Epilepsy affects approximately two million people in the U.S. About five percent of physician visits and 20% of neurological visits are by people seeking medical advice for the treatment of seizures. Approximately two-thirds of epileptic seizures begin in childhood; however, the incidence increases again after age 60, with a peak incidence in persons greater than 70 years of age. The term epilepsy is derived from Greek words meaning to “seize upon” or “take hold of.” The medical definition of epilepsy is an intermittent derangement of the nervous system caused by a sudden, excessive, disorderly discharge of cerebral neurons. Seizures refer to any paroxysmal disturbance in consciousness, behavior, or motor activity.

The clinical presentations of epileptic seizures are classified by symptomatology and electrophysiological findings according to the International Classification of Epileptic Seizures. The classification is as follows:

I. Partial seizures (seizures begin locally)
   A. Simple (without impairment of consciousness)
      1. With motor symptoms
      2. With special sensory or somatosensory symptoms
      3. With psychic symptoms
   B. Complex (with impairment of consciousness)
      1. Simple partial onset followed by impairment of consciousness with or without automatisms
      2. Impaired consciousness at onset with or without automatisms
   C. Secondarily generalized (partial onset evolving to generalized tonic–clonic seizures)

II. Generalized seizures (bilaterally symmetrical and without focal onset)
   A. Absence
   B. Myoclonic
   C. Clonic
   D. Tonic
   E. Tonic–clonic
   F. Atonic
   G. Infantile spasms

III. Unclassified seizures

IV. Status epilepticus

The goal of epilepsy therapy is to provide a seizure-free state. General principles of anticonvulsant therapy include deciding whether or not to treat, selecting the appropriate drug for a patient's particular seizure type, initiating therapy slowly and titrating to avoid drug toxicity, starting with monotherapy before adding another drug, choosing a simple regimen when possible, assessing patient compliance, monitoring blood levels, and deciding how long to treat. The American Academy of Neurology has guidelines for discontinuing antiepileptic drugs (AEDs) in seizure-free patients after physicians have assessed the risks and benefits to such patients and society. Patients who may be considered for anticonvulsant therapy discontinuation with the lowest risk for seizure recurrence from two to five years are those patients who have experienced a single
type of partial seizure or primary generalized tonic–clonic seizures; patients who have had a normal neurologic examination/normal IQ; and for whom EEG has normalized with treatment. Drug treatments for the chronic management of seizures depend on seizure type. This review will focus on oral anticonvulsants that were approved by the FDA over the past 25 years.

### Adjunct Anticonvulsants

Several oral anticonvulsant agents have been released into the market during the past 25 years. These agents are recommended as monotherapy or adjunctive therapy for seizures refractory to conventional first-line anticonvulsant therapies.

#### Valproic acid

Valproic acid was FDA-approved in 1978 for monotherapy or adjunctive treatment of simple and complex absence seizures as well as complex partial seizures. Valproic acid is chemically unrelated to other drugs used in seizure disorders. Its mechanism of action is not established, but it seems to be related to the increase in levels of GABA in the brain. Valproic acid is also responsible for the blockade of voltage-dependent sodium channels and the potentiation of GABAergic transmission. Valproic acid has peak serum concentrations within 1-4 hours. It is primarily metabolized hepatically with urine excretion. Its therapeutic serum level is 50 to 150 mcg/ml. More than 29% of patients experienced gastrointestinal side effects in placebo-controlled trials. Fatal hepatic failure has occurred in patients receiving valproic acid; therefore, liver function tests should be monitored prior to therapy and periodically during the first six months.

Valproic acid was associated with a lower study withdrawal rate (4%) than phenytoin (9%) and carbamazepine (4%), in 167 children with newly diagnosed epilepsy after three years’ follow-up. Valproate had similar efficacy as carbamezapine for secondarily generalized tonic–clonic seizures in 274 patients in clinical trials after one to five years’ follow-up.

#### Gabapentin

Gabapentin was FDA-approved in 1994 as combination therapy for the management of partial seizures with or without secondary generalization. Gabapentin is an oral antiepileptic with an unknown mechanism of action. However, it has similar properties in common with other anticonvulsants in animals. Although structurally related to GABA, it does not interact with GABA receptors. Gabapentin is thought to potentiate GABA responses and also act through the blockade of voltage-dependent sodium channels.

Gabapentin has a unique pharmacokinetic profile including minimal protein binding, primarily renal excretion, and dose-dependent oral absorption. More than 10% of patients in placebo-controlled trials experienced somnolence, dizziness, and ataxia. In a multicenter, placebo-controlled, parallel-group study of 306 patients with refractory partial epilepsy, gabapentin was associated with a 50% reduction in seizure frequency in 18–26% of groups compared to 8% of placebo control group ($P<=0.00001$).

#### Lamotrigine

Lamotrigine was FDA-approved in 1995 as adjunctive therapy in adults with partial seizures or adjunctive therapy in generalized seizures of Lennox–Gastaut syndrome in pediatric and adult patients. It is also indicated for conversion to monotherapy in adults with partial seizures who are receiving hepatic-enzyme-inducing anticonvulsants. Lamotrigine has shown antiseizure activity similar to that of phenytoin and carbamazepine.
in animal studies, and although its structure is different from phenytoin and carbamazepine, it also inhibits sodium currents in a voltage- and use-dependent manner. Lamotrigine blocks the influx of sodium ions into rapidly firing neurons. Through this mode of action, and perhaps through some other mechanisms, it inhibits presynaptic release of the excitatory neurotransmitters glutamate and aspartate.\(^5,8,13\)

Lamotrigine is metabolized by gluconoric acid conjugation to inactive metabolites. It has predominantly urinary excretion, with a small amount excreted fecally. The half-life of lamotrigine is 33 hours, and it offers once-daily administration.\(^5\)

In controlled clinical trials, adverse effects occurring in more than 10% of patients who received lamotrigine as adjunctive therapy included dizziness, rash, rhinitis, and gastrointestinal effects. In a comparative clinical trial, it was found to have efficacy similar to carbamazepine for partial seizures with or without secondary generalization or for primary generalized tonic–clonic seizures. The incidence of sleepiness in those treated with carbamazepine was 4% versus no incidence due to lamotrigine \((P<0.05)\).\(^14\)

**Tiagabine**

Tiagabine was approved in 1997 as an adjunctive treatment for partial seizures. Tiagabine is a nipecotic acid derivative linked to a lipophilic anchor, which enables tiagabine to cross the blood–brain barrier. Its precise mechanism of action is unknown. It was designed to enhance the inhibitory actions of GABA by blocking its uptake, thereby prolonging its action after synaptic release.\(^5,8,15\)

Tiagabine has 95% oral absorption and 96% protein binding. It is metabolized by thiophene oxidation and gluconoration.\(^5\) Dizziness, somnolence, nervousness, and gastrointestinal upset occurred in more than 10% of patients in placebo-controlled trials. The efficacy of tiagabine as add-on therapy for the treatment of partial seizures was evaluated in a double-blind, randomized, placebo-controlled U.S. multicenter trial. Patients were randomized to placebo \((n=107)\) or tiagabine \((n=210)\) 32 mg daily. Tiagabine resulted in a 50% seizure-reduction rate within four weeks in 21% of treated patients, compared to 5.8% of those in placebo groups \((P<0.01)\).\(^16\)

**Topiramate**

Topiramate was FDA-approved in 1998 for adjunctive treatment of adult onset of partial-onset epilepsy. The exact mechanism of action of topiramate is not known, although its actions include the blockade of sodium channels, attenuation of kainate-induced responses, and the enhancement of the inhibitory actions of GABA by acting at a unique modulatory site. Topiramate is also known to inhibit the enzyme carbonic anhydrase.

The anticonvulsant properties of topiramate are similar to those of phenytoin and carbamazepine. Topiramate does not counteract chemically induced seizures and has little effect on seizure threshold.\(^5,8,17\) Topiramate offers high bioavailability and low protein binding. Adverse effects occurring in more than 10% of patients in placebo-controlled trials included dizziness, somnolence, ataxia, nervousness, speech problems, nausea, paresthesia, tremor, and nystagmus. Topiramate was associated with a 50% seizure-frequency reduction in 43% of the treatment group compared to 18% of the placebo group in a placebo-controlled trial of adult patients with partial-onset seizures \((P<0.001)\).\(^18\)

**Levetiracetam**

Levetiracetam was FDA-approved in 1999 as adjunctive therapy in adult patients with partial-onset seizures. Levetiracetam is a pyrrolidone derivative and chemically unrelated to other AEDs. Its precise mechanism of action is unknown and does not appear to be related to any known mechanism involved in inhibitory and excitatory neurotransmission. Animal studies have shown that levetiracetam has protective properties against secondarily generalized activity from focal seizures induced by pilocarpine and kainic acid, two chemicals that mimic some features of human complex partial seizures with secondary generalization.\(^19,20\) Levetiracetam offers 100% oral absorption with low protein binding. It is primarily renally excreted unchanged.

The most commonly reported adverse effects (greater than 10%) in placebo-controlled trials were somnolence, asthenia, depression, and infection.\(^19\) The efficacy of levetiracetam was evaluated in a double-blind, placebo-controlled, parallel-group study conducted at multicenters in the U.S. Patients were randomized to levetiracetam 1000 mg daily \((n=97)\), levetiracetam 3000 mg daily \((n=101)\), and placebo \((n=95)\). The number of study participants who had a 50% reduction in weekly partial-onset seizure frequency were: levetiracetam, 1000-mg daily treatment group: 37.1%; levetiracetam, 3000-mg daily treatment group: 39.6%; and placebo, 7.4% \((P<0.001)\) for both levetiracetam groups compared to placebo.\(^21\)

**Oxcarbazepine**

Oxcarbazepine (OXC) was FDA-approved in 2000 for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults and as adjunctive ther-
Oxcarbazepine is metabolized to the active metabolite 10-hydroxy-carbamazapine. Central nervous system disorders including headache, dizziness, somnolence, ataxia, nystagmus, and abnormal gait were commonly reported in more than 10% of patients in placebo-controlled trials. Nausea, vomiting, and abdominal pain were also commonly reported.

The use of OXC as monotherapy was compared to phenytoin (PHT) in patients with newly diagnosed partial seizures or generalized tonic–clonic seizures without partial onset who had had a minimum of two seizures within the previous six months (n=287). The proportion of seizure-free patients with partial seizures was 56% for OXC and 53% for PHT. The proportion of seizure-free patients with generalized seizures without partial onset was 64% for OXC and 68% for PHT. The mean number of seizures was 3.57 for OXC versus 2.13 for PHT during maintenance.

The efficacy of OXC in patients with newly diagnosed partial seizures with or without secondarily generalized seizures or generalized tonic–clonic seizures was compared with that of valproic acid (VPA, n=249). In all patients with partial seizures, 46% and 48% of OXC and VPA patients were seizure-free, respectively. However, in the sub-group of patients with secondarily generalized seizures, 28% of OXC and 63% of VPA patients were seizure-free. Among patients with generalized tonic–clonic seizures, 72% and 62% of OXC and VPA patients, respectively, were seizure-free. Mean seizure frequency per week was 0.17 for the OXC patients versus 0.40 for the VPA patients, and the mean number of seizures during the study period was 3.57 for OXC and 10.96 for VPA (P=0.87).

The antiepileptic efficacy and side effects of oxcarbazepine were evaluated (n=40). Patients with chronic seizure disorders who were treated unsatisfactorily with PHT monotherapy were randomized to either OXC or carbamazepine (CBZ). Eighteen (45% of the study popu-
The overall seizure frequency for both groups was lower than during treatment with PHT. The number of side effects was significantly higher for CBZ than OXC (P<0.05). Sedation and dizziness occurred more frequently with CBZ than with OXC. Five patients in each treatment group had been seizure-free for one year prior to this trial and showed no relapse during the study.24

Zonisamide
Zonisamide was FDA-approved in 2000 for use as adjunctive therapy in the treatment of partial seizures in adults. The precise mechanism of action is unknown. However, in vitro pharmacological studies suggest that zonisamide blocks sodium channels and reduces voltage-dependent, transient inward currents (T-type Ca2+ currents), consequently stabilizing neuronal membranes and suppressing neuronal hypersynchronization.5 Zonisamide has approximately 40% binding to plasma proteins and primarily renal excretion after acetylation. Adverse events that occurred in more than 10% of zonisamide-treated patients compared to placebo were dizziness, headache, somnolence, and anorexia. Rare fatal skin reactions (i.e., Stevens-Johnson syndrome and toxic epidermal necrolysis) have occurred in patients taking zonisamide. Patients should be observed frequently. The effectiveness of zonisamide as adjunctive therapy was evaluated in multicenter placebo-controlled trials. Zonisamide was associated with a 32.3% median reduction in partial seizures compared to 9.6% for placebo.25

Drug Interactions

Tiagabine
Tiagabine has no known clinically significant effect on plasma levels of phenytoin, carbamazepine, valproate, phenobarbital, and primidone. Hepatic-enzyme-inducing AEDs (e.g., carbamazepine) increase tiagabine clearance, shortening its half-life to 4–7 hours (7–9 hours in non-induced patients). Valproate had no effect on tiagabine pharmacokinetics. In vitro, a 40% increase in free tiagabine was observed in patients taking valproate chronically. The clinical relevance of this finding is unknown. In pharmacokinetic studies, no interactions were observed with commonly prescribed non-AEDs including cimetidine, theophylline, warfarin, digoxin, and oral contraceptives.5,8

Levetiracetam
Potential drug interactions between levetiracetam and existing AEDs were assessed during placebo-controlled clinical studies. The data indicate that levetiracetam
does not influence the plasma concentration of existing AEDs and that these AEDs do not influence the pharmacokinetics of levetiracetam.19

Sulfonamides

Drug interactions for zonisamide: Drugs that induce liver enzymes increase the metabolism and clearance of zonisamide and decrease its half-life. Concurrent administration with therapy that either induces or inhibits CYP3A4 would be expected to alter serum concentrations of zonisamide.5,8 Zonisamide is not expected to interfere with the metabolism of other drugs that are metabolized by the CYP450 isoenzymes.

Summary

Numerous medications are currently available for the management of epileptic disorders. Seizure type, drug efficacy, and safety are factors to consider when selecting an anticonvulsant. Monotherapy offers the advantages of fewer adverse effects, the avoidance of drug interactions, improved compliance, and decreased costs.

Over the past 25 years, several anticonvulsant agents have been recommended as adjunctive therapy in patients with seizures refractory to monotherapy. Valproic acid is commonly used in children with epileptic

Table 7 Zonisamide Drug Interactions

<table>
<thead>
<tr>
<th>CYP3A4 inducers (increase metabolism)</th>
<th>CYP3A4 inhibitors (decrease metabolism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Cannabinoids</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>Cimetidine</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>Danazol</td>
</tr>
<tr>
<td>Nelfinavir</td>
<td>Dirithromycin</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Metronidazole</td>
</tr>
<tr>
<td>Rifampin</td>
<td>Quinidine</td>
</tr>
<tr>
<td>Sulfinpyrazone</td>
<td>Ranitidine</td>
</tr>
<tr>
<td></td>
<td>Sertraline</td>
</tr>
<tr>
<td></td>
<td>Valproic acid</td>
</tr>
<tr>
<td></td>
<td>Verapamil</td>
</tr>
<tr>
<td></td>
<td>Zafirlukast</td>
</tr>
</tbody>
</table>

Table 8 Anticonvulsant Dosages

<table>
<thead>
<tr>
<th>Drug5</th>
<th>Adults</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial Dose</td>
<td>Maintenance Dose</td>
</tr>
<tr>
<td><strong>Adjuvants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>&lt;15 mg/kg qd</td>
<td>60 mg/kg qd</td>
</tr>
<tr>
<td>Felbamate</td>
<td>1200 mg qd</td>
<td>3600 mg qd</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>900–1800 mg qd</td>
<td>&lt; 2400 mg qd</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>0.6 mg/kg qd</td>
<td>5–15 mg/kg qd</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>4 mg qd</td>
<td>&lt;56 mg qd</td>
</tr>
<tr>
<td>Topiramate</td>
<td>50 mg qd</td>
<td>&lt;400 mg qd</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>500 mg bid</td>
<td>3000 mg qd</td>
</tr>
<tr>
<td>Oxcarbazepine7</td>
<td>1.2 g qd</td>
<td>&lt;2.4 g qd</td>
</tr>
<tr>
<td>Sulfonamide</td>
<td>100 mg qd</td>
<td>300–400 mg qd</td>
</tr>
</tbody>
</table>

Adult dose based on 70kg; pediatric dose based on 20kg; qd = Once every day; bid = twice a day; tid = three times a day; hs = at bedtime; ND = not determined.
disorders. Felbamate was approved as monotherapy or adjunctive treatment of partial seizures, but incidents of aplastic anemia and acute hepatic failure limit its use. Gabapentin has a favorable pharmacokinetic profile that includes minimal protein binding, few drug interactions, and primarily renal excretion. Its side-effect profile is limited to central nervous system effects. Lamotrigine offers an option to patients converting from monotherapy with a hepatic-enzyme-inducing anticonvulsant agent. Tiagabine, an adjunctive agent for partial seizures, has not demonstrated clinically important interactions with drugs metabolized through hepatic cytochrome P450 pathways. Topiramate may be displaced by the hepatic enzyme inducers, phenytoin and carbamazepine. Levetiracetam is a newer anticonvulsant with a favorable tolerability profile and low potential for drug interactions. Oxcarbazepine is a homologue of carbamazepine that has been shown to be as effective as phenytoin and valproic acid at reducing the frequency of generalized tonic-clonic and partial seizures. Zonisamide is a newer adjunctive agent for partial seizures. It is chemically classified as a sulfonamide, and it carries a risk of severe rash.

References


Disclosure
Dr. Tucker has declared that she has no commercial relationship to disclose relating to this activity.