REVIEW ARTICLE

CHOOSING ANTI-EPILEPTICS IN CHILDREN: NEVER AN EASY TASK

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Introduction

Treating epilepsy in general is challenging at all ages because the goal of therapy is to ensure efficacy in controlling seizures over long term and to optimize patient's quality of life. In children this task is even more difficult due to need of rapidly controlling the seizures in order to avoid developmental arrest or regression and to carefully consider benefits versus side effects involved in long term use of antiepileptic drugs (AED). The purpose of this article is to summarize the progress that has been made in the field of AED pharmacokinetics and to provide the practicing pediatrician or general neurologist with a helpful tool in making an optimal decision.

General principles of AED therapy

The decision to treat a child after a first or second seizure may differ compared with an adult, due to the favorable prognosis in many pediatric epilepsy syndromes and lifestyle factors. Several AEDs are used off-label in the pediatric age range and some treatments are specific for pediatric epilepsy syndromes such as adrenocorticotropic hormone (ACTH), steroids or a ketogenic diet. (1-6) Before deciding which AED to use several factors have to be taken into consideration:

• Pharmacodynamics, which is the study of what a drug does to the body, and pharmacokinetics, which is the study of what the body does to a drug, should be careful reviewed before starting AED's in children, specially in polytherapy and when other co morbidities are present.

• Choice of AEDs based on seizure semiology (focal versus generalized) and a general theme for AED choice based on this distinction is summarized in Table 1. Some AEDs can be used for both partial and generalized seizures. Special precautions should be taken in using AED's that might aggravate specific type of seizures. For example, carbamazepine and oxcarbazepine can worsen generalized seizures. Lamotrigine has been reported to worsen myoclonic seizures. Tiagabine, a drug no longer used, was associated with non-convulsive status epilepticus.

Table 1: Anti-epileptic drug classification based on seizure semiology

Generalized Seizures	Focal Seizures with/ without generalization
Phenobarbital	Phenytoin
Phenytoin	Ethosuximide
Topiramate	Vigabatrin
Benzodiazepines (Status epilepticus)	Carbamazepine
Valproate	Gabapentin
Felbamate	Oxcarbazepine
Lamotrigine	Zonisamide
Levetiracetam	Levetiracetam

Classification of AED

AEDs can be classified into "old" and "new", or based on their mechanism of action and seizure semiology (focal with or without secondary generalization and generalized). In this review the AED's will be discussed in their order of discovery (summarized in Table 2).

Table 2: AED's classification based on chronologic order of discovery

Old AED's	New AED's
Acetazolamide, 1988	Vigabatrin, 1989
Carbamazapine, 1965	Lamotrigine, 1991
Clobazam, 1979	Gabapentin, 1993
Clonazepam, 1974	Piracetam, 1993
Ethosuximide,1955	Topiramate, 1995
Phenobarbitone, 1912	Tiagabine, 1998
Phenytoin, 1938	Fosphenytoin, 1999
Primidone, 1952	Oxcarbazepine, 2000
Sodium Valproate, 1973	Pregabalin, 2004
	Zonisamide, 2005
	Rufinamide, 2007
	Eslicarbazepine, 2009
	Retigabine, 2011
	Stiripentol, 2007

First Generation AEDs

Phenobarbital (PB): It is effective, easy to use and readily available worldwide. (3,7-10). PB appears to be efficacious for every seizure type except absence seizures. It is primarily indicated for the management of generalized tonic clonic seizures (GTCS) and partial seizures. PB remains the first choice of drug in the treatment of neonatal seizures. It can be administered parenterally and is one of the third drug in the treatment of status epilepticus in children, rarely in adult. PB causes liver enzyme induction and acceleration of the metabolism of other drugs, including AEDs and a long elimination t 1/2 (1.5 days in children), allowing once-daily dosing. (7,8) The primary disadvantage of PB is its side-effect profile, more specifically its potential impact on behavior and cognition. (9,10) PB has been reported to cause osteomalacia and hypocalcemia when administered for longer than 6 months. (11,12).

Phenytoin (PHT) : PHT is indicated for the treatment of GTCS and simple partial and complex partial seizures. PHT can be administered parenterally and it is usually the second line of treatment for status epilepticus after lorazepam. (1,7,13-15) It can be used in neonates. Intravenous administration of PHT may cause venous irritation and pain, as well as thrombophlebitis. (14,15) Fosphenytoin, an ester of PHT, offers the efficacy of PHT with significantly less risks related to intravenous administration. Since PHT is a liver-enzyme inducer, it may have significant interactions with other agents, including AEDs. (7,14,15) PHT is not effective against myoclonic seizures, tonic or atonic drop attacks and absence seizures, which it may exacerbate. PHT is a strong enzyme inducer. Its pharmacokinetic profile is nonlinear elimination kinetics, thus frequent monitoring of serum levels is necessary to avoid toxicity. (1,13) PHT can cause a range of adverse effects: hypersensitivity reactions (rash, severe allergic reactions, neurologic (e.g., ataxia, diplopia, drowsiness, lethargy, sedation and encephalopathy, cerebellar atrophy) and chronic (e.g., gingival hyperplasia, hirsutism and dysmorphism) and due to its teratogenic risk should be avoided in pregnancy. Osteomalacia as well as cerebellar atrophy is a known side effect of PHT. (1,7,13-15) PHT is still one of the less sedating AEDs.

Ethosuximide (ESM): ESM is still considered a first-line treatment for absence seizures, particularly for children with childhood absence epilepsy, with only this seizures type. (16,) ESM may also be effective as adjunctive treatment for myoclonic seizures (17), drop attacks (18) , and negative myoclonus . ESM does not control GTCS. Enzyme inducers, such as PHT, PB and carbamazepine (CBZ), may accelerate the elimination of ESM, while valproic acid (VPA) inhibits its metabolism. (19) One of ESM's main advantages is its favorable side-effect profile, including the absence of cognitive impairment. Most patients tolerate ESM well, but some may experience gastrointestinal complaints (mild or severe) and drowsiness that is usually dose-related. Dizziness and headaches can occur, unclear if dose related or not. Rare idiosyncratic leukopenia, aplastic anemia, thrombocytopenia or skin rashes and psychosis.

Benzodiazepines : Benzodiazepines are known for their anxiolytic and sedative effects. Diazepam, a long-acting agent, is the first used as an anticonvulsant. (8) Clonazepam, an intermediate acting agent, as well as lorazepam and midazolam, two short-acting benzodiazepines, are used for their anticonvulsant properties. (1,20-22) Intravenous lorazepam is usually the first-line treatment for status epilepticus. Midazolam is frequently used as an intravenous infusion for the control of refractory status epilepticus in an intensive care unit setting. Rectal diazepam is indicated in children and young adults for outpatient control of prolonged seizure or cluster. It can be used also for acute management of prolonged febrile seizure in children. Clonazepam is frequently used in the treatment of myoclonic seizures, or as an adjunct for Lennox-Gastaut syndrome (LGS), infantile spasms or drop seizures. Clobazam is used as a long-term treatment for different seizure types and may cause less sedation. (20-22) The main disadvantages for the use of benzodiazepines include sedation (less for clobazam) and the development of tolerance. Cardiovascular and respiratory function should be monitored, mainly in acute setting and with repeat administration due to its cumulative effect. (20-22)

Carbamazepine (CBZ): CBZ is a non-sedative, safe and efficacious AED and is used widely in the management of partial seizures and GTCS. Conversely, CBZ may exacerbate idiopathic generalized epilepsy and it should be avoided in patients with absence or myoclonic seizures. (5,23-27) Auto-induction of microsomal enzymes is a unique pharmacokinetic feature of CBZ. This results in an increase in clearance during the first 2 months of treatment. CBZ induces the metabolism of other AEDs, such as VPA, ESM, lamotrigine (LTG), topiramate (TPM), and zonisamide (ZNS). (5,23-25) Common adverse effects include drowsiness, nausea, diplopia or blurred vision, headache, dizziness, ataxia, mild leukopenia and hyponatremia. (22)

Valproate (VPA): VPA's major advantages include a broad spectrum of action against many seizure types and a relatively low sedative effect. VPA is considered first-line treatment for primarily generalized idiopathic seizures such as absence, generalized tonic-clonic and myoclonic seizures. (3,28,29) It has proven efficacy in the treatment of partial seizures and it is also considered effective in LGS and infantile spasms. (29) CBZ, PHT and PB may lower VPA levels significantly. Elimination of LTG, PB and ESM is markedly inhibited by VPA, resulting in significantly elevated blood levels if doses are not adjusted. VPA may also displace PHT and diazepam from protein binding sites, resulting in toxicity at therapeutic total concentrations of these drugs. (29) Common adverse effects related to VPA include a dose-related tremor, nausea, vomiting, weight gain and/or anorexia. Other side effects include drowsiness, thrombocytopenia, impaired coagulation, hyperammonemia, encephalopathy and alopecia. The most feared, although uncommon, adverse

effects include fatal hepatotoxicity (30,31)and acute hemorrhagic pancreatitis (2,3). Fatal hepatotoxicity was shown to have an incidence of 1 in 600 before the age of 3 years, particularly in children on polytherapy or with congenital metabolic disorders, mental retardation or organic brain disease. (30,31)

New or second generation AED's

Felbamate (FBM) : FBM may also be effective in the treatment of absence seizures, juvenile myoclonic epilepsy (JME), Landau Kleffner Syndrome and infantile spasms. Its primary current indication in children is for adjunctive treatment of LGS. FBM was associated with a relatively high incidence of two life-threatening adverse effects: aplastic anemia and liver failure. (32-34), The risk is estimated to be 1 in 4700. The risk of fatal hepatotoxic effects has been estimated to be 1 in 22,000, which does appear to exceed the risk associated with VPA in monotherapy. (30,31) Fatal aplastic anemia has been reported in adults only, whereas hepatotoxicity appears to have to age predilection.

Gabapentin (GBP) **:** GBP is effective against partial and secondarily generalized seizures, but not against primarily generalized seizures, including absence seizures. (3,24) GBP may be the AED of choice in patients with seizures and acute intermittent porphyria. (35,36) It is rarely used now in the treatment of epileptic seizure, but it is widely used for other neurological condition like neuropathic pain and fibromyalgia and possible psychiatric disorders. (36)

Lamotrigine (LTG): LTG may aggravate myoclonic seizures, particularly in JME. (6,13, 37,38) It is effective in the treatment of LGS and in children with newly diagnosed absence seizures. (39). A major limiting factor for the use of LTG is its need for slow titration schedule, particularly when fast seizure control is required; this may necessitate the use of a bridge medication, such as clonazepam, until a therapeutic dose is achieved. The metabolism of LTG is markedly accelerated by the use of inducing drugs such as PB, CBZ and PHT, and markedly inhibited by VPA. Dosing with LTG and either VPA or an inducing drug can be complicated. (37,38) LTG itself does not significantly affect the metabolism of other drugs. In children taking VPA concurrently, LTG should be introduced at a much lower dose and titrated very carefully. (37,38) The adverse effect of significant concern is a rash (37) , which can evolve into potentially lethal SJS. The association between LTG and rash, is more frequent in children. There is good evidence that the likelihood of a rash increases with faster titration rates, especially in the presence of VPA, an inhibitor of the elimination of LTG. This observation has led to the current recommendation for very slow titration. (37,38)

Topiramate (TPM): TPM is primarily indicated in the treatment of GTCS or partial-onset seizures and in the treatment of seizures (drop attacks) associated with LGS. There is also evidence that it may potentially be useful in the treatment of infantile spasms. (28,40,41) and JME. (28,41) The most common adverse effects of TPM in children include somnolence and fatigue, problems with concentration and word finding, decreased appetite and weight loss. TPM may frequently induce or aggravate metabolic acidosis and should be administered with caution and under monitoring in patients with renal disease and those on a ketogenic diet or Zonisamide. (40) Nephrolithiasis has occurred in 1.5% of patients; hypohydrosis (decreased sweating) may also occur and can lead to hyperthermia. (41)

Vigabatrin (VGB) : VGB has emerged as a potential first-choice AED against infantile spasms, particularly in patients with tuberous sclerosis. (42) In adults is used for partial seizures. The main concern is the occurrence of irreversible visual field constriction, with bilateral optic disc pallor and subtle peripheral retinal atrophy. (5,20,42,43) This has prompted the recommendation of initial and periodic ophthalmological examinations (approximately every 3 months) in patients treated with VGB, and it has markedly limited the use of VGB beyond infantile spasms. (20,42) The most common adverse effects of VGB include fatigue, headache, drowsiness, dizziness, ataxia, tremor, depression, weight gain and hyperactivity in children.

Levetiracetam (LEV) : LEV is currently indicated for the treatment of partial seizures and has recently been approved for the treatment of myoclonic seizures in JME. There is growing evidence that LEV has a broad spectrum of action and is effective in all seizure types of idiopathic generalized epilepsy (IGE). (13,20,24,44) LEV was initially developed as a cognition-enhancing agent (i.e., a non-tropic drug) for the treatment of Alzheimer's disease and it is structurally and chemically unrelated to other AEDs. (13,20,24,44) LEV has no significant pharmacokinetic interactions with other AEDs. It is usually well tolerated and has a rather benign adverse-effect profile (20,45) . Behavioral changes such as mood changes, as well as occasional psychosis, are the main concerns.(20,45) In children behavioral changes can be controlled with concomitant administration of vitamin B6.

Table 3: AED's dosages in children and formulations (2)

AED	Initial dose (mg/kg/day)	Maintenance dose	Daily dose
Phenobarbital	5 mg/kg/day	Same	Once or twice
Phenytoin	4-5 mg/kg/day	4-8 mg/kg/day	Twice or three-times
Ethosuximide	250-500 mg/day	15-20 mg/kg/day	Twice or three-times
Diazepam	2-5 years: 0.5 mg/kg 6-11 years: 0.3 mg/kg 12+ years 0.2 mg/kg	Same Same	Three-times
Lorazepam	0.05-0.1 mg/kg per dose	Same	NA
Clonazepam	0.01 mg/kg/day	0.1 mg/kg/day	Twice of three-times
Clobazam	0.25 mg/kg/day	1 mg/kg/day	Once or twice
Carbamazepine	5-10 mg/kg/day	15-20 mg/kg/day	Twice or three-times
Valproic acid	10-15 mg/kg/day	15-30 mg/kg/day	Twice or three-times
Felbamate	15 mg/kg/day	15-45 mg/kg/day	Twice or three-times
Topiramate	0.5-1.0 mg/kg/day	4-8 mg/kg/day	Twice
Vigabatrin	40 mg/kg	80-100 mg/kg/day (150 mg/kg/day for infantile spasms)	Twice
Levetiracetam	20 mg/kg/day	40-60 mg/day	Twice
Oxcarbazepine	8-10 mg/kg/day	20-30 mg/kg/day	Twice
Zonisamide	1-2 mg/kg/day	4-8 mg/kg/day (Max: 12mg/kg/day)	Once or twice

Oxcarbazepine (OXC): OXC is indicated for the treatment of partial seizures. There is also evidence that OXC is effective for the treatment of GTCS (38) although, like CBZ, it is contraindicated in IGE due to the potential for seizure activation. OXC may induce similar adverse effects as CBZ and has a favorable adverse-effect profile in children.(46) Recent evidence is indicative of potentially serious dermatological reactions and multiorgan hypersensitivity reactions in patients taking OXC; cases of SJS and toxic epidermal necrolysis have been reported in children and adults. In addition, hyponatremia is another concern with OXC, although in children it has been reported in less than 1%. It usually occurs within 3 months of therapy. (38,46)

Zonisamide (ZNS): ZNS is indicated in the treatment of partial seizures. It was also found to be effective in patients with LGS. (1,3,16) Common adverse effects of ZNS include sleepiness, loss of appetite, weight loss and ataxia. Oligohydrosis (decreased sweating) and hyperthermia have been reported in pediatric patients, although many cases occurred after exposure to elevated environmental temperatures. (1,3,16)

Dosage of AED

Usual dosages of AED's commonly used in children are summarized in Table 3.

Childhood epileptic syndromes and AED choices

In the pediatric age group, variety of epileptic syndromes have been identified and thus the treatment can be tailored accordingly.

Partial seizures : Overall, most AEDs have documented efficacy against partial seizures, and none could be shown to be more effective than any other. (3) CBZ, OXC and LEV could be considered as drugs of first choice.

Generalized tonic-clonic seizures : GTCS may occur in the context of an IGE, undetermined epilepsies without evidence of focality or focal epilepsies with rapid secondary generalization. If the patient has an IGE, the drugs of choice would be VPA, LTG or TPM because of the available evidence, and due to the possible exacerbation of seizures or epileptiform EEG abnormalities with other agents. (1,3) LEV, ZNS, CBZ or PHT, which are potentially effective, could be considered as further choices. (1,3) CBZ and PHT should be avoided if an IGE is suspected. (1,3)

Absence epilepsies: childhood & juvenile absence epilepsy: Randomized comparisons of AED treatments for absence seizures revealed no difference in efficacy between VPA and ESM. Children with absence seizures may be divided into two age categories; those under the age of 10 years and those over the age of 10 years. (1,3) Concomitant GTCS are more likely to occur after the age of 10 years in patients diagnosed with Childhood Absence Epilepsy (CAE) and are common in Juvenile Absence Epilepsy. (3) The incidence of VPA-induced fatal hepatotoxicity is highest in infants and young children, especially in combination therapy. (3) The incidence of severe hypersensitivity reaction associated with LTG also appears to be inversely age related. (3) ESM represent the drug of first choice in patients less than 10 years of age who only have absence seizures, as is usually the case in CAE. Ethosuximide does not protect against GTCS and VPA is recommended in such cases. LTG, which is also effective against absence seizures and GTCS, is quite safe in this age group and is a valuable alternative to VPA (3). It may be chosen over VPA in adolescent females.

Juvenile myoclonic epilepsy : JME is one of the most common forms of IGE, accounting for 5-10% of all epilepsies. It is best to consider IGE as a continuum of syndromes that can include GTCS, myoclonic and absence seizures in various proportions and with different ages of onset and resolution. (3) JME usually represents a lifelong condition requiring continuation of AEDs. VPA remains the drug of choice for JME. However, the side-effect profile of VPA is a concern, especially in women of childbearing age. (1,3) There is growing evidence that LEV is effective in all seizure types of IGE and is the most promising alternative to VPA of all the new AEDs. Other options include LTG, which has a much lower incidence of severe idiosyncratic reactions in adults and has few other side effects. LTG is quite effective against GTCS, but it should be kept in mind that it may aggravate myoclonic seizures. (1,3) Inversely, clonazepam is very effective against myoclonic seizures but less effective against GTCS. TPM has been shown to be effective against GTCS in JME, but its role against myoclonic seizures remains to be established. (3)

Benign rolandic epilepsy with centro-temporal spikes: Benign rolandic epilepsy with centro-temporal spikes (BRECTS), an idiopathic localization-related epilepsy, is the most common epilepsy syndrome in children from 3-12 years of age. The syndrome is characterized by brief, simple partial, hemifacial motor seizures, frequently with associated somatosensory symptoms, which have a tendency to evolve into GTCS. Both seizures and EEG findings are potentiated by sleep. BRECTS is usually associated with excellent prognosis and outcome, although there is growing evidence that it may, at times, have a substantial impact on the child's behavior or cognition. In many cases, treatment is not necessary. Many AEDs were reported efficacious, including OXC and CZP.

Infantile spasms : Infantile spasms is a catastrophic childhood seizure disorder which require prompt diagnosis and treatment. (5,23,47) ACTH and VGB are the most effective agents in the treatment of infantile spasms, but concerns remain about the risk/benefit profiles of these drugs. (23,47) Irreversible restriction of visual fields was reported after administration of VGB, but it remains the drug of choice in infantile spasm and TS. (23,47)

Lennox-Gastaut syndrome: Seizures associated with LGS do not respond well to treatment, in particular the tonic and astatic seizures. TPM and LTG are commonly used as the drugs of first choice . FBM may be one of the most effective drugs in patients with LGS, but its side-effect profile makes it a drug of third choice. VPA can be considered a drug of second choice in these patients. Owing to the age of onset of after 2-3 years, the risk of hepatic failure from VPA is relatively low in these patients, especially in monotherapy. Benzodiazepines are also effective against all types of seizures including tonic seizures, but they can, at times, cause tonic status epilepticus. CBZ has been reported to worsen seizures in LGS and ZNS showed some promising effect. In patients with recurrent seizures after two or three initial drug trials, it is now common to try the ketogenic diet. (1,3) In a recently reported double-blind, add-on trial, rufinamide, a newly developed AED, has been shown to have good responder rates for astatic seizures in patients with

LGS. (48) Vagal nerve stimulator is also used in the treatment of astatic seizures associated with LGS. (49) Surgical intervention with corpus calosotomy can be an option in refractory cases with astatic seizures being the predominant seizures.

Landau-Kleffner Syndrome & Continuous Spike Waves of Sleep (CSWS): These two epileptic encephalopathy syndromes appear to have more similarities than differences. Both are characterized by slowing or regression of development and abnormal inter-ictal, sleep activated, epileptiform discharges on the EEG, with or without clinical seizures, in children 3-8 years of age. (3) Afflicted children have normal development before the onset of seizures. In LKS, the loss of function is primarily an acquired aphasia, while in CSWS there is a broader range of cognitive and behavioral deterioration. (3) Treatment is similar for these disorders. Seizures usually respond to various AEDs, although the challenge is the suppression of abnormal EEG activity and the improvement of cognitive regression that may often require ACTH or steroids. (3)

Neonatal seizures: Neonatal seizures have very heterogeneous underlying etiologies and can represent a symptom of any brain pathology. They are more often focal tonic or clonic-myoclonic and virtually never generalized, but a multifocal seizure in neonates can be considered the equivalent of generalized seizure in older ages. (3) PB and PHT, two of the oldest AEDs, together with a benzodiazepine, remain the first-line choices (1,3,7) , but LEV is emerging as a promising dose at this age group and with possible less side effects. Interaction between PB and PHT remain a concern at all ages but specially in infants. When neonatal seizures remain intractable, and no etiology has been identified, specific metabolic underlying etiologies requiring special treatment should be considered. Examples include pyridoxine-dependent seizures, folinic acid-dependent seizures, or glucose transporter deficiency syndrome that may respond to the ketogenic diet.

Conclusion

Treating epilepsy can be challenging for the reasons highlighted in this review. Antiepileptic medications therapy is long (usually more than 2 years) and serious and life threatening side effect can occur. We do recommend treating epilepsy in children primarily based on specific epileptic syndrome if this is possible and avoiding medications that might aggravate specific types of seizures. Choosing the AED with least possible side effect is recommended. When polytherapy is indicated, AED?s with different mechanisms of action are indicated. We recommend clinical observation of the AED?s efficacy with frequent blood levels monitoring in the acute settings or when compliance or toxicity is suspected. In children a metabolic/genetic/oncologic cause for seizure should be suspected in the appropriate clinical setting, especially in newborn period. Unlike adults, children with epilepsy have increase chances to outgrow their symptoms, in the appropriate clinical setting. Decision of initiating or discontinuing anti-seizure medications should be done only after careful evaluation and under direct supervision of a neurologist.

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