The New Antiepileptic Drugs: Where Do They Belong in Our Armamentarium?

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Abstract Eight new antiepileptic drugs (AEDs)—ezogabine, eslicarbazepine acetate, stiripentol, vigabatrin, perampanel, lacosamide, rufinamide, and clobazam—have been approved by the US Food and Drug Administration over the past decade, adding significantly to the armamentarium of AEDs available to treat epilepsy in adults and children. This article reviews the indications, mechanisms of action, pharmacokinetics, efficacy, safety, ease of use, tolerability, drug interactions, and dosing of these agents. This information provides neurologists who treat patients with epilepsy with a greater understanding of how both to incorporate the newest AEDs into clinical practice and to counsel patients and their families regarding the risks, benefits, and possible therapeutic alternatives.

Epilepsy is a common and serious condition. A variety of new antiepileptic drugs (AEDs) that suppress or prevent seizures are now available to clinicians, yet about 30%–40% of children and adults with seizure disorders remain resistant to drug treatment. A high seizure burden in early childhood contributes to severe cognitive, behavioral, and motor developmental delays.

Not all refractory seizures can be resolved with surgery; some patients continue to have seizures following resection, ablation, or neuromodulation. The introduction of each new AED raises valid expectations in patients and physicians for more effective treatment of epilepsy. Safety, tolerability, and lack of drug interactions are important, but improved efficacy is a crucial feature for a new AED. Selection of an AED is based primarily on efficacy for specific seizure types and epileptic syndromes. Because different AEDs may be similarly effective, the choice of one AED over another often rests on other properties, such as their side-effect profile and tolerability, potential for drug interactions, pharmacokinetic properties, and cost. Over the past decade, many new drugs have been added to the therapeutic armamentarium for epilepsy. Some of these represent structural modifications of preexisting compounds, others modify neurotransmitter function, and many more are clinically useful even though their mode of action is unclear. The pharmacokinetics of these drugs differ widely. Nonetheless, the primary goal of therapy is allowing freedom from seizures without causing side effects.

During the 2014 Annual Meeting of the American Epilepsy Society, distinguished experts in managing seizure disorders in both adults and children reviewed the benefits, risks, and potential uses of the latest AEDs. The primary objectives were to understand the pharmacology of these agents; to identify any drug-to-drug interactions, adverse effects, and tolerability; and to recognize appropriate opportunities in day-to-day clinical practice to treat epilepsy. During this symposium, both approved and off-label uses of these medications were discussed.
eslicarbazepine may exert therapeutic effects via augmentation of γ-aminobutyric acid (GABA)-mediated currents.\(^3\)

**Pharmacokinetics**

Eslicarbazepine has a linear pharmacokinetic profile when given at doses ranging from 600 mg to 1,200 mg. It is rapidly absorbed; the median time to maximum blood levels is 0.5–2 hours, and oral bioavailability is 60%. The volume of distribution is 2–3 L/kg. Eslicarbazepine is 80% bound to plasma proteins, and clinically important interactions with other drugs through displacement from these proteins have not been expected. The drug is excreted by the kidneys, with an elimination half-life of 6–10 hours.

Eslicarbazepine undergoes extensive hepatic oxidation and glucuronidation. Oxidation by the cytochrome P (CYP) 450 isoenzyme system involved in its metabolism does not occur; therefore, the coadministration of eslicarbazepine with inhibitors or inducers of the CYP450 system does not impact its pharmacokinetics.\(^4\) Administration of eslicarbazepine also does not affect the circulating concentrations of other antiepileptic medications. Patients with renal or hepatic impairment require dosage adjustment.

**Dosing and Tolerability**

Eslicarbazepine is taken orally in three equally divided daily doses, with or without food. The dose is gradually titrated upward to minimize the risk of adverse effects. The maximum daily starting dose is 100 mg three times daily (300 mg/d). The dose is increased by 150 mg weekly, depending on patient response and tolerability, to an effective maintenance dose of 600–1,200 mg/d. The maximum total maintenance dose is 1,200 mg/d.

In the RESTORE 1 study, the median percent reduction in total seizure frequency with administration of 1,200 mg of eslicarbazepine was 44.3% versus 17.5% with placebo (\(P < 0.001\)).\(^5\) In the RESTORE 2 study, the median percentage seizure reductions were greater in eslicarbazepine-treated patients (600 mg, 27.9% [\(P = 0.007\)]; 900 mg, 39.9% [\(P < 0.001\)]) as compared with placebo (15.9%).\(^6\) Both studies concluded that adjunctive eslicarbazepine therapy was effective and generally well tolerated in adults with refractory partial-onset seizures.

**Side Effects**

The most common dose-related side effects related to eslicarbazepine therapy include somnolence, confusion, dizziness, tremor, amnesia, vertigo, speech disorders, and asthenia. The problems with subsequent usage include dose-dependent prolongation of QT interval; urologic symptoms, including urinary retention; and confusional states, irritability, and other psychiatric symptoms.

More serious side effects include discoloration of the skin, nails, sclera, and mucous membranes. The package labeling includes a black-box warning that describes the potential for retinal pigmentation and possible decreased visual acuity. If a patient develops discoloration of the nails, lips, skin, and/or mucosa, a change to an alternative medication should be considered seriously. The discoloration gradually subsides with discontinuation of eslicarbazepine therapy.

Retinal abnormalities caused by eslicarbazepine are similar to those of retinal pigment dystrophies, which result in damage to the photoreceptors and vision loss. Eslicarbazepine should be used in patients who have responded inadequately to several alternative treatments and for whom the benefits outweigh the potential risk of vision loss. All patients taking eslicarbazepine should undergo systematic visual monitoring by an ophthalmologist at baseline and every 6 months thereafter. Patients who fail to show substantial clinical benefit after adequate titration should discontinue use of the drug.

**ESLICARBZEPINE ACETATE**

Based on a presentation by Martin J. Brodie, MBCoB, MRCP, MD, FRCP.

Eslicarbazepine acetate is approved by the US Food and Drug Administration (FDA) for adjunctive treatment of focal seizures, with or without secondary generalization, in adults. Structurally, the drug belongs to the dibenzazepine family and is closely related to carbamazepine and oxcarbazepine.

Eslicarbazepine shares the dibenzazepine nucleus with carbamazepine and oxcarbazepine, differing from these drugs by a 5-carboxamide substitute at the 10,11 position. Because of this configuration, eslicarbazepine is not metabolized into the carbamazepine 10,11-epoxide, an active and potentially toxic compound. As a result, eslicarbazepine has very low enzyme-inducing activity of the CYP450 enzymatic system and does not induce its own metabolism.\(^7\)

**Mechanism of Action**

Eslicarbazepine inhibits voltage-gated sodium channels in a manner similar to that of carbamazepine and oxcarbazepine.\(^8–10\) Eslicarbazepine has a greater affinity for the inactive state of the sodium channel than it does for its resting state, meaning that it could be more selective for rapidly firing neurons.\(^8\) It may selectively target the area of the brain where the focal seizure occurs, causing fewer neurologic side effects overall. It also inhibits high- and low-affinity voltage-gated inward calcium currents.

**Pharmacokinetics**

Eslicarbazepine acetate is a prodrug that is rapidly and extensively metabolized to its major active metabolite eslicarbazepine and two minor active metabolites, (R)-licarbazepine and oxcarbazepine. It has a high bioavailability and a half-life of 20 hours, which allows once-daily oral dosing. Eslicarbazepine has linear pharmacokinetics at clinical doses up to 1,200 mg/d. Active metabolites are metabolized further to inactive glucuronides. Metabolites are eliminated unchanged or conjugated via the kidneys. The elimination half-life is approximately 16 hours, and steady-state serum levels are reached in approximately 4–5 days.\(^11\)

Clearance of eslicarbazepine increases with concurrent carbamazepine treatment in a dose-dependent manner and with coadministration of barbiturates and phenytoin.\(^12\) Eslicarbazepine increases the clearance of carbamazepine (14%), lamotrigine (12%), and topiramate (16%), but it has no effect on the clearance of...
clobazam, valproate, levetiracetam, gabapentin, phenytoin, or phenobarbital. It induces the metabolism of warfarin and statins and weakly induces CYP3A4. Administration of eslicarbazepine decreases the effectiveness of oral contraceptives.  

**Dosing and Tolerability**

In adults over 18 years of age, the starting oral dose is 400 mg once daily for 1 week, then 800 mg once daily. The maximum recommended maintenance dose is 1,200 mg once daily. In clinical trials, seizure frequency was significantly reduced with administration of eslicarbazepine at 800 mg (35%) and 1,200 mg (39%) when compared with placebo (15%; \( P < 0.0001 \)). Chung et al 14 demonstrated that the median percentage reduction in seizure frequency was significantly greater (\( P < 0.05 \)) in recipients of eslicarbazepine acetate (800 and 1,200 mg/d) than in placebo-treated patients not given concomitant carbamazepine (32.6% and 38.9% vs 16.7%). Certain adverse events (eg, dizziness, diplopia, abnormal coordination, nausea, and vomiting) appear to be more common in eslicarbazepine recipients receiving concomitant carbamazepine than in those not taking carbamazepine.  

**Side Effects**

The most frequent adverse reactions related to eslicarbazepine therapy include dizziness, somnolence, nausea, headache, diplopia, vomiting, fatigue, vertigo, ataxia, blurred vision, and tremor. Idiosyncratic rash and pruritus have been reported in 0.5%, 1.2%, and 3.2% of patients receiving 400, 800, and 1,200 mg/d of eslicarbazepine, respectively. Prolongation of the PR interval and dose-dependent, clinically significant hyponatremia (1%–2%) have been reported, as have potentially serious dermatologic reactions. Dosage reduction is advised in cases of renal impairment (creatinine clearance [CrCl] < 50 mL/min). Unlike carbamazepine and oxcarbazepine, eslicarbazepine is not metabolized to a 10,11-epoxide, a metabolite that may be responsible for enzyme induction and some serious adverse effects. In addition, eslicarbazepine does not require a complicated titration schedule and is

### Properties of Newer Antiepileptic Drug (AED) Therapies

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<th><strong>Ezogabine</strong></th>
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<tr>
<td>• Broad-spectrum AED</td>
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<tr>
<td>• First-in-class KCNQ agonist</td>
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<td>• Daily dose: 600–1,200 mg PO in 3 divided doses</td>
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<tr>
<td>• May cause skin discoloration and/or retinal pigmentation (FDA black-box warning)</td>
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<tr>
<td>• Overall assessment: Third/fourth-line AED reserved for patients ≥ 18 years of age with focal seizures refractory to other drugs</td>
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<tr>
<th><strong>Eslicarbazepine acetate</strong></th>
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<tr>
<td>• Narrow-spectrum AED</td>
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<tr>
<td>• Structurally related to carbamazepine and oxcarbazepine and equally efficacious</td>
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<tr>
<td>• Daily dose: 800–1,200 mg PO in a single dose</td>
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<tr>
<td>• Tends to be well tolerated</td>
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<tr>
<td>• Overall assessment: Useful first-line AED for adults ≥ 18 years of age with focal seizures; similar to carbamazepine and oxcarbazepine but offering simpler dosing titration and once-daily use</td>
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<td>• Not FDA approved; orphan-drug status in the United States</td>
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<tr>
<td>• GABA receptor modulator</td>
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<tr>
<td>• Daily dose: 50–100 mg/kg (maximum, 4 g) PO in 2–3 divided doses</td>
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<tr>
<td>• Overall assessment: Niche drug for use with clobazam and valproate as adjunctive therapy of refractory generalized tonic-clonic seizures in patients with severe myoclonic epilepsy in infancy (Dravet syndrome) whose seizures are not adequately controlled</td>
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<th><strong>Vigabatrin</strong></th>
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<td>• Broad-spectrum AED</td>
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<td>• Daily dose: 4–12 mg PO in a single dose</td>
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<tr>
<td>• May cause permanent vision loss (FDA black-box warning)</td>
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<tr>
<td>• Overall assessment: Drug of choice for patients with epilepsy spasms and tuberous sclerosis</td>
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<tr>
<th><strong>Perampanel</strong></th>
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<tr>
<td>• Broad-spectrum AED</td>
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<tr>
<td>• Daily dose: up to 150 mg/kg PO in 2 divided doses; for refractory complex partial seizures, 1,000 mg PO twice daily for patients 10–16 years old and 1,500 mg PO twice daily for those &gt; 16 years of age or weighing &gt; 60 kg</td>
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<tr>
<td>• May cause aggression and hostility (FDA black-box warning)</td>
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<tr>
<td>• Overall assessment: Useful adjunctive therapy for patients ≥ 12 years of age with partial-onset seizures, with or without generalized seizures, particularly for those refractory to other AEDs</td>
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<th><strong>Lacosamide</strong></th>
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<tr>
<td>• Broad-spectrum AED</td>
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<tr>
<td>• Daily dose: 45 mg/kg (maximum, 3,200 mg) PO in 2 divided doses</td>
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<tr>
<td>• Overall assessment: Indicated for adjunctive treatment of Lennox-Gastaut syndrome in patients ≥ 4 years of age; possibly useful as a third-line AED for treating focal epilepsy</td>
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<th><strong>Clobazam</strong></th>
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<tr>
<td>• Broad-spectrum AED</td>
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<tr>
<td>• Potentiation of GABAergic neurotransmission resulting from binding at the benzodiazepine site of the GABA ( \alpha ) receptor</td>
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<td>• Daily dose: for patients weighing ≤ 30 kg, 5–20 mg PO in 2 divided doses; for those weighing &gt; 30 kg, 10–40 mg PO in 2 divided doses</td>
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<tr>
<td>• Overall assessment: Currently approved only for treatment of Lennox-Gastaut syndrome in patients ≥ 2 years of age but may be useful as adjunctive therapy of Dravet syndrome and as second- or third-line therapy of focal epilepsy</td>
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KCNQ = potassium channel, voltage-dependent; PO = orally (per os); GABA = γ-aminobutyric acid; FDA = US Food and Drug Administration; AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid; IV = intravenous
Stiripentol is a pentenol derivative that has no structural relationship to other known anticonvulsant medications and that belongs to the group of aromatic aliphatic alcohols. Its anticonvulsant activity was shown in several rodent and rabbit models during the 1980s. Pharmacologic findings led to development of stiripentol as an AED. It is indicated for use with clobazam and valproate for adjunctive therapy of refractory generalized tonic-clonic seizures in infants with severe myoclonic epilepsy (Dravet syndrome) whose seizures are not adequately controlled with clobazam and valproate.

Mechanism of Action

Stiripentol directly acts as a positive allosteric modulator on the GABA type A (GABA_A) receptor, thereby enhancing inhibitory neurotransmission. Most of the in vivo actions of stiripentol during adjunctive therapy probably are indirect and mediated by inhibition of CYP450 enzymes (eg, CYP3A4, CYP1A2, and CYP2C19). As a result, stiripentol increases the plasma concentrations of a wide variety of AEDs, including phenytoin, carbamazepine, phenobarbital, valproate, and clobazam, and decreases plasma concentrations of their metabolites (including the toxic ones). Such drug interactions may partially explain the antiepileptic effects of stiripentol in humans and the surprisingly good tolerability related to high plasma concentrations of carbamazepine and clobazam.

Pharmacokinetics

Stiripentol has nonlinear pharmacokinetics. It is absorbed rapidly; the time to peak plasma concentration is 1.5 hours. It is extensively bound to circulating plasma proteins (~99%). Its elimination half-life is dose-dependent and ranges from 4.5 to 13 hours, increasing with dose. Clearance decreases with repeated administration (possibly due to inhibition of CYP450 isoenzymes) and falls markedly at higher doses. It undergoes extensive hepatic metabolism through demethylation (ie, primarily by CYP1A2, CYP2C19, and CYP3A4) and glucuronidation. Metabolites excreted in the urine account for 73% of the elimination, and 13%–24% of the unchanged drug is excreted through feces.

Dosing and Tolerability

The initial daily stiripentol dose is 50 mg/kg, given in two or three divided doses, up to 100 mg/kg per day (maximum dose, 4 g). Stiripentol is used only with clobazam and valproate; the dosages of clobazam and valproate may need downward adjustment (possibly by up to 50%).

Two large, multicenter, double-blinded, placebo-controlled trials (STICLO France and STICLO Italy) involving children with Dravet syndrome showed a change in seizure frequency of ~70% when stiripentol was used with valproate and clobazam.

A retrospective study reported a 63% decrease in total seizure frequency, a reduced incidence of status epilepticus, and a relatively better tolerability profile in children with Dravet syndrome who received stiripentol with valproate and clobazam. Currently, stiripentol is approved in Europe, Canada, and Japan; in the United States, it has orphan-drug status.

Side Effects

Stiripentol inhibits CYP450 isoenzymes CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4, leading to reduced metabolism of coadministered drugs. Thus, AED dosage adjustments are required if signs or symptoms of overdose or adverse reactions occur. For example, the daily dose of valproate should be reduced by 30% per week if loss of appetite and weight occur; likewise, the clobazam dose should be decreased by 25% per week if signs and symptoms of drowsiness, hypotonia, and hyperexcitability are noted. Caution is advised when combining stiripentol with drugs metabolized by CYP2C19 (eg, citalopram, omeprazole) or CYP3A4 (eg, antihistamines, calcium-channel blockers, statins, codeine).

Vigabatrin

Based on a presentation by Elinor Ben-Menachem, MD, PhD.

Vigabatrin is γ-vinyl GABA. It is indicated as monotherapy for pediatric patients (age, 1 month to 2 years) with infantile spasms for whom the potential benefits outweigh the risk of vision loss. Patients with tuberous sclerosis respond best to this drug. In addition, vigabatrin is approved for adjunctive treatment of refractory complex partial seizures in patients ≥10 years of age who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss.

Mechanism of Action

Vigabatrin irreversibly inhibits GABA transaminase (GABA-T), resulting in greater levels of the inhibitory compound GABA within the brain. No direct correlation between plasma concentration and efficacy has been established. The duration of drug effect is presumed to depend upon the rate of GABA-T resynthesis rather than on the rate of drug elimination from the systemic circulation. Levels of vigabatrin remain longer in cerebrospinal fluid (3 days) than in blood (1 day).

Pharmacokinetics

Vigabatrin is rapidly absorbed. Its serum half-life is about 7.5 hours. It does not bind to plasma proteins and is widely distributed throughout the body. It is not significantly metabolized and is eliminated primarily through renal excretion. Vigabatrin induces CYP2C9 and can reduce serum phenytoin levels by 16%–20%, but it does not induce other hepatic CYP450 enzyme systems.

Dosing and Tolerability

In children with infantile spasms who are 1 month to 2 years of age, the initial daily dose of vigabatrin is 50 mg/kg given in two divided doses. The dosage may be titrated upward by 25–50 mg/kg per day every 3 days up to a maximum of 150
mg/d given in two divided daily doses. Adults with refractory complex partial seizures may be given 500 mg/d of the drug orally in two divided doses. The total daily dose may be increased in 500-mg increments at weekly intervals, depending upon response, to 1.5 g given twice daily.

A unique randomized, placebo-controlled study by Appleton et al. demonstrated the efficacy of vigabatrin in treating West syndrome, confirming it as the drug of first choice in treating infantile spasms. In this study, spasms were reduced by 78% (95% confidence interval [CI] = 55%–89%) in patients given vigabatrin compared with 26% (95% CI = 55%–65%) in those given placebo (P = 0.020). At the end of the study, 38% of the patients treated with vigabatrin were spasm-free.

In open-label studies, vigabatrin has been effective in infants with infantile spasms and tuberous sclerosis. In a randomized, multicenter study, Chiron et al. compared use of vigabatrin with oral corticosteroid administration in newly diagnosed patients with infantile spasm and tuberous sclerosis. All 11 infants given vigabatrin and 5 of 11 infants given hydrocortisone were spasm-free (P < 0.01). Mean time to disappearance of infantile spasms was 3.5 days on vigabatrin versus 13 days on hydrocortisone (P < 0.01). Thus, vigabatrin should be considered the treatment of choice for infantile spasm due to tuberous sclerosis.

According to Ben-Menachem and Sander, several well-controlled European studies of refractory complex partial seizures demonstrated that vigabatrin therapy reduces seizure frequency. Vigabatrin was well tolerated, and mostly mild adverse effects were reported.

**Side Effects**

The most commonly reported side effects of vigabatrin therapy are irritability, nervousness, dizziness, headache, depression, and weight gain. Vacuolation, characterized by fluid accumulation and separation of the outer layers of myelin, has been observed in cerebral white-matter tracts in adult and juvenile rats following administration of vigabatrin. This lesion, referred to as intramyelinc edema (IME), was seen at doses within the human therapeutic range. Administration of the drug to rats during the neonatal and juvenile stages of development produced vacuolar changes in the cerebral gray matter (areas including the thalamus, midbrain, deep cerebellar nuclei, substantia nigra, hippocampus, and forebrain), which are considered distinct from the IME observed in vigabatrin-treated adult animals.

Vigabatrin has serious potential adverse effects, and its official prescribing information carries a black-box warning. It may cause permanent, bilateral, concentric, visual-field constriction in ≥ 30% of patients. In some cases, vigabatrin may damage the central retina, decreasing visual acuity. The onset of visual loss is unpredictable and can occur anytime during treatment. The risk of visual loss increases with increasing dose and cumulative exposure, but no dose or exposure is free of this risk. A formal ophthalmologic assessment is required every 3 months during therapy, but monitoring alone cannot reliably prevent vision damage. Visual assessment also is required about 3–6 months after discontinuation of therapy. Once detected, visual loss is irreversible. Visual loss could worsen despite discontinuation of the drug.

Because of the risk of permanent vision loss, vigabatrin is available only through a special restricted distribution program. In a retrospective study published by Wild et al., the frequency of vigabatrin-attributed visual field loss was associated with length of treatment, mean daily dose of vigabatrin, and male gender. In addition, static perimetry was more effective than kinetic perimetry in detecting visual field loss.

**Mechanism of Action**

Perampanel is a noncompetitive antagonist of the excitatory, ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid (AMPA) glutamate receptor on postsynaptic neurons, which is believed to be the source of its anticonvulsant property.

**Pharmacokinetics**

Perampanel is rapidly and completely absorbed following oral administration. Its time to peak plasma concentration is 1 hour. It is 96% protein-bound. The drug is extensively metabolized via primary oxidation and sequential glucuronidation by the liver. Its primary metabolism is mediated by CYP3A and/or CYP3A5. The elimination half-life is 105 hours; perampanel is excreted in the feces (48%) and urine (22%).

**Dosing and Tolerability**

Perampanel is a controlled substance (Schedule C-III) that is taken once daily at bedtime. The usual starting dose is 2 mg in patients not currently taking enzyme-inducing AEDs (eg, carbamazepine, oxcarbazepine, or phenytoin) and 4 mg in patients who are taking enzyme-inducing AEDs. Based on clinical response and tolerability, the dose may be increased by up to 2-mg increments to a maximum dose of 4–12 mg/d. Dosage increases should not occur more frequently than once a week.

Dosing adjustments may be needed in various populations. In patients with hepatic impairment, for example, dose increments should be made every 2 weeks. In those with mild or moderate hepatic impairment, the suggested maximum doses are 6 and 4 mg/d, respectively. Perampanel therapy is not recommended in patients with severe hepatic (Child-Pugh Class C) or renal impairment (CrCl < 30 mL/min). In the elderly, the dose should be increased slowly in increments of 2 mg/d and no more frequently than every 2 weeks. Perampanel increases the clearance of levonorgestrel at doses of...
12 mg/d and may therefore decrease the efficacy of contraceptives containing this progestin. Co-administration of CYP450 inducers may decrease plasma levels of perampanel.

**Side Effects**

The most common side effects of perampanel therapy include dizziness, somnolence, headache, fatigue, irritability, weight gain, and falls. As compared with 3% of patients given placebo, 5% and 10% of patients given 8 and 12 mg/d of perampanel, respectively, experienced falls. Dose-related neuropsychiatric events associated with the administration of perampanel have included aggression, anger, homicidal thoughts, hostility, and irritability; these symptoms most often have been reported during the first 6 weeks of therapy in patients with or without pre-existing psychiatric disease. In some cases, these events were serious and/or life-threatening. Close monitoring is recommended, especially during dosage adjustments and use of higher doses.

**LACOSAMIDE**

Based on a presentation by John R. Pollard, MD.

Lacosamide is indicated as monotherapy or adjunctive therapy of partial-onset seizures, with or without secondary generalization, in patients ≥ 17 years of age. A multicenter, double-blind, randomized, placebo-controlled trial by Chung et al34 showed that adjunctive treatment with 400 or 600 mg/d of lacosamide reduced seizure frequency in patients with uncontrolled partial-onset seizures, with 400 mg/d of lacosamide providing the best balance of efficacy and tolerability.

**Mechanism of Action**

In vitro, lacosamide stabilizes hyperexcitable neuronal membranes and inhibits repetitive neuronal firing by enhancing the slow inactivation of sodium channels with no effects on their fast inactivation.

**Pharmacokinetics**

Lacosamide is completely absorbed; the time to peak plasma concentration is 1–4 hours. Its protein binding is < 15%. It undergoes hepatic oxidation via CYP3A4, CYP2C9, and CYP2C19. The elimination half-life is 13 hours, and 40% of the unchanged drug is excreted by the kidneys.37

An open-label trial demonstrated that use of lacosamide with an oral contraceptive containing ethinyl estradiol and levonorgestrel has a low potential for drug-drug interactions.34 Therefore, co-administration of the two drugs is unlikely to result in contraceptive failure or loss of seizure control.

**Dosing and Tolerability**

For monotherapy in patients with partial-onset seizures, the initial recommended oral dose of lacosamide is 100 mg twice daily. Based on individual patient response and tolerability, the dose should be increased at weekly intervals by 50 mg twice daily, up to a recommended maintenance dose of 150–200 mg twice daily. When used as adjunctive therapy, the initial recommended dose is 50 mg twice daily; the dose should be increased at weekly intervals by 50 mg twice daily until the goal maintenance dose of 100–200 mg twice daily is reached. In patients with severe renal impairment (CrCl ≤ 30 mL/min), the maximum recommended dose is 300 mg/d. Use of this drug is not recommended for patients with severe hepatic impairment.

Lacosamide also is available as an intravenous (IV) preparation that can be used for loading doses; however, IV therapy should be used only temporarily under medical supervision. Clinical study experience of IV lacosamide has been limited to 5 days of consecutive treatment. In patients with renal impairment who are using strong CYP3A4 and/or CYP2C9 inhibitors concomitantly, dosage reduction may be necessary.

Lacosamide therapy may be effective and may represent a possible therapeutic option in children affected by Lennox-Gastaut syndrome. Grosso et al39 showed that 33% of children with Lennox-Gastaut syndrome responded well to lacosamide adjunctive therapy, and the overall seizure reduction rate was 29%. The percentage reductions from baseline in tonic seizures and drop-attacks rates were 31% and 20%, respectively. Current evidence on the use of IV lacosamide in patients with acute seizures and status epilepticus is restricted to retrospective case reports and case series but is promising.40

Stephen et al41 showed that in patients with partial-onset seizures, lacosamide is an effective (26.2% of patients treated with the drug were deemed seizure-free) and well-tolerated adjunctive AED when combined with appropriate doses of traditional sodium-channel blockers or agents with other mechanisms of action. Seizure freedom was more likely when lacosamide was used as a first add-on than when it was given as a later treatment.41

Sake and others42 conducted a pooled analysis of lacosamide clinical trial data that was grouped by mechanism of action of concomitant antiepileptic drugs. Adjunctive use of lacosamide led to significant seizure reduction over placebo regardless of the inclusion of traditional sodium-channel blockers in the concomitant AED regimen.

**Side Effects**

Most adverse events noted in patients taking lacosamide have been dose-related. The most common side effects include dizziness, fatigue, ataxia, headache, nausea, vomiting, diplopia, and blurred vision. Serious side effects include prolongation of the PR interval, atrial arrhythmia, and syncope. Use caution when using lacosamide in patients with conduction problems (eg, first/second-degree AV block, sick sinus syndrome without a pacemaker), sodium channelopathies (eg, Brugada syndrome), myocardial ischemia, heart failure, or structural heart disease or when other drugs that prolong the PR interval are used concomitantly. An electrocardiogram is recommended before treatment is begun and when a steady-state maintenance level is reached.

**RUFINAMIDE**

Based on a presentation by Joan A. Conry, MD, Professor of Neurology and Pediatrics, Children’s National Medical Center, Washington, DC.

Rufinamide is FDA-approved for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients ≥ 4 years of age.
Mechanism of Action

Rufinamide is a triazole-derivative antiepileptic agent whose exact mechanism of action is unknown. In vitro, use of the drug prolongs the inactive state of the sodium channels, thereby limiting repetitive firing of sodium-dependent action potentials that mediate anticonvulsant effects.

Pharmacokinetics

Absorption of the drug after oral administration is slow, but it increases when rufinamide is taken with food. It is 34% bound to proteins and extensively metabolized via carboxylesterase-mediated hydrolysis. Rufinamide is a weak inhibitor of CYP2E1 and weak inducer of CYP3A4. The elimination half-life is 6–10 hours; the drug is excreted by the kidneys.

Dosing and Tolerability

In children ≥ 4 years of age who have Lennox-Gastaut syndrome, the initial dose should be 10 mg/kg per day, given in two equally divided doses. The dose should be increased by about 10 mg/kg every other day to a target dose of 45 mg/kg per day or 3,200 mg/d, whichever is lower, given in equally divided doses.

In terms of seizure types and epilepsy syndromes, Grosso et al14 demonstrated that in children under 4 years of age, the highest seizure reduction rate with rufinamide was observed in those with epileptic spasms (46%) and drop attacks (42%). Seizure reduction also was observed in patients with tonic seizures (35%) and those with focal seizures (30%).43 In terms of epilepsy syndromes, rufinamide was effective in patients with Lennox-Gastaut syndrome. Results were poor for those affected by Dravet syndrome. Thus, rufinamide may be a safe and effective drug for a broad range of seizures and epilepsy syndromes in infants and young children.

Thome-Souza et al44 evaluated the use of rufinamide in one pediatric center; the cohort was large, and the follow-up was long. Use of rufinamide led to a median seizure frequency reduction of 59.2%. Seizure reduction was greater in patients having a genetic etiology (66.2%) than in those with a structural/metabolic cause (45.5%; P = 0.005). A prospective, open-label, add-on treatment study done by Cusmai et al15 showed that in a population of patients with severely refractory epilepsy due to neuronal migration disorders, rufinamide appeared to be effective and generally well tolerated. In that study, there was a 50%–99% seizure reduction and 3% seizure freedom.

Side Effects

The most commonly observed adverse reactions associated with rufinamide therapy are headache, dizziness, fatigue, somnolence, and nausea. Because it may cause shortening of the QT interval, therapy is contraindicated in patients with familial short QT syndrome.

CLOBAZAM

Based on a presentation by Joan A. Conry, MD.

Clobazam is approved for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients > 2 years of age.

Mechanism of Action

Clobazam is a 1,5 benzodiazepine that binds to stereospecific benzodiazepine receptors (specifically, the GABA A sub-unit) on the postsynaptic GABA neuron at several sites within the central nervous system, including the limbic system and the reticular formation in the brainstem. Enhancement of the inhibitory effect of GABA on neuronal excitability increases neuronal membrane permeability to chloride ions, resulting in hyperpolarization and stabilization.

Pharmacokinetics

Clobazam is rapidly absorbed after oral administration and peaks 0.5–4 hours after single or multiple doses are taken. Clobazam is lipophilic and distributes rapidly throughout the body. It has a protein binding of 80%–90%. It is broken down to a metabolite known as N-desmethylclobazam, which has about one-fifth the activity of clobazam. The mean half-life is 36–42 hours for clobazam and 71–82 hours for its main metabolite. Clobazam is metabolized in the liver, and the major metabolic pathway involves CYP3A4. CYP2C19 is involved in the metabolism of N-desmethylclobazam. Slow metabolizers have a significant increase of N-desmethylclobazam. The drug is eliminated by the kidneys. There appears to be no significant effect of other AEDs on the metabolism of clobazam, although this medication is a CYP3A4 inducer.

Dosing and Tolerability

The dose of clobazam depends on patient body weight. The total daily dose should be divided into two daily doses. For patients weighing ≤ 30 kg, give 5 mg/d of clobazam to start and slowly increase the dose up to 20 mg/d, as tolerated. For patients weighing > 30 kg, give 10 mg/d to start and increase the dose up to 40 mg/d, as tolerated. Dosage adjustment is needed for older patients, known slow CYP2C19 metabolizers, and individuals with liver disease or problems.

Conry et al46 demonstrated that in patients with Lennox-Gastaut syndrome with difficult-to-treat seizures, adjunctive clobazam therapy produced sustained seizure freedom and substantial seizure improvements at stable dosages through 3 years of therapy.46 Ogunbemiro and Aarons47 suggested that the most effective treatment for Dravet syndrome is clobazam plus valproic acid or clobazam plus stiripentol.

Side Effects

The most commonly reported side effects of clobazam use include lethargy and sedation.48 In general, these effects tend to be dose-related, with higher doses producing more reports of adverse reactions. Clobazam is a benzodiazepine, and so abrupt discontinuation should be avoided. Withdrawal symptoms may occur if use of the drug is not tapered slowly. Tolbert et al49 noted that after short- or long-term (≤ 5 years) use of clobazam, no withdrawal-related adverse effects or status epilepticus occurred when dosages were tapered over 3 weeks.

REFERENCES

2. Rogawski MA, Bazil CW. New molecular


