




# Persistent Underdosing of Benzodiazepines for Status Epilepticus: The Weight Is the Hardest Part

Epilepsy Currents  
2021, Vol. 21(5) 351–352  
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DOI: 10.1177/15357597211036821  
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## Keywords

status epilepticus, benzodiazepine

### Patterns of benzodiazepine underdosing in the Established Status Epilepticus Treatment Trial

Sathe AG, Underwood E, Coles LD, et al. *Epilepsia*. 2021; 62(3):795-806. doi: 10.1111/epi.16825. Epub 2021 Feb 10. PMID: 33567109; PMCID: PMC8075113

**Objective:** This study was undertaken to describe patterns of benzodiazepine use as first-line treatment of status epilepticus (SE) and test the association of benzodiazepine doses with response to second-line agents in patients enrolled in the Established Status Epilepticus Treatment Trial (ESETT). **Methods:** Patients refractory to an adequate dose of benzodiazepines for the treatment of SE were enrolled in ESETT. Choice of benzodiazepine, doses given prior to administration of second-line agent, route of administration, setting, and patient weight were characterized. These were compared with guideline-recommended dosing. Logistic regression was used to determine the association of the first dose of benzodiazepine and the cumulative benzodiazepine dose with the response to second-line agent. **Results:** Four hundred sixty patients were administered 1170 doses of benzodiazepines (669 lorazepam, 398 midazolam, and 103 diazepam). Lorazepam was most frequently administered intravenously in the emergency department, midazolam intramuscularly or intravenously by the emergency medical services personnel, and diazepam rectally prior to ambulance arrival. The first dose of the first benzodiazepine (N = 460) was lower than guideline recommendations in 76% of midazolam administrations and 81% of lorazepam administrations. Among all administrations, >85% of midazolam and >76% of lorazepam administrations were lower than recommended. Higher first or cumulative benzodiazepine doses were not associated with better outcomes or clinical seizure cessation in response to second-line medications in these benzodiazepine-refractory seizures. **Significance:** Benzodiazepines as first-line treatment of SE, particularly midazolam and lorazepam, are frequently underdosed throughout the United States. This broad and generalizable cohort confirms prior single site reports that underdosing is both pervasive and difficult to remediate (ESETT [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01960075) identifier: NCT01960075.).

## Commentary

Status epilepticus is a neurologic emergency where early and appropriate intervention is a critical determinate of outcome. Current practice guidelines are clear that first-line treatment should be a benzodiazepine administered as soon as possible, in a single dose appropriate for the patient's weight.<sup>1</sup> Evidence-based guidelines in place since 2016 provide specific dosing and route recommendations: intramuscular midazolam (10 mg for >40 kg, 5 mg for 13–40 kg), intravenous lorazepam (.1 mg/kg to maximum of 4 mg), or intravenous diazepam (.2 mg/kg to maximum of 10 mg), with acceptable alternatives of intravenous phenobarbital, rectal diazepam, or intranasal midazolam.<sup>1</sup> Fears that benzodiazepines would worsen outcomes by inducing respiratory depression have been refuted in studies of both children and adults.<sup>1,2</sup> Nevertheless, compliance with these guidelines in studies of real-world practice has

been demonstrably poor. In 2019, the Established Status Epilepticus Treatment Trial (ESETT) investigators analyzed pre-trial enrollment administration of lorazepam, midazolam, and diazepam in the prehospital environment and emergency department and found that 70% of the time the first dose was too low.<sup>3</sup> Instead of single full dose, a common pattern of multiple small doses was observed.<sup>3</sup> Similarly, a study of over 1500 patients treated for status epilepticus with midazolam by first responders between 2013 and 2018 found none received the recommended 10 mg dose.<sup>4</sup> The underdosing was significant, with the majority receiving only 5 mg.<sup>4</sup> These reported failures were widely discussed in the epilepsy community with calls to educate ourselves and our colleagues in emergency medical services and emergency departments, as well as to update local policies and procedures.

Disappointingly, this updated examination of the appropriateness of benzodiazepine administration for out-of-hospital






status found little interval improvement.<sup>5</sup> The authors again looked at dosing of benzodiazepine as a first line for status epilepticus in an updated cohort of children and adults enrolled in ESETT through 2018. After the gap in benzodiazepine dosing was observed in the initial cohort, the investigators state they redoubled their efforts to educate study sites on evidence-based best practices. Despite these efforts to improve guideline compliance among 460 subjects enrolled from 57 US hospitals, only 1 in 3 received a first benzodiazepine dose that was within the minimum recommended range.<sup>5</sup> As with the prior report, most patients received 2–3 doses of benzodiazepine, each lower than recommended. Lorazepam was primarily given intravenously in the emergency department, but only 24% of doses were within guidelines. Midazolam was most often administered by emergency medical services and was adequately dosed only 14% of the time. The one outlier in an otherwise consistent pattern of underdosing: rectal diazepam administered by family or caregivers prior to EMS arrival. In the prior 2019 analysis of benzodiazepine dosing in ESETT enrollees, the authors suggested that systematic underdosing reflected a culture of medical practice that could be addressed with education.<sup>4</sup> Thus, prior to the current analyses, they provided updated instruction to site investigators on the guidelines as well as tools to increase guideline compliance.<sup>5</sup> This disappointing outcome should not discourage further efforts to educate emergency medical service providers and physicians who treat status epilepticus but does invite consideration of what other barriers are present.

Accurate weight-based medication dosing in an emergency carries inherent challenges. This is particularly true when the patient is unable to communicate their weight. First responders and emergency department personnel must often rely on family member reports, visual estimates, or indirect calculations based on factors like height, in the absence of means or time to formally weigh a patient. This challenge can be particularly fraught in a patient who is supine, unresponsive, and convulsing; however, it is not unique to seizure emergencies. An analysis of acute stroke patients receiving tissue plasminogen activator (tPA), which similarly requires weight-based dosing, found significant errors in estimated weight were common.<sup>6</sup> Weights were wrong 20% of the time as reported by patients, 38% as estimated by ED physicians, 42% as estimated by nurses, and 20% when calculated by anthropometric measurement.<sup>6</sup> Similar to benzodiazepines and status epilepticus, errors in weight resulted in suboptimal tPA dosing, a third of the time which contributed to poorer outcomes.<sup>6</sup> In a survey of US paramedics related to weight-based medication in out-of-hospital pediatric emergencies, 35% reported relying on

parent reported weight and another 35% reported “I don’t get a weight, I just give a smaller dose”.<sup>7</sup> Remember that even once a weight is reported or estimated, there may be still be a need to convert pounds to kilograms, then to a volume (ml), and then to dilute or draw up an appropriate dose for administration—all this in an environment that is high stress, emotionally charged, and potentially chaotic. Compare this to the provider in the office setting who has an accurate weight, time, and means to calculate accurate dosing. Consider the accuracy with which this provider prescribes rectal diazepam in a ready-to-use, fixed dose package, and it is easier to understand why caregiver administered diazepam was the outlier high rate of dosing within the guidelines. Improving access to patient transports and emergency department beds that measure weight might be one step to optimizing care of patients with status epilepticus. Closing the gap between the guidelines and current practice will take more time, more effort, and more creativity—but we cannot afford to wait.

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