Introduction

Status epilepticus (SE) is a neurological emergency with considerable morbidity, mortality, and healthcare costs (1). The predominant definition of SE is five or more minutes of continuous clinical and/or electrographic seizure activity, or recurrent activity without recovery to baseline between seizures (2,3). The primary goal of therapy is rapid cessation of seizure activity through pharmacological measures. Guidelines uniformly position benzodiazepines as the mainstay of emergent initial therapy, and optimization of benzodiazepine therapy prior to initiating second-line agents is critical (2,3). This article provides an overview of optimal benzodiazepine use in the emergent care of SE and to highlight the role of emergency medicine pharmacists (EMPs).

The role of pharmacists in SE and other medical emergencies

Pharmacists’ inherent focus on medications improves patient outcomes and decreases medication errors (4). High-risk patients and time-dependent emergencies
Contribute to the dynamic environment of the emergency department (ED), where unique medication-related challenges solidify the importance of EMPs (4,5). Various professional organizations, including the American Society of Health-System Pharmacists (ASHP), the American College of Medical Toxicology (ACMT), and the American College of Emergency Physicians (ACEP) endorse EMPs as key stakeholders in optimizing efficient, safe, and effective medication use in the ED (6-8). The positive impact of EMPs in the care of critically ill patients has been demonstrated for acute ischemic stroke, myocardial infarction, trauma and resuscitation, cardiac life support, sepsis, rapid sequence intubation and initiation of post-intubation sedation and analgesia (4-6,9,10).

To date, two studies have evaluated the impact of pharmacist involvement in SE. The first study by Villamar and colleagues did not exclusively study pharmacists but rather included pharmacy residents as part of a bundled, multidisciplinary alert system which reduced the overall time to administration of second-line antiseizure medications following initial benzodiazepine therapy (11). In this study, the pharmacy resident ensured timely verification of medication orders, facilitated procurement of medications from the central pharmacy, assisted with the bedside admixture of antiseizure medications, and completed therapeutic drug monitoring as needed (12). A second study found that the presence of a pharmacist was potentially associated with faster administration of benzodiazepines and second-line antiseizure medications, as well as more appropriate benzodiazepine dosing, but was not powered to reach statistical significance with only 22 enrolled participants (13).

After adequate doses of benzodiazepines have been given, pharmacists can participate in a comprehensive medical and pharmaceutical work-up, including a review of chronic and pre-hospital medications, which is essential to identify potential precipitating causes, guide subsequent treatment modalities, and aid in the timely use of second-line treatments. Outside of the clinical setting, pharmacists also have a key role in quality improvement initiatives, such as the analysis of current institutional practices, identifying barriers to guideline adherence, reviewing medication safety incidents, emergency preparedness, development of local treatment protocols for ED and pre-hospital personnel, inventory and formulary management, and providing multidisciplinary education (6).

### Optimizing benzodiazepines for SE

Multiple anti-epileptic drugs have been studied for SE; however, guidelines consistently suggest benzodiazepines are the agents of choice for emergent initial treatment (2,3). Amongst individual benzodiazepines, there are alternative routes of administration and pharmacokinetic advantages that allow for timely, patient-specific treatment (Table 1). Medication timing and dosing are pillars of emergent therapy; delaying administration may lead to refractory SE, poor clinical outcomes, and neuronal death (14,16,17). By extension, proper selection of a benzodiazepine and optimization of its dose are essential to ensure treatment success prior to initiating second-line therapies.

### Timing of benzodiazepine administration

Emergent control of seizures by rapid initiation of treatment is pivotal in determining the clinical course of SE. A multicenter prospective observational study of 218 patients demonstrated that delayed benzodiazepine administration by greater than 10 minutes from seizure onset was associated with a higher need for continuous infusion of intravenous (IV) anesthetics, a longer convulsion duration (49 minutes longer in the delayed group), and higher mortality (66% vs. 34%; adjusted odds ratio of 11) (17). Similarly, a 2021 study found that ED patients with generalized convulsive SE were significantly less likely to be admitted to the intensive care unit or hospital when early seizure control was achieved (18). These findings uncover challenges with interpreting the landmark ESETT trial, which highlighted timely administration of benzodiazepines and its impact on the effectiveness of subsequent benzodiazepine-refractory interventions (19,20). In this trial, appropriate benzodiazepine therapy was not administered within the guideline-recommended time-frames, and therefore subsequent second-line agents were being administered when neuronal damage may have already begun. Participants had an estimated delay of 27 minutes from the onset of SE to the first dose of benzodiazepine, and the median duration of seizure at enrollment was 62 minutes for levetiracetam, 59 minutes for fosphenytoin, and 61.5 minutes for valproate, all of which could have contributed to the trial’s apparent futility in its primary outcome (19,20). Robust formal data is lacking.
for pharmacists improving the time to benzodiazepine administration, but their impacts have been previously demonstrated in accelerating the first-dose of antibiotics for sepsis, analgesia for trauma patients, sedation and analgesia following intubation, thrombolysis for ischemic stroke, and door-to-balloon time for myocardial infarction (4-6,9,10). Akin to other time-dependent emergencies in the ED, these studies project a potential role of EMPs in the facilitation of prompt medication administration for SE.

### Benzodiazepine dosing for SE

Optimized benzodiazepine dosing is an equally critical component of effective therapy in SE, where studies have highlighted that there are quantifiable harms to underdosing benzodiazepine therapy (21,22). Adverse effects that are commonly considered with benzodiazepines include respiratory depression and hypotension, which are identified as barriers to guideline-recommended doses; however, due to ongoing seizure activity itself carrying such risks, in a small randomized, controlled trial, these effects were observed less frequently in those treated with benzodiazepines compared to those who received placebo (21). Out-of-hospital complications when benzodiazepines are administered by prehospital personnel (hypotension, cardiac dysrhythmia, or respiratory intervention) occurred in 10.6% of the patients treated with lorazepam, 10.3% of the patients treated with diazepam, and 22.5% of the patients

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (2,3,14)</th>
<th>Pharmacokinetics (14)</th>
<th>Guideline recommendation in the emergent stage of SE (2,3)</th>
<th>Other considerations (14,15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>IV: 0.1 mg/kg (up to 4 mg per dose), may repeat dose once in 5–10 minutes</td>
<td>IV: onset, 2 minutes; duration: 4–6 hours</td>
<td>Neurocritical Care: class I, level A</td>
<td>Lorazepam has a long central nervous system half-life. IM administration is not recommended due to erratic absorption and slow time to peak levels. American Epilepsy Society: level A</td>
</tr>
<tr>
<td>Midazolam</td>
<td>IM‡: 0.2 mg/kg (up to 10 mg per dose) once</td>
<td>IM: onset, 5–15 minutes; duration, 2–6 hours</td>
<td>Neurocritical Care: class I, level A</td>
<td>IM midazolam is superior to IV lorazepam for prehospital seizure cessation, and is the preferred benzodiazepine in patients without IV access. American Epilepsy Society: IM, level A; intranasal, level B; buccal, level B</td>
</tr>
<tr>
<td>Diazepam</td>
<td>IV: 0.15–0.20 mg/kg (up to 10 mg per dose), may repeat dose once in 5 minutes</td>
<td>IV: onset, 1–3 minutes; duration, 15–30 minutes</td>
<td>Neurocritical Care: class lla, level A</td>
<td>Give IV undiluted. American Epilepsy Society: IV, level A; rectal, level B</td>
</tr>
</tbody>
</table>

| Alternate: intranasal, 0.2 mg/kg (up to 15 mg per dose); buccal, 0.5 mg/kg (up to 30 mg per dose) | Intranasal: onset, 3–10 minutes; duration, 23 minutes | American Epilepsy Society: IM, level A; intranasal, level B; buccal, level B | | |
| Alternate: rectal, 0.2–0.5 mg/kg (up to 20 mg per dose) once | Rectal: onset, 2–10 minutes; duration, 15–30 minutes | American Epilepsy Society: IV, level A; rectal, level B | | |

†, first-line therapy options include: IM midazolam, IV lorazepam, IV diazepam. If none of the first-line options are available, consider using rectal diazepam, intranasal midazolam, and IV phenobarbital (2); ‡, midazolam also available as continuous IV infusion for refractory SE. IV, intravenous; IM, intramuscular; SE, status epilepticus; D5W, 5% dextrose in water.
given placebo (P=0.08) (21). A database study by Rao et al. found that less than a third of patients at their institution received adequate doses of benzodiazepines, with a resultant association with progression to refractory SE and/or non-convulsive SE with coma. In both cases, escalating doses of benzodiazepines were inversely correlated with a poorer outcome (22).

In the ESETT trial, the initial dose of benzodiazepine (n=460) was lower than guideline recommendations in 76% of midazolam administrations and 81% of lorazepam administrations (19,20). When reflecting on the methodology of the ESETT trial, it becomes apparent that benzodiazepines were not administered at guideline-recommended doses, limiting the ability to extrapolate results to clinical practice. Where it is known that benzodiazepines are often administered sub-optimally, EMPs can play a significant role in ensuring guideline-recommended administration of benzodiazepines in the emergent setting of SE, both at the bedside and in developing institutional treatment protocols.

**Selection of an appropriate benzodiazepine**

IV lorazepam is a first-line option for emergent initial therapy and was the most widely-used benzodiazepine in the ESETT trial, which enrolled patients from 57 hospital EDs across the United States (19,20). An important pharmacologic characteristic of benzodiazepines is their ability to achieve high therapeutic concentrations in the central nervous system (14). Lorazepam, diazepam, and midazolam are lipid-soluble and cross the blood-brain barrier; however, lorazepam conveys an advantage through its long duration of action in the central nervous system, resulting in prolonged seizure control (14). In order to readily administer lorazepam in the setting of SE, consideration must also be given to its formulation. Propylene glycol is the solvent used in injectable lorazepam and diazepam and is safe at guideline-recommended doses (14,23). However, injectable lorazepam and diazepam warrant close monitoring for signs of propylene glycol toxicity particularly with renal or hepatic dysfunction, co-intoxication with other toxic alcohols, or if patients proceed to receiving large doses of parenteral phenytoin or phenobarbital for treatment of SE, as these agents are also formulated with propylene glycol (23). Life-threatening iatrogenic toxicities including lactic acidosis, hyperosmolality, hypotension, and multisystem organ dysfunction have been identified in case reports and observational studies (23,24). Treatment of known or suspected propylene glycol toxicity involves discontinuing the offending agent, administration of fomepizole, and dialysis in severe cases (23,25). Despite such challenges, for patients where placement of an IV line is attainable, IV lorazepam is the preferred benzodiazepine in the emergent setting of SE; both Neurocritical Care and American Epilepsy Society guidelines list lorazepam as a level A recommendation for initial management (2,3).

Midazolam conveys a unique advantage in its intramuscular (IM) route of administration, often resulting in efficient administration in pre-hospital settings or where obtaining IV access is challenging, such as for patients with ongoing convulsions. The RAMPART trial was critical to demonstrating evidence for midazolam’s place in therapy without established IV access, and the effect of timing and route of administration on SE outcomes (26). This trial compared IV lorazepam to IM midazolam for treatment of SE in adult and pediatric patients with a primary outcome of cessation of seizure activity prior to arrival to the ED without the need for rescue therapy. The authors reported 73.4% in the IM midazolam group and 63.4% in the IV lorazepam group for the primary outcome (95% confidence interval: 4.0% to 16.1%; P<0.001 for non-inferiority and superiority) (26). The placement of an IV line delayed the mean administration time of lorazepam, which offset its more rapid effects compared to IM midazolam; overall, IM midazolam had a mean time of effect of 4.5 minutes from enrolment compared to 6.4 minutes for IV lorazepam; therefore, the finding of superiority could be attributable to midazolam being a superior molecule over lorazepam, but may instead be related to the speed of administration as a key determinant of success (26). Midazolam can also be administered intranasally; however, administration requires the use of a mucosal atomization device, and no more than 1 milliliter of medication should be instilled in each nostril, which is a limitation to adequately dosing adult patients (15). Buccal midazolam is also a reasonable therapy option in the pre-hospital setting, where IV access may be challenging and where IM injections are undesirable. IM midazolam is the preferred route and is awarded a level A recommendation by the American Epilepsy Society guidelines, whereas intranasal and buccal routes are assigned Level B (2).

IV diazepam is an option for initial management of SE, though its shorter duration of action compared to IV lorazepam may render it less preferable (14). Prospective randomized controlled trials directly comparing
benzodiazepines are lacking, though a Cochrane Review concluded IV lorazepam compared to diazepam or phenytoin alone decreases the risk that SE will continue, or require a different drug or general anesthesia in the ED setting (27). Diazepam can also be given rectally, though rectal administration is often impractical. Further, randomized controlled trials have shown superiority for intranasal midazolam over rectal diazepam when considering time-to-seizure cessation, though studies have primarily been conducted in a pediatric population (28,29). Per the Neurocritical Care guidelines, lorazepam and midazolam are both given a class I recommendation, while diazepam is considered class IIa (3).

**Conclusions**

The primary goal of therapy for SE is rapid cessation of seizure activity through pharmacological measures, and efficient administration of appropriately-dosed benzodiazepines is outlined by both the Neurocritical Care and American Epilepsy Society guidelines as the first-line option in achieving this goal. Pharmacists have a role in optimizing medication management by supporting efficient selection of an appropriate benzodiazepine agent and adhering to guideline-recommended doses to avoid the progression to refractory SE. The involvement of pharmacists in development of institutional policies and order sets can also help tailor appropriate guideline-based dosing of benzodiazepines in the ED.

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**Footnote**

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