



Seizure Rescue Medication Use among US Pediatric Epilepsy Providers: A Survey of the Pediatric Epilepsy Research Consortium

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Objective To assess how pediatric neurologists prescribe home seizure rescue medications to treat acute prolonged seizures and clusters of seizures in children.

Study design A brief, email survey was sent to the members of the Pediatric Epilepsy Research Consortium assessing seizure rescue medication prescribing practices for patients of different age groups, cognitive abilities, and seizure type. Survey responses were anonymous.

Results Thirty-six respondents (of 76 surveyed; 47% response rate) completed the survey. Rectal diazepam was the most commonly chosen rescue medication for a prolonged convulsive seizure in a severely developmentally delayed 16-year-old (44%) and typical and delayed 7-year-old (44% and 61%, respectively), 3-year-old (78% and 86%, respectively), and 9-month-old (83%) patients. Most responders (69%) indicated that developmentally typical 16-year-olds would be prescribed intranasal midazolam. For clusters of seizures, clonazepam orally disintegrating tablets were the most frequent first-line option in all age groups, except developmentally delayed 3-year-old and 9-month-old children, for whom rectal diazepam was chosen more commonly. Medication dosing generally followed standard dosing guidelines with very few exceptions.

Conclusions Rectal diazepam remains the most frequently used rescue medication for prolonged seizures for nearly all age groups, except in developmentally typical teenagers, for whom intranasal midazolam is used more often. Clonazepam orally disintegrating tablets are the most frequently used medication for treatment of clusters of seizures, except in younger patients. Further work is necessary to establish best practices for type and administration route of seizure rescue medications. (*J Pediatr* 2019;212:111-6).

Seizure rescue medications are an important tool for the management of children with epilepsy. Despite improvements in the treatment of epilepsy, status epilepticus remains the most common neurologic emergency in children.¹ Rescue medications have been shown to safely reduce the length of prolonged seizures and the likelihood of recurrent seizures.²⁻⁸ A growing body of literature suggesting that delay in administration of medications for status epilepticus leads to worse outcomes^{9,10} highlights the importance of having first-line medications immediately accessible. These medications represent an especially important intervention in nonmedical (eg, home, school) settings.^{11,12} Rescue drug availability has empowered parents and other caregivers to initiate a treatment pathway before trained medical personnel arrive and potentially abort a dangerous seizure emergency.

The safety of rescue medications is clear. Studies have demonstrated the very low overall risk of adverse effects (eg, respiratory suppression) with these drugs.^{13,14} Despite the well-known benefit of this group of medications, there remains only 1 Food and Drug Administration (FDA)-approved drug for the use in clusters of seizures (rectal diazepam, [Diatat]). Multiple other benzodiazepines (eg, midazolam, clonazepam, lorazepam) are frequently used for the same indication on an off-label basis. A number of studies have compared these medications against each other to demonstrate one's benefit over another, but a lack of randomized, controlled trials has left providers without a definitive answer regarding the best drug to use. Furthermore, although the importance of prompt treatment of prolonged seizures is universally stressed, no specific guidelines about which rescue medications to use are available to guide practitioners. To complicate this issue further, a number of routes of administration are also available (ie, intranasal [IN], buccal, intramuscular, and rectal), all with their own supporting literature.

We hypothesized that this cadre of medication options has led to significant variability in prescribing patterns among providers who treat children with epilepsy. Given the lack of clinical evidence to guide pediatric seizure rescue medication choice, we surveyed the experts—pediatric neurologists and epileptologists—to assess seizure rescue medication prescribing tendencies and variability. Specifically, for a variety of developmental ages and cognitive abilities, along with seizure types (prolonged convulsive vs recurrent clusters),

FDA	Food and Drug Administration
IN	Intranasal
ODT	Orally disintegrating tablet
PERC	Pediatric Epilepsy Research Consortium

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we asked experts to choose their preferred seizure rescue medication, dosage, and administration route.

Methods

A REDCap email survey was sent to all members of the Pediatric Epilepsy Research Consortium (PERC), a group of US pediatric epilepsy providers that includes pediatric epileptologists and pediatric neurologists. Responses were identifiable only by the respondent's geographic region of practice. The survey consisted of a total of 35 queries, which included a combination of multiple-choice and free-text questions (Figure 1). The first section of the survey presented respondents with multiple different clinical scenarios assessing their single, best choice of rescue medication for either prolonged seizures or clusters of seizures in patients of varying ages (16, 7, and 3 years, and 9 months), each with and without a history of developmental delay. The remainder of the survey addressed other prescribing patterns, including dosage of each medication, timing of medication administration, other instructional practices, and demographic information. Descriptive statistics were used to evaluate the data obtained.

Results

Of a total of 76 PERC members surveyed, we received 36 responses (47% response rate). Thirty-four of the responders identified themselves as pediatric epileptologists and 2 identified themselves as pediatric neurologists. The group had a wide range of experience with 1-30 years of practice after training (median, 7.5 years). All regions of the US were represented with 16 from the Midwest (44%), 9 from the Northeast (25%), 8 from the West (22%), 2 from the Southeast (6%), and 1 from the Southwest (3%).

Figure 2 provides the details of survey responses. In 16-year-old developmentally typical patients with prolonged convulsive seizures, providers were more likely to prescribe IN midazolam (69%) than any other rescue medication. In contrast, 44% of providers would prescribe rectal diazepam to severely developmentally delayed 16-year-olds and only 39% recommended IN midazolam for prolonged convulsive seizures. With decreasing patient age, the likelihood of recommending rectal diazepam for prolonged convulsive seizures increased. For example, 47% of developmentally typical 7-year-old children would be given rectal diazepam and 36% prescribed IN midazolam. This trend continued in children ages 3 years and 9 months with 78%-86% of providers indicating that rectal diazepam would be chosen. Buccal diazepam and clonazepam orally disintegrating tablets (ODTs) were less commonly indicated as choices with up to 8% of providers indicating these choices for any of the patient scenarios.

The choice of rescue treatment for recurrent clusters of seizures differed notably. Clonazepam ODT was the first medication choice in 16-year-olds regardless of their devel-

1. The following patients present to your clinic for evaluation of prolonged convulsive seizures. Which rescue medication would you prescribe for a...

*16 year old, developmentally typical child,
16 year old developmentally delayed child,
7 year old, developmentally typical child,
7 year old developmentally delayed child,
3 year old, developmentally typical child,
3 year old, developmentally delayed child,
9 month old child.*

2. The same patients present to your clinic for clusters of seizures; which rescue medication would you prescribe?

3. What dosing do you use for each of the rescue medications that you prescribe?

4. At what length of seizure do you recommend using rescue medications; *for patients <2 years old, 2-5 years old, 6-13 years old, and >14 years old?*

5. What factors most influence your choice of rescue medication?

6. Do you routinely test a rescue medication in the hospital before outpatient use?

7. What is the youngest age you feel comfortable prescribing rescue medication for outpatient use?

8. Do you advise repeating a dose of rescue medication for continued seizure activity after the first dose?

If yes, at what time and what dose?

9. Do you prescribe rectal medication for developmentally typical school aged children or older?

10. Do you advise calling 911 after administration of a rescue medication?

If yes, in which patients or circumstances do you recommend calling?

Figure 1. Complete list of survey questions sent to participants.

opment. Seven-year-old developmentally typical patients would be prescribed clonazepam by 47% of providers, whereas only 33% of the same-aged patients with developmental delay would be given clonazepam. That difference was accounted for by the increased preference for rectal diazepam. This trend continued in the 3-year-old patient example, again with an increased likelihood of using rectal diazepam in the group with developmental delays.

Prescribers indicated that dosage for each medication largely followed standard dosing guidelines (Table I). Specifically, all responders indicated that they used standard doses of rectal diazepam, clonazepam ODTs, and buccal lorazepam. Only 12.5% (1/8), 3% (1/33), and 17% (3/18) indicated that they used alternative dosing of buccal diazepam, IN midazolam, and buccal midazolam, respectively.

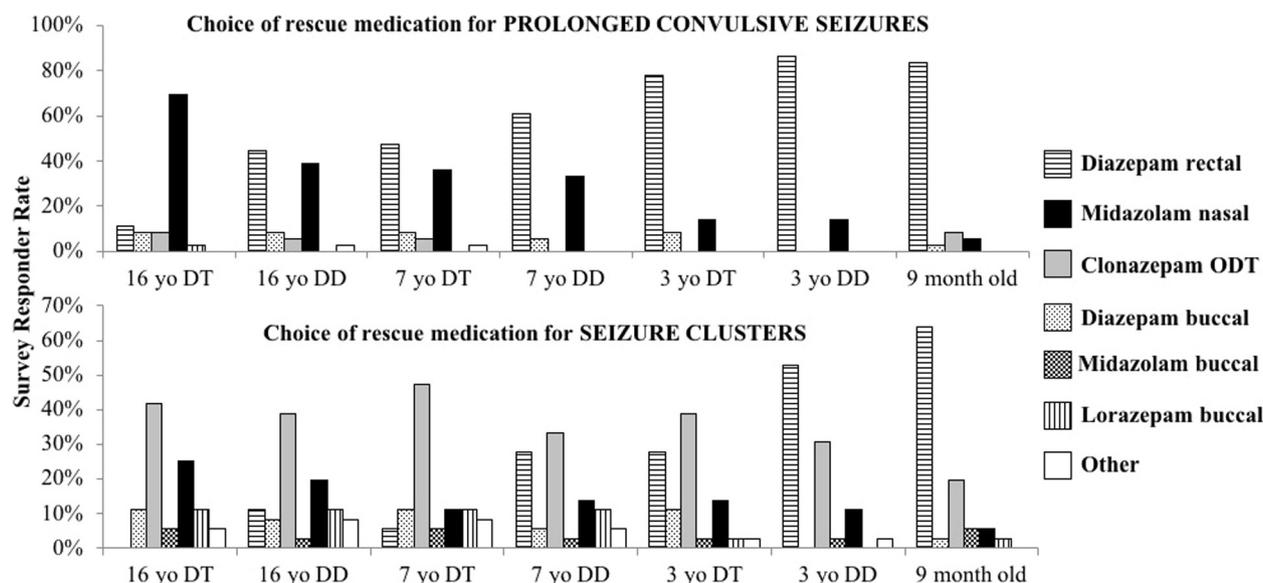


Figure 2. The response of choice of rescue medications for different ages/developmental level for patients with either prolonged or clusters of seizures. *DD*, developmentally delayed; *DT*, developmentally typical; *yo*, years of age.

The remainder of survey responses are summarized in **Table II**. For prolonged convulsive seizures clinicians indicated that they recommended that seizures be treated at a median of 5 minutes of seizure activity for all age categories (IQR 3-5, 3-5, 4-5, 4-5 minutes, for <2 years, 2-5 years, 6-13 years, and ≥14 years age groups, respectively). The most compelling reasons for choice of rescue medication was (1) the medication's ability to preserve the patient's dignity and (2) ease of use. Most providers (78%; 28/36) indicated that they do not routinely test rescue medications on their patients in the hospital before prescribing them. Four respondents (11%) indicated that they did test rescue medications, but only on patients less than 6 months of age, 3 (8%) did so for patients less than 1 year of age, and 1 respondent (3%) tested rescue medications on all patients. The minimum age that prescribers felt comfortable prescribing rescue medications was a median of 4 months (IQR, 2-6 months). A majority of prescribers (81%; 29/36) recommend that rescue medications be repeated for continued seizure activity following administration of the first dose. Seventy-two percent (21/29) of those approved patients of any age receiving a second dose. Some providers indicated that they would advise repeat doses only in patients 2 years and older (21%; 6/29) or 6 years and older (7%; 2/29). Among

those who recommended a repeat dose, they suggested such at a median of 5 minutes of additional seizure activity. Eighty-three percent (24/29) recommended that a full dose be repeated and 10% (3/29) recommend a half dose. Respondents most commonly (39%) advised calling 911 after the first use of rescue medications in any age. Fewer (8%) advised calling only in young children receiving their first ever dose of rescue medication. Others recommended doing so when there was a lack of response to medication (11%). Additional comments made by the respondents indicated that the choice of rescue medications was often patient specific and can often be tailored based on the treatment history.

Discussion

Our study demonstrates the current prescribing practices of seizure rescue medications among a group of pediatric epilepsy providers in the US. Although we expected variability in the choice of medications used between different scenarios, our data suggest some consistent patterns in prescribing tendencies. The study showed that there was preference to prescribe IN midazolam for convulsive seizures in older patients (16-year-olds) with a shift toward

Table I. "Standard" pediatric doses of rescue medications

Medications	Dose
Diazepam rectal	0.5 mg/kg for 2-5 years of age, 0.3 mg/kg for 6-11 years of age, 0.2 mg/kg for ≥12 years of age, max 20 mg
Diazepam buccal	0.5 mg/kg, nearest 2.5 mg increment, max 10 mg
Clonazepam ODT	0.01-0.03 mg/kg, max 2 mg
Midazolam IN	0.2 mg/kg, max 10 mg
Midazolam buccal	2.5 mg for 6 mo-1 year of age, 5 mg for 1-5 years of age, 7.5 mg for 5-10 years of age, 10 mg for ≥10 years of age
Lorazepam buccal	0.1 mg/kg, max 4 mg

Table II. Responses to prescribing practice questions

Survey questions	Response
At what length of seizure in minutes do you recommend using rescue medications?	
For patients <2 years of age	5 (3-5)
For patients 2-5 years of age	5 (3-5)
For patients 6-13 years of age	5 (4-5)
For patients >14 years of age	5 (4-5)
Do you routinely test rescue medication in the hospital before outpatient use?	
No	78 (28/36)
Yes, in patients <6 months of age	11 (4/36)
Yes, in patients <1 year of age	8 (3/36)
Yes, in all patients	3 (1/36)
What is the youngest age patient in months you feel comfortable prescribing rescue medications to for outpatient use?	4 (2-6)
Do you advise repeating a dose of rescue medication for seizures continuing after an initial dose?	
No	19 (7/36)
Yes	81 (29/36)
Yes, in patients ≥ 2 years of age	21 (6/29)
Yes, in patients ≥ 6 years of age	7 (2/29)
Yes, in all patients	72 (21/29)
After how many minutes of additional convulsive seizure activity do you usually recommend redosing with a rescue medication?	5 (5-10)
When repeating a rescue medication, what dose do you recommend?	
A full dose	83 (24/29)
One-half of a dose	0 (3/29)
Variable	7 (2/29)

Values are median (IQR) or percent (n/N).

using rectal diazepam with diminishing age, especially in the presence of developmental delay. Similarly, the preference for recurrent seizures clusters was to use clonazepam ODTs for older children and, again, rectal diazepam for younger children and those with developmental delay. Our findings provide novel insights. The lack of choices of FDA-approved medications and, as a result, the lack of formal guidelines for choosing a rescue medication, make this information valuable. Furthermore, an expanding body of evidence suggesting that delays in administration of benzodiazepines during the early stages of status epilepticus creates a more difficult clinical situation^{9,10} and presses the need for prescribing guidance.

Surveys regarding the use of rescue medications have been performed in the past. A similar 2009 UK survey performed by the Epic Clinical Network, a group of pediatric neurologists, identified patients with epilepsy, noted their epilepsy type, and which rescue medication they were prescribed and its dosage.¹⁵ Parents were then sent a survey polling their experience with rescue medications. Fifty-one percent of patients were prescribed buccal midazolam and 38% rectal diazepam. Whether prescribing patterns differed by age was not noted. That study noted a shift to a greater use of buccal midazolam secondary to previous studies^{5,6} supporting buccal midazolam's use over rectal diazepam. The Practices in Emergency and Rescue Medication for Epilepsy Managed with Community Administered Therapy (PERFECT) initiative surveyed a group of European pediatric neurologists, pediatricians, and epilepsy nurses regarding their knowledge of the state of nonhospital treatment of prolonged or repetitive seizures.¹⁶ Findings focused on the gaps in healthcare providers' knowledge of outpatient guidelines for treatment of seizure emergencies and the

practical use of rescue medications rather than providers' medication choice and dosing.

A recent US study surveyed families of children with epilepsy¹⁷ and found that most patients (87%) with epilepsy were prescribed a rescue medication, although many (39%) did not receive training on its usage and 36% of families were unfamiliar with when to administer the drug. This study also found that a majority of families indicated that they would prefer a nonrectally administered medication. Interestingly, however, that survey identified that families of children with normal development (90%) were more likely to have this preference than families with children with developmental delay (65%). No reason was cited for this difference. This preference for a buccal or nasal route of administration was similarly demonstrated in a UK patient phone survey in which families vastly preferred them vs drugs requiring rectal administration.¹⁸

The preference of our surveyed providers for use of IN midazolam in teenagers is well supported by a study by Arya et al.¹⁹ This meta-analysis evaluating the efficacy of rescue medications showed that intramuscular and IN midazolam are the most efficacious options for aborting prolonged seizures or seizure clusters. Although the preference for IN midazolam is well-supported, it falls into some conflict with our survey's results stating that ease of use is one of the most important factors influencing choice of medication. Currently, there is no proprietary delivery device for IN rescue medications, often making administration a tricky process of drawing up medication from an IV vial, switching syringe tips, and preparing IN delivery, all while one's child continues to have ongoing seizure activity. Conversely, rectal diazepam is offered in a very easy to use delivery device, likely a driving factor behind its frequent use. Although there is

abundant pharmacokinetic evidence to suggest that some routes of administration are superior in their onset of action to others, the results of the landmark Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) trial point to the importance of a speedy delivery route,²⁰ perhaps even overshadowing the importance of the onset of action.

Our study found that the most common reason for choosing a medication was the medication's ability to preserve patient dignity. We interpret this to mean avoidance of embarrassing patient exposure, an essentially unavoidable effect of any rectally administered medication. Despite this factor being the most important one to be identified, rectal diazepam remained the overall most commonly prescribed medication. This issue seems probably most relevant to older school-age patients, especially teenagers, for whom our surveyed providers tended to prescribe the most IN midazolam. It is unclear why rectal diazepam seems to be more acceptable in patients with developmental delay and why it remained the primary option for young school-aged children. The collective preferences of our surveyed providers would suggest that an easy-to-use form of an effective, nonrectal (eg, IN) delivery device would likely become the drug of choice for prolonged seizures.

Rectally administered medications pose a special problem for some schools. Given the need for nonmedical personnel to administer rescue medications, the administration of rescue drugs has already been the focus of some legal debate,^{21,22} although laws in the US and essentially every European country clearly support their use. School personnel's concerns are then further amplified by the need for rectal administration, a procedure that has allegedly been tied to claims of sexual assault in the past.

We found that clusters of seizures are treated in a quite different way than prolonged seizures. The term "seizure cluster" is heterogeneously defined and used variably among providers. Broadly, it refers to repeated seizures (≥ 3), recurring over a course of minutes to days. Clonazepam was a very frequent choice of rescue medication here. The elimination half-life of clonazepam of 30-40 hours²³ is postulated to be a principal reason behind its use for this indication. Clonazepam's use as a maintenance medication for epilepsy is well-established.²⁴ However, aside from a single study²³ examining its efficacy in pediatric patients, oral clonazepam is not strongly supported by recent evidence. The ease with which clonazepam is administered, specifically the ODT formulation, is likely the driving factor for its use despite its lack of supportive evidence.

Only 7 respondents indicated that cost played a part of their choice of rescue medication. Given the expense of some rescue medications compared with the low cost of others, perhaps this should be more of a focus. A recent report indicated that IN and buccal midazolam were cost effective options compared with rectal diazepam, which costs upwards of USD300.²⁵

Our group recommended the use of rescue medications at 5 minutes, a relatively standard practice adhering to the International League Against Epilepsy's most recent revised

definition of status epilepticus²⁶ and other similar survey results.¹⁷ In line with previous survey results,²⁷ the use of test dosing rescue medications in the hospital was rarely recommended. Most providers advised repeating a dose of rescue medication for continued seizure after the first dose administration. This practice adheres to the available standardized algorithms for the initial treatment of status epilepticus^{28,29} and is supported by evidence suggesting 2 doses of benzodiazepine are typically well-tolerated.⁹

Our study was limited by its relatively small sample size and response rate with an overrepresentation of the Midwest region and underrepresentation of the Southwest and Southeast regions. In addition, data were gathered by a survey of hypothetical patients and may not match precisely what truly happens in the respondents' practices. Finally, because seizures and epilepsy are treated by providers beyond those with special expertise in epilepsy, our survey is not likely representative of what happens across all patients with epilepsy. Our intent, however, was to ascertain the patterns of epilepsy professionals in hopes of understanding the most expert practices.

Rescue medications allow for prompt treatment early in the course of a seizure and can help to abate the dangerous consequences of prolonged seizures. Prescriptions for them are best accompanied by a seizure action plan, family education, and collaboration between the child's school and care team. The current prescribing patterns will likely (and hopefully) evolve with the much-needed addition of FDA-approved rescue medications and randomized controlled trials supporting them. ■

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