTG, LEV, VPA, TPM	CBZ, GBP, OXC, PHT, PGB, TGB, VGB
BECTS	CBZ, LTG, LEV, OXC, VPA	CBZ, CLB, GBP, LTG, LEV, OXC, VPA, TPM	

Table 3. Continued

Panayiotopoulos syndrome	CBZ, LTG, LEV, OXC, VPA	CBZ, CLB, GBP, LTG, LEV, OXC, VPA, TPM	
Late-onset childhood occipital epilepsy (Gastaut type)	CBZ, LTG, LEV, OXC	CBZ, CLB, GBP, LTG, LEV, OXC, VPA, TPM	
Infantile spasms not due to tuberous sclerosis	Discuss with or refer to a tertiary paediatric epilepsy specialist Steroid (prednisolone or tetracosactide) or VGB		
Infantile spasms due to tuberous sclerosis	Discuss with or refer to a tertiary paediatric epilepsy specialist VGB or steroid (prednisolone or tetracosactide)		
Dravet syndrome	Discuss with, or refer to a tertiary paediatric epilepsy specialist VPA, TPM	CLB, stiripentol	CBZ, GBP, LTG, OXC, PHT, PGB, TGB, VGB
Lennox-Gastaut syndrome	Discuss with or refer to a tertiary paediatric epilepsy specialist VPA	LTG	CBZ, GBP, OXC, PGB, TGB, VGB
Landau-Kleffner syndrome	Refer to a tertiary paediatric epilepsy specialist Steroids, LTG, VPA		
Continuous spike-wave in slow sleep	Refer to a tertiary paediatric epilepsy specialist Steroids, CLB, VPA, LTG, ESM	LEV, TPM	CBZ, OXC, VGB
Myoclonic-astatic epilepsy	Refer to a tertiary paediatric epilepsy specialist VPA, LEV	LTG, TPM	CBZ, OXC

licence for patients aged 12 years and older but as adjunctive therapy from two years. Vigabatrin has a monotherapy licence for use in the management of children with infantile spasms (West syndrome) in the UK. Topiramate now has a licence for use as monotherapy in children aged six years and above. The licence for levetiracetam is currently as monotherapy for patients aged four years and above; this drug also has a licence as adjunctive therapy for treating focal seizures from one month of age and myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy (JME). Pregabalin, zonisamide and lacosamide have licences for use as adjunctive therapy in people aged 18 years and above. Perampanel has a license for adjunctive therapy of focal seizures over the age of 12 years. Of these new AEDs, lamotrigine, topiramate and levetiracetam would appear to have the broadest spectrum of action, being effective against many generalised and focal seizure types, and relatively free of serious side effects, other than lamotrigine producing an allergic or idiosyncratic rash, that rarely develops into Stevens-Johnson syndrome^{7,8}. Lamotrigine can be effective in controlling typical absence seizures⁹ but not as effective in suppressing myoclonic seizures. Levetiracetam also has a broad spectrum of action against different seizure types and its safety profile would appear to be relatively impressive, with hostility/aggression as the only significant and possibly drug-limiting side effects.

Vigabatrin is also a very effective drug in the treatment of infantile spasms¹⁰ to the point where it is recognised as a drug of first choice^{11,12}, particularly when the underlying cause is tuberous sclerosis¹³⁻¹⁵. Vigabatrin is also useful for focal seizures, with or without secondary generalisation, and appears to be particularly effective in children who have an underlying structural lesion such as focal cortical dysplasia or even low-grade tumours. However, the drug may exacerbate myoclonic and typical absence seizures¹⁶⁻²⁰. The drug also appears to have a relatively impressive short-term safety profile. Rarely, however, behavioural effects may occur, which manifest as either agitation or a change in muscle tone and an increased appetite; these effects are transient and resolve once the dose is reduced or the drug withdrawn. However, the peripheral visual field constriction reported to occur in up to 40% of adult patients treated with vigabatrin²¹ is clearly of concern and, consequently, this drug is now only rarely (possibly never) prescribed to adults or older children for focal seizures. At the current time, visual field defects have been reported in children but it is not known whether children are likely to be at a higher or lower risk of developing a visual field defect and also whether any visual field constriction is more or less likely to be reversible than in adults. The reported incidence is 20–25% and has been derived from older children treated with this drug for focal seizures but this figure may be higher or lower because it is often very difficult to accurately obtain formal visual field assessment (perimetry) in children with a cognitive age of <9 years. Limited data also suggest the occurrence to be related to dose and duration of treatment²². The drug should only be prescribed in children after careful consideration of the risk:benefit ratio.

Efficacy and safety data on the use of gabapentin in children are limited, although it does appear to be effective in focal seizures²³⁻²⁵. Of all the new AEDs, gabapentin appears to be the least potent in treating focal seizures in children and the one with the lowest chance of rendering children seizure free²⁴. In adults the drug is effective in focal seizures with and without evolution to bilaterally convulsive seizures^{26,27}; there is little information on generalised tonic-clonic seizures, although it would appear to have no effect (beneficial or detrimental) in typical absences²⁸. Adverse events appear to be both mild and infrequent with gabapentin, and there are no known drug interactions. Unfortunately, it often has to be administered three times a day (which has implications for some school children), and as yet there is only a capsule formulation that restricts its use in children. A 'mixed fruit'-flavoured suspension is available in the US.

Topiramate is effective in focal onset seizures and also in the Lennox-Gastaut syndrome²⁹⁻³³ (tonic and atonic seizures seem to respond best). Topiramate may also be effective as

monotherapy in both focal and primary generalised tonic-clonic seizures³⁴ and also in treating Dravet syndrome. The drug does appear to be associated with a number of acute and predominantly dose-related side effects, particularly on the central nervous system. These include dizziness, drowsiness, irritability, 'fatigue', word-finding difficulties/mild cognitive impairment and, rarely, acute depressive and psychotic illness. These can be minimised by slow introduction. Paraesthesiae, renal calculi and glaucoma have also been reported but predominantly in adults; theoretically there is an increased incidence of renal calculi if children are receiving a combination of either topiramate and zonisamide or topiramate with the ketogenic diet over a long period (in excess of 12 or 18 months). Insomnia, anorexia and weight loss are additional reported side effects with topiramate³⁴.

There are few randomised clinical data on the use of tiagabine³⁴ in children. As with all new AEDs the drug has been shown to be more effective than placebo in suppressing focal onset seizures in adults and some adolescents, without apparently causing any severe adverse effects^{35,36}. Like vigabatrin, tiagabine also has a direct effect on GABA-ergic neurotransmission (and GABA levels) and although it is theoretically possible that tiagabine *might* also affect visual field function, reports suggest that this drug does not produce the same visual field defect that is seen with vigabatrin. A number of anecdotal reports have suggested that the drug may precipitate non-convulsive status epilepticus^{37,38}.

Oxcarbazepine, structurally similar to carbamazepine, was licensed for use in the UK in 2002. Its spectrum of action is almost identical to carbamazepine, but by not being metabolised to the 11-epoxide metabolite it is associated with fewer adverse side effects than carbamazepine (i.e. less ataxia, diplopia and nausea). However, hyponatraemia is reported to occur more frequently with oxcarbazepine – although rarely with any significant clinical effects. The drug is available as a standard (not slow or sustained) release tablet and liquid suspension. Finally, there is some evidence that oxcarbazepine will not be complicated by an idiosyncratic rash, even if the child has previously developed a rash with carbamazepine. Like carbamazepine, oxcarbazepine may exacerbate the absence and myoclonic seizures that occur in the generalised epilepsies³⁹.

There is a clear dose-response relationship with lamotrigine, gabapentin, topiramate, levetiracetam and probably pregabalin, tiagabine and zonisamide but not with vigabatrin³⁹, and none appear to be associated with either significant tolerance or tachyphylaxis. Finally, there is as yet no established plasma 'therapeutic range' for these new drugs; and as there is no correlation between plasma levels of vigabatrin and its clinical efficacy (due to its pharmacokinetic properties), such measurements are not helpful as a guide to dosage. Whether a random level can be usefully used to ascertain compliance remains to be determined – although this is probably useful where major non-compliance is possible.

Until 1994/5 felbamate was available in the UK on a compassionate, named-patient basis. Early reports from the US had suggested that it was effective for focal seizures in adults^{40,41} and generalised seizures associated with the Lennox-Gastaut syndrome in children⁴³. Unfortunately, a large number of patients developed aplastic anaemia, some with a fatal outcome. A severe, presumed idiosyncratic, hepatitis has also been reported. As a result of these serious adverse reactions, the drug is only available in the UK on a limited named-patient basis. However, in the US, the prescribing of felbamate continues to increase (slowly), but obviously with close monitoring of haematological and hepatic function. This re-emergence of felbamate has not been reported to be accompanied by a corresponding increase in additional cases of aplastic anaemia or hepatitis.

Zonisamide appears to have a broad spectrum of action, if data from Japan and the USA (where the drug has been used for over a decade) are to be believed, with reported benefits in treating

patients with drug-resistant focal seizures, primary generalised tonic-clonic seizures, refractory myoclonic and absence seizures and even refractory infantile spasms^{44,45}. Its mechanism of action, and therefore its reported adverse side effects, appears to be similar, but less severe, to that of topiramate. Currently, in the UK, the drug only has a licence as an add-on treatment for treating focal seizures in patients aged 18 years and above; however, it is expected to receive a paediatric licence as adjunctive therapy within the near future (2013/14).

Rufinamide is licensed in the UK for treatment of seizures associated with Lennox-Gastaut syndrome. A randomised double-blind placebo-controlled trial of 139 participants aged 4–30 years showed significant benefit in most seizure types, particularly atonic ('drop') and absence seizures⁴⁶.

Many other drugs have been used in paediatric epilepsy, usually in an attempt to control multiple and refractory seizure types. Acetazolamide, a diuretic and carbonic anhydrase inhibitor, is considered by many to be a useful add-on drug (usually in combination with carbamazepine) in treating focal seizures⁴⁷. Pyridoxine (vitamin B₆) is clearly the treatment of choice in the rare inherited disorder of pyridoxine-dependent seizures⁴⁸, but it has also been used in West syndrome (infantile spasms)⁴⁹. A three-week trial of oral pyridoxine should also be used in any child under 18 months of age with frequent seizures (including infantile spasms) that have been resistant to 'conventional' AEDs. If there has been no obvious or sustained response to pyridoxine, and there remains a high suspicion of pyridoxine-dependent epilepsy, the child should then receive a three- or four-week course of pyridoxal phosphate. Biotin should also be used in infants and young children with refractory seizures pending the result of a serum biotinidase level. Folinic acid should also be used for any infant with neonatal-onset seizures that have been resistant to both conventional antiepileptic medication and pyridoxine and where no cause has been found for the epilepsy.

The high-fat, low-carbohydrate ketogenic diet is a historical treatment that has gained more credibility as an effective management of children with drug resistant epilepsy⁵⁰. A randomised controlled trial has demonstrated definitive efficacy over no change in treatment. More relaxed forms of the diet have raised the possibility of it being available to use over a wide age range.

Steroids, given either as prednisolone or less commonly hydrocortisone or adrenocorticotrophic hormone (ACTH)⁵¹ (this drug is no longer available in the UK and has been replaced by the synthetic steroid, tetracosactide, see Chapter 23), are frequently used in treating different seizure types or epilepsy syndromes, including acute epileptic encephalopathies. The mechanism of action of steroids is unclear but they may be very effective, particularly in the following situations:

- infantile spasms (West syndrome)
- continuous spike-wave in slow sleep (CSWSS), also called electrical status epilepticus of slow sleep (ESESS)
- Dravet syndrome
- Lennox-Gastaut syndrome, particularly in non-convulsive (atypical absence) status
- other, rare epileptic encephalopathies.

Intravenous immunoglobulins have been used with varying (usually very limited), success in intractable epilepsies including children with both the West^{52,53} and Lennox-Gastaut syndromes^{54,55}. There are marked variations in the frequency of courses, duration of treatment

and doses of this particular therapy and there is as yet no established or universally accepted mechanism of action.

Which drug?

Drug choice in childhood epilepsy should, wherever possible, be evidence based as in older individuals. However, there are few randomised controlled trials on which to base drug choice within the epilepsy syndromes. This in part reflects the logistical and ethical difficulties as well as the expense in conducting paediatric trials. Nevertheless, the principal should still be to try and base treatment strategies on robust evidence. The EMA has recently revised guidelines on the development of AEDs in children. They state that focal epilepsies in children older than four years of age have a similar clinical expression to focal epilepsies in adolescents and adults. In refractory focal epilepsies, the results of efficacy trials performed in adults could to some extent be extrapolated to children, provided the appropriate dose and safety data are established. In children under four years of age, short-term assessment of response by using video-EEG monitoring may be sufficient once efficacy has been demonstrated in older children. For syndromes limited to childhood, sufficient experience needs to be gained in this population before a new medicinal product may be registered for these indications in children⁵⁶; predictably such experience is likely to be largely anecdotal unless data can be obtained from well-conducted national or international randomised controlled trials.

Many studies are conducted on the basis of seizure type rather than syndrome, are limited in duration and reveal little in the way of long-term effects. The HTA (in 2004) suggested that older drugs such as sodium valproate or carbamazepine should be used as first line over and above newer anticonvulsants unless there was a contraindication⁵⁷. The NICE guidelines for the diagnosis and management of epilepsy in primary and secondary care, originally published in 2004, underwent a pharmacological review in 2012¹². These took a GRADE approach to evaluating evidence and guidance produced was based also on the cost effectiveness of AED use.

Many paediatric epilepsies and epilepsy syndromes are associated with generalised seizures, and for these the current drug of choice (at least in the UK) is usually sodium valproate. This was confirmed by the SANAD (Standard and New Antiepileptic Drugs) study, which showed sodium valproate to be superior in the treatment of generalised seizures over topiramate and lamotrigine where sodium valproate would have been the physicians' choice (arm B). Many of the individuals in this study had genetic generalised epilepsy⁵⁸. Further, a recent randomised double-blind trial in the treatment of childhood absence epilepsy comparing ethosuximide, sodium valproate and lamotrigine showed superior efficacy of sodium valproate and ethosuximide over lamotrigine, but some neuropsychological advantage to ethosuximide⁵⁹. There has been increasing concern about the effect of sodium valproate on the unborn child of mothers taking the medication – both an increased risk of malformations, as well as cognitive delay in later childhood. For this reason the medication is not recommended as first line in girls of child-bearing age, and when considered, the risks of taking the medication need to be weighed against the risk of the epilepsy itself in each individual.

Epilepsies associated with focal seizures are slightly less common in children in contrast to adults and for these individuals carbamazepine is the usual preferred treatment. Data from the SANAD study⁶⁰ arm A where carbamazepine would have been physicians' choice demonstrated that lamotrigine was at least as effective and associated with fewer adverse side effects than carbamazepine, oxcarbazepine, topiramate and gabapentin. Although SANAD was inclusive of children in the protocol, few children were recruited to this arm, and in the majority

those included had symptomatic focal epilepsy, which is less common than idiopathic focal epilepsy in children.

A follow-on study, SANAD II, commenced in April/May 2013. In this study the ‘standard’ drug in the generalised or unclassified arm will be sodium valproate (the ‘winner’ in SANAD I) and the ‘new’ comparator drug will be levetiracetam. In the focal arm, lamotrigine will be the ‘standard’ drug (the ‘winner’ in SANAD I) and the ‘new’ comparator drugs will be levetiracetam and zonisamide. The results will be interesting and should hopefully be published in 2017/18.

One major syndrome to consider is West syndrome, characterised by infantile spasms and hypsarrhythmia on EEG; most, but not all children also demonstrate developmental plateau or even regression, particularly if the diagnosis is delayed. It is recommended that hormonal treatments (ACTH, tetracosactide or prednisolone) or vigabatrin should be used as first-line monotherapy drugs in treating infantile spasms^{11,12}. Vigabatrin is particularly effective in treating infantile spasms caused by tuberous sclerosis¹² but appears to be slightly less effective than tetracosactide or prednisolone in treating spasms due to other aetiologies^{61,62}. However there are currently differences of opinion regarding the treatment of infantile spasms, in part reflecting clinicians’ concerns over drug safety and in part availability of medication. In the US, ACTH or prednisolone is the preferred treatment⁶¹; until recently vigabatrin has not been freely available, whereas in many European countries vigabatrin is widely used. Which is used will depend on family and physician choice, weighing up the risk:benefit of the treatment involved. Although use of vigabatrin in adults and older children has been associated with visual field constriction, this appears to be related to dose and duration of treatment²¹ and does not necessarily prevent or reduce the use of this drug in treating infantile spasms when weighed up against the risk of short-term high-dose steroids.

In Dravet syndrome, previously called severe myoclonic epilepsy of infancy, medications of choice are sodium valproate, clobazam and topiramate. Furthermore a well-constructed randomised crossover study demonstrated stiripentol, a cytochrome P450 inhibitor, to be significantly more effective than placebo when added to sodium valproate and clobazam⁶³; however, this drug may be associated with significant somnolence as well as loss of appetite. Of greater note is the observation that medications acting on sodium channels (e.g. lamotrigine, phenytoin) may cause aggravation of seizures in this syndrome^{64,65} and therefore should be avoided.

Several studies have been conducted evaluating treatments against placebo in Lennox-Gastaut syndrome as add-on therapy. A Cochrane Review was able to evaluate seven randomised controlled trials. All but two studies evaluated different therapies. Overall the authors concluded that no study to date had shown any one drug to be effective over and above another but lamotrigine, rufinamide, clobazam, topiramate and felbamate may be helpful as add-on therapy⁶⁶. Therefore until further research has been undertaken clinicians will need to continue to consider each patient individually, taking into account the potential benefit of each therapy weighed against the risk of adverse effects.

There is still probably a clear need for novel AEDs in childhood epilepsy. These must be effective (preferably with a broad spectrum of action against a wide range of seizure types), safe and be available in child-friendly formulation. However, while the advent of the new AEDs should be welcomed, it is important to use the older, ‘conventional’ AEDs appropriately and initially, particularly in view of the limited data on both monotherapy efficacy and long-term safety for newer compounds. In this regard, it is common for a child to be falsely described as being refractory to treatment because they have been prescribed the wrong drug for their epilepsy syndrome. The classic example is the use of carbamazepine or oxcarbazepine for juvenile-onset absence or juvenile myoclonic epilepsy, when it is known to exacerbate both

the myoclonic and absence seizures which characterise these syndromes. Further, when initiating teenage girls on medication that may need to be lifelong, the possibility of pregnancy and the effects of AEDs *in utero* need to be taken into consideration and individuals counselled accordingly; this is particularly important when discussing and prescribing sodium valproate.

Summary and conclusions

- The choice of AED in treating the childhood epilepsies will be determined by the epilepsy syndrome (and therefore the specific seizures that help to define the syndrome), safety profile and, to a slightly lesser extent, its ease of use (formulation and dosing regimen)
- Sodium valproate appears to remain the most effective AED in treating generalised seizures
- Lamotrigine, closely followed by carbamazepine or oxcarbazepine, appears to be the most effective and ‘best tolerated’ AED in treating focal seizures
- The major benefit of the newer AEDs seems to be their lower (and also milder) incidence of adverse side effects although there are some exceptions
- It is important to be aware of drugs that may exacerbate some seizure types
- The temptation should be strongly resisted to indulge in polypharmacy; it is always easier to add another drug than to withdraw one. There are no convincing data that the simultaneous use of three AEDs results in better seizure control than two drugs. ‘Polypharmacy’ increases the risk and incidence of adverse side effects; in addition, three drugs, in causing drowsiness and disturbing sleep patterns, may paradoxically cause a deterioration in seizure control, as well as an increase in adverse side effects. Consequently the prescribing mantra must be ‘if I add, what can I take away’ to avoid dangerous polypharmacy.

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