

## Managing Pediatric Epilepsy Syndromes With New Antiepileptic Drugs

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**ABSTRACT.** The management of epilepsy in the pediatric patient requires careful evaluation, classification, and pharmacologic treatment. Despite best efforts on the part of clinicians, approximately 25% of children remain refractory to appropriate medical therapies. The development of an improved classification system and the emergence of several new antiepileptic drugs have enabled some progress in this area, specifically in children with disorders such as Lennox-Gastaut syndrome and infantile spasms, which are notoriously difficult to control. However, limited data are available that define the optimal use of new antiepileptic agents in pediatric patients. To most effectively treat children with epilepsy syndromes, further research must be completed to validate the positive effects described in case reports, open-label clinical trials, and early controlled clinical trials. *Pediatrics* 1999;104:1106-1116; *epilepsy, pediatrics, anti-epileptic drugs.*

ABBREVIATIONS. AED, antiepileptic drug; EEG, electroencephalography/electroencephalographic; GABA, gamma-aminobutyric acid; CNS, central nervous system.

It is estimated that 0.5% to 1% of children have epilepsy<sup>1</sup>; in the majority of epilepsy syndromes, onset occurs during infancy or childhood. Therefore, the challenging task of diagnosing, classifying, and managing epilepsy in the pediatric population is an important one. Despite recent advances in pharmacologic therapy and the development of an improved classification system, 25% of children who are diagnosed with epilepsy remain refractory to traditional therapy.<sup>2</sup> Furthermore, the use of new antiepileptic drugs (AEDs) in children is somewhat limited by a lack of firm data outlining the appropriate use of these agents in the pediatric population. This reviews available case reports and clinical trial data related to the use of newer AEDs in the chronic management of epilepsy syndromes in pediatric patients.

### CLASSIFICATION OF CHILDHOOD EPILEPSIES

The appropriate classification of seizure disorders is crucial to the overall management of children with

epilepsy. Unfortunately, not all cases are easily classified and not all epilepsy syndromes are well defined. Despite its limitations, the current classification system offers definite advantages to the clinicians involved and the patients they treat.<sup>3</sup>

The International Classification of Epilepsies and Epileptic Syndromes was developed in 1989 in response to a global need for refinement of the current classification system; it is used in conjunction with the International Classification of Epileptic Seizures. This revised system recognizes the various epilepsy syndromes, defined as "a cluster of signs and symptoms customarily occurring together," rather than seizure type alone, which allows for more accurate diagnosis and more effective tailoring of drug therapies. In some instances, proper classification affords clinicians greater prognostic insight during the earlier stages of management of the disorder.<sup>3</sup>

Table 1 outlines the most recent categories identified for classification of epilepsies in childhood, as set forth in 1989 by the Commission on Classification and Terminology of the International League Against Epilepsy.<sup>3,4</sup> General categories initially are separated by the focal or generalized onset of seizures, with further subdivisions made based on idiopathic, symptomatic, or cryptogenic nature of the disorder. Specific syndromes within each subdivision are classified according to a collection of criteria, including type of seizure, cause, anatomy, precipitating factors, age of onset, severity, chronicity, diurnal and circadian cycling, and sometimes prognosis.<sup>3</sup>

Although this classification scheme is not without its imperfections (eg, some syndromes are less stringently defined than others; it is not all-encompassing), it still provides physicians with a means of more effectively analyzing each patient and more easily making therapeutic decisions. Modifications to this system have been proposed for both semiology and anatomic considerations in adults<sup>5</sup> and because of the difficulty establishing the subtle signs of alteration of the level of consciousness in children.<sup>6,7</sup>

### TAILORING DRUG THERAPY IN CHILDHOOD EPILEPSY

The pharmacologic management of seizure disorders in pediatric patients requires careful consideration of a variety of factors. Once the epilepsy syndrome has been properly identified, the most appropriate AED, if one is indicated, must be selected based on efficacy data, adverse effects and pharmacokinetic profiles, and previous clinical experience. The clinician also must keep in mind that

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**TABLE 1.** The International League Against Epilepsy Classification of Epilepsy Syndromes of Childhood

Localization-related Epilepsy Syndromes	
Idiopathic (with age-related onset)	
	Benign childhood epilepsy with centrotemporal (rolandic) spikes
	Childhood epilepsy with occipital paroxysms
	Primary reading epilepsy
Symptomatic	
	Chronic progressive epilepsia partialis continua of childhood (Kojewnikow's syndrome)
Topographic syndromes	
	Temporal lobe
	Frontal lobe
	Parietal lobe
	Occipital lobe
Cryptogenic (symptomatic with lack of clear etiology)	
Generalized Epilepsy Syndromes	
Idiopathic (with age-related onset)	
	Benign neonatal familial convulsions
	Benign neonatal convulsions
	Benign myoclonic epilepsy in infancy
	Childhood absence epilepsy (pyknoepilepsy)
	Juvenile absence epilepsy
	Juvenile myoclonic epilepsy (Janz syndrome)
	Epilepsy with generalized tonic-clonic seizures on awakening
Cryptogenic or symptomatic	
	West's syndrome (infantile spasms)
	Lennox-Gastaut syndrome
	Epilepsy with myoclonic-astatic seizures
	Epilepsy with myoclonic absences
Symptomatic (nonspecific etiology)	
	Early myoclonic encephalopathy
	Early infantile epileptic encephalopathy with suppression burst
	Other
Symptomatic (specific syndromes)	
	Includes any disease that has seizures as a primary clinical finding
Epilepsies and Syndromes Undetermined as to Whether Focal or Generalized	
Neonatal seizures	
	Severe myoclonic epilepsy in infancy
	Epilepsy with continuous spike waves during slow wave sleep
	Acquired epileptic aphasia (Landau-Kleffner syndrome)
Special Syndromes	
Febrile convulsions	

From Aicardi.<sup>1</sup>

differences exist between adults and children. Factors such as hepatic metabolism, renal elimination, and volume of distribution vary among children and will fluctuate over time, requiring dose adjustments as the child matures. This appears to be less of a problem with agents that are eliminated unchanged via renal excretion.<sup>8</sup>

A current drawback to the management of pediatric patients involves the lack of published data from controlled clinical trials in children to enable specific labeling for use in the various syndromes of pediatric epilepsy when the AEDs initially are released. This shortcoming stems from both ethical and practical issues regarding the inclusion of this population in premarketing trials. As a result, much of the current AED use in children is off-label and based on safety and efficacy data derived from adult trials, along

with smaller, uncontrolled studies in children, which have provided some early pharmacokinetic data. The problem of a lack of published data in children was addressed in 1994 at a National Institutes of Health workshop.<sup>9</sup> Recommendations for designing and implementing appropriate trials in this population were made, and instances in which adult data can be extrapolated were identified (Table 2).<sup>9</sup> The general consensus indicated that improvements in the provision of information related to pediatric use were necessary but that neither the availability of new agents nor the safety of the children should be compromised in the process.<sup>9</sup> This has led to the encouragement of changes in the current strategy for designing clinical trials.<sup>10,11</sup>

It is expected that because of the new guidelines for drug development and the increase in new agents released throughout the past several years drug therapy options for pediatric patients with epilepsy will expand and the overall management of seizures in children will improve.

#### NEW AEDs IN THE PEDIATRIC POPULATION

For many years, therapy with standard AEDs was the only option for the pharmacologic treatment of children and adults with epilepsy. Although these drugs generally were effective in controlling seizures, their usefulness was hampered by unfavorable adverse effect profiles and unwanted drug interactions. Several new AEDs have been introduced during the 1990s and are presented here in alphabetical order (Table 3).<sup>2</sup> Although in the majority of cases these drugs are approved by the US Food and Drug Administration for use only in adults, the availability of these new agents has broadened the therapeutic options for all patients who suffer from

**TABLE 2.** National Institute of Neurological Disorders and Stroke Consensus on the Development of New Antiepileptic Drugs for Pediatric Patients

Recommendations for the Development of AEDs for Children	
AEDs are needed for pediatric epilepsy; trials for new AEDs should include trials for children.	
If a drug is shown to be effective for partial seizures in adults, this is sufficient to justify its approval for use in partial seizures in children, provided that safety and pharmacokinetic considerations are appropriate.	
Because AEDs that are approved for use in adults are certain to be used in children, pharmacokinetic data and dosing schedules for children should be provided to the professional community at the time of drug approval.	
Putative AEDs should be tested in immature animals as well as adult animals to identify agents that may be age specific.	
New models should be developed for specific age-related syndromes.	
The development and standardization of new outcome measures of drug effects, especially in the areas of cognition and behavior, are recommended for the evaluation of new AEDs in pediatric epilepsy.	
Postmarketing surveillance of long-term developmental, cognitive, and other safety issues needs to be developed for all new AEDs.	
Governmental agencies, such as the NINDS, are strongly urged to identify and track patients for AED development.	

From Sheridan and Jacobs.<sup>9</sup>

Abbreviations: AEDs, antiepileptic drugs; NINDS, National Institute of Neurological Disorders and Stroke.

**TABLE 3.** Pharmacokinetic Properties of New Oral Antiepileptic Drugs\*

Drug	Oral Absorption	Kinetic	Protein Binding	Active Metabolites	Half-life (h)	Hepatic Enzyme Activity	Elimination	AED Interaction
Felbamate	Complete	Linear	30%	Unknown	14-23	None	50% unchanged in urine; 50% liver	Induced by CBZ, PHT; VPA, PHT, CBZ metabolism decreased
Gabapentin	Complete	Linear	NS	None	5-7	None	Renal	None
Lamotrigine	Complete	Linear	55%	None	6-114	? Increases 10,11 epoxide-CBZ	Renal as glucuronide conjugate	Induced by PHT, CBZ; inhibited by VPA
Tiagabine	Complete	Linear	96%	None	5-8	None	Liver	None
Topiramate	Complete	Linear	0-15%	None	18-23	Inhibition	Renal	Induced by PHT, CBZ; may increase PHT
Vigabatrin‡	Complete	Linear	NS	S(+) Enantiomer	5-11	None	Renal	May decrease PHT, PB levels

From Pellock and Watemberg.<sup>2</sup>

\* Pharmacokinetic parameters are derived from adult and pediatric data.

‡ Investigational in the United States.

Abbreviations: CBZ, carbamazepine; NS, not significant; PB, phenobarbital; PHT, phenytoin; VPA, valproic acid.

epilepsy, especially those with refractory seizures. It is important to note that these newer agents should not be considered as first line therapy, and, if used, pediatricians should be co-managing patients with child neurologists.

*Felbamate*

Felbamate, which was approved for use in the United States in August 1993, is a dicarbamate AED indicated for the treatment of partial seizures in adults, with or without secondary generalization, and for the adjunctive treatment of partial and generalized seizures in children with Lennox-Gastaut syndrome. Although its mechanism of action is not clearly defined, it is thought to block both the N-methyl-D-aspartate receptor, altering calcium permeability, and voltage-dependent sodium channels.<sup>12</sup> The initial recommended dose of felbamate as adjunctive therapy in children is 15 to 45 mg/kg/d, depending on seizure control and tolerability; however, some children require much higher doses (>90 mg/kg/d).<sup>13</sup>

Despite the cautious use of felbamate after reports of widespread and potentially fatal cases of aplastic anemia<sup>14</sup> and hepatotoxicity,<sup>15</sup> it remains a viable treatment option for children who are unable to achieve seizure control with traditional AED therapy, especially those with Lennox-Gastaut syndrome. No cases of felbamate-associated aplastic anemia have been reported in children aged 13 years and younger.<sup>16</sup> Hepatotoxicity has been noted in children but not with the propensity for infants aged 2 years and younger, as observed with valproate.<sup>17</sup> Because of the risks associated with this AED, initiation of felbamate therapy in this patient population is best left to the pediatric neurologist.

**Clinical Evidence**

Two major studies have been completed that examined the use of felbamate in patients with Lennox-Gastaut syndrome.<sup>18,19</sup> This seizure disorder begins in patients aged 1 to 6 years, may follow infantile spasms, and is characterized by the presence of multiple seizure types, most often tonic-axial, atonic, and atypical absence seizures, which tend to be refractory to pharmacologic therapy. Children with this syn-

drome exhibit characteristic electroencephalographic (EEG) abnormalities, including generalized slow spike and waves; such children generally have mental retardation and a poor prognosis.<sup>3,20,21</sup>

In a pivotal double-blind, placebo-controlled, add-on study that aided in the approval of felbamate in pediatric patients, 73 patients (aged 4 to 36 years) with Lennox-Gastaut syndrome were randomized to receive either felbamate 15 mg/kg/d or placebo.<sup>19</sup> Felbamate was titrated over 2 weeks to the lower of two doses, 45 mg/kg/d or 3600 mg/d, and was then maintained at the highest tolerated dose for an additional 8 weeks. Patients who received felbamate demonstrated greater seizure reduction and higher global evaluation scores (eg, improved quality of life) during the maintenance phase compared with patients who received placebo. The greatest reduction was noted for atonic seizures (34% vs 9% reduction; *P* = .01).

These findings were sustained in an open-label, follow-up study of 70 of the original 73 patients.<sup>18</sup> Patients who were randomized to receive felbamate in the controlled trial sustained improvement, and 58% of patients who switched from placebo achieved a 50% or greater reduction in seizure frequency. These improvements were sustained for 12 months in 51% of patients.

Evidence of the efficacy of felbamate in the treatment of partial seizures is plentiful.<sup>22-28</sup> During several clinical trials as both add-on therapy and monotherapy, felbamate improved seizure control in adults and children with partial seizures.

One open-label, add-on study was conducted of 30 children with complex partial and/or secondarily generalized seizures who failed trials of carbamazepine, phenytoin, valproate, and a barbiturate.<sup>23</sup> Felbamate 15 mg/kg/d was added to the current regimen and titrated to a maximum of 45 mg/kg/d or 3600 mg/d (lesser of the two) as tolerated. Seven patients experienced a 70% decrease in seizure frequency, 8 patients reported a 50% to 70% decrease, and 15 patients experienced a reduction of <50%. Overall, patients aged 10 years and older were more likely to have a >50% reduction in seizure frequency (*P* = .011). This evidence, combined with strong data on adult patients, supports the use of felbamate in

children with complex partial seizures who are refractory to other first- and second-line agents.

Felbamate also has been reported to be useful in the management of infantile spasms, or West's syndrome. Children with West's syndrome generally exhibit three characteristic clinical findings: infantile spasms, stunted psychomotor/mental development, and hypsarrhythmia (an EEG abnormality with random, high-voltage slow waves and spikes); unfortunately, they have a poor overall prognosis.<sup>3,29</sup> West's syndrome traditionally has been treated with corticotropin or oral corticosteroids, but various alternative therapies have been used to achieve seizure control in treatment-resistant infants.<sup>20</sup>

One small open-label study was conducted that examined the use of felbamate as add-on therapy in 11 children aged 6 to 45 months who had treatment-resistant infantile spasms (insufficient seizure control with two or more AEDs).<sup>30</sup> Felbamate therapy was initiated at 15 mg/kg/d and titrated to 45 mg/kg/d by weeks 3 to 6. Two patients required larger doses of 60 and 75 mg/kg/d.

In patients who were receiving valproate at the start of the study, the dose was decreased by 25% on felbamate initiation. Valproate then was tapered and discontinued in all patients. The median follow-up for all patients was 22 weeks. The median decrease in seizure frequency, as measured by seizure counts from baseline and treatment video EEG segments, was 72%. The median decrease in electrodecremental events was 73%. A reduction in clinical spasms was noted in seven patients overall ( $P < .05$ ), as was a decrease in electrodecremental events.

Caregiver data revealed improvement in the frequency of infantile spasms in 10 patients ( $P < .05$ ). Greater clinical improvement was observed in patients who had an earlier onset of seizures ( $P = .02$ ). Felbamate treatment was generally well tolerated and resulted in increased alertness in seven patients. Dose-related adverse effects included weight loss in 1 patient and increased vomiting in a child with gastroesophageal reflux. Both effects resolved with a reduction in the felbamate dose. Several case reports of children aged 5 to 24 months with refractory infantile spasms describe improvement in or complete control of seizures after 2 to 4 days of therapy with 15 to 45 mg/kg/d of felbamate; all the children were reported to be more alert.<sup>29</sup>

### Toxicity Profile

Estimated rates of occurrence of aplastic anemia and hepatotoxicity, for which a black box warning appears in the product labeling, are outlined in Table 4.<sup>14</sup> Another estimate of the true incidence of felbamate-associated aplastic anemia, which was derived

from an in-depth examination of the first 31 reported cases, indicated that the most probable incidence is approximately 127 cases per million treated (~1:8000). In all, 31 cases of aplastic anemia were reported to the US Food and Drug Administration between January 1994 and January 1995; 7 resulted in death.<sup>31</sup> Aside from these two potentially fatal reactions, the most commonly reported adverse events during clinical trials in children receiving felbamate were anorexia, somnolence, insomnia, vomiting, weight loss, nausea, and gait abnormalities.<sup>14-18</sup> In clinical practice, insomnia, anorexia, and weight loss occur often and are particularly distressing in this patient population.

### Gabapentin

Gabapentin, a gamma-aminobutyric acid (GABA) analog, is indicated for the adjunctive treatment of partial and secondarily generalized seizures in adults. Gabapentin, which was originally designed to mimic GABA, is inactive at GABA receptors. The actual mechanism of action of gabapentin may be multimodal. Several mechanisms of action have been hypothesized, including competition with the endogenous amino acids leucine, isoleucine, valine, and phenylalanine for transport; induction of increased GABA concentrations and synthesis in the brain; modulation of calcium and/or sodium channels; inhibition of monoamine neurotransmitter release; and induction of increased serotonin levels.<sup>32</sup>

Gabapentin has gained popularity since its release in February 1994, partly because of its ability to be titrated quickly, its mild adverse effect profile, its lack of enzyme-altering properties, and its general lack of significant drug-drug interactions (renal elimination), all of which are preferred clinical properties. The drug also has demonstrated important efficacy in children with otherwise refractory partial seizures. The optimal therapeutic dose of gabapentin in pediatric patients ranges from 30 to >90 mg/kg/d<sup>2</sup> with higher doses of gabapentin proving to be particularly effective in reducing seizure frequency in refractory childhood partial epilepsy.<sup>33</sup>

### Clinical Evidence

In adult controlled studies, the efficacy of gabapentin as add-on therapy,<sup>34-38</sup> and, more recently, monotherapy<sup>39,40</sup> in refractory partial and/or secondarily generalized seizures has been evaluated with favorable results. Additional favorable data were obtained from two small-scale studies that examined the long-term efficacy ( $\leq 4$  years) of gabapentin in this same population.<sup>41,42</sup> Gabapentin also has been studied in adult patients with generalized seizures<sup>43</sup>; although the results indicated a trend toward a reduction in seizure frequency, no statistically significant improvement was noted. Therefore, the clinical usefulness of gabapentin in patients with epilepsy generally is limited to the treatment of drug-resistant partial seizures, with or without secondary generalization.

Data from trials in children are similar to those from adult trials. Two double-blind, placebo-controlled, multicenter studies evaluated the effec-

TABLE 4. Risk of Aplastic Anemia and Hepatotoxicity Associated With Felbamate Therapy

Adverse Event	Overall Risk	Risk of Death
Aplastic anemia	1:3000	1:10 000
Hepatotoxicity	1:7000	1:12 500
Combined risk	1:2000	1:5500

From Bourgeois.<sup>14</sup>

tiveness of gabapentin in controlling childhood absence seizures in a total of 33 treatment-naive children (aged 2 to 16 years) and showed no greater efficacy than placebo with gabapentin 15 to 20 mg/kg/d.<sup>44</sup> All patients tolerated the drug.

An open-label, add-on study of gabapentin in 32 children with treatment-resistant partial seizures, with or without secondary generalization, produced positive results.<sup>45</sup> Children aged 2 to 16 years received gabapentin 10 to 50 mg/kg/d (mean, 24.5 mg/kg/d) for a period of 2 weeks to 9 months. Eleven patients (34.4%) had a 50% or greater decrease in the frequency of seizures; 4 patients had a 25% to 50% reduction; and 6 patients continued to respond to gabapentin (>50% seizure reduction) for 6 months. Adverse effects generally were mild, but 4 patients experienced significant behavioral changes, typically hyperactivity or aggression. Three patients required discontinuation of gabapentin. However, all 15 patients who reported behavioral changes were mentally retarded and had a history of attention deficit and/or behavioral problems before initiation of gabapentin. Based on these results and those from adult trials, as well as the agent's favorable pharmacokinetic and tolerability profiles, gabapentin is a useful alternative in pediatric patients who have refractory partial seizures. Initial reports of two studies of gabapentin in children are similarly encouraging. Both refractory seizures and benign epilepsy with centrotemporal spikes (rolandic) showed significant improvement when treated with adjunctive gabapentin versus placebo.

Our clinical experience with gabapentin use in children reveals that it is safe and effective, with a dose-dependent increase in serum levels and efficacy. Patients who were treated with a mean gabapentin dose of 21.5 mg/kg/d had mean blood levels of 5.04 µg/mL, whereas groups that received mean doses of 44.5 and 75.7 mg/kg/d had levels of 9.05 and 12.72 µg/mL, respectively. The drug's efficacy generally was superior in the patients who were treated with higher gabapentin doses, but neurotoxic adverse effects may increase at higher doses.<sup>33,46</sup>

An extremely impressive response to gabapentin by patients with resistant partial epilepsy and mental retardation was of particular importance. Patients on concomitant AEDs may require a reduction in dose or a change of medications to allow increased gabapentin doses, because of dynamic (not pharmacokinetic) interactions that produce adverse effects, including behavioral effects. It is recommended that doses begin with 10 to 20 mg/kg/d and be increased by approximately 10 mg/kg/d to evaluate their efficacy at 30 mg/kg/d. Then, as needed, the dose may be increased to 60 mg/kg/d in refractory patients and to approximately 100 mg/kg/d in patients who are uncontrolled but tolerate gabapentin. Titration can be achieved by advancing the doses every few days.

#### Toxicity Profile

As demonstrated in clinical trials, gabapentin lacks significant adverse effects, a major advantage when treating children with epilepsy. Behavioral changes

have been reported and are generally manifested as combinations of aggression, hyperexcitability, and tantrums.<sup>45,47-49</sup> In practice, this appears to be a reaction observed in <10% of the children treated, and it is more common although not constantly observed in children with previous behavioral difficulties, including those who are mentally retarded. Symptoms are reversible on discontinuation of gabapentin. Other adverse effects observed in clinical trials included somnolence, dizziness, fatigue, ataxia, nystagmus, and weight gain.<sup>35-44</sup>

#### Lamotrigine

Lamotrigine is a triazine AED that is proposed to exert its effect by blocking voltage-dependent sodium channels.<sup>50</sup> However, this mechanism does not explain its broad range of clinical usefulness. For adult patients, the drug currently is indicated for adjunctive treatment of partial seizures or monotherapy in patients currently receiving single drug therapy with an enzyme-inducing AED. Lamotrigine is also indicated as add-on therapy for the treatment of generalized seizures in Lennox-Gastaut syndrome. Effective maintenance doses in children range from 1 to 15 mg/kg/d, and the doses must be titrated carefully to limit adverse effects.<sup>13,51,52</sup>

The broad dosing range for lamotrigine is explained by the metabolic effect of other AEDs on its metabolism, because valproate inhibits its conversion, whereas its half-life is shortened by enzyme-inducing AEDs such as carbamazepine, phenytoin, and phenobarbital. Lamotrigine is a useful agent in the armamentarium of AEDs, but caution must be exercised in its use with children because of the association with serious rashes that occur with concomitant valproate use and rapid dose titration. Nevertheless, the use of lamotrigine in children is important, because it may confer great benefit, especially in those children with Lennox-Gastaut syndrome and other refractory partial and generalized epilepsy syndromes.

#### Clinical Evidence

Lamotrigine has proved to be effective in controlling a variety of seizure types in both children and adults. Its usefulness as an add-on therapy in reducing seizure frequency in adult patients who have refractory partial seizures, with or without secondary generalization, has been demonstrated in several double-blind, placebo-controlled trials.<sup>53-58</sup> Lamotrigine also has proved effective in treating patients with primary generalized seizures, including tonic-clonic, absence, myoclonic, and atonic, and in patients with Lennox-Gastaut syndrome or with seizures secondary to brain injury.<sup>59-65</sup>

A synergistic effect on seizure control is achieved when lamotrigine is given in combination with valproate, but this AED combination increases the probability of serious lamotrigine-induced rash.<sup>60</sup> Much lower lamotrigine doses are required in patients who receive valproate resulting from the inhibition of lamotrigine metabolism by valproate. Because this combination of lamotrigine and valproate is common, especially in patients with Lennox-Gastaut syn-

drome, it is imperative that caution be exercised. Lamotrigine should be initiated at 0.2 mg/kg/d (with valproate) or 2 mg/kg/d (no valproate) and titrated slowly.<sup>2,52</sup> Maintenance doses range from 1 to 5 mg/kg/d (with valproate) to 5 to 15 mg/kg/d (no valproate). Lamotrigine monotherapy can successfully be achieved in some patients and is generally tolerated better than combined therapy with standard AEDs (eg, carbamazepine).<sup>60,66</sup>

Much of the data regarding the use of lamotrigine in children are in the form of case reports and open-label trials. Lamotrigine is effective in reducing seizure frequency in a broad range of partial and generalized seizure types and childhood epileptic syndromes. Experience with lamotrigine includes the childhood syndromes of juvenile myoclonic epilepsy,<sup>67,68</sup> infantile spasms,<sup>69</sup> Rett's syndrome,<sup>70</sup> absence seizures,<sup>71</sup> and Lennox-Gastaut syndrome.<sup>64</sup> However, myoclonic seizures may not respond to lamotrigine therapy.<sup>52,72</sup>

Results were presented from five open-label trials involving 285 pediatric patients aged 1 to 13 years with treatment-resistant epilepsy.<sup>59</sup> Patients were observed and seizure counts were measured for a 3-month baseline period. Lamotrigine then was initiated at 0.5 mg/kg/d (concomitant valproate) to 2 mg/kg/d (no valproate) and titrated to 5 to 15 mg/kg/d. After 12 weeks of lamotrigine therapy, 34% of all evaluable patients experienced a 50% or greater decrease in seizure frequency.

Patients with absence (53% with a  $\geq 50\%$  decrease) and atypical absence (50% with a  $\geq 50\%$  decrease) seizures appeared to have the most significant improvement during this time. Of the 32 children evaluated at 48 weeks, 41% experienced a 50% or greater improvement in seizure frequency. Global evaluations reported improvement in 69% of children at 12 weeks and 74% at 48 weeks. Safety data revealed a 13% discontinuation rate because of adverse events; rash accounted for a 7.4% discontinuation rate.

In one open-label, long-term continuation study of 155 treatment-refractory patients aged 2 to 19 years, lamotrigine 1 to 15 mg/kg/d was administered as add-on therapy or monotherapy ( $N = 34$ ) for as long as 4 years.<sup>51</sup> Of the original 155 patients who entered the continuation phase, 95 completed therapy for a minimum of 144 weeks, 73% of whom maintained improvement.

Overall, lamotrigine reduced seizure frequency throughout the 4-year period and was well tolerated, with some patients reporting an improvement in global functioning with lamotrigine therapy. This added benefit of lamotrigine therapy (eg, increased attention, alertness) has been reported in pediatric and adult trials and is especially pronounced in children who have concomitant developmental and/or attention problems.<sup>63,73</sup> Earlier open studies that evaluated lamotrigine therapy in a total of 334 adults and children with refractory seizures support these positive results,<sup>74-76</sup> as do results from a compassionate use protocol of 13 children and adolescents with severe, uncontrolled seizure disorders.<sup>77</sup>

Until recently, data supporting the efficacy of lamotrigine in children with Lennox-Gastaut syndrome

were largely limited to abstracts and open-label studies.<sup>76,78-81</sup> In a double-blind, placebo-controlled trial of lamotrigine in 169 patients aged 3 to 25 years with Lennox-Gastaut syndrome, patients received either lamotrigine 50 to 400 mg/d (1 to 15 mg/kg/d), based on weight and absence or presence of valproate, or placebo as add-on therapy for 16 weeks.<sup>64</sup> On final evaluation, 33% of the lamotrigine recipients and 16% of the placebo recipients achieved a seizure reduction of 50% or greater ( $P = .01$ ).<sup>64</sup> A second report of efficacy in children and adolescents with refractory generalized epilepsy corroborates these results.<sup>82</sup> Childhood epilepsies such as Lennox-Gastaut syndrome, which tend to be refractory to pharmacologic therapy, represent one of the more promising areas for lamotrigine therapy.

### Toxicity Profile

The adverse effect associated with lamotrigine that is of greatest concern has been rash, which occurs in as many as 10% to 12% of patients, usually during the first 2 to 8 weeks of treatment, and it may progress to the potentially life-threatening Stevens-Johnson syndrome or toxic epidermal necrolysis. Six incidences of Stevens-Johnson syndrome were reported in pooled data from lamotrigine clinical trials involving >1200 pediatric patients. One additional patient with erythema multiforme was not included, because hospitalization did not occur. Most patients either were receiving concomitant valproic acid or lamotrigine that had been titrated rapidly.<sup>52</sup> Therefore, it is recommended that lamotrigine therapy be discontinued immediately after a rash is recognized<sup>83</sup>; exceptions may include instances where the rash is considered to be nondescript or limited and those that occur after 3 months of lamotrigine treatment.<sup>2</sup> Risk factors for the development of a potentially serious lamotrigine-associated rash include young age, rapid titration, and administration with valproate. Other common adverse events that have been observed with lamotrigine therapy include dizziness, diplopia, headache, ataxia, blurred vision, nausea, somnolence, and vomiting.<sup>56</sup> Most adverse effects are transient or dose-related. Lamotrigine has been well tolerated in the pediatric population and may actually have a beneficial effect on the well being of children with epilepsy.

### Tiagabine

Tiagabine is a nipecotic acid derivative that selectively inhibits the reuptake of GABA into the neurons and glia.<sup>84</sup> It was approved for use in the United States in September 1997 for the adjunctive treatment of partial seizures. Dosing in children is titrated upward beginning at approximately 0.1 mg/kg/d. As adjunctive therapy in adult patients, higher doses (32 to 56 mg/d) tend to be more effective than lower doses.<sup>85</sup>

### Clinical Evidence

Results have been encouraging in adult trials that examined the efficacy of add-on therapy<sup>86,87</sup> and monotherapy<sup>88</sup> with tiagabine in patients with partial seizures. Decreases in the frequency of both partial

and secondarily generalized seizures were noted, and tiagabine was well tolerated. These efficacy and safety data continued to be true with long-term drug therapy.<sup>89</sup> Cognitive and quality of life studies reveal neither detrimental nor positive influences of tiagabine.<sup>90,91</sup>

At present, there are limited data on tiagabine for pediatric patients. Preliminary results of tiagabine as add-on therapy or monotherapy in children with partial seizures are promising.<sup>92</sup> The children, who first participated in a single-dose pharmacokinetic analysis, then participated in an open-label, long-term pilot study.<sup>92</sup> Tiagabine 0.1 mg/kg/d was administered for the first 2 weeks of the study. Doses then were increased by 0.1 mg/kg/d every 2 weeks until an optimal effect was achieved. Of the 21 patients who continued therapy for at least 6 months, 90% achieved a >50% decrease in seizure frequency. Patients in whom monotherapy was possible ( $N = 16$ ) remained seizure-free for at least 2 months. The average monotherapy dose administered was 0.31 mg/kg/d.

A second open-label study examined the safety and preliminary efficacy of tiagabine in children aged 2 to 15 years who had treatment-refractory partial or generalized epilepsy.<sup>93</sup> After a 3-week placebo period, tiagabine 0.25 mg/kg/d was administered and titrated to 1.5 mg/kg/d. Of the 47 patients who received tiagabine, 20 completed the study; 17 of these 20 entered a long-term extension study. At the time of this initial report, a moderate reduction in seizure frequency was noted in patients with partial seizures; however, this improvement was not statistically significant. Because of its mechanism of action, tiagabine might be expected to be a successful treatment for infantile spasms. Unfortunately, no clinical studies are available at present to support this expectation.

### Toxicity Profile

The most common adverse events experienced by adults and children were somnolence, dizziness, and headache.<sup>86,89</sup> In one pediatric study, tiagabine was well tolerated; no patients withdrew because of adverse events.<sup>92</sup> Somnolence was the most frequently reported effect after a single dose of tiagabine in children.<sup>94</sup> In one study, 3 of 47 children discontinued therapy because of adverse events (eg, ataxia, somnolence, and depression).<sup>93</sup> Two children in this study were hospitalized because of serious adverse effects, but both recovered and remained on therapy. Nonconvulsive status epilepticus, or twilight state, which resolved on dose reduction, was reported in adults taking higher doses (48 to 60 mg/d) of tiagabine, but at a rate that was almost the same as placebo.<sup>95,96</sup>

### Topiramate

Topiramate is a sulfamate-substituted monosaccharide. Its mechanism appears to involve three distinct actions: 1) blockade of voltage-dependent sodium channels, 2) potentiation of GABA-mediated effects, and 3) antagonism of glutamate, an excitatory amino acid, receptors. The drug currently is indi-

cated as adjunctive treatment for partial seizures in adults. Its role in children is still being defined, but available data support its potential role in multiple childhood epilepsy syndromes. In add-on therapy and monotherapy trials in children, initial doses of 1 mg/kg/d were used, with target maintenance doses ranging from 3 to 6 mg/kg/d.<sup>97</sup>

### Clinical Evidence

Topiramate has been studied extensively in the United States and abroad to identify its role in the management of partial seizures as both monotherapy<sup>98,99</sup> and add-on therapy in adults<sup>98,100-105</sup>; the results have been favorable. Data available from studies in childhood epilepsies suggest it is useful in patients with Lennox-Gastaut syndrome, infantile spasms, and refractory partial seizures.<sup>97,106-109</sup>

Add-on therapy with topiramate was evaluated in an open-label, multicenter study of 18 patients aged 4 to 30 years with Lennox-Gastaut syndrome.<sup>107</sup> After a 2-week baseline phase, topiramate was initiated at 1 mg/kg/d and titrated to 3, 6, and 9 mg/kg/d at weekly intervals as tolerated. Topiramate therapy produced a reduction of 50% or greater in seizure frequency in 6 of 8 patients (75%) who were able to continue therapy; a positive effect on attention and interaction was noted in all patients. The most frequent cause of topiramate discontinuation in these children was central nervous system (CNS) adverse effects, followed by a lack of efficacy.

These beneficial results prompted researchers to begin a double-blind, placebo-controlled, multicenter trial of topiramate adjunctive therapy for the Lennox-Gastaut syndrome.<sup>108</sup> Ninety-eight patients aged 2 to 42 years were randomized to receive placebo or topiramate in addition to their current AED regimen after a 28-day baseline period.

Topiramate was initiated at 1 mg/kg/d and titrated to 6 mg/kg/d over 21 days. The median percent reduction in drop attacks was significantly better for the topiramate group when compared with the placebo group ( $P = .04$ ). The global evaluation scores, as measured by parents/guardians, also were significantly better for the topiramate group ( $P = .04$ ). The CNS adverse effects were the most common, but no patients discontinued therapy because of adverse events.

Results also are available from a double-blind, placebo-controlled trial of topiramate adjunctive therapy in 86 pediatric patients aged 2 to 16 years with refractory partial seizures.<sup>106</sup> Topiramate therapy was initiated at 50 mg/d for all patients and titrated over 8 weeks to 175 to 400 mg/d, depending on weight. Overall, patients in the topiramate group experienced a greater median decrease in seizure frequency when compared with patients receiving placebo (33% vs 11%;  $P = .034$ ). Thirty-nine percent of patients who received topiramate had a 50% or greater reduction in seizure frequency compared with 20% in the placebo group ( $P = .08$ ); global improvement scores also were favorable. No patients stopped topiramate therapy because of adverse effects; CNS effects were the most common.

An open-label, monotherapy substitution study is

ongoing in children aged 8 to 10 years who have partial seizures that are well controlled on traditional AEDs but who are experiencing intolerable adverse effects that warrant a change in therapy.<sup>97</sup> Five children are enrolled; 2 have been successfully titrated to monotherapy with topiramate 3 mg/kg/d and remain seizure-free.

### Toxicity Profile

In adults, the primary adverse effects of topiramate in clinical trials were somnolence, dizziness, fatigue, abnormal thinking, headache, diplopia, ataxia, speech difficulties, psychomotor slowing, nystagmus, paresthesia, impaired concentration, and confusion.<sup>99,101,105-105</sup> These same problems have been noted in children receiving topiramate. Weight loss and nephrolithiasis, which is caused by the ability of topiramate to inhibit carbonic anhydrase, also have occurred in adult patients.

Behavioral adverse effects were most problematic in children, along with anorexia and sleep disorders.<sup>97</sup> Clinical experience suggests that slow titration helps decrease adverse effects; nevertheless, reported speech or language processing difficulty should prompt clinicians who care for children to suspect topiramate-related cognitive interference.

### INVESTIGATIONAL AGENT

#### Vigabatrin

Although vigabatrin is not currently available in the United States, its proven efficacy in a wide variety of pediatric epilepsy syndromes, particularly infantile spasms, warrants its mention. Vigabatrin is a specific, irreversible, GABA-aminotransferase inhibitor. This enzyme is responsible for the metabolism of GABA in the CNS.<sup>110</sup> Controlled trials in adults have shown that vigabatrin is well tolerated and effective as add-on therapy<sup>111-113</sup> and as monotherapy compared with carbamazepine<sup>114-115</sup> in adult patients with partial seizures. In children, it has proved safe and efficacious in a wide variety of seizure disorders, including partial seizures, generalized seizures, and in some patients with Lennox-Gastaut syndrome; however, it may exacerbate myoclonic seizures.<sup>116-119</sup> Particular attention has been paid to the beneficial effects of vigabatrin in children with infantile

spasms, or West's syndrome, especially those spasms caused by tuberous sclerosis.<sup>120-122</sup> Pediatric doses commonly used in clinical trials ranged from 50 mg/kg/d to 150 mg/kg/d. Adverse effects related to vigabatrin use generally are CNS effects; they include hyperactivity (the most common reason for medication discontinuation in one study), weight gain, facial edema, drowsiness, insomnia, ataxia, somnolence, and stupor.<sup>117,118</sup> Recently recognized visual field constriction has been identified in children and will limit its use.<sup>123</sup>

### FUTURE NEEDS IN PEDIATRIC EPILEPSY

Because of the vast clinical experience that has been gained with the use of conventional AEDs, these agents remain first-line therapy in the management of seizure disorders. The newer AEDs, however, broaden the therapeutic options in treating patients with refractory epilepsy and those who cannot tolerate conventional therapy. To advance the management of childhood epilepsy syndromes to an acceptable level, further research must be performed to more appropriately outline the use of these drugs and other agents in the pediatric population. Guidelines for such research already have been made available by the National Institutes of Health Consensus Panel<sup>9</sup> and the Committee on Drugs of the American Academy of Pediatrics.<sup>124</sup> In addition, the agents currently available for adult use must be better formulated to allow for their easier administration and titration in children. New agents are of suboptimal clinical value if their appropriate administration is hindered by lack of a useful dosage form. Most importantly, all patients who experience seizures must undergo a thorough evaluation and classification to determine the most appropriate course of action to manage their disorder effectively.

The treatment of epilepsy in children has come a long way in the past few years, and much of this improvement can be attributed to the development of new AEDs. A summary of the practice parameters for using these new AEDs in pediatric practice is provided in Table 5.<sup>2,13,14,18,35-45,47-49,51,56,83,86,89,92,94,95,97,99,101,103-105,125</sup> The launching of further studies to outline pharmacokinetic properties and to validate the usefulness of these agents in children is the logical next step.

TABLE 5. Guidelines for the Use of New Antiepileptic Drugs

Drug	FDA-Approved Indications(s)	Pediatric Dose	Adverse Effects
Felbamate	Treatment of partial seizures with or without secondary generalization in adults; adjunctive treatment of partial and generalized seizures in children with Lennox-Gastaut syndrome	15-→75 mg/kg/d	Anorexia, <i>aplastic anemia</i> ,* gait abnormalities, <i>hepatotoxicity</i> ,* insomnia, nausea, somnolence, vomiting, weight loss
Gabapentin	Adjunctive treatment of partial and secondarily generalized seizures in adults	30-→90 mg/kg/d	Ataxia, behavioral changes, dizziness, fatigue, nystagmus, somnolence, weight gain
Lamotrigine	Adjunctive treatment of partial seizures in adults; adjunctive treatment of generalized seizures in children with Lennox-Gastaut syndrome	1-→15 mg/kg/d	Ataxia, diplopia, dizziness, headache, nausea, <i>rash (potentially Stevens-Johnson syndrome)</i> ,* somnolence, vomiting
Tiagabine	Adjunctive treatment of partial seizures	32-56 mg/d	Dizziness, headache, somnolence, twilight state
Topiramate	Adjunctive treatment of partial seizures in adults	3-→10 mg/kg/d	Abnormal thinking, ataxia, confusion, diplopia, dizziness, fatigue, headache, impaired concentration, nystagmus, paresthesia, psychomotor slowing, somnolence, speech difficulties

\* Black box warning.

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## BRAIN STRUCTURE AND NEUROCOGNITIVE AND BEHAVIORAL FUNCTION IN ADOLESCENTS WHO WERE BORN VERY PRETERM

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**ABSTRACT.** *Background.* Infants born very preterm (<33 weeks) are at increased risk of neurocognitive deficits. Their neurodevelopmental outcome up to age 8 years can be predicted by neonatal ultrasonography, but little is known of their later function. We investigated the effect of very preterm birth on brain structure and neurocognitive and behavioral functioning in adolescence.

*Methods.* A cohort of 105 infants born before 33 weeks of gestation in 1979–1980 had ultrasonographic scans at University College Hospital, London, and were prospectively examined at 2, 4, and 8 years. At age 14 to 15 years, 72 of those who remained in UK (cases) and 21 age-matched full-term controls underwent brain magnetic resonance imaging (MRI), as well as neurological, cognitive, and behavioral assessment. MRI images were assessed by 2 neuroradiologists unaware of ultrasonographic findings or case or control status.

*Findings.* Of the 72 cases, 40 had unequivocally abnormal MRI and 15 had equivocal scans. Of the 21 controls, 1 had abnormal and 5 equivocal MRI. Abnormalities of ventricles, corpus callosum, and white matter were especially common in cases. More brain lesions were identified by MRI than by neonatal ultrasonography. The cases had significantly more reading, adjustment, and neurological impairments than controls, but their behavior was significantly related to MRI abnormality.

*Interpretation.* Individuals born very preterm show an excess of neurocognitive and behavioral problems in adolescence, and more than half have abnormal MRI brain scans.