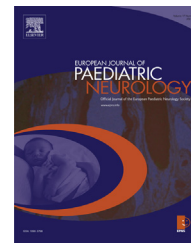




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Review article

Advancing the management of childhood epilepsies



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ABSTRACT

Childhood epilepsies comprise a heterogeneous group of disorders and syndromes that vary in terms of severity, prognosis and treatment requirements. Effective management requires early, accurate recognition and diagnosis, and a holistic approach that addresses each individual's medical and psychosocial needs within the context of their overall health status and quality of life. With increasing understanding of underlying aetiologies, new approaches to management and treatment are emerging. For example, genetic testing is beginning to provide a tool to aid differential diagnosis and a means of predicting predisposition to particular types of epilepsy. Despite the availability of an increasing number of antiepileptic drugs (AEDs) – due not only to the development of new AEDs, but also to changes in regulatory requirements that have facilitated clinical development – seizure control and tolerability continue to be suboptimal in many patients, and there is therefore a continuing need for new treatment strategies. Surgery and other non-pharmacological treatments (e.g. vagus nerve stimulation, ketogenic diet) are already relatively well established in paediatric epilepsy. New pharmacological treatments include generational advances on existing AEDs and AEDs with novel modes of action, and non-AED pharmacological interventions, such as immunomodulation. Emerging technologies include novel approaches allowing the delivery of medicinal agents to specific areas of the brain, and 'closed-loop' experimental devices employing algorithms that allow treatment (e.g. electrical stimulation) to be targeted both spatially and temporally. Although in early stages of development, cell-based approaches (e.g. focal targeting of adenosine augmentation) and gene therapy may also provide new treatment choices in the future.

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1. Introduction

Epilepsy in childhood has a prevalence of approximately 0.5–0.8% and comprises a heterogeneous group of disorders including a variety of epilepsy syndromes that range in severity from benign to progressive and catastrophic.^{1–4} These syndromes are categorised on the basis of a number of features including seizure type(s), age of onset, clinical features, genetics, brain abnormalities, electroencephalogram (EEG) expression, response to treatment, and prognosis.⁵ Effective management of paediatric epilepsies requires early, accurate recognition and diagnosis in order to ensure prompt and appropriate treatment, but also requires a holistic, comprehensive approach to patient care that encompasses the child’s psychosocial as well as medical needs.

The objectives of this paper are to outline current challenges in the management of childhood epilepsies and ways in which these are being addressed, including how the knowledge base for paediatric epilepsy is expanding, and how treatment options – both antiepileptic drug (AED) and non-AED – are being advanced.

2. Current management issues in paediatric epilepsy

2.1. Importance of differential diagnosis and syndromic classification

Epilepsy in childhood can be difficult to recognise and diagnose correctly, particularly since there is no definitive diagnostic

test. Unusual mannerisms, movements and behaviours in infants, children and teenagers are common and may have a variety of causes, only some of which may result from electrical changes in the brain and therefore, by definition, be epileptic seizures.⁵ For example, in a prospective study of 380 children referred to a ‘fits, faints and funny turns’ clinic, only 23% were given a final diagnosis of one of the childhood epilepsies, with syncope being the commonest cause of a non-epileptic event

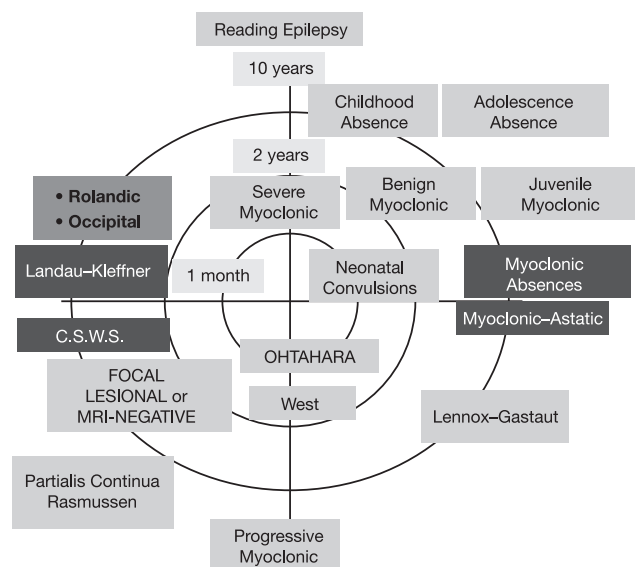


Fig. 1 – Diversity and age dependence of epilepsy syndromes in childhood. CSWS, continuous spikes and waves during slow sleep; MRI, magnetic resonance imaging.

(accounting for 42% of all diagnoses) and 14% of events being unclassified and managed without a diagnostic label or treatment.⁵ Misdiagnosis of epilepsy is therefore common, with one study demonstrating that almost 40% of children referred to a tertiary epilepsy service with paroxysmal events did not in fact have epilepsy.³ The opposite is also true: epilepsy is often misdiagnosed as not being epilepsy. Furthermore, since childhood epilepsy is characterised by a plethora of syndromes (Fig. 1),⁶ accurate diagnosis of a specific syndrome may be problematic, even when epilepsy is correctly recognised.

Differential diagnosis of specific syndromes may be crucial to manage a patient's condition and to guide prognosis.⁷ For example, differentiation of Lennox–Gastaut syndrome (LGS), myoclonic-astatic epilepsy and Dravet syndrome is of considerable importance from prognostic, therapeutic and genetic counselling perspectives, since AEDs that are effective for LGS may exacerbate myoclonic seizures in patients with Dravet syndrome (e.g. lamotrigine).⁸ Further, the risk of familial recurrence is higher for Dravet syndrome and myoclonic-astatic epilepsy than it is for LGS⁹; a high proportion of children with myoclonic-astatic epilepsy (at least 50%) have a good prognosis, whereas the prognoses of Dravet syndrome and LGS are less favourable.⁷

2.2. Treatment challenges

Even when a childhood epilepsy syndrome has been accurately diagnosed, treatment can be challenging. With over 20 AEDs currently available, choice of treatment must be made on an individual basis, taking into account the patient's seizure history, comorbidities and associated co-medications, as well as psychosocial aspects. It is also important to recognise that AEDs are in fact 'antiseizure' rather than 'antiepileptic', and thus target the symptoms of epilepsy, rather than the underlying cause. Since epilepsy involves more than just seizures (e.g. intellectual disability, behavioural disturbances), effective management must address all aspects of the condition, and these should be taken into account when making any treatment decision. Moreover, AEDs often have important side effects that must be avoided where possible or otherwise managed effectively. Treatment therefore involves balancing the control of seizures and comorbidities against the negative effects of treatment, which may adversely affect the patient's quality of life as much as the condition itself.

The ideal AED would be considered to be effective on multiple seizure types, cause no exacerbation of other seizure types, have no side effects, display predictable pharmacokinetics and not interact with other AEDs. Such an agent does not currently exist, although the search for better AEDs and novel therapeutic approaches continues.

2.3. The need for evidence to inform treatment decisions

Evidence-based guidelines have been published to help physicians choose appropriate newer AEDs in paediatric patients.^{10–13} However, to fully endorse new treatments for paediatric epilepsy, there is a need for well-designed randomised controlled trials (RCTs). Regulatory requirements for paediatric epilepsy have become increasingly specific^{14,15}

and only a limited number of well-designed RCTs have been performed in the childhood epilepsies.^{16–21} However, RCTs only provide limited information, since they are primarily designed to demonstrate safety and efficacy for regulatory purposes. In addition, they rarely provide direct head-to-head comparative data (the Standard And New Antiepileptic Drugs [SANAD] trial^{22,23} being an exception) or syndrome-specific efficacy data. Controlled data are particularly scarce for rare but severe childhood epilepsy syndromes and infantile epileptic encephalopathies, for which available clinical evidence is often limited to anecdotal case series.^{24,25}

3. Identifying realistic treatment goals: what does 'refractory' mean?

Before starting treatment with a new AED, treatment goals should, if possible, be defined, but these should be realistic and it is important to recognise that they may vary between patients, parents and clinicians. There is great variability in the prognosis of childhood epilepsies. Some syndromes have a good prognosis, either in terms of remission (e.g. Panayiotopoulos syndrome²⁶) or seizure control (e.g. idiopathic generalised epilepsy²⁷). For others, prognosis is either inconsistent (e.g. myoclonic-astatic epilepsy) or poor (e.g. LGS, Dravet syndrome).²⁸ Variability in prognosis directly affects treatment decisions; firstly, the decision of whether or not to treat at all, and secondly, the decision of which treatment to use. Since any AED is associated with the risk of side effects, the potential benefits of a particular therapy must be weighed against the potential risk of these effects. Existing comorbidities and their associated co-medications must also be taken into consideration when choosing AED treatment. For example, depression is a particularly common psychiatric comorbidity in epilepsy patients, requiring careful treatment.^{29,30} Although the overall objective of antiepileptic treatment is freedom from seizures, this must always be placed within the context of the patient's quality of life. This is particularly important for epilepsy syndromes with a poor prognosis, such as LGS, where complete seizure freedom is usually unrealistic and treatment success must therefore be seen in terms of achieving a favourable balance between control of seizures versus control of comorbidities, in order to optimise the patient's general health status and quality of life.³¹

Attempts to provide a definition for drug resistance have been hampered by questions such as the number of drugs that should be tried before a patient is considered refractory, the extent to which side effects may be considered acceptable, and the number of years that are necessary to establish drug resistance.³² The International League Against Epilepsy (ILAE) has proposed a definition of 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'.³³ It is hoped that this might provide an operational definition for clinical and research purposes, although it is acknowledged that the criteria for refractoriness may change with the emergence of

new data and alternative treatments,³⁴ and that such a definition might not be valid in very young children (<1 year). Refractoriness can also be difficult to identify and measure, since there may be ongoing natural fluctuations in seizure frequency, regardless of the intervention used, which may give a misleading impression of response.³⁵ The methods and timings used to monitor seizures may therefore give a false indication of the benefit/risk of stopping or starting a new treatment. Documentation of seizures (e.g. using an electronic diary) is essential when assessing efficacy during follow-up.

The biological mechanisms underlying pharmacoresistance are poorly understood, but are likely to be multifactorial and variable, comprising both genetic and environmental factors.^{32,36,37} For example, there is evidence for a potential mechanism whereby AEDs are limited in their ability to access the seizure focus in the brain by overexpression of P-glycoprotein and other efflux transporters in the cerebrovascular endothelium.³⁷ Since P-glycoprotein is encoded by the multi-drug resistance gene (*MDR1* or *ABCB1*), it has been suggested that there may be an association between variants of this gene and medical intractability in epilepsy.³⁷ In addition, expression of P-glycoprotein has been found to be highly inducible by environmental factors, including heat shock, arsenite, growth factors, sodium butyrate and protein kinase C agonists.³⁷ Similarly, major vault protein (a marker of drug resistance) has also been shown to be upregulated in refractory epilepsy.³⁸

Regardless of the mechanisms underlying treatment resistance, it appears to be worth persisting in trying new AED treatments in patients who have failed to respond adequately to other agents, since some may subsequently achieve seizure reduction and a small number seizure freedom. For example, a retrospective analysis was conducted to investigate the effects of 265 introductions of previously unused AEDs (by addition [$n = 125$] or substitution [$n = 140$]) in 155 patients with a history of uncontrolled epilepsy of at least 5 years' duration.³⁹ Overall, the introduction of a new AED resulted in seizure freedom in 16% of cases – seizure freedom being defined as a minimum period of follow-up without seizures of 12 months. A 50–99% reduction in seizures was experienced in a further 21% of cases. In some patients who failed to respond to a first new AED, the introduction of a second or third new AED was successful, so that, by the end of the study,

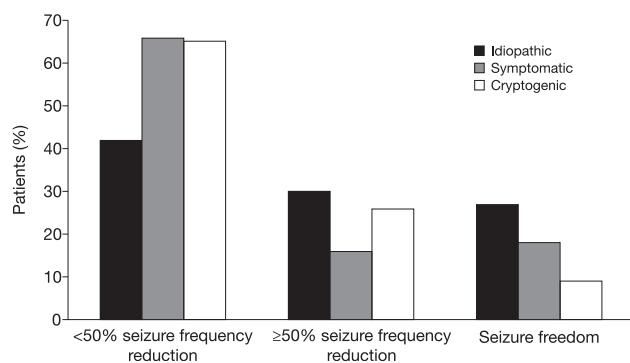


Fig. 2 – Evidence of benefit in persisting to try new AEDs in refractory patients: Effects of 285 additions of new agents in 155 patients with refractory epilepsy of ≥5 years' duration.³⁹

28% of patients had achieved seizure freedom by the addition of a previously unused AED (Fig. 2).³⁹ Other groups have reported similar findings.^{40–43} In addition, studies have shown that some refractory patients who are not eligible for surgical treatment may experience a reduction in seizure frequency, and even seizure freedom, after long-term follow-up, partly due to the natural history of the disease, but also optimisation of AED treatment, suggesting that patients presenting for presurgical assessment may be at a 'nadir' in terms of disease course and drug resistance.^{44,45} It is, however, important to point out that some epilepsy patients will remain refractory to treatment, the chance of responding to therapy – and especially of becoming seizure free – being very low once more than five AEDs have been tried.⁴²

Although it appears to be worth persisting with new AED treatments in patients with seemingly intractable epilepsy, it is also important to recognise that the most appropriate treatment goal for some patients with refractory epilepsy and severe multiple comorbidities will be the optimisation of care, focussing primarily on the patient's quality of life.

4. Improving management practice

When considering treatment for a child with epilepsy, it is important to weigh the medical aspects of the condition against its psychosocial aspects. This involves finding a balance not only between seizure control and the side effects of treatment, but also between maintaining hope that a successful treatment can eventually be found ('never give up') and accepting that the degree of seizure control achieved might be 'as good as it can get'. Overall, a holistic, individualised, multidisciplinary approach to treatment is required in order to optimise patients' quality of life. This should not only take into consideration the patient's medical needs, but also their particular psychosocial setting, in terms of living situation, interpersonal relationships and educational needs, as well as their priorities and aspirations.

It is also important to recognise that treatment goals may change as a patient makes the transition from childhood to adulthood. Adolescence, in particular, is a time of great physical, emotional and social change; and all these aspects can have a bearing on how epilepsy is treated and managed.³¹ For example, since adolescents are often image-conscious and subject to peer pressure, AED side effects (e.g. weight gain and rash) can seriously impair their self-esteem and quality of life, and may result in medication non-compliance.^{46–48} Individualisation of AED treatment is therefore particularly important, taking into account the patient's specific needs and priorities wherever possible. The range of individuals moving through adolescence with epilepsy is wide, and priorities will therefore differ. Whereas for many individuals with epilepsy, seizure freedom remains a primary goal, for children with complex needs, the International Classification of Functioning, Disability and Health provides a useful biopsychosocial framework to help define different treatment goals for different ages, creating a dynamic system to address possible influences on patient outcomes (Table 1).^{49,50}

Table 1 – Application of the international classification of functioning, disability and health model in the global assessment of patients with Lennox–Gastaut syndrome at different stages of life. Reprinted from Arzimanoglou et al., 2009⁴⁹ with permission from Elsevier.

Dimensions of ICF	4-year-old patient	12-year-old patient	35-year-old patient
Body functions and structures	<ul style="list-style-type: none"> Do the causes of LGS alone predict mental retardation and other neurological disorders or can seizure control prevent cognitive or behavioural decline? Is freedom from seizures possible? What is the effect of medication? Does control of seizures contribute to paradoxical change in behaviour? 	<ul style="list-style-type: none"> Can there be a further effect on cognition with improvement in seizures? Is freedom from seizures possible? What is the effect of medication on behaviour or cognition? 	<ul style="list-style-type: none"> Can better control of seizures result in improved mental or behavioural functions? Is freedom from seizures still possible? Do antiepileptic drugs that failed in the past now have a different effect? Does control of seizures contribute to paradoxical change in behaviour?
Activity and participation	<ul style="list-style-type: none"> Pre-school education Injuries Interaction with peers 	<ul style="list-style-type: none"> Integration and schooling Relationships with peers School trips Out-of-school activities 	<ul style="list-style-type: none"> Self-independence Mobility Working Social interaction
Environmental factors	<ul style="list-style-type: none"> Burden on the family with brothers and sisters Parental employment 	<ul style="list-style-type: none"> Attitude of school Burden on the family Residential schooling? Risks of sudden unexpected death? 	<ul style="list-style-type: none"> Living outside the family Partnership Risks of sudden unexpected death?

ICF, international classification of functioning, disability and health; LGS, Lennox–Gastaut syndrome.

5. Advancing the knowledge base

5.1. Elucidation of aetiologies and new epilepsy syndromes and the emerging role of genetic testing

There is an increasing understanding of (possibly treatable) aetiologies and new epilepsy syndromes that should be considered when a child presents with refractory epilepsy. These include glucose transporter protein type 1 (GLUT-1) deficiency syndrome, brain-specific folate transport defect, pyridoxine-dependent epilepsy (PDE), and surgically remediable epilepsies.

GLUT-1 deficiency syndrome is an inborn disorder of cerebral glucose transport associated with early infantile epilepsy and microcephaly, which has recently been proposed as a cause of refractory absence seizures in childhood.⁵¹ Diagnosis is based on finding low levels of glucose in the cerebrospinal fluid, in the absence of hypoglycaemia, and identification of the mutation in SLC2A1 on chromosome 1.⁵² Importantly, the condition can be treated successfully with the ketogenic diet, since ketones provide an alternative ‘fuel’ for the brain.^{52,53} It has also recently been shown to be effectively treated with a modified Atkins diet, which is less restrictive, more palatable and easier to manage than the ketogenic diet.⁵⁴ Similarly, mutations in the folate receptor 1 gene (FOLR1), which codes for folate receptor alpha, have been shown to cause a previously unrecognised type of childhood brain-specific folate transport defect, characterised by progressive movement disturbance, psychomotor decline and epilepsy.⁵⁵ Folinic acid therapy has been shown to be able to reverse the clinical symptoms of the condition and improve associated brain abnormalities and function.⁵⁵

PDE is a rare autosomal recessive disorder resulting from mutations in the gene that encodes antiquitin (ALDH7A1), which causes intractable seizures in neonates and infants.^{56,57} Patients with PDE are usually resistant to AEDs, but respond to administration of pyridoxine.⁵⁶ Different seizure types are associated with PDE and episodes of status epilepticus are frequently reported. Intellectual disability is also common, but EEG and neuroimaging abnormalities are not pathognomonic.⁵⁶ Although PDE is highly treatable, until recently there has been no diagnostic test, other than a trial of pyridoxine and a subsequent period of withdrawal should there have been a response. However, screening for elevated urinary L-α-amino-adipic semialdehyde (α-AASA), together with DNA analysis for antiquitin deficiency, have been determined as potential means of identifying the condition, and it has been recommended that measurement of urinary α-AASA be performed for all neonates with intractable seizures.⁵⁷

The characterisation of genetic aetiologies has raised the possibility of genetic testing to help aid the identification and differential diagnosis of existing epilepsies; also, to help elucidate the potential risks of epilepsy in other family members. Mutations of the sodium channel neuronal type 1 α subunit gene (SCN1A) are associated with several childhood epilepsies, most notably Dravet syndrome, but ranging in severity from febrile seizures to severe epileptic encephalopathies.⁵⁸ The association between SCN1A mutations and Dravet syndrome is particularly strong, with 70–80% of Dravet patients being carriers.⁵⁹ The diagnosis, however, is made on electroclinical characteristics, the distinction between this and other syndromes such as LGS remaining important, as they require different approaches to treatment; for example, although lamotrigine is an effective treatment for LGS, it can exacerbate seizures associated with Dravet syndrome.⁸

Screening for *SCN1A* has implications for genetic counselling, since the majority of mutations occur *de novo*.⁷

Similar to *SCN1A*, X-linked mutations of the protocadherin 19 gene (*PCDH19*) are associated with several conditions in females, ranging from mild epilepsy to epileptic encephalopathies.⁶⁰ Due to an unusual mode of transmission (thought to involve ‘cellular interference’), heterozygous females are affected while hemizygous males are spared.⁶¹ Types of epilepsies resulting from *PCDH19* mutations include epilepsy and mental retardation limited to females (EFMR)⁶² and Dravet syndrome.^{59,63} Cognitive prognosis with epilepsies resulting from *PCDH19* mutations is frequently poor.⁶¹ Female patients with such mutations have a 50% risk of transmitting the mutation, but only to female offspring, resulting in global risk of transmission of 25%.⁶¹ It may therefore be possible to offer prenatal diagnosis using only a foetal sex determination from maternal blood.^{61,64}

Mutations in at least two genes have been associated with X-linked infantile spasms: the Aristaless-related gene (*ARX*) and the cyclin-dependent kinase-like 5 gene (*CDKL5*).⁶⁵ *CDKL5* mutations are particularly important in the aetiology of female patients with severe mental retardation and a seizure disorder starting in the first 6 months of life.^{65,66} *CDKL5* analysis is therefore recommended for girls with severe, early-onset, epileptic encephalopathies.⁶⁶

Mutations of the mitochondrial DNA polymerase γ gene (*POLG*) often manifest in children as Alpers’ syndrome and are associated with the risk of valproate-induced liver failure.^{67–69} Epilepsy resulting from *POLG* mutations is commonly characterised by an early predominance of epileptiform discharges over the occipital region, although EEG and magnetic resonance imaging (MRI) findings vary between patients and stages of the disease.⁶⁸ It has been suggested that *POLG* analysis be considered in any child or adolescent presenting or developing drug-resistant seizures with or without status epilepticus or *epilepsia partialis continua*, particularly when there is a history of psychomotor regression.⁶⁸ Due to the risk of hepatic failure, it is also recommended that *POLG* genetic testing precede valproate therapy in paediatric patients with a typical phenotype.⁶⁹

Genetic testing is currently expensive and has had little therapeutic impact to date. This aside, a positive diagnosis gives closure to a family, and allows more accurate genetic counselling. The emergence of new tests will soon make it easier and cheaper to investigate many epilepsy-relevant genes in one step.^{70,71} The ethical and legal, as well as economic, implications of this technology are likely to receive increasing attention in the near future.

5.2. Epigenetic effects of epilepsy treatments

Epigenetic modifications of DNA and its histone proteins can change the overall structure of chromatin and thereby regulate the transcriptional status of a genetic locus.⁷² There is emerging evidence that some epilepsy treatments may have additional epigenetic effects. For example, valproic acid has been shown to affect chromatin remodelling by inhibiting histone deacetylases, which appears to confer anticancer and neuroprotective effects,⁷³ although serum levels of valproic acid used in epilepsy treatment are not high enough to have this effect.

Levetiracetam also appears to act as a histone deacetylase inhibitor, mediating anti-inflammatory, antioxidative and anti-apoptotic effects, and it may therefore provide a potential new approach to treating inflammatory diseases affecting the peripheral nerve.⁷⁴ There is also increasing interest in the potential of using epigenetic agents to modify chromatin structure specifically in order to alter the disease course of epilepsy.⁷⁵

6. Advancing AED treatment

6.1. Advancing the evidence base

During the early history of AED development, the primary objective was the control of seizures; but experience with thalidomide in the 1960s shifted the focus of drug development onto safety and tolerability, resulting in much stricter regulatory control.⁷⁶ This led to increasing reliance on RCTs as the ‘gold standard’ of clinical evidence.⁷⁶ Although RCTs are still of primary importance in the regulation of drug development and the formulation of treatment guidelines, there has been growing acknowledgement of their limitations – particularly because they often do not reflect the individualised approach to treatment required in clinical practice.⁷⁶ RCTs provide a specific type of clinical evidence required for regulatory approval and are typically designed with strict dosing schedules and carefully selected patient populations, in order to minimise the influence of confounding factors and thus allow the efficacy and safety of a test product to be revealed. In order to help inform clinical practice, however, information on how the agent behaves under ‘real-world’ conditions is required and there is therefore a need for other types of clinical data, to supplement and complement controlled evidence from clinical trials.⁷⁶ This is particularly important for a chronic condition such as epilepsy, for which patients require long-term (often life-long) treatment. Information is firstly required on the long-term efficacy and safety of AEDs; for example, to monitor whether long-term usage is associated with the occurrence of seizure aggravation or the development of rare side effects, which may take time to emerge (e.g. the emergence of visual field defects with vigabatrin⁷⁷). Practical guidance on optimal dosing is also needed, in terms of dosage and titration schedule; for example, an observational, single-centre study reported that, in certain clinical circumstances, topiramate treatment comprising rapid titration followed by low maintenance dosing may be beneficial for paediatric patients with difficult-to-treat epilepsy.⁷⁸ Information is also required on whether there is any synergy or interaction between the AED in question and other drugs; and on the potential benefit(s) of the new agent, relative to other AEDs. If new formulations of an AED are developed, then information on their pharmacokinetics, efficacy and safety will also be needed.

There has been recognition that the level of evidence required for regulatory approval has hampered the development of drugs for rare medical conditions. As a result of this, the Orphan Drug Act (1983) was passed in the USA to encourage pharmaceutical companies to target rare conditions, such as epileptic encephalopathies.⁷⁶ Similar legislation was subsequently enacted in the EU, and in 2007 the US Food and Drug Administration (FDA) and European Medicines

Agency (EMA) agreed a common application process to simplify Orphan Drug development. This process included a lessening of the phase III statistical burden in order to prove efficacy, in recognition of the limitations of low patient numbers with rare conditions. Examples of AEDs that have been granted Orphan Drug status include stiripentol (for treatment of Dravet syndrome) and rufinamide (for adjunctive treatment of seizures associated with LGS in patients aged ≥ 4 years).

The clinical development of rufinamide provides a good illustration of the issues involved in developing a new AED for a rare epileptic condition. Rufinamide is a triazole derivative that is structurally unrelated to other AEDs.⁷⁹ Originally granted Orphan Drug status in 2004 for the adjunctive treatment of seizures associated with LGS in patients aged ≥ 4 years, it received authorisation for this indication in Europe in January 2007,⁸⁰ and in the USA in November 2008.⁸¹ Since marketing authorisation was obtained on the basis of a single multicentre, randomised, double-blind, placebo-controlled, parallel-group trial, conducted in 138 LGS patients,⁸² the EMA requested that a post-marketing patient registry be set up, in order to assess the long-term safety of the drug. As a result, a European registry was established to provide long-term data on AED use in LGS.⁸³ The primary objective of the registry (which is currently ongoing) is to evaluate safety during the use of rufinamide and other AEDs in combination therapy to treat LGS, but it will also allow assessment of other aspects of LGS management, such as healthcare resource utilisation.⁸³

In addition to the registry, several studies have been conducted specifically to assess the efficacy and safety of adjunctive rufinamide when used to treat LGS in clinical practice.^{84–87} A comparison of these studies with the original clinical trial⁸² and a long-term, open-label extension to the trial⁸⁸ revealed that a 'lower and slower' dosing strategy tends to be adopted in clinical practice, which does not appear to compromise efficacy, but may provide improvements in tolerability.⁸⁹ 'Naturalistic' clinical practice studies can therefore provide valuable, pragmatic information for the practicing physician, which helps bridge the gap between clinical trials and everyday clinical practice. Furthermore, since patients receiving rufinamide are likely to be children, or to have comorbid conditions that may make swallowing tablets difficult, an oral suspension formulation of rufinamide was subsequently developed,⁹⁰ which was approved by the FDA and EMA in 2011 for the adjunctive treatment of seizures associated with LGS in patients ≥ 4 years.^{80,81}

6.2. Advancing treatment choices

The advancement of treatment options for epilepsy involves not only the development of new AEDs with novel modes of action, but also the reassessment and exploration of ways in which existing AEDs are used, since traditional therapies may prove to have additional benefits when used in new therapeutic settings. For example, bromides appear to be effective in patients with epilepsy resulting from SCN1A mutations, such as Dravet syndrome.^{91–94} Similarly, a small observational study has recently indicated that fenfluramine, an amphetamine-like drug previously used as a treatment for

obesity, may also be effective as an add-on treatment for Dravet syndrome.⁹⁵

Generational AEDs may provide improvements on existing AEDs in terms of efficacy and/or tolerability. Indeed, many AEDs have resulted from structural advances of existing agents.⁷⁶ For example, pregabalin has been developed as a structural advance on gabapentin, resulting in more potent efficacy, longer duration of anticonvulsant action and a more predictable pharmacokinetic profile than its predecessor.^{96,97} Similarly, brivaracetam has been rationally developed as a structural advance on levetiracetam, possessing a binding affinity for the synaptic vesicle protein 2A that is 10-fold higher than levetiracetam and additionally acting as a sodium channel inhibitor.^{98,99} Eslicarbazine acetate, a new-generation, single-enantiomer member of the dibenz[b,f]azepine family of AEDs, is a structural advance on carbamazepine.^{100,101} Importantly, despite their structural similarity, eslicarbazine acetate avoids the generation of toxic epoxide metabolites associated with carbamazepine,^{100,102} thereby maintaining efficacy while potentially offering a more favourable safety and tolerability profile.

Despite the availability of an increasing number of agents, up to 30% of patients are drug-resistant^{103,104} and there is therefore a continuing drive to develop AEDs with novel modes of action, since these may allow previously refractory patients to be treated effectively. A recent approach has been to target the neuronal voltage-gated potassium channel (e.g. retigabine).^{105,106} Another new approach has been to target ionotropic glutamate receptors via the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor (e.g. perampanel), since this has been found to be the predominant mediator of excitatory neurotransmission in the central nervous system (via transduction of the glutamate signal into depolarisation of the post-synaptic neuron), and to play a critical role in the generation and spread of epileptic activity.¹⁰⁷

Although the development of new AEDs continues to be a central focus in improving the management of epilepsy, it has increasingly been recognised that there may be flaws in how AED development is approached, both in terms of the animal models used to screen potential new agents and in terms of the way in which AEDs are targeted to treat the symptoms of epilepsy, rather than the underlying epileptogenic process.¹⁰⁸ These limitations have driven research to develop alternative approaches to epilepsy management.

7. Immunomodulation

Recent years have seen an increasing recognition of the aetiological significance of autoantibodies in a number of previously unexplained epilepsies and this has encouraged investigation into immunomodulation as a novel approach to treatment. For example, antibodies to cell-surface membrane proteins, such as N-methyl-D-aspartic acid (NMDA) receptors and voltage-gated potassium channels, have been found in patients with limbic encephalitis, as well as in some patients with epilepsy as their primary or sole condition of acute onset.^{109,110} Such patients may not respond to AED therapy but have been found to respond to immunotherapies, including corticosteroids and intravenous

immunoglobulin.^{110,111} Other autoantibodies that have been detected in epilepsy patients include those targeting AMPA and γ -aminobutyric acid-B (GABA[B]) receptors.¹¹² Similarly, antibodies to glutamic acid decarboxylase have been found in patients with temporal lobe epilepsy and antibodies to epi-tempin have been reported in approximately 90% of patients with faciobrachial dystonic seizures.^{113,114}

In addition to limbic encephalitis, conditions giving rise to epilepsy that have been successfully treated with immunotherapy include anti-NMDA receptor encephalitis, fever-induced refractory epileptic encephalopathy in school-age children (FIRES) and Rasmussen encephalitis.^{115–119} Anti-NMDA receptor encephalitis is difficult to recognise, particularly in paediatric patients, since it has variable neuroimaging manifestations and can be confused with neurological conditions that have similar features.¹¹⁷ Treatment with steroids and plasma exchange have been reported to improve the clinical course of the condition, and it is recommended that children presenting with explosive-onset epilepsy, unilateral imaging abnormalities and neurocognitive decline be investigated for autoantibodies to NMDA receptors.¹¹⁷

FIRES is a recently defined epileptic encephalopathy, initiated by febrile status epilepticus, which develops into pharmacoresistant epilepsy associated with dramatic cognitive decline and behavioural difficulties.^{115,116,118} Although use of the ketogenic diet has demonstrated some efficacy in FIRES,¹²⁰ there has also recently been a report of a case associated with elevated voltage-gated potassium channel complex antibodies, which responded favourably to immunomodulation: initially with intravenous methylprednisolone followed by oral prednisolone; later with monthly intravenous immunoglobulin infusions and low-dose azathioprine.¹¹⁸

Rasmussen encephalitis is a rare, severe, immune-mediated brain disorder that is associated with focal epilepsy and progressive neurological dysfunction (including progressive hemiparesis and cognitive dysfunction).¹¹⁹ Its pathogenesis is thought to involve both autoantibodies and cytotoxic T-cells.¹¹⁹ Immunotherapies that have shown efficacy in the treatment of Rasmussen encephalitis include corticosteroids and/or intravenous immunoglobulin, plasmapheresis and tacrolimus, although there is currently insufficient evidence to support the use of one type of immunotherapy over the others.¹¹⁹

8. Surgery and other non-pharmacological approaches to treatment

Surgery for children with refractory epilepsy has become an important treatment option over the past 30 years, with approximately 25% of intractable paediatric patients estimated to have surgically remediable epilepsy syndromes.^{121,122} The ILAE Subcommittee on Paediatric Epilepsy Surgery has proposed criteria for the referral and evaluation of children for epilepsy surgery, but recognises that there is currently insufficient class 1 evidence to recommend specific practice guidelines.¹²³

Modern neuroimaging techniques, such as MRI, single-photon emission computed tomography and fluorodeoxyglucose-positron emission tomography, have expanded the understanding of underlying aetiologies and consequently the

types of operation that are possible. Today, the aetiologies of paediatric epilepsy for which surgery is used range from cortical dysplasia, tumours and perinatal strokes to rarer syndromes, including hemimegalencephaly, tuberous sclerosis complex and Rasmussen encephalitis.^{122,124} Furthermore, improvements in technology, surgical procedures and clinical practice have resulted in enhanced and sustained seizure free outcomes in paediatric epilepsy surgery patients.¹²² Indeed, over 80% of patients with focal, subhemispheric and hemispheric epilepsy syndromes achieve a favourable seizure outcome following surgery.¹²¹ Moreover, early identification of intractable patients with surgically remediable epilepsy syndromes may allow surgery to be conducted prior to cessation of neural plasticity, thereby potentially permitting enhanced cognitive function and psychosocial development.¹²¹

The ketogenic diet is a high-fat, adequate-protein, low-carbohydrate diet that has been used since the 1920s to treat children with epilepsy who are resistant to AEDs, but which has undergone a resurgence in popularity over recent years.^{125,126} The diet creates ketosis by mimicking the biochemical changes associated with starvation, and thereby provides an alternative fuel for the brain in the form of ketones.^{53,125} Although proven to be an effective medical therapy for intractable childhood epilepsy,¹²⁷ the ketogenic diet is restrictive and not without side effects, and consequently requires a high degree of medical and dietetic monitoring.¹²⁸ More relaxed, less restrictive dietary therapies (modified Atkins diet, low glycaemic index diet) have been shown to be effective and well-tolerated alternative therapies for intractable paediatric and adult epilepsy.^{129–134}

Vagus nerve stimulation was approved by the FDA in 1997 for adjunctive treatment of pharmacoresistant focal epilepsy and is the first FDA-approved device for treating epilepsy.¹³⁵ It is approved in the USA as an adjunctive treatment for refractory epilepsy in patients aged ≥ 12 years with complex partial seizures¹³⁶ and its use in paediatric epilepsy has been endorsed in treatment guidelines elsewhere.¹³⁷ Vagus nerve stimulation involves periodic electrical stimulation of the left vagus nerve by a contact wrapped around the nerve trunk in the neck.¹³⁵ The precise mechanism by which vagus nerve stimulation modulates seizures is unclear; but it has been shown to reduce the number of seizures by 30–40%, seizure freedom being achieved in $\leq 10\%$ of patients.^{135,138} The side effect profile of vagus nerve stimulation is more favourable than that of many AEDs.¹³⁵

Deep brain stimulation, involving bilateral stimulation of the anterior nuclei of the thalamus, was originally developed for the treatment of Parkinson's disease, but has also been developed as a potential treatment for refractory epilepsy.¹³⁵ The Stimulation of the Anterior Nucleus of the Thalamus in Epilepsy (SANTE) trial was a multicentre, randomised, double-blind study, in which 110 adult patients with medically refractory focal seizures were randomised to receive stimulation or no stimulation for a 3-month blinded phase, after which all patients received unblinded stimulation.¹³⁹ In the last month of the blinded phase, the stimulated group experienced a 29% greater reduction in seizures versus the unstimulated group ($p = 0.002$) (Fig. 3).¹³⁹ After 2 years, median reduction in seizure frequency was 56%, 54% of patients had

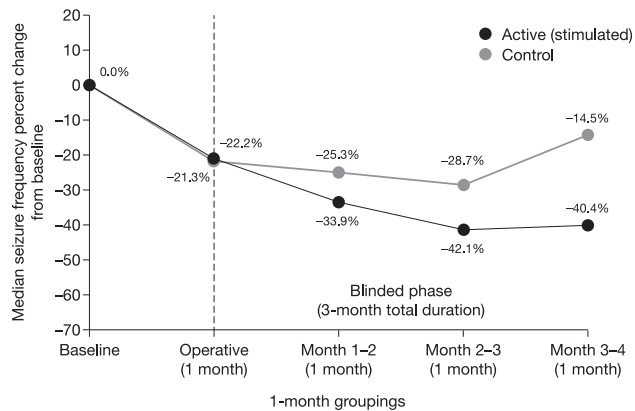


Fig. 3 – Results from the stimulation of the anterior nucleus of the thalamus in epilepsy (SANTE) trial: Unadjusted median total seizure frequency percentage change from baseline by 1-month groupings and treatment group during the blinded phase.¹³⁹ Reproduced with permission from John Wiley and Sons.

achieved $\geq 50\%$ seizure frequency reduction and 14 patients were seizure free for ≥ 6 months.¹³⁹ Two patients experienced acute, transient stimulation-associated seizures, and stimulated patients were more likely to report depression or memory problems than unstimulated patients, but complication rates were otherwise modest.¹³⁹ Deep brain stimulation of other areas of the brain (e.g. the hippocampus¹⁴⁰) is also being investigated. This technique is emerging as an important treatment option for drug-refractory epilepsy.¹⁴¹

9. Future directions of epilepsy management

Current AED treatment strategies have a number of limitations. For example, it is often difficult for AEDs to cross the blood–brain barrier, which can result in an ‘efficacy ceiling’. Since AEDs are non-targeted, non-epileptic parts of the brain are exposed to their effects, resulting in the risk of central nervous system side effects. Similarly, there is the risk of systemic toxicity.

Such limitations have led to research into alternative approaches to epilepsy management, both in terms of the delivery of existing pharmacological therapies and the development of non-pharmacological treatments. It is likely that these kinds of novel approaches will become an important part of how childhood epilepsies are treated and managed in the future, although their role in current paediatric epilepsy management is limited.

9.1. Novel delivery approaches

Novel delivery approaches have been developed to allow more targeted delivery of AEDs and other molecules to epileptic foci (e.g. adenosine – see ‘Cell-based approaches and gene therapy’ below). These include invasive approaches, such as convection-enhanced delivery,¹⁴² intrahippocampal delivery,¹⁴³ intracerebroventricular delivery^{144,145} and transmeningeal delivery^{146,147}; also, the use of erodible

microspheres,¹⁴⁸ encapsulated cells¹⁴⁹ and implanted eluting devices.¹⁵⁰ In addition, non-invasive delivery approaches have been developed, such as transmucosal drug delivery.¹⁵¹

9.2. Experimental devices

Experimental devices include a number of non-pharmacological approaches to treatment. As previously mentioned, vagus nerve stimulation and deep brain stimulation already have a place in the management of epilepsy. These represent ‘open-loop’ systems, in that they apply electrical stimulation continuously or at regular intervals, regardless of the underlying seizure pattern. By contrast, ‘closed-loop’ systems actively record biological signals using various algorithms (e.g. EEG), process these signals in real time to detect evidence of imminent seizure onset, and then trigger an intervention, thus providing a responsive form of electrical stimulation.¹³⁵ In addition to EEG,^{152,153} other algorithms used in closed-loop systems include accelerometers,¹⁵⁴ video detection¹⁵⁵ and frequency and vector analyses.¹⁵⁶ The NeuroPace system (NeuroPace Inc, Mountain View, CA, USA) is one such closed-loop system that is currently in late-stage clinical development. Consisting of a cranially implanted pulse generator, one or two quadripolar subdural strip or depth leads, and an external programmer, the system uses an electrocorticographic algorithm to detect evidence of a seizure and applies cortical electrical stimulation in response to seizure detection.^{157–160} A multicentre, randomised, double-blind, controlled trial assessed the safety and effectiveness of the system as an adjunctive treatment for focal-onset seizures in adults with medically refractory epilepsy.¹⁶⁰ A total of 191 patients were implanted with the device and randomised to receive stimulation in response to seizure detections (treatment) or no stimulation (sham).¹⁶⁰ Efficacy and safety were assessed over a 12-week blinded period, after which all patients received 84 weeks of responsive stimulation. During the blinded period, seizures were significantly reduced in the treatment group versus sham (-37.9% vs -17.3% ; $p = 0.012$) and there was no difference between groups in adverse events.¹⁶⁰ During the open-label period, seizure reduction was sustained in the treatment group and seizures were significantly reduced in the sham group associated with initiation of stimulation.¹⁶⁰ Treatment was also associated with significant improvements in overall quality of life ($p < 0.02$) and no deterioration in mood or neuropsychological function was observed.¹⁶⁰ By providing a treatment that is responsive and specific (physically and temporally), this type of closed-loop therapy overcomes important limitations of AED treatment and may provide a useful alternative treatment for refractory epilepsy.

Other non-pharmacological experimental devices that are being investigated as potential treatments for epilepsy include focal cooling of the brain using a thermoelectric device,¹⁶¹ transcranial direct current stimulation¹⁶² and transcranial magnetic stimulation.^{163,164} In some cases, these are being combined with seizure anticipation/detection techniques (e.g. real time EEG) in closed-loop systems.^{161,163}

9.3. Cell-based approaches and gene therapy

Several cell-based approaches are currently being investigated as a means of correcting the production and balance of

neurotransmitters and nucleosides in the brain, although these are only in early stages of development. For example, galanin is an endogenous neuropeptide that inhibits glutamate release in the hippocampus, thereby acting as a powerful inhibitor of seizure activity.¹⁶⁵ The NsGene EC Biodelivery™ platform (NsGene A/S, Ballerup, Denmark) uses a membrane-encapsulated human genetically modified galanin-producing cell line to deliver galanin directly into the brain.¹⁶⁶ The neuromodulator adenosine has increasingly been recognised as a potential disease-modifying treatment for epilepsy, since it can directly alter the seizure threshold and plays a key role in postictal depression of seizure activity and in keeping a seizure focus localised.¹⁶⁷ In order to augment endogenous levels of adenosine, focal targeting is required, due to the risk of systemic side effects. Several cell-based approaches to adenosine augmentation are currently being explored in animal models, including brain implants of cells engineered to release adenosine that have been embedded in a cell encapsulation device, and the direct transplantation of stem cells engineered to release adenosine.¹⁶⁸ Transplantation of GABAergic cells is also being investigated in various models of temporal lobe epilepsy.¹⁶⁹

Gene therapy is also being employed as a means of correcting levels of neurotransmitters in the brain. Recombinant adeno-associated viral vectors have been used in the direct bilateral microinjection of neuropeptide Y-expressing apparatus into the hippocampus in rat models of temporal lobe epilepsy, resulting in attenuation of epileptogenesis versus controls, and a significant reduction in spontaneous seizure frequency versus pre-injection baseline in 40% of animals.¹⁷⁰ Similarly, adeno-associated virus type 2 vectors have been used to enhance GABA(A) receptor alpha-1 subunit levels in hippocampal dentate gyrus in an animal model of temporal lobe epilepsy, resulting in a threefold increase in mean seizure free time following status epilepticus, and a 60% reduction in the number of animals developing recurrent spontaneous seizures in the first 4 weeks following status epilepticus.¹⁷¹

10. Conclusions

The management of epilepsy in childhood is challenging both in terms of its recognition and diagnosis, and also in terms of selecting the most appropriate treatment approach, since – uniquely in the paediatric patient – this has implications not only for the individual's current health status, but also, potentially, for their longer-term development. Accurate diagnosis is crucial in order to ensure that the correct type of treatment is used, and also to guide prognosis and help inform treatment expectations.

An increasing understanding of the aetiologies underlying childhood epilepsies, and the elucidation of new epilepsy syndromes, has opened up further possibilities in terms of both diagnosis (e.g. genetic testing) and treatment. Although the choice of AEDs has expanded greatly over recent years, a high proportion of patients remain refractory to treatment and AED side effects are often problematic; therefore, the need continues for new AEDs with improved tolerability as well as efficacy. There is, however, also a need to recognise and accept the limitations of AED treatment, and to consider alternative

approaches to treatment and management. Some such approaches – such as surgery, vagus nerve stimulation and the use of specific diets – are already relatively well established in paediatric epilepsy; whereas others – including immunomodulation, novel delivery approaches and experimental ‘closed-loop’ devices – are just beginning to emerge as potentially useful treatment alternatives for epilepsy. Other fields – such as epigenetics, cell-based technologies and gene therapy – are still in early stages of understanding and development, but may provide further therapeutic options in the future.

As treatment options continue to expand, it is important to recognise that effective management of epilepsy involves far more than the treatment of seizures. This is particularly true for the paediatric patient, whose medical needs must always be addressed alongside their psychosocial needs, within the wider context of their growth, development, and quality of life.

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