Drugs for Epilepsy

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I. OVERVIEW

Approximately 10% of the population will have at least one seizure in their lifetime. Globally, epilepsy is the third most common neurologic disorder after cerebrovascular and Alzheimer’s disease. Epilepsy is not a single entity but an assortment of different seizure types and syndromes originating from several mechanisms that have in common the sudden, excessive, and synchronous discharge of cerebral neurons. This abnormal electrical activity may result in a variety of events, including loss of consciousness, abnormal movements, atypical or odd behavior, and distorted perceptions that are of limited duration but recur if untreated. The site of origin of the abnormal neuronal firing determines the symptoms that are produced. For example, if the motor cortex is involved, the patient may experience abnormal movements or a generalized convulsion. Seizures originating in the parietal or occipital lobe may include visual, auditory, and olfactory hallucinations. Medications are the most widely used mode of treatment for patients with epilepsy. In general, seizures can be controlled with one medication in approximately 75% of patients. Patients may require more than one medication in order to optimize seizure control, and some patients may never obtain total seizure control. A summary of antiepilepsy medications is shown in Figure 12.1.

II. ETIOLOGY OF SEIZURES

In most cases, epilepsy has no identifiable cause. Focal areas that are functionally abnormal may be triggered into activity by changes in physiologic factors, such as an alteration in blood gases, pH, electrolytes, and blood glucose and changes in environmental factors, such as sleep deprivation, alcohol intake, and stress. The neuronal discharge in epilepsy results from the firing of a small population of neurons in a specific area of the brain referred to as the “primary focus.” Neuroimaging techniques, such as magnetic resonance imaging, positron emission tomography scans, and single photon emission coherence tomography, may identify areas of concern (Figure 12.2). Epilepsy can be due to an underlying genetic, structural, or metabolic cause or an unknown cause. Though multiple specific epilepsy syndromes that include symptoms other than seizures have been classified, a discussion of these syndromes is beyond the scope of this chapter.

Figure 12.1
Summary of agents used in the treatment of epilepsy. Drugs arranged alphabetically.
A. Genetic epilepsy

These seizures result from an inherited abnormality in the central nervous system (CNS). Some genetic mutations have been identified in epilepsy syndromes. Obtaining a detailed family history may provide important information for assessing the possibility of a genetic link to seizures.

B. Structural/metabolic epilepsy

A number of causes, such as illicit drug use, tumor, head injury, hypoglycemia, meningeal infection, and the rapid withdrawal of alcohol from an alcoholic, can precipitate seizures. In cases when the cause of a seizure can be determined and corrected, medication may not be necessary. For example, a seizure that is caused by a drug reaction is not epilepsy and does not require chronic therapy. In other situations, antiepilepsy medications may be needed when the primary cause of the seizures cannot be corrected.

C. Unknown cause

When no specific anatomic cause for the seizure, such as trauma or neoplasm, is evident, a patient may be diagnosed with seizures where the underlying cause is unknown. Most cases of epilepsy are due to an unknown cause. Patients can be treated chronically with antiepilepsy medications or vagal nerve stimulation.

III. CLASSIFICATION OF SEIZURES

It is important to correctly classify seizures to determine appropriate treatment. Seizures have been categorized by site of origin, etiology, electrophysiologic correlation, and clinical presentation. The nomenclature developed by the International League Against Epilepsy is considered the standard way to classify seizures and epilepsy syndromes (Figure 12.3). Seizures have been classified into two broad groups: focal and generalized.

A. Focal

Focal seizures involve only a portion of the brain, typically part of one lobe of one hemisphere. The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neurons in the brain. Focal seizures may progress to become generalized tonic–clonic seizures.

1. Simple partial: These seizures are caused by a group of hyperactive neurons exhibiting abnormal electrical activity and are confined to a single locus in the brain. The electrical discharge does not spread, and the patient does not lose consciousness or awareness. The patient often exhibits abnormal activity of a single limb or muscle group that is controlled by the region of the brain experiencing the disturbance. The patient may also show sensory distortions. This activity may spread. Simple partial seizures may occur at any age.
2. **Complex partial:** These seizures exhibit complex sensory hallucinations and mental distortion. Motor dysfunction may involve chewing movements, diarrhea, and/or urination. Consciousness is altered. Simple partial seizure activity may spread to become complex and then spread to a secondarily generalized convulsion. Complex partial seizures may occur at any age.

**B. Generalized**

Generalized seizures may begin locally and then progress to include abnormal electrical discharges throughout both hemispheres of the brain. Primary generalized seizures may be convulsive or nonconvulsive, and the patient usually has an immediate loss of consciousness.

1. **Tonic–clonic:** These seizures result in loss of consciousness, followed by tonic (continuous contraction) and clonic (rapid contraction and relaxation) phases. The seizure may be followed by a period of confusion and exhaustion due to the depletion of glucose and energy stores.

2. **Absence:** These seizures involve a brief, abrupt, and self-limiting loss of consciousness. The onset generally occurs in patients at 3 to 5 years of age and lasts until puberty or beyond. The patient stares and exhibits rapid eye-blinking, which lasts for 3 to 5 seconds. An absence seizure has a very distinct three-per-second spike and wave discharge seen on electroencephalogram.

3. **Myoclonic:** These seizures consist of short episodes of muscle contractions that may recur for several minutes. They generally occur after wakening and exhibit as brief jerks of the limbs. Myoclonic seizures occur at any age but usually begin around puberty or early adulthood.

4. **Clonic:** These seizures consist of short episodes of muscle contractions that may closely resemble myoclonic seizures. Consciousness is more impaired with clonic seizures as compared to myoclonic.

5. **Tonic:** These seizures involve increased tone in the extension muscles and are generally less than 60 seconds long.

6. **Atonic:** These seizures are also known as drop attacks and are characterized by a sudden loss of muscle tone.

**C. Mechanism of action of antiepilepsy medications**

Drugs reduce seizures through such mechanisms as blocking voltage-gated channels (Na⁺ or Ca²⁺), enhancing inhibitory γ-aminobutyric acid (GABA)-ergic impulses and interfering with excitatory glutamate transmission. Some antiepilepsy medications appear to have multiple targets within the CNS, whereas the mechanism of action for some agents is poorly defined. Antiepilepsy medications suppress seizures but do not “cure” or “prevent” epilepsy.
IV. DRUG SELECTION

Choice of drug treatment is based on the classification of the seizures, patient-specific variables (for example, age, comorbid medical conditions, lifestyle, and personal preference), and characteristics of the drug (such as cost and drug interactions). For example, focal-onset seizures are treated with a different set of medications than primary generalized seizures, although the list of effective agents overlaps. The toxicity of the agent and characteristics of the patient are major considerations in drug selection. In newly diagnosed patients, monotherapy is instituted with a single agent until seizures are controlled or toxicity occurs (Figure 12.4). Compared to those receiving combination therapy, patients receiving monotherapy exhibit better medication adherence and fewer side effects. If seizures are not controlled with the first medication, monotherapy with an alternate medication or the addition of medications should be considered (Figure 12.5). Failing that, other medical management (vagal nerve stimulation, surgery, etc.) should be considered. Awareness of the antiepilepsy medications available and their mechanisms of action, pharmacokinetics, potential for drug–drug interactions, and adverse effects is essential for successful treatment of the patient.

V. ANTIENZYMENOSE MEDICATIONS

During the past 20 years, the Food and Drug Administration has approved many new antiepilepsy medications (Figure 12.1). Some of these agents are thought to have potential advantages over drugs approved prior to 1990 in terms of pharmacokinetics, tolerability, and reduced risk for drug–drug interactions. However, studies have failed to demonstrate that the newer drugs are significantly more efficacious than the older agents. For that reason, the antiepilepsy medications are described below in alphabetical order, rather than attempting to rank them by efficacy. Figure 12.6 summarizes pharmacokinetic properties of the antiepilepsy medications, and Figure 12.7 shows common adverse effects. Suicidal behavior and suicidal ideation have been identified as a risk with antiepilepsy medications. In addition, virtually, all antiepilepsy medications have been associated with multiorgan hypersensitivity reactions, a rare idiosyncratic reaction characterized by rash, fever, and systemic organ involvement.

A. Benzodiazepines

Benzodiazepines bind to GABA inhibitory receptors to reduce firing rate. Most benzodiazepines are reserved for emergency or acute seizure treatment due to tolerance. However, clonazepam [klo-NAZ-e-pam] and clobazam [KLOE-ba-zam] may be prescribed as adjunctive therapy for particular types of seizures. Diazepam [dye-AZ-e-pam] is also available for rectal administration to avoid or interrupt prolonged generalized tonic–clonic seizures or clusters when oral administration is not possible.
Figure 12.5
Therapeutic indications for the anticonvulsant agents. Benzodiazepines = diazepam and lorazepam.
### Figure 12.6
Summary of the pharmacokinetics of antiepilepsy medications used as chronic therapy.

<table>
<thead>
<tr>
<th>ANTIEPILEPSY MEDICATION</th>
<th>PROTEIN BINDING*</th>
<th>HALF-LIFE</th>
<th>ACTIVE METABOLITE</th>
<th>MAJOR ORGAN OF ELIMINATION</th>
<th>DRUG INTERACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Moderate</td>
<td>6–15</td>
<td>CBZ-10,11-epoxide</td>
<td>Liver</td>
<td>✔</td>
</tr>
<tr>
<td>Eslicarbazepine acetate</td>
<td>Low</td>
<td>8–24</td>
<td>Eslicarbazepine</td>
<td>Kidney</td>
<td>✔</td>
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<tr>
<td>Ethosuximide</td>
<td>Low</td>
<td>25–26</td>
<td></td>
<td>Liver</td>
<td>✔</td>
</tr>
<tr>
<td>Ezogabine</td>
<td>Moderate</td>
<td>7–11</td>
<td>monoacetylated</td>
<td>Liver</td>
<td>✔</td>
</tr>
<tr>
<td>Fosphenytoin**</td>
<td>High</td>
<td>12–60</td>
<td>phenytoin</td>
<td>Liver</td>
<td>✔</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Low</td>
<td>5–9</td>
<td></td>
<td>Kidney</td>
<td></td>
</tr>
<tr>
<td>Lacosamide</td>
<td>Low</td>
<td>13</td>
<td></td>
<td>Various</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Low</td>
<td>25–32</td>
<td></td>
<td>Liver</td>
<td>✔</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Low</td>
<td>6–8</td>
<td></td>
<td>Hydrolysis</td>
<td></td>
</tr>
<tr>
<td>Oxcarbazepine**</td>
<td>Low</td>
<td>5–13</td>
<td>Monohydroxy</td>
<td>Liver</td>
<td>✔</td>
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<tr>
<td>Phenobarbital</td>
<td>Low</td>
<td>72–124</td>
<td></td>
<td>Liver</td>
<td>✔</td>
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<tr>
<td>Phenytoin</td>
<td>High</td>
<td>12–60</td>
<td></td>
<td>Liver</td>
<td>✔</td>
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<tr>
<td>Primidone</td>
<td>High</td>
<td>72–124</td>
<td>Phenobarbital, PEMA</td>
<td>Liver</td>
<td>✔</td>
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<tr>
<td>Perampanel^</td>
<td>High</td>
<td>105</td>
<td></td>
<td>Liver</td>
<td>✔</td>
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<td>Pregabalin</td>
<td>Low</td>
<td>5–6.5</td>
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<td>Kidney</td>
<td>✔</td>
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<td>Rufinamide</td>
<td>Low</td>
<td>6–10</td>
<td></td>
<td>Liver</td>
<td>✔</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>High</td>
<td>7–9</td>
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<td>Liver</td>
<td>✔</td>
</tr>
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<td>✔</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Low</td>
<td>7.5</td>
<td></td>
<td>Kidney</td>
<td>✔</td>
</tr>
<tr>
<td>Valproic Acid (Divalproex)</td>
<td>Moderate/High</td>
<td>6–18</td>
<td>Various</td>
<td>Liver</td>
<td>✔</td>
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<tr>
<td>Zonisamide</td>
<td>Low</td>
<td>63</td>
<td></td>
<td>Liver</td>
<td>✔</td>
</tr>
</tbody>
</table>

*Low = 60% or less, Moderate = 61%-85%, High = >85%; ^Newly approved. Limited data in patients available. **Prodrug.

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**B. Carbamazepine**

*Carbamazepine* [kar-ba-MA-z-a-peen] blocks sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus and preventing their spread. *Carbamazepine* is effective for treatment of focal seizures and, additionally generalized tonic–clonic seizures, trigeminal neuralgia, and bipolar disorder. *Carbamazepine* is absorbed slowly and erratically following oral administration and may vary from generic to generic, resulting in large variations in serum concentrations of the drug. It induces its own
metabolism, resulting in lower total carbamazepine blood concentrations at higher doses. Carbamazepine is an inducer of the CYP1A2, CYP2C, and CYP3A and UDP glucuronosyltransferase (UGT) enzymes, which increases the clearance of other drugs (Figure 12.8). Hyponatremia may be noted in some patients, especially the elderly, and may necessitate a change in medication. Carbamazepine should not be prescribed for patients with absence seizures because it may cause an increase in seizures.

C. Eslicarbazepine

*Eslicarbazepine* [es-li-car-BAZ-a-peen] acetate is a prodrug that is converted to the active metabolite eslicarbazepine (S-licarbazepine) by hydrolysis. S-licarbazepine is the active metabolite of oxcarbazepine (see below). It is a voltage-gated sodium channel blocker and is approved for partial-onset seizures in adults. Eslicarbazepine exhibits linear pharmacokinetics and is eliminated via glucuronidation. The side effect profile includes dizziness, somnolence, diplopia, and headache. Serious adverse reactions such as rash, psychiatric side effects, and hyponatremia occur rarely.

D. Ethosuximide

*Ethosuximide* [eth-oh-SUX-i-mide] reduces propagation of abnormal electrical activity in the brain, most likely by inhibiting T-type calcium channels. It is only effective in treating absence seizures.

E. Ezogabine

*Ezogabine* [e-ZOG-a-been] is thought to open voltage-gated M-type potassium channels leading to stabilization of the resting membrane potential. Ezogabine exhibits linear pharmacokinetics and no drug interactions at lower doses. Possible unique side effects are urinary retention, QT interval prolongation, blue skin discoloration, and retinal abnormalities.

F. Felbamate

*Felbamate* [FEL-ba-mate] has a broad spectrum of anticonvulsant action with multiple proposed mechanisms including the blocking of voltage-dependent sodium channels, competing with the glycine coagonist binding site on the N-methyl-D-aspartate (NMDA) glutamate receptor, blocking of calcium channels, and potentiating GABA action. It is an inhibitor of drugs metabolized by CYP2C19 and induces drugs metabolized by CYP3A4. It is reserved for use in refractory epilepsies (particularly Lennox-Gastaut syndrome) because of the risk of aplastic anemia (about 1:4000) and hepatic failure.

G. Gabapentin

*Gabapentin* [GA-ba-pen-tin] is an analog of GABA. However, it does not act at GABA receptors, enhance GABA actions or convert to GABA. Its precise mechanism of action is not known. It is approved as adjunct therapy for focal seizures and treatment of postherpetic neuralgia. Gabapentin exhibits nonlinear pharmacokinetics (see Chapter 1) due to its uptake by a saturable transport system from the gut. Gabapentin does not bind to plasma proteins

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**Figure 12.7**

Notable adverse effects of antiseizure medications.
and is excreted unchanged through the kidneys. Reduced dosing is required in renal disease. Gabapentin is well tolerated by the elderly population with partial seizures due to its relatively mild adverse effects. It may also be a good choice for the older patient because there are few drug interactions.

H. Lacosamide

Lacosamide [la-KOE-sa-mide] in vitro affects voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing. Lacosamide binds to collapsin response mediator protein-2 (CRMP-2), a phosphoprotein involved in neuronal differentiation and control of axonal outgrowth. The role of CRMP-2 binding in seizure control is unknown. Lacosamide is approved for adjunctive treatment of focal seizures. It is available in an injectable formulation. The most common adverse events that limit treatment include dizziness, headache, and fatigue.

I. Lamotrigine

Lamotrigine [la-MOE-tri-jeen] blocks sodium channels, as well as high voltage-dependent calcium channels. Lamotrigine is effective in a wide variety of seizure types, including focal, generalized, absence seizures, and Lennox-Gastaut syndrome. It is also used to treat bipolar disorder. Lamotrigine is metabolized primarily to the 2-N-glucuronide metabolite through the UGT1A4 pathway. As with other antiepilepsy medications, general inducers increase lamotrigine clearance leading to lower lamotrigine concentrations, whereas valproate results in a significant decrease in lamotrigine clearance (higher lamotrigine concentrations). Lamotrigine dosages should be reduced when adding valproate to therapy. Slow titration is necessary with lamotrigine (particularly when adding lamotrigine to a regimen that includes valproate) due to risk of rash, which may progress to a serious, life-threatening reaction.

J. Levetiracetam

Levetiracetam [lee-ve-tye-RA-se-tam] is approved for adjunct therapy of focal onset, myoclonic, and primary generalized tonic–clonic seizures in adults and children. The exact mechanism of anticonvulsant action is unknown. It demonstrates high affinity for a synaptic vesicle protein (SV2A). The drug is well absorbed orally and excreted in urine mostly unchanged, resulting in few to no drug interactions. Levetiracetam can cause mood alterations that may require a dose reduction or a change of medication.

K. Oxcarbazepine

Oxcarbazepine [ox-kar-BAY-zeh-peen] is a prodrug that is rapidly reduced to the 10-monohydroxy (MHD) metabolite responsible for its anticonvulsant activity. MHD blocks sodium channels, preventing the spread of the abnormal discharge. It is also thought to modulate calcium channels. It is approved for use in adults and children with partial-onset seizures. Oxcarbazepine is a less potent inducer of CYP3A4 and UGT than carbamazepine. The adverse effect of hyponatremia limits its use in the elderly.
L. Perampanel

Perampanel [per-AM-pa-nel] is a selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid antagonist resulting in reduced excitatory activity. Perampanel has a long half-life enabling once-daily dosing. It is approved for adjunctive treatment of partial-onset seizures in patients 12 years or older. Perampanel is a newer antiepileptic agent, and limited data are available in patients.

M. Phenobarbital and primidone

The primary mechanism of action of phenobarbital [fee-noe-BAR-bih-tal] is enhancement of the inhibitory effects of GABA-mediated neurons (see Chapter 9). Primidone is metabolized to phenobarbital (major) and phenylethylmalonamide, both with anticonvulsant activity. Phenobarbital is used primarily in the treatment of status epilepticus when other agents fail.

N. Phenytoin and fosphenytoin

Phenytoin [FEN-i-toin] blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery. It is effective for treatment of focal and generalized tonic-clonic seizures and in the treatment of status epilepticus. Phenytoin induces drugs metabolized by the CYP2C and CYP3A families and the UGT enzyme system. Phenytoin exhibits saturable enzyme metabolism resulting in nonlinear pharmacokinetic properties (small increases in the daily dose can produce large increases in plasma concentration, resulting in drug-induced toxicity; Figure 12.9). Depression of the CNS occurs particularly in the cerebellum and vestibular system, causing nystagmus and ataxia. The elderly are highly susceptible to this effect. Gingival hyperplasia may cause the gums to grow over the teeth (Figure 12.10). Long-term use may lead to development of peripheral neuropathies and osteoporosis. Although phenytoin is advantageous due to its low cost, the actual cost of therapy may be much higher, considering the potential for serious toxicity and adverse effects.

Fosphenytoin [FOS-phen-i-toin] is a prodrug that is rapidly converted to phenytoin in the blood within minutes. Whereas fosphenytoin may be administered intramuscularly (IM), phenytoin sodium should never be given IM, as it causes tissue damage and necrosis. Fosphenytoin is the drug of choice and standard of care for IV and IM administration of phenytoin. Because of sound-alike and look-alike trade names, there is a risk for prescribing errors. The trade name of fosphenytoin is Cerebyx®, which is easily confused with Celebrex®, the cyclooxygenase-2 inhibitor, and Celexa®, the antidepressant.

O. Pregabalin

Pregabalin [pree-GA-ba-lin] binds to the α2-δ site, an auxiliary subunit of voltage-gated calcium channels in the CNS, inhibiting excitatory neurotransmitter release. The exact role this plays in treatment is not known, but the drug has proven effects on focal-onset seizures, diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. More than 90% of pregabalin is eliminated renally. Dosage adjustments are needed in renal dysfunction. It has no significant metabolism and few drug interactions. Weight gain and peripheral edema have been reported.
**P. Rufinamide**

*Rufinamide* [roo-FIN-a-mide] acts at sodium channels. It is approved for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children over age 4 years and in adults. *Rufinamide* is a weak inhibitor of CYP2E1 and a weak inducer of CYP3A4 enzymes. Food increases absorption and peak serum concentrations. Serum concentrations of *rufinamide* are affected by other antiepilepsy medications. As with other antiepilepsy medications, it is induced by *carbamazepine* and *phenytoin* and inhibited when given with *valproate*. Adverse effects include the potential for shortened QT intervals. Patients with familial short QT syndrome should not be treated with *rufinamide*.

**Q. Tiagabine**

*Tiagabine* [ty-AG-a-been] blocks GABA uptake into presynaptic neurons permitting more GABA to be available for receptor binding, and therefore, it enhances inhibitory activity. *Tiagabine* is effective as adjunctive treatment in partial-onset seizures. In postmarketing surveillance, seizures have occurred in patients using *tiagabine* who did not have epilepsy. *Tiagabine* should not be used for indications other than epilepsy.

**R. Topiramate**

*Topiramate* [toe-PEER-a-mate] has multiple mechanisms of action. It blocks voltage-dependent sodium channels, reduces high-voltage calcium currents (L type), is a carbonic anhydrase inhibitor, and may act at glutamate (NMDA) sites. *Topiramate* is effective for use in partial and primary generalized epilepsy. It is also approved for prevention of migraine. It inhibits CYP2C19 and is induced by *phenytoin* and *carbamazepine*. Adverse effects include somnolence, weight loss, and paresthesias. Renal stones, glaucoma, oligohydrosis (decreased sweating), and hyperthermia have also been reported.

**S. Valproic acid and divalproex**

Possible mechanisms of action include sodium channel blockade, blockade of GABA transaminase, and action at the T-type calcium channels. These varied mechanisms provide a broad spectrum of activity against seizures. It is effective for the treatment of focal and primary generalized epilepsies. *Valproic acid* [val-PRO-ik A-sid] is available as a free acid. *Divalproex* [dye-val-PRO-ex] *sodium* is a combination of *sodium valproate* [val-PROE-ate] and *valproic acid* that is converted to *valproate* when it reaches the gastrointestinal tract. It was developed to improve gastrointestinal tolerance of *valproic acid*. All of the available salt forms are equivalent in efficacy (*valproic acid* and *sodium valproate*). Commercial products are available in multiple-salt dosage forms and extended-release formulations. Therefore, the risk for medication errors is high, and it is essential to be familiar with all preparations. *Valproate* inhibits metabolism of the CYP2C9, UGT, and epoxide hydrolase systems (Figure 12.8). Rare hepatotoxicity may cause a rise in liver enzymes, which should be monitored frequently. Teratogenicity is also of great concern.
T. Vigabatrin

Vigabatrin [vye-GA-ba-trin] acts as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T). GABA-T is the enzyme responsible for metabolism of GABA. Vigabatrin is associated with visual field loss ranging from mild to severe in 30% or more of patients. Vigabatrin is only available through physicians and pharmacies that participate in the restricted distribution SHARE program.

U. Zonisamide

Zonisamide [zoe-NIS-a-mide] is a sulfonamide derivative that has a broad spectrum of action. The compound has multiple effects, including blockade of both voltage-gated sodium channels and T-type calcium currents. It has a limited amount of carbonic anhydrase activity. Zonisamide is approved for use in patients with focal epilepsy. It is metabolized by the CYP3A4 isozyme and may, to a lesser extent, be affected by CYP3A5 and CYP2C19. In addition to typical CNS adverse effects, zonisamide may cause kidney stones. Oligohidrosis has been reported, and patients should be monitored for increased body temperature and decreased sweating. Zonisamide is contraindicated in patients with sulfonamide or carbonic anhydrase inhibitor hypersensitivity.

VI. STATUS EPILEPTICUS

In status epilepticus, two or more seizures occur without recovery of full consciousness in between episodes. These may be focal or primary generalized, convulsive or nonconvulsive. Status epilepticus is life threatening and requires emergency treatment usually consisting of administration of a fast-acting medication such as a benzodiazepine, followed by a slower-acting medication such as phenytoin.

VII. WOMEN’S HEALTH AND EPILEPSY

Women of childbearing potential with epilepsy require assessment of their antiepilepsy medications in regard to contraception and pregnancy planning. Several antiepilepsy medications increase the metabolism of hormonal contraceptives, potentially rendering them ineffective. These include phenytoin, phenobarbital, carbamazepine, topiramate, oxcarbazepine, rufinamide, and clobazam. These medications increase the metabolism of contraceptives regardless of the delivery system used (for example, patch, ring, implants, and oral tablets). Pregnancy planning is vital, as many antiepilepsy medications have the potential to affect fetal development and cause birth defects. All women considering pregnancy should be on high doses (1 to 5 mg) of folic acid prior to conception. Divalproex and barbiturates should be avoided. If possible, women already taking divalproex should be placed on other therapies prior to pregnancy and counseled about the potential for birth defects, including cognitive (Figure 12.11) and behavioral abnormalities and neural tube defects. The pharmacokinetics of antiepilepsy medications and the frequency and severity of seizures may change during pregnancy. Regular monitoring by both an obstetrician and a neurologist is important. All women with epilepsy should be encouraged to register with the Antiepileptic Drug Pregnancy Registry. Figure 12.12 summarizes important characteristics of the antiepilepsy medications.

Figure 12.11
Cognitive function at 3 years of age after fetal exposure to doses of antiepileptic drugs. The means (black squares) and 95% confidence intervals (horizontal lines) are given for the children’s IQ as a function of the antiepileptic drugs.
<table>
<thead>
<tr>
<th>DRUG</th>
<th>MECHANISM OF ACTION</th>
<th>ADVERSE EFFECTS AND COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Carbamazepine</strong></td>
<td>Blocks Na(^+) channels</td>
<td>Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has also been associated with Stevens-Johnson syndrome. Blood dyscrasias: neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemia.</td>
</tr>
<tr>
<td><strong>Divalprox</strong></td>
<td>Multiple mechanisms of action</td>
<td>Weight gain, easy bruising, nausea, tremor, hair loss, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects have been observed. Broad spectrum of antiseizure activity.</td>
</tr>
<tr>
<td><strong>Eilcarbazepine acetate</strong></td>
<td>Blocks Na(^+) channels</td>
<td>Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.</td>
</tr>
<tr>
<td><strong>Ethosuximide</strong></td>
<td>Blocks Ca(^2+) channels</td>
<td>Drowsiness, hyperactivity, nausea, sedation, GI upset, weight gain, lethargy, SLE, and rash. Blood dyscrasias can occur; periodic CBCs should be done. Abrupt discontinuance of drug may cause seizures.</td>
</tr>
<tr>
<td><strong>Ezogabine</strong></td>
<td>Enhances K(^+) channels</td>
<td>Urinary retention, neuropsychiatric symptoms, dizziness, somnolence, QT prolongation, reports of blue skin discoloration, and retina changes.</td>
</tr>
<tr>
<td><strong>Felbamate</strong></td>
<td>Multiple mechanisms of action</td>
<td>Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia and hepatic failure. Broad spectrum of antiseizure activity. Requires patient to sign informed consent at dispensing.</td>
</tr>
<tr>
<td><strong>Gabapentin</strong></td>
<td>Unknown</td>
<td>Mild drowsiness, dizziness, ataxia, weight gain, and diarrhea. Few drug interactions. One hundred percent renal elimination.</td>
</tr>
<tr>
<td><strong>Lacosamide</strong></td>
<td>Multiple mechanisms of action</td>
<td>Dizziness, fatigue, and headache. Few drug interactions; Schedule V.</td>
</tr>
<tr>
<td><strong>Lamotrigine</strong></td>
<td>Multiple mechanisms of action</td>
<td>Nausea, drowsiness, dizziness, headache, and diplopia. Rash (Stevens-Johnson syndrome—potentially life threatening). Broad spectrum of antiseizure activity.</td>
</tr>
<tr>
<td><strong>Levetiracetam</strong></td>
<td>Multiple mechanisms of action</td>
<td>Sedation, dizziness, headache, anorexia, fatigue, infections, and behavioral symptoms. Few drug interactions. Broad spectrum of antiseizure activity.</td>
</tr>
<tr>
<td><strong>Oxcarbazepine</strong></td>
<td>Blocks Na(^+) channels</td>
<td>Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.</td>
</tr>
<tr>
<td><strong>Perampanel</strong></td>
<td>Blocks AMPA glutamate receptors</td>
<td>Gingival hyperplasia, confusion, slurred speech, double vision, ataxia, sedation, dizziness, and hirsutism. Stevens-Johnson syndrome—potentially life threatening. Not recommended for chronic use. Primary treatment for status epilepticus (fosphenytoin).</td>
</tr>
<tr>
<td><strong>Phenytoin</strong></td>
<td>Blocks Na(^+) channels</td>
<td>Gingival hyperplasia, confusion, slurred speech, double vision, ataxia, sedation, dizziness, and hirsutism. Stevens-Johnson syndrome—potentially life threatening. Not recommended for chronic use. Primary treatment for status epilepticus (fosphenytoin).</td>
</tr>
<tr>
<td><strong>Pregabalin</strong></td>
<td>Multiple mechanisms of action</td>
<td>Weight gain, somnolence, dizziness, headache, diplopia, and ataxia. One hundred percent renal elimination.</td>
</tr>
<tr>
<td><strong>Rufinamide</strong></td>
<td>Unknown</td>
<td>Shortened QT interval. Multiple drug interactions.</td>
</tr>
<tr>
<td><strong>Tiagabine</strong></td>
<td>Blocks GABA uptake</td>
<td>Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions.</td>
</tr>
<tr>
<td><strong>Topiramate</strong></td>
<td>Multiple mechanisms of action</td>
<td>Paresthesia, weight loss, nervousness, depression, anorexia, anxiety, tremor, cognitive complaints, headache, and oligohidrosis. Few drug interactions. Broad spectrum of antiseizure activity.</td>
</tr>
<tr>
<td><strong>Vigabatrin</strong></td>
<td>Irreversible binding of GABA-T</td>
<td>Vision loss, anemia, somnolence, fatigue, peripheral neuropathy, weight gain. Available only through SHARE pharmacies.</td>
</tr>
<tr>
<td><strong>Zonisamide</strong></td>
<td>Multiple mechanisms of action</td>
<td>Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia, and oligohidrosis. Broad spectrum of antiseizure activity.</td>
</tr>
</tbody>
</table>

**Figure 12.12**
Summary of antiepileptic drugs. AMPA = \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CBC = complete blood count; GABA = \(\gamma\)-aminobutyric acid; GABA-T = \(\gamma\)-aminobutyric acid transaminase; GI = gastrointestinal; SLE = systemic lupus erythematosus.
Study Questions

Choose the ONE best answer.

12.1 A 9-year-old boy is sent for neurologic evaluation because of episodes of apparent inattention. Over the past year, the child has experienced episodes during which he develops a blank look on his face and his eyes blink for 15 seconds. He immediately resumes his previous activity. Which one the following best describes this patient’s seizures?

A. Simple partial.
B. Complex partial.
C. Tonic–clonic.
D. Absence.
E. Myoclonic.

Correct answer = D. The patient is experiencing episodes of absence seizures. Consciousness is impaired briefly and they generally begin in children aged 4 to 12 years. Diagnosis includes obtaining an EEG that shows generalized 3-Hz waves.

12.2 A child is experiencing absence seizures that interrupt his ability to pay attention during school and activities. Which of the following therapies would be most appropriate for this patient?

A. Ethosuximide.
B. Carbamazepine.
C. Diazepam.
D. Carbamazepine plus primidone.
E. Watchful waiting.

Correct answer = A. The patient has had many seizures that interrupt his ability to pay attention during school and activities, so therapy is justified. Monotherapy with primary agents is preferred for most patients. The advantages of monotherapy include reduced frequency of adverse effects, fewer interactions between antiepileptic drugs, lower cost, and improved compliance. Carbamazepine and diazepam are not indicated for absence seizures.

12.3 Which of the following drugs is most useful for the treatment of absence seizures?

A. Topiramate.
B. Tiagabine.
C. Levetiracetam.
D. Lamotrigine.
E. Zonisamide.

Correct answer = D. Of the drugs listed, lamotrigine has the best data for use in absence seizures and would be the best choice. Tiagabine is only used for focal-onset seizures. Topiramate, levetiracetam, and zonisamide may be options if the lamotrigine does not work.

12.4 A 25-year-old woman with myoclonic seizures is well controlled on valproate. She indicates that she is interested in becoming pregnant in the next year. With respect to her antiepilepsy medication, which of the following should be considered?

A. Leave her on her current therapy.
B. Consider switching to lamotrigine.
C. Consider adding a second antiepilepsy medication.
D. Decrease her valproate dose.

Correct answer = B. Valproate is a poor choice in women of child-bearing age. A review of the medication history of this patient is warranted. If she has not tried any other antiepilepsy medication, then consideration of another antiepilepsy medication may be beneficial. Studies show that valproate taken during pregnancy can have a detrimental effect on cognitive abilities in children.

12.5 A woman with myoclonic seizures is well controlled with lamotrigine. She becomes pregnant and begins to have breakthrough seizures. What is most likely happening?

A. Her epilepsy is getting worse.
B. Lamotrigine concentrations are increasing.
C. Lamotrigine concentrations are decreasing.
D. Lamotrigine is no longer efficacious for this patient.

Correct answer = C. Pregnancy alters the pharmacokinetics of lamotrigine. As pregnancy progresses, most women require increased dosages to maintain blood concentrations and seizure control.
12.6 A 42-year-old man undergoes a neurologic evaluation because of episodes of apparent confusion. Over the past year, the man has experienced episodes during which he develops a blank look on his face and fails to respond to questions. Moreover, it appears to take several minutes before the man recovers from the episodes. Which one of the following best describes this type of seizure?
A. Focal (simple partial).
B. Focal (complex partial).
C. Tonic–clonic.
D. Absence.
E. Myoclonic.

Correct answer = B. The patient is experiencing episodes of complex partial seizures. Complex partial seizures impair consciousness and can occur in all age groups. Typically, staring is accompanied by impaired consciousness and recall. If asked a question, the patient might respond with an inappropriate or unintelligible answer. Automatic movements are associated with most complex partial seizures and involve the mouth and face (lip-smacking, chewing, tasting, and swallowing movements), upper extremities (fumbling, picking, tapping, or clasping movements), vocal apparatus (grunts or repetition of words and phrases), as are complex acts (such as walking or mixing foods in a bowl).

12.7 A 52-year-old man has had several focal complex partial seizures over the last year. Which one of the following therapies would be the most appropriate initial therapy for this patient?
A. Ethosuximide.
B. Levetiracetam.
C. Diazepam.
D. Carbamazepine plus primidone.
E. Watchful waiting.

Correct answer = B. The patient has had many seizures, and the risks of not starting drug therapy would be substantially greater than the risks of treating his seizures. Because the patient has impaired consciousness during the seizure, he is at risk for injury during an attack. Monotherapy with primary agents is preferred for most patients. The advantages of monotherapy include reduced frequency of adverse effects, absence of interactions between antiepileptic drugs, lower cost, and improved compliance. Ethosuximide and diazepam are not indicated for complex partial seizures.

12.8 A patient with focal complex partial seizures has been treated for 6 months with carbamazepine but, recently, has been experiencing breakthrough seizures on a more frequent basis. You are considering adding a second drug to the antiseizure regimen. Which of the following drugs is least likely to have a pharmacokinetic interaction with carbamazepine?
A. Topiramate.
B. Tiagabine.
C. Levetiracetam.
D. Lamotrigine.
E. Zonisamide.

Correct answer = C. Of the drugs listed, all of which are approved as adjunct therapy for refractory focal complex partial seizures, only levetiracetam does not affect the pharmacokinetics of other antiepileptic drugs, and other drugs do not significantly alter its pharmacokinetics. However, any of the listed drugs could be added depending on the plan and the patient characteristics. Treatment of epilepsy is complex, and diagnosis is based on history and may need to be reevaluated when drug therapy fails or seizures increase.

12.9 Which of the following is a first-line medication for generalized tonic–clonic seizures?
A. Ethosuximide.
B. Felbamate.
C. Vigabatrin.
D. Ezogabine.
E. Topiramate.

Correct answer = E. Topiramate is a broad spectrum anti-epilepsy medication that is indicated for primary generalized tonic–clonic seizures. Ethosuximide should only be used for absence seizures. Felbamate is reserved for refractory seizures due to the risk of aplastic anemia and liver failure. Vigabatrin is not indicated for generalized seizures and is associated with visual field defects. Ezogabine is indicated for focal seizures and has been implicated in retinal abnormalities.

12.10 A 75-year-old woman had a stroke approximately 1 month ago. She is continuing to have small focal seizures where she fails to respond appropriately while talking. Which of the following is the most appropriate treatment for this individual?
A. Phenytoin.
B. Oxcarbazepine.
C. Levetiracetam.
D. Phenobarbital.

Correct answer = C. Levetiracetam is renally cleared and prone to very few drug interactions. Elderly patients usually have more comorbidities and are taking more medications than younger patients. Oxcarbazepine may cause hyponatremia, which is more symptomatic in the elderly. Phenytoin and phenobarbital have many drug interactions and a side effect profile that may be especially troublesome in the elderly age group including dizziness that may lead to falls, cognitive issues, and bone health issues.