With new antiepileptic drugs (AEDs) released at a rate of nearly 1 per year for the past decade, clinicians have been blessed with—and occasionally confused by—a growing list of medical treatment options for the child with epilepsy. The AEDs added since 1993 include: felbamate, gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide. These new drugs have greatly expanded the range of alternatives to the standard AEDs and their unfavorable side-effect profiles and potential drug interactions. Many of the new choices do not have specific pediatric indications, pharmacokinetic information, and side-effect data, and they cannot boast a long track record of clinical use. Despite these factors, the new agents are of necessity playing valuable roles in everyday clinical practice. This is especially true in cases where the child has failed to achieve satisfactory control after treatment with a first- or second-choice medication such as phenytoin, carbamazepine, valproate, ethosuximide, or phenobarbital/primidone.

Although the new AEDs lack a solid scientific base of evidence, such as Class I, clinicians still require information to guide their decision making with regard to the wealth of AED choices for refractory seizures. This article attempts to translate clinical experience into such guidance, first by reviewing key differences between childhood and adult epilepsy and then by suggesting a seizure- and syndrome-specific approach to AED selection in children.

**WHY CHILDREN ARE DIFFERENT FROM ADULTS**

In selecting therapies for pediatric seizure control, clinicians should first recall that epilepsy in children differs considerably from epilepsy in adults (Table 1). The 3 areas of difference most relevant to drug selection involve pharmacokinetics, adverse-event profiles, and the fact that children exhibit a characteristic set of epilepsy syndromes and seizure types, with equally characteristic responses to specific AEDs.

**PHARMACOKINETICS**

Factors affecting the absorption, volume of distribution, hepatic metabolic degradation, and excretion of drugs may vary considerably with age. In infants, AEDs typically have shorter half-lives and larger volumes of distribution. Because of this, the clearance of AEDs is approximately twice as high in infants than in adults. In children, the clearance is about 50% higher.
With topiramate, for example, the clearance in non-induced infants (average age 26 months) was 1.19 L/kg/day compared to 0.66 L/kg/day in 4- to 17-year-olds and 0.46 L/kg/day in adults. Similarly, with levetiracetam, clearence was 2.1 L/kg/day in children 6 to 12 years of age compared to 1.6 L/kg/day in adults. These types of differences are significant because the maintenance dose needed to attain a given steady-state serum level will be directly proportional to the clearance.

Although pharmacokinetic data on dosing of AEDs in children are scarce, pediatric neurologists have evaluated the adult data and used their clinical experience and the data from the few small and uncontrolled pediatric trials to build a general consensus on AED pediatric dosing. Gabapentin, eg, is generally started at 10 to 20 mg/kg/day on the first day, then increased daily or every 2 to 3 days up to 30 to 100 mg/kg/day. A higher-end maintenance dose of 60 to 100 mg/kg/day will produce a steady-state level of about 10 to 18 mg/L. Topiramate in children 2 to 16 years of age has an initial dose of 0.5-1 mg/kg/day, given nightly for the first week; it is then titrated at 1- to 3-mg/kg/day increments at 1- or 2-week intervals until the recommended daily dose of 5 to 9 mg/kg/day is attained.

Clinicians are referred to recent reviews for details on pediatric dosing of the new AEDs and discussions of the AEDs with the most favorable pharmacokinetic profiles; these are the drugs that are most suitable for once- or twice-daily administration, have fewer interactions, and are available in parenteral form.

With all the AEDs, a critical point to remember is that interactions with other medications may alter the pharmacokinetics. In 1 pediatric study, lamotrigine monotherapy led to a half-life of about 22 hours while coadministration with valproate doubled the lamotrigine half-life and coadministration with an inducer reduced the half-life to 8 hours. Such interactions require an increase in the initiation, titration, and maintenance doses of lamotrigine when this new agent is administered with inducing AEDs (eg, an initiation dose of 2 mg/kg/day). To limit the chances of a serious rash and hypersensitivity, a careful reduction of lamotrigine dose is required when it is coadministered with valproate (eg, an initiation dose of 50.2 mg/kg/day).

ADVERSE EFFECTS

Awareness of age-related drug side effects is also necessary for safe and effective use of the new AEDs. In most cases, side effects witnessed in adult populations are worse in children. For example, while gabapentin normally does not produce significant behavioral side effects in adults, several investigators have now reported tantrums, aggression, hyperactivity, or defiance in some children treated with this gamma-aminobutyric acid analog. Many of these cases involved children with previous behavioral difficulties and the changes were reversible.

Lamotrigine is another agent that may have age-related side effects. As made clear in the black box of the package insert label for this product, the drug has been associated with serious hypersensitivity reaction in about 1 of 100 children compared to 1 of 1000 adults. Although a slow titration of lamotrigine and careful coadministration with valproate (as described above) may actually reduce the rate of rashes and Stevens-Johnson syndrome or toxic epidermal necrolysis, special attention is still required in young children.

In some cases, the new AEDs may produce fewer side effects in children than in adults. The most recent data with felbamate, eg, show that not a single patient under 18 years of age has died from aplastic anemia. In the estimated 110,000 patients treated, the upper...
limit mortality risk from this condition was 1 in 16 000. Although thousands of children were exposed to felbamate, the youngest patient diagnosed with aplastic anemia was 14 years old. Further, the overall risk of hepatotoxic death with this new AED was 1 in 22 000, a level comparable to that seen in adults taking valproate in polytherapy—but much less worrisome than the fatal hepatotoxicity rate of 1 in 618 seen in patients 0 to 2 years of age on valproate polytherapy.9

**Pediatric Epilepsy Syndromes**

As with the older AEDs, each of the newer agents is gradually carving out a unique efficacy profile in relation to the various seizure syndromes. Some of the agents, such as felbamate, lamotrigine, topiramate, and possibly zonisamide, possess a relatively broad spectrum of efficacy in pediatric epilepsy syndromes. Other agents, such as gabapentin and tiagabine, are clearly narrow-spectrum agents (Table 2). This emerging picture of drug efficacy is based on relatively few large double-blind clinical studies. One of the rare double-blind studies in generalized tonic-clonic seizures, for instance, showed topiramate to be highly effective for this indication. The understanding of ideal indications is expected to evolve as additional studies are done and as clinical experience grows. Still, even with the current limited use of these agents, the practical clinical impact of these agents as adjuncts or secondary drugs for children who do not respond to standard therapy should not be underestimated.

**Making the Treatment Decisions**

A lack of compelling clinical data, although far from the ideal situation, cannot stop a clinician from offering one of the new AEDs to a child who has failed to respond to standard medications. A clinical judgment based on all information available and personal clinical experience should guide the decision. Consultation with a pediatric neurologist is recommended. Suggestions for specific sequences of medications for various seizure types and epilepsy syndromes are presented here. These suggestions are founded on an overall consideration of the safety, efficacy, and pharmacokinetic issues just reviewed. Although a few of the major trials involving the new AEDs are cited here, these recommendations also rely on the combined experiences of the large consulting practice at Children’s Hospital in Boston and those of our colleagues at other tertiary centers.

**Partial Seizures**

Most neurologists in the United States still use carbamazepine as the drug of first choice for newly diagnosed partial seizures, simple and complex, with or without generalization. Table 2 presents emerging efficacy profiles for the new antiepileptic drugs. Partial seizures, such as absence seizures and generalized tonic-clonic seizures, are discussed in this section. Other types of seizures, such as benzodiazepines and benzodiazepine agonists, are discussed in separate sections.

<table>
<thead>
<tr>
<th>Type</th>
<th>Felbamate</th>
<th>Gabapentin</th>
<th>Lamotrigine</th>
<th>Topiramate</th>
<th>Tiagabine</th>
<th>Vigabatrin</th>
<th>Levetiracetam</th>
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<tr>
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</tr>
</tbody>
</table>

yes = some evidence indicating efficacy in this condition; no = minimal or no evidence suggesting efficacy in this condition; ? = efficacy possible but not reported. Adapted from Baur B. New antiepileptic drugs in children: which ones for which seizures? Clin Neuropharm. 2000;23:119-132. Used with permission.
nosed partial seizures with or without secondary generalization. Oxcarbazepine may have some advantages over carbamazepine, but higher price may limit this option. Second choices after carbamazepine failure currently include gabapentin, lamotrigine, topiramate, and valproate—with the exact choice determined by seizure frequency, gender, age, and the clinician’s perception of side-effect risk. For example, lamotrigine may be used in adolescents but not in young children because of the age-related risks previously described. Valproate may be a less desirable option in an adolescent girl because of concerns about that drug’s gender-specific toxicity, such as possible polycystic ovary syndrome. However, topiramate may be selected for focal onset seizures based on a perception of its higher efficacy balanced with a relatively safe side-effect profile. Possible third-line agents include tiagabine, zonisamide, phenytoin, levetiracetam, phenobarbital, and primidone.

**GENERALIZED TONIC-CLONIC SEIZURES**

The treatment decision is often difficult for the patient who has had 2 or 3 generalized tonic-clonic seizures with a normal electroencephalogram and no evidence of a focus. Is this a true generalized epilepsy or is there a hidden focal onset? With any evidence of primary generalized epilepsy, such as spike waves, clinicians may feel justified reluctance to use carbamazepine or phenytoin because of the possibility of exacerbating these seizures. However, several older studies show these drugs to be effective. Valproate is currently the first-line choice based on its broad spectrum of action. Topiramate and lamotrigine are 2 other broad-spectrum agents with proven efficacy; these are now the second-line choices for treating difficult cases. Phenobarbital, primidone, and zonisamide can be considered as third-line choices.

**CHILDHOOD ABSENCE EPILEPSY**

For children younger than 10 years of age, ethosuximide is usually the drug of first choice if there are no convulsive seizures. With convulsive seizures, and any time after the age of 10 years, valproate should be considered. The rationale for this approach involves findings that about 50% of patients with untreated absence seizures will go on to develop generalized tonic-clonic seizures; thus, in the typical 6- or 7-year-old child with absence seizures and a minimal near-term chance of generalized tonic-clonic seizures, treatment with ethosuximide is recommended. Because ethosuximide provides no protection against the generalized tonic-clonic seizures that are more likely in older patients, an agent such as valproate is recommended in children older than 10 years of age. Lamotrigine should be considered a strong second choice in all cases of childhood absence epilepsy. Topiramate and zonisamide may also work as third-line agents but their exact roles are still not well delineated. Methylximide, acetazolamide, and benzodiazepines are other agents to consider.

**JUVENILE MYOCLONIC EPILEPSY**

For the seizure triad in patients with juvenile myoclonic epilepsy (ie, myoclonic, generalized tonic-clonic, and absence) valproate is still the most effective first-line therapy. Unfortunately, patients with this condition frequently need to take medication for decades, and the exposure to valproate side effects over this long period is unwelcome. As next-line alternatives, topiramate and lamotrigine can be considered, especially in those cases involving generalized tonic-clonic seizures. The choice depends to a large degree on the likelihood of myoclonic seizures in the particular patient and on the clinician’s view of relative drug efficacy in these seizures. Another therapeutic option is combining a low dose of clonazepam, which is very effective against myoclonic seizures, with lamotrigine or topiramate. Third-line choices may include phenobarbital, primidone, zonisamide, and felbamate. Rare cases of progressive myoclonic epilepsy are still treated mainly with valproate, sometimes combined with clon...
azepam; zonisamide is increasingly viewed as another option in this condition.

LENNOX-GASTAUT AND RELATED SYNDROMES

In Lennox-Gastaut syndrome and related disorders, such as myoclonic atonic epilepsy, valproate remains the drug of first choice. In newly diagnosed cases, topiramate has become the clear drug of second choice among child neurologists. Lamotrigine is another second-line option. After 2 or 3 drug failures or if standard treatment proves intolerable, the ketogenic diet should be strongly considered. Because of its efficacy in Lennox-Gastaut syndrome and because toxicity in this age group might be lower than assumed, felbamate is another potential third-line choice. Zonisamide has been reported to be potentially effective, and benzodiazepines are often used as add-ons for patients with this syndrome. Further options include ethosuximide, methsuximide, adrenocorticotropic hormone (ACTH), corticotosteroids, pyridoxine (vitamin B6), and vigabatrin. Vagal nerve stimulation has been used quite successfully for drop attacks.

INFANTILE SPASMS

The top treatments for infantile spasms generally are ACTH, vigabatrin, and valproate. The choice of agent can be complicated by drug side effects, drug availability, and varying patient presentations. In idiopathic or cryptogenic cases, for example, ACTH is often the drug of first choice, although it does have significant side effects and can be difficult to obtain. In patients with an identifiable lesion or tuberous sclerosis, vigabatrin might be considered first. Topiramate has emerged as a clear drug of second choice in spasms. Less effective third-line agents might include lamotrigine, tiagabine, and the benzodiazepines. As with any child who is younger than 2 years of age and has refractory seizures of unknown origin, children who have infantile spasms may also benefit from a trial of pyridoxine.

BENIGN EPILEPSY OF CHILDHOOD WITH CENTROTEMPORAL SPIKES

When a patient with benign partial seizures requires therapy, the first choices are currently gabapentin or valproate. Although not currently available in the United States, sulthiame might also be considered a first-line agent based on a recent report of efficacy. Carbamazepine is also still commonly employed as a first- or second-line agent in this common focal epilepsy of childhood, but clinicians should remain aware that this drug can actually aggravate benign epilepsy. Other possible choices include phenytoin, phenobarbital, primidone, and benzodiazepines. Lamotrigine and topiramate can also be considered.

NEONATAL SEIZURES

The treatment of neonatal seizures has changed little in the past 30 years. Phenobarbital remains the drug of choice, with phenytoin added if the seizures persist. Other drugs that have been used include benzodiazepines, primidone, valproate, and pyridoxine. None of the new AEDs have been systematically tested in neonatal seizures.

CONCLUSION

Clinicians are faced with a lack of extensive scientific guidance for the potential pediatric uses of the many AEDs introduced in the 1990s. Despite these stubborn gaps in the evidence base, the new AEDs already constitute much of the second line of defense for pediatricians and pediatric neurologists seeking nonsurgical options for refractory patients. As the safety and efficacy profiles of these agents are clarified, the pharmacologic treatment options for children with epilepsy will likely multiply and the long-term outcomes will improve.

QUESTIONS & ANSWERS

When is combination therapy appropriate?

Dr Bourgeois: At this point I am an advocate for monotherapy in most situations, with possible exceptions in 3 specific situations: in patients with partial seizures, where the benefit of combining valproate and lamotrigine has been verified; in patients with more than one seizure type, such as those with juvenile myoclonic epilepsy who cannot tolerate valproate, so they might receive topiramate or lamotrigine plus a low dose of clonazepam; and in those children who simply worsen again when you try to take away the first drug after adding a second drug.

Dr Lesser: Simultaneously increasing 1 drug while decreasing the other might avoid this last problem. Also, keep in mind that patients taking primi-
done are actually getting, because of the active metabolites, 2 or 3 AEDs. In this case, it's an advantage.

Given the recent evidence showing associations between valproic acid and endocrinopathies or teratogenicities, how have treatment options changed for adolescent girls?

Dr Riviello: Recent studies actually show some of the same endocrinologic abnormalities with other drugs such as carbamazepine. Valproate has been around for 22 years, and we're only seeing these things now. Who knows what will happen with the newer medications?

Dr Bourgeois: Yes, the longer a drug is available, the higher the chances of finding such effects. But further studies with valproate in different populations of women are still needed and the possibility of teratogenicity with valproate means that we need to explore this with the newer drugs. Although valproate teratogenicity is potentially severe, it can be diagnosed early and managed.

Dr Lesser: We can also prescribe folic acid to our patients of child-bearing age to prevent some of these problems. Since the maximal risk occurs in the first few weeks of pregnancy, it may be important to begin folic acid ahead of time.

Dr Bourgeois: Folate may indeed reduce the risk of spina bifida, and certainly there are no disadvantages to folate. That's why it's the right thing to do. But we still can't be completely comfortable giving valproate. We can't tell patients by exactly how much the risk is reduced or that they won't need an ultrasound. Because of the endocrinologic problems, I ask my adolescent patients about painful or irregular periods.

Dr Riviello: Some clinicians say that if women put on valproate, weight gain can be used as an indicator of a potential problem.

Dr Bourgeois: Overall, I am increasingly reluctant to give valproate to women of childbearing age where I have a valid alternative such as, in select cases and syndromes, topiramate and lamotrigine. This is true in juvenile myoclonic epilepsy, for example, where half the patients will be girls who will need medication for many years.

Are there other situations where topiramate or lamotrigine would be appropriate first choices for therapy?

Dr Bourgeois: Until we get results from new studies, valproate is still the treatment of choice in many syndromes. In boys with juvenile myoclonic epilepsy, for example, valproate remains the drug of choice until side effects develop. I recently had such a patient who developed hair loss and asked for a change, so we switched him to topiramate and we will add clonazepam should the myoclonic seizures persist.

Dr Lesser: I always caution patients starting valproate about side effects such as weight gain and hair loss. They need to know alternatives are available.

Aside from the cost disadvantage, what are the potential advantages of oxcarbazepine over carbamazepine?

Dr Bourgeois: The main advantage is fewer drug interactions. At one time the reduced risk for neonatal rash also seemed important, but this may eliminate the need for CBCs (evaluation of complete blood count) once or twice a year. Now, however, we are hearing that you may need to monitor sodium with oxcarbazepine therapy, so the potential advantage of fewer blood draws is gone. The half-lives of these 2 drugs are actually fairly similar, about 10 hours for oxcarbazepine and 10 to 15 hours for carbamazepine.

So, overall, the differences are rather modest.

REFERENCES