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

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ABSTRACT

This clinical policy from the American College of Emergency Physicians is the revision of a 2004 policy on critical issues in the evaluation and management of adult patients with seizures in the emergency department.[1] A writing subcommittee reviewed the literature to derive evidence-based recommendations to help clinicians answer the following critical questions: (1) In patients with a first generalized convulsive seizure who have returned to their baseline clinical status, should antiepileptic therapy be initiated in the emergency department to prevent additional seizures? (2) In patients with a first unprovoked seizure who have returned to their baseline clinical status in the emergency

department, should the patient be admitted to the hospital to prevent adverse events? (3) In patients with a known seizure disorder in which resuming their antiepileptic medication in the emergency department is deemed appropriate, does the route of administration impact recurrence of seizures? (4) In emergency department patients with generalized convulsive status epilepticus who continue to have seizures despite receiving optimal dosing of a benzodiazepine, which agent or agents should be administered next to terminate seizures? A literature search was performed, the evidence was graded, and recommendations were given based on the strength of the available data in the medical literature.

INTRODUCTION

There is a diagnostic process for evaluating generalized convulsions. A variety of clinical conditions may lead to events that resemble convulsive seizures but in fact are not. Examples include the brief stiffening or rhythmic jerks that sometimes accompany syncope or concussion, rigors, psychogenic nonepileptic seizures, and many other clinical conditions. Even after thorough evaluation in the emergency department (ED), the correct categorization of a clinical event as a seizure may be difficult.

The terminology for seizures and epilepsy is not straightforward and continues to evolve. In this document, generalized convulsive seizure, or simply seizure, refers to generalized movements with unresponsiveness reflecting excessive synchronous cortical electrical activity. Patients in the ED may have seizures that are secondary to causes such as electrolyte disturbances, withdrawal, toxins, infections, central nervous system (CNS) mass lesions, or other etiologies; these are classified as acute symptomatic or provoked seizures. By definition, an acute symptomatic seizure occurs at the time of or within 7 days of an acute neurologic, systemic, metabolic, or toxic insult. A remote symptomatic seizure results from a CNS or systemic insult that occurred more than 7 days in the past. An unprovoked seizure occurs in the absence of acute precipitating factors and includes remote symptomatic seizures, as well as seizures that are not established to have a cause. Epilepsy is defined as recurrent unprovoked seizures.[2,3] Table 1 provides definitions and examples of provoked and unprovoked seizures.

Other than in the discussion on status epilepticus, antiepileptic medication in this document refers to a medication prescribed for seizure prevention, not the episodic use of agents such as benzodiazepines. For example, a benzodiazepine administered to decrease the occurrence of alcohol withdrawal seizures is not regarded as use of an antiepileptic medication in this document. A detailed review of the dosing and route of administration of benzodiazepines in seizing patients is outside the scope of this document; however, these dosing strategies have been studied extensively, particularly in the prehospital setting. A prehospital study compared dosing of 10 mg intramuscular midazolam to 4 mg intravenous (IV) lorazepam administered in the prehospital environment for status epilepticus in adults and in children weighing greater than 40 kg and noted equivalent efficacy.[4]

Table 1. Classification of seizures.

Classification	Definition	Examples
Provoked seizure acute symptomatic seizure	Provoked seizure equivalent to acute symptomatic seizure; seizure occurs at time of or within 7 days of an acute neurologic, systemic, metabolic, or toxic insult	Seizures from hyponatremia or other electrolyte abnormalities, withdrawal, toxic ingestions, encephalitis, CNS mass lesions, and many others
Unprovoked seizure including remote symptomatic seizure	Seizure occurs without acute precipitating factors; unprovoked seizures include but are not limited to remote symptomatic seizures if seizure is thought to result from CNS or systemic insult that occurred more than 7 days in the past	Idiopathic seizures; epilepsy (if recurrent); seizure attributed to history of stroke, traumatic brain injury, or other past events

CNS, central nervous system.

The American College of Emergency Physicians' (ACEP) 2004 clinical policy on seizures[1] addressed 2 critical questions on laboratory testing and neuroimaging: (1) 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? (2) Which new-onset seizure patients who have returned to a normal baseline require a head computed tomography (CT) scan in the ED? The committee agreed that these areas were no longer controversial and did not re-address these questions in the current draft. Laboratory testing and neuroimaging are also discussed in several other recent guidelines.[5-7]

METHODOLOGY

This clinical policy was created after careful review and critical analysis of the medical literature. Searches of MEDLINE, MEDLINE InProcess, Cochrane Systematic Review Database, and Cochrane Database of Clinical Trials were performed. All searches were limited to English-language sources, human studies, and adults. All searches excluded pediatric or children, head trauma, brain mass or brain tumor, and immunocompromised immune system. Specific key words/phrases and years used in the searches are identified under each critical question. In addition, relevant articles from the bibliographies of included studies and more recent articles identified by committee members and reviewers were included.

This policy is a product of the ACEP clinical policy development process, including expert review, and is based on the existing literature; when literature was not available, consensus of emergency physicians was used. Expert review comments were received from emergency physicians, neurologists, and individual members of the American Epilepsy Society, the American Academy of

Neurology, the Epilepsy Foundation of America, the National Association of Epilepsy Centers, and ACEP's Quality and Performance Committee. The draft was also open to comments from ACEP membership through *EM Today*. Their responses were used to further refine and enhance this policy; however, their responses do not imply endorsement of this clinical policy. Clinical policies are scheduled for revision every 3 years; however, interim reviews are conducted when technology or the practice environment changes significantly. ACEP was the funding source for this clinical policy.

Assessment of Classes of Evidence

All articles used in the formulation of this clinical policy were graded by at least 2 subcommittee members and assigned a Class of Evidence. In doing so, subcommittee members assigned design classes to each article, with design 1 representing the strongest study design and subsequent design classes (eg, design 2, design 3) representing respectively weaker study designs for therapeutic, diagnostic, or prognostic clinical reports, or meta-analyses (Appendix A). Articles were then graded on dimensions related to the study's methodological features, including but not necessarily limited to randomization processes, blinding, allocation concealment, methods of data collection, outcome measures and their assessment, selection and misclassification biases, sample size, and generalizability. Using predetermined formulas related to the study's design, methodological quality, and applicability to the critical question, articles received a final Class of Evidence grade (ie, Class I, Class II, Class III, or Class X) (Appendix B). Articles identified with fatal flaws or that were not applicable to the critical question received a Class of Evidence grade "X" and were not used in formulating recommendations for this policy. Grading was done with respect to the specific critical questions; thus, the level of evidence for any one study may vary according to the question. As such, it was possible for a single article to receive different Classes of Evidence as different critical questions were answered from the same study. Question-specific Classes of Evidence grading may be found in the Evidentiary Table included at the end of this policy.

Translation of Classes of Evidence to Recommendation Levels

Strength of recommendations regarding each critical question were made by subcommittee members using results from strength of evidence grading, expert opinion, and consensus among subcommittee members according to the following guidelines:

Level A recommendations. Generally accepted principles for patient care that reflect a high degree of clinical certainty (ie, based on evidence from 1 or more Class of Evidence I or multiple Class of Evidence II studies).

Level B recommendations. Recommendations for patient care that may identify a particular strategy or range of strategies that reflect moderate clinical certainty (ie, based on evidence from 1 or more Class of Evidence II studies or strong consensus of Class of Evidence III studies).

Level C recommendations. Recommendations for patient care that are based on evidence from Class of Evidence III studies or, in the absence of any adequate published literature, based on expert consensus. In instances where consensus recommendations are made, "consensus" is placed in parentheses at the end of the recommendation.

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

When possible, clinically oriented statistics (eg, likelihood ratios, number needed to treat [NNT]) were presented to help the reader better understand how the results may be applied to the individual patient. For a definition of these statistical concepts, see Appendix C.

This policy is not intended to be a complete manual on the evaluation and management of patients with seizures but rather a focused examination of critical issues that have particular relevance to the current practice of emergency medicine.

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 adequate empirical data 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 or management options available to the emergency physician. ACEP clearly recognizes the importance of the individual physician's judgment and patient preferences. Rather, this guideline defines for the physician those strategies for which medical literature exists to provide support for answers to the critical questions addressed in this policy.

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

Inclusion Criteria. This guideline is intended for adult patients aged 18 years and older presenting to the ED with generalized convulsive seizures.

Exclusion Criteria. This guideline is not intended for pediatric patients, patients with complex partial seizures, patients with acute head trauma or multisystem trauma, patients with brain mass or brain tumor, immunocompromised patients, or patients with eclampsia.

CRITICAL QUESTIONS

1. In patients with a first generalized convulsive seizure who have returned to their baseline clinical status, should antiepileptic therapy be initiated in the ED to prevent additional seizures?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations.

(1) Emergency physicians need not initiate antiepileptic medication* in the ED for patients who have had a first *provoked* seizure. Precipitating medical conditions should be identified and treated.
(2) Emergency physicians need not initiate antiepileptic medication* in the ED for patients who have had a first *unprovoked* seizure without evidence of brain disease or injury.
(3) Emergency physicians may initiate antiepileptic medication* 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.

* Antiepileptic medication in this document refers to medications prescribed for seizure prevention.

Key words/phrases for literature searches: seizures, seizure disorder, emergency department, adults, antiepileptic medications, new onset seizure, first seizure, epilepsy, immediate treatment, delayed treatment, and variations and combinations of the key words/phrases; years January 2000 through December 2009, and January 2010 through April 2011.

The physician must weigh several issues in the decision to initiate antiepileptic medication in patients who have had an apparent first seizure. As described previously, there is a diagnostic process for evaluating convulsive events. Ultimately, the decision to initiate treatment depends on 2 variables: (1) the probability that the event clearly represented a seizure, and (2) the risk of seizure recurrence.

The question of risk of a subsequent seizure is complex. The epidemiologic literature on seizure recurrence is derived primarily from epilepsy studies that track seizure recurrence over months to years, not days to weeks. Studies of seizure recurrence typically exclude patients with provoked seizures. There is little information addressing seizure recurrence in ED patients over shorter timelines. The challenge to the clinician is offering patients an accurate assessment of their risk and involving them in decisionmaking.[8] Initiation of antiepileptic medication should be considered separately for patients with an acute symptomatic (provoked) seizure and patients with an unprovoked seizure.

Diagnosis and treatment of any underlying medical condition is of primary importance. To our knowledge, there are no studies that have investigated benefit from initiation of antiepileptic medication in the ED in patients with provoked seizures from acute medical conditions who have returned to their baseline clinical status. The clinical principle is that such a patient needs treatment of the primary condition and does not benefit from initiation of an antiepileptic medication. Significant medical history such as cancer or immunosuppression may prompt additional diagnostic testing. Though this policy does not specifically address neuroimaging, immediate noncontrast computed tomography (CT) is possibly useful, especially when there is an abnormal examination result, predisposing history, or focal onset of the seizures.[1,6] If a structural lesion is discovered, this should be weighed in decisionmaking.

There remains division within the medical community on the issue of initiating antiepileptic medication for the patient who has experienced a first unprovoked seizure. When a patient presents to the ED after a seizure, a thorough history may reveal that what is thought to be a first seizure may in fact be one of several similar events. If other events have occurred, the possibility of recurrent unprovoked seizures, that is, epilepsy, should be considered and might influence treatment decisions. Practice patterns of neurologists often include obtaining EEG, magnetic resonance imaging, or other studies not typically available in the ED, with the idea that additional information may allow risk stratification and aid in the decision to initiate medication.[5,7,9] Approximately one third to one half of patients with a first unprovoked seizure will have a recurrent seizure within 5 years.[10,11] However, for patients with a single unprovoked seizure, outpatient studies indicate that initiation of treatment within days to weeks after a seizure prolongs time to a subsequent event, but outcomes at 5 years are no different.[12,13] In these studies, it was estimated that for patients with a first unprovoked generalized seizure, it would be necessary to treat 14 patients to prevent a single seizure recurrence within the first 2 years.[13] For patients with 2 or 3 recurrent unprovoked seizures on separate occasions, the risk of seizure recurrence within 5 years increases substantially from about one third to about three quarters of patients.[10] For the patient with a first unprovoked seizure, the strategy of waiting until a second seizure before initiating antiepileptic medication is considered appropriate.

Patients with a first seizure may have a past medical history of stroke, trauma, tumor, or other CNS disease or injury, and thus the seizure may represent a remote symptomatic seizure, a type of unprovoked seizure. Many of these conditions are thought to provide anatomic or physiologic substrate for recurrent seizures. A history of CNS injury (inclusive of stroke and traumatic brain injury) increases the possibility of further seizures and should be weighed in decisionmaking. Because seizure recurrence rate is higher in these patients, treatment is considered appropriate after 1 seizure.[9] For patients with evidence of preexisting brain disease or injury and an abnormal EEG result, the NNT to prevent a single additional seizure in the following first year is approximately 5.[13]

2. In patients with a first unprovoked seizure who have returned to their baseline clinical status in the ED, should the patient be admitted to the hospital to prevent adverse events?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. Emergency physicians need not admit patients with a first unprovoked seizure who have returned to their clinical baseline in the ED.

Key words/phrases for literature searches: seizures, seizure disorder, emergency, adults, new-onset seizures, first seizure, epilepsy, prognosis, hospital admission, and variations and combinations of the key words/phrases; years January 2000 through August 2011.

The available literature considers seizure recurrence and mortality within 24 hours after initial seizure as adverse events. Conceivably, some of these outcomes might be mitigated with hospital admission. Although studies demonstrate the general risk of seizure recurrence and mortality for patients during various time intervals after initial seizure, the immediate need for admission and observation after ED evaluation has not been specifically addressed. Since the last clinical policy[1] was published, 1 Class II study[14] evaluated the probability of early seizure recurrence in the first 24 hours after initial seizure, 1 Class III observational study[15] addressed the appropriateness of discharge after initial ED workup, and 2 Class III reviews[7,16] offered recommendations.

There is limited evidence available that addresses mortality and seizure recurrence in the 24 hours after a first seizure. The majority of evidence focuses on recurrence and mortality during a longer time frame in unprovoked seizures.[17] Seizures from many different etiologies are included in other studies and make them less generalizable to a population of patients with unprovoked seizures. However, they should serve to heighten emergency physicians' awareness of the increased risk for seizure recurrence and mortality in patients with provoked seizures and prompt investigation to establish the etiology of a seizure when possible.[18-21]

In terms of early seizure recurrence, Choquet et al[14] published a Class II study of 1,025 patients admitted to 2 urban EDs with provoked and unprovoked seizures, with the goal of observing early seizure recurrence at 6 and 24 hours. The mean time to first early seizure recurrence was 121 minutes (SD 96 minutes; median 90 minutes). More than 85% of early seizures recurred within 360 minutes. In subgroup analysis, nonalcoholic patients with new-onset seizures had the lowest early seizure recurrence (9.4%), and alcoholic patients with a history of seizures had the highest early seizure recurrence (25.2%; P=.01). Univariate analysis found age greater than or equal to 40 years, alcoholism, hyperglycemia, and Glasgow Coma Scale (GCS) score less than 15 to be associated with early seizure recurrence.[14]

With regard to appropriateness for discharge, Breen et al[15] published a Class III study of 232 patients with possible seizures who were referred to a first-time seizure clinic; 53% were referred from the ED. Three percent of patients experienced an injury related to the seizure, and 19% were admitted. Antiepileptic therapy was not immediately started after the first seizure. Nine percent of the total 232 patients experienced a repeated seizure while waiting for their 6-week seizure clinic appointment. Admission status among the patients with a repeated seizure was not specified. All of the discharged patients had a GCS score of 15. No data were reported about early seizure recurrence in the 19% of patients who were admitted. This study is further limited because 18% of patients were lost to follow-up.

Dunn et al[16] proposed a disposition algorithm for patients with uncomplicated first generalized seizure that uses glucose, CT scan (if indicated and done), ECG, and blood tests for renal function, electrolyte level, calcium level, and blood count. They proposed that the patient with normal results may be discharged, provided the following criteria are satisfied: full recovery without abnormal neurologic signs and/or symptoms, normal vital signs, received advice not to drive, availability of a responsible adult to watch him or her, follow-up arranged, and follow-up likely. A practice guideline echoes these recommendations, though the algorithm has not been prospectively studied.[7]

3. In patients with a known seizure disorder in which resuming their antiepileptic medication in the ED is deemed appropriate, does the route of administration impact recurrence of seizures?

Patient Management Recommendations

Level A recommendations. None specified.

Level B recommendations. None specified.

Level C recommendations. When resuming antiepileptic medication in the ED is deemed appropriate, the emergency physician may administer IV or oral medication at their discretion.

Key words/phrases for literature searches: seizures, seizure disorder, epilepsy, status epilepticus, emergency department, adults, outcomes, anticonvulsants, antiepileptic drugs, intravenous administration, oral administration, parenteral administration, intranasal administration, intramuscular administration, rectal administration, oral loading and antiepileptic, and variations and combinations of the key words/phrases; years January 2000 through September 2011.

The emergency physician is often faced with determining how best to resume antiepileptic medications in patients with known seizure disorders. The goal of this critical question was to determine the current state of the literature on oral versus parenteral dosing strategies for seizure patients regardless of their current medications. Dosing strategies often become an issue in the ED under one of 2 circumstances: (1) the patient could in theory benefit from rapid administration of prescribed medication (loading) to improve the likelihood of a safe, seizure-free discharge, or (2) the patient has a contraindication to oral administration medications. Patients who might potentially benefit from loading in the ED include those noted to have a subtherapeutic serum level of medication or to be noncompliant with a medication when a serum level cannot be readily assessed.

The literature reviewed for this clinical question is limited because the only studies found did not use early seizure recurrence as a primary outcome measure. Most studies investigated loading dose strategies with attainment of drug levels rather than for the purpose of preventing seizure recurrences. Serum levels of the drug were used as a surrogate outcome measure for efficacy. The exceptions are ED studies of

Table 2. Loading dose and route of administration strategies for antiepileptic medications in the ED when resuming antiepileptic medication in the ED is deemed appropriate.* This information may not be consistent with FDA labeling.

Drug (With Selected References)	Loading Dose and Route of Administration	Adverse Effects	Seizure Recurrence Rate	Notes
Carbamazepine[24] Tegretol Equetro	8 mg/kg oral suspension, single oral load; IV not available	Common drowsiness, nausea, dizziness	Not studied	Oral tablet has slow/erratic absorption
Gabapentin[25] Neurontin Gralise	900 mg/day oral (300 mg tid) for 3 days; IV not available	Somnolence, dizziness, ataxia, and fatigue	No difference from slower load	Adjunct for partial seizures
Lacosamide[26] Vimpat	Oral and IV formulations available and safe; loading dosages not studied	Mild to moderate dizziness, headache, back pain, somnolence, and injection site pain	Not studied	Adjunct for partial seizures; withdrawal seizures with abrupt discontinuation
Lamotrigine[27] Lamictal	6.5 mg/kg single oral load if on lamotrigine for >6 mo without a history of rash or intolerance in the past and only off lamotrigine for <5 days; IV not available	Mild, transient nausea	Not studied	Frequent and serious rashes; do *not* load if history of rash or patient not previously on lamotrigine
Levetiracetam[28,29] Keppra	1,500 mg oral load; rapid IV loading safe and well tolerated in doses up to 60 mg/kg	Fatigue, dizziness, rarely pain at infusion site	No seizures within 24 h of loading in study of oral loading	
Phenytoin[23,30,31] Dilantin Phenytek	20 mg/kg divided in maximum doses of 400 mg every 2 h orally, or 18 mg/kg IV at maximum rate of 50 mg/min	IV is faster to load but more serious adverse effects than oral, including hypotension, bradyarrhythmias, cardiac arrest, and extravasation injuries	No significant difference in recurrence between oral and IV loading	Oral is cheaper but takes >5 h to reach therapeutic levels; IV requires filter, infusion pump
Fosphenytoin[30,31] Cerebyx	18 PE/kg IV at maximum rate of 150 PE/min; IM administration possible	Fewer adverse events in head-to-head analysis between IV fosphenytoin and IV phenytoin load		Generic now available with significant cost reduction
Valproate[32] Depacon	Up to 30 mg/kg IV at max rate of 10 mg/kg/min IV	Transient local irritation at injection site	Not studied	

h, hour; *IM*, intramuscular; *IV*, intravenous; *kg*, kilogram; *mg*, milligram; *min*, minute; *mo*, month; *PE*, phenytoin equivalent; *tid*, 3 times a day.
*As a resource for drug recognition by the practitioner, both the generic and trade names are provided for each of the medications in the table. Also included is information on available routes of administration.

oral loading of phenytoin.[22,23] Most of the patients enrolled in the phenytoin studies were no longer actively seizing. Seizure recurrence after antiepileptic medication loading in these studies was an infrequent event, so even these phenytoin studies are not powered to determine a difference in seizure prevention. In the meantime, studies about attaining therapeutic serum levels might suffice as a surrogate outcome measure for efficacy. Information from studies about a variety of agents is summarized in Table 2; the information may not be consistent with Food and Drug Administration (FDA) labeling.

In summary, for antiepileptic medications given in the ED setting for patients with a known seizure disorder in which resuming their antiepileptic medication is deemed appropriate, there is a lack of evidence to support one route of administration (oral versus parenteral) over the other in terms of preventing early recurrent seizure. Pending future studies, the choice of administration is at the discretion of the emergency physician. Though loading with antiepileptic medication is commonly done, there is lack of evidence to support or refute this practice.

4. In ED patients with generalized convulsive status epilepticus who continue to have seizures despite receiving optimal dosing of a benzodiazepine, which agent or agents should be administered next to terminate seizures?

Patient Management Recommendations

Level A recommendations. Emergency physicians should administer an additional antiepileptic medication in ED patients with refractory status epilepticus who have failed treatment with benzodiazepines.

Level B recommendations. Emergency physicians may administer intravenous phenytoin, fosphenytoin, or valproate in ED patients with refractory status epilepticus who have failed treatment with benzodiazepines.

Level C recommendations. Emergency physicians may administer intravenous levetiracetam, propofol, or barbiturates in ED patients with refractory status epilepticus who have failed treatment with benzodiazepines.

Key words/phrases for literature searches: seizures, seizure disorder, epilepsy, emergency department, adults, outcome,

benzodiazepines, anticonvulsants, and variations and combinations of the key words/phrases; years January 2000 through December 2009, and January 2010 through April 2011.

Up to 5% of adults with epilepsy will have 1 episode of status epilepticus in their lifetime. Generalized status epilepticus can also occur in patients without epilepsy as a result of clinical conditions such as infection, hemorrhage, or trauma. For this critical question, status epilepticus is defined as unremitting convulsive seizure activity lasting 20 minutes or more or intermittent seizures without regaining full consciousness. A generalized convulsive seizure lasting for 5 minutes has been proposed as defining status epilepticus,[33] but studies cited here generally used a longer period as inclusion criteria. These are typically patients who have failed first-line treatment with optimal dosing of benzodiazepines. Patients who continue to have generalized convulsive status epilepticus should be given an additional anticonvulsant agent. Simultaneously, one should search for treatable causes of status epilepticus, including, but not limited to, hypoglycemia, hyponatremia, hypoxia, drug toxicity, and systemic or CNS infection. If a provoking cause is discovered for status epilepticus, condition-specific treatment should be given. Other etiologies such as ischemic stroke, intracerebral hemorrhage, and withdrawal syndromes also need to be addressed if present.

The Neurocritical Care Society's Status Epilepticus Guideline Writing Committee recommended urgent control of seizures with any of the following: valproate, levetiracetam, or phenobarbital, in addition to phenytoin/fosphenytoin. Valproate was recommended for both emergent treatment of seizures and refractory status epilepticus based on high-level evidence.[34] The European Federation of Neurological Societies' evidence-based guideline for status epilepticus in adults recommended anesthetic doses of midazolam, propofol, or barbiturates for status epilepticus refractory to benzodiazepines and phenytoin.[35]

Although some studies show benefit of valproate over phenytoin, the available data do not conclusively demonstrate the superiority of any drug in treating refractory status epilepticus. Adverse drug effects, drug shortages, patient allergies, and inconvenience of delivery have made newer agents more attractive in some cases than fosphenytoin and phenytoin for second-line treatment. Regardless of the agent chosen, the goal is to control seizure activity as quickly as possible.

Phenytoin/Fosphenytoin

Traditionally, the drug used for status epilepticus after benzodiazepines has been phenytoin and, more recently, fosphenytoin. A survey published in 2003 of 106 neurologists of the Critical Care and Epilepsy Sections of the American Academy of Neurology found that 95% recommended phenytoin or fosphenytoin for seizures that do not respond to benzodiazepines.[36] However, phenytoin and its prodrug, fosphenytoin, have numerous drawbacks. The 1998 Veterans Affairs cooperative study showed only a 56% success in terminating status epilepticus when diazepam followed by phenytoin was used.[37] Although uncommon, especially for fosphenytoin, both phenytoin and fosphenytoin may cause cardiovascular compromise with rapid infusion. In addition, these agents may not effectively treat toxin-induced seizures.

Valproate

IV valproate has been advocated as an alternative to phenytoin and even as first-line therapy for status epilepticus. IV valproate has been shown to be at least as effective as phenytoin for refractory status epilepticus, with potentially fewer adverse effects. In a Class II study, Misra et al[38] treated 68 patients with convulsive status epilepticus with valproate or phenytoin either as first- or second-line therapy in a crossover design if initial treatment failed. In both groups, valproate was more effective than phenytoin in controlling seizures. As a second-line agent, seizure control was achieved in 79% (15/19) of patients with valproate versus 25% (3/12) with phenytoin, an absolute risk reduction of 54% (95% confidence interval [CI] 23% to 85%; NNT 1.9). In another Class II study, Agarwal et al[39] randomized patients with status epilepticus refractory to 20 mg of IV diazepam to receive 20 mg/kg of either valproate (40 mg per minute) or phenytoin (50 mg per minute). Within 20 minutes of infusion, both groups had equal success in seizure cessation: 88% with valproate and 84% with phenytoin. However, 12% of the phenytoin group experienced hypotension versus none in the valproate group.[39]

Class III studies support the efficacy of valproate for status epilepticus. Peters and Pohlmann-Eden[40] studied a case series of 102 adult patients who received IV valproate (4 mg/kg to 16 mg/kg) for status epilepticus or acute repeated seizures. The patients with status epilepticus responded within 15 minutes in 77% of cases; those with repeated seizures had an 85% response rate. The study by Limdi et al[41] followed 63 adult patients with refractory status epilepticus. Patients were chosen to receive IV valproate at an average dose of 30 mg/kg and a rate up to 500 mg per minute. In more than half of the cases (63%), status epilepticus ceased, as demonstrated clinically or by EEG. Another Class III study showed that valproate (30 mg/kg infused at 6 mg/kg per hour followed by infusion at rate 1 to 2 mg/kg per hour) stopped seizures within an hour in 88% of cases of status epilepticus refractory to IV diazepam and intramuscular phenobarbital.[42] Gilad et al[43] performed a Class III trial of adults with status epilepticus or acute repetitive seizure patients. Patients were randomized to valproate at 30 mg/kg versus phenytoin 18 mg/kg over 20 minutes. Of the 74 patients enrolled, 88% in each group had resolution of seizures within 20 minutes of infusion. Valproate appears to be safe and effective in refractory status epilepticus and was not associated with hypotension. In conclusion, it appears that IV valproate is an acceptable treatment option for refractory status epilepticus and may work as well as phenytoin.

Levetiracetam

Another drug with efficacy in managing status epilepticus is levetiracetam. Tripathi et al[44] performed a Class III prospective study of 82 patients older than 14 years and with refractory status epilepticus who had already received lorazepam and phenytoin.

Patients were assigned to either valproate or levetiracetam, both at 30 mg/kg IV load delivered at 5 mg/kg per minute. Seizure cessation, evaluated blindly, after infusion was similar in both groups (valproate 68%; levetiracetam 73%). Multiple observational studies lend credence to the efficacy of levetiracetam in status epilepticus. Ruegg et al[45] published a Class III retrospective experience in treating 24 patients with status epilepticus. Seizures ceased with administration of IV levetiracetam in 67% of cases. In a Class III observational study, a 1,500 mg IV load of levetiracetam led to resolution of status epilepticus in 7 of 9 patients within 30 minutes.[46] Uges et al[47] performed a Class III study with levetiracetam 2,500 mg IV over 5 minutes for status epilepticus patients who had failed benzodiazepines and subsequent phenytoin or valproate. Seizures ceased in 10 of 11 patients, but time to cessation was not clear and 3 of those patients experienced prolonged seizures during the 24-hour period. There were no serious adverse effects attributable to the infusion. Both Tripathi et al[44] and Uges et al[47] technically used levetiracetam after initial treatment with benzodiazepines followed by phenytoin or valproate; therefore, it is unclear whether levetiracetam would work as second line, rather than third, in refractory generalized convulsive status epilepticus.

More recent studies, all Class III, have examined retrospectively the use of levetiracetam for status epilepticus that has failed initial treatment with benzodiazepines. A small study by Berning et al[48] showed only a 38% efficacy within 30 minutes with IV levetiracetam at a dose of 20 mg/kg. Two larger studies showed efficacies of 44% (95% CI 29% to 59%) within 3 minutes of drug administration[49] and as high as 73% (95% CI 58% to 88%) extending to 24 hours postadministration.[50] The only adverse effects noted were nausea and transient transaminitis in individual separate cases.[48] All of this experience suggests a potential role for levetiracetam as treatment for status epilepticus refractory to benzodiazepines, but definite proof awaits prospective randomized controlled trials.

Propofol

Propofol is increasingly used in refractory status epilepticus, but controlled data are limited. A Class III study showed that propofol was as effective as pentobarbital in treating status epilepticus refractory to benzodiazepines, but the propofol group required fewer mechanical ventilation days, at 4 compared with 14 in the pentobarbital arm.[51] In this study, propofol was bolus loaded at 2 mg/kg, followed by a 5 mg/kg per hour infusion. Carley and Crawford[52] published a Class III systematic review of 6 studies showing that propofol may be effective at terminating the motor or EEG findings of status epilepticus. In those studies, the bolus dosing of 2 mg/kg was followed by a 3 to 7 mg/kg per hour infusion. In a Class III series, propofol caused less hypotension, defined as requiring pressors, than barbiturates, 42% versus 77%.[53] Development of formal recommendations for the use of propofol in status epilepticus awaits future studies.

Barbiturates

Barbiturates, notably phenobarbital, have also been recommended for treatment of status epilepticus but have fallen out of favor.[54] In the only Class I study, the Veterans Affairs cooperative trial of refractory status epilepticus, initial treatment with phenobarbital as initial medication was effective in terminating seizures 58.2% of the time.[37] Several Class III studies attest to its efficacy in status epilepticus. In a 1988 study, phenobarbital was found to be as effective as a combination of diazepam and phenytoin for untreated convulsive status epilepticus.[55] In a study by Claassen et al,[53] pentobarbital (bolus 13 mg/kg; infusion of 2 to 3 mg/kg per hour) was more successful than propofol (2 mg/kg bolus; infusion of 3 to 4 mg/kg per hour) in terminating status epilepticus, 73% versus 92%. The main limitation of barbiturates is the increased adverse effects profile, particularly hypotension and respiratory depression.

Table 3. IV medication options if generalized convulsive status epilepticus continues after optimal benzodiazepine administration; many of these are off-label use of the drugs and may be inconsistent with FDA label recommendations.*

Drug and Selected References	Dose	Adverse Effects
Phenytoin[37] (Phenytek) (Dilantin)	18-20 mg/kg administered no faster than 50 mg/kg; some recommend to increase to total 30 mg/kg if seizures continue	Soft tissue injury with extravasation, hypotension, cardiac dysrhythmias, purple glove syndrome
Fosphenytoin[36] (Cerebyx)	18-20 PE/kg administered no faster than 150 PE/min	Hypotension, cardiac dysrhythmias
Valproate[32,39] (Depacon)	20 to 30 mg/kg at rate of 40 mg/min (faster administration rates also reported)	Dizziness, thrombocytopenia, liver toxicity, hyperammonemia
Leviteracetam[44-46] (Keppra)	30–50 mg/kg IV load at 100 mg/min	Nausea, rash
Propofol[51] (Diprivan)	2 mg/kg; may repeat in 3-5 min; maintenance infusion of 5 mg/kg/h	Injection site pain, heart failure, respiratory support required
Phenobarbital[37,55] (Luminal) (and other barbiturates)	10-20 mg/kg; may repeat 5-10 mg/kg at 10 min (dosage differs for other barbiturates)	Respiratory depression, hypotension

h, hour; *kg*, kilogram; *mg*, milligram; *min*, minute; *PE*, phenytoin equivalent.
*As a resource for drug recognition by the practitioner, both the generic and trade names are provided for each of the medications in the table.

Conclusion

Evidence suggests that valproate works as well in status epilepticus after benzodiazepine administration as a second-line agent as phenytoin and fosphenytoin. The advantage of valproate over phenytoin or fosphenytoin is that it can be given more quickly, with fewer adverse effects.[41] Therefore, valproate may be considered for refractory convulsive status epilepticus if benzodiazepines fail as an alternative to phenytoin or fosphenytoin.

Making definitive recommendations on the treatment of refractory status epilepticus is difficult. There is a lack of prospective controlled randomized trials in this area. Newer agents, such as levetiracetam and propofol, may have a role in refractory status epilepticus that remains to be defined. Levetiracetam is safe, with low incidence of hypotension and respiratory depression when given as an IV load. Propofol can be useful in intubated patients who continue to seize, provided they do not exhibit hypotension. Barbiturates, although effective, are difficult to deliver quickly without causing hypotension.[53] In addition, there is the issue of multifactorial etiologies for status epilepticus from an acute condition that presents undifferentiated to the ED. Table 3 summarizes IV medication options if generalized status epilepticus continues after optimal benzodiazepine administration.

Future Directions

Basic questions remain to be addressed by prospective studies enrolling ED patients in contemporary clinical practice. It is unknown how successful emergency physicians are in delineating provoked seizures from unprovoked seizures. Multiple studies address seizure recurrence and mortality over time periods of months to years in patients with an apparent unprovoked seizure. Though these studies provide an idea of seizure recurrence risk, further studies are needed to address early seizure recurrence and early morbidity and mortality in ED patients. With regard to the question of patients with known seizure disorder who present to the ED after a seizure, future research should focus on the patient-centered outcome of recurrence of seizures in a time frame that is applicable to the ED (ie, hours or days, not months or years). Such research will help to determine whether it is necessary to load these patients in the ED. Recommendation of the optimal agent for treatment of refractory status epilepticus awaits further studies. Medications such as lacosamide may be useful in treating status epilepticus and need more study. Future studies might also include EEG performed in the ED to detect subtle or transformed status epilepticus, sometimes referred to as nonconvulsive status epilepticus.

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Relevant industry relationships are those relationships with companies associated with products or services that significantly impact the specific aspect of disease addressed in the critical questions.

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Appendix A. Literature classification schema.*

Design/Class	Therapy†	Diagnosis‡	Prognosis§
1	Randomized, controlled trial or meta-analysis of randomized trials	Prospective cohort using a criterion standard or meta-analysis of prospective studies	Population prospective cohort or meta-analysis of prospective studies
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)

*Some designs (eg, surveys) will not fit this schema and should be assessed individually.
†Objective is to measure therapeutic efficacy comparing interventions.
‡Objective is to determine the sensitivity and specificity of diagnostic tests.
§Objective is to predict outcome, including mortality and morbidity.

Appendix B. Approach to downgrading strength of evidence.

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

Appendix C. Likelihood ratios and number needed to treat.*

LR (+)	LR (−)	
1.0	1.0	Useless
1-5	0.5-1	Rarely of value, only minimally changes pretest probability
10	0.1	Worthwhile test, may be diagnostic if the result is concordant with pretest probability
20	0.05	Strong test, usually diagnostic
100	0.01	Very accurate test, almost always diagnostic even in the setting of low or high pretest probability

LR, likelihood ratio.
*Number needed to treat (NNT): number of patients who need to be treated to achieve 1 additional good outcome; NNT=1/absolute risk reductionx100, where absolute risk reduction is the risk difference between 2 event rates (ie, experimental and control groups).

Evidentiary Table.

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Turner and Benger[7]	2009	Professional society guideline	Literature review; search of MEDLINE, CINAHL, EMBASE, and Cochrane	None specified	Echoes recommendations of Dunn et al[16]	Systematic review but limited explanation of search strategy, articles included and excluded; no data or evidentiary table	III
Hauser et al[10]	1998	Prospective cohort	Observational	Seizure recurrence	Risk of seizure recurrence 33% within 5 y after a first unprovoked seizure; if 2 or more unprovoked seizures, risk increases to about 75%	Possible subject dropouts; time frame to initiation of therapy does not reference ED encounter	III
Musicco et al[11]	1997	Multicenter, randomized, open label	Randomized observational trial	Seizure recurrence	Starting treatment after a first unprovoked seizure reduces risk of seizures for 2 y but does not affect outcomes at 5 y	Did not address treatment initiated in ED ("immediate" treatment meant drug therapy initiated within 7 days); EEG results influenced decision to treat in some patients; treatment decision used data not available in ED	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Choquet et al[14]	2008	Prospective, observational study	All patients >18 y with seizure presenting to 2 EDs; all patients observed for at least 6 h; if admitted followed for 24 h; if discharged followed via hospital databases, patient/family follow-up, social service databases; compared patients early seizure recurrence to those with none, using bivariate and multivariate analysis; predictive model was created	Early seizure recurrence at 6 h and 24 h	1,025 patients admitted to the EDs with seizure, follow-up data available for all but 12 patients; mean time to first seizure recurrence was 121 (SD 96 min) (median 90 min), >85% of early seizure recurrence occurred within 360 min; nonalcoholic patients with new-onset seizures had lowest early seizure recurrence (9.4%) and alcoholic patients with history of seizures had highest early seizure recurrence (25.2%), *P*=.01; univariate analysis found age ≥40 y, alcoholism, hyperglycemia, and GCS score <15 to be associated with early seizure recurrence; multivariate analysis created scoring tool	Not specifically designed to study need for hospitalization; did not study treatment in ED, CT findings, or psychosocial conditions in relation to early seizure recurrence	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Breen et al[15]	2005	Prospective, observational	Descriptive study	Described epidemiology, clinical characteristics, and initial management of adults with new-onset seizure	232 patients in final analysis referred to clinic, 124 (53%) via the ED; no laboratory test was significantly associated with final diagnosis of seizure; in ED patients referred to seizure clinic CT result was abnormal in 1 patient (only 17% of patients received CT, missing data in 19% of these); 19% admitted to hospital, 3% had injury related to seizure; 18% (42 patients) did not show to seizure clinic; 9% had seizure before seizure clinic visit in 6 wk; final diagnosis of seizure in 52% of patients referred to clinic (other diagnoses=syncope [28%], nonepileptic seizure [2%], hyperventilation [1%], panic attack [1%], arrhythmia [1%]); 42 patients (22%) had CT in clinic with abnormal results in 8 patients (19%) and report not available in 8 patients (19%); 56% of all initial seizures found to be related to alcohol, recreational drugs, or sleep deprivation	Concluded that adults with first-time seizure can be discharged and managed on an outpatient basis unless persistent abnormal neurologic examination results, abnormal investigation results or observations are present; not clear how data support this; recurrence was 9% in 6 wk; no mortality data reported; no explanation of whether patients who failed follow-up to seizure clinic were followed for recurrence, morbidity, and mortality	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Dunn et al[16]	2005	Review article	Literature review with goal of management algorithm; search of MEDLINE, CINAHL, EMBASE, and Cochrane	None specified	Creates algorithm that uses glucose, CT (with specific indications), ECG, and blood chemistries to determine need for admission; if all of the above results are normal then discharge criteria include: full recovery without abnormal neurologic signs/symptoms, normal vital signs, has received advice to not drive, has a responsible adult to watch him/her, has follow-up arranged and will likely go to follow-up	Systematic review but limited explanation of search strategy, articles included/excluded, no data or evidentiary table	III
Gallop[23]	2010	Secondary review	Phenytoin use in the ED	Efficacy of IV versus oral phenytoin in the ED	In the nonemergency situation it is possible to achieve therapeutic serum concentrations after an oral loading dose; however, the time to reach therapeutic levels after oral loading is much longer than after IV loading; not possible to comment on the efficacy of oral compared with IV loading for preventing seizures since rate of seizure recurrence in the studies is low; prevention of further seizures not used as an outcome measure; no consensus if oral loading is best achieved with a single dose or in divided doses; low-quality studies suggest that IV loading may be associated with more frequent or severe adverse effects, which may depend on dose, concentration, and rate of administration	One reviewer; no inclusion/exclusion noted; no methods to combine data from studies; does summarize key data on critical question	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Purcell et al[24]	2007	Prospective cohort	Safety/efficacy of rapid load of oral suspension of carbamazepine at 8 mg/kg in the ED	Serum levels and adverse effects	36 patients; loading was 93% successful based on mean 3-h carbamazepine level; adverse effects occurred in 58% of patients, most commonly drowsiness (26%) and nausea (23%); other adverse effects included dizziness, nystagmus, abdominal pain, vomiting, ataxia, and double vision	Study of oral suspension only; tablets not studied (thought to be unreliably absorbed)	III
Fisher et al[25]	2001	Double-blind, parallel group, dose-initiation trial with placebo lead-in	Gabapentin slow initiation (300 mg on day 1, 600 mg on day 2, then 900 mg/day) or gabapentin rapid initiation (900 mg/day)	Adverse events, tolerability	No clinically meaningful differences in incidence of fatigue, ataxia, or somnolence; the slow initiation group experienced slightly more dizziness than the rapid initiation group (15.2% of 276 subjects versus 10.5% of 294 subjects)	Efficacy not assessed, study looked at only 5 days of treatment; however, no differences in number of seizures between the 2 groups	III
Biton et al[26]	2008	Double-blind, double-dummy, randomized	IV versus oral lacosamide in partial-onset seizures	Adverse events, tolerability	59 patients; adverse effects included dizziness, headache, back pain, somnolence, and injection site pain; tolerability profile of IV lacosamide was consistent with that of oral lacosamide; all adverse effects were considered mild or moderate; no serious adverse effects reported	Indicated for partial seizures only; inpatient study; patients not loaded with lacosamide	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Lardizabal et al[27]	2003	Observational pilot safety study	Oral loading of lamotrigine in patients off of lamotrigine for 5 days and no history of rash with previous use	Serum concentration, adverse effects	24 patients; no serious adverse effects; all patients reached target blood levels; 2 had mild, transient nausea	Case series of epilepsy monitoring unit patients; not ED patients	III
Koubeissi et al[28]	2008	Observational pilot safety study	Oral loading of levetiracetam	Adverse effects, serum concentration, seizure	37 patients; 89% denied adverse effects; other 11% reported transient irritability, imbalance, tiredness, or lightheadedness; no seizures occurred within 24 h of loading; all patients were able to be discharged 3 to 30 h after loading	Retrospective case series of epilepsy monitoring unit patients, not ED patients	III
Wheless et al[29]	2009	Prospective open-label safety study	Rapid IV loading of levetiracetam in pediatric patients	Serum levels, adverse events	45 patients divided equally into 3 dosing groups; 20, 40, and 60 mg/kg (corresponding maximum doses of 1, 2, and 3 g); postinfusion serum levetiracetam concentrations were 14 to 189 mg/mL; no significant changes in blood pressure, no local infusion site reactions, and no ECG abnormalities	Pediatric patients and some young adults but no subset analysis done for adults aged 18 y and older; single-center, inpatient study	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Swadron et al[30]	2004	Prospective, randomized controlled trial	Oral phenytoin vs IV phenytoin vs IV fosphenytoin	Time to therapeutic level, adverse drug events, length of stay	45 patients; mean times to reach therapeutic drug concentrations were 5.62 h, 0.24 h, and 0.21 h in the PO, IV phenytoin, and IV fosphenytoin groups, respectively; a total of 17, 27, and 32 adverse drug events were observed, respectively, with significantly fewer events in the PO group (P=.02, P=.01); the average time to safe ED discharge was significantly shorter for the IV groups compared with the PO group	Not blinded; completion and dropouts not reported; small sample size but large effect size; clinical research center used to observe patients may not be generalizable to ED	III
Rudis et al[31]	2004	Cost-effectiveness analysis of randomized prospective trial	Oral phenytoin vs IV phenytoin vs IV fosphenytoin	Adverse events, cost, length of stay	The mean number of adverse events per patient for oral phenytoin, IV phenytoin, and IV fosphenytoin was 1.06, 1.93, and 2.13, respectively; mean time to safe ED discharge in the 3 groups was 6.4 h, 1.7 h, and 1.3 h; cost per patient was $2.83, $21.16, and $175.19, respectively	Same study from Swadron et al, 2004; cost analysis obsolete now that fosphenytoin is generic	III
Limdi et al[32]	2007	Prospective open-label safety study	Safety of rapid IV loading of valproate	Local and systemic tolerability, serum levels	40 patients; no significant changes in heart rate or blood pressure, local irritation occurs but is transient	Case series of epilepsy monitoring unit patients, not ED patients; safe and well tolerated at rates up to 10 mg/kg/min and doses up to 30 mg/kg	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Meierkord et al[35]	2010	Structured review	Structured review of MEDLINE, EMBASE, and CENTRAL 1996–2005 to create recommendations for the treatment of status epilepticus in adults by the European Federation of Neurological Societies	Control of refractory status epilepticus that has failed with benzodiazepines	Recommendation is for phenytoin after benzodiazepines; if continued refractory, proceed to barbiturates, midazolam, or propofol	Phenytoin considered first-line treatment with benzodiazepines	III
Claassen et al[36]	2003	Survey	Surveyed 106 critical care and epilepsy members of the American Academy of Neurology	Drug preferences for status epilepticus after initial treatment with benzodiazepines fails	95% (95% CI 91% to 99%) preferred phenytoin or fosphenytoin as second line; there was no agreement on third-line treatment	Only 29% of members responded; survey was in 2001	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Treiman et al[37]	1998	Randomized controlled trial	Patients with generalized status epilepticus randomized to 1 of 4 treatments IV: lorazepam, phenobarbital, diazepam and phenytoin, or phenytoin alone	Cessation of seizure activity within 20 min	N=384; success rates: lorazepam 65%, phenobarbital 58%, diazepam and phenytoin 56%, phenytoin 44%; pairwise, lorazepam was significantly superior to phenytoin	Not clear whether refractory to initial treatment with benzodiazepines	I
Misra et al[38]	2006	Randomized controlled study	Treatment of convulsive status epilepticus with IV phenytoin 18 mg/kg vs valproate 30 mg/kg	Control of seizures up to 24 h after infusion	In convulsive status epilepticus, IV valproate (23/35, 66%) was more effective than phenytoin (14/33; 42%) with NNT 4.3 (95% CI 2.2 to 395); more respiratory depression and hypotension in phenytoin group	Not blinded; unclear what if any initial treatment patients received before study drugs	II

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Agarwal et al[39]	2007	Randomized controlled trial; patients matched for age and gender	In patients with benzodiazepine-refractory status epilepticus, IV loading 20 mg/kg of valproate or phenytoin	Seizure cessation based on motor activity or EEG within 20 min; and adverse effects	Both drugs efficacious with status epilepticus cessation: valproate 88%, phenytoin 84%; 12% of phenytoin group became hypotensive	No blinding to treatment group; negative study	II
Peters and Pohlmann-Eden[40]	2005	Retrospective observational series	102 patients who received IV valproate at range of 4 mg/kg to 16 mg/kg in seizure emergencies	Interruption of seizures within 15 min	102 patients entered; valproate efficacious in 27/35 or 77% (95% CI 63% to 91%) in those with status epilepticus	Protocol not completely standardized; not all patients in status epilepticus	III
Limdi et al[41]	2005	Retrospective case series	Reviewed records of patients with status epilepticus who received IV valproate at doses ranging from 10 mg/kg to 78 mg/kg	Cessation of seizures on EEG or neurologic examination during 12 h postinfusion	Valproic acid efficacy was 63% (95% CI 51% to75%) without serious adverse effects	Valproate was first-line drug in 22% of cases; no standardization of dose or medication with benzodiazepines	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Chen et al[42]	2009	Prospective nonrandomized observational trial	Patients with refractory convulsive status epilepticus who failed IV diazepam and IM phenobarbital were given valproate 30 mg/kg IV at 6 mg/kg/h	Cessation of motor activity within 1 h of starting infusion	Valproate controlled seizures within 1 h in 88% (95% CI 78% to 97%)	No control; children included in data; endpoint not completely clear	III
Gilad et al[43]	2008	Prospective, nonrandomized, open-label, controlled study	Patients with status epilepticus or acute repetitive seizures were given either IV phenytoin 18 mg/kg or valproate 30 mg/kg	Cessation of seizures within 20 min	Enrolled 74 patients, with control of seizures in 88% regardless of treatment group	Study drugs were first-line treatment; no benzodiazepines administered; no randomization; unbalanced design	III
Tripathi et al[44]	2010	Prospective nonrandomized trial	Convenience allocation of patients with refractory status epilepticus (had received lorazepam and phenytoin already); assigned to IV valproate 30 mg/kg vs levetiracetam 30 mg/kg	Cessation of seizure (EEG) after infusion	82 patients entered, with equal efficacy between the 2 treatments; valproate 68% vs levetiracetam 73%	No standardization of first-line treatment; finances used for allocation	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Ruegg et al[45]	2008	Retrospective case series	Chart review of patients who received levetiracetam 20 mg/kg IV for seizures	Cessation of seizure by EEG	In the refractory status epilepticus group, efficacy was 67% (16/24) [95% CI 48% to 86%]	No standardization of first-line treatment	III
Fattouch et al[46]	2010	Prospective observational series	Elderly (aged ≥65 y) patients with video EEG-documented status epilepticus loaded with levetiracetam 1,500 mg in ≤15 min	Cessation of seizure based on video EEG monitoring	9 patients treated: 8/9, 89% (95% CI 68% to 100%) had reduction in seizures; in 7/9, 78% (95% CI 51% to 100%) of seizures ceased	Levetiracetam may have been used first line for status epilepticus; unclear what was initial treatment; no controls; mixture of convulsive and nonconvulsive status epilepticus	III
Uges et al[47]	2009	Prospective open-label trial of patients with status epilepticus refractory to benzo-diazepines	Patients with status epilepticus refractory to benzodiazepines were given levetiracetam 2,500 mg IV over 5 min	Safety; patients were observed 24 h for cardiac, respiratory, dermal, or allergic adverse events	11 patients were enrolled, with 10 (83% [95% CI 62% to 100%]) having seizures terminate within 24 h; 1 patient with flushing and 1 patient with unrelated oxygen desaturation	Not efficacy study; drug given inconsistently with respect to other anticonvulsants; levetiracetam technically was given third line after benzodiazepines and valproate or phenytoin	III
Berning et al[48]	2009	Retrospective case series	Chart review of 8 patients who received levetiracetam 20 mg/kg IV for status epilepticus after benzodiazepines (1 group)	Termination of seizure activity on EEG within 30 min	Efficacy was 3/8 (38%), 95% CI 4% to 72%	Only 8 patients; benzodiazepine dose was only 2 mg lorazepam; older population (aged ≥63 y)	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Eue et al[49]	2009	Retrospective case series	Chart review of 43 patients with status epilepticus who failed benzodiazepines and received IV levetiracetam	Termination of seizure activity clinically or on EEG within 3 min	Efficacy was 19/43 (44%), 95% CI 29% to 59%	Dosage not standardized; average age of population 67 y	III
Gamez-Leyva et al[50]	2009	Retrospective case series	Chart review of 33 adult patients with status epilepticus who had not responded to IV benzodiazepines and received a median of 1,000 mg IV levetiracetam over 15 to 30 min	Absence of seizures within 24 h of drug infusion	Efficacy was 24/33 (73%), 95% CI 58% to 88%	Only 6 (18%) patients had generalized as opposed to focal status epilepticus; unclear how quickly the drug worked	III
Rossetti et al[51]	2011	Randomized controlled multicenter trial	Prospective; patients with status epilepticus refractory to benzodiazepines were randomized to starting IV doses of propofol 2 mg/kg vs pentobarbital 5 mg/kg titrated upward based on EEG results	Control of seizures using EEG within the first day; tolerability	Same efficacy; propofol 43% vs pentobarbital 22% (NS); difference in tolerability	Underpowered study (n=23)	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Carley and Crawford[52]	2002	Structured review	MEDLINE search from 1966 through 2001 identified 6 studies (4 studies with adults, 1 study with children, 1 study with unknown patient population) addressing whether IV propofol is effective in resistant status epilepticus	Cessation of seizures	No standardization of treatment; propofol appeared to quickly terminate seizures (2.6 min in 1 series)	Cases identified retrospectively; only 1 study with a control group (total N=16); very small sample sizes	III
Claassen et al[53]	2002	Structured review	Searched MEDLINE and OVID for studies of refractory status epilepticus treated with IV midazolam, propofol, or pentobarbital	Immediate treatment failure at 1 and 6 h after initial loading; adverse effect was measured as hypotension requiring pressors	193 patients in 28 studies were included; fewer treatment failures in pentobarbital group at 8% vs propofol 27%, or midazolam 20% ($P<.01$); pressors were required more often in the pentobarbital group, 77% vs propofol 42% and midazolam 30%	None of the studies were prospective randomizations; all were open label without blinded observers	III

Evidentiary Table (continued).

Study	Year	Design	Intervention(s)/ Test(s)/Modality	Outcome Measure/Criterion Standard	Results	Limitations/Comments	Class
Shaner et al[55]	1988	Randomized controlled trial	Patients with generalized convulsive status epilepticus treated with IV phenobarbital vs combined diazepam and phenytoin	Time spent in active convulsions	N=36; quicker resolution of seizure activity in the phenobarbital (5.5 min) vs the diazepam/phenytoin (15 min) group but not significant	Result was $P<.10$	III

CI, confidence interval; *CINAHL*, Cumulative Index to Nursing and Allied Health Literature; *CT*, computed tomography; *ECG*, electrocardiogram; *ED*, emergency department; *EEG*, electroencephalogram; *EMBASE*, Excerpta Medical database; *g*, gram; *GCS*, Glasgow Coma Scale; *h*, hour; *IM*, intramuscular; *IV*, intravenous; *kg*, kilogram; *mg*, milligram; *min*, minute; *mL*, milliliter; *NNT*, number needed to treat; *NS*, not significant; *PO*, by mouth; *SD*, standard deviation; *vs*, versus; *wk*, week; *y*, year.