The treatment of epilepsy is dependent on proper diagnosis of seizure type and epilepsy syndrome. Classic medications available before 1990 popularly used for the treatment of epilepsy in childhood include phenobarbital, primidone, phenytoin, carbamazepine, valproic acid, and ethosuximide. The two classic drugs most commonly used today are carbamazepine and valproate, with ethosuximide remaining a drug of choice for children with absence seizures without associated generalized convulsive or myoclonic seizures. Recent extended-release formulations of both

---

Dr. Pellock is professor and chair of the Division of Child Neurology and vice chair of the Department of Neurology at the Virginia Commonwealth University School of Medicine, Richmond, VA.

Address reprint requests to Division of Child Neurology, VCU Children's Pavilion, 1001 East Marshall Street, First Floor, PO Box 980211, Richmond, VA 23298-0211.

Dr. Pellock is a consultant for, receives grant or research support from, and is on the Speaker's Bureaus of Abbott Laboratories, Accordia, AstraZeneca, Aventis, Carter Wallace, CoSenSys, Elan Pharmaceuticals, Eli Lilly and Company, GlaxoSmithKline, Novartis, NPS Pharmaceuticals, Ortho McNeil/Johnson & Johnson, Pfizer, Roche Laboratories, Schwarz Pharma, UCB Pharma, Harris, Bertek, and Excel.
valproate and carbamazepine, as well as more child-friendly preparations in the form of sprinkles, have allowed easier use and better compliance with existing classic medications.4 Because of incomplete seizure control and bothersome side effects associated with the medications previously noted in a significant percentage of patients, additional antiepileptic drugs (AEDs) were developed and became available during the 1990s.2 Beginning with felbamate in 1993, which was initially approved for use in treatment of partial seizures with or without secondary generalization and then in children for the treatment of Lennox-Gastaut syndrome,5 nearly 20 AEDs are now available for either acute or chronic treatment of seizures.

This article reviews the new AEDs most commonly used in children and briefly discusses the salient features of these medications, allowing pediatricians to become more familiar with these new therapeutic options. The sidebar lists the new medications available for the treatment of epilepsy approved since 1993.

Felbamate is rarely used in children because of potential adverse hematologic and hepatic life-threatening side effects.6 Tiagabine has not been fully developed for use in children, although as a primary GABAergic drug, it may have promise not only for epilepsy but for pain and spasticity.7 Vigabatrin is not available in the United States but may, in fact, be the drug of choice for the treatment of infantile spasms associated with tuberous sclerosis; retinal toxicity seen in approximately one-third of children and adults treated with vigabatrin has kept this drug from receiving approval by the FDA.8 Because of their limited use, these drugs are not discussed in this article. It is of note, however, that the drugs discussed may not be fully approved for children of all ages or may have limited approval as adjunctive therapies rather than monotherapies. All of the AEDs approved for adults have shown efficacy in both adjunctive and monotherapy studies, but sufficient data has not been presented to the FDA to enable full labeling for all appropriate seizure types in adults and children.9

GABAPENTIN
Gabapentin is a gamma-aminobutyric acid (GABA) analog and has shown efficacy for the treatment of partial and secondarily generalized seizures to achieve elevated blood levels.2 Clinical evidence of efficacy has been demonstrated in both refractory and benign partial seizures in children, both as adjunctive therapy and monotherapy. Children require daily doses from 20 to 100 mg/kg or greater to reach higher blood levels, which are sometimes more efficacious in treatment of those patients with refractory epilepsy.11 It is recommended that doses begin at 10 to 20 mg/kg per day and be increased to between 30 and 60 mg/kg per day in most patients, divided into three or four doses. Titration may be done safely using weekly increases in dose.

The primary adverse reactions to gabapentin are various types of neurotoxicity. Typical adverse effects seen in clinical trials included somnolence, dizziness, fatigue, ataxia, nystagmus, and weight gain. Some children, particularly those who are developmentally delayed and those with prior behavioral abnormalities, have demonstrated behavioral changes manifested by aggression, hyperexcitability, and tantrums.12

When rash is diagnosed as being innocent or unrelated to suspected lamotrigine, there is probably no need to discontinue medication.

LAMOTRIGINE
Lamotrigine is a broad-spectrum AED with a spectrum similar to that of valproate.13,14 Its efficacy is thought to be in part related to its effect in blocking voltage-dependent sodium channels with a secondary effect in reducing the release of excitatory amino acids, especially glutamate. Its broader spectrum of activity suggests that other mechanisms may also be present.15 Lamotrigine has demonstrated effi-
cacy in both partial and generalized seizures, including absence.13,14,16 Although it has few interactions with other drugs, its metabolism is markedly affected by the presence of hepatic inducers (ie, phenobarbital, phenytoin, carbamazepine) or inhibitors (ie, valproate). Clinical evidence for its efficacy has been demonstrated in numerous clinical trials in adults and children for the treatment of partial seizures, seizures associated with Lennox-Gastaut syndrome, childhood absence, and generalized epilepsy specialized syndromes including juvenile myoclonic epilepsy. Unfortunately, lamotrigine is associated with exacerbation of myoclonic seizures in children and adults with encephalopathic epilepsy.

Correct dosing in children ranges from 1 to 15 mg/kg per day, depending on co-medications. For those on monotherapy or those receiving both an inducer and inhibitor, typical doses range between 5 and 10 mg/kg per day, administered in divided doses. Multiple preparations, including a dispersible tablet friendly to children, are available. Slow-dose titration is mandatory because of the association of increased risk of serious, life-threatening rash seemingly more common in those receiving rapid-dose titration.14

The most common side effects of lamotrigine are neurotoxic symptoms. These commonly include dizziness, diplopia, headache, ataxia, blurred vision, nausea, somnolence, and vomiting. The greatest concern associated with lamotrigine administration is rash, which initially was reported in up to 10% of patients, although most were benign. Potentially life-threatening rash, including Stevens Johnson syndrome or toxic epidermal necrolysis, has occurred in both children and adults. It is more common, however, in children who begin lamotrigine with concomitant valproate, those who received more rapid titration of dosing, and perhaps in those with previous history of hypersensitivity reactions. This serious rash usually manifests in the first 2 to 8 weeks of treatment. Unfortunately, it may appear to be a nondescript rash initially and may then progress to significant during a few days.13 When rash is diagnosed as being innocent or unrelated to lamotrigine, there is probably no need to discontinue medication. When potentially life-threatening

When potentially life-threatening rash is suspected because of desquamation, mucous membrane ulcerations, or associated signs of hypersensitivity, immediate discontinuation of lamotrigine is recommended.

...
LEVETIRACETAM

Levetiracetam is a pyrrolidine derivative with an unknown mechanism of action. A chemically related compound, piracetam, has anticonvulsant properties against myoclonic seizures.\textsuperscript{18} This drug has few pharmacokinetic interactions and is primarily excreted renally. Although its half-life is 6 to 8 hours, it is typically administered twice daily, even in children. Clinical trials demonstrated its efficacy against partial seizures in adults initially. Additional evidence found it to be a more broad-spectrum drug, including activity against myoclonic and absence seizures in some patients. Maintenance doses in children are from 10 to 50 mg/kg per day, typically beginning at 5 to 10 mg/kg per day and titrating at weekly intervals.

The primary toxicity of levetiracetam is that of neurologic side effects including asthenia, somnolence, and dizziness. Some children and adults have experienced agitation, aberrant behavior, and psychosis. These reactions seem to be more common in those with pre-existing behavioral abnormality.\textsuperscript{19,20} Additional

Nephrolithiasis and metabolic acidosis have been reported infrequently [in patients taking topiramate], especially in those patients with limited fluid intake. A peculiar syndrome of

studies in the treatment of pediatric and other types of epilepsy besides partial seizures are ongoing.

OXCARBAZEPINE

Oxcarbazepine is structurally related to carbamazepine as the 10-keto derivative of carbamazepine that is not metabolized into the 10,11 epoxide but is metabolized to its active product, a monohydroxy derivative. The 10,11 epoxide of carbamazepine is thought to be responsible for many of

the idiosyncratic side effects of carbamazepine, including aplastic anemia, serious rash, and hepatic reactions. Oxcarbazepine shows the greatest activity against partial and convulsive seizures that are secondarily generalized.\textsuperscript{21} In adults, dosing begins at 300 mg per day and typically ranges between 900 and 1,200 mg per day, with some patients receiving as much as 2,400 mg per day. In children, doses of 10 to 60 mg/kg or greater per day have been administered with significant efficacy noted. Oxcarbazepine is less of an inducing agent than carbamazepine and is less affected by both inducing and inhibitory AEDs.\textsuperscript{21}

Neurotoxicity is the most commonly reported side effect, with tiredness, headache, dizziness, and ataxia most frequent. Skin rash is exceedingly rare and hypersensitivity reactions are much less common than with carbamazepine, occurring in approximately 20% to 25% of those patients showing similar reactions to carbamazepine.\textsuperscript{22} Hyponatremia may occur with chronic use and should be considered in high-risk patients.

TOPIRAMATE

Topiramate is a broader-spectrum AED and a sulfamate-substituted monosaccharide. It has multiple modes of action, including voltage-dependent sodium channel effects, GABA-mediated effects, glutamate antagonisms, calcium channels effects, and a carbonic anhydrase-inhibitory effect.\textsuperscript{23} It has shown effectiveness in partial seizures in adults and children, along with seizures associated with Lennox-Gastaut syndrome and other generalized seizures, including
myoclonic and absence epilepsy. It has demonstrated some efficacy in some children with infantile spasms.24

Topiramate is 70% renally excreted unchanged and is induced by hepatic inducers, such as phenytoin, carbamazepine, and phenobarbital. Phenytoin levels also may become elevated as topiramate doses are increased, especially in patients with higher blood concentrations before addition of topiramate. Topiramate induces hepatic metabolism at higher doses and may affect birth-control preparations.23

Topiramate’s side-effect profile is primarily neurotoxicity, with reports including somnolence, dizziness, fatigue, abnormal thinking, headache, diplopia, ataxia, speech difficulties, psychomotor slowing, nystagmus, paraesthesia, impaired concentration, and confusion. Speech- and language-processing deficits peculiarly are seen with this agent at higher doses.22,23,23 Recent studies indicate slower titrations and overall lower doses are more favorable. Fewer behavioral and cognitive adverse effects develop if lower doses can be used, especially when given as monotherapy.26 It is recommended that dosing begin at 0.5 to 1 mg/kg per day, with titration at 1- to 2-week intervals up to 6 to 8 mg/kg given in two daily doses. Patients with refractory epilepsy may require higher dosing. Weight loss may occur, sometimes favorably. Nephrolithiasis and metabolic acidosis have been reported infrequently, especially in those patients with limited fluid intake. A peculiar syndrome of decreased sweating with accompanying fever (oligohydrosis) has been noted in children in warm climates taking topiramate.27

ZONISAMIDE

Although relatively newly approved in the United States, zonisamide has been available in Japan for more than a decade and has proven efficacious in both partial and generalized seizures.28 It has demonstrated a clinical effect on voltage-dependent sodium channels and also affects T-type calcium channels, explaining its broader range of efficacy.29,30 Zonisamide has a half-life of 50 to 69 hours, therefore, once daily dosing is acceptable as the drug undergoes reductive biotransformation in the liver.2

Particularly important to pediatricians is the efficacy of zonisamide in the treatment of infantile spasms30 and myoclonic seizures,31 both notably resistant to many therapies. It is approved, however, for the treatment of partial seizures.32 The typical starting dose in adults and older children is 100 mg per day but ranges from 1 to 5 mg/kg per day in younger children depending on the urgency of treatment. Children with infantile spasms receive initial doses of 5 mg/kg per day or greater. Typical maintenance dose ranges from 4 to 8 mg/kg per day and is dependent upon the presence of inducing AED co-therapy.28

The side-effect profile of zonisamide is primarily neurotoxicity, with reports of somnolence, ataxia, anorexia, confusion, abnormal thinking, and hyperthermia were reported in children receiving zonisamide; they were responsive to hydration.31 Additional studies are ongoing to demonstrate the full clinical efficacy of this agent.

CONCLUSIONS

The new AEDs offer additional treatments for those patients nonresponsive to classic medications, whose side effects are intolerable, or for those who are at high risk for side effects with one of the existing classic drugs. AEDs with a more narrow spectrum of activity for partial seizures, along with those of a broader spectrum, have been developed. (Sidebar, see page 387.) Both pharmacokinetic and adverse-effect advantages are seen with many of these agents. The cost of the newer AEDs is almost always greater than classic AEDs, especially when generic equivalents are available. None of the new drugs are yet available in intravenous formulations.

All of the newer agents are classified as category C regarding teratogenesis because insufficient numbers of births to women receiving monotherapy with one of these new agents were reported. Theoretically, those agents with fewer toxic metabolites may prove safer to the unborn fetus, but post-marketing surveillance is necessary to prove this assumption. As always, fewer adverse effects — especially those of neurotoxicity, behavioral abnormalities, and cognitive interferences — are reported when AEDs are used as monotherapies in the lowest efficacious doses.

Classic management of epilepsy begins with establishing a seizure and syndrome diagnosis.34 This requires knowledge of the exact behavior during the ictus and its electroencephalogram (EEG) characterization. The epilepsy syndrome is further defined by age of onset, etiology, genetic influence, natural history, and likelihood of remis-
sion or refractoriness of seizures to treatment. The first assumption of diagnosis leads to choosing an AED, if it is warranted, because recurrent seizures are likely to occur. As stated previously, most clinicians choose carbamazepine for treatment of partial seizures and many undefined convulsions. If these seizures are associated with a generalized EEG abnormality, carbamazepine actually may make seizures worse or lead to the appearance of new seizure types, such as absence or myoclonic seizures.

For generalized epilepsy syndromes, valproate is the drug with the greatest proven efficacy. Its use in young children with possible metabolic abnormalities needs to be assessed carefully, and the potential for some adverse effects makes it a second-line drug for some clinicians. Enteric-coated valproate is always more preferred to valproic acid because of decreased gastroenteric side effects.

Comparing the side effects of AEDs shown in the sidebar (see page 387) for more safety. Adjunctive treatment with multiple AEDs will lead to a greater number of pharmacodynamic adverse effects than may be predicted on pharmacokinetic basis. Ease of administration is an important factor for some patients, and they may choose a treatment according to its form — liquid, capsule, tablet, sprinkle, chewable, or extended release.

**PRACTICAL EXPERIENCE**

I give parents and patients who are old enough to make an informed decision a choice of appropriate AEDs when considering initial or replacement medication for the treatment of epilepsy. We discuss efficacy, adverse effects, and ease of use. Cosmetic side effects are typically the most important to adolescents, whereas rare but potentially life-threatening adverse effects are of more concern to parents. I usually suggest two or three choices with appropriate information to begin the decision process. Package inserts,
effects should be recognized. Multiple reviews\(^1\text{-}^3\) along with the Web site from the American Epilepsy Society Clinical Pharmacology Task Force\(^6\) are available for further information.

**REFERENCES**


