STATEMENT OF EDITORIAL PURPOSE

The Epilepsy Board Review Manual is a study guide for trainees and practicing physicians preparing for board examinations in epilepsy. Each manual reviews a topic essential to the current management of patients with epilepsy.

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Antiepilepsy Drugs: Pharmacodynamics and Principles of Drug Selection

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Antiepilepsy Drugs: Pharmacodynamics and Principles of Drug Selection

Jeannine M. Conway, PharmD, and Thomas R. Henry, MD

INTRODUCTION

Pharmacologic management of seizures in individual patients mainly involves drug selection based on the individual patient’s epilepsy syndrome and risks for toxicity with particular agents, followed by ongoing surveillance for antiseizure efficacy and adverse effects. These aspects of the interaction between particular drugs and individuals’ brains and other organ systems are considered the pharmacodynamics of antiepileptic drugs (AEDs), in distinction to the absorption, distribution, and elimination of drugs and drug-drug interactions, or pharmacokinetics, of AEDs. Drug selection by epilepsy syndrome may be informed by randomized prospective trials with explicit entry criteria that define a syndrome and report efficacy of an AED versus placebo with statistically rigorous analyses, and by expert consensus statements.1,2 In addition to warnings and toxicity information issued by the U.S. Food and Drug Administration (FDA), expert consensus statements also play a major role in avoiding and managing adverse effects of AEDs.3

PRINCIPLES OF DRUG SELECTION AND DOSING

INITIAL MONOTHERAPY

A dilemma encountered by prescribers is determining which antiepileptic medication should be prescribed first. The majority of the data indicate that, particularly for focal seizures, medications are essentially equally efficacious, but some statistically significant differences can be found in tolerability and side effects.4–7 The great majority of industry-sponsored clinical trials are designed as placebo-controlled, add-on therapy, prospective trials in subjects whose seizures are not well controlled by their current medications. The inclusion criteria may vary slightly, but they most often include adults with a diagnosis of complex partial seizures. As a result, most AEDs are launched initially to market to be used as adjunctive therapy with an existing AED regimen (Table 1). It is therefore difficult to extrapolate the results of those studies to all patients seen in clinic, as many may not be refractory and may not be adults.
### Table 1. Antiepileptic Drug FDA-Approved Indications

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA-Approved Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First generation</strong></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>POS, GTC seizures, mixed seizure patterns*</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Absence seizures*</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Not an FDA-approved medication</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Control of GTC seizures (grand mal) and CPS (psychomotor, temporal lobe) and prevention and treatment of seizures occurring during or following neurosurgery</td>
</tr>
<tr>
<td>Valproic acid†</td>
<td>Monotherapy and adjunctive therapy in the treatment of adult patients and pediatric patients down to age 10 years with CPS that occur either in isolation or in association with other types of seizures; also indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures in adults and children aged ≥ 10 years, and adjunctively in adults and children aged ≥ 10 years with multiple seizure types that include absence seizures</td>
</tr>
<tr>
<td><strong>Second generation</strong></td>
<td></td>
</tr>
<tr>
<td>Clobazam</td>
<td>Adjunctive treatment of seizures associated with LGS in patients aged ≥2 years</td>
</tr>
<tr>
<td>Felbamate</td>
<td>Monotherapy or adjunctive therapy in the treatment of POS, with and without generalization, in adults with epilepsy and as adjunctive therapy in the treatment of partial and generalized seizures associated with LGS in children</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Adjunctive therapy in the treatment of POS with and without secondary generalization in patients over age 12 years with epilepsy; also indicated as adjunctive therapy in the treatment of POS in pediatric patients aged 3–12 years</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Adjunctive therapy for the following seizure types in patients aged ≥2 years: POS, primary GTC seizures, generalized seizures of LGS; indicated for conversion to monotherapy in adults (age ≥16 years) with POS who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Adjunctive therapy in the treatment of POS in adults and children aged ≥1 month with epilepsy and as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents aged ≥12 years with JME; also indicated as adjunctive therapy in the treatment of primary GTC seizures in adults and children aged ≥6 years with idiopathic generalized epilepsy</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>Monotherapy or adjunctive therapy in the treatment of POS in adults and as monotherapy in the treatment of POS in children aged ≥4 years with epilepsy, and as adjunctive therapy in children aged ≥2 years with POS</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Adjunctive therapy for adult patients with POS</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>Adjunctive treatment of seizures associated with LGS in children aged ≥4 years and adults</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>Adjunctive therapy in adults and children aged ≥12 years in the treatment of POS</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Initial monotherapy in patients aged ≥2 years with POS or primary GTC seizures; safety and effectiveness in patients who were converted to monotherapy from a previous regimen of other anticonvulsant drugs have not been established in controlled trials; also indicated as adjunctive therapy for adults and pediatric patients ages 2–16 years with POS or primary GTC seizures, and in patients aged ≥2 years with seizures associated with LGS</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Adjunctive therapy for adult patients with refractory CPS who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss and monotherapy for pediatric patients with infantile spasms for whom the potential benefits outweigh the potential risk of vision loss</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Adjunctive therapy in the treatment of POS in adults with epilepsy</td>
</tr>
<tr>
<td><strong>Third generation</strong></td>
<td></td>
</tr>
<tr>
<td>Ezogabine</td>
<td>Adjunctive treatment of POS in patients aged ≥18 years</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Adjunctive therapy in the treatment of POS in patients with epilepsy aged ≥17 years</td>
</tr>
<tr>
<td>Perampanel</td>
<td>Adjunctive therapy for the treatment of POS with or without secondarily generalized seizures in patients with epilepsy aged ≥12 years</td>
</tr>
</tbody>
</table>

AED = antiepileptic drug; CPS = complex partial seizures; GTC = generalized tonic-clonic; JME = juvenile myoclonic epilepsy; LGS = Lennox-Gastaut syndrome; POS = partial-onset seizures.

*Age of patients not specified by label.

†Age not specified in enteric-coated valproate label; extended-release approved for children aged ≥ 10 years. Avoid use in children under 2 years due to risk of hepatotoxicity.
A recent study by Brodie and colleagues has provided additional insight into how patients respond to medications prescribed initially after a new diagnosis of epilepsy. They followed 1098 newly diagnosed patients for a median duration of 7.5 years. Causes of epilepsy were idiopathic for 23%, symptomatic for 41%, and cryptogenic for 35%. Their analysis revealed that 4 patterns emerge: early and sustained seizure freedom (37%), delayed and sustained seizure freedom (22%), fluctuation between periods of seizure freedom and relapse (16%), and never seizure-free for any complete year (25%).

Selecting an Agent
An initial medication is selected based on the patient’s seizure type or syndrome (Table 2). Joint statements from American Academy of Neurology and American Epilepsy Society, and most recently from the NICE guidelines from the United Kingdom, also provide guidance on selecting medications for various seizure syndromes. Once the seizure type or syndrome has been determined, other patient-specific factors should be taken into consideration. These include age, health conditions, concurrent medications, medication insurance coverage and cost considerations, and the patient’s ability and preference to take the medication as prescribed. An understanding of the pharmacokinetic properties of the various AEDs is useful to differentiate the medications available. Table 3 summarizes typical dosing for AEDs.

SUBSEQUENT THERAPY
If the first prescribed AED does not adequately control seizures, a second medication should be considered. There is adequate data to support the newer AEDs as adjunctive treatment. Ideally, the first medication should remain at the current (and/or tolerated) dose, while the second medication is titrated up to a therapeutic dose. Once the new drug is at steady-state, the first medication can be tapered off, depending on how the patient is responding to the new regimen. If the first AED resulted in a treatment emergent side effect, such as a significant rash or other hypersensitivity reaction, discontinuing it immediately is likely the most appropriate action. A second AED could be initiated with an oral or intravenous loading dose to provide adequate seizure protection.
### Table 3. Dosing of Antiepileptic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Forms</th>
<th>Available Strengths</th>
<th>Typical Oral Dosing Range and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbamazepine (Carbatrol, Tegretol, Tegretol XR)</strong></td>
<td>Capsule (ER)</td>
<td>100, 200, 300 mg</td>
<td>Child (initial, monotherapy): 5–10 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>Oral suspension</td>
<td>100 mg/5 mL</td>
<td>Adult (initial, monotherapy): 5 mg/kg/day</td>
</tr>
<tr>
<td></td>
<td>Tablet (IR)</td>
<td>200 mg</td>
<td>Child (typical maintenance): 10–40 mg/day</td>
</tr>
<tr>
<td></td>
<td>Chewable tablet</td>
<td>100 mg</td>
<td>Adult (typical maintenance): 1000–2000 mg/day</td>
</tr>
<tr>
<td></td>
<td>Tablet (ER)</td>
<td>100, 200, 400 mg</td>
<td>Adult/Child age ≥2 years &gt;30 kg (adjunct): Initially 10 mg orally daily (in 2 divided doses), titrating to 20 mg daily (2 divided doses) on day 7 and to 40 mg daily (2 divided doses) on day 14. Adult/Child age ≥2 years ≤30 kg (adjunct): Initially 5 mg orally daily (in 2 divided doses), titrating to 10 mg daily (2 divided doses) on day 7 and to 20 mg daily (2 divided doses) on day 14.</td>
</tr>
<tr>
<td><strong>Clobazam (Onfi)</strong></td>
<td>Tablet</td>
<td>5, 10, 20 mg</td>
<td>Adult: 0.5 mg orally TID initially; may increase daily dose by 0.5–1 mg orally every 3 days to a maximum total daily dose of 20 mg (in 3 divided doses). Child (up to age 10 years, or 30 kg): Initially 0.01–0.03 mg/kg/day orally divided into 2 to 3 daily doses; may increase by 0.25–0.5 mg every 3 days to a maximum total daily dose of 0.1–0.2 mg/kg/day (in 3 divided doses).</td>
</tr>
<tr>
<td></td>
<td>ODT</td>
<td>0.5, 1, 2 mg</td>
<td>Adult/Child age ≥2 years &gt;30 kg (adjunct): Initially 10 mg orally daily (in 2 divided doses), titrating to 20 mg daily (2 divided doses) on day 7 and to 40 mg daily (2 divided doses) on day 14. Adult/Child age ≥2 years ≤30 kg (adjunct): Initially 5 mg orally daily (in 2 divided doses), titrating to 10 mg daily (2 divided doses) on day 7 and to 20 mg daily (2 divided doses) on day 14.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.125, 0.25, 0.5, 1, 2 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Clonazepam (Klonopin)</strong></td>
<td>Tablet</td>
<td>0.5, 1, 2 mg</td>
<td>Adult (adjunct): 2–10 mg orally BID–QID</td>
</tr>
<tr>
<td></td>
<td>ODT</td>
<td>0.125, 0.25, 0.5, 1, 2 mg</td>
<td>Adult (adjunct): 0.2 mg/kg rectally (round up to available rectal dose); may repeat in 4–12 hours, no more than 1 episode every 5 days, and 5 episodes per month. Child: varies by age and severity; refer to PI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.25, 1, 2 mg</td>
<td>Child: varies by age and severity; refer to PI</td>
</tr>
<tr>
<td></td>
<td>Oral solution</td>
<td>5 mg/5 mL</td>
<td>Child: varies by age and severity; refer to PI</td>
</tr>
<tr>
<td><strong>Diazepam (Diastat)</strong></td>
<td>Rectal gel</td>
<td>2.5, 5, 7.5, 10, 12.5, 15, 20 mg</td>
<td>Adult (adjunct): 2–10 mg orally BID–QID</td>
</tr>
<tr>
<td></td>
<td>Oral solution</td>
<td>5 mg/5 mL</td>
<td>Adult (adjunct): 0.2 mg/kg rectally (round up to available rectal dose); may repeat in 4–12 hours, no more than 1 episode every 5 days, and 5 episodes per month. Child: varies by age and severity; refer to PI</td>
</tr>
<tr>
<td><strong>Divalproex (Depakote)</strong></td>
<td>Capsule (sprinkle)</td>
<td>125 mg</td>
<td>Adult (adjunct): 10–15 mg/kg/day orally; may increase dosage 5–10 mg/kg/wk to achieve optimal clinical response (maximum 60 mg/kg/day or less with a therapeutic range of 50–100 µg/mL). Child age 10–18 years (adjunct): 10–15 mg/kg/day orally; may increase dosage 5–10 mg/kg/wk to achieve optimal clinical response (maximum 60 mg/kg/day or less with a therapeutic range of 50–100 µg/mL).</td>
</tr>
<tr>
<td></td>
<td>Tablet (ER)</td>
<td>250, 500 mg</td>
<td>Adult (adjunct): 2–10 mg orally BID–QID</td>
</tr>
<tr>
<td></td>
<td>Tablet (DR)</td>
<td>125, 250, 500 mg</td>
<td>Adult (adjunct): 2–10 mg orally BID–QID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Child: varies by age and severity; refer to PI</td>
</tr>
<tr>
<td><strong>Ethosuximide (Zarontin)</strong></td>
<td>Capsule</td>
<td>250 mg</td>
<td>Adult (absence seizure): 500 mg orally adjusted by 250-mg increments every 4–7 days to desired therapeutic effect (doses &gt;1.5 g/day must be supervised by the patient’s physician). Child age 3–6 years (absence seizure): 250 mg orally daily, increase daily dose by 250 mg every 4–7 days as needed (doses &gt;1.5 g/day must be supervised by the patient’s physician). Child age &gt;6 years (absence seizure): 500 mg orally daily; increase daily dose by 250 mg every 4–7 days as needed (doses &gt;1.5 g/day must be supervised by the patient’s physician).</td>
</tr>
<tr>
<td></td>
<td>Oral solution</td>
<td>250 mg/5 mL</td>
<td>Adult (absence seizure): 500 mg orally adjusted by 250-mg increments every 4–7 days to desired therapeutic effect (doses &gt;1.5 g/day must be supervised by the patient’s physician). Child age 3–6 years (absence seizure): 250 mg orally daily, increase daily dose by 250 mg every 4–7 days as needed (doses &gt;1.5 g/day must be supervised by the patient’s physician). Child age &gt;6 years (absence seizure): 500 mg orally daily; increase daily dose by 250 mg every 4–7 days as needed (doses &gt;1.5 g/day must be supervised by the patient’s physician).</td>
</tr>
</tbody>
</table>

(continued on page 5)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Forms</th>
<th>Available Strengths</th>
<th>Typical Oral Dosing Range and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ezogabine (Potiga)</td>
<td>Tablet</td>
<td>50, 200, 300, 400 mg</td>
<td>Adult (age ≥18 years, adjunct): Start with 100 mg TID for 1 week; increase to maintenance dose at weekly intervals by no more than 150 mg/day; optimal effective dose between 200 mg TID to 400 mg TID</td>
</tr>
</tbody>
</table>
| Felbamate (Felbatol)  | Tablet       | 400, 600 mg         | Child age 2–14 years (Lennox-Gastaut): 15 mg/kg/day in 3 to 4 divided doses; increase by 15 mg/kg/day increments at weekly intervals; maximum dose of 45 mg/kg/day or 3600 mg/day (whichever is less)  
|                       | Oral suspension | 600 mg/5 mL     | Adult/Child 14+ years (initial): 1200 mg/day in 3 to 4 divided doses; may increase in 600-mg increments every 2 weeks to 2400–3600 mg/day  
|                       |               |                    | Adult (maintenance): 3600 mg/day |
| Gabapentin (Neurontin)| Capsule      | 100, 300, 400 mg    | Adult (adjunct): 300 mg TID; may increase up to 1800 mg/day in divided doses  
|                       | Oral solution | 250 mg/5 mL        | Child age 3–12 years (initial): 10–15 mg/kg/day in 3 divided doses  
|                       | Tablet        | 100, 300, 400, 600, 800 mg | Child age 3–4 years (maintenance): Titrate upwards over 3 days to 40 mg/kg/day in 3 divided doses  
| Lacosamide (Vimpat)   | Tablet        | 50, 100, 150, 200 mg| Adult age 17+ years (adjunct): Oral, IV: start with 50 mg orally BID, and increase by 50 mg BID every week to an initial therapeutic dose of 100 mg BID; maximum recommended dose is 200 mg BID; when switching from oral to IV formulations, the total daily dose and frequency should be the same; IV therapy should only be used temporarily for short periods of time |
|                       | Oral solution | 10 mg/mL           | Dose depends on presence of valproic acid or enzyme-inducing AED and type of seizure; refer to PI |
|                       | Injection solution | 10 mg/mL       |
| Lamotrigine (Lamictal)| Tablet (IR)  | 25, 100, 150, 200 mg| Adult (adjunct): Start with 500 mg orally BID; increase daily doses by 1000 mg every 2 weeks; target of 3000 mg/day  
|                       | Tablet (ER)  | 25, 50, 100, 200 mg | Child: Dose varies by type of seizure and age; refer to PI  
|                       | Chewable tablet | 2, 5, 25 mg     | Adult age 16+ years (adjunct): Initial dose of 1000 mg once daily; may be adjusted in increments of 1000 mg every 2 weeks to a maximum recommended daily dose of 3000 mg  
|                       | ODT          | 25, 50, 100, 200 mg |
| Levetiracetam (Keppra, Keppra XR) | Tablet | 250, 500, 750, 1000 mg | Adult (adjunct): 8–10 mg/kg/day in 2 divided doses; consider using 16–20 mg/kg/day divided in 2 divided doses if weight <20 kg  
|                       | Oral solution | 100 mg/mL        | Child age 4–16 years (initial conversion): 8–10 mg/kg/day in 2 divided doses  
|                       | Tablet (ER)  | 500, 750 mg       | Child age 4–16 years (target maintenance): range depends on patient weight (continued on page 6)  
| Oxcarbazepine (Trileptal, Oxtellar) | Tablet | 150, 300, 600 mg | Adult (initial): 300 mg BID  
|                       | Oral suspension | 300 mg/5 mL     | Adult (maintenance): 600 mg BID  
|                       | Tablet (ER)  | 150, 300, 600 mg |

(continued on page 6)
### Table 3. Dosing of Antiepileptic Drugs (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Forms</th>
<th>Available Strengths</th>
<th>Typical Oral Dosing Range and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perampanel (Fycompa)</strong></td>
<td>Tablet</td>
<td>2, 4, 6, 8, 10, 12 mg</td>
<td>Initial: 2 mg once daily at bedtime, if patient is not on enzyme inducer; 4 mg once daily at bedtime, if patient is on enzyme-inducing AED; may increase by a maximum of 2 mg daily every week (or 2 weeks) to a maximum of 12 mg once daily</td>
</tr>
<tr>
<td><strong>Phenobarbital (Luminal)</strong></td>
<td>Oral elixir</td>
<td>20 mg/5 mL</td>
<td>Adult (maintenance): 50–100 mg orally BID–TID</td>
</tr>
<tr>
<td></td>
<td>Tablet</td>
<td>15, 16.2, 30, 32.4, 60, 64.8, 97.2, 100 mg</td>
<td>Child (maintenance): 15–50 mg orally BID–TID</td>
</tr>
<tr>
<td><strong>Phenytoin (Dilantin, Phenytek)</strong></td>
<td>Capsule (ER)</td>
<td>30, 100, 200, 300 mg</td>
<td>Due to wide interindividual variability in metabolism and absorption, regimen must be individualized</td>
</tr>
<tr>
<td></td>
<td>Capsule (IR)</td>
<td>100 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Oral suspension</td>
<td>100 mg/4 mL, 125 mg/5 mL</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chewable tablet</td>
<td>50 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Pregabalin (Lyrica)</strong></td>
<td>Capsule</td>
<td>25, 50, 75, 100, 150, 200, 225, 300 mg</td>
<td>Adult (adjunct): Initial dose no greater than 75 mg orally BID or 50 mg orally TID (150 mg/day) and increase to a maximum dose of 600 mg/day in divided doses (BID or TID) based on response and tolerability</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Children: Safety and efficacy not established</td>
</tr>
<tr>
<td><strong>Primidone (Mysoline)</strong></td>
<td>Tablet</td>
<td>50, 250 mg</td>
<td>Adult age 8+ years (adjunct or monotherapy): 100–125 mg orally every night for 3 days, then increase dose by 100–125 mg/day (divided doses) every 3 days to reach a dose of 250 mg TID–QID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Child age &lt;8 years (adjunct or monotherapy): 50 mg orally every night for 3 days, then increase dose by 50 mg/day (divided doses) every 3 days to reach a dose of 125–250 mg TID</td>
</tr>
<tr>
<td><strong>Rufinamide (Banzel)</strong></td>
<td>Tablet</td>
<td>200, 400 mg</td>
<td>Adult: Initial dose of 400–800 mg/day in 2 equally divided doses and increase by 400–800 mg/day every 2 days until a maximum of 3200 mg/day in 2 equally divided doses is reached</td>
</tr>
<tr>
<td></td>
<td>Oral suspension</td>
<td>40 mg/mL</td>
<td>Children age 4+: Initial dose of 10 mg/kg/day in 2 equally divided doses and increase by 10 mg/kg increments every other day to a target dose of 45 mg/kg/day or 3200 mg/day, whichever is less, administered in 2 equally divided doses</td>
</tr>
<tr>
<td><strong>Tiagabine (Gabitril)</strong></td>
<td>Tablet</td>
<td>2, 4, 12, 16 mg</td>
<td>Adult (adjunct): 4 mg orally daily; may increase dosage by 4–8 mg/day at weekly intervals to a maximum dose of 56 mg/day (in 2–4 divided doses)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Child age 12–18 years (adjunct, with enzyme-inducing AEDs): 4 mg orally daily; may increase dosage by 4 mg/day after 7 days, then total daily dose may be increased by 4–8 mg/day at weekly intervals to a maximum dose of 32 mg/day (in 2–4 divided doses) (continued on page 7)</td>
</tr>
</tbody>
</table>
Table 3. Dosing of Antiepileptic Drugs (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage Forms</th>
<th>Available Strengths</th>
<th>Typical Oral Dosing Range and Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>Capsule (sprinkle)</td>
<td>15, 25 mg</td>
<td>Adult and child age &gt;2 years (initial monotherapy): 25 mg orally BID (AM and PM); may increase each dose by 25 mg weekly; maximum dose of 200 mg orally BID</td>
</tr>
<tr>
<td></td>
<td>Tablet</td>
<td>25, 50, 100, 200 mg</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>Capsule</td>
<td>250 mg</td>
<td>Adult (adjunct): 10–15 mg/kg/day orally (in 2–3 divided doses if total daily dose &gt;250 mg); may increase dosage 5–10 mg/kg/week to achieve optimal clinical response (maximum 60 mg/kg/day or less with a therapeutic range of 50–100 µg/mL)</td>
</tr>
<tr>
<td>(Depakene)</td>
<td>Oral syrup</td>
<td>250 mg/5 mL</td>
<td>Child age 10–18 years (adjunct): Dose as an adult</td>
</tr>
<tr>
<td>(Stavzor)</td>
<td>Capsule (DR)</td>
<td>125, 250, 500 mg</td>
<td>Child age &lt;10 years: Safety and efficacy not established</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Powder for oral solution</td>
<td>500 mg/packet</td>
<td>Adult (adjunct): 500 mg BID; may increase dosage by 500 mg/day at 1-week intervals to the usual maintenance dose of 1500 mg BID</td>
</tr>
<tr>
<td>(Sabril)</td>
<td>Tablet</td>
<td>500 mg</td>
<td>Child age 1 month–2 years (infantile spasms): Initial dose of 50 mg/kg/day (in 2 divided doses); can titrate 25–50 mg/kg/day every 3 days to maximum dose of 150 mg/kg/day</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Capsule</td>
<td>25, 50, 100 mg</td>
<td>Age 16+ years (adjunct): 100 mg/day orally; may increase dosage by 100 mg/day every 2 weeks to the usual effective dosage range of 100–600 mg/day in 1 to 2 divided doses; no additional benefit seen with doses &gt;400 mg/day</td>
</tr>
<tr>
<td>(Zonegran)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AED = antiepileptic drug; BID = twice daily; DR = delayed release; ER = extended release; IR = immediate release; ODT = orally disintegrating tablet; PI = package insert; QID = 4 times daily; TID = 3 times daily.

TOXICITY

Side Effects

In the case of AEDs, side effects are concentration-related, idiosyncratic, or due to chronic exposure. Table 4 provides a summary of side effects for the various agents. Concentration-related side effects result from an exaggeration of the pharmacologic effects of a medication. Sedation, ataxia, and headache are examples. These side effects generally are reversible with a dose reduction. It may be difficult to achieve the fine balance between controlling seizures and side effects for some patients, and multiple trials of different medications may be necessary.

Some patients remain on AEDs for decades, and chronic exposure side effects must be considered. Some chronic effects impact weight. Valproic acid is highly associated with weight gain, as are gabapentin and pregabalin, while topiramate and zonisamide are associated with weight loss. Bone health and the impact of AEDs on bone density have been of great concern over
the past decade. Unfortunately, it is not entirely clear which AEDs decrease bone density and what the mechanism of bone loss is. In the case of the enzyme-inducing AEDs (carbamazepine, phenytoin, phenobarbital), it is thought that induction of vitamin D metabolism could be responsible, but research has not consistently demonstrated this.17,18 While the data are not entirely conclusive, it is appropriate to ensure that patients are consuming adequate amounts of calcium and vitamin D.

### Table 4. Adverse Effects of Antiepileptic Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Acute Side Effects</th>
<th>Chronic Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbamazepine</strong></td>
<td>Diplopia, dizziness, drowsiness, nausea, unsteadiness, lethargy</td>
<td>Blood dyscrasias, rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyponatremia</td>
</tr>
<tr>
<td><strong>Clobazam</strong></td>
<td>Common side effects: somnolence or sedation, drooling, constipation, cough, urinary tract infection, aggression, insomnia, dysarthria, fatigue</td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Divalproex</strong></td>
<td>Tremors, unsteadiness</td>
<td>Hepatic failure, pancreatitis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CNS depression</td>
</tr>
<tr>
<td><strong>Ethosuximide</strong></td>
<td>Ataxia, drowsiness, GI distress, unsteadiness, hiccoughs</td>
<td>Blood dyscrasias, rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Behavior changes, headache</td>
</tr>
<tr>
<td><strong>Ezogabine</strong></td>
<td>Common side effects: dizziness, fatigue, confusion, hallucination, vertigo, tremor, problems with coordination, double vision, problems paying attention, memory impairment, lack of strength, urinary retention, QT prolongation</td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Felbamate</strong></td>
<td>Anorexia, nausea, vomiting, insomnia, headache</td>
<td>Aplastic anemia, acute hepatic failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Gabapentin</strong></td>
<td>Dizziness, fatigue, somnolence, ataxia</td>
<td>Pedal edema</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Weight gain, breast enlargement</td>
</tr>
<tr>
<td><strong>Lacosamide</strong></td>
<td>Dizziness, nausea, fatigue, ataxia, abnormal vision, diplopia, vertigo, and nystagmus</td>
<td>Not established</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Lamotrigine</strong></td>
<td>Diplopia, dizziness, unsteadiness, headache</td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Levetiracetam</strong></td>
<td>Sedation, behavioral disturbance</td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Oxcarbazepine</strong></td>
<td>Sedation, dizziness, ataxia, nausea</td>
<td>Rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyponatremia, hemic and lymphatic system (bone marrow depression, agranulocytosis, aplastic anemia, pancytopenia, neutropenia), pancreatitis, and/or lipase and/or amylase increase, metabolism and nutrition disorders (folic acid deficiency)</td>
</tr>
<tr>
<td><strong>Perampanel</strong></td>
<td>Dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, gait disturbance, and balance disorder, hostility and aggression</td>
<td>Not established</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Not established</td>
</tr>
<tr>
<td><strong>Phenobarbital</strong></td>
<td>Ataxia, hyperactivity, headache, unsteadiness, sedation, nausea</td>
<td>Blood dyscrasias, rash</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Behavior changes, connective tissue disorders, intellectual blunting, metabolic bone disease, mood change, sedation</td>
</tr>
</tbody>
</table>
The body of evidence showing that the enzyme-inducing AEDs have a negative effect on cholesterol levels and cardiac risk factors is growing, and the patient’s risk for cardiac events should also be considered when prescribing an AED.19–21

Idiosyncratic reactions are the most worrisome of the side effects. These reactions are unpredictable and can range from minor (pedal edema) to life-threatening, including hepatic failure and angranulocytosis. When these reactions occur, discontinuation of the offending agents is almost always required.22 Recently, there has been progress identifying genetic causes of drug reactions. Patients who carry the HLA-B*1502 allele are at high risk to develop severe cutaneous drug reactions when exposed to carbamazepine and phenytoin. This allele is significantly more prevalent in patients of Asian descent.23 The FDA recommends genetic testing in patients of Asian descent before initiating carbamazepine. Anticonvulsant hypersensitivity and drug reaction with eosinophilia and systemic symptoms (DRESS) are different
terms for essentially the same clinical diagnoses and are reported with several AEDs. Symptoms include hematologic abnormalities, other organ involvement including liver dysfunction, and skin rash. With the exception of the genetic testing for carbamazepine, there are no laboratory tests that can predict which patients are likely to develop hypersensitivity reactions. Once a patient experiences a hypersensitivity reaction, a new medication must be selected cautiously as cross-reactivity may occur. There is evidence that cross-reactivity occurs between the aromatic AEDs, phenytoin, carbamazepine, and oxcarbazepine approximately 30% of the time.

Teratogenicity

Determining if a medication causes birth defects is a complex research question. It is critical to collect data prospectively and with a large enough sample size to truly capture whether exposure to medications increases the risk of birth defects. The literature is also challenging to interpret because of variability in how research groups have tracked and defined what they reported as birth defects. In the past 12 months, several groups have published data that are helping better characterize the teratogenicity of AEDs. The North American Pregnancy Registry recently analyzed 4899 women on AED monotherapy and 442 women with epilepsy and no AED exposure. The AEDs associated with higher risk of birth defects compared to unexposed patients were topiramate, valproate, and phenobarbital. This analysis did not detect any correlation of birth defects to doses of AEDs. An analysis of data from 3909 women on monotherapy carbamazepine, lamotrigine, valproic acid, or phenobarbital from the EURAP database did demonstrate increased risks of malformations based on dose of AEDs. The reference group was women on lamotrigine taking less than 300 mg/day. AED doses that had statistically higher odds for major congenital malformations were: carbamazepine >1000 mg/day, phenobarbital ≥150 mg/per day, valproic acid ≥700 to <1500 mg per day, and valproic acid ≥1500 mg per day. Data on the newer medications is lacking in this data set. A recent report from Denmark examined 1532 pregnancies (of 837,795 live births, nationally) exposed to lamotrigine, oxcarbazepine, topiramate, gabapentin, or levetiracetam. They found no difference between the infants exposed versus the infants not exposed. The numbers of infants exposed to individual medications was quite low, and that limited the ability to detect if certain medications are more problematic. These new studies help clarify that monotherapy is best at the lowest dose possible.

The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) study group is investigating the effects of monotherapy AED exposure during pregnancy on children. There were enough women taking carbamazepine, lamotrigine, phenytoin, and valproate monotherapy to further investigate the impact of those medications on children at age 3 years. This study found that, while controlling for maternal IQ, the children exposed to valproate had statistically significantly lower IQs. A further analysis of verbal and non-verbal abilities determined that children exposed to valproate had lower scores as compared to the other AEDs. Additionally, the verbal abilities for each of the AED-exposed groups were lower than the normative data. The investigators followed-up with the children at age 4.5 years and found that the differences persist: children exposed to valproate have reduced IQs and all 4 AED exposure groups have reduced verbal abilities.

Pre-pregnancy planning discussions with women should include balancing the risks of seizures with
possible medication effects, and valproate should be avoided if possible. Folic acid supplementation should be initiated prior to conception at a dose of at least 0.4 µg/day. Consultation and monitoring by an obstetrician is recommended. For women who are not planning conception, ensuring they are using adequate contraception is critical. Many AEDs interact with hormonal contraceptives, regardless of the route of delivery, including implants, patches, and vaginal rings. Patient education is crucial, so that the risks engendered by unplanned pregnancies are minimized.

Suicidality

All prescribers should be aware of the FDA warning issued in 2008 regarding suicidal behavior and ideation and AEDs. This warning was based on a meta-analysis of pooled data from 199 clinical trials of carbamazepine, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tiagabine, topiramate, valproate, and zonisamide. The FDA has applied the warning to all AEDs, even those not included in this analysis. There is debate among the epilepsy community as to whether this warning is appropriate and warranted. Regardless, depression is not uncommon in patients with epilepsy, and prescribers should discuss mood and assess for adverse effects of AEDs.

SUMMARY OF ANTIEPILEPTIC DRUGS

Information comparing or contrasting the various AEDs is summarized in Table 3 and Table 4. Here, notable aspects of the various medications are discussed. For information about the pharmacokinetic characteristics of AEDs, refer to the previous article in this series (Epilepsy Board Review Manual, Volume 1, Part 5).

FIRST-GENERATION DRUGS

Generally, the first-generation AEDs all undergo hepatic metabolism. The majority of them are highly bound to protein, they are all involved in numerous drug interactions, and most exhibit nonlinear pharmacokinetics.

Acetazolamide

Acetazolamide is a carbonic anhydrase inhibitor that has acedotally been used to treat catamenial epilepsy. Benzodiazepines

Benzodiazepines are frequently used to treat cluster seizures or prolonged seizures. Lorazepam and diazepam are available as intravenous solutions, oral solutions (intensols), and tablets. Additionally, diazepam is available as a rectal gel for home treatment of cluster seizures. It is currently under investigation for intramuscular delivery via an autoinjector. These medications are usually dosed intermittently and reserved as rescue therapy aimed at preventing emergency department visits or hospitalization. There is increasing evidence that midazolam delivery intramuscularly in the ambulance has comparable efficacy to intravenous lorazepam at prehospital seizure cessation. An intranasal delivery formula of midazolam is also under investigation as an alternative to rectal diazepam. Clonazepam is indicated for daily, regular dosing for myoclonic, akinetic, and Lennox-Gastaut seizures, but tolerance develops and loss of efficacy may occur.

Carbamazepine

Carbamazepine induces its own hepatic clearance (autoinduction) and has an active metabolite (carbamazepine-10, 11-epoxide) that also exerts some antiseizure effects. Carbamazepine’s primary metabolic pathway is CYP 3A4, which is
responsible for metabolizing numerous medications. Carbamazepine causes enzyme induction, resulting in many drug interactions.\(^{45}\) The efficacy of carbamazepine has been demonstrated in many studies. A Veterans Affairs Epilepsy Cooperative study demonstrated that it was as efficacious as phenytoin, phenobarbital, and primidone, but better tolerated than phenobarbital and primidone.\(^{46}\) A subsequent VA study demonstrated that carbamazepine was better at controlling focal seizures and better tolerated than valproic acid.\(^{47}\) Most recently, carbamazepine was shown to be as efficacious as lamotrigine and gabapentin but not as well tolerated in an elderly veteran population with new-onset seizures.\(^{48}\)

**Ethosuximide**

Ethosuximide is primarily indicated to treat absence seizures, which usually begin in childhood. In a recent study that compared ethosuximide, valproic acid, and lamotrigine, both ethosuximide and valproic acid demonstrated similar efficacy for absence seizures, but ethosuximide was better tolerated.\(^{49}\)

**Phenytoin**

Phenytoin is unusual due to its saturable, non-linear metabolism, resulting in greater than expected blood concentrations when increasing doses. Depending on the patient, very small increases in dose (10%–30%) can cause a greater than doubling of the blood concentration.\(^{52}\) The primary metabolic pathways are CYP 2C9 and 2C19. The CYP 2C9 pathway becomes saturated first, and then the CYP 2C19 pathway becomes involved. Several polymorphisms of CYP 2C9 and 2C19 have been identified,\(^{53}\) but there is no current recommendation to routinely test patients prior to initiating phenytoin treatment. This leads to substantial interpatient variability and unpredictability between dose and concentration. Prescribers must be cautious when adjusting doses because small (10%–20%) changes can potentially result in very large changes in blood levels and side effects. Intravenous phenytoin has a pH of 11 and is incompatible in many intravenous solutions. It must be infused no faster than 50 mg/min, and patients should have electrocardiographic monitoring for potential arrhythmias.\(^{54}\) Fosphenytoin is a pro-drug of phenytoin and is rapidly hydrolyzed by phosphatases into phenytoin. This allows for a better tolerated intravenous formulation that can be delivered more quickly and safely. It can also be administered intramuscularly if necessary.\(^{55}\)

**Primidone**

Primidone is metabolized into 2 active metabolites: phenylethylmalonamide and phenobarbital. As a result, it has a side effect and drug interaction profile similar to phenobarbital. While primidone was first clinically used in 1952, the study that established its efficacy was the VA Cooperative Study that compared primidone to carbamazepine, phenytoin, and phenobarbital.\(^{50}\)
Valproic Acid
Valproic acid is available in many formulations, requiring the prescriber to be vigilant that the product desired is the one prescribed (and dispensed from the pharmacy). Valproic acid is available as syrup, a liquid-filled capsule, and a delayed-release capsule. To overcome the frequent gastrointestinal upset, it is also available as divalproex sodium (2 valproic acid molecules bound to sodium), which dissociates into valproic acid. It is available as a sprinkle, an enteric-coated tablet (delays medication release until after passing through the stomach), and an extended-release tablet (designed to release the medication over 24 hours). It is also important to note that the extended-release formulation is not equivalent to the enteric-coated formulation. Only 80% to 90% of the dose in the extended-release formulations is released. The intravenous formulation is valproate sodium, the sodium salt form of valproic acid. While valproic acid is a broad-spectrum AED and used for several seizure types, it is less frequently being recommended for use in women with child-bearing potential (see Teratogenicity section). As valproic acid doses increase, the protein binding sites saturate, resulting in a less than expected increase in blood concentrations as the doses get higher.

SECOND-GENERATION DRUGS
The second- (and third-) generation AEDs offer new mechanisms of action, fewer drug interactions, and different adverse effect profiles as compared to the first-generation agents.

Clobazam
Clobazam has been used internationally for 30 years, but only recently has received FDA approval. It is a benzodiazepine indicated for use in patients with Lennox-Gastaut syndrome. The metabolite can accumulate in patients who have lower levels of functional CYP 2C19 enzyme, and they should be started on lower doses.

Felbamate
In 1993, felbamate was the first new AED to be approved in 15 years. During the first 12 to 18 months of use, cases of aplastic anemia (33 patients) and hepatic failure (18 patients) were reported. This has resulted in felbamate being reserved for patients whose seizures remain uncontrolled despite multiple trials of AEDs in which the benefit of adding felbamate outweighs the risks. Liver function tests and hematologic evaluations should be done as clinically appropriate. It was investigated in patients with focal seizures and seizures associated with Lennox-Gastaut syndrome.

Gabapentin
The first AED that did not interact with other medications was gabapentin. Its use as an AED is limited by a short half-life that requires frequent dosing (3 to 4 times a day) to maintain consistent exposure. It is completely eliminated from the body through the kidneys. As patients age and their kidney function declines, the interval between doses can be extended.

Lamotrigine
Lamotrigine is notable for its significant drug interaction with valproic acid and for potentially increasing the risk of developing a severe rash. The half-life of lamotrigine with no interacting medications is approximately 25 hours. Valproic acid inhibits the clearance of lamotrigine, resulting in an increase in the half-life (~70 hrs), while enzyme-inducers (phenytoin, carbamazepine, phenobarbital) increase the clearance, resulting in a decrease in the half-life (~12 hrs). This requires conservative
lamotrigine dosing when adding it to a regimen that contains valproic acid. If a patient currently taking lamotrigine requires the addition of valproic acid, the patient should be closely monitored and a significant dose reduction of lamotrigine will likely be required. Relatively low doses of valproic acid have been shown to significantly inhibit lamotrigine.69 Beyond the use of lamotrigine as adjunctive treatment for focal seizures, there is evidence that lamotrigine is efficacious as adjunctive treatment for primary generalized seizures70 and as monotherapy treatment for focal or primary generalized seizures.71 It can also be considered for treatment of juvenile myoclonic epilepsy,72 particularly in women with child-bearing potential. Lamotrigine is approved for conversion to monotherapy by the FDA.

Levetiracetam

The second AED that does not interact with other medications is levetiracetam. It has become one of the first-line agents because of its convenient dosing (twice a day) and decreasing cost since becoming available generically several years ago. Its use is limited by its side effects. A recent report of patients enrolled in open-label, long-term follow-up found that the most common side effects resulting in discontinuation were depression, insomnia, anxiety, and nervousness.73 Levetiracetam is frequently used as monotherapy clinically. A meta-analysis from 2011 concluded there was adequate data to support adjunctive use, but there was not enough data to support monotherapy.74 A recent prospective, open-label, randomized, multicenter study that compared lamotrigine and levetiracetam monotherapy in newly diagnosed patients, with either focal or generalized seizures, showed no difference in efficacy or tolerability between the medications.75

Oxcarbazepine

Oxcarbazepine is an analog of carbamazepine that is approved for monotherapy use by the FDA. It is rapidly metabolized to an active metabolite, the monohydroxylated derivative (MHD). If monitoring of blood levels is desired, the MHD level should be measured. Oxcarbazepine does not induce liver enzymes to the same extent as carbamazepine, resulting in less clinically significant drug interactions.76 Hyponatremia can occur and may result in discontinuation of the medication.77 If a patient had a hypersensitivity reaction to carbamazepine, there is a 25% to 30% risk that a hypersensitivity reaction will occur with oxcarbazepine.78 There is evidence to support oxcarbazepine being prescribed as either monotherapy or adjunctive therapy for focal seizures for both adults and children.79-81

Pregabalin

Pregabalin is the third AED that does not interact with other medications. It is primarily used for neuropathic pain due to shingles, fibromyalgia, diabetes, and spinal cord injuries. Approximately 90% of a dose is eliminated in the urine unchanged. A recent meta-analysis of pregabalin monotherapy data determined there was no available data assessing pregabalin use in patients with generalized tonic-clonic seizures.82 The limited data assessing monotherapy for focal seizures show similar tolerability as compared to lamotrigine and slightly less efficacy, but there were study design limitations.83

Rufinamide

The clearance of rufinamide is increased by the enzyme-inducers (phenytoin, carbamazepine, phenobarbital) and inhibited by valproic acid. The mechanism of the interaction with valproic acid is not entirely clear.84 The molecule is insoluble in
water and dissolution is slow and erratic, resulting in lower bioavailability for the higher strength tablets. The FDA approval was based on 138 subjects with generalized seizures with Lennox-Gastaut. An additional study of patients with focal seizures demonstrated efficacy, but to a smaller magnitude compared to the previous study.

Tiagabine
Clinical experience with tiagabine has resulted in a number of reports of tiagabine-induced non-convulsive status epilepticus. In 2005 the FDA issued a warning about seizures in patients taking tiagabine for non–seizure-related reasons. This has resulted in very limited prescribing for primary generalized seizures, and data supports use as an add-on treatment in refractory partial onset seizures.

Topiramate
Topiramate is notable for its effects on cognition, including word finding difficulty. Weight loss, kidney stones, and paresthesias can also occur with topiramate treatment. It has multiple mechanisms of action and also is indicated for migraine prophylaxis and weight loss (in combination with phentermine). There is evidence to support monotherapy use for both focal and primary generalized tonic-clonic seizures.

Vigabatrin
While vigabatrin has been used internationally for about 35 years, due to visual field defects and potentially permanent vision changes, vigabatrin is subject to a risk evaluation and mitigation strategy through the FDA. Vigabatrin is only available through the manufacturer via the Share program, which requires prescribers to register and work with the manufacturer to monitor for vision changes and efficacy. Patients must also enroll with the program for safety monitoring and to obtain the medication. The new guidelines for infantile spasms place vigabatrin after adrenocorticotropic hormone as the only 2 medications with evidence of efficacy.

Zonisamide
Zonisamide is a multi-mechanism AED with weak carbonic anhydrase inhibition that shares a very similar side effect profile with topiramate. Additionally, if patients are allergic to sulfa medications, zonisamide should not be prescribed. It has a very long half-life, which may be preferable for patients who have difficulty taking medications more than once a day. Initially, the higher than expected rates of renal calculi in clinical studies resulted in delaying zonisamide’s development in the United States; however, additional studies provided evidence that the rates were not excessively high.

THIRD-GENERATION DRUGS
Ezogabine
While ezogabine was under investigational studies, its generic name was retigabine; that is still the generic name approved by the European Union. Ezogabine brings a new mechanism of action to the AED choices as a potassium channel agonist. Unlike other AEDS, ezogabine exerts an effect on urinary bladder muscles and causes urinary retention. Current evidence supports adjunctive therapy for focal seizures.

Lacosamide
Lacosamide is also free of significant drug interactions with other AEDs. Its mechanism of action is attributed to slow inactivation of sodium channels. Lacosamide was studied with total daily
doses of 200, 400, and 600 mg. In this study, efficacy was seen with the 200-mg and 400-mg doses, but without additional response at the 600-mg dose. Side effects were greater at the 600-mg dose. An additional study compared 200 mg versus 400 mg and found no difference in efficacy between the doses. A third study compared 400 mg versus 600 mg and demonstrated they were similarly efficacious. Post hoc analysis of the clinical trials indicates that lacosamide is best tolerated when used in combination with non–sodium channel blocking AEDs. Patients did not tolerate higher dosages of lacosamide when also taking phenytoin, carbamazepine, oxcarbazepine, and lamotrigine.

**Perampanel**

As a recently approved AED, perampanel has a unique mechanism of action as the first AMPA inhibitor reducing the action of glutamate. It is also notable for its long half-life, which enables once-daily dosing. Three clinical trials have been conducted evaluating a variety of doses. While a new mechanism of action provides options for patients, perampanel appears to have some significant psychiatric effects that will require close monitoring, including aggression, hostility, irritability, and anger.

**OTHER CONSIDERATIONS**

Many of the AEDs are now available as generic products. There is much concern that generic AEDs are not truly equivalent to the innovator products. The American Academy of Neurology has issued a statement that opposes AED substitution without prescriber consent. Bioequivalence is determined by the rate and extent a generic medication is absorbed as compared to the innovator formulation. Generally, these studies are conducted as single-dose fed and fasting randomized cross-over (and occasionally multiple-dose) studies in healthy adults. If the rate and absorption 90% confidence intervals are within 80% to 125% of the innovator product, they are determined to be bioequivalent (FDA guidance).

Most of the data to date indicating that there may be problems with switching from branded AEDs to a generic is observational and lacks the rigor of a randomized, placebo-controlled clinical study design. A 2010 meta-analysis found only 9 randomized controlled trials that were available for their analysis, and all were published between 1986 and 1997. The Agency for Healthcare Research Quality conducted a comparative effectiveness review to examine the data surrounding effectiveness and safety of antiepileptic medications in patients with epilepsy. As part of the review, they examined the data available on innovator versus generic drugs. The strength of evidence for the 18 articles that met inclusion criteria was rated primarily as low or insufficient. They did not detect a difference between generics and innovators in terms of seizure occurrence, seizure frequency, blood concentrations, or adverse events.

There are continuing discussions between the neurology community and the FDA as to how equivalence should be best determined. It is important to recognize that there is no requirement for bioequivalence testing between generic manufacturers. In lieu of data either supporting or disproving generic-to-generic equivalency, it is best if a patient can be maintained on the same manufacturer, if possible. A generic manufacturer can be specified by the prescriber by indicating “dispense as written, medically necessary.” The laws surrounding if and how a pharmacist can substitute when dispensing medication vary by state.
REFERENCES


51. Sulzbacher S, Farwell JR, Temkin N, et al. Late cognitive...


