

Antiseizure Drugs

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CASE STUDY

A 23-year-old woman presents to the office for consultation regarding her antiseizure medications. Seven years ago, this otherwise healthy young woman had a tonic-clonic seizure at home. She was rushed to the emergency department, at which time she was alert but complained of headache. A consulting neurologist placed her on levetiracetam, 500 mg bid. Four days later, electroencephalography (EEG) showed rare right temporal sharp waves. Magnetic resonance imaging (MRI) was normal. One year after this episode, a repeat EEG

was unchanged, and levetiracetam was gradually increased to 1000 mg bid. The patient had no significant adverse effects from this dosage. At age 21, she had a second tonic-clonic seizure while in college; further discussion with her roommate at that time revealed a history of two recent episodes of 1–2 minutes of altered consciousness with lip smacking (*focal impaired awareness seizure*, formerly *complex partial seizure*). A repeat EEG showed occasional right temporal spikes. What is one possible strategy for controlling her present symptoms?

Epilepsy is a chronic disorder of brain function characterized by the recurrent and unpredictable occurrence of seizures. Approximately 1% of the world's population has epilepsy, which is the fourth most common neurologic disorder after migraine, stroke, and Alzheimer's disease. Seizures that occur in people with epilepsy are transitory alterations in behavior, sensation, or consciousness caused by an abnormal, synchronized electrical discharge in the brain. Many cases of epilepsy are the result of damage to the brain, as occurs in traumatic brain injury, stroke, or infections, whereas in other cases, the epilepsy is caused by a brain tumor or developmental lesion such as a cortical or vascular malformation; these epilepsies are referred to as "symptomatic." In other cases, genetic factors are believed to be the root cause. Genetic epilepsies are often called *idiopathic*. In most cases, the inheritance is complex (polygenic). Rarely, a single gene defect can be identified. A wide diversity of genes may be affected, including (1) those encoding voltage-gated ion channels and synaptic receptors such as GABA_A receptors, (2) components of the neurotransmitter release machinery including syntaxin binding protein (STXB1), (3) neural adhesion molecules such as PCDH19, and (4) proteins involved in synapse development such as leucine-rich glioma inactivated-1 (LGI1).

The antiseizure drugs described in this chapter are usually used chronically to prevent the occurrence of seizures in people with epilepsy. These drugs are also, on occasion, used in people who do not have epilepsy—to prevent seizures that may occur as part of an acute illness such as meningitis or in the early period following either neurosurgery or traumatic brain injury. In addition, certain antiseizure drugs are used to terminate ongoing seizures such as in status epilepticus or prolonged febrile seizures or following exposure to seizure-inducing nerve toxins. Seizures are occasionally caused by an acute underlying toxic or metabolic disorder, such as hypocalcemia, in which case appropriate therapy should be directed toward correcting the specific abnormality.

DRUG DEVELOPMENT FOR EPILEPSY

Most antiseizure drugs have been identified by tests in rodent (rat or mouse) models. The **maximal electroshock (MES)** test, in which animals receive an electrical stimulus, with tonic hindlimb extension as the end point, has been the most productive model. The MES test led to the identification of many of the sodium

channel-blocking antiseizure drugs. Another model, the **pentyl-enetetrazol (PTZ)** test, in which animals receive a dose of the chemical convulsant PTZ (an antagonist of GABA_A receptors) sufficient to cause clonic seizures, has also been widely used. Animals with a genetic susceptibility to absence-like episodes are useful in identifying drugs for the treatment of absence seizures. In the kindling model, mice or rats repeatedly receive a mild electrical stimulus in the amygdala or hippocampus over the course of a number of days, causing them to develop a permanent propensity for limbic seizures when they later are stimulated. The **kindling model** can be used to assess the ability of a chemical compound to protect against focal seizures. In addition to empirical screening of chemical compounds in such animal models, a few antiseizure drugs have been identified by in vitro screening against a molecular target. Examples of targets that have been used to identify approved antiseizure drugs include γ -aminobutyric acid (GABA) transaminase (vigabatrin), GAT-1 GABA transporter (tiagabine), AMPA receptors (perampanel), or the synaptic vesicle protein SV2A (brivaracetam).

CLASSIFICATION OF SEIZURES

Epileptic seizures are classified into two main categories: (1) *focal onset seizures* (in the past called “partial” or “partial onset” seizures), which begin in a local cortical site, and (2) *generalized onset seizures*, which involve both brain hemispheres from the onset (Table 24–1). *Focal seizures* can transition to *bilateral tonic-clonic seizures* (formerly called “secondarily generalized”). *Focal aware seizures* (previously “simple partial seizures”) have preservation of consciousness; *focal impaired awareness seizures* (formerly “complex partial seizures”) have impaired consciousness. *Tonic-clonic convulsions* (previously termed “grand mal”) are what most people typically think of as a seizure: the person

loses consciousness, falls, stiffens (the tonic phase), and jerks (clonic phase). Tonic-clonic convulsions usually last for less than 3 minutes but are followed by confusion and tiredness of variable duration (“postictal period”). *Generalized tonic-clonic seizures* involve both hemispheres from the onset; they occur in patients with idiopathic generalized epilepsies, in some classifications referred to as genetic generalized epilepsies, and have been referred to as primary generalized tonic-clonic seizures. *Generalized absence seizures* (formerly called “petit mal”) are brief episodes of unconsciousness (4–20 seconds, usually <10 seconds) with no warning and immediate resumption of consciousness (no postictal abnormality). Generalized absence seizures most commonly occur in children with childhood absence epilepsy, a specific idiopathic generalized epilepsy syndrome beginning between 4 and 10 years (usually 5–7 years); most remit by age 12. Other important epilepsy syndromes are infantile spasms (West’s syndrome), Lennox-Gastaut syndrome, juvenile myoclonic epilepsy, and Dravet’s syndrome. The major seizure type in infantile spasms is the epileptic spasm, which consists of a sudden flexion, extension, or mixed extension-flexion of predominantly proximal and truncal muscles. Limited forms, such as grimacing, head nodding, or subtle eye movements, can occur. Myoclonic seizures are sudden, brief (<100 milliseconds), involuntary, single or multiple contractions of muscles or muscle groups of variable topography (axial, proximal limb, distal limb). Myoclonus is less regularly repetitive and less sustained than is clonus.

TREATMENT OF EPILEPSY

Antiseizure drugs used in the chronic treatment of epilepsy are administered orally; the objective is to prevent the occurrence of seizures. The choice of medication depends either on the type of seizures that the patient exhibits or on the patient’s syndromic classification. Appropriately chosen antiseizure drugs provide adequate seizure control in about two-thirds of patients. In designing a therapeutic strategy, the use of a single drug is preferred, especially in patients who are not severely affected; such patients can benefit from the advantage of fewer adverse effects using monotherapy. For patients with hard-to-control seizures, multiple drugs are usually used simultaneously. Patients who do not achieve seizure control following adequate trials with two or more appropriate drugs are considered “pharmacoresistant.” The basis for pharmacoresistance is not well understood. In children, some severe seizure syndromes (catastrophic childhood epilepsies) associated with progressive brain damage are very difficult to treat. Focal seizures may also be refractory to medications. In some cases, the epilepsy can be cured by surgical resection of the affected brain region. The most commonly performed epilepsy surgery is temporal lobe resection for mesial temporal lobe epilepsy; extratemporal cortical resection, when indicated, is less successful. When seizures arise from cortical injury, malformation, tumor, or a vascular lesion, lesionectomy may be curative. In addition to medications and surgery, several electrical stimulation devices are used in the treatment of

TABLE 24–1 International League Against Epilepsy classification of seizure types.

Focal onset (formerly partial onset) seizures
Focal aware seizure (formerly <i>simple partial seizure</i>)
Focal impaired awareness seizure (formerly <i>complex partial seizure</i>)
Focal-to-bilateral tonic-clonic seizure (formerly <i>partial seizure secondarily generalized</i> or <i>grand mal seizure</i>)
Generalized onset seizures
Generalized tonic-clonic seizure (formerly <i>primary generalized tonic-clonic seizure</i> or <i>grand mal seizure</i>)
Generalized absence seizure (formerly <i>petit mal seizure</i> ; occurs, for example, in absence epilepsy)
Myoclonic seizure (occurs, for example, in juvenile myoclonic epilepsy and Dravet’s syndrome)
Atonic seizure (<i>drop seizure</i> or <i>astatic seizure</i> ; occurs, for example, in the Lennox-Gastaut syndrome)
Epileptic spasms (as in infantile spasms also known as West’s syndrome)

Lennox-Gastaut syndrome, Dravet’s syndrome, and juvenile myoclonic epilepsy are epilepsy syndromes in which there are multiple different seizure types.

epilepsy. The vagus nerve stimulator (VNS) is an implanted programmable pulse generator with a helical electrode that is wrapped around the left vagus nerve in the neck. The device, which continuously delivers open-loop stimulation according to a duty cycle, is approved for the treatment of drug-refractory focal seizures but may also be a good option for symptomatic (or cryptogenic) generalized epilepsies of the Lennox-Gastaut type, including those with intractable atonic seizures. Another device for the treatment of medically refractory focal epilepsy is the responsive neurostimulator (RNS). The RNS is a closed-loop system that detects a pattern of abnormal electrical activity in the seizure focus and then delivers electrical stimulation to prevent seizure occurrence. Other devices, using various paradigms of electrical stimulation, are in clinical development. One of these, a deep brain stimulation device, has been approved in Canada and Europe but not in the USA.

MECHANISMS OF ACTION

Antiseizure drugs protect against seizures by interacting with one or more molecular targets in the brain. The ultimate effect of these interactions is to inhibit the local generation of seizure discharges, both by reducing the ability of neurons to fire action potentials at high rate as well as reducing neuronal synchronization. In addition, antiseizure drugs inhibit the spread of epileptic activity to nearby and distant sites, either by strengthening the inhibitory surround mediated by GABAergic interneurons or by reducing glutamate-mediated excitatory neurotransmission (the means through which a presynaptic neuron depolarizes and excites a postsynaptic follower neuron). The specific actions of antiseizure drugs on their targets are broadly described as: (1) modulation of voltage-gated sodium, calcium, or potassium channels; (2) enhancement of fast GABA-mediated synaptic inhibition; (3) modification of synaptic release processes; and (4) diminution of fast glutamate-mediated excitation. These actions can be viewed in the context of the balance between excitation mediated by glutamatergic neurons and inhibition mediated by GABAergic neurons. A propensity for seizure generation occurs when there is an imbalance favoring excitation over inhibition, which can result from either excessive excitation or diminished inhibition or both. Treatments, therefore, that either inhibit excitation or enhance inhibition have antiseizure actions to reduce seizure generation. Inhibition of excitation can be produced by effects on intrinsic excitability mechanisms in excitatory neurons (eg, sodium channel blockers) or on excitatory synaptic transmission (eg, modification of release of the excitatory neurotransmitter glutamate; AMPA receptor antagonists). Enhancement of inhibition is produced by increased activation of GABA_A receptors, the mediators of inhibition in cortical areas relevant to seizures. Some drug treatments (eg, benzodiazepines, phenobarbital) act as positive allosteric modulators of GABA_A receptors, whereas others (eg, tiagabine, vigabatrin) lead to increased availability of neurotransmitter GABA. Voltage-gated potassium channels of the K_v7 type also serve as an inhibitory influence on epileptiform activity. Retigabine (ezogabine), a positive allosteric modulator of K_v7 channels,

exerts a unique antiseizure action by virtue of its ability to enhance the natural inhibitory influence of these channels. The specific sites at excitatory and inhibitory neurons and synapses where currently available antiseizure drugs act to exert these diverse actions are illustrated in Figure 24–1. Table 24–2 lists the various targets at which currently available antiseizure drugs are thought to act and the drugs that act on those targets. For some drugs, there is no consensus as to the specific molecular target (eg, valproate, zonisamide, rufinamide) or there may be multiple targets (eg, topiramate, felbamate).

PHARMACOKINETICS

Chronic antiseizure drug administration prevents the occurrence of seizures, which can, on occasion, be life threatening. Therefore, adequate drug exposure must be continuously maintained. However, many antiseizure drugs also have a narrow therapeutic window; dosing must therefore avoid excessive, toxic exposure. An understanding of the pharmacokinetic properties of the drugs is essential. It is also necessary for the clinician to be cognizant of special factors that affect dosing; these factors include nonlinear relationships between dose and drug exposure and the influence of hepatic or renal impairment on clearance (see Chapters 3 and 4). Further, drug–drug interactions occur with many of the agents—a special issue since the drugs are often used in combination. For some antiseizure drugs, drug–drug interactions are complex (see Chapter 66). For example, addition of a new drug may affect the clearance of the current medication such that the dose of the current medication must be modified. Further, the current medication may necessitate a different dosing of the new drug—different from dosing in a drug-naïve subject. Many antiseizure drugs are metabolized by hepatic enzymes, and some, such as carbamazepine, oxcarbazepine, eslicarbazepine acetate, phenobarbital, phenytoin, and primidone, are strong inducers of hepatic cytochrome P450 and glucuronyl transferase enzymes. A new antiseizure drug may increase the concentration of an existing drug by inhibiting its metabolism; alternatively, the new drug may reduce the concentration by inducing the metabolism of the existing drug. Other antiseizure drugs are excreted in the kidney and are less susceptible to drug–drug interactions. Some antiseizure drugs have active metabolites. The extent of conversion to the active forms can be affected by the presence of other drugs. Some antiseizure drugs, such as phenytoin, tiagabine, valproate, diazepam, and perampanel, are highly (>90%) bound to plasma proteins. These drugs can be displaced from plasma proteins by other protein-bound drugs, resulting in a temporary rise in the free fraction. Since the free (unbound) drug is active, there can be transient toxicity. However, systemic clearance increases along with the increased free fraction, so the elevation in free concentration is eventually corrected. Some antiseizure drugs, notably levetiracetam, gabapentin, and pregabalin, are not known to have drug interactions. Antiseizure drugs can also interact with other medications. Importantly, oral contraceptive levels may be reduced by strong inducers, resulting in failure of birth control.

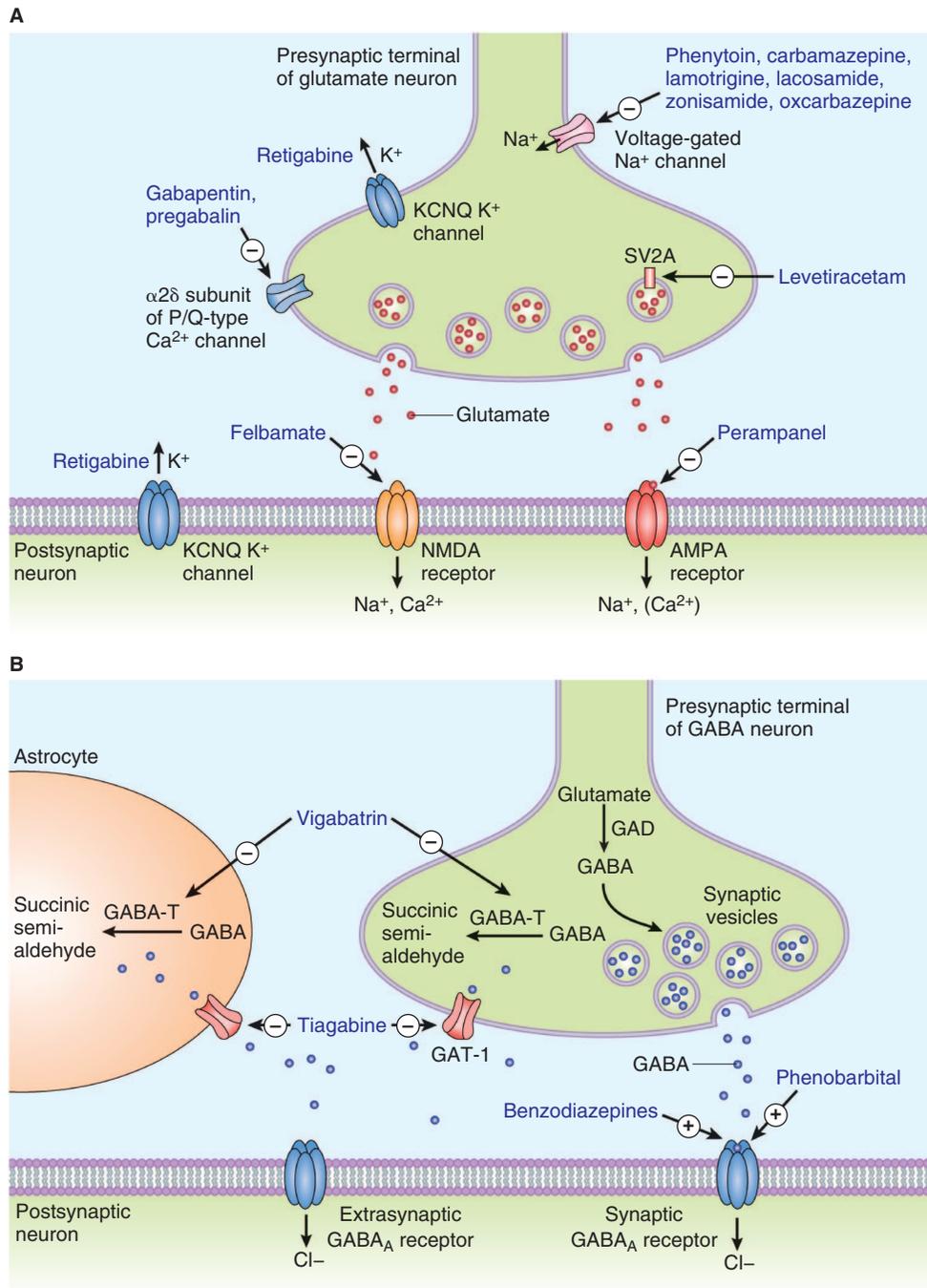


FIGURE 24-1 Molecular targets for antiseizure drugs at the excitatory glutamatergic synapse (**A**) and the inhibitory GABAergic synapse (**B**). Presynaptic targets diminishing glutamate release include Na_v1.6 voltage-gated sodium channels (carbamazepine, monohydroxy derivative [MHD], phenytoin, lamotrigine, and lacosamide), K_v7 voltage-gated potassium channels (retigabine [ezogabine]), and α_{2δ} (gabapentin and pregabalin). Postsynaptic targets at excitatory synapses are AMPA receptors (perampanel), T-type Ca_v voltage-gated calcium channels (ethosuximide, dimethadione), and K_v7 voltage-gated potassium channels (retigabine [ezogabine]). At inhibitory synapses and in astrocytes, vigabatrin inhibits GABA-transaminase (GABA-T) and tiagabine blocks GABA transporter 1 (GAT-1). Phenobarbital, primidone (via metabolism to phenobarbital), and benzodiazepines are positive allosteric modulators of synaptic GABA_A receptors; high GABA levels resulting from blockade of GABA-T may act on extrasynaptic GABA_A receptors.

TABLE 24–2 Molecular targets of antiseizure drugs.

Molecular Target	Antiseizure Drugs That Act on Target
Voltage-gated ion channels	
Voltage-gated sodium channels (Na _v)	Phenytoin, fosphenytoin ¹ , carbamazepine, oxcarbazepine ² , eslicarbazepine acetate ³ , lamotrigine, lacosamide; possibly topiramate, zonisamide, rufinamide
Voltage-gated calcium channels (T-type)	Ethosuximide
Voltage-gated potassium channels (K _v 7)	Retigabine (ezogabine)
GABA inhibition	
GABA _A receptors	Phenobarbital, primidone, benzodiazepines including diazepam, lorazepam, and clonazepam; possibly topiramate, felbamate, ezogabine
GAT-1 GABA transporter	Tiagabine
GABA transaminase	Vigabatrin
Synaptic release machinery	
SV2A	Levetiracetam, brivaracetam
α2δ	Gabapentin, gabapentin enacarbil ⁴ , pregabalin
Ionotropic glutamate receptors	
AMPA receptor	Perampanel
Mixed/unknown ⁵	Valproate, felbamate, topiramate, zonisamide, rufinamide, adrenocorticotropin

¹Fosphenytoin is a prodrug for phenytoin.

²Oxcarbazepine serves largely as a prodrug for licarbazepine, mainly S-licarbazepine.

³Eslicarbazepine acetate is a prodrug for S-licarbazepine.

⁴Gabapentin enacarbil is a prodrug for gabapentin.

⁵There is no consensus as to the mechanism of valproate; felbamate, topiramate, zonisamide, and rufinamide may have actions on as yet unidentified targets in addition to those shown in the table.

Modified from Rogawski MA, Löscher W, Rho JM: Mechanisms of action of antiseizure drugs and the ketogenic diet. *Cold Spring Harb Perspect Med* 2016;6:a022780.

Antiseizure drugs must have reasonable oral bioavailability and must enter the central nervous system. These drugs are predominantly distributed into total body water. Plasma clearance is relatively slow; many antiseizure drugs are therefore considered to be medium to long acting, such that they are administered twice or three times a day. Some have half-lives longer than 12 hours. A few, such as zonisamide and perampanel, can often be administered once daily. For some drugs with short half-lives, extended-release preparations are now available; as a result, compliance is better. In the remainder of the chapter, the most widely used antiseizure drugs, as well as some that are used only in special circumstances, are reviewed. The focal (partial onset) seizure medications are described first, followed by medications for generalized onset seizures and certain epileptic syndromes.

DRUGS USED FOR FOCAL (PARTIAL ONSET) SEIZURES

Carbamazepine is a prototype of the antiseizure drugs primarily used in the treatment of focal onset seizures. In addition to being effective in the treatment of focal seizures, carbamazepine is indicated for the treatment of tonic-clonic (grand mal) seizures. This indication derives from studies in patients whose focal onset seizures progressed to bilateral tonic-clonic seizures (previously called “secondarily generalized tonic-clonic seizures”). Drugs like carbamazepine *exacerbate* certain seizure types in idiopathic

generalized epilepsies, including myoclonic and absence seizures, and are generally avoided in patients with such a diagnosis. There is evidence from anecdotal reports and small studies indicating that carbamazepine, phenytoin, and lacosamide may be effective and safe in the treatment of generalized tonic-clonic seizures in idiopathic generalized epilepsies. The most popular drugs for the treatment of focal seizures are carbamazepine, lamotrigine, phenytoin, and lacosamide; levetiracetam is also commonly used. Phenobarbital is useful if cost is an issue. Vigabatrin and felbamate are third-line drugs because of risk of toxicity.

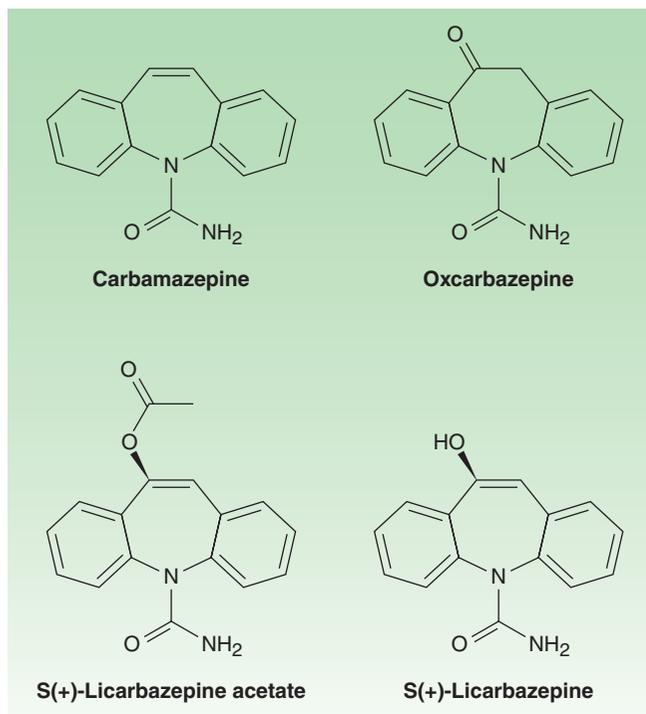
CARBAMAZEPINE

Carbamazepine is one of the most widely used antiseizure drugs despite its limited range of activity as a treatment for focal (partial onset) and focal-to-bilateral tonic-clonic seizures. It was initially marketed for the treatment of trigeminal neuralgia, for which it is highly effective; it is usually the drug of first choice for this condition. In addition, carbamazepine is a mood stabilizer used to treat bipolar disorder.

Chemistry

Structurally, carbamazepine is an iminostilbene (dibenzazepine)—a tricyclic compound consisting of two benzene rings fused to an azepine group. The structure of carbamazepine is similar to that of

tricyclic antidepressants such as imipramine, but unlike the tricyclic antidepressants, carbamazepine does not inhibit monoamine (serotonin and norepinephrine) transporters with high affinity; therefore, carbamazepine is not used as an antidepressant despite its ability to treat bipolar disorder.



Mechanism of Action

Carbamazepine is a prototypical sodium channel-blocking antiseizure drug that is thought to protect against seizures by interacting with the voltage-gated sodium channels (Na_v1) responsible for the rising phase of neuronal action potentials (see Chapters 14 and 21). In the normal state, when neurons are depolarized to action potential threshold, the sodium channel protein senses the depolarization and, within a few hundred microseconds, undergoes a conformational change (gating) that converts the channel from its closed (resting) nonconducting state to the open conducting state that permits sodium flux (Figure 24–2). Then, within less than a millisecond, the channel enters the inactivated state, terminating the flow of sodium ions. The channel must then be repolarized before it can be activated again by a subsequent depolarization. Brain sodium channels can rapidly cycle through the resting, open, and inactivated states, allowing neurons to fire high-frequency trains of action potentials.

Sodium channels are multimeric protein complexes, composed of (1) a large α subunit that forms four subunit-like homologous domains (designated I–IV) and (2) one or more smaller β subunits. The ion-conducting pore is contained within the α subunit, as are the elements of the channel that undergo conformational changes in response to membrane depolarization. Carbamazepine and other sodium channel-blocking antiseizure drugs such as phenytoin and lamotrigine bind preferentially to the channel

when it is in the inactivated state, causing it to be stabilized in this state. During high-frequency firing, sodium channels cycle rapidly through the inactivated state, allowing the block to accumulate. This leads to a characteristic use-dependent blocking action in which high-frequency trains of action potentials are more effectively inhibited than are either individual action potentials or the firing at low frequencies (see Chapter 14, Figures 14–9 and 14–10). In addition, sodium channel-blocking antiseizure drugs exhibit a voltage dependence to their blocking action because a greater fraction of sodium channels exist in the inactivated state at depolarized potentials. Thus, action potentials, which are superimposed on a depolarized plateau potential as characteristically occurs with seizures, are effectively inhibited. The use dependence and voltage dependence of the blocking action of drugs like carbamazepine provide the ability to preferentially inhibit action potentials during seizure discharges and to less effectively interfere with ordinary ongoing action potential firing (Figure 24–3). Such action is thought to allow such drugs to prevent the occurrence of seizures without causing unacceptable neurologic impairment. It is noteworthy that sodium channel-blocking antiseizure agents act mainly on action potential firing; the drugs do not directly alter excitatory or inhibitory synaptic responses. However, the effect on action potentials translates into reduced transmitter output at synapses.

Clinical Uses

Carbamazepine is effective for the treatment of focal and focal-to-bilateral tonic-clonic seizures. As noted earlier, there is anecdotal evidence that carbamazepine may be effective in the treatment of generalized tonic-clonic seizures in idiopathic generalized epilepsies but must be used with caution as it can exacerbate absence and myoclonic seizures. Carbamazepine is also effective for the treatment of trigeminal and glossopharyngeal neuralgia, and mania in bipolar disorder.

Pharmacokinetics

Carbamazepine has nearly 100% oral bioavailability, but the rate of absorption varies widely among patients. Peak levels are usually achieved 6–8 hours after administration. Slowing absorption by giving the drug after meals causes a reduction in peak levels and helps the patient tolerate larger total daily doses. Extended-release formulations may also decrease the incidence of adverse effects.

Distribution is slow, and the volume of distribution is approximately 1 L/kg. Plasma protein binding is approximately 70%. Carbamazepine has a very low systemic clearance of approximately 1 L/kg/d at the start of therapy. The drug has a notable ability to induce its own metabolism, often causing serum concentrations to fall after a few weeks of treatment. Typically, the half-life of 36 hours observed in subjects after an initial single dose decreases to as little as 8–12 hours in subjects receiving continuous therapy. Considerable dosage adjustments are thus to be expected during the first weeks of therapy.

Carbamazepine is metabolized in the liver, and only about 5% of the drug is excreted unchanged. The major route of metabolism is conversion to carbamazepine-10,11-epoxide, which has

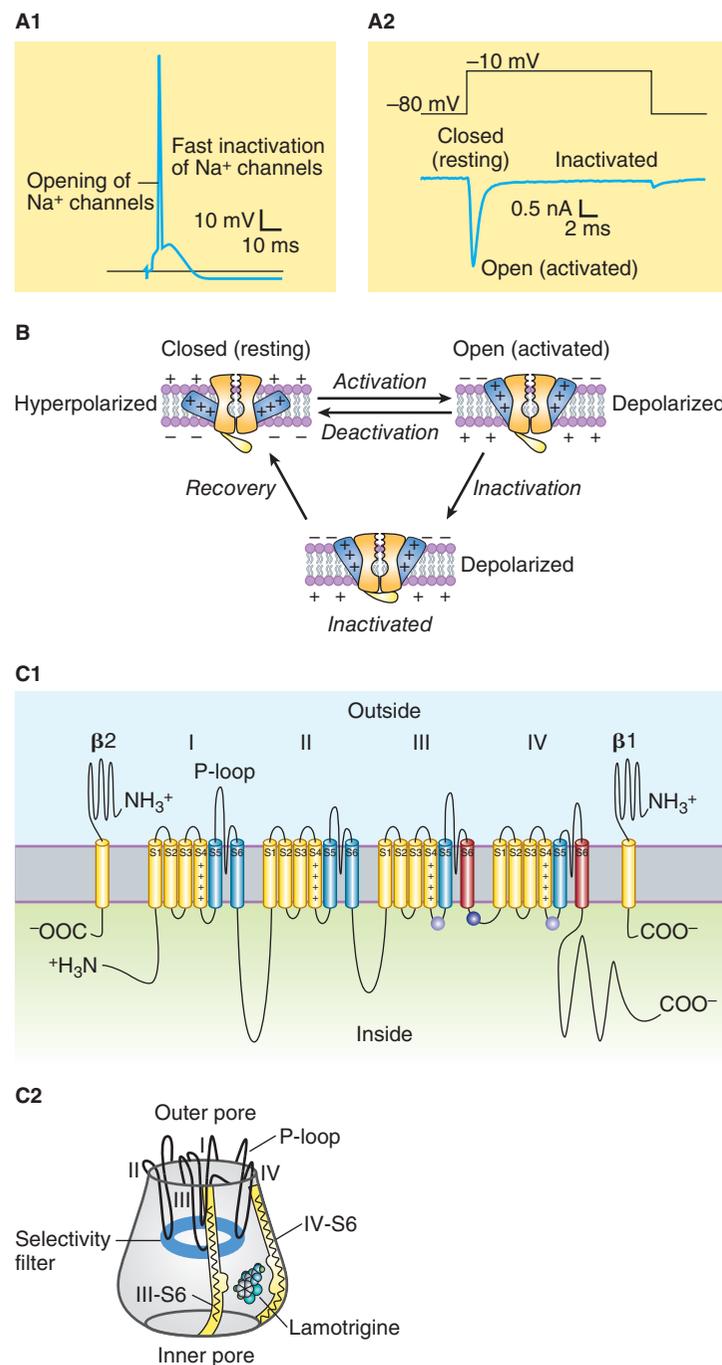


FIGURE 24-2 (A1) Voltage-gated sodium channels mediate the upstroke of action potentials in brain neurons. Fast inactivation of sodium channels (along with the activation of potassium channels) terminates the action potential. (A2) Voltage-clamp recording of sodium channel current following depolarization, illustrating the time course of sodium channel gating. (B) Schematic illustration of the voltage-dependent gating of sodium channels between closed, open, and inactivated states. (C1) Primary structures of the subunits of sodium channels. The main α subunit, consisting of four homologous repeats (I–IV), is shown flanked by the two auxiliary β subunits. Cylinders represent α -helical transmembrane segments. Blue α -helical segments (S5, S6) form the pore region. +, S4 voltage sensors; grey circles, inactivation particle in inactivation gate loop; III-S6 and IV-S6 (red) are regions of antiepileptic drug binding. (C2) Schematic illustration of the sodium channel pore composed of the homologous repeats arrayed around the central channel pore through which sodium flows into the neuron. The S5 and S6 transmembrane α -helical segments from each homologous repeat (I–IV) form the four walls of the pore. The outer pore mouth and ion selectivity filter are formed by re-entrant P-loops. The key α -helical S6 segments in repeat III and IV, which contain the antiepileptic drug binding sites, are highlighted. A lamotrigine molecule is illustrated in association with its binding site.

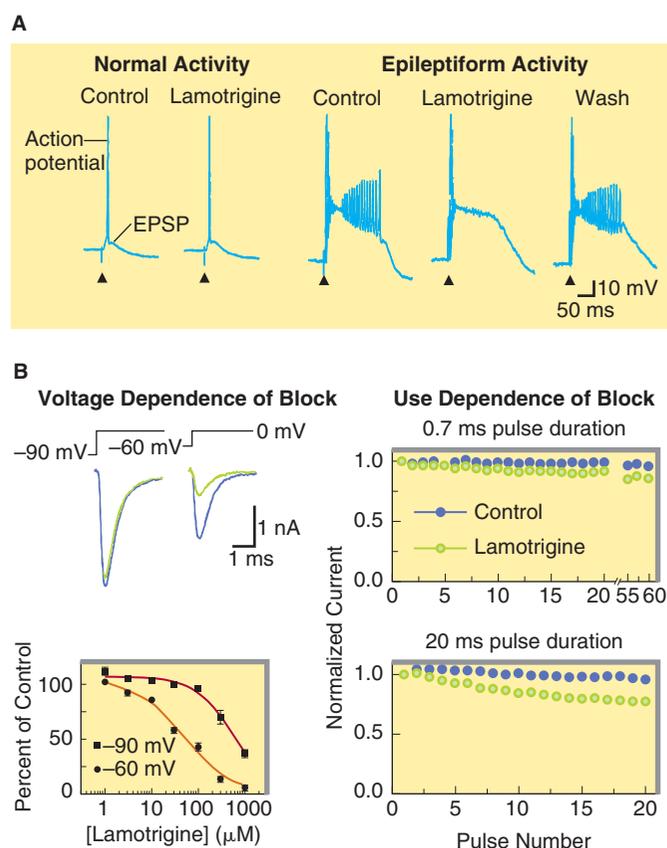


FIGURE 24-3 (A) Selective effect of a clinically relevant concentration of lamotrigine ($50 \mu\text{M}$) on action potentials and epileptic-like discharges in rat hippocampal neurons as assessed with intracellular recording. In normal recording conditions, lamotrigine has no effect on action potentials or on the evoked excitatory postsynaptic potentials (EPSPs) that elicit the action potential. In epileptic-like conditions (low magnesium), activation elicits initial spikes followed by repetitive epileptiform spike firing (afterdischarge). Lamotrigine inhibits the pathologic discharge but not the initial spikes. EPSPs were elicited by stimulation of the Schaffer collateral/commissural fibers (triangles). (B) Voltage and use dependence of block of human $\text{Na}_v1.2$ voltage-activated sodium channels. Sodium currents elicited by depolarization from a holding potential of -90 mV (where there is little inactivation) are minimally affected by $100 \mu\text{M}$ of lamotrigine, whereas there is strong block of current elicited from -60 mV (where there is more substantial inactivation). Trains of 0.7 -millisecond (ms) duration pulses from -90 mV (minimal inactivation) are minimally blocked in a use-dependent fashion by $100 \mu\text{M}$ of lamotrigine, whereas 20 -ms pulses (marked inactivation) show substantial use dependence. (Adapted, with permission, from Xie X, Hagan RM: Cellular and molecular actions of lamotrigine: Possible mechanisms of efficacy in bipolar disorder. *Neuropsychobiology* 1998;38:119.)

been shown to have antiseizure activity. This reaction is primarily catalyzed by CYP3A4, although CYP2C8 also plays a role and CYP3A5 may be involved. The contribution of this and other metabolites to the clinical activity of carbamazepine is unknown.

Dosage Recommendations & Therapeutic Levels

Carbamazepine is available in oral forms (tablets and suspensions), and an intravenous formulation is available for temporary replacement of oral therapy. The drug is effective in children, in whom a dosage of 15 – 25 mg/kg/d is appropriate. In adults, the typical daily maintenance dose is 800 – 1200 mg/d , and the maximum recommended dose is 1600 mg/d , but rarely patients have required doses up to 2400 mg/d . Higher dosage is achieved by giving multiple divided doses daily. Extended-release preparations permit twice-daily dosing for most patients. In patients in

whom the blood is drawn just before the morning dose (trough level), therapeutic concentrations are usually 4 – 8 mcg/mL . Although many patients complain of diplopia at drug levels above 7 mcg/mL , others can tolerate levels above 10 mcg/mL , especially with monotherapy. Drug initiation should be slow, with gradual increases in dose.

Drug Interactions

Carbamazepine stimulates the transcriptional up-regulation of CYP3A4 and CYP2B6. This autoinduction leads not only to a reduction in steady-state carbamazepine concentrations but also to an increased rate of metabolism of concomitant antiseizure drugs including primidone, phenytoin, ethosuximide, valproic acid, and clonazepam. Some antiseizure drugs such as valproic acid may inhibit carbamazepine clearance and increase steady-state carbamazepine blood levels. Other antiseizure drugs, notably phenytoin

and phenobarbital, may decrease steady-state concentrations of carbamazepine through enzyme induction. These interactions may require dosing changes. No clinically significant protein-binding interactions have been reported.

Adverse Effects

Carbamazepine may cause dose-dependent mild gastrointestinal discomfort, dizziness, blurred vision, diplopia, or ataxia; sedation occurs only at high doses, and rarely, weight gain can occur. The diplopia often occurs first and may last less than an hour during a particular time of day. Rearrangement of the divided daily dose can often remedy this complaint. A benign leukopenia occurs in many patients, but there is usually no need for intervention unless neutrophil count falls below $1000/\text{mm}^3$. Rash and hyponatremia are the most common reasons for discontinuation. Stevens-Johnson syndrome is rare, but the risk is significantly higher in patients with the HLA-B*1502 allele. It is recommended that Asians, who have a 10-fold higher incidence of carbamazepine-induced Stevens-Johnson syndrome compared to other ethnic groups, be tested before starting the drug.

OXCARBAZEPINE

Oxcarbazepine is the 10-keto analog of carbamazepine. Unlike carbamazepine, it cannot form an epoxide metabolite. Although it has been hypothesized that the epoxide is associated with carbamazepine's adverse effects, little evidence is available to document the claim that oxcarbazepine is better tolerated. Oxcarbazepine is thought to protect against seizures by blocking voltage-gated sodium channels in the same way as carbamazepine. Oxcarbazepine itself has a half-life of only 1–2 hours; its antiseizure activity resides almost exclusively in the active 10-hydroxy metabolites, *S*(+)- and *R*(-)-licarbazepine (also referred to as monohydroxy derivatives or MHDs), to which oxcarbazepine is rapidly converted and both of which have half-lives similar to that of carbamazepine (8–12 hours). The bulk (80%) of oxcarbazepine is converted to the *S*(+) form. The drug is mostly excreted as the glucuronide of the 10-hydroxy metabolite.

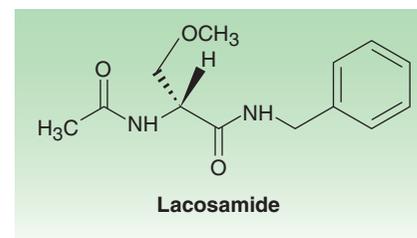
Oxcarbazepine is less potent than carbamazepine, both in animal tests and in patients; clinical doses of oxcarbazepine may need to be 50% higher than those of carbamazepine to obtain equivalent seizure control. Some studies report fewer hypersensitivity reactions to oxcarbazepine, and cross-reactivity with carbamazepine does not always occur. Furthermore, the drug appears to induce hepatic enzymes to a lesser extent than carbamazepine, minimizing drug interactions. Although hyponatremia may occur more commonly with oxcarbazepine than with carbamazepine, most adverse effects of oxcarbazepine are similar to those of carbamazepine.

ESLICARBAZEPINE ACETATE

Eslicarbazepine acetate, a prodrug of *S*(+)-licarbazepine, provides an alternative to oxcarbazepine, with some minor differences. Like oxcarbazepine, eslicarbazepine acetate is converted to

eslicarbazepine but the conversion occurs more rapidly and it is nearly completely to the *S*(+) form, with only a small amount of the *R*(-) isomer (5%) formed by chiral inversion. Whether there is a benefit to the more selective conversion to *S*(+)-licarbazepine is uncertain, especially since both enantiomers act similarly on voltage-gated sodium channels. The effective half-life of *S*(+)-licarbazepine following oral administration of eslicarbazepine acetate is 20–24 hours so the prodrug can be administered once daily, which is a potential advantage. The drug is administered at a dosage of 400–1600 mg/d; titration is typically required for the higher doses. *S*(+)-Licarbazepine is eliminated primarily by renal excretion; dose adjustment is therefore required for patients with renal impairment. Minimal pharmacokinetic effects are observed with coadministration of carbamazepine, levetiracetam, lamotrigine, topiramate, and valproate. The dose of phenytoin may need to be decreased if used concomitantly with eslicarbazepine acetate. Oral contraceptives may be less effective with concomitant eslicarbazepine acetate administration.

LACOSAMIDE



Lacosamide is a sodium channel-blocking antiseizure drug approved for the treatment of focal seizures. It has favorable pharmacokinetic properties and good tolerability. The drug is widely prescribed.

Mechanism of Action

Early studies suggested that lacosamide enhances a poorly understood type of sodium channel inactivation called slow inactivation. Recent studies, however, contradict this view and indicate that the drug binds selectively to the fast inactivated state of sodium channels—as is the case for other sodium channel-blocking antiseizure drugs, except that the binding is much slower.

Clinical Uses

Lacosamide is approved for the treatment of focal onset seizures in patients age 17 years and older. In clinical trials with more than 1300 patients, lacosamide was effective at doses of 200 mg/d and had greater and roughly similar overall efficacy at 400 and 600 mg/d, respectively. Although the overall efficacy was similar at 400 and 600 mg/d, the higher dose may provide better control of focal-to-bilateral tonic-clonic (secondarily generalized) seizures; however, this dose is associated with a greater incidence of adverse effects. Adverse effects include dizziness, headache, nausea, and diplopia. The drug is typically administered twice daily, beginning

with 50-mg doses and increasing by 100-mg increments weekly. An intravenous formulation provides short-term replacement for the oral drug. The oral solution contains aspartame, which is a source of phenylalanine and could be harmful in people with phenylketonuria.

Pharmacokinetics

Oral lacosamide is rapidly and completely absorbed in adults, with no food effect. Bioavailability is nearly 100%. The plasma concentrations are proportional to oral dosage up to 800 mg. Peak concentrations occur from 1 to 4 hours after oral dosing, with an elimination half-life of 13 hours. There are no active metabolites, and protein binding is minimal. Lacosamide does not induce or inhibit cytochrome P450 isoenzymes, so drug interactions are minimal.

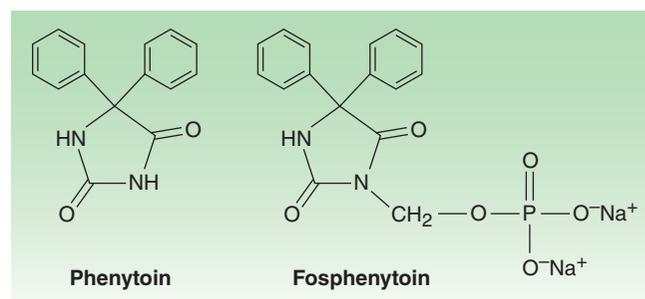
PHENYTOIN

Phenytoin, first identified to have antiseizure activity in 1938, is the oldest nonsedating drug used in the treatment of epilepsy. It is prescribed for the prevention of focal seizures and generalized tonic-clonic seizures and for the acute treatment of status epilepticus. Phenytoin was identified by testing in laboratory animals in a search for better tolerated barbiturates.

Chemistry

Phenytoin, sometimes referred to as diphenylhydantoin, is the 5,5-diphenyl-substituted analog of hydantoin. Hydantoin is a five-membered ring molecule similar structurally to barbiturates, which are based on a six-member ring. Phenytoin free base ($pK_a = 8.06\text{--}8.33$) is poorly water soluble, but phenytoin sodium does dissolve in water (17 mg/mL). Phenytoin is most commonly prescribed in an extended-release capsule containing phenytoin sodium and other excipients to provide a slow and extended rate of absorption with peak blood concentrations from 4 to 12 hours. This form differs from the prompt phenytoin sodium capsule form that provides rapid rate of absorption with peak blood concentration from 1.5 to 3 hours. In addition, the free base is available as an immediate-release suspension and chewable tablets. Phenytoin is available as an intravenous solution containing propylene glycol and alcohol adjusted to a pH of 12. Absorption after intramuscular injection is unpredictable, and some drug precipitation in the muscle occurs; this route of administration is not recommended.

With intravenous administration, there is a risk of the potentially serious “purple glove syndrome” in which a purplish-black discoloration accompanied by edema and pain occurs distal to the site of injection. **Fosphenytoin** is a water-soluble prodrug of phenytoin that may have a lower incidence of purple glove syndrome. This phosphate ester compound is rapidly converted to phenytoin in the plasma and is used for intravenous administration and treatment of status epilepticus. Fosphenytoin is well absorbed after intramuscular administration, but this route is rarely appropriate for the treatment of status epilepticus.



Mechanism of Action

Phenytoin is a sodium channel-blocking antiseizure drug that acts in a similar fashion to carbamazepine and other agents in the class.

Clinical Uses

Phenytoin is effective in preventing focal onset seizures and also tonic-clonic seizures, whether they are focal-to-bilateral tonic-clonic (secondarily generalized) or occurring in the setting of an idiopathic generalized epilepsy syndrome. Phenytoin may worsen other seizure types in primary generalized epilepsies, including absence epilepsy, juvenile myoclonic epilepsy, and Dravet's syndrome.

Pharmacokinetics & Drug Interactions

Absorption of phenytoin is highly dependent on the formulation. Particle size and pharmaceutical additives affect both the rate and the extent of absorption. Therefore, while absorption from the gastrointestinal tract is nearly complete in most patients, the time to peak may range from 3 to 12 hours. Phenytoin is extensively (~90%) bound to serum albumin and is prone to displacement in response to a variety of factors (eg, hyperbilirubinemia or drugs such as warfarin or valproic acid), which can lead to toxicity. Also, low plasma albumin (such as in liver disease or nephrotic syndrome) can result in abnormally high free concentrations and toxicity. Small changes in the bound fraction dramatically affect the amount of free (active) drug. Increased proportions of free drug are also present in the neonate and in the elderly. Some agents such as valproic acid, phenylbutazone, and sulfonamides can compete with phenytoin for binding to plasma proteins. Valproic acid also inhibits phenytoin metabolism. The combined effect can result in marked increases in free phenytoin. In all of these situations, patients may exhibit signs of toxicity when total drug levels are within the therapeutic range. Because of its high protein binding, phenytoin has a low volume of distribution (0.6–0.7 L/kg in adults).

Phenytoin is metabolized by CYP2C9 and CYP2C19 to inactive metabolites that are excreted in the urine. Only a small proportion of the dose is excreted unchanged. The elimination of phenytoin depends on the dose. At low blood levels, phenytoin metabolism follows first-order kinetics. However, as blood levels rise within the therapeutic range, the maximum capacity of the liver to metabolize the drug is approached (saturation kinetics). Even small increases in dose may be associated with large changes

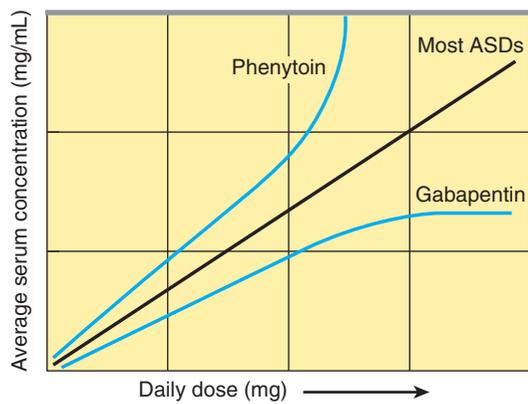


FIGURE 24-4 Relationship between dose and exposure for antiseizure drugs (ASDs). Most antiseizure drugs follow linear (first-order) kinetics, in which a constant fraction per unit time of the drug is eliminated (elimination is proportional to drug concentration). In the case of phenytoin, as the dose increases, there is saturation of metabolism and a shift from first-order to zero-order kinetics, in which a constant quantity per unit time is metabolized. A small increase in dose can result in a large increase in concentration. Orally administered gabapentin also exhibits zero-order kinetics, but in contrast to phenytoin where metabolism can be saturated, in the case of gabapentin, gut absorption, which is mediated by the large neutral amino acid system L transporter, is susceptible to saturation. The bioavailability of gabapentin falls at high doses as the transporter is saturated so that increases in blood levels do not keep pace with increases in dose.

in phenytoin serum concentrations (Figure 24-4). In such cases, the half-life of the drug increases markedly, steady state is not achieved in routine fashion (since the plasma level continues to rise), and patients quickly develop symptoms of toxicity.

The half-life of phenytoin in most patients varies from 12 to 36 hours, with an average of 24 hours in the low to mid therapeutic range. Much longer half-lives are observed at higher concentrations. At low blood levels, 5–7 days are needed to reach steady-state blood levels after every dosage change; at higher levels, it may be 4–6 weeks before blood levels are stable. Phenytoin—like carbamazepine, phenobarbital, and primidone—is a major enzyme-inducing antiseizure drug that stimulates the rate of metabolism of many coadministered antiseizure drugs, including valproic acid, tiagabine, ethosuximide, lamotrigine, topiramate, oxcarbazepine and MHDs, zonisamide, felbamate, many benzodiazepines, and perampanel. Autoinduction of its own metabolism, however, is insignificant.

Therapeutic Levels & Dosing

The therapeutic plasma level of phenytoin for most patients is between 10 and 20 mcg/mL. A loading dose can be given either orally or intravenously, with either fosphenytoin sodium injection (preferred) or phenytoin sodium injection. When oral therapy is started, it is common to begin adults at a dosage of 300 mg/d, regardless of body weight. This may be acceptable in some patients, but it frequently yields steady-state blood levels below

10 $\mu\text{g/mL}$, which is the minimum therapeutic level for most patients. If seizures continue, higher doses are usually necessary to achieve plasma levels in the upper therapeutic range. Because of the kinetic factors discussed earlier, toxic levels may occur with only small increments in dosage. The phenytoin dosage should be increased in increments of no more than 25–30 mg/d in adults, and ample time should be allowed for the new steady state to be achieved before further increasing the dosage. A common clinical error is to increase the dosage directly from 300 mg/d to 400 mg/d; toxicity frequently occurs at a variable time thereafter. In children, a dosage of 5 mg/kg/d should be followed by readjustment after steady-state plasma levels are obtained.

Two types of oral phenytoin are currently available in the USA, differing in their respective rates of dissolution. The predominant form is the sodium salt in an extended-release pill intended for once- or twice-a-day use. In addition, the free acid is available as an immediate-release suspension and chewable tablets. Although a few patients being given phenytoin on a long-term basis have been proved to have low blood levels from poor absorption or rapid metabolism, the most common cause of low levels is poor compliance. As noted, fosphenytoin sodium is available for intravenous or intramuscular use and usually replaces intravenous phenytoin sodium, a much less soluble form of the drug.

Toxicity

Early signs of phenytoin administration include nystagmus and loss of smooth extraocular pursuit movements; neither is an indication for decreasing the dose. Diplopia and ataxia are the most common dose-related adverse effects requiring dosage adjustment; sedation usually occurs only at considerably higher levels. Gingival hyperplasia and hirsutism occur to some degree in most patients; the latter can be especially unpleasant in women. Long-term use is associated in some patients with coarsening of facial features and with mild peripheral neuropathy, usually manifested by diminished deep tendon reflexes in the lower extremities. Long-term use may also result in abnormalities of vitamin D metabolism, leading to osteomalacia. Low folate levels and megaloblastic anemia have been reported, but the clinical importance of these observations is unknown.

Idiosyncratic reactions to phenytoin are relatively rare. A skin rash may indicate hypersensitivity of the patient to the drug. Fever may also occur, and in rare cases, the skin lesions may be severe and exfoliative. Lymphadenopathy may rarely occur; this must be distinguished from malignant lymphoma. Hematologic complications are exceedingly rare, although agranulocytosis has been reported in combination with fever and rash.

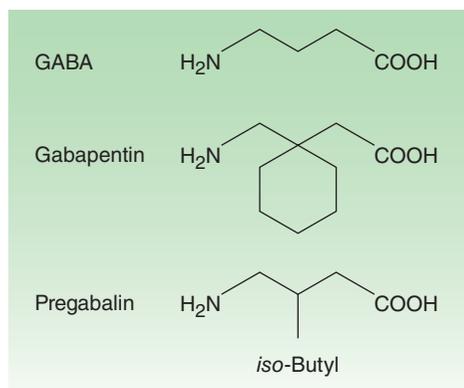
MEPHENYTOIN, ETHOTOIN, & PHENACEMIDE

Many congeners of phenytoin have been synthesized, but only three have been marketed in the USA, and one of these (phenacemide) has been withdrawn. The other two congeners, mephenytoin and ethotoin, like phenytoin, appear to be most effective

against focal and generalized tonic-clonic seizures. No well-controlled clinical trials have documented their effectiveness, and the drugs are rarely used. The incidence of severe reactions such as dermatitis, agranulocytosis, or hepatitis is higher for mephenytoin than for phenytoin. Mephenytoin is metabolized to 5-ethyl-5-phenyl-hydantoin (nirvanol) via demethylation; nirvanol contributes most of the antiseizure activity of mephenytoin.

GABAPENTIN & PREGABALIN

Gabapentin and pregabalin, known as “gabapentinoids,” are amino acid-like molecules that were originally synthesized as analogs of GABA but are now known not to act through GABA mechanisms. They are used in the treatment of focal seizures and various nonepilepsy indications, such as neuropathic pain, restless legs syndrome, and anxiety disorders.



Mechanism of Action

Despite their close structural resemblance to GABA, gabapentin and pregabalin do not act through effects on GABA receptors or any other mechanism related to GABA-mediated neurotransmission. Rather, gabapentinoids bind avidly to $\alpha 2\delta$, a protein that serves as an auxiliary subunit of voltage-gated calcium channels but may also have other functions. The precise way in which binding of gabapentinoids to $\alpha 2\delta$ protects against seizures is not known but may relate to a decrease in glutamate release at excitatory synapses.

Clinical Uses

Gabapentin and pregabalin are effective in the treatment of focal seizures; there is no evidence that they are efficacious in generalized epilepsies. Indeed, gabapentin may aggravate absence seizures and myoclonic seizures. Gabapentin is usually started at a dose of 900 mg/d (in three divided doses), but starting doses as high as 3600 mg/d can be used if a rapid response is required. Some clinicians have found that even higher dosages are needed to achieve improvement in seizure control. The recommended starting dose of pregabalin is 150 mg/d, but a lower starting dose (50–75 mg/d) may avoid adverse effects that can occur on drug initiation; the effective maintenance dose range is 150 to 600 mg/d. Although comparative studies are lacking, gabapentinoids are generally

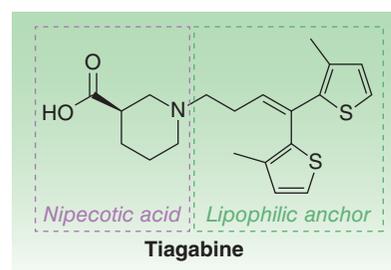
considered less effective than other antiseizure drugs for the treatment of focal seizures. Gabapentinoids are frequently used in the treatment of neuropathic pain conditions, including postherpetic neuralgia and painful diabetic neuropathy, and in the treatment of anxiety disorders. Pregabalin is also approved for the treatment of fibromyalgia. Gabapentin and pregabalin are generally well tolerated. The most common adverse effects are somnolence, dizziness, ataxia, headache, and tremor. These adverse effects are most troublesome at initiation of therapy and often resolve with continued dosing. Both gabapentinoids can cause weight gain and peripheral edema.

Pharmacokinetics

Gabapentin and pregabalin are not metabolized and do not induce hepatic enzymes; they are eliminated unchanged in the urine. Both drugs are absorbed by the L-amino acid transport system, which is found only in the upper small intestine. The oral bioavailability of gabapentin decreases with increasing dose because of saturation of this transport system. In contrast, pregabalin exhibits linear absorption within the therapeutic dose range. This is explained, in part, by the fact that pregabalin is used at much lower doses than gabapentin so it does not saturate the transport system. Also, pregabalin may be absorbed by mechanisms other than the L-amino acid transport system. Because of dependence on the transport system, absorption of gabapentin shows patient-to-patient variability and dosing requires individualization. Pregabalin bioavailability exceeds 90% and is independent of dose so that it may produce a more predictable patient response. Gabapentinoids are not bound to plasma proteins. Drug-drug interactions are negligible. The half-life of both drugs is relatively short (ranging from 5 to 8 hours for gabapentin and 4.5 to 7.0 hours for pregabalin); they are typically administered two or three times per day. Sustained-release, once-a-day preparations of gabapentin are available. The gabapentin prodrug gabapentin enacarbil is also available in an extended-release formulation. This prodrug is actively absorbed by high-capacity nutrient transporters, which are abundant throughout the intestinal tract, and then converted to gabapentin presumably within the intestine, so there is dose-proportional systemic gabapentin exposure over a wide dose range.

TIAGABINE

Tiagabine, a selective inhibitor of the GAT-1 GABA transporter, is a second-line treatment for focal seizures. It is contraindicated in generalized onset epilepsies.



Mechanism of Action

Tiagabine is a lipophilic, blood-brain barrier-permeant analog of nipecotic acid, a GABA uptake inhibitor that is not active systemically. The chemical structure of tiagabine consists of the active moiety—nipecotic acid—and a lipophilic anchor that allows the molecule to cross the blood-brain barrier. Tiagabine is highly selective for the GAT-1 GABA transporter isoform, the most abundant GABA transporter expressed in brain, and has little or no activity on the other sodium- and chloride-dependent GABA transporters, GAT-2, GAT-3, or BGT-1. The action of the GABA that is released by inhibitory neurons is normally terminated by reuptake into the neuron and surrounding glia by these transporters. Tiagabine inhibits the movement of GABA from the extracellular space—where the GABA can act on neuronal receptors—to the intracellular compartment, where it is inactive. This action of tiagabine causes prolongation of GABA-mediated inhibitory synaptic responses and potentiation of tonic inhibition; the latter is caused by the action of GABA on extrasynaptic GABA receptors. Tiagabine is considered a “rationally designed” antiseizure drug because it was developed with the understanding that potentiation of GABA action in the brain is a possible antiseizure mechanism.

Clinical Uses

Tiagabine is indicated for the adjunctive treatment of focal seizures, with or without secondary generalization. In adults, the recommended initial dose is 4 mg/d with weekly increments of 4–8 mg/d to total doses of 16–56 mg/d. Initial dosages can be given twice a day, but a change to three times a day is recommended above 30–32 mg/d. Divided doses as often as four times daily are sometimes required. Adverse effects and apparent lack of efficacy limit the use of this drug. Minor adverse events are dose related and include nervousness, dizziness, tremor, difficulty concentrating, and depression. Excessive confusion, somnolence, or ataxia may require discontinuation. Psychosis occurs rarely. The drug can *cause* seizures in some patients, notably those taking the drug for other indications. Rash is an uncommon idiosyncratic adverse effect.

Pharmacokinetics

Tiagabine is 90–100% bioavailable, has linear kinetics, and is highly protein bound. The half-life is 5–8 hours and decreases in the presence of enzyme-inducing drugs. Food decreases the peak plasma concentration but not the area under the concentration curve (see Chapter 3). To avoid adverse effects, the drug should be taken with food. Hepatic impairment causes a slight decrease in clearance and may necessitate a lower dose. The drug is oxidized in the liver by CYP3A. Elimination is primarily in the feces (60–65%) and urine (25%).

RETIGABINE (EZOGABINE)

Retigabine (US Adopted Name: ezogabine), a potassium channel opener, is a third-line treatment for focal seizures. Because retigabine causes pigment discoloration of the retina and skin,

its use is limited to those who have failed to respond to other agents.

Mechanism of Action

Retigabine is an allosteric opener of KCNQ2-5 (K_v7.2-K_v7.5) voltage-gated potassium channels, which are localized, in part, in axons and nerve terminals. Opening KCNQ potassium channels in presynaptic terminals inhibits the release of various neurotransmitters, including glutamate, which may be responsible for the seizure protection.

Clinical Use

Doses of retigabine range from 600 to 1200 mg/d, with 900 mg/d expected to be the most common. The drug is administered in three divided doses, and the dose must be titrated beginning at 300 mg/d. Most adverse effects are dose-related and include dizziness, somnolence, blurred vision, confusion, and dysarthria. Urinary symptoms, including retention, hesitation, and dysuria, believed to be due to effects of the drug on KCNQ potassium channels in detrusor smooth muscle, may occur. They are generally mild and usually do not require drug discontinuation. In 2013, reports began to appear of blue pigmentation, primarily on the skin and lips, but also on the palate, sclera, and conjunctiva. The skin dyspigmentation is due to the presence of coarse melanin granules within dermal cells and not to deposition of the drug within the tissue. The skin discoloration has not been associated with more serious adverse effects but may be of cosmetic significance. In addition, however, retinal pigment abnormalities can occur independent of skin changes. Of particular concern are postmarketing reports of macular abnormalities characterized as vitelliform lesions, such as those seen in macular degeneration or dystrophy. Decreased visual acuity has been reported, but documentation is lacking. Nevertheless, because of the ophthalmologic adverse reactions, regulatory agencies have recommended use of retigabine only in cases where other antiseizure drugs are not adequate or not tolerated.

Pharmacokinetics

Absorption of retigabine is not affected by food, and kinetics are linear; drug interactions are minimal. The major metabolic pathways in humans are N-glucuronidation and N-acetylation. The drug neither inhibits nor induces the major CYP enzymes involved in drug metabolism.

DRUGS EFFECTIVE FOR FOCAL SEIZURES & CERTAIN GENERALIZED ONSET SEIZURE TYPES

Correct diagnosis is critical to antiseizure drug selection. The agents described in the previous section are effective for the treatment of focal onset seizures, including focal-to-bilateral tonic-clonic seizures (secondarily generalized tonic-clonic seizures), but some can worsen certain seizure types in generalized epilepsy syndromes. A variety of drugs were shown initially to be effective

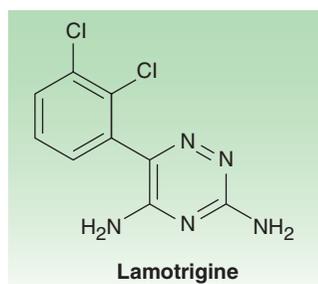
in the treatment of focal onset seizures and are primarily used to treat these types of seizures; in addition, these drugs have also found uses in the treatment of certain generalized onset seizure types. These drugs are described below.

LAMOTRIGINE

Lamotrigine is considered a sodium channel-blocking antiseizure drug; it is effective for the treatment of focal seizures, as are other drugs in this category. In addition, clinical trials of lamotrigine have demonstrated effectiveness in the treatment of generalized tonic-clonic seizures (in idiopathic generalized epilepsy) and in the treatment of generalized absence epilepsy. In the latter, lamotrigine is not as effective as ethosuximide or valproate. The drug is generally well tolerated; however, it can produce a potentially fatal rash (Stevens-Johnson syndrome). Although adverse effects are similar to those of other sodium channel-blocking antiseizure drugs, lamotrigine paradoxically may cause insomnia instead of sedation. Lamotrigine causes fewer adverse cognitive effects than carbamazepine or topiramate. It can also improve depression in patients with epilepsy and reduces the risk of relapse in bipolar disorder.

Chemistry

Lamotrigine was developed when investigators thought that the antifolate effects of certain antiseizure drugs such as phenytoin might contribute to their effectiveness. Several phenyltriazines were developed; although their antifolate properties were weak, some were active in seizure screening tests. The antifolate activity of lamotrigine is not believed to contribute to its therapeutic activity in epilepsy.



Mechanism of Action

The action of lamotrigine on voltage-gated sodium channels is similar to that of carbamazepine. The mechanism by which lamotrigine is effective against absence seizures is not known.

Clinical Uses

Although most controlled studies have evaluated lamotrigine as add-on therapy, the drug is effective as monotherapy for focal seizures, and lamotrigine is now widely prescribed for this indication because of its excellent tolerability. Despite being less effective than ethosuximide and valproate for absence epilepsy, lamotrigine

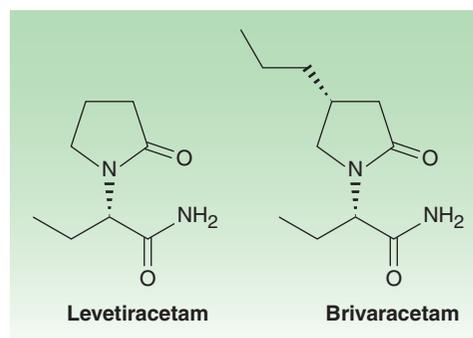
may be prescribed because of its tolerability or in females of childbearing age because it has fewer fetal risks than valproate. Lamotrigine is also approved for primary generalized tonic-clonic seizures and generalized seizures of the Lennox-Gastaut syndrome. Adverse effects include dizziness, headache, diplopia, nausea, insomnia, somnolence, and skin rash. The rash is a typical hypersensitivity reaction. Although the risk of rash may be diminished by introducing the drug slowly, pediatric patients are at greater risk. Serious rash occurs in approximately 0.3–0.8% of children age 2–17 years, whereas in adults, the rate is 0.08–0.3%.

Pharmacokinetics

Lamotrigine is almost completely absorbed and has a volume of distribution of 1–1.4 L/kg. Protein binding is only about 55%. The drug has linear kinetics and is metabolized primarily by glucuronidation in the liver to the inactive 2-*N*-glucuronide, which is excreted in the urine. Lamotrigine has a half-life of approximately 24 hours in normal volunteers; this decreases to 13–15 hours in patients taking enzyme-inducing drugs. Lamotrigine is effective in the treatment of focal seizures in adults at dosages typically between 100 and 300 mg/d. The initial dose is 25 mg/d, increasing to 50 mg/d after 2 weeks; thereafter, titration can proceed by 50 mg/d every 1–2 weeks to a usual maintenance dose of 225–375 mg/d (in two divided doses). Therapeutic serum levels have not been established, but toxicity is infrequent with levels < 10 mcg/mL. The combination of lamotrigine and valproate is believed to be particularly efficacious. However, valproate causes a two-fold increase in the half-life of lamotrigine and can increase blood levels correspondingly, leading to a risk of skin rash if valproate is added to a stable regimen of lamotrigine. In patients receiving valproate, the initial dose of lamotrigine must be reduced to 12.5–25 mg every other day, with increases of 25–50 mg/d every 2 weeks as needed to a usual maintenance dose of 100–200 mg/d.

LEVETIRACETAM

Levetiracetam is a broad-spectrum antiseizure agent and one of the most commonly prescribed drugs for epilepsy, primarily because of its perceived favorable adverse effect profile, broad therapeutic window, favorable pharmacokinetic properties, and lack of drug-drug interactions.



Mechanism of Action

Levetiracetam is an analog of piracetam, which is purported to be a cognition enhancer. In animal testing, levetiracetam is not active in the MES or PTZ tests, but it does have activity against seizures in the 6-Hz and kindling models. Levetiracetam binds selectively to SV2A, a ubiquitous synaptic vesicle integral membrane protein, which may function as a positive effector of synaptic vesicle exocytosis. The drug accesses the luminal side of recycling synaptic vesicles by vesicular endocytosis. Binding to SV2A in the vesicle reduces the release of the excitatory neurotransmitter glutamate during trains of high-frequency activity.

Clinical Uses

Levetiracetam is effective in the treatment of focal seizures in adults and children, primary generalized tonic-clonic seizures, and the myoclonic seizures of juvenile myoclonic epilepsy. Adult dosing can begin with 500 or 1000 mg/d. The dosage can be increased every 2–4 weeks by 1000 mg to a maximum dosage of 3000 mg/d. The drug is dosed twice daily. Adverse effects include somnolence, asthenia, ataxia, infection (colds), and dizziness. Less common but more serious are behavioral and mood changes, such as irritability, aggression, agitation, anger, anxiety, apathy, depression, and emotional lability. Oral formulations include extended-release tablets; an intravenous preparation is also available.

Pharmacokinetics

Oral absorption of levetiracetam is rapid and nearly complete, with peak plasma concentrations in 1.3 hours. Food slows the rate of absorption but does not affect the amount absorbed. Kinetics are linear. Protein binding is less than 10%. The plasma half-life is 6–8 hours, but may be longer in the elderly. Two-thirds of the drug is excreted unchanged in the urine and the remainder as the inactive deaminated metabolite 2-pyrrolidone-*N*-butyric acid. The metabolism of levetiracetam occurs in the blood. There is no metabolism in the liver, and drug interactions are minimal.

BRIVARACETAM

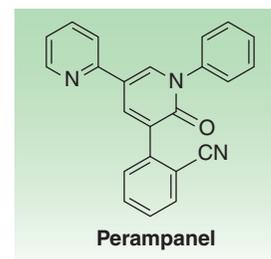
Brivaracetam, the 4-*n*-propyl analog of levetiracetam, is a high-affinity SV2A ligand recently approved for the treatment of focal (partial) onset seizures. Whether it will prove to have the broad-spectrum activity of levetiracetam remains to be demonstrated; given the similarity of the mechanisms of action, however, a broad spectrum is expected. Brivaracetam is active in animal models of generalized epilepsies. It improved or abolished the photoparoxysmal response (abnormal occurrence of cortical spikes or spike and wave discharges on EEG in response to intermittent light stimulation) in patients with generalized epilepsies. In addition, the drug reduced the frequency of generalized seizures in a small number

of patients with generalized seizures included in a clinical trial. Brivaracetam exhibits linear pharmacokinetics over a wide dose range (10–600 mg, single oral dose). It is rapidly and completely absorbed after oral administration; has an elimination half-life of 7–8 hours, which allows twice-daily dosing; and has low plasma protein binding (<20%).

Coadministration of brivaracetam with carbamazepine may increase exposure to carbamazepine epoxide, the active metabolite of carbamazepine, possibly leading to adverse effects; carbamazepine dose reduction should be considered. Similarly, coadministration of brivaracetam with phenytoin may increase phenytoin levels. Coadministration of other antiseizure drugs is unlikely to affect brivaracetam exposure. Brivaracetam provides no added therapeutic benefit when administered in conjunction with levetiracetam; both drugs act on SV2A.

PERAMPANEL

Perampanel is an orally active AMPA receptor antagonist approved for the treatment of focal seizures and primary generalized tonic-clonic seizures in idiopathic generalized epilepsies.



Mechanism of Action

Perampanel is a potent noncompetitive antagonist of the AMPA receptor, a subtype of the ionotropic glutamate receptor that is the main mediator of synaptic excitation in the central nervous system (Figure 24–1). AMPA receptors are critical to local generation of seizure activity in epileptic foci and are also responsible for the neuron-to-neuron spread of excitation. Partial blockade of AMPA receptors by therapeutic concentrations of perampanel reduces the likelihood of seizure occurrence. In generalized convulsive seizures, whether occurring as a secondarily generalized convulsion following a focal seizure or as a primary generalized seizure, excitatory cortical neurons engage subcortical centers, including the thalamus, that relay the excitation throughout both hemispheres. This spread of excitation to distant sites is mediated by AMPA receptors at the excitatory synapses that long axons make on their distant targets. Perampanel is therefore well suited to inhibit this spread of excitation, which may account for its activity in preventing secondary and primary generalized convulsive seizures. Perampanel binds to an allosteric site on the extracellular side of the channel, acting as a wedge to prevent channel opening.

Clinical Use

A typical maintenance dose of perampanel for patients 12 years of age and older is 4, 6, or 8 mg/d. Higher doses may be needed in patients who are receiving CYP3A4-inducing antiseizure drugs. Perampanel use is often associated with behavioral adverse reactions including aggression, hostility, irritability, and anger. The frequency of these adverse effects increases in a dose-dependent fashion, and they occur more often in younger patients and in those with learning disabilities or dementia. Alcohol use may exacerbate the level of anger. Other common adverse effects are dizziness, somnolence, and headache. Falls are more common at higher doses.

Pharmacokinetics

Perampanel has a long half-life, typically ranging from 70 to 110 hours, which permits once-daily dosing. Because of the long half-life, steady state is not achieved for 2–3 weeks; the prescriber should make dosage changes no more frequently than at 2-week (or longer) intervals. The kinetics are linear in the dose range of 2–12 mg/d. The half-life is prolonged in moderate hepatic failure. Absorption is rapid and the drug is fully bioavailable. Although food slows the rate of absorption, the extent is not affected. Perampanel is 95% bound to plasma proteins. The drug is extensively metabolized via initial oxidation by CYP3A4 and subsequent glucuronidation.

Drug Interactions

The most significant drug interactions with perampanel are with potent CYP3A4 inducer antiseizure drugs such as carbamazepine, oxcarbazepine, and phenytoin. Concomitant use with such agents increases the clearance of perampanel by 50–70%, which may require the use of higher perampanel doses. Of somewhat lesser concern is the potential for strong CYP3A4 inhibitors to increase the levels of perampanel. Perampanel may decrease the effectiveness of levonorgestrel-containing hormonal contraceptives.

PHENOBARBITAL

In 1903, chemists in Germany discovered that lipophilic derivatives of barbituric acid induced sleep in dogs. Phenobarbital was introduced into the clinical market in 1912 as a sleeping aid; it was serendipitously found to be useful in the treatment of epilepsy. In comparison with anesthetic barbiturates such as pentobarbital, phenobarbital is preferred in the chronic treatment of epilepsy because it is less sedative at antiseizure doses. Intravenous pentobarbital, however, is frequently used to induce general anesthesia in the treatment of drug-refractory status epilepticus. Phenobarbital is the oldest of the currently available antiseizure drugs; however, the drug is no longer a first choice in the developed world because of its sedative properties and many drug interactions. It is still useful for neonatal seizures.

Chemistry

Four barbituric acid derivatives were once used for epilepsy: phenobarbital, mephobarbital, metharbital, and primidone. Only phenobarbital and primidone remain in common use.

Mechanism of Action (see also Chapter 22)

Barbiturates such as phenobarbital act as positive allosteric modulators of GABA_A receptors at low concentrations (see Figure 22–6); at higher concentrations, the drugs directly activate GABA_A receptors. In contrast to benzodiazepines, which augment the frequency of GABA_A receptor chloride channel opening, barbiturates increase the mean open duration of the channel without altering either channel conductance or opening frequency. Phenobarbital also exerts other actions on synaptic function and intrinsic neuronal excitability mechanisms; some of these could be relevant to its clinical antiseizure activity, including block of AMPA receptors or voltage-activated calcium channels.

Clinical Uses

Phenobarbital is useful in the treatment of focal seizures and generalized tonic-clonic seizures. Evidence-based comparisons of phenobarbital with phenytoin and carbamazepine have shown no difference in seizure control, but phenobarbital was more likely to be discontinued due to adverse effects. Phenobarbital may be useful in the treatment of myoclonic seizures, such as in juvenile myoclonic epilepsy, but it is not a drug of first choice. Phenobarbital may worsen absence seizures and infantile spasms. Long-term administration of phenobarbital leads to physical dependence such that seizure threshold is reduced upon withdrawal. The drug must be discontinued gradually over several weeks to avoid the occurrence of severe seizures or status epilepticus.

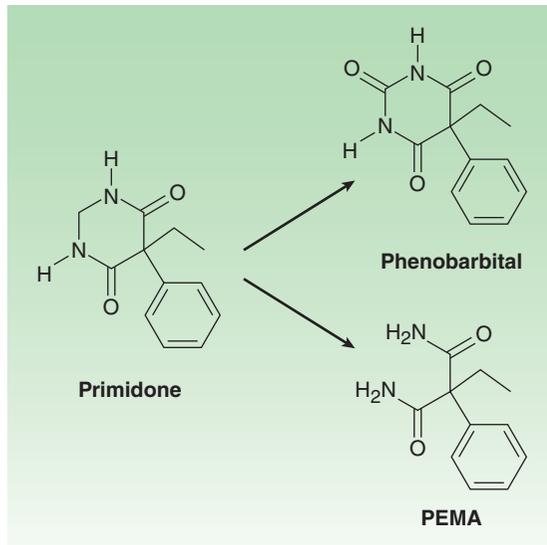
Pharmacokinetics, Therapeutic Levels, & Dosage

For pharmacokinetics, drug interactions, and toxicity of phenobarbital, see Chapter 22. The dose of phenobarbital is individualized based on clinical response. Dosing information from clinical trials is limited. Doses in the range of 60–200 mg, divided two or three times daily, are typically used. The minimally effective dose may be 60 mg/d, and the median effective dose range may be 100–150 mg/d. The accepted serum concentration reference range is 15 to 40 mcg/mL, although many patients tolerate chronic levels above 40 mcg/mL. Mean steady-state plasma phenobarbital levels with 60 and 100 mg/d dosing are 14 and 21 mcg/mL, respectively.

PRIMIDONE

Primidone (2-desoxyphenobarbital) is a derivative of phenobarbital. In the early 1950s, the drug was found to have antiseizure activity in animal models; subsequent evidence showed it to be clinically active in the treatment of epilepsy. It was widely used until the 1960s, but was then largely abandoned

because of its high incidence of adverse effects. It is effective for the treatment of essential tremor and is still used for this indication.



Mechanism of Action

Primidone is metabolized to phenobarbital and phenylethylmalonamide (PEMA). All three compounds are active antiseizure agents. Although phenobarbital is roughly equally active in the MES and PTZ animal tests, primidone has greater activity in the MES test than the PTZ test, indicating that it acts more like the sodium channel-blocking antiseizure drugs than phenobarbital. Also, in animal models, primidone causes relatively less acute motor impairment than phenobarbital. With chronic treatment, phenobarbital is thought to mediate most of the antiseizure activity of primidone. Attempts to determine the relative contributions of the parent drug and its two metabolites have been conducted in newborn infants, in whom drug-metabolizing enzyme systems are very immature and in whom primidone is only slowly metabolized. In these patients, primidone is effective in controlling seizures, confirming that it has intrinsic antiseizure activity. This conclusion was reinforced by studies in older patients initiating treatment with primidone, in which seizure control was obtained before phenobarbital concentrations reached the therapeutic range.

Clinical Uses

Primidone is effective against focal seizures and generalized tonic-clonic seizures, but its overall effectiveness is less than drugs such as carbamazepine and phenytoin because of a high incidence of acute toxicity on initial administration and because of chronic sedative effects at effective doses. Primidone is also used in some movement disorders (see Chapter 28).

Pharmacokinetics

Primidone is completely absorbed, usually reaching peak concentrations about 3 hours after oral administration. Primidone is only 30% bound to plasma proteins. The volume of distribution

is 0.6 L/kg. As shown in the text figure, primidone is metabolized by oxidation to phenobarbital, which accumulates slowly, and by scission of the heterocyclic ring to form PEMA. Both primidone and phenobarbital also undergo subsequent conjugation and excretion. Primidone has a larger clearance than most other antiseizure drugs (2 L/kg/d), corresponding to a half-life of 6–8 hours. PEMA clearance is approximately half that of primidone, but phenobarbital has a very low clearance (see Table 3–1). The appearance of phenobarbital corresponds to the disappearance of primidone. During chronic therapy, the phenobarbital levels derived from primidone are usually two to three times higher than the primidone levels.

Therapeutic Levels & Dosage

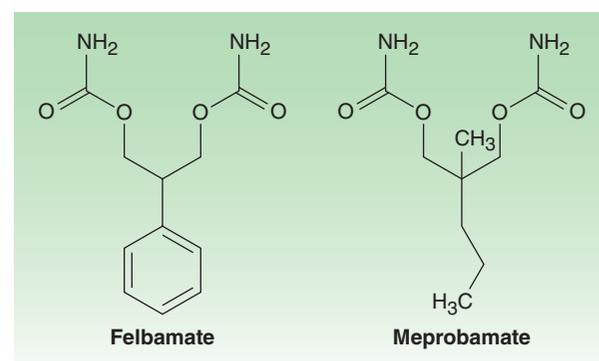
Primidone is most efficacious when plasma levels are in the range of 8–12 mcg/mL. Concomitant levels of its metabolite, phenobarbital, at steady state, usually vary from 15 to 30 mcg/mL. Dosages of 10–20 mg/kg/d are necessary to obtain these levels. Primidone should be started at a low daily dose, which is then gradually escalated over several days to a few weeks to avoid prominent sedation and gastrointestinal complaints. When adjusting doses of the drug, the parent drug reaches steady state rapidly (30–40 hours), but the active metabolites phenobarbital and PEMA reach steady state much more slowly, at approximately 20 days and 3–4 days, respectively.

Toxicity

The dose-related adverse effects of primidone are similar to those of its metabolite, phenobarbital, except that many patients experience severe adverse effects on initial dosing including drowsiness, dizziness, ataxia, nausea, and vomiting. Tolerance to these adverse effects develops in hours to days and can be minimized by slow titration.

FELBAMATE

Felbamate is a dicarbamate that is used in the treatment of focal seizures and in the Lennox-Gastaut syndrome. It is structurally related to the sedative-hypnotic meprobamate. Felbamate is generally well tolerated; some patients report *improved* alertness. However, because the drug can cause both aplastic anemia and severe hepatitis, felbamate is used only for patients with refractory seizures who respond poorly to other medications. Despite the seriousness of the adverse effects, thousands of patients worldwide use this medication.



Felbamate appears to have multiple mechanisms of action. It produces a use-dependent block of *N*-methyl-D-aspartate (NMDA) receptors, with selectivity for those containing the GluN2B (NR2B) subunit; the drug also produces a barbiturate-like potentiation of GABA_A receptor responses. Oral felbamate is well absorbed (> 90%). Of the absorbed dose, 30–50% is excreted unchanged in the urine. The remainder is metabolized by CYP3A4 and CYP2E1 in the liver. The mean terminal half-life of 20 hours in monotherapy decreases to 13–14 hours in the presence of phenytoin or carbamazepine. The typical starting dose of felbamate is 400 mg three times a day. The dose may be escalated slowly to a maximum dose of 3600 mg/d, although some patients have received doses as high as 6000 mg/d. Effective plasma levels range from 30 to 100 mcg/mL. In addition to its usefulness in focal seizures, felbamate ameliorates atonic seizures as well as other seizure types in the Lennox-Gastaut syndrome. Felbamate decreases the clearance of phenytoin and valproic acid and increases their blood levels; dose reductions of these drugs may be necessary when felbamate is initiated. Felbamate reduces levels of carbamazepine but increases levels of the metabolite carbamazepine epoxide, which may be associated with adverse effects including dizziness, diplopia, or headache.

DRUGS EFFECTIVE FOR GENERALIZED ONSET SEIZURES

A limited number of antiseizure drugs are first-line agents in the treatment of patients who exhibit multiple generalized onset seizure types. Valproate is especially effective and is considered the first-choice treatment for such patients. However, it has various troublesome side effects and is a known human teratogen; its use is avoided in women of childbearing potential. Other drugs that may have broad activity in generalized epilepsies are topiramate and zonisamide.

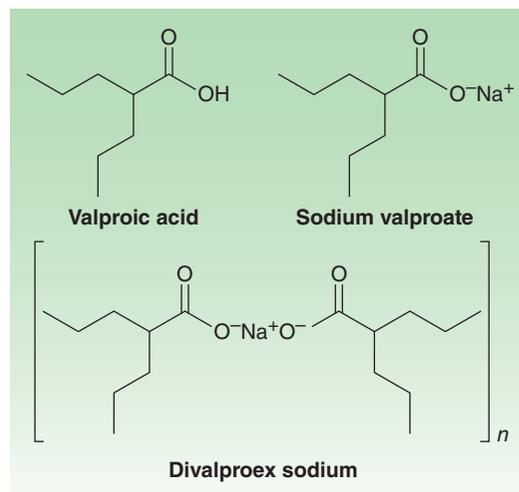
VALPROATE AND DIVALPROEX SODIUM

Valproate is a first-line broad-spectrum antiseizure drug that is thought to offer protection against many seizure types. In addition, it is used as a mood stabilizer in bipolar disorder and as prophylactic treatment for migraine. Valproate was found to have antiseizure properties when used as a solvent in the search for other drugs effective against seizures.

Chemistry

Valproic acid is a short-chain branched fatty acid that is liquid at room temperature; it is formulated as an oral syrup solution or in gelatin capsules. More commonly, however, the drug is used in a coordination complex—referred to as divalproex sodium—composed of equal parts of valproic acid and the salt sodium valproate. An extended-release divalproex formulation in a hydrophilic polymer matrix allows once-a-day oral administration. Valproic acid has a pK_a value of 4.56 and is therefore fully ionized at body pH; for that reason, the active form of the drug

is the valproate ion, regardless of whether valproic acid or the salt of the acid is administered. Valproic acid is one of a series of fatty carboxylic acids that have antiseizure activity; this activity appears to be greatest for carbon chain lengths of five to eight atoms. The amides and esters of valproic acid are also active antiseizure agents.



Mechanism of Action

The mechanism or mechanisms whereby valproate exerts its therapeutic actions are not known. Valproate has broad-spectrum efficacy in animal models, conferring seizure protection in diverse chemoconvulsant seizure models, the MES test, and the kindling models. The time course of valproate's antiseizure activity is poorly correlated with blood or tissue levels of the parent drug, an observation that has led to speculation regarding the active species.

Clinical Uses

Valproate is one of the most versatile and effective antiseizure drugs. It is widely used for myoclonic (such as in juvenile myoclonic epilepsy), atonic (as in Lennox-Gastaut syndrome), and generalized onset tonic-clonic seizures. Valproate is also effective in the treatment of generalized absence seizures and is often preferred to ethosuximide when the patient has concomitant generalized tonic-clonic seizures. Valproate is also effective in focal seizures, but it may not be as effective as carbamazepine or phenytoin. Intravenous formulations can be used to treat status epilepticus.

Pharmacokinetics

Valproate is well absorbed after an oral dose, with bioavailability greater than 80%. Peak blood levels are observed within 2 hours. Food may delay absorption, and the drug may have improved tolerability if it is administered after meals. Valproate is highly bound to plasma proteins, but protein binding becomes saturated as the concentration increases at the upper end of the therapeutic range, resulting in an increase in the plasma free fraction of valproate from 10% at plasma concentrations up to 75 mcg/mL to 30% at levels greater than 150 mcg/mL. Such increases lead to an apparent

increase in the clearance of total valproate at high doses. The half-life varies from 9 to 18 hours; extended-release formulations are therefore preferred. Because valproate is highly protein bound, it is largely confined to blood plasma; the drug has a low volume of distribution of approximately 0.15 L/kg. Approximately 20% of the drug is excreted as a direct conjugate.

Dosing and Therapeutic Levels

An initial daily dose of 15 mg/kg is recommended with slow titration to the therapeutic dose. Dosages of 25–30 mg/kg/d may be adequate in some patients, but others may require 60 mg/kg/d or even more. Therapeutic levels of valproate range from 50 to 100 mcg/mL, but concentrations up to 150 mcg/mL are generally tolerated and may be required.

Drug Interactions

Valproate inhibits the metabolism of several drugs, including phenobarbital and ethosuximide, leading to higher steady-state concentrations of these agents. Levels of phenobarbital may rise steeply, causing stupor or coma. Valproate displaces phenytoin from plasma proteins, causing an increase in the free fraction of phenytoin, and total phenytoin concentrations in the therapeutic range may be associated with toxicity. Although valproate does not increase levels of carbamazepine itself, levels of carbamazepine epoxide may be increased. Valproate can dramatically decrease the clearance of lamotrigine, resulting in a two- to three-fold prolongation of lamotrigine's half-life.

Toxicity

The most common dose-related adverse effects of valproate are nausea, vomiting, and other gastrointestinal complaints such as abdominal pain and heartburn. The drug should be started gradually to avoid these symptoms. A fine tremor is frequently seen at higher levels. Other reversible adverse effects occurring in some patients include weight gain, increased appetite, and hair loss.

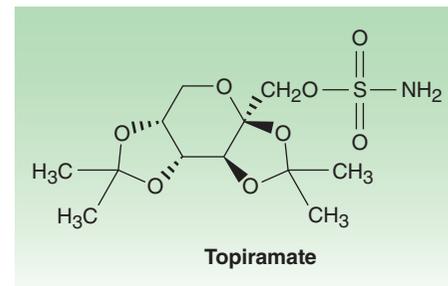
Valproate rarely causes idiosyncratic hepatic toxicity that may be severe and has been fatal. The risk is greatest for patients under 2 years of age and for those taking multiple medications. Initial aspartate aminotransferase values may not be elevated in susceptible patients, although these levels do eventually become abnormal. Most fatalities have occurred within 4 months after initiation of therapy. The other observed idiosyncratic adverse effect with valproate is thrombocytopenia, although documented cases of abnormal bleeding are lacking. Valproate can interfere with conversion of ammonia to urea. It can cause lethargy associated with increased blood ammonia concentrations. Fatal hyperammonemic encephalopathy has occurred in patients with genetic defects in urea metabolism; the drug is contraindicated in these patients.

Treatment with valproate during the first trimester of pregnancy is associated with a 1–2% risk of neural tube defects including spina bifida. In addition, an increased incidence of cardiovascular, orofacial, and digital abnormalities has been noted. Finally, cognitive impairment in offspring has been reported.

These observations must be strongly considered in the choice of drugs in women of child-bearing potential.

TOPIRAMATE

Topiramate is a broad-spectrum antiseizure drug whose chemical structure is that of a sulfamate-substituted monosaccharide derived from D-fructose. It is used in the treatment of focal seizures, primary generalized seizures, and seizures in the Lennox-Gastaut syndrome. Topiramate is also commonly used for migraine headache prophylaxis.



Mechanism of Action

Topiramate likely acts through several cellular targets, which may account for its broad-spectrum activity in epilepsy and migraine. Possible sites of action relevant to its clinical activities are (1) voltage-gated sodium channels; (2) GABA_A receptor subtypes; and (3) AMPA or kainate receptors. The drug is a weak inhibitor of carbonic anhydrase isoenzymes II and IV, but this is not thought to account for its antiseizure effects. In rare cases, the inhibition of carbonic anhydrase may cause metabolic acidosis of clinical importance.

Clinical Uses

Topiramate is effective in the treatment of focal seizures in adults and children and in primary generalized tonic-clonic seizures. The drug is approved for the Lennox-Gastaut syndrome and may be effective in juvenile myoclonic epilepsy, infantile spasms, Dravet's syndrome (severe myoclonic epilepsy in infancy), and even childhood absence seizures. The initial dose in newly diagnosed patients is typically 100 mg/d, but maintenance doses usually range from 200 to 400 mg/d. Most clinicians begin at a low dose (25–50 mg/d) and increase slowly to prevent adverse effects. Cognitive side effects commonly occur with topiramate and are a frequent reason for discontinuation. Affected patients experience impaired expressive language function (dysnomia and diminished verbal fluency), impaired verbal memory, and a general slowing of cognitive processing. These effects are unlike other antiseizure drugs and often occur without sedation or mood change. The incidence of cognitive side effects increases in a dose-dependent fashion, reaching 26% at a dose of 400 mg/d; however, some patients are completely unaffected even at higher dosages. Another troublesome adverse effect that commonly occurs with topiramate

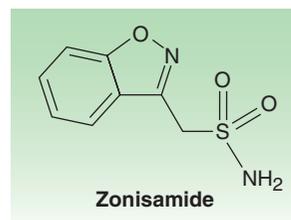
is paresthesias, typically occurring during initiation of therapy or at high doses; the symptoms may resolve with continuing treatment. Other dose-related adverse effects that occur frequently in the first 4 weeks of topiramate therapy are somnolence, fatigue, dizziness, nervousness, and confusion. Acute myopia and angle-closure glaucoma may require prompt drug withdrawal. Urolithiasis occurs in 0.5–1.5% of patients on long-term therapy and is more common in men. In some patients, carbonic anhydrase inhibition is associated with reduced serum bicarbonate that is usually asymptomatic but may result in nonspecific symptoms such as fatigue, anorexia, or nausea and vomiting. The potential for chronic untreated hyperchloremic non-anion gap metabolic acidosis for bone health is unknown. Decreased sweating (oligohydrosis) and an elevation in body temperature may occur during exposure to hot weather, mostly in children. Long-term topiramate therapy is often associated with significant weight loss, primarily due to a reduction in body fat mass. In clinical trials, 85% of adults receiving topiramate lost weight, which on average amounted to 5% of mean baseline body weight. Greater weight loss occurs in those with higher pretreatment weight. Weight loss is gradual and typically peaks at 12–18 months after initiation of therapy. Beneficial changes in lipid profile, glycemic control, and blood pressure may accompany the weight loss. Data in humans suggest a link between topiramate use in the first trimester of pregnancy and oral cleft formation in newborns (relative risk 16- to 21-fold).

Pharmacokinetics

Topiramate is rapidly absorbed (about 2 hours) and is 80% bioavailable. There is minimal food effect on absorption, minimal (15%) plasma protein binding, and only moderate (20–50%) metabolism; no active metabolites are formed. The drug is primarily excreted in the urine (50–80% is unchanged). The monotherapy half-life is 20–30 hours, but drops to 12–15 hours when administered with concomitant enzyme-inducing drugs. Immediate-release formulations are usually administered in two daily doses. Extended-release formulations are available that have been approved for once-daily administration. Although increased levels are seen with renal failure and hepatic impairment, there is no age or gender effect, no autoinduction, and no inhibition of metabolism, and kinetics are linear. Drug interactions do occur and can be complex, but the major effect is on topiramate levels rather than on the levels of other antiseizure drugs. Birth control pills may be less effective in the presence of topiramate, and alternative modes of contraception are recommended in women taking more than 200 mg/d; however, oral contraceptives with a higher content of ethinyl estradiol (50 mcg) may be satisfactory.

ZONISAMIDE

Zonisamide is a broad-spectrum antiseizure drug that is effective for focal and generalized tonic-clonic seizures in adults and children and may also be effective in some myoclonic epilepsies and in infantile spasms. There are reports of improvement in generalized onset tonic-clonic seizures and atypical absence seizures.



There is little information on the mechanism of action of zonisamide. Although it does block voltage-gated sodium channels, other actions may also contribute to its antiseizure activity. Zonisamide has high bioavailability, modest protein binding (>50–60%), and a half-life of 1–3 days, so it can be administered once daily. The drug is extensively metabolized by acetylation to form *N*-acetyl-zonisamide, which is excreted in the urine unchanged, and by CYP3A4 to form 2-sulfamoylacetylphenol, which is excreted as the glucuronide. Maintenance doses are 200–400 mg/d in adults (maximum 600 mg/d) and 4–8 mg/kg/d in children (maximum 12 mg/kg/d). Adverse effects include drowsiness, cognitive impairment, renal stones, and potentially serious skin rashes. Zonisamide has no clinically significant effects on the pharmacokinetics of other antiseizure drugs. However, antiseizure drugs such as carbamazepine, phenytoin, and phenobarbital that induce CYP3A4 increase the clearance of zonisamide, shortening its half-life; concomitant use with CYP3A4-inducing agents may therefore require an increase in zonisamide dose. Zonisamide, like topiramate, contains sulphur: zonisamide is a sulfonamide, whereas topiramate contains the same sulfonamide structure but is strictly a sulfamate. They have similar pharmacologic actions, including carbonic anhydrase inhibition like acetazolamide, which is also a sulfonamide. Both zonisamide and topiramate are associated with weight loss. They also both (rarely) cause kidney stones and oligohydrosis. Whether these actions are related to the common sulfonamide structure is not known.

DRUGS EFFECTIVE FOR GENERALIZED ABSENCE SEIZURES

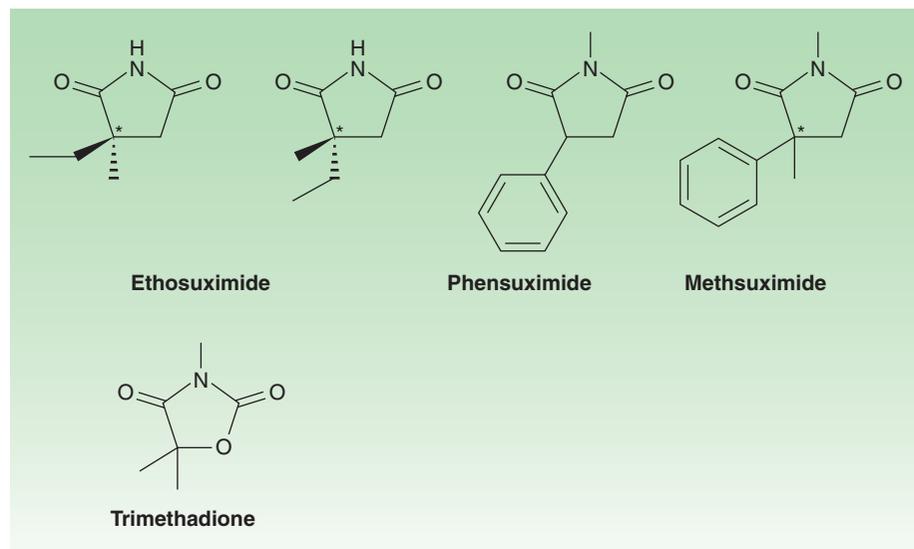
Ethosuximide and valproate are effective and well-tolerated treatments for generalized absence seizures in childhood absence epilepsy; lamotrigine is possibly effective. Ethosuximide is considered in this section along with trimethadione, which is of historical interest.

ETHOSUXIMIDE

Ethosuximide is a first-line drug for the treatment of generalized absence seizures. It can be used as monotherapy unless generalized tonic-clonic seizures are also present, in which case valproate is preferred or ethosuximide can be combined with another drug effective against generalized tonic-clonic seizures.

Chemistry

Ethosuximide was introduced in 1958 as the third of three marketed succinimides; the other two, phensuximide and methsuximide, are rarely used. Ethosuximide and methsuximide have asymmetric carbons (asterisks in below figure) and are used as racemates.



Mechanism of Action

Ethosuximide is thought to act by inhibition of low-voltage-activated T-type calcium channels in thalamocortical neurons that underlie the 3-Hz spike-wave discharges of generalized absence seizures. Other ion channels affected include voltage-gated sodium channels, calcium-activated potassium channels, and inward rectifier potassium channels; these actions may contribute to the efficacy of ethosuximide in absence epilepsy.

Clinical Uses

Studies in the mid-1970s provided evidence that monotherapy with ethosuximide is effective in the treatment of childhood generalized absence seizures. There is also evidence that it is effective in the treatment of atypical absence and epileptic negative myoclonus, a rare seizure type characterized by interruption of ongoing electromyographic activity contralateral to a lateralized spike-and-wave discharge. If ethosuximide in monotherapy does not lead to seizure control, the drug can be used in combination with valproate or other agents such as benzodiazepines.

Pharmacokinetics

Absorption is complete following administration of the oral dosage forms. Peak levels are observed 3–7 hours after oral administration of the capsules. Ethosuximide is not protein bound. During long-term administration, approximately 20% of the dose is excreted unchanged by the kidney. The remaining drug is metabolized in the liver, principally by CYP3A hydroxylation, to inactive metabolites. Ethosuximide has a very low total body clearance (0.25 L/kg/d). This corresponds to a half-life of approximately 40 hours, although values from 18 to 72 hours have been reported.

Therapeutic Levels & Dosage

In children, a common starting dose is 10–15 mg/kg/d, with titration according to clinical response to a maintenance dose of

15–40 mg/kg/d. In older children and adults, the initial dose is 250 or 500 mg/d, increasing in 250-mg increments to clinical response to a maximum of 1500 mg/d. While dosing is based on titration to maximal seizure control with acceptable tolerability, the accepted therapeutic serum concentration range is 40–100 mcg/mL (although plasma levels up to 150 mcg/mL may be necessary and tolerated in some patients). There is a linear relationship between ethosuximide dose and steady-state plasma levels. While the long half-life could allow once-daily dosing, ethosuximide is generally administered in two or even three divided doses to minimize adverse gastrointestinal effects.

Drug Interactions & Toxicity

Administration of ethosuximide with valproic acid results in a decrease in ethosuximide clearance and higher steady-state concentrations owing to inhibition of ethosuximide metabolism. No other important drug interactions have been reported. The most common dose-related adverse effect of ethosuximide is gastric distress, including pain, nausea, and vomiting. When an adverse effect does occur, temporary dosage reductions may allow adaptation. Other dose-related adverse effects are transient lethargy or fatigue and, much less commonly, headache, dizziness, hiccup, and euphoria. Behavioral changes are usually in the direction of improvement. Non-dose-related or idiosyncratic adverse effects of ethosuximide are extremely uncommon.

TRIMETHADIONE

Trimethadione is an oxazolidinedione antiseizure drug introduced in 1945. It is no longer marketed in the USA but is available elsewhere. Trimethadione is effective in the treatment of generalized absence seizures and was the drug of choice for this seizure type until the introduction of ethosuximide. Trimethadione has numerous dose-related and idiosyncratic side effects, including hemeralopia (day blindness). Because of the high propensity for

side effects, trimethadione and the related oxazolidinediones paramethadione and dimethadione, the major metabolite of trimethadione, are now rarely used.

DRUGS EFFECTIVE FOR MYOCLONIC SEIZURES SUCH AS IN THE SYNDROME OF JUVENILE MYOCLONIC EPILEPSY

Valproate is the drug of first choice for the treatment of myoclonic seizures. Other drugs effective in the treatment of this seizure type are levetiracetam, zonisamide, topiramate, and lamotrigine.

DRUGS EFFECTIVE FOR ATONIC SEIZURES SUCH AS IN THE LENNOX-GASTAUT SYNDROME

Valproate in combination with lamotrigine and a benzodiazepine is the most widely used treatment for atonic seizures. Topiramate, felbamate, and lamotrigine are used in the treatment of Lennox-Gastaut syndrome; clinical trials have shown improvement in atonic seizures. The sodium channel-blocking antiseizure drugs phenobarbital and vigabatrin should be used with caution because they may worsen atonic seizures. Clobazam and rufinamide, discussed in this section, are also used in the treatment of seizures associated with Lennox-Gastaut syndrome and have been demonstrated in clinical trials to reduce the frequency of atonic seizures.

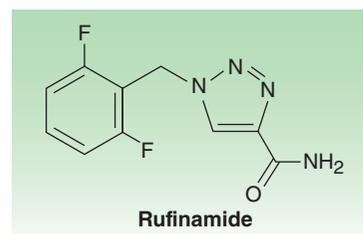
CLOBAZAM

Clobazam is widely used for the treatment of focal seizures in many countries, although it is not approved for that indication in the United States, where its only approved use is for treatment of seizures associated with Lennox-Gastaut syndrome in patients 2 years of age or older. Clobazam is a 1,5-benzodiazepine and structurally different from other marketed benzodiazepines, which are 1,4-benzodiazepines. Like the 1,4-benzodiazepines, however, clobazam is a positive allosteric modulator of GABA_A receptors and has similar pharmacologic activities and adverse effects. In addition, while tolerance occurs to clobazam in animal models within days to weeks of chronic administration, retrospective studies assessing the extent of tolerance in the clinical setting have suggested that tolerance is not a prominent issue in clinical treatment. Side effects that occur in a dose-dependent fashion include somnolence and sedation, dysarthria, drooling, and behavioral changes, including aggression. Withdrawal symptoms may occur with abrupt discontinuation. Clobazam has a half-life of 18 hours and is effective at dosages of 0.5–1 mg/kg/d. Clobazam is metabolized in the liver by CYP and non-CYP transformations, with up to 14 metabolites; however, the major metabolite is desmethylclobazam (norclobazam). With long-term administration of clobazam, levels of norclobazam, which has a longer half-life than clobazam, are 8- to 20-times higher than those of the parent.

Norclobazam has antiseizure activity, although it is weaker than clobazam. Nevertheless, because norclobazam levels are so much higher at steady state, seizure protection during chronic therapy is likely mainly due to norclobazam. Clobazam is a moderate inhibitor of CYP2D6 and has been shown to significantly increase the levels of drugs metabolized by this isoenzyme such as phenytoin and carbamazepine. Reduced dosing may be required when these antiseizure drugs are used in combination with clobazam.

RUFINAMIDE

Rufinamide is a triazole derivative identified by screening in animal seizure models. It is effective for atonic seizures in Lennox-Gastaut syndrome, but there is also some evidence of efficacy in the treatment of focal seizures. In the USA and Europe, rufinamide is only approved for treatment of seizures associated with the Lennox-Gastaut syndrome.



Mechanism of Action

In mice and rats, rufinamide is protective in the MES test and, at higher doses, in the PTZ test. Its only known action that is relevant to seizure protection is as a blocker of voltage-gated sodium channels.

Clinical Uses

In the Lennox-Gastaut syndrome, rufinamide is effective against all seizure types but especially against atonic seizures. Some clinical data suggest it may be effective against focal seizures. Treatment in children is typically started at 10 mg/kg/d in two equally divided doses and gradually increased to 45 mg/kg/d to a maximum of 3200 mg/d. Adults can begin with 400–800 mg/d in two equally divided doses up to a maximum of 3200 mg/d as tolerated. The drug should be given with food. The most common adverse events are somnolence and vomiting.

Pharmacokinetics

Rufinamide is well absorbed, and plasma concentrations peak between 4 and 6 hours. The half-life is 6–10 hours, and minimal plasma protein binding is observed. Although cytochrome P450 enzymes are not involved, the drug is extensively metabolized to inactive products. Most of the drug is excreted in the urine; an acid metabolite accounts for about two-thirds of the dose. Most drug-drug interactions are minor except that valproate may decrease the clearance of rufinamide; dosing with valproate, particularly in children, may need to be decreased, typically by 50%.

DRUGS EFFECTIVE FOR DRAVET'S SYNDROME

Dravet's syndrome (severe myoclonic epilepsy of infancy) is a rare genetic epileptic encephalopathy characterized by diverse generalized and focal seizure types, including myoclonic seizures, tonic-clonic seizures, absence seizures, atonic seizures, and one-sided hemiconvulsive and focal seizures. Mutations of the *SCN1A* gene encoding Na_v1.1 voltage-dependent sodium channels cause 79% of diagnosed cases of Dravet's syndrome. Although drugs such as clobazam, valproate, and topiramate are used, none of these is very effective. Stiripentol is not approved in the USA but is widely used in Europe. In patients with *SCN1A* gene mutations, sodium channel-blocking antiseizure drugs are contraindicated because they worsen seizures.

STIRIPENTOL

Stiripentol is an aromatic allylic alcohol that has activity in the treatment of Dravet's syndrome. Clinical studies indicate that it reduces the frequency of prolonged seizures in children with this condition. Stiripentol is often used in conjunction with clobazam or valproate; whether it has activity by itself has not been studied in clinical trials. The drug has various actions on GABA-mediated neurotransmission including acting as a positive allosteric modulator of GABA_A receptors. It is a potent inhibitor of CYP3A4, CYP1A2, and CYP2C19 and dramatically increases the levels of clobazam and its active metabolite norclobazam; it also inhibits valproate metabolism. These drug-drug interactions have been proposed as the basis for the clinical effectiveness of stiripentol, and elevations in concomitant drugs likely contribute to some extent to efficacy. However, stiripentol has activity in various animal seizure models, indicating that it has antiseizure activity in its own right. Dosing is complex, typically beginning with a reduction in concomitant medications. Stiripentol is then started at 10 mg/kg/d and is increased gradually as tolerated. The most frequent adverse effects are sedation/drowsiness, reduced appetite, slowing of mental function, ataxia, diplopia, nausea, and abdominal pain. Stiripentol exhibits nonlinear pharmacokinetics, decreasing in clearance as the dose increases.

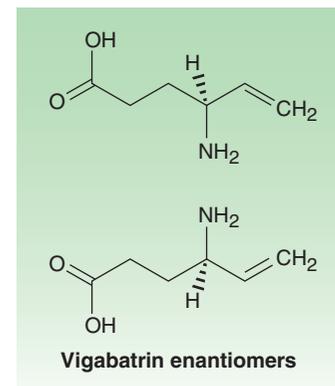
DRUGS EFFECTIVE FOR INFANTILE SPASMS (WEST'S SYNDROME)

Infantile spasms are treated with adrenocorticotrophic hormone (ACTH) by intramuscular injection or oral corticosteroids such as prednisone or hydrocortisone. Vigabatrin is also often used and is particularly effective in cases associated with tuberous sclerosis. Other antiseizure medications that may be helpful are valproate, topiramate, zonisamide, or a benzodiazepine such as clonazepam or nitrazepam. ACTH and corticosteroids are associated with substantial morbidity, and vigabatrin, as discussed below, has a risk of permanent loss of vision. The goal of treatment is cessation of seizures, and this generally requires ACTH, corticosteroids, or vigabatrin and is not generally achieved with the safer antiseizure

agents. The mechanism of action of ACTH and corticosteroids in the treatment of infantile spasms is unknown.

VIGABATRIN

Vigabatrin is an analog of GABA, designed as an inhibitor of GABA transaminase (GABA-T), the enzyme responsible for the metabolism of synaptically released GABA. Vigabatrin is effective in the treatment of focal seizures (but not generalized seizures) and in the treatment of infantile spasms. Because it may cause irreversible visual loss, it is usually reserved for patients with seizures refractory to other treatments.



Mechanism of Action

Vigabatrin is a specific, irreversible inhibitor of GABA-T, producing a sustained increase in the extracellular concentrations of GABA in the brain. This paradoxically leads to inhibition of synaptic GABA_A receptor responses, but also prolongs the activation of extrasynaptic GABA_A receptors that mediate tonic inhibition. Vigabatrin is effective in a wide range of animal seizure models. Vigabatrin is marketed as a racemate; the *S*(+) enantiomer is active and the *R*(-) enantiomer appears to be inactive.

Clinical Uses

Vigabatrin is useful in the treatment of infantile spasms, especially when associated with tuberous sclerosis. The drug is also effective against focal seizures. The half-life is approximately 6–8 hours, but the pharmacodynamic activity of the drug is more prolonged and not well correlated with the plasma half-life because recovery from the drug requires synthesis of replacement GABA-T enzyme. In infants, the dosage is 50–150 mg/kg/d. In adults, vigabatrin is started at an oral dosage of 500 mg twice daily; a total of 2–3 g/d may be required for full effectiveness. The most important adverse effect of vigabatrin is irreversible retinal dysfunction. Patients may develop permanent bilateral concentric visual field constriction that is often asymptomatic but can be disabling. Minimal evidence also suggests that vigabatrin also can damage the central retina. The onset of vision loss can occur within weeks of starting treatment or after months or years. Other adverse effects are somnolence, headache, dizziness, and weight gain. Less common but more troublesome adverse effects are agitation, confusion, and psychosis; preexisting mental illness is a relative contraindication.

OTHER DRUGS USED IN MANAGEMENT OF SEIZURES AND EPILEPSY

BENZODIAZEPINES

Seven benzodiazepines play roles in the treatment of seizures and epilepsy (see also Chapter 22). All produce their functional effects by positive allosteric modulation of GABA_A receptors; however, subtle structural differences among the benzodiazepines result in differences in their pharmacokinetic properties. Certain benzodiazepines are the first-line acute treatment for seizures, either in status epilepticus or acute repetitive seizures (seizure clusters). However, two prominent aspects of benzodiazepines limit their usefulness in the chronic therapy of epilepsy. The first is their pronounced sedative effects; however, in children, there may be a paradoxical hyperactivity, as is the case with other sedative agents such as barbiturates. The second problem is tolerance, in which seizures may respond initially but recur within a few months. As a result of these limitations, benzodiazepines are infrequently used in the chronic treatment of epilepsy.

Diazepam given intravenously is a first-line treatment for status epilepticus. It is also used in a rectal gel formulation for the treatment of acute repetitive seizures (seizure clusters). The drug is occasionally given orally on a long-term basis, although it is not considered very effective in this application, because of the development of tolerance. **Lorazepam** is more commonly used in the treatment of status epilepticus because it has a more prolonged duration of action after bolus intravenous injection. There is evidence that intramuscular **midazolam**, which is water soluble, is preferred in the out-of-hospital treatment of status epilepticus because the delay required to achieve intravenous access may be avoided. **Clonazepam** is a long-acting benzodiazepine that on a milligram basis is one of the most potent antiseizure agents known. It has documented efficacy in the treatment of absence, atonic, and myoclonic seizures. As is the case for all benzodiazepines, sedation is prominent, especially on initiation of therapy; starting doses should be small. Maximal tolerated doses are usually in the range of 0.1–0.2 mg/kg/d, but many weeks of gradually increasing daily doses may be needed to achieve these dosages in some patients. **Nitrazepam** is not marketed in the USA but is used in many other countries, especially for infantile spasms and myoclonic seizures. **Clorazepate dipotassium** is approved in the USA for the treatment of focal seizures. Drowsiness and lethargy are common adverse effects, but as long as the drug is increased gradually, dosages as high as 90 mg/d can be given. **Clobazam** is described earlier in this chapter under atonic seizures.

CARBONIC ANHYDRASE INHIBITORS

Carbonic anhydrases are enzymes that catalyze the interconversion between CO₂ and bicarbonate (see Chapter 15). Inhibitors of carbonic anhydrases, particularly the cytosolic forms CA II and CA VII, exhibit antiseizure activity. Bicarbonate efflux through GABA_A receptors can exert a depolarizing (excitatory) influence

that is especially relevant during intense GABA_A receptor activation, as occurs during seizures, when there is diminution of the hyperpolarizing chloride gradient. Carbonic anhydrase inhibition prevents the replenishment of intracellular bicarbonate and depresses the depolarizing action of bicarbonate.

The prototypical carbonic anhydrase inhibitor is the sulfonamide acetazolamide (see Chapter 15), which has broad-spectrum antiseizure activity in animal models. In addition, acetazolamide is believed to have clinical antiseizure activity, at least transiently, against most types of seizures including focal and generalized tonic-clonic seizures and especially generalized absence seizures. However, acetazolamide is rarely used for chronic therapy because tolerance develops rapidly, with return of seizures usually within a few weeks. The drug is often used in the intermittent treatment of menstrual seizure exacerbations in women. The usual dosage is approximately 10 mg/kg/d to a maximum of 1000 mg/d.

Another sulfonamide carbonic anhydrase inhibitor, **sulthiame**, became established in the treatment of focal seizures in the 1950s and has also been reported to be effective in benign focal epilepsy with centrotemporal spikes (BECTS) and infantile spasms, but results of controlled trials are not available. Its use has declined in routine practice, other than in a few countries in Europe and in Israel. It is not available in the USA.

As noted previously, topiramate and zonisamide are sulfur-containing molecules with weak carbonic anhydrase activity. There is little evidence that this activity is a major factor in their therapeutic effects.

ADDITIONAL TOPICS

THERAPEUTIC DRUG MONITORING

The pharmacokinetic behavior of most antiseizure drugs varies markedly from patient to patient so that dosing must be individualized. Therapeutic drug concentration monitoring is often used as an aid to dosing. Established reference ranges are available for most of the older antiseizure drugs (Table 24–3). Such ranges are generally not available for newer drugs, although there may be information on blood levels associated with efficacy. In all cases, the ranges should be interpreted flexibly given individual variability in response. Drug levels can be helpful (1) to guide dose adjustments when there is a change in drug formulation, (2) when breakthrough seizures occur, (3) when an interacting medication is added to or removed from a patient's regimen, (4) during pregnancy, (5) to establish an individual therapeutic concentration range when a patient is in remission, (6) to determine whether adverse effects are related to drug levels, and (7) to assess adherence.

STATUS EPILEPTICUS

Status epilepticus is clinically defined as abnormally prolonged or repetitive seizures. Status epilepticus presents in several forms: (1) **convulsive status epilepticus** consisting of repeated generalized

TABLE 24-3 Serum concentrations reference ranges for some antiseizure drugs.

Antiseizure Drug	Reference Range ¹	
	μM	mcg/mL
OLDER DRUGS		
Carbamazepine	15–45	4–12
Clobazam	0.1–1.0	0.03–0.30
Clonazepam	60–220 nmol/L	19–70 ng/mL
Ethosuximide	300–600	40–100
Phenytoin	40–80	10–20
Phenobarbital	65–172	15–40
Primidone	Primidone: 37–55	Primidone: 8–12
	Phenobarbital: 65–129	Phenobarbital: 15–30
Valproate	300–600	40–100
NEWER DRUGS (Post-1990)		
Eslicarbazepine acetate ²	20–140	5–35
Retigabine (Ezogabine)	No data	
Felbamate	125–250	30–60
Gabapentin	70–120	12–21
Lacosamide	40–80	10–20
Lamotrigine	10–60	3–15
Levetiracetam	70–270	12–46
Oxcarbazepine ²	20–140	5–35
Perampanel	0.14–1.14	0.05–0.4
Pregabalin ³	18–52	2.8–8.2
Rufinamide ⁴	37–168	9–40
Stiripentol ⁴	34–51	8–12
Tiagabine	0.05–0.53	0.02–0.2
Topiramate	15–60	5–20
Vigabatrin	6–279	0.8–36
Zonisamide	47–188	10–40

¹These data are provided only as a general guideline. Many patients will respond better at different levels, and some patients may have drug-related adverse events within the listed reference ranges.

²Monohydroxy metabolites (combination of eslicarbazepine and R-licarbazepine).

³Not well established.

⁴Not well established; values given were associated with positive response.

tonic-clonic seizures with persistent postictal depression of neurologic function between seizures; (2) **nonconvulsive status epilepticus**, a persistent change in behavior or mental processes with continuous epileptiform EEG but without major motor signs; and (3) **focal status epilepticus**, with or without altered awareness. Convulsive status epilepticus is a life-threatening emergency that requires immediate treatment. Traditionally, convulsive status epilepticus was defined as more than 30 minutes of either (1) continuous seizure activity or (2) two or more sequential seizures without full recovery of consciousness between seizures.

Because persistent seizure activity is believed to cause permanent neuronal injury and because the majority of seizures terminate in 2 to 3 minutes, it is now generally accepted that treatment should be begun when the seizure duration reaches 5 minutes for generalized tonic-clonic seizures and 10 minutes for focal seizures with or without impairment of consciousness. It is noteworthy that convulsive status epilepticus may evolve to nonconvulsive status epilepticus.

The initial treatment of choice is a benzodiazepine, either intravenous lorazepam or diazepam, although there is evidence that intramuscular midazolam may be equally effective. Lorazepam is less lipophilic than diazepam (logP values of 2.4 and 2.8, respectively) and does not undergo as rapid redistribution from brain to peripheral tissues as does diazepam. Clinically effective diazepam concentrations in the brain following an intravenous bolus fall rapidly as the drug exits the central compartment into peripheral fat. Lorazepam has less extensive peripheral tissue uptake, allowing clinically effective concentrations to remain in the central compartment for much longer. Although lorazepam is now used more frequently than diazepam because of the perceived pharmacokinetic advantage, recent appraisals of the clinical data have not found evidence to favor lorazepam. In the prehospital setting, rectal diazepam, intranasal midazolam, or buccal midazolam are acceptable alternative first treatments if the preferred options are not available. If seizures continue, a second therapy is administered. Intravenous fosphenytoin or phenytoin is most common in the USA, although there is no evidence that these choices are superior to intravenous valproate or levetiracetam. Phenobarbital is also an acceptable second therapy, but it has a long half-life causing persistent side effects including severe sedation, respiratory depression, and hypotension. Lacosamide is available in an intravenous formulation, but there is little published experience to assess its efficacy. If the second therapy fails to stop the seizures, an additional second-line agent is often tried. Refractory status epilepticus occurs when seizures continue or recur at least 30 minutes after treatment with first and second therapy agents. Refractory status epilepticus is treated with anesthetic doses of pentobarbital, propofol, midazolam, or thiopental. Case reports indicate that ketamine may be effective. If status epilepticus continues or recurs 24 hours or more after the onset of anesthesia, the condition is considered super-refractory. Often, super-refractory status epilepticus is recognized when anesthetics are withdrawn and seizures recur. There are no established therapies for super-refractory status epilepticus other than to reinstitute general anesthesia.

Treatment of focal status epilepticus is similar to therapy for convulsive status epilepticus, although in some cases simply instituting oral antiseizure drug therapy is sufficient. Focal status epilepticus must be distinguished from absence status epilepticus, which is a prolonged, generalized absence seizure that usually lasts for hours or even days. Absence status epilepticus can often be effectively treated with a benzodiazepine followed by intravenous valproate or oral or nasogastric ethosuximide. Absence status epilepticus can occur when an inappropriate antiseizure drug, such as tiagabine or carbamazepine, is used in a patient with idiopathic generalized epilepsy.

ACUTE REPETITIVE SEIZURES (SEIZURE CLUSTERS)

Acute repetitive seizures, also referred to as seizure clusters, are groups of seizures that occur more frequently than the patient's habitual frequency. The clusters can occur rapidly over several minutes, or they may occur over a longer time period of 1 or 2 days. In acute repetitive seizures, there is complete recovery between seizures so that patients do not meet the definition of status epilepticus. However, the condition is concerning nevertheless because, in the absence of treatment, prolonged seizures or status epilepticus can occur. Acute repetitive seizures can be treated in the emergency department with intravenous benzodiazepines or other antiseizure drugs. In the USA, diazepam rectal gel is the only approved treatment for out-of-hospital treatment of acute repetitive seizures. Outside the USA, rectal paraldehyde is sometimes used. Administering rectal medications can be difficult, time consuming, and an embarrassing experience for the patient and caregivers; such products are generally limited to use in children because of the social stigma and the mechanical difficulties of positioning adults. Buccal (oromucosal) midazolam, in which the treatment solution is administered to the buccal mucosa using an oral syringe, is commonly used in Europe and elsewhere in the world. Intranasal midazolam, diazepam, and lorazepam have also been shown to be efficacious; these drugs are not approved for this route of administration in the USA, but some clinicians use intranasal midazolam or oral benzodiazepines on an off-label basis.

TERATOGENICITY (SEE ALSO CHAPTER 59)

Most women with epilepsy who become pregnant require continued antiseizure drug therapy for seizure control. No antiseizure drug is known to be completely safe for the developing fetus.

Valproate is a known human teratogen. First-trimester exposure is associated with an approximately three-fold increased risk of major congenital malformations, most commonly spina bifida (absolute risk, 6–9%). Phenobarbital use during pregnancy is also associated with an elevated risk of major congenital malformation, most often cardiac defects. First-trimester in utero exposure to topiramate is associated with an approximately 10-fold increase in oral clefts risk (absolute risk, 1.4%). If possible, valproate, phenobarbital, and topiramate should be avoided in women of childbearing potential, and if the drugs cannot be eliminated, they should be used at the lowest dose possible because the risk, at least for valproate, has been shown to be dose-dependent. Other antiseizure drugs may present a lower risk of major congenital malformations (or the risk is poorly understood), but the risk for most drugs, including carbamazepine, phenytoin, and levetiracetam is not zero. In addition to congenital malformations, there is evidence that first-trimester exposure is associated with cognitive impairment. In particular, fetal exposure to valproate is associated with a dose-dependent reduction in cognitive

abilities across a range of domains including IQ. Fetal exposure to lamotrigine or levetiracetam may be safer with regard to cognition than other antiseizure drugs, and these two agents also have the lowest risks of major congenital malformations. Polytherapy may increase the risk of neurodevelopmental deficits, particularly when one of the drugs is valproate. In addition, there is evidence that valproate exposure may be associated with an increased risk of autism spectrum disorder.

BREASTFEEDING

Some antiepileptic drugs such as primidone, levetiracetam, gabapentin, lamotrigine, and topiramate penetrate into breast milk in relatively high concentrations. For example, in one study, plasma concentrations of lamotrigine in breastfeeding infants were 18.3% of maternal plasma concentrations. Other antiseizure drugs that are highly protein bound, such as valproate, phenobarbital, phenytoin, and carbamazepine, do not penetrate into breast milk substantially. Case series have not reported adverse effects on the newborn of antiseizure drug exposure via breast milk, although there are some reports of sedation with the barbiturates and benzodiazepines. As a general rule, breastfeeding should not be discouraged given the lack of evidence of harm and the known positive benefits.

SUICIDALITY

An analysis of suicidal behavior during clinical trials of antiseizure drugs was carried out by the US Food and Drug Administration in 2008. The presence of either suicidal behavior or suicidal ideation was 0.37% in patients taking active drugs and 0.24% in patients taking placebo. This led to an alert of an increased risk of suicide in people taking antiseizure drugs. Following the report, several studies have addressed the issue in various ways but have not provided convincing data that, as a class, antiseizure drugs induce suicide-related behaviors. Some data suggest a possible association of lamotrigine, levetiracetam, and topiramate with suicidality, but further research is needed. Patients treated with antiseizure drugs and their families should be informed of the risk of suicidality.

WITHDRAWAL

Antiseizure drugs may not need to be taken indefinitely. Children who are seizure free for periods longer than 2–4 years while on antiseizure medications will remain so when medications are withdrawn in 70% of cases. The risk of recurrence depends on the seizure syndrome. Resolution of seizures is common for generalized absence epilepsy but not for juvenile myoclonic epilepsy. Other risk factors for recurrence are an abnormal EEG, the presence of neurologic deficits, or when seizure control

had been difficult to achieve. There is little information on antiseizure drug withdrawal in seizure-free adults. Withdrawal is believed to be more likely to be successful in patients with generalized epilepsies who exhibit a single seizure type, whereas longer duration of epilepsy, an abnormal neurologic examination, an abnormal EEG, and certain epilepsy syndromes, including juvenile myoclonic epilepsy, are associated with increased risk of recurrence. Drugs are generally withdrawn slowly over a 1- to 3-month period or longer. Abrupt cessation may be associated with return of seizures and even a risk of status epilepticus. Some drugs are more easily withdrawn than others. Physical dependence occurs with barbiturates and benzodiazepines, and there is a well-recognized risk of rebound seizures with abrupt withdrawal.

ANTISEIZURE DRUGS IN DEVELOPMENT

Several potential new antiseizure drugs are in late clinical development; these are Staccato (thermal aerosol inhaled) alprazolam, for acute repetitive seizures; intranasal midazolam, for acute repetitive seizures; allopregnanolone, for status epilepticus; ganaxolone, for status epilepticus and rare epilepsy syndromes; cannabidiol, for epileptic encephalopathies and focal seizures; cannabidivarin, for focal seizures; cenobamate (YKP3089), for focal seizures; fenfluramine, for Dravet's syndrome; and stiripentol, for Dravet's syndrome. Other drugs are in earlier stages of development; current information can be found on the Epilepsy Foundation website at http://www.epilepsy.com/etp/pipeline_new_therapies.

SUMMARY ANTISEIZURE DRUGS

Type, Drug	Mechanism of Action	Pharmacokinetics	Clinical Applications	Toxicities, Interactions
SODIUM CHANNEL BLOCKERS				
• Carbamazepine	Sodium channel blocker	Rapidly absorbed orally, with bioavailability 75–85% • peak levels in 4–5 h • plasma protein binding 75% • extensively metabolized in liver, in part to active carbamazepine-10, 11-epoxide • $t_{1/2}$ of parent in adults initially 25–65 h, decreasing to 12–17 h with autoinduction	Focal and focal-to-bilateral tonic-clonic seizures; trigeminal neuralgia	<i>Toxicity:</i> Nausea, diplopia, ataxia, hyponatremia, headache • <i>Interactions:</i> Phenytoin, valproate, fluoxetine, verapamil, macrolide antibiotics, isoniazid, propoxyphene, danazol, phenobarbital, primidone, many others
• <i>Oxcarbazepine:</i> Similar to carbamazepine; 100% bioavailability; 1–2 h $t_{1/2}$ but active metabolites with $t_{1/2}$ of 8–12 h; fewer interactions reported				
• <i>Eslicarbazepine acetate:</i> Similar to oxcarbazepine but shown to be effective when given once daily and may be more rapidly converted to the active metabolite				
• Lamotrigine	Sodium channel blocker	Nearly complete (~90%) absorption • peak levels in 1–3 h • protein binding 55% • extensively metabolized; no active metabolites • $t_{1/2}$ 8–35 h	Focal seizures, generalized tonic-clonic seizures, absence seizures, other generalized seizures; bipolar depression	<i>Toxicity:</i> Dizziness, headache, diplopia, rash • <i>Interactions:</i> Valproate, carbamazepine, oxcarbazepine, phenytoin, phenobarbital, primidone, succinimides, sertraline, topiramate
• Lacosamide	Sodium channel blocker, slow blocking kinetics	Complete absorption • peak levels in 1–2 h • protein binding <30% • no active metabolites • $t_{1/2}$ 12–14 h	Focal seizures	<i>Toxicity:</i> Dizziness, headache, nausea • small increase in PR interval • <i>Interactions:</i> Minimal
• Phenytoin, fosphenytoin	Sodium channel blocker	Absorption is formulation dependent • highly bound to plasma proteins • no active metabolites • dose-dependent elimination, $t_{1/2}$ 12–36 h • fosphenytoin is for IV, IM routes	Focal seizures, tonic-clonic seizures	<i>Toxicity:</i> Diplopia, ataxia, gingival hyperplasia, hirsutism, neuropathy • <i>Interactions:</i> Phenobarbital, carbamazepine, isoniazid, felbamate, oxcarbazepine, topiramate, fluoxetine, fluconazole, digoxin, quinidine, cyclosporine, steroids, oral contraceptives, others

(continued)

Type, Drug	Mechanism of Action	Pharmacokinetics	Clinical Applications	Toxicities, Interactions
BROAD SPECTRUM				
• Valproate	Unknown	Nearly complete (>90%) absorption • peak levels formulation dependent • highly (90%) bound to plasma proteins • extensively metabolized in liver • $t_{1/2}$ 5–16 h	Generalized tonic-clonic seizures, partial seizures, absence seizures, myoclonic seizures, other generalized seizure; migraine prophylaxis	<i>Toxicity:</i> Nausea, tremor, weight gain, hair loss, teratogenic, hepatotoxic • <i>Interactions:</i> Phenobarbital, phenytoin, carbamazepine, lamotrigine, felbamate, rifampin, ethosuximide, primidone
• Levetiracetam	SV2A ligand	Nearly complete (~95%) absorption • peak levels in 1–2 h • not bound to plasma proteins • minimal metabolism in blood to inactive metabolite; ~66% excreted unchanged in urine • $t_{1/2}$ 6–11 h	Focal seizures, generalized tonic-clonic seizures, myoclonic seizures	<i>Toxicity:</i> Nervousness, dizziness, depression, seizures • <i>Interactions:</i> Rare
<i>Brivaracetam: Similar to levetiracetam but interaction with carbamazepine</i>				
• Topiramate	Multiple actions	Bioavailability ~80% • peak levels in 2–4 h • minimal (15%) plasma protein binding • variable metabolism; no active metabolites; 20–70% excreted unchanged in the urine • $t_{1/2}$ 20–30 h, but decreases with concomitant drugs	Focal seizures, primary generalized seizures, Lennox-Gastaut syndrome; migraine prophylaxis	<i>Toxicity:</i> Somnolence, cognitive slowing, confusion, paresthesias • <i>Interactions:</i> Phenytoin, carbamazepine, oral contraceptives, lamotrigine, lithium?
• Zonisamide	Unknown	Nearly complete (>90%) absorption • peak concentrations in 2–6 h • modest (40–60%) plasma protein binding • moderate (> 50%) metabolism in liver; 30% excreted unchanged in urine • $t_{1/2}$ 50–70 h	Focal seizures, generalized tonic-clonic seizures, myoclonic seizures	<i>Toxicity:</i> Drowsiness, cognitive impairment, confusion, skin rashes • <i>Interactions:</i> Minimal
• Rufinamide	Sodium channel blocker and other mechanisms	Well absorbed orally • peak concentrations in 4–6 h • low (35%) plasma protein binding • $t_{1/2}$ 6–10 h • no active metabolites • mostly excreted in urine	Lennox-Gastaut syndrome; focal seizures	<i>Toxicity:</i> Somnolence, vomiting, pyrexia, diarrhea • <i>Interactions:</i> Not metabolized via P450 enzymes, but antiseizure drug interactions may be present
GABAPENTINOIDS				
• Gabapentin	$\alpha 2\delta$ ligand (Ca^{2+} channel and possibly other sites)	Bioavailability 50%, decreasing with increasing doses • peak concentrations in 2–3 h • not bound to plasma proteins • not metabolized; 100% excreted unchanged in urine • $t_{1/2}$ 5–9 h	Focal seizures; neuropathic pain; postherpetic neuralgia; anxiety	<i>Toxicity:</i> Somnolence, dizziness, ataxia • <i>Interactions:</i> Minimal
• Pregabalin	$\alpha 2\delta$ ligand (Ca^{2+} channel and possibly other sites)	Nearly complete (~90%) absorption • peak concentrations in 1–2 h • not bound to plasma proteins • not metabolized; 98% excreted unchanged in urine • $t_{1/2}$ 4.5–7 h	Focal seizures; neuropathic pain; postherpetic neuralgia; fibromyalgia; anxiety	<i>Toxicity:</i> Somnolence, dizziness, ataxia • <i>Interactions:</i> Minimal
BARBITURATES				
• Phenobarbital	Positive allosteric modulator of GABA _A receptors • reduces excitatory synaptic responses	Nearly complete (>90%) absorption • peak concentrations in 0.5–4 h • modest (55%) plasma protein binding • extensively metabolized in liver; no active metabolites; 20–25% excreted unchanged in urine • $t_{1/2}$ 75–140 h	Focal seizures, generalized tonic-clonic seizures, myoclonic seizures, neonatal seizures; sedation	<i>Toxicity:</i> Sedation, cognitive issues, ataxia, hyperactivity • <i>Interactions:</i> Valproate, carbamazepine, felbamate, phenytoin, cyclosporine, felodipine, lamotrigine, nifedipine, nimodipine, steroids, theophylline, verapamil, others
• Primidone	Sodium channel blocker-like but converted to phenobarbital	Nearly complete (>90%) absorption • minimal (10%) plasma protein binding • peak concentrations in 2–6 h • extensively metabolized in liver; 2 active metabolites (phenobarbital and phenylethylmalonamide); 65% excreted unchanged in urine • $t_{1/2}$ 10–25 h	Generalized tonic-clonic seizures, partial seizures	<i>Toxicity:</i> Sedation, cognitive issues, ataxia, hyperactivity • <i>Interactions:</i> Similar to phenobarbital

(continued)

Type, Drug	Mechanism of Action	Pharmacokinetics	Clinical Applications	Toxicities, Interactions
ABSENCE SEIZURE-SPECIFIC				
• Ethosuximide	Inhibit low-threshold calcium channels (T-type)	Nearly complete (>90%) absorption • peak concentrations in 3–7 h • not bound to plasma proteins • extensively metabolized in liver; no active metabolites; 20% excreted unchanged in urine • $t_{1/2}$ 20–60 h	Absence seizures	<i>Toxicity:</i> Nausea, headache, dizziness, lethargy • <i>Interactions:</i> Valproate, phenobarbital, phenytoin, carbamazepine, rifampicin
BENZODIAZEPINES				
• Diazepam	Positive allosteric modulator of GABA _A receptors	Nearly complete (>90%) oral or rectal absorption • peak concentrations in 1–1.5 h • IV for status epilepticus • highly (95–98%) bound to plasma proteins • extensively metabolized to several active metabolites • $t_{1/2}$ of active metabolite N-desmethyldiazepam up to 100 h	Status epilepticus, seizure clusters; sedation, anxiety, muscle relaxation (muscle spasms, spasticity), acute alcohol withdrawal	<i>Toxicity:</i> Sedation • <i>Interactions:</i> Additive with sedative-hypnotics
• Clonazepam	Positive allosteric modulator of GABA _A receptors	Bioavailability >80% • peak concentrations in 1–4 h • highly (86%) bound to plasma proteins • extensively metabolized in liver; no active metabolites • $t_{1/2}$ 12–56 h	Absence seizures, myoclonic seizures, infantile spasms	<i>Toxicity:</i> Similar to diazepam • <i>Interactions:</i> Additive with sedative-hypnotics
<ul style="list-style-type: none"> • Lorazepam: Similar to diazepam • Clobazam: Indications include absence seizures, myoclonic seizures, infantile spasms 				
GABA MECHANISMS OTHER THAN BARBITURATES AND BENZODIAZEPINE				
• Tiagabine	GAT-1 GABA transporter inhibitor	Nearly complete (~90%) absorption • peak concentrations in 0.5–2 h • highly (96%) bound to plasma proteins • extensively metabolized in liver; no active metabolites; <2% excreted unchanged in urine • $t_{1/2}$ 2–9 h	Focal seizures	<i>Toxicity:</i> Nervousness, dizziness, depression, seizures • <i>Interactions:</i> Phenobarbital, phenytoin, carbamazepine, primidone
• Vigabatrin	Irreversible inhibitor of GABA transaminase	Complete absorption • peak concentrations in 1 h • not bound to plasma proteins • not metabolized; eliminated unchanged in urine • $t_{1/2}$ 5–8 h (not relevant because of irreversible action)	Focal seizures, infantile spasms	<i>Toxicity:</i> Drowsiness, dizziness, psychosis, visual field loss • <i>Interactions:</i> Minimal
POTASSIUM CHANNEL OPENER				
• Retigabine (ezogabine)	Opens KCNQ potassium channels	Bioavailability ~60% • peak concentrations in 0.5–2 h • moderately (~80%) bound to plasma proteins • extensively metabolized in liver; 36% excreted unchanged in urine • $t_{1/2}$ 7–11 h	Focal seizures	<i>Toxicity:</i> Dizziness, somnolence, confusion, blurred vision • <i>Interactions:</i> minimal
AMPA RECEPTOR BLOCKER				
• Perampanel	Noncompetitive block of AMPA receptors	Complete absorption • peak concentrations in 0.5–3 h • highly (95%) bound to plasma proteins • extensively metabolized in liver • $t_{1/2}$ 25–129 h	Focal and focal-to-bilateral tonic-clonic seizures, generalized tonic-clonic seizures	<i>Toxicity:</i> Dizziness, somnolence, headache; psychiatric syndromes • <i>Interactions:</i> Substantial, with increased clearance caused by CYP3A

PREPARATIONS AVAILABLE



GENERIC NAME	AVAILABLE AS
Carbamazepine forms	
Carbamazepine	Generic, Tegretol
Carbamazepine injection	Carnexiv
Clobazam	Onfi
Clonazepam	Generic, Klonopin
Clorazepate dipotassium	Generic, Tranxene
Diazepam forms	
Diazepam	Generic, Valium, others
Diazepam rectal gel	Diastat Acudial
Eslicarbazepine acetate	Aptiom, Stedesa
Ethosuximide	Generic, Zarontin
Ethotoin	Peganone
Felbamate	Generic, Felbatol
Fosphenytoin	Generic, Cerebyx
Gabapentin	Generic, Neurontin, Gralise
Gabapentin enacarbil	Horizant
Lacosamide forms	
Lacosamide	Vimpat
Lacosamide injection	Vimpat injection
Lamotrigine forms	
Lamotrigine	Generic, Lamictal
Lamotrigine extended release	Generic, Lamictal XR
Levetiracetam	Generic, Keppra, Spritam
Lorazepam	Generic, Ativan
Mephenytoin	Mesantoin (discontinued in United States)

GENERIC NAME	AVAILABLE AS
Methsuximide	Celontin
Oxcarbazepine	Generic, Trileptal, Oxtellar XR
Pentobarbital sodium	Generic, Nembutal Sodium
Perampanel	Fycompa
Phenobarbital	Generic, Luminal Sodium, others
Phenytoin	Phenytoin, Dilantin, others
Pregabalin	Lyrica
Primidone	Generic, Mysoline
Retigabine (ezogabine)	Potiga, Trobalt
Rufinamide	Banzel
Stiripentol	Diacomit
Tiagabine	Generic, Gabitril
Topiramate forms	
Topiramate	Generic, Topamax
Topiramate extended release	Trokendi XR, Qudexy XR
Trimethadione	Tridione
Valproate/valproic acid forms	
Valproic acid	Generic, Depakene
Divalproex sodium delayed release	Generic, Depakote
Divalproex sodium extended release	Depakote ER
Valproate sodium injection	Generic, Depacon
Vigabatrin	Sabril
Zonisamide	Generic, Zonegran

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CASE STUDY ANSWER

Lamotrigine was gradually added to the regimen to a dosage of 200 mg bid. Since then, the patient has been seizure-free for almost 2 years but now comes to the office for a medication review. Gradual discontinuation of levetiracetam is

planned if the patient continues to do well for another year, although risk of recurrent seizures is always present when medications are withdrawn.