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Evaluation and Management of Seizures in the Emergency Department

Introduction

Seizures are a common complaint in both children and adults presenting to the emergency department (ED).[1,2,3] Epilepsy is a disorder of the brain characterized by an ongoing predisposition to generate epileptic seizures. Approximately 65 million people worldwide have epilepsy, with 40-70 new cases per 100,000 people annually in industrialized countries.[4,5] Seizures may stop prior to physician evaluation, may be ongoing upon presentation, or may occur after the patient is brought to the ED. Patients may be experiencing a seizure for the first time in their lives or may be suffering from chronic epilepsy.

While a seizure is defined as the occurrence of signs or symptoms due to abnormal or synchronous electrical activity in the brain,[6,7] an accurate diagnosis of seizure can be difficult to make in an acute setting. When seizures are accompanied by sudden loss of consciousness and rhythmic movements, they are readily recognized as such by lay people. Yet not all that shakes is a seizure. Presentations without involuntary movements and with subtle mental status changes or when pathological movements resemble normal activity may be challenging to diagnose rapidly even for a seasoned clinician. Seizures must be differentiated from other types of involuntary movements, such as chorea (and its severe form ballism), dystonia, various tremors, asterixis, tics, and myoclonus. Tonic-clonic (stiffening of muscles followed by jerking movements) is a term commonly used to describe a pattern of movements observed in generalized seizure activity.

General ED Considerations

From a practical perspective, it is important for emergency physicians to address the following when confronted with a possible seizure patient:

- Did the patient have a seizure or some mimic?
- How likely is the patient to experience another seizure in the near future, and are there interventions likely to reduce that possibility?
- Is the seizure idiopathic (a symptom of epilepsy) or is it a sign of another pathological process?
- Is it status epilepticus?
- How should patients presenting in known or suspected status epilepticus be evaluated and treated?
- What are the antiepileptic drugs useful in emergency situations, and what are their prominent side effects?

EXECUTIVE SUMMARY

- Patients with initial onset of seizure are at increased risk of seizure recurrence within two years if they have a prior brain insult, if their electroencephalogram shows epileptiform abnormalities, if they show abnormal brain imaging, or if their seizure occurred at night.
- Comorbidities of epilepsy include injury, drowning, depression associated with high suicide rates, and sudden unexplained death in epilepsy.
- Seizure recurrences may cause serious psychological and social consequences, including loss of employment and loss of driving privileges.
- Respiratory depression can occur after treatment of status epilepticus with benzodiazepines, but the rate of respiratory depression is higher if status epilepticus is untreated.
- Teratogenic effects have been reported with various antiepileptic drugs, but it appears that valproic acid especially should be avoided during the first trimester of pregnancy.
- Nonconvulsive status epilepticus in a comatose patient cannot be diagnosed without an electroencephalogram.
- Heavy alcohol intake may be related to the development of seizures, apart from reversible metabolic abnormalities and withdrawal symptoms.
- Seizures may be implicated in drowning, accidental injury, and more severe injury, including fractures, burns, and soft tissue injury.

• What are the complications of epilepsy, including sudden unexpected death in epilepsy (SUDEP)?

• What are non-epileptic seizures (pseudoseizures)?

Did This Patient Have a Seizure?

The diagnostic uncertainty as to whether the patient actually experienced a seizure can arise in several distinct ways depending on the patient's presentation. (*See Table 1.*)

The differentiation between syncope and seizure is not always straightforward. Patients who seize are more likely to exhibit tonic-clonic activity, although some jerking/clonic activity may occur during or following syncope. Following syncope, consciousness generally should be restored promptly, as opposed to postictal confusion or neurologic deficits following a seizure that may take minutes to hours to resolve. Patients are more likely to injure themselves following a seizure than they are following a simple faint. Tongue biting and urinary incontinence have been associated with seizure more than with fainting.

Video electroencephalography (vEEG) or SPECT imaging is considered the gold standard for definitive diagnosis of epilepsy, but these modalities generally are not available to the emergency physician. During an episode, the absence of epileptiform activity on the vEEG supports the diagnosis of pseudoseizures or psychogenic non-epileptic seizures (PNES).[8]

The term "pseudoseizure" has fallen into disfavor in some circles; instead, PNES is preferred, defined as "paroxysmal episodes clinically resembling an epileptic seizure, but not caused by ictal epileptiform activity." Psychogenic movement disorders (PMD) are defined as the occurrence of abnormal movements that do not result from a known general or neurologic cause. Both are common and may be diagnosed by some psychiatrists as conversion disorder.[9]

Acute Interventions

Once the clinician decides that the patient's presentation is caused by a seizure, the clinician should determine whether the seizure was provoked, for example as from a drug intoxication, central nervous system (CNS) infection, or withdrawal state, or unprovoked. Provoked seizures have a much higher mortality short term than unprovoked seizures.[6] Unprovoked seizures are further subgrouped based on the presence or absence of an identifiable non-acute brain lesion.[1]

Patients who present with a seizure requiring immediate stabilization and airway management are clearly different from the young adult patient who presents following the first seizure of their life and is completely back to baseline with a normal neurological examination in the ED. Laboratory tests rarely reveal clinically important abnormalities in this latter population in the absence of historical clues, such as significant vomiting and diarrhea, weight loss, or lassitude.

We prefer to obtain neuroimaging in the ED, either non-contrast head computed tomography (CT) or non-contrast magnetic resonance imaging (MRI) of the head in first-time seizure patients, although if close follow-up is available, outpatient neuroimaging may be reasonable.

Inpatient admission is necessary if either a significant secondary cause of seizure or a dangerous seizure mimic is suspected. The patient's ability to care for him- or herself and to follow up also plays an important role in deciding on the disposition.

Patients seen in the ED for first-time seizure are at heightened risk of having another seizure sometime in their lifetime. One study found that the risk of seizure recurrence following a seizure of unknown cause with none of the risk factors (*see Executive Summary*) at one, three, and five years was 10%, 24%, and 29%, respectively.[10]

The question arises, then, whether treatment with antiepileptic drugs (AEDs) is indicated following an ED visit for a first unprovoked seizure. (*See Table 2.*) Adults with a first unprovoked seizure but without high-risk features should be educated on seizure safety, including counseling on driving and avoidance of substances and behaviors that lower seizure threshold (street drugs, alcohol, certain medications such as tramadol, sleep deprivation, and strobing lights, for example) and generally are not started on an AED. These drugs may decrease absolute risk of seizure recurrence by 35% but not affect quality of life or mortality.[1,2]

If a patient experiences a second or subsequent seizure, an AED generally should be started, with the choice

Table 1. Initial Differential Diagnosis When Seizure Is a Consideration

Presentation	Differential Diagnosis	Comments
Sudden loss of consciousness with complete spontaneous recovery	Syncope (different etiologies: neurocardiogenic, arrhythmogenic, pulmonary embolism, hypovolemia, etc.), brain concussion with concussion seizure, seizure	Brief extremity shaking is commonly observed in syncope, including neurocardiogenic syncope.[8,20] Some patients may describe an aura resembling visual hallucinations.[8] Tongue biting is much less common in syncope as compared to a seizure.[10] Secondary trauma is common after a seizure.[4] Altered mental status, if present after loss of consciousness, generally rules out syncope.
Ongoing or recurrent loss of consciousness with tonic-clonic activity	Status epilepticus, recurrent seizures, non-convulsive seizures	Prior history of non-convulsive seizures, if available, is helpful. Certain features suggesting preserved volitional activity (purposeful movements, speech, tightly closed eyes) may clue the clinician to psychogenic nonepileptic seizures, but are not absolutely diagnsostic.[21]
Altered mental status without abnormal movements	Non-convulsive status epilepticus, postictal state, metabolic or endocrine derangements, intoxicants, infection, central nervous system trauma, etc.	Improvement in mental status after administration of benzodiazepines suggests seizure activity but is not diagnostic; maintaining a broad differential is important; EEG can be very helpful in difficult cases.
Unilateral neurodeficit	Stroke, transient ischemic attack, aortic dissection, hypoglycemia, shock, complex migraine, Todd's paralysis	Seizure at the onset of stroke-like symptoms is a relative contraindication for administration of tPA for an acute stroke. Transient ischemic attack can mimic focal motor seizures.[8]
Uncontrolled movements without alteration in mental state	Focal seizure, chorea, ballism	Chorea can be a presenting symptom of an acute stroke.
Aura	Migraine, seizure, brain tumor, syncope, psychosis	

ideally made jointly with the patient and consulting neurologist. The risk of yet additional seizures in a patient who has had ensuing seizures has been shown to be very high: 57% by one year and 73% by four years.[2] Patients already on AEDs who present following another seizure represent a distinct group frequently evaluated in the ED. The clinician should ascertain if this seizure represents a typical manifestation of the patient's epilepsy or possibly the onset of a new problem. Noncompliance with medications is common, often because of AED side effects,[2,5,11] and can have fatal consequences for patients with epilepsy.[12] Measuring the serum levels of many antiepileptic drugs is reasonable even if the results are not immediately available, as it may be helpful to the patient's neurologist in follow-up.[2]

In compliant patients, the reasons for breakthrough seizures include drug-resistant epilepsy,[13,14] acute gastrointestinal illness causing malabsorption of the AED, introduction of another medication (especially a cytochrome P450 inducer that interferes with AED metabolism[2]), switching between different brands of the same antiepileptic,[15] or even switching between lots of the same antiepileptic drug from the same manufacturer.[15] Commonly prescribed AEDs, such as phenytoin, have the potential of actually worsening certain epilepsy syndromes.[16] Some AEDs have rather narrow therapeutic profiles and can cause severe symptoms and seizures at toxic levels.[17]

If after careful examination the seizure is determined to be typical in character and frequency for the patient who is at baseline in the ED and is not injured, any investigation beyond checking the AED level is unlikely to be beneficial. Options for patients with escalating seizure frequency include increasing the dose of an AED or starting another AED.[14,17,18] Onset of a seizure pattern or frequency that is unusual for the patient, or that meets criteria for status epilepticus, mandates consideration of neuroimaging and inpatient admission.

Symptom of Epilepsy or Sign of Another Pathological Process?

A seizure can be a presenting sign of a wide variety of disorders, many of which are life-threatening, including in those patients with an established diagnosis of epilepsy.[19] Patients presenting with seizures as a result of acute stroke, CNS infection, or trauma have 30-day mortality that is nine times greater than patients with unprovoked seizures.[6] Any condition resulting in reduction of blood flow to the brain, either due to a drop in systemic blood pressure, such as cardiac arrhythmia, increased blood viscosity as in acute leukemia, or local vasospasm can present with a seizure. Congenitally hypoplastic CNS vasculature or acquired stenosis can accentuate or localize seizures. Hypoglycemia can result in a seizure followed by focal neurological deficit, perhaps from sustained cerebral vasospasm brought on by catecholamine surge.

The emergency physician evaluating a patient presenting with seizures should always keep in mind the possibility of

Table 2. Management of First-Time Seizure in Adults

Initial workup	• Rule out status epilepticus, evaluate for traumatic injuries.[4] • Rule out provoked seizure[6]: alcohol- or drug-related; space-occupying intracranial lesion; stroke;[44] withdrawal state; electrolyte or glucose disturbances; bacterial, auto-immune encephalitis; bacterial, viral, or parasitic central nervous system infection.[7] • In the third trimester of pregnancy and early postpartum, always consider the possibility of eclampsia; keep in mind that some women will not know or share their pregnant state. • Consider timing and type of neuroimaging: emergent non-contrast CT of brain if space-occupying lesion or trauma is a concern, contrast CT of brain for brain abscess, parasitic lesion, or malignancy, CTA of brain and neck if acute stroke or neck arterial dissection is suspected, MRI of brain for more subtle pathology and to guide initial therapy.[6] • Lumbar puncture should follow neuroimaging if there are no contraindications and central nervous system infection or inflammation remains a concern.
Decision to start an antiepileptic drug after first unprovoked seizure	• Generally, starting an antiepileptic drug (AED) after the first seizure does not improve quality of life or prognosis.[1] • Patients who are at higher risk of recurrence based on seizure type (nocturnal seizure), seizure duration (patients presenting in status epilepticus), significantly abnormal brain imaging, or epileptiform abnormalities on EEG are at higher risk of early recurrence and should be considered for AED.[1,2,17,27]
Information for patients	• Correct information on driving and avoidance or modification of other dangerous activities, such as lying down in a bathtub unsupervised, is essential but is commonly omitted at discharge.[1] • Patients with seizures are at higher risk of causing a motor vehicle accident than the general population.[4] • The Epilepsy Society has a webpage that answers questions with regard to various scenarios arising for someone living with epilepsy. AEDs do not prevent development of epilepsy.[2] AEDs can reduce the number of seizures the patient experiences and may reduce the risk of untimely death.[2,12] • The patient's family members should be educated on what to do and what not to do if the patient has another seizure. • Explicit follow-up instructions should be given.
Special populations	• The American Academy of Neurology has published guidelines for AED choice and special concerns for patients with HIV infection and pregnant women.[28,29] • Physicians should be familiar with non-convulsive seizure presentations, which range from acute and fluctuating confusional state to coma.[2] Patients presenting with a first seizure and meeting criteria for status epilepticus are also a special group.[13]

underlying illness manifesting as seizure.[21] (*See Table 3.*) Following initial evaluation and stabilization, blood tests, imaging studies (CT or MRI), and performance of lumbar puncture for cerebrospinal fluid analyses may aid in establishing a diagnosis.

Important medications with risk of seizures in overdose or in therapeutic doses in susceptible individuals include tramadol,[22] lithium, theophylline, lidocaine, and lindane. (*See Table 4.*)

Seizures have rarely been described with administration of many general anesthetics, including those used in the ED for sedation, with etomidate probably having a somewhat higher risk, while propofol and ketamine are less apt to cause seizures.[1] Any severe overdose that causes circulatory collapse or coma (such as severe salicylate toxicity) can be accompanied by seizure activity.

Serotonin syndrome usually resulting from multiple drug-drug interactions causing increased serotonergic activity in the CNS can cause recurrent generalized seizures.

Toxic substance-induced seizures tend to respond to treatment with benzodiazepines, with the important exception of isoniazid, which requires specific treatment with pyridoxine.[23]

Alcohol use and abuse can contribute to seizures in several different ways, including withdrawal, metabolic disturbances such as hyponatremia, lowering seizure threshold, increasing chances of neurotrauma, CNS infection, and noncompliance with AEDs.[24] A review and meta-analysis of alcohol consumption and unprovoked seizures found that the threshold for alcohol consumption and the onset of epilepsy was the daily ingestion of 24 grams of ethanol (about two drinks).[25] This risk is separate from the well-known risk of seizures due to alcohol withdrawal. The pathophysiology by which seizures occur in alcohol users is poorly understood, and may be related to cerebral atrophy, ionic imbalance, or a proposed "kindling" theory by which repeated withdrawal leads to the gradual lowering of the epileptogenic threshold.[25]

Status Epilepticus

Status epilepticus affects between 50,000 and 150,000 Americans every year, making it the second most common neurological emergency in the United States after stroke.[26,27] It describes a prolonged, self-sustained generalized tonic-clonic seizure lasting more than five minutes, or two or more shorter episodes over 30 minutes, and without the patient regaining full consciousness in between.[26] This change in definition from the prior requirement of seizure activity lasting for more than 20-30 minutes comes from a realization that most seizures are brief, and once a seizure lasts for five minutes it is likely to be prolonged.[26] The 20-30 minute cut-off represents the time at which ongoing

Table 3. Life-Threatening Conditions Commonly Presenting as Seizures

Cause	Type	Comment
Electrolyte derangements	Hypoglycemia, extreme hyperglycemia, hypo- or hypernatremia (severe and rapidly developing), severe hypo- or hypercalcemia, severe hypomagnesemia	Early bedside glucose measurement and an ECG are essential in any patient with present or recent altered mental status. Severe hypocalcemia can result in tetany that can be difficult to distinguish from seizure activity. Hypokalemia can cause life-threatening arrhythmia resulting in recurrent syncope and severe muscle weakness. Rapid bedside tests have been developed for serum electrolyte measurement.
Intracranial space-occupying lesion	Traumatic Intracranial hemorrhage, brain abscess, central nervous system malignancy, central nervous system parasitic disease	Red flags vary depending on specific condition; non-contrast CT of the brain is usually the first study obtained in adults.[6]
Central nervous system infection	Meningitis, infectious encephalitis, subdural empyema, and parasitic infections, such as cysticercosis or toxoplasmosis	Travel history and patient's immunological status can be important clues; any suspicion of bacterial meningitis or herpes encephalitis necessitates prompt appropriate antibiotic administration. Encephalopathy and low Glasgow Coma Scale on presentation are especially worrisome.[7]
Stroke	Both ischemic and hemorrhagic stroke, venous sinus thrombosis, brain vasculitis	Todd's paralysis can be difficult to distinguish from stroke initially.
Eclamspia		Rarely may present several weeks postpartum; need to distinguish from breakthrough seizures in women with epilepsy.
Noninfectious encephalitis	Many types, including limbic, Hashimoto, uremia,[13] autoimmune (such as anti-NMDA, cerebral lupus, or associated with thrombotic thrombocytopenic purpura)[32]	Initially psychiatric complaints may predominate, delaying the diagnosis.
Withdrawal	Alcohol, benzodiazepines, barbiturates, gamma hydroxybutyrate	Can herald development of life-threatening delirium. Any patient presenting to the ED with seizures should be questioned about drug and alcohol use.

seizure activity itself can damage the brain.

Status epilepticus can be convulsive (either generalized or focal) and, thus, readily apparent, or non-convulsive (non-convulsive status epilepticus [NCSE]). The latter diagnosis cannot be made without performing an EEG.[30] NCSE is further subdivided into NCSE proper that can be of "wandering confused" or comatose variety[13] and deep coma with epileptic discharges.[30] In approximately 30% of cases, status epilepticus fails to respond to administration of benzodiazepines and another AED and thus meets criteria for refractory status epilepticus (RSE).[13,27]

Mortality rates for status epilepticus in adults are estimated at up to 20%[26,31] and depend on underlying cause, the duration of status epilepticus, and the age of the patient.[31,32] Recently published Neurocritical Care Society and American Epilepsy Society guidelines propose a rational approach to diagnosis and treatment of patients presenting in status epilepticus.[13,22,26,27,31,32,33,34,35]

While what follows appears to be a step-wise process, in reality many of the described steps will be occurring simultaneously or in parallel. Given the deleterious effect of ongoing convulsive and non-convulsive seizures, patients who present in status epilepticus should receive immediate attention. The clinician should strive to control the seizures as soon as possible while keeping in mind side effects of AEDs. If there is any doubt as to whether or not a comatose patient is experiencing seizures, EEG monitoring should be initiated as soon as possible.[13]

Causes of Status Epilepticus

Status epilepticus is quite common among neurologic emergencies, with an incidence as high as 41 per 100,000 per year, and fewer than 50% of patients have experienced previous seizures.[32] Generalized tonic-clonic seizures tend not to last for more than two to three minutes. In adults with preexisting epilepsy, noncompliance with AEDs is a major cause for status epilepticus. Stroke, anoxia, CNS infection, tumor, trauma, alcohol, and drug overdose are all common causes. Status epilepticus may occur in patients without previous seizure disorder, and, conversely, with prolonged seizures, neuronal death, and alteration of networks may cause recurrent seizures after an episode of status epliepticus.[32] Less common causes include a variety of immunologic disorders, such as cerebral lupus, Goodpasture syndrome, or thrombocytopenic purpura. A variety of infections can cause status epilepticus, including but not limited to West Nile encephalitis, HIV-related infections, neurosyphilis, cat-scratch disease, and measles encephalitis.

Approach to Known or Suspected Status Epilepticus

The following section will present two representative scenarios for adult status epilepticus.

Table 4. Some Poisonings That Can Cause Seizures[45]

Toxin	Examples	Comments
Sodium channel blockers	Tricyclic antidepressants, carbamazepine, chloroquine, quinine, local anesthetics	Associated with life-threatening dysrhythmias, distinct ECG abnormalities, altered mental status
Sympathomimetics	Cocaine, amphetamines	Severe hypertension, tachycardia, hyperthermia, delirium; resembles alcohol or benzodiazepine withdrawal
Bupropion		Recurrent seizures, psychosis
Camphor		Sources include Vick's VapoRub®, imported folk remedies
Anticholinergics	Diphenhydramine, scopolamine, atropine, toxic plants (jimson weed), many other substances	Presentation can resemble sympathomimetic overdose except for dry skin and urinary retention
Isoniazid		Refractory seizures and status epilepticus that respond to administration of vitamin B6 (pyridoxine)
Cholinesterase inhibitors	Organophosphates (insecticides, nerve agents), carbamates	Hypersecretory state, respiratory failure Transdermal toxicity may necessitate decontamination of victims to protect health personnel
Theophylline		Pronounced nausea and vomiting, electrolyte abnormalities Obtain serial serum levels

Scenario 1. A patient presents unconscious with either ongoing or frequent intermittent seizure activity lasting more than five minutes.

In this scenario, airway protection is paramount. Oxygen should be administered as necessary, the patient should be placed on a cardiac monitor, IV or IO access should be established, and blood glucose should be checked. Intravenous thiamine then IV dextrose should be given.[26] If there are any signs of trauma present, cervical spine protection should be considered. The patient may require intubation, especially prior to leaving the ED for imaging or other reasons. The possibility of non-epileptic seizures should be considered. If a wide complex tachycardia is present, consider bicarbonate administration if sodium channel blocker overdose such as a cyclic antidepressant is a possibility.

An appropriately dosed benzodiazepine should be given as a first-line agent: lorazepam 2 to 4 mg IV, diazepam 5 to 10 mg IV, or midazolam 10 mg IM if there is any delay with establishing an intravenous line.[22] In patients without an established IV, midazolam IM will terminate seizures faster than lorazepam given IV, likely because of the time it takes to start an IV.[22] If there are historical clues suggesting isoniazid overdose, IV vitamin B6 (pyridoxine) 70 mg/kg up to 5 grams should be administered.

In women of childbearing age, the possibility of eclampsia should always be considered. The patient with eclampsia should be given magnesium sulfate 4 to 6 grams IV followed by infusion of 1-3 g/hour.

If seizures continue, consider repeating the parenteral benzodiazepine dose once. Consider bedside electrolyte measurement if available. If not, serum should be sent for chemistry, hematology, toxicology, and AED levels as appropriate. If suspicion for expanding intracranial lesion exists (signs of trauma, other signs of increasing intracranial pressure), non-contrast CT scan of the head must be obtained as soon as possible.

If seizures continue and no obvious cause is evident, choose one of the following as the second-line agent: phenytoin or fosphenytoin (20 mg/kg or 20 PE/kg up to a maximum of 1,500 mg), valproate (40 mg/kg, maximum 3,000 mg),[17] or levetiracetam (60 mg/kg up to a maximum of 4,500 mg).

If seizures continue, IV phenobarbital can be given at 15 to 30 mg/kg and usually will require simultaneous initiation of ventilator support. If seizures continue, general anesthesia with IV propofol (1 to 2 mg/kg load then 20 to 40 mcg/kg/min) or pentobarbital (5 to 15 mg/kg load followed by 0.5 to 5 mg/kg/hr) should be started with close attention paid to hemodynamics, as some patients may need pressors. EEG monitoring will be needed in all patients reaching this stage.

Any suspicion for CNS infection should prompt administration of broad spectrum IV antibiotics and acyclovir as well as performance of lumbar puncture after head CT is done. Status epilepticus that continues for 24 hours after induction of general anesthesia is defined as super-refractory status epilepticus.[35]

Scenario 2. A patient presents with altered mental status as a result of NCSE. While initial steps, AEDs, and critical care are largely the same as in convulsive status epilepticus, EEG is critical to diagnosing this condition. NCSE can present either as a fluctuating state of confusion and speech disturbances possibly mimicking delirium, psychiatric disease, or stroke, or as deep coma.[13,27,30] In patients with minor disturbances of the level of alertness, heavy sedation should be avoided if possible.[13,27] Just as in convulsive status epilepticus, a reversible secondary cause, such as stroke or encephalitis,[8] should be sought when appropriate.

Disposition. Patients presenting in status epilepticus and still with altered mental status after ED treatment should be admitted to an intensive care setting for frequent neurological checks and careful monitoring. Those who are hemodynamically stable and

have mental status that is back to baseline and whose workup did not reveal a dangerous condition may be stable for a medical floor or observation unit admission.

Approximately 35% of patients with super-refractory status epilepticus die, while another 35% return to their prior neurologic state. A variety of AEDs, inhalational anesthetics, other medications including ketamine, and desperation therapies including electroconvulsive therapy, deep brain stimulation, hypothermia,[33] and other neurosurgical procedures have been utilized in these patients.[35]

Antiepileptic Drugs

AEDs are a diverse group of medications used to treat seizures as well as some other neurologic and psychiatric conditions, including trigeminal neuralgia, chronic pain syndromes, and certain mood disorders. (*See Table 5.*) In patients diagnosed with epilepsy or with two unprovoked seizures more than 24 hours apart, AEDs generally are recommended.[17] The choice of AED ideally is made jointly with the doctor who will be following the patient. Patients who have frequent breakthrough seizures despite taking an AED either can be switched to a different medication or have another medication added. We recommend extreme caution for ED physicians in stopping an AED unless a severe side effect develops for fear of breakthrough seizures or status epilepticus development.[17] AEDs achieve symptomatic relief of seizures in approximately 75% of patients, while about half of those treated report some side effects.[17] Importantly, current AEDs do not prevent or reverse epilepsy.[1,17] All AEDs have side effects and some of those can be life-threatening.[5] Patients are frequently noncompliant with prescribed AEDs with the potential for increased morbidity and mortality.

While there are many choices available now for initial monotherapy in adults who require an AED, no agent is clearly superior.[18,36] All AEDs are associated with the potential for increased suicidality,[5,17] especially in patients with underlying psychiatric disorders. Any medication can cause severe and life-threatening allergic reactions. AEDs that cause sedation increase the risk of accidental injury in patients taking them, especially if combined with other CNS depressing substances or medications. Patients and their families should be educated to seek immediate care for any new psychiatric complaint and to report any new rash or mucous membrane lesions.

It is useful to consider broad categories of AED effects. Type A effects can be attributed to the known mechanism of action of antiepileptic drugs: dizziness, unsteadiness, ataxia, gait difficulties, nystagmus, tremor, or diplopia. Cognitive dysfunction, such as memory problems or difficulty concentrating, tends to be most prominent with benzodiazepines or barbiturates. Type B effects are adverse reactions that cannot be ascribed directly to the known mechanism of action of a drug, such as cutaneous reactions, pancreatitis, hepatic or hematologic reactions, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, or drug rash with eosinophilia with systemic symptoms (DRESS), as occurs with carbamazepine, phenytoin, or lamotrigine use. Type C reactions are related to the cumulative dose of the drug, for example decreased bone mineral density or folate deficiency with phenytoin and barbiturates, or weight gain with valproate or gabapentin. Type D effects encompass teratogenic effects, as with valproate and phenobarbital. Type E effects are related to drug interactions affecting drug metabolism.[12]

Certain characteristics of specific medications are worth noting. Phenytoin is not useful for myoclonic seizures, and neither phenobarbital, levetiracetam, nor phenytoin are effective for absence seizures. The relatively new AEDs levetiracetam and gabapentin tend not to cause dermatologic/hypersensitivity reactions. Nor do they affect hepatic enzyme function. The following medications have target plasma concentrations so that their levels can be measured: carbamazepine, felbamate, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, primidone, and valproate.[2] However, levels are not always useful for optimizing dosages. They may be more useful for monitoring a patient's compliance with therapy and adherence to their treatment protocols. Hypoventilation, hypotension, and cardiac rhythm disturbance are the prominent adverse effects of any drug used to treat status epilepticus.

Drug-resistant epilepsy has been defined broadly as failure to achieve seizure control with trials of two appropriate antiepileptic drugs. This may be a result of medication noncompliance, sleep deprivation, or alcohol or drug abuse rather than ineffectiveness of the medications themselves. Psychogenic seizures may account for up to 2% of resistant cases. It may be that the wrong AED has been prescribed because the seizure has been misclassified. For example, absence epilepsy or myoclonic seizures can be worsened with phenytoin, carbamazepine, gabapentin, and others.[14]

Pregnancy is a particular concern in the management of seizures. The risk of major congenital malformations in the offspring of women with epilepsy may be increased by taking AEDs in the first trimester. Avoidance of valproic acid especially is recommended in the first trimester of pregnancy.[29] Valproate has been linked to a higher rate of spontaneous abortion, neural tube defects, cleft palate, hypospadias, and atrial septal defect, as well as developmental delays and autism during childhood.[37]

Other AEDs have been linked to adverse effects, although in lesser numbers. Lamotrigine has been associated with cleft lip or cleft palate. Phenytoin, phenobarbital, and primidone have been reported in the past to be associated with cleft palate and hare lip and possible reduced cognitive outcomes. It has been recommended that AED polytherapy during pregnancy be avoided.[29]

Complications of Epilepsy

Patients with epilepsy suffer from increased morbidity and mortality compared to the general population.[4,30,38] Part of this increase is due to underlying disorders causing secondary epilepsy, such as brain tumors.[39] Status epilepticus has high mortality, as noted earlier.[32] Suicide risk is higher in patients with epilepsy, likely due to a combination of the pathological changes caused by the disease and the AEDs used to treat it.[38,39]

Patients with epilepsy, especially those with convulsive tonic-clonic seizures,

Table 5. Antiepileptic Drugs

Drug Name	Indications	Precautions	Important Side Effects	Adult Dosing	Drug-Drug Interactions	Special Populations
Phenytoin/ Fosphenytoin	Convulsive seizures; has been used for seizure prophylaxis after severe head injury, although the benefit is not clear[36]	Contraindicated in pronounced sinus bradycardia, sino-atrial and atrioventricular block; can induce hyperglycemia and ketoacidosis. Rapid intravenous administration of phenytoin can cause hypotension and cardiac arrhythmias.	Severe allergic reactions, vertigo, unsteadiness, osteoporosis	Load IV or PO 15-20 mg/kg; IV loading of phenytoin requires cardiac monitoring and should not be faster than 50 mg/min in adults; phenytoin is tissue toxic if extravasates; oral loading can be divided in 3 doses every 4 hours or given as a single dose; fosphenytoin is parenteral only, is a phenytoin prodrug, and its dose is expressed in phenytoin sodium equivalents (PE), it can be loaded IV at 150 PE/min and can be given IM; maintenance phenytoin therapy 300-400 mg/ day extended release (ER) PO divided TID or QID	Multiple drug-drug interactions	Drug-drug interaction with lopinavir/ritonavir in HIV patients Interacts with other antiretroviral drugs as well: amprenavir, darunavir, efavirenz, nelfinavir
Valproate	Convulsive seizures, absence seizures	Avoid in patients with mitochondrial disorders	Teratogenicity, hepatotoxicity (can be fatal), pancreatitis, hyperammonemic encephalopathy (occurs with therapeutic serum valproate levels), weight gain	Standard loading dose is 15-20 mg/kg IV, in status epilepticus use up to 40 mg/kg IV (maximum 3 g); maintenance therapy with 30-60 mg/kg/day PO divided BID-TID	Phenytoin, carbamazepine, phenobarbital, and carbapenem antibiotics all reduce serum valproate levels	In HIV patients, zidovudine dose needs to be reduced. Avoid in pregnancy if possible
Carbamazepine	Convulsive seizures	Avoid in patients with prior aplastic anemia; causes tricyclic-like sodium channel blockade in overdose	Severe allergic reaction, disequilibrium	No IV formulation; start with 200 mg ER PO BID, increase by 200 mg weekly to maintenance dose of 400-600 mg ER PO BID	Multiple drug-drug interactions; Tegretol suspension is not to be taken together with any other medications	
Phenobarbital	Convulsive seizures	Habit forming; small amounts are excreted in human milk	Sedation, severe allergic reactions	15-20 mg/kg IV loading in status epilepticus only; maintenance dose is 60 mg PO BID-TID	Multiple drug-drug interactions	Withdrawal is a concern in infants born to mothers who receive phenobarbital in their third trimester of pregnancy
Levetiracetam	Convulsive seizures, seizure prophylaxis after severe head injury (controversial),[36] myoclonic epilepsy	Generally well tolerated	Psychiatric and behavior side effects including aggression	50-60 mg/kg (maximum 4.5 g) IV loading in status epilepticus only; maintenance dose is 500-1,500 mg PO BID	No significant drug-drug interactions, although recently an interaction with methotrexate has been established	
Lacosamide	Partial seizures		Dizziness and ataxia	Start at 100 mg PO BID, increase by 100 mg/day every week to maintenance dose of 150-200 mg PO BID	Caution when administered concomitantly with PR-prolonging medications, such as calcium channel blockers or beta-blockers	

Table 5. Antiepileptic Drugs (continued)

Drug Name	Indications	Precautions	Important Side Effects	Adult Dosing	Drug-Drug Interactions	Special Populations
Lamotrigine	Convulsive seizures	Patients should seek immediate medical attention for any new rash while taking lamotrigine; avoid administering together with valproate	Severe allergic reactions; FDA black box warning for life-threatening allergic rashes	Complex dose escalation depending on many individual factors — consult clinical pharmacist	Multiple drug-drug interactions, including with valproate	HIV patients receiving ritonavir/atazanavir need lamotrigine dose increased by 50% Interaction with lopinavir/ritonavir
Topiramate	Convulsive seizures	Avoid administering together with valproate, acetazolamide, or metformin	Nephrolithiasis, unsteadiness; increased risk of bleeding; metabolic acidosis; somnolence; visual disturbances (acute myopia, visual field defects)	Start 25 mg PO BID, increase by 50 mg/day every week to maintenance dose of 200 mg PO BID	Multiple drug-drug interactions	Reduces effectiveness of oral contraceptives
Zonisamide	Partial seizures	Avoid concomitant CNS depressant substances and medications; zonisamide is a sulfonamide derivative	Nephrolithiasis, sedation, metabolic acidosis	Start 100 mg PO daily, increase every two weeks by 100 mg/day to maintenance dose of 200-400 mg/day; may be divided q12 hr after first week	Avoid co-administration with other carbonic anhydrase inhibitors (such as acetazolamide or topiramate) and metformin	
Gabapentin	Partial seizures; adjunctive use only	Avoid co-administration with other CNS depressants	Gastroparesis, sedation, weight gain; withdrawal symptoms possible with rapid discontinuation	Start 300 mg PO daily, increase over two days to maintenance dose of 300 mg PO TID	Does not affect metabolism of other antiepileptics	
Oxcarbazepine	Partial seizures		Hyponatremia, severe allergic reaction, unsteadiness, cognitive problems	Start 300 mg PO BID, if AED naive increase every three days by 300 mg/day to maintenance dose of 600 mg PO BID	Multiple drug-drug interactions	
Perampanel	Partial seizures; adjunctive use only	Avoid use with other CNS depressants; abuse potential	Severe psychiatric and behavioral disturbances	Complex dose escalation depending on many individual factors — consult clinical pharmacist, maintenance dose 8-12 mg PO qhs	Multiple drug-drug interactions	

are at higher risk than the general population for certain types of accidental trauma, specifically related to driving and falls.[4] Head injury sustained during a fall from standing from a tonic-clonic seizure is much more likely to result in intracranial hemorrhage or a skull fracture than one in an otherwise neurologically intact patient.[4] Certain AEDs, such as phenytoin, can cause accelerated osteoporosis,[32] increasing a chance of a long bone fracture after a fall. Some AEDs cause sedation or disequilibrium, especially when combined with other CNS depressants or at supratheraputic plasma levels and as such increase the probability of accidental trauma.

Drowning is a risk to seizure patients, and appropriate counseling regarding not lying in a bathtub and not swimming while unsupervised is essential.

Sudden unexplained death in epilepsy patients (SUDEP) is defined as unexpected non-traumatic and non-drowning death in a patient with epilepsy without another structural or toxicological cause and not related to status epilepticus.[40,41] It is one of the leading causes of death in patients with chronic epilepsy and the second most important neurological cause of years of life lost behind only stroke.[31] It usually is nocturnal, frequently but not always follows a seizure, and is more common after a generalized tonic-clonic seizure.[42] To date, SUDEP mechanisms are not understood and no definite association with either electrocardiogram (ECG) abnormalities or to a particular AED is known.[40,43] No modifiable risk factors have been identified, with the exception of the degree of epilepsy control, as patients experiencing more seizures are at higher risk of sudden death.[12,39]

As there are no effective means of predicting or preventing SUDEP, discussing it with individuals and families is difficult and controversial.[39] Most

episodes occur during sleep, and the patient is found prone, suggesting suffocation as a contributing factor. If there is a suggestion that a person is having nocturnal seizures without being aware of them, such as tongue biting, muscle soreness, confusion on awakening, or urinary incontinence, a sound or seizure monitor may be considered.[38]

Non-epileptic Seizures

Psychogenic non-epileptic seizures (PNES) are encountered regularly by emergency physicians, although their true prevalence in ED patients presenting with seizures is not known.[9] While various etiologies and triggers, such as prior sexual or physical abuse, have been proposed, their cause remains unknown.[9,21] Non-epileptic seizures lack ictal brain activity and so a seizure is presumed to be non-epileptogenic if a vEEG during the episode is normal. PNES patients also may have comorbid epilepsy, are distinct from those volitionally attempting to feign a seizure for secondary gain, and are thought to be suffering from psychiatric illness, perhaps a form of conversion disorder.[8,21]

In our experience, once the diagnosis of PNES is reasonably certain and the patient is medically stable, involving psychiatry in patient care early can make a positive difference in the frequency of PNES. Given underlying complex neuropsychiatric mechanisms, "confronting" or admonishing patients for their PNES episodes is not helpful. An ongoing PNES episode can be extremely difficult to distinguish from status epilepticus for ED physicians and neurologists alike, exposing these patients to interventions carrying risk of significant morbidity, such as multiple AED administration, repeat neuroimaging, and even endotracheal intubation.

ED physicians should use extreme caution in diagnosing PNES based on clinical features alone, and epileptic seizures are the most common missed medical diagnosis.[8] For example, patients with frontal lobe epilepsy can present with bilateral tonic posturing without losing consciousness, pelvic thrusting, crying, and lack of postictal confusion.[8] Myoclonic and temporal lobe epilepsy attacks also can present with bilateral arm movements and preserved consciousness. Moreover, epileptic activity coming from a small focus in deep brain structures or in a patient taking AEDs may not be picked up on video EEG with routine electrode placement.[8] Case reports of seizures predictably triggered by certain decision-making activities (backgammon playing) or audio stimuli from a certain voice from TV,[16] as well as cases of encephalitis presenting with prominent psychiatric overtures[8,16] call for careful consideration prior to ascribing patient shaking to a psychiatric illness.

Summary and Conclusion

Seizures are a common presenting complaint in ED patients. Many serious diseases, such as strokes, brain tumors, and CNS infections, can result in provoked seizures and some of these carry high mortality. Generalized or focal shaking associated with brief or prolonged altered mental status can be seen in variety of medical conditions and does not necessarily represent seizures. Patients with primary seizures require careful evaluation to decide whether or not to start an AED. Neuroimaging techniques, including non-contrast head CT, CT head with intravenous contrast, CT angiogram of the brain, and various MRI of the brain, are used to exclude provoked seizure, work up neurotrauma resulting from a seizure, and to risk-stratify patients for AED administration and appropriate disposition. Convulsive and non-convulsive status epilepticus is a medical emergency requiring aggressive diagnostic and therapeutic measures to terminate seizure activity as soon as possible while minimizing morbidity and mortality.

Diagnosis of non-epileptic seizures generally requires an EEG to be performed during the episode. Clinicians should keep in mind the possibility of a serious medical disorder, most commonly epilepsy or certain forms of encephalitis masquerading as a psychiatric disease. Antiepileptic drugs can reduce the number of seizures that a patient will have, but do not reverse epilepsy, and all have various medical and psychiatric side effects. Noncompliance with antiepileptic drugs is common and puts patients at risk for morbidity and mortality. Compared to the general population, patients with epilepsy are at increased risk for untimely death resulting from underlying disorders, traumatic injuries, status epilepticus, and sudden unexplained death in epilepsy.

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CME/CE Questions

1. Which of these conditions can present with transient altered mental status and extremity shaking?
   a. Neurocardiogenic syncope
   b. Brain concussion
   c. Pulmonary embolism
   d. All of the above

2. A patient presents with left hemiparesis and altered mental status. Which metabolic derangement can be the cause?
   a. Metabolic acidosis
   b. Hypoglycemia
   c. Hypokalemia
   d. Hyperammonemia
   e. Hypocalcemia

3. Which of the following is true of uncontrolled movements without altered mental status?
   a. They are always a sign of psychiatric disorder.
   b. They may be a sign of acute stroke.
   c. They always require sedation.
   d. They always represent a focal seizure.

4. While treating a patient with status epilepticus, the physician should:
   a. never administer medications intramuscularly.
   b. repeat appropriate dose of a benzodiazepine three times.
   c. give vitamin B6 intravenously to a continuously seizing patient treated for tuberculosis as an outpatient.
   d. never give barbiturates after benzodiazepines have been given.

5. To reduce the risk of untimely death in a patient with chronic epilepsy, the physician should:
   a. perform a head CT every time the patient presents to the ED after a seizure
   b. tell the patient to lie in a bathtub instead of taking a shower.
   c. make sure that the patient is on an appropriate antiepileptic drug and is compliant with it.
   d. perform an ECG looking for telltale signs of oncoming sudden death in epilepsy.

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EMERGENCY MEDICINE **REPORTS**

Evaluation and Management of Seizures in the Emergency Department

Initial Differential Diagnosis When Seizure Is a Consideration

Presentation	Differential Diagnosis	Comments
Sudden loss of consciousness with complete spontaneous recovery	Syncope (different etiologies: neurocardiogenic, arrhythmogenic, pulmonary embolism, hypovolemia, etc.), brain concussion with concussion seizure, seizure	Brief extremity shaking is commonly observed in syncope, including neurocardiogenic syncope. Some patients may describe an aura resembling visual hallucinations. Tongue biting is much less common in syncope as compared to a seizure. Secondary trauma is common after a seizure. Altered mental status, if present after loss of consciousness, generally rules out syncope.
Ongoing or recurrent loss of consciousness with tonic-clonic activity	Status epilepticus, recurrent seizures, non-convulsive seizures	Prior history of non-convulsive seizures, if available, is helpful. Certain features suggesting preserved volitional activity (purposeful movements, speech, tightly closed eyes) may clue the clinician to psychogenic nonepileptic seizures, but are not absolutely diagnsostic.
Altered mental status without abnormal movements	Non-convulsive status epilepticus, postictal state, metabolic or endocrine derangements, intoxicants, infection, central nervous system trauma, etc.	Improvement in mental status after administration of benzodiazepines suggests seizure activity but is not diagnostic; maintaining a broad differential is important; EEG can be very helpful in difficult cases.
Unilateral neurodeficit	Stroke, transient ischemic attack, aortic dissection, hypoglycemia, shock, complex migraine, Todd's paralysis	Seizure at the onset of stroke-like symptoms is a relative contraindication for administration of tPA for an acute stroke. Transient ischemic attack can mimic focal motor seizures.
Uncontrolled movements without alteration in mental state	Focal seizure, chorea, ballism	Chorea can be a presenting symptom of an acute stroke.
Aura	Migraine, seizure, brain tumor, syncope, psychosis	

Management of First-Time Seizure in Adults

Initial workup	• Rule out status epilepticus, evaluate for traumatic injuries. • Rule out provoked seizure: alcohol- or drug-related; space-occupying intracranial lesion; stroke; withdrawal state; electrolyte or glucose disturbances; bacterial, auto-immune encephalitis; bacterial, viral, or parasitic central nervous system infection. • In the third trimester of pregnancy and early postpartum, always consider the possibility of eclampsia; keep in mind that some women will not know or share their pregnant state. • Consider timing and type of neuroimaging: emergent non-contrast CT of brain if space-occupying lesion or trauma is a concern, contrast CT of brain for brain abscess, parasitic lesion, or malignancy, CTA of brain and neck if acute stroke or neck arterial dissection is suspected, MRI of brain for more subtle pathology and to guide initial therapy. • Lumbar puncture should follow neuroimaging if there are no contraindications and central nervous system infection or inflammation remains a concern.
Decision to start an antiepileptic drug after first unprovoked seizure	• Generally, starting an antiepileptic drug (AED) after the first seizure does not improve quality of life or prognosis. • Patients who are at higher risk of recurrence based on seizure type (nocturnal seizure), seizure duration (patients presenting in status epilepticus), significantly abnormal brain imaging, or epileptiform abnormalities on EEG are at higher risk of early recurrence and should be considered for AED.
Information for patients	• Correct information on driving and avoidance or modification of other dangerous activities, such as lying down in a bathtub unsupervised, is essential but is commonly omitted at discharge. • Patients with seizures are at higher risk of causing a motor vehicle accident than the general population. • The Epilepsy Society has a webpage that answers questions with regard to various scenarios arising for someone living with epilepsy. AEDs do not prevent development of epilepsy. AEDs can reduce the number of seizures the patient experiences and may reduce the risk of untimely death. • The patient's family members should be educated on what to do and what not to do if the patient has another seizure. • Explicit follow-up instructions should be given.
Special populations	• The American Academy of Neurology has published guidelines for AED choice and special concerns for patients with HIV infection and pregnant women. • Physicians should be familiar with non-convulsive seizure presentations, which range from acute and fluctuating confusional state to coma. Patients presenting with a first seizure and meeting criteria for status epilepticus are also a special group.

Life-Threatening Conditions Commonly Presenting as Seizures

Cause	Type	Comment
Electrolyte derangements	Hypoglycemia, extreme hyperglycemia, hypo- or hypernatremia (severe and rapidly developing), severe hypo- or hypercalcemia, severe hypomagnesemia	Early bedside glucose measurement and an ECG are essential in any patient with present or recent altered mental status. Severe hypocalcemia can result in tetany that can be difficult to distinguish from seizure activity. Hypokalemia can cause life-threatening arrhythmia resulting in recurrent syncope and severe muscle weakness. Rapid bedside tests have been developed for serum electrolyte measurement.
Intracranial space-occupying lesion	Traumatic Intracranial hemorrhage, brain abscess, central nervous system malignancy, central nervous system parasitic disease	Red flags vary depending on specific condition; non-contrast CT of the brain is usually the first study obtained in adults.
Central nervous system infection	Meningitis, infectious encephalitis, subdural empyema, and parasitic infections, such as cysticercosis or toxoplasmosis	Travel history and patient's immunological status can be important clues; any suspicion of bacterial meningitis or herpes encephalitis necessitates prompt appropriate antibiotic administration. Encephalopathy and low Glasgow Coma Scale on presentation are especially worrisome.
Stroke	Both ischemic and hemorrhagic stroke, venous sinus thrombosis, brain vasculitis	Todd's paralysis can be difficult to distinguish from stroke initially.
Eclamspia		Rarely may present several weeks postpartum; need to distinguish from breakthrough seizures in women with epilepsy.
Noninfectious encephalitis	Many types, including limbic, Hashimoto, uremia, autoimmune (such as anti-NMDA, cerebral lupus, or associated with thrombotic thrombocytopenic purpura)	Initially psychiatric complaints may predominate, delaying the diagnosis.
Withdrawal	Alcohol, benzodiazepines, barbiturates, gamma hydroxybutyrate	Can herald development of life-threatening delirium. Any patient presenting to the ED with seizures should be questioned about drug and alcohol use.

Some Poisonings That Can Cause Seizures

Toxin	Examples	Comments
Sodium channel blockers	Tricyclic antidepressants, carbamazepine, chloroquine, quinine, local anesthetics	Associated with life-threatening dysrhythmias, distinct ECG abnormalities, altered mental status
Sympathomimetics	Cocaine, amphetamines	Severe hypertension, tachycardia, hyperthermia, delirium; resembles alcohol or benzodiazepine withdrawal
Bupropion		Recurrent seizures, psychosis
Camphor		Sources include Vick's VapoRub®, imported folk remedies
Anticholinergics	Diphenhydramine, scopolamine, atropine, toxic plants (jimson weed), many other substances	Presentation can resemble sympathomimetic overdose except for dry skin and urinary retention
Isoniazid		Refractory seizures and status epilepticus that respond to administration of vitamin B6 (pyridoxine)
Cholinesterase inhibitors	Organophosphates (insecticides, nerve agents), carbamates	Hypersecretory state, respiratory failure Transdermal toxicity may necessitate decontamination of victims to protect health personnel
Theophylline		Pronounced nausea and vomiting, electrolyte abnormalities Obtain serial serum levels

Antiepileptic Drugs

Drug Name	Indications	Precautions	Important Side Effects	Adult Dosing	Drug-Drug Interactions	Special Populations
Phenytoin/ Fosphenytoin	Convulsive seizures; has been used for seizure prophylaxis after severe head injury, although the benefit is not clear[36]	Contraindicated in pronounced sinus bradycardia, sino-atrial and atrioventricular block; can induce hyperglycemia and ketoacidosis. Rapid intravenous administration of phenytoin can cause hypotension and cardiac arrhythmias.	Severe allergic reactions, vertigo, unsteadiness, osteoporosis	Load IV or PO 15-20 mg/kg; IV loading of phenytoin requires cardiac monitoring and should not be faster than 50 mg/min in adults; phenytoin is tissue toxic if extravasates; oral loading can be divided in 3 doses every 4 hours or given as a single dose; fosphenytoin is parenteral only, is a phenytoin prodrug, and its dose is expressed in phenytoin sodium equivalents (PE), it can be loaded IV at 150 PE/min and can be given IM; maintenance phenytoin therapy 300-400 mg/ day extended release (ER) PO divided TID or QID	Multiple drug-drug interactions	Drug-drug interaction with lopinavir/ritonavir in HIV patients Interacts with other antiretroviral drugs as well: amprenavir, darunavir, efavirenz, nelfinavir
Valproate	Convulsive seizures, absence seizures	Avoid in patients with mitochondrial disorders	Teratogenicity, hepatotoxicity (can be fatal), pancreatitis, hyperammonemic encephalopathy (occurs with therapeutic serum valproate levels), weight gain	Standard loading dose is 15-20 mg/kg IV, in status epilepticus use up to 40 mg/kg IV (maximum 3 g); maintenance therapy with 30-60 mg/kg/day PO divided BID-TID	Phenytoin, carbamazepine, phenobarbital, and carbapenem antibiotics all reduce serum valproate levels	In HIV patients, zidovudine dose needs to be reduced. Avoid in pregnancy if possible
Carbamazepine	Convulsive seizures	Avoid in patients with prior aplastic anemia; causes tricyclic-like sodium channel blockade in overdose	Severe allergic reaction, disequilibrium	No IV formulation; start with 200 mg ER PO BID, increase by 200 mg weekly to maintenance dose of 400-600 mg ER PO BID	Multiple drug-drug interactions; Tegretol suspension is not to be taken together with any other medications	
Phenobarbital	Convulsive seizures	Habit forming; small amounts are excreted in human milk	Sedation, severe allergic reactions	15-20 mg/kg IV loading in status epilepticus only; maintenance dose is 60 mg PO BID-TID	Multiple drug-drug interactions	Withdrawal is a concern in infants born to mothers who receive phenobarbital in their third trimester of pregnancy
Levetiracetam	Convulsive seizures, seizure prophylaxis after severe head injury (controversial),[36] myoclonic epilepsy	Generally well tolerated	Psychiatric and behavior side effects including aggression	50-60 mg/kg (maximum 4.5 g) IV loading in status epilepticus only; maintenance dose is 500-1,500 mg PO BID	No significant drug-drug interactions, although recently an interaction with methotrexate has been established	
Lacosamide	Partial seizures		Dizziness and ataxia	Start at 100 mg PO BID, increase by 100 mg/day every week to maintenance dose of 150-200 mg PO BID	Caution when administered concomitantly with PR-prolonging medications, such as calcium channel blockers or beta-blockers	

Drug Name	Indications	Precautions	Important Side Effects	Adult Dosing	Drug-Drug Interactions	Special Populations
Lamotrigine	Convulsive seizures	Patients should seek immediate medical attention for any new rash while taking lamotrigine; avoid administering together with valproate	Severe allergic reactions; FDA black box warning for life-threatening allergic rashes	Complex dose escalation depending on many individual factors — consult clinical pharmacist	Multiple drug-drug interactions, including with valproate	HIV patients receiving ritonavir/ atazanavir need lamotrigine dose increased by 50% Interaction with lopinavir/ritonavir
Topiramate	Convulsive seizures	Avoid administering together with valproate, acetazolamide, or metformin	Nephrolithiasis, unsteadiness; increased risk of bleeding; metabolic acidosis; somnolence; visual disturbances (acute myopia, visual field defects)	Start 25 mg PO BID, increase by 50 mg/ day every week to maintenance dose of 200 mg PO BID	Multiple drug-drug interactions	Reduces effectiveness of oral contraceptives
Zonisamide	Partial seizures	Avoid concomitant CNS depressant substances and medications; zonisamide is a sulfonamide derivative	Nephrolithiasis, sedation, metabolic acidosis	Start 100 mg PO daily, increase every two weeks by 100 mg/day to maintenance dose of 200-400 mg/day; may be divided q12 hr after first week	Avoid co-administration with other carbonic anhydrase inhibitors (such as acetazolamide or topiramate) and metformin	
Gabapentin	Partial seizures; adjunctive use only	Avoid co-administration with other CNS depressants	Gastroparesis, sedation, weight gain; withdrawal symptoms possible with rapid discontinuation	Start 300 mg PO daily, increase over two days to maintenance dose of 300 mg PO TID	Does not affect metabolism of other antiepileptics	
Oxcarbazepine	Partial seizures		Hyponatremia, severe allergic reaction, unsteadiness, cognitive problems	Start 300 mg PO BID, if AED naive increase every three days by 300 mg/day to maintenance dose of 600 mg PO BID	Multiple drug-drug interactions	
Perampanel	Partial seizures; adjunctive use only	Avoid use with other CNS depressants; abuse potential	Severe psychiatric and behavioral disturbances	Complex dose escalation depending on many individual factors — consult clinical pharmacist, maintenance dose 8-12 mg PO qhs	Multiple drug-drug interactions	

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