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21

Treatment of Seizure Disorders

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MAJOR DRUG CLASSES

u0490 u0495 u0500 u0505 u0510 u0515 u0520 u0525 u0530 u0535 u0540 u0545

- Voltage-gated ion channel modulators
  - Voltage-gated sodium channel blockers
  - T-type voltage-gated calcium channel blockers
  - Gabapentinoids (α2δ 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

b0035 t0020

ABBREVIATIONS

ACTH	Adrenocorticotropin
ARS	Acute repetitive seizures
DEE	Developmental and epileptic encephalopathy
EEG	Electroencephalogram
GABA	γ-Aminobutyric acid
GAT-1	GABA transporter
mTOR	Mechanistic target of rapamycin
PAM	Positive allosteric modulator
TSC	Tuberous sclerosis complex

s0130

THERAPEUTIC OVERVIEW

p0695 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 years and in adults over age 50 years. 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.

p0700 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.

p0705 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).

p0710 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.

p0715 **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 terminate 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.

p0720 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.

p0725 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

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BOX 21.1 Causes of Seizures and Epilepsy

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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

s0015 u0040 u0045 u0050 u0055 u0060 u0065 u0070 u0075 u0080 u0085

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

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.

p0730 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 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.

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Pathophysiology

p0735 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.

p0740 Genetic factors play a role in many forms of epilepsy. Most epilepsies likely have a complex oligogenic or polygenic architecture. Even in epilepsies that are acquired, such as in traumatic brain injury, genetic factors probably play a role but are not yet defined. There are a large number of rare Mendelian epilepsies (Box 21.2). The most severe and intractable forms of epilepsy occur together with developmental and

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BOX 21.2 Examples of Monogenic Epilepsies

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Disorder	Mutation(s)
Focal Epilepsies	
Familial focal epilepsy with variable foci (autosomal dominant nocturnal frontal lobe epilepsy, familial temporal lobe epilepsy)	Negative regulator of mTOR pathway *DEPDC5*
Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE)	Nicotinic acetylcholine receptor subunit genes *CHRNA4, CHRNB2,* or *CHRNA2*
Benign familial neonatal seizures (may have generalized seizures)	Voltage-gated M-current potassium channel genes *KCNQ2* or *KCNQ3*
Migrating partial epilepsy of infancy (MPEI)	Voltage-gated sodium channel α2 subunit gene *SCN2A*
Autosomal dominant epilepsy with auditory features (ADPEAF)	Eptempin gene *LGI1*
Autosomal dominant juvenile myoclonic epilepsy	$GABA_A$ receptor subunit gene *GABRA1*
Developmental and Epileptic Encephalopathies	
Dravet syndrome	Voltage-gated sodium channel gene *SCN1A*; rarely *PCDH19, GABRA1, GABRG2, HCN1, KCNA2, SCN1B*
Ohtahara syndrome (early-onset infantile encephalopathy)	Syntaxin binding protein gene *STXBP1*; *KCNQ2, SCN2A, SCN8A*
Epilepsy in infancy with migrating focal seizures	Sodium-activated potassium channel gene *KCNT1, SCN2A*
PCDH19 X-linked sex-limited early infantile epileptic encephalopathy	Cell adhesion nonclustered δ2 protocadherin gene *PCDH19*
Glucose transporter type 1 deficiency syndrome (severe infantile metabolic encephalopathy)	Glucose transporter 1 (GLUT1) gene *SLC2A1*
SLC6A1 epileptic encephalopathy	GABA transporter (GAT-1) gene *SLC6A1*
CDKL5 deficiency disorder	Cyclin-dependent kinase-like 5 gene *CDKL5*
DEND (developmental delay, epilepsy, and neonatal diabetes) syndrome	Kir6.2 ATP-sensitive potassium channel (K_{ATP}) subunit *KCNJ11*
Genetic Generalized Epilepsies	
Childhood absence epilepsy	$GABA_A$ receptor γ2 subunit gene *GABRG2*
Autosomal dominant juvenile myoclonic epilepsy	$GABA_A$ receptor α1 subunit gene *GABRA1*
Glucose transporter type 1 deficiency syndrome (epilepsy with early onset absence seizures, paroxysmal exertional dyskinesia, and often normal intellect)	Glucose transporter 1 (GLUT1) gene *SLC2A1*

$GABA_A$, γ-Aminobutyric acid type A.

intellectual disability. They are referred to as **developmental and epileptic encephalopathies (DEEs)**. In some cases, the DEE is acquired as a result, for example, of a perinatal stroke, infection, or trauma. In other circumstances, the DEE is a component of a genetic syndrome, such as tuberous sclerosis complex (TSC), that has other associated structural or metabolic brain abnormalities. Often, the genetic epilepsy has seizures as its only clinical manifestation, and there is no apparent structural or metabolic disorder of the brain. Such **idiopathic (genetic) generalized epilepsies** include childhood absence epilepsy, juvenile myoclonic epilepsy, juvenile absence epilepsy, generalized tonic-clonic seizures alone (formerly generalized tonic-clonic seizures on awakening), and BECTS.

p0745 In Mendelian (monogenic) epilepsies, the mutations are commonly de novo. Sequence changes are the most frequent mutations, but chromosomal deletions or duplications and copy number variants account for some cases. Somatic mutations leading to focal epilepsy can arise during the course of prenatal brain development. These noninherited mutations, such as in mechanistic target of rapamycin (mTOR) pathway genes, result in a mosaic of affected cells intermixed with unaffected cells.

p0750 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**. Other monogenic epilepsies are caused by mutations in transporter genes and components of the synaptic machinery, such as syntaxin binding protein STXBP1, which also may regulate excitability However, some monogenic epilepsies are caused by mutations in nonexcitability genes, including components of the mTOR pathway such as DEPDC5; neural adhesion molecules, such as PCDH19 (protocadherin 19); and proteins involved in synapse development, such as LGI1 (leucine-rich glioma inactivated 1).

p0755 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 $GABA_A$ 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.

p0760 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.

p0765 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 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.

THERAPEUTIC OVERVIEW b0040

Focal Onset (Partial Onset) Seizures s0140

- Focal aware seizure (formerly simple partial seizure) u0550
  - Sensory, motor, autonomic, or psychic symptoms, without altered awareness u0555
- Focal impaired awareness seizure (formerly complex partial seizure) u0560
  - Dreamy disaffective state with or without automatisms, with altered awareness u0565
- Focal to bilateral tonic-clonic seizure (formerly secondarily generalized tonic-clonic seizure or grand mal seizure) u0570
  - 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) u0575

Generalized Onset Seizures s0145

- Generalized tonic-clonic seizure (formerly primary generalized tonic-clonic seizure or grand mal seizure) u0580
  - Similar to focal to bilateral tonic-clonic seizure except that onset is in both hemispheres; occurs in patients with genetic (idiopathic) generalized epilepsies u0585
- Generalized absence seizures u0590
  - 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 u0595
- Other types of generalized onset seizures u0600
  - Myoclonic seizure: rapid shock-like (jerking) muscle contraction u0605
  - Atonic seizure (drop seizure or astatic seizure): loss of muscle tone u0610
  - Epileptic spasm: sudden flexion, extension or flexion-extension of neck, trunk, arms, and legs u0615

MECHANISMS OF ACTION s0150

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 require treatment with special agents. This is the case for infantile spasms (West syndrome), an epileptic encephalopathy of infancy characterized by epileptic spasms, EEG hypsarrhythmia, and intellectual disability. p0850

Epileptic activity may occur as a consequence of either decreased inhibition or increased excitation of neurons. Agents used for the p0855

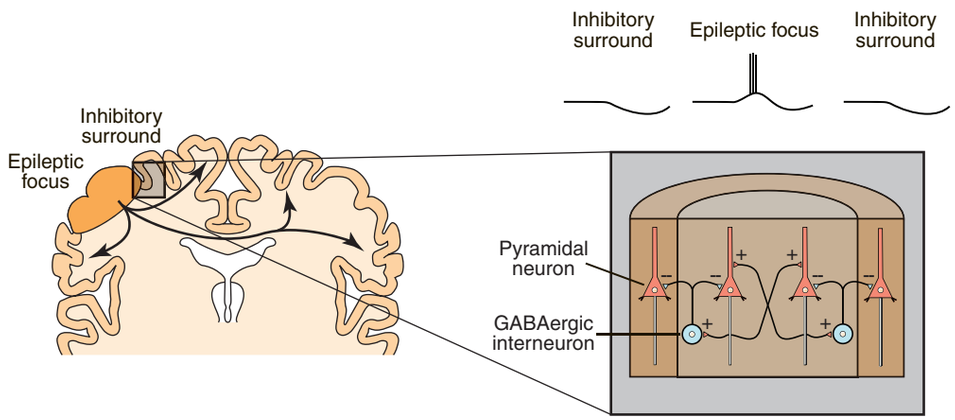

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FIG. 21.1 Seizure Generation and Spread in a Focal Seizure. Epileptiform activity begins in a localized area (epileptic focus) and spreads to adjacent and contralateral cortical regions. Epileptic activity reflects the synchronized activity of excitatory (+) 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.

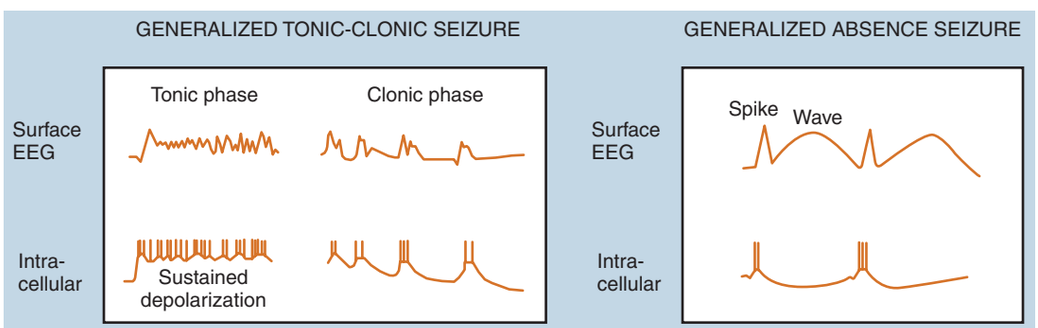

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FIG. 21.2 Comparison of the Electrical Behavior of the Surface Electroencephalogram *(EEG)* and Single-Neuron Recording During Generalized Tonic-Clonic and Absence Seizures on a Time Scale of Hundreds of Milliseconds. Surface EEG signals are field 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.

treatment of epilepsy depress aberrant neuronal firing primarily by 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.

s0155

Voltage-Gated Ion-Channel Modulators

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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

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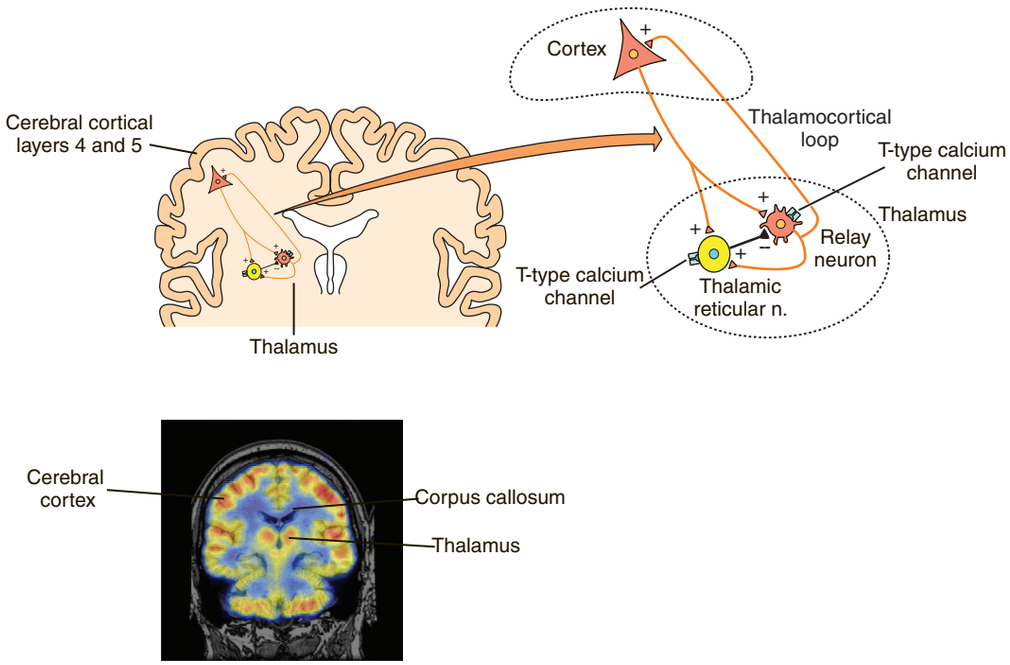

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FIG. 21.3 Thalamocortical Circuitry Generating Absence Seizures According to the "Corticoreticular" Theory. The thalamus and cortex are both essential for the spike-wave discharges of absence seizures; bilateral synchrony depends on the corpus callosum 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

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depolarized conditions of the epileptic discharge allows these drugs to inhibit seizures without affecting normal brain function at therapeutic concentrations.

p0865 **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.

p0870 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.

p0875 **Ezogabine** (retigabine) 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. K_v7 is encoded by KCNQ genes. Mutations in KCNQ2 and KCNQ3 are pathogenic for diverse monogenic epilepsies (Box 21.2).

GABA Enhancers

s0160

p0880 GABA, the major inhibitory neurotransmitter in the brain, causes fast inhibition through its action on $GABA_A$ receptors (see 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. **Stiripentol** acts by a similar mechanism. 1,4-Benzodiazepines, such as **diazepam**, **lorazepam**, **midazolam**, 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. The 1,5-benzodiazepine **clobazam** is a $GABA_A$ receptor PAM that acts similarly to 1,4-benzodiazepines. The activity of benzodiazepines is

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b0020

BOX 21.3 Mechanisms of Action of Antiseizure Drugs

s0020 **Voltage-Gated Ion-Channel Modulators**

s0025 ***Voltage-Gated Sodium-Channel Blockers***

u0090 • Phenytoin
u0095 • Carbamazepine
u0100 • Oxcarbazepine
u0105 • Eslicarbazepine acetate (prodrug)
u0110 • Lamotrigine
u0115 • Lacosamide

s0030 ***T-Type Calcium-Channel Blocker***

u0120 • Ethosuximide

s0035 ***α2δ Ligands***

u0125 • Gabapentin
u0130 • Pregabalin

s0040 ***Voltage-Gated Potassium-Channel Opener***

u0135 • Ezogabine (retigabine)

s0045 **GABA Enhancers**

s0050 ***$GABA_A$ Receptor Positive Modulators***

u0140 • Phenobarbital
u0145 • Primidone
u0150 • Diazepam, lorazepam, clonazepam, clobazam
u0155 • Stiripentol
u0160 • Ganaxolone

s0055 ***GABA Transporter (GAT-1) Inhibitor***

u0165 • Tiagabine

s0060 ***GABA Transaminase Inhibitor***

u0170 • Vigabatrin

s0065 ***Glutamate AMPA Receptor Antagonist***

u0175 • Perampanel

s0070 ***SV2A Ligand***

u0180 • Levetiracetam
u0185 • Brivaracetam

s0075 **Mixed/Unknown**

u0190 • Valproate
u0195 • Topiramate
u0200 • Zonisamide
u0205 • Felbamate
u0210 • Rufinamide
u0215 • Cenobamate
u0220 • Cannabidiol
u0225 • Fenfluramine
u0230 • Adrenocorticotropin

GABA, γ-Aminobutyric acid.

restricted to specific synaptic $GABA_A$ receptor subtypes. **Ganaxolone** is a neuroactive steroid $GABA_A$ receptor PAM. Such agents act broadly on $GABA_A$ receptor subtypes, including synaptic and extrasynaptic isoforms.

p0885 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

s0165

p0890 AMPA receptors are a type of ionotropic glutamate receptor that mediates 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

s0170

p0895 **Levetiracetam** and **brivaracetam** exert their antiseizure activity by binding to SV2A, a ubiquitous synaptic vesicle membrane glycoprotein 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

s0175

p0900 The mechanisms of action of many antiseizure drugs involve mixed effects or are poorly understood. These compounds include **valproate**, **topiramate**, **zonisamide**, **felbamate**, **rufinamide**, **cenobamate**, **cannabidiol**, **fenfluramine**, and **adrenocorticotropin** (ACTH).

p0905 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 NMDA-type ionotropic glutamate receptors, although the relationship between this latter action and the antiseizure activity of felbamate is poorly defined. **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. **Cenobamate** is a low-efficacy positive allosteric modulator of $GABA_A$ receptors, with effects on both phasic and tonic inhibitory currents, and a sodium channel blocker. **Cannabidiol** has multiple actions, none of which are clearly linked to an antiseizure action (see Chapter 30). **Fenfluramine** is a potent serotonin release agent and reuptake blocker, with less potent actions on norepinephrine release and reuptake. The available evidence indicates that both enantiomers of fenfluramine participate in its therapeutic activity and the major metabolite norfenfluramine may also contribute. Fenfluramine and norfenfluramine metabolites interact with diverse serotonin receptors. There is no agreement which, if any, of these contribute to the antiseizure activity.

p0910 **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.

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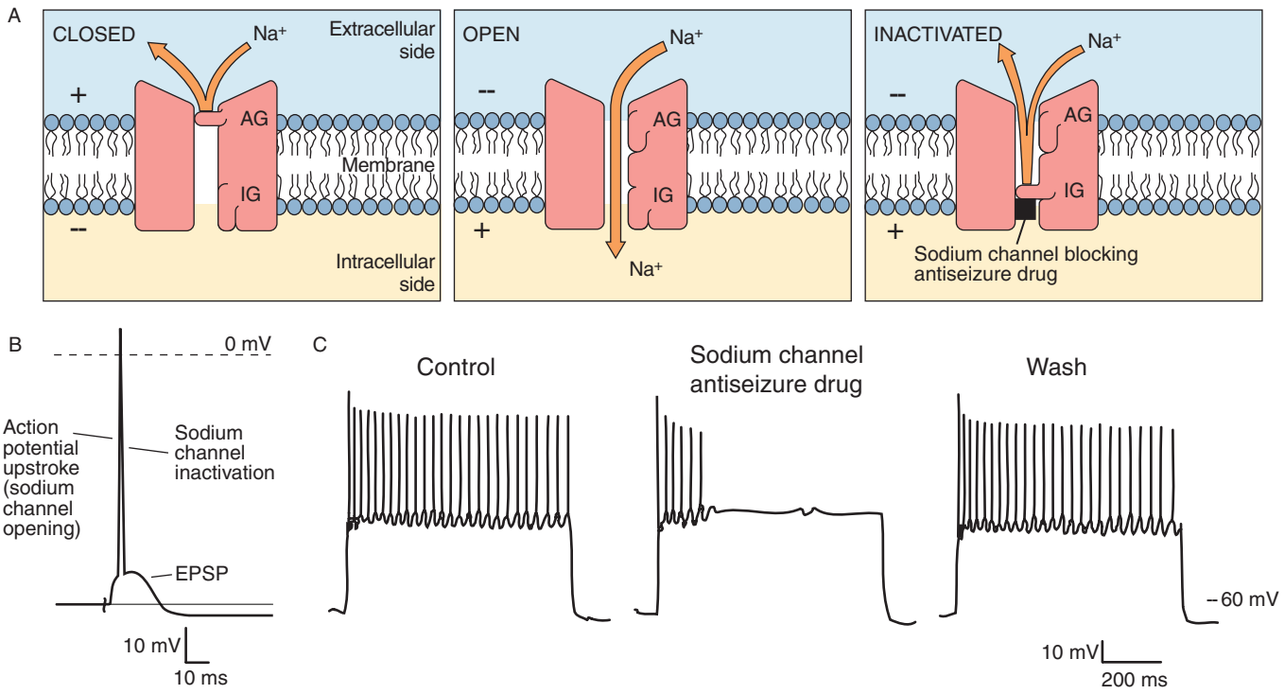

f0025 **FIG. 21.4** Action of Sodium-Channel Blocking Antiseizure Drugs on Voltage-Gated Sodium Channels. (A) At hyperpolarized membrane potentials, the sodium-channel activation gate *(AG)* is closed, blocking sodium influx. Depolarization of the neuron causes AG to open, allowing sodium flux. Within less than 1 millisecond, the inactivation gate *(IG)* closes, terminating sodium flux. When the membrane potential is repolarized, the AG closes (not shown), and after 1 to 2 milliseconds, 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.

s0180 ## RELATIONSHIP OF MECHANISMS OF ACTION TO CLINICAL RESPONSE

s0185 ### Drugs Used in the Treatment of Focal Seizures

p0915 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.

s0190 ### Drugs Used in the Treatment of Focal Seizures With Efficacy in Certain Generalized Seizure Types

p0920 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.

p0925 **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.

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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 (retigabine)

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 or valproic acid)
- Topiramate
- Zonisamide

Absence Seizures
- Ethosuximide
- Valproate (divalproex sodium or valproic acid)
- Lamotrigine

Myoclonic Seizures
- Valproate (divalproex sodium or valproic acid)
- Levetiracetam
- Zonisamide
- Topiramate
- Lamotrigine

Clonazepam, clobazam

Atonic Seizures (as in Lennox-Gastaut syndrome)
- Valproate (divalproex sodium or valproic acid)

Lamotrigine
- Rufinamide
- Clobazam
- Topiramate
- Felbamate
- Cannabidiol
- Fenfluramine

Dravet Syndrome
- Valproate (divalproex sodium or valproic acid)
- Stiripentol
- Clobazam
- Cannabidiol
- Fenfluramine
- Topiramate

Infantile Spasm Syndrome (West Syndrome)
- Adrenocorticotropic hormone
- Vigabatrin

Status Epilepticus
- Intravenous lorazepam or diazepam, intramuscular midazolam
- Intravenous levetiracetam, fosphenytoin or valproate sodium
- Intravenous phenobarbital, 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
- Nasal midazolam, diazepam, lorazepam

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 early-onset developmental epileptic encephalopathy that usually presents before 8 years of age with multiple seizure types, including atonic (drop) seizures. Seizures in Lennox-Gastaut syndrome are difficult to treat and usually require drug combinations. **Valproate** is generally considered the first-line therapy. If ineffective, **lamotrigine** is often added. Other agents used are **rufinamide**, **clobazam**, **topiramate**, **felbamate**, **cannabidiol**, and **fenfluramine**. Sodium-channel blocking antiseizure drugs other than lamotrigine are not used, as they may worsen atonic seizures.

Drugs Used in the Treatment of Dravet Syndrome

Dravet syndrome, also known as severe myoclonic epilepsy of infancy, is a rare DEE with multiple seizure types, including focal seizures, atypical absence seizures, and myoclonic seizures. There is also motor dysfunction, behavioral disorder, and cognitive impairment. First-line treatment is often with **valproate**. If seizures continue, **clobazam**, **stiripentol**, or the newer agents **fenfluramine** or **cannabidiol** may be added. Other drugs used in the treatment of Dravet syndrome include topiramate, levetiracetam, and zonisamide. Ethosuximide may be used to treat atypical absence seizures. Sodium channel blocking antiseizure drugs may aggravate seizures in Dravet syndrome and are generally contraindicated.

Drugs Used in the Treatment of Other Epilepsy Syndromes

Everolimus, an inhibitor of mTOR signaling, is used in the treatment of seizures associated with TSC, which is caused by loss-of-function mutations in the TSC1 gene encoding the protein hamartin or in the

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TSC2 gene encoding tuberin. The mutations lead to constitutive mTOR activation, resulting in the abnormal cerebral cortical development with multiple focal structural malformations. **Everolimus** confers sustained improvement in seizure status and in some cases seizure freedom.

p0950 **Ganaxolone** is approved for the treatment of seizures associated with CDKL5 deficiency disorder, but its mechanism of action as a $GABA_A$ receptor PAM is compatible with broad-spectrum activity.

s0215

Drugs Used in the Treatment of Status Epilepticus and Acute Seizures

p0955 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 **levetiracetam**, **fosphenytoin** or **phenytoin**, and **valproate** are appropriate choices. **Phenobarbital** is highly effective but is generally not used because 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.

p0960 **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 superrefractory. 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.

p0965 **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. Until recently, **diazepam rectal gel** was the only approved treatment for ARS in the United States. 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. Now, **nasal spray** devices that administer **midazolam** and **diazepam** are available in the United States. **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. **Nasal lorazepam** has also been shown to be efficacious but is not approved for administration by this route in the United States. Some clinicians use oral benzodiazepines on an off-label basis.

s0220

PHARMACOKINETICS

p0970 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.

p0975 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 (phenobarbital and phenylethylmalonic acid), oxcarbazepine (licarbazepine), diazepam (nordiazepam and others), clobazam (N-desmethylclobazam, also called norclobazam), and fenfluramine (norfenfluramine). Some antiseizure drugs are prodrugs that require activation, most notably fosphenytoin, which is converted to phenytoin, and eslicarbazepine acetate, which is converted to *S*(−)-licarbazepine. 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.

p0980 Some antiseizure drugs, including phenytoin, tiagabine, valproate, diazepam, perampanel, stiripentol, and ganaxolone 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. AU:5

p0985 **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.

p0990 **Oxcarbazepine** is completely absorbed and extensively metabolized by hepatic cytosolic enzymes to its active 10-hydroxy metabolite licarbazepine, which is responsible for its clinical effects. Following repeated dosing, 19% of licarbazepine is in the R(+)-form. Both enantiomeric forms of licarbazepine [*R*(+) and *S*(−)] have antiseizure activity. Oxcarbazepine is administered twice daily. An extended-release form for once-daily administration is available. **Eslicarbazepine acetate** is a prodrug for *S*(−)-licarbazepine, which undergoes minor chiral inversion so that 5% of the circulating licarbazepine is in the *R*(+)-form. Eslicarbazepine acetate is available as a marketed antiseizure drug recommended for once-daily administration.

p0995 **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.

p1000 **Lamotrigine** is well absorbed and has negligible first-pass metabolism so that its bioavailability is greater than 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

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t0010

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	0.2–2
Cannabidiol	56–61	>94	M	0.3[b]
Carbamazepine	3–55	75	M	4–12
Cenobamate	50–60	60	M, R	15–23[c]
Clobazam	10–30; 36–46 (N-desmethylclobazam)	70–90	M	0.03–0.30; 0.3–3.0 (N-desmethylclobazam)
Eslicarbazepine acetate	<2 hours conversion to eslicarbazepine	30	M	3–35 (based on licarbazepine value for oxcarbazepine)
Ethosuximide	30–60	<10	M, R	40–100
Fenfluramine	20	50	M, R	<0.15–0.20[d]
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
Levetiracetam	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	0.05–0.4
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
Stiripentol	4.5–13[e]	99	M, R	4–22
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.
[b]No reference range available. Value given is mean plasma concentration in children and adult clinical trial responders receiving a mean dose of 27.1 mg/kg/day.
[c]No reference range available. Range bounds are mean steady-state plasma concentrations for trial subjects receiving daily doses of 200 mg and 400 mg.
[d]No reference range available. Many patients achieve good response with levels <0.1 μg/mL.
[e]Nonlinear pharmacokinetics.
M, Metabolized by liver; *R*, renal elimination (>3%); $t_{1/2}$, half-life.

regimen does not increase the risk, as the patient is desensitized to the immunotoxic effect that causes Stevens-Johnson syndrome.

p1005 AU:6 **Phenytoin** metabolism is characterized by saturation (zero order) kinetics (see 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.

p1010 **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.

p1015 **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 (~75%), and eliminating saturation kinetics inasmuch as MCT-1 is expressed at high levels in the intestine.

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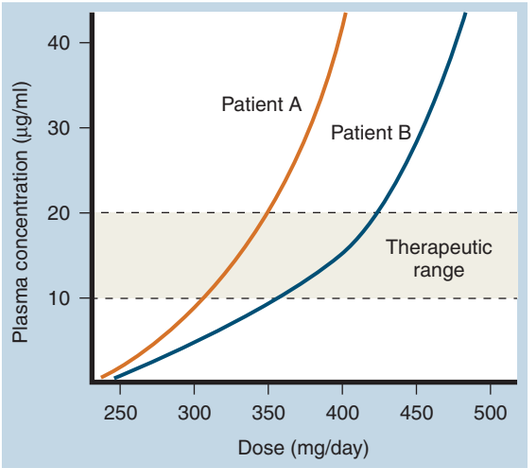

f0030 **FIG. 21.5 Relationship Between the Dose and Steady-State Plasma Concentration of Phenytoin Is Illustrated for Two Patients.** In both patients, there is a linear relationship between the dose and plasma concentration at low doses. As the dose increases, there is saturation of metabolism and a 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.

p1020 **Levetiracetam** is nearly completely absorbed and is not bound to plasma proteins. It is partially metabolized by hydrolysis of the acetamide group to the inactive acid metabolite ucb L057 (24% of the dose), and approximately two-thirds of an administered dose is excreted unchanged by the kidneys. **Brivaracetam** is also nearly completely absorbed and only weakly bound to plasma proteins (≤20%). It is extensively metabolized to inactive metabolites. The major metabolic pathway (56%) is hydrolysis by hepatic and extrahepatic amidase. A lesser amount of brivaracetam (28%) undergoes CYP2C19-mediated hydroxylation to form hydroxy-brivaracetam.

p1025 **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.

p1030 **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.

p1035 **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 p1040 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 p1045 extensively metabolized; typically 40% to 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 p1050 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 s0225

Antiseizure drugs have dose-limiting adverse effects that can be p1055 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 p1060 are presented in Chapter 17. AU:7

Cannabidiol causes sedation and somnolence as well as gastroin- p1065 testinal adverse reactions, including decreased appetite, diarrhea, and vomiting. Pharmaceutical cannabidiol is formulated in sesame oil, which may contribute to the gastrointestinal side effects. The most frequent cause of discontinuation is dose-related elevations of liver transaminases (alanine aminotransferase and aspartate aminotransferase). Cannabidiol may cause seizure aggravation when not used in conjunction with clobazam. In Europe and Great Britain, it is indicated for use as adjunctive therapy of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in conjunction with clobazam.

Carbamazepine often causes nausea and visual disturbances dur- p1070 ing 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

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anemia (pancytopenia), which is a rare (less than 1 in 50,000), idiosyncratic (non–dose related) complication that usually occurs early in treatment. **Oxcarbazepine** and **eslicarbazepine acetate** are associated with similar adverse effects as carbamazepine. All three drugs may cause hyponatremia, which is usually asymptomatic, but the elderly are more frequently affected and the risk is greater with oxcarbazepine and eslicarbazepine acetate than with carbamazepine. Multiorgan hypersensitivity reactions have been reported with oxcarbazepine, and cross-reactivity with carbamazepine is not uncommon.

p1075 **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.

p1080 **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.

p1085 **Fenfluramine** may cause fibrosis of the mitral and aortic valves leading to regurgitation. The phenomenon is believed to be due to the action of norfenfluramine, the major metabolite of fenfluramine, stimulating serotonin 5-HT_{2B} receptors, which are located on both mitral and aortic valves. The valvulopathy is due to proliferation of valve myofibroblasts. Fenfluramine may also cause pulmonary hypertension.

p1090 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.

p1095 **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.

p1100 **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.

p1105 **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.

p1110 **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.

p1115 **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.

p1120 **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.

p1125 **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.

p1130 **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 (~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.

p1135 **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.

p1140 **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.

p1145 Common adverse effects of the antiseizure drugs are listed in the Clinical Problems Box.

Antiseizure Drugs During Pregnancy

s0230

p1150 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

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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.

p1155 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.

s0235

NEW DEVELOPMENTS

p1160 Several potential new drug treatments for seizures and epilepsy are in clinical development. **XEN1101**, a potent Kv7.2/Kv7.3 (KCNQ2/KCNQ3) potassium channel opener, is being studied for the treatment of focal seizures in adults. **Darigabat**, a subtype selective α2 α3 α5 $GABA_A$ receptor positive modulator, is also being studied in focal epilepsy. Various treatments for ARS are under investigation, including thermal aerosol (inhaled) **alprazolam** and buccal **diazepam**. Diverse drug treatments are being studied for rare childhood epilepsy syndromes. **Ganaxolone** is being studied for seizures in TSC and Lennox-Gastaut syndrome, and for the treatment of status epilepticus. **Fenfluramine** is being studied in CDKL5 deficiency disorder. **Carisbamate** is in development for Lennox-Gastaut syndrome. Drugs specifically in development for Dravet syndrome include the cholesterol 24-hydroxylase inhibitor **soticlestat**, the selective 5-HT_C receptor agonist **lorcaserin**, the antihistamine **clemizole** (which also is believed to interact with serotonin signaling), and extended-release formulations of the acetylcholinesterase inhibitor **huperzine A**. Other drugs for rare DEEs in development include the persistent sodium channel blocker **PRAX-562** for SCN2A DEE and SCN8A DEE. **NBI-921352**, a selective blocker of the Nav1.6 sodium channel (encoded by SCN8A), is also in clinical development for SCN8A DEE. Several gene therapies are in early clinical development or are expected to enter development soon for monogenic DEEs. **STK-001** and **CO-3527** are antisense oligonucleotide designed to upregulate SCN1A expression in Dravet syndrome. **PRAX-222** is an antisense oligonucleotide designed to decrease SCN2A expression in gain-of-function SCN2A epilepsy. **ETX101** is an adeno-associated virus capsid that delivers a transgene coding for an engineered SCN1A-specific transcription factor to upreglate SCN1A in GABA neurons in Dravet syndrome. Cellular therapies are also being investigated. **NRTX-1001** is a cell therapy consisting of GABA-secreting interneurons derived from human pluripotent stem cells for transplantation to treat mesial temporal lobe epilepsy.

s0240

CLINICAL RELEVANCE FOR HEALTHCARE PROFESSIONALS

p1165 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

b0045

Brivaracetam s0245
- Somnolence, dizziness, fatigue; increased carbamazepine epoxide u0620

Cannabidiol s0250
- Somnolence, fatigue, decreased appetite, diarrhea; transaminase elevations; increased levels of the active clobazam metabolite N-desmethylclobazam, with the potential for excessive sedation u0625

Carbamazepine s0255
- Induction of its own metabolism; nausea, dizziness, blurred vision, ataxia (dose-related); rash and rarely Stevens-Johnson syndrome; hyponatremia; leukopenia; aplastic anemia; hepatic failure u0630

Cenobamate s0260
- Somnolence, dizziness, headache, fatigue, and diplopia; QT shortening; drug reaction with eosinophilia and systemic symptoms (DRESS) u0635

Clobazam s0265
- Somnolence, sedation, lethargy; increases levels of phenytoin and carbamazepine; cannabidiol increases levels of active metabolite N-desmethylclobazam; concomitant use with opioids may result in profound sedation, respiratory depression, coma, and death u0640

Ethosuximide s0270
- Abdominal pain and vomiting; valproate increases ethosuximide levels; abrupt discontinuation may precipitate absence status epilepticus u0645

Felbamate s0275
- Anorexia; aplastic anemia; hepatic failure u0650

Fenfluramine s0280
- Valvular heart disease (aortic or mitral regurgitation), pulmonary hypertension; fatigue, lethargy, somnolence, diarrhea, loss of appetite, pyrexia, and weight loss; dose should be reduced in the presence of stiripentol u0655

Gabapentin and Pregabalin s0285
- At initiation of therapy: sedation, fatigue, dizziness, ataxia u0660

Ganaxolone s0290
- Somnolence, sedation u0665

Lacosamide s0295
- Dizziness, headache, nausea, vomiting, diplopia; prolonged PR interval u0670

Lamotrigine s0300
- Dizziness, blurred vision, headache, insomnia; rash, Stevens-Johnson syndrome, toxic epidermal necrolysis; hepatic failure; risk of serious arrhythmias in patients with certain underlying cardiac disorders, including second- and third-degree heart block, Brugada syndrome, arrhythmogenic ventricular cardiomyopathy, and bundle branch block with left anterior or posterior fascicular block u0675

Levetiracetam s0305
- Irritability, aggression u0680

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CLINICAL PROBLEMS—CONT'D

s0310 u0685
Oxcarbazepine
- Nausea and vomiting, dizziness, blurred vision, ataxia (dose-related); rash and rarely Stevens-Johnson syndrome; hyponatremia; leukopenia; aplastic anemia

s0315 u0690
Perampanel
- Behavioral adverse effects: irritability, aggression, hostility, anger; dizziness, somnolence, headache, falls; increases clearance of carbamazepine, oxcarbazepine, phenytoin

s0320 u0695
Phenobarbital
- Fatigue, dizziness, ataxia, confusion; in children: hyperactivity; hepatic failure, rash, Stevens-Johnson syndrome; many drug interactions; rebound seizures on abrupt discontinuation

s0325 u0700
Phenytoin
- Nystagmus (benign sign); diplopia and ataxia (dose-related); cognitive impairment; hirsutism, coarsening of facial features, gingival hyperplasia; saturation metabolism kinetics

s0330 u0705
Stiripentol
- Somnolence, decreased appetite; increases levels of clobazam and its active metabolite N-desmethylclobazam

s0335 u0710
Tiagabine
- Fatigue, dizziness, somnolence, irritability; spike-wave status epilepticus

s0340 u0715
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)

s0345 u0720
Valproate (divalproex sodium)
- Nausea, vomiting, and other gastrointestinal complaints; fine tremor; hair loss; weight gain; thrombocytopenia; teratogenicity (neural tube defects such as spina bifida, distinctive facial features, congenital heart defects and other musculoskeletal abnormalities); hepatic failure, pancreatitis, hyperammonemia, aplastic anemia; many drug interactions

s0350 u0725
Vigabatrin
- Fatigue, somnolence; irreversible visual loss

s0355 u0730
Zonisamide
- Anorexia and weight loss; kidney stones; heat stroke (children)

TRADE NAMES

b0050 p1400

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) u0735
- Brivaracetam (Briviact) u0740
- Cannabidiol (Epidiolex) u0745
- Carbamazepine (Tegretol, Carbatrol,[a] Equetro,[a] Carnexiv[b]) u0750
- Cenobamate (Xcopri) u0755
- Clobazam (Onfi) u0760
- Clonazepam (Klonopin) u0765
- Diazepam (Valium, Diastat Acudial,[c] Valtoco[d]) u0770
- Divalproex sodium (Depakote) u0775
- Eslicarbazepine acetate (Aptiom) u0780
- Ethosuximide (Zarontin) u0785
- Everolimus (Afinitor) u0790
- Ezogabine (Potiga) u0795
- Felbamate (Felbatol) u0800
- Fenfluramine (Fintepla) u0805
- Fosphenytoin (Cerebyx) u0810
- Gabapentin (Neurontin, Gralise[a,e]) u0815
- Gabapentin enacarbil (Horizant[a]) u0820
- Ganaxolone (Ztalmy) u0825
- Lacosamide (Vimpat) u0830
- Lamotrigine (Lamictal) u0835
- Levetiracetam (Keppra, Keppra XR,[a] Spritam) u0840
- Lorazepam (Ativan) u0845
- Methsuximide (Celontin) u0850
- Midazolam (Nayzilam[d]) u0855
- Oxcarbazepine (Trileptal, Oxtellar XR[a]) u0860
- Perampanel (Fycompa) u0865
- Phenobarbital (Luminal) u0870
- Phenytoin (Dilantin) u0875
- Pregabalin (Lyrica) u0880
- Primidone (Mysoline) u0885
- Rufinamide (Banzel) u0890
- Stiripentol (Diacomit) u0895
- Tiagabine (Gabitril) u0900
- Topiramate (Topamax, Trokendi XR,[a] Qudexy XR,[a] Eprontia) u0905
- Valproic acid (Depakene) u0910
- Valproate sodium injection (Depacon[b]) u0915
- Vigabatrin (Sabril) u0920
- Zonisamide (Zonegran, Zonisade) u0925

[a] Extended release.
[b] Intravenous.
[c] Rectal.
[d] Nasal
[e] Gastroretentive.

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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 to 5 seconds and occur 10 to 20 times during the school day. An EEG shows synchronized three-per-second spike-wave discharges generalized over the entire cortex. Which antiseizure 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 statement 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

FURTHER READING

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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-care/treatments

The American Epilepsy Society website provides information of antiseizure medications, evidence-based guidelines for the treatment of seizure disorders, and drug alerts and US Food and Drug Administration (FDA) news.

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.