Clinical Decision Making In Seizures And Status Epilepticus

Abstract

Seizures and status epilepticus are frequent neurologic emergencies in the emergency department, accounting for 1% of all emergency department visits. The management of this time-sensitive and potentially life-threatening condition is challenging for both prehospital providers and emergency clinicians. The approach to seizing patients begins with differentiating seizure activity from mimics and follows with identifying potential secondary etiologies, such as alcohol-related seizures. The approach to the patient in status epilepticus and the patient with nonconvulsive status epilepticus constitutes a special clinical challenge. This review summarizes the best available evidence and recommendations regarding diagnosis and resuscitation of the seizing patient in the emergency setting.

January 2015
Volume 17, Number 1

Authors

Felipe Teran, MD
Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; Faculty, Emergency Department, Clinica Alemana, Santiago, Chile

Katrina Harper-Kirksey, MD
Anesthesiology Critical Care Fellow, Department of Anesthesiology, Stanford Hospital and Clinics, Stanford, CA

Andy Jagoda, MD, FACEP
Professor and Chair, Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai, New York, NY; Medical Director, Mount Sinai Hospital, New York, NY

Peer Reviewers

J. Stephen Huff, MD
Professor of Emergency Medicine and Neurology, University of Virginia, Charlottesville, VA

Jason MckMullan, MD
Assistant Professor, Department of Emergency Medicine, University of Cincinnati, Cincinnati, OH

CME Objectives

Upon completion of this article, you should be able to:
1. Describe the diagnostic approach to patients who have recovered from a seizure and patients in status epilepticus.
2. Recognize and treat patients with alcohol withdrawal seizures.
3. Choose appropriate pharmacologic therapy for seizure states.

Prior to beginning this activity, see “Physician CME Information” on the back page.

Research Editors

Michael Guthrie, MD
Emergency Medicine Residency, Icahn School of Medicine at Mount Sinai, New York, NY

Federica Stella, MD
Emergency Medicine Residency, Giovanni e Paolo Hospital in Venice, University of Padua, Italy

International Editors

Giorgio Carbone, MD
Chief, Department of Emergency Medicine Ospedale Gradenigo, Torino, Italy

Amin Antoine Kazzi, MD, FAAEM
Associate Professor and Vice Chair, Department of Emergency Medicine, University of California, Irvine, USA

Hugo Peralta, MD
Chair of Emergency Services, Hospital Italiano, Buenos Aires, Argentina

Dhanad Samunski, MD, FAAEM
Attending Physician, Emergency Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; Faculty of Medicine, Chulalongkorn University, Thailand

Suzanne Y.G. Peeters, MD
Emergency Medicine Residency Director, Haga Teaching Hospital, The Hague, The Netherlands

Editor-In-Chief

Andy Jagoda, MD, FACEP
Professor and Chair, Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai, Medical Director, Mount Sinai Hospital, New York, NY

Associate Editor-In-Chief

Kaushal Shah, MD, FACEP
Associate Professor, Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

Editorial Board

William J. Brady, MD
Professor of Emergency Medicine and Medicine, Chair, Medical Emergency Response Committee, Medical Director, Emergency Management, University of Virginia Medical Center, Charlottesville, VA

Mark Clark, MD
Assistant Professor of Emergency Medicine, Program Director, Emergency Medicine Residency, Mount Sinai Saint Luke’s, Mount Sinai Roosevelt, New York, NY

Peter DeBlieux, MD
Professor of Clinical Medicine, Interim Public Hospital Director of Emergency Medicine Services, Louisiana State University Health Science Center, New Orleans, LA

Nicholas Genes, MD, PhD
Assistant Professor, Department of Emergency Medicine, Icahn School of Medicine at Mount Sinai, New York, NY

Michael A. Gibbons, MD, FACEP
Professor and Chair, Department of Emergency Medicine, Carolinas Medical Center, University of North Carolina School of Medicine, Chapel Hill, NC

Steve A. Godwin, MD, FACEP
Professor and Chair, Department of Emergency Medicine, Assistant Dean, Simulation Education, University of Florida COM, Jacksonville, Jacksonville, FL

Gregory L. Henry, MD, FACEP
Clinical Professor, Department of Emergency Medicine, University of Michigan Medical School; CEO, Medical Practice Risk Assessment, Inc., Ann Arbor, MI

John M. Howell, MD, FACEP
Clinical Professor of Emergency Medicine, George Washington University, Washington, DC; Director of Academic Affairs, Best Practices, Inc, Inova Fairfax Hospital, Falls Church, VA

Kriten Hoshiai, MD, MPH, MBA
Chief of Emergency Medicine, Baylor College of Medicine, Houston, TX

Eric Labe, MD
Chief of Emergency Medicine, King’s County Hospital; Professor of Clinical Emergency Medicine, SUNY Downstate College of Medicine, Brooklyn, NY

Keith A. Marcell, MD
Research Faculty, Department of Emergency Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA

Charles V. Pollack, Jr., MA, MD, FACEP
Professor and Chair, Department of Emergency Medicine, Pennsylvania Hospital, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Michael S. Rado, MD, MPH
Assistant Professor of Emergency Medicine, Weill Medical College of Cornell University, New York; Research Director, Department of Emergency Medicine, New York Hospital Queens, Flushing, NY

Ali S. Raja, MD, MBA, MPH
Associate Professor and Chair, Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN

Stephen H. Thomas, MD, MPH
George Kaiser Family Foundation Professor & Chair, Department of Emergency Medicine, University of California, San Francisco School of Medicine, Tulsa, OK

David M. Walker, MD, FACEP, FAAP
Assistant Professor of Emergency Medicine, Emory University School of Medicine, Emory University Hospital, Atlanta, GA

Ron M. Wallis, MD
Professor of Emergency Medicine and Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston, MA

Research Editors

Michael Guthrie, MD
Emergency Medicine Residency, Icahn School of Medicine at Mount Sinai, New York, NY

Federica Stella, MD
Emergency Medicine Residency, Giovanni e Paolo Hospital in Venice, University of Padua, Italy

International Editors

Giorgio Carbone, MD
Chief, Department of Emergency Medicine Ospedale Gradenigo, Torino, Italy

Amin Antoine Kazzi, MD, FAAEM
Associate Professor and Vice Chair, Department of Emergency Medicine, University of California, Irvine, USA

Hugo Peralta, MD
Chair of Emergency Services, Hospital Italiano, Buenos Aires, Argentina

Dhanad Samunski, MD, FAAEM
Attending Physician, Emergency Medicine, King Chulalongkorn Memorial Hospital, Bangkok, Thailand; Faculty of Medicine, Chulalongkorn University, Thailand

Suzanne Y.G. Peeters, MD
Emergency Medicine Residency Director, Haga Teaching Hospital, The Hague, The Netherlands

Critical Care Editors

William A. Knight, IV, MD, FACEP
Assistant Professor of Emergency Medicine and Surgery, Medical Director, EM Midlevel Provider Program, Associate Medical Director, Neuroscience ICU, University of Cincinnati, Cincinnati, OH

Scott D. Weingart, MD, FCCM
Associate Professor of Emergency Medicine, Director, Division of ED Critical Care, Icahn School of Medicine at Mount Sinai, New York, NY

Senior Research Editors

James Dammali, PharmD, BCPS
Clinical Pharmacist, Emergency Room, St. Joseph’s Hospital and Medical Center, Phoenix, AZ

Joseph D. Toscano, MD
Chairman, Department of Emergency Medicine, San Ramon Regional Medical Center, San Ramon, CA

CME Objectives

Upon completion of this article, you should be able to:
1. Describe the diagnostic approach to patients who have recovered from a seizure and patients in status epilepticus.
2. Recognize and treat patients with alcohol withdrawal seizures.
3. Choose appropriate pharmacologic therapy for seizure states.

Prior to beginning this activity, see “Physician CME Information” on the back page.

EB MEDICINE
PRAC TICE
EBMEDICINE.NET
AN EVIDENCE-BASED APPROACH TO EMERGENCY MEDICINE
Case Presentations

A 19-year-old man with no serious medical history presents to the ED after reports of seizure-like activity. According to the patient’s mother, he was lying on the sofa when he became unresponsive and began having tonic-clonic activity in all extremities. The episode lasted 30 seconds, included urine incontinence, and was followed by a 20-minute period of confusion. He said there have been no previous episodes; however, the mother reports that he once had a febrile seizure as a child. The patient denies drug use and infectious symptoms. On arrival, the patient is awake and completely responsive, with a normal neurologic examination. You wonder if this patient needs neuroimaging and whether he should be admitted to the hospital for a workup...

You receive a notification from EMS that they are bringing in a 22-year-old man who was “found down” and has been having tonic-clonic seizures on and off, without return to baseline, for at least 30 minutes. EMS gives an ETA of 10 minutes. The paramedics have been unable to secure an IV line and they ask you if diazepam should be given IM or rectal… or should they give lorazepam IM or midazolam IM instead? On arrival to the ED, the patient is actively seizing. His blood glucose is 162 mg/dL. He is given a total of 10 mg of IM midazolam while an intravenous line is established. While seizure activity slows, it does not completely abate, even after a fosphenytoin load of 1400 PE is given over 10 minutes. The nurse asks you, “Doctor, what’s next?”

An 80-year-old woman is brought to the ED after having a first-time, witnessed, generalized tonic-clonic seizure about an hour before. Paramedics report no medications given in the field. You quickly assess the patient, who appears confused, with reactive pupils, moving extremities, and no evidence of focal deficits. After the nurse confirms a normal blood sugar of 120 mg/dL, you immediately take the patient for a head CT, which shows evidence of old lacunar infarcts and atrophy, but no midline deviation, edema, or any other finding to explain her altered mental status. By the time the results of basic metabolic testing are back (with no abnormalities), it’s been over 2 hours since your patient has had any evidence of convulsive seizure activity, which seems a little long for a postictal period. You wonder if you are missing something...

Introduction

Seizure can be defined as a sudden change in behavior, characterized by an alteration in sensory perception or motor activity. Seizures are caused by abnormal, excessive, and synchronous electrical firing in groups of neurons. Convulsion refers specifically to the motor manifestations of this abnormal electrical activity. The clinical spectrum of seizures is wide and includes focal or generalized motor activity, altered mental status, sensory or psychic experiences, and autonomic disturbances.

Seizures may be classified according to whether they are caused by an underlying process (provoked) or not (unprovoked). Acute central nervous system (CNS) insults, toxins, or acute metabolic derangements can trigger provoked seizures.

Epilepsy is a condition of recurrent unprovoked seizures. For example, a patient who suffers head trauma might have an acute seizure but would not be considered to have epilepsy unless there are recurrent unprovoked events as a result of the brain injury.

The term ictus refers to the period during which a seizure occurs. Postictal period refers to the interval immediately following the seizure but before the patient returns to baseline mental status. An aura is a focal seizure and is defined by the area of the brain where the seizure originates (eg, a patient with a temporal lobe focus may have a déjà vu experience before the focal event spreads into a generalized tonic-clonic seizure).

Seizures are also classified as partial or generalized (see Table 1, page 3). Partial seizure (also known as focal seizure) occurs due to abnormal neuronal firing within a limited and confined population of neurons in 1 brain hemisphere, whereas generalized seizure denotes an abnormal neuronal firing throughout both brain hemispheres. Partial seizures are further classified as simple when they do not involve a change in mental status and complex when there is some degree of impaired consciousness. Furthermore, generalized seizures can be classified according to the specific type of motor activity (ie, tonic, clonic, tonic-clonic, or myoclonic).

Status Epilepticus

During a convulsive event, metabolic acidosis, hypotension, hypoxia, hypoglycemia, hyperthermia, rhabdomyolysis, and pulmonary edema may develop. Clinical data indicate that permanent neuronal damage may occur after 30 minutes of epileptic activity, even with control of blood pressure, respiration, and body temperature. Thus, status epilepticus (SE) has traditionally been defined as unremitting seizure activity lasting at least 30 minutes or intermittent seizures without recovery of full consciousness. However, irreversible neuronal injury and pharmacoresistance may occur before this traditionally defined time parameter, and spontaneous cessation of epileptic activity is unlikely to occur after 5 minutes of ongoing activity. Consequently, it is now generally accepted that SE be defined as a seizure lasting for 5 minutes or more, or recurrent seizure activity without an interictal return to baseline.

SE is categorized into 2 basic categories: (1) generalized convulsive status epilepticus (GCSE) and (2) nonconvulsive status epilepticus (NCSE). GCSE is a medical emergency, with mortality directly correlated with the duration of the event. It
is typically characterized by seizures with tonic or tonic-clonic activity.\textsuperscript{2,10}

A patient is considered to be in refractory status epilepticus (RSE) when the seizure does not terminate after treatment with a benzodiazepine and a second antiepileptic drug (AED). One retrospective cohort study of 74 patients in GCSE found that 30\% of them progressed to RSE.\textsuperscript{11}

**Nonconvulsive Status Epilepticus**

NCSE presents clinically as an alteration in behavior that is associated with continuous epileptiform discharges on electroencephalogram (EEG). The altered mental status may range from a subtle change to coma, and may be associated with subtle motor signs such as twitching, blinking, eye deviation, persistent aphasia, or somatosensory findings.\textsuperscript{12} NCSE should also be considered in patients in coma of undetermined etiology. A prospective study of 236 patients in coma revealed that 8\% actually carried the diagnosis of NCSE.\textsuperscript{13}

Infections, benzodiazepine withdrawal, and electrolyte abnormalities have been associated with NCSE in patients with and without a pre-existing diagnosis of epilepsy.\textsuperscript{14,15} NCSE has been reported in all age groups, with incidence rates of between 2 and 20 cases per 100,000 individuals, and it can be the first manifestation of a seizure disorder.\textsuperscript{16,17} EEG makes the definitive diagnosis. However, because of the wide spectrum of clinical presentations, NCSE continues to represent a diagnostic challenge to even the most experienced clinicians. According to the presence or absence of consciousness impairment and the type of motor activity, NCSE can be classified into 4 subtypes (see Table 2). NCSE may persist after a convulsive event and should be suspected in a patient who appears to have a prolonged postictal period.

In addition to simple partial SE, distinct forms of NCSE include absence SE and complex partial SE, and subtle convulsive SE. Absence SE and complex partial SE may present with variable degrees of impaired consciousness and very subtle motor activity (such as isolated blinking). A particularly challenging type is subtle SE, which evolves from GCSE as muscles fatigue or neurons become exhausted; its prognosis is much worse than other types of NCSE.\textsuperscript{16} The diagnosis of subtle convulsive status is made in the presence of EEG changes and evidence of previous overt epileptic seizures or GCSE. A United States Department of Veterans Affairs (VA) Cooperative Study demonstrated a substantially worse outcome in subtle SE than in GCSE (with mortality rates of 65\% and 27\%, respectively).\textsuperscript{18}

**Table 1. Classification Of Seizures**

<table>
<thead>
<tr>
<th>Partial Seizures:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Simple partial seizure classification of symptoms</td>
</tr>
<tr>
<td>◦ Motor</td>
</tr>
<tr>
<td>◦ Somatosensory</td>
</tr>
<tr>
<td>◦ Autonomic</td>
</tr>
<tr>
<td>◦ Psychic</td>
</tr>
<tr>
<td>• Complex partial seizure classification</td>
</tr>
<tr>
<td>◦ With focal onset prior to alteration in consciousness</td>
</tr>
<tr>
<td>◦ Without focal onset prior to alteration in consciousness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Generalized Seizures:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Primary generalized nonconvulsive seizure classification</td>
</tr>
<tr>
<td>◦ Absence</td>
</tr>
<tr>
<td>• Primary generalized convulsive seizure classifications</td>
</tr>
<tr>
<td>◦ Tonic-clonic</td>
</tr>
<tr>
<td>◦ Clonic</td>
</tr>
<tr>
<td>◦ Tonic</td>
</tr>
<tr>
<td>◦ Myoclonic</td>
</tr>
<tr>
<td>◦ Atonic</td>
</tr>
<tr>
<td>• Secondary generalized seizure classifications</td>
</tr>
<tr>
<td>◦ Convulsive</td>
</tr>
<tr>
<td>◦ Nonconvulsive</td>
</tr>
</tbody>
</table>

**Status Epilepticus:**

| Convulsive generalized seizure classifications |
| Primary generalized |
| Secondary generalized |
| Convulsive focal seizures |
| Nonconvulsive seizure classifications |
| Primary generalized (absence) |
| Simple partial |
| Partial with or without secondary generalization (complex partial) |
| Subtle |

**Table 2. Clinical Features In Subtypes Of Nonconvulsive Status Epilepticus\textsuperscript{16}**

<table>
<thead>
<tr>
<th>Status Epilepticus Subtype</th>
<th>Phenomenology</th>
</tr>
</thead>
<tbody>
<tr>
<td>With Altered Consciousness</td>
<td></td>
</tr>
<tr>
<td>• Absence status epilepticus</td>
<td>Impaired consciousness of variable degree (eg, disorientation, slow speech, hallucinations) and slight jerking movements</td>
</tr>
<tr>
<td>• Complex partial status epilepticus</td>
<td>Impaired consciousness (usually confusion and strange behavior) and automatisms</td>
</tr>
<tr>
<td>• Subtle status epilepticus</td>
<td>Impaired consciousness with no or subtle movements (such as rhythmic twitching of arms, legs or facial muscles or nystagmus-type eye jerking)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>With Normal Consciousness</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• Simple partial status epilepticus</td>
<td>Preserved consciousness; acoustic, aphasic, gustatory, olfactory or visual symptoms; or altered behavior</td>
</tr>
</tbody>
</table>
Complex partial status epilepticus should be treated initially in the same way as GCSE. Prehospital treatment is recommended. For the adult patient presenting to the ED with a first seizure, assess likelihood that acute treatment is needed. Phenytoin should be loaded rapidly, with an infusion rate of 50 mg/min; this regimen is as effective as IV lorazepam. In GCSE, the preferred treatment is IV administration of 0.1 mg/kg lorazepam. Out-of-hospital IV administration of benzodiazepines in GCSE is as safe as placebo treatment using other drugs. Emergency clinicians may administer IV levetiracetam, propofol, or barbiturates in ED if indicated. When resuming AEDs in the ED is deemed appropriate, emergency clinicians may administer IV or oral medication at their discretion. If IV lorazepam is not available, 10 mg of diazepam, directly followed by 18 mg/kg phenytoin or equivalent fosphenytoin, may be given instead. Immediate noncontrast CT is possibly useful to assess for structural lesion, especially when there is an abnormal neurological examination result, predisposing history, or focal onset of the seizures. Emergency clinicians need not initiate AEDs in the ED for patients who have had a first provoked seizure, or who have had a first unprovoked seizure without evidence of brain disease or injury. Emergency clinicians may initiate AEDs in the ED, or defer in coordination with other providers, for patients who experienced a first unprovoked seizure with a remote history of brain disease or injury. Emergency clinicians need not admit patients with a first unprovoked seizure who have returned to their clinical baseline in the ED. When resuming AEDs in the ED is deemed appropriate, emergency clinicians may administer IV or oral medication at their discretion. Emergency clinicians may administer IV levetiracetam, propofol, or barbiturates in ED patients with refractory status epilepticus who have failed treatment with benzodiazepines. Immediate noncontrast CT is possibly useful to assess for structural lesion, especially when there is an abnormal neurological examination result, predisposing history, or focal onset of the seizures. For adults presenting to the ED with a first seizure, assess likelihood that acute management is changed because of the results of a neuroimaging study. For adults presenting with seizure, CT scans resulted in a change of acute management in 9% to 17% of patients. Immediate noncontrast CT is possibly useful for emergency patients presenting with seizure to guide appropriate acute management, especially where there is an abnormal neurologic examination, predisposing history, or focal seizure onset. For the adult patient presenting to the ED with a first seizure, assess likelihood that acute management is changed because of the results of a neuroimaging study. For adults presenting with seizure, CT scans resulted in a change of acute management in 9% to 17% of patients. Immediate noncontrast CT is possibly useful for emergency patients presenting with seizure to guide appropriate acute management, especially where there is an abnormal neurologic examination, predisposing history, or focal seizure onset. Consensus guideline

### Table 3. Evidence-Based Resources Pertinent To Seizure Management In The Emergency Department

<table>
<thead>
<tr>
<th>Guideline</th>
<th>Methodology</th>
<th>Main Recommendations(^a)</th>
</tr>
</thead>
</table>
| 2014 American College of Emergency Physicians Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department with Seizures\(^b\) | Consensus guideline | - Emergency clinicians need not initiate AEDs in the ED for patients who have had a first provoked seizure, or who have had a first unprovoked seizure without evidence of brain disease or injury. (Level C)  
- Emergency clinicians may initiate AEDs in the ED, or defer in coordination with other providers, for patients who experienced a first unprovoked seizure with a remote history of brain disease or injury. (Level C)  
- Emergency clinicians need not admit patients with a first unprovoked seizure who have returned to their clinical baseline in the ED. (Level C)  
- When resuming AEDs in the ED is deemed appropriate, emergency clinicians may administer IV or oral medication at their discretion. (Level C)  
- Emergency clinicians may administer IV levetiracetam, propofol, or barbiturates in ED patients with refractory status epilepticus who have failed treatment with benzodiazepines. (Level C)  
- Immediate noncontrast CT is possibly useful to assess for structural lesion, especially when there is an abnormal neurological examination result, predisposing history, or focal onset of the seizures. (Level B) |
| 2007 Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology\(^c\) | Expert evidence-based review | - For the adult patient presenting to the ED with a first seizure, assess likelihood that acute management is changed because of the results of a neuroimaging study.  
- For adults presenting with seizure, CT scans resulted in a change of acute management in 9% to 17% of patients. Immediate noncontrast CT is possibly useful for emergency patients presenting with seizure to guide appropriate acute management, especially where there is an abnormal neurologic examination, predisposing history, or focal seizure onset. (Level C) |
| 2010 European Federation of Neurological Societies Guideline on the Management of Status Epilepticus in Adults\(^d\) | Consensus guideline | - In GCSE, the preferred treatment is IV administration of 0.1 mg/kg lorazepam. (Level A)  
- If IV lorazepam is not available, 10 mg of diazepam, directly followed by 18 mg/kg phenytoin or equivalent fosphenytoin, may be given instead. (Level A)  
- Phenytoin should be loaded rapidly, with an infusion rate of 50 mg/min; this regimen is as safe as anticonvulsant treatment using other drugs. (Level A)  
- Prehospital treatment is recommended.  
- Out-of-hospital IV administration of benzodiazepines in GCSE is as safe as placebo treatment. (Level A)  
- Complex partial status epilepticus should be treated initially in the same way as GCSE.  
- In GCSE and subtle SE, it is suggested to proceed immediately to the infusion of anesthetic doses of midazolam, propofol, or barbiturates because of the progressive risk of brain and systemic damage. (Level C) |

Abbreviations: AEDs, antiepileptic drugs; CT, computed tomography; ED, emergency department; GCSE, general convulsive status epilepticus; IV, intravenous; SE, status epilepticus.

\(^a\) Levels of evidence for each set of recommendations are defined in their respective source documents.


testing and imaging for these patients are retrospective data analyses. Two areas of particularly limited evidence are the risk of seizure recurrence and determination of the need for outpatient observation and follow-up versus hospital admission.

Guidelines pertaining to the appropriate choice of AED in SE patients treated in the ED are limited by the lack of subject randomization and outcome reporting of AED levels rather than patient-oriented outcomes (ie, seizure cessation or recurrence). There is not enough good-quality evidence to make definitive recommendations as to the utility of ED-based EEG in patients who appear to have stopped seizing, although a growing body of literature supports early consideration of nonconvulsive or subtle SE when patients do not return to baseline as expected. Evidence outlining recommended treatment modality and agents of choice for patients with RSE is based mainly on small case series, retrospective studies, and survey data from critical care neurologists and epileptologists.

**Epidemiology**

Seizures account for 1% of all ED visits in the United States, with a large majority being unrelated to epilepsy. An analysis of etiologies for patients presenting to the ED with seizures over a 12-year period found that 41% were unknown, 19% were related to alcohol or drugs, 8% were associated with head injury, and only 7% of patients had a pre-existing diagnosis of epilepsy. Other less frequently diagnosed pathologies included brain tumors (3%), metabolic abnormalities (3%), stroke (3%), and neurocysticercosis (1%). Patients presenting to the ED with seizures have a bimodal distribution, with the highest incidence among infants and individuals aged >75 years. This is explained by the high prevalence of febrile seizures in infants and structural brain damage in the elderly. The prevalence of epilepsy in the United States population is approximately 6 per 1000. Up to 50% of patients with epilepsy have recurrent seizures despite initiation of therapy and, even with optimal pharmacologic therapy, up to 10% of patients will have intractable epilepsy.

**Status Epilepticus**

One prospective study involving 236 patients suggested an incidence rate of SE (both GCSE and NCSE) of 41 per 100,000. Up to 5% of adults with epilepsy will have at least 1 episode of SE in their lifetime. The most common causes of SE include subtherapeutic AED levels or pre-existing neurologic conditions. Some patients can experience SE as a result of infection, hemorrhage, stroke, trauma, hypoxia, metabolic abnormalities, or drug or alcohol withdrawal, even with no prior history of epilepsy. Estimated rates of mortality for SE range from 10% to 40% and are related to the underlying etiology.

For example, refractory GCSE associated with bacterial meningitis has a higher mortality than GCSE caused by AED or alcohol withdrawal.

**Pathophysiology**

The basic pathophysiologic changes seen in seizures are characterized by an abnormal electrical discharge of cortical neurons caused by disequilibrium of the neuronal cell membrane. Under normal neurophysiology, neuronal cell membranes are kept stable due primarily to electrochemical gradients across the membranes and regulation of inhibitory mediators such as gamma-aminobutyric acid (GABA). Several pathologic processes (such as infection, toxins, or electrolyte imbalances) can affect this equilibrium and trigger a seizure. Most drugs used to interrupt seizures act on GABA\_A subtype receptors, therefore enhancing inhibitory activity.

At the neuronal level, reduced inhibition and enhanced excitation created during seizure activity reinforce an environment that favors ongoing seizure activity. Persistent seizure activity results in gradual reduction of GABA\_A receptors secondary to receptor internalization and degradation. This process leads to a decrease of endogenous GABAergic inhibition, resulting in sustained epileptic activity. Pharmacoresistance to GABAergic drugs (such as benzodiazepines, barbiturates, and propofol) is likely related to this loss of postsynaptic GABA receptors. Furthermore, N-methyl-D-aspartate (NMDA) receptors are upregulated at the synaptic membrane, resulting in increased numbers of excitatory NMDA receptors, further facilitating sustained neuronal excitability. This is the basis for the old adage, “seizures beget seizures.”

Seizures produce a number of physiologic consequences, including an increase in body temperature, an increase in serum glucose, and lactic acidosis. Elevated lactate occurs within 60 seconds of a convulsive event and normalizes within 1 hour after ictus. A rise in the peripheral white blood cell count without an increase in bands is also often seen.

**Prognosis And Progression Of Seizure Disorder**

One relevant question for the emergency clinician treating the seizing patient is whether the number or duration of seizures carries any significance with regard to the potential for recurrence and how this might influence cognitive outcomes. Patients with provoked seizures show equal incidence of later development of epilepsy, regardless of whether or not treatment with AEDs was initiated immediately after the inciting event. For patients with unprovoked seizures, the evidence is less straightforward.

Whether recurrent or prolonged seizure activity
can lead to cognitive deterioration remains a subject of debate. In general, current data challenge the idea of a common seizure-dependent mechanism for epilepsy progression and intellectual impairment. While some studies have proposed that SE alone may result in cognitive impairment, independent of the inciting cause, most recent studies demonstrate that the majority of patients with epilepsy do not show a progressive disorder. The rare cases of intellectual decline and progressive worsening of seizures are limited to specific epileptic events (e.g., mesial temporal lobe epilepsy, which can follow a progressive course induced by recurrent seizure activity). 

**Differential Diagnosis**

The first step in the approach to a patient suspected of having had a seizure is differentiation of true seizures (aka neurogenic seizures) from other conditions that can mimic them. A common clinical scenario for the emergency clinician is the patient who presents with a history of having had a seizure-like episode, usually involving sudden loss of consciousness and some type of motor activity. Observations from witnesses may hold the key to the diagnosis. As a general rule, no single clinical feature or diagnostic modality is 100% confirmatory for occurrence of a neurogenic seizure. A prospective study that assessed which clinical aspects help distinguish seizures from syncope found a seizure to be 5 times more likely than syncope if the patient was disoriented after the event and 3 times more likely if the patient was aged < 45 years. Remarkably, incontinence and trauma were not discriminative findings between seizure, syncope, and nonepileptic attack disorder. Additional studies have shown that postictal confusion, tongue biting, cyanosis, confirmed unresponsiveness, preceding déjà vu or jamais vu, head or eye turning to one side, and rhythmic limb shaking or dystonic posturing are also strong markers of seizure.

**Convulsive Syncope**

Based on observational studies in blood donors, up to 40% of patients with syncope will have some component of motor activity, most commonly involving tonic extension of the trunk or myoclonic jerks of the extremities. This phenomenon has been observed in patients in a seated position. These events are termed convulsive syncope and are usually not associated with tonic-clonic movements, tongue biting, cyanosis, incontinence, or postictal confusion. Nausea or sweating before the event makes seizure much less likely than syncope.

**Cardiac Dysrhythmias**

Symptomatic dysrhythmias can present with sudden loss of consciousness as a result of cerebral hypoperfusion and hypoxia, which can lead to seizure activity. Specifically, prolonged QT syndrome has been misdiagnosed as a seizure disorder. A careful history may identify preceding cardiac symptoms, such as palpitations, lightheadedness, or diaphoresis. An electrocardiogram (ECG) may be diagnostic, but, when it is not clear, a concurrent cardiac workup may be indicated. Moreover, seizure may also result in dysrhythmia-related syncope.

**Nonepileptic Attacks**

Also referred to as nonepileptic spells, these are nonepileptic paroxysmal neurologic events that may resemble seizures in appearance but do not result from abnormal cortical discharge. Etiologies for these include breath-holding spells, involuntary movements, decerebrate or decorticate posturing, and psychogenic seizures.

Psychogenic seizures (also known as pseudoseizures or nonepileptic seizures) have been reported in 12% to 18% of patients with transient loss of consciousness and can exist concomitantly in patients with neurogenic seizures. Psychogenic seizures are rarely caused by malingering but instead are more commonly a conversion disorder. Characteristic features of a psychogenic seizure include out-of-phase tonic-clonic activity, forward pelvic thrusting, and voluntary eye movements away from the examiner.

**Prehospital Care**

Prehospital management of the seizing patient focuses on assessing oxygenation and perfusion and protecting the patient from injury. Based on evidence from a retrospective study of 1656 patients, there is no need for the use of spinal precautions in patients who experience a seizure that is not associated with major trauma. Management of the patient who is no longer seizing focuses on identifying precipitants and preparing for possible recurrence. The majority of seizures are of short duration and are self-limited, so little intervention is required. In most cases, prehospital personnel will arrive at least 5 minutes after the onset of seizure activity. Therefore, patients who are still seizing on arrival of emergency medical services (EMS) should be managed under the presumption of SE; EMS should be aware of the clinical findings suggestive of nonepileptic spells. If the patient remains confused or unresponsive, paramedics should consider managing the patient as if he were still seizing and immediately measure the patient’s blood sugar.

There are several well-designed prehospital trials on seizure management. In 2007, Holsti et al compared intranasal midazolam to rectal diazepam in pediatric patients, concluding that the intranasal route was more effective at terminating seizures (30 min vs 11 min; P = .003). They also found that patients in the rectal diazepam group were more likely...
to experience a recurrent seizure in the ED (odds ratio [OR], 8.4; 95% confidence interval [CI], 1.6%-43.6%) and to require intubation in the ED (OR, 12.2; 95% CI, 2%-75.4%). Chamberlain et al compared treatment of ongoing seizures using intramuscular midazolam versus intravenous diazepam. Patients who were administered midazolam received the medication sooner (3 min vs 7.8 min) and had more rapid control of seizures (7.8 min vs 11.2 min). In 2001, the Prehospital Treatment of Status Epilepticus (PHTSE) trial randomized the administration of diazepam 5 mg IV, lorazepam 2 mg IV, and placebo in 205 adult patients with GCSE. Seizures were terminated by the time of arrival to the ED in 59% of patients treated with lorazepam, 43% treated with diazepam, and 21% of those who received placebo (P = .001), strongly supporting the use of prehospital benzodiazepines.

Most recently, the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) provided what is considered the most definitive evidence, to date, regarding best route of administration and optimal benzodiazepine for initial treatment of seizures and SE in both children and adults. This double-blind randomized clinical trial enrolled 893 patients over 19 months and compared the efficacy of intramuscular midazolam with intravenous lorazepam in patients treated by paramedics for SE. In the study, seizures were terminated without rescue therapy upon arrival to the ED in 329 (73.4%) of 448 patients allocated to intramuscular midazolam treatment and in 282 (63.4%) of 445 patients allocated to intravenous lorazepam treatment. No difference in complications as found between the 2 groups (including need for endotracheal intubation and recurrent seizures). These results indicate that early administration of intramuscular midazolam is the best option for the prehospital treatment of SE, especially when no intravenous access is immediately available.

**Emergency Department Evaluation**

In approaching the seizing patient, the emergency clinician is often constrained by the paucity of reliable history in a patient who may be unable to cooperate during the initial examination. Medical alert bracelets, old medical records, and medication lists or containers can often provide critical clues to assessing these patients.

**Clinical History**

Identifying the circumstances surrounding the event (such as progression and duration of symptoms) will provide important clues towards determining whether the event was a seizure or a mimic. Witnesses and paramedics are valuable resources. Obtain any history of trauma, either prior to the seizure or during the ictal episode itself, as this may direct management. Comorbid disease may play an important role in the genesis of seizures. A history of neurosurgery, especially a shunt or other CNS hardware, may prompt aggressive testing if the patient has concomitant fever or headache. A history of renal failure, immunosuppression, or recent electrolyte abnormality may drive specific laboratory investigations. Patients with a psychiatric history may have psychogenic seizures, but they may also suffer from hyponatremia due to pathologic water intoxication or as an adverse effect of a psychiatric medication. Those with depression or psychosis may be at higher risk for drug- or toxin-related seizures.

Noncompliance with anticonvulsants is the most common cause for the ED presentation of recurrent seizures. The use of anticoagulants should increase suspicion for intracranial bleeding. Seizures with metabolic causes are most commonly attributed to hypoglycemia and occur primarily in diabetics.

The patient’s social history is also important. Alcohol abuse puts the patient at risk for a number of etiologies that may cause a seizure, including brain injury and withdrawal. Certain recreational drugs (such as cocaine, phencyclidine, and ecstasy) are known to decrease the seizure threshold. Finally, common causes of adult-onset partial seizures in the developing world are neurocysticercosis and malaria, both of which should be considered in travelers and immigrants.

**Physical Examination**

An accurate set of vital signs is the foundation of any physical examination. While a low-grade fever is common immediately after a prolonged convulsion, a persistently high temperature suggests infection or drug reaction. Hypertension with bradycardia may be the result of rising intracranial pressure and impending herniation. Irregular heart rate or carotid bruises may accompany a stroke, which is a common cause of new-onset seizures in the elderly. Anticholinergic and sympathomimetic syndromes may suggest a drug-related seizure, which may make a significant difference in management.

If the patient presents while actively seizing, observe the specifics of the motor activity. Focal abnormalities and eye deviation are signs of an epileptic focus. Anecdotally, pupils are often reported to be dilated during or after a seizure; persistent mydriasis may reflect anticholinergic or sympathomimetic toxicity. Some patients in NCSE are mistakenly assumed to be postictal instead of actively seizing.

Mental status should be carefully documented and observed for change. When possible, recruit family members or contacts who know the patient’s baseline mental status. Postictal confusion usually resolves within 1 hour; failure to improve should prompt a search for alternate explanations (see Table 4, page 8).
A thorough neurologic examination is the key component of the evaluation. Neurologic deficits may represent an old lesion, new intracranial pathology, or postictal neurologic compromise (Todd paralysis). In the case of Todd paralysis that does not quickly resolve, the physician must rule out a new structural lesion. Other physical findings suggestive of a recent seizure include hyperreflexia and extensor plantar responses, both of which should resolve during the immediate postictal period.

Seizures are often associated with injury, and the patient must be evaluated for both soft-tissue and skeletal trauma. Head trauma and tongue lacerations are frequent. Seizure activity can also produce dislocations and fractures. Posterior shoulder dislocations are extremely rare, but, when present, should prompt suspicion that a seizure has occurred. Seizure-induced fractures are rare (<0.6%), but commonly missed. The humerus, thoracic spine, and femur are most commonly involved.

### Diagnostic Studies

#### Laboratory Studies

When relevant, a thorough history and physical examination can predict causative laboratory abnormalities. Patients with persistent alteration of mental status, those in SE, and those who have fever or new neurologic deficit are unique in that they require extensive diagnostic testing. This includes serum glucose, electrolytes, urea nitrogen, creatinine, magnesium, calcium, complete blood count, pregnancy tests in women of childbearing age, AED levels, liver function tests, and drugs-of-abuse screening. If an arterial blood gas analysis is obtained in a convulsing patient (though it is not routinely indicated), it may show an anion gap that has been found sufficiently sensitive or specific to be used in the ED.

### Table 4. Differential Diagnosis Of Altered Mental Status In The Patient Who Has Seized

- Postictal period
- Nonconvulsive status epilepticus or subtle convulsive status epilepticus (can mimic the following):
  - Hypoglycemia
  - Central nervous system infection
  - Central nervous system vascular event
  - Drug toxicity
  - Psychiatric disorder
  - Metabolic encephalopathy
  - Migraine
  - Transient global amnesia

### Toxicological Testing

A drug-of-abuse screen and alcohol level should be considered in patients with first-time seizures, although there is no evidence that such testing changes outcome. A positive drug-of-abuse screen does not prove causation, and the patient would still require an EEG and neuroimaging study to direct management. The screen may, however, suggest an etiology and help with future medical and psychiatric disposition. Seizure due to alcohol intoxication or withdrawal is a diagnosis of exclusion, as alcoholics are at increased risk for electrolyte abnormalities and traumatic injuries.

### Other Laboratory Testing

Both creatine phosphokinase and prolactin have been investigated as markers of seizures. Neither has been found sufficiently sensitive or specific to be used in the ED.

### Electrocardiogram

Patients who continue to seize and patients suspected of overdose may benefit from cardiac...
monitoring. An ECG is also an early screen for drug toxicity. Tricyclic cardiotoxicity may manifest as a QRS complex > 0.1 second or a rightward shift of the terminal 40 ms of the frontal plane QRS complex (a prominent R wave in lead AVR). The ECG can also identify a prolonged QT, a delta wave, Brugada pattern, or heart block, which might contribute further insight into the seizure etiology.

**Neuroimaging**

There is general agreement that neuroimaging is indicated in patients with a first-time nonepileptic seizure. The literature suggests that computed tomography (CT) will change acute management of patients with a new seizure in up to 17% of cases. Table 5 summarizes useful criteria in determining who will benefit from an emergency CT.

Magnetic resonance imaging (MRI) is generally the diagnostic test preferred by neurologists in evaluating first-time seizure because it is better than CT in identifying small lesions. MRI is not better than CT for detecting acute hemorrhage, however, and there are no ED-based studies that have evaluated MRI utility in seizure management.

**Lumbar Puncture**

Lumbar puncture should be considered in patients with fever, severe headache, or persistent altered mental status. Asymptomatic patients with a history or strong suspicion of immunocompromise are also candidates for a lumbar puncture. In a prospective cohort, Sempere et al reported on 8 human immunodeficiency virus (HIV) patients whose seizures were found to be caused by CNS infection, 2 of whom were afebrile with no meningeal signs. This literature review uncovered no cases of bacterial CNS infection presenting as isolated seizure without fever or abnormal neurologic examination in immunocompetent individuals. Theoretically, an exception may occur in cases of partially treated meningitis.

A transient cerebrospinal fluid pleocytosis of up to 20 white blood cells/mm$^3$ has been reported in up to 23% of patients with seizures. However, the emergency clinician is obligated to assume that the presence of white blood cells in the cerebrospinal fluid of a seizing patient represents meningitis until proven otherwise.

**Electroencephalography**

The EEG is the definitive test for diagnosing a seizure disorder, although its sensitivity varies depending on timing and location of the seizure focus. It can certainly be helpful when the diagnosis is in doubt, such as in acute confusion states and coma, as well as for the diagnosis of NCSE. One study found that continued electrical activity occurred in 14% of patients initially treated for GCSE. In the VA Cooperative trial, performance of early EEG found that continued electrical activity occurred in 25% of patients whose seizure was thought, by bedside observation, to have terminated.

Delay in diagnosis of subtle SE was strongly associated with mortality in an intensive care unit study of 72 patients. A 2013 prospective observational trial by Zehtabchi, et al assessed the prevalence of nonconvulsive seizures (NCS) in patients with altered mental status presenting to the ED. The study excluded all cases with correctable causes (ie, hypoglycemia or electrolyte abnormalities), as well as patients who were unable to undergo EEG or who were hemodynamically unstable. Trained technicians performed EEG in the ED and results were interpreted by the on-call study epileptologist. In a convenience sample of 259 patients, 78% of the EEGs were found to have some abnormality (95% CI, 73-83), with the most common being background slowing (58%; 95% CI, 52-68), indicating underlying encephalopathy. NCS was detected in 5% (95% CI, 3-8) of patients. Interestingly, a regression analysis showed a strong effect of age (P < .001; adjusted OR, 1.66 [95% CI, 1.36-2.02] per 10-year age increment). The interrater agreement for EEG interpretations was modest (kappa statistic, 0.45; 95% CI, 0.36-0.54), presenting a potential challenge to accurate diagnosis and highlighting the importance of having access to a trained electroencephalographer. With technology for point-of-care EEG already available in the market, the findings of this study suggest that emergency clinicians should consider EEG in the assessment of the patient with altered mental status in whom there is clinical concern of NCS. However, despite the potential diagnostic and therapeutic value, the incorporation of bedside EEG in the ED still poses logistic difficulties, such as the availability of EEG technicians and on-call epileptologists, as well as several technical pitfalls (such as artifact from interference with other equipment in the ED). Further studies to determine the feasibility, accuracy, and cost-effectiveness of this technology are needed.

**Table 5. Factors Associated With Abnormal Computed Tomography Findings In Patients Presenting To The Emergency Department With Seizure**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Focal abnormality</td>
<td>on neurological examination</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
</tr>
<tr>
<td>Closed head injury</td>
<td></td>
</tr>
<tr>
<td>Neurocutaneous disorder</td>
<td></td>
</tr>
<tr>
<td>Focal onset of seizure</td>
<td></td>
</tr>
<tr>
<td>Absence of a history of alcohol abuse</td>
<td></td>
</tr>
<tr>
<td>History of cysticercosis</td>
<td></td>
</tr>
<tr>
<td>Altered mental status</td>
<td></td>
</tr>
<tr>
<td>Patient aged &gt; 65 y</td>
<td></td>
</tr>
<tr>
<td>Seizure duration &gt; 15 min</td>
<td></td>
</tr>
</tbody>
</table>
Treatment

Stabilization
Management of the patient in SE prioritizes pharmacologic intervention and ensured perfusion and oxygenation to the brain. Jaw thrust and nasopharyngeal airways are simple measures that can improve oxygenation. The patient should be placed on a monitor along with continuous pulse oximetry and capnography. Intravenous access should be established and is best secured with a nondextrose solution, as dextrose will precipitate phenytoin if administered concurrently (fosphenytoin can be safely administered with dextrose solutions).

If, at any time, breathing or ventilation is compromised, rapid sequence intubation is recommended using a short-acting paralytic agent, such as succinylcholine. Long-acting paralyzing agents are contraindicated unless bedside EEG monitoring is available. Prolonged pharmacologic paralysis can mask persistent electrical status of the brain, lulling the physician into a false sense of security.

The emergency clinician must approach SE from multiple directions at once. It is critical to consider the treatable etiologies (eg, intracranial infections and lesions, metabolic abnormalities, drug toxicities, and eclampsia). For hypoglycemic adult patients, 50 cc of 50% dextrose should be given intravenously. Thiamine 100 mg with dextrose is recommended in patients who appear malnourished. When infection is suspected, consider early (empiric) antibiotics, since head CT and lumbar puncture may be delayed pending patient stabilization. A noncontrast head CT is recommended for all first-time seizure patients, once they have been stabilized, to exclude surgically reversible etiologies such as an epidural or subdural hemorrhage. While an EEG is not typically necessary in SE for initial diagnosis, it plays an important role in posttreatment monitoring, particularly in RSE or when there is concern for NCSE.

Pharmacologic Therapy For Status Epilepticus
Traditionally, pharmacologic therapy of SE has been divided into first-, second-, and third-line therapies. The benzodiazepines are generally the initial intervention of choice, followed by phenytoin or valproic acid. Third-line interventions include infusions of benzodiazepines, propofol, or barbiturates.

Benzodiazepines
Early and aggressive therapy with benzodiazepines has confirmed benefit in the management of SE, and intravenous benzodiazepines remain the first-line drugs of choice for SE. Intravenous lorazepam has been shown to be equally as effective as phenobarbital and superior to phenytoin alone in the termination of seizures. The VA Cooperative Study was a head-to-head trial comparing 4 treatment arms in convulsive SE: diazepam (0.15 mg/kg) followed by phenytoin (18 mg/kg); lorazepam alone (0.1 mg/kg); phenytoin alone (18 mg/kg); and phenobarbital alone (15 mg/kg). This randomized double-blind study found no outcome difference between the 4 treatments; however, lorazepam was the easiest to administer so it was recommended as the first-line agent in GCSE management.

Lorazepam and diazepam are both effective at terminating initial seizures. However, lorazepam has a smaller volume of distribution and, thus, the anticonvulsant activity of lorazepam lasts up to 12 hours, while that of diazepam only lasts for 20 minutes. Lorazepam also binds more tightly to receptors in the brain, increasing duration of action and reducing the risk of recurrent seizures. In a 2005 meta-analysis, a Cochrane review found that intravenous lorazepam was superior to intravenous diazepam for the cessation of seizure and the prevention of recurrence. Lorazepam is generally recommended at a dose of 0.1 mg/kg (up to 4 mg per dose), to be repeated in 5 to 10 minutes if seizure activity is not terminated. Two-thirds of patients respond to the initial treatment.

As previously discussed in the Prehospital Care section (page 6), options for patients with no vascular access include intramuscular lorazepam, intramuscular midazolam, and rectal diazepam. Of these options, intramuscular midazolam is preferred because it is water-soluble, nonirritating, and rapidly absorbed. At least one trial has shown it to be as effective as intravenous diazepam, with no additional adverse outcomes. Additionally, as shown in the RAMPART study (a double-blind randomized noninferiority clinical trial that compared the efficacy of intramuscular midazolam with intravenous lorazepam), early administration of midazolam is the best option for the prehospital treatment of SE.

Phenytoins
Phenytoin and its prodrug, fosphenytoin, are the most commonly recommended second-line therapies for patients with persistent seizure activity. Phenytoin is limited by the rate at which it can be delivered, as well as by known adverse effects. Phenytoin slows the recovery of voltage-activated sodium channels, thus decreasing repetitive action potentials in neurons. Although rare, this effect on the myocardium can lead to QT prolongation and arrhythmias; for this reason, cardiac monitoring is recommended during infusion. A more common effect is hypotension (primarily due to the propylene glycol diluent), with incidence directly related to the dose and rate of infusion. Other relatively benign side effects include confusion and ataxia, both of which usually resolve with supportive care, but which can impose significant patient safety concerns.
Valproic Acid

Valproic acid is unique among older AEDs because it is effective in treating all forms of seizures, including absence, partial, and primary generalized. Its mechanism is similar to that of phenytoin and carbamazepine, in that it prolongs recovery of voltage-activated sodium channels from inactivation. Intravenous valproate has been proposed as an effective second-line treatment for SE.7,113,114 The recommended intravenous loading dose for valproate is 20 to 30 mg/kg at a rate of 40 mg/min, although faster bolus infusions, over 5 to 10 minutes, have been safely administered.105,114-116

Valproate has an excellent safety profile.117-119 It is generally well tolerated, with mild side effects. The notable exception is hepatotoxicity, which usually develops with chronic use over the first 6 months of therapy. There is also a rare, fatal, idiosyncratic hepatotoxicity in 1 out of 49,000 adults.120,121 Therefore, the drug is not recommended in patients with hepatic dysfunction.

Levetiracetam

Levetiracetam is a second-generation AED used to treat generalized and partial seizures. It is non-sedating, has a low incidence of hypotension and respiratory depression, and has few interactions with other drugs.1 It is not metabolized by the liver and may, therefore, be suitable in patients with liver disease. While its efficacy has not been studied in comparison with other routinely used agents, case reports suggest that a 30 to 50 mg/kg intravenous load at 100 mg/min may be safe and effective in the management of SE.1,122,123

Pharmacologic Therapy For Refractory Status Epilepticus

In up to 30% of patients, first- and second-line anticonvulsants fail to terminate SE.1,18 In these cases, there are several options, although there is little evidence to support the superiority of one agent over another. Expert opinion and case series recommend infusions of midazolam, propofol, or barbiturates.3,24 Use of these agents as a continuous infusion necessitates definitive airway management and pressor agents, as needed, for the attenuation of cardiopulmonary depression associated with some of these drugs.3

Benzodiazepines

Midazolam is water-soluble and continuous infusion allows for high CNS penetration. It has a short duration of action and it is easy to titrate. It also causes less hypotension than propofol or barbiturates. The loading dose is 0.2 mg/kg, followed by an infusion of 0.05 to 0.6 mg/kg/h.118,120 When compared with propofol or pentobarbital in a meta-analysis of RSE that included 193 patients, intravenous midazolam was effective in 80% of cases. While this was less effective than propofol or pentobarbital, it was also associated with a lower rate of hypotension than the other 2 medications.118,120,121,124 Lorazepam has also been used as a continuous intravenous infusion; however, the data on its use in SE are limited and its long half-life makes withdrawal more difficult.16

Propofol

Propofol is a global CNS depressant that acts as a direct GABA agonist as well as an NMDA antagonist. In an underpowered retrospective study comparing intravenous midazolam and propofol in 14 patients, mortality was 57% in the propofol group and 17% in the intravenous midazolam group.125 This same
study showed that propofol was equally as effective as pentobarbital in treating RSE; however, the propofol group required 4 mechanical ventilation days, compared with 14 in the pentobarbital group.\textsuperscript{120} Propofol also tends to cause less hypotension than barbiturates.\textsuperscript{120} Propofol is dosed as an intravenous bolus of 1 to 2 mg/kg, followed by a continuous infusion at 30 to 200 mcg/kg/min.\textsuperscript{1}

Propofol is limited in its long-term and high-dose use by the propofol infusion syndrome of hypotension, hyperlipidemia, and metabolic acidosis.\textsuperscript{127,128} Propofol can also cause nonepileptic jerking movements and even induce seizures with abrupt discontinuation, so EEG monitoring is recommended.\textsuperscript{129}

**Barbiturates**

Barbiturates (eg, phenobarbital or pentobarbital) have mostly fallen out of favor in the management of RSE due to their high side-effect profile. One retrospective cohort study of 74 patients found that phenobarbital offered no additional benefit to seizure control in patients who did not respond to lorazepam and phenytoin. Another retrospective chart review of 14 patients showed improved termination of RSE with pentobarbital, in comparison with propofol and midazolam, but no difference in mortality.\textsuperscript{11,120}

Introduced in 1912, phenobarbital is the oldest AED still in use. It is notably the only barbiturate that possesses anticonvulsant properties at subhypnotic doses. In the past, it was advocated as a first-line intervention, but its use is in decline today. Phenobarbital works on the GABA receptor with a mechanism similar to that of benzodiazepines, and it has generally shown the same efficacy as a first-line agent in conjunction with both diazepam and phenytoin or with lorazepam alone.\textsuperscript{18,130,131} The main drawback of phenobarbital is its potential to induce profound respiratory depression and hypotension as a result of its vasodilatory and cardiodepressant effects. It also has a long half-life, which can make complications and titration difficult to manage.\textsuperscript{132} Phenobarbital is dosed at 10 to 20 mg/kg, with allowance for repeat dosing of 5 to 10 mg/kg after 10 minutes of continued seizure activity.

Pentobarbital is the first metabolite of thiopental and is much shorter-acting than phenobarbital. It is highly lipid-soluble and will accumulate in fat stores, leading to prolonged elimination.\textsuperscript{1} In a prospective study of 10 intensive care unit patients in RSE, high-dose thiopental terminated seizures in all patients. However, one-third of the patients needed either dobutamine or norepinephrine to support their blood pressure during therapy. The authors also noted prolonged recovery time from the medication after seizures had been suppressed.\textsuperscript{133}

Pentobarbital is loaded at a dose of 5 to 15 mg/kg over 1 hour, followed by an infusion of 0.5 to 5 mg/kg/h.\textsuperscript{1} Pentobarbital can compromise cardiovascular status, and its use necessitates EEG monitoring due to suppression of motor activity. Fluid boluses should be used to treat pentobarbital-induced hypotension and norepinephrine should be considered in case of persistent hypotension.\textsuperscript{134,135}

A systematic review that included a total of 28 studies did not find sufficient evidence to support the superiority of pentobarbital, propofol, or midazolam.\textsuperscript{120} Pentobarbital had less treatment failure but caused more hypotension than either propofol or midazolam. Midazolam and propofol are more familiar to most emergency medicine and critical care clinicians and are, therefore, often recommended due to the ease of access and familiarity.

**Other Pharmacologic Therapies**

Other medications that have been used to treat SE in case series include lidocaine, chloral hydrate, and etomidate.\textsuperscript{1,24,136-139} As of now, these medications have not been validated for general use and should only be considered when other, more standard therapies have failed.

Lacosamide (in both oral and intravenous formulations) is used in the treatment of partial epilepsies, and case reports suggest potential benefit in patients with NCSE.\textsuperscript{1,140} Lastly, as mentioned previously, during the course of sustained SE, NMDA receptors are increasingly expressed. Therefore, NMDA channel blockers (such as ketamine) have also been used for the treatment of SE when GABAergic anticonvulsants fail.\textsuperscript{1,141,142}

**Putting It All Together**

When a patient presents with GCSE, the time to termination of seizure may depend on the time it takes for the clinician to choose a drug and administer it. Intramuscular midazolam is preferred if no intravenous access is available at arrival. The ability of the ED to rapidly provide the resources needed to treat SE depends upon development of a prearranged treatment algorithm. See the Clinical Pathway for Status Epilepticus Management, page 15. Preselection of medications for first-line use and for RSE will prevent delays when patients present. With a lack of strong evidence to determine a preferred treatment for RSE, individual EDs may make choices in conjunction with their neurology and critical care services based upon drug availability and staff familiarity with given drugs.

Upon presentation to the ED, continued seizure treatment begins with the stabilization of the airway, establishment of intravenous access, placement on continuous cardiac monitoring, and pulse oximetry. Initial medications of choice are lorazepam 0.1 mg/kg IV (up to 4 mg/dose), diazepam 5 to 10 mg/dose IV, or midazolam 0.2 mg/kg/dose IV (usually 10 mg is given). Approximate onset
times (and therefore interval for repeating doses) are 3 to 5 minutes for lorazepam, 2 minutes for diazepam, and 2 to 3 minutes for midazolam.

If benzodiazepines do not terminate seizure activity, phenytoin or fosphenytoin (20 mg/kg or 20 PE/kg, respectively) should be given. If the patient continues to seize, an additional 5 to 10 (PE) mg/kg may be given. Intravenous valproate (20-30 mg/kg) may be considered if the patient is known to have been on valproate in the past. If seizure activity continues, the patient is considered to be in RSE. Management choices include infusions of midazolam, propofol, or barbiturates titrated against an EEG burst suppression pattern for at least 24 hours.3

**Nonconvulsive Status Epilepticus**

Most forms of NCSE, with the exception of subtle SE, have favorable outcomes and, therefore, generally require less aggressive treatment strategies than GCSE.16 Subtle SE, or NCSE that arose from GCSE, should be treated similarly to GCSE. In fact, some authors advocate for avoidance of anesthetic drugs in most NCSE patients, arguing that it may have a greater risk of morbidity and mortality than continuing nonconvulsive seizure activity.16,143-145 Generally, NCSE is rapidly terminated with first-line benzodiazepine therapy.146 Doses may be repeated if seizure activity persists beyond 10 minutes. In refractory cases, first-line therapy is typically followed by administration of intravenous valproate (20-30 mg/kg at a rate of 40 mg/min) or phenobarbital (15-20 mg/kg at a rate of 50 mg/min).15,16,147

**Special Circumstances**

**Emergency Department Initiation Of Antiepileptic Therapy**

Based on the best available evidence, the current ACEP Clinical Policy states that emergency clinicians do not need to initiate an AED in patients who have had a first provoked seizure or a first unprovoked seizure without evidence of brain disease or injury. For patients with a history of stroke, brain trauma, tumor, or other CNS disease or injury, the guideline states that AED therapy may be initiated, but advises that it is best done by a neurologist in coordination with the patient’s primary care provider. The reason for beginning AEDs in this group of patients is their higher probability of recurrence.

**Patients With A History Of Seizure**

Investigation of potential precipitants (such as sleep deprivation; infection; or new medications, especially those that can lower the seizure threshold or affect later AED metabolism) is key to managing the patient with a known seizure disorder who has a typical event while on medications.

AED noncompliance and subtherapeutic AED levels in a patient who has had a seizure are commonly encountered in the ED. Literature to support the recommendation of one route of administration over another (oral vs parenteral) is inconclusive, mainly because most available studies used AED serum concentration levels instead of early seizure recurrence as a primary outcome measure. Within this limited evidence, most studies have compared phenytoin and fosphenytoin in oral and intravenous routes. Swadron et al performed an ED-based randomized trial to assess the effectiveness and safety of oral phenytoin in comparison with intravenous phenytoin and intravenous fosphenytoin. Oral loading had fewer adverse drug events (eg, hypotension) than either of the intravenous loading methods. However, as expected, therapeutic plasma concentrations were achieved significantly faster with the intravenous route.148 This study did not find any significant difference between phenytoin and fosphenytoin with regard to adverse drug events.

Some emergency clinicians still prefer parenteral loading of phenytoin or fosphenytoin to ensure adequate serum level on discharge. However, there is no good evidence that this practice decreases risk of seizure recurrence.24

**Alcohol-Related Seizures**

Alcohol-related seizures present in the setting of chronic alcohol dependence.149 Of seizure patients presenting to an ED, 20% to 40% have seizures related to alcohol abuse. Seizures occur in approximately 10% of patients who withdraw from alcohol, and alcohol withdrawal has been reported as a causative factor in 3% to 20% of patients with SE.105,150-152 Therefore, it has been suggested that all patients presenting with seizures should be screened using a structured questionnaire (ie, CAGE) whenever possible.149 In more than 50% of cases, alcohol-related seizures occur as an adjunct to other risk factors (such as pre-existing epilepsy, structural brain lesions, and the use of recreational drugs).149

The diagnostic yield for CT after first alcohol-related seizure is high. A 1988 Denver study reported head CT results in 259 patients with a first alcohol-related convulsion. A clinically significant lesion was found in 16 (6.2%) patients, 7 of whom were alert and had nonfocal neurologic examinations and no history of trauma. Nearly 4% had CT findings that changed clinical management (eg, subdural hematoma, aneurysm, subarachnoid hemorrhage, and neurocysticercosis). In these patients, the history and physical examination did not predict the CT abnormality. This study emphasizes that an alcoholic with a first-time seizure should not be presumed to have an alcohol withdrawal seizure (AWS), and it underscores the need to consider neuroimaging in this special group of patients.159
Clinical Pathway For Non–Status Epilepticus Seizure Management

Patient who has seized and returned to baseline

First-time seizure?

YES

• Assess for drug use, head trauma, illness, medications, pregnancy, hypoglycemia, and focality on neurologic examination (Class II)
• Obtain electrolytes and serum glucose (Class II)
• Consider need for complete blood count; liver function tests; serum calcium, magnesium, and phosphorus; drugs-of-abuse screen, and blood alcohol level (Class III)

NO

Same as past events?

YES

Check AED level and assess for factors that lower seizure threshold (Class III)

NO

Give intravenous, oral, or intramuscular (fosphenytoin only) loading dose (Class III)

Is the patient on phenytoin and subtherapeutic?

YES

• Discharge for outpatient workup (Class III)
• Do not start AEDs (Class III)

NO

Perform CT in the ED or arrange for outpatient CT (Class II)

Focal neurologic examination or immunocompromised patient?

YES

Perform CT in the ED (Class III)

NO

Same as past events?

• Assess for drug use, head trauma, illness, medications, pregnancy, hypoglycemia, and focality on neurologic examination (Class II)
• Obtain electrolytes and serum glucose (Class II)
• Consider need for complete blood count; liver function tests; serum calcium, magnesium, and phosphorus; drugs-of-abuse screen, and blood alcohol level (Class III)

NO

Class of Evidence Definitions

Each action in the clinical pathways section of Emergency Medicine Practice receives a score based on the following definitions.

<table>
<thead>
<tr>
<th>Class</th>
<th>Always acceptable, safe</th>
<th>Definitely useful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>Proven in both efficacy and effectiveness</td>
<td></td>
</tr>
</tbody>
</table>

Level of Evidence:
- One or more large prospective studies are present (with rare exceptions)
- High-quality meta-analyses
- Study results consistently positive and compelling

<table>
<thead>
<tr>
<th>Class</th>
<th>Safe, acceptable</th>
<th>Probably useful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class II</td>
<td>Generally higher levels of evidence</td>
<td>Nonrandomized or retrospective studies: historic, cohort, or case control studies</td>
</tr>
</tbody>
</table>
- Less robust randomized controlled trials
- Results consistently positive

<table>
<thead>
<tr>
<th>Class</th>
<th>May be acceptable</th>
<th>Possibly useful</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class III</td>
<td>Considered optional or alternative treatments</td>
<td>Case series, animal studies, consensus panels</td>
</tr>
</tbody>
</table>
- Occasionally positive results

| Indeterminate | Continuing area of research | No recommendations until further research |
- Higher studies in progress
- Results inconsistent, contradictory
- Results not compelling

Level of Evidence:
- Evidence not available

Abbreviations: AED, antiepileptic drug; CT, computed tomography; ED, emergency department.

This clinical pathway is intended to supplement, rather than substitute for, professional judgment and may be changed depending upon a patient’s individual needs. Failure to comply with this pathway does not represent a breach of the standard of care.

Copyright © 2015 EB Medicine. 1-800-249-5770. No part of this publication may be reproduced in any format without written consent of EB Medicine.
Clinical Pathway For Status Epilepticus Management

Status epilepticus diagnosed

On arrival:

- Finger-stick glucose test (give IV dextrose if glucose < 60 mg/dL) (Class III)
- Assess airway, breathing, and circulation; obtain vital signs; monitor pulse oximetry; and perform electrocardiogram (Class III)

Administer first-line therapy:

- Lorazepam 4 mg IV push over 2 min (may be repeated) or
- Diazepam 10 mg IV or rectal (may be repeated) or
- Midazolam 10 mg IV (or IM if no IV access) (Class III)

Administer second-line therapy:

- Fosphenytoin 20 PE/kg IM or IV at 150 mg/min (may give additional 5 PE/kg) or
- Phenytoin 20 mg/kg IV at a maximum rate of 50 mg/min (may give additional 5-10 mg/kg) or
- Valproate 20-30 mg/kg IV (Class III)

Consult primary care physician or neurologist for disposition (Class III)

Consider NCSE in patients who have not fully returned to baseline (Class III)

Patient is in refractory status epilepticus; administer third-line therapy:

- Intubation and EEG monitoring recommended (Class III)
- Midazolam: loading dose 0.2 mg/kg IV bolus (maintenance 0.05-0.6 mg/kg/h) or
- Propofol: loading dose 1-2 mg/kg IV bolus (maintenance 50-100 mcg/kg/min) or
- Pentobarbital: loading dose 20 mg/kg IV at 50 mg/min (Class III)

Abbreviations: EEG, electroencephalography; IM, intramuscular; IV, intravenous; PE, phenytoin equivalents; NCSE, nonconvulsive status epilepticus.

For class of evidence definitions, see page 14.
Alcohol Withdrawal Seizures

AWSs are usually generalized events and occur between 6 and 48 hours after cessation of drinking. Recurrent seizures have been reported in 13% to 60% of these patients, with most occurring within 12 hours of onset.154,156,161 The patient may or may not have other signs of alcohol withdrawal (such as tachycardia, confusion, or tremors) that may indicate a likelihood of developing a seizure.

The diagnosis of AWS is based on a history of recurrent events temporally related to stopping (or significantly decreasing) alcohol intake and should be pursued after the consideration of concurrent risk factors. A first-time withdrawal seizure must be evaluated as any first-time seizure, even in alcoholics who claim to have had seizures in the past but for whom no documentation of previous seizures or of an appropriate workup is available. Metabolic disorders, toxic ingestion, infection, and structural abnormalities need to be ruled out by history, physical examination, and diagnostic testing (including electrolytes, glucose, and brain CT).154,157

Once a person with an AWS is brought to the ED, clinical findings cannot predict who is likely to have a recurrent seizure in the ED.159 Benzodiazepines are the treatment of choice in AWS. They offer cross-tolerance with alcohol by acting at the GABA receptor site and reduce the signs and symptoms of AWS. All benzodiazepines appear to be equally efficacious; however, longer-acting agents may be preferred to shorter-acting drugs in preventing seizures. Many hospitals have developed institutional algorithms based on a benzodiazepine of choice for the management of alcohol-related seizures.

There is also good evidence to recommend benzodiazepines in a patient who is no longer actively seizing. A double-blind, placebo-controlled study of 186 patients showed that lorazepam 2 mg IV decreases the short-term recurrence of seizures related to alcohol withdrawal and reduces the need for hospitalization. The number needed to treat in this study to prevent 1 further withdrawal seizure at 6 hours was 5.160 Phenytoin does not have a role in managing pure alcohol-related seizures in the ED.153,155,158-160

Once a diagnosis of AWS is made and other seizure disorders are assessed for and eliminated, management focuses on patient safety, minimizing the risk for a second withdrawal seizure, and patient education. Management of these patients also includes observation for 4 to 6 hours after administration of lorazepam and, ideally, referral to a detoxification center.

Toxins

Toxins can alter the brain equilibrium of excitation-inhibition in a variety of ways to cause seizures. Most drug-induced seizures, particularly those resulting from cocaine and other stimulants, respond best to benzodiazepine therapy. Seizures can also be precipitated by use of narcotics and withdrawal from benzodiazepines or barbiturates.

Cases of RSE pose a particular challenge because the mechanism of SE may be different from SE with other causes. Some toxins (eg, isoniazid) cause depletion of GABA neurotransmitter and, since some of the typical pharmacologic agents act by sensitizing the GABA receptor, they are less effective. In these cases, early administration of pyridoxine may be advantageous because it replenishes GABA in the brain. It is initially dosed at 5 g IV in adults and 70 mg/kg IV in children.161

Phenytoin is ineffective for most drug-induced seizures and, in some cases, it may be harmful (eg, in theophylline or tricyclic overdose).162 Barbiturates or propofol are good options.161

Posttraumatic Seizures

The risk of developing a seizure disorder after a traumatic brain injury is related to the severity of the injury. The incidence after minor traumatic brain injury (Glasgow Coma Scale [GCS] score > 12) is 1.5%, while the incidence increases to 17% after a severe traumatic brain injury (GCS score < 9).163

Although the incidence of posttraumatic seizures in the first week after a severe traumatic brain injury is decreased to < 4% with early treatment with phenytoin, after the first week, there is no statistical difference in seizure incidence whether or not patients are treated with phenytoin.164 For this reason, although the incidence of an early posttraumatic seizure is decreased with AED use, there is no change in outcome. Thus, prophylactic AEDs are not indicated to prevent late posttraumatic seizures.164

Pregnancy

Seizures in pregnancy can be classified as 1 of 3 types: (1) those that occur in epileptics who happen to be pregnant, (2) new-onset seizures in pregnant patients, and (3) seizures that occur in the setting of eclampsia.

The most complete prospective observational study of pregnant women with epilepsy is the International Registry of Antiepileptic Drugs and Pregnancy (EURAP). Of 1956 pregnancies, over half were seizure-free; 17.3% had an increase in seizure frequency; and 15.9% had a decrease in frequency.165 In a previous study, a larger increase in seizure frequency was attributed to the discontinuation of AEDs.166 Overall, there is not an increased risk of SE during pregnancy.3,167 However, factors that may lower the seizure threshold in women who are pregnant include noncompliance, sleep deprivation, nausea, and vomiting.94

The serum concentration of AEDs tends to decrease during pregnancy due to an increase in hepatic and renal clearance and a pregnancy-related increase in the volume of distribution.168 This de-
crease in serum drug level is balanced by the fact that free (unbound) drug levels may actually be increased due to the decrease in concentration of serum proteins that normally occurs in pregnancy.

While there are few data guiding the use of AEDs for SE during pregnancy, the risks to the fetus from SE-related hypoxia and acidosis are greater than the potential teratogenicity of anticonvulsant medications and, therefore, patients who are actively seizing should be managed as the non-pregnant patient. In patients who are more than 24 weeks pregnant, fetal monitoring during and after a seizure should be arranged.

**New-Onset Seizure During Pregnancy**

Pregnant patients with new-onset seizures (not with eclampsia) should be worked up as any new-onset seizure patient, with a metabolic profile, EEG, and head CT with appropriate abdominal shielding. Precipitating etiologies, such as infections and drug toxicities, should also be investigated. If no source is identified, anticonvulsants should be withheld and the patient referred for close follow-up.

**Eclampsia**

Eclampsia is the major consideration in pregnant patients of > 20 weeks' gestation (and up to 6 weeks postpartum) who present with new-onset seizures. Magnesium has been demonstrated to be the therapy of choice in the treatment of acute eclamptic seizures and for prevention of recurrent eclamptic seizures. A systematic review of 4 good-quality trials involving 823 women found magnesium sulfate to be substantially more effective than phenytoin with regard to recurrence of convulsions and maternal death. Complications (such as respiratory depression and pneumonia) were less likely with magnesium than phenytoin. Magnesium sulfate was also associated with benefits for the baby, including fewer admissions to the neonatal intensive care unit. Eclamptic seizures refractory to magnesium may respond to benzodiazepines or barbiturates with or without phenytoin. In the eclamptic patient, magnesium sulfate 4 g IV should be given over 20 minutes, followed by a 2 g/h infusion (some centers use intramuscular regimens). Control the patient’s blood pressure if it is very high (systolic blood pressure > 160 mm Hg; diastolic blood pressure > 110 mm Hg) and contact an obstetrician. According to the American College of Obstetrics and Gynecology (ACOG) and the National High Blood Pressure Education Program: Working Group Report on High Blood Pressure in Pregnancy, agents of choice for control of blood pressure in the emergency setting include hydralazine (first-line) and labetalol.

---

**Disposition**

The need for hospital admission is obvious in patients who are clinically ill; however, a dilemma arises when determining disposition for the patient who returns to a normal baseline after a first-time seizure. The best predictor of seizure recurrence is the causative etiology combined with EEG findings. This information often requires modalities that are not routinely available in the ED. A decision as to whether a patient needs to receive AED therapy or should be admitted is, therefore, challenging and requires shared decision-making with the patient, as there are few ED-based studies to direct disposition.

One study investigated the incidence of seizure recurrence within 24 hours of ED presentation. This was a retrospective review of all adult patients admitted to the hospital during a 2-year period with a first-time seizure. The authors reported a 19% seizure recurrence rate within 24 hours of presentation, which decreased to 9% if patients with alcohol-related events or focal lesions on CT were excluded. The applicability of these results is limited because patients with recurrent seizures were not well described, making it impossible to assess whether recurrence could have been predicted based on physical findings or comorbid factors. At present, there is insufficient evidence to guide the decision to admit. We recommend this decision be tailored to the patient, taking into consideration the patient’s access to follow-up care and social risk factors (eg, alcoholism or lack of health insurance). Patients with comorbidities, including age > 60 years, known cardiovascular disease, history of cancer, or history of immunocompromise, should be considered for admission to the hospital.

**Considerations For Safety On Discharge**

Patients and their families should be counseled and instructed on basic safety measures to prevent complications (such as trauma) during seizures. For example, patients should be advised to avoid swimming or cycling following a seizure, at least until they have been reassessed by their neurologist and their antiepileptic therapy optimized, if needed. A particularly important point for seizure patients is education against driving. Although evidence remains controversial on this issue, there is general agreement that uncontrolled epileptic patients who drive are at risk for a motor vehicle crash, with potential injury or death to themselves and others. For this reason, most states do not allow these patients to drive unless they have been seizure-free on medications for 1 year. According to population survey data, 0.01% to 0.1% of all motor vehicle crashes are attributable to seizures. While physicians are required to report patients with seizures to driving authorities in 6 states (California, Delaware, Nevada, New Jersey, Oregon, Oregon,
and Pennsylvania).\textsuperscript{178} mandatory reporting has not been proven to reduce the risk of motor vehicle crash in patients with epilepsy.\textsuperscript{179}

**Summary**

Seizures are a manifestation of CNS injury, and acute management focuses on identifying correctable underlying etiologies and terminating the event. Epilepsy is a condition of recurrent unprovoked seizures; however, the majority of patients seen in EDs with seizures do not have epilepsy, and over half of the patients seen in the ED who are in SE have no seizure history. Morbidity and mortality in SE is associated with duration, emphasizing the importance of early recognition and treatment. A clear history is often not immediately available for patients with seizures, so the emergency clinician must be vigilant for evidence of comorbid disease, alcohol and drug use or dependence, and medication noncompliance. Regarding laboratory evaluation, adult patients with new-onset seizures who are otherwise healthy and have returned to baseline require only a serum glucose, sodium level, and pregnancy test. Further testing is indicated in patients with fever, comorbid disease, or new neurological deficit. Emergency neuroimaging and EEG are indicated in select cases. Intramuscular midazolam is indicated when there is no intravenous access. Intravenous lorazepam is the first-line agent for seizure control. Second-line therapies include a phenytoin, valproic acid, and possibly levetiracetam (particularly in patients with liver disease). Institutions should establish standard treatment protocols for seizures and SE that take into account staff familiarity with the available drugs. While most seizures are successfully terminated after first- or second-line therapies, up to 30\% of patients will have refractory disease and require induction of coma with either a propofol, barbiturate, or benzodiazepine infusion.

**Case Conclusions**

The 19-year-old man brought in by his mother remained seizure-free during a short observation period in the ED. His blood glucose and serum electrolytes were all within normal limits. Since his mental status completely returned to baseline and the neurologic examination was normal, he was discharged with next-day neurology follow-up for outpatient head CT and EEG.

After the fosphenytoin load failed to terminate his seizures, the 22-year-old man was found to be in RSE and required aggressive management, including intubation and deep sedation. His girlfriend arrived at bedside and informed you that he had a seizure history and had recently been noncompliant with his valproate. You decided to send for phenytoin and valproate levels, which, not surprisingly, returned subtherapeutic. You loaded the patient with intravenous valproate and intubated with propofol and succinylcholine, following with a propofol drip.

Because your 80-year-old patient’s postictal period seemed too long, you consulted neurology and obtained a bedside EEG that showed 3/sec spike-and-wave activity. A diagnosis of NCSE was made and the patient was treated with intravenous lorazepam, which resulted in a normalization of her EEG and resolution of the altered mental status. On further questioning, you learned that she was on daily alprazolam for years and had run out. A diagnosis of NCSE due to benzodiazepine withdrawal was made.

**Cost-Effective Strategies**

- **Inform patients about generic options.** Many patients are not aware that generic alternatives are available for some medications, with significant differences in cost compared to brand-name drugs. It is especially important to address this in patients at risk of falling into noncompliance for economic reasons.
- **Consider oral phenytoin loading.** Given the lack of evidence that intravenous loading is more effective than oral loading, oral loading is an acceptable strategy and negates the need for intravenous and cardiac monitoring. The time to reach peak serum AED levels will be slower (4 to 6 hours); however, the risk of side effects (neurologic, cardiac, and tissue-related) will be decreased. If intravenous loading is done, it should be done slowly over 1 hour, not at the expedited rate used for managing SE.
- **Choose the type and timing of neuroimaging carefully.** The ACEP Clinical Policy supports outpatient neuroimaging for patients who have had a new-onset seizure and have returned to a normal baseline. Neurologists generally prefer an MRI to a CT in evaluating these patients. To avoid redundant testing, in select patients with coordinated care, an outpatient MRI could constitute best practice.
- **Limit your laboratory testing.** Extensive metabolic panels are not indicated for uncomplicated first-time seizure patients. Patients with a history of seizures who have stopped taking their medication do not necessarily need an AED serum level or other laboratory test; they just need to be restarted on their medication.
- **Check the intravenous site.** When giving a parenteral dose of phenytoin, check the intravenous site yourself to be sure that it is large enough and has good flow. Ensuring that the vein is secure could save the patient from unnecessary pain and, potentially, from a necrotizing extravasation.
1. “The patient was no longer shaking, so I assumed he was no longer seizing.”
While a tonic-clonic seizure will be more clinically evident, patients presenting with partial seizures involving the nonmotor areas of the brain may be more difficult to recognize.

2. “The patient was seizing – I never thought she was hypoglycemic.”
Missing hypoglycemia on the evaluation of a seizing or postictal patient is a pitfall that should never occur. Check blood glucose together with vital signs in all patients who are seizing or who appear to be postictal.

3. “I never expected the patient to be so hyponatremic.”
Patients with seizure disorders can seize for many reasons, and a systematic evaluation is always required in order to catch underlying infectious or metabolic causes of seizure. This is particularly true in patients with multiple comorbidities (such as renal failure).

4. “I assumed the patient knew that he shouldn’t drive.”
All patients who have had a seizure should be explicitly advised not to drive or engage in activity that puts them at risk. Discharge all seizure patients with directed safety instructions regarding driving and operating machinery. Given the unpredictable nature of seizures, even a brief seizure can result in death or severe injuries to the patient or others. Patients with recent seizures should be advised not to drive until their seizures are controlled and, ideally, not until they follow up with their neurologist, AED levels are rechecked, and therapy is optimized.

5. “I forgot to ask about other medications.”
Always inquire about new medications in patients on AEDs. Most AEDs are metabolized in the liver, so taking them in conjunction with other hepatically metabolized medications may reduce the AED serum level to a nontherapeutic range. Many commonly used drugs (including antibiotics, antipsychotics, and antidepressants) can lower the seizure threshold and explain a breakthrough seizure that occurs despite compliance with therapy.

6. “The patient was in a coma – I never suspected he could actually be seizing.”
Never forget that NCSE can present as coma and maintain a low threshold for obtaining a bedside EEG.

7. “I assumed the patient seized because her AED blood level was low.”
AED serum levels are a guide to therapy but not an absolute. Many patients are well controlled at low serum levels but have breakthrough seizures due to physical or mental stressors such as sleep deprivation. In these cases, treatment consists not of increasing the AED dose but eliminating the stressor.

8. “I thought the best way to address the hypoxia was to focus on treating the seizure.”
Oxygenation and perfusion are fundamental to successful management of the patient in SE. Hypoxia and hypotension are the 2 most consistent predictors of increased morbidity and mortality in all types of emergencies involving the brain. Particularly in patients with prolonged seizures, standard emergency medicine interventions (such as securing the airway and ensuring oxygenation) should not be delayed.

9. “I thought the seizure would stop on its own.”
Time is brain, and failing to aggressively control seizure activity increases morbidity. While most seizures cease without intervention, some patients need medications. Have a benzodiazepine dose readily available in case it is needed; intramuscular midazolam is an excellent option when intravenous access is not available.

10. “I was too busy treating the patient to talk to EMS.”
EMS personnel often have key information needed to care for a patient. Many patients are either postictal or under the effect of benzodiazepine treatment when they arrive to the ED, so they are not able to fully cooperate during the evaluation. It is always important to get as much information as possible from the EMS crew, including type of convolution, medication, and doses that were given in the field.
References

Evidence-based medicine requires a critical appraisal of the literature based upon study methodology and number of subjects. Not all references are equally robust. The findings of a large, prospective, randomized, and blinded trial should carry more weight than a case report.

To help the reader judge the strength of each reference, pertinent information about the study will be included in bold type following the reference, where available. In addition, the most informative references cited in this paper, as determined by the authors, will be noted by an asterisk (*) next to the number of the reference.


69. Pesola GR, Westfall RE. New-onset generalized seizures in patients with AIDS presenting to an emergency department. Acad Emerg Med. 1998;5(9):905-911. (Retrospective review; 146 patients)


124. Kaplan PW. No, some types of nonconvulsive status epilepticus cause little permanent neurologic sequelae (or: “the cure may be worse than the disease”). *Neurophysiol Clin.* 2000;30(6):377-382. (Review)


138. Schoenenberger RA, Heim SM. Indication for computed


CME Questions

Take This Test Online!

Current subscribers receive CME credit absolutely free by completing the following test. Each issue includes 4 AMA PRA Category 1 Credits™, 4 ACEP Category I credits, 4 AAFP Prescribed credits, and 4 AAOA Category 2A or 2B credits. Monthly online testing is now available for current and archived issues. To receive your free CME credits for this issue, scan the QR code below with your smartphone or visit www.ebmedicine.net/E0115.

1. Regarding prehospital care of the patient with seizures, which of the following statements is FALSE?

a. Patients do not need to be transported with spinal precautions unless there is evidence of trauma.

b. Benzodiazepines should not be the first choice for seizure control due to the risk of respiratory depression.

c. Intranasal midazolam is available in some EMS systems and is a good alternative in the absence of IV access.

d. The main priorities are airway management, intravenous access, and protecting the patient from injury.

2. A 73-year-old nursing home patient with a history of epilepsy presents with fever, cough, and ongoing seizure activity. Which testing is appropriate for this patient?

a. Chest x-ray

b. Blood cultures

c. AED levels

d. Sodium and glucose levels

e. All of the above

4 AMA PRA Category 1 Credits™, 4 ACEP Category I credits, 4 AAFP Prescribed credits, and 4 AAOA Category 2A or 2B credits.
3. A 55-year-old woman with a history of breast cancer presents for evaluation after having a focal seizure at home. She has never had seizures in the past. On further interrogation, the patient states that, over the past month, she has experienced paresthesias of her left arm. What would be the best diagnostic approach for this patient?
   a. Urgent EEG and laboratory testing
   b. Basic laboratory testing and brain CT
   c. Laboratory testing and lumbar puncture
   d. Only basic laboratory testing is needed unless there is a clear focal deficit on neurologic examination

4. In which of the following patients would you consider initiating an AED after completing the assessment in the ED?
   a. A 19-year-old student with no medical history who presents with a first-ever seizure after pulling 3 all-nighters in a row studying for finals
   b. An alcoholic with adult-onset seizures who presents after a seizure
   c. A 25-year-old who presents for evaluation after having a seizure following head trauma, with normal neurologic examination and unremarkable brain CT
   d. A 30-year-old with a history of 3 unprovoked seizures over the last 2 months, who presents with a tonic-clonic seizure, has a normal brain CT and examination, and will be following up with neurology in 1 week

5. Which of the following AEDs is the best first choice for SE?
   a. Lorazepam IV
   b. Diazepam IV
   c. Phenytoin IV
   d. Fosphenytoin IV

6. You have admitted a 25-year-old patient with a history of epilepsy for SE after self-discontinuing his outpatient AEDs. He appears to have responded to a 4 mg loading dose of lorazepam and fosphenytoin. However, when you open his eyes he has eye deviation to the left. What is the most important step in this patient’s management?
   a. Intubation.
   b. Consult neurology for an EEG.
   c. Begin a lorazepam drip.
   d. Add an additional anticonvulsant anesthetic and consider intubation.

7. A 35-year-old man is brought to the ED by his wife after having a witnessed tonic-clonic seizure at home. He has no known medical problems and never had a seizure in the past. He is currently asymptomatic and has a normal neurologic examination. You perform basic laboratory testing and a head CT, all of which result normal. What would be the most appropriate disposition for this patient?
   a. Admit to telemetry for observation of possible recurrent seizures.
   b. Discharge home after phenytoin load in the ED and a prescription to start oral phenytoin.
   c. Admit to neurology service for urgent inpatient EEG.
   d. Discharge patient with close follow-up.

8. In a patient with a history of alcohol dependency and adult-onset seizures who presents to the ED with a seizure, which of the following statements is FALSE?
   a. These patients have a significantly higher mortality than the general population.
   b. The diagnostic yield of brain CT is high in patients presenting with a first alcohol-related seizure.
   c. Screening for hypoglycemia and electrolyte abnormalities (ie, hyponatremia) is important in these patients, as these conditions can often coexist and precipitate or perpetuate seizures.
   d. Phenytoin IV load is the treatment of choice in these patients.

9. Which of the following AEDs is the first choice for seizure in third-trimester pregnant patients with eclampsia?
   a. Lorazepam IV
   b. Diazepam IV
   c. Phenytoin IV
   d. Magnesium IV

10. A 53-year-old woman with a history of diabetes and no history of seizure disorder presents after witnessed jerking of her extremities. On arrival to the ED, she is diaphoretic and appears to be postictal. What is the first initial step in this patient’s management?
    a. Finger-stick blood glucose
    b. Fosphenytoin (or phenytoin) load
    c. Repeat dose of lorazepam
    d. Lactate

Receive this exclusive resource **absolutely free** when you take advantage of this limited-time offer to extend your subscription with a $50+ savings.

Each year, your *Emergency Medicine Practice* subscription includes 12 monthly, information-packed, evidence-based print issues; 48 hours of CME credit per year; and full online access to searchable archives of over 140 issues, clinical pathways, risk management advice, cost-effective care tips, and more. Lock in your low subscription price today and continue to receive all these great benefits for up to five years at the discounted price!

With your paid renewal, you also receive the "*Emergency Medicine Practice* Audio Series Vol. II" absolutely free. In this audio series, Dr. Steve Carroll brings you updated information on 4 critical topics, including TIA, novel oral anticoagulant agents, acute aortic syndromes, and syncope. Each section condenses the information you need to know into easily digestible 15-minute sessions. The audio summaries are available as MP3 downloads on our website when you renew with this offer, and they are easy to add to your iPhone, iPod, tablet, or other audio devices. Here’s how to receive your maximum savings:

<table>
<thead>
<tr>
<th>SUBSCRIPTION EXTENSION</th>
<th>REGULAR PRICE</th>
<th>TOTAL DISCOUNTED PRICE</th>
<th>AUDIO SERIES VOL. II</th>
<th>TOTAL SAVINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Year</td>
<td>$329</td>
<td>$279 <strong>Save $50</strong></td>
<td><em><strong>FREE!</strong></em></td>
<td>$50</td>
</tr>
<tr>
<td>2 Year</td>
<td>$658</td>
<td>$538 <strong>Save $120</strong></td>
<td><em><strong>FREE!</strong></em></td>
<td>$120</td>
</tr>
<tr>
<td>3 Year</td>
<td>$987</td>
<td>$777 <strong>Save $210</strong></td>
<td><em><strong>FREE!</strong></em></td>
<td>$210</td>
</tr>
<tr>
<td>4 Year</td>
<td>$1316</td>
<td>$996 <strong>Save $320</strong></td>
<td><em><strong>FREE!</strong></em></td>
<td>$320</td>
</tr>
<tr>
<td>5 Year</td>
<td>$1645</td>
<td>$1195 <strong>Save $450</strong></td>
<td><em><strong>FREE!</strong></em></td>
<td>$450</td>
</tr>
</tbody>
</table>

Renew your subscription today using the Promotion Code **RHEAC** and lock in these low rates for up to five years! Your free MP3 download of the “*Emergency Medicine Practice* Audio Series Vol. II” will be available within 24 hours upon receipt of your order. This offer is valid for 30 days. Call 1-800-249-5770 for fastest service and be sure to mention promotion code **RHEAC** to receive your free resource. You can also go to [www.ebmedicine.net/RHEAC](http://www.ebmedicine.net/RHEAC) to order online.

*Use Promotion Code: RHEAC at checkout to secure your discount*
# SPECIAL SAVINGS:
The 2012-2015 Lifelong Learning And Self-Assessment Study Guides

Receive FREE article reprints,* CME, and more when you order yours today!

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>AMOUNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>The 2015 Lifelong Learning And Self-Assessment Study Guide</td>
<td>$199</td>
</tr>
<tr>
<td></td>
<td>$149</td>
</tr>
<tr>
<td>The 2014 Lifelong Learning and Self-Assessment Study Guide</td>
<td>$199</td>
</tr>
<tr>
<td></td>
<td>$149</td>
</tr>
<tr>
<td>The 2013 Lifelong Learning And Self-Assessment Study Guide</td>
<td>$199</td>
</tr>
<tr>
<td></td>
<td>$149</td>
</tr>
<tr>
<td>The 2012 Lifelong Learning And Self-Assessment Study Guide</td>
<td>$199</td>
</tr>
<tr>
<td></td>
<td>$149</td>
</tr>
</tbody>
</table>

• Full reprints of the original articles*
• 35 AMA PRA Category 1 Credits™ or 35 ACEP Category I CME Credits.
• A handy summary of key points so you get the “must know” information for each article.
• An in-depth discussion of each article to clarify and elaborate on the key points.
• Sample questions to help you quiz yourself on your knowledge of the material.
• Answers and explanations to the sample questions that drive home the main points.
• A critical discussion and critique of the article that answers the question, “What does this article really tell us?”
• 100% money-back guarantee: If, for any reason, you are not completely satisfied, simply call us to receive a full and immediate refund. No questions asked.

SPECIAL SAVINGS: The 2012-2015 Lifelong Learning And Self-Assessment Study Guides

Receive FREE article reprints,* CME, and more when you order yours today!

<table>
<thead>
<tr>
<th>DESCRIPTION</th>
<th>AMOUNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>The 2015 Lifelong Learning And Self-Assessment Study Guide</td>
<td>$199</td>
</tr>
<tr>
<td></td>
<td>$149</td>
</tr>
<tr>
<td>The 2014 Lifelong Learning and Self-Assessment Study Guide</td>
<td>$199</td>
</tr>
<tr>
<td></td>
<td>$149</td>
</tr>
<tr>
<td>The 2013 Lifelong Learning And Self-Assessment Study Guide</td>
<td>$199</td>
</tr>
<tr>
<td></td>
<td>$149</td>
</tr>
<tr>
<td>The 2012 Lifelong Learning And Self-Assessment Study Guide</td>
<td>$199</td>
</tr>
<tr>
<td></td>
<td>$149</td>
</tr>
</tbody>
</table>

• Full reprints of the original articles*
• 35 AMA PRA Category 1 Credits™ or 35 ACEP Category I CME Credits.
• A handy summary of key points so you get the “must know” information for each article.
• An in-depth discussion of each article to clarify and elaborate on the key points.
• Sample questions to help you quiz yourself on your knowledge of the material.
• Answers and explanations to the sample questions that drive home the main points.
• A critical discussion and critique of the article that answers the question, “What does this article really tell us?”
• 100% money-back guarantee: If, for any reason, you are not completely satisfied, simply call us to receive a full and immediate refund. No questions asked.

EASY WAYS TO ORDER

1. Go online to: www.ebmedicine.net/NHLAC
2. Call 1-800-249-5770 or 678-366-7933

Use Promotion Code: NHLAC at checkout to secure your discount
Renew your subscription to Emergency Medicine Practice now for $279
(a savings of $50 off our regular subscription rate)
You'll also get a free binder to hold all your 2015 issues! Use CME dollars to renew your subscription and get organized at the same time.

Call us at 1-800-249-5770 and use promotion code RGEAJ or go online to www.ebmedicine.net/RGEAJ to take advantage of this limited-time offer.

Physician CME Information


Accreditation: EB Medicine is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the ACCME.

Credit Designation: EB Medicine designates this enduring material for a maximum of 4 AMA PRA Category 1 Credits™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

ACEP Accreditation: Emergency Medicine Practice is approved by the American College of Emergency Physicians for 48 hours of ACEP Category I credit per annual subscription.

AAFP Accreditation: This Medical Journal activity, Emergency Medicine Practice, has been reviewed and is acceptable for up to 48 Prescribed credits by the American Academy of Family Physicians per year. AAFP accreditation begins July 31, 2014. Term of approval is for one year from this date. Each issue is approved for 4 Prescribed credits. Credit may be claimed for one year from the date of each issue. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AOA Accreditation: Emergency Medicine Practice is eligible for up to 48 American Osteopathic Association Category 2A or 2B credit hours per year.

Needs Assessment: The need for this educational activity was determined by a survey of medical staff, including the editorial board of this publication; review of morbidity and mortality data from the CDC, AHA, NCHS, and ACEP; and evaluation of prior activities for emergency physicians.

Target Audience: This enduring material is designed for emergency medicine physicians, physician assistants, nurse practitioners, and residents.

Objectives: Upon completion of this article, you should be able to: (1) distinguish between generalized convulsive and refractory status epilepticus; (2) recognize alcohol withdrawal seizures; and (3) choose appropriate pharmacologic therapy for various seizure states.

Goals: Upon completion of this activity, you should be able to: (1) demonstrate medical decision-making based on the strongest clinical evidence; (2) cost-effectively diagnose and treat the most critical ED presentations; and (3) describe the most common medicolegal pitfalls for each topic covered.

Discussion of Investigational Information: As part of the journal, faculty may be presenting investigational information about pharmaceutical products that is outside Food and Drug Administration–approved labeling. Information presented as part of this activity is intended solely as continuing medical education and is not intended to promote off-label use of any pharmaceutical product.

Faculty Disclosure: It is the policy of EB Medicine to ensure objectivity, balance, independence, transparency, and scientific rigor in all CME-sponsored educational activities. All faculty participating in the planning or implementation of a sponsored activity are expected to disclose to the audience any relevant financial relationships and to assist in resolving any conflict of interest that may arise from the relationship. In compliance with all ACCME Essentials, Standards, and Guidelines, all faculty for this CME activity were asked to complete a full disclosure statement. The information received is as follows: Dr. Teran, Dr. Harper-Kirksey, Dr. Huff, Dr. McMullan, Dr. Damilini, Dr. Toscano, and their related parties report no significant financial interest or other relationship with the manufacturer(s) of any commercial product(s) discussed in this educational presentation.

Dr. Jagoda reported work as a consultant for Banyan Biomarkers, Inc. and The Brain Trauma Foundation.

Commercial Support: This issue of Emergency Medicine Practice did not receive any commercial support.

Earning Credit: Two Convenient Methods: (1) Go online to www.ebmedicine.net/CME and click on the title of the article. (2) Mail or fax the CME Answer And Evaluation Form (included with your June and December issues) to EB Medicine.

Hardware/Software Requirements: You will need a Macintosh or PC to access the online archived articles and CME testing.

Additional Policies: For additional policies, including our statement of conflict of interest, source of funding, statement of informed consent, and statement of human and animal rights, visit http://www.ebmedicine.net/policies.