Epilepsy is one of the most common and serious neurologic disorders. According to an Institute of Medicine report,1 in 26 people will have epilepsy over his or her lifetime. Approximately 30% of people with epilepsy do not attain complete control of their seizures, even after trying several medications.2 Neurosurgery may be a therapeutic option for some patients, but several contraindications to surgery can prevent a good outcome.3 For patients with refractory epilepsy who are not good neurosurgical candidates, new antiepileptic drugs (AEDs) may offer some hope, especially when such medications have novel structures or new molecular targets. In addition to new brand-name agents, generic versions of existing medications are becoming increasingly prevalent. Controversies about the true equivalence of original brand-name agents and their generic counterparts have been debated for years, and physicians must judge use of these generic medications according to the best available evidence.

At the Annual Fundamentals Symposium offered during the 66th Annual Meeting of the American Epilepsy Society, a series of presentations focused on the best use of the newest AEDs. Speakers also addressed controversies in managing generic medications in patients with epilepsy. Experts in the field discussed use of newer AEDs in patients with refractory epilepsy, matching novel agents to specific epileptic syndromes, the adverse effects related to use of these drugs, and the administration of generic drugs based on a firm understanding of the best scientific data available.

The session was chaired by Michael Privitera, MD, Professor of Neurology, University of Cincinnati College of Medicine, and Director, Epilepsy Center, UC Neuroscience Institute, Cincinnati, Ohio.

MECHANISM OF ACTION OF THE NEW AEDs

Based on a presentation by Misty D. Smith, PhD, Research Assistant Professor of Pharmacology and Toxicology, Investigator in the Anticonvulsant Drug Development Program, University of Utah, Salt Lake City, Utah

Since 2007, eight AEDs have been approved by the US Food and Drug Administration (FDA) and/or the European Union (EU). In chronologic order of introduction, those drugs are stiripentol, lacosamide, rufinamide, eslicarbazepine acetate, vigabatrin, ezogabine (retigabine), clobazam, and perampanel (Tables 1 and 2).

When considering the mechanism of action of an AED, it is important to remember that we do not have full knowledge of all potential sites of action within in vivo systems. These drugs likely have multiple sites of action, and no one action of any given AED completely accounts for its observed clinical effects (ie, efficacy, toxicity, tolerability).

Most established AEDs affect either reduction of excitatory neurotransmission; enhancement of inhibitory neurotransmission of γ-aminobutyric acid (GABA); or modification of sodium, potassium, or calcium ion conductance. To increase the likelihood of improved seizure control, the new AEDs are structurally novel, able to engage new molecular targets, or next-generation compounds.

Stiripentol

Stiripentol is an aromatic alcohol that is structurally unrelated to other AEDs. In 2007, the European Medicine Agency authorized marketing of the drug for adjunctive therapy with clobazam and valproic acid to treat refractory generalized
tonic-clonic seizures in young patients with myoclonic epilepsy in infancy (Dravet syndrome).¹

The exact mechanism of action of stiripentol is unknown, but it likely is diverse. Stiripentol has been shown to enhance neurotransmission of GABA in slices of neonatal rat hippocampi.² The drug seems to increase the duration of opening of GABA₆ receptors in a manner somewhat like that of barbiturates, and there may be some interaction with benzodiazepines as well. Stiripentol is active in δ-containing recombinant GABA₆ receptors insensitive to benzodiazepines; it also may increase central GABA by interfering with uptake and metabolism.³ Stiripentol also inhibits a variety of cytochrome P (CYP) 450 enzymes, resulting in decreased metabolism of such AEDs as phenytoin, carbamazepine, and diazepam.⁴⁻⁶

**Lacosamide**

In 2008, lacosamide was approved by the FDA for adjunctive treatment of partial-onset seizures in patients over 17 years of age. Lacosamide was the first AED to enhance the slow inactivation state of voltage-gated sodium channels.⁸,¹⁰ Under normal conditions, the majority of sodium channels are in a closed, resting state. When stimulated, these channels depolarize and open; within milliseconds, they recover to a resting state and then to long-term inactivation. Most traditional sodium-channel blockers (eg, phenytoin, carbamazepine) work by inactivating fast-gated sodium channels. By targeting the slow inactivated sodium channel, lacosamide may regulate sodium-channel availability over the long term by decreasing the available pool of sodium channels and facilitating action potential burst termination.¹¹

Lacosamide also binds with collapsin response mediator protein, but it is unclear whether this binding contributes to anticonvulsant activity.⁹

**Rufinamide**

Rufinamide was the first drug to reach the American market with a pediatric indication before its use was approved in adults. The FDA approved rufinamide in November 2008 for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in patients 4 years of age and older.

Rufinamide possesses a novel triazole structure somewhat similar to that of lamotrigine. The drug prolongs the inactivated state of voltage-gated sodium channels, thereby limiting repetitive firing of sodium-dependent action potentials.¹² Like all AEDs, however, rufinamide’s mechanism of action is incompletely understood. Most sodium-channel blockers are not very effective against atonic seizures; rufinamide, however, has been more successful, leading many experts to suspect that additional mechanisms of action are involved.¹⁰

**Eslicarbazepine Acetate**

Eslicarbazepine acetate, the only next-generation compound discussed at the American Epilepsy Society session on new anticonvulsants, is a third-generation...
<table>
<thead>
<tr>
<th>Drug name</th>
<th>T&lt;sub&gt;max&lt;/sub&gt;, h</th>
<th>t&lt;sub&gt;½&lt;/sub&gt;, h</th>
<th>Protein bound, %</th>
<th>Dosage&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Major side effects</th>
<th>Drug interactions</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stiripentol</td>
<td>1.5</td>
<td>4.5–13</td>
<td>99</td>
<td>50–100 mg/kg daily; maximum dose, 4 g</td>
<td>Ataxia, drowsiness, weight loss</td>
<td>CYP450 inhibitor; prolongs metabolism of other AEDs (eg, phenytoin, diazepam, carbamazepine)</td>
<td>Not FDA approved</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>0.5–4</td>
<td>13</td>
<td>15</td>
<td>50–100 mg/d in at least two divided doses; maintenance dose, 200–400 mg/d</td>
<td>Dizziness</td>
<td>Other CYP inducers affect lacosamide's metabolism</td>
<td>Large fluctuations in serum concentrations</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>4–6</td>
<td>6–10</td>
<td>26–35</td>
<td>400–800 mg/d in two equally divided doses, followed by increases of 400–800 mg/d every other day, up to a maximum of 3,200 mg/d in two equally divided doses</td>
<td>QT-interval shortening, fatigue, headache, nausea</td>
<td>Inducers affect rufinamide's metabolism; valproic acid may increase rufinamide's serum concentration by up to 50%</td>
<td>Nonlinear dose versus serum concentration relationship; food intake increases bioavailability</td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>2–3</td>
<td>20–40</td>
<td>40</td>
<td>400 mg every other day for first 2 weeks, then 400 mg daily</td>
<td>Dizziness, headache, diplopia</td>
<td>CYP inducer, resulting in a 12%–16% increase in clearance of carbamazepine, lamotrigine, and topiramate</td>
<td>Prodrug, with 100% of dose converted to its main metabolite, eslicarbazepine; not FDA approved</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>1</td>
<td>7.5</td>
<td>0</td>
<td>Adults: 500 mg twice daily, followed by weekly increases of 500 mg, up to 3 g/d; for infantile spasms, 50 mg/kg in two divided daily doses to start, followed by 25–50 mg/kg per day every 3 days up to 150 mg/kg daily</td>
<td>Peripheral vision loss</td>
<td>May enhance effects of central nervous system depressants</td>
<td>Half-life of biologic activity exceeds elimination half-life; biologic half-life depends upon GABA-T resynthesis</td>
</tr>
<tr>
<td>Ezogabine (retigabine)</td>
<td>0.5</td>
<td>8</td>
<td>80</td>
<td>100 mg three times daily, followed by weekly increases of not more than 150 mg/d, up to 200–400 mg three times daily</td>
<td>Urinary retention, dizziness, somnolence</td>
<td>Unusual two-way interaction with lamotrigine</td>
<td>Limited experience in clinical practice</td>
</tr>
<tr>
<td>Clobazam</td>
<td>1–3</td>
<td>10–30</td>
<td>85</td>
<td>Patients up to 30 kg: 5 mg once daily for 1 week, followed by 5 mg twice daily for 1 week and then 10 mg twice daily; patients over 30 kg: 10 mg once daily for 1 week, followed by 10 mg twice daily for 1 week and then 20 mg twice daily</td>
<td>Similar to benzodiazepine toxicity</td>
<td>Other inducers affect the metabolism of clobazam; polymorphisms exist, with slow metabolizers having increased adverse effects</td>
<td>Extensive experience in clinical practice in Europe; may be less sedating and slower to develop tolerance than other benzodiazepines</td>
</tr>
<tr>
<td>Perampanel</td>
<td>0.5–1.5</td>
<td>70–100</td>
<td>96</td>
<td>2 mg once daily at bedtime, followed by increases of 2 mg/d at not less than weekly intervals, up to 4–8 mg once daily at bedtime</td>
<td>Dizziness, headache, somnolence, dose-related neuropsychiatric disturbances</td>
<td>CYP enzyme inducers (carbamazepine, phenytoin, oxcarbazepine) may decrease plasma perampanel levels by 50%–67% levonorgestrel-containing contraceptives may be less effective</td>
<td>Long half-life means that it can take 14 days to reach steady state; absorption delayed 2 hours when taken with food; limited clinical experience</td>
</tr>
</tbody>
</table>

AEDs = antiepileptic drugs; FDA = US Food and Drug Administration; GABA = γ-aminobutyric acid

<sup>a</sup>Oral dosage; lacosamide also may be given intravenously
Ezogabine (Retigabine)

Ezogabine (known as retigabine in Europe) is the first AED to target and open a voltage-gated potassium channel. By targeting the low-threshold KCNQ (Kv7) channel, ezogabine has a hyperpolarizing effect on neurons and reduces neuronal hyperexcitability. At supratherapeutic concentrations, it also enhances GABA$_{A}$-activated currents.

The drug was approved in 2011 as adjunctive therapy for patients over 18 years of age who have been diagnosed with partial seizures and refractory partial epilepsy. A notable side effect related to ezogabine therapy is urinary retention due to the presence of voltage-gated potassium channel subunits Kv7.2–Kv7.5 in the bladder urothelium.

Clobazam

Clobazam is a structurally unique 1,5-benzodiazepine, meaning the nitrogen atoms in a heterocyclic ring are in the 1 and 5 positions rather than the 1 and 4 positions of older benzodiazepines. It was first approved in Australia in 1970; it has been used for years in Europe. The drug was approved by the FDA in 2011 for adjunctive therapy of Lennox-Gastaut syndrome in patients > 2 years of age. Use of this medication has resulted in up to a 70% reduction in drop seizures in these patients.

Like other benzodiazepines, clobazam potentiates GABAergic neurotransmission by binding to the benzodiazepine site of the GABA$_{A}$ receptor. In comparison with 1,4-benzodiazepines, clobazam is less lipophilic and acidic, better tolerated, and less sedating. In addition, patients using clobazam develop tolerance to the drug more slowly than do those using other AEDs.

Perampanel

Perampanel is the first inotropic $\alpha$-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor antagonist. As such, it provides researchers with a tool for better understanding the role of the AMPA receptor in refractory seizure disorders and represents a new therapy for epilepsy. As a selective noncompetitive antagonist of neuronal AMPA receptors, perampanel reduces fast excitatory signaling in the brain critical to generation and spread of epileptic activity. The drug was first approved in the EU; in October 2012, perampanel was approved by the FDA for treatment of partial-onset seizures.

Understanding the mechanisms of action of AEDs can assist neurologists in making logical selections of an AED for either monotherapy or polytherapy, and it may prevent drug selections that worsen patient outcomes. Established AEDs have diverse targets; however, about a third of epilepsy patients remain refractory to drug treatment, and failure of one medication predicts the failure of medications in the future.

We can only hope that as we continue to find new medications, we will see continued benefits for our individual patients and for patients with epilepsy as a whole.

**CLINICAL PHARMACOKINETICS AND DRUG INTERACTIONS**

Based on a presentation by Cecilie Johannessen Landmark, PhD, Associate Professor of Pharmacy and Biomedical Science, Faculty of Health Sciences, Oslo University College and Akerhus University College of Applied Sciences, Oslo, Norway

The term pharmacokinetics refers to all processes of a drug after administration, including absorption, distribution, metabolism, and excretion. Each pharmacokinetic process has distinct parameters to consider, such as the area under the curve (AUC), steady-state concentration, half-life, and volume of distribution (V$_{d}$).

When considering the pharmacokinetic properties of any medication, especially anticonvulsants, one must keep in mind that pharmacokinetics vary by age, gender, physiologic changes (eg, pregnancy), ethnicity, and environmental factors. There is often a 10-fold difference in pharmacokinetic variability among patients given the same dose of an AED.

Much of this variability is determined by pharmacokinetic interactions. Such interactions between AEDs may cause no significant change or may lead to toxicity and adverse effects. The efficacy of one or more drugs may be increased or lost. For example, giving valproic acid and lamotrigine together may result in a synergistic effect. On the other hand, giving two sodium-channel blockers may potentiate their adverse effects. Because
Effects of Antiepileptic Drug Combinations

<table>
<thead>
<tr>
<th>Enzyme-inducing drugs:</th>
<th>Decrease serum concentrations of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Other enzyme inducers</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Valproate</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Lamotrigine</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Tiagabine</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Zonisamide</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Lacosamide</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Rufinamide</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Enzyme-inhibiting drugs:</th>
<th>Increase serum concentrations of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Other enzyme inhibitors</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Carbamazepine</td>
</tr>
<tr>
<td>Stiripentol</td>
<td>Rufinamide</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Ethosuximide</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Phenytoin</td>
</tr>
</tbody>
</table>

Lacosamide is well absorbed, but its maximum concentration in the blood ($T_{\text{max}}$) is reached 0.5–4 hours following administration. Lacosamide serum concentrations have shown high fluctuations during the day, with a steep increase during the first 3 hours after administration.30 Fluctuations during the day may be reduced by taking the drug three times daily instead of two. Such dosing also may improve tolerability in patients who experience adverse reactions from lacosamide.

Lacosamide is available in both oral and intravenous (IV) forms and is predominantly excreted renally.31

Rufinamide

There is a nonlinear relationship between dose and serum concentrations of rufinamide, and its absorption after oral administration is dose-dependent. The bioavailability of the drug depends upon food intake, with less absorption occurring in the absence of food. Rufinamide is not highly protein-bound (26%–35%).

The metabolism of rufinamide is non–CYP-dependent hydrolysis with a short half-life; however, the drug has other enzyme-inducing properties, and various inducers affect its metabolism. For example, valproic acid inhibits the metabolism of rufinamide, leading to up to a 50% increase in rufinamide serum concentrations.32 The concentration-dose relationship is nonlinear, and children have about 19% lower serum levels than do adults due to increased clearance.33

Therapeutic drug monitoring is especially recommended when this drug is used, as serum concentrations differ markedly between patients.

Eslicarbazepine Acetate

Eslicarbazepine acetate is a prodrug; 100% of a dose is converted into its active metabolite, eslicarbazepine. Its $T_{\text{max}}$ is 2–3 hours. Protein binding is about 40%, with a $V_d$ of 2.7 L/kg. There is a linear relationship between dose and serum concentration. This medication can induce other CYP isoenzymes, leading to a 12%–16% increase in clearance of carbamazepine, lamotrigine, and topiramate. It also can induce the metabolism of oral contraceptives. Excretion of eslicarbazepine is lower in patients with renal or hepatic impairment.13,14,34,35

Vigabatrin

The pharmacokinetics of this irreversible GABA-transaminase inhibitor are easily learned, because it has a low potential for pharmacokinetic interactions. Vigabatrin is 100% bioavailable, with no protein binding and a $T_{\text{max}}$ of 1 hour. The drug has been used in Europe for many years. Although only more recently did it become available in the United States, vigabatrin has been used to a limited extent, because it has caused irreversible peripheral vision loss in many patients.36

Because vigabatrin is a suicide inhibitor of GABA-transaminase, the half-life of biological activity exceeds the half-life of the drug concentration in the serum.37 The half-life of biologic activity likely depends most on the regeneration of GABA transaminase, which may take up to 6 days from drug administration.38

Ezogabine

Ezogabine has a higher $V_d$ (6.2 L/kg) than do many other medications. It is metabolized by UGT and N-acetylation. This medication can cause an unusual two-way interaction with lamotrigine, leading to a 20% increase in clearance.39,40

Clobazam

Clobazam is not a new drug outside of the United States—it has long been used in Europe. The bioavailability of clobazam is close to 100%, with moderately high protein binding at 85% and a $V_d$ of 1 L/kg. Clobazam is metabolized not only by CYP3A4 but also by CYP2C19. This is important, since there are polymorphisms of this enzyme that could lead to pharmacogenetic variability. In patients with slow CYP metabolism, use of this drug may lead to increased adverse effects akin to benzodiazepine toxicity. Lower doses are called for in patients with renal or hepatic impairment.36,41

Perampanel

Perampanel is generally well absorbed, but that absorption can be delayed by 2 hours when it is taken with food. It is also

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Source: Cecilie Johannessen Landmark, PhD; used with permission
96% protein-bound, in a manner similar to that of valproic acid. This means there are possible displacement interactions between perampanel and other highly bound AEDs.

Perampanel also has a high \( V_d \) at 77 L/kg. Perampanel has a long half-life, reaching steady-state serum levels after 14 days. Clearance of perampanel can be increased two- to threefold by concomitant use of carbamazepine, oxcarbazepine, or phenytoin. Perampanel is also an inducer of oral contraceptives in women. There is limited experience with this drug in clinical practice.\(^{18,42}\)

**Impact on Clinical Care and Practice**

The impact of drug interactions vary due to considerable differences in pharmacokinetics between patients. In clinical practice, therapeutic drug monitoring is helpful for adjusting dosage if interactions occur. Wherever possible, avoiding potentially harmful drug interactions is the best course, along with a discussion with the patient of all potential interactions (Table 4).\(^{16,43}\)

### Efficacy and Adverse Effects of Newer AEDs in Approved Indications

Based on a presentation by R. Edward Faught, Jr, MD, Professor of Neurology, Emory University, and Chief of Service, Neurology, Emory University Hospital Midtown, Atlanta, Georgia

Well-known reports have suggested the increasing futility of attempting more antiepileptic therapy after a patient has failed two or three AEDs. The results of lesser-known studies, however, have suggested that it may be worthwhile to keep trying new medications in patients with refractory epilepsy. Rates of response (defined as at least a 50% reduction in seizures) have demonstrated that even after administration of many ineffective AEDs, at least 26.5% of patients have responded favorably to the use of a new AED.\(^{44,45}\)

What most people with epilepsy truly want, however, is to be free of seizures. Whereas <20% of patients will attain this goal after trying a third or fourth drug, others experience improvement, showing that there is always some hope of a meaningful benefit, even in people with refractory epilepsy.

#### Lacosamide

A meta-analysis of clinical trials of lacosamide demonstrated a leveling of dose response after about 400 mg/d was given.\(^{46}\) There seemed to be a linear relationship between dose and side effects, as discerned by the number of patients leaving the clinical trial. Almost 25% of patients suffered dizziness, the most common side effect, when taking 400 mg/d of lacosamide. This side effect seemed to worsen when lacosamide was combined with another sodium-channel blocker. Other side effects included vertigo, ataxia, balance disorders, coordination abnormalities, and diplopia.

The recommended dosage of lacosamide is 50 mg given twice daily for the first week; thereafter, the dosage is increased in weekly intervals by 100 mg/d in two divided doses, as tolerated, until a goal of 200–400 mg/d in two divided doses is reached. A more conservative method involves simply cutting these doses in half and taking twice as long to titrate the dose upward.

Advantages of lacosamide include the patient’s ability to take the drug just twice a day, although it may be better tolerated if taken three times daily. Use of the drug has been related to few, if any, drug interactions. Lacosamide adds particularly well to levetiracetam, topiramate, or pregabalin. A relatively low rate of somnolence, rash, or cognitive side effects has been noted with its use.

Disadvantages of lacosamide use include its modest effectiveness—treatment at 400 mg/d has led to seizure reduction just 20% greater than that observed with placebo (however, the placebo response was high at >20%). Dizziness caused by the drug limits the physician’s ability to use it with phenytoin, carbamazepine, oxcarbazepine, or lamotrigine, because these combinations tend to worsen dizziness. Monotherapy with lacosamide is not proven, however, and dosage levels for use of this drug as a single agent are not established.

#### Ezogabine

Ezogabine has the unique method of action of facilitating and prolonging potassium-channel opening, thereby inhibiting repetitive neuronal firing.\(^{18}\) Use of 1,200 mg/d resulted in a linear decrease in seizure frequency of up to 35.2%.\(^{47}\) Side effects are generally dose-related and include somnolence, dizziness, and confusion.

Ezogabine has an unusual side effect for an AED, urinary retention, which can be severe. In one study, 8% of treated patients had some complaint of voiding difficulty, and 2% had experienced urinary retention.\(^{48}\) Caution is advised for use of the drug in patients with an enlarged prostate or other problems with urinary voiding. The recommended starting dose is 100 mg three times a day, which should then be titrated upward to a total daily dose of 600–1,200 mg in three divided doses.

Benefits of ezogabine therapy include a novel mechanism of action, no significant drug interactions, renal excretion, a low rate of rash, and a low incidence of cognitive complaints. Drawbacks include only modest efficacy, the need to dose three times daily, and urinary retention.

#### Rufinamide

Rufinamide therapy is particularly successful for treating atonic seizures or “drop attacks.” Previously, the most commonly used drugs for this indication included felbamate, lamotrigine, and topiramate.

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**TABLE 4**

<table>
<thead>
<tr>
<th>Propensity of Selected Antiepileptic Drugs to Interact with Other Therapeutic Agents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug</td>
</tr>
<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Clobazam</td>
</tr>
<tr>
<td>Eslicarbazepine acetate(^a)</td>
</tr>
<tr>
<td>Ezogabine (retigabine)</td>
</tr>
<tr>
<td>Lacosamide</td>
</tr>
<tr>
<td>Perampanel</td>
</tr>
<tr>
<td>Rufinamide(^a)</td>
</tr>
<tr>
<td>Vigabatin</td>
</tr>
</tbody>
</table>

\(^a\) Antiepileptic drugs that may cause drug interactions and have enzyme-inducing properties

Source: Johannessen and Patsalos\(^{46}\); Bialer et al\(^{47}\)
Felbamate is the most effective of these three drugs; however, it reduces just over 40% of such seizures.59 Rufinamide has a similar success rate in the treatment of atonic seizures in patients with Lennox-Gastaut syndrome but offers a better side-effect profile. Dosing for children starts at 10 mg/kg per day given in two divided doses (target dose, 45 mg/kg per day). In adults, the starting dose is 200 mg twice daily (maximum dose, 3,200 mg/d). Rufinamide is prone to interact with other AEDs.

Clobazam

Clobazam was designed to produce less somnolence and tolerance than other benzodiazepines. In patients weighing > 30 kg, dosing ranges from 10 to 40 mg/d given in two divided doses. A conservative starting dose would be 5 mg/d given for 1 week, followed by 5-mg/d increases at weekly intervals to reach a goal of 20 mg/d. At a dose of 1 mg/kg, the reduction in weekly drop seizures was relatively impressive (68%).23 Clobazam often is added to regimens including valproic acid, felbamate, lamotrigine, or topiramate.

**EMERGING USES OF THE NEWER AEDs IN STATUS EPILEPTICUS AND EPILEPSY**

Based on a presentation by Howard P. Goodkin, MD, PhD, Shure Professor of Neurology and Pediatrics, Division Director of Pediatric Neurology, and Co-Vice Chair for Research in the Department of Neurology, University of Virginia, Charlottesville, Virginia

Off-label uses of drugs are sometimes regarded with suspicion, especially by those outside of the medical profession. Prescribing medications for an indication not specified by the drug company, however, is sanctioned by the FDA. Regulations on drug labeling, as delineated in the Kefauver-Harris Amendment to the Federal Food, Drug, and Cosmetic (FD&C) Act of 1962,50 restrict only the marketing of that drug, stating that “an FDA-approved drug may be labeled, promoted, and advertised only for those uses for which the drug’s safety and effectiveness have been established.” The FD&C Act does not limit how a physician may use an approved drug, stating that “unapproved or more precisely ‘unlabeled’ uses may be appropriate and rational in certain circumstances, and may, in fact, reflect approaches to drug therapy that have been extensively reported in the medical literature.”50 Off-label use of medication is both an accepted medical practice and quite common, with 21% of prescriptions written for off-label use.51 Off-label prescription relies on medical judgment and should be performed in “good faith, in the best interest of the patient, and without fraudulent intent.”52 Physicians should consider the existence of an equally effective on-label alternative and the rationale for off-label use, including published scientific evidence and the standard of care regarding the patient’s condition.52

Off-label use of medication is both an accepted medical practice and quite common, with 21% of prescriptions written for off-label use.

Within the field of epilepsy, common off-label uses include extension to other syndromes or seizure types, use in status epilepticus, and use of a medication in a pediatric or adult population.

**Lacosamide**

Emerging uses of lacosamide include prescribing for generalized seizures in adults, extending the use of lacosamide to children, and using the drug in patients with status epilepticus.

The use of lacosamide in generalized seizures is supported by case reports and series, as well as evidence of a > 50% decrease in the frequency of epileptic incidents in 18 of 24 patients with generalized tonic-clonic seizures.53

At least four studies have investigated the use of lacosamide in children, with two studies examining use of the drug for focal epilepsy and two investigating its use for a mix of focal and general epilepsy.54–57 Investigators noted 30%–50% reductions in seizure frequency with lacosamide use, but patients frequently dropped out of studies because of side effects.

Results on the use of lacosamide in status epilepticus are conflicting. In one study,58 all seven cases of status epilepticus improved within 24 hours of IV lacosamide administration. In another,59 none of the treated patients experienced resolution of signs and symptoms within the study criteria of 4 hours of IV lacosamide use, and only two experienced a decrease in seizure frequency in the days following. The authors noted one, and possibly two, cases of angioedema related to lacosamide administration. The results of a retrospective study showed cessation of status epilepticus in 17 of 38 patients (response rate, 45%) given lacosamide, with no adverse events.60 In another study, 25 of 31 patients (81%) who received lacosamide had cessation of status epilepticus.61

**Rufinamide**

Therapeutic trends now include adjunctive treatment of focal seizures in children and adults. Multiple small case reports and case series describe electroclinical syndromes such as malignant migrating partial epilepsy, epilepsy with myoclonic absence, Dravet syndrome, myoclonic astatic epilepsy, West syndrome, multifocal encephalopathy with bifrontal spike-wave discharges, and other unspecified symptomatic or cryptogenic generalized epilepsy.62–69 In almost all cases, responses ranged and varied, and no clear picture emerged from the data.

Various studies have investigated the use of rufinamide for adjunctive treatment of focal seizures in children and adults. The largest was a 24-week, multicenter, phase II clinical study of 647 patients 15–65 years of age that featured a 12-week prospective baseline phase before randomization into a double-blind, parallel group, five-arm treatment phase.70 A large proportion of subjects completed the study. The primary endpoint of a linear trend for dose response was established, with a similar rate of adverse events ob-
served between treatment and placebo arms; headache, fatigue, and dizziness were among the most common adverse events.

A subsequent randomized, double-blind, placebo-controlled, parallel-group, multicenter study was performed, in which rufinamide doses were titrated up to a dose of 3,200 mg/d and then maintained for an 84-day treatment phase. A significant difference between the treatment and placebo groups was found ($P = 0.007$). Side effects were also greater in the treatment group, with dizziness, fatigue, nausea, somnolence, and diplopia being the most frequent adverse events.71

**Clobazam**

Additional uses for clobazam currently being investigated include treatment of other electroclinical syndromes, monotherapy for focal or generalized seizure in adults, and adjunctive therapy for focal or generalized seizure in adults and children. Other possible indications for the future include status epilepticus and febrile seizures.

Case series have described the use of clobazam in West syndrome, Dravet syndrome, myoclonic astatic epilepsy, Landau-Kleffner syndrome, Jeavons syndrome, and unspecified epileptic encephalopathies.72–75

Because clobazam has existed since 1970, more primary studies have been done on this drug than on previously discussed AEDs. The largest trial to address the potential use of clobazam in adults and children with focal or generalized seizures was a double-blind, crossover study involving 129 patients in 1987.76 In all, 20 patients became seizure-free. Adverse reactions included drowsiness, dizziness, depressive mood, and aggressiveness. Another double-blind crossover study done in 1990 that focused on the treatment of children found a > 50% reduction in seizure frequency among 11 of 21 patients.77

**Summary**

Case series suggest an emerging role for lacosamide in treating adults with generalized seizures, children with epilepsy, and patients with status epilepticus. Case series suggest an emerging role for rufinamide in treating several electroclinical syndromes, and the results of double-blind, placebo-controlled studies support a role for rufinamide in the adjunctive treatment of focal seizures. Results from case series suggest a possible role for clobazam in treating several electroclinical syndromes, febrile seizures, and some forms of status epilepticus. Outcomes from double-blind, placebo-controlled trials support a role for clobazam in the adjunctive treatment of focal and generalized seizures in both children and adults.

### GENERIC AEDs: FACTS AND FICTION

**Based on a presentation by Michael D. Privitera, MD, Professor of Neurology, University of Cincinnati College of Medicine, and Director, Epilepsy Center, UC Neuroscience Institute, Cincinnati, Ohio**

Several million doses of generic AEDs are taken every day by people with epilepsy. Not only do these medications benefit individual patients due to their lower costs, but the FDA estimates that $56.7 billion were saved in 2002 alone due to generic substitution, signifying the power of generic drugs in combating healthcare costs.

For years, neurologists and patient advocates have expressed concern that FDA rules on generic medication allow too much variability across formulations of anticonvulsants and, in turn, that these variations cause health problems. According to the FDA, there is no reliable documentation of generic drugs causing problems, and the agency maintains that formulations are safely interchangeable.

In 2007, the American Academy of Neurology (AAN) reiterated the concerns of many of its constituents, stating that small variations in concentrations between name brands and their generic equivalents could cause toxic effects or seizures when taken by people with epilepsy; however, the AAN did not cite evidence for this claim.78 In 2009, the US Senate Appropriations Committee insisted that the FDA report how it was funding studies to resolve questions of AED generic equivalence.79

**Definitions of Equivalence**

When discussing the controversy of equivalence between generics and brand-name medications, it is important to be clear about certain terminology. The term *bioequivalence* means that the pharmacokinetic parameters of the AUC and the maximum serum concentration ($C_{\text{max}}$) fall within a certain range. The term bioequivalence usually is used to compare a single generic with a brand-name drug. *Therapeutic equivalence* means that two products have an equal clinical benefit for a patient. In the case of an AED, this means that two drugs would have equal tolerability and seizure control. Finally, the term *switchability* means that there is no change in therapeutic effect when one drug is exchanged for another.

These terms have meanings that are similar, but, in fact, the differences may be quite significant. For example, the FDA requires rigorous testing of bioequivalence, but it does not demand proof of therapeutic equivalence. It is assumed that if the plasma concentration-time curve and $C_{\text{max}}$ fall within specified limits, therapeutic equivalence will follow. Typically, bioequivalence studies are done using one dose in healthy adults—not in people with epilepsy or those using concomitant medications or with comorbid conditions. As long as both the AUC and $C_{\text{max}}$ fall within 80%–125% of those of the brand-name drug, the generic drug passes FDA standards. Most generic drugs do very well in meeting those standards.

**The Crux of the Problem**

The argument of many neurologists essentially is that the FDA standards of bioequivalence do not reliably lead to actual therapeutic equivalence or switchability. The research literature is full of retrospective studies supporting this position. In Canada, switching from a brand-name AED to its generic equivalent has been associated with a higher rate of switching back to the original medication, when compared with statins for treating...
hyperlipidemia or selective serotonin reuptake inhibitors for treating depression, presumably due to lack of tolerability or diminished efficacy when switching AEDs. Furthermore, use of generic AEDs has been associated with a greater need for emergency services. In another study, switching to generics was found to have no effect on epilepsy-related events.

An assessment of five generic carbamazepine products was performed on data obtained via the Freedom of Information Act. A model using these data demonstrated AUC variations of up to 21% and variations in C_max reaching 40%.

On the other hand, there are several caveats to these retrospective studies. Switchbacks may have resulted from incorrect attribution to the generic medication by physicians or patients. There was no control in these studies for adherence, stress, or sleep deprivation. There is also a possible placebo effect, in which the statement by physicians that a generic might not perform as well as a brand-name drug helped to bring about those results. There has been no rigorous assessment of seizure frequency or blood levels of AEDs.

Improving Equivalence Research

Given the current state of evidential equipoise regarding the true therapeutic equivalence and switchability of generic and brand-name AEDs, an opportunity exists for better controlled studies. Three such study protocols have been designed and are currently being enacted. All of these studies are investigating the generic forms of lamotrigine.

The FDA funded the first two research projects, which are combined to form the Equivalence Among Antiepileptic Drug Generic and Brand Products in People with Epilepsy (EQUIGEN) studies. The most disparate generic products were recommended using the abbreviated new drug application data given to the FDA for generic approval plus dissolution characteristics. The first study looked at chronic dosing in people with epilepsy, comparing a high-range generic with a low-range generic. The study of chronic medication dosing is more like real life, but there was a concern that such a chronic study may introduce more variables that enhance or minimize pharmacokinetic differences. Mixing one dose of a drug could alter the bioequivalence results. The second study, then, was a single-dose study in patients with epilepsy to allow for the potential effects of concomitant medications.

The third study is being managed by the University of Maryland. Called BEEP, it is comparing the brand-name drug Lamictal with the most commonly dispensed generic version of lamotrigine, marketed by Teva.

Results of these studies are expected early in 2013. This research is focusing on bioequivalence rather than therapeutic equivalence. Even if bioequivalence is solidly established, the question of therapeutic equivalence will remain. A series of studies still needs to be done on therapeutic equivalence as well.

Although more data are pending, it is recommended that physicians research cost differences and recognize that patients who are pregnant, have a history of status epilepticus, or are seizure-free and driving a vehicle are at higher risk than others. Patients should be counseled about unauthorized formulation substitution and the need to call their physician if the pills in a newly refilled prescription look different from those obtained previously. This opportunity can also be used to counsel patients on medication adherence and avoidance of such triggers as alcohol and sleep deprivation.

CONCLUSION

Over the past few years, new medications have been approved to treat epilepsy. Many of these new drugs have novel mechanisms of action, such as targeting AMPA receptors or voltage-gated potassium channels. In addition to their indications for medication-resistant partial seizures or Lennox-Gastaut syndrome, many of these drugs have additional emerging uses. Such off-label uses include status epilepticus as well as idiopathic generalized seizures.

In addition to understanding new brand-name therapeutics, physicians also must learn the best way to integrate generic medications into their practices. Potential risks of switching from a brand-name drug to a generic medication or between different generics and potential cost savings related to such switches must be discussed with patients.

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