CHAPTER 100 Seizures

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PERSPECTIVE

A *seizure* is the clinical manifestation of excessive, abnormal cortical neuron activity. The physical manifestation depends on the area of brain cortex involved and, to a lesser extent, on the specific underlying abnormality. Patients who have recurring seizures without consistent provocation have *epilepsy*, although this term encompasses many disparate clinical syndromes. Seizures also may occur as a predictable response to certain toxic, pathophysiologic, or environmental stresses; these are *reactive* or *secondary seizures*, and patients who experience them do not have epilepsy. In the United States, 10% of people experience at least one seizure in their lifetime; the cumulative incidence of epilepsy is 3%.[1]

The evaluation of patients with seizures, whether ongoing or recent, in the emergency department (ED) may be complex and difficult. A careful history must be elicited to determine the presence of ictal events that represent epilepsy or exposure to ictogenic stimuli (e.g., alcohol, cocaine), significant underlying illness (e.g., meningitis, hypoxemia, hypoglycemia, intracranial mass), or contributing causes (e.g., sleep deprivation in an epileptic). The physical examination should focus on the identification of focal neurologic abnormalities, systemic illness, and signs of toxic exposure. If the patient continues to experience seizure activity, airway protection and abortive therapy must be provided. Laboratory and radiographic evaluation that is guided by historical and physical findings may be limited or unnecessary in some cases. Finally, the appropriate disposition of a patient presenting to the ED with a seizure or with a history of recent seizure requires an understanding of the underlying illness, likelihood of recurrence, indications for maintenance pharmacologic therapy, and state reporting regulations.

In addition to the distinction between primary (epileptic) and secondary (reactive) seizures, many other classifications of ictal events have been proposed.[2-7] Seizures are termed *generalized* or *focal* (*partial*) depending on their clinical manifestations. The former type of seizure results from the abnormal electrical event that simultaneously involves both cerebral hemispheres and is accompanied by loss of consciousness; in the latter, abnormal activity is limited to part of one cerebral hemisphere only. Generalized seizures usually are characterized by rhythmic, tonic-clonic muscle contractions, or *convulsions*, although *nonconvulsive generalized seizures* also occur. Partial seizures can be differentiated further into seizures during which cognition is maintained (*simple partial*) and seizures during which cognition is impaired (*complex partial*). The term *cognition* is defined as involving at least two of the five features—perception, attention, emotion, memory, and executive function[8,9]—and replaces the previously used term *consciousness*, which is both difficult to define and difficult to document. Finally, partial seizures may become generalized (*partial with secondary generalization*).

Inexperienced witnesses may provide histories that are insufficient for accurate categorization of seizures. However, when an accurate history is available, secondary (reactive) seizures typically are generalized, not partial, in nature. The definitive differentiation among these classifications may require electroencephalogram (EEG) recording *during* the seizure, sometimes in association with simultaneous video recording.

Seizures in children, as in adults, are classified as primary (idiopathic) and secondary (symptomatic or reactive). The term *cryptogenic* is used sometimes when seizures are thought to be secondary but no cause has been identified. The history is the most important diagnostic tool in evaluating seizures in children. The actual seizure activity usually is not observed, and the emergency physician must rely on a detailed and accurate history for diagnosis.

Other important terms to describe ictal events include *status epilepticus*, in which seizures occur serially without an intervening return to a normal neurologic condition; *spasm*, which is a specific, debilitating seizure syndrome that occurs in infants; and *myoclonus*, which refers to rhythmic, shock-like muscle contractions also typical for specific seizure syndromes. The *postictal period* is an interval after a seizure, of variable duration, usually characterized by impaired consciousness but sometimes also marked by self-limited focal paralysis or neurogenic pulmonary edema.

PRINCIPLES OF DISEASE

The pathophysiology of seizures at the neuronal level is incompletely understood, with most of what is known coming from animal studies in which either electrical or pharmacologic stimulation is applied directly to brain cortex. To produce generalized ictus, stimuli must be applied to both hemispheres simultaneously. Some studies show the concept of recruitment, which occurs when the initiating neurons' abnormal, increased electrical activity activates adjacent neurons and propagates until the thalamus and other subcortical structures are recruited. The clinical seizure activity typically, but not always, reflects the focus of initiation.[9-11]

What prompts such initiation is unclear. Proposed mechanisms include disruption of normal structure—whether congenital, maturational, or acquired (as with scar tissue)—and disruption of local metabolic or biochemical function. The latter mechanism is better elucidated because the roles of two neurotransmitters—acetylcholine, which is excitatory to cortical neurons, and γ-aminobutyric acid (GABA), which is inhibitory—have been more fully characterized. In sensitive neurons, such as those at an ictogenic focus, subtle changes in the local concentrations of these neurotransmitters can produce sustained membrane depolarization, ultimately followed by local hyperpolarization and recruitment. Recruitment may follow contiguous paths or extend along diverse integrated circuits that are deep and cross the midline.[9-11]

When the ictal discharge extends below the cortex to deeper structures, the reticular activating system in the brainstem may be affected, altering consciousness. In generalized seizures, the focus often is subcortical and midline, which explains the prompt loss of consciousness and bilateral involvement.[9,12] Seizures typically are self-limited; at some point, the hyperpolarization subsides, and the electrical discharges from the focus terminate. This termination may be related to reflex inhibition, loss of synchrony, neuronal exhaustion, or alteration of the local balance of acetylcholine and GABA in favor of inhibition.[9,12]

The systemic manifestations of convulsive ictal activity include hypertension, tachycardia, tachypnea, and hyperglycemia from sympathetic stimulation. With more prolonged convulsions, skeletal muscle damage, lactic acidosis, and, rarely, frank rhabdomyolysis may ensue.[9,10,13] Autonomic discharge and bulbar muscle involvement may result in urinary or fecal incontinence, vomiting (with significant aspiration risk), tongue biting, and airway impairment.

CLINICAL FEATURES

Primary Seizures in Adults

Primary ictal events in adults include events of genetic and of idiopathic origin. Onset is typically during childhood or adolescence, but occasionally idiopathic seizures may begin de novo in adulthood. Because idiopathic seizures are rare, a first-time seizure in an adult requires a thorough ED evaluation.

Focal seizures in adults may be classified as simple partial or complex partial. Simple partial seizures are limited in electrical focus to one cerebral hemisphere and do not cause loss of cognition. Although the specific function of the initiating neurons determines the clinical manifestation of the ictal event (i.e., motor, somatosensory, special sensory, autonomic, or psychic), such clinical manifestations are not sufficiently specific for anatomic localization without an EEG. Typical features of simple partial seizures include focal clonic movements; paresthesias; visual, auditory, olfactory, or gustatory experiences; sweating and flushing; dysphasia; a sense of déjà vu; or a sense of unwarranted fear.[9,11] Motor signs, which by definition remain ipsilateral in simple partial seizures, may spread contiguously in a stepwise fashion (*Jacksonian march*) as neuron recruitment occurs in the motor cortex. There is generally no postictal state after a simple partial seizure.

Complex partial seizures are ictal events that involve impairment of cognition, either at onset or evolving from focal activity. Amnesia for the ictal event is a consistent feature of complex partial seizures, although during the episode the patient may remain responsive to the surroundings. Complex partial seizures typically involve automatisms that are specific to the affected person, such as lip smacking, repeated swallowing or uttering verbal phrases, or picking at clothing. Complex partial seizures generally are associated with an aura, such as a specific smell, taste, visual hallucination, or intense emotional feeling. In contrast with those experiencing generalized seizures, these patients may continue with ongoing motor activity, such as driving an automobile, riding a bicycle, or playing a musical instrument (reactive automatisms), and they may react to their surroundings in a semiappropriate manner.[9] Partial seizures may progress rapidly to generalized seizures. A postictal state is common after complex partial seizures and may persist for hours.[9,11]

Generalized seizures in adults may be convulsive or nonconvulsive. By definition, patients lose consciousness in a generalized seizure, and no aura is present. Some patients may experience a brief, vague prodrome or dysphoric state just before the ictal event. Convulsive generalized seizures are typified by the tonic-clonic, or grand mal, seizure, in which the patient loses consciousness, stiffens with generalized muscular hypertonus, and then rhythmically and violently contracts multiple, bilateral, and usually symmetrical muscle groups. The muscular force may be sufficiently vigorous to result in posterior shoulder dislocation or fractures of thoracic spine vertebral bodies; significant tongue and buccal injuries also may be incurred from biting with repeated jaw muscle contractions. Dysautonomia, including transient apnea, is a potential manifestation of convulsive generalized seizures; urinary incontinence is more common than fecal incontinence. A generalized convulsive seizure generally lasts 1 to 2 minutes and is followed by a postictal state, headache, and drowsiness that may persist for hours. This state must be differentiated in the ED from altered consciousness attributable to other causes.

Nonconvulsive generalized seizures include absence, or petit mal, seizures; myoclonic seizures; tonic seizures; and atonic seizures. Absence seizures in adults are subclassified further as *typical* or *atypical*. Typical absence ictus is characterized by the sudden cessation of normal, conscious activity followed by a nonconvulsive, dissociative state that persists for a few seconds to several minutes before suddenly terminating. Eye movements, blinking, or automatisms may be present. There is no aura and no postictal state. If the seizure occurs midsentence, then the patient typically will resume speaking at precisely the point of interruption without awareness of the intervening event. Absence seizures typically begin in childhood but occasionally develop in adults. Atypical absence seizures are marked by more complicated motor signs, coexistence with other forms of generalized seizures, inconsistent postictal confusion, and irregular EEG abnormalities.[9,11]

Atonic seizures are characterized by focal diminution of muscle tone (limb or head) or generalized loss of postural tone in which the head falls forward and then the body slumps to the ground ("drop attack"), usually landing buttocks first (although this can vary depending on the axis of gravity at the time of the fall). Recovery occurs immediately, and there is either no loss or an extremely brief loss of consciousness. In *myoclonic-atonic seizures*, a brief (less than 100 msec) myoclonic jerk of muscle group of variable anatomy occurs before the episode of atonia.[9] Because typically no postictal state is associated with these episodes, an altered level of consciousness in a patient presenting to the ED after an atonic or myoclonic-atonic seizure should prompt an investigation for head trauma or a toxic or metabolic abnormality.

Status epilepticus is defined as serial seizure activity without interictal recovery or prolonged, continuous seizure activity. Traditionally, status epilepticus was defined as seizure activity lasting longer than 30 minutes, which is the estimated duration necessary for neuronal injury.[14,15] However, because an isolated tonic-clonic seizure rarely lasts more than a few minutes, an operational definition of status epilepticus has been

advocated as either a continuous seizure lasting more than 5 minutes, or more than two discrete seizures without intervening recovery of consciousness.[16] Although it is recognized that the underlying cause of status epilepticus is the predominant factor determining morbidity and mortality, prolonged seizure activity does cause neuronal injury and therefore warrants prompt abortive therapy. Furthermore, status epilepticus may become refractory to treatment over time.[14,17]

The most common cause of status epilepticus is discontinuation of anticonvulsant medication. This situation may be compounded by barbiturate withdrawal when phenobarbital therapy is abruptly withdrawn. Patients may present for the first time with a primary seizure disorder in status. Many other causes of status epilepticus have been documented[9,15,18,19] (Box 100-1). After prolonged status epilepticus or after incomplete treatment, the patient may exhibit very subtle manifestations of continued seizure activity, such as small-amplitude twitching of the extremities or jerking of the eyes, or any visible motor activity may cease while seizure activity detectable on the EEG continues.[9,20-22] Recognition of the latter scenario, termed *nonconvulsive status epilepticus*, requires a high index of clincial suspicion. Prompt treatment is essential; otherwise, neuronal damage can result.

All classes of primary seizures may recur sporadically, randomly, or predictably. Cyclic recurrence has been reported with awakening, sleep deprivation, emotional or physical stress, alcohol, and menses, among other factors. Seizures also may be triggered by specific senory stumuli, the most common of which is visual stimulation in the form of flashing lights, such as strobe lights, television, and video games.[9,23] Seizures also can be caused by auditory, gustatory, tactile or startle triggers that are specific to the affected person. The most common cause of recurrent primary seizures is medication noncompliance.[9,11]

Reactive Seizures in Adults

Reactive or secondary seizures do not result from genetic or idiopathic causes. The conditions that cause reactive seizures may be static (e.g., anatomic scarring), progressive (e.g., degenerative cortical disorders), or transient (e.g., acute electrolyte derangements).

Seizures Caused by Metabolic Derangements

Hypoglycemia is a common metabolic cause of reactive seizures. Ictal activity can occur when the plasma glucose level is less than 45 mg/dL, although some patients may manifest neurologic disturbances even at higher levels.[24] A rapid bedside glucose test should be an integral part of the ED evaluation of the patient exhibiting seizure activity. Convulsive and nonconvulsive seizures and generalized and partial seizures all may occur during hypoglycemia.[24] Patients at the extremes of age are particularly susceptible to glucose stress during acute illness. Hypoglycemia also may result from insulin reaction, a deliberate insulin or hypoglycemic agent overdose, alcoholism, poor nutrition, and sepsis. Hypoglycemic seizures respond to glucose therapy; anticonvulsants are unnecessary.

Cation derangements, notably hyper- and hyponatremia, hypomagnesemia, and hypocalcemia, are other common metabolic causes of ictal activity.[25,26] Hypo-osmolar and hyperosmolar states can precipitate seizures. Disorders of sodium—the primary cation in the extracellular fluid compartment and the primary determinant of serum osmolarity—are most common. Hyponatremia is the most frequently identified electrolyte disorder in hospitalized patients, and sodium levels less than 120 mEq/L often are associated with seizures.[27,28] The rate at which the sodium level decreases, and not the absolute magnitude of the decrease, determines the risk for neurologic manifestation.[27,29] Correcting hyponatremia should be undertaken slowly in the ED, to avoid osmotic demyelination. If seizures are persistent, administration of hypertonic (3%) saline may be indicated.[27] Hypernatremia will result in cerebral edema and seizures in the setting of rapid elevation of serum sodium to greater than 160 mEq/L or during aggressive correction of subacute hyponatremia.[25,29]

Hypercalcemia reduces neuronal excitability and rarely causes seizures; significant hypocalcemia (7.5 mEq/L) is associated, however, with ictal activity. Hypocalcemia may result

BOX 100-1 ETIOLOGY OF STATUS EPILEPTICUS: COMMON CAUSATIVE DISORDERS

Metabolic Disturbances
Hepatic encephalopathy
Hypocalcemia
Hypoglycemia or hyperglycemia
Hyponatremia
Uremia

Infectious Processes
CNS abscess
Encephalitis
Meningitis

Withdrawal Syndromes
Alcohol
Antiepileptic drugs
Baclofen
Barbiturates
Benzodiazepams

CNS Lesions
Acute hydrocephalus
Anoxic or hypoxic insult
Arteriovenous malformations
Brain metastases
Cerebrovascular accident
Chronic epilepsy
Eclampsia
Head trauma
Intracerebral hemorrhage
Neoplasm
Neurosurgery
Posterior reversible leukoencephalopathy
Remote structural injury

Intoxication
Bupropion
Camphor
Clozapine
Cyclosporine
Flumazenil
Fluoroquinolones
Imipenem
Isoniazid
Lead
Lidocaine
Lithium
Metronidazole
Theophylline
Tricyclic antidepressants

CNS, central nervous system.

from hypoparathyroidism, renal failure, or acute pancreatitis and typically is associated with hypomagnesemia, which also can precipitate seizures, particularly at serum levels less than 1 mEq/L. Hypomagnesemia is seen most often as a result of poor nutrition, especially in alcoholic patients. Patients with significant hypomagnesemia or hypocalcemia should be treated empirically for both disorders.[25,26]

Nonketotic hyperosmolar hyperglycemia also is associated with seizure activity. Partial seizures, including partial status, predominate. These seizures do not respond to anticonvulsants; rather, they are best managed with gradual correction of fluid deficits and glucose excess.[30-32]

Seizures may complicate the course and treatment of renal failure.[33] Ictal activity occasionally complicates uremic encephalopathy, is more common in conjunction with acute fluid and electrolyte shifts during dialysis (*dialysis disequilibrium syndrome*), and can occur as a complication of immunosuppressive therapy after renal transplantation.

Thyroid hormones lower seizure threshold, and consequently Graves' disease and thyrotoxicosis may occasionally manifest as seizures, including status epilepticus.[9,34,35] Seizures also occur with hypoparathyroidism as a direct result of secondary hypocalcemia.[36]

Seizures Caused by Infectious Diseases

Infectious diseases can cause seizures independent of a purely febrile mechanism. These seizures generally result from primary central nervous system (CNS) infections but occasionally arise from other septic sources. The most important ictogenic infections are meningitis, encephalitis, cerebral abscess, cerebral parasitosis, and human immunodeficiency virus (HIV) disease and associated opportunistic infections, with their protean CNS manifestations.

Seizures can occur as a result of the acute inflammatory response or as sequelae to bacterial or viral meningitis. During the acute course of their illness, up to 40% of patients with meningitis will have at least one seizure; this is more common at the extremes of age but is rarely associated with residual epilepsy.[9,37,38] By contrast, seizures occur in up to 50% of patients with a brain abscess, and epilepsy develops in 40% of the survivors.[9,39] After meningitic seizures are terminated with benzodiazepines, phenytoin should be initiated temporarily.[9]

Viral meningoencephalitides, the most common of which are caused by the herpes simplex virus, also are associated with seizures. These seizures may be generalized or partial, often recur during the acute phase of the illness, and may persist after the illness resolves.[9]

The parasitic CNS infection neurocysticercosis is relatively common in areas of the United States in which the population includes immigrants from Latin America. Seizures complicate 50 to 90% of neurocysticercosis cases.[40] Latent syphilis also may be a cause of adult-onset seizures. Primary HIV disease of the CNS, its attendant infectious and mass lesion complications, such as from toxoplasmosis and lymphoma, and the demyelinating infection progressive multifocal leukoencephalopathy constitute a significant cause of generalized and partial seizures.[41] Choosing an antiepileptic drug for an HIV-infected patient with seizures should be done in consultation with infectious disease and neurology specialists, because of the well-recognized increase in adverse effects of and interactions between antiepileptic drugs and antiviral medications.

Seizures Caused by Drugs and Toxins

The list of substances reported to cause seizures either as an idiosyncratic side effect of therapeutic use or as a manifestation of toxic overdose is extensive.[18,42] The recognition of this etiologic category is crucial in the ED setting. Seizure activity should be viewed as a dire sign of toxicity and may herald the onset of life-threatening instability.

Seizures may occur after therapeutic doses of antimicrobials, cardiovascular agents, neuroleptics, and sympathomimetics.[43] Seizures also may result from exposure to plant toxins, insecticides and rodenticides, and hydrocarbons. Certain over-the-counter supplements also have been associated with seizures, either alone or through adverse interactions with prescription medications.[44,45] The most common drug-associated and toxin-associated seizures occur, however, in conjunction with illicit drugs, such as cocaine, amphetamines, and phencyclidine; with overdoses of anticholinergic agents, such as cyclic antidepressants and antihistamines; as a manifestation of withdrawal from ethyl alcohol and sedative-hypnotics; and with toxic levels and deliberate overdoses of diverse medications including aspirin, theophylline, meperidine, isoniazid, lithium, and the anticonvulsants phenytoin and carbamazepine.[42,46] Standard ED therapeutic measures usually are effective for management of toxic seizures. In some cases, specific antidotal therapy is available, such as alkalinization for cyclic antidepressant and salicylate overdoses, pyridoxine (vitamin B_6) for isoniazid overdose, and hemodialysis for salicylate and lithium toxicity.

Because of its prevalence in urban ED patient populations, cocaine toxicity warrants special mention.[47] Seizures may occur after isolated recreational use or chronic abuse, after overdose, and in "body packers" and "body stuffers."[48] Cocaine-related seizures may be a manifestation of direct CNS toxicity or an indirect result of hypoxemia from cardiac toxicity.[49] Seizures in cocaine-intoxicated patients must be managed as part of the overall toxic reaction, which often includes high fever, rhabdomyolysis, and cardiac arrhythmias. A benzodiazepine is the appropriate initial therapeutic agent.

Ethyl alcohol is another common toxic cause of seizures. Ictal events may occur with acute inebriation but are more common during withdrawal from alcohol.[50] Withdrawal seizures typically are generalized, are recurrent, and may begin within 6 hours of cessation of or decrease in alcohol consumption. Through a phenomenon termed *kindling*, the risk and severity of seizures increase with each episode of withdrawal. Kindling implies that with each episode of alcohol withdrawal, the seizure threshold is lower. Alcoholic patients with seizures must be evaluated for other related, concomitant ictogenic problems (e.g., hypoglycemia, electrolyte derangements, head trauma, co-ingestion of other toxins, pregnancy). The preferred treatment for alcohol-associated seizures is with benzodiazepines; these drugs substitute for the GABA-enhancing effect of ethanol in the CNS.

Seizures Caused by Trauma

Post-traumatic seizures can occur acutely as a result of blunt or penetrating head trauma or as a post-traumatic sequela. Immediate post-traumatic seizures occur within 24 hours of injury. Epidural, subdural, and intracerebral hematomas and traumatic subarachnoid hemorrhages all can be acutely ictogenic, particularly as intracranial pressure rises. More often, however, the onset of seizure activity is delayed for at least several hours. Early post-traumatic seizures occur within 1 week of injury, whereas late post-traumatic seizures occur after 1 week. Immediate and early post-traumatic seizures are more common in children than in adults, and children also are more likely than adults to present in status epilepticus in the immediate or early post-traumatic phase.[51,52] Within the first year after significant head trauma, the incidence of seizures is at least 12 times that in the general population.[53]

The severity of head injury correlates with the likelihood of post-traumatic seizures. The incidence of seizures after injury with neurologic deficit without dural violation is 7 to 39%; when the dura is disrupted, the incidence is 20 to 57%.[53] Imaging studies should be performed urgently because the likelihood of identifying significant cerebral edema, cerebral contusions, hematomas, and depressed skull fractures is relatively high.[52,54] Antiepileptic drugs are recommended for prophylaxis against post-traumatic seizures occurring within the first 7 days after severe brain injury in adults; however, they have not been shown to be effective in preventing late post-traumatic seizures.[51,55,56]

Seizures Associated with Malignancy or Vasculitis

Seizures are a common manifestation of primary and metastatic CNS neoplasms. They also may complicate cancer treatment as a result of postsurgical scarring or chemotherapy-related electrolyte derangements, hematologic abnormalities, or immunosuppression. Although any CNS tumor can be ictogenic, low-grade and slow-growing primary neoplasms (e.g., well-differentiated gliomas and oligodendrogliomas) are implicated most commonly.[57] In such cases, seizures, which most often are partial with secondary generalization, may be the initial clinical manifestation. A new-onset seizure in a patient with a non-CNS primary malignancy, such as melanoma and tumors of the lung, breast, colon, germ cells, or renal cells, should prompt consideration of CNS metastasis and warrants neuroimaging.

Seizures also may be the presenting manifestation of CNS vasculitis in patients with systemic lupus erythematosus and polyarteritis nodosa. These commonly are complex partial seizures that give a general indication of the acute inflammatory focus. Sometimes secondary generalization follows.[58]

Seizures Caused by Strokes, Arteriovenous Malformations, and Migraines

Ischemic or hemorrhagic stroke is the cause of new-onset seizures in 40 to 54% of elderly patients.[59] The overall incidence of seizures with stroke ranges from 4 to 15%; more than one half occur within the first week after stroke. The incidence of epilepsy after stroke is 4 to 9%.[60,61] Seizures that occur acutely with stroke are thought to result from local metabolic alterations in the CNS; these events are transient, and the seizures often are focal and self-limited. Seizures that develop later are more likely to be generalized.

Seizures also occur in conjunction with unruptured cerebrovascular aneurysms and arteriovenous malformations.[9] Arteriography may be required to confirm the diagnosis; unruptured arteriovenous malformations are easier to detect on an enhanced cranial computed tomography (CT) scan than are smaller, unruptured aneurysms. Seizures also may arise in concert with vascular headaches, either coincidentally, by migrainous activation of an epileptic focus, or after vascular headache has induced cerebral infarction that becomes an epileptic focus.[62]

Seizures Caused by Degenerative Disease of the Central Nervous System

In approximately 5% of patients with multiple sclerosis, focal or generalized seizures develop during the course of their illness. These seizures must be differentiated from the tonic spasms that may occur in multiple sclerosis. Patients with demyelinating disease also should be evaluated for the other types of reactive seizures.[9]

CNS degeneration associated with aging, including dementia and Alzheimer's disease, increases the risk of reactive seizures and epilepsy.[59,63] The elderly also are more likely to have other ictogenic problems (e.g., stroke, brain neoplasm, toxic and metabolic disturbances, blunt head trauma from falls). Maintenance treatment of elderly patients with epilepsy often is complicated by drug-drug interactions, and breakthrough seizures may result even when patients are compliant. Although the incidence of unprovoked seizures increases after age 60 years, ED management of these patients must include a thorough evaluation for causes of secondary seizures.[59]

Gestational Seizures

Seizures associated with pregnancy are divided into two categories: *gestational epilepsy*, in which hormonal and metabolic changes exacerbate underlying epilepsy or adversely influence serum levels of anticonvulsants, and *eclampsia* or *toxemia*, which is a gestational hypertensive encephalopathy manifested by seizures, hypertension, coma, proteinuria, and edema. For the former, antiepileptic therapy should be tailored by the patient's neurologist and obstetrician to maximize seizure control and minimize the risk of teratogenic effects.[64] Convulsive generalized status epilepticus in pregnancy jeopardizes both mother and fetus. The definitive treatment for eclamptic seizures is magnesium sulfate. Simultaneous reduction in blood pressure using hydralazine, labetalol, or nifedipine is recommended.[65]

Psychogenic Nonepileptic Seizures

Psychogenic seizures, or pseudoseizures, are functional events that may be associated with alterations in consciousness, abnormal movements and behaviors, and autonomic changes. They are not the result of abnormal CNS electrical activiy. Psychogenic seizures may be primarily motor and mimic convulsive generalized seizures, including refractory status epilepticus, or they may be nonconvulsive and mimic either absence or complex partial seizures. Although certain features of convulsive psychogenic seizures may suggest the diagnosis, no clinical criteria are 100% specific; simultaneous video and EEG recordings may be required to confirm the diagnosis.[9]

The ED evaluation of these patients is difficult, because seizures and pseudoseizures can coexist. All but obviously functional abnormalities should be treated as for true ictus pending formal neurologic evaluation. Many patients with pseudoseizures are not deliberately attempting to mislead the examining physician. The long-term treatment of patients with confirmed pseudoseizures may include direct confrontation, intensive psychotherapy, and a placebo.

Postictal States

The postictal state that follows most generalized seizures typically is characterized by a decreased level of arousal and responsiveness, disorientation, amnesia, and headache. These conditions may persist for only a few minutes or for many hours and may not be consistent from seizure to seizure. The most important consideration in ED management of the postictal state is to monitor and investigate the altered mental status after a seizure; otherwise, dangerous underlying metabolic or toxic abnormalities may be overlooked. At the minimum, airway positioning maneuvers, pulse oximetry, rapid glucose determination, and cardiac rhythm monitoring are necessary.

Two unusual postictal manifestations may provoke particular consternation in the ED: postictal paralysis and neurogenic pulmonary edema. Postictal paralysis, or *Todd's paralysis*, may

follow generalized or complex partial seizures and is a focal motor deficit that may persist up to 24 hours. Weakness of one extremity or a complete hemiparesis may occur; in the latter case, the patient must be safely restrained to avoid falls caused by a combination of weakness and diminished responsiveness resulting from the postictal state. Todd's paralysis is associated with a high likelihood of an underlying structural cause for the seizure.

Neurogenic pulmonary edema is a relatively common, although often subclinical, complication of any structural CNS insult, including seizure, trauma, and hemorrhage.[66] Neurogenic pulmonary edema probably is caused by centrally mediated sympathetic discharge and generalized vasoconstriction, coupled with increased pulmonary capillary membrane permeability. After a seizure, neurogenic pulmonary edema can be confused clinically and radiographically with aspiration pneumonia. Neurogenic pulmonary edema is managed with ventilatory support, including positive end-expiratory pressure and other aggressive measures to reduce intracranial pressure. Hypoxia or other clinical evidence of pulmonary congestion after a seizure should prompt consideration of neurogenic pulmonary edema.[67]

DIAGNOSTIC STRATEGIES

First-Time Seizures

The essential components of the seizure evaluation in the ED setting are discussed in Chapter 16. An accurate and thorough history of the ictal event, any known or potential precipitants or exposures, and the patient's medical problems must be obtained. A thorough physical examination, including a complete neurologic examination, is essential. Any identified focal neurologic deficits must be monitored for progression or resolution. Appropriate ancillary studies may be comprehensive, but if precipitants (e.g., hypoglycemia, intoxication) are known, studies may be comparatively limited. Although the Academy of Neurology recommends neuroimaging, by either CT or magnetic resonance imaging (MRI), for all adults presenting with an apparent unprovoked first seizure,[68] the usefulness of emergent imaging depends on the clinical situation.

An emergent cranial CT scan is indicated when a serious structural lesion is suspected on clinical grounds, including presence of a new focal deficit, persistent altered mental status, fever, recent trauma, persistent headache, history of cancer, anticoagulant use, suspicion or known history of AIDS, age older than 40 years, and partial-complex seizure.[69] A reasonable approach may be to obtain scans on an outpatient, follow-up basis in patients who have recovered completely from the ictal event and in whom no apparent cause has been elucidated; if reliable follow-up care is unlikely or even questionable, the CT scan should be obtained in the ED to ensure its completion. In patients with known epilepsy and recurrent seizures, the same considerations apply, but in addition, epileptic patients with a change in seizure pattern, prolonged postictal state, or persistent abnormal mental status should be scanned in the ED.

The decision to initiate anticonvulsant therapy after a single seizure depends on the etiology of the seizure. Seizures due to structural lesions, such as stroke, tumor, or head injury, are likely to recur and may warrant antiepileptic medication. However, such patients also are likely to be admitted to the hospital if the lesion is newly discovered. For patients with a single unprovoked seizure, most authorities now agree that antiepileptic therapy should not be initiated; rather, the patient should be discharged with referral for neurologic consultation.[9,70] The rationale for this approach is threefold. First, the diagnosis may be incorrect, especially if the seizure-like activity was not witnessed by ED personnel. It is estimated that 20 to 25% of patients diagnosed as having seizures are found to have been misdiagnosed, with the most frequent alternative diagnoses being cardiovascular and psychopathologic.[71-74] Second, the patient may not have a recurrent seizure. It is estimated that less than 50% of patients who have had a single unprovoked seizure will experience a recurrent seizure within 2 years.[9,70,75,76] Furthermore, whereas treatment decreases the risk of early recurrent seizure, it does not affect long-term prognosis of epilepsy,[70,77,78] nor does it have an impact on patient quality of life,[79] with the exception of driving limitations, which are prolonged in a patient with a recurrent seizure. Third, antiepileptic medications have side effects that may outweigh the benefit of treatment, especially in women of childbearing age, owing to the teratogenic risk of antiepileptic drugs, and in patients with liver, kidney, or hematologic disorders and patients already receiving multiple medications.

Recurrent Seizures

The initial approach to stabilization of a patient with a known seizure disorder does not differ from that for a new-onset patient; this includes a rapid blood glucose determination. The most common cause of seizures in a patient with a diagnosed seizure disorder is noncompliance with medications.[9] However, supratherapeutic and toxic levels of some anticonvulsants, such as carbamazepine, phenytoin, and lamotrigine, whether attained chronically or after acute overdose, can also *cause* seizures.[80-83] Accordingly, it is prudent to check the serum drug level, if this test is available, before giving a full loading dose of anticonvulsants to patients on long-term therapy. Meanwhile, a thorough history and physical examination should focus on intercurrent illness or trauma, drug or alcohol use, potential adverse drug-drug interactions with anticonvulsants, a recent change in anticonvulsant dosing regimens, and any change in ictal pattern or characteristics. Clinical indications should dictate the selection of other laboratory or radiographic tests.

DIFFERENTIAL CONSIDERATIONS

Even when a "seizure" is witnessed in the ED, other abnormal movements and states of consciousness can be confused with ictal activity. The most common misdiagnoses are cardiovascular (syncope) and psychogenic, but other considerations in the differential diagnosis include hyperventilation and breath-holding, certain toxic and metabolic states, transient ischemic attacks, narcolepsy, and some movement disorders.[9,11,72,73,84]

Syncope—whether vasodepressive (e.g., "vagal" or micturition syncope), orthostatic, or arrhythmogenic (e.g., paroxysmal ventricular tachycardia or fibrillation, long Q-T syndrome)—may be confused with ictal events; differentiating among these may be particularly difficult when episodes are recurrent—hence the consideration "fit versus faint." Generally, ictal tonic-clonic movements are much more forceful and are more prolonged than the "twitches" sometimes associated with fainting. In addition, most seizures are characterized by a postictal state, which, with the important exception of atonic drop attack ictus, is not a feature of syncope. The cause of an unwitnessed, unprovoked loss of consciousness with a fall, after which the patient presents to the ED, may be difficult to classify. Retrograde amnesia suggests an ictal diagnosis. Hyperventilation syndrome can be associated with mood disturbances, paresthesias, and posturing movements of the distal extremities. Manifestations of toxic and metabolic disorders

that may mimic ictus include delirium tremens and alcoholic blackouts, the alteration in consciousness associated with hypoglycemia and acute intermittent porphyria, the buccolingual spasms of phencyclidine intoxication, and the tonic spasms caused by tetanus, strychnine, and camphor.[11] Nonictal CNS events, such as transient ischemic attacks, transient global amnesia, and atypical migraines, may manifest in a manner similar to that in absence seizures and postictal states such as Todd's paralysis. Carotid sinus hypersensitivity, which can even result from a too-tight necktie, may cause drop attacks.[85] Narcolepsy (recurrent irresistible daytime sleepiness), especially when it occurs with cataplexy (sudden falls), may be associated with hallucinations and abnormal movements. It can be differentiated from seizure activity by the history and response to stimulation. Movement disorders, such as hemiballismus and tics, usually are associated with other neurologic problems. Finally, dissociative states such as fugue and panic attacks can be confused with seizures. An EEG is an appropriate diagnostic option in unclear cases.

MANAGEMENT

Immediate Management

ED management of a patient experiencing a seizure begins with active, anticipatory airway management. In generalized ictus, the gag reflex is suppressed, and vomiting often is complicated by aspiration of gastric contents. The patient should be placed in a left lateral decubitus position, and any dentures should be removed. A bite-block should be placed to protect the tongue and allow access for suctioning.

If the patient is persistently apneic or if an unavoidable airway threat is present, endotracheal intubation is warranted for definitive protection. A benzodiazepine should be used as an induction agent in the hope that its action may terminate the seizure or obviate the need for tracheal intubation. Trismus may necessitate use of a short-acting neuromuscular blocking agent to facilitate intubation.

In general, the first-line pharmacologic agent for treatment of any active seizure is a parenteral benzodiazepine. Because benzodiazepines directly enhance GABA-mediated neuronal inhibition, they affect clinical and electrical manifestations of seizures. Benzodiazepines are effective in terminating ictal activity in a majority of patients and have been shown to be more effective than phenytoin in terminating status epilepticus.[86,87] Although phenobarbital appears to be as effective as the benzodiazepine lorazepam in terminating status epilepticus, the associated high risk of hypoventilation and hypotension limits its use as a first-line agent.[87]

Benzodiazepines available in the ED setting include diazepam (Valium), lorazepam (Ativan), and midazolam (Versed) (Table 100-1). All three may be used in patients of any age, and all share the following characteristics: rapid efficacy (seconds to minutes), relatively short duration of anticonvulsant action, a sedative effect, and the potential for hypotension and respiratory depression. Lorazepam has emerged as the drug of choice for the initial management of epilepsy, because it terminates seizure rapidly (within 2 minutes) and has a longer duration of action (4 to 6 hours, compared with 20 minutes for diazepam), thus necessitating fewer repeat doses.[88-91] For this reason, it also is the preferred agent for control of alcohol withdrawal seizures.[92,93] Lorazepam is available intramuscularly and as a sublingual preparation for out-of-hospital control of seizures in children.[9] An advantage of diazepam is that it is in liquid form at room temperature and is therefore available premixed in resuscitation kits, and it can be administered quickly and without a need for reconstitution by the intravenous, endotracheal, or intraosseous route. It also is available in a rectal gel formulation. Its onset of action with intravenous administration is within 10 to 20 seconds, but a 50% chance of recurrent seizure within 2 hours if diazepam is used alone has been noted.[87] Midazolam's onset of action is within 1 minute; it is available in both intranasal and buccal formulations,[94] and among the benzodiazepines it has the least cardiovascular effect.[91]

Second-line abortive anticonvulsant therapy consists of phenytoin (Dilantin) and phenobarbital. Phenytoin reduces the repetitive firing of action potentials through sodium channel blockade, thereby stabilizing neuronal membranes.[9] Phenytoin neither sedates patients nor causes respiratory depression, but rapid intravenous administration of phenytoin in its propylene glycol diluent may cause hypotension and cardiac bradydysrhythmias, as well as local vascular injury, including venous thrombosis and localized tissue necrosis (purple glove syndrome).[95-97] It should therefore be administered through a 20 gauge or larger line proximal to the forearm, at a rate no faster than 50 mg/minute, and the patient should have a cardiac monitor. Phenytoin's onset of action is within 10 to 30 minutes, and intravenous administration typically requires at least 20 minutes.[98] The duration of action is approximately 24 hours. Continued benzodiazepine dosing is appropriate until phenytoin achieves adequate brain levels.

Fosphenytoin is a water-soluble prodrug form of phenytoin, with a more physiologic pH. Its main advantages are that it is not likely to precipitate during intravenous infusion and that it also can be administered intramuscularly, although the volume required for full loading by the intramuscular route may be in the range of 20 mL or more.[99] Although fosphenytoin can be infused more rapidly, the time to therapeutic concentration of the active drug is the same as for intravenous phenytoin.[100] The hemodynamic advantages of fosphenytoin over intravenous phenytoin have not proved to be significant.[101,102] Its use is most appropriate when intravenous access is not obtainable or when the intravenous line is of small gauge, as is often the case in children or the elderly.[88] If levels of phenytoin or phenobarbital are subtherapeutic in a patient already being treated for seizures, loading doses can be given intravenously; alternatively, an adjusted oral dosing schedule can be prescribed to boost the serum level over 24 to 48 hours. Oral loading of phenytoin is associated with fewer adverse events than those noted with loading with either intravenous phenytoin or fosphenytoin,[101] but its use may be limited when therapeutic activity is required urgently.

Phenobarbital is similar to benzodiazepines in that it binds to and enhances the inhibitory neurotransmitter GABA, thereby acting as a CNS depressant that decreases ictal and physiologic cortical electrical activity. Sedation and depression of respiratory drive and blood pressure must be anticipated,[91] and, for this reason, nonsedating phenytoin is preferred. The onset of action of phenobarbital is within 15 to 30 minutes, and the duration of action is 48 hours.

Valproic acid administered intravenously has recently been recognized as a safe and effective treatment for seizures, especially in patients with allergies to phenytoin, the elderly, and patients with cardiorespiratory instability who might be at increased risk of adverse events from phenytoin.[103-105] Valproic acid administered intravenously has been shown to be as effective as phenytoin given intravenously in patients with benzodiazepine-refractory status epilepticus, with fewer cardiopulmonary side effects.[106] Hyperammonemic encephalopathy after valproic acid loading has been reported and should be evaluated by determination of serum ammonia level in a patient who does not regain consciousness after seizure resolution.[19,107] Appropriate ED dosing regimens for the

Table 100-1 Drugs Used in the Abortive Treatment of Status Epilepticus in the Emergency Department

GENERIC NAME	BRAND NAME	ADULT DOSE	COMMENTS
Diazepam	Valium	5–10 mg IV every 10 minutes, up to 30 mg per 8-hour period	May be given per rectum in pediatrics (0.3–0.5 mg/kg)
Lorazepam	Ativan	0.1 mg/kg IV (usually 4 mg in adult); may repeat in 10 minutes, then 0.01–0.1 mg/kg per hour infusion	Preferred benzodiazepine owing to its longer duration of action
Midazolam	Versed	0.2 mg/kg IV bolus, then 0.05–0.6 mg/kg per hour infusion	May be given intranasally (0.2 mg/kg)
Phenytoin	Dilantin	20 mg/kg IV at <50 mg/minute	Cardiac and blood pressure monitoring during infusion; large-bore intravenous line
Fosphenytoin	Cerebyx	20 PE/kg IV at 150 mg PE/minute	Cardiac monitoring Less risk of infusion site reaction; may be given IM
Phenobarbital	Luminal	20 mg/kg IV, then 5–10 mg/kg every 20 minutes, up to 2 g	May be given as IM loading dose
Valproate	Depakote	20–40 mg/kg at ≤6 mg/kg per minute	Unlabeled use
Propofol	Diprivan	1–2 mg/kg IV bolus, then 5–10 mg/kg per hour infusion	Intubation required; monitor hemodynamics
Pentobarbital	Numbutal	10–20 mg/kg IV load over 1–2 hours, then 0.5–1 mg/kg per hour infusion	Intubation required; monitor hemodynamics
Isoflurane	Forane, Terrell	Via general endotracheal anesthesia	Monitor with EEG

EEG, electroencephalogram; PE, phenytoin equivalent.
Data from Lowenstein DH: Treatment options for status epilepticus. Current Opin Pharmacol 5:334, 2005; Engel J Jr, Pedley TA (eds): Epilepsy: A Comprehensive Textbook, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2008.

benzodiazepines, phenytoin, fosphenytoin, phenobarbital, and valproic acid are listed in Table 100-1.

Although such agents are being given to abort ongoing seizure activity, ED management must include a search for other underlying reversible causes. This search may prompt administration of dextrose for hypoglycemia, pyridoxine (vitamin B_6) for isoniazid overdose, sodium for hyponatremia, or magnesium for eclampsia.

Eclampsia complicates 1 in 1000 deliveries in the United States[108] and can occur ante partum (91% of cases occur after 28 weeks of gestation), in the peripartal period, or up to 4 weeks post partum.[109,110] Abortive treatment for eclamptic seizures is with magnesium sulfate, which is superior to either diazepam or phenytoin in limiting maternal mortality and preventing further seizures in eclampsia.[111,112] The loading dose of magnesium sulfate is 4 to 6 g, followed by an infusion of 2 g/hour for 24 hours.[65,111,113] Because hypermagnesemia may cause respiratory arrest, it is essential to monitor patients for hyporeflexia, which precedes respiratory compromise. In the uncommon event of excessive neuromuscular blockade secondary to respiratory compromise caused by magnesium sulfate, 1 g of 10% calcium gluconate is an effective reversal agent.[65] Simultaneous reduction in blood pressure in the eclamptic patient, using hydralazine, labetalol, or nicardipine, is recommended.[65]

Nonpregnant patients who continue having seizures in the ED despite management with benzodiazepines, phenytoin, or phenobarbital are likely to meet the clinical criteria for refractory status epilepticus. Additional therapeutic measures include use of valproate, midazolam infusion, propofol infusion, barbiturate coma, and general inhalational anesthesia. Valproate, which increases GABA concentration, may be given intravenously in status epilepticus (see Table 100-1).[22] Another alternative is the use of propofol, a nonbarbiturate anesthetic agent with hypnotic and anticonvulsant activity. Studies suggest that propofol acts at a location other than the benzodiazepine-binding site and modifies the chloride channel by a mechanism that is different from, and possibly synergistic with, those for benzodiazepines and barbiturates. Propofol usually is administered as an intravenous loading dose of 1 to 3 mg/kg; this is followed by an infusion of 1 to 15 mg/kg per hour,[114] with continuous EEG monitoring to ensure persistent burst suppression.[115]

Barbiturate coma is effective in terminating seizures by facilitating GABA, although it also suppresses all brainstem function. Neurologic consultation is advisable beforehand, however, because barbiturate coma may induce respiratory arrest, myocardial depression, and hypotension while decreasing intracranial pressure and increasing cerebral perfusion. The preferred agent for barbiturate coma is pentobarbital (see Table 100-1). Patients require intubation and ventilatory support, continuous cardiac monitoring, and invasive hemodynamic monitoring. Pressors may be required to support the blood pressure.[116]

Isoflurane anesthesia is one final alternative in the management of refractory ictus. Halothane is associated with more hemodynamic and hepatotoxic complications. Isoflurane suppresses electrical seizure foci and is easily titratable. Patients managed with barbiturate coma or inhalational anesthesia require intubation and mechanical ventilation. Intubation of a patient with ongoing seizure activity is best facilitated by using a benzodiazepine as an induction agent and lidocaine (1 mg/kg) as a pretreatment medication. Lidocaine reduces the increase in intracranial pressure that reflexively results from laryngoscopy and intubation.

The visible manifestations of convulsive ictus are extinguished by neuromuscular blockade. When a seizing patient is paralyzed and intubated, it cannot be assumed that pharmacologic therapy has terminated the seizure. Anticonvulsants should be administered, and EEG monitoring of the patient should be arranged. Without EEG, detection of seizure activity in a heavily sedated or paralyzed patient is difficult.

Long-Term Management

Identifying a new-onset seizure disorder in the ED should prompt consideration of the need for further management in the following three areas: pharmacologic, psychosocial, and legal. The primary dilemma concerns whether to initiate prophylactic anticonvulsant therapy after one seizure. The deci-

sion to treat should be based on (1) ensuring that the diagnosis of seizure is correct, (2) ascertaining the likelihood of seizure recurrence, (3) assessing the benefit versus risk of anticonvulsant therapy, and (4) discussing with the patient their approach to risk. Even when witnessed in the ED, apparent ictal activity may not be a seizure. Diagnosing a seizure is more difficult when the event resolved before the patient's arrival at the ED and is based on witness reports. In patients diagnosed with a seizure, 20 to 25% are subsequently found to have been misdiagnosed.[72,74,117]

The risk of seizure recurrence is difficult to estimate in the ED setting. In patients with an initial unprovoked seizure, the 2-year risk of recurrence without treatment generally is considered to be less than 50%.[70,75,76] The presence of EEG abnormalities suggests greater risk, but this information usually is unavailable in the ED setting. Other factors associated with an increased risk of recurrence are partial (versus generalized) ictus, status epilepticus, a history of intracranial surgery or trauma, and the presence of a persistent neurologic abnormality, such as Todd's paralysis.

The presence of specific underlying conditions may affect the decision to institute long-term therapy. For example, it would be reasonable to initiate antiepileptic therapy for an initial seizure in an HIV-positive patient when the seizure is thought not to be due to correctable factors such as drug toxicity or metabolic derangement.[41,70] Alcohol-related seizures are notoriously unresponsive to anticonvulsants. Prophylaxis against post-traumatic seizures beyond the first week after injury probably is unnecessary,[118] but the occurrence of early post-traumatic seizures should prompt at least short-term initiation of therapy.[119] Furthermore, if a patient not receiving antiepileptic therapy presents to the ED with a second seizure, then initiating treatment is warranted because of the estimated 70% risk of recurrent events.[120]

The side effects of anticonvulsants can be debilitating for the patient (Table 100-2). These effects must be considered before such therapy is initiated, particularly in women of reproductive age, because some anticonvulsants are teratogenic and furthermore may precipitate failure of oral contraceptives.

In the absence of specific underlying conditions that increase risk of recurrence, most authorities do not recommend initiation of anticonvulsant therapy from the ED after a single unprovoked seizure in adults.[11,78,79,121] If the seizure was provoked, the decision should be based on whether the provoking factor can be corrected; if it cannot, anticonvulsant therapy should be instituted. The anticonvulsant dosing regimen for a patient with known epilepsy should be modified only in consultation with the patient's physician (Table 100-3).

Drug monotherapy is always preferable in anticonvulsant regimens. The choice of drug to initiate antiepileptic therapy

Table 100-2 Important Adverse Effects and Drug-Drug Interactions of Anticonvulsants

GENERIC NAME	TRADE NAME	IMPORTANT ADVERSE EFFECTS	P-450 LIVER ENZYME METABOLIZERS*
Carbamazepine	Tegretol	Rash, leukopenia, hyponatremia, cardiac dysrhythmias (elderly), weight gain	Inducer
Clonazepam	Klonipin	Sedation, ataxia, irritability	No
Ethosuximide	Zarontin	Sedation, ataxia, nausea, anorexia	
Felbamate	Felbatol	Rare fatal aplastic anemia, hepatotoxicity, headache, anorexia, vomiting, insomnia	Inducer
Fosphenytoin	Cerebyx	Nystagmus, ataxia, sedation, headache	Inducer
Gabapentin	Neurontin	Sedation, ataxia, tremor	No
Lamotrigine	Lamictal	Hypersensitivity reaction (risk of renal failure, liver failure, DIC), rash (SJS, TEN), ataxia, headache, nausea	Inducer and inhibitor†
Levetiracetam	Keppra	Emotional lability, sedation, dizziness, infections (colds)	No
Oxcarbazepine	Trileptal	Hyponatremia, rash, dizziness, headache, fatigue	Inducer and inhibitor
Phenobarbital	Luminal	Sedation, depression, cognitive slowing, decline in libido, osteomalacia	Inducer
Phenytoin	Dilantin	Gingival hyperplasia, hirsutism, nystagmus, ataxia, sedation, nausea, osteoporosis, leukopenia, phenytoin hypersensitivity syndrome‡	Inducer
Pregabalin	Lyrica	Weight gain	No
Primidone§	Mysolline	Sedation, depression, cognitive slowing, decline in libido, acute toxicity after first dose	Inducer
Tiagabine	Gabitril	Dizziness, depression, tremor, poor concentration	No
Topiramate	Topamax	Cognitive slowing, anorexia, nephrolithiasis, paresthesias, metabolic acidosis, rare glaucoma	Inducer
Valproate	Depakote	Thrombocytopenia, tremor, weight gain, male-pattern hair loss, rare hepatotoxicity, osteoporosis	No
Zonisamide	Zonegran	Sedation, cognitive slowing, ataxia, anorexia, rash	No

*All inducers of liver enzymes reduce the efficacy of oral contraceptives.
†OCP also reduces Lamictal serum levels.
‡Phenytoin hypersensitivity syndrome includes rash, fever, hepatitis, lymphoid hyperplasia, and blood dyscrasias. Side effects of intravenous phenytoin include hypotension, arterioventricular block, and purple glove syndrome (edema, pain, and discoloration of the limb distal to the site of infusion).
§Primidone is a congener of phenobarbital.
DIC, disseminated intravascular coagulation; OCP, oral contraceptive pills; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.
Data from Engel J Jr, Pedley TA (eds): Epilepsy: A Comprehensive Textbook, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2008; Harden CL, Leppik I: Optimizing therapy of seizures in women who use oral contraceptives. Neurology 67:S56, 2006; French JA, et al: Efficacy and tolerability of the new antiepileptic drugs I: Treatment of new onset epilepsy: Report of the Therapeutics and Technology Assessment Subcommittee and Quality Standards Subcommittee of the American Academy of Neurology and the American Epilepsy Society [see comment]. Neurology 62:1252, 2004; and Mattson RH: Efficacy and adverse effects of established and new antiepileptic drugs. Epilepsia 36:S13, 1995.

Table 100-3 Drugs Used for Long-Term Anticonvulsant Therapy in Adults

DRUG	INDICATIONS	MAINTENANCE DOSE (MG/DAY)*	FORMULATION	THERAPEUTIC RANGE (mcg/mL)	DAILY DOSES
Carbamazepine	Partial, generalized	800–1600	PO	4–12	2–3
Clonazepam	Absence	1.5–8	PO	20–80	2–3
Ethosuximide	Absence	750–1250	PO	40–100	2
Felbamate	Refractory epilepsy only	2400–3600	PO	N/A	3–4
Fosphenytoin	Partial, generalized	4–6 PE/kg/day	IV, IM	10–20	
Gabapentin	Partial	900–3600	PO	N/A	3
Lamotrigine	Partial, generalized, absence	100–500	PO	N/A	2
Levetiracetam	Partial, generalized, absence	1000–3000	PO, IV	N/A	2
Oxcarbazepine	Partial, generalized	1200–2400	PO	N/A	2
Phenobarbital	Partial, generalized	90–150	PO, IV	20–40	2–3
Phenytoin	Partial, generalized	300–400	PO, IV, IM	10–20	1–3
Pregabalin	Partial	150–600	PO	N/A	2–3
Primidone‡	Partial, generalized	750–1250	PO	5–12	3–4
Tiagabine	Partial (adjunct)	32–56§	PO	N/A	2–4
Topiramate	Partial, generalized	200–400	PO	N/A	2
Valproate	Partial, generalized, absence	1000–3000	PO, IV	50–100	1–3
Zonisamide	Partial, generalized, absence	100–400	PO	20–30†	1–2

*Adjust dose for hepatic or renal disease and with use of other medications.
†Some studies indicate a range of 10–50 mg/L.
§If patient is not taking enzyme-reducing AED, then daily dose should be halved (16–28).
PE, phenytoin equivalents.
Data from Engel J Jr, Pedley TA (eds): Epilepsy: A Comprehensive Textbook, 2nd ed. Philadelphia, Lippincott Williams & Wilkins, 2008; Mattson RH: Efficacy and adverse effects of established and new antiepileptic drugs. Epilepsia 36:S13, 1995; Perucca E: Clinical pharmacology and therapeutic use of the new antiepileptic drugs. Fundam Clin Pharmacol 15:405, 2001; and Drugs for Epilepsy. Treatment Guidelines from the Medical Letter 6:37, 2008.

is complex and depends on numerous factors, including the type of seizure, any comorbid conditions, other medications the patient is taking, and the potential for pregnancy, and is best determined in consultation with a neurologist, ideally after MRI neuroimaging and an EEG.[68] However, if an antiepileptic drug is to be initiated in the ED, then the choice is among the three medications with the strongest evidence for efficacy in the treatment of a tonic-clonic seizure of either generalized-onset or partial onset with secondary generalization: carbamazepine, phenytoin, and valproate.[122] It is essential to inform women of childbearing age that carbamazepine and phenytoin decrease the efficacy of oral contraceptive pills, so a second form of contraception should be used until consultation with a neurologist. Valproate, although not altering the efficacy of oral contraceptives, carries a high risk of teratogenic effects and is therefore not an ideal first-line agent for women of childbearing years.[123,124]

The psychological and social implications of the new diagnosis of a seizure disorder should not be underestimated. Fear of seizures and stigmatization are common; employability and insurability may be adversely affected. Although the emergency physician is not usually in a suitable position to arrange for counseling, referral to local epilepsy support groups may be helpful.

The diagnosis of a new-onset seizure disorder has legal implications as well. Each state has regulations regarding driving privileges in patients with seizures, and some states require reporting by the physician. Accordingly, ED management should ensure compliance with such regulations, including informing patients about any restrictions. Patients also should be advised to refrain from hazardous or isolated activities until cleared to do so by their primary care physician. The need for a "medical alert" bracelet or other medical condition identifier should be stressed.

Finally, patients and their families should be counseled about seizure first aid, safety precautions such as avoiding swimming alone or operating dangerous machinery, and triggers for recurrence such as photic stimuli, sleep deprivation, and alcohol.

KEY CONCEPTS

- The possibility of reactive seizures should be considered in all patients who present to the ED with seizures or recent history of seizures, including patients with a history of epilepsy. The most common cause of reactive seizures is hypoglycemia. The most common cause of recurrent primary seizures is medication noncompliance.
- Nonconvulsive seizures may be confused with nonictal states, including psychiatric disorders. The presence of repetitive eye movements, blinking, or automatisms suggests the diagnosis.
- Neuroimaging is recommended for patients with seizures in whom head trauma, elevated intracranial pressure, intracranial mass, persistently abnormal mental status or focal neurologic abnormality, or HIV disease is suspected.
- Primary abortive therapy for seizures in the ED setting is with a benzodiazepine; second-line agents include phenytoin and phenobarbital.

The references for this chapter can be found online by accessing the accompanying Expert Consult website.