21

Treatment of Seizure Disorders

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MAJOR DRUG CLASSES

- Voltage-gated ion channel modulators
  - Voltage-gated sodium channel blockers
  - T-type voltage-gated calcium channel blockers
  - Gabapentinoids ($\alpha 2\delta$ ligands)
  - K_v7 voltage-gated potassium channel openers
- GABA enhancers
  - $GABA_A$ receptor modulators
  - GABA transporter inhibitors
  - GABA transaminase inhibitors
- AMPA receptor antagonists
- SV2A ligands
- Mixed-acting compounds

ABBREVIATIONS

ACTH	Adrenocorticotropin
ARS	Acute repetitive seizures
EEG	Electroencephalogram
GABA	γ-Aminobutyric acid
GAT-1	GABA transporter

THERAPEUTIC OVERVIEW

Epilepsy is a chronic episodic disorder of brain function characterized by the unpredictable occurrence of **seizures**. Epileptic seizures are transitory alterations in behavior, sensation, or consciousness caused by abnormal, excessive, or synchronous neuronal activity in the brain that can be detected with the electroencephalogram (EEG). Approximately 0.8% of the population suffers from epilepsy. Epilepsy can occur at any age, but onset is more frequent in children younger than about age 10 and in adults over age 50. Recurrent seizures, if frequent, interfere with a patient's ability to carry out day-to-day activities. However, daily oral use of antiseizure medications allows approximately 70% of patients to remain seizure free.

Seizures are classified into two major types: **focal onset** (formerly **partial onset**) **seizures** and **generalized onset seizures**. Focal seizures arise in a localized region in one cerebral hemisphere and are accompanied by EEG abnormalities that are restricted to the epileptic focus. In contrast, generalized seizures are associated with EEG features indicating simultaneous hemispheric activation.

Focal seizures are further classified as **aware**, **impaired awareness**, or **focal to bilateral tonic-clonic**. The seizures are termed **aware** (formerly **simple**) if consciousness is preserved and **impaired awareness** (formerly **complex**) if consciousness is impaired or lost. In impaired awareness seizures, motor activity often appears as a complicated and seemingly purposeful movement referred to as an **automatism**. If a focal seizure spreads to encompass both hemispheres, the focal seizure can transition to a **bilateral tonic-clonic seizure** (formerly **secondarily generalized**) resulting in tonic-clonic manifestations, which involve rigid extension of the trunk and limbs (tonic phase) followed by rhythmic contractions of the arms and legs (clonic phase).

In generalized seizures, both hemispheres are involved at the onset. There are various types of generalized seizures, including **generalized tonic-clonic seizures**, which are similar to focal to bilateral tonic-clonic seizures except that they do not begin focally; **absence seizures**, characterized by impaired consciousness and minimal motor manifestations; and other types of seizures, including **myoclonic**, **clonic**, **tonic**, or **atonic (astatic)**, depending on the specific clinical manifestations. The classification of seizures and their characteristics are presented in the Therapeutic Overview Box.

Status epilepticus, clinically defined as abnormally prolonged or repetitive seizures, presents in several forms, including (1) **tonic-clonic (convulsive) status epilepticus**, (2) **nonconvulsive status epilepticus**, (3) **focal status epilepticus**, and (4) **absence status epilepticus**. Convulsive status epilepticus is a life-threatening medical 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 the majority of seizures terminates in 2 to 3 minutes, it is now generally accepted that treatment should begin when the seizure duration reaches 5 minutes for generalized tonic-clonic seizures and 10 minutes for focal seizures with or without impairment of awareness.

Convulsive status epilepticus can lead to systemic hypoxia, acidemia, hyperpyrexia, cardiovascular collapse, and renal shutdown. Nonconvulsive status epilepticus, a persistent change in behavior or mental processes with continuous epileptiform EEG but without major motor signs, also requires urgent treatment.

All people are capable of experiencing seizures. Brain insults such as fever, hypoglycemia, hypocalcemia, hyponatremia, and extreme lactic acidosis, or exposure to certain drugs or toxins, can trigger a seizure, but if the condition is corrected, seizures do not recur, and the condition is not considered epilepsy. Epilepsy is a disease (also variously described as a disorder) characterized by an enduring predisposition to epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition. The diverse causes of seizures and epilepsy are listed in Box 21.1.

The goal of antiseizure drug therapy is to prevent seizures while minimizing adverse effects. If seizures continue after drug therapy is initiated, the dose may be increased until unacceptable adverse effects

Abstract

Antiseizure drugs are used chronically to treat epilepsy and on an as needed basis to terminate status epilepticus and acute repetitive seizures.

Key Words

acute repetitive seizures
antiepileptic drug
antiseizure drug
epilepsy
seizure
status epilepticus

BOX 21.1 Causes of Seizures and Epilepsy

Causes of Seizures

In newborns:
- Neonatal hypoxia; intracranial hemorrhage; maternal drug use

In infants and children:
- Fever; infections (meningitis or encephalitis)

In adults and the elderly:
- Traumatic brain injury; stroke; metabolic disturbances (hypoglycemia, hypocalcemia, hypomagnesemia, hyponatremia, lactic acidosis, uremia); drugs, alcohol, and toxins including withdrawal from barbiturates and other central nervous system depressants

Causes of Epilepsy
- Traumatic brain injury
- Status epilepticus
- Genetic syndromes with seizures in conjunction with intellectual disability, brain structural or metabolic abnormalities, or congenital malformations
- Genetic syndromes with isolated seizures (idiopathic)
- Congenital malformations
- Birth and perinatal injuries
- Stroke
- Brain tumor
- Infections such as neurocysticercosis
- Alzheimer's disease and other degenerative neurological conditions

BOX 21.2 Examples of Monogenic Epilepsies

Disorder	Mutation(s)
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	Nicotinic acetylcholine receptor subunit genes *CHRNA4, CHRNB2,* or *CHRNA2*
Autosomal dominant juvenile myoclonic epilepsy	$GABA_A$ receptor subunit gene *GABRA1*
Benign familial neonatal seizures	Voltage-gated potassium channel genes *KCNQ2* or *KCNQ3*
Familial febrile seizures and Dravet syndrome	Voltage-gated sodium channel genes *SCN1A* and rarely *SCN8A*

$GABA_A$, γ-Aminobutyric acid type A.

prevent further dosage increases, at which point another drug can be substituted or a second drug added. 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 so that a trial of discontinuation may be warranted. Resolution of seizures is common for certain syndromes, such as childhood absence epilepsy and benign epilepsy of childhood with centrotemporal spikes (BECTS), but infrequent for others, such as juvenile myoclonic epilepsy. Resolution is unlikely in adults with an abnormal neurologic examination or an abnormal EEG so that drug treatment will likely be required for the life of the patient.

Pathophysiology

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**. Mesial temporal lobe epilepsy associated with hippocampal sclerosis is a symptomatic epilepsy that is a common cause of medication refractory seizures.

In 40% of all epilepsies, genetic factors are believed to be the root cause. In some cases, the epilepsy is a component of a genetic syndrome, such as tuberous sclerosis, that has other associated structural or metabolic brain abnormalities. In other cases, the genetic epilepsy has seizures as its only clinical manifestation, and there is no apparent structural or metabolic disorder of the brain. Such **idiopathic** epilepsies include benign epilepsy of childhood with centrotemporal spikes (BECTS), benign familial neonatal convulsions, childhood absence epilepsy, and juvenile myoclonic epilepsy. In most genetic epilepsies, the inheritance is complex (polygenic); rarely, a single gene defect can be identified. Some monogenic epilepsies and associated gene mutations are listed in Box 21.2. In some cases, these genetic epilepsies are benign, and in other cases, they are severe and termed **epileptic encephalopathies**.

It is noteworthy that many of the genes in the monogenic epilepsies encode subunits of ion channels, which are the fundamental mediators of neuronal excitability. These types of epilepsies can be considered **channelopathies**. However, some monogenic epilepsies are caused by mutations in non–ion channel genes, including neural adhesion molecules, such as PCDH19 (protocadherin 19), and proteins involved in synapse development, such as LGI1 (leucine-rich glioma inactivated 1).

The cellular and molecular events leading to the development of focal epilepsies in cases of cortical injury are poorly understood. There is better understanding of the physiology of the seizures. Focal seizures are thought to occur as a consequence of the loss of **surround inhibition**, a process that normally prevents the activation of neurons adjacent to a focus (Fig. 21.1). This loss of surround inhibition may result from impaired γ-aminobutyric acid (GABA) transmission, loss of GABA interneurons, changes in GABA type A ($GABA_A$) receptors, or alterations in intracellular chloride or bicarbonate ion concentrations. Excessive glutamate-mediated excitation may also lead to focal seizures. Impaired GABA-mediated inhibition or excessive glutamate-mediated excitation predisposes to abnormal hypersynchronous activity manifest as epileptiform discharges, which, if they encompass a large enough area of cortex, are associated with the motor, sensory, psychic, or autonomic symptoms of a focal seizure.

Generalized seizures involve both hemispheres and thalamic synchronizing mechanisms. In tonic-clonic convulsions, the **tonic phase** of muscle contraction is thought to reflect prolonged neuronal depolarization as a consequence of the loss of GABA-mediated inhibition and the dominance of excitatory glutamate neurotransmission. As the seizure evolves, neurons repolarize and afterhyperpolarizations are apparent, which reflect the reappearance of GABA-mediated inhibition and diminished glutamate excitation, producing the **clonic phase**. Drugs that increase surround inhibition and prevent the spread of synchronous activity are effective in the treatment of focal seizures.

Our understanding of the onset of generalized tonic-clonic seizures is limited. However, there are some clues concerning the cellular mechanisms underlying absence seizures, which are characterized by the sudden appearance of spike-wave discharges synchronized throughout the brain. The EEGs recorded during an absence seizure compared with a generalized tonic-clonic seizure are shown in Fig. 21.2. Studies support a major role of **thalamocortical circuits** in the pathogenesis of absence seizures with abnormal oscillations generated by excitatory glutamatergic cortical pyramidal and thalamic relay neurons and inhibitory GABAergic thalamic reticular neurons (Fig. 21.3). Thalamic relay neurons project to the cortex, and cortical pyramidal neurons project back to the thalamus

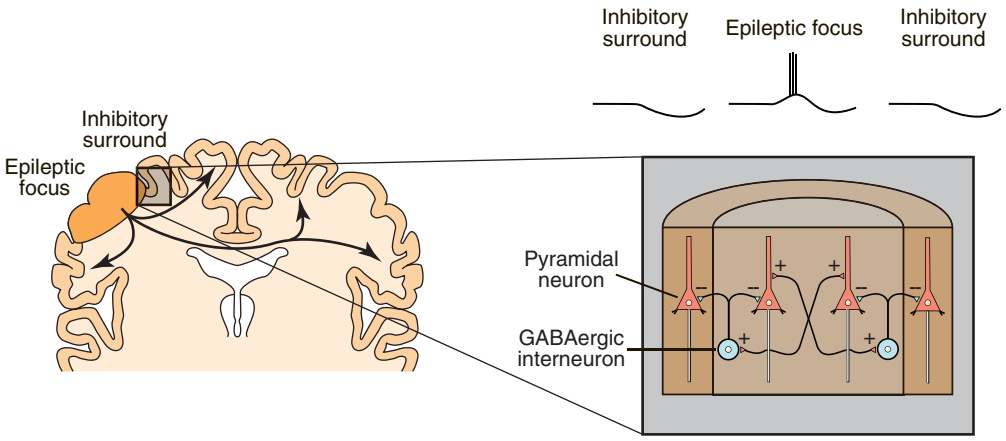

FIG. 21.1 Seizure Generation and Spread in a Focal Seizure. Epileptiform activity begins in a localized area (epileptic focus) and spreads to adjacent and contralateral cortical regions. Epileptic activity reflects the synchronized activity of excitatory (+) glutamate cortical pyramidal neurons. Spread is restrained by inhibitory (–) γ-aminobutyric acid (GABA) interneurons. Seizure spread is believed to reflect the loss of surround inhibition. Antiseizure drugs that enhance GABA inhibition restrain seizure spread. Spread can also be prevented by sodium-channel blocking drugs (Fig. 21.4) and AMPA receptor antagonists.

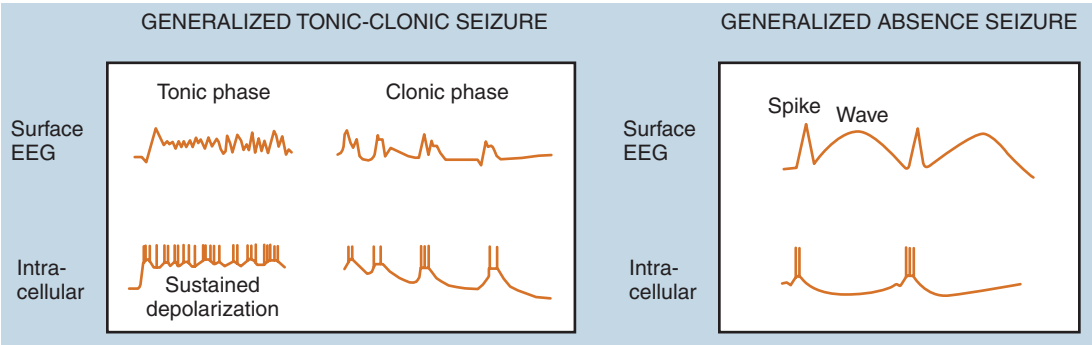

FIG. 21.2 Comparison of the Electrical Behavior of the Surface Electroencephalogram (EEG) and Single-Neuron Recording During Generalized Tonic-Clonic and Absence Seizures on a Time Scale of Hundreds of Milliseconds. Surface EEG signals are field responses detected with flat metal electrodes on the scalp. Intracellular recordings represent the membrane potential changes of individual cortical neurons. A generalized tonic-clonic seizure begins with a tonic phase consisting of rhythmic high-frequency discharges recorded in the surface EEG; cortical neurons undergo sustained depolarization, which generates high-frequency action potential firing. Subsequently, the seizure converts to a clonic phase, characterized by groups of spikes on the EEG; cortical neurons exhibit periodic depolarizations with clusters of action potentials on the crests. In an absence seizure, 3-Hz spike-and-wave discharges are recorded in the surface EEG. During the spike phase, cortical neurons generate short-duration depolarizations, which trigger a brief burst of action potentials. During the wave phase, cortical neurons are hyperpolarized. Recognizing the differences between the single neuron electrical events in tonic-clonic and absence seizures helps in understanding why antiseizure drugs that inhibit sustained repetitive firing of action potentials (see Fig. 21.4) are effective in the treatment of tonic-clonic, but not absence, seizures.

in a recurrent excitatory loop. Thalamic relay neurons exhibit spike-wave discharges that generate normal cortical rhythms and participate in the generation of sleep spindles. The normal bursting pattern of these neurons results from the activation of low voltage-gated T-type calcium channels during depolarization, followed by GABA release from thalamic reticular neurons and hyperpolarization. The circuit transitions to abnormal rhythmicity at the onset of an absence seizure. T-type calcium channels in relay neurons and thalamic reticular neurons play a critical role in the pathological behavior of absence seizures, as blockade of these channels, most notably by ethosuximide, is effective for the treatment of such seizures.

MECHANISMS OF ACTION

Selection of the correct antiseizure drug depends on accurate diagnosis of the patient's seizure type and epilepsy syndrome. Focal onset seizures must be distinguished from generalized onset seizures because some drugs effective for focal seizures do not prevent and may exacerbate some generalized seizure types. Certain epilepsy syndromes, such as infantile spasms, require treatment with special agents.

Epileptic activity may occur as a consequence of either decreased inhibition or increased excitation of neurons. Agents used for the treatment of epilepsy depress aberrant neuronal firing primarily by

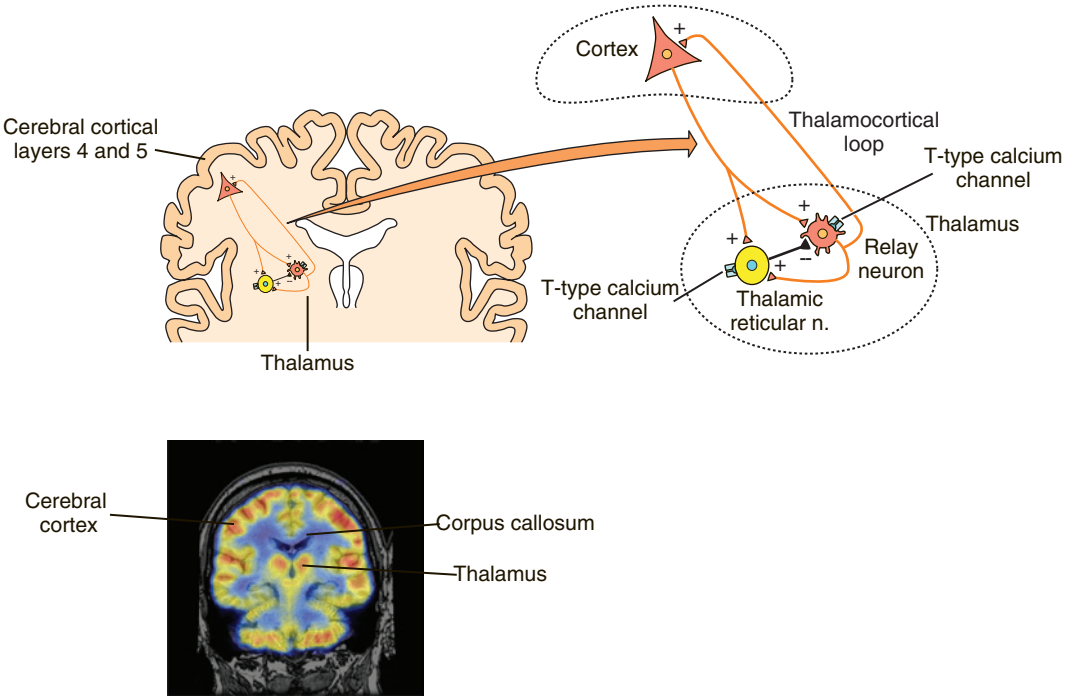

FIG. 21.3 Thalamocortical Circuitry Generating Absence Seizures According to the "Corticoreticular" Theory. The thalamus and cortex are both essential for the spike-wave discharges of absence seizures; bilateral synchrony depends on the corpus callosum connecting the two hemispheres. Spike-wave bursts are likely initiated in the cortex (the perioral region of the somatosensory cortex has been implicated) by the discharge of a network of massively interconnected excitatory neurons in the presence of insufficient γ-aminobutyric acid (GABA) inhibition. This initial event is followed by entrainment of the thalamus leading to synchronized oscillations in which the thalamus and cortex drive each other. Excitatory (+) glutamate thalamic relay neurons project to the cortex, and excitatory glutamate cortical neurons project back to the thalamus, forming a recurrent loop. The thalamic reticular nucleus, a shell-like structure covering the thalamus, is composed of GABA interneurons that provide massive inhibitory (–) input to thalamic relay neurons and may contribute to the pathological oscillations. T-type voltage-gated calcium channels are necessary for burst firing in thalamic relay neurons and thalamic reticular neurons. Shown below the diagram is a coronal fluorodeoxyglucose positron emission tomography image of a human brain superimposed on T1 magnetic resonance image, illustrating the location of the relevant structures. (Courtesy of Johnson KA, Becker JA. *Whole Brain Atlas*. http://www.med.harvard.edu/aanlib/cprt.html)

THERAPEUTIC OVERVIEW

Focal Onset (Partial Onset) Seizures

Focal aware seizure (formerly simple partial seizure)

Sensory, motor, autonomic, or psychic symptoms, without altered awareness

Focal impaired awareness seizure (formerly complex partial seizure)

Dreamy disaffective state with or without automatisms, with altered awareness

Focal to bilateral tonic-clonic seizure (formerly secondarily generalized tonic-clonic seizure or grand mal seizure)

Evolution of focal aware or focal impaired awareness seizure to convulsion with rigid extension of trunk and limbs (tonic phase) and rhythmic contractions of arms and legs (clonic phase)

Generalized Onset Seizures

Generalized tonic-clonic seizure (formerly primary generalized tonic-clonic seizure or grand mal seizure)

Similar to focal to bilateral tonic-clonic seizure except that onset is in both hemispheres; occurs in patients with genetic (idiopathic) generalized epilepsies

Generalized absence seizures

Abrupt loss of consciousness with staring and cessation of ongoing activity with or without eye blinks; occurs in patients with genetic (idiopathic) generalized epilepsies, including childhood absence epilepsy

Other types of generalized onset seizures

Myoclonic seizure: rapid shock-like (jerking) muscle contraction

Atonic seizure (drop seizure or astatic seizure): loss of muscle tone

Epileptic spasm: sudden flexion, extension or flexion-extension of neck, trunk, arms, and legs

BOX 21.3 Mechanisms of Action of Antiseizure Drugs

Voltage-Gated Ion-Channel Modulators

Voltage-Gated Sodium-Channel Blockers

Phenytoin
Carbamazepine
Oxcarbazepine
Eslicarbazepine acetate (prodrug)
Lamotrigine
Lacosamide

T-Type Calcium-Channel Blocker

Ethosuximide

α2δ Ligands

Gabapentin
Pregabalin

Voltage-Gated Potassium-Channel Opener

Retigabine (ezogabine)

GABA Enhancers

$GABA_A$ Receptor Positive Modulators

Phenobarbital
Primidone
Benzodiazepines including diazepam, lorazepam, and clonazepam

GABA Transporter (GAT-1) Inhibitor

Tiagabine

GABA Transaminase Inhibitor

Vigabatrin

Glutamate AMPA Receptor Antagonist

Perampanel

SV2A Ligand

Levetiracetam
Brivaracetam

Mixed/Unknown

Valproate
Topiramate
Zonisamide
Felbamate
Rufinamide
Adrenocorticotropin

GABA, γ-Aminobutyric acid.

altering ion channel activity, enhancing GABA-mediated inhibitory neurotransmission, or dampening glutamate-mediated excitatory neurotransmission. Although some drugs have a single mechanism of action, several of these agents have more than one mechanism. Antiseizure drugs classified according to mechanisms of action are listed in Box 21.3.

Voltage-Gated Ion-Channel Modulators

The **voltage-gated sodium-channel blockers** are widely used antiseizure drugs with demonstrated effectiveness for focal seizures. These drugs include **phenytoin**, **carbamazepine**, **oxcarbazepine**, **eslicarbazepine acetate** (a prodrug), **lamotrigine**, and **lacosamide**. These agents reduce the repetitive firing of neurons by producing a use-dependent and voltage-dependent blockade of sodium channels (Fig. 21.4). By prolonging the inactivated state of the sodium channel and thus the relative refractory period, these drugs do not alter the first action potential in a train but rather reduce the likelihood of repetitive action potentials. Neurons retain their ability to generate action potentials at the lower frequencies common during normal brain function. The discrimination between normal firing from usual membrane potential levels and high-frequency firing under the abnormally depolarized conditions of the epileptic discharge allows these drugs to inhibit seizures without affecting normal brain function at therapeutic concentrations.

T-type calcium channels provide for rhythmic firing of thalamic neurons and are thought to be involved in generating spike-wave discharges in absence seizures. **Ethosuximide** inhibits T-type calcium channels, thus suppressing absence seizures.

The **α2δ auxiliary subunit of voltage-gated calcium channels** modulates the trafficking and biophysical properties of these membrane channels but can also be non–channel associated and interact with proteins in the extracellular matrix and alter synaptogenesis. Although the specific role of α2δ in seizure disorders is unclear, this protein is the primary target of the **gabapentinoid** drugs **gabapentin** and **pregabalin**. These compounds have a close structural resemblance to GABA but do not affect GABA receptors or any other mechanism related to GABA-mediated neurotransmission. Rather, the gabapentinoids appear to exert their antiseizure and analgesic activity by interacting with α2δ, although how this action protects against seizures is unknown.

Ezogabine opens K_v7 voltage-gated potassium channels ($K_v7.2$–$K_v7.5$) but does not affect the cardiac channel ($K_v7.1$). Potassium channels are inhibitory and cause neuronal hyperpolarization when activated. Both $K_v7.2$ and $K_v7.3$ contribute to the M-current, a potassium-channel current that increases as the membrane potential in neurons approaches action potential threshold and serves as a "brake" on epileptic burst firing.

GABA Enhancers

GABA, the major inhibitory neurotransmitter in the brain, causes fast inhibition through its action on $GABA_A$ receptors (Chapter 17) to reduce circuit hyperexcitability. Barbiturates including **phenobarbital** exert antiseizure activity in part by acting as positive allosteric modulators (PAMs) of $GABA_A$ receptors to prolong the duration of channel openings upon receptor activation by GABA. The **benzodiazepines**, such as **diazepam**, **lorazepam**, and **clonazepam**, are also PAMs of $GABA_A$ receptors, acting at a site distinct from that of the barbiturates to increase the frequency of channel openings upon receptor activation by GABA.

Several drugs increase GABAergic inhibition by either decreasing the reuptake of GABA or by inhibiting its catabolism. **Tiagabine** blocks GABA reuptake into presynaptic neurons and glia by inhibiting the GABA transporter (GAT-1), while **vigabatrin** is an irreversible inhibitor of GABA transaminase, the enzyme that inactivates GABA.

AMPA Receptor Antagonist

AMPA receptors mediate glutamate excitation in the brain and are critical for both the local generation of seizure activity in epileptic foci and for the spread of excitation to distant sites. Activation of these tetrameric ion channels by glutamate leads to sodium (and in some receptors, calcium) influx, contributing to the excitatory postsynaptic potential (EPSP). **Perampanel** is a potent noncompetitive antagonist of AMPA receptors that binds to an allosteric site on the extracellular side of the channel, acting as a wedge to prevent channel opening.

SV2A Ligands

Levetiracetam and **brivaracetam** exert their antiseizure activity by binding to SV2A, a ubiquitous synaptic vesicle membrane glycoprotein

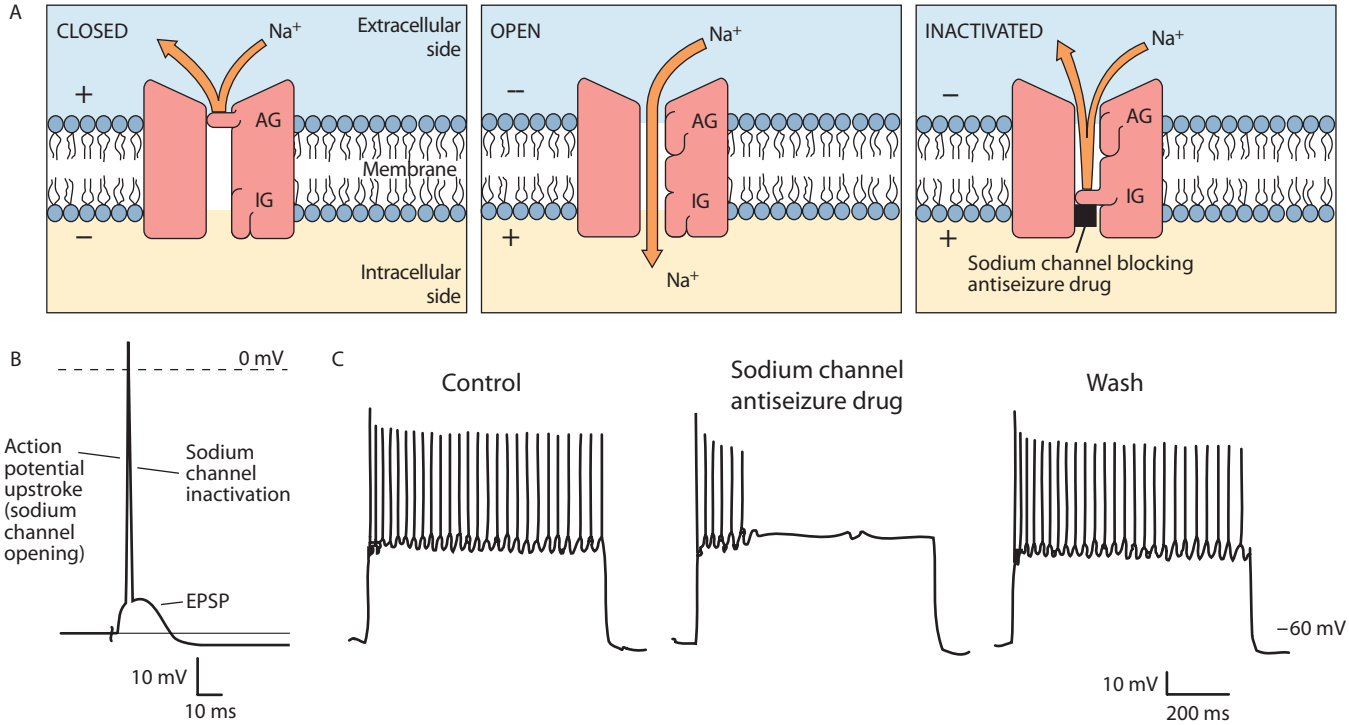

FIG. 21.4 Action of Sodium-Channel Blocking Antiseizure Drugs on Voltage-Gated Sodium Channels. (A) At hyperpolarized membrane potentials, the sodium-channel activation gate (AG) is closed, blocking sodium influx. Depolarization of the neuron causes AG to open, allowing sodium flux. Within less than 1 ms, the inactivation gate (IG) closes, terminating sodium flux. When the membrane potential is repolarized, the AG closes (not shown), and after 1–2 ms, the IG opens, and the channel reverts to its closed (resting) state, where it can be opened again by depolarization. Sodium-channel blocking drugs selectively bind to and stabilize the inactivated state of the channel. (B) Membrane potential changes in a neuron activated by an excitatory postsynaptic potential (EPSP) generated by stimulation of excitatory (glutamate) afferents. When the depolarization of the EPSP reaches threshold, an action potential is generated. The upstroke of the action potential results from sodium influx through voltage-gated channels opened by the EPSP depolarization. The downstroke is largely due to sodium-channel inactivation. (C) Depolarization of a neuron in vitro causes a high-frequency train of action potentials. In the presence of a sodium-channel blocking drug, the train terminates because sodium channels are progressively inhibited in a use-dependent fashion as the sodium channels cycle into the inactivated state where drug binding occurs. Wash out of the drug restores the ability of the neuron to discharge long trains.

involved in exocytosis. The precise role of SV2A in the exocytotic process is not well understood, but evidence suggests that it interacts with synaptotagmin, a trigger for calcium-mediated exocytosis. It is possible that the binding of levetiracetam and brivaracetam to SV2A reduces the release of glutamate during trains of high-frequency activity as occurs during epileptic activity.

Mixed-Acting Compounds

The mechanisms of action of many antiseizure drugs involve mixed effects or are poorly understood. These compounds include **valproate**, **felbamate**, **topiramate**, **zonisamide**, **rufinamide**, and **adrenocorticotropin** (ACTH).

The antiseizure effects of **valproate** have been attributed to increases in the turnover of GABA in a regionally selective manner, which might be associated with enhanced synaptic or extrasynaptic inhibition, but this mechanism is not well established and there is no consensus on the drug's antiseizure mechanism. **Felbamate** acts as a PAM at $GABA_A$ receptors and blocks glutamate NMDA receptors, although the relationship between this latter action and the antiseizure activity of felbamate is questionable. **Topiramate** may modulate voltage-gated sodium channels and glutamate receptors and may potentiate GABA activity, but again, the relationship between these actions and antiseizure activity is not well understood. **Zonisamide** blocks voltage-gated sodium and T-type calcium channels, while **rufinamide** also modulates voltage-gated sodium-channel activity but may also have other actions.

ACTH, which is used for the treatment of infantile spasms, stimulates glucocorticoid (cortisol) synthesis and release from the adrenal cortex. The cortisol could influence infantile spasms through an antiinflammatory action or in some other fashion. Synthetic glucocorticoids such as prednisone and prednisolone also have therapeutic activity in the treatment of infantile spasms.

RELATIONSHIP OF MECHANISMS OF ACTION TO CLINICAL RESPONSE

Drugs Used in the Treatment of Focal Seizures

The **sodium-channel blockers** (except lamotrigine), **gabapentinoids**, and **tiagabine** are used exclusively for the treatment of focal seizures and focal to bilateral tonic-clonic seizures (Box 21.4). Some of these drugs have also shown efficacy in generalized onset tonic-clonic seizures, including **oxcarbazepine** and **phenytoin**. These drugs may exacerbate certain types of generalized onset seizures, including absence and myoclonic seizures, and seizures in Dravet syndrome.

BOX 21.4 Drugs Effective for Specific Seizure Types

Focal Seizures Exclusively
Carbamazepine
Oxcarbazepine
Eslicarbazepine acetate
Lacosamide
Phenytoin
Gabapentin
Pregabalin
Tiagabine
Vigabatrin (also infantile spasms)
Ezogabine

Focal Seizures and Certain Generalized Seizure Types
Lamotrigine
Levetiracetam
Brivaracetam (evidence only available in focal seizures)
Perampanel
Phenobarbital
Primidone
Felbamate

Broad Spectrum (Generalized Seizures and Focal Seizures)
Valproate (divalproex sodium)
Topiramate
Zonisamide

Absence Seizures
Ethosuximide
Divalproex sodium
Lamotrigine

Myoclonic Seizures
Divalproex sodium
Levetiracetam
Zonisamide
Topiramate
Lamotrigine

Atonic Seizures
Valproate (divalproex sodium)
Clobazam
Rufinamide
Topiramate
Felbamate
Lamotrigine

Dravet Syndrome
Clobazam
Valproate (divalproex sodium)
Topiramate
Stiripentol

West Syndrome
Adrenocorticotropic hormone
Vigabatrin

Status Epilepticus
Intravenous lorazepam or diazepam, intramuscular midazolam
Intravenous fosphenytoin or phenytoin
Intravenous phenobarbital, valproic acid, lacosamide, levetiracetam
For refractory status epilepticus, anesthesia with intravenous pentobarbital, propofol, midazolam, thiopental, ketamine

Acute Repetitive Seizures (Seizure Clusters)
Diazepam rectal gel
Rectal paraldehyde
Buccal (oromucosal) midazolam
Intranasal midazolam, diazepam, lorazepam

Drugs Used in the Treatment of Focal Seizures With Efficacy in Certain Generalized Seizure Types

Some antiseizure drugs are effective for the treatment of both focal seizures and certain generalized seizures. For example, **lamotrigine** is first choice for focal seizures and is also useful in treating absence seizures, although it is not as effective as ethosuximide or valproate. **Levetiracetam** is also first choice for focal seizures and is probably useful for myoclonic seizures. **Brivaracetam**, a drug related to levetiracetam, likely has the same spectrum of activity as levetiracetam but has not been studied in the treatment of other seizure types. **Perampanel** is useful in the treatment of focal and focal to bilateral tonic-clonic seizures and in the treatment of generalized onset tonic-clonic seizures. **Phenobarbital** is effective in the treatment of focal seizures, focal to bilateral tonic-clonic seizures, generalized onset tonic-clinic seizures, and other seizure types, but it is not effective in absence seizures and is not commonly used because it is sedating and has many drug-drug interactions. **Primidone** is not commonly used, as it is metabolized to phenobarbital and has many of the same issues. **Felbamate** is effective for the treatment of focal seizures, focal to bilateral tonic-clonic seizures, generalized onset tonic-clinic seizures, and seizures associated with Lennox-Gastaut syndrome in children but is rarely used because of the risk of aplastic anemia and hepatic failure.

Valproate, **topiramate**, and **zonisamide** have the broadest spectrum among antiseizure drugs and are useful in the treatment of focal seizures and diverse generalized seizure types. Valproate is especially effective and considered the first choice for patients who exhibit multiple generalized seizure types. It is widely used for myoclonic, atonic, and generalized tonic-clonic seizures. Valproate is also effective in focal seizures, but it may not be as effective as carbamazepine or phenytoin.

Drugs Used in the Treatment of Absence Seizures

Ethosuximide and **valproate** are the drugs of choice for absence seizures. Although less effective than these two drugs, **lamotrigine** also has activity in the treatment of absence seizures and may be prescribed because of its greater tolerability or fewer fetal risks than valproate.

Drugs Used in the Treatment of Lennox-Gastaut Syndrome

Lennox-Gastaut syndrome is a severe type of childhood epilepsy with multiple seizure types, including atonic (drop) seizures. Seizures in Lennox-Gastaut syndrome are difficult to treat and usually require drug combinations. **Valproate**, in combination with **lamotrigine** and a benzodiazepine such as **clonazepam**, is the most widely used combination. **Topiramate**, **clobazam**, **rufinamide**, **felbamate**, and **lamotrigine** are

also used. Sodium-channel blocking antiseizure drugs other than lamotrigine are not used, as they may worsen atonic seizures.

Drugs Used in the Treatment of Status Epilepticus and Acute Seizures

The initial treatment of choice for status epilepticus is a benzodiazepine administered intravenously; **lorazepam** or **diazepam** are most commonly used. Recent evidence indicates that intramuscular **midazolam** delivered with an autoinjector system is equally effective and may be easier and more rapid to administer in an out-of-hospital setting. If seizures continue, or if there is a concern that seizures may recur, a second therapy is administered. Intravenous **fosphenytoin** or **phenytoin** is most common in the United States, although there is no evidence that these choices are superior to intravenous **valproate** or **levetiracetam**. **Phenobarbital** is also an acceptable second therapy, but it causes persistent sedation and may have serious cardiorespiratory adverse effects, including 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 therapy agent is often tried.

Refractory status epilepticus occurs when seizures continue or recur at least 30 minutes following treatment with first and second therapy agents. Refractory status epilepticus is treated with anesthetic doses of pentobarbital, propofol, midazolam, thiopental, or ketamine, usually in combination. If status epilepticus continues or recurs 24 hours or more after the onset of anesthesia, the condition is considered super-refractory. Often superrefractory status epilepticus is recognized when anesthetics are withdrawn and seizures recur. There are no established therapies for superrefractory status epilepticus other than to reinstitute general anesthesia.

Acute repetitive seizures (ARS), or seizure clusters, are groups of seizures that occur more frequently than usual, typically three or more seizures within 24 hours. There is complete recovery between seizures so that patients do not meet the definition of status epilepticus. However, ARS can progress to status epilepticus and may be associated with other medical complications, including injury. Optimal management of ARS begins at home, before the need for emergency room care arises. In the United States, **diazepam rectal gel** is the only approved treatment for ARS. Although it has been demonstrated to be effective, administering the rectal gel can be a cumbersome, time-consuming, and embarrassing experience for the patient and caregivers. Rectal gel is most commonly used in children and rarely in adults because of stigma and difficulty positioning the patient. **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 United States, but some clinicians use intranasal midazolam or oral benzodiazepines on an off-label basis.

PHARMACOKINETICS

Antiseizure drugs used in the chronic therapy of epilepsy must be orally bioavailable. Even fosphenytoin and benzodiazepines, including midazolam, which are primarily administered parenterally, have excellent oral bioavailability and can be administered orally if necessary.

Seizures are a disorder of brain circuits; consequently, antiseizure agents must cross the blood-brain barrier to be active. Many antiseizure drugs are metabolized by the hepatic cytochrome P450 (CYP) system, and several have active metabolites, including primidone and diazepam. Some of these agents are prodrugs that require activation, including oxcarbazepine, which is activated to S-licarbazepine, and fosphenytoin, which is converted to phenytoin. Some antiseizure drugs, including gabapentin, pregabalin, vigabatrin, and levetiracetam, are not metabolized and are excreted unchanged in the urine. These drugs have a low propensity for drug-drug interactions.

Some antiseizure drugs, including phenytoin, tiagabine, valproate, diazepam, and perampanel, are highly (>90%) bound to plasma proteins and can be displaced by other protein-bound drugs, resulting in a transitory rise in the active free fraction that may be associated with adverse effects until metabolism or renal excretion reduces the free levels. The usual clinical laboratory determination of blood concentrations represents the total drug exposure (bound plus free) in plasma and may fail to reveal the cause of such toxicity. In states of hypoalbuminemia, free levels may be increased, leading either to toxicity, more rapid hepatic metabolism, or both. The half-life ($t_{1/2}$) of antiseizure drugs varies with the age of the patient and exposure to other drugs. The pharmacokinetic parameters of antiseizure agents are summarized in Table 21.1. The pharmacokinetics of the benzodiazepines are presented in Chapter 17.

Carbamazepine is nearly completely metabolized by CYP3A4 (although CYP2C8 and CYP3A5 may contribute) in the liver to produce carbamazepine-10,11-epoxide, which is relatively stable, accumulates in the blood, and has antiseizure activity. Carbamazepine also induces its own metabolism, with the rate of metabolism increasing during the first 4 to 6 weeks. After this time, larger doses become necessary to maintain constant plasma concentrations.

Oxcarbazepine is a prodrug and completely absorbed and extensively metabolized by hepatic cytosolic enzymes to its active 10-hydroxy metabolite licarbazepine, which is responsible for its clinical effects; both enantiomeric forms of licarbazepine [*R*(+) and *S*(−)] have antiseizure activity. Oxcarbazepine is administered twice daily. **Eslicarbazepine acetate** is a prodrug for *S*(−)-licarbazepine and is available as a marketed antiseizure drug recommended for once-daily administration.

Ethosuximide has a long half-life, which allows for once-a-day dosing. However, it has significant gastrointestinal side effects that are frequently intolerable with once-a-day dosing and may be mitigated with divided dosing, which reduces the peak plasma concentration and thereby reduces the incidence of side effects.

Lamotrigine is well absorbed and has negligible first-pass metabolism so that its bioavailability is >95%. However, it has a variable half-life, dependent on concomitant medications. Lamotrigine with valproate is considered to be a particularly effective combination, but valproate inhibits the metabolism of lamotrigine, decreasing its clearance by 60% so that plasma lamotrigine levels are increased. The interaction is a consequence of the effect of valproate on the UGT1A4 glucuronidation of lamotrigine. The addition of lamotrigine to a patient already taking valproate must be done especially slowly to avoid a skin rash (potentially Stevens-Johnson syndrome or toxic epidermal necrolysis) caused by lamotrigine levels rising too rapidly. In contrast, the addition of valproate to a patient already on a stable lamotrigine regimen does not increase the risk, as the patient is desensitized to the immunotoxic effect that causes Stevens-Johnson syndrome.

Phenytoin metabolism is characterized by saturation (zero order) kinetics (Chapter 3). At low doses, there is a linear relationship between the dose and the plasma concentration of the drug. At higher doses, however, there is a much greater rise in plasma concentration for a given increase in dose (nonlinear) because when plasma concentrations rise above a certain value, the liver enzymes that catalyze phenytoin metabolism become saturated. The dose at which this transition occurs varies from patient to patient but is usually between 400 and 600 mg/day (Fig. 21.5). Because of the unusual pharmacokinetic properties of phenytoin, dosing must be individualized.

TABLE 21.1 Pharmacokinetic Parameters

Drug	$t_{1/2}$ (Hours)[a]	Bound to Plasma Proteins (%)	Disposition	Therapeutic Concentration Range (μg/mL)
Brivaracetam	7–8	17	M, R	Not available
Carbamazepine	3–55	75	M	4–12
Clobazam	10–30; 36–46 (N-desmethylclobazam)	70–90	M	0.03–0.30; 0.3–3.0 (N-desmethylclobazam)
Eslicarbazepine acetate	<2 h conversion to eslicarbazepine	30	M	3–35 (based on licarbazepine value for oxcarbazepine)
Ethosuximide	30–60	<10	M, R	40–100
Felbamate	16–22	25	M, R	30–60
Gabapentin	5–9	<3	R	2–20
Lacosamide	13	<15	M, R	10–20
Lamotrigine	7–70	55	M, R	3–15
Leviracetam	6–8	0	M, R	12–46
Oxcarbazepine	7–15 (licarbazepine)	60 (parent), 40 (licarbazepine)	M	3–35 (licarbazepine)
Perampanel	51–129; with inducing comedications, 25	95	M	0.1–1
Phenobarbital	53–118	55	M, R	10–40
Phenytoin	12–36	90	M, R	10–20
Pregabalin	5–7	0	R	0.9–14.2
Primidone	6–8	10	M, R	5–10 (primidone), 10–40 (phenobarbital)
Rufinamide	6–10	35	M	30–40
Tiagabine	7–9	96	M	20–200
Topiramate	10–30	15	R	5–20
Valproate	8–17	90	M	50–100
Vigabatrin	5–8	0	R	0.8–36
Zonisamide	60–65	40	M, R	10–40

[a]Age dependent.
M, Metabolized by liver; *R*, renal elimination (>3%); $t_{½}$, half-life.

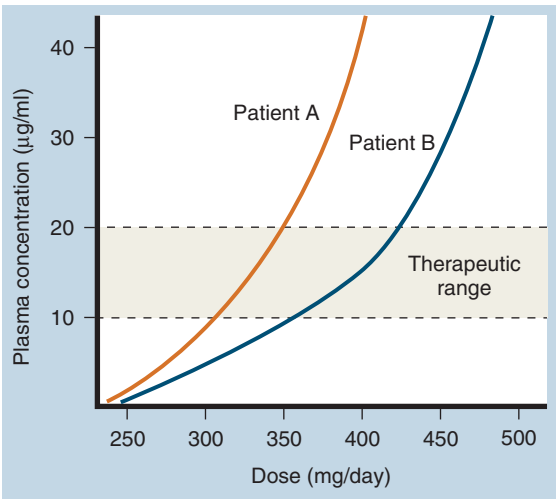

FIG. 21.5 Relationship between the dose and steady-state plasma concentration of phenytoin is illustrated for two patients. In both patients, there is a linear relationship between the dose and plasma concentration at low doses. As the dose increases, there is saturation of metabolism and a shift from first-order to zero-order kinetics, in which a small increase in dose results in a large increase in concentration. This transition occurs at different doses in the two patients so that Patient A would not tolerate an increase in dose from 300 mg/day to 400 mg/day, whereas Patient B would require the higher dose to obtain a therapeutic plasma concentration.

Valproate has a relatively short half-life and is metabolized by both the hepatic microsomal cytochrome P450 system and mitochondria to approximately the same extent. In excess of 25 metabolites have been identified, but valproic acid glucuronide and 3-oxo-valproic acid are the most abundant.

Gabapentin is absorbed in the proximal small intestine by the L-amino acid transport system. Bioavailability is dose limited because of transporter saturation (<60%). Gabapentin blood levels increase linearly with dose, up to about 1.8 g per day. Plasma levels continue to increase at higher doses, but less than expected. Once absorbed, gabapentin is not bound to plasma proteins and is not metabolized. It has a relatively short half-life in the circulation and is excreted unchanged by the kidneys. **Pregabalin** is absorbed throughout the small intestine and by the ascending colon; it is not subject to saturation. Pregabalin is absorbed more rapidly and has higher bioavailability than gabapentin (>90%). Gabapentin can be administered as a gastroretentive formulation, which swells in gastric fluid and remains in the upper gastrointestinal tract, gradually releasing gabapentin over approximately 10 hours. The prodrug **gabapentin enacarbil** is absorbed through the small intestine by the proton-linked monocarboxylate transporter MCT-1, increasing the bioavailability somewhat (about 75%), and eliminating saturation kinetics inasmuch as MCT-1 is expressed at high levels in the intestine.

Levetiracetam is nearly completely absorbed and is not bound to plasma proteins. It is partially metabolized by hydrolysis of the acetamide group to the acid metabolite ucb L057 (24% of the dose), and

approximately two-thirds of an administered dose is excreted unchanged by the kidneys.

Perampanel is completely absorbed following oral administration and exhibits linear dose-proportional kinetics. Plasma protein binding is 95%–96%. Perampanel is extensively metabolized, primarily by CYP3A4 followed by glucuronidation. Clearance is increased with inducing drugs such as carbamazepine, oxcarbazepine, and phenytoin, and the concomitant use of these drugs reduces perampanel exposure, necessitating higher doses of perampanel. Because of the long half-life and the propensity for adverse effects, the dose should be up titrated slowly, generally no more rapidly than 2 mg in a 2-week interval.

Phenobarbital is a weak acid that is absorbed with a bioavailability of >90% and rapidly distributed to all tissues. The drug is metabolized by hepatic CYP (CYP2C9 with minor contributions from CYP2C19 and CYP2E1) and by N-glucosidation. Phenobarbital is a major inducer of CYP, accelerating its own metabolism and that of other drugs taken concurrently. Phenobarbital dosing may need upward adjustment as a result of autoinduction. Approximately 20%–40% of an administered dose is excreted unchanged, while the metabolites are excreted as glucuronide conjugates in the urine. Phenobarbital has a long half-life and is usually administered on a once-daily schedule.

Primidone is an analogue of phenobarbital with antiseizure activity but is metabolized slowly to phenobarbital, which gradually accumulates to plasma concentrations comparable to those in patients receiving therapeutic doses of phenobarbital itself. Another active metabolite is phenylethylmalonamide (PEMA). Because of its metabolism to phenobarbital, primidone leads to cytochrome P450 induction. Approximately 65% of the administered dose of primidone is excreted unchanged in the urine.

Tiagabine is well absorbed (bioavailability >90%), but its rate of absorption is decreased by the presence of food. Tiagabine is oxidized primarily by CYP3A4 to inactive metabolites excreted in both the urine and feces. Drug-drug interactions with tiagabine are minimal. However, CYP3A4 induction by the concurrent administration of drugs such as phenobarbital, carbamazepine, or phenytoin increases the clearance of tiagabine by approximately 60%, resulting in approximately a 50% decreased half-life.

Topiramate is well absorbed (bioavailability >80%), and it is not extensively metabolized; typically 40%–50% is excreted unchanged by the kidneys. Elimination is accelerated in the presence of enzyme-inducing antiseizure drugs.

Zonisamide is well absorbed (bioavailability >90%) and undergoes moderate metabolism in the liver, primarily by acetylation (20%) and reduction by CYP3A4 (50%). Zonisamide binds extensively to erythrocytes, resulting in an approximate eightfold higher concentration in erythrocytes than the plasma.

PHARMACOVIGILANCE: ADVERSE EFFECTS AND DRUG INTERACTIONS

Antiseizure drugs have dose-limiting adverse effects that can be avoided by reducing the dose. In addition, there are diverse serious idiosyncratic reactions, including allergic reactions, that are rare but can be life-threatening. These usually occur within several weeks or months of starting a new drug and tend to be dose-independent. Most antiseizure drugs should be introduced slowly to minimize adverse effects.

The adverse effects associated with the use of the benzodiazepines are presented in Chapter 17.

Carbamazepine often causes nausea and visual disturbances during initiation of therapy, but these effects can be minimized by slow titration. With high initial doses or rapid dose escalation, carbamazepine has been associated with rash. In some cases, the dermatological reactions are serious (Stevens-Johnson syndrome and toxic epidermal necrolysis); these reactions are more common in patients of Chinese ancestry, and there is a strong association with the inherited HLA-B*1502 variant. Testing for this variant is recommended in patients of Chinese ancestry. HLA-B*3101 has also been associated with increased risk of the serious skin reactions and is present in a broader ethnic population. It may be worthwhile to test for this allele prior to initiating carbamazepine therapy in all ethnic groups. Carbamazepine causes leukopenia in 12% of children and 7% of adults, which may be transient or persistent and does not usually require discontinuation of treatment. The most problematic hematological effect is aplastic anemia (pancytopenia), which is a rare (less than 1 in 50,000), idiosyncratic (non–dose related) complication that usually occurs early in treatment. **Oxcarbazepine** is associated with similar adverse effects as carbamazepine. Both drugs may cause hyponatremia, which is usually asymptomatic, but the risk is greater with oxcarbazepine. Multiorgan hypersensitivity reactions have been reported with oxcarbazepine, and cross-reactivity with carbamazepine is not uncommon.

Ethosuximide causes a variety of dose-related side effects including nausea, vomiting, sleep disturbance, drowsiness, and hyperactivity. Psychotic behaviors can be precipitated, and blood dyscrasias and bone marrow suppression have been reported, but rarely.

Lamotrigine produces dose-related side effects that include dizziness, headache, diplopia, nausea, and sleepiness. A rash can occur as either a dose-related or idiosyncratic reaction. The rash may progress to Stevens-Johnson syndrome, toxic epidermal necrolysis, or angioedema, which can be life-threatening. Slow dose titration is essential to reduce the risk of developing a rash.

Phenytoin has many dose-related adverse effects, including ataxia and nystagmus, commonly detected when total plasma concentrations exceed 20 μg/mL. Other adverse effects of long-term therapy are hirsutism, coarsening of facial features, gingival hyperplasia, and osteomalacia. Less common reactions are hepatitis, a lupus-like connective tissue disease, lymphadenopathy, and pseudolymphoma. Because of the propensity for adverse effects and the availability of safer agents with fewer drug-drug interactions, phenytoin is rarely prescribed except for patients who initiated therapy prior to the availability of newer agents.

Valproate may cause nausea, vomiting, and lethargy, particularly early in therapy. The availability of an enteric-coated formulation containing valproate in the form of divalproex sodium has led to a decrease in the incidence of gastrointestinal side effects. Today, the divalproex form is almost always used for oral dosing. Common adverse effects of valproate are weight gain, alopecia, and tremor. Elevation of liver enzymes and blood ammonia levels is common. Fatal hepatitis may occur, but overall the risk is small (approximately 1 in 40,000). The risk is increased considerably in patients younger than 2 years of age treated with multiple antiseizure drugs. Two uncommon dose-related adverse effects of valproate are thrombocytopenia and changes in coagulation parameters resulting from depletion of fibrinogen.

Felbamate is used only in patients with seizures uncontrolled by other medications because of the risk of potentially fatal aplastic anemia, which occurs in approximately 1 in 5000 patients and is more common in individuals with blood dyscrasias and autoimmune disease. Felbamate use has also been associated with hepatic failure, but the risk may not be greater than that of valproate. Felbamate treatment is also associated with typical antiseizure drug adverse effects of anorexia, headache, nausea, dizziness, and gait disturbance. The drug is not sedative and often causes insomnia.

The gabapentinoids **gabapentin** and **pregabalin** are relatively safe drugs that are well tolerated and devoid of pharmacokinetic interactions with other agents. They can produce transient fatigue, dizziness, somnolence, and ataxia, which are dose related and usually transitory,

as well as edema and weight gain. Gabapentinoids can exacerbate myoclonic seizures.

Levetiracetam is generally well tolerated, but the drug can cause sedation and behavioral adverse effects, including irritability. In some patients, agitation and aggression have been a problem, particularly for those who are intellectually disabled and have a history of behavioral disturbances. Psychotic-like reactions can occur, especially in individuals with a previous psychiatric illness.

Perampanel is generally well tolerated but can cause dizziness, somnolence, headaches, and falls. Because of the tendency to produce sedation, administration at bedtime is advised. Some patients receiving perampanel experience troubling adverse behavioral effects, including irritability, aggression, hostility, anger, and homicidal ideation and threats. The incidence of these symptoms increases with dose, and younger patients are at greater risk.

Phenobarbital is highly sedative, although the sedation may resolve with chronic therapy. Cognitive disturbances are not uncommon, particularly in children. Additional adverse effects in children include hyperactivity, irritability, decreased attention, and mental slowing.

Tiagabine produces abdominal pain and nausea and should be taken with food to minimize these effects. Additional major side effects include dizziness, lack of energy, somnolence, nervousness, tremor, and difficulty concentrating. Tiagabine can also impair cognition and produce confusion and in some circumstances may have proconvulsant actions causing nonconvulsive status epilepticus.

Topiramate often leads to cognitive disturbances characterized by impairment in working memory, cognitive processing speed, motor speed, and verbal fluency and naming. It may also produce nervousness, weight loss, and diplopia. Renal stones have been reported, likely as a consequence of the ability of topiramate to cause a metabolic acidosis resulting from carbonic anhydrase inhibition.

Vigabatrin is only used in exceptional cases where other treatments have failed, or in catastrophic infantile spasms, as it can cause permanent bilateral concentric visual field constriction that is often asymptomatic but can be disabling. In addition, vigabatrin can damage the central retina. Other adverse effects are somnolence, headache, dizziness, and weight gain. Vigabatrin can worsen myoclonic seizures and cause nonconvulsive status epilepticus.

Zonisamide adverse effects include lethargy, dizziness, ataxia, anorexia, and weight loss. Zonisamide is a carbonic anhydrase inhibitor and, like topiramate, is rarely associated with renal stones. In children, oligohydrosis may lead to hyperthermia and heat stroke.

Common adverse effects of the antiseizure drugs are listed in the Clinical Problems Box.

Antiepileptic Drugs During Pregnancy

Seizures during pregnancy present risks to the mother and fetus. Therefore most women with epilepsy who become pregnant require antiseizure drug therapy. If at all possible, valproate, phenobarbital, and topiramate should be avoided, most importantly at the time of conception and early in the pregnancy. Valproate exposure during pregnancy is associated with neural tube defects and other malformations including cardiac, orofacial/craniofacial, and skeletal and limb malformations. In addition, there is evidence of reduced cognitive ability in the offspring, and there may be an increased risk of autism spectrum disorders. The risk with valproate increases with dose. Phenobarbital use during pregnancy is associated with a risk of major congenital malformations, including cardiac defects. Topiramate increases the risk of oral clefts. Other antiseizure drugs may also present a risk of congenital malformations, but the risk may be lower than that of valproate, phenobarbital, and topiramate. Lamotrigine is often considered for use in pregnancy, as pregnancy registries have failed to find evidence of a substantial increase in the risk of major birth defects. The prevalence of malformations following levetiracetam exposure is not significantly different from lamotrigine and the rate in controls. Based on current evidence, lamotrigine and levetiracetam present the lowest level of risk to the fetus, whereas the risk with valproate is clear. Despite the risks, most pregnant patients exposed to antiseizure drugs deliver normal infants. Children of mothers who have epilepsy are at increased risk for malformations even if antiseizure drugs are not used during pregnancy. Whenever possible, women with epilepsy should be counseled before they become pregnant. It is recommended that the lowest possible doses of antiseizure drug be used during pregnancy.

Newborn infants of mothers who have received enzyme-inducing antiseizure drugs during pregnancy may develop a deficiency of vitamin K–dependent clotting factors, which can result in serious hemorrhage during the first 24 hours of life. This situation can be prevented by administering vitamin K to the newborn by intramuscular injection shortly after birth.

NEW DEVELOPMENTS

Several potential new drug treatments for seizures and epilepsy are in clinical development. Many of the treatments are being studied for rare childhood epilepsy syndromes. For example, **cannabidiol**, a nonpsychoactive component of the cannabis plant, is being studied for the treatment of Dravet syndrome and Lennox-Gastaut syndrome. **Fenfluramine** is also being studied for these two syndromes. **Stiripentol**, which is available in Europe, Canada, and Japan as a treatment for Dravet syndrome, is being evaluated for marketing in the United States. The neurosteroid **allopregnanolone** and related compounds, which act as positive modulators of synaptic and extrasynaptic $GABA_A$ receptors, are being studied for various clinical indications. Allopregnanolone is being evaluated for refractory status epilepticus and its 3β-methyl analogue **ganaxolone** for status epilepticus and rare epilepsy syndromes. Various treatments for ARS are under investigation, including thermal aerosol (inhaled) **alprazolam** and intranasal **midazolam** and **diazepam**. Finally, the carbamate **cenobamate** (YKP3089) is being studied for focal seizures.

CLINICAL RELEVANCE FOR HEALTHCARE PROFESSIONALS

Individuals with seizure disorders often require long-term medication. Because many of these antiseizure drugs induce CYPs, it is incumbent on all healthcare professionals to ensure that their patients present a complete drug history. It is also incumbent on healthcare professionals to be aware of the primary adverse reactions associated with the antiseizure drugs so that they can recognize issues readily when they arise.

CLINICAL PROBLEMS

Carbamazepine
Induction of its own metabolism; nausea, dizziness, blurred vision, ataxia (dose-related); rash and rarely Stevens-Johnson syndrome; hyponatremia; leukopenia; aplastic anemia; hepatic failure

Divalproex (Valproate)
Nausea, vomiting, and other gastrointestinal complaints; fine tremor; hair loss; weight gain; thrombocytopenia; teratogenicity; hepatic failure, pancreatitis, hyperammonemia, aplastic anemia; many drug interactions

Ethosuximide
Abdominal pain and vomiting; valproate increases ethosuximide levels; abrupt discontinuation may precipitate absence status epilepticus

Felbamate
Anorexia; aplastic anemia; hepatic failure

Gabapentin and Pregabalin
At initiation of therapy: sedation, fatigue, dizziness, ataxia

Lacosamide
Dizziness, headache, nausea, vomiting, diplopia; prolonged PR interval

Lamotrigine
Dizziness, blurred vision, headache, insomnia; rash, Stevens-Johnson syndrome, toxic epidermal necrolysis; hepatic failure

Levetiracetam
Irritability, aggression

Oxcarbazepine
Nausea and vomiting, dizziness, blurred vision, ataxia (dose-related); rash and rarely Stevens-Johnson syndrome; hyponatremia; leukopenia; aplastic anemia

Perampanel
Behavioral adverse effects: irritability, aggression, hostility, anger; dizziness, somnolence, headache, falls; increases clearance of carbamazepine, oxcarbazepine, phenytoin

Phenobarbital
Fatigue, dizziness, ataxia, confusion; in children: hyperactivity; hepatic failure, rash, Stevens-Johnson syndrome; many drug interactions; rebound seizures on abrupt discontinuation

Phenytoin
Nystagmus (benign sign); diplopia and ataxia (dose-related); cognitive impairment; hirsutism, coarsening of facial features, gingival hyperplasia; saturation metabolism kinetics

Tiagabine
Fatigue, dizziness, somnolence, irritability; spike-wave status epilepticus

Topiramate
Impaired expressive language function, impaired verbal memory, slowing of cognition; paresthesias at initiation of therapy; anorexia and weight loss; kidney stones; heat stroke (children); metabolic acidosis; acute close-angle glaucoma; teratogenicity (oral clefts)

Vigabatrin
Fatigue, somnolence; irreversible visual loss

Zonisamide
Anorexia and weight loss; kidney stones; heat stroke (children)

TRADE NAMES

Many antiseizure drugs are available in generic form, but some are proprietary. Trade names for some branded products available in the United States are shown in this table.

Acetazolamide (Diamox)
Carbamazepine (Tegretol, Carbatrol,[a] Equetro,[a] Carnexiv[b])
Clobazam (Onfi)
Clonazepam (Klonopin)
Diazepam (Valium, Diastat Acudial[c])
Divalproex (Depakote)
Eslicarbazepine acetate (Aptiom)
Ethosuximide (Zarontin)
Ezogabine (Potiga)
Felbamate (Felbatol)
Fosphenytoin (Cerebyx)
Gabapentin (Neurontin, Gralise[a,e])
Gabapentin enacarbil (Horizant[a])
Lacosamide (Vimpat)
Lamotrigine (Lamictal)
Levetiracetam (Keppra, Keppra XR,[a] Spritam)
Lorazepam (Ativan)
Methsuximide (Celontin)
Oxcarbazepine (Trileptal, Oxtellar XR[a])
Perampanel (Fycompa)
Phenobarbital (Luminal)
Phenytoin (Dilantin)
Pregabalin (Lyrica)
Primidone (Mysoline)
Rufinamide (Banzel)
Stiripentol (Diacomit)[d]
Tiagabine (Gabitril)
Topiramate (Topamax, Trokendi XR,[a] Qudexy XR[a])
Valproic acid (Depakene)
Valproate sodium injection (Depacon[b])
Zonisamide (Zonegran)

[a]Extended release.
[b]Intravenous.
[c]Rectal.
[d]Not yet available in United States.
[e]Gastroretentive.

SELF-ASSESSMENT QUESTIONS

1. A 6-year-old girl and her mother come to see you because the girl's teacher observed episodes of staring and inability to communicate. These episodes last 3–5 seconds and occur 10–20 times during the school day. An EEG shows synchronized three-per-second spike-wave discharges generalized over the entire cortex. Which antiepileptic medication would you try first in this young girl?
   A. Phenytoin
   B. Clonazepam
   C. Primidone
   D. Carbamazepine
   E. Ethosuximide
2. A young patient's seizures have been well controlled with phenytoin for many years, but he recently had two seizures. You determine that the phenytoin concentration in his blood is low because of his recent growth, and increase the phenytoin dose, calculating it based on his weight gain (same mg/kg as before). Several weeks later, the patient calls and tells you that he has not had any seizures, but he is having trouble walking and is dizzy. Which of the following statements best describes what has happened?
   A. The patient did not follow your instructions and has been taking too many pills.
   B. After the dose increase, phenytoin was eliminated by zero-order kinetics, and plasma concentrations were in the toxic range.
   C. His metabolism of phenytoin has increased as a result of induction of liver microsomal enzymes.
   D. His phenytoin concentrations are too low.
   E. An inner ear infection has developed.
3. What is the best initial treatment for a 3-year-old girl experiencing generalized tonic-clonic seizures daily?
   A. Brain surgery to remove the focus of her seizures
   B. Monotherapy with primidone
   C. Treatment with carbamazepine
   D. Treatment with phenytoin
   E. No drug therapy at this time
4. Generalized tonic-clonic seizures are characterized by a sustained depolarization of cortical neurons with high-frequency repetitive action potential firing. An antiseizure drug that acts by which of the following mechanisms is best suited to treat such seizures?
   A. A voltage-gated sodium-channel blocker
   B. A T-type calcium-channel blocker
   C. A $GABA_A$ receptor positive modulator
   D. A GABA transporter inhibitor
   E. A GABA transaminase inhibitor
5. A 45-year-old woman with newly diagnosed epilepsy is started on an antiseizure drug. She initially does well, but she has two seizures approximately 4 weeks after the start of treatment. She has taken the same number of pills each day, but during therapeutic drug monitoring, it is noticed that the plasma level of her drug has decreased. Which antiseizure drug is she taking?
   A. Ethosuximide
   B. Primidone
   C. Phenytoin
   D. Carbamazepine
   E. Valproic acid

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WEBSITES

http://www.epilepsy.com/learn/treating-seizures-and-epilepsy
This site is maintained by the Epilepsy Foundation and is an excellent resource for both healthcare professionals and patients, as it has links to many resources.

https://www.aesnet.org/clinical_resources/guidelines
The American Epilepsy Society website presents current evidence-based guidelines for the treatment of seizure disorders.

https://www.aan.com/Guidelines/Home/ByTopic?topicId=23
The American Academy of Neurology also maintains evidence-based guidelines for the treatment of seizure disorders.