

Diagnosis and Acute Management of Seizure in Adults

Minal J. Bhanushali, MD

Sandra J. Helmers, MD

A 34-year-old man with a history of seizure disorder presented to the emergency department (ED) due to an increase in seizure frequency. He reports having had 4 generalized tonic-clonic seizures over the past 24 hours. His last seizure occurred approximately 45 minutes before he presented to the ED. He had a 6-year history of partial epilepsy, which was being treated with carbamazepine 400 mg twice daily. He reported having experienced nausea, vomiting, and diarrhea over the past week, which made him unable to take his medication during this time. There was no history of fever, recent use of any new medications, alcohol abuse, or head trauma.

Examination in the ED revealed normal vital signs except for a borderline low blood pressure of 100/60 mm Hg. General examination was remarkable for lateral tongue bites; his neck was supple. On neurologic examination he appeared lethargic but was able to follow simple commands. Pupils were equal and reactive with no eye deviation. Corneal, oculocephalic, cough, and gag reflexes were intact. He localized to pain and moved all extremities symmetrically. Deep tendon reflexes were depressed uniformly; toes showed flexor responses bilaterally. Notable laboratory values included a random blood glucose level of 96 mg/dL (normal, 65–100 mg/dL), white blood cell count of 12,000 cells/ μ L (normal, 3600–11,000 cells/ μ L), hematocrit of 56% (normal, 45%–54%), sodium level of 132 mEq/L (normal, 136–144 mEq/L), and a carbamazepine level of 1.2 mg/L (therapeutic level, 4–12 mg/L).

While in the ED, the patient experienced a witnessed generalized tonic-clonic seizure lasting for 2 minutes. Vital signs remained within normal limits. Lorazepam 2 mg and fosphenytoin 650 mg phenytoin equivalents (PE; 10 mg PE/kg) were administered intravenously. The patient was admitted to the medical floor for further management.

An epileptic *seizure* is a temporary alteration in brain function due to excessive and hypersynchronous neuronal activity that may result in uncontrolled body movements or a convulsion and alteration of consciousness. *Epilepsy* is a chronic condition characterized by a tendency to have recurrent unprovoked seizures (2 or more). Approximately 2.5 million people in the United States have epilepsy, and 100,000 new cases are diagnosed each year.¹ Common reasons for hospitalization in patients who present to medical care with seizure are new-onset seizures and increased frequency of seizures in persons diagnosed with epilepsy. In 2005, there were nearly 1.4 million hospital admissions directly or indirectly related to seizures or convulsions (eg, trauma due to seizures, aspiration pneumonias due to seizures, fever or alcohol use leading to seizures), and 277,000 of these admissions had epilepsy as a primary admitting diagnosis.² Timely evaluation and management of patients who present with seizure is essential to control seizures and prevent progression to status epilepticus, a life-threatening

emergency with significant morbidity and a mortality rate of up to 22%.³ This article reviews the evaluation and management of adult patients with new-onset or recurrent seizure in the acute care setting.

CLASSIFICATION

The International League Against Epilepsy (ILAE) classification system for seizures identifies 3 broad types: localization related (partial or focal), generalized, and unclassified (**Table 1**).⁴ Localization-related seizures start focally and may or may not spread to other parts of the brain. These are further subdivided into simple (associated with normal awareness), complex (associated with impaired awareness), and partial

At the time this article was written, Dr. Bhanushali was a clinical neurophysiology fellow, Emory University School of Medicine, Atlanta, GA; she is currently an assistant professor, Department of Neurology, Michigan State University, East Lansing, MI. Dr. Helmers is an associate professor, Department of Neurology, Emory University School of Medicine.

TAKE HOME POINTS

- A seizure is a temporary alteration in brain function due to excessive and hypersynchronous neuronal activity, whereas epilepsy is a chronic condition with a tendency to have recurrent unprovoked seizures.
- A careful review of history is essential to distinguish nonepileptic paroxysmal events mimicking seizure from an epileptic seizure, which may be provoked or unprovoked.
- Neuroimaging and routine electroencephalogram (EEG) should be considered in all patients with new-onset seizures.
- Acute management of seizures is directed to prevent aspiration and secondary trauma, to achieve timely seizure control with benzodiazepines with or without intravenous antiepileptic drugs, and to prevent progression to status epilepticus.
- Continuous EEG monitoring is required for patients in status epilepticus on benzodiazepine or propofol infusion.
- Patients with a normal neurologic examination, no risk factors, and no known structural brain lesion may not require antiepileptic drugs after a first unprovoked seizure.
- Checking a serum antiepileptic drug level prior to giving an additional loading dose is recommended.

seizures evolving into secondary generalized seizures. Generalized seizures involve both hemispheres of the brain at onset. Unclassified seizures include all seizures that cannot be classified due to incomplete data or that defy classification into the other 2 categories. The ILAE classification system is used to identify the seizure type or syndrome and thereby guide management (ie, neuroimaging, choice of an antiepileptic drug).

STATUS EPILEPTICUS

Status epilepticus traditionally has been defined as at least 30 minutes of persistent seizures (partial or generalized) or a series of recurrent seizures without complete return to full consciousness between the seizures. However, Lowenstein and colleagues⁵ have suggested defining generalized convulsive status epilepticus as more than 5 minutes of either continuous seizures or 2 or more discrete seizures with incomplete recovery of consciousness in between. This definition has been endorsed by epileptologists and neurologists and is widely

Table 1. International League Against Epilepsy Classification of Seizure Type (1981)

Localization-related seizures (partial or focal seizures)

Simple partial seizures with

Motor signs (focal clonic movements)

Somatosensory (tingling or numbness) or sensory symptoms

Visual (light flashes or hallucinations)

Auditory (buzzing)

Olfactory (abnormal or putrid smells)

Gustatory (metallic taste)

Autonomic symptoms

Psychic symptoms (eg, déjà vu feeling, feeling of fear, epigastric discomfort)

Complex partial seizures

Partial seizures with secondary generalization

Generalized seizures (convulsive or nonconvulsive)

Absence seizures

Myoclonic seizures

Clonic seizures

Tonic seizures

Tonic-clonic seizures

Atonic seizures

Unclassified epileptic seizures

used.⁶ Seizures associated with nonmotor manifestations include absence status epilepticus and complex partial status epilepticus (nonconvulsive status), which may present with acute confusion or encephalopathy.^{7,8} The possibility of nonconvulsive status should be considered in patients who have a prolonged altered level of consciousness following convulsive seizures.⁹

INITIAL EVALUATION AND DIAGNOSIS OF SEIZURES

The initial evaluation of a patient who presents following a reported seizure focuses on determining whether an epileptic seizure actually occurred, and if it did, whether it was provoked or unprovoked. The **Figure** shows a common approach to a differential diagnosis for first seizure. Syncope, migraine, and psychogenic nonepileptic seizures (ie, paroxysmal behavior patterns initiated by psychological mechanisms) can commonly be mistaken for epileptic seizures, and differentiating them clinically can be challenging.¹⁰ Electroencephalogram (EEG) or video EEG monitoring (for psychogenic nonepileptic seizures) can occasionally help in making a diagnosis. However, determining whether the event was an epileptic seizure or a nonepileptic event mimicking an epileptic convulsion is typically based on a detailed history.

After the patient is stabilized, a careful review of events preceding, during, and after the seizure should be obtained from the witness or the patient (if possible), with particular attention to prodromal symptoms, auras, and a description of the seizure (Table 1). Prodromal symptoms include a sense of nervousness and anxiety for hours or days before a seizure and are not associated with epileptiform activity on EEG. The term *aura* is used to describe a sensation immediately preceding a seizure, and auras are associated with epileptiform correlates on EEG.¹¹

Once a seizure has been established to be epileptic, the next step is to identify if the seizure was provoked or unprovoked by determining whether an underlying cause associated with seizures is present. Provoked seizures are commonly secondary to a systemic cause such as a metabolic disturbance, medications, intoxication, alcohol withdrawal, or an intracranial lesion (eg, stroke, intracranial bleed, trauma, infection, tumor). Past medical history should be elicited to determine whether the patient has risk factors for seizures and epilepsy, including prior seizures or symptoms suggestive of seizures, febrile seizures, meningitis, head injury, vascular disease or stroke, alcohol withdrawal, and a family history of epilepsy. A history of prior seizures favors the diagnosis of epilepsy. Detailed review of medications may be obtained, including recent dose changes (eg, discontinuation of benzodiazepines or barbiturates or use of high doses of meperidine or bupropion) and use of antiepileptic drugs. Physical examination should be performed with emphasis on injury pattern, cardiovascular system (looking for arrhythmias and hypotension), and skin (looking for neurocutaneous stigmata). Neurologic examination occasionally reveals focal deficits, which may be a postictal phenomenon (Todd's paralysis) or may indicate the presence of a structural brain lesion.

Distinguishing if a seizure was provoked is important in determining treatment. In the case of a provoked seizure, treating the underlying condition is necessary to control the current seizure and prevent the recurrence of seizures. Also, prolonged use of antiepileptic medications may not be indicated in this situation.

Role of Diagnostic Tests

Ancillary tests that may be useful in patients with seizures include blood and cerebrospinal fluid analysis, EEG, and neuroimaging. According to the clinical policy statement of the American College of Emergency Physicians (ACEP) as well as practice parameters issued by the American Academy of Neurology (AAN), laboratory testing (complete blood count, comprehensive metabolic profile, cerebrospinal fluid analysis, urine analysis) has a low yield in patients with new-onset seizure who have

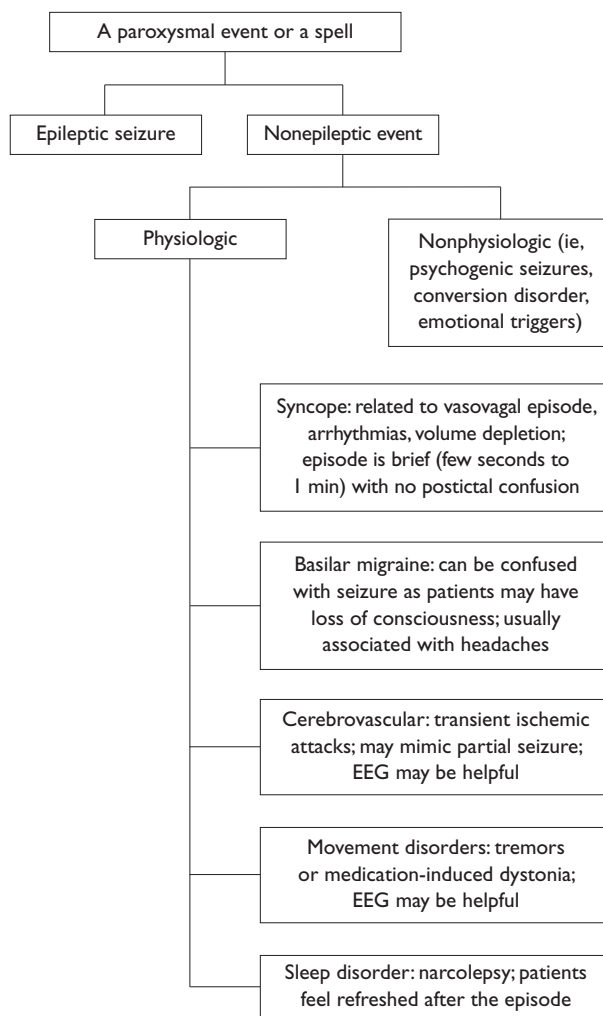


Figure. Common conditions that mimic epileptic seizures. EEG = electroencephalogram. (Data from Carreno M. Recognition of nonepileptic events. *Semin Neurol* 2008;28:297-304.)

returned to baseline.^{12,13} Serum glucose abnormalities and hyponatremia are the most frequent abnormalities identified.¹² There are no prospective trials to support or refute more in-depth testing such as serum calcium, magnesium, or phosphate levels, blood counts, or drugs of abuse testing, although these tests may be helpful depending on clinical circumstances.¹² Pregnancy testing in young women with new-onset seizures has implications on further testing (ie, radiation exposure from computed tomography [CT] scan), diagnosis (ie, eclampsia), and choice of antiepileptic medications.¹² In patients with known epilepsy, serum antiepileptic drug levels should be measured to assess for subtherapeutic or supratherapeutic levels and guide management.

Performing serum prolactin assay after a seizure

can rarely be helpful in differentiating epileptic seizures from nonepileptic psychogenic seizures as serum prolactin may rise shortly after an epileptic seizure.¹⁴ However, the increase in prolactin is not constant, and a normal prolactin level does not exclude epileptic seizures. Also, some patients have increased baseline prolactin levels, and the test does not exclude concurrent psychogenic seizures.¹⁵

Current evidence does not support routine lumbar puncture in adults presenting with an apparently unprovoked seizure.¹³ However, it is recommended in febrile patients¹⁶ as well as in all immunocompromised patients (even if they are afebrile) with new-onset seizures.¹⁷

The AAN practice parameters¹² recommend performing neuroimaging (CT scan or magnetic resonance imaging of the brain) in all patients with new-onset seizures. Emergent head CT is recommended in patients with a history or findings of trauma, history of malignancy, immunocompromised state, fever, persistent headaches, history of anticoagulation, or history of new focal neurologic deficits or focal onset of seizures with or without generalization.¹⁸ In nonemergent situations, magnetic resonance imaging is the preferred modality as it is more sensitive.¹³ In patients with known epilepsy, repeat neuroimaging may be considered with onset of new focal neurologic deficits or a change in the character of seizures.

In patients with new-onset seizures, EEG helps predict the risk of seizure recurrence, diagnose and classify the epileptic syndrome, guide the choice of an appropriate antiepileptic drug, and determine prognosis.^{19,20} Epileptiform activity on EEG manifested as generalized spike and wave discharges or focal spikes is associated with greater risk of recurrence. However, a normal EEG does not exclude the presence of a seizure disorder. On average, approximately 30% of individuals clinically diagnosed with seizures have a normal EEG.²¹ The diagnostic yield of a routine EEG is reported to be 29%.^{4,22} A routine EEG should be considered in all patients with unprovoked new-onset seizures.¹³ An emergent EEG with continuous monitoring is recommended for patients in persistent coma, refractory status epilepticus with pharmacologically induced coma, or nonconvulsive status. EEG is the definitive test for diagnosing nonconvulsive status. In situations requiring an emergent EEG, consultation with a neurologist is recommended.¹²

MANAGEMENT

Acute Management of Seizures

The goals of acute management of seizures are to prevent aspiration and secondary trauma, to achieve

timely seizure control with benzodiazepines with or without intravenous (IV) antiepileptic drugs, and to prevent progression to status epilepticus. If the patient is actively seizing, he or she should be placed in a lateral decubitus position with the head positioned at a 30-degree angle to minimize aspiration, and any objects that can injure the patient should be moved. It is important to observe the seizure type. Oxygen should be administered by nasal cannula or facemask. An oropharyngeal airway kit and bag valve mask should be ready at bedside, and IV access should be established. Pharmacologic therapy is 0.1 mg/kg of IV lorazepam administered in 2-mg increments over 2 to 3 minutes (maximum of 8 mg). Alternatively, 0.2 mg/kg of IV diazepam at a rate of 5 mg/min can be used.²³ If IV access cannot be established, lorazepam can be administered intramuscularly. Diazepam is available in intramuscular and rectal gel formulation as well. Because benzodiazepines can cause respiratory depression, blood oxygen saturation and respiratory rate should be monitored closely. Blood glucose can be measured by fingerstick, if deemed necessary.¹² If the patient is hypoglycemic, dextrose 50% in water should be administered intravenously. In patients with a history of alcohol use, 100 mg of thiamine should be injected prior to glucose administration.¹² Most seizures terminate within 2 to 3 minutes and do not require further acute treatment.

If a seizure continues for more than 5 minutes or the patient has 2 or more generalized tonic-clonic seizures within 1 hour, aggressive management is warranted as these patients progress rapidly to status epilepticus. Early intervention is associated with an 80% response rate, and rates progressively decline with increased time to treatment.²⁴ IV lorazepam at a dose of 0.1 mg/kg along with parenteral (IV/intramuscular) fosphenytoin at a loading dose of 20 mg phenytoin equivalents (PE)/kg should be administered; the rate of fosphenytoin should not exceed 150 mg PE/min.^{22,25,26} Although the incidence of cardiac arrhythmias and hypotension is lower with fosphenytoin as compared with IV phenytoin, cardiac monitoring is recommended while administering the bolus dose.²⁷ If fosphenytoin (or phenytoin) is contraindicated (allergy), alternative antiepileptic drugs available in IV preparations include phenobarbital, valproate, and levetiracetam.

All patients with seizures presenting to the hospital must be placed under seizure precautions to minimize the risk of physical injury. These include nursing orders for placing the bed in the lowest position, putting side rails up and padding them, and making sure that

oropharyngeal airway, oxygen, and suction are available at bedside.

Management of Status Epilepticus

If a patient continues to seize after these interventions, he or she should be intubated and transferred to the intensive care unit.²³ An IV infusion of phenobarbital with a loading dose of 15 to 20 mg/kg can be started. Seizures that continue in spite of administration of an initial benzodiazepine and second-line antiepileptic drug (ie, phenytoin or phenobarbital) are considered refractory status epilepticus, and aggressive management with benzodiazepine or propofol infusion is needed for faster control.²⁸ Commonly used medications are lorazepam initiated with a 0.1 mg/kg loading dose followed by infusion of 0.1 to 0.2 mg/kg; midazolam initiated with a 0.2 mg/kg loading dose followed by 0.1 to 0.2 mg/kg/hour infusion; or propofol initiated with a 3 to 5 mg/kg loading dose followed by 2 to 10 mg/kg/hour infusion.²⁸⁻³¹ However, arterial blood pressure needs to be monitored carefully because of the risk for significant hypotension with IV infusions of benzodiazepines or propofol; use of vasopressors or administration of the loading dose in segments may be warranted. Occasionally, patients with refractory status epilepticus require pharmacologic induction of coma by barbiturate infusion or general anesthesia. Continuous EEG monitoring is required, and infusion rates are titrated to maintain the patient in a burst-suppression pattern. In addition, cardiac monitoring and blood pressure monitoring for hypotension is warranted. Complications of prolonged seizures such as lactic acidosis, hyperpyrexia, electrolyte disturbance, rhabdomyolysis, and renal failure are addressed accordingly. After acute control of seizures by the above measures, identification and treatment of the underlying cause is necessary to maintain long-term control.

Initiation of an Antiepileptic Drug

The decision to start an antiepileptic drug in a patient with new-onset seizure depends mainly on his or her risk for recurrence. Seizures provoked secondarily are managed by treating the underlying etiology (eg, hypoglycemic seizures are treated with glucose), and antiepileptic drugs are not indicated. If a patient presents with new-onset, apparently unprovoked seizure, no risk factors (outlined below), and a normal neurologic examination at baseline, the probability of seizure recurrence is less than 10% in the first year and approximately 24% by the end of 2 years after a single seizure.³² AAN practice parameters as well as ACEP clinical policies recommend against initiation of an antiepileptic drug

in patients with a normal neurologic examination, no risk factors, and no known structural brain lesion after first unprovoked seizure.^{12,13} However, the decision is individualized on the basis of clinical judgment. Seizures associated with a structural brain lesion and partial-onset seizures are associated with a risk of recurrence up to 65%, and antiepileptic drugs are indicated after a single seizure.³³ If a patient has concomitant risk factors such as a history of previous central nervous system insult, family history of seizures, spike and wave pattern on EEG, or presence of Todd's postictal paresis, initiation of an antiepileptic drug is considered after a single seizure.³²

Several factors should be considered when choosing an appropriate antiepileptic drug. First, seizure treatment should be initiated with a single antiepileptic drug. Potential benefits of monotherapy include fewer adverse events, better tolerability, minimal drug interactions, and improved compliance.³⁴ Second, it is necessary to correctly identify the seizure type and epileptic syndrome prior to initiating therapy. If a clinician is uncertain of the seizure type, consultation with a neurologist is helpful after the acute management of seizure. In adults, partial-onset seizures are more common than primary generalized seizures.³⁵ These patients can be initiated on a classic antiepileptic drug such as carbamazepine, phenytoin, valproate, or phenobarbital or a second-generation antiepileptic drug such as lamotrigine, gabapentin, oxcarbazepine, or topiramate. The newer antiepileptic drugs tend to have improved side-effect profiles, drug interaction profiles, and dosing regimens (**Table 2**).³⁶ In generalized epilepsies, valproate, lamotrigine, or topiramate have shown efficacy.^{36,37} Levetiracetam is approved as adjunctive therapy for generalized seizures.³⁸

A third consideration in selecting an antiepileptic drug is comorbidities. If a patient has concomitant migraine headaches, initiating an antiepileptic drug such as valproate or topiramate can be considered, while in those with a history of bipolar disease, lamotrigine or valproate may be preferred.

Medication noncompliance is one of the most common reasons for recurrent seizures in patients with epilepsy. Measuring the serum antiepileptic drug level is recommended prior to administering additional medication as this practice has been shown to prevent undue toxicity and is associated with shorter hospital stay, and decreased morbidity.³⁹ Additionally, albumin level, plasma protein binding, and distribution of plasma volume (eg, in pregnancy, dialysis) influence total antiepileptic drug levels in the serum. Therefore, assessing a free level of the drug is preferable in these circumstances. Several days may be required to obtain serum levels of newer antiepileptic drugs.

Table 2. Commonly Used Antiepileptic Drugs

Medication	Starting Dose	Metabolism	Efficacy in Types of Seizure	Adverse Effects
Carbamazepine	5–8 mg/kg/day	Hepatic	Partial-onset	Bone marrow suppression, hepatitis, hyponatremia
Phenytoin and fosphenytoin (IV or IM only)	Loading: 10–15 mg/kg/day Maintenance: 5 mg/kg/day	Hepatic	Partial-onset	Gum hyperplasia, hirsutism, acne, rash, blood dyscrasias IV: cardiac arrhythmias, hypotension (lower incidence with fosphenytoin)
Valproate (orally and IV)	5–15 mg/kg/day	Hepatic	Primary generalized and partial-onset	Weight gain, alopecia, tremor, hepatitis, thrombocytopenia, pancreatitis, polycystic ovarian failure, neural tube defects in pregnant woman, rash
Oxcarbazepine	300–600 mg/day	Hepatic (70%)	Partial-onset	Hyponatremia, rash
Lamotrigine	50–75 mg/day (titration pack)	Hepatic (90%)	Primary generalized	Rash and hypersensitivity reaction (increased with concomitant use of valproate), insomnia
Levetiracetam	500–1000 mg/day	Renal (66%), hydrolysis (34%)	Adjunct to partial-onset and primary generalized	Behavior change
Topiramate	25–50 mg/day	Renal (40%–70%)	Adjunct to partial-onset and primary generalized	Nephrolithiasis, glaucoma, reduced sweating, weight loss, metabolic acidosis, word finding difficulties
Zonisamide	100–200 mg/day	Hepatic metabolism and renal clearance	Adjunct to partial-onset	Contraindicated in patients allergic to sulfonamides; decreased sweating and hyperthermia, nephrolithiasis, sedation, fatigue

IM = intramuscular; IV = intravenous.

Patient Discharge and Disposition

Patients with provoked seizures, abnormal neurologic examination, or prolonged postictal state need further work-up in the hospital, and status epilepticus requires admission to the intensive care unit. However, patients who return to baseline mental status and have a normal neurologic examination can be discharged from the ED with an outpatient follow-up.¹² At the time of discharge, patients must be informed about restrictions on driving, which vary from state to state. The Epilepsy Foundation of America's web site (www.epilepsyfoundation.org) is a helpful online resource for patient information and for determining driving laws in a given state (www.epilepsyfoundation.org/living/wellness/transportation).

CONCLUSION

Evaluation, diagnosis, and management of seizures in the hospital or ED is complex. Timely and accurate management is essential to prevent progression to status epilepticus or seizure recurrence. Partnership between a hospital physician and neurologist will help facilitate recognition and care of patients presenting with seizure. **HP**

Corresponding author: Minal Bhanushali, MD, Department of Neurology and Ophthalmology, Michigan State University, 138 Service

Road, Suite B445, East Lansing, MI 48824; minal.bhanushali@hc.msu.edu.

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