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# Benzodiazepine Selection in the Management of Status Epilepticus
## A Review

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**ABSTRACT**
The choice and route of administration of benzodiazepines for the treatment of acute status epilepticus (SE) in both prehospital and emergency department (ED) settings often vary by provider and institution. Prehospital and ED care often involves intramuscular, intravenous, or rectal administration of these medications. Diazepam, lorazepam, and midazolam are available as parenteral formulations in the United States. A literature review of clinical trials and SE treatment guidelines was conducted in an attempt to identify which benzodiazepine and route are the best treatment option for adult patients with SE. For initial treatment of SE in adults, intravenous lorazepam is the recommended drug of choice. However, evidence suggests that intramuscular midazolam has at least equal efficacy in prehospital settings and may be more appropriate for use in this environment. Despite the support of multiple clinical trials and treatment guidelines, inconsistencies in the treatment of acute SE continue to occur in both the prehospital and ED settings.
**Key words:** benzodiazepine, seizure, status epilepticus

ONE MILLION emergency department (ED) visits annually in the United States are due to seizure activity, accounting for 1% of total ED visits (Pallin, Goldstein, Pelletier, Green, & Camargo, 2008). Although the majority of these are self-limiting, 120,000–200,000 of these cases are status epilepticus (SE; Lowenstein, 2006). Status epilepticus is a seizure event lasting more than 5 min, or repeated seizure activities for more than 5 min without full recovery of neurological status between events as defined by the Neurocritical Care Society (NCCS) (Brophy et al., 2012). It often presents as generalized tonic-clonic movements or rhythmic jerking of the extremities and is associated with mental status impairment. Nonconvulsive, or "subtle SE," can also occur and may present as fine motor movements or tremors that can be best diagnosed on an electroencephalogram (EEG).

Status epilepticus carries a 19%–27% mortality rate and a strong association with poor outcomes (Brophy et al., 2012). Survival is

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improved with a shorter duration of seizure activity, suggesting the importance of urgent seizure cessation (Drislane et al., 2009). Prolonged length of seizure time is also associated with poor functional outcomes, and patients who receive insufficient therapy have higher mortality rates (Brophy et al., 2012). This phenomenon is commonly described as that "time is brain." Neuroprotective measures are essential for the initial cessation of seizure activity, and providers must be aware of the most efficacious medications and routes of administration that are available.

The choice of therapy for the initial treatment of acute SE is widely variable in the United States (Cook et al., 2012). Benzodiazepines are recommended as the initial treatment option by experts, although the evidence for the specific drug and route of administration is limited (Brophy et al., 2012). In fact, a survey of international experts revealed that there was not a unanimous agreement on any of three simulated patient cases (Riviello et al., 2013). Because no clear standard exists, selection of the particular agent should account for ease of administration, care environment (i.e., prehospital vs. in-hospital), and drug characteristics. To elucidate these differences, we undertook a review of the available options and evidence for use in adult patients.

## ROUTES OF ADMINISTRATION

Acute seizure activity is usually accompanied by altered mental status and/or motor deficits that render oral administration of rescue medication impossible. Treatment of acute SE therefore requires the use of medications that do not need to be swallowed. Several benzodiazepines are available that meet this criterion and have been tested with a number of nonoral routes. In the United States, diazepam, lorazepam, and midazolam are all available in a sterile solution that can be given via either intravenous or intramuscular injection (National Institutes of Health, 2014). Diazepam is also available as a Food and Drug Administration (FDA)-approved gel for rectal administration, although in theory the injectable formulations could also be given rectally. Clonazepam is available in quick-dissolving wafers that can be placed in the mouth and absorbed via buccal membranes (Meierkord et al., 2010). Intranasal administration of midazolam has also been shown effective for achieving control of seizures when administered as the concentrated injectable formulation via an atomizer device (Wolfe & McFarlane, 2006).

When evaluating route of administration, it is important to note that when nasal, buccal, rectal, and oral routes are used, the larger proportion of drug enters the enteric circulation and is metabolized in the liver before reaching systemic blood (Katzung, Masters, & Trevor, 2012). This means that dosing must be adjusted accordingly when compared with injections and that onset of activity will be delayed. However, intranasal and rectal routes require fewer technical steps and are attractive options for laypersons and prehospital providers.

Intramuscular administration of benzodiazepines leads to more rapid systemic levels of medication than those given via oral, enteric, and rectal routes because the drug bypasses the first-pass metabolism in the liver (Katzung et al., 2012). Lorazepam has a slower distribution from muscle tissue than midazolam and diazepam, which makes it less ideal for administration via this route (Katzung et al., 2012). Administration of medication via intramuscular injection is more practical than achieving intravenous access in a patient who is seizing. Commercial autoinjectors containing diazepam and midazolam are not yet available for general medical use in the United States but are used in military applications as part of an antidote for nerve gas (National Institutes of Health, 2014).

Laypersons, family members, and nonmedical caregivers are often involved in the early care of patients who are seizing, and ready-to-use formulations are important for success in these cases. Rectal diazepam gel is currently the only commercially available nonoral product.

## DRUG COMPARISON

See Table 1 for a comparison of clinical and chemical properties of this class of drugs. Benzodiazepines must enter the brain to terminate seizure activity. Regardless of the route of administration, all drugs in this class cross the blood–brain barrier readily once they reach systemic circulation. Although midazolam and diazepam have the highest affinity for the central nervous system (CNS) based on observed volume of distribution among the parenteral agents, their rapid onset of 3–5 min is followed by a secondary redistribution into blood and body tissues (Katzung et al., 2012). This drop in concentrations of cerebrospinal fluid approximately 30 min after administration could lead to recurrence of seizure activity (Katzung et al., 2012). Lorazepam has a slightly slower onset due to delayed entry into the CNS, but secondary redistribution does not occur, which leads to more prolonged concentrations in the brain.

Each of these agents is metabolized in the liver, and metabolites are then excreted in bile and urine (Brunton, Chabner, & Knollmann, 2011). Among the parenteral agents, lorazepam is the only compound that is converted directly to inactive metabolites during its first stage of biotransformation. Diazepam, midazolam, and clonazepam are all converted in varying amounts to metabolites that are also pharmacologically active (Brunton et al., 2011). Clinically, this can lead to disproportionately extended duration of activity and increased accumulation with repeat dosing in patients with diminished liver function because multiple stages of metabolism are required to terminate drug activity. As such, lorazepam should be preferred in patients with reduced hepatic function, such as elderly patients and those with cirrhosis or hepatitis.

Consideration for physical characteristics is also important in the understanding of drug delivery. Midazolam is the only agent that is inherently soluble in aqueous solution without requiring the use of concentrated propylene glycol (Brunton et al., 2011). Concentrated solutions of diazepam and lorazepam are both viscous and hyperosmolar as a result of this excipient. The high viscosity makes them less ideal for use in intranasal atomizer devices, and the high osmolarity contributes to injection site pain. Finally, lorazepam injection has poor chemical stability at room temperature (McMullan et al., 2013), making storage in ambulances and emergency kits logistically challenging due to lack of refrigeration.

## PRIMARY LITERATURE IN ADULTS

In addition to consideration of the physical and logistical characteristics of each agent, it is important to evaluate their individual efficacy in patients who are actively seizing. A search was conducted using CINAHL, MEDLINE, and Cochrane Library databases on studies involving benzodiazepine use and routes of administration for management of acute SE. All studies through 2014 were reviewed; exclusive pediatric studies and those not published in English were excluded. See Table 2 for an overview of the selected studies and their results. In addition, the most current SE treatment guidelines in both the United States and Europe were reviewed.

Leppik et al. (1983) conducted the first study with a head-to-head comparison of benzodiazepine use in patients with SE. A double-blind randomized trial was conducted with 81 patients. Patient selection included adults with convulsive, partial, absence, partial complex, and partial elementary seizure activity. Those with terminal illness, cardiac arrhythmia, hypotension, metabolic disorders (i.e., hypoglycemia), childbearing potential, and a history of sensitivity to benzodiazepines, as well as those who had received treatment of SE prior to study referral, were excluded. A 2-ml study drug of either 5 mg of diazepam or 2 mg of lorazepam was provided in an amber syringe used to blind the provider. A second equivalent dose of the same study drug was provided in the event and a repeat dose was indicated after 10 min for recurrent seizures. Most patients were given a loading dose of phenytoin 30 min after initial treatment regardless of recurrence. Because no

**Table 1.** Comparison of benzodiazepines

| Drug | Dosing | Recommended maximum single doses | Available formulations | Role in therapy | Notes |
|---|---|---|---|---|---|
| Lorazepam | Intravenous: 0.1 mg/kg<br>May repeat every 5 min | 4 mg | 2 mg in 1-ml injection | Drug of choice for the intravenous treatment of SE | Contains propylene glycol<br>Dilute 1:1 with saline prior to intravenous push |
| Midazolam | Intramuscular, IV or intranasal: 0.2 mg/kg<br>May repeat every 10 min | Weight less than 40 kg: 5 mg<br>Weight 40 kg or more: 10 mg | 10 mg in 2-ml injection<br>2 mg in 2-ml injection<br>5 mg in 5-ml injection | Drug of choice for intramuscular or intranasal administration if intravenous access not available | Use an atomizer device for nasal administration<br>Split dose per each nostril, maximum 1 ml per side |
| Diazepam | Intravenous: 0.15 mg/kg<br>Rectal (age based)<br>2–5 years: 0.5 mg/kg<br>6–11 years: 0.3 mg/kg<br>More than 11 years: 0.2 mg/kg | 10 mg | 10 mg in 2-ml injection | Rectal formulation available for layperson caregivers | Intravenous formulation contains propylene glycol<br>Rectal formulation should not be repeated; alternate route is recommended if SE persists |

*Note*: SE = status epilepticus.

**Table 2.** Adult studies of benzodiazepine efficacy

| Citation | Patient population | Intervention | Results | Limitations | Conclusions |
|---|---|---|---|---|---|
| Leppik et al., 1983 | 70 patients with SE in a single ED | 5 mg of diazepam intravenously vs. 2 mg of lorazepam intravenously, repeated as necessary one time | Seizure cessation: 76% with diazepam, 89% with lorazepam; not statistically significant | Small study; comorbidities not well matched | Lorazepam should be considered at least equivalent to diazepam |
| Treiman et al., 1998 | 518 patients from 22 hospitals | Four different intravenous regimens: lorazepam alone, phenobarbital alone, phenytoin alone, and diazepam plus phenytoin | Lorazepam superior to phenobarbital; all other analyses showed no significant difference | Most patients were older men; definition of SE was 20 min of activity | Lorazepam was most effective in paired comparison and took the least amount of time to infuse |
| Alldredge et al., 2001 | 205 prehospital patients in the San Francisco area | Intravenous doses of 5 mg of diazepam, 2 mg of lorazepam, or placebo | Active treatment was better than placebo for cessation and resulted in fewer complications; duration was shorter with lorazepam | Single center; delays in intravenous access not reported | Lorazepam was favored, and prehospital treatment of seizure was safer than placebo |
| Silbergleit et al., 2012 | 893 patients throughout the United States | 4 mg of lorazepam intravenously vs. 10 mg of midazolam via intramuscular autoinjector | Similar rates of seizure cessation and adverse effects, shorter "time to drug" in the intramuscular group | Autoinjector not commercially available, subtle SE not included | Intramuscular midazolam is at least as effective as intravenous lorazepam and is easier to administer in the prehospital setting |

*Note.* SE = status epilepticus.

clinical standard for benzodiazepine administration existed, it was considered ethically sound to provide treatment with either diazepam or lorazepam. Convulsive SE was defined as three or more generalized seizures within an hour without recovery, absence status as confused state with spikes on an EEG, partial complex status as confused with clinical seizures and/or EEG spikes, and elementary status as partial seizures without loss of consciousness. Retrospectively, only 70 patients fit all criteria and were selected for study; 33 were treated with diazepam and 37 with lorazepam, with no statistical difference in age or type of seizure. Seizure activity ceased with a single dose of diazepam in 58% of 33 episodes compared with 78% of 37 episodes after lorazepam administration, which did not reach statistical significance. In patients with recurrent seizures requiring a second dose, six of 13 patients in the diazepam group experienced seizure cessation versus four of eight patients in the lorazepam group, also not reaching statistical significance. Overall, treatment with diazepam was successful 76% of the time in patients who were given either one or two doses and 89% of the time in patients treated with lorazepam. There was no significant difference noted in the onset of action, measured by the time the drug was given until the time of seizure cessation. Adverse effects were also studied between the two groups including respiratory depression/arrest, sedation, and hypotension, which were similar between the groups in approximately 12% of patients. Although the comparison of efficacy between intravenous diazepam and lorazepam did not reach statistical significance, Leppik et al. (1983) concluded that lorazepam was "at least as effective as diazepam in the initial treatment of SE" (p. 1454). A recommendation was made for further clinical experience to determine if lorazepam should replace diazepam for initial treatment. Patient characteristics and comorbidities were not well matched among the treatment arms as the authors mentioned that several patients in the lorazepam group had significant comorbidities; such matching issues are common among research involving emergency interventions. Although it was a small sample size, this double-blind study was a welcome addition to the medical literature and sparked the conversation of alternate benzodiazepine use in patients with SE.

To follow, Treiman et al. (1998) conducted a large-scale, multicenter, double-blind study on patients with SE at 16 Veterans Affairs hospitals and six university hospitals between 1990 and 1995. Patients were considered to be in SE that presented with seizure activity for more than 10 min or two or more generalized convulsive seizures without any full recovery in between. Patients in subtle SE who were in a persistent comatose state with ictal changes on the EEG with or without convulsive movements were also included in the study. Patients younger than 18 years, those who were pregnant, those requiring surgical intervention, and those with specific contraindications to the administration of benzodiazepine use were excluded. Blood work was obtained prior to administration to screen for antiepileptic drugs. Drug kits containing lorazepam, phenobarbital, phenytoin, and diazepam followed by phenytoin were numbered randomly and distributed to several locations within the treatment sites. Patients selected for the study were treated with the lowest numbered treatment kit at the closest location. Each drug kit was identical and contained three treatment boxes in the event that repeat treatment was needed. Continuous EEG monitoring was performed if available, as well as frequent vital signs and documentation of level of consciousness and seizure activity. Treatment was considered successful if seizure activity ceased within 20 min of treatment and there was no recurrence at 20–60 min posttreatment. A total of 518 patients were studied, the majority of them being male veterans with a mean age of 58 years. A total of 384 patients presented with convulsive SE and 134 with subtle SE. Drug dosage, drug serum concentration, length of drug infusion time, drug side effects, and treatment outcome (successful or unsuccessful) were all recorded for each

patient. A variation was found in the frequency of successful treatment among the four treatments studied. Lorazepam was successful in 52.2% of patients, phenobarbital in 49.2%, diazepam followed by phenytoin in 43.1%, and phenytoin alone in 36.8%. A paired comparison between lorazepam and phenobarbital revealed lorazepam to be effective more often with a statistically significant $p$ value of 0.001. Recurrence of SE was noted in 11% of patients, and there were no significant differences in the rates of recurrence among the four treatments. Side effects were evaluated, and although hypotension requiring treatment occurred more in the subtle SE group, there was no significant difference in side effects among the four treatments. Outcomes 30 days posttreatment were evaluated; the subtle SE group had a higher mortality and inpatient hospitalization rate, but no significant differences between the four treatment groups were appreciated. The authors concluded their study with the recommendation of using intravenous lorazepam for initial management of patients with SE because it was the most effective drug in paired comparisons and took the least amount of time to infuse. Regardless of which drug was used, treatment was only effective in two thirds of patients; the authors identified this as a need for the development of more effective therapies. The population studied was lacking in variation, being that the majority of patients were older and male, but the study did have a large sample size. In addition, the criterion for SE diagnosis of 20 min or more of seizure activity is not consistent with more current guidelines now available. Overall, this was a well-designed study that provided valuable information for treatment guidelines and set the stage for additional studies.

Historically, there has been very little literature on out-of-hospital treatment; this was addressed in a 2001 study comparing lorazepam, diazepam, and placebo for the treatment of SE in the prehospital setting (Alldredge et al., 2001). This randomized, double-blind trial investigated not only a comparison of the two different benzodiazepines but also the efficacy and safety of treating patients with SE prior to hospital arrival. Paramedics of the San Francisco Department of Public Health and 10 area hospitals were involved in the trial. Between 1994 and 1999, 205 adult patients presenting with tonic-clonic seizure activity in SE were enrolled in the study. Status epilepticus in this particular study was defined as "continuous or repeated seizure activity for more than five minutes without recovery of consciousness" (p. 632). For the study, we excluded patients with concurrent bradycardia, hypotension, atrioventricular blocks, or asthma or chronic obstructive pulmonary disease, pregnant patients, patients with tachyarrhythmias, and patients with a history of or sensitivity to benzodiazepine use. Each patient enrolled in the study received 5 mg of diazepam, 2 mg of lorazepam, or placebo intravenously. Because of the fact that delaying treatment until ED arrival was routine practice at that time, administering placebo was not considered to be an ethical concern. For recurrent or continued seizures, a second dose was given after 4 min. The study kits contained identical contents and colored glass syringes to ensure blinding. Open-label diazepam was available in the event of a life-threatening situation. Paramedics recorded the presence of seizure activity, level of consciousness, respiratory status, and cardiovascular function every 5 min. Seizure cessation prior to arrival in the ED was the primary outcome measured, which was determined by clinically evident seizures or those witnessed on the EEG in a comatose patient. Secondary outcomes included duration of SE, out-of-hospital and transfer complications, neurological outcome and discharge, and disposition of the patient from the ED. Demographics among the three treatment groups did not vary significantly. Status epilepticus was terminated prior to arrival in the ED in 59% of patients in the lorazepam group, 43% in the diazepam group, and 21% in the placebo group. The odds ratio indicated that seizure cessation was more likely with lorazepam and diazepam than that with placebo and favored lorazepam over diazepam but did not reach significance.

It was also noted that the duration of SE was shorter in the lorazepam group than in both the placebo and diazepam groups, but it only reached significance when lorazepam versus placebo was compared. Out-of-hospital complications including respiratory or cardiovascular compromise occurred in 10% of patients in both the lorazepam and diazepam groups and 23% of the placebo group. In addition, patients with seizure cessation prior to arrival in the ED had a much lower rate of admission to the hospital (73% vs. 32%). Alldredge et al. (2001) concluded that the trial provided clear evidence that intravenous benzodiazepine use is safe and effective in the prehospital setting and lorazepam was favored over diazepam. Also of note, the incidence of complications such as respiratory or cardiovascular compromise was actually lower in patients treated with benzodiazepines than those treated with placebo despite the known side effects of cardiorespiratory depression with benzodiazepine use. This trial was important because it encouraged the use of antiepileptics for the prehospital treatment of SE—a change from the previously common practice of delaying treatment until arrival in the ED.

Another prehospital trial was conducted in 2012, referred to as RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial). Designed and conducted by the Neurological Emergencies Treatment Trials network and funded by the National Institute of Neurological Disorders and Stroke (NINDS), it was one of the first double-blind randomized trials of its kind (Silbergleit et al., 2012). This trial was part of an investigational new drug application with the FDA in which the Department of Defense (DOD) provided autoinjectors with active medication and placebo to the NINDS, although the DOD played no role in the study itself. RAMPART was a massive trial across the United States involving 4,314 paramedics, 33 emergency medical services agencies, and 79 receiving facilities. The study subjects included both pediatric patients of 13 kg or more and adults presenting in SE in the prehospital setting. The definition of SE used for the purpose of the study was convulsive seizures at the time of treatment, with continuous seizure activity for greater than 5 min as reported by reliable witnesses, or having intermittent seizures without regaining consciousness for more than 5 min. Patients with an acute precipitant of seizure such as major trauma, hypoglycemia, cardiac arrest, or heart rate less than 40 beats/min were excluded, as well as those with known allergies to benzodiazepines, those with known pregnancies, and prisoners. A total of 893 subjects were enrolled between 2009 and 2011, and the two treatment groups were well balanced in terms of demographics, clinical presentation, and diagnosis. Study kits were provided to all participating paramedics containing two drug bundles each consisting of an investigational intramuscular midazolam autoinjector and a prefilled intravenous syringe. Adults and children weighing more than 40 kg received either 10 mg of intramuscular midazolam followed by intravenous placebo or intramuscular placebo followed by 4 mg of intravenous lorazepam. Subjects in both groups initially received the autoinjector, followed by the intravenous injection after venous or intraosseous access was achieved. The study boxes contained voice recorders that were used to track oral statements from the paramedics describing the time of intramuscular administration, when intravenous access was established, when the intravenous study drug was given, whether any rescue treatments were given, when convulsions ceased, and whether convulsions were still present upon arrival to the ED. The primary outcome measured was cessation of seizure activity prior to ED arrival without rescue medication, which was determined by the clinical judgment of the ED physician upon physical examination of the patient. Secondary outcomes included time from study-box opening to seizure cessation, time from active drug administration to seizure cessation, frequency and duration of hospitalization, admissions to the intensive care unit (ICU), frequency of endotracheal intubation within 30 min of arrival to the ED, and acute seizure recurrence. The

NINDS hypothesized that the intramuscular midazolam group would not be inferior to that of the intravenous lorazepam group by more than a prespecified amount. Secondary outcomes were compared using a two-sided test in a superiority framework. Prior to arrival to the ED, 74% of patients who had received intramuscular midazolam had seizure cessation versus 64% of patients who had received intravenous lorazepam, with $p$ values of less than 0.001 for noninferiority and superiority. Notably, a larger proportion of subjects in the intravenous lorazepam group never received the study medication due to difficulty obtaining venous access: 31 subjects versus five subjects in the intramuscular midazolam group. With regard to the secondary outcomes, the frequency of intubation, length of stay, ICU admission, recurrent seizures, and other safety outcomes were similar between the two groups. Rates of discharge from the ED were higher and rates of admission were lower in the intramuscular midazolam group, reaching statistical significance with a $p$ value of 0.01. It was also noted that the time to administration was lower in the intramuscular midazolam group, but onset of action was lower in the intravenous lorazepam group. Overall, the NINDS concluded that its hypothesis was correct that intramuscular midazolam is at least as effective as intravenous lorazepam in subjects with SE. This is at least, in part, due to the difficulty in obtaining intravenous access in a patient actively seizing in a prehospital environment. In addition, lorazepam has poor stability in unrefrigerated conditions compared with midazolam, which added impetus to the study. Challenges in the prehospital setting, paired with the equal efficacy and safety of midazolam and lorazepam, led to the recommendation by the NINDS for intramuscular midazolam as an alternative to the intravenous route in prehospital care. This study was limited to patients presenting in convulsive SE alone—Future trials may include other presentations such as subtle SE.

Limited research exists on rectal administration of benzodiazepines for the treatment of acute seizures in adults. Cereghino, Cloyd, and Kuzniecky (2002) address this need in their prospective double-blind, placebo-controlled parallel trials by the NINDS. A viscous solution of diazepam to be given rectally was developed in order to allow a layperson to easily administer it to an individual experiencing an acute seizure. To test the efficacy of this medication, it was compared head-to-head against a placebo. Subjects included in this study were those having acute repetitive seizure (ARS), defined as an episode of multiple complex, partial, or generalized seizures, and had experienced at least two to four of these episodes within the past year. The subject's caregiver initiated treatment at the time the ARS episode was identified. Outcomes measured included seizure frequency, time to next seizure, and the caregiver's overall evaluation of the outcome. Adverse events such as respiratory depression were also recorded, as determined by the study nurse at a posttreatment visit. Demographic characteristics had no statistical significance. Ninety-six adults were enrolled in the study, with 70 patients experiencing an ARS episode that was treated with the test medication. Patients in the rectal diazepam group had proven significant reduction in seizure frequency, longer duration until the next seizure, and higher incidence of remaining seizure free than those in the placebo group. A higher proportion of patients did experience adverse events, mainly somnolence and dizziness, in the diazepam group than in the placebo group. These were considered clinically unimportant. Overall, this study demonstrated that diazepam rectal gel is safe and effective in adult patients experiencing repetitive seizures and can be easily administered by nonmedical caregivers.

## PEDIATRIC LITERATURE AND CONSIDERATIONS

A review of pediatric literature is beyond the scope of this article, but it is important to note that management approaches should be the same regardless of the age of the patient. Weight-based doses are prudent, and dose-dependent side effects such as respiratory and

cardiovascular depression should be noted. Almost the entirety of data regarding the use of intranasal midazolam for the management of seizure is published in pediatric literature. Wolfe & MacFarlane (2006) reviewed the evidence for intranasal midazolam in seizure management and established that it is as effective as intravenous diazepam and is both more effective and more socially acceptable than rectal diazepam. Expert guidelines also recommend administration of empirical pyridoxine because in the presence of a rare genetic syndrome known as pyridoxine-dependent epilepsy, seizures may not respond to standard treatments (Brophy et al., 2012).

## TREATMENT GUIDELINES

The 2012 NCCS guidelines for the evaluation and management of SE addressed the need for "emergent, targeted treatment to reduce patient morbidity and mortality" as well as the continued controversy on type of treatment (Brophy et al., 2012). They described the treatment of SE in three phases: emergent initial, urgent, and refractory therapies. The clear-cut definition of SE, as stated formerly, was developed in an attempt to avoid confusion by providers leading to undertreatment of patients presenting with SE. In addition, patients should be classified as either convulsive or nonconvulsive, and an attempt to identify the etiology of the seizure activity must be made emergently and corrected if possible. The NCCS considers benzodiazepines as the recommended emergent initial treatment, with intravenous lorazepam being the preferred agent if available. Midazolam is the preferred medication for intramuscular injection and diazepam for rectal administration. The guidelines recognize that there are no controlled trials for optimal dosage ranges but do suggest initial doses of 0.1 mg/kg of lorazepam intravenously, 0.15 mg/kg of diazepam intravenously, and 0.2 mg/kg of midazolam intramuscularly (Brophy et al., 2012). Additional management of patients with SE should include supportive measures if respiratory depression or hypotension occurs.

The *European Journal of Neurology* published SE management guidelines in 2010, which reaffirm the need for immediate and effective treatment (Meierkord et al., 2010). However, the recommended treatment pathway slightly differs from that of the NCCS. Again, benzodiazepines are recognized as the drug class of choice for initial management of SE. A starting dose of 0.1 mg/kg of lorazepam, which can then be repeated after 10 min if needed, is recommended (Meierkord et al., 2010). However, in some European countries such as France, intravenous lorazepam is not available. In this situation, the guidelines recommend 10 mg of diazepam directly followed by 18 mg/kg of phenytoin. For prehospital use, there is no preference stated and either 2 mg of intravenous lorazepam or 5 mg of intravenous diazepam can be given. Notably, these recommendations were written before the completion of the RAMPART trial that specifically evaluated prehospital treatment of SE.

## NONBENZODIAZEPINE TREATMENTS

Once benzodiazepines have been administered for emergent treatment of SE, patients are typically given additional antiepileptics as either maintenance therapy for epilepsy management or an escalation in therapy to halt continued seizures. Almost all patients receive two drugs in the initial phase of treatment for SE, and the NCCS refers to these second-agent therapies as the "urgent treatment" phase of care (Brophy et al., 2012). Similar to benzodiazepine research, large-scale and high-quality evidence is limited with regard to the particular agent of choice. Levetiracetam, phenytoin, phenobarbital, and valproate sodium all earned Class IIb recommendation evidence (Brophy et al., 2012). In cases refractory to initial treatment, propofol, general anesthetics, and pentobarbital are recommended by the NCCS, with mechanical ventilation as necessary to achieve seizure control. The guiding principle for management should focus on a standardized protocol-based approach that escalates until seizures are halted.

## CONCLUSION

Status epilepticus carries both high mortality and morbidity rates, and early intervention to halt seizure activity is the first priority of care, even to the point where aggressive medication use is recommended despite the risk of requiring respiratory or cardiovascular support as a result of antiepileptic administration. Benzodiazepines are recommended universally as the first-line therapy to address acute SE, and the choice of agent and route should account for drug properties, technical requirements, and comparative efficacy. In the prehospital setting, intramuscular injections of midazolam can be considered first-line therapy due to its effectiveness in a large-scale clinical trial along with practicality and drug properties that make it most suitable for this environment, particularly if autoinjectors are made widely available. When intravenous access is available, the literature suggests that lorazepam shows the best efficacy for seizure cessation while providing consistent CNS concentrations along with a favorable safety profile. Continued research should focus on drugs or combinations of drugs that achieve consistent cessation of seizure activity. In addition, limited data exist to describe the effect of drug selection on long-term outcomes in these patients. Because of evidence of low rates of respiratory and cardiovascular compromise with benzodiazepine use in SE, it may be worthwhile to conduct research on higher doses of benzodiazepine use in an effort to increase efficacy.

## REFERENCES


Alldredge, B. K., Gelb, A. M., Isaacs, S. M., Corry, M. D., Allen, F., Ulrich, S. K., . . . Lowenstein, D. H. (2001). A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *The New England Journal of Medicine*, *345*(9), 631–637.

Brophy, G. M., Bell, R., Claassen, J., Alldredge, B., Bleck, T. P., Glauser, T., . . . Vespa, P. M. (2012). Guidelines for the evaluation and management of status epilepticus. *Neurocritical Care*, *17*(1), 3–23.

Brunton, L. L., Chabner, B. A., & Knollmann, B. C. (2011). *Goodman & Gilman's the pharmacological basis of therapeutics* (12th ed.). New York, NY: Mcgraw-Hill.

Cereghino, J. J., Cloyd, J. C., & Kuzniecky, R. I. (2002). Rectal diazepam gel for treatment of acute repetitive seizures in adults. *Archives of Neurology*, *59*, 1915–1919.

Cook, A. M., Castle, A., Green, A., Lesche, C., Morrison, C., Rhoney, D., . . . Murphy-Human, T. (2012). Practice variations in the management of status epilepticus. *Neurocritical Care Society*, *17*, 24–30. doi:10.1007/s12028-012-9711-3

Drislane, F. W., Blum, A. S., Lopez, M. R., Gautam, S., & Schomer, D. L. (2009). Duration of refractory status epilepticus and outcome; loss of prognostic utility after several hours. *Epilepsia*, *50*(6), 1566–1571.

Katzung, B. G., Masters, S. B., & Trevor, A. J. (2012). *Basic & clinical pharmacology* (12th ed.). Philadelphia, PA: McGraw-Hill.

Leppik, I. E., Derivan, A. T., Homan, R. W., Walker, J., Ramsay, R. E., & Patrick, B. (1983). Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA*, *249*, 1452–1454.

Lowenstein, D. H. (2006) The management of refractory status epilepticus: An update. *Epilepsia*, *47*(1), 35–40.

McMullan, J. T., Pinnawin, A., Jones, E., Denninghoff, K., Siewart, N., Spaite, D. W, . . . Silbergleit, R. (2013). The 60-day temperature-dependent degradation of midazolam and lorazepam in the prehospital environment. *Prehospital Emergency Care*, *17*(1), 1–7.

Meierkord, H., Boon, P., Engelsen, B., Gocke, K., Shorvon, S., Tinuper, P., & Holtkamp, M. (2010). EFNS guideline on the management of status epilepticus in adults. *European Journal of Neurology*, *17*(3), 348–355.

National Institutes of Health. (2014). DailyMed. Retrieved from http://dailymed.nlm.nih.gov

Pallin, D. J., Goldstein, J. S., Pelletier, A. J., Green, A. R., & Camargo, C. A. Jr. (2008). Seizure visits in US emergency departments: Epidemiology and potential disparities in care. *International Journal of Emergency Medicine*, *1*(2), 97–105. doi:10.1007/s12245-0008-0024-4

Riviello, J. J., Claassen, J., LaRoche, S. M., Sperling, M. R., Alldredge, B., Bleck, T. P., . . . Brophy, G. M. (2013). Treatment of status epilepticus: An international survey of experts. *Neurocritical Care Society*, *18*(2), 193–200. doi:10.1007/s12028-012-9790-1

Silbergleit, R., Durkalski, V., Lowenstein, D., Conwit, R., Pancioli, A., Palesch, Y., & Barsan, W. A. (2012). Intramuscular versus intravenous therapy for prehospital status epilepticus. *The New England Journal of Medicine*, *366*(7), 591–600.

Silbergleit, R., Lowenstein, D., Durkalski, V., & Conwit, R. (2013). Lessons from the RAMPART study—And which is the best route of administration of benzodiazepines in status epilepticus. *Epilepsia*, *54*(6), 74–77.

Treiman, D. M., Meyers, P. D., Walton, N. Y., Collins, J. F., Colling, C., Rowan, A. J., . . . Mamdani, M. B. (1998). A comparison of four treatments for generalized convulsive status epilepticus. *The New England Journal of Medicine*, *339*, 792–798.

Wolfe, T. R., & Macfarlane, T. C. (2006). Intranasal midazolam therapy for pediatric status epilepticus. *American Journal of Emergency Medicine*, *24*, 343–346.



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