

Clinical Policy: Critical Issues in the Evaluation and Management of Adult Patients Presenting to the Emergency Department With Seizures

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This clinical policy was developed by the ACEP Clinical Policies Committee and the Clinical Policies Subcommittee on Seizures. For a complete listing of subcommittee and committee members, please see page 614.

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This clinical policy focuses on critical issues in the evaluation and management of adult patients with seizures. The medical literature was reviewed for articles that pertained to the critical questions posed. Subcommittee members and expert peer reviewers also supplied articles with direct bearing on this policy. This clinical policy focuses on 6 critical questions:

- I. What laboratory tests are indicated in the otherwise healthy adult patient with a new-onset seizure who has returned to a baseline normal neurologic status?
- II. Which new-onset seizure patients who have returned to a normal baseline require a head computed tomography (CT) scan in the emergency department (ED)?
- III. Which new-onset seizure patients who have returned to normal baseline need to be admitted to the hospital and/or started on an antiepileptic drug?
- IV. What are effective phenytoin or fosphenytoin dosing strategies for preventing seizure recurrence in patients who present to the ED after having had a seizure with a subtherapeutic serum phenytoin level?
- V. What agent(s) should be administered to a patient in status epilepticus who continues to seize after having received benzodiazepine and phenytoin?
- VI. When should electroencephalographic (EEG) testing be performed in the ED?

Recommendations for patient management are provided for each 1 of these topics on the basis of strength of evidence (Level A, B, or C). *Level A recommendations* represent patient management principles that reflect a high degree of clinical certainty; *Level B recommendations* represent patient management principles that reflect moderate clinical certainty; and *Level C recommendations* represent other patient management strategies based on preliminary, inconclusive, or conflicting evidence, or based on consensus of the members of the Clinical Policies Committee. This clinical policy is intended for physicians working in hospital-based EDs.

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INTRODUCTION

Epilepsy is defined as recurrent unprovoked seizures. There are an estimated 2.5 million patients with epilepsy in the United States, based on a prevalence of about 6.6 per

1,000 Americans.¹ Up to 28% of all epilepsy patients require treatment in emergency departments (EDs) annually.² Patients with seizures or presenting complaints related to seizures represent approximately 1% to 2% of all ED visits in the United States.³ An estimated 2% to 5% of the population will have at least 1 nonfebrile seizure during their lifetime.¹ In addition to patients who have an established seizure diagnosis, another 150,000 patients are diagnosed with a seizure each year, most often in the ED.⁴

A seizure can be the result of an acute process, in which case it is referred to as an “acute symptomatic seizure,” or it can result from a past intracranial insult such as stroke, trauma, or anoxia, in which case it is referred to as a “remote symptomatic seizure.” Responsibilities of the emergency physician in evaluating and treating patients include providing stabilization and interventions to stop the seizure, preventing seizure-related complications, identifying life-threatening processes for which a seizure may be a symptom (eg, electrolyte abnormalities, intracranial hemorrhage, meningitis), determining an appropriate and timely disposition (eg, hospital admission or outpatient follow-up), and minimizing future seizure-related morbidity and mortality.

Status epilepticus is a life-threatening form of seizure. Generalized tonic-clonic status epilepticus occurs in 50,000 to 150,000 patients per year in the United States and most commonly occurs at the extremes of age.⁵ Between 5% to 17% of patients will have a seizure while in the ED, and up to 7% of patients in the ED will have status epilepticus. The reported mortality rate for patients in status epilepticus ranges from 5% to 22% and has been reported to be as high as 65% in those patients refractory to first-line therapies.⁵⁻⁸

Despite its frequency, there is no universally accepted definition of status epilepticus. According to the World Health Organization, status epilepticus is “a condition characterized by an epileptic seizure that is sufficiently prolonged or repeated at sufficiently brief intervals so as to produce an unvarying and enduring epileptic condition.”⁹ Status epilepticus has traditionally been defined as at least 30 minutes of persistent seizures or a series of recurrent seizures without complete return to full consciousness between the seizures. Some authors have proposed shortening the time criteria for diagnosing status epilepticus from 30 minutes to 5 minutes.⁷ Even when properly treated, patients with status epilepticus can have serious morbidity and mortality.¹⁰ Status epilepticus is more easily recognized when it is

convulsive. To diagnose nonconvulsive status epilepticus (ie, complex partial status and absence status) and subtle convulsive status epilepticus (often the terminal stage of convulsive status), emergency physicians need to maintain a high index of suspicion.¹¹

This policy is a scheduled revision of the American College of Emergency Physicians (ACEP) seizure clinical policy.¹² This policy is not intended to be a complete manual on the evaluation and management of adult patients with seizures, but rather a focused look at critical issues that have particular relevance to the practice of emergency medicine. In an attempt to maximize the usefulness of this policy, this revision is organized into “critical questions” that were determined by the committee members to represent some of the most important and controversial issues related to the evaluation and management of adult patients who present to the ED with a seizure or a seizure-related complaint. It is the goal of the Clinical Policies Committee to provide an evidence-based recommendation when the medical literature provides enough quality information to answer a “critical question.” When the medical literature does not contain enough quality information to answer a “critical question,” the members of the Clinical Policies Committee believe that it is equally important to alert emergency physicians to this fact.

Recommendations offered in this policy are not intended to represent the only diagnostic and management options that the emergency physician should consider. ACEP clearly recognizes the importance of the individual clinician's judgment. Rather, they define for the clinician those strategies for which medical literature exists to provide strong support for their utility in answering the crucial questions addressed in this policy.

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature. All articles were graded by at least 2 subcommittee members for strength of evidence. The medical literature (1960 to 2002) was reviewed for articles that pertained to each critical question posed. Subcommittee members and expert peer reviewers also supplied articles with direct bearing on this policy.

The reasons for developing clinical policies in emergency medicine and the approaches used in their development have been enumerated.¹³ This policy is a product of the ACEP clinical policy development process, including expert review, and is based on the existing lit-

erature; where literature was not available, consensus of emergency physicians was used. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly.

During the review process, all articles used in the formulation of this clinical policy were classified by the subcommittee members into 3 classes of evidence on the basis of the design of the study, with design 1 representing the strongest evidence and design 3 representing the weakest evidence for therapeutic, diagnostic, and prognostic clinical reports respectively (Appendix A). Articles were then graded on 6 dimensions thought to be most relevant to the development of a clinical guideline: blinded versus nonblinded outcome assessment, blinded or randomized allocation, direct or indirect outcome measures (reliability and validity), biases (eg, selection, detection, transfer), external validity (ie, generalizability), and sufficient sample size. Articles received a final grade (I, II, III) on the basis of a predetermined formula taking into account design and grade of study (Appendix B). Articles with fatal flaws were given an "X" grade and not used in the creation of this policy. An Evidentiary Table was constructed and is included at the end of this policy.

Clinical findings and strength of recommendations regarding patient management were then made according to the following criteria:

Level A recommendations. Generally accepted principles for patient management that reflect a high degree of clinical certainty (ie, based on "strength of evidence class I" or overwhelming evidence from "strength of evidence class II" studies that directly address all the issues).

Level B recommendations. Recommendations for patient management that may identify a particular strategy or range of management strategies that reflect moderate clinical certainty (ie, based on "strength of evidence class II" studies that directly address the issue, decision analysis that directly addresses the issue, or strong consensus of "strength of evidence class III" studies).

Level C recommendations. Other strategies for patient management that are based on preliminary, inconclusive, or conflicting evidence or, in the absence of any published literature, based on panel consensus.

There are certain circumstances in which the recommendations stemming from a body of evidence should not be rated as highly as the individual studies on which they are based. Factors such as heterogeneity of results, uncertainty about effect magnitude and consequences,

strength of prior beliefs, and publication bias, among others, might lead to such a downgrading of recommendations.

Scope of Application. This guideline is intended for physicians working in hospital-based EDs.

Inclusion Criteria. This guideline is intended for adult patients presenting to the ED with seizures.

Exclusion Criteria. This guideline is not intended for pediatric patients.

CRITICAL QUESTIONS

I. What laboratory tests are indicated in the otherwise healthy adult patient with a new-onset seizure who has returned to a baseline normal neurologic status?

When confronted with an otherwise healthy adult patient who has had a first-time seizure, the emergency physician must determine if the seizure was the result of an acute event that requires immediate attention. The decision of which patients with a new-onset seizure need laboratory testing is determined by the information gathered through a careful history and physical examination. Patients with a first-time seizure that is suspected to be the result of concurrent alcohol use or alcohol withdrawal should be approached in a similar fashion.¹⁴ The diagnosis of an alcohol withdrawal seizure should be a diagnosis of exclusion, especially in patients presenting with a first-time seizure.

Laboratory studies: The history and physical examination will predict the majority of patients who will have a laboratory abnormality.¹⁵⁻¹⁸ Patients with altered mental status, fever, or a new focal neurologic deficit require more extensive evaluation. The controversial question is which laboratory tests are indicated in an otherwise healthy adult patient who presents to the ED after having a first-time seizure and is alert, oriented, and has no abnormal clinical findings.

The literature suggests that laboratory testing is of very low yield in patients with a new-onset seizure who have returned to baseline. Glucose abnormalities and hyponatremia are the most frequent abnormalities identified and are usually predicted by the history and physical examination.^{15-17,19} In 1 prospective study of 163 patients, 1 unexpected case of hypoglycemia was discovered.¹⁶ In a prospective study of 136 patients, Turnbull et al¹⁵ found 4 cases of hypoglycemia and 4 cases of hyperglycemia. Two of the cases of hypoglycemia were not suspected on the basis of the history and physical examination. Tardy et al¹⁸ found 1 case of

unsuspected hypoglycemia in 247 patients. Sempere et al¹⁷ found 1 case of unsuspected hyponatremia in a patient with psychogenic water ingestion in a cohort of 98 patients that was prospectively studied. Tardy et al,¹⁸ in a retrospective review of patients with new-onset seizures, found 4 cases of hyponatremia, only 1 of which was not suspected on the basis of history and physical examination.

There are no prospective studies in either children or adults at this time to support more in-depth routine laboratory testing such as serum calcium, magnesium, or phosphate levels of otherwise healthy patients evaluated in the ED.²⁰ Of note, Turnbull et al¹⁵ did find 2 patients with hypocalcemia in 136 patients with new-onset seizure who were prospectively studied; 1 with cancer, and 1 with renal failure. Tardy et al¹⁸ reported 1 case of hypocalcemia, but clinical correlation was not provided. There are inconclusive data to direct appropriate laboratory testing in patients with known medical disorders such as renal insufficiency or malnutrition, and in patients taking diuretics.

Identification of pregnancy in a patient with a first-time seizure is important because it may affect testing, disposition, and initiation of antiepileptic drug therapy. In 1 study of 59 patients with new-onset seizures in pregnancy, 14 patients were diagnosed with gestational epilepsy (ie, seizure disorder that occurs only during pregnancy).²¹

A drug of abuse screen is a consideration in patients with a first-time seizure; however, there are no prospective studies that demonstrate a benefit of routine use.²²⁻²⁴ Dhuna et al,²² in a retrospective review, reported that 69 of 90 admitted patients with cocaine-related seizures had no prior seizure history. Pesola and Westfal²⁴ reported 4 cases of cocaine-related seizures in 120 patients studied, although not all patients received the same tests nor was a direct correlation demonstrated.

Lumbar puncture: There are no prospective studies that support performing a lumbar puncture as part of the diagnostic evaluation in the ED on patients who are alert, oriented, afebrile, and not immunocompromised. There are no adult studies, but in 1 retrospective pediatric case series of 503 cases of meningitis in children aged 2 months to 15 years, there was no case of occult bacterial meningitis manifesting solely as a simple seizure.²⁵ Sempere et al¹⁷ reported that 5 of 9 patients with a first seizure who had a fever had a central nervous system infection.

There is evidence to support performing a lumbar puncture in patients who are immunocompromised

and who have a first-time seizure, even if they are afebrile.^{17,24,26} In a retrospective cohort of 100 consecutive HIV-positive patients, 14 cases of central nervous system infections were identified on lumbar puncture; however, clinical correlation was not provided.²⁶ In a prospective cohort, Sempere et al¹⁷ reported on 8 HIV-positive patients found to have a central nervous system infection as a cause of their seizure, 2 of whom were afebrile with no meningeal signs.

Patient Management Recommendations: What laboratory tests are indicated in the otherwise healthy adult patient with a new-onset seizure who has returned to a baseline normal neurologic status?

Level A recommendations. None specified.

Level B recommendations.

1. Determine a serum glucose and sodium level on patients with a first-time seizure with no comorbidities who have returned to their baseline.
2. Obtain a pregnancy test if a woman is of childbearing age.
3. Perform a lumbar puncture, after a head computed tomography (CT) scan, either in the ED or after admission, on patients who are immunocompromised.

Level C recommendations. None specified.

II. Which new-onset seizure patients who have returned to a normal baseline require a head CT scan in the ED?

The indications and timing of head CT scans in patients with a first-time seizure are controversial. Three percent to 41% of patients with a first-time seizure have abnormal head CT scan results.^{18,27} In 1 retrospective review, 22% of patients with a first-time seizure who had a normal neurologic examination had abnormal head CT scan results.²⁷ In a study of 259 patients with suspected alcohol withdrawal seizure, 58% had abnormal CT scan results, of which 16 (6%) had a clinically significant lesion.²⁸ Of the 16 patients with abnormal CT scan results, 7 were alert, had a normal neurologic examination, and no signs of head trauma. Management changed in 10 patients as a result of the abnormal finding.²⁸

The question remains whether identifying the abnormality in patients with nonfocal neurologic examinations who are evaluated in the ED has an effect on outcome. This, of course, depends on the outcome measure used; clearly, identifying a lesion may direct disposition and argues in favor of ED neuroimaging. For example, Tardy et al¹⁸ reported that 23% of patients with a new-onset seizure had an acute stroke or tumor demon-

strated on CT scan. Pesola and Westfal²⁴ reported that 6 of 26 HIV-positive patients had an acute lesion found on CT scan, 2 of which were not suspected on physical examination.

In a multidisciplinary collaboration between emergency medicine, neurology, and neuroradiology, an evidence-based clinical policy on neuroimaging of patients with a first-time seizure was published in 1996.²⁹ The timing of imaging was categorized into “emergent,” “urgent,” and “routine” on the basis of an outcome measure of identifying an immediate life-threatening process. It was recommended that a head CT scan be performed in the ED whenever an acute intracranial process is suspected, in patients with a history of acute head trauma, history of malignancy, immunocompromise, fever, persistent headache, history of anticoagulation or a new focal neurologic examination, age older than 40 years, or focal onset before generalization. This multidisciplinary document allowed for a deferred neuroimaging study as an outpatient in those patients with a first-time seizure who were alert and returned to baseline. This recommendation was based on the absence of studies demonstrating an outcome benefit from ED imaging. Unfortunately, concerns in timely follow-up and social issues are the intangible factors that the emergency physician must consider when deciding on required tests.

Patient Management Recommendations: Which new-onset seizure patients who have returned to a normal baseline require a head CT scan in the ED?

Level A recommendations. None specified.

Level B recommendations.

1. When feasible, perform a neuroimaging of the brain in the ED on patients with a first-time seizure.
2. Deferred outpatient neuroimaging may be used when reliable follow-up is available.

Level C recommendations. None specified.

III. Which new-onset seizure patients who have returned to normal baseline need to be admitted to the hospital and/or started on an antiepileptic drug?

In trying to answer the question of which patients need to be admitted to the hospital, it is necessary to identify the outcome measure that will be used in assessing the correctness of the decision. Examples of outcome measures include recurrence of seizure within 24 to 72 hours, underlying life-threatening etiology of the seizure, or morbidity/mortality within 24 to 72 hours. There is a paucity of literature on the evaluation

of patients with new-onset seizures in the ED, and most of this literature uses an abnormal laboratory or diagnostic test as the outcome measure. There are no studies that have looked at the 24-hour morbidity or mortality of first-time seizure patients discharged from the ED. There are no prospective studies and only 1 retrospective study that looked at the recurrence rate in the first 24 hours of admitted patients.¹⁸ The majority of studies that look at recurrence rates begin by excluding patients with acute symptomatic seizures, whereas the majority of studies that look at diagnostic testing group all types of seizure patients together. The focus of this question is patients who are alert with a normal neurologic examination.³⁰

The chance of a patient having a recurrent event after 1 unprovoked seizure varies depending on the patient's age and the seizure's underlying etiology.³⁰⁻³³ Seizure etiology, combined with electroencephalographic (EEG) findings, are the best predictors of recurrence. When no etiology is identified and the EEG findings are normal, the recurrence rate is 14% at 1 year and 24% at 2 years.³¹ Patients who have structural lesions on CT scan, or patients with focal seizures that secondarily generalize, have a risk of recurrence of up to 65% and are the group of patients that probably benefits from initiating antiepileptic drug therapy.³²

There is limited literature to help the emergency physician decide which patient with a new-onset seizure needs to be admitted to the hospital. Krumholz et al³⁴ reported that 63 of 200 seizure patients seen in an ED required hospitalization; however, this retrospective study failed to provide a complete data set on the patients or outcome data. In a retrospective review, Henneman et al²⁷ reported that 136 (46%) of 294 adult patients seen in the ED with a first-time seizure required admission and 48 (15%) of the 294 adult patients had a recurrent seizure while in the ED; however, clinical data on these patients were not provided.

There is only 1 study that specifically investigated the incidence of seizure recurrence within 24 hours of ED presentation. Tardy et al¹⁸ performed a retrospective review of all adult patients seen over a 2-year period who were admitted to the hospital with a first-time seizure. The study suffers from its retrospective design, and it is unclear to what extent selection bias affects its findings. The authors reported a 19% seizure recurrence rate within 24 hours of presentation, decreasing to 9% if those patients with alcohol-related events or focal lesions on CT scan were excluded. Unfortunately, those patients with recurrent seizures are not well de-

scribed, and it is not possible to assess from the data provided whether a recurrence could have been predicted on the basis of physical findings or comorbid factors.

A corollary to admitting a patient with a new-onset seizure to the hospital is the decision to initiate anti-epileptic drug therapy in the ED. This decision is based on the underlying cause of the seizure that requires the results of laboratory testing, a neuroimaging study, and an EEG. All of these data are rarely available before ED discharge. Consequently, both the decision to admit to the hospital and to initiate antiepileptic drug therapy must be based on the predicted risk for seizure recurrence, with the understanding that even if an anti-epileptic drug is initiated seizure recurrence may not be changed.³¹ In a prospective nonrandomized cohort, Hauser et al³¹ reported that antiepileptic drug treatment did not decrease the incidence of recurrence after a first unprovoked seizure and was associated with an increased risk of having a second seizure. Another study has demonstrated a decreased incidence of seizure recurrence after a first unprovoked seizure; however, 20% of the “treated” patients were noncompliant with their treatment and there was no placebo group.³³

Patient Management Recommendations: Which new-onset seizure patients who have returned to normal baseline need to be admitted to the hospital and/or started on an antiepileptic drug?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations.

1. Patients with a normal neurologic examination can be discharged from the ED with outpatient follow-up.
2. Patients with a normal neurologic examination, no comorbidities, and no known structural brain disease do not need to be started on an antiepileptic drug in the ED.

IV. What are effective phenytoin or fosphenytoin dosing strategies for preventing seizure recurrence in patients who present to the ED after having had a seizure with a subtherapeutic serum phenytoin level?

Most laboratories report a “therapeutic” serum phenytoin level between 10 to 20 mg/L. The term “therapeutic” serum phenytoin level is misleading because many patients remain seizure free at serum levels less than 10 mg/L and some patients require a serum level greater than 20 mg/L to control their seizures.

A serum phenytoin level greater than or equal to 10 mg/L can be achieved by any of the common contemporary dosing strategies. Intravenous loading of either

phenytoin or fosphenytoin usually achieves a serum phenytoin level greater than or equal to 10 mg/L within minutes after completion of the infusion.³⁵⁻³⁸ Intramuscular administration of fosphenytoin generally produces a therapeutic serum phenytoin level within 1 hour of administration.³⁹⁻⁴¹ Oral loading of phenytoin as a single dose and in divided doses has been reported to achieve a therapeutic serum phenytoin level between 3 to 8 hours after the initial ingestion.⁴²⁻⁴⁵ Oral phenytoin dosing at the appropriate daily maintenance dose, without a loading dose, can achieve a serum phenytoin level greater than or equal to 10 mg/L in 3 to 7 days. Some patients may not achieve a serum phenytoin level greater than or equal to 10 mg/L unless the daily maintenance dose is increased. Because these are all effective strategies, serum phenytoin levels do not need to be rechecked before ED discharge, but follow-up and monitoring of serum phenytoin levels on an outpatient basis are important.⁴⁶⁻⁴⁸

Irrespective of the route of administration, dose-related adverse effects associated with phenytoin and fosphenytoin include ataxia, nystagmus, tremor, and somnolence.⁴⁰ Fosphenytoin, the disodium phosphate ester of phenytoin, is a parenteral phenytoin pro-drug that is rapidly converted to phenytoin by blood and tissue phosphatases after intravenous and intramuscular injection.³⁹ Many of the adverse local and systemic effects, including phlebitis, purple glove syndrome, tissue necrosis, impairment of myocardial contractility, dysrhythmias, hypotension, and cardiac arrest, that have been reported with intravenous administration of phenytoin occur much less frequently with intravenous administration of fosphenytoin.⁴⁹⁻⁵⁵ This difference in adverse effects is believed to be in part related to the fact that parenteral phenytoin preparations contain propylene glycol (40%) and ethanol (10%) and are adjusted to a pH of 12. Fosphenytoin, which is more water soluble, does not contain these same diluents. Although fosphenytoin appears to have a better safety profile than intravenously administered phenytoin, its acquisition costs are considerably more than those for both intravenous and oral phenytoin preparations.⁵⁶⁻⁵⁹

To date, there are no published studies specifically designed to compare the rate of seizure recurrence using any combination of the common contemporary phenytoin dosing strategies. Most pharmacokinetic studies use achievement of a therapeutic serum phenytoin level as the primary outcome measure.

The most important measure of a particular anti-epileptic drug dosing strategy should be efficacy in pre-

venting seizure recurrence when viewed in conjunction with adverse events. Data on the risk of seizure recurrence are commonly reported in years rather than days.⁶⁰ The baseline rate of seizure recurrence within a few days to a few weeks of ED discharge for the patient population of interest is unknown. Without knowing the background prevalence of short-term seizure recurrence, individual studies that address the rate of seizure recurrence are difficult to interpret and compare.

Most studies lacked a standardized measurement of efficacy and adverse events. Most studies included patients with many different etiologies for their seizures, despite the fact that the underlying cause of seizures is an important variable in determining the rate of seizure recurrence. Studies that did report adverse effects often did not evaluate for their severity. Many studies used a fixed dose of phenytoin that was not adjusted for the patient's weight.

There are no published studies that address the rate of seizure recurrence within a few days in patients who are started or restarted on daily oral maintenance dosing without administering a loading dose. The rate of seizure recurrence was estimated in 2 class III studies, 1 involving intravenous phenytoin loading and 1 involving oral phenytoin loading. Cranford et al⁶¹ reported the results of a convenience sample of 139 patients with seizures who were administered intravenous phenytoin at varying doses for status epilepticus, serial seizures, isolated seizures when withdrawal from antiepileptic drugs was suspected, and as prophylaxis after subarachnoid hemorrhage. Ninety-nine patients were classified as having preexisting epilepsy, atypical alcohol withdrawal, or "miscellaneous conditions." Of these patients, 59 had serial seizures, 17 had 2 or less seizures, and 9 patients did not have their seizure frequency recorded. The rate of seizure recurrence in these patients was 8%, 10%, and 11%, respectively. Of these 81 patients that may have been representative of the patient population of interest, approximately 8% had a recurrent seizure.

One study investigated oral loading doses of phenytoin where the rate of seizure recurrence was reported. Osborn et al⁴² administered a single 18-mg/kg oral dose of phenytoin capsules or suspension to 44 patients who presented to the ED after 1 or more recent seizures, had undetectable serum phenytoin levels, were awake, and had the ability to take oral phenytoin. Patients were observed for at least 8 hours, and no patient had a seizure.

Weaknesses shared by the 2 studies were a lack of a double-blind, randomized design; small study size;

failure to exclude patients with alcohol withdrawal seizures; the lack of objective measures of baseline seizure frequency; inclusion of a heterogeneous population of patients with different types of seizures; and an inadequate record of adverse effects associated with phenytoin dosing.^{42,61}

Patient Management Recommendations: What are effective phenytoin or fosphenytoin dosing strategies for preventing seizure recurrence in patients who present to the ED after having had a seizure with a subtherapeutic serum phenytoin level?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Administer an intravenous or oral loading dose of phenytoin or intravenous or intramuscular fosphenytoin, and restart daily oral maintenance dosing.

V. What agent(s) should be administered to a patient in status epilepticus who continues to seize after having received benzodiazepine and phenytoin?

Many different agents have been used to treat patients with status epilepticus who continue to seize despite the administration of benzodiazepines and phenytoins.⁶²⁻⁶⁴

Although intravenous phenytoin is an accepted therapy for patients whose seizures cannot be successfully terminated with benzodiazepines, few controlled trials have addressed its use in status epilepticus. The 1998 Treiman et al⁸ study (VA Cooperative Study) showed a 56% success in terminating status epilepticus using a diazepam/phenytoin combination. The 1988 Shaner et al⁶⁵ study evaluated the use of diazepam and phenytoin in 18 patients in a clinical trial comparing this regimen with 18 patients treated with phenobarbital. The use of diazepam and phenytoin was associated with longer seizure duration than with the use of phenobarbital (5 minutes versus 9 minutes; $P < .06$). Complications in these 2 treatment groups were comparable. Other than 1 abstract demonstrating efficacy, there have been no published prospective studies of fosphenytoin in the treatment of status epilepticus patients who have not improved with benzodiazepine treatment.⁶⁶

The issue of high-dose phenytoins in the treatment of status epilepticus is addressed in a case series and 1 published guideline.^{63,67} Osorio and Reed⁶⁷ reported that of 13 status epilepticus patients who were given high-dose phenytoin (mean dose 24 mg/kg), 5 (38%) did not require pentobarbital therapy. The Epilepsy Foundation of America's Working Group on Status

Epilepticus recommends, on the basis of consensus, that up to 30 mg/kg of phenytoin be given before using another antiepileptic drug.⁶³

One prospective, double-blind, randomized study, the VA Cooperative Study, and 1 nonblinded study have examined the efficacy of phenobarbital in seizures and status epilepticus.^{8,65} The VA Cooperative Study showed phenobarbital to be equally efficacious in the management of status epilepticus when compared with lorazepam, phenytoin, and phenytoin plus diazepam.⁸ The problem with phenobarbital is its potential to induce profound respiratory depression and hypotension from its vasodilatory and cardiodepressant effects. Shaner et al⁶⁵ compared the use of diazepam and phenytoin with the use of phenobarbital and optional phenytoin in 36 patients in status epilepticus. Status epilepticus duration was noted to be shorter with the use of phenobarbital, and 61% of phenobarbital patients did not require the addition of phenytoin in order to terminate status epilepticus. Complication rates were comparable in the 2 treatment groups, suggesting phenobarbital as an alternative to diazepam and phenytoin. There is 1 other study that compared phenobarbital to phenytoin in treating neonatal seizures, but it is of questionable relevance in discussing adult status epilepticus.⁶⁸

Intravenous valproate has been shown to be effective in a small French study of patients in status epilepticus.⁶⁹ In this study, valproate was used to treat status epilepticus irrespective of initial antiepileptic drug therapy, and seizure termination was achieved within 20 minutes of infusion for 83% of the patients. Another European study, from Spain, demonstrated 58% control of status epilepticus in pediatric patients.⁷⁰ Intravenous valproate has also been reported in other small case series to be effective in the treatment of myoclonic seizures and in generalized convulsive and nonconvulsive status epilepticus.⁷¹⁻⁷³ Limdi and Faught⁷² reported that 16 of 20 patients with intractable seizures were effectively treated with a rapid infusion of intravenous valproate. Sinha and Naritoku⁷³ reported that 13 hypotensive geriatric patients were effectively infused with intravenous valproate without an exacerbation of their hypotension; 30% achieved seizure control.

Intravenous propofol has been reported to be effective in an emergency medical services case report from Finland, as well as in hospitalized patients from Switzerland and the West Indies.⁷⁴⁻⁷⁶ In 1 US study of 16 patients that compared propofol with high-dose barbiturates, propofol was noted to terminate fewer cases

of status epilepticus (63% versus 82%; *P* not significant), but the time to termination was much shorter with the use of propofol (3 minutes versus 123 minutes; *P* < .002).⁷⁷ In a study of 20 refractory status epilepticus patients from Virginia, the use of propofol was compared with midazolam.⁷⁸ Propofol achieved a 64% rate of seizure suppression compared with 67% for midazolam.

The continuous infusion of benzodiazepines has been used to treat both pediatric and adult patients with refractory status epilepticus. In 1 open-label study in 40 pediatric patients, continuous infusions of diazepam and midazolam were compared, with the endpoint being a 6-hour period free of seizures.⁷⁹ Both drugs were equally effective in controlling refractory status epilepticus (86% and 89%, respectively), but higher seizure recurrence and mortality rates were seen with the infusion of midazolam. In a review article that included 54 adult status epilepticus patients, the use of a continuous intravenous midazolam infusion effectively treated 80% of patients, but its use was associated with a greater rate of breakthrough seizures than were the infusions of propofol and pentobarbital (51% versus 15% and 12%, respectively).⁸⁰ The infusion of midazolam was, however, associated with less hypotension than were the other 2 infusions (30% versus 44% and 77%, respectively). Two other studies examined the use of a continuous intravenous midazolam infusion in adults, 1 with 33 patients, and 1 with 7 patients whose outcome was compared with 13 patients treated with a propofol infusion.^{78,81} In the study of 33 patients in nonconvulsive status epilepticus, an infusion of intravenous midazolam was effective in treating 82% of patients.⁸¹ In 6 patients treated with a midazolam infusion, the rate of seizure suppression was 67%.⁷⁸

The use of a continuous intravenous infusion of pentobarbital has been studied in multiple adult case series.^{77,80,82} In a nonrandomized small study of 16 patients in refractory status epilepticus, there was no statistical difference between pentobarbital and propofol in terminating the seizure. There was a trend in favor of pentobarbital, although the time to seizure termination favored propofol.⁷⁷ In a comprehensive review of the literature by Claassen et al,⁸⁰ 106 patients treated with intravenous pentobarbital were identified, and pentobarbital had a treatment success rate of 92% compared with 80% for intravenous midazolam and 73% for intravenous propofol. Pentobarbital, however, was associated with the highest rate of hypotension requiring pressors compared with propofol and midazolam

(77% versus 42% and 30%, respectively). In a case series of 44 patients with refractory status epilepticus treated with pentobarbital, patients with significant toxic and metabolic derangements or anoxia as the cause of the refractory status epilepticus were least likely to be controlled compared with those with chronic epilepsy, infections, tumors, stroke, or trauma.⁸²

Patient Management Recommendations: What agent(s) should be administered to a patient in status epilepticus who continues to seize after having received a benzodiazepine and a phenytoin?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Administer 1 of the following agents intravenously: “high-dose phenytoin,” phenobarbital, valproic acid, midazolam infusion, pentobarbital infusion, or propofol infusion.

VI. When should EEG testing be performed in the ED?

Recommendations have been made to obtain an emergency EEG for persistent altered consciousness, refractory status epilepticus, pharmacologically managed sedation and coma, and for the diagnosis of viral encephalitis, as well as for a variety of other clinical conditions including coma and brain death.^{83,84} Although uncommon, acute confusional states, behavioral changes, other psychiatric disturbances, or encephalopathy may result from continuing seizures. The term nonconvulsive status epilepticus is used to describe those seizures in which the primary manifestation of the seizure is not motor in nature; nonconvulsive status includes absence status epilepticus and complex partial status epilepticus.^{85,86} It has recently been recognized that an altered level of consciousness after a motor seizure may be the result of either nonconvulsive status or subtle convulsive status epilepticus.⁸⁷⁻⁸⁹ A high index of clinical suspicion is necessary to suspect these events, and EEG is the definitive test.

The most compelling argument for emergent EEG is for the detection of generalized convulsive status epilepticus that may have evolved into subtle status epilepticus with continuing abnormal EEG discharges. The ongoing electrical seizure activity may cause cell injury even in the absence of convulsive movements and with conventional advanced life support.¹⁰ A recent trial examining treatments for generalized convulsive status epilepticus used EEG early in the clinical course and found that 25% of patients had evidence of continuing electrical seizures when generalized con-

vulsions were thought to have been terminated by bedside observation.⁸ This “subtle status epilepticus” was regarded as an evolution of suboptimally treated or nonterminated convulsive status epilepticus and was actively treated in this study. Others have also noted that nonconvulsive status epilepticus may persist after control of generalized convulsive status epilepticus and suggest that EEG monitoring be immediately available after the control of convulsive status epilepticus.⁸⁹ Continuous EEG monitoring for patients with status epilepticus that is refractory to optimal doses of a benzodiazepine and phenytoin is recommended as well.⁹⁰

Although physicians generally agree that the excessive, abnormal electrical activity associated with status epilepticus may in itself cause cerebral injury, the concept still generates controversy.^{91,92}

The detection of nonconvulsive status epilepticus in comatose patients in ICUs is another area of active research. In comatose patients without clinical signs of seizure activity, up to 8% met criteria for nonconvulsive status epilepticus in 1 study.⁹³ Others have described EEG status epilepticus in comatose patients as well.⁹⁴ The duration and delay in diagnosis of nonconvulsive status epilepticus was strongly linked to mortality in another ICU-based study.⁹⁵ These studies were performed on patients in ICUs with continuous EEG-monitoring techniques. The application of these studies to patients in the ED and effect of any treatment on patient outcome remains unclear.

Despite differing recommendations, a recently published multicenter survey of management of patients with seizures revealed that EEG was uncommonly performed in EDs.³

A survey of medical directors of accredited North American clinical EEG laboratories and directors of facilities offering accredited EEG fellowships revealed that the majority of facilities required neurologic consultation or other specialized consultation before emergent EEG could be obtained. The survey revealed no clear consistency between centers regarding which clinical syndromes were appropriate for emergent EEG study. Furthermore, an average response time from request to initial EEG reading of approximately 3 hours exceeds ideal availability for treatment of time-critical conditions.⁸⁴

No clear recommendation for ordering emergency EEG may be made on the basis of available data. Local access to neurologic and EEG expertise, access to technical personnel and equipment, other technical considerations, and local practice patterns will likely continue

to limit performance of EEGs in EDs. The widespread practice of neurologic consultation before obtaining an EEG seems reasonable given that EEG interpretation is a specialized province within the specialty of neurology.

Patient Management Recommendations: When should EEG testing be performed in the ED?

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Consider an emergent EEG in patients suspected of being in nonconvulsive status epilepticus or in subtle convulsive status epilepticus, patients who have received a long-acting paralytic, or patients who are in a drug-induced coma.

This clinical policy was developed by the ACEP Clinical Policies Committee and the Clinical Policies Subcommittee on Seizures.

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Evidentiary Table.

Study	Design	Outcome Measure	Findings	Limitations	Class
Huff et al ³	Multicenter retrospective review	Seizure occurrence/termination	EEG uncommonly performed in ED in this sample of seizure patients	Retrospective review; EEG performed at discretion of consulting physicians likely does not reflect practice of emergency physicians	III
Treiman et al ⁸	Multicenter, randomized, double-blind trial	Termination of status epilepticus	518 status epilepticus patients from ED, ward, and ICU; 74% overt status epilepticus; 26% subtle status epilepticus; absence of clinical or EEG seizure within 20 min of treatment start; seizure did not recur 20 to 60 min after start of treatment; effectiveness of IV treatments: overt status epilepticus: lorazepam: 65%; phenobarbital: 58%; diazepam and phenytoin: 56%; phenytoin: 44%; lorazepam is significantly superior to phenytoin; subtle status epilepticus: no significant differences	VA population; large number of patients with anoxic brain damage	I
Ng et al ¹⁴	Prospective observational	Descriptive	308 first seizures compared with 294 control patients; risk of having an unprovoked seizure increased with increased alcohol use: the greater the alcohol consumption the greater the odds ratio of a seizure; no support for the withdrawal hypothesis was found in a statistical model devised to test the hypothesis in terms of the timing of alcohol-related seizures; questions of existence of withdrawal seizures per se and supports the need to eliminate symptomatic causes of seizures before labeling a patient as having withdrawal seizures	Does not present diagnostic testing or specific etiologies	II
Turnbull et al ¹⁵	Prospective; standardized data collection: CBC count, electrolytes, BUN, creatinine, Mg, calcium	Abnormal diagnostic test	136 patients over 3-y period, ages 12 to 86 y; 11 (8%) correctable lab abnormalities: 4 hypoglycemia, 4 hyperglycemia, 2 hypocalcemia, 1 hypomagnesemia; of the 11 cases, only 2 cases of hypoglycemia were not suspected on history or physical examination; hypocalcemic patients: 1 had cancer and 1 had renal failure; case of hypomagnesemia was in an alcoholic; idiopathic, alcohol withdrawal, cerebral infarction most common etiologies	Mixed group of seizure patients; alcohol withdrawal included; no CT results provided; no analysis of clinical presentations (awake vs altered mental status)	III
Eisner et al ¹⁶	Prospective study; CBC count, electrolytes, BUN, creatinine, Mg, calcium; CT in patients with new-onset seizure	Abnormal diagnostic test	163 patients; only 24 with new-onset seizures; most common etiologies: antiepileptic drug noncompliance, new onset, alcohol; 19 of 25 patients with new-onset seizures had CT: 5 were abnormal; history and physical examination predicted all abnormalities except 1 hypoglycemia and 1 subdural	Small number of patients with new-onset seizures; no outcome	III

Evidentiary Table (continued).

Study	Design	Outcome Measure	Findings	Limitations	Class
Sempere et al ¹⁷	Prospective cohort; all patients seen by a neurologist, ECG, CBC count, glucose, electrolytes, creatinine, CT with contrast if unenhanced CT was normal, which if still normal was followed by an MRI; HIV testing and EEG on select patients	Abnormal diagnostic test	98 patients, ≥ 15 y; 27 idiopathic, 23 stroke, 11 alcohol withdrawals, 9 CNS infections, 8 tumors, 6 vascular malformations; 4 trauma; 3 drug toxicity, 2 subdurals, 2 hyperglycemia, 1 uremia, 1 hyponatremia (low idiopathic rate probably secondary to extensive workup); 8 patients with HIV; 5 had treatable infections: 2 toxicologic, 1 cryptococcal, 1 herpes zoster meningitis, 1 cytomegalovirus encephalitis, 1 alcohol withdrawal, 2 idiopathic; incidence of stroke and tumors increased with age; 9 patients were febrile, 5 of the 9 had a CNS infection; 97% patients with a focal examination had a symptomatic seizure; 34% had a structural lesion on CT (40% had a nonfocal examination); 2 HIV patients who were afebrile and no meningeal signs had positive LP results: 1 crypto, 1 herpes zoster; 5 other immunocompetent patients with positive LP results were febrile; hyponatremia not suspected in 1 patient with unknown psychogenic water drinking; all other metabolic abnormalities were suspected by history	Not all patients had LP; did not document seizure recurrence or use of antiepileptic drug	II
Tardy et al ¹⁸	Retrospective study 3-y	Abnormal diagnostic tests; seizure recurrence	247 patients; all had CT, 209 had EEG; etiologies: 24% unknown, 20% alcohol, 13% stroke, 10% tumor, 10% intoxication; 4.9% metabolic abnormalities: 5 cases hypoglycemia, 4 hyponatremia, 1 hypocalcemia, 1 hypercalcemia, 1 hypernatremia; in 3 cases history and physical examination did not predict the abnormality (1 hypoglycemia, 1 hyponatremia, 1 hypocalcaemia); 85 (34%) of 247 patients had focally abnormal CT (34%); highest in patients >60 y; 17% of patients with normal neurologic examinations had a focal CT; 55 (81%) of 68 patients with a focal neurologic examination had a focal lesion on CT; early recurrence was 18.5%: focal lesions on CT did not significantly increase rate; early recurrence was 12% in patients without alcohol or focal lesion on CT; recurrence rate was 8.5% in "unknown" group	Timing of the repeat seizure not provided (ie, in first hours or late); does not describe the 3 cases of metabolic abnormality that were not predicted by history and physical examination; does not provide historical information to help predict recurrence	III
Powers ¹⁹	Retrospective cohort	Abnormal diagnostic test	126 seizures: 55 patients with new-onset seizure, 1 due to hypoglycemia in patient with diabetes; 8 of 18 patients with alcohol-related seizures had magnesium <1.5 mEq/L; concludes that abnormalities can be identified by history and physical examination	Retrospective; no CT results; small number of patients with new-onset seizure	III
American Academy of Neurology ²⁰	Evidence-based clinical policy	First-time seizure in child 1 mo to 21 y; excluded obvious head trauma or CNS infection	Laboratory studies: Option: Laboratory tests should be ordered on the basis of individual clinical circumstances that include suggestive historic or clinical findings such as vomiting, diarrhea, dehydration, or failure to return to baseline alertness. Toxicologic screening should be considered across the entire pediatric age range if there is any question of drug exposure or substance abuse.	Recommendations are for children	III

Evidentiary Table (continued).

Study	Design	Outcome Measure	Findings	Limitations	Class
			<p>LP: Option: In the child with a first non-febrile seizure, LP is of limited value and should be used primarily when there is concern about possible meningitis or encephalitis.</p> <p>EEG: Standard: The EEG is recommended as part of the neurodiagnostic evaluation of the child with an apparent first unprovoked seizure.</p> <p>Neuroimaging studies: Guideline: If a neuroimaging study is obtained, MRI is the preferred modality.</p> <p>Option: Emergent neuroimaging should be performed in a child of any age who exhibits a postictal focal deficit that does not quickly resolve or who has not returned to baseline within several hours after the seizure.</p> <p>Option: Nonurgent imaging studies with MRI should be seriously considered in any child with a significant cognitive or motor impairment of unknown etiology, unexplained abnormalities on neurologic examination, a seizure of partial onset with or without secondary generalization, an EEG that does not represent a benign partial epilepsy of childhood or primary generalized epilepsy, or in children aged <1 y.</p>		
Knight and Rhind ²¹	Descriptive study of patients seen in an epilepsy clinic over a 20-y period	New-onset seizure during pregnancy that only occurs during pregnancy	59 patients with 153 pregnancies; 14 patients with gestational epilepsy (seizures occurring only in relation to pregnancy); patients followed up for 6 mo to 16 y	Questionable if gestational epilepsy exists as a specific entity; no CT correlation; no systematic evaluation described	III
Dhuna et al ²²	Retrospective review	Seizure related to cocaine use	945 patients admitted for cocaine-related medical issues; 98 (10%) with seizures; 69 diagnosed with cocaine-related seizure with no prior seizure history; 70% were single, generalized; all had normal CT scan results	Selection bias; limited information on the workup patients received; no information on total number of patients with new-onset seizures admitted during this period	III
Olson et al ²³	Retrospective review of poison center consultations	Seizure associated with drug ingestion	191 cases: 55 TCA, 55 cocaine or other stimulants, 14 antihistamines, 10 theophylline	No information on total number of overdoses seen; no information regarding concomitant etiologies for the seizure (eg, metabolic profile, CT)	III
Pesola and Westfal ²⁴	Retrospective review of HIV versus non-HIV patients with new-onset seizures compared; history, physical examination, CBC count, electrolytes, Mg	Abnormal diagnostic test	26 HIV patients with new-onset seizures; etiology: 8 idiopathic, 8 HIV encephalopathy, 5 CNS toxicologic, 2 alcohol withdrawal, 2 PML, 1 central nervous system lymphoma; of the 120 patients without HIV, idiopathic and alcohol withdrawal were the most common etiologies; 4 had acute cocaine intoxication; 2 hypoglycemia; 1 hyperglycemia with hypoxia; 6 patients (40%) had acute lesion necessitating admission (5 toxicologic, 1 lymphoma); only 2 of 6 had findings on physical examination; recommend HIV with new-onset seizures; need a CT and LP either in ED or after admission	Not all patients had the same tests; does not report incidence of recurrence of seizures while in the hospital	III

Evidentiary Table (continued).

Study	Design	Outcome Measure	Findings	Limitations	Class
Green et al ²⁵	Retrospective cohort	Seizure in patient with signs or symptoms of meningitis	503 consecutive patients aged 2 to 15 y; no cases of bacterial meningitis identified in patient; simple seizure was the sole presentation	Retrospective study; relatively small number because seizure due to occult bacteremia probably is a very rare event; pediatric study	III
Holtzman et al ²⁶	Retrospective cohort of consecutive patients	Abnormal diagnostic test	100 patients: 32 mass lesion, 24 HIV encephalopathy, 13 cryptococcal meningitis, 1 herpes zoster meningitis, 2 hyponatremia, 1 renal failure, 3 stroke, 23 no cause	Retrospective design; no follow-up; no correlation between abnormalities on diagnostic testing and clinical presentation	III
Henneman et al ²⁷	Retrospective chart review over a 5-y period; excluded head trauma, hypoglycemia, alcohol or recreational drug-related seizures; standardized evaluation included history and physical examination, CBC count, electrolytes, BUN, creatinine, glucose, calcium, head CT; febrile patients had an LP	Abnormal diagnostic test; seizure recurrence; "need for admission as judged by a retrospective evaluation of the ED and hospital course"	333 total adults; 136 (46%) of 294 adult patients were admitted; 146 (44%) no etiology; 41 (12%) stroke; 38 (11%) cerebral cystercerosis; significant abnormality: 23% examination; 8% CBC; 6% SMA-7; 1% calcium; 41% CT, 8% LP; 134 (41%) of 325 had abnormal CT scan results; 30 (22%) had a normal physical examination; 7 patients (5%) were judged to have needed admission but would have been discharged on the basis of ED evaluation; however, of these patients 2 developed rhabdomyolysis, 2 had recurrent seizures without sequelae, 1 had liver disease, 1 had history consistent with TIA, 1 had a history of stroke; 15% had recurrent seizures in the ED: 36 (11%) had 1 recurrent seizure and 12 (4%) had multiple seizures; recommends urine be dipped for blood to detect evidence of rhabdomyolysis	Limited follow-up of those patients discharged from the ED (181 [54%] of 333); 5 returned within 1 mo with a repeat seizure; follow-up based on medical records; did not capture those who presented to another ED or who died; does not provide data on the history of those patients with metabolic abnormalities; group with abnormal LP results not well described	III
Earnest et al ²⁸	Retrospective and prospective consecutive patients thought to have an alcohol withdrawal seizure	Abnormal head CT results	137 patients in the prospective arm, 122 in the retrospective arm; all patients were determined to have a "probable first alcohol withdrawal seizure"; 151 (58%) had an abnormal CT: 16 (6%) had a clinically significant intracranial lesion; clinical management was changed in 10 (4%) cases; 11 patients were alert with a normal neurologic examination; 7 (44%) of the 11 were alert with normal neurologic examination and no signs of head trauma	No follow-up; no other laboratory tests provided or alcohol levels	II
American College of Emergency Physicians, American Academy of Neurology, American Association of Neurological Surgeons, American Society of Neuroradiology ²⁹	Evidence-based practice guideline	Change in treatment (not in disposition)	Categorizes CT into emergent, urgent, and routine. Urgent are scans either in the ED or scheduled as part of the disposition from the ED; recommendations based on no class I articles, 18 class II, and 33 class III; emergent: performed when a serious structural lesion is suspected (new focal deficits, persistent altered mental status, fever, recent trauma, persistent headache, history of cancer, anticoagulation, suspicion or known HIV); should be considered in patients >40 y or partial-onset seizure; urgent: considered in patients who have completely recovered from their seizure and no clear-cut cause has been identified	No outcome data to support the recommendations	III

Evidentiary Table (continued).

Study	Design	Outcome Measure	Findings	Limitations	Class
Annegers et al ³⁰	Retrospective review of a prospectively collected database	Seizure recurrence	424 patients initially seen between 1935 and 1979; EEG obtained in 50% within 10 days; 257 had antiepileptic drug started at time of initial event; recurrence in 220/424 patients: 9% by 1 mo, 21% by 3 mo, 30% by 6 mo, 36% by 1 y, 48% by 3 y, 56% by 5 y; "idiopathic" had the most favorable outcome (26% at 1 y); history of perinatal injury had highest rate (92% by 1 y); 16% with a normal EEG had a recurrence in 1 y; abnormal neurologic examination predicted recurrence; recurrence risk at 1 y was similar with and without antiepileptic drug; initial partial seizure, abnormal EEG, abnormal neurologic examination increased chances of a recurrence	By definition, does not address symptomatic seizures; not all patients received the same diagnostic tests; CT results not provided; no discussion if patients were admitted or workup as an outpatient; no data on morbidity from treatment versus nontreatment; study did not address which patients were evaluated in the ED or recurrence within the first week	II
Hauser et al ³¹	Prospective cohort	Seizure recurrence	208 patients recruited within 24 h and interviewed within 30 d; recurrence risk was 14% at 1 y, 29% at 3 y, 34% at 5 y; remote symptomatic at greater risk than idiopathic seizures, 10% versus 26% respectively at 1 y; abnormal neurologic examination and normal EEG <i>did not</i> predict recurrence; Todd's paralysis did predict recurrence (76%); abnormal EEG predicted increased risk; antiepileptic drug treatment was not shown to affect recurrence rate (in fact, it was associated with an increased rate); increased recurrence associated with abnormal EEG, acute symptomatic seizure	By definition, does not address symptomatic seizures, implying that a workup was performed but that workup is not presented; observational study with no standardization of treatment; patients placed on antiepileptic drug had higher recurrence rate but design did not measure equality of groups, therefore no conclusion can be made; study did not address which patients were evaluated in the ED or had recurrence within the first week	II
Berg and Shinnar ³²	Meta-analysis	Seizure recurrence at 2 y	36% seizure recurrence rate at 2 y in prospective studies; increased risk associated with abnormal neurologic examination and abnormal EEG; 24% recurrence in idiopathic with normal EEG; 65% in remote symptomatic with abnormal EEG; partial seizures associated with an increased risk	By definition, does not address symptomatic seizures, implying that a workup was performed but that workup is not presented	I
FIRST Group ³³	Randomized, multicenter trial; excluded patients with acute symptomatic seizures	Seizure recurrence within 2 y	397 patients, aged 2 to 70 y; 36/204 not treated and 75/193 treated had recurrence (ie, 2.8 times higher risk of relapse if not treated); cumulative risk of recurrence at 2 y was 25%; 51% if not treated; however, in the treatment group, 20% stopped their antiepileptic drug; in this 20% the relapse rate was only 27%; age (<16 y) and EEG (presence of epileptiform abnormalities) were predictors of relapse	By definition, does not address symptomatic seizures, implying that a workup was performed but that workup is not presented; antiepileptic drug choice left to clinician; plasma levels in the therapeutic range had to be reached within 1 mo but no mention if levels remained therapeutic from that point on; 20% of treatment group stopped their antiepileptic drug although the group as a whole reported to have a lower relapse rate; no placebo group in the treatment group; no discussion of ED or initial management; patients with >1 seizure within 24 h were excluded	I
Carducci et al ³⁵	Convenience sample	Serum level	38 patients loaded with 18 mg/kg; a serum phenytoin level was >10 mg/L in 37 (97%) of 38 patients immediately after the infusion; in 29 (94%) of 31 patients at 4 h after infusion; no patient had a seizure recurrence but only 49% were followed up for 12 to 24 h after infusion	Adverse events not reported	III

Evidentiary Table (continued).

Study	Design	Outcome Measure	Findings	Limitations	Class
Kugler et al ³⁶	Meta-analysis	Serum levels	108 patients received IV fosphenytoin and 10 patients received IM fosphenytoin (>15 mg/kg); therapeutic levels were achieved within 10 min of rapid IV loading and within 30 min of slow IV or IM loading	Abstract	III
Leppik et al ³⁷	Convenience sample	Serum level and rate of recurrence	159 doses to 139 patients (15-18 mg/kg); 28 (100%) of 28 patients with an undetectable level achieved a therapeutic level after infusion; rate of seizure recurrence was similar in patients who did and did not have a seizure recurrence: 6% if antiepileptic drug withdrawal, 11% epilepsy cause unknown, 18% miscellaneous causes	Adverse events not reported	III
Leppik et al ³⁸	Multicenter, randomized, double-blind trial	Response latency	78 adult ED or ICU patients in status epilepticus; 89% versus 76% of seizures controlled with lorazepam versus diazepam ($P=NS$); adverse events in 13% and 12%, respectively	Small sample	I
Wilder et al ⁴⁰	Convenience sample	Serum level; control of status epilepticus	14 patients were loaded with 10.9-17 mg/kg intravenously and started on oral phenytoin 24 h later; 10 patients with status epilepticus were loaded intravenously with 8.1-16.6 mg/kg; at 12 h after the loading dose 9 (64%) of 14 patients had a therapeutic level, and no "major" seizures occurred after oral phenytoin was started; 9 (90%) of 10 patients had cessation of status epilepticus and a phenytoin level >10 mg/L within 30 min	Wide range of mg/kg dosing was used; adverse events were poorly reported; rate of seizure recurrence could not be calculated	III
Osborn et al ⁴²	Convenience sample	Serum level	44 patients; 94% had had a seizure within 24 h of presentation; loaded orally with 18-mg/kg capsules or suspension; 20 (48%) of 41 patients had a therapeutic serum level at 3-5 h after loading; 21 (55%) of 38 patients had a therapeutic serum level at 6-10 h after loading; no seizure recurrence in any patient >8 h postingestion observation period	45% had history of alcohol use within past 24 h and some had recognized alcohol withdrawal; limited follow-up: there were trends toward serum levels continuing to increase within the first 24 h; rate of seizure recurrence after 8 h not reported	III
Ratanakorn et al ⁴³	Prospective volunteer study and case series	Serum level	19 healthy volunteers and 14 patients with seizures; 18.7 mg/kg to males and 24.8 mg/kg to female patients with seizures; in volunteers and patients with seizures the average serum level was therapeutic in 2.62 ± 1.25 and 2.04 ± 0.44 h postingestion, respectively	Patients with recent seizures were studied; rate of seizure recurrence not reported	II
Record et al ⁴⁴	Retrospective, convenience sample	Serum level	20 patients; 15.4-22.8 mg/kg in 2-4 divided doses and given over 6-12 h; 16 (80%) of 20 patients had a documented serum level >10 mg/L at a mean of 10.75 h after the last dose	Rate of seizure recurrence not reported	III

Evidentiary Table (continued).

Study	Design	Outcome Measure	Findings	Limitations	Class
Wilder et al ⁴⁵	Convenience sample	Serum level	15 patients were given 1,000 mg in divided doses (400 mg, 300 mg, 300 mg) at 2 h intervals; 8 patients were given 1,000 mg as a single dose and another 38 were dosed in divided doses as above 5 (33%) of 15 patients and 10 (66%) of 15 patients had a serum level ≥ 10 within 8 h and 24 h of the first dose, respectively; no patient who received the loading dose in divided doses developed gastrointestinal upset; there were no "serious adverse reactions"	Dose administered was not weight based; rate of seizure recurrence not reported	III
Buchanan et al ⁴⁶	Prospective volunteer study	Serum level	12 volunteers were given 100 mg orally at 6 AM, noon, and 6 PM and another 12 were given 300 mg orally at 6 AM; the serum mean levels reached steady state at 7-8 d after starting medications regardless of the dosing method; 5 (20%) of 24 patients had a serum level ≥ 10 mg/L at that time	Dose administered was not weight based	II
Gugler et al ⁴⁷	Prospective	Serum level	6 volunteers on separate occasions were given 1-time doses of 300 mg orally and 300 mg intravenously, as well as 300 mg orally for 14 d; no patient on 300 mg orally for 14 d reached a serum level > 10 mg/L	Volunteer study; rate of seizure recurrence not reported	II
Svensmark et al ⁴⁸	Prospective	Serum level	4 volunteers plus 12 patients with seizures received oral maintenance doses between 200-700 mg/d; 6 patients with seizures received IV maintenance doses of 300-700 mg/d; in the patients receiving daily maintenance doses, it took 6-9 d to reach a level of 10 mg/L; it took 18 h for the serum level after oral dosing to reach the same levels as those after IV dosing	Rate of seizure recurrence not reported; adverse events not reported; poor reporting of data	III
Earnest et al ⁵²	Convenience sample	Serum level	200 patients; 500-1,500 mg; 200 (100%) of 200 patients had a serum phenytoin level > 10 mg/L; adverse events: 29 (15%) of 200 patients had local irritation; 3 (2%) of 200 patients had bradycardia; 4 (2%) of 200 patients had dysrhythmias	Rate of seizure recurrence not reported	II
Cranford et al ⁶¹	Convenience sample	Serum level; rate of seizure recurrence	139 patients were treated on 137 occasions for repetitive seizures and on 22 occasions for prophylaxis after subarachnoid hemorrhage with IV phenytoin (15-18 mg/kg); all patients given 1,000 mg regardless of weight, had a 2-h level ≥ 10 mg/L; with a dose of 18 mg/kg, almost all the patients had a level > 10 mg/L at 24 h after infusion; seizures were controlled in 80% of patients; if there were anoxic or metabolic disturbances, seizures were controlled in $< 40\%$ of patients; 46% developed hypotension	Poor reporting of time of seizure recurrence	II
Shaner et al ⁶⁵	Randomized, nonblinded trial	Cumulative seizure; time response latency; frequency of complications	36 consecutive ED patients in status epilepticus; cumulative convulsive time, response latency shorter for patients receiving phenobarbital; similar complication rates	Small sample size, nonblinded, single center	II

Evidentiary Table (continued).

Study	Design	Outcome Measure	Findings	Limitations	Class
Osorio and Reed ⁶⁷	Case series	Termination of status; complications	17 inpatients with refractory status epilepticus; 76% of patients received high-dose phenytoin, 38% of them stopped seizing; 70% of patients required phenobarbital; hypotension occurred in all phenobarbital patients, which responded to dopamine	Case series, small sample size, single center	III
Painter et al ⁶⁸	Randomized, single-blinded trial	End of seizure measured by EEG	59 neonatal ICU neonates with EEG-confirmed seizures; phenobarbital and phenytoin are equally effective in neonates (43% vs 45%); less than half of seizures were controlled by single drug alone	Single blinded, few patients, single center	II
Giroud et al ⁶⁹	Case series	Seizure termination	23 ED admissions for status epilepticus; age >2 y; IV valproic acid ended seizures within 20 min for 19 (83%) of 23 cases	Case series, small sample size, single center	III
Hovinga et al ⁷¹	Case series	Pharmacokinetic model of valproate to determine loading and maintenance dosing	3 pediatric patients; 20-mg/kg loading dose should produce a concentration of 75 mg/L; adjust dose on response and serum concentration	Case series, small sample size, single center	III
Limdi and Faught ⁷²	Case series	Seizure termination; changes in pulse rate, blood pressure, respiratory rate, levels of alertness; local IV site irritation	20 repetitive seizure patients receiving rapid infusion of IV valproic acid; infusion of IV valproic acid at rates of 33–555 mg/min was well tolerated; no serious adverse effects; may have contributed to hypotension in 2 patients	Case series, small sample size, single center	III
Sinha and Naritoku ⁷³	Case series	Changes in vital signs, dosing of other vasopressors, loading dose, rates, serum levels, adverse events	13 status epilepticus patients with hypotension who received IV valproate; valproate loading of patients with cardiovascular instability is well tolerated; only 30% of patients had seizures controlled	Nonrandomized, small sample size, single center	III
Stecker et al ⁷⁷	Nonrandomized trial	Absence of clinical or seizure on EEG for 12 h after treatment	16 adult inpatients with refractory status epilepticus; seizure control was not significantly different between propofol and barbiturate groups; mean time to seizure control for propofol was 2.6±0.75 min; mean time to seizure control for barbiturates was 123±33 min	Nonrandomized, small sample size, single center	III
Prasad et al ⁷⁸	Retrospective review	Absence of clinical or EEG seizure	14 ICU patients treated primarily with propofol; 6 ICU patients treated primarily with midazolam; seizure control was not significantly different between propofol and midazolam groups (64% vs 67% for clinical, 78% vs 67% for EEG); no significant difference in complications	Nonrandomized, small sample size, single center	III
Claassen et al ⁸⁰	Systematic review	Frequency of immediate seizure treatment failure (1–6 h after administration) and mortality	193 patients with refractory status epilepticus; patients treated with midazolam had more frequent breakthrough seizures and more frequent changes to other IV antiepileptic drugs; pentobarbital had lowest frequencies of breakthrough seizures and drug changes	Small number of cases; vast majority of patients treated with pentobarbital titrated to EEG; background suppression may be reason for good results for pentobarbital	III

Evidentiary Table (continued).

Study	Design	Outcome Measure	Findings	Limitations	Class
Claassen et al ⁸¹	Retrospective chart review	Elimination of clinical and EEG seizure activity	81 episodes of refractory status epilepticus treated with continuous IV midazolam; immediate seizure control with midazolam occurred in <1 h in >80% of the cases; however, breakthrough seizures, detectable only by EEG, occurred in more than half of the patients	All patients having continuous EEG may skew results	III
Krishnamurthy and Drislane ⁸²	Retrospective chart review	Relapse of clinical or electrographic seizures after medication discontinuation	44 episodes of refractory status epilepticus in 40 patients; patients with refractory status caused by significant toxic and metabolic derangements or anoxia were least likely to be effectively treated with IV pentobarbital compared with those with chronic epilepsy, infections, tumors, stroke, or trauma (91% vs 29%)	Data obtained from retrospective chart reviews	III
Quigg et al ⁸⁴	Survey	EEG response time	Average response time from EEG request to preliminary reading was 3 h; no clear consensus when emergent EEG is indicated between centers	Survey of accredited EEG laboratories may not reflect community practice; 46 respondents of 84 EEG laboratories reflects a 55% survey response rate	III
DeLorenzo et al ⁸⁹	Retrospective review of prospectively constructed database	Abnormal diagnostic test	48% of study patients (total 164) were found to have persistent electrographic seizures with continuous EEG monitoring	ICU population may not represent ED patient population; relationship to clinical outcome not clear	III
Bleck ⁹⁰	Expert opinion	Not applicable	Review of treatment for status epilepticus with recommendation of EEG monitoring for refractory status epilepticus	Opinion	III
Towne et al ⁹³	Retrospective review of prospectively created database	Abnormal diagnostic test	8% of comatose patients (total 236) in an ICU population were found to have unsuspected nonconvulsive status epilepticus	ICU population of questionable application to ED patients; relationship to outcome not clear	III
Lowenstein and Aminoff ⁹⁴	Retrospective observational	Abnormal diagnostic test	EEG-only seizure activity found in a few comatose ICU patients (5 of 46) who did not exhibit clinical seizure activity	ICU population of questionable application to ED patients; relationship to outcome not clear	III
Young et al ⁹⁵	Retrospective review	Abnormal diagnostic test	Retrospective review of 49 patients encountered over 3 y with abnormal continuous EEG monitoring suggestive of nonconvulsive status epilepticus; seizure duration and delay in diagnosis correlated with poor prognosis	ICU population of questionable application to ED patients	III

VA, Veterans Affairs; IV, intravenous; BUN, blood urea nitrogen; Mg, magnesium; MRI, magnetic resonance imaging; LP, lumbar puncture; CNS, central nervous system; TCA, tricyclic antidepressant; PML, progressive multifocal leukoencephalopathy; SMA-7, Sequential Multiple Analyzer-7; TIA, transient ischemic attack; NS, not significant.

APPENDIX A.

Literature classification schema.*

Design/ Class	Therapy [†]	Diagnosis [‡]	Prognosis [§]
1	Randomized, controlled trial or meta-analyses of randomized trials	Prospective cohort using a criterion standard	Population prospective cohort
2	Nonrandomized trial	Retrospective observational	Retrospective cohort Case control
3	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)	Case series Case report Other (eg, consensus, review)

*Note: some designs (eg, surveys) will not fit this schema and should be assessed individually.

[†]Objective to measure therapeutic efficacy comparing ≥2 interventions.

[‡]Objective to determine the sensitivity and specificity of diagnostic tests.

[§]Objective to predict outcome including mortality and morbidity.

APPENDIX B.

Approach to downgrading strength of evidence.

Downgrading	Design/Class		
	1	2	3
None	I	II	III
1 level	II	III	X
2 levels	III	X	X
Fatally flawed	X	X	X