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Epilepsy

Epilepsy is a common neurologic condition characterized by at least 1 unprovoked seizure and a high risk for recurrent seizures. Distinguishing epilepsy from conditions that can mimic seizures is important for accurate diagnosis and effective treatment. This article reviews the evaluation of patients suspected of having epilepsy and discusses behavioral strategies and pharmacologic and surgical therapies that can help reduce morbidity associated with recurrent seizures.

CME/MOC activity available at Annals.org.

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doi:10.7326/ANNALS-25-00494

This article was published at Annals.org on 8 April 2025.

CME Objective: To review current evidence for epidemiology, diagnosis, evaluation, management, and practice improvement for epilepsy.

Funding Source: American College of Physicians.

Disclosures: All relevant financial relationships have been mitigated. The disclosure form is available with the article online.

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Epidemiology

What is epilepsy?

Epilepsy, the tendency for recurrent seizures, is a neurologic condition that is commonly encountered in general medicine. The lifetime risk for a single seizure is 10% (1). Epilepsy affects 1% to 2% of the general population (1). The technical definitions of seizure and epilepsy have historically been complex. In 2014, a more practical definition was adopted by the International League Against Epilepsy (ILAE), whereby epilepsy was defined as a disease characterized by 1 of the following: 1) at least 2 unprovoked (reflex) seizures occurring at least 24 hours apart; 2) 1 unprovoked (reflex) seizure, with a probability of further seizures similar to the general recurrence risk after 2 unprovoked seizures (≥60%) occurring over the next 10 years (for example, a single unprovoked seizure in the presence of other factors, such as abnormal structural findings on brain imaging or epileptiform findings on electroencephalography [EEG], to increase recurrence risk to that of patients who have had 2 unprovoked seizures); or 3) diagnosis of an epilepsy syndrome, defined as "a cluster of features incorporating seizure types, EEG and imaging features that tend to occur together" (2).

The ILAE defines "unprovoked" as the "absence of a temporary or reversible factor lowering the [seizure] threshold and producing a seizure at that point in time" (**Table**) (2). For example, a seizure associated with concussion, fever, or alcohol withdrawal might be considered a provoked seizure, precluding an epilepsy diagnosis, whereas stimuli that trigger a reflexive seizure, such as photic stimuli or causes that "produce an enduring tendency to have seizures" (for example, a brain tumor), would not preclude the diagnosis. Nonetheless, the ILAE acknowledged that not recognizing a provoking factor does not preclude such a factor (2, 3).

What are signs and symptoms of seizures, and how is epilepsy classified?

Seizures are caused by electrical disturbances in the brain. Symptoms vary depending on the origin and spread pattern of the electrical disturbance; they may begin with sensory, motor (usually uncontrollable movements), cognitive, or emotional changes and may progress to altered awareness.

Seizures can be initially classified based on their location of onset (focal or generalized [**Figure**]). Patients with focal-onset seizures may have motor manifestations (such as uncontrollable twitches or jerks on 1 side of the face or body) or nonmotor manifestations (including sudden emotional disturbances, such as feelings of elation or anger, or the inability to understand language) (4). Generalized-onset seizures also can be subdivided into those with motor manifestations (tonic-clonic, clonic, or tonic) and those without (absence) (4). Seizures with uncertain onset are classified as "unknown onset" (4).

The updated classification system recommends a patient be assessed for awareness "of self and environment during the seizure, even if" they are unable to move (4). Although generalized-onset seizures are always associated with absence of awareness (previously characterized less precisely as "consciousness"), focal seizures may be associated with retention or absence of awareness. Focal-onset aware seizures were previously known as "simple partial seizures," and focal-onset seizures with impaired awareness were previously known as "complex partial seizures." Accurate classification is important in helping to identify appropriate treatment (4).

What are causes and risk factors for isolated seizures and epilepsy?

Seizures can be caused by various factors (**Table**), including metabolic abnormalities (such as electrolyte imbalance

1. Falco-Walter J. Epilepsy–definition, classification, pathophysiology, and epidemiology. Semin Neurol. 2020;40:617-623. [PMID: 33155183]
2. Fisher RS, Acevedo C, Arzimanoglou A, et al. ILAE official report: a practical clinical definition of epilepsy. Epilepsia. 2014;55:475-482. [PMID: 24730690]
3. Fisher RS, Cross JH, French JA, et al. Operational classification of seizure types by the International League Against Epilepsy: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:522-530. [PMID: 28276060]
4. Scheffer IE, Berkovic S, Capovilla G, et al. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017;58:512-521. [PMID: 28276062]

Table. **Potential Causes of Seizures or Epilepsy**

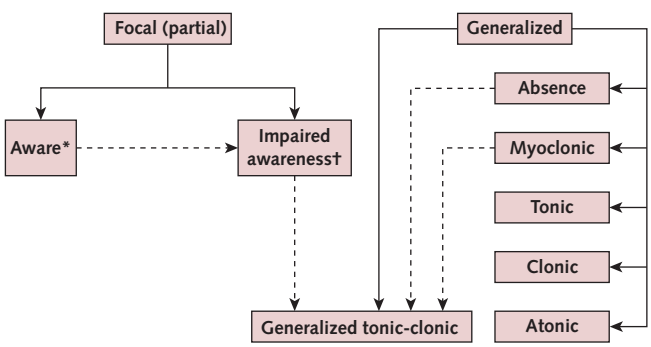
Seizure-Provoking Factors	*Epilepsy Risk Factors*	*Seizure Triggers*
Metabolic: • Hyponatremia or hypernatremia • Hypocalcemia or hypercalcemia • Hypomagnesemia • Hypoglycemia • Hyperammonemia or hepatic failure • Uremia or kidney failure Structural: • Acute head trauma, meningitis, encephalitis, stroke, or hypoxia/ischemia Substances: • Alcohol intoxication or withdrawal • Recreational drug use Medication-related: • Benzodiazepine withdrawal • Baclofen withdrawal • Fluoroquinolones • Carbapenems • Cefepime • Metronidazole • Tramadol • Meperidine • Morphine • Bupropion • Clozapine* • Lithium* • Tricyclic antidepressants* • Typical antipsychotic agents*	Febrile seizures Family history (especially first-degree relatives) Past meningitis/encephalitis (including due to immunologic disorders) History of structural brain lesion (such as stroke or tumor) Past significant head trauma (loss of consciousness or amnesia lasting >30 min, penetrating skull injury) History of brain surgery Preterm birth Birth injury, asphyxia, or stroke Neurologic developmental delay Intellectual disability Genetic causes (presents in childhood)	Sleep deprivation† Fever Emotional stress Acute infection (nonneurologic) Hyperventilation Photic stimulation Music, reading, eating (only in specific reflex epilepsies) Hormonal changes (e.g., menstrual changes)

** Can be used in patients with epilepsy if needed.*
† Typically does not trigger seizures in patients without epilepsy and is not considered a provoking factor.

or hypoglycemia), structural lesions in the brain, substances (for example, alcohol can lower the seizure threshold), and adverse effects of certain medications. The **Table** also lists common triggers, including sleep deprivation, emotional stressors, and photic stimulation.

Risk factors for epilepsy include structural causes that can be developmental or acquired changes to the central nervous system (CNS) (**Table**). Acquired causes include focal brain or systemic infections that induce CNS changes, such as encephalitis, meningitis, HIV infection, neurocysticercosis, cerebral malaria (5), and TORCH infections (toxoplasmosis, rubella, cytomegalovirus, herpes, and other agents transmitted

Figure. **Common seizure types based on International League Against Epilepsy classification.**



The dashed arrows represent the possibility of one seizure type transitioning directly into another when a patient is seizing. Note that generalized tonic-clonic seizures may start out focal or generalized.
* Previously known as simple partial seizures.
† Previously known as complex partial or focal dyscognitive seizures.

5. Bhalla D, Godet B, Druet-Cabanac M, et al. Etiologies of epilepsy: a comprehensive review. Expert Rev Neurother. 2011;11:861-876. [PMID: 21651333]

during pregnancy or at term); structural lesions or changes due to stroke, tumor, or past head trauma (loss of consciousness or amnesia lasting >30 minutes, penetrating skull injury); and chronic alcohol or other substance use. Developmental risk factors include white matter and cortical damage associated with preterm birth; birth injury, asphyxia, or stroke; and neurologic developmental delay or intellectual disability (for example, neuronal migrational abnormalities) (6). Genetic causes include juvenile myoclonic epilepsy, the most common cause of idiopathic epilepsy in adults, which often manifests in adolescence and young adulthood (for example, during college years due to associated triggers) (7); tuberous sclerosis complex; and Lafora disease. Epilepsy can also be caused by metabolic changes from often inborn errors of metabolism, such as Alpers disease, Menkes disease, or pyridoxine-dependent seizures (5). Finally, immunologic disorders, such as Rasmussen syndrome or autoimmune encephalitis, can increase risk for epilepsy (7).

Despite the aforementioned causes and risk factors, approximately one third to one half of patients with epilepsy may not have an identified cause, making prognostication difficult (7).

What is the risk for recurrent seizures in people with a first unprovoked seizure?

In adults who have had a single, apparently unprovoked seizure, the recurrence risk is believed to be 21% to 45% (8). After 2 unprovoked seizures, the risk for a third seizure is approximately 73% (9). However, the risk for recurrence can vary widely depending on the underlying context. A first seizure due to an underlying brain insult, such as a stroke or trauma, can carry a risk for recurrence equivalent to that of someone with 2 unprovoked seizures (10). Other factors that increase risk for recurrence include a seizure occurring in sleep or an abnormal finding on EEG or brain imaging (8). Although immediate treatment after a first seizure seems to reduce the risk for recurrence over the subsequent 2 years, initiating treatment after a first seizure versus delaying treatment until occurrence of a subsequent seizure does not seem to improve seizure remission after 3 years (8). Nonetheless, one of the strongest predictors of favorable long-term outcomes for patients with epilepsy is a positive response to the first anticonvulsant (11).

What are potential complications and the long-term prognosis for people with epilepsy?

Patients with epilepsy have increased mortality and morbidity, with the risk for premature death estimated to be twice that of the general population (12). However, even in patients who have a recognized epilepsy syndrome, determination of prognosis can be challenging because it varies depending on seizure type and risk for recurrence, which can be difficult to predict. Juvenile myoclonic epilepsy is a well-recognized polygenic syndrome long considered to be a lifelong condition; however, a recent study found that 32% of patients were seizure-free with at least 5 years of antiseizure medication (ASM) use, and when these patients subsequently had ASMs withdrawn, more than half maintained full remission (13).

Patients with epilepsy can sustain physical injuries from seizures, such as falls with fractures. Drownings occur at 10 times the rate in the general population; these can occur with or without concurrent seizures and in bathtubs or bodies of water (14). These risks are higher in patients with refractory seizures versus those with well-controlled epilepsy, suggesting the importance of optimizing seizure control (12). One cross-sectional study comparing injuries in patients receiving inadequate epilepsy treatment versus patients receiving treatment per evidence-based guidelines found that patients receiving suboptimal treatment were 8 times more likely to have had burns, fractures, and/or dental injuries (15).

6. Robinson S. Systemic prenatal insults disrupt telencephalon development: implications for potential interventions. Epilepsy Behav. 2005;7:345-363. [PMID: 16061421]
7. Wirrell E. Evaluation of first seizure and newly diagnosed epilepsy. Continuum (Minneap Minn). 2022;28:230-260. [PMID: 35393959]
8. Krumholz A, Wiebe S, Gronseth GS, et al. Evidence-based guideline: management of an unprovoked first seizure in adults: report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2015;84:1705-1713. [PMID: 25901057]
9. Hauser WA, Rich SS, Lee JR, et al. Risk of recurrent seizures after two unprovoked seizures. N Engl J Med. 1998;338:429-434. [PMID: 9459646]
10. Stroink H, Brouwer OF, Arts WF, et al. The first unprovoked, untreated seizure in childhood: a hospital based study of the accuracy of the diagnosis, rate of recurrence, and long term outcome after recurrence. Dutch study of epilepsy in childhood. J Neurol Neurosurg Psychiatry. 1998;64:595-600. [PMID: 9598673]
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12. Thurman DJ, Logroscino G, Beghi E, et al; Epidemiology Commission of the International League Against Epilepsy. The burden of premature mortality of epilepsy in high-income countries: a systematic review from the Mortality Task Force of the International League Against Epilepsy. Epilepsia. 2017;58:17-26. [PMID: 27888514]
13. Pietrafusa N, La Neve A, de Palma L, et al. Juvenile myoclonic epilepsy: long-term prognosis and risk factors. Brain Dev. 2021;43:688-697. [PMID: 33781581]
14. Bain E, Keller AE, Ho J, et al. Drowning in epilepsy: a population-based case series. Epilepsy Res. 2018;145:123-126. [PMID: 29957568]
15. Elavarasi A, Parihar J, Kapoor S, et al. Seizure-related injuries in inadequately treated epilepsy patients: a case-control study. Seizure. 2020;83:17-20. [PMID: 33075672]

Sudden unexpected death in epilepsy (SUDEP) occurs in approximately 1.4 in 1000 adults with epilepsy each year (16). Associated risk factors include frequency of tonic-clonic seizures, nocturnal seizures, living or sleeping alone, and nonadherence to ASM therapy (16).

Epidemiology... Epilepsy is a common disease characterized by at least 1 unprovoked seizure and a high risk for recurrent seizures. Seizures can be focal or generalized and are classified based on the level of patient awareness and motor activity. Epilepsy can have structural, genetic, metabolic, infectious, or immunologic causes; however, only 30% of patients have an identifiable cause. Patients with epilepsy have twice the morbidity and mortality of the general population, with higher rates of injuries and drownings. Control of seizure recurrence is associated with improved outcomes.

CLINICAL BOTTOM LINE

Diagnosis and Evaluation

What features of the history and examination raise suspicion about seizures and epilepsy?

Before a diagnosis of seizure or epilepsy can be established, clinicians need to elicit a history of the episode from the patient, a witness to the episode, or both. Seizure symptoms vary widely and can be sensory (numbness, tingling, pain), motor (uncontrolled movements), or emotional (fear, sadness, elation, laughing) in nature. Consciousness and awareness may be altered, leading to an inability to interact normally. Some patients may seem to be conscious but have difficulty responding verbally to questions and integrating new memories. Patients may also exhibit automatic behaviors, such as lip smacking, chewing, or swallowing. When the electrical disturbance involves wider areas of the cerebral cortex, other motor manifestations may emerge, including stiffening (tonic), jerking (clonic), or twitching (myoclonic) movements on 1 or both sides of the body. Loss of tone, incontinence, and tongue biting may occur. Confusion and disorientation may linger for several minutes after the seizure. Symptoms can be brief, or, in the case of longer-duration seizures, a return to normal cognitive function may take hours or days. Patients with absence seizures may stare or blink repetitively with few motor manifestations; they may not be aware that a seizure has occurred unless they are told. Lack of recall may also occur with focal impaired (or complex partial) seizures.

In patients with suspected seizures, the clinician should elicit elements of the history that help distinguish the different types of seizure and should elicit whether similar events have occurred in the past, as both of these have implications for treatment. If a patient can recognize or describe 1 or more symptoms that precede any alteration of awareness, a seizure is likely to be of focal onset. The clinician should clarify whether the patient remains aware of themselves and their environment and whether symptoms consistent with an aura are present. If an episode was witnessed, the history should clarify whether there was motor activity and the nature of the movements at onset and progression of the seizure.

Many patients presenting for a "first seizure" experience similar episodes before the incident presentation. In one study of patients specifically referred to a "first seizure clinic," 41% had had 1 or more events before presentation (17). For patients presenting with recurrent seizures, many of the same historical details should be verified, as a more comprehensive clinical

16. Mesraoua B, Tomson T, Brodie M, et al. Sudden unexpected death in epilepsy (SUDEP): definition, epidemiology, and significance of education. Epilepsy Behav. 2022;132:108742. [PMID: 35623204]
17. Firkin AL, Marco DJ, Saya S, et al. Mind the gap: multiple events and lengthy delays before presentation with a "first seizure". Epilepsia. 2015;56:1534-1541. [PMID: 26332423]

picture often emerges after repeated history taking.

The history should include a review of seizure and epilepsy risk factors and a detailed review of systems to evaluate for symptoms that might indicate common causes of seizures (**Table**), including pregnancy complications and premature birth, complicated childhood febrile seizures, developmental delay, infections such as meningitis or encephalitis at any age, head trauma (which may be minor, particularly if it is recurrent), and a family history of epilepsy or neurologic illnesses. The history should also elicit signs and symptoms of other conditions in the differential diagnosis that may mimic seizures (**Appendix Table 1**, available at Annals.org), such as previous episodes of altered awareness or behavior (possibly representing previously unrecognized seizures) or infectious symptoms, along with any primary witness or bystander observations.

The physical examination should look for findings consistent with underlying causes of seizures or conditions in the differential diagnosis as well as focal findings that indicate the presence of an abnormal intracranial structure. Blurred disc margins on an ocular examination could indicate increased intracranial pressure. Hemiatrophy of a limb or digit suggests incomplete contralateral cerebral development from an intrauterine insult.

What conditions can mimic seizures?

One of the biggest challenges in evaluating seizures is ensuring that the description of the episode is consistent with a seizure before performing a seizure or epilepsy diagnostic work-up. There are various intermittent movements that can look like seizures; furthermore, the language that we use to describe these movements (such as "jerking" or "twitching") can lead to anchoring bias (diagnostic certainty where none should exist).

Appendix Table 1 presents conditions that can mimic seizures according to the age at which they tend to present. Most of these fall into 6 broad categories of disorders:

1. Disorders associated with transient cerebral hypoperfusion, such as vasovagal syncope or cardiac causes (for example, cardiac dysrhythmias or long QT syndrome). If prolonged, these may lead to convulsive syncope with limb jerks, bladder or bowel incontinence, and retrograde amnesia. In vasovagal syncope, some people may have a prodrome of blurred vision, ringing or distant-sounding hearing, and lightheadedness, which may be mistaken for a seizure aura.
2. Transient ischemic attacks (TIAs). Although the time course of the event (30 to 60 minutes for TIAs vs. 1 to 2 minutes for seizures) may provide clues, physicians may mistake the lingering negative symptoms (weakness, numbness, impaired function) for indications of postictal or Todd paralysis.
3. Movement disorders. Periodic limb movements of sleep, tics, and parasomnias can be mistaken for nocturnal seizures, particularly because patients may have little or no awareness that the events have occurred.
4. Migraine. Some people with migraine experience confusion as part of the episodic headache event.
5. Behavioral or psychiatric disorders. Examples include psychogenic nonepileptic seizures (PNES) and panic attacks. Panic attacks can produce feelings of fear or impending doom that may be reminiscent of simple partial seizures originating in the temporal lobe.
6. Vertigo.

In particular, PNES warrants discussion as the disorder carries substantial morbidity and mortality risk, which can be improved if properly diagnosed and treated (18). Although experienced by patients and described by witnesses and bystanders as seizures, PNES is not due to abnormal neuronal epileptiform activity but is instead associated with underlying psychological disorders and comorbidities, such as anxiety, depression, traumatic life events, and personality disorders (19). Eight percent to 60% of people diagnosed with PNES also have epilepsy (20). Therefore, it is important to ensure that a thorough evaluation for epilepsy has been done in all patients with or

18. Marcolini E, Tolchin B. Functional seizures. Emerg Med Clin North Am. 2021;39:123-132. [PMID: 33218653]
19. Beimer NJ, LaFrance WC Jr. Evaluation and treatment of psychogenic nonepileptic seizures. Neurol Clin. 2022;40:799-820. [PMID: 36270692]
20. Kutlubaev MA, Xu Y, Hackett ML, et al. Dual diagnosis of epilepsy and psychogenic nonepileptic seizures: systematic review and meta-analysis of frequency, correlates, and outcomes. Epilepsy Behav. 2018;89:70-78. [PMID: 30384103]

suspected of having PNES. To definitively diagnose PNES, video EEG monitoring is used to capture a clinical event identical to an episode as experienced by the patient; the lack of concordant electrographic seizure findings helps to confirm the diagnosis. Patients with PNES are not "faking" their symptoms; episodes of PNES are believed to be involuntary, and events can occur even when patients believe themselves to be unobserved (18). Reassurance can improve manifestations of the disorder, with some achieving remission immediately when the diagnosis is thoughtfully explained, or over time with a multidisciplinary approach that includes neurologists and behavioral health providers (18).

What laboratory or imaging studies should the initial evaluation of a first or recurrent seizure include?

For many patients, evaluation of a first seizure occurs in an emergency department.

Laboratory testing (see the **Box**: Seizure Evaluation) should evaluate for common metabolic abnormalities, the presence of toxins (especially alcohol, cocaine, and amphetamines), signs of infection (urinalysis, urine culture, chest radiography as clinically warranted), and pregnancy in patients capable of biological pregnancy. Although an elevated serum prolactin level is suggestive of seizure, it does not distinguish between epileptic seizures and syncope (21). Nevertheless, some clinicians use it in an attempt to distinguish PNES from seizure, but the level is reliably elevated only if drawn within 10 to 20 minutes after an episode of seizure, which is often not the case by the time the patient presents for evaluation (21). Thus, measuring serum prolactin is not recommended except in specific circumstances.

Structural neuroimaging, ideally with magnetic resonance imaging (MRI) or a computed tomography (CT) scan of the head if MRI is not available, should be done in patients presenting for a first seizure to evaluate for structural abnormalities. For those with recurrent seizure, clinicians should ensure that a high-resolution MRI was obtained within the previous year.

When should EEG be ordered, and what type is most helpful?

EEG should be done in any patient for whom a seizure or epilepsy is suspected. There are 3 major types of noninvasive EEGs: routine EEG (rEEG), ambulatory EEG (aEEG), and continuous EEG (cEEG). Each of these may have video recording obtained simultaneously.

Routine EEGs may be more readily obtained in an office or emergency

Seizure Evaluation

First seizure
- History and physical examination
- Levels of serum glucose, sodium, calcium, phosphorus, magnesium, blood urea nitrogen, creatinine, and alcohol; liver function tests; complete blood count; toxicology screen; and pregnancy test for women of childbearing age
- Lumbar puncture if the patient is febrile or has nuchal rigidity or immunocompromise
- Electroencephalogram
- Computed tomography or magnetic resonance imaging of the head
- Consider HIV test

Breakthrough seizure
- History and physical examination
- Same laboratory tests as above, plus trough anticonvulsant levels
- Assessment for infection (urinalysis, chest radiography, lumbar puncture as noted above)
- No need for neuroimaging unless the seizure type is new or there is a change in seizure symptoms or frequency
- Electroencephalogram if the patient does not return to baseline

21. Chen DK, So YT, Fisher RS; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Use of serum prolactin in diagnosing epileptic seizures: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology. 2005;65:668-675. [PMID: 16157897]

department setting and involve 20 to 40 minutes of brain wave recording. Interictal discharges (such as spikes or sharp waves) on an rEEG suggest the patient is capable of having seizures but do not necessarily confirm that the episode in question was a seizure as these changes can be seen in approximately 3% of people without epilepsy (7). The diagnostic sensitivity of a single rEEG is only 30% to 50%.

Many neurologists prefer aEEG monitoring because of the higher likelihood of capturing an electrographic seizure (26% greater than single EEG) (22). aEEG monitoring provides cEEG recording in an outpatient setting for several days at a time. Patients are asked to activate an event marker when an event occurs and provide a written description of the event. The monitoring can be arranged for a high-risk period to increase the yield (23). Although not available in all EEG laboratories, aEEG is available through many commercial vendors. Nevertheless, some patients find it cumbersome to wear the aEEG to work or school or find the video monitoring intrusive.

Continuous EEG recording with event capture, whether done in an ambulatory or inpatient setting, is the gold standard test for diagnosing epilepsy, but it can produce false-negative results, particularly when a patient is taking an ASM. Inpatient cEEG recording may be required to allow ASMs to be discontinued in a monitored setting or if prolonged or recurrent seizures cause emergent hospitalization. It is typically done in consultation with an epilepsy specialist. cEEG is also used to identify a seizure focus in anticipation of surgical treatment.

When should clinicians refer patients to a specialist for diagnosis and evaluation?

Given the large number of seizure mimics, many clinicians refer patients with a first seizure to a general neurologist to confirm the diagnosis and to help classify the seizure type. Referral to the emergency department can expedite evaluation of severe cases. In regions where neurologists are scarce, the emergency department might provide patients with expedited access to an on-site neurologist or, if available, to a telehealth neurologist.

Diagnosis and Evaluation... Diagnosis and evaluation of a patient with potential epilepsy begins by establishing that the presenting event is a seizure and then assessing risk for recurrence. The history should elicit features of the event, underlying risk factors and causes of seizures, and features that distinguish it from other conditions that can mimic seizures. Work-up typically includes laboratory testing to identify potential causes and a head MRI or CT scan. cEEG is preferred to document the CNS foci. Referral to a neurologist or an epilepsy specialist is warranted if the diagnostic picture is complex.

CLINICAL BOTTOM LINE

Management

What is the overall approach to management and treatment?

The initial diagnosis of seizure or epilepsy is distressing for many patients. Thus, patient education and counseling on emotional, lifestyle, and functional impacts is an essential component of management. This should include a discussion about general safety measures, driving restrictions and transportation options, and adjustment to the diagnosis. Referral to a mental health provider may be appropriate, even at the first postseizure visit.

For a patient presenting with a first seizure, the main goal is to determine the likelihood of a second seizure and

22. Keezer MR, Simard-Tremblay E, Veilleux M. The diagnostic accuracy of prolonged ambulatory versus routine EEG. Clin EEG Neurosci. 2016;47:157-161. [PMID: 26376916]
23. González Otárula KA, Schuele S. Ambulatory EEG-video. Epilepsy Behav. 2024;151:109615. [PMID: 38176091]

whether pharmacologic therapy might be appropriate versus expectant management. For patients with epilepsy, developing a therapeutic strategy to achieve seizure freedom is critical to optimizing quality of life.

Many measures of seizure freedom are used for research purposes, such as the Engel Classification and the ILAE Classification. However, these measures may not be clinically useful because what are deemed to be "good" or "bad" outcomes on these measures may not align well with patient ratings (24). Thus, therapeutic effectiveness may be better measured by assessing patients' self-reported satisfaction with their current level of seizure freedom and whether and how it limits them vocationally, socially, and personally. Establishing a baseline of seizure types and average frequency is crucial to monitoring progression and therapeutic response.

Are there behavioral changes that can reduce risk for recurrent seizure?

Patients should be advised to refrain from behaviors and avoid conditions that trigger or provoke seizures (**Table**); counseling should be provided to explain the importance of adequate sleep and avoiding emotional and psychological stressors, photic stimulation, and alcohol and recreational drug use. Several dietary regimens have been studied for the treatment of epilepsy, including ketogenic diets; however, data are limited and primarily focused on patients with childhood or ASM-resistant seizures, and genetic factors seem to be associated with responsiveness (25). The mechanisms leading to seizure reduction are not well understood but are believed to be related to increases in ketone bodies and polyunsaturated fatty acids.

When should pharmacologic agents be considered?

As previously mentioned, data suggest that initiating treatment after a first seizure does not improve the probability of seizure remission over 3 years compared with a strategy of delaying treatment until after a subsequent seizure (8). Treatment with ASMs is recommended for recurrent unprovoked seizures, but whether to recommend an ASM after a single seizure depends on the presence of other risk factors, such as prior stroke or brain injury, an abnormal EEG or brain imaging study, and whether the seizure was provoked (8).

How should clinicians select from the many pharmacologic agents for epilepsy?

One of the strongest predictors of favorable long-term outcomes for patients with epilepsy is a positive response to the first ASM (11). However, the first or second prescribed medication is ineffective in up to one third of patients with epilepsy, and achieving seizure freedom becomes increasingly less likely with each unsuccessful ASM (26).

Although there are more than 20 approved ASMs, few head-to-head trials of ASMs are available. Moreover, most ASM clinical trials have studied participants with focal-onset seizures because this is the most commonly encountered seizure type in adults (27, 28). Once ASMs are approved for commercial use, further clinical trials in other subtypes of seizures are rarely performed; thus, most ASMs have proven efficacy for focal-onset seizures, as shown in **Appendix Table 2** (available at Annals.org) (27–29). Moreover, many newer ASMs were studied in clinical trials that used an add-on therapy approach (for ethical reasons), are U.S. Food and Drug Administration (FDA)–approved as such, and are never tested as monotherapy. Thus, initial treatment should be based on the available efficacy data for that seizure type; associated adverse effects; teratogenicity for women of childbearing age; and, importantly, any drug–drug interactions (30, 31).

A 2018 systematic review of available data commissioned by the American

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31. Asadi-Pooya AA, Beniczky S, Rubboli G, et al. A pragmatic algorithm to select appropriate antiseizure medications in patients with epilepsy. Epilepsia. 2020;61:1668-1677. [PMID: 32697354]

Academy of Neurology (AAN) and the American Epilepsy Society to update their practice guideline suggests that lamotrigine should (level B recommendation) and levetiracetam and zonisamide may (level C recommendation) be considered to decrease seizure frequency in adults with new-onset focal epilepsy; lamotrigine (level B recommendation) and gabapentin (level C recommendation) may be considered in patients aged 60 years or older. The review found no high-quality studies to suggest that clobazam, eslicarbazepine, ezogabine, felbamate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, perampanel, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, or zonisamide is effective in treating new-onset epilepsy in adults of various ages. The review thus concluded that lamotrigine, levetiracetam, and zonisamide may be considered first-line ASMs for "patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures" (28).

In most circumstances, levetiracetam is the first ASM used in the emergency department because it has an intravenous formulation and can therefore be loaded quickly, is primarily eliminated renally, and has minimal potential for drug–drug interactions. For patients who do not respond to the first agent or who have unacceptable adverse effects, use of a second agent is indicated, either as an adjunct to the first or with plans for a cross-taper to allow for monotherapy. Because new ASMs were "added on" in clinical trials to participants' baseline ASM, there may not necessarily be synergism between the new ASM and baseline therapy and these combinations should not be overinterpreted (**Appendix Table 2**). Nevertheless, various ASMs have different mechanisms of action. If a patient's seizures do not respond to monotherapy, it may help to add a second agent with a different mechanism of action. Titration of ASMs and addition of adjunctive agents are usually done by neurologists or epilepsy specialists due to the complexity.

Patients should be advised that ASMs are not effective unless they are taken regularly enough to produce a consistent serum concentration. Patients are more likely to adhere to once-daily treatment regimens. For patients who use smartphones or computer apps for scheduling, programming daily reminders can improve adherence. Cost and formulary restrictions affect access and adherence. Many pharmaceutical companies provide patient assistance programs, particularly in the United States.

How should ASMs be monitored?

Therapeutic drug monitoring is not always helpful when adjusting ASMs as some patients can have dose-related effects even at "therapeutic values" whereas others may have good efficacy and no clinical adverse effects at supratherapeutic values. Nevertheless, it is helpful to document the serum concentration once an effective dose is identified to help future decision making should the patient develop clinical adverse effects or breakthrough seizures.

All ASMs work by passing through the blood–brain barrier and can cause dose-related adverse effects similar to those from alcohol, including fatigue, blurred or double vision, slurred speech, confusion, incoordination, and ataxia. Symptoms tend to worsen with dose increases, when ASMs are taken on an empty stomach, or once the patient's specific maximal tolerable threshold is surpassed. This can be mitigated by suggesting that patients take ASMs within 10 minutes of beginning or ending a meal, with more gradual dose titration than approved by the FDA, and with closer monitoring for signs of overmedication (nystagmus, cerebellar signs, or gait ataxia).

Appendix Table 2 summarizes dosing, adverse effects, and precautions for ASMs. It is helpful for nonepilepsy specialists to familiarize themselves with first-line ASMs, particularly levetiracetam as it is often initially prescribed; its unique adverse effects include irritability, sleeplessness, depression, anxiety,

and rarely psychosis. Lamotrigine has a black box warning about Stevens–Johnson syndrome and a more recent FDA warning about cardiac rhythm and conduction abnormalities (32), although one study found the risk (44 cases per 100 000 people exposed) to be similar to that with phenytoin (46 cases per 100 000 people exposed) (33). As discussed later, ASMs may have drug–drug interactions that affect management in patients with other comorbidities.

What devices are available to treat seizures, and when should they be considered?

The vagus nerve stimulator (VNS) is indicated for add-on therapy in adults and children who have focal to bilateral tonic-clonic (partial onset) seizures and patients who have medically refractory epilepsy but are not considered optimal candidates for resective brain surgery (34). The device consists of a pulse generator that is surgically implanted subcutaneously in the anterior chest wall and a wire lead subcutaneously connecting the generator to the left vagus nerve sheath in the neck. The generator can be programmed to provide stimulation at set intervals and with set parameters and can also be triggered via an external handheld magnet. Patients who have an aura or their caregivers can trigger the device in hopes of aborting progression or shortening seizure duration (34, 35), although evidence of effectiveness is primarily for regular, programmed activation of the device (35). Ictal tachycardia in some patients can result from propagation of an electrical seizure to the right insular cortex, and the latest generation of devices can also deliver stimulation automatically when tachycardia is detected (34). The VNS may allow tapering or discontinuation of some ASMs but requires surgical placement and several weeks to months of sequential programming and other device care. Adverse effects include hoarseness, pain, and a sensation of shortness of breath.

The second implantable device that is currently approved is the Responsive Neurostimulation (RNS) System, which is programmable and also responsive to seizures (36). A pulse generator is implanted along the convexity of the skull, and several strip leads are placed within or on top of the brain. The device can be programmed to deliver stimulation in response to identified ictal patterns, but identification of these loci can be lengthy and complex. RNS can improve seizure control and reduce ASM use; adverse effects are primarily related to surgical implantation (for example, intracranial hemorrhage sometimes leading to permanent neurologic deficits, infection) (36).

When should surgery be considered?

Resective surgery should be considered for all patients with medically refractory epilepsy. If a person's seizures all originate in one specific region of the brain, and if that region is not otherwise providing function or benefit, removal of the epileptogenic focus should, in theory, prevent seizures. This intervention requires identification of foci for all seizure types in a given patient; despite detailed techniques to identify functional zones in a patient's brain, the associated adverse effects of resective surgery are not fully predictable (37). It carries all of the attendant risks of brain surgery, including intracranial hemorrhage, infection, and potential development of a new neurologic deficit. Weighing benefits of surgery versus risks can be challenging, although multiple studies suggest that surgery is associated with shorter epilepsy duration, so earlier consideration in patients with medically refractory epilepsy may be warranted (38).

What are optimal ASM choices for patients receiving chemotherapy or HIV medications?

Many antiretroviral medications and chemotherapeutic agents are metabolized by the hepatic P450 system (**Appendix Table 2**). Thus, ASMs that induce or inhibit the P450 system

32. French JA, Perucca E, Sander JW, et al. FDA safety warning on the cardiac effects of lamotrigine: an advisory from the ad hoc ILAE/AES task force. Epilepsy Curr. 2021;21:153575972199-6344. [PMID: 33641454]
33. Frey N, Bodmer M, Bircher A, et al. The risk of Stevens–Johnson syndrome and toxic epidermal necrolysis in new users of antiepileptic drugs. Epilepsia. 2017;58:2178-2185. [PMID: 29027197]
34. González HFJ, Yengo-Kahn A, Englot DJ. Vagus nerve stimulation for the treatment of epilepsy. Neurosurg Clin N Am. 2019;30:219-230. [PMID: 30898273]
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36. Matias CM, Sharan A, Wu C. Responsive neurostimulation for the treatment of epilepsy. Neurosurg Clin N Am. 2019;30:231-242. [PMID: 30898274]
37. Lunney M, Wahby S, Sauro KM, et al. Patient satisfaction with epilepsy surgery: what is important to patients? Epileptic Disord. 2018;20:364-373. [PMID: 30361186]
38. Bjellvi J, Olsson I, Malmgren K, et al. Epilepsy duration and seizure outcome in epilepsy surgery: a systematic review and meta-analysis. Neurology. 2019;93:e159-e166. [PMID: 31182508]

should be avoided. Both conditions also place patients at risk for opportunistic infections which may require complex regimens, including hepatically metabolized drugs (39). Renally cleared levetiracetam is therefore considered the first choice for ASMs, with lacosamide as a second agent in patients receiving antiretroviral or chemotherapeutic agents (40).

Does treatment need to be modified for patients who are pregnant or lactating or who require contraception?

Because the rate of unplanned (not unwanted) pregnancy in women with epilepsy parallels the rate among women without epilepsy, it is imperative for all pregnancy-capable patients to be counseled about and encouraged to utilize contraception until pregnancy is desired; simultaneously, they should be prescribed ASMs with lower risks to the fetus. Lamotrigine and levetiracetam have specifically been shown to carry low risk (41). Use of long-acting reversible contraceptive options, such as an intrauterine device, is preferred (42) as many ASMs that interfere with the P450 system can make hormonal contraceptives less effective, and hormonal contraceptives can also make ASMs metabolized by the P450 system less effective.

If an ASM controls seizures for a woman with epilepsy before pregnancy, it can be effective during pregnancy as long as therapeutic levels are maintained. However, many pregnancy changes can lead to decreases in serum ASM levels, including increase in steroid reproductive hormones (causing hepatic P450 induction and enhanced degradation of some ASMs), increase in creatinine clearance (enhances excretion of renally cleared ASMs), and changes in protein binding and volume of distribution. ASMs can also have late-term effects on fetal metabolism and clearance of ASMs crossing the placenta. Thus, levels should be closely monitored during pregnancy and the dosage should be adjusted as needed (43).

Evidence is inconclusive about whether risks for pregnancy-associated complications, such as preterm birth, pregnancy-induced hypertension, or late-term bleeding, are increased in women with epilepsy (44). Breastfeeding in women with epilepsy is considered to be safe as long as the patient can receive adequate sleep, possibly by pumping and allowing another adult to provide some feedings (41).

What is the role of hormone therapy?

Catamenial epilepsy is the clustering of seizures associated with the female reproductive cycle due to neuroactive properties of endogenous steroid hormones in combination with their cyclical levels (45). The higher the serum estradiol–progesterone ratio, the greater the tendency for seizures. Thus, seizures tend to cluster before the onset of menses, before ovulation, and/or (for patients with anovulatory cycles) throughout the entire second half of the cycle (45). For these patients, progesterone or oral contraceptive pills may reduce the perturbations in endogenous hormones and thus the cyclic seizure exacerbations (46).

What are associated comorbid conditions in patients with epilepsy?

Cognitive impairment can occur in patients with epilepsy (47) due to the underlying CNS lesions caused by epilepsy and because frequent or prolonged seizures can lead to disturbances of cortical function during and after a seizure or the associated transient or chronic metabolic or hypoxic derangements from seizures. ASMs themselves may also cause cognitive dysfunction (48). Patients with temporal lobe epilepsy may have associated cognitive deficits related to the laterality of the seizure focus; for example, language deficits may be seen in patients with temporal lobe epilepsy arising in the dominant hemisphere for language, even if epilepsy is well controlled.

39. Birbeck GL, French JA, Perucca E, et al.; Quality Standards Subcommittee of the American Academy of Neurology; Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy. Evidence-based guideline: antiepileptic drug selection for people with HIV/AIDS: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Ad Hoc Task Force of the Commission on Therapeutic Strategies of the International League Against Epilepsy. Neurology. 2012;78:139-145. [PMID: 22218281]
40. Siddiqi O, Birbeck GL. Safe treatment of seizures in the setting of HIV/AIDS. Curr Treat Options Neurol. 2013;15:529-543. [PMID: 23657845]
41. Li Y, Meador KJ. Epilepsy and pregnancy. Continuum (Minneap Minn). 2022;28:34-54. [PMID: 35133310]
42. Voinescu PE, Pennell PB. Delivery of a personalized treatment approach to women with epilepsy. Semin Neurol. 2017;37:611-623. [PMID: 29270934]
43. Moise AC, Gerard EE. Antiseizure medications in pregnancy. Obstet Gynecol Clin North Am. 2023;50:251-261. [PMID: 36822708]
44. Harden CL, Hopp J, Ting TY, et al; American Academy of Neurology; American Epilepsy Society. Practice parameter update: management issues for women with epilepsy–focus on pregnancy (an evidence-based review): obstetrical complications and change in seizure frequency: report of the Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society. Neurology. 2009;73:126-132. [PMID: 19398682]
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46. Stephen LJ, Harden C, Tomson T, et al. Management of epilepsy in women. Lancet Neurol. 2019;18:481-491. [PMID: 30857949]
47. Witt J-A, Helmstaedter C. Cognition in the early stages of adult epilepsy. Seizure. 2015;26:65-68. [PMID: 25799904]
48. Schmidt D, Schachter SC. Drug treatment of epilepsy in adults. BMJ. 2014;348:g254. [PMID: 24583319]

Mood disorders, such as depression and anxiety, occur more frequently in patients with epilepsy (48), either as primary conditions or secondary to ASMs. Twenty percent to 30% of people with epilepsy have concomitant depression, and patients with both have a 3-fold increase in suicide attempts (49). Thus, all patients with epilepsy should be screened regularly for depression and suicidality. Fear of having a seizure in public can lead to social isolation and decreased social support (50). People with active seizures can be prohibited from driving, which can diminish quality of life and further limit work and social opportunities (51). Patients may be reluctant to seek help for a coexistent mood disorder because of the stigma associated with both mood disorders and epilepsy. Depression seems to be more common in patients with temporal lobe epilepsy than other seizure types (52). Coincident epilepsy and mood disorders may also increase risk for recurrent or breakthrough seizures (53).

Both women and men with epilepsy have higher rates of certain hormone-related conditions. Reproductive endocrine disorders, such as polycystic ovary syndrome, occur more than twice as often in women with epilepsy than in the general population (54). In addition to hormonal changes, menopause is also associated with sleep disturbances that can affect seizures (55). Men with epilepsy can have low sexual function, and those receiving enzyme-inducing ASMs, such as phenytoin and carbamazepine, may have decreased testosterone bioactivity (56).

Some ASMs can also affect appetite and cholesterol, which can exacerbate existing medical conditions such as hypertension, dyslipidemia, and diabetes. Older ASMs such as phenytoin, carbamazepine, valproate, and phenobarbital can cause disturbances in calcium homeostasis, increasing the risk for early osteopenia and osteoporosis; patients with these exposures should receive regular screenings with bone densitometry.

What are strategies to promote safety and prevent seizure-related injuries and morbidity?

Patients with epilepsy can sustain physical injuries from seizures (falls with fractures) and can drown, either in their own bathrooms or when participating in recreational activities. Counseling should include the use of emergency stop valves in bathtubs (49). The topic of injury prevention should be routinely integrated into office visits and reinforced. Preventive strategies should be balanced against restrictions that stigmatize or prevent patients from fulfilling their goals and ambitions. Most of the reasonable safety measures can be framed as applying to people in general, such as wearing a helmet when biking, skiing, or skating or swimming in pools or open bodies of water only when a lifeguard is on duty.

SUDEP affects 1 in 1000 adult patients with epilepsy each year (16). Risk factors include greater frequency of tonic-clonic seizures and nocturnal seizures, living or sleeping alone, and nonadherence to ASMs (16). The AAN practice guideline recommends educating patients and families about SUDEP and approaches to mitigate the risk (57).

The most complicated aspect of counseling relates to driving given its implications for the patient's ability to work or transport children to school and feelings of stigma (58). There is no reliable method to predict which patients with epilepsy are likely to have seizures while driving (59). There are also no well-designed studies that conclusively prove that drivers with epilepsy have higher rates of motor vehicle accidents (51). However, the risk to the public is deemed high enough that patients' driving privileges are typically restricted until they have been event-free for an interval ranging from a few months to as long as 2 years depending on the state; an up-to-date listing of laws by state is provided at www.epilepsy.com/lifestyle/driving-and-transportation/laws. These restrictions are broadly based on episodes of altered awareness rather

49. Mesraoua B, Deleu D, Hassan AH, et al. Dramatic outcomes in epilepsy: depression, suicide, injuries, and mortality. Curr Med Res Opin. 2020;36:1473-1480. [PMID: 32476500]
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51. Naik PA, Fleming ME, Bhatia P, et al. Do drivers with epilepsy have higher rates of motor vehicle accidents than those without epilepsy? Epilepsy Behav. 2015;47:111-114. [PMID: 25960422]
52. Garcia C. Depression in temporal lobe epilepsy: a review of prevalence, clinical features, and management considerations. Epilepsy Res Treat. 2012;2012:809843. [PMID: 22957244]
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55. Sveinsson O, Tomson T. Epilepsy and menopause: potential implications for pharmacotherapy. Drugs Aging. 2014;31:671-675. [PMID: 25079452]
56. Devinsky O. Neurologist-induced sexual dysfunction: enzyme-inducing antiepileptic drugs. Neurology. 2005;65:980-981. [PMID: 16217046]
57. Harden C, Tomson T, Gloss D, et al. Practice guideline summary: sudden unexpected death in epilepsy incidence rates and risk factors: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology. 2017;88:1674-1680. [PMID: 28438841]
58. Jayagopal LA, Samson KK, Taraschenko O. Driving with drug-resistant and controlled seizures from a patient's perspective: assessment of attitudes and practices. Epilepsy Behav. 2018;81:101-106. [PMID: 29449138]

than seizures explicitly. Most states do not require clinicians to report seizure occurrence, although many require submission of a medical report either as a 1-time event or periodically. Clinicians should familiarize themselves with the restrictions that apply to patients in their practice region. Many patients drive even without a valid driver's license, but ensuring that appropriate counseling has been provided and documented is important (58).

Can ASM treatment be withdrawn?

Studies in adults are limited, but a recently updated practice advisory from the AAN recommends discussion between patients and clinicians at the 2-year seizure-free time point to consider the risks and benefits of ASM withdrawal (60), recognizing that a recurrent seizure may affect driving privileges.

When should clinicians refer patients to a neurologist or an epilepsy specialist to help with management?

Referral to a neurologist or an epilepsy specialist may be warranted after a first seizure if the risk for recurrent seizure and the need for an ASM is unclear and/or to help with initiation or titration of ASMs. A referral may also be helpful for complex management issues related to comorbidities or drug–drug interactions or when a patient with previously well-controlled seizures has a breakthrough seizure or develops a different seizure pattern to help in identifying the cause of the breakthrough event and management, particularly if a patient is already using 2 ASMs at adequate dosages. Patients should be referred if a device and surgery for epilepsy are being considered (61).

Referral to a neurologist or an epilepsy specialist with expertise in women's issues is also recommended to help with contraception options, preconception counseling, and management during pregnancy (42). Similarly, patients who may have more complex nonepilepsy comorbidities or require treatments that may interfere with seizure control or ASM levels may benefit from referral.

Management... For patients at risk for recurrent seizures, the goal is to optimize seizure freedom and implement safety strategies (including prevention of falls, fractures, and drownings) that optimize quality of life and functional independence. Selection from among the many available ASMs should be based on available efficacy data for patients' seizure type, adverse effect profile, and risk for drug–drug interactions, although lamotrigine, levetiracetam, and zonisamide are considered first-line therapy. Alternative or combination ASMs, addition of a seizure abortive device, and surgery are potential options for patients with treatment failure. Adverse cognitive and psychological effects, including depression and suicide, are more common in patients with epilepsy and should be addressed.

CLINICAL BOTTOM LINE

Practice Improvement

What do professional organizations recommend?

The AAN has developed an epilepsy quality measurement set with guidelines for documentation of seizures, discussion of safety factors, and screening for behavioral health disorders, among other steps. In the most recent update in 2015, the AAN added "referral to a comprehensive epilepsy center every two years" for patients with treatment-resistant epilepsy (62).

59. Xu Y, Zhou Z, Shanthosh J, et al. Who is driving and who is prone to have traffic accidents? A systematic review and meta-analysis among people with seizures. Epilepsy Behav. 2019;94:252-257. [PMID: 30978638]
60. Gloss D, Pargeon K, Pack A, et al; AAN Guideline Subcommittee. Antiseizure medication withdrawal in seizure-free patients: practice advisory update summary: report of the AAN Guideline Subcommittee. Neurology. 2021;97:1072-1081. [PMID: 34873018]
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In the Clinic
Tool Kit

Epilepsy

Patient Information

https://medlineplus.gov/epilepsy.html
Information from the National Institutes of Health's MedlinePlus.

www.ninds.nih.gov/health-information/disorders/epilepsy-and-seizures
Health information on epilepsy and seizures from the National Institute of Neurological Disorders and Stroke.

www.cdc.gov/epilepsy/index.html
Information on treatment and management of epilepsy from the Centers for Disease Control and Prevention.

Information for Health Professionals

www.neurology.org/doi/10.1212/WNL.0000000000001487
Guidelines on the management of an unprovoked first seizure in adults from the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society.

www.neurology.org/doi/10.1212/WNL.0b013e3182a393d1
Evidence-based guideline update on vagus nerve stimulation for the treatment of epilepsy from the Guideline Development Subcommittee of the American Academy of Neurology.

www.aan.com/practice/epilepsy-seizures-quality-measures
Quality measures for patients from the American Academy of Neurology.

WHAT YOU SHOULD KNOW ABOUT EPILEPSY

What Is Epilepsy?

Epilepsy is a brain disorder that causes seizures. Seizures occur when there is abnormal electrical activity in your brain cells. People with epilepsy have had 2 or more seizures or are at high risk for having repeated multiple seizures in their lifetime. The cause of epilepsy is not always known. Your risk increases if you:

- Have a family history of epilepsy
- Were born prematurely
- Had unexplained fevers as a child
- Have had infections, such as meningitis
- Have had a head injury
- Have had a stroke or a brain tumor
- Have certain rare genetic conditions

What Are the Warning Signs?

Seizures are the main symptoms. Signs can differ depending on the type of seizure. They can include changes in mental status, such as:

- Unexplained fear, sadness, or laughing
- Feeling unusual or different from normal
- Losing awareness or passing out
- Trouble responding to questions
- Feeling confused and disoriented
- Uncontrolled stiffening, jerking, or twitching
- Numbness, tingling, or pain
- Tongue biting
- Loss of bladder control

How Is It Diagnosed?

Your doctor will first need to rule out all other possible causes of your seizures. You will be asked about your medical history, your symptoms, and what happens when you have a seizure. Your doctor will then complete a physical examination. Testing may be needed, including:

- An EEG, which is a test that measures brain waves
- Imaging tests, such as an MRI
- Blood tests to rule out other causes of seizure

How Is It Treated?

Antiseizure medicines are usually used to reduce or stop seizures. It is important to take these medicines as directed. It is also important to avoid seizure "triggers," such as lack of sleep and drug or alcohol use. If these treatments do not help with your symptoms, your doctor may refer you to a specialist to explore other options. These may include:

- An electrical device implanted in your chest to help reduce seizures
- Surgery to remove the damaged part of your brain that is causing the seizures
- Hormone medicines in women if seizures are related to hormone changes

Questions for My Doctor

- What is causing my seizures?
- How can I tell if I will have another seizure?
- What are the side effects of the medicines?
- Is it safe for me to drive?
- Can I still do the things I enjoy?
- Could my seizures cause long-term damage?
- Should I wear a medical alert bracelet?
- Are there other lifestyle changes I need to make because of my epilepsy?

For More Information

ACP℠
American College of Physicians
Leading Internal Medicine, Improving Lives

MedlinePlus
www.nlm.nih.gov/medlineplus/epilepsy.html

National Institute of Neurological Disorders and Stroke
www.ninds.nih.gov/health-information/disorders/epilepsy-and-seizures

Patient Information

Appendix Table 1. **Common Seizure Mimics***

Seizure Mimics	*Clinical Clues*
Childhood to adulthood	
Rage attacks	Rage reactions occur predominantly in older children and teens and, although triggered by minor stimuli, are characteristically out of proportion Patients are often aggressive during these periods, which can last for ≥30 min
Tics	Involuntary, sudden, rapid, repetitive, nonrhythmic, simple, or complex movements or vocalizations that often occur multiple times per day These are interruptible and can be suppressed, albeit often for only a matter of seconds Tics abate during sleep
REM sleep disorders	Abnormal motor activity, typically in the last third of sleep, when the person acts out their dreams The person can recall the event The events are not as stereotypical as seizures
Periodic leg movements in sleep	Repetitive stereotyped flexion of toes, ankles, knees, and hips Resolve with waking
Postural orthostatic tachycardia syndrome or orthostatic intolerance	Episodic periods of lightheadedness, chest pain, blurred vision, abdominal pain Comes on with standing and resolves with sitting or lying down
Panic attacks	Brief episodes, lasting only minutes, with sudden feeling of impending doom, accompanied by shortness of breath, choking sensation, palpitations, chest pain, paresthesia, dizziness, sweating, trembling, and feeling faint Patient is very frightened but aware No postictal sleepiness or confusion
Narcolepsy/cataplexy	Excessive daytime sleepiness, cataplexy (loss of tone in response to strong emotion), hypnagogic hallucinations, and sleep paralysis
Migraine with aura	Most common aura is visual, typically in one visual field, and is characteristically a scintillating scotoma, which is then followed by a migraine headache Visual phenomena with occipital seizures are more commonly colored and of various shapes
Psychogenic nonepileptic spells	Two main sets of symptoms: 1) unresponsive periods without motor phenomena, or 2) motor phenomena with bizarre, irregular jerking and thrashing Often prolonged (>15–30 min) Often minimal postictal phase Frequent and refractory from onset
Paroxysmal kinesigenic dyskinesia	Brief (<1 min) attacks of abnormal movement, triggered by a sudden voluntary movement The movements are most commonly dystonic but may be choreiform Affects limbs on one or both sides No altered awareness Family history may be present
Episodic ataxia (autosomal dominant)	Brief episodes of cerebellar ataxia triggered by sudden movement, emotion, or illness May have associated dysarthria, nystagmus, titubation, and nausea
Adults	
Transient ischemic attacks	Sudden onset of focal neurologic symptoms that typically reflect loss of function (i.e., paresis, speech problems), which then resolve completely within 24 h, and usually within 30–60 min Seizures more commonly present with positive symptoms due to an excess of neuronal discharge (visual: flashing lights, zigzag shapes, lines, shapes, objects; somatosensory: pain, paresthesia, or motor features [e.g., clonic activity]); transient ischemic attacks most commonly involve loss or reduction of neuronal function (e.g., loss of vision, hearing, sensation, or limb power)
Any age	
Vasovagal syncope	Typically triggered by prolonged standing, dehydration, change in posture, warm environment, or emotional upset (e.g., blood draw) Preceded by lightheadedness, blurred vision, ringing in ears, pallor, diaphoresis, abdominal discomfort Loss of tone, which may be followed by brief myoclonic jerks or tonic posturing Rapid return to awareness, but lightheadedness may remain for a brief period thereafter

Continued on following page

Appendix Table 1–**Continued**

Seizure Mimics	*Clinical Clues*
Cardiac syncope–long QT	Sudden loss of consciousness with pallor, atonia, or tonic posturing Often triggered by fright, exercise, surprise, and immersion in water Family history of syncope may be present
Neurogenic syncope (Chiari malformation, colloid cyst of the third ventricle)	Headache and sensory symptoms associated with collapse Exacerbated by straining

REM = rapid eye movement.
** Conditions in the differential diagnosis that primarily present in children are not included in the table. Vertigo, another condition in the differential diagnosis noted in the text, is also not included in the table. Adapted with permission from Wolters Kluwer Health, Inc.: Wirrell E. Evaluation of first seizure and newly diagnosed epilepsy. Continuum (Minneap Minn). 2022;28:230-260. doi:10.1212/CON.0000000000001074*

Appendix Table 2. **Selected Antiseizure Medications***

Medication†	Mechanism (Metabolism)	Evidence of Efficacy for Seizure Type						Dosing	Metabolism/ Elimination (Drug–Drug Interactions)	Adverse Effects	Precautions/ Additional Notes
		Focal	Generalized, Tonic-Clonic	Generalized, Absence	Generalized, Myoclonic	Lennox–Gastaut Syndrome	Dravet Syndrome				
Brivaracetam	Binding SV2A	Class I trial evidence	–	–	–	–	–	Initial dose: 50–100 mg/d Titration: 50 mg/d as needed Target: 100 mg/d; maximum, 200 mg/d	Hepatic (moderate)	Somnolence, dizziness, fatigue, irritability	Controlled substance May be helpful in patients who develop adverse behavioral effects from levetiracetam
Carbamazepine (Carbatrol, Tegretol, Tegretol-XR, Epitol)‡	Blocking sodium channels	Class I trial evidence	Suggestive but not trial proven	Not effective	Not effective	–	–	Initial dose: 200 mg/d Titration: 200 mg/d every 3 d Target: 400–800 mg/d	Hepatic (high)	Nausea, dizziness, sedation, tiredness, diplopia, incoordination, hyponatremia, mild leukopenia	Causes autoinduction May exacerbate absence, myoclonic, atonic seizures Rare aplastic anemia Rare lupus-like syndrome, hepatotoxicity May be affected by CYP3A4 inhibitors
Cannabidiol	Enhancing GABA, modulation of intracellular calcium	Class IV evidence	–	–	–	Class I trial evidence	Class I trial evidence	Initial dose: 5 mg/kg/d Titration: Increase by 5 mg/kg/d per week Target: 10 mg/kg/d; maximum, 20 mg/kg/d	Hepatic (high)	Sedation, fatigue, decreased appetite, diarrhea	Class I for tuberous sclerosis Can increase liver enzyme levels (liver enzymes and total bilirubin should be measured before treatment and at 1, 3, and 6 mo after initiation of therapy)
Cenobamate	Blocking sodium channels	Class I trial evidence	–	–	–	–	–	Initial dose: 12.5 mg/d Titration: Increase to 25 mg/d after 2 wk, 50 mg/d 2 wk later, then by 50 mg/d every 2 wk Target: 100–200 mg/d; maximum, 400 mg/d	Hepatic (high)	Somnolence, dizziness, fatigue, DRESS (risk decreased with slowed titration rate)	Long half-life Many drug interactions, including decreasing efficacy of OCPs Controlled substance
Clobazam	Enhancing GABA	Suggestive but not trial proven	Suggestive but not trial proven	Suggestive but not trial proven	Suggestive but not trial proven	Class I trial evidence	–	Initial dose: 10 mg/d Titration: 10 mg/d every 2 wk as needed Target: 20–40 mg/d	Hepatic (high)	Drowsiness, nystagmus, incoordination, unsteadiness, dysarthria	Long half-life, but withdrawal seizures may occur with abrupt discontinuation
Eslicarbazepine	Blocking sodium channels	Class I trial evidence	–	Not effective	Not effective	–	–	Initial dose: 400 mg/d Titration: 400 mg/d per week as needed Target: 800–1200 mg/d; maximum, 1600 mg/d	~40% hepatic, 60% renal unchanged (moderate)	Dizziness, somnolence, headache, diplopia, nausea, vomiting, fatigue, ataxia	Prodrug; weak inducer of CYP3A4 (may make OCPs less effective) and weak inhibitor of CYP2C19 (may increase plasma phenytoin concentrations)

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Appendix Table 2–**Continued**

Medication†	*Mechanism (Metabolism)*	*Evidence of Efficacy for Seizure Type*						*Dosing*	*Metabolism/ Elimination (Drug–Drug Interactions)*	*Adverse Effects*	*Precautions/ Additional Notes*
		Focal	*Generalized, Tonic-Clonic*	*Generalized, Absence*	*Generalized, Myoclonic*	*Lennox–Gastaut Syndrome*	*Dravet Syndrome*				
Ethosuximide (first-line agent *only* for childhood absence epilepsy) (Zarontin)	Blocking T-type calcium channels	Not effective	Not effective	Class I trial evidence	Not effective	–	–	Initial dose: 250-500 mg/d Titration: 250 mg/d per week as needed Target: 750 mg/d; maximum, 1500 mg/d	Hepatic (moderate)	Nausea, abdominal discomfort, anorexia, vomiting, insomnia, behavior changes, fatigue, ataxia	Psychosis, depression, hallucinations may occur SLE, rare aplastic anemia, agranulocytosis, rare autoimmune thyroiditis
Felbamate (Felbatol)‡	NMDA antagonism, blocking Na channels, enhancing GABA	Class I trial evidence	Suggestive but not trial proven	–	–	Class I trial evidence	–	Initial dose: 1200 mg/d Titration: 600–1200 mg/d per week; maximum, 3600 mg/d	~50% hepatic, 40%–50% unchanged in urine (high)	GI irritation with anorexia, nausea, vomiting (co-administer with food), insomnia, irritability, weight loss	Black box warning for estimated risk for aplastic anemia of 1 in 5000 to 8000; risk for hepatic failure of 1 in 26 000 to 54 000; perform CBC and LFTs before start, every 2 wk for 6 mo, then periodically thereafter‡ Serious hematologic reactions, hepatotoxicity; avoid with hepatic disease; decrease dose by half with CKD; inhibitor of CYP2C19, inducer of CYP3A4‡
Gabapentin (Neurontin)	Binding X2Y calcium channel subunit	Class I trial evidence	Not effective	Not effective	Not effective	–	–	Initial dose: 300-400 mg/d Titration: 300–400 mg/d Target: 1200 mg/d; maximum, 4800 mg/d	None (low)	Drowsiness, dizziness, ataxia, tiredness, weight gain, peripheral edema	Decrease dose if CrCl <60 mL/min Does not interact with other anticonvulsants Low teratogenicity
Lacosamide (Vimpat)	Blocking sodium channels	Class I trial evidence	–	Not effective	Not effective	–	–	Initial dose: 100 mg/d Titration: 100 mg/d per week as needed Target: 200 mg/d; maximum, 600 mg/d	~60% hepatic, 40% unchanged in urine (low)	Dizziness, nausea, vomiting, diplopia, fatigue, sedation, especially at high doses or when used with other sodium channel medications Diplopia, blurred vision, AV block, PR prolongation, DRESS, dependence	Can produce dose-dependent PR interval prolongation (EKG should be done before treatment initiation) Controlled substance
Lamotrigine (first-line agent) (Lamictal, Lamictal XR, Lamictal ODT)‡	Blocking sodium channels	Class I trial evidence	Class I trial evidence	Suggestive but not trial proven	Class IV evidence	Class I trial evidence	–	Initial dose (monotherapy): 25 mg/d for 2 wk Titration (monotherapy): 50 mg/d for 2 wk, then increase by 50 mg/d every 1–2 wk Target: 200–300 mg/d	Hepatic (moderate)	Dizziness, blurred/double vision, unsteadiness, nausea, headache, tremor	Increased risk for rash if titrated too quickly Must slow taper in presence of valproic acid; can increase dose escalation in presence of P450 inducers (DPH, PB, CBZ) SJS, TEN rare idiosyncratic adverse effects Low risk if used as monotherapy in pregnancy

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Appendix Table 2—**Continued**

Medication†	*Mechanism (Metabolism)*	*Evidence of Efficacy for Seizure Type*						*Dosing*	*Metabolism/ Elimination (Drug–Drug Interactions)*	*Adverse Effects*	*Precautions/ Additional Notes*
		Focal	*Generalized, Tonic-Clonic*	*Generalized, Absence*	*Generalized, Myoclonic*	*Lennox–Gastaut Syndrome*	*Dravet Syndrome*				
Levetiracetam (first-line agent) (Keppra, Keppra XR)	Binding SV2A	Class I trial evidence	Class I trial evidence	Suggestive but not trial proven	Class I trial evidence	–	–	Initial dose: 500 mg/d Titration: 500 mg/d per week as needed Target: 1000 mg/d; maximum, 4000 mg/d	~30% nonhepatic, 66% unchanged in urine (low)	Somnolence, dizziness, asthenia, irritability, hostility, depression, anxiety, rare psychosis	Exclusively renally cleared with few drug interactions, so drug of choice in patients receiving retroviral therapy or chemotherapy Low risk if used as monotherapy in pregnancy
Oxcarbazepine (Trileptal) (first-line agent)	Blocking sodium channels	Class I trial evidence	–	Not effective	Not effective	–	–	Initial dose: 300–600 mg/d Titration: 300 mg/d per week as needed Target: 600–1200 mg/d; maximum, 2400 mg/d	Hepatic (moderate)	Hyponatremia common, usually asymptomatic, but may be symptomatic if patient is also taking a diuretic Drowsiness, headache, fatigue, blurred/double vision, nausea, ataxia	May reduce efficacy of OCP May exacerbate absence seizures, myoclonic seizures, and other generalized epilepsies
Perampanel	AMPA antagonism	Class I trial evidence	Class I trial evidence	–	Class IV evidence	–	–	Initial dose: 2 mg/d Titration: 2 mg/d every 3 wk Target: 4 mg/d; maximum, 8 mg/d	Hepatic (moderate)	Dizziness, somnolence, headache, fatigue, ataxia, blurred vision	Black box warning for aggression and hostility Controlled substance Long half-life May decrease efficacy of OCP
Phenobarbital	Enhancing GABA	Class I trial evidence	Suggestive but not trial proven	Not effective	Class IV evidence	–	–	Initial dose: 30–60 mg/d Titration: 30–60 mg/d every 1–2 wk as needed Target: 120–180 mg/d	>70% hepatic, 20%–25% renal (high)	Sedation, decreased concentration, mood changes (depression)	Potent P450 inducer Long half-life Long-term use causes decreased bone density, Dupuytren contractures Contraindicated in pregnancy
Phenytoin (Dilantin, Phenytek)‡	Blocking sodium channels	Class I trial evidence	Suggestive but not trial proven	Not effective	Not effective	–	–	Initial dose: 200–400 mg/d Titration: No titration needed; dose adjustment in 30- to 60-mg/d increments as needed for seizure control Target: 200–400 mg/d	Hepatic (high)	Intravenous preparation may cause phlebitis, "purple glove syndrome" Gingival hyperplasia, peripheral neuropathy, hirsutism, ataxia	Potent P450 inducer Cardiovascular risk with rapid infusion Contraindicated in pregnancy Has saturable nonlinear kinetics Free level increases with hepatic and/or renal failure and in presence of other highly protein-bound medications Long-term use causes cerebellar atrophy, peripheral neuropathy, decreased bone density

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Appendix Table 2–**Continued**

Medication†	*Mechanism (Metabolism)*	*Evidence of Efficacy for Seizure Type*						*Dosing*	*Metabolism/ Elimination (Drug-Drug Interactions)*	*Adverse Effects*	*Precautions/ Additional Notes*
		Focal	*Generalized, Tonic-Clonic*	*Generalized, Absence*	*Generalized, Myoclonic*	*Lennox–Gastaut Syndrome*	*Dravet Syndrome*				
Pregabalin (Lyrica)	Binding X2Y calcium channel subunit	Class I trial evidence	Not effective	Not effective	Not effective	–	–	Initial dose: 75–150 mg/d Titration: 75–150 mg/d per week as needed Target: 300 mg/d; maximum, 600 mg/d	None (low)	Dizziness, somnolence, increased appetite, weight gain, peripheral edema	May cause myoclonus at high doses
Rufinamide (Banzel)	Blocking sodium channels	Class I trial evidence‡	Suggestive but not trial proven	–	–	Class I trial evidence	–	Initial dose: 400 mg/d Titration: 400 mg/d every 2 d Target: 3200 mg/d	Hepatic (moderate)	Shortened QT interval, status epilepticus, diplopia, blurred vision, anemia, leukopenia	Avoid with severe hepatic disease Consider decreased dose with mild to moderate hepatic disease Weak inducer of CYP3A4; weak inhibitor of CYP2E1
Tiagabine (Gabitril)	Enhancing GABA	Class I trial evidence	Not effective	Not effective	Not effective	–	–	Initial: 4 mg/d Titration: 4 mg/d per week Target: 24 mg/d; maximum, 56 mg/d	Hepatic (high)	Dizziness, nervousness, tremor, depression, emotional lability	Associated with episodes of nonconvulsive status epilepticus or encephalopathy, even in people with no history of epilepsy
Topiramate (Topamax)	Blocking sodium channels, AMPA/glutamate antagonism, enhancing GABA	Class I trial evidence	Class I trial evidence	Not effective	–	Class I trial evidence	–	Initial: 25 mg/d Titration: 25 mg/d per week Target: 100 mg/d; maximum, 400 mg/d	~30% hepatic, 70% unchanged in urine (low)	Adverse cognitive effects (cognitive slowing, word-finding difficulty, reduced verbal fluency) Kidney stones in 1.5%; decreased appetite and weight loss	Rare secondary angle closure in glaucoma Dual action of migraine prevention High risk for teratogenesis
Valproic acid (first-line agent) (Stavzor, Depakene)‡ Divalproex sodium (Depakote, Depakote ER)‡	Blocking sodium channels, enhancing GABA, blocking T-type calcium channels	Class I trial evidence	Suggestive but not trial proven	Class I trial evidence	Suggestive but not trial proven	Suggestive but not trial proven	Suggestive but not trial proven	Initial: 500 mg/d Titration: 250–500 mg/d per week as needed Target: 1000–2000 mg/d	Hepatic (high)	Alopecia, elevated blood ammonia level, PCOS, thrombocytopenia, menstrual disturbances	Potential CYP inhibitor (increases serum concentrations of PB, DPH, lamotrigine), and coadministration with lamotrigine significantly increases risk for SJS Relatively contraindicated in pregnancy; in utero exposure associated with dose-dependent teratogenesis, increased risk for reduced verbal IQ and autism Idiosyncratic hepatotoxicity and pancreatitis Long-term use associated with brain atrophy, reversible parkinsonism, gait disorder

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Appendix Table 2–**Continued**

Medication†	*Mechanism (Metabolism)*	*Evidence of Efficacy for Seizure Type*						*Dosing*	*Metabolism/ Elimination (Drug–Drug Interactions)*	*Adverse Effects*	*Precautions/ Additional Notes*
		Focal	*Generalized, Tonic-Clonic*	*Generalized, Absence*	*Generalized, Myoclonic*	*Lennox–Gastaut Syndrome*	*Dravet Syndrome*				
Vigabatrin	Enhancing GABA	Class I trial evidence	Not effective	Not effective	Not effective	–	–	Initial: 1000 mg/d Titration: 500 mg/d per week as needed Target: 3000 mg/d; maximum, 6000 mg/d	None (low)	Sedation, fatigue, dizziness, ataxia, irritability, behavior changes, psychosis, depression	Serious potential risk for progressive and permanent bilateral concentric visual field constriction leading to vision loss Risk increases with increased daily dose and increased duration of therapy Class I infantile spasms
Zonisamide (Zonegran)	Blocking sodium channels, blocking T-type calcium channels	Class I trial evidence	Suggestive but not trial proven	Suggestive but not trial proven	Suggestive but not trial proven	–	–	Initial: 100 mg/d Titration: 100 mg/d every 1–2 wk as needed Target: 200 mg/d; maximum, 600 mg/d	~65% (moderate)	Sedation, ataxia, nausea, dizziness, fatigue, anorexia with weight loss Cognitive slowing at high doses Depression, psychosis, kidney stones in up to 4%	Avoid with sulfonamide hypersensitivity Rare oligohidrosis, hyperthermia, and metabolic acidosis, more often in children

AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AV = atrioventricular; CBC = complete blood count; CBZ = carbamazepine; CKD = chronic kidney disease; CrCl = creatinine clearance; CYP = cytochrome P450; DPH = diphenhydramine; DRESS = drug reaction with eosinophilia and systemic symptoms; EKG = electrocardiography; ER = extended-release; GABA = γ-aminobutyric acid; GI = gastrointestinal; HF = heart failure; LFT = liver function test; NMDA = N-methyl-D-aspartic acid; OCP = oral contraceptive pill; ODT = orally disintegrating tablets; PB = phenobarbital; PCOS = polycystic ovary syndrome; SJS = Stevens–Johnson syndrome; SLE = systemic lupus erythematosus; TEN = toxic epidermal necrolysis; XR = extended-release.

** Data are from references 27, 28, and 29.*

† All antiseizure medications have central nervous system adverse effects (including drowsiness, dizziness, headache, insomnia, anxiety, asthenia, and tremor), as well as hypersensitivity reactions, nausea, vomiting, and depression. Clinicians should avoid abrupt discontinuation, exercise additional caution in elderly patients and during pregnancy, monitor for depression, and be alert for complex interactions between medications.

‡ Black box warning.