



# New Drugs for Pediatric Epilepsy

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The last 2 decades have witnessed an unprecedented period of new antiepileptic drug (AED) development. Newer-generation AEDs have been developed with the intention of improving the ease of use, decreasing drug interactions, decreasing adverse side effects, and identifying drugs with unique mechanisms of action, some of which may bear relevance to potential neuroprotective activity. Drug trials have also been refined in some cases to evaluate AED efficacy in children and against distinct epilepsy syndromes. This progress provides many new treatment options for the child neurologist facing children with epilepsy but also introduces the burden of determining appropriate AED choices. Here we highlight 6 new antiepileptic medications recently approved or pending approval for use in the United States: lacosamide, rufinamide, vigabatrin, retigabine, brivaracetam, and clobazam. For each of these medications, we present information regarding the history of drug development, proposed mechanism(s) of action, pharmacokinetics and recommended dosing, evidence for clinical efficacy, tolerability, and when, available, any unique features that are relevant for the pediatric population.

Semin Pediatr Neurol 17:214-223 © 2010 Published by Elsevier Inc.

Epilepsy is a common pediatric neurologic disorder that affects approximately 0.5% to 1% of all children.<sup>1-3</sup> Although nearly 60% of epilepsy syndromes in children remit,<sup>4,5</sup> large population-based studies suggest that 8% to 28% of children with at least 2 seizures develop seizures refractory to medical management.<sup>6,7</sup> For these children, dietary treatments and surgical intervention including vagus nerve stimulation<sup>8</sup> or epilepsy surgery<sup>9</sup> may be an option; however, for the majority of patients, hope for seizure control lies in new drug development.

Thirty-one anticonvulsants are approved for use in Europe or the United States; 11 of these medications were approved by the Food and Drug Administration (FDA) only within the last 20 years, marking an unprecedented period of antiepileptic drug (AED) development. Despite the availability of new options, the failure rate of the first AED used in children with newly diagnosed epilepsy remains as high as 20% to 40%.<sup>10</sup> These failures have been attributed to both a high incidence of adverse effects and/or a lack of drug efficacy. Newer AED development has focused on improving the ease of use, diminishing drug interactions, decreasing adverse side effects, and identifying drugs with unique mechanisms of action, some of which have been implicated in neuroprotective actions.<sup>11</sup>

The luxury of current options requires the child neurologist to consider AED options carefully based on each of these aspects and thereby choose the appropriate treatment. In this review, we highlight 6 new antiepileptic medications, including 3 that have been recently approved by the US Food and Drug Administration (lacosamide, rufinamide, and vigabatrin), and 3 are expected to be approved in the near future (retigabine, brivaracetam, and clobazam). Some of these medications have been available outside of the United States and have been used by child neurologists for select pediatric populations for decades. Others are recently developed, and only limited clinical information is currently available. For each of these medications, we present information regarding the history of drug development, proposed mechanism(s) of action, pharmacokinetics and dosing (Table 1), evidence for clinical efficacy, tolerability, and, when available, any unique attributes that may be relevant to pediatric populations.

## Lacosamide

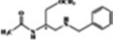
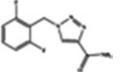
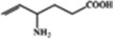
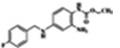
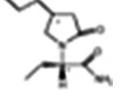
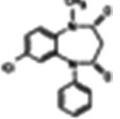
### History

After N-acetyl-D-L-alanine benzylamide was noted to be effective in animal models of epilepsy in 1982, subsequent evaluation of over 100 compound derivatives led to the discovery of lacosamide.<sup>12</sup> The European Commission approved the use of lacosamide in August 2008, and the FDA followed suit in the United States in October 2008 with an indication for the adjunctive treatment of partial-onset seizures.

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Table 1 New AEDs: Pharmacokinetic Properties and Dosing Recommendations<sup>99-105</sup>

	<b>Absorption</b>	<b>Protein Binding</b>	<b>PK</b>	<b>Peak Plasma Concentration</b>	<b>Plasma Half-Life</b>	<b>Metabolism</b>	<b>Clearance</b>	<b>Significant Drug Interactions</b>	<b>Recommended Dosing by Age: Initial (max)</b>
Lacosamide 	~100	<19	Linear	1-2 h	~13 h	Limited metabolism by CYP2C19	Renal (40% unchanged)	None	Not yet evaluated in young children > 16 y: 50 mg BID (400 mg/d)
Rufinamide 	>85*	~34	Nonlinear†	4-6 h	6-10 h	Hydrolysis	Renal (<2% unchanged)	Decreased by CYP inducers (ie, PB, PRM, PHT, CBZ). Increases PHT. May decrease OCP. Increased by VPA, especially in children.	>4 y: 10 mg/kg/d div BID (45 mg/kg/d) Adults: 400-800 mg/d div BID (3,200 mg)
Vigabatrin 	60-70	Nil	Linear	2 h	5-8 h‡	None	Renal (100% unchanged)	Decreases PHT	IS: <2 y: 50 mg/kg/d (150 mg/kg/d) CPS: 10-15 kg: 0.5-1 g/d, 16-30 kg: 1-1.5 g/d, 31-50 kg: 1.5-3 g/d, >50 kg 2-3 g/d Adults: 500 mg BID (3 g/d)
Retigabine 	60	<80	Linear	1-2 h§	8-10 h	Hydrolysis, acetylation, and glucuronidation	Renal	Decreased by CYP inducers. Increased by and increases LTG.	NA (Doses ranging from 600-1,200 mg/d have been investigated in adults)
Brivaracetam 	~100	<20	Linear	1-2 h	7-8 h	Hydrolysis and CYP-mediated hydroxylation	Renal (<5% unchanged)	Decreased by CYP inducers. Increases CBZ.	NA (doses ranging from 5-150 mg/d have been investigated in adults)
Clobazam 	87	82-90	Linear	1-2.5 h§	33-35 h	CYP2C19	Renal (<10% unchanged)	Decreased by CBZ. May effectively decrease VPA.	<2 y: 0.5-1 mg/kg/d (2 mg/kg/d) 2-16 y: 5 mg/d (40 mg/d) Adults: 5-15 mg/d (80 mg/d)

PK, pharmacokinetics; CYP, cytochrome p450; PB, phenobarbital; PRM, primidone; PHT, phenytoin; CBZ, carbamazepine; VGB, vigabatrin; VPA, valproic acid; LTG, lamotrigine; OCP, oral contraceptive; IS, infantile spasms; CPS, complex partial seizures.

\*Facilitated by food; †lesser increase in plasma concentration with increasing dose; ‡the effective half-life is the resynthesis rate of GABA-transaminase; §slowed by food; ||may be longer in infants and shorter in young children.

## Proposed Mechanism of Action

Lacosamide is a functionalized amino acid molecule thought to exert 2 novel mechanisms of action, including enhancement of slow inactivation of voltage-gated sodium channels (VGSCs) and a functional interaction with the collapsin-response mediator protein 2 (CRMP-2), but this latter putative action has yet to be validated. VGSCs are composed of multiple alpha subunits that surround a central pore spanning the extracellular membrane. Depolarization induces a conformational change that occurs within milliseconds and subsequently leads to the obstruction of the pore blocking further sodium ion flow on the intracellular side (so-called "fast-inactivation"). With prolonged depolarization, conformational changes occur within the membrane-bound portion of the channel causing a similar deactivation but with a slower time course (so-called "slow-inactivation"). Lacosamide has been shown to selectively enhance the entry of VGSCs to the slow inactive state, thereby increasing the fraction of channels unavailable for depolarization.<sup>13-15</sup> To reopen the channel from either deactivated states, the membrane potential must be hyperpolarized; this is a recovery process that occurs quickly for the fast inactivation process and more slowly (up to seconds) for the slow inactivation process.<sup>16</sup> Unique from other anticonvulsant medications known to act on VGSCs (eg, carbamazepine, lamotrigine, phenytoin, oxcarbazepine, topiramate, and felbamate), lacosamide does not affect fast inactivation of VGSCs.<sup>14</sup>

CRMP-2 is part of a signal transduction cascade of neurotrophic factors involved in neuronal differentiation, morphogenesis, polarization, and axonal outgrowth. CRMP-2 has been shown to be induced *in vitro* by neurotrophic factors, such as brain-derived neurotrophic factor and neurotrophin-3.<sup>15</sup> The effect of lacosamide on CRMP-2 has been postulated to be responsible for neuroprotective effects against apoptosis and glutamate-induced excitotoxicity noted in animal models,<sup>15</sup> but whether this interaction in fact occurs remains unknown.

## Clinical Evidence

Three large (each with over 400 patients enrolled) multicenter randomized, placebo-controlled trials have been performed in adult patients, one of which included patients 16 years or older. Each of these studies had similar design, with the goal of evaluating safety and efficacy of lacosamide when administered concomitantly with 1 to 3 AEDs in patients with refractory partial epilepsy. At doses over 400 mg/d, 38% to 41% of patients had a >50% reduction in seizures, which was significant compared with placebo.<sup>17-20</sup> A separate study noted similar efficacy at 6 months.<sup>21</sup>

Although preclinical animal studies suggested broad-spectrum efficacy, lacosamide has only been studied clinically in patients with partial-onset epilepsy.<sup>22</sup> Interestingly, and consistent with the drug's known mechanism on sodium channels undergoing prolonged depolarization, limited case reports suggest that lacosamide may have efficacy in some cases of refractory convulsive and nonconvulsive status epilepticus.<sup>23,24</sup>

## Tolerability

The most common adverse effects noted in the clinical trials were dose-related central nervous system (CNS) side effects common to many AEDs. Specifically, dizziness, headache, nausea, and diplopia were reported in greater than 10% of patients receiving 400 mg/d.<sup>25</sup> The efficacy rates of 400 mg/d and 600 mg/d dosing regimens were noted to be similar, but there was less tolerability at higher doses, resulting in the recommended maximum daily dose of 400 mg for adults.<sup>17,20</sup> Notably, significant weight loss has been reported in a small percentage of patients.<sup>21</sup>

## Pediatric Issues

Unfortunately, lacosamide has not been studied specifically in children younger than 16 years of age. Of particular concern for pediatric patients is the possible impact of lacosamide on normal brain development if used in very young children, given the known interaction with CRMP-2, which is highly expressed during early development in the CNS.<sup>15</sup>

## Rufinamide

### History

Rufinamide was granted orphan drug status in October 2004 by the FDA and was targeted for use in patients with Lennox-Gastaut syndrome (LGS), a highly refractory childhood epilepsy syndrome classically characterized by mixed generalized seizure types, a characteristic slow spike-and-wave pattern on electroencephalography, and mental retardation.<sup>26</sup> Rufinamide was approved in Europe in 2007 for use as adjunctive therapy in children and adults with LGS and approved by the US FDA in November 2008 as adjunctive treatment of seizures associated with LGS in children 4 years and older and adults. Remarkably, rufinamide is the first new AED available in the United States with an approved pediatric indication before an adult indication.<sup>27</sup>

## Proposed Mechanism of Action

Rufinamide is a novel triazole derivative, structurally unrelated to existing AEDs.<sup>28</sup> The antiepileptic mechanisms of rufinamide are still under investigation. *In vitro* preclinical animal studies suggest that rufinamide reduces the recovery of sodium channels from an inactivated state, thereby decreasing the frequency of sustained repetitive firing in neurons.<sup>27</sup> Oral rufinamide has shown anticonvulsant activity in generalized and partial epilepsy mice models.<sup>28,29</sup>

## Clinical Evidence

Several large, well-designed placebo controlled studies have been performed in patients of varying age evaluating rufinamide's efficacy for partial-onset seizures and generalized seizures associated with LGS. Two double-blind, randomized, placebo-controlled studies evaluated the efficacy of rufinamide as an add-on treatment in adolescent and adult patients with refractory partial epilepsy. The first trial, performed in 313 patients greater than 15 years of age, found

that 28.2% of patients taking rufinamide at 3,200 mg/d had at least 50% reduction in seizures compared with 18.6% on placebo ( $P = 0.04$ ).<sup>30</sup> The second study, performed in 647 patients at least 16 years of age, evaluated dose-dependent efficacy at 200 mg/d, 400 mg/d, 800 mg/d, and 1,600 mg/d doses. This study found a significant linear trend in dose response for reduced seizure frequency in favor of rufinamide ( $P = .003$ ).<sup>31</sup>

Rufinamide has been evaluated for use in children. One small open-label retrospective observational study was performed in 60 patients aged 1 to 60 years with mixed refractory epilepsy syndromes, LGS, generalized epilepsy, or partial epilepsy.<sup>32</sup> Various doses were used, and the authors compared a 12-week observation period with a 4-week baseline period. Among all patients, 46.7% had at least a 50% reduction in seizures, and 8.3% were seizure free. At 18 months, 26.7% exhibited continued improved seizure control.<sup>32</sup> The highest responder rate (35.5%) was noted among the patients with LGS.

A second, larger, international, multicenter, double-blind, placebo-controlled, randomized trial evaluated rufinamide in 138 patients aged 4 to 30 years (median age 12 years) with refractory LGS treated with 1 to 3 medications.<sup>33</sup> Patients were randomized to receive rufinamide versus placebo as adjunctive therapy for 12 weeks to a goal of  $\sim 45$  mg/kg/d. Among patients receiving rufinamide, 31.1% experienced at least a 50% reduction in seizures compared with 10.9% of those receiving placebo ( $P = .0045$ ).

## Tolerability

A pooled analysis of 7 clinical trials among 391 total children aged 3 to 16 years revealed the most common adverse effects to be somnolence, vomiting, and headache.<sup>34</sup> In our experience, we have found that many of these side effects can be mitigated by slowing the titration of the drug with dose increases spaced every 5 to 7 days. Importantly, cognitive assessments have been formally evaluated in 189 adults and adolescent patients (aged 15-64 years) taking rufinamide for refractory partial seizures. The cognitive tests were designed to test attentional abilities, central information processing, psychomotor speed, and working memory. In this study, no difference in pre- or posttreatment performance at doses of 200 mg/d, 400 mg/d, 800 mg/d, or 1,600 mg/d were evident.<sup>35</sup>

## Pediatric Issues

Notably, rash can occur in children taking rufinamide.<sup>36</sup> Five possible cases of AED hypersensitivity syndrome have been reported with rufinamide, all in children less than 12 years of age. Each case occurred in the first 4 weeks of treatment, and all patients recovered quickly after drug discontinuation.<sup>34</sup> Dosing considerations should also be considered for children less than 30 kg because they may have larger pharmacokinetic interindividual variability, particularly with treatment with valproate, requiring a lower maximal daily dose.<sup>37</sup>

# Vigabatrin

## History

Vigabatrin was first marketed in 1989 at which time it was approved for use in the United Kingdom. The FDA approved vigabatrin for use as adjunctive treatment for adults with refractory complex partial seizures and for infantile spasms in January 2009. Infantile spasms is a severe infantile epilepsy syndrome characterized by difficult-to-treat seizures, a characteristic and markedly abnormal electroencephalographic pattern termed hypsarrhythmia, and a high risk of mental retardation. Although many different treatments have been used historically, vigabatrin is currently the only FDA-approved medication for the treatment of infantile spasms.

## Proposed Mechanism of Action

Vigabatrin is a structural analog of gamma-aminobutyric acid (GABA), which is the primary inhibitory neurotransmitter in the CNS. Vigabatrin irreversibly and competitively binds to GABA transaminase, rendering this enzyme inactive and thereby blocking degradation of GABA. Vigabatrin may also stimulate GABA release.<sup>38</sup> In vivo nuclear magnetic resonance measurements in humans showed that brain GABA increases by more than 40% within 2 hours after oral administration.<sup>39</sup>

## Clinical Evidence

Many limited clinical trials have been performed evaluating the clinical efficacy of vigabatrin for use in infantile spasms and partial seizures. One larger, randomized study designed to evaluate low-dose (18-36 mg/kg/d) versus high-dose (100-148 mg/kg/d) vigabatrin for the treatment of infantile spasms found an increased efficacy of high-dose vigabatrin among the 142 patients who were able to complete the trial, with 35.8% of patients in the high-dose group responding compared with 10.7% in the low-dose group ( $P < .001$ ).<sup>40</sup> This study, although limited by stringent study design, also showed that spasm cessation was greatest in patients with tuberous sclerosis complex (74%) and cryptogenic patients (72%) compared with other symptomatic etiologies (50%). A small retrospective chart review in 31 TSC patients with infantile spasms similarly found 74% responded to vigabatrin.<sup>41</sup> Most experts now agree that vigabatrin should be considered first-line therapy for patients with infantile spasms related to tuberous sclerosis complex<sup>42</sup> and possibly cortical dysplasias.<sup>41</sup>

Another large randomized double-blind trial comparing vigabatrin with hormonal treatments for infantile spasms in 107 infants found that hormonal treatment was associated with better early control at 2 weeks (73% with hormonal vs prednisolone or synthetic adrenocorticotrophic hormone (ACTH) vs 54% with vigabatrin,  $P = .043$ ) and improved developmental outcomes at 12 to 14 months in patients with cryptogenic etiologies.<sup>43,44</sup> However, follow-up of these patients revealed that the improved developmental outcome was no longer evident at 4 years.<sup>45</sup> A smaller study in 28 infants with cryptogenic infantile spasms found no difference

in response to treatment with seizure cessation or electroencephalographic normalization or relapse rate between ACTH and vigabatrin but did find improved cognitive outcome in the patients treated with ACTH within 1 month of onset of spasms.<sup>46</sup> Given these findings, many experts believe that ACTH should be considered first-line treatment for patients with infantile spasms caused by a cryptogenic etiology.

A Cochrane review evaluated 11 trials testing doses of 1,000 to 6,000 mg/d, which included 982 observations in 747 adult patients with refractory partial seizures and found a relative risk of 2.58 for at least a 50% reduction in seizure frequency compared with controls.<sup>47</sup> One of the larger trials included was a double-blind, placebo-controlled study in 182 adult patients with refractory partial epilepsy treated with 3 g/d of vigabatrin. This study found 43% of vigabatrin-treated patients versus 19% of patients receiving placebo had at least 50% seizure reduction.<sup>48</sup> Dose responses were assessed in a double-blind, placebo-controlled randomized study in 174 adult patients with refractory partial epilepsy and found a significant dose-response relationship at 1 g/d, 3 g/d, and 6 g/d compared with placebo (24%, 51%, and 54% vs 7%, respectively;  $P = .0248$ ,  $P < .001$ , and  $P < .001$ ).<sup>49</sup>

## Tolerability

Major safety concerns limit the use of vigabatrin. In particular, irreversible, bilateral concentric peripheral field constriction has been shown in 30% to 50% of treated patients.<sup>50-52</sup> However, because of difficulties and inconsistencies with formal visual field testing in young infants and children, the true incidence of visual changes associated with vigabatrin remains uncertain. Most patients with abnormalities received treatment for at least 6 months, and those treated for more than 2 years have been reported to have stable visual fields.<sup>53</sup> Bilateral nasal defects may be the first clinical indication of retinal toxicity; central visual acuity appears to be consistently spared.<sup>38</sup> Although typically asymptomatic, the concentric peripheral visual loss may involve ~20 to 40 axial degrees for each eye and may have implications for driving in cognitively normal patients. Because of these risks, patients receiving vigabatrin treatment are required to receive baseline perimetry testing. Adults are to be tested at baseline and every 6 months thereafter. Infants are to be tested at baseline and every 3 months for the first 18 months and then every 6 months thereafter on treatment. This may be a significant access issue for many patients, and the treating neurologist may reserve the right to waive these requirements.

More recently, new T2 and diffusion weighted imaging (DWI) signal abnormalities on brain magnetic resonance imaging have been noted exclusively in some infants treated with vigabatrin. Two small retrospective studies identified new basal ganglia, thalamic, brainstem, and dentate nucleus DWI or T2 hyperintense lesions in 33% to 35% of infant patients treated with vigabatrin.<sup>54,55</sup> These findings were all asymptomatic, reversible with discontinuation of therapy, and associated with younger ages and higher doses of treatment. A larger multicenter retrospective chart review of magnetic resonance imaging from 205 infants (0-24 months)

from 668 children and adults found that 22% of infants treated with vigabatrin versus 4% of those naive to the medication had new magnetic resonance imaging signal abnormalities ( $P < .001$ ). These changes were not present in older children or adults.<sup>56</sup>

More typical symptomatic side effects associated with vigabatrin consist primarily of mild-to-moderate fatigue and drowsiness.<sup>47</sup> Mild adverse effects were reported in 13% of children, including symptoms of trembling, excessive sleepiness, swallowing and motor problems, and irritability.<sup>41</sup>

## Pediatric Issues

The efficacy for infantile spasms can typically be ascertained within 2 to 12 weeks of treatment, well before visual field changes are thought to occur. Given the great potential for significant benefit from rapid, aggressive treatment, many insist on initiating treatment in patients with active infantile spasms swiftly and subsequently choose whether to discontinue treatment once responsiveness has been ascertained.<sup>38</sup> When considered for use against partial seizures, careful baseline evaluation and repeat assessments of visual fields are typically warranted.

## Retigabine

### History

Retigabine is a novel investigational AED being developed in the United States as an adjunctive treatment for partial epilepsy. Two-phase III clinical trials have been completed with the final reports expected in late 2010.

### Proposed Mechanism of Action

Retigabine potently and selectively opens voltage-gated KCNQ2/3 and KCNQ3/5 potassium channels, likely by stabilizing the open conformation and thus leading to cellular membrane hyperpolarization.<sup>57-59</sup> This drug, however, also exhibits nonspecific activity at very high concentrations, blocking voltage-gated sodium and calcium conductances and augmenting synthesis of GABA.<sup>59</sup> Preclinical studies in animal models show broad-spectrum anticonvulsant activity as well as limited neuroprotective effects.<sup>36,59</sup>

### Clinical Evidence

The efficacy of retigabine versus placebo as an add-on treatment was evaluated in a single large phase II, multicenter, randomized double-blind placebo-controlled trial in 537 patients aged 16 to 70 years with inadequately controlled partial-onset seizures (already being treated with at least 1 AED). In this study, patients were randomly assigned to placebo or titrated to daily doses of 600, 900, or 1200 mg/d over 2 to 6 weeks. At 900 and 1200 mg/d, significantly more patients had at least a 50% reduction in seizures compared with placebo (32% and 33% vs 16%,  $P = .021$  and  $P = .016$ ).<sup>60</sup>

Two-phase III placebo-controlled trials evaluated the efficacy of retigabine at 1,200 mg/d against placebo (Restore 1 trial) and 600 and 900 mg a day against placebo (Restore 2 trial). A total of 841 patients aged 18 to 75 years old with

refractory partial seizures participated in these studies. Early reports showed a dose-dependent response; at 1,200/d, the responder rate was 45.0% versus 18% for placebo ( $P < .001$ ).<sup>61</sup> At 600 and 900 mg/d, 31.5% and 39.3% of patients reportedly had at least a 50% reduction in seizures compared with 17.3% of patients receiving placebo ( $P < .01$  and  $P < .001$ ).<sup>61</sup>

## Tolerability

In the aforementioned trials, the most common adverse effects (seen in  $>5\%$  of patients and significantly increased relative to placebo) included somnolence, fatigue, confusion, and dizziness. These adverse effects were largely dose dependent and did result in discontinuation in some patients.<sup>60,61</sup>

## Pediatric Issues

Interestingly, loss-of-function mutations involving *KCNQ2/3* genes have been identified in autosomal dominant neonatal epilepsy, validating the impact of these channels on the regulation of normal neuronal excitability.<sup>62</sup> In this autosomal dominant genetic epilepsy syndrome, patients typically develop focal tonic-clonic or generalized seizures on day of life 3, which spontaneously remit by 1 month. Patients with this condition develop normally, and seizure control is readily achieved with traditional AEDs. However, 10% to 15% of patients may subsequently develop epilepsy, and therapy-resistant epileptic encephalopathy may rarely be seen.<sup>63</sup> The role of retigabine in the treatment of patients with known *KCNQ2/3* mutations remains uncertain.

## Brivaracetam

### History

Brivaracetam is largely regarded as a success story in rational drug development.<sup>64</sup> Chance observation led to the discovery that the (*S*)-isomer of levetiracetam offered protection in several animal models of epilepsy. Subsequent studies identified a novel binding target for levetiracetam, the neuron-specific synaptic vesicle protein 2 A (SV2A). This protein is believed to participate in presynaptic vesicle fusion and exocytosis mechanisms although its precise role remains uncertain.<sup>65</sup> Additional structure-activity studies revealed that a substitution in the fourth position of the pyrrolidine ring of levetiracetam results in increased binding affinity with SV2A. This finding ultimately led to the development of the 4-*n*-propyl analog, brivaracetam, which exhibits a 13-fold higher binding affinity than levetiracetam to SV2A.<sup>64</sup> In 2005, brivaracetam gained orphan status as an agent to treat progressive and symptomatic myoclonic seizures in Europe as well as in the United States because of initial promising results for the treatment of photosensitive epilepsy.<sup>66</sup>

### Proposed Mechanism of Action

As with levetiracetam, it is unclear what the specific binding of brivaracetam to SV2A actually leads to, but SV2A appears to be essential for coordination of exocytosis of presynaptic vesicles into the synaptic cleft.<sup>36,61</sup> Brivaracetam has also been

found to inhibit VGSCs.<sup>61</sup> In preclinical trials, brivaracetam was shown to have broad-spectrum anticonvulsant activity in a variety of animal seizure models and to be more potent than levetiracetam in protecting against secondarily generalized seizures.<sup>36,61</sup>

## Clinical Evidence

A small placebo-controlled single-dose study in adults (aged 18-60 years) showed that 17 of 18 (94%) of patients with photosensitive epilepsy responded to brivaracetam compared with 8 of 18 (44%) patients who received placebo. This study evaluated doses at 10, 20, 40, or 80 mg/d and found a dose-dependent suppression of the photoparoxysmal electroencephalographic response.<sup>66</sup>

Furthermore, 2 phase II clinical trials evaluating the efficacy of brivaracetam as add-on treatment in adults with refractory partial-onset seizures have been performed. However, the results have yet to be published. In the first study involving 208 patients (aged 16-65 years), doses of 5, 20, or 50 mg/d were administered for 7 weeks. The responder rates at these doses were reported to be 32.0%, 44.2%, and 55.8%, respectively, compared with 16.7% for placebo.<sup>67</sup> In the second study, doses of 50 and 150 mg/d were compared with placebo in 157 adult patients with refractory partial seizures, and although the responder rates were higher for both doses compared with placebo, neither reached statistical significance.<sup>68</sup>

Two large phase III randomized double-blind, placebo-controlled multicenter, multinational trials assessing the efficacy and safety of brivaracetam in adult patients with refractory partial-onset seizures over a 12-week period have recently been completed, but the results are still pending as of this writing. The first study compared doses of 5, 20, and 50 mg/d with placebo, and early reports indicated that brivaracetam significantly reduced the number of partial seizures compared with placebo.<sup>69</sup> The second study that compared 20, 50, and 100 mg/d doses with placebo failed to reach its primary efficacy endpoint.

Two further studies evaluating the use of brivaracetam as an add-on treatment in 106 patients with Unverricht-Lundborg disease have recently been completed.<sup>61</sup> Both reportedly failed to meet their respective endpoint, but nevertheless showed some promising results in a subset of patients.

## Tolerability

A pooled analysis of the phase II clinical studies revealed that brivaracetam was well tolerated, and reported adverse effects were similar to placebo at all doses examined (5-150 mg/d).<sup>70</sup> The most frequent adverse effects were nausea, vomiting, fatigue, nasopharyngitis, anorexia, convulsion, dizziness, headache, somnolence, and insomnia. Despite this, however, there were no significant differences between any of these symptoms compared with placebo.

## Pediatric Issues

To date, no clinical trials evaluating brivaracetam in children younger than 16 years of age have been performed. The re-

ported low side effect profile and potent broad-spectrum efficacy of brivaracetam against a variety of refractory seizure types make it an appealing option for use in pediatric populations.

## Clobazam

### History

Clobazam was originally synthesized in the 1960s for the treatment of anxiety. It is currently approved for use as an AED in more than 100 countries. Clobazam is a 1,5-benzodiazepine that was initially developed to reduce side effects associated with the traditional 1,4-benzodiazepines. In December 2008, the FDA granted orphan drug status to clobazam for the adjunctive treatment of LGS. Clobazam is not yet approved for use in the United States, but FDA approval is anticipated by the end of 2010.<sup>71</sup>

### Proposed Mechanism of Action

Although traditional benzodiazepines possess a 1,4-structure, clobazam is the only clinically used 1,5-benzodiazepine (ie, nitrogen atoms occupying the 1 and 5 positions and a keto group is in the 4 position). Anticonvulsant effects are attributed to the enhancement of GABAergic neurotransmission via 3 specific mechanisms: allosteric activation of the GABA<sub>A</sub> receptor and upregulation of the GABA transporters 1 and 3 (GAT1 and GAT3). Clobazam has also been shown to have decreased affinity to the GABA<sub>A</sub> subunits that mediate the sedative properties of traditional 1,4-benzodiazepines, which may explain in part the relative paucity of such side effects seen with this unconventional compound.<sup>72</sup>

### Clinical Evidence

Because clobazam has been available internationally for over 40 years, there is much clinical experience to draw from. Over 50 trials have been conducted evaluating the efficacy of clobazam as an AED. To summarize these, we review primarily the largest studies and meta-analyses.

A current 4-armed multinational placebo-controlled phase II study evaluated clobazam as add-on treatment in 238 patients with LGS at 3 doses (0.25, 0.5, and 1.0 mg/kg) in both children and adults (aged 2-60 years) has been completed, but results have not yet been published. Early reports claimed that the 2 highest doses of clobazam showed a significant reduction in drop seizures compared with placebo.<sup>71</sup>

A recent review that analyzed data from 20 studies including more than 300 patients with LGS<sup>73</sup> calculated a cumulative greater than 50% seizure reduction in greater than 50% of patients, with the highest efficacy seen against atonic seizures and bilateral myoclonus. These authors also reported a striking 10% of patients achieving seizure freedom. Among studies that included long-term follow-up, 42% of patients maintained benefit for more than 1 year.

A 2008 Cochrane Database review was performed to evaluate the cumulative evidence for clobazam as an add-on agent in refractory partial-onset or generalized epilepsy.<sup>74</sup> This review identified 4 crossover studies involving a total of

196 participants and designed with adequate double-blind methods with a minimum treatment period of 8 weeks. Although the studies differed in estimations of efficacy, these reviewers concluded that clobazam may reduce seizure frequency, particularly partial-onset seizures.

A large multicenter, double-blind trial in 235 pediatric patients (aged 2-16 years with newly diagnosed epilepsy or failure of 1 drug) evaluated the efficacy of clobazam versus carbamazepine or phenytoin as monotherapy and found that seizure control and retention rates at 1 year were equivalent for the 3 drugs.<sup>75</sup>

### Tolerability

The most common side effects reported with clobazam are similar to those seen with classic benzodiazepines, such as somnolence and lethargy, reported in 71% and 26% of patients, respectively, in 1 study.<sup>76</sup> The development of tolerance and the sedative, muscle relaxant, and behavioral effects seen with classical benzodiazepines are thought to be less prominent with clobazam,<sup>73-75</sup> and this drug is noted to have no addictive potential.<sup>73</sup>

### Pediatric Issues

Although not noted to be a significant side effect, "severe behavioral change" was reported in 1 pediatric study, resulting in drug withdrawal in 2 children.<sup>77</sup> Another larger study in children also noted increased behavioral side effects with clobazam,<sup>75</sup> suggesting that this may be a limiting factor in younger populations. Despite this concern, because of the longstanding international experience in over 3000 patients (including many children), clobazam is arguably one of the safest AEDs for use in the pediatric population.<sup>73</sup>

## Conclusions

The overarching goal guiding all epileptologists is to achieve complete seizure freedom without adverse effects. Although this aim can be particularly challenging in pediatric patients, there is greater urgency given the evidence from animal studies indicating that earlier seizure control may improve future epilepsy outcomes.<sup>78,79</sup> It is well established that in pediatric epileptic encephalopathies, the duration of disease<sup>80-82</sup> and possibly even the degree of interictal activity<sup>83</sup> are negatively correlated with long-term cognitive outcome. For example, in tuberous sclerosis complex, epilepsy duration appears to predict a worse epilepsy prognosis.<sup>84</sup> Furthermore, the adverse cognitive effects of many AEDs may have a disproportionate impact in pediatric populations during critical periods of language development and formal education.<sup>85</sup>

Given the unique physiology of infants and children, the dynamic developmental profile of the maturing brain, and the heterogeneity of distinct pediatric epilepsy syndromes, information regarding AED efficacy in adult populations cannot be easily extrapolated to children.<sup>86</sup> To date, 28 well-characterized epilepsy syndromes have been described in children with unique electroclinical features.<sup>87</sup> Although few large, well-designed double-blind, randomized, placebo-

controlled trials have been performed to evaluate AED efficacy in children, available data indicate improved efficacy for particular drugs used to treat properly diagnosed epilepsy syndromes.<sup>88-97</sup> Furthermore, expert opinion supports the use of specific AEDs for specific epilepsy syndrome.<sup>98</sup>

Fortunately, many of the AEDs recently approved and expected to be approved in the near future have been designed with particular attention to these concerns. Rational drug design now targets novel mechanisms for seizure control and improved tolerability. As more sophisticated medications are developed, trial designs are also becoming more refined, allowing for evaluation in pediatric populations with complex, age-specific epilepsy syndromes. Each of these developments opens a new door for hope for patients, families, and providers such that our goals for seizure-freedom and drug safety may be reached, even in the most challenging pediatric epilepsy cases.

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