Antiepileptic Drugs: The Old and the New

Oliver L. Hung, MD*, Richard D. Shih, MD

During the past decade, 8 new antiepileptic drugs (AEDs) have been approved by the Food and Drug Administration (FDA) for the treatment of seizures (Table 1). In contrast, during the preceding 8 decades, only 6 principal AEDs existed for the treatment of generalized and partial seizures, with no new drugs approved from 1978 to 1993. With this new generation of antiepileptic medications, emergency physicians must be familiar with their therapeutic usage and potential adverse reactions. This article provides an overview of these new AEDs as well as the preexisting AEDs.

AEDs: OLD GENERATION

Carbamazepine (Tegretol)

Carbamazepine, which is structurally similar to tricyclic antidepressants, is used to treat partial and generalized tonic-clonic seizures. The mechanism of action of this drug is similar to that of phenytoin, that is, involves slowing the rate of reactivation of voltage-dependent sodium channels after depolarization. The most common side effects are diplopia, headache, dizziness, and nausea. Benign maculopapular or morbilliform rashes occur in 10% of patients.1 Less common skin eruptions include erythema multiforme and Stevens-Johnson syndrome. A reversible leukopenia also occurs in 10% of patients; however, only 2% of the patients require discontinuation of the medication. Aplastic anemia is rare and occurs in 0.5 per 100,000 treatment-years. Carbamazepine is an inducer of the cytochrome P450 system (3A and 2C9) and increases the metabolism of valproic acid, ethosuximide, corticosteroids, warfarin, phenothiazines, and cyclosporine.

There is no parenteral version of carbamazepine. Oral loading may be possible; one study suggested that a single loading dose of carbamazepine, 8 mg/kg, by suspension or in tablet formulation successfully achieved therapeutic concentrations without significant gastrointestinal (GI) tract side effects within 2 and 5 hours, respectively.2

Clonazepam (Klonopin)

The benzodiazepine clonazepam is used in the treatment of absence seizures, myoclonic jerks, and tonic-clonic seizures. However, the tendency of this drug to
cause excessive sedation and the eventual development of tolerance to clonazepam has limited its usefulness; it is mainly used for the treatment of refractory myoclonic seizures.

**Ethosuximide (Zarontin)**

Ethosuximide is considered a first-line AED for patients with generalized absence seizures. The mechanism of action of this drug is related to its ability to reduce calcium currents in specific thalamic neurons. The primary side effects are on the GI tract (nausea, vomiting, abdominal pain) or central nervous system (CNS) (sedation, headache).

**Phenobarbital (Phenobarbitone)**

Phenobarbital is effective for the treatment of partial and generalized tonic-clonic seizures. Introduced in 1912, phenobarbital is the oldest AED still in use. The primary mechanism of action involves the potentiation of the $\gamma$-aminobutyric acid type A (GABA$_A$) receptor. Potentiation is mediated by the promotion of GABA to the receptor and by directly increasing the duration for which the chloride channels remain open. Phenobarbital is the only barbiturate that possesses anticonvulsant properties at sub-hypnotic doses (Table 2). Although phenobarbital is as effective as phenytoin and carbamazepine in preventing seizures, it is considered a second-line AED because of its significant CNS side effects, including excessive fatigue in adults and hyperactivity.

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<td>Lamotrigine</td>
<td>Partial seizure</td>
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<td>Levetiracetam</td>
<td>Partial seizure</td>
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<td>Oxcarbazepine</td>
<td>Partial seizure</td>
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<td>Tiagabine</td>
<td>Partial seizure</td>
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<td>Topiramate</td>
<td>Partial seizure</td>
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and aggression in children. Phenobarbital is also a potent inducer of many cytochrome P450 enzymes (1A2, 2A, and 3C), which can result in clinically significant increased metabolism of many medications, including AEDs (carbamazepine, ethosuximide, lamotrigine, tiagabine, zonisamide), antiarrhythmics, antihypertensive agents, corticosteroids, theophylline, estrogens, warfarin, and phenothiazines. Phenobarbital exists in both an oral and a parenteral preparation. However, the administration of loading doses of phenobarbital by intravenous (IV) or oral route is usually impractical and seldom attempted (except in treating patients with status epilepticus) because of the high risk of excessive sedation and respiratory depression.

**Phenytoin (Dilantin) and Fosphenytoin (Cerebyx)**

Phenytoin is effective for the treatment of partial and tonic-clonic seizures. The drug slows the rate of reactivation of voltage-dependent sodium channels after depolarization. The principal side effects include gingival hyperplasia, hirsutism, acne, and facial coarsening. At plasma concentrations greater than 20 μg/mL, phenytoin may produce neurologic symptoms, including nystagmus, ataxia, dysarthria, and lethargy. Phenytoin is an inducer of the cytochrome P450 system (2C9, 19, and 3A4) and may decrease serum concentrations of benzodiazepines, ethosuximide, felbamate, lamotrigine, oxcarbazepine, tiagabine, topiramate, and zonisamide.

The IV administration of phenytoin may result in hypotension or cardiac arrhythmias (3.5% incidence). This risk is related to the rate of administration and the total dose infused and is attributed to phenytoin and its diluents propylene glycol and ethanol. In addition, local irritation from IV phenytoin infusions may result in infusion site reactions (e.g., phlebitis, purple glove syndrome, and tissue necrosis). The risk of both hemodynamic complications and infusion site reactions may be decreased by limiting the IV infusion rate to 50 mg/min (25 mg/min in patients with cardiovascular disease) and ensuring that the infusion is given through a well-placed line with a good flow.

Phenytoin has been used as a first-line drug in the management of seizures in the emergency department (ED) because it is formulated in both oral and parenteral preparations and can rapidly achieve therapeutic concentrations. A loading dose of IV phenytoin, 20 mg/kg at 50 mg/min, by continuous infusion can achieve therapeutic concentrations in approximately 30 minutes. Similarly, a therapeutic concentration of phenytoin can be achieved after an oral dose of phenytoin, 20 mg/kg. In an ED study, 64% of patients (N = 44) achieved therapeutic phenytoin concentrations greater than 10 μg/mL within 8 hours after oral loading. Another study evaluated single oral phenytoin administration in both volunteers and hospitalized patients.

### Table 2

<table>
<thead>
<tr>
<th>New Anticonvulsants</th>
<th>Carbamazepine</th>
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<tr>
<td>Felbamate</td>
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<td>Increase</td>
<td>Increase</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>None</td>
<td>None</td>
<td>None</td>
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<tr>
<td>Lamotrigine</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Topiramate</td>
<td>None</td>
<td>Increase</td>
<td>None/Decrease</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>None/Increase</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>None</td>
<td>None</td>
<td>None</td>
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All volunteers (N = 19) receiving phenytoin, 15mg/kg, achieved therapeutic phenytoin concentrations of greater than 10 µg/mL within 4 hours. Meanwhile, the hospitalized patients (N = 14) received a higher single dose of oral phenytoin (18.7 mg/kg for males and 24.8 mg/kg for females), and all of them achieved therapeutic phenytoin concentrations within 4 hours and maintained therapeutic concentrations during a 24-hour observation period. The mean peak phenytoin concentrations were 23.9 ± 5.5 µg/mL for males and 21.5 ± 5.1 µg/mL for females.7

Fosphenytoin is a parenteral phenytoin prodrug that is metabolized to phenytoin and has the same pharmacologic activity as phenytoin in the treatment of seizures.8 Fosphenytoin is more water soluble than phenytoin and therefore, does not require dilution with propylene glycol and alcohol. Consequently, this drug lacks phenytoin’s serious adverse effects such as hypotension, cardiac arrhythmias, and infusion site reactions. In addition, fosphenytoin can be administered intravenously or as an intramuscular injection. Fosphenytoin is administered in the form of phenytoin sodium equivalents (PSEs). The loading dose is the same as that for phenytoin, 15 to 20 PSEs/kg, but the maximum rate of infusion is much higher, 150 mg/min for adults or 3 mg/kg/min for children. The main advantage of fosphenytoin is the decreased risk of serious adverse effects and its ability to be administered as an intramuscular injection. The main disadvantage of fosphenytoin is its higher cost when compared with phenytoin; however, because fosphenytoin is now available generically, the cost difference is minimal.

Valproic Acid (Depakote)

Valproic acid is unique among the older AEDs because of its effectiveness in treating all types of seizures, including absence, partial, and generalized tonic-clonic seizures. The mechanism of action is similar to that of both phenytoin and carbamazepine in that it prolongs the recovery of voltage-activated sodium channels from inactivation. In addition, valproic acid stimulates GABA synthesis by activating glutamic acid decarboxylase and inhibiting GABA degradation enzymes. The most common side effects are GI tract disturbances, including anorexia, vomiting, tremor, and weight gain. Hepatotoxic reactions include transient reversible elevations of aminotransferases (frequent), reversible hyperammonemia (20% of all patients), toxic hepatitis, and a Reye-like syndrome.9 The incidence of fatal idiosyncratic hepatotoxicity is 1 in 49,000 adults and 1 in 800 children.10 Acute pancreatitis has also been associated with the use of valproic acid. In 1997, an IV formulation of valproic acid was approved for use by the FDA. IV valproic acid has been successfully used to treat status epilepticus.11–13

AEDs: NEW GENERATION

As a group, the new-generation AEDs seem to be better tolerated, with less-severe side effects (with the exception of felbamate and lamotrigine), and have fewer drug interactions than the traditional AEDs (Table 3). Most of these medications are only approved as adjunctive treatments for seizures. Their efficacy as a single treatment of seizures is currently being investigated.

Felbamate (Felbatol)

In 1993, felbamate was approved for the adjunctive treatment of partial seizures in adults and Lennox-Gastaut syndrome in children and adults. This drug is structurally similar to the anxiolytic meprobamate but does not possess any muscle-relaxing properties. The exact mechanism of action of this drug is not known. The drug is
postulated to act by interaction with \textit{N}-methyl-\textit{d}-aspartate class of glutamate receptor.\textsuperscript{14} Felbamate inhibits the enzyme CYP2C19 and induces CYP3A4. The concurrent administration of felbamate increases serum concentrations of phenytoin, phenobarbital, and valproic acid and decreases serum concentrations of carbamazepine. The use of felbamate has been associated with the development of aplastic anemia and hepatic failure. The risk of aplastic anemia is estimated at 127 per million users.\textsuperscript{15} The risk of hepatic failure is 1 in 30,000 users.\textsuperscript{16} Consequently, felbamate has been largely replaced by other alternative AEDs.

\textbf{Overdose}

Few cases of overdose have been reported; overdoses mostly result in a mild CNS depression that resolves with supportive care.\textsuperscript{17,18} An overdose of felbamate and valproate has been reported to result in felbamate crystalluria and acute renal failure that was successfully treated with IV hydration.\textsuperscript{19} Another overdose of felbamate in a 3-year-old child was associated with restlessness, ataxia, hematuria, and crystalluria.\textsuperscript{20}

\textbf{Gabapentin (Neurontin)}

Gabapentin’s exact mechanism of action is unknown but is thought to be related to its properties as a GABA agonist and its ability to bind to a specific voltage-sensitive calcium channel in the brain. Gabapentin has been shown to be an effective adjunct for the treatment of partial seizures with or without secondary generalized tonic-clonic seizures.\textsuperscript{21} The drug also has been demonstrated to be effective in the treatment of painful neuropathies and is approved for the treatment of postherpetic neuralgia. Investigational uses include monotherapy of refractory partial seizure disorders, treatment of spasticity in multiple sclerosis, and treatment of tremor. Potential psychiatric uses include the treatment of mood disorders and attenuation of disruptive behaviors in patients with dementia.

Gabapentin is not metabolized and is excreted unchanged by the kidneys, making it one of the preferred AEDs in patients with hepatic disease.\textsuperscript{21} Adverse reactions are generally mild. Leukopenia has been reported in approximately 1.1\% of gabapentin-treated patients.\textsuperscript{21} The manufacturer has reported that purpuras frequently occur

\begin{table}[h]
\centering
\caption{Pharmacokinetics of the new AEDs}
\begin{tabular}{|c|c|c|c|c|}
\hline
Drugs & t\textsubscript{max} (h)\textsuperscript{a} & Half-life (h) & Metabolism & Elimination \\
\hline
Felbamate & 1.0–4.0 & 20.0–23.0 & Partly metabolized in liver to inactive metabolites & 90\% urine (metabolized 40\%) \\
Gabapentin & 1.5–4.0 & 5.0–7.0 & None & 100\% urine \\
Lamotrigine & 2.2–3.0 & 13.0–30.0 & 76\% glucuronidation & 94\% urine \\
Topiramate & 2.0–3.0 & 20.0–30.0 & Hydroxylation, hydrolysis, glucuronidation & 55\%–97\% urine, unchanged 62\% urine \\
Zonisamide & 2.0–6.0 & 63.0 & Inactive metabolites & — \\
Levetiracetam & 1.0 & 6.0–8.0 & Insignificant, hepatic 24\%, enzymatic hydrolysis & 91\% urine \\
Oxcarbazepine & 4.5 & 1.0–2.5 & 10-hydroxy carbazepine (active) & 95\% urine metabolites \\
Tiagabine & 0.75 & 7.0–9.0 & CYP3A & 25\% urine (unchanged & metabolites) 63\% fecal \\
\hline
\end{tabular}
\textsuperscript{a} Time after dosing when maximum serum concentration is achieved.
\end{table}
with gabapentin therapy, which are most often described as bruises resulting from physical trauma.\textsuperscript{21} Gabapentin is devoid of any significant drug interactions.\textsuperscript{21}

\textbf{Overdose}
Overdose of gabapentin generally results in mild CNS depression. Treatment includes supportive therapy and appropriate GI tract decontamination. Severe withdrawal symptoms have been described in patients after the abrupt cessation of high-dose gabapentin treatment.\textsuperscript{22}

\textbf{Levetiracetam (Keppra)}

In 1999, levetiracetam was approved for the treatment of partial seizures with or without secondary generalization. The precise mechanism of action is unknown. Like gabapentin, levetiracetam is not hepatically metabolized and is excreted renally; it is a preferred agent in patients with hepatic disease and should be avoided in patients with renal disease. This drug has no known clinically significant drug interactions and has mild adverse effects.\textsuperscript{23} Levetiracetam is available in an IV formulation and is thus a consideration in patients already receiving levetiracetam presenting in status epilepticus secondary to medication noncompliance or in patients with known hepatic disease.

\textbf{Overdose}
Overdose data are limited, but overdose seems to result in mild CNS depression. Treatment of levetiracetam overdose includes supportive therapy, including appropriate GI tract decontamination.

\textbf{Topiramate (Topamax)}

In 1997, topiramate was approved for the treatment of refractory partial seizures in adults. This drug is a derivative of \(\alpha\)-fructose, but its mechanism of action is unclear. Topiramate enhances the inhibitory effect of GABA, blocks sodium channels, and antagonizes kainate/AMPA receptor subtype of the glutamate receptor.\textsuperscript{24} This drug is also a weak carbonic anhydrase inhibitor. The adverse reactions are generally mild. Patients taking topiramate have a slightly increased risk (1.5\%) of developing renal calculi.\textsuperscript{24,25} Reports describing the development of acute angle-closure glaucoma in patients on this medication are rare.\textsuperscript{24,26,27} Topiramate may reduce the effectiveness of oral contraceptives, increase phenytoin concentrations, and decrease serum digoxin and valproic acid concentrations. Topiramate should be avoided in patients with a history of nephrolithiasis or in those taking carbonic anhydrase inhibitors.

\textbf{Overdose}
Most cases of overdoses of topiramate result in mild CNS toxicity. Two cases involving overdoses of 20 and 40 g of topiramate have resulted in status epilepticus, transient hypotension, metabolic acidosis, and coma. Both patients fully recovered with supportive care.\textsuperscript{28} Treatment of topiramate overdose includes supportive therapy, including appropriate GI tract decontamination. IV benzodiazepines should be administered for topiramate-induced seizures.

\textbf{Tiagabine (Gabitril)}

Tiagabine was approved in 1997 for the treatment of partial seizures. It is a chemical derivative of nipecotic acid, a compound found in betel nut. This drug inhibits the reuptake of GABA by binding to recognition sites associated with the GABA uptake carrier. Adverse reactions are generally mild. However, 5\% of patients receiving tiagabine
experienced some form of status epilepticus and 33% of patients with a history of status epilepticus had a recurrence during tiagabine treatment.\textsuperscript{29} Tiagabine is metabolized by the CYP3A4 enzyme but does not seem to affect the serum concentrations of other drugs.

**Overdose**

Clinical experience with tiagabine overdose is limited. CNS depression and agitation were reported as common symptoms after overdose of up to 800 mg.\textsuperscript{29} Status epilepticus after 400 mg ingestion (normal maximum daily dose is 56 mg) has also been reported after tiagabine overdose.\textsuperscript{29} A retrospective case series of tiagabine overdoses observed that coma and seizures were common findings. Treatment of tiagabine overdose should include supportive therapy including GI tract decontamination with activated charcoal.\textsuperscript{30} IV benzodiazepines should be administered for tiagabine-induced seizures or tiagabine-induced agitation.

**Zonisamide (Zonegran)**

Zonisamide is a sulfonamide derivative approved in 2000 as an adjunct for the treatment of partial seizures in adults. The exact mechanism of action is not fully understood and is thought to involve the blockade of sodium and T-type calcium channels.\textsuperscript{31} Acute psychosis occurred in 2% of patients taking zonisamide.\textsuperscript{32} The other side effects include decreased sweating, hyperthermia, and renal calculi. Children seem to be more susceptible to developing hyperthermia than adults. Zonisamide is metabolized by CYP3A4 enzyme and may be affected by other drugs that induce or inhibit this isoenzyme (phenytoin, carbamazepine, and phenytoin). It does not seem to affect the plasma concentrations of other drugs. Few cases of overdose have been reported.

**Overdose**

Bradycardia, hypotension, respiratory depression, seizures, and coma have been reported after zonisamide overdose.\textsuperscript{32} Bradycardia was reported in a 26-year-old woman who became comatose after ingesting an unknown amount of zonisamide, clonazepam, and carbamazepine in a suicide attempt. The zonisamide plasma level was 100.1 μg/mL 31 hours postingestion.\textsuperscript{29} Multiple episodes of generalized tonic-clonic seizures as well as cardiac arrest occurred in an 18-year-old woman after a single-drug ingestion of 4.8 g of zonisamide (normal maximum daily dose is 600 mg) in a suicide attempt. The patient’s rhythm changed to a perfusing wide complex tachycardia after cardioresuscitative measures but the patient developed severe cerebral edema and brain death.\textsuperscript{32}

**Lamotrigine (Lamictal)**

Lamotrigine was approved in 1998 as an adjunct for the treatment of refractory partial seizures and Lennox-Gastaut syndrome. The exact mechanism of action is not fully understood and may involve the inhibition of glutamate release by inhibition of voltage-sensitive sodium channels.\textsuperscript{33} Lamotrigine carries an FDA black box warning for the development of life-threatening rashes. About 10% of patients develop erythema and maculopapular rash. An estimated 1% of pediatric patients and 0.3% of adult patients develop a life-threatening rash (eg, Steven-Johnson syndrome, toxic epidermal necrolysis).\textsuperscript{34} The risk is increased with the concomitant administration of valproic acid. The development of any type of bullous or vesicular rash should prompt the immediate discontinuation of this AED. The metabolism of lamotrigine is enhanced by carbamazepine, phenobarbital, and phenytoin and reduced by valproic acid.
Lamotrigine itself does not cause significant induction or inhibition of hepatic drug-metabolizing enzymes.

**Overdose**
CNS depression is the most common effect of lamotrigine overdose. Overdoses of up to 15 g of lamotrigine have been reported to result in fatalities.33

**Oxcarbazepine (Trileptal)**
Oxcarbazepine was approved in 1999 for monotherapy and adjunct therapy for patients with partial seizures. This drug is the 10-keto derivative of carbamazepine and is quickly metabolized to its active metabolite, 10,11-dihydro-10-hydroxycarbamazepine. Oxcarbazepine has a mechanism of action similar to carbamazepine and seems less likely than carbamazepine to producing CNS side effects, skin rash, or leukopenia. In addition, monitoring of drug levels and blood cell counts is not necessary. Oxcarbazepine seems to induce hepatic enzymes to a lesser extent than carbamazepine. However, oxcarbazepine seems to be more likely than carbamazepine in causing a dose-related hyponatremia.35,36

**Overdose**
Overdose data are limited. Hypotension, tinnitus, seizures, and bradycardia were reported in one case of oxcarbazepine overdose. A 33-year-old woman developed bradycardia (heart rate = 27/min), tinnitus, hypotension (systolic blood pressure = 60 mm Hg), and a witnessed partial seizure after an unintentional ingestion of oxcarbazepine, 3300 mg, (normal dose is 2400 mg/day) and recovered after supportive therapy.37

**SUMMARY**
With a few exceptions, the new AEDs seem to cause fewer adverse effects and have decreased potential for toxicity in overdose when compared with the older generation of medications. However, their efficacy in preventing seizures has not been fully established. The new drugs are only approved for use for adjunctive therapies for the treatment of seizures. Indications for the ED administration of these drugs are limited, and their administration should only be considered with neurologic consultation.

**KEY CONCEPTS**
- Fosphenytoin has a better safety profile than phenytoin and can be safely given intramuscularly, with rapid achievement of therapeutic serum levels.
- Valproic acid is available in an IV formulation, which should be used in noncompliant patients on valproic acid who seize, and considered for treating status epilepticus refractory to primary therapies.
- Most AEDs are metabolized in the liver and attention must be given to avoid inducing drug interactions with their use.
- Levetiracetam and gabapentin are renally excreted and can be safely used in patients with hepatic disease.
- In general, the new-generation AEDs do not cause serious morbidity in overdose, and treatment is primarily supportive.
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