Treatment of seizures in childhood

The field of pediatric epilepsy is a rewarding yet challenging area of medicine. A fairly significant proportion of children remain refractory to current antiepileptic drugs, and may require alternative treatment options. Challenges also arise because many of the antiepileptic drugs available for use since 1993 are US FDA approved only for use over the age of 2–4 years, hence presenting a medicolegal conundrum to the treating physician. However, their more favorable side-effect profile and tolerability have led to their widespread use even in those less than 2 years of age. This review briefly outlines their indications, pharmacokinetic profile and dosages, and covers evidence-based guidelines for therapy in common epilepsy syndromes of childhood.

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Epilepsy is a common disorder of childhood occurring with an incidence in the range 46–60 out of 100,000 in the Western world. It is most common in the first year of life, and declines progressively after the age of 10 years. Based on clinical and electrophysiologic findings, two main forms of epilepsy are recognized: localization-related (partial) and generalized. The question of 'when to treat' has been addressed fairly extensively, and the general consensus of opinion is that seizure treatment can be deferred after a single unprovoked seizure, as antiepileptic drugs (AEDs) do not eliminate recurrence and do not have an effect on long-term remission [1]. Meta-analyses suggest that the chance of recurrence after a single generalized seizure is 30–50%, and after a second event is 70–80% [2–4].

The definition of epileptic seizure has been suggested as 'transient occurrence of signs/symptoms owing to abnormal excessive or synchronous neuronal activity in the brain'. The International League Against Epilepsy (ILAE) has proposed that epilepsy be defined as 'disorder of the brain characterized by an enduring predisposition to generate epileptic seizure and by the neurobiological, cognitive, psychological and social consequences of this condition.'

Antiepileptic drugs

Antiepileptic drugs are the preferred initial treatment modality for most seizures of childhood. The goals of treatment for epilepsy in children include seizure control with few adverse effects, though in a given case, consideration of tolerability, efficacy, cost, safety profile, pharmacokinetics and patient-specific variables will play a role in selection. Monotherapy is the preferred modality of treatment over polytherapy, and in the event of failure with one, replacement with a second drug is preferable to addition of a second medication.

■ Newer AEDs

Several new AEDs have been introduced since 1993, and many have been used effectively in the control of pediatric epilepsy. Many have favorable pharmacokinetic and a side-effect profile that makes them easier to use than the older generation of seizure medications.

Felbamate

Felbamate was introduced for use in 1993 and has found use as an add-on treatment in Lennox–Gastaut syndrome (LGS). Class III evidence exists for use in partial epilepsy, infantile spasms, juvenile myoclonic epilepsy (JME) and Landau–Kleffner syndrome. The initial dose is 15 mg/kg/day, and doses as high as 90 mg/kg/day have been employed in childhood. It is available as a suspension of 600 mg/5 ml and tablets of 400 and 600 mg. It is approved for use in children between the ages of 2 and 16 years for the treatment of LGS.

Between the years of 1994 and 1997, felbamate was associated with 34 cases of aplastic anemia, of which in 13 instances it was fatal. The risk of this occurrence in those being administered felbamate is one in 5000, and no cases have been reported in children less than 13 years of

age. Most patients who developed this side effect also had exposure to other AEDs, and a third had serological evidence of an immune disorder in the past. Currently, written consent is recommended in the USA, with documented baseline hematologic and liver profile parameters, prior to drug initiation. It also carries a one in 7000 risk of hepatotoxicity, with fatality rates of one in 25,000–34,000 [5]. More common side effects include anorexia and gait disturbance.

Gabapentin

Gabapentin has been in use since 1994. It potentiates GABA release and inhibits GABA transminase. It has US FDA approval for use in children over 12 years of age. At doses ranging from 10 to 90 mg/kg/day, gabapentin has been found to be useful as an adjunct in partial epilepsy, with response rate ranging from 8.4 to 26.4% [6,7], as well as in refractory partial seizures [8]. These studies did not focus on the pediatric population, and recent guidelines suggest paucity of evidence to suggest efficacy in pediatric patients with partial epilepsy. On the other hand, there is no evidence that it is useful in primary generalized epilepsy in children either. Side effects include drowsiness, and involuntary movements such as choreoathetosis and myoclonus [9,10]. Formulations include: solution: 250 mg/5 ml; tablet: 600 and 800 mg; and capsules: 100, 200 and 400 mg.

Lamotrigine

Lamotrigine (LTG) was approved for use in the USA in 1994. It acts by blocking the use of voltage-dependent sodium channels and reducing the release of glutamate. In pediatric patients, LTG has been shown to reduce the frequency of seizures in those with partial epilepsy poorly responsive to conventional medications in placebo-controlled double-blind trials – 44% during LTG treatment compared with 13% during placebo treatment in the maintenance period [11]. It has a place in reducing the incidence of generalized seizures in LGS [12]. Regarding its use in patients with idiopathic generalized tonic-clonic seizures, a 2006 study by Trevathan *et al.* in 45 children has noted that 48% on LTG were seizure free, as opposed to 17% of controls [13]. However, exacerbation of myoclonic jerks or *de novo* appearance with initiation of LTG has also been documented [14].

Side effects are mostly confined to the CNS, except for skin rash, which occurred in 10–17% of people, usually in the first 2–8 weeks of treatment. Stevens–Johnsons syndrome occurs in 0.5% of children. It should be noted that LTG use with valporate (VPA) increases the risk of serious skin rash, as does high initiation dose and rapid upward titration. Ataxia, dizziness, diplopia, somnolence and headaches are the other adverse events most commonly identified. Use of extended-release LTG also caused a significant (p = 0.0037) decrease in seizure frequency in a recent study of 239 patients, where it was added on to an ongoing regime of AEDs [15].

The half-life is 15–60 h, and approximately 55% is protein bound. It is not a cytochrome P450 enzyme inducer, and hence has favorable drug interactions with other AEDs. The initiation dose is 1–2 mg/kg/day when not used in conjunction with VPA, and 0.2 mg/kg/day when used in combination, with a maintenance dose of 5–15 mg/kg/day in the former situation and 1–5 mg/kg in the latter. It has FDA approval for use over the age of 2 years. Formulations include: chewable tablet: 5 and 25 mg; and regular tablet: 25, 100, 150 and 200 mg.

Levetiracetam

Levetiracetam (LEV) was approved for use in the USA market in 1999, and received FDA approval as add-on therapy in children of 4 years of age or older with partial epilepsy in 2005. At doses of 20–40 mg/kg/day there is class III evidence to suggest its utility in refractory partial epilepsy [16], and class IV evidence of its place in treatment of JME [17,18], but few objective data of class I nature exist regarding its use in new-onset epilepsy exists.

Its exact mechanism of action has not been clearly elucidated, but *in vivo* and *in vitro* studies with recordings from the hippocampus have pointed to the fact that LEV does not inhibit neuronal hyperexcitabililty, but does cause prevention of burst firing by preventing hypersynchronization and propagation of impulses. It has no action on sodium/T-type calcium currents, and does not modulate levels of GABA or glutamate. It does bind to SV2A – a synaptic vesicle protein that has a role in vesicle exocytosis – though how this is relevant to epilepsy in not clear. LEV is less than 10% protein bound, and 66% is excreted renally. It has a half-life of 6–8 h.

Adverse effects include behavior changes, hostility and aggression, which occur in 2% of cases and may be reason for discontinuation by care givers [19]. It is marketed as tablets of 250, 500 and 750 mg, and a liquid preparation of 100 mg/ml. A parenteral preparation has recently been marketed and has found a place in the treatment of status epilepticus (see 'Status epilepticus in childhood' section).

Oxcarbazepine

Oxcarbazepine (OXC), a homologue of carbamazepine (CBZ), has been marketed in the USA since 2000. It is a prodrug and its monohydroxy derivative is the active metabolite. The half-life of OXC is 8–16 h, and approximately 40% is protein bound. OXC metabolism is largely unaffected by induction of the cytochrome P450 system. The usual initiation dose is 10 mg/kg/day and maintenance range is 25–30 mg/kg/day, with maximum dosage of 60 mg/kg/day. It is available as a 300 mg/5 ml suspension and tablets of 150, 300 and 600 mg. The mechanism of action involves blockage of voltage-sensitive sodium channels. It is FDA approved for use in children over the age of 4 years.

Expert opinion in the USA and guidelines from the ILAE suggest it is can be considered for monotherapy in partial epilepsy and benign rolandic epilepsy of childhood. Class I evidence also exists for its adjunctive role in refractory partial epilepsy [20]. Similar to CBZ, it has the propensity to aggravate generalized tonic-clonic seizures.

Adverse effects include ataxia, diplopia and drowsiness. Hyponatremia (0.4–1% in adults) has rarely been described in the pediatric population. A 24–33% risk of cross-sensitivity with CBZ exists [21], wherein individuals who develop a hypersensitivity reaction to CBZ will also respond similarly with OXC.

Tiagabine

Tiagabine has been approved for use in the USA since 1997. In one study with class II evidence, it reduced the seizure frequency by half in 26% of children with partial epilepsy. Tonic seizures and atypical absences responded best in the primary generalized category, with median percentage reductions in the weekly seizure rate of 77 and 63%, respectively [22]. However, it also has the propensity to exacerbate certain seizure types, especially myoclonic and generalized tonic-clonic varieties. It does not have application in the treatment of infantile spasms or LGS.

It prevents the uptake of the inhibitory neurotransmitter GABA into presynaptic neuronal and glial cells. It has a half-life of 7–9 h in uninduced adults, and 2–3 h in those receiving enzyme-inducing AEDs. Adverse events include asthenia, nervousness, dizziness and somnolence. It is available in tablet form of 2, 4, 12, 16 and 20 mg.

Topiramate

Topiramate was introduced for use in 1996. The available data support its use in infantile spasms, LGS, JME, refractory partial epilepsy, as monotherapy in newly diagnosed partial/generalized epilepsy and as adjuvant therapy in partial and primary generalized epilepsy [23–25]. Expert opinion in the USA suggests it can be used after VPA in generalized epilepsy, as second-line therapy after CBZ, phenytoin (PHT) and OXC in cryptogenic partial epilepsy, after VPA and LTG in JME, and as a second-line agent in infantile spasms [26].

Formulations include tablets of 25, 100 and 200 mg with sprinkle caps of 15 and 25 mg. The usual initiation dose is 1.0 mg/kg/day, and maintenance dose ranges from 3 to 10 mg/kg/day. Adverse effects include behavior side effects including decreased attention and concentration, somnolence, nephrolithiasis, hypohidrosis, anorexia and weight loss. It has FDA approval for use in children over the age of 2 years.

Vigabatrin

Vigabatrin (VGB) binds irreversibly to GABA transaminase, resulting in a decrease in the synaptic breakdown of GABA. It has been found to be useful as an add-on therapy in refractory partial epilepsy of childhood, infantile spasms (especially in those with tuberose sclerosis) and LGS [27]. The usual efficacious dose is 50–150 mg/kg/day. VGB is eliminated primarily via the kidneys, with approximately 65% of the administered dose found unchanged in the urine within 24 h. Kinetics are dose-linear within the range of usual therapeutic doses. It has a half-life of 7–9 h. Since it does not induce hepatic enzymes, it is has limited interactions with other antiepileptics. Common side effects include fatigue, weight gain and tremor. It is currently not marketed in the USA due to its potential to cause irreversible, visual field constriction – hence, no guidelines exist for use by the American Academy of Neurology (AAN) or the American Epilepsy Society (AES).

Zonisanide

Insufficient evidence exists, per the ILAE, regarding use of zonisanide (ZNS) as monotherapy in new-onset partial epilepsy, new-onset primary generalized epilepsy including absence syndromes, benign epilepsy of childhood with central temporal spikes, or JME [6]. The AAN and AES state that 'insufficient evidence' exists regarding its use in pediatric refractory partial epilepsy. It acts by GABA-mediated inhibition of neurons and modulation of sodium and T-type calcium channels. It has been shown to be useful as adjunctive treatment in refractory partial and generalized epilepsy of childhood, with a

response rate of 58.3% in the first 8 weeks of therapy [19]. It has been widely used in Japan since 1989, and most of the initial studies have been conducted there, although the American experience has validated its place in the treatment of infantile spasms [28].

Zonisanide blocks sodium channels and reduces T-type calcium channel current, which inhibits inward calcium influx and thus reduces neuronal bursts. It also modulates neurotransmitters including GABA, dopamine and serotonin, which alters neuronal activity.

The usual initiation dose is 2–4 mg/kg/day, and the maintenance dose varies from 5 to 8 mg/kg/day. It has low-to-moderate protein binding (40%) and a half-life of 63 h [29]. It is available as a capsule of 25, 50 and 100 mg.

Common side effects include agitation, irritability and weight loss (9%). Renal calculi occur in 1% of cases, although hyperthermia and oligohydramnios may occur more commonly in the pediatric than adult population. It has FDA approval for use over the age of 16 years.

■ Antiepileptics that can aggravate certain seizure types

Typical absence epilepsy of childhood can be aggravated by CBZ, PHT, VGB and phenobarbital (PHB) (at high doses). CBZ has been known to precipitate absence status, increase the myoclonic jerks associated with Angelman's syndrome, infantile spasms, severe myoclonic epilepsy of infancy (Dravet's syndrome) and the massive myoclonus that characterizes JME. On the other hand benzodiazepines can cause tonic status in LGS and infantile spasms. LTG can cause exacerbation of seizures in severe myoclonic epilepsy. As can be seen, the idiopathic and symptomatic generalized epilepsies of childhood are most prone to such exacerbation, and hence caution should be exercised in these situations when choosing an AED [30,31].

Selection of drugs using evidence-based medicine
Partial onset seizures

As of 2006, 25 randomized controlled trials (RCT) were conducted to study the efficacy of single antiepeleptic use in children. The drugs studied include CBZ (RCT = 11), LTG, OXC, topiramate, VPA (RCT = 7), VGB, clonazepam, PHB and PHT. However, very few class I evidence trials exists for the use of a specific AED in children. OXC emerged as the drug with the most data regarding efficacy and effectiveness on the basis of available literature.

CBZ, PB, PHT, topiramate (TPM) and VPA were described as 'possibly efficacious', while LEV and VGB were classified as 'potentially efficacious' [32].

Primary generalized

The following epilepsy syndromes, classified under primary generalized epilepsy, have the potential to respond well to AEDs:

■ Idiopathic general tonic-clonic seizures – a total of 20 RCTs were documented to study the use of monotherapy in children, with none of them meeting criteria for class I studies. No single AED emerged as the drug of choice, while CBZ, PB, PHT, TPM and VPA have been designated as 'possibly efficacious', with class IV evidence to suggest that CBZ, OXC and PHT have the potential to worsen generalized tonic-clonic seizures.

■ Absence epilepsy – six RCTs were conducted to study monotherapy in children with absence seizures or childhood absence epilepsy. ESM, LTG and VPA were noted to be possibly efficacious, with meta-analysis finding 'insufficient evidence to inform clinical practice' [33].

■ JME – no Class I, II or III studied exist to study monotherapy in JME. Class IV evidence suggests CZP, LEV, LTG, TPM, VPA and ZNS may have some efficacy.

■ Newly diagnosed epilepsy in the emergency department – only one study so far has addressed the issue of choosing an AED without exclusion of seizure type [39], albeit confining itself to one of three available medications. In this study, TPM, CBZ and VPA demonstrated equivalent efficacy. In the USA, interestingly enough, CBZ is often selected as the drug of first choice although, in a French study [40], VPA emerged as the drug of choice in adult males and VPA/LTG in adult females. The utility of AEDs after a first seizure has been addressed previously in this review.

Benign rolandic epilepsy

Children with benign epilepsy with centrotemporal spikes: three RCTs and no meta-analyses investigated drug therapy in children with benign epilepsy of childhood with centrotemporal spikes. CBZ and VPA can be considered as candidate drugs for this condition. In Europe, sulthiame is extensively used for this epilepsy category, though lack of FDA approval in the USA has limited its use here.

Infantile spasms

Expert opinion suggests use of adrenocorticotropic hormone, VGB and topiramate in the treatment of spasms. VGB is almost universally effective in those with spasms associated with tuberose sclerosis complex. Recent practice parameters from the Child Neurology Society meeting endorse use of adrenocorticotropic hormone as the first-line therapy ('probably effective') and VGB as 'possibly effective'. Ketogenic diet (KD) and early surgical evaluation have been recommended by some.

Lennox–Gastaut syndrome

Expert opinion inclines towards the use of VPA, TPM or LTG as first-line options, followed by trials of drug combinations [33]. AAN and AES guidelines recommend the use of LTG and TPM in the treatment of 'drop attacks' associated with spasms. ZNS, LEV, KD and felbamate [34–36] have been suggested as second-line options.

Febrile seizures

Rectal diazepam is the treatment of choice for acute treatment of a prolonged febrile seizure or a cluster of febrile seizures. The FDA has not approved its use in children less than 2 years of age, but it is widely used in clinical practice. VPA and PHB have been shown to be effective oral AEDs that are useful in preventing febrile seizures [37]. However, potential risks outweigh the benefits of long-term treatment. Contrary to popular view, use of antipyretics does not significantly reduce the incidence of febrile events [38]. Furthermore, there is no evidence to suggest that treatment of febrile seizures reduces the chance of developing epilepsy.

Status epilepticus in childhood

The incidence of status epilepticus is greatest in the first year of life (18–20/100,000/year) with progressive decrease with age in the 10–14 year age group (2/100,000) [41,42].

The vast majority of seizures terminate in less than 2 min, with status epilepticus being variably defined as seizure activity ranging from 30 min to 5 months, for example the VA Cooperative Trial on Treatment of Generalized Convulsive Status Epilepticus used a duration of 10 min as inclusion criteria [43]. Recently, a decrease in the duration has been proposed, with literature to suggest that seizures that do not terminate within 5–10 months are unlikely to spontaneously remit [44]. Refractory status is variably defined as seizures that continue despite use of 2–3 intravenously administered medications or those that last an inordinate length of time, such as more than 30 min, 1 h or 2 h.

Prehospital treatment can influence outcome; for example, early use of benzodiazepines can terminate it and lead to decreased in-patient stay [45]. In this regard, buccal midazolam has been found to be more effective than rectal diazepam in outpatient seizure treatment [46].

The first-line treatment of status epilepticus in hospital consists of benzodiazepines, with addition of phenytoin/fosphenytoin as second-line drug and PHB/VPA/LEV (the latter having been reported as effective in adults) being variably used for third-line medication. The treatment thereafter may include continuous infusion of midazolam, propofol or pentobarbital. There is no prospective evidence to suggest that one of the above three is more effective than the other, or that a combination is more likely to resolve the status. A reasonable period of 12–24 h of infusion should be maintained before initiating a change .The role of benzodiazepines as the agent of choice has been well validated by Trieman *et al.*, who compared adults with SE by administering four different regimes. The subgroup that received lorazepam had cessation of seizures in 64.9%, and in an intention-to-treat analysis was as effective as diazepam plus PHT or PHB alone [47]. The failure of first- or second-line of medications predicts a high rate of failure to a subsequent regime of medications (7% response rate).

Other important aspects to management of status include airway protection, attention to metabolic imbalances, circulatory issues, electroencephalogram (EEG) monitoring, cerebral edema, rhabdomyolysis and temperature regulation. The clinician should be satisfied that the EEG demonstrates burst suppression pattern, and that the bursts are nonepileptiform, before concluding that the continuous infusion therapy is successful.

Perhaps the most important factor in successful treatment of status epilepticus is the early and efficacious use of appropriate medication in adequate dosage. Status epilepticus carries a high mortality of 2.7–5.2% [41].

Midazolam and pentobarbital have been effectively used. Midazolam is used at a maintenance dose of 0.1–0.4 mg/kg/h. A preliminary bolus of 0.2 mg/kg as slow infusion may be employed.

The maintenance dose of pentobarbital is 0.3–3.0 mg/kg/h, with bolus of 3.0 mg/kg at a rate of 0.2–0.4 mg/kg/min.

In a recent, albeit small study, intravenous LEV was used as adjunctive treatment of status epilepticus in children. Three out of four who received

it responded with seizure freedom, and one had a 50% reduction in seizure frequency [48]. Similar response has been noted in the adult literature with use of an oral formulation as well, with response in generalized, focal and nonconvulsive status [49]. The use of levatiracetam has several advantages over traditional medications used in refractory status epilepticus, such as propofol, midazolam and pentobarbital, as it does not affect blood pressure or cause respiratory depression.

Neonatal seizures

Neonatal seizures occur at a high incidence of 2.84 per 1000 births. They are associated with a relatively high morbidity and mortality, but clear-cut guidelines and practice parameters do not exist to guide the practicing clinician. In a recent multicenter retrospective study by Bartha *et al.* [50], 82% used PHB as the first-line drug, followed by lorazepam and phenytoin. A total of 6% of neonates required two anticonvulsants. However, no conclusive data exists regarding use of PHB in this age group. The response to PHB in a study by Conell *et al.* [51] was 44% for electrographic seizures, and 6.6% for clinical and electrographic cessation, while approximately a third had neither remission of clinical or electrographic events. In 1999, Painter *et al.* showed that both PHB and PHT were comparable in terms of efficacy in this age group, but no comparison to placebo was made [52]. Pyridoxine use has been noted to be curative in the setting of B6 deficiency/dependency.

At present, there is little evidence from randomized, controlled trials to support the use of any of the anticonvulsants currently used in the neonatal period. Expert opinion in the USA points towards the use of PHB as a first-line option, with lorazepam or fosphenytoin as appropriate substitutes. After the seizures have stopped, the panel recommended continuing preventive treatment for 1–2 months.

Toddlers and school-age children on PHB have a higher incidence of behavior issues, language, memory problems and comprehension, hence making a case for switch to one of the newer AEDs for use in this age group.

Although seizure-induced neuronal injury has been well studied in animal models, strong evidence in humans is lacking [53]. It is common practice to initiate seizure treatment in the neonatal period after observation of clinical events, although a clear-cut, positive effect on cognitive outcome or decrease in future epilepsy has not been documented.

Other treatment options
■ Surgical treatment

Approximately 20–30% of pediatric epilepsy patients are drug resistant, despite the advent of modern drug options [54–56]. If the seizures can not be adequately controlled by appropriate treatment with two AEDs, it may be time to consider whether the patient is a surgical candidate. For some conditions, surgery may be considered even earlier, such as for tumors, for instance dysembryoplastic neuroepithelial tumors or certain conditions including mesial temporal sclerosis, Rasmussen syndrome and malformations of cortical development such as hemimeganencephaly. Epilepsy surgery should be carried out by a comprehensive multispecialist team including a neurologist/epileptologist, neurosurgeon, neuropsychologist, neuroradiologist and physiatrist.

The workup for the proper candidate of surgery may include EEG/long-term EEG with video monitor recording, MRI of brain, PET/SPECT scan, magnetoencephalography, neuropsychological evaluation, Wada test/functional MRI, EEG and cortical mapping.

Surgical techniques include focal resection, hemispherectomy, multiple subpial transection and electrical stimulations, including vagus nerve stimulation (VNS) and deep-brain stimulation.

Focal resection

The most common surgical technique is focal resection, which is used for partial seizures caused by focal lesion, such as cortical dysplasia, tuberose sclerosis and tumor, or nonlesional resection, such as epileptogenic focus without detectible structural lesions. Hemispherectomy can be considered for Rasmussen syndrome, hemimeganencephaly, Sturge–Weber syndrome and extensive unilateral cortical dysplasia.

Focal resection can be curative or palliative. The efficacy of resection is associated with careful preoperative work-up. The best result is from temporal lobe epilepsy, with a long-term epilepsy-free rate from 66 to 88% [57,58]. If seizure-free more than 6 months to 1 year, most likely patients can be weaned off AEDs [59,60]. The outcome of epilepsy secondary to dysembryoplastic neuroepithelial tumors depends on the location [61].

Extratemporal epilepsy has less favorable results, with a long-term seizure-free rate for occipital lobe resection at 46–69.2% [62–64], frontal lobe resection at 27–30.1% [62–65] and parietal lobe resection at 46–51.8% [62,66]. The rates of long-term seizure freedom after hemispherectomy is approximately 61–66% [62,67].

Complications may include intracranial hemorrhage, increased intracranial pressure, infection, hydrocephalus and neurological deficit, depending on the location of resection. Mortality is very rare.

Nonresective surgery

For those intractable epileptic patients who are not resective surgical candidates, palliative surgery can be considered. Callosotomy can be partial or complete, and has been used for primary generalized epilepsy or secondary generalized epilepsy, especially for frequent drop attack. The reduction in seizure severity has been seen in up to 60–70% of patients [68,69]. Complications include intracranial hemorrhage, infection and disconnection syndromes, which are rare and temporary.

Multiple subpial transection is another palliative surgical technique, which is mostly useful for intractable focal seizures from clinically important cortex. Significant improvement has been observed in 33–46% [70].

Deep-brain stimulation is a new technique for treatment of seizures. Electrodes are inserted in the deep-brain structures, such as in the anterior nucleus of thalamus, centromedian nucleus of thalamus, subthalamic nucleus, cerebellum, pallidum and medial temporal lobe. As to which location is most effective, this is unknown at the present time; however, of them, cerebellum may be the least effective. Best results are obtained in nonfocal generalized tonic-clonic seizures and atypical absences of the LGS. Deep-brain stimulation is potentially an excellent alternative add-on therapy, but still needs to be extensively evaluated for its utility in children.

■ Ketogenic diet

The KD has been utilized for treatment of epilepsy since the 1920s. The mechanism of action has not been clearly elucidated, although experimental models suggest that the KD elevation in rats causes an increase in mean voltage (maximal shock) needed to produce a convulsion. This may be accomplished by increase in β-hydroxy butyrate levels, which subsequently leads to alteration in the rate-limiting step of the tricarboxylic acid cycle and elevated GABA levels [71].

The efficacy in retrospective studies was as high as 67%, while prospective multicenter studies have shown that 40% of children have at least a 50% reduction in seizure frequency [72]. Although it has been traditionally associated with treatment of refractory epilepsy, early use (while patients are on zero to one anticonvulsant) has also been shown to be clinically useful with

significant reduction in seizures at 6 months and 1 year [73]. Furthermore, its efficacy in infants has also been documented, with a recent study showing that 19.4% of subjects became seizure-free, and an additional 35.5% had greater than 50% reduction in seizure frequency. Interestingly, children who were on the diet for less than an year showed a decrease in seizures 3–6 years later, though whether this was related to diet or other interventions was not clear [59]. Use of the modified Atkin's diet was also found to be helpful in children with epilepsy, and when recently studied in a prospective fashion, 65% had a 50% reduction in seizure frequency [75]. It has been used for a wide variety of seizure types, including myoclonic-astatic seizures, Dravet's syndrome, infantile spasms, respiratory chain complex defects and Lafora body disease [54,76,77]. Case reports comment on its use in Rett syndrome [55]. Caution should be exercised in ruling out certain conditions such as pyruvate carboxylase deficiency prior to initiation of the diet.

The KD can be commenced at home or in the hospital. No difference has been noted in seizure freedom for those who initiated the diet at home versus those who had a period of initial hospitilazation, but gradual initiation may have better tolerability and fewer adverse effects. However, initial hospitalization may help in identifying side effects such as hypoglycemia and metabolic acidosis. It consists of inducing ketosis by giving diet consisting of 3–4 parts fat to 1 part carbohydrate/protein. Some studies have shown that a 4:1 ratio may be more effective [56].

Adverse effects include dehydration, acidosis, hypoglycemia, renal stones and elevation of liver enzymes, hyperlipidemia, bone demineralization, cardiomyopathy and deficiencies of vitamins and trace minerals [71]. The child may feel socially isolated due to the fact that their diet may preclude them from participating in family meals and other celebrations, and hence multiple aspects need to be discussed with the family and child prior to embarking on this form of treatment.

■ Vagal nerve stimulator

Vagal nerve stimulator is an alternative procedure for patients who are refractory to pharmacological treatment, experience intolerable side effects of AEDs or who are not candidates for resective surgery. VNS received approval by the FDA in 1997 for adjunctive therapy in the treatment of medically intractable epilepsy.

Stimulator device is surgically placed under the skin in the upper part of the chest and connects with an electrode that coils around the

vagus nerve on the left side of the neck. The stimulator can be programmed for different intensity, duration or frequency of stimuli. A hand-held magnet can produce immediate electric current to stop a seizure or reduce the severity of seizures. Therefore, VNS can both abort seizures and have prophylactic effect. This effect increases over time in chronic treatment, to a maximum up to 2 years [78]. VNS is most effective for the patients with drop attack, especially in LGS, though it can also been noted to be useful in both focal and generalized epilepsy. The exact mechanism of action remains unknown. However, recent studies showed the efficacy of VNS is associated with thalamic and limbic circuitry [79,80]. VNS is essentially a palliative treatment and the number of patients who become seizure free is very small. A significant reduction in the frequency and severity of seizures can be expected in approximately a third

of patients [81]. In the USA, VNS is approval for children older than 12 years of age, but there is no limit in the EU.

The complications of VNS include bleeding, infection, reversible paralysis of left vocal cord and other common complications of surgery. During stimulation, the patients may experience hoarseness, coughing, tingling in the neck or dysphagia. These side effects are usually mild and gradually become less prominent over time [82].

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Executive summary

- Despite the use of new antiepileptic drugs (AEDs), a significant proportion of children with epilepsy remain refractory to current drug regimes.
- Alternative treatment options such as resective surgery, ketogenic diet and vagal nerve stimulator constitute an important part of the treatment armamentarium.
- New-onset seizures in a child treatment of the first seizure does not lead to decrease in the incidence of epilepsy.

Application of the 'new' antiepileptic medications in the treatment of select epilepsy syndromes of childhood

- Partial onset seizures – oxcarbazepine emerged as the drug with the most data regarding efficacy and effectiveness.
- Infantile spasms – adrenocorticotropic hormone is 'probably' effective in the treatment of spasms and resolution of hyps- arrythmias although clear-cut guidelines as to dosage and duration of treatment are lacking. Vigabatrin is 'possibly' effective.
- Absence epilepsy – ethosuximide, lamotrigine and valproate have emerged as drugs that are possibly efficacious.
- Juvenile myoclonic epilepsy – levetiracetam, valproate, zonisanide, topiramate and lamotrigine may be efficacious.
- Lennox–Gastaut syndrome – valproate, topiramate and lamotrigine may be considered drugs of first choice on the basis of expert opinion.
- Febrile seizures – rectal diazepam is useful in the treatment of prolonged seizures.
- Potential risks outweigh the benefits of long-term treatment with antiepileptics.
- Neonatal seizures – no clear consensus exists regarding best practice in this age group, with phenobarbital and phenytoin being widely used. None of the new AEDs have been approved for treatment in this age group, although off-label use is widespread.

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