Epilepsy

New Antiepileptic Drugs: Lacosamide, Rufinamide, and Vigabatrin

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Opinion statement

The treatment of epilepsy is complicated by the multiple seizure types and epilepsy syndromes needing therapy. In addition, seizures in up to 30% of epilepsy patients are resistant to available medications. The three newest antiepileptic medications (lacosamide, rufinamide, and vigabatrin) all putatively have novel mechanisms of action, which might increase the chance of treatment success in patients failing previous antiepilepsy drug trials and the chance of successful synergy with currently available medications. In our experience, all three drugs generally are well tolerated, although the risk for serious long-term complications with vigabatrin presents special challenges and precautions. Lacosamide is approved for the adjunctive therapy of complex partial seizures in adults and also is available in an intravenous formulation. Rufinamide is a new treatment option for seizures associated with Lennox-Gastaut syndrome, and although it is not FDA approved for partial seizures, it has shown efficacy for that indication as well. Vigabatrin has been approved in adults for drug-resistant complex partial seizures and in infants as a treatment option for infantile spasms.

Introduction

Epilepsy

Epilepsy, or recurrent unprovoked seizures, is among the most common neurologic disorders, with a prevalence of about 1% in the general population [1]. A recently published meta-analysis of studies assessing epilepsy prevalence estimates the prevalence of persons in need of treatment for epilepsy at approximately 4.9 per 1000 in developed countries and in urban populations of developing countries [2]. The epilepsy prevalence in rural parts of developing countries is estimated to be twice that number. The prevalence of drug-resistant, or medically refractory, epilepsy is estimated to be about 30% in people with active epilepsy. The International League Against Epilepsy (ILAE) appointed a taskforce to define drug resistance, and a recent publication of this work reports that drug-resistant epilepsy may be defined as "failure of adequate trials of two tolerated and appropriately chosen and used anti-epileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom"[3••]. The seizures of these patients continue to drive the ongoing search for novel treatments for epilepsy.

Status epilepticus

Status epilepticus (SE), or the occurrence of repetitive seizures without pause, is a major neurologic emergency. The incidence of SE is estimated to be 18.3 per 100,000 person-years [4]. SE carries a high risk for permanent morbidity or mortality. Adding to our armamentarium of antiepileptic drugs (AEDs) effective in treating SE is of great importance. Often, options for treating SE are limited to AEDs available in intravenous (IV) formulations.

Treatment

Pharmacologic treatment

- Epilepsy is a serious illness, and before 1989 there were few alternatives for treatment. Development of antiepileptic medications also has been hindered by side effects inherent in many central nervous system-active medications, including fatigue and dizziness. With the acceleration of AED development, a greater push has been made to develop medicines that are both efficacious and well tolerated. The aim of ideal drug therapy treatment therefore includes efficacy (including improved treatment of our drug-resistant population); safety; tolerability; affordability; absence of chronic adverse effects, such as weight gain and effects on bone; fewer drug-drug interactions; and dosing convenience. The three most recently available AEDs in the United States are rufinamide, lacosamide, and vigabatrin. This review encompasses the most recent relevant information regarding treatment of epilepsy patients with these drugs, including details on patient selection, drug dosages, major drug-drug interactions, and major adverse effects for each drug.

Clinical trials

- Table 1 provides a summary of the main points of selected clinical trials of lacosamide, rufinamide, and vigabatrin. Included are the results of the trials of rufinamide for the adjunctive treatment of partial seizures, although this agent is not yet approved for this purpose.

When to consider using a newly approved antiepileptic drug

- In our experience, most epileptologists will use a newly approved AED when a patient has failed at least three other anticonvulsants either in monotherapy or in combination. Bearing in mind that the ILAE has defined drug-resistant epilepsy as failure of trials of two antiepileptic medications, some will initiate a trial of a newly approved drug sooner. This is especially true for situations such as Lennox-Gastaut syndrome (LGS), which is a devastating diagnosis. Rufinamide is not usually considered a first-line drug for treatment of LGS, and most pediatric neurologists will use this medicine after an adequate trial of valproic acid and levetiracetam. In the event of seizure freedom with the addition of rufinamide, most pediatric neurologists will consider weaning the other medications, especially

Table 1. Selected clinical trials of rufinamide, lacosamide, and vigabatrin

Study	Drug	Population treated	Study design	Dose/range tested	Efficacy
Martin et al., 2009 [5]	Rufinamide	Adults with partial seizures: simple, complex, and secondarily generalized	Double-blind, placebo-controlled, randomized, parallel-group, multicenter	3200 mg/d added to stable dose of 1–2 concomitant AEDs; dose escalated over the first 7-d period	Median reduction in partial seizure frequency was 20.4% vs placebo group, with mean increase of 1.6%
Glauser et al., 2008 [6]	Rufinamide	Children and adults age 4–30 y with Lennox-Gastaut syndrome	Double-blind, randomized, placebo-controlled	45 mg/kg/d divided twice daily; median dosage, 1800 mg/d; titration period, 14 d	32.7% decrease in total seizure frequency; 43.5% decrease in tonic/atonic seizures; significant decrease in absence seizures
Ben-Menachem et al., 2007 [7]	Lacosamide	Adults age 18–65 y with simple or complex partial seizures with or without secondary generalization	Multicenter, double-blind, placebo-controlled	6-wk dose titration into four arms 1:1:1:1: 200 mg, 400 mg, 600 mg, placebo. Dose increased by 100 mg/wk to goal; added to stable dose of 1–2 other concomitant AEDs	Median reduction: 26% in 200-mg/d, 39% in 400-mg/d, and 40% in 600-mg/d treatment groups, compared with 10% in placebo group.
French et al., 1996 [8]	Vigabatrin	Adults with medically refractory CPS	Double-blind, randomized, placebo-controlled adjunct trial	3 g total daily dose as add-on therapy to existing medications	43% of patients reported a ≥50% reduction in seizure occurrence
Dean et al., 1999 [9]	Vigabatrin	Adults with medically refractory CPS	Parallel group study	1 vs 3 vs 6 g total daily dose, all doses as add-on to existing medications	24% of patients taking 1 g/d had a ≥50% reduction in seizures (not statistically significant); 51% of patients taking 3 g/d and 54% taking 6 g/d had a ≥50% reduction in seizures (both significantly different from placebo, not significantly different from each other
Chiron et al., 1997 [10]	Vigabatrin	Infants with IS due to TS	Crossover trial; comparison steroid treatment arm	150 mg/kg/d	After 1 month, 100% of vigabatrin-treated patients were spasm-free, compared with 45% of steroid-treated children
Appleton et al., 1999 [11]	Vigabatrin	Infants with newly diagnosed IS from any cause	Placebo comparison group; 5-d treatment phase	50–150 mg/kg/d as first-line monotherapy	In first 5 d of treatment, 35% of vigabatrin-treated children were spasm-free, compared with 10% of placebo-treated children

AEDs antiepileptic drugs; *CPS* complex partial seizures; *IS* infantile spasms; *TS* tuberous sclerosis.

if the patient has experienced side effects. In our experience though, seizure freedom with the addition of rufinamide for LGS is uncommon. In the case of infantile spasms, most pediatric neurologists will start vigabatrin as a first-line drug, especially in children with tuberous sclerosis and spasms. Very few medications are available for treating this type of epilepsy, and tuberous sclerosis patients are exquisitely sensitive to vigabatrin. In our practice, we consider adding lacosamide adjunctively for partial-onset seizures when a patient has proven to be drug resistant with the failure of adequate trials of two or three drugs in monotherapy or in combination. We typically use combinations of drugs with different biological mechanisms and thus consider using lacosamide even when patients are already on other sodium channel-blocking agents, such as phenytoin or carbamazepine, as lacosamide offers a different mechanism of action. Pediatric neurologists are not routinely using lacosamide at this time.

Risk of suicidal behavior and ideation with the use of antiepileptic drugs

- The incidence of depression is higher in the epileptic population than in the general population. Additionally, AEDs are increasingly used to treat a variety of psychiatric diseases, such as bipolar mood disorder and depression. Recently the *Journal of the American Medical Association* reported on the risk of suicide and attempted suicide in patients using AEDs. This was a cohort study evaluating patients aged 15 years and older starting a regimen of AEDs. Patients had to have been continuously enrolled in a health plan for 6 months before study entry and were excluded if they had a preceding diagnosis of HIV, cancer, or previous suicide attempts. None of the drugs under discussion in this article was studied; however, this study essentially confirmed the previous US Food and Drug Administration (FDA) meta-analysis demonstrating increased risk of suicidal ideation or behavior with all the AEDs compared with placebo [12, 13]. Clinicians should caution patients about this increased risk and assess for symptoms of depression, including suicidal ideation, as a part of routine patient care.

Lacosamide

Lacosamide was approved for the adjunctive treatment of partial-onset seizures in October 2008.

Standard dosage   The adult dosage of lacosamide is a 200- to 400-mg total daily dose, divided twice daily. The efficacy and dosage of lacosamide in the pediatric population have not been established. Lacosamide is FDA approved for the adjunctive treatment of partial seizures with or without secondary generalization in patients ≥17 years of age. We find that a titration slower than recommended reduces the number of reports of dizziness with this drug and start our patients at a dosage of no more than 50 mg twice daily for 1 to 2 weeks, before escalating the dosage by 50-mg/wk increments until efficacy or a total daily dose of 400 mg is achieved. There is evidence for greater efficacy at a total daily dose of 600 mg, but in our experience, as was shown in

clinical trials, pushing the dose beyond this is not well tolerated, mostly because of dizziness [14]. Some of our patients have been able to tolerate a higher dose with reduction of concomitant AEDs, which is an approach that may be considered in this group.

Contraindications

According to product prescribing information published by the manufacturer, there are no contraindications except for known hypersensitivity to lacosamide [15].

Main drug interactions

No significant drug interactions are reported. One open-label study conducted with healthy subjects showed no appreciable interaction between carbamazepine and lacosamide [16, Class III].

Main side effects

The most commonly reported side effects of lacosamide are nausea, vomiting, and dizziness. Ataxia and diplopia are less commonly reported. There is, however, a potential for cardiac rhythm and conduction abnormalities. These are seen at low rates but deserve mention as they constitute a serious side effect. FDA prescribing information cautions against the use of lacosamide in patients who have known cardiac conduction problems, especially marked first-degree atrioventricular (AV) block, second-degree or higher AV block, and sick sinus syndrome without a pacemaker. Dose-dependent increases in the PR interval were observed in clinical trials. Symptoms associated with atrial fibrillation and flutter, such as shortness of breath, rapid pulse, and palpitations, have been reported in 0.5% of treated patients, especially in those with concomitant heart disease or diabetic neuropathy. Syncope was reported in short-term trials of lacosamide in 1.2% of patients with diabetic neuropathy compared with placebo, but not in otherwise healthy epileptic patients. Obtaining an electrocardiogram before and after titration of lacosamide to target doses is recommended [15].

Metabolism and use in patients with hepatic and renal disease: Lacosamide has a half-life of about 13 h and is metabolized to the inactive form *O*-desmethyl-lacosamide via demethylation. Food does not affect absorption. Protein binding is reported to be less than 15%. Of note, the plasma levels of AEDs that are cytochrome P-450 (CYP) inducers (eg, carbamazepine) and those that are CYP inhibitors (eg, valproate) are not appreciably affected by coadministration of lacosamide, nor are the levels of lacosamide altered when used in combination with these agents. Of particular interest, levels of ethinylestradiol and levonorgestrel and lacosamide were unaffected when coadministered [17]. The metabolite is excreted renally and is dialyzable. In patients with renal disease with creatinine clearance less than 30 mL/min or those with end-stage renal disease, the maximum dosage is 300 mg/d. Patients with mild to moderate liver disease also should have their dosage adjusted to 300 mg/d [15].

Special points

Lacosamide's mechanism of action is purported to be an enhancement of slow inactivation of voltage-gated sodium channels. Also described is a possible functional interaction with collapsin-response mediator protein 2 (CRMP2) [18].

Of the three drugs under current discussion, lacosamide is the only one available in an IV formulation. As mentioned earlier, effective treatment of SE nearly always requires IV preparations of medication. The use of IV lacosamide preparations in our neurologic intensive care unit is limited by cost, and currently these preparations are used in patients who have failed other approved combinations of AEDs for ongoing seizure activity. Our critical care neurologist infuses according to FDA recommendations at divided doses over a 30- to 60-minute interval, although recently published

reports show tolerability with 15-minute infusions in alert patients [19]. The mechanisms of action of the agents currently in wide use for SE (benzodiazepines, phenytoin, and barbiturates) are different from that of lacosamide. This newer agent has potential to offer a viable alternative for treating SE [20]. One case report of successful treatment of nonconvulsive SE with lacosamide was published [21, Class IV]. Potential neuroprotective properties in SE also have been reported [17]. Lacosamide is effective in the pilocarpine, cobalt-homocysteine, and electrical stimulation models of SE [17, 22]. Currently, there is no FDA indication for treating SE with lacosamide. The safety and tolerability of IV lacosamide also has been investigated [19]. Its use may be in patients who present to the hospital with seizures and potentially have missed doses of oral lacosamide, with an urgent need for replacement.

Lacosamide also has been studied as an antinociceptive agent for diabetic neuropathic pain, with two positive studies [23, 24, Class I], but it is not yet FDA approved for this indication.

Pediatric considerations	Lacosamide has not been studied as thoroughly in children. As is the case with numerous other anticonvulsants, many pediatric neurologists use lacosamide in older school-age children and teens, extrapolating from the adult data to a target dose of 200 to 400 mg. For children with a potential for generalized seizures, most pediatric neurologists avoid the use of lacosamide because, similar to other partial seizure drugs, such as carbamazepine and phenytoin, it may potentiate generalized seizures.
Cost/cost-effectiveness	*Cost estimate:* Lacosamide is listed in the current edition of the *2009 Red Book*, but no pricing information is given [25]. Based on average wholesale pricing (AWP) tables, lacosamide costs an average of $260 for 60 50-mg tablets and $400 for 60 100-mg tablets.

Cost-effectiveness: There is scant literature on the cost-effectiveness of these newer agents. One recently published paper described a cost analysis for lacosamide as adjunctive treatment with quality-adjusted life-years (QALYs) [26]. The authors concluded that the cost of the drug fell within the calculated willingness to pay for an additional QALY. According to another recent publication, the most definitive statement that can be made after review of a total of 212 studies, including systematic reviews and Cochrane reviews, is that there is scant evidence from trials to support the use of newer over older drugs, or to support the use of one newer drug over another. What may be concluded is that if older drugs have caused significant side effects that in turn increase the cost of medical care, or older drugs have been ineffective while newer drugs have produced a treatment response, then an argument may be made for greater cost-effectiveness [27].

Rufinamide

Standard dosage	Rufinamide received FDA approval in November 2008 for the adjunctive treatment of seizures associated with LGS. The drug was analyzed in a randomized, double-blinded, placebo-controlled trial, which showed a favorable safety and tolerability profile in this population [28, Class II]. The drug is approved for treating LGS-related seizures in pediatric and adult populations, but there are no data for efficacy or dosing in children younger than 4 years.

Adult dosing: The recommended starting dose is 400 to 800 mg/d divided twice daily. If there is no urgent need for more rapid titration, we find that a slower dose escalation of 400 mg/wk is better tolerated to a maximum dosage of about 45 mg/kg/d, with an average dosage in adults of 3200 mg/d.

With slower titrations, symptoms of somnolence, fatigue, and dizziness are reduced.

Pediatric dosing: Dose recommendations are 10 mg/kg/d divided twice daily with increases at a rate of 10 mg/kg every other day to a target dosage of 45 mg/kg/d or 3200 mg/d (whichever is less). Some pediatric neurologists push the dose to 60 mg/kg/d if the drug is tolerated and shows efficacy.

Contraindications	Familial short QT syndrome. The clinical significance of QT shortening as a side effect of the administration of rufinamide is not known. However, in familial short QT syndrome there is a risk of sudden cardiac death. Therefore, the use of rufinamide in this population is contraindicated [29].
Main drug interactions	According to FDA prescribing information, rufinamide is 34% albumin bound and has minimal drug-drug interactions. It is not metabolized by the CYP system but is a weak inhibitor of CYP2E1 and a weak inducer of CYP3A4 [29]. Of particular interest in an epileptic population are rufinamide's interactions with other AEDs, although these are estimated to be minimal. Carbamazepine and lamotrigine plasma levels are lowered by rufinamide, whereas phenobarbital and phenytoin serum levels are increased. Primidone, phenytoin, phenobarbital, and carbamazepine all decrease the plasma concentration of rufinamide, whereas valproate increases the plasma levels of rufinamide. Importantly, rufinamide may lower the efficacy of oral contraceptives.
Main side effects	The most commonly encountered side effects include somnolence, fatigue, dizziness, headache, and nausea [30]. Blurred vision, loss of appetite, and rash are less common. Shortened QT interval is seen in a dose-dependent fashion and reported in clinical trials at a rate of 50%.
Special points	Rufinamide is a triazole derivative whose mechanism of action is postulated to involve the suppression of neuronal hyperexcitability by prolonging the inactivation phase of voltage-gated sodium channels [29]. It currently is FDA approved for the adjunctive treatment of seizures associated with LGS in both pediatric (age >4 years) and adult populations. There also is an application on file for approval for the adjunctive treatment of pharmacologically refractory complex partial seizures.
Pediatric considerations	Several pediatric studies were performed to assess the efficacy of rufinamide, especially because it has an indication for patients with LGS, commonly diagnosed in childhood. Glauser et al. [6, Class I] studied 139 patients between 4 and 30 years old and found that rufinamide was effective and well tolerated, especially in tonic-atonic (drop attack) seizures, with a 42.5% median percentage reduction. Rufinamide is effective for Lennox-Gastaut and generalized seizures. Rufinamide usually is taken with food to help absorption and elimination does not appear to be affected by renal impairment. Children may report headache, nausea, and sedation, which are dose dependent. Anecdotally, some patients have noted that their seizures may worsen on this medication, but the likelihood of seizure exacerbation is not known. The starting dosage for rufinamide is 10 mg/kg/d and usually is titrated up to a maximum of 45 mg/kg/d, although some pediatric neurologists have used it off label to 60 mg/kg/d in patients with no side effects.
Cost/cost-effectiveness	*Cost estimates:* $45 for 30 200-mg tablets, $360 for 120 400-mg tablets [25]. *Cost effectiveness:* One recent study compared the cost of adding rufinamide with the cost of adding topiramate or lamotrigine to treatment with older AEDs [31]. This study showed a higher cost for rufinamide, but an acceptable cost-effectiveness ratio when factors such as treatment success are

taken into consideration. The primary outcome measure in this study was a greater than 50% reduction in total seizure and drop attack frequency.

Vigabatrin

Standard dosage   Vigabatrin is thought to offer a novel mechanism of antiseizure activity. Although its exact mechanism of action is not known, vigabatrin is an irreversible inhibitor of γ-aminobutyric acid (GABA) transaminase, the enzyme responsible for the metabolism of the inhibitory neurotransmitter GABA in the central nervous system [32••]. The resultant increased levels of GABA within the central nervous system are thought to be the major contributor to vigabatrin's antiseizure effect [32••,33, Class III]. Currently, vigabatrin is available in the United States only through a restricted distribution program (more information is available by calling 1-888-45-SHARE). Vigabatrin is available in either an oral solution (for children 1 month to 2 years of age) or a bioequivalent tablet formulation.

Medically refractory complex partial seizures: The recommended starting dosage of vigabatrin in adults is 500 mg orally twice daily. The total daily dose then may be titrated upward by 500 mg/wk to a recommended maximal dosage of 1500 mg twice daily. Vigabatrin, as an add-on therapy in adult patients (18–60 years old) with complex partial seizures (with or without secondary generalization), has been shown to be effective in reducing seizure frequency by 50% or more in approximately 50% of patients tested [34–41, Class I]. Both single-blind and open, multicenter studies have reported the efficacy of add-on vigabatrin therapy in treating refractory epilepsy in children and adolescents [42,43, Class II–III], although the drug is not yet FDA approved for complex partial seizure patients younger than 18 years.

Infantile spasms: A typical starting dosage is 50 mg/kg/d divided twice daily. The total daily dosage then may be titrated upward by 50 mg/kg/d per week to a maximum total dosage of 150 to 200 mg/kg/d. Vigabatrin has been shown to be an effective treatment for new-onset infantile spasms [44, Class I] and in children 1 month to 2 years of age with drug-refractory West syndrome from several different etiologies [45, Class III]. Vigabatrin may be especially effective in cases of infantile spasms associated with tuberous sclerosis complex [46,47, Class II]. Currently, there is no consensus on whether vigabatrin offers treatment benefit compared with adrenocorticotropic hormone (ACTH) or prednisone [48,49•, Class I].

Special dosing considerations: The vigabatrin dosage should be reduced in patients with mild, moderate, or severe renal impairment. A dose reduction should be considered in healthy patients aged 65 years or older because of documented decreases in drug clearance in this age group.

Contraindications   There are no specific contraindications to the use of vigabatrin, other than a proven allergy to the medication.

Main drug interactions   *Carbamazepine:* Jedrzejczak et al. [50, Class IV] found an increase in serum carbamazepine concentration of at least 10% in 46 of 66 patients who received vigabatrin in addition to stable-dose carbamazepine therapy. The mean increase in serum carbamazepine levels was 24.2%. However, a separate study of 15 patients showed that the plasma clearance of carbamazepine was increased by 35% in the presence of vigabatrin [51, Class IV]. Given this conflicting information, when vigabatrin is added to carbamazepine therapy, serum levels of carbamazepine should be monitored and the carbamazepine dosage adjusted as needed.

Phenytoin/fosphenytoin: The addition of vigabatrin to phenytoin therapy may result in a decrease in serum phenytoin levels. This effect may not become significant until the third to fourth week of concurrent therapy [34,52, Class IV]. Serum phenytoin levels should be considered when either adding or stopping adjunctive vigabatrin therapy.

Main side effects   Vigabatrin use has been associated with two severe adverse events: irreversible peripheral visual field loss (more in adults than children) and cerebral intramyelinic edema (more in children than adults). Currently, more is known about the risks and clinical significance of vigabatrin-associated visual field loss (VAVFL), but the scientific knowledge base for the occurrence of intramyelinic edema is expected to continue to develop.

VAVFL: The estimated risk of VAVFL in adult patients with refractory epilepsy treated with vigabatrin is 30% to 40% after 6 months or more of therapy. The typical deficit is a bilateral concentric peripheral field loss of 20 to 40 axial degrees. Many patients remain asymptomatic, but the loss is irreversible, even after drug cessation [53–56].

Three major risk factors have been identified for the occurrence of VAVFL: 1) male gender, 2) length of treatment, and 3) cumulative vigabatrin dose. The risk of VAVFL increases rapidly in the first 2 years of treatment and the first 2 kg of cumulative vigabatrin intake but seems to plateau thereafter [53,54]. There likely is less risk of VAVFL in patients treated with vigabatrin as infants. One recent study found a much lower incidence of VAVFL in children aged 6 to 12 years who had been treated with vigabatrin for infantile spasms [57].

White matter vacuolation and intramyelinic edema: The association between white matter vacuolation and intramyelinic edema was first identified in animal studies. Reports of similar changes in humans were published only recently [58,59]. To date, these changes have been found among infants treated with vigabatrin (estimated incidence of 22%), rather than adults or older children [59]. The MRI abnormalities likely are transient and asymptomatic, although the clinical implications for ongoing neural development remain unclear [60].

Additional adverse effects to consider: Worsening of depression, suicidal ideation, and abnormal changes in behavior have been reported with the use of vigabatrin. Anemia; changes in hemoglobin, hematocrit, and red blood cell indices; peripheral edema; increased risk of somnolence or fatigue during daily activities; and peripheral neuropathy (in adults) also have been reported [61].

Special points   *Clinical management of risk:* Although the development of guidelines for clinical management of risk is beyond the scope of this review, there are several recent publications that present ideas for guidelines that are well worth review [36,52,60]. In general, each of these guidelines involves 1) the weighing of potential benefits and risks for each patient before initiating vigabatrin; 2) consistent postinitiation monitoring for the occurrence of severe adverse effects, and the limiting of further exposure to the drug if they occur; and 3) early cessation of the drug if no clinical benefit is documented.

Other potential uses for this medication: Vigabatrin also is reported to be effective in treating cocaine dependence [62, Class I], panic disorder [63, Class III], spasticity associated with spinal cord lesions [35, Class II], stiff-man syndrome [64,65, Class IV], multiple sclerosis in adults [35, Class II], and metabolic diseases with leukodystrophy in children [66, Class III]. Investigation is continuing.

Pediatric considerations	Of the three new medications discussed, vigabatrin is the most studied in the pediatric population. This is a result of its indications for epileptic spasms that occur predominantly in infants and children. Vigabatrin is one of the two most effective medications for epileptic spasms; the other is ACTH. It is especially successful in treating epileptic spasms in tuberous sclerosis patients (see earlier). In addition, vigabatrin may be used as a partial seizure medication, although most pediatric neurologists prescribe it specifically for tuberous sclerosis patients who have complex partial seizures.

Many pediatric neurologists prescribe vigabatrin rather than ACTH because of ACTH's undesirable side effect profile, including immune suppression, hypertension, hyperglycemia, and gastric complications. Furthermore, many parents cannot use ACTH because of its cost or because it is given intramuscularly (requiring family teaching on injection methods). In children, the main side effects of vigabatrin are visual field loss and irritability, which often are cumulative and dose dependent. Currently, to obtain vigabatrin through the pharmaceutical company, the patient must have quarterly ophthalmologic visits to check for visual field deficits. This requirement may be an issue in young infants, in whom visual field testing and/or electroretinograms are difficult to perform or validate. As discussed, the literature contains reports of white matter vacuolization in patients; therefore, some physicians perform maintenance MRI testing every year or two while a patient is on vigabatrin. Most will maintain a patient on vigabatrin for 6 months to 1 year spasm-free, then wean him or her off the drug because of the potential visual field effects.

Cost/cost-effectiveness	*Cost estimates:* There is no listing or price information for vigabatrin in the *2009 Red Book.* The estimated monthly cost for a typical vigabatrin regimen according to AWP is $30.82 per 500-mg tablet [25]. *Cost-effectiveness:* One cost-effectiveness study compared the cost of vigabatrin treatment with epilepsy surgery and found the two are comparable if the cost of the surgery is distributed over the patient's expected lifetime [67].

Disclosure

Dr. Strom has been a subinvestigator for a trial of lacosamide for Schwarz Pharma and is the current chair of the physicians advisory board of the Colorado Epilepsy Foundation. No other potential conflicts of interest relevant to this article were reported.

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