Update on Antiepileptic Drugs 2019

By Bassel W. Abou-Khalil, MD, FAAN

EDITOR’S NOTE
The article “Update on Antiepileptic Drugs 2019” by Dr Abou-Khalil was first published in the February 2016 Epilepsy issue of Continuum: Lifelong Learning in Neurology as “Antiepileptic Drugs” and has been updated by Dr Abou-Khalil for this issue.

ABSTRACT
PURPOSE OF REVIEW: This article is an update from the article on antiepileptic drug (AED) therapy published in the last Continuum issue on epilepsy and is intended to cover the vast majority of agents currently available to the neurologist in the management of patients with epilepsy. Treatment of epilepsy starts with AED monotherapy. Knowledge of the spectrum of efficacy, clinical pharmacology, and modes of use for individual AEDs is essential for optimal treatment for epilepsy. This article addresses AEDs individually, focusing on key pharmacokinetic characteristics, indications, and modes of use.

RECENT FINDINGS: Since the previous version of this article was published, three new AEDs, brivaracetam, cannabidiol, and stiripentol, have been approved by the US Food and Drug Administration (FDA), and ezogabine was removed from the market because of decreased use as a result of bluish skin pigmentation and concern over potential retinal toxicity. Older AEDs are effective but have tolerability and pharmacokinetic disadvantages. Several newer AEDs have undergone comparative trials demonstrating efficacy equal to and tolerability at least equal to or better than older AEDs as first-line therapy. The list includes lamotrigine, oxcarbazepine, levetiracetam, topiramate, zonisamide, and lacosamide. Pregabalin was found to be less effective than lamotrigine. Lacosamide, pregabalin, and eslicarbazepine have undergone successful trials of conversion to monotherapy. Other newer AEDs with a variety of mechanisms of action are suitable for adjunctive therapy. Most recently, the FDA adopted a policy that a drug’s efficacy as adjunctive therapy in adults can be extrapolated to efficacy in monotherapy. In addition, efficacy in adults can be extrapolated for efficacy in children 4 years of age and older. Both extrapolations require data demonstrating that an AED has equivalent pharmacokinetics between its original approved use and its extrapolated use. In addition, the safety of the drug in pediatric patients has to be demonstrated in clinical studies that can be open label. Rational AED combinations should avoid AEDs with unfavorable pharmacokinetic interactions or pharmacodynamic interactions related to mechanism of action.
SUMMARY: Knowledge of AED pharmacokinetics, efficacy, and tolerability profiles facilitates the choice of appropriate AED therapy for patients with epilepsy.

INTRODUCTION

Antiepileptic drugs (AEDs) are the mainstay of epilepsy therapy. Until 1993, the choice of AED was limited to seven or eight major agents. However, more than 17 new AEDs have been approved and marketed since then. With such a large choice of AEDs, much guidance is needed in the choice of AEDs for initial therapy, later replacement monotherapy, or adjunctive therapy. Considerations in AED choice must include the spectrum of efficacy of the AED (TABLE 11-1), its pharmacokinetic properties (TABLE 11-2), its safety and tolerability profile, and its efficacy against comorbidities, as relevant to the patient’s specific circumstances. This article addresses each AED, focusing on indications, tolerability, and clinical use. Relevant pharmacokinetic properties are also discussed. This article focuses on AED use in adults; however, salient features related to use in children are highlighted throughout the text. TABLE 11-3 summarizes AED dosing in children, and TABLE 11-4 summarizes teratogenicity data for AEDs. The order in which AEDs are presented is roughly based on the order in which AEDs were marketed, although related AEDs will be discussed together with their oldest relative.

PHENOBARBITAL

Phenobarbital has been in clinical use since 1912, although initially used as a sedative and sleep aid. Its main mechanism of action is through binding the y-aminobutyric acid (GABA)-A receptor, prolonging the opening of the associated chloride channel. It is available as an oral preparation as well as a parenteral solution. It has excellent oral bioavailability and relatively low protein binding. It is mostly metabolized in the liver, but approximately one-quarter of the dose is eliminated unchanged in the urine. It has a long half-life of approximately 80 to 100 hours. Phenobarbital is a potent hepatic P450 enzyme inducer, accelerating the metabolism of medications processed by this enzyme system and reducing their plasma concentration. This affects its use in combination therapy because it may render concomitant AEDs less effective if they are metabolized by the liver.

Phenobarbital is effective against focal seizures and generalized tonic-clonic seizures but is not effective against generalized absence seizures. The parenteral solution has been used effectively for status epilepticus.

The suggested maintenance dose is 1 mg/kg/d to 2.5 mg/kg/d, but a much lower starting dose is recommended, such as 30 mg to 60 mg at bedtime. The dose can be increased by 30 mg to 60 mg every 2 weeks as needed, depending on seizure control and tolerability. A once-daily dose at bedtime may reduce sedation and is adequate because of its long half-life. The recommended serum concentration is 15 mg/L to 40 mg/L.

Phenobarbital’s main adverse effects are sedation, decreased concentration, and mood changes, particularly depression. In children, it can cause hyperactivity. Long-term use is associated with decreased bone density, Dupuytren contractures, plantar fibromatosis, and frozen shoulder. It is not recommended in pregnancy because of teratogenicity with increased risk of

KEY POINTS

- Phenobarbital, primidone, phenytoin, and carbamazepine are potent inducers of liver enzymes, reducing the efficacy of drugs metabolized by the cytochrome P450 enzyme system.
- Long-term phenobarbital use is associated with decreased bone density, Dupuytren contractures, plantar fibromatosis, and frozen shoulder.
cardiac malformations in the exposed fetus. Evidence also exists of decreased cognitive abilities in males exposed in utero. Phenobarbital is a controlled substance.

**Place in Therapy**

Because of its adverse effect on cognitive function and its enzyme induction, phenobarbital is used very infrequently as first-line therapy in developed countries. However, its low cost and wide availability make it the only affordable AED in much of the developing world. In addition, there has been some debate about adverse cognitive effects; one study in rural China reported no major negative cognitive effects, and some cognitive gains, likely related to improved seizure control.  

### TABLE 11-1 Spectrum of Efficacy of Select Antiepileptic Drugs

<table>
<thead>
<tr>
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<tbody>
<tr>
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<td>Class I trials</td>
<td>Suggested, but not proven in Class I trials</td>
<td>Not effective</td>
<td>Class IV evidence</td>
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<td>Phenytoin</td>
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<td>Carbamazepine</td>
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<td>Eslicarbazepine acetate</td>
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<td>Clobazam</td>
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<td>Class I trialsLennox-Gastaut syndrome</td>
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<td>Felbamate</td>
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<td>Gabapentin</td>
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<td>Not effective</td>
<td>Not effective</td>
<td></td>
</tr>
<tr>
<td>Pregabalin</td>
<td>Class I trials</td>
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</table>

CONTINUED ON PAGE 511
PRIMIDONE
Primidone is converted in the liver to phenobarbital and phenylethylmalonamide, which is also an active metabolite. It is available only as an oral preparation. When used in monotherapy, about 25% of oral primidone is converted to phenobarbital. The half-life of primidone is 10 to 15 hours in monotherapy and 6.5 to 8.3 hours with enzyme inducers. Primidone is a potent enzyme inducer.

Primidone is effective against focal seizures and generalized tonic-clonic seizures. Anecdotal evidence also exists of efficacy against myoclonic seizures. Primidone is also effective in controlling essential tremor.

In addition to sedation and other adverse effects of phenobarbital, primidone use is associated with an acute toxic reaction unrelated to phenobarbital, with potentially debilitating drowsiness, dizziness, ataxia, nausea, and vomiting.

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<td>Class I trials</td>
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FDA = US Food and Drug Administration.

a Blank cells in this column represent no convincing or Class I data.
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<tr>
<th>Antiepileptic Drug</th>
<th>Oral Bioavailability</th>
<th>Protein Binding&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Metabolism</th>
<th>Half-life&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Potential for Pharmacokinetic Interactions</th>
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<td>Extensive</td>
<td>Intermediate</td>
<td>Moderate</td>
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<td>~65%</td>
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<td>Rufinamide</td>
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<td>Extensive</td>
<td>Short</td>
<td>Moderate</td>
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<tr>
<td>Perampanel</td>
<td>Good</td>
<td>Low</td>
<td>Extensive</td>
<td>Long</td>
<td>Moderate</td>
</tr>
<tr>
<td>Cannabidiol</td>
<td>Low</td>
<td>High</td>
<td>Extensive</td>
<td>Long</td>
<td>High</td>
</tr>
</tbody>
</table>

<sup>a</sup> Low: <50%; intermediate: 50% to 85%; high: >85%.

<sup>b</sup> Short: <10 hours; intermediate: 10 to 30 hours; long: >30 hours.
Place in Therapy

Primidone was the least-tolerated agent in the large cooperative US Department of Veterans Affairs trial comparing the efficacy and tolerability of carbamazepine, phenobarbital, phenytoin, and primidone. As a result, it is infrequently used. In view of the acute toxic adverse effects, primidone should be started at a low dose, for example 50 mg to 125 mg at bedtime, then increased gradually by 50 mg to 125 mg every 3 to 7 days to 250 mg 3 times a day.

PHENYTOIN

Phenytoin has been in clinical use since 1938 when its efficacy in the maximum electroshock animal model was discovered. Phenytoin binds to the active state of the sodium channel to prolong its fast inactivated state, thus reducing high-frequency firing as might occur during a seizure, while allowing normal action potentials to occur. It is available as an oral preparation and a parenteral solution, and a phenytoin prodrug, fosphenytoin, is available for IV and IM administration.

Phenytoin bioavailability is reduced with coadministration of calcium, antacids, and nasogastric feedings. It is highly protein bound at approximately 90%. It is metabolized in the liver, mostly by cytochrome P450 (CYP) 2C9 and, to a lesser extent, CYP 2C19. Phenytoin’s metabolism is saturable, resulting in nonlinear kinetics. As the serum concentration increases, it reaches a point within the recommended therapeutic range after which the half-life starts increasing. Beyond that point, the phenytoin plasma level increases disproportionately with an increase in the dose (FIGURE 11-1).

Phenytoin is a potent enzyme inducer that reduces the efficacy of drugs metabolized by the P450 enzyme system. Phenytoin is also affected by a number of agents that reduce its metabolism and cause it to accumulate. These include amiodarone, fluoxetine, fluvoxamine, isoniazid, and azole antifungal agents. The phenytoin protein-free fraction may increase with hepatic and renal failure, in low-protein states, during pregnancy, in old age, and in the presence of highly protein-bound drugs, such as valproate, that compete for protein binding. This is of clinical relevance when decisions are made based on total phenytoin serum concentration.

Phenytoin is effective against focal seizures and generalized tonic-clonic seizures. Phenytoin is not effective against generalized myoclonic or generalized absence seizures and may even exacerbate these seizures; hence, it is not a drug of choice in idiopathic generalized epilepsy.

The usual phenytoin initiation dose is 200 mg/d to 400 mg/d, initially given as a bedtime dose. Titration is primarily based on clinical response but also takes into consideration the serum concentration. The recommended “therapeutic” serum concentration is 10 mg/L to 20 mg/L; the protein-free recommended “therapeutic” serum concentration is 1 mg/L to 2 mg/L. Protein-free phenytoin levels should be checked in clinical situations where the protein-free fraction is expected to be increased. In view of nonlinear kinetics, small increments (eg, 30 mg to 60 mg) should be used when the phenytoin level is in the “therapeutic range” but the clinical situation warrants optimization of therapy. Extended-release capsules are preferred. Dosing 2 times a day may be needed when seizures are drug resistant. Phenytoin can be loaded orally at 18 mg/kg divided into 3 doses given 2 to 3 hours apart (or even as a single dose if needed).

The IV preparation of phenytoin is associated with local reactions, including burning pain, phlebitis, cellulitis, and, rarely, the purple glove syndrome. IM
administration is contraindicated because of erratic absorption and sterile abscess formation. The phenytoin water-soluble prodrug fosphenytoin is preferred for parenteral use. It has a lower incidence of local reactions with IV administration. It is also well absorbed after IM administration, which can be considered in the absence of IV access. When administered intravenously in an awake individual, it may be associated with paresthesia and pruritis, most often in the groin region. IV administration of either phenytoin or fosphenytoin can be associated with hypotension and arrhythmias, so ECG and blood pressure

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>Starting Total Daily Dose</th>
<th>Titration</th>
<th>Target Total Daily Dose; Usual Maximal Effective Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>1–3 mg/kg/d</td>
<td>1 mg/kg/d every 1–2 weeks</td>
<td>3 mg/kg/d; up to 8 mg/kg/d</td>
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<td>Phenytoin</td>
<td>5–7 mg/kg/d</td>
<td>No titration needed</td>
<td>6–8 mg/kg/d; up to 10 mg/kg/d (may be guided by serum concentration)</td>
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<td>Carbamazepine</td>
<td>10–20 mg/kg/d</td>
<td>Increase weekly using 100 mg increments</td>
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<tr>
<td>Oxcarbazepine</td>
<td>8–10 mg/kg/d</td>
<td>5–10 mg/kg/d every 3–7 days as needed</td>
<td>30–50 mg/kg/d; usually &lt;60 mg/kg/d</td>
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<tr>
<td>Eslicarbazepine acetate</td>
<td>10–20 mg/kg/d (200–400 mg/d depending on weight)</td>
<td>200–400 mg/wk as needed</td>
<td>20–60 mg/kg/d (400–1200 mg/d depending on weight)</td>
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<td>Valproate</td>
<td>15 mg/kg/d</td>
<td>5–10 mg/kg/d every week</td>
<td>30 mg/kg/d; up to 60 mg/kg/d with enzyme-inducing antiepileptic drugs</td>
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<td>Ethosuximide</td>
<td>10–15 mg/kg/d</td>
<td>5 mg/kg/d every week as needed</td>
<td>20–30 mg/kg/d; up to 40 mg/kg/d</td>
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<td>Clobazam</td>
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<td>0.1 mg/kg/d every week as needed</td>
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<td>Felbamate</td>
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<td>15 mg/kg/d every week</td>
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<td>Gabapentin</td>
<td>10–15 mg/kg/d</td>
<td>10 mg/kg/d every day</td>
<td>40 mg/kg/d; up to 50 mg/kg/d</td>
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</table>

Lamotrigine

Monotherapy for weeks 1 and 2: 0.3 mg/kg/d

Monotherapy for weeks 3 and 4: 0.6 mg/kg/d; week 5 and on: increase by 0.6 mg/kg/d every 1–2 weeks

Maintenance dose for monotherapy: 4.5–7.5 mg/kg/d

With valproate: 0.15 mg/kg/d

With valproate for weeks 3 and 4: 0.3 mg/kg/d; week 5 and on: increase by 0.3 mg/kg/d every 1–2 weeks

With valproate: 1–5 mg/kg/d

With enzyme inducer: 0.6 mg/kg/d

With enzyme inducer for weeks 3 and 4: 1.2 mg/kg/d; week 5 and on: increase by 1.2 mg/kg/d every 1–2 weeks

With enzyme inducers: 5–15 mg/kg/d

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monitoring are recommended, and the rate of IV administration should not exceed 50 mg/min for phenytoin and 150 mg/min for fosphenytoin. Phenytoin is less sedating than phenobarbital but nevertheless may have cognitive adverse effects in some individuals, even within the therapeutic range. Adverse effects that occur with high concentrations include ataxia, incoordination, dysarthria, nystagmus, and diplopia. A paradoxical increase in seizures has been documented with concentrations exceeding 30 mg/L. Idiosyncratic reactions include allergic rash (almost 6% in a study based on CONTINUED FROM PAGE 514

<table>
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<tr>
<th>Antiepileptic Drug</th>
<th>Starting Total Daily Dose</th>
<th>Titration</th>
<th>Target Total Daily Dose; Usual Maximal Effective Dose</th>
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</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>1–3 mg/kg/d</td>
<td>1–3 mg/kg/d every 1–2 weeks</td>
<td>5–9 mg/kg/d</td>
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<td>Levetiracetam</td>
<td>20 mg/kg/d (infants 1 month to &lt;6 months of age: 14 mg/kg/d)</td>
<td>10 mg/kg/d every 1–2 weeks</td>
<td>Children 4 years to &lt;16 years: 60 mg/kg/d; children 6 months to &lt;4 years: 50 mg/kg/d; infants 1 month to &lt;6 months: 42 mg/kg/d</td>
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<td>Brivaracetam</td>
<td>1–2 mg/kg/d</td>
<td>Dose adjustment based on response</td>
<td>1–5 mg/kg/d (pediatric patients weighing &gt;50 kg [110 lb]: initial dose of 50–100 mg/d with maximum dose of 200 mg/d)</td>
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<tr>
<td>Zonisamideb</td>
<td>1 mg/kg/d</td>
<td>2 mg/kg/d every 2 weeks as needed</td>
<td>Usual dose of 4–8 mg/kg/d with maximum dose of 12 mg/kg/d</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>20 mg/kg/d</td>
<td>20 mg/kg/d every week as needed</td>
<td>40–60 mg/kg/d</td>
</tr>
<tr>
<td></td>
<td>Infantile spasms: 50 mg/kg/d</td>
<td>Infantine spasms: Increase to 100 mg/kg/d after 5 days</td>
<td>Infantine spasms: 100 mg/kg/d; maximum dose is 150 mg/kg/d</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>10 mg/kg/d; in the presence of valproate, the starting dose should be ~5 mg/kg/d</td>
<td>Increase by 10 mg/kg/d every other day; in the presence of valproate, titration rate should be ~5 mg/kg/d every other day</td>
<td>45 mg/kg/d; in the presence of valproate, target dose should be 20–30 mg/kg/d</td>
</tr>
<tr>
<td>Perampanel</td>
<td>2 mg/d</td>
<td>Increase by 2 mg as needed, no more frequently than weekly</td>
<td>8–12 mg/d</td>
</tr>
<tr>
<td>Cannabidiol</td>
<td>5 mg/kg/d</td>
<td>Increase by 5 mg/kg/d every week as needed</td>
<td>20 mg/kg/d</td>
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</table>

* Generally applicable to children younger than 12 years of age. The dosing is provided for antiepileptic drugs that have at least been tested in children.

b Not US Food and Drug Administration-approved for children.
clinical practice)\textsuperscript{5} and, rarely, Stevens-Johnson syndrome, toxic epidermal necrolysis, or hypersensitivity syndrome with fever, rash, lymphadenopathy, eosinophilia, and liver and renal impairment. Adverse effects associated with long-term use include gingival hyperplasia, acne, hirsutism, cerebellar atrophy, decreased bone density, anemia, and peripheral neuropathy.

**Place in Therapy**
Phenytoin was the most frequently used AED for many years, but its use has declined considerably since the appearance of newer AEDs with improved

<table>
<thead>
<tr>
<th>Antiepileptic Drug Teratogenicity\textsuperscript{a}</th>
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<tbody>
<tr>
<td><strong>Antiepileptic Drug</strong></td>
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<tr>
<td>Phenobarbital\textsuperscript{c}</td>
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<tr>
<td>Phenytoin</td>
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<tr>
<td>Carbamazepine</td>
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<tr>
<td>Oxcarbazepine</td>
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<tr>
<td>Eslicarbazepine acetate</td>
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<tr>
<td>Valproate\textsuperscript{e}</td>
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<td>Ethosuximide</td>
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<td>Clobazam</td>
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<td>Felbamate</td>
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<td>Gabapentin</td>
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<td>Pregabalin</td>
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<td>Lamotrigine</td>
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<td>Topiramate</td>
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<td>Tiagabine</td>
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<td>Levetiracetam</td>
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<td>Brivaracetam</td>
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<td>Zonisamide</td>
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<td>Lacosamide</td>
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<td>Vigabatrin</td>
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<tr>
<td>Rufinamide</td>
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<tr>
<td>Perampanel</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Data are extracted from North American and European registries.\textsuperscript{1,2} When the two registries differed in malformation rate, a weighted average was used.

\textsuperscript{b} Low: <3%; intermediate: 3.1% to 6%; high: 6.1% to 9%; very high: >9%.

\textsuperscript{c} An additional negative effect is decreased IQ in male offspring.

\textsuperscript{d} The two registries had different results.

\textsuperscript{e} Additional negative effects are decreased verbal IQ and autism.
CARBAMAZEPINE

Carbamazepine’s mechanism of action is similar to that of phenytoin. It blocks the sodium channel in a voltage-dependent and use-dependent fashion, reducing high-frequency neuronal firing.

Carbamazepine was only available as an oral preparation until a parenteral preparation was approved in 2016 as temporary replacement therapy when oral administration is not feasible. Carbamazepine has good oral bioavailability. Its protein binding of about 75% is not of clinical importance. It is metabolized in the liver, mainly by CYP 3A4; the most important metabolite is carbamazepine-10,11-epoxide. It is an active metabolite also responsible for some adverse effects. Carbamazepine is a potent enzyme inducer, reducing the levels of drugs as well as endogenous substances metabolized by the CYP enzyme system. Carbamazepine also induces its own metabolism, a process known as autoinduction, which results in increased clearance over 2 to 4 weeks, with shortened half-life and lower serum concentration. Carbamazepine may accumulate when coadministered with inhibitors of CYP 3A4, such as erythromycin and other macrolide antibiotics (except azithromycin), fluoxetine, propoxyphene, and grapefruit juice. Carbamazepine epoxide levels increase with concomitant use of some inhibitors, such as valproate and felbamate.

Carbamazepine is effective against focal seizures and generalized tonic-clonic seizures. However, it may exacerbate absence, myoclonic, and atonic seizures. Hence, it is not a good choice in idiopathic generalized epilepsy. It has US Food and Drug Administration (FDA) indications for trigeminal neuralgia and for acute mania and bipolar disorder. The starting dose is 100 mg 2 times a day or 200 mg at bedtime when the extended-release preparation is used. The dose can be increased by 200 mg every 3 days to a target total daily dosage of 400 mg to 800 mg in two divided doses, and the dose can be increased further, if needed, for persistent seizures. When immediate-release formulations of carbamazepine are used, administration in 3 divided doses is recommended, although patients may have difficulty adhering to this more complex dosing schedule. The
extended-release preparation, indicated for dosing 2 times a day, provides steadier levels with evidence for improved tolerability as well as efficacy. The recommended therapeutic range of carbamazepine concentration is 4 mg/L to 12 mg/L.

Adverse effects noted with carbamazepine include nausea, headache, dizziness, sedation, and tiredness. Cognitive impairment has been reported on neuropsychological testing. With elevated levels, there may be blurred vision, diplopia, nystagmus, unsteadiness, incoordination, and tremor. Hyponatremia may occur. Weight gain and decreased bone density are reported with long-term use. Mild leukopenia seen in 10% to 20% of patients is usually benign, although it may be persistent; the more serious aplastic anemia is rare (estimated at 1 in 200,000). It is advisable to check a complete blood cell count and liver enzymes before initiating therapy, after 2 to 3 months of treatment, then every 6 to 12 months as needed depending on the clinical setting. Idiosyncratic adverse experiences include rash, which may be less common than with phenytoin. Stevens-Johnson syndrome and toxic epidermal necrolysis are rare but more likely with the HLA-B*502 allele in individuals of Asian descent, for whom genetic testing of HLA-B polymorphisms is indicated prior to initiation. Other rare idiosyncratic adverse effects include a lupuslike syndrome, hepatotoxicity, and hypersensitivity syndrome with fever, rash, and organ involvement. Carbamazepine use in polytherapy has been associated with increased risk of spina bifida in infants exposed during gestation. Abrupt withdrawal may be associated with severe rebound seizures.

**Place in Therapy**

Carbamazepine had the best balance of efficacy and tolerability in the large cooperative US Department of Veterans Affairs study that also included phenytoin, phenobarbital, and primidone. As a result, it became the standard treatment for focal seizures. No drug has been demonstrated to be more effective than carbamazepine, but its use has declined with the marketing of new AEDs that have pharmacokinetic advantages. Lamotrigine, oxcarbazepine, and gabapentin have better tolerability than immediate-release carbamazepine. However, comparative trials using extended-release carbamazepine have failed to show superior tolerability of lamotrigine, levetiracetam, zonisamide, or lacosamide. Nevertheless, enzyme induction and pharmacokinetic interactions have been issues favoring newer AEDs. On the other hand, economic considerations favor the less-expensive carbamazepine.

**OXCARBAZEPINE**

Oxcarbazepine is a structural analogue of carbamazepine, but the minor structural differences have resulted in major differences in metabolism and induction of metabolic pathways. Like carbamazepine and phenytoin, oxcarbazepine binds to the sodium channel, inhibiting high-frequency repetitive neuronal firing. Oxcarbazepine is only available as an oral preparation.

Oxcarbazepine has excellent oral bioavailability. It is very rapidly converted to the monohydroxy derivative, which has two enantiomers, the active S-licarbazepine, responsible for most of oxcarbazepine’s antiseizure activity (80%), and R-licarbazepine (less active but contributes to adverse effects). Its protein binding is not clinically important. The half-life of oxcarbazepine is only 1 to 3.7 hours, and that of the monohydroxy derivatives is 8 to 10 hours.
Oxcarbazepine is a weak inducer of CYP 3A4, which is responsible for estrogen metabolism, and reduces the efficacy of the oral contraceptive pill at high doses, usually greater than 900 mg/d. It is a weak inhibitor of CYP 2C19, thus raising the phenytoin level when used at high doses. It does not induce its own metabolism. Unlike carbamazepine, it is not affected by CYP 3A4 inhibitors, such as erythromycin, fluoxetine, propoxyphene, and grapefruit juice.

Oxcarbazepine is effective against focal seizures. It may exacerbate absence and myoclonic seizures and should be avoided in patients with generalized epilepsy. It can be started at the dose of 300 mg 2 times a day, but in the absence of urgency, it is better to start at 150 mg 2 times a day. The dose can be titrated by 300 mg per week as needed. The highest dose used in clinical trials was 1200 mg 2 times a day. An extended-release preparation is available, allowing for once-daily dosing. The recommended therapeutic range for the monohydroxy derivative is 15 mg/L to 35 mg/L. Conversion from carbamazepine can be made overnight by using 300 mg of oxcarbazepine for every 200 mg of carbamazepine when the carbamazepine dose is 800 mg or less. A slower conversion and lower ratio are advisable with higher carbamazepine doses. Conversion from carbamazepine may be accompanied by reduction in sodium concentration and increased levels of concomitant medications metabolized by the CYP enzyme system.

Oxcarbazepine may cause drowsiness, headache, and fatigue. Higher doses can cause dizziness, blurred vision, diplopia, nausea, vomiting, and ataxia. Rash may occur in 2% to 4% of individuals; oxcarbazepine has 25% cross-reactivity with carbamazepine. Oxcarbazepine is more likely to cause hyponatremia than carbamazepine is18,19; symptomatic hyponatremia is more likely in older individuals and those taking a diuretic. Abrupt withdrawal may be associated with severe rebound seizures.20

Place in Therapy
Oxcarbazepine is approved as a first-line monotherapy for focal seizures. Multiple comparative monotherapy trials for new-onset focal epilepsy have demonstrated that oxcarbazepine is equal in efficacy to phenytoin and immediate-release carbamazepine but with possibly superior tolerability.21,22 Combining oxcarbazepine with other classic sodium channel blockers, such as carbamazepine, lamotrigine, and phenytoin, may limit tolerability because of dizziness, diplopia, and ataxia.

ESLICARBZEPINE ACETATE
Eslicarbazepine acetate was approved for marketing in the United States in 2014, but it is listed here because it represents a third-generation relative of carbamazepine and oxcarbazepine. It is a prodrug rapidly converted to the active metabolite S-licarbazepine, also known as eslicarbazepine, the active enantiomer of the monohydroxy derivative of oxcarbazepine. Eslicarbazepine acts by blocking sodium channels and stabilizing the inactive state of the voltage-gated sodium channel. A 2015 study suggested that, unlike carbamazepine, it may enhance slow inactivation of voltage-gated sodium channels.23 It is available only as an oral preparation.

Eslicarbazepine is metabolized to inactive compounds, but more than 50% is excreted in the urine as unchanged eslicarbazepine. The half-life of

KEY POINTS
- The HLA-B1502 allele is predictive of a carbamazepine-induced severe rash in individuals of Asian descent.
- Oxcarbazepine is more likely to cause hyponatremia than carbamazepine. Older individuals taking a diuretic are at particularly high risk.
Eslicarbazepine is 13 to 20 hours in plasma and 20 to 24 hours in CSF, justifying once-daily dosing. Unlike oxcarbazepine, eslicarbazepine acetate is not followed by a CSF spike, which is suspected to be responsible for acute adverse effects. Eslicarbazepine is a weak inducer of CYP 3A4, potentially decreasing plasma concentrations of estrogen and other molecules metabolized by this enzyme, and a weak inhibitor of CYP 2C19, potentially increasing the plasma concentration of phenytoin and other drugs metabolized by this enzyme.

Eslicarbazepine acetate is effective against focal seizures. The recommended starting dose is 400 mg once daily, to be increased to 800 mg once daily after 1 week. If needed, the dose can be increased again to 1200 mg/d after 1 week. In a 2015 successful conversion to monotherapy study, a dose of 1600 mg/d was used.

Eslicarbazepine acetate has adverse effects similar to oxcarbazepine, although less frequent. The most common dose-related adverse effects are dizziness, somnolence, headache, diplopia, nausea, vomiting, fatigue, and ataxia. Hyponatremia was less commonly reported than in oxcarbazepine trials. Sodium levels of 125 mEq/L or lower were reported in up to 1.5% of individuals taking 1200 mg/d. Rash occurs in up to 3% of individuals at 1200 mg/d.

Place in Therapy
Eslicarbazepine acetate was first approved by the FDA as adjunctive treatment for focal seizures. A monotherapy indication followed after successful completion of a conversion to monotherapy trial. Like oxcarbazepine, it should be avoided in idiopathic generalized epilepsy. Theoretical considerations suggest eslicarbazepine acetate could be considered a first-line monotherapy for focal seizures, with tolerability advantages over immediate-release oxcarbazepine. However, financial considerations may be an obstacle.

Valproic Acid/Divalproex Sodium (Valproate)
Valproate has multiple mechanisms of action, including GABA potentiation, blocking of T-type calcium channels (predictive of efficacy against absence seizures), and blocking of sodium channels. It is available as oral preparations (mainly in the form of divalproex sodium, a complex of valproate and sodium valproate) and parenteral valproate sodium preparation. Oral bioavailability is almost complete, although slightly less for the extended-release preparation. It is highly protein bound at about 90%. The free fraction increases with increasing total concentration and with coadministration of phenytoin, with which it competes for protein binding.

Valproate is extensively metabolized by conjugation and oxidation. The half-life in adults is 13 to 16 hours but shorter at about 9 hours with enzyme-inducing drugs. It is a potent inhibitor, reducing the clearance of phenobarbital, lamotrigine, rufinamide, and carbamazepine epoxide.

Valproate has a wide spectrum of efficacy against all focal and generalized seizures, including generalized absence and myoclonic seizures. The divalproex sodium formulation also has FDA indications for migraine prophylaxis and bipolar disorder. It should be started at a low dose to improve tolerability. The extended-release divalproex sodium preparation, which can be administered once daily, is preferred. The recommended starting dose is 500 mg at bedtime for the extended-release divalproex sodium preparation or 250 mg 2 times a day for the delayed-release and immediate-release preparations. The dose can be
increased gradually as needed to achieve seizure control, up to 1000 mg/d to 2000 mg/d. It should be avoided in women of childbearing potential because of teratogenic risk. The recommended therapeutic range is 50 mg/L to 100 mg/L. A protein-free concentration should be checked at high levels and in other circumstances in which the protein-free fraction is expected to rise.

The adverse effects of valproate include gastric irritation with nausea, vomiting, and anorexia. Other adverse effects include diarrhea, fatigue, drowsiness, tremor, weight gain, hair loss, peripheral edema, and confusion. Tolerability is generally improved with the extended-release formulation.26–28 Dose-related thrombocytopenia may occur. Endocrine effects are most recognized in women and include polycystic ovary syndrome, hyperandrogenism, hyperinsulinemia and insulin resistance.29,30 Reversible parkinsonism, gait disorder, dementia, and brain atrophy have been described with chronic use in seniors. Encephalopathy and hyperammonemia may occur in polytherapy.

Idiosyncratic hepatotoxicity and pancreatitis are potentially life threatening but rare. Risk factors are polytherapy and young age. Valproate is associated with a dose-related teratogenicity rate higher than any other marketed AED, with risk of major malformations higher than 30% at doses greater than 1100 mg/d.31 In utero exposure is also associated with dose-dependent reduced verbal IQ and autism.32–33

**Place in Therapy**
Valproate remains the most effective AED for idiopathic generalized epilepsy with generalized tonic-clonic seizures and should remain a drug of first choice for men with generalized epilepsy.34 Although equally effective as ethosuximide for generalized absence seizures, it has more cognitive adverse effects.35 A large cooperative US Department of Veterans Affairs study found it less well tolerated and less effective than carbamazepine for complex partial seizures (focal impaired awareness seizures), although equally effective for secondarily generalized tonic-clonic seizures (focal to bilateral tonic-clonic seizures).36

**ETHOSUXIMIDE**
Ethosuximide blocks T-type calcium currents, which predicts efficacy against absence seizures. It has an excellent oral bioavailability (greater than 90%). Protein binding is very low. Ethosuximide is extensively metabolized in the liver. It has a long half-life of 30 to 60 hours.

Ethosuximide is a narrow-spectrum AED, selective for generalized absence seizures. The starting dose is 250 mg/d for patients between 3 and 6 years of age and 250 mg 2 times a day for those older than 6 years of age. The dose can be increased by 250 mg every week as needed for persistent seizures, not to exceed 500 mg 3 times a day. The recommended therapeutic range is 40 mg/L to 100 mg/L.

Adverse effects include nausea, abdominal discomfort, anorexia, vomiting, diarrhea, drowsiness, insomnia, nervousness, dizziness, fatigue, ataxia, and behavior changes. Most adverse effects are dose related and are helped by administration of divided doses with meals. Headaches, psychosis, depression, and hallucinations are not clearly dose related. Idiosyncratic adverse experiences include rash, Stevens-Johnson syndrome, systemic lupus erythematosus, rare aplastic anemia, thrombocytopenia, agranulocytosis, and rare autoimmune thyroiditis.
Place in Therapy
Ethosuximide is the AED of choice for absence epilepsy with generalized absence seizures as the only seizure type, a status supported by the large multicenter double-blind randomized controlled trial comparing ethosuximide, valproic acid, and lamotrigine.37

BENZODIAZEPINES
Benzodiazepines act mainly on the GABA-A receptor, increasing the frequency of GABA-mediated chloride channel openings. Clobazam is the only 1,5-benzodiazepine, referring to the position of nitrogen atoms in the heterocyclic ring; other benzodiazepines are 1,4-benzodiazepines. Only clonazepam and clobazam, used for chronic epilepsy management, are discussed here. In the United States, they are available only as oral preparations.

Both have good oral bioavailability. Both are highly protein bound. However, they differ in their metabolism.38 Clonazepam is converted to inactive metabolites, while clobazam is metabolized in the liver to the active N-desmethylclobazam. Both clonazepam and clobazam have long half-lives, justifying once-daily dosing. Both clonazepam and clobazam are broad-spectrum agents, although their FDA indication is limited to generalized seizure types.

Drowsiness is a common adverse effect that improves over time. It is less likely with clobazam. With increasing doses, nystagmus, incoordination, unsteadiness, and dysarthria may occur. Tolerance may develop to the therapeutic effect of benzodiazepines, but this appears less likely with clobazam. Withdrawal seizures may occur with abrupt discontinuation. All benzodiazepines are controlled substances.

Place in Therapy
Both clonazepam and clobazam are typically used as adjunctive therapy and have limited data to support monotherapy use. The clobazam FDA indication is for adjunctive treatment of seizures associated with Lennox-Gastaut syndrome.

FELBAMATE
Felbamate was the first second-generation AED approved in the United States in 1993. It has multiple mechanisms of action, including N-methyl-D-aspartate (NMDA) receptor antagonism, GABA enhancement, and sodium channel blocking. It is available as an oral preparation.

Felbamate has excellent oral bioavailability; its protein binding is not clinically significant. It is metabolized in the liver to inactive metabolites, with a half-life of 20 to 23 hours. It is an inhibitor of CYP 2C19, CYP 1A2, and β-oxidation, inhibiting the metabolism of phenobarbital, phenytoin, valproate, carbamazepine epoxide, and warfarin, and it is a weak inducer of CYP 3A4, decreasing carbamazepine levels and reducing oral contraceptive efficacy.

Felbamate is a broad-spectrum agent effective against focal seizures as well as generalized seizures in the setting of Lennox-Gastaut syndrome. The recommended starting dose is 600 mg 2 times a day, with subsequent titration by 600 mg to 1200 mg per week up to 1200 mg 3 times a day.

The most common adverse effect of felbamate is gastrointestinal irritation with anorexia, nausea, and vomiting, which can be helped by administration with food. Felbamate may also cause insomnia, irritability, headache, and weight loss. The most concerning toxicity is the potentially lethal aplastic anemia,
with an estimated risk of 1 in 5000 to 1 in 8000 patients, and hepatic failure, with an estimated risk of 1 in 26,000 to 1 in 54,000 patients. Both are unlikely after 1 year of treatment, and aplastic anemia has not been reported in patients younger than 13 years of age. These two serious adverse effects have resulted in a boxed warning suggesting that felbamate should be used only for severe epilepsy where treatment benefits outweigh the risk. It is recommended to check a complete blood cell count and liver function test prior to starting felbamate and to repeat the tests every 2 weeks in the first 6 months of treatment. The frequency of monitoring can be reduced considerably after 1 year of treatment.

**Place in Therapy**
Although felbamate was approved for monotherapy, it is not indicated as a first-line treatment because of its potential serious idiosyncratic toxicity. Adjunctive therapy or alternative monotherapy can be considered when other appropriate and safer options have failed.

**GABAPENTIN**
Gabapentin binds to the alpha-2-delta subunit of voltage-gated calcium channels, reducing the influx of calcium and associated neurotransmitter release under hyperexcitable conditions. It is available as an oral preparation only.

Gabapentin bioavailability is low and variable between subjects and even in the same subject. Because of its active saturable transport system from the gut, its bioavailability decreases with increasing doses, from 60% after a single dose of 300 mg to 29% for 1600 mg 3 times a day. Protein binding is negligible. It is eliminated unchanged in the urine. Its half-life is 5 to 7 hours. It has no known interactions, other than potential antacid interference with its absorption.

Gabapentin is a narrow-spectrum agent against focal seizures. It may cause exacerbation of myoclonus. It is also FDA approved for the treatment of postherpetic neuralgia. An extended-release preparation (gabapentin enacarbil) has been approved for the treatment of restless legs syndrome, and another (gastroretentive dosage form) has been approved for the management of postherpetic neuralgia.

The recommended starting dose of gabapentin is 300 mg/d to 400 mg/d, to be increased by 300 mg to 400 mg every day up to 300 mg to 400 mg 3 times a day. The dose can be increased as needed up to 4800 mg/d in 3 divided doses.

Adverse effects include drowsiness, dizziness, ataxia, tiredness, and weight gain. It may cause myoclonus. It may cause cognitive slowing in the elderly and emotional lability in children. Peripheral edema is more likely with increasing age. Gabapentin was recently reclassified as a controlled substance in some states.

**Place in Therapy**
Gabapentin can be used as adjunctive treatment for focal seizures. It is often chosen for its anecdotal benefit in the treatment of headache and other pain and its benefit for sleep. Although approved in Europe for initial monotherapy, a large randomized comparative trial found it less effective than lamotrigine.

**PREGABALIN**
Pregabalin is structurally related to gabapentin and has a similar mechanism of action. It is also available only as an oral preparation. Unlike gabapentin, pregabalin has very good oral bioavailability, which is independent of dose. Like
gabapentin, it has no protein binding and is not metabolized in humans, and it has no known interactions. It is excreted unchanged in the urine. Its half-life is about 6 hours.

Pregabalin is a narrow-spectrum drug against focal seizures. The official FDA epilepsy indication is adjunctive therapy for adult patients with partial onset seizures. Like gabapentin, pregabalin has a narrow spectrum of efficacy against focal seizures and may exacerbate generalized myoclonic and absence seizures. It also has an FDA indication for neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. The starting dose is 75 mg 1 time (at bedtime) or 2 times a day. The dose can then be increased by 75 mg to 150 mg every week as needed, until seizure control, appearance of adverse effects, or reaching a maximum dose of 300 mg 2 times a day.

The adverse effects of pregabalin include dizziness, somnolence, increased appetite, weight gain, and peripheral edema. Myoclonus may occur with higher doses in some individuals. Pregabalin is a controlled substance because of the potential for abuse.

Place in Therapy
Pregabalin is indicated as adjunctive therapy for focal seizures. It was inferior to lamotrigine as first-line therapy and should probably not be used as a first-line treatment. However, a conversion-to-monotherapy study was successful.

LAMOTRIGINE
Lamotrigine blocks sodium channels, like phenytoin and carbamazepine, but must have other unrecognized actions to explain efficacy against absence seizures. It is available as an oral preparation only.

Lamotrigine has an excellent oral bioavailability. Its protein binding is not clinically significant. It is extensively metabolized in the liver, predominantly by glucuronidation, and then eliminated in the urine. The half-life is about 24 hours in monotherapy, at least twice as long when used with valproate, and about half as long when used with an enzyme inducer. Estrogen and pregnancy increase lamotrigine clearance.

Lamotrigine is a broad-spectrum AED, although its FDA indications are limited to focal seizures, generalized tonic-clonic seizures, and Lennox-Gastaut syndrome. It is less effective against generalized absence seizures than valproate and ethosuximide. It may be effective against myoclonic seizures in some patients but may exacerbate these seizures in others. Lamotrigine also has an FDA indication for maintenance treatment in bipolar I disorder.

Lamotrigine requires a very slow titration to avoid the development of rash. In monotherapy, it should be initiated with 25 mg/d for 2 weeks, followed by 50 mg/d for 2 weeks, then 100 mg/d. The dose can then be increased as needed by 100 mg every 2 weeks. The titration rate is half as fast with adjunctive valproic acid but can be twice as fast in the presence of an enzyme inducer and absence of valproic acid. A serum concentration is helpful to guide further titration if seizures are still not controlled at a dose of 600 mg/d. The suggested therapeutic range is 2 mg/L to 20 mg/L. The extended-release preparation allows once-daily dosing and reduces toxicity from peak levels. It may even improve efficacy when used 2 times a day in patients who are drug resistant.

Dose-related adverse effects include dizziness, blurred vision, diplopia, unsteadiness, nausea and vomiting, headache, and tremor. A serum
concentration is indicated for symptoms that could be consistent with lamotrigine toxicity, particularly if the baseline concentration was greater than 10 mg/L. Rash is seen in about 3% of patients, with a higher incidence in children, with coadministration of valproic acid, and with faster titration and higher doses. The risk of rash is increased in patients with a prior rash when on carbamazepine or phenytoin. Stevens-Johnson syndrome, toxic epidermal necrolysis, hypersensitivity syndrome, and hemophagocytic lymphohistiocytosis are rare serious idiosyncratic adverse effects.

Place in Therapy
Lamotrigine is an important first-line AED for focal seizures and generalized tonic-clonic seizures. Several comparative trials have favored lamotrigine over other AEDs for focal seizures in the balance of tolerability and efficacy. However, it was inferior to valproic acid for idiopathic generalized epilepsy and inferior to ethosuximide for generalized absence seizures. Lamotrigine is less sedating and has fewer cognitive adverse effects than traditional AEDs. Its monotherapy use is associated with one of the lowest rates of teratogenicity, favoring its use in women of childbearing age. Lamotrigine may have pharmacodynamic interactions with other classic sodium channel blockers, resulting in adverse effects at lower than expected serum concentrations. However, its combination with valproate can be synergistic, with greater efficacy than predicted.

TOPIRAMATE
Topiramate has multiple mechanisms of action, including antagonism of α-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid (AMPA)/kainate receptors, augmentation of GABA activity, and blocking of voltage-gated sodium channels. It is also a weak carbonic anhydrase inhibitor, but this mechanism does not contribute significantly to its efficacy. It is available as an oral preparation. Topiramate has an excellent oral bioavailability. Its protein binding is not clinically significant. It is partially metabolized in the liver, with about 70% eliminated unchanged in the urine. Its half-life is approximately 21 hours. It is a mild inducer of CYP 3A4, reducing the efficacy of the oral contraceptive at a dose greater than 200 mg/d, and a mild inhibitor of CYP 2C19.

Topiramate is a broad-spectrum AED effective against focal and generalized tonic-clonic seizures. A pilot trial suggested it is not effective for generalized absence seizures. It is FDA approved for migraine prophylaxis and as a weight-loss preparation in combination with phentermine. It is also frequently used off-label for bipolar disorder. Topiramate has to be titrated gradually to manage cognitive adverse effects. It is suggested to start with 25 mg/d and increase the dose by 25 mg every week up to 100 mg/d. Further titration by 25 mg to 50 mg every week can be considered, up to 400 mg/d in 2 divided doses. Extended-release preparations with once-daily dosing may improve tolerability.

Topiramate is less well tolerated than lamotrigine, the main tolerability issue being cognitive adverse effects, including cognitive slowing, decreased attention and memory, impaired executive function, word-finding difficulty, and reduced verbal fluency. Patients may not be aware of these cognitive difficulties. Other adverse effects include sedation, fatigue, dizziness, ataxia, and depression. Kidney stones occur in about 1.5% of individuals. Decreased appetite and weight loss may also occur. Paresthesia in the hands and feet can occur with initiation and with dose increase but usually resolve. This is due to the carbonic anhydrase
inhibition activity of this drug. Oligohidrosis, hyperthermia, and metabolic acidosis may occur, more commonly in children. Acute myopia and secondary angle-closure glaucoma are reported rarely. Hyperammonemia may occur when topiramate is used in conjunction with valproate. Topiramate is associated with increased birth defects at a rate of approximately 4%, particularly oral clefts.52

Place in Therapy
Although topiramate is FDA approved for initial monotherapy for focal seizures and generalized tonic-clonic seizures, it is not a drug of first choice because of its cognitive adverse effects, unless its use is justified by comorbidity, such as headache or obesity. It is effective as adjunctive therapy for focal and generalized seizures and Lennox-Gastaut syndrome.

TIAGabine
Tiagabine inhibits GABA reuptake at the synapse. It is available as an oral preparation only.

Tiagabine has an excellent oral bioavailability. It is 96% protein bound, but this is of limited importance because dosing decisions are not dependent on the level, and its serum concentration is so low that it does not significantly compete for protein binding. It is extensively metabolized in the liver. Its half-life is 7 to 9 hours in monotherapy, shortened to 2 to 5 hours in the presence of an enzyme inducer.

Tiagabine has a narrow spectrum of efficacy against focal seizures only. It may exacerbate generalized absence and myoclonic seizures. It is used off-label in the management of spasticity in multiple sclerosis, in the treatment of addiction, and to increase deep sleep proportion. It should be started at 4 mg at bedtime and increased by 4 mg every week to an initial target dose of 8 mg 3 times a day. The dose can be increased further by 4 mg every week up to 12 mg to 16 mg 3 times a day. A higher dose may be used in the presence of an enzyme inducer.

The most common adverse effects are dizziness, asthenia, nervousness, tremor, depression, and emotional lability, which are more common during titration. Tiagabine may be associated with dose-related episodes of nonconvulsive status epilepticus or encephalopathy, which may occur even in the absence of epilepsy.53,54

Place in Therapy
Tiagabine should be reserved for use as adjunctive therapy for focal seizures.

Leventiracetam
Levetiracetam’s main mechanism of action is binding to the synaptic vesicle protein SV2A. This seems to result in nonspecific decrease in neurotransmitter release in a state of neuronal hyperactivation.55 Levetiracetam is available in oral and IV formulations.

Levetiracetam has an excellent oral bioavailability and very low protein binding. It has no hepatic metabolism; 66% is excreted unchanged in the urine, and the rest is hydrolyzed to inactive compounds. The half-life is 6 to 8 hours. It has no known significant pharmacokinetic interactions.

Levetiracetam is a broad-spectrum drug, effective against focal seizures, generalized tonic-clonic seizures, and generalized myoclonic seizures. Levetiracetam is the only AED with Class I evidence for efficacy against myoclonic seizures. It is best to start with 500 mg/d in 2 divided doses or once
at bedtime with the extended-release preparation. The dose can then be increased as needed and as tolerated up to 3000 mg/d to 4000 mg/d.

The most common adverse effects include somnolence, dizziness, and asthenia. Irritability and hostility may occur, more often in children. Depression may also occur.

**Place in Therapy**
Although levetiracetam is not FDA approved for monotherapy in the United States, it is used widely as a first-line treatment for focal and generalized tonic-clonic seizures and is approved for initial monotherapy in Europe. It is also an excellent adjunctive treatment in view of its safety and absence of interactions. The IV preparation has been used as a second-line agent in the treatment of status epilepticus.56–58

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**BRIVARACETAM**
Brivaracetam is structurally related to levetiracetam and has a similar mechanism of action through binding to SV2A but with approximately 20-fold higher affinity and greater selectivity. It also has a higher brain permeability than levetiracetam. It is available in oral and IV formulations.

Brivaracetam has an excellent bioavailability after oral administration. It is weakly bound to plasma proteins. Its half-life is approximately 9 hours. It is renally excreted after extensive metabolism, primarily by hydrolysis and to a lesser extent hydroxylation mainly via CYP 2C19. Brivaracetam has more interactions than levetiracetam. Its clearance is increased by enzyme inducers. It may increase carbamazepine epoxide and may also increase phenytoin concentration by up to 20%.

Although brivaracetam has a broad spectrum of efficacy in preclinical models, human Class I trials have only been conducted in patients with focal seizures. Pooled analyses demonstrated efficacy greater than placebo at 50 mg/d, 100 mg/d, and 200 mg/d administered in 2 divided doses as adjunctive therapy.59

The recommended starting dose is 50 mg 2 times a day, followed by adjustment based on response and tolerability, either down to 25 mg 2 times per day or up to 100 mg 2 times a day. The most commonly reported adverse experiences occurring more often than placebo were somnolence, dizziness, and fatigue. Irritability was reported only in 3.2% of patients receiving brivaracetam compared with 1.1% of those receiving placebo.

**Place in Therapy**
Brivaracetam is FDA approved for the treatment of partial onset seizures in patients 16 years of age and older. This indication includes monotherapy and adjunctive use of the drug, although it has not specifically undergone monotherapy trials. The avenue for this approval is via a new pathway for monotherapy approval put forth by the FDA in a General Advice Letter in September 2016, stating that for approved antiseizure drugs "it is acceptable to extrapolate the efficacy and safety of drugs approved as adjunctive therapy for the treatment of partial onset seizures (POS) to their use as monotherapy for the treatment of POS."60

Brivaracetam is not effective when added to levetiracetam.61 One small open-label study suggested that behavioral adverse effects from levetiracetam may improve after switching to brivaracetam.62

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**KEY POINTS**
- Tiagabine may be associated with dose-related episodes of nonconvulsive status epilepticus or encephalopathy, even in subjects who do not have epilepsy.
- Levetiracetam is the only antiepileptic drug with Class I evidence of efficacy against generalized myoclonic seizures.
- Brivaracetam may have fewer behavioral side effects than levetiracetam.
ZONISAMIDE
Zonisamide is structurally related to sulfonamides. It has multiple mechanisms of action, including blocking T-type calcium channels (predictive of efficacy against absence seizures), blocking sodium channels, and weak inhibition of carbonic anhydrase activity. It is available only as an oral preparation.

Zonisamide has excellent oral bioavailability. Protein binding is not clinically significant. It is metabolized in the liver to inactive metabolites. It has a long half-life of about 60 hours. It is not a hepatic enzyme inducer or inhibitor.

Zonisamide is considered a broad-spectrum AED, although Class I trials have only been conducted in patients with focal seizures. The starting dose is 100 mg at bedtime for 2 weeks, then 200 mg at bedtime. The dose can be increased by 100 mg every 2 weeks as needed, up to 600 mg/d once at bedtime or in 2 divided doses. The suggested therapeutic range for plasma concentration is 10 mg/L to 40 mg/L.

Adverse effects include sedation, ataxia, dizziness, nausea, fatigue, agitation/irritability, and anorexia. Weight loss may occur. Cognitive slowing and difficulty with concentration may be seen, particularly at higher doses, but are less pronounced than with topiramate. Rarely, depression and psychosis may occur. Serious rash, such as Stevens-Johnson syndrome and toxic epidermal necrolysis, occurs rarely. Kidney stones occur in up to 4% of patients but may be prevented with adequate hydration. Oligohidrosis, hyperthermia, and metabolic acidosis occur rarely, more often in children.

Place in Therapy
Zonisamide is indicated as initial monotherapy for focal seizures in Europe. In Japan, it is also indicated as monotherapy for generalized seizures. The official FDA indication is for adjunctive therapy for focal seizures. Zonisamide is rarely the first-choice agent for initial monotherapy because of its cognitive adverse effects. However, its long half-life could be an advantage, reducing the impact of a missed dose.

LACOSAMIDE
Lacosamide blocks sodium channels, enhancing slow inactivation, unlike most classic sodium channel blockers, which enhance fast sodium channel inactivation. It is available in oral as well as parenteral formulations.

Oral bioavailability is excellent. Protein binding is not clinically significant. Lacosamide is converted in the liver to inactive metabolites, but approximately 40% is eliminated unchanged in the urine. The half-life is approximately 13 hours.

Lacosamide appears to be a narrow-spectrum AED against focal seizures. However, preliminary data suggest that it does not exacerbate absence or myoclonic seizures. The starting dose is 100 mg/d (once at bedtime or in 2 divided doses) for 1 week, then 100 mg 2 times a day. The dose can then be titrated as needed by 100 mg every 1 to 2 weeks until seizures are controlled, side effects appear, or a dose of 600 mg/d is reached.

The most common adverse effects include dizziness, headache, nausea, vomiting, diplopia, fatigue, and sedation, all of which are more common at higher doses. These adverse effects are also more likely when lacosamide is used in conjunction with other sodium channel blockers. Lacosamide may produce a
dose-dependent prolongation in PR interval, which could be clinically significant in patients with known conduction problems, or if it is combined with other drugs that have a similar effect.

**Place in Therapy**

Lacosamide is indicated as monotherapy and as adjunctive therapy for focal seizures. The parenteral formulation is indicated as short-term replacement when oral administration is not feasible in patients taking oral lacosamide; several anecdotal reports also exist of efficacy in status epilepticus. When lacosamide is used as adjunctive therapy, it may have greater efficacy and better tolerability if it is combined with a non-sodium channel drug.63

**VIGABATRIN**

Vigabatrin is an irreversible inhibitor of GABA transaminase, resulting in accumulation of GABA. It is available as an oral formulation. Vigabatrin has excellent oral bioavailability and no protein binding. It is not significantly metabolized and is eliminated unchanged in the urine. The half-life is 10.5 hours in young adults and 5 to 6 hours in infants. However, its duration of action outlasts its presence in serum.64 Vigabatrin is a weak inducer of CYP 2C9.

Vigabatrin is a narrow-spectrum drug effective against focal seizures. It may worsen absence and myoclonic seizures in idiopathic generalized epilepsy. However, it is effective against infantile spasms, particularly in the presence of tuberous sclerosis. The starting adult dose is 500 mg 2 times a day, then it is titrated by 500 mg per week up to 1.5 g 2 times a day. The dose can be increased further, as needed, up to 3 g 2 times a day, but this increases the risk of adverse effects with a low chance of additional therapeutic benefit.

Common vigabatrin adverse effects include sedation, fatigue, dizziness, and ataxia. Irritability, behavior changes, psychosis, and depression may also be observed. Weight gain may occur. The most concerning adverse effect is a progressive and permanent bilateral concentric visual field constriction, which may occur in up to 30% to 40% of individuals.65 The risk increases with increased daily dose and increased duration of therapy.66

**Place in Therapy**

Vigabatrin use is reserved for adjunctive therapy in subjects who have failed several alternative treatments and monotherapy in infants with infantile spasms. Because of the visual toxicity, periodic visual assessment is recommended at baseline and every 3 months, and treatment should be continued only if considerable benefit is observed in the first 3 months.

**RUFINAMIDE**

Rufinamide is a sodium channel blocker, although additional mechanisms of action are likely. It is available only as an oral preparation. Oral bioavailability is very good with food but is decreased in the absence of food. Protein binding is not clinically significant. It is metabolized by enzymatic hydrolysis to an inactive metabolite eliminated in the urine. The half-life is approximately 6 to 10 hours. It is a weak inhibitor of CYP 2E1 and a weak inducer of CYP 3A4 and uridine diphosphate glucuronyltransferase (UDP-GT). The addition of

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**KEY POINTS**

- Zonisamide’s long half-life of about 60 hours may be an advantage in reducing the impact of a missed dose.
- Lacosamide may produce a dose-dependent prolongation in PR interval, which could be clinically significant in patients with known conduction problems, or if it is combined with other drugs that have a similar effect.
- Long-term vigabatrin use may be associated with irreversible visual field constriction; hence, it should only be continued if it produces a remarkable improvement in seizure control.
valproate decreases rufinamide clearance and increases rufinamide levels by up to 70%.

Rufinamide is a broad-spectrum AED, but its efficacy against focal seizures was not sufficient for an FDA indication. The starting dose is 400 mg/d, after which it is increased by 400 mg every other day until seizure control or until a daily dose of 3200 mg is reached (in 2 divided doses).

The adverse effects of rufinamide include dizziness, fatigue, somnolence, and headache. Vomiting may occur in children. Rufinamide may cause a shortening of the QT interval.

Place in Therapy
Rufinamide is FDA indicated as adjunctive treatment for seizures associated with Lennox-Gastaut syndrome.

EZOGABINE (RETIGABINE)
Ezogabine (known as retigabine outside the United States) was a promising new AED with a novel mechanism of action as a potassium channel opener. However, long-term use was associated with bluish pigmentation in the skin, nails, and retina. Its use declined to the point that its maker withdrew it from the market in 2017, which is why it will not be discussed further here.

PERAMPANEL
Perampanel is a selective noncompetitive AMPA glutamate receptor antagonist. It is available as an oral preparation. It has excellent oral bioavailability and is 95% protein bound. It is extensively metabolized in the liver. It has a long half-life of about 105 hours. At a dose of 12 mg (not 8 mg), it accelerates the metabolism of levonorgestrel, a progesterone component of the oral contraceptive pill.67 Perampanel is effective for focal seizures and generalized tonic-clonic seizures.68

The adverse effects of perampanel include dizziness, somnolence, headache, fatigue, ataxia, and blurred vision. Aggression and hostility may occur, with an estimated incidence of about 20% at a dose of 12 mg/d, resulting in a boxed warning.69 Behavioral changes were more common in patients with intellectual disability.70

Place in Therapy
Perampanel is indicated for focal seizures (adjunctive and monotherapy) and as adjunctive treatment for primary generalized tonic-clonic seizures. Although there is no FDA indication for myoclonic seizures, several case reports and case series suggest particular efficacy in progressive myoclonic epilepsies, which are usually resistant to therapy.71–74

CANNABIDIOL
Cannabidiol was marketed in the United States in November 2018. It is a cannabinoid but does not interact with the cannabinoid receptor CB1 and does not share the psychoactive properties of tetrahydrocannabinol. Its exact mechanisms of action are not known, but it may enhance GABA activity through allosteric modulation of the GABA-A receptor and enhancement of currents elicited by low GABA concentrations.75 Its bioavailability is increased by administration with a high-fat meal. It is highly protein bound
Cannabidiol is metabolized in the liver, primarily by CYP2C19 and CYP3A4 enzymes, and converted to an active then an inactive metabolite. Its clearance is increased by inducers and decreased by inhibitors of CYPC19 and CYP3A4. It interacts with several AEDs, most notably with clobazam, increasing the concentration of its active metabolite N-desmethylclobazam. Cannabidiol is available only as an oral solution. The recommended starting dose is 5 mg/kg/d in 2 divided doses for 1 week, then 10 mg/kg/d in 2 divided doses. Its most common adverse effects are sedation, fatigue, decreased appetite, and diarrhea. It may produce an increase in liver enzymes, particularly when used in conjunction with valproate or with valproate and clobazam. Liver enzymes and total bilirubin levels should be obtained before treatment and at 1, 3, and 6 months after initiation of treatment.

Place in Therapy
Cannabidiol is FDA indicated for the treatment of seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients 2 years of age and older based on blinded controlled trials. Open-label trials also suggest efficacy for other forms of epilepsy. Artisanal cannabidiol formulations are used without prescription by many patients with epilepsy in the United States.

STIRIPENTOL
Stiripentol was FDA approved in 2018 for the treatment of seizures associated with Dravet syndrome in patients also taking clobazam. Its mechanism of action may involve both direct interaction with the GABA-A receptor and inhibition of CYP enzyme activity resulting in increased concentration of clobazam and its active metabolite. At the time of publication, it was not being marketed in the United States.

USE OF ANTIEPILEPTIC DRUGS IN COMBINATION
If the first AED fails because of lack of tolerability, it should be replaced with an alternative monotherapy. If the first AED fails because of lack of efficacy, options of replacement monotherapy or adjunctive therapy seem to be equal. Substitution monotherapy is favored when the first AED was not well tolerated or was totally ineffective. Substitution monotherapy would also be preferable in elderly patients who already take other medications, in women of childbearing potential contemplating pregnancy, in patients with compliance challenges, and when financial restrictions exist. Add-on therapy would be preferred if the first AED was well tolerated and partially effective or if the projected add-on agent has not been tested in monotherapy. The add-on therapy should not have negative pharmacokinetic interactions with the first AED or other concomitant medications. For example, the use of an enzyme inducer with an AED whose metabolism can be induced will reduce its efficacy. Enzyme inhibition is less of a problem as long as dosing accommodations are made. Evidence exists that combining two AEDs with different mechanisms of action is associated with greater balance of tolerability and efficacy. In particular, combining two sodium channel blockers tends to be associated with pharmacodynamic interactions such that adverse effects may be seen even though serum concentrations are in the therapeutic range. Several combinations seem to have synergistic efficacy in animal models, but only one combination has been demonstrated to be synergistic in humans, the combination of lamotrigine and valproate.
CONCLUSION
In conclusion, many AEDs are available for the treatment of epilepsy, with specific advantages and disadvantages. Some AEDs have additional efficacy in the treatment of comorbidities such as migraine or bipolar disorder. Considerations in AED choice include the AED’s efficacy profile as well as patient-specific factors. AED combinations should avoid unfavorable pharmacokinetic and pharmacodynamic interactions.

The most notable developments since the last version of this article are the FDA approval of three new AEDs, new practice guidelines for the efficacy and tolerability of the new AEDs, and new extrapolation policies of the FDA. The pediatric extrapolation policy allows efficacy data against focal seizures in adults to apply to children 4 years of age or older, although safety studies would still be needed for pediatric approval. Based on this policy, lacosamide, eslicarbazepine, brivaracetam, and perampanel were approved for the treatment of focal seizures in children aged 4 years and older. The FDA also allowed extrapolation of monotherapy use of a drug proven effective as adjunctive therapy. There has also been increasing awareness of autoimmune pathophysiology underlying epilepsy in many patients, often requiring immunotherapy for optimal management.

Improved understanding of the underlying pathophysiology of epilepsy in individual patients will allow more specific AED therapy in the future.

REFERENCES


60 Data on File (FDA General Advice Letter, dated 09/13/2016).


