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REVIEW

Treatment of Seizure Clusters in Epilepsy: A Narrative Review on Rescue Therapies

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ABSTRACT

Epilepsy is a common neurological disorder in the United States, affecting approximately 1.2% of the population. Some people with epilepsy may experience seizure clusters, which are acute repetitive seizures that differ from the person's usual seizure pattern. Seizure clusters are unpredictable, are emotionally burdensome to patients and caregivers (including care partners), and require prompt treatment to prevent progression to serious outcomes, including status epilepticus and associated morbidity (e.g., lacerations, fractures due to falls) and mortality. Rescue medications for community use can be administered to terminate a seizure cluster, and benzodiazepines are the cornerstone of rescue treatment. Despite the effectiveness of benzodiazepines and the importance of a rapid treatment approach, as many as 80% of adult patients do not use rescue medication to treat seizure clusters. This narrative review provides an update on rescue medications used for treatment of seizure clusters, with an emphasis on clinical development and study programs for diazepam rectal gel, midazolam nasal spray, and diazepam nasal spray. Results from long-term clinical trials have shown that treatments for seizure clusters are effective. Intranasal benzodiazepines provide ease of use and patient and caregiver satisfaction in pediatric and adult patients. Adverse events attributed to acute rescue treatments have been characterized as mild to moderate, and no reports of respiratory depression have been attributed to treatment in long-term safety studies. The implementation of an acute seizure action plan to facilitate optimal use of rescue medications provides an opportunity for improved management of seizure clusters, allowing those affected to resume normal daily activities more quickly.

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PLAIN LANGUAGE SUMMARY

Some people with epilepsy who take antiseizure medications may still have seizures. These seizures might happen in clusters. Seizure clusters are emergencies that need to be treated quickly to lower the risk of status epilepticus and hospitalization. Also, these clusters can be stressful. Approved rescue medications are diazepam rectal gel, midazolam nasal spray, and diazepam nasal spray. They can all be used by family and other caregivers, and nasal sprays may be preferred in a public setting. All of these treatments can be used for adults, but each has a different age limit for children. Overall, these therapies are underused; however, all have been shown to work in stopping seizure clusters and have mild to moderate side effects. Nasal treatments offer ease of use and satisfaction for patients and caregivers (care partners). However, data for some effects and patient groups are not available for all treatments. Seizure action plans are designed to give step-by-step instructions about when and how to use rescue medication. Increased use of action plans may improve at-home treatment of seizure clusters and allow patients to perform their normal daily activities and avoid injury or hospitalizations.

Keywords: Acute repetitive seizures; Benzodiazepines; Diazepam; Midazolam; Intranasal; Nasal spray; Rectal gel

Key Summary Points

Patients with epilepsy may experience seizures clusters, which are acute repetitive seizures that differ from the person's usual seizure pattern.

Rapid treatment is critical to minimize the emotional burden of seizure clusters and to reduce the risk of status epilepticus and hospitalizations.

Diazepam rectal gel, midazolam nasal spray, and diazepam nasal spray are specifically approved rescue medications for treatment of seizure clusters.

Rescue medications differ according to route of administration and formulation, which may influence the time needed for administration and cessation of seizure activity as well as patient and caregiver experiences with treatment.

Seizure action plans can guide appropriate treatment during a seizure cluster to empower patients and caregivers and reduce anxiety.

INTRODUCTION

Epilepsy affects 1.2% of the population in the USA (approx. three million adults and 500,000 children) [1], and as many as 30–40% of these individuals have drug-resistant epilepsy [2, 3]. Some people with epilepsy may experience seizure clusters (acute repetitive seizures, serial seizures), which are acute episodes of increased repetitive seizures, irrespective of type or grouping, that differ from the person's usual seizure pattern [3–5]. Seizure clusters are a rare condition and have been designated as an orphan indication in the USA [6]. The term seizure cluster is not classified as a clinical indication by the European Union (EU, European Medicines Agency) [3]. The prevalence of seizure clusters varies among populations with epilepsy, with an estimated 3.0% of people from a large, population-based sample [7, 8] but was notably higher among patients with drug-resistant epilepsy at an epilepsy center [7, 9]. Seizure clusters can persist for hours and extend beyond a single day [3], although most recurrences of seizures within a cluster have been reported within 6–24 h of the first seizure for an untreated seizure cluster [10]. Risk factors for seizure clusters include high seizure frequency, history of status epilepticus, and drug-resistant epilepsy [7].

Consequences of Seizure Clusters

Seizure clusters are unpredictable and cause emotional burdens for patients and caregivers

(care partners) [11]. In a 2017 survey of adult patients with seizure clusters, 75% indicated that they live in fear that a seizure can occur at any time, and 80% indicated that seizure clusters create a significant emotional burden [11]. Moreover, 62% of caregivers of pediatric or adult patients felt that the patient lived in fear of seizures, and 71% felt that seizure clusters were emotionally burdensome to the patient. Seventy-one percent of adult patients felt that seizure clusters had an impact on their expectations about performing daily living activities, and 58% of caregivers reported a moderate to major negative impact of seizure clusters on their own quality of life. The unpredictable nature of seizure clusters can lead to patient worry about loss of independence (e.g., driving [driving privileges for people with epilepsy and required length of time without seizures vary across states/countries] [12, 13]) and control of seizure clusters [11].

Seizure clusters are associated with a greater overall burden of epilepsy, including increased hospitalization, morbidity, and mortality [14, 15]. One study reported greater rates of status epilepticus in patients who experienced seizure clusters (44%) compared with those who did not (13%) [16]. Repetitive seizures, as well as prolonged seizures, can lead to neuronal death [17], and seizure clusters may increase the risk in patients for sudden unexpected death in epilepsy (SUDEP) [18]. In a long-term prospective study, patients with a history of seizure clusters had a 3.5-fold higher mortality risk than those without seizure clusters [19].

Annual healthcare costs associated with epilepsy are variable and can range into the tens of thousands of dollars, depending on use of emergency and hospital services (including transportation), although indirect costs, such as lost wages from employment, represent the majority of total costs incurred [20]. In a retrospective chart review, patients with seizure clusters who consistently used rescue medication incurred lower medical costs for a 12-month period compared with patients who did not ($13,265 vs $21,790 in 2013 USD) [21]. Additionally, the annual costs for a patient to obtain acute seizure rescue medication is roughly one-tenth the cost of a single hospitalization [20, 22].

Importance of Prompt Treatment

The characteristics of a seizure cluster vary from patient to patient. Seizure clusters are distinct from the patient's usual seizure pattern where the seizure type, frequency, duration, and severity are easy for caregivers to identify when they are familiar with the patient [23, 24]. Recognizing the beginning of a seizure cluster provides an opportunity to administer prompt treatment. Delays in the treatment of seizure emergencies are often associated with negative patient outcomes. Seizure clusters become less responsive to treatment when they continue unabated over time [14], and could evolve to prolonged seizures or status epilepticus. Benzodiazepines are the cornerstone of treatment for seizure clusters [25]. However, prolonged seizures can disrupt the normal expression of inhibitory and excitatory receptors at the neuronal cell membrane, resulting in greater cellular excitation (Fig. 1) [26]. Internalization of the γ-aminobutyric acid A receptor at the level of the cellular membrane contributes to the

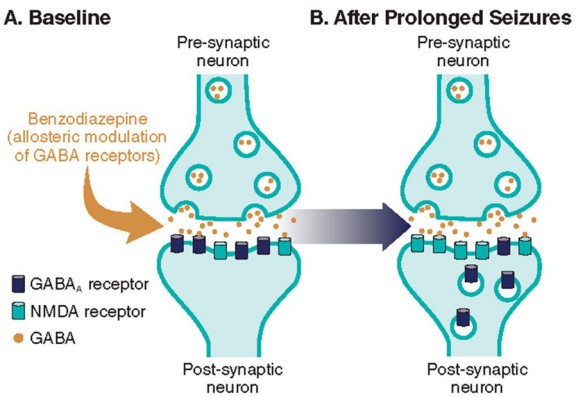


Fig. 1 Pathophysiology of seizure. Localization of key receptors that influence neuronal excitation during normal (**a**) and prolonged seizure conditions (**b**). During seizures, γ-aminobutyric acid A ($GABA_A$) receptors are internalized, and *N*-methyl-D-aspartic acid (NMDA) receptors accumulate in the postsynaptic membrane, resulting in loss of inhibition and increased excitation. These changes favor self-sustaining seizures and resistance to benzodiazepines [26]

attenuated antiseizure effect despite benzodiazepine administration during prolonged seizures or when rescue treatment is delayed [26]. Prolonged seizure durations of status epilepticus have been observed when initial treatment with benzodiazepines is delayed more than 30 min after seizure onset [26]. Thus, early benzodiazepine treatment for other seizure emergencies, such as seizure clusters, would be expected to yield the best results.

Traditional Treatment Options

For much of the past 2 decades (1997–2019), US Food and Drug Administration (FDA)-approved rescue medication was limited to diazepam rectal gel (Diastat®; Bausch Health US, LLC [Bridgewater, NJ, USA]), which was the first approved rescue medication for seizure clusters [27, 28]. However, the rectal route of administration has mechanical restrictions (e.g., patient positioning and medication administration) [29] during a seizure, in addition to social and privacy considerations [27]. Other formulations of benzodiazepines, which are not approved for use as rescue medications, may have variable absorption. Routes of administration for rescue therapies vary and have utilized oral tablets, orally disintegrating tablets (ODTs)/wafers, intranasal atomized solutions, and other delivery formulations of benzodiazepines [25, 27]. Orally administered lorazepam and clonazepam as well as intranasal administration of atomized midazolam are common examples of therapies used off-label as rescue medications for seizure clusters [30]. In the EU, diazepam in a solution formulation that is administered rectally has received a broad indication to treat febrile convulsions in patients 1 year of age or older [31–33]. Additionally, buccally administered midazolam is approved in 27 EU-member countries, the UK, Japan, and Israel for the treatment of prolonged, acute, convulsive seizures in children and adolescents (3 months to less than 18 years of age) [27, 34, 35].

Oral Tablets and ODT/Wafers Several factors can influence absorption and bioavailability of oral medications, including first-pass metabolism, gastric emptying, and gastrointestinal motility [36, 37]. There are also risks for aspiration when using oral antiseizure medications (ASMs) during a seizure, including the potential for caregiver injury from biting [27]. Administration of oral rescue medication during a drowsy state, especially for those patients in the postictal state, also may present an elevated risk for aspiration. The use of ODT/wafers and other formulations with buccal or sublingual routes of administration are associated with variable absorption and bioavailability [25, 27].

Intranasal Atomized Intravenous Solutions Benzodiazepine solutions for injection are not designed for intranasal use and have a relatively low concentration of drug (e.g., 1 or 5 mg/mL) [38]. This requires administration of a larger volume of liquid to ensure adequate drug dosing. As such, intranasal administration of injectable formulations can result in meaningful amounts of drug passing through the nasal cavity into the gastrointestinal tract or leakage from the nasal cavity. Ideally, benzodiazepine medications for intranasal use should be concentrated so they achieve a therapeutic dosage absorbed from the nasal mucosa, owing to the relatively small surface area of the nasal cavity [25]. The low pH (approx. 3) of intravenous (IV) formulations of midazolam makes the pharmacokinetics of acidic compounds less desirable for intranasal administration [25].

The lack of optimal acute seizure rescue treatment options demonstrated a gap in therapy and substantial clinical need. In a Harris poll published in 2017, 80% of patients did not use a rescue medication for treatment of seizure clusters, despite availability and recommendations for its use by clinicians [11]. Thirty-one percent of patients utilized the emergency department within the year preceding the survey [11].

The purpose of this narrative review is to serve as an update on acute rescue medications used to treat seizure clusters with the general neurologist in mind. In addition, evidence is provided that may help facilitate the practical use and choice of rescue medication as a means to improving control of seizure clusters in patients with epilepsy. This article is based on previously conducted studies and does not contain any new studies with human

participants or animals performed by any of the authors.

AVAILABLE MEDICATIONS USED AS RESCUE THERAPY

Several limitations related to rectal administration of the diazepam gel formulation led to the development of improved routes of administration for pediatric and adult patients with epilepsy [25]. Midazolam nasal spray (Nayzilam®; UCB, Inc. [Smyrna, GA, USA]) and diazepam nasal spray (Valtoco®; Neurelis, Inc. [San Diego, CA, USA]) were approved by the FDA in 2019 and 2020, respectively, for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from usual seizure patterns in patients with epilepsy [39, 40]. Diazepam rectal gel is approved by the FDA for use in patients aged 2 years or older [28], diazepam nasal spray is approved for those aged 6 years or older [39], and midazolam nasal spray is approved for patients aged 12 years or older [40].

Diazepam Rectal Gel

Diazepam rectal gel is provided in a prefilled, unit-dose system, with doses ranging from 2.5 to 20 mg [28]. Each twin pack contains two doses of diazepam rectal gel along with lubricating jelly [28], which can be stored for up to 4 years [41]. Dosage is determined according to patient age and weight (0.5 mg/kg for ages 2–5 years, 0.3 mg/kg for ages 6–11 years, and 0.2 mg/kg for ages 12 years or older) [28]. Rectal administration involves placing the patient in the lateral recumbent position, preparation of the soft-tip applicator with lubricant, and partially disrobing and exposing the patient for access to the rectum to administer the drug (Table 1) [28].

Clinical Development of Diazepam Rectal Gel

Intravenous benzodiazepines are established as an ASM based on their use as an effective treatment of seizure clusters in the hospital setting, but there was a gap in therapy for patients outside the hospital setting and need for therapies that could be administered by nonmedical caregivers in the community [25]. Diazepam rectal gel was developed to provide a simpler alternative treatment for seizure clusters that could be used more widely outside the hospital in a community setting [42]. Diazepam rectal gel is easily absorbed by most patients and is associated with relatively rapid elevations in diazepam levels (bioavailability, 90%) [25, 43].

Diazepam Rectal Gel: Effectiveness and Safety Profile

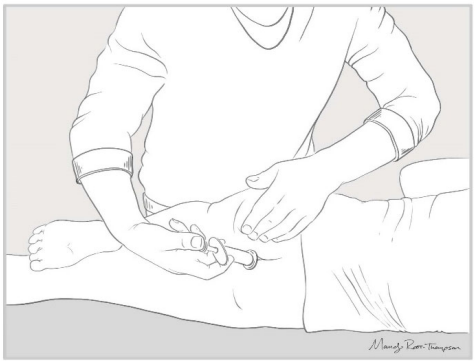
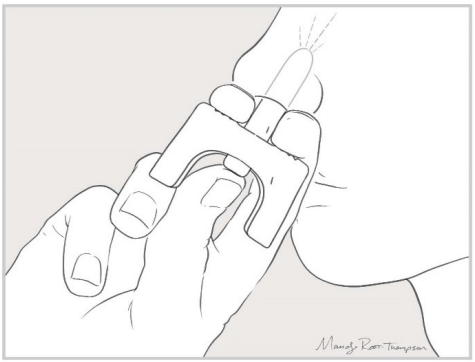
Diazepam rectal gel was investigated in two randomized, double-blind, placebo-controlled trials comprising 205 treated patients total (diazepam rectal gel, $n = 101$; placebo, $n = 104$) [24, 44]. Compared with placebo, diazepam rectal gel was more effective at reducing seizure frequency (seizures per hour; median approx. 0 vs approx. 0.3; $P < 0.001$) [24] and number of seizures over a 12-h period (median 0 vs 2; $P = 0.029$) [44]. In both studies, the most frequent treatment-emergent adverse event (TEAE; those that arise during treatment) was somnolence (33% [24] and 13% [44]), and there were no reports of respiratory depression [24, 44].

In an open-label safety study with 149 patients, 17% reported somnolence, with 9% attributed to treatment [45]. No serious TEAEs or deaths were attributed to diazepam rectal gel. Two patients experienced hypoventilation that did not require treatment, and three discontinued owing to TEAEs. Of 1578 seizure clusters, 77% were controlled throughout the 12-h observation period [45].

Patient and Caregiver Perspectives on Diazepam Rectal Gel

In the placebo-controlled studies, caregivers completed global assessments of rescue treatment, and assessments were generally more favorable with diazepam rectal gel than with placebo [24, 44]. In the long-term open-label safety study, caregiver assessments of diazepam rectal gel remained highly positive at 12- and 24-month visits [45].

Table 1 Practical steps for administration of FDA-approved rescue medications

Treatment	Administration
Rectal 	**Step 1:** Put person on their side where they can't fall. **Step 2:** Remove medicine from package and remove the cap (including seal pin) from syringe. **Step 3:** Lubricate rectal tip with lubricating jelly. **Step 4:** Turn person on side facing you. **Step 5:** Bend upper leg forward and separate buttocks to expose rectum. **Step 6:** Gently insert syringe tip into rectum. **Step 7:** Slowly count to 3 while gently pushing plunger in until it stops. **Step 8:** Slowly count to 3 before removing syringe from rectum. **Step 9:** Slowly count to 3 while holding buttocks together to prevent leakage.
Intranasal 	**Step 1:** Peel open the blister packaging and remove the device. **Step 2:** Hold the nasal spray unit with thumb on the plunger. **Step 3:** Place the tip into 1 nostril. **Step 4:** Press the plunger firmly.

Important: For intranasal spray, if the dose requires 2 devices, give the second spray in the other nostril to provide the full dose.
FDA, US Food and Drug Administration.

Midazolam Nasal Spray

Benzodiazepines are hydrophobic and have poor water solubility [25], and midazolam nasal spray uses organic solvents to solubilize midazolam in an aqueous spray solution that has a more neutral pH than the IV formulation of midazolam [40]. Midazolam nasal spray can be stored at room temperature for up to 2 years, and each box contains two 5-mg doses [40, 46]. For treatment of seizure clusters, one 5-mg dose is administered into one nostril irrespective of patient weight. If necessary, a second 5-mg dose can be administered in the other nostril 10 min after the first dose (Table 1) [40].

Clinical Development of Midazolam Nasal Spray

A phase 1, open-label, randomized, five-way crossover study was conducted in healthy adult volunteers to compare the pharmacokinetics and pharmacodynamics of midazolam nasal spray (2.5–7.5 mg/0.1 mL) with an injectable form of midazolam administered intravenously or intranasally (5 mg/1 mL) [40, 47]. The absolute bioavailability for all

doses of midazolam nasal spray was greater than with intranasal administration of midazolam solution for injection (62–73% vs 50%). Peak concentration (C_{max}) of midazolam nasal spray ranged from 59 to 93 ng/mL compared with 55 ng/mL achieved with intranasal midazolam solution. The elimination half-life of midazolam for the nasal spray (3.6–3.8 h), intranasal solution (3.6 h), and IV formulation (4.0 h) was similar [47]. Pharmacokinetic variability (percent geometric coefficient of variation, %GCV) of midazolam nasal spray in healthy adults was low to moderate, with inter- and intraindividual variability of 16–22% and 33–38%, respectively [48]. In a population pharmacokinetic analysis, doses greater than 15 mg failed to increase plasma levels of midazolam further as a result of reduced relative bioavailability, which may be protective in the event of overdosing [48].

Midazolam Nasal Spray: Safety and Effectiveness Profile

The safety and efficacy of midazolam nasal spray in patients experiencing seizure clusters were investigated in three phase 3 clinical trials (Acute Rescue Therapy in Epilepsy with Midazolam Intranasal Spray [ARTEMIS-1, ARTEMIS-2, ARTEMIS-EMU]) [49–51]. ARTEMIS-1, a double-blind, randomized, placebo-controlled trial, comprised test-dose and comparative phases [49]. In the test-dose phase consisting of 292 patients, rates of TEAEs (at least one), serious TEAEs, and treatment-related TEAEs (TEAEs considered related to treatment by the investigator) were 51%, 5%, and 37%, respectively. Four percent discontinued owing to a treatment-related TEAE, and 1% (2 patients) discontinued because of respiratory depression with decreased oxygen saturation. Current labeling instructions suggest considering a test dose for patients at risk of respiratory depression [40]. More patients in the midazolam nasal spray group achieved the primary endpoint of seizure termination within 10 min of treatment and no seizure recurrence from 10 min to 6 h following treatment (54% with midazolam vs 34% with placebo) [49].

ARTEMIS-2 was an open-label extension trial of ARTEMIS-1 ($n = 161$ patients) [50]. Fifty-seven percent of patients experienced at least one TEAE, 11% a serious TEAE, and 35% a treatment-related TEAE; 1% discontinued the study owing to a treatment-related TEAE [50]. Sedation with midazolam nasal spray has been reported to be greatest 15–120 min after administration, with a return to baseline approximately 240 min after dosing [48]. Of 1998 seizure clusters, 769 (38%) received a second dose of midazolam nasal spray within 6 h of the first dose, suggesting that a single dose was effective for most clusters [50].

ARTEMIS-EMU was a double-blind, randomized, placebo-controlled trial in patients admitted to an Epilepsy Monitoring Unit [51]. The rates of TEAEs (52%) and treatment-related TEAEs (42%) were comparable to results in ARTEMIS-1 and ARTEMIS-2, with no reports of serious TEAEs or discontinuations owing to TEAEs. A greater proportion of patients who received midazolam nasal spray were seizure-free 6 h after active treatment compared with placebo (55% vs 39%, respectively; $n = 31$ per group), although this difference was not statistically significant [51].

Patient and Caregiver Perspectives on Midazolam Nasal Spray

Psychosocial outcomes for patients and caregivers were assessed in the ARTEMIS-2 trial [52]. Patient satisfaction with midazolam nasal spray, as measured by the Treatment Satisfaction Questionnaire for Medication, numerically increased from baseline to last visit in all domains (effectiveness, side effects, convenience, global satisfaction). In addition, repeated use of midazolam nasal spray was associated with reduced anxiety in both patients and caregivers, and approximately four out of five patients and caregivers were confident to travel with an intranasal spray. Small improvements in Short Form-12 Health Survey version 2 domains of general health, physical functioning, role-physical, role-emotional, and bodily pain, as well as the physical health component, were reported for patients and caregivers [52].

Diazepam Nasal Spray

Diazepam nasal spray contains dodecyl maltoside (Intravail®; Neurelis, Inc. [San Diego, CA, USA]), an alkylsaccharide excipient that facilitates diazepam absorption across the nasal mucosa [25, 53]. Dodecyl maltoside transiently increases nasal epithelial permeability by relaxing tight intercellular junctions [25]. In a study with sumatriptan, dodecyl maltoside has been shown to increase bioavailability while decreasing time to C_{max} [53]. Vitamin E is used to solubilize diazepam for delivery in an aqueous spray [25]. Diazepam nasal spray is stable at room temperature, with a shelf life longer than 2 years [54]. Diazepam nasal spray comes in 5-, 10-, 15-, and 20-mg doses (15- and 20-mg doses require two sprayers of 7.5 or 10 mg each: one for each nostril), and dose is based on patient age and weight (0.3 mg/kg for patients aged 6–11 years; 0.2 mg/kg for patients aged 12 years or older) [39]. Each blister pack contains one full dose, and there are two blister packs (doses) per carton [39]. Administration involves proper handling of the sprayer and positioning of the nozzle in the nostril (Table 1) [55]. If needed, a second dose may be given at least 4 h after the first dose, using the second blister pack [29].

Clinical Development of Diazepam Nasal Spray

Diazepam nasal spray was approved by the FDA through the 505(b)(2) regulatory pathway, which utilizes a reference drug (diazepam rectal gel) for support of safety and effectiveness [56]. In one of the trials for diazepam rectal gel, two or three doses of diazepam rectal gel (based on age) were administered, with the second dose 4 h after the first dose and, for adults, another at 12 h in order to maintain plasma levels of diazepam (150–300 ng/mL) [24], which contributed to the FDA label requirements of 4 h between first and second doses of diazepam nasal spray [57]. As part of the 505(b)(2) pathway, diazepam nasal spray inherited the same labeling for use as the rectal gel [56]. In the summary of findings, the FDA stated that the intranasal administration route of diazepam nasal spray was clinically superior because it "provides a major contribution to patient care over the rectal route of administration by providing a significantly improved ease of use" [58].

The pharmacokinetics of diazepam nasal spray was investigated in phase 1 studies conducted in healthy volunteers [43, 59, 60] and patients with epilepsy [61]. An open-label, three-way crossover study compared the bioavailability and other pharmacokinetic variables of two intranasal formulations of diazepam (nasal solution [the formulation for diazepam nasal spray] and nasal suspension) with IV formulation of diazepam [59]. Bioavailability of diazepam nasal spray (10 mg) was 97%, whereas that of the nasal suspension (10 mg) was 67%. C_{max} of diazepam nasal spray and the nasal suspension were 272 and 221 ng/mL, respectively [59], which were in a therapeutic range associated with reductions in electroencephalogram spike counts [62]. The half-life of diazepam was similar for both intranasal formulations (diazepam nasal spray, 49.2 h; nasal suspension, 56.2 h) and the IV formulation (56.2 h) [59], suggesting that diazepam was effectively absorbed using the intranasal route.

An open-label, randomized crossover study assessed the dose proportionality and pharmacokinetics of diazepam nasal spray [60]. Diazepam nasal spray administered in 5-, 10-, and 20-mg doses achieved mean C_{max} of 85.6, 133.6, and 235.3 ng/mL, respectively, which was suggestive of dose proportionality, although a formal analysis of dose proportionality was inconclusive owing to intersubject variability [60]. An open-label, randomized, single-dose, three-treatment, three-period, six-sequence crossover study compared bioavailability and safety of diazepam nasal spray with orally and rectally administered diazepam [43]. Pharmacokinetic variability (%GCV) of diazepam was 2- to 4-fold lower with nasal spray (44–81%) than rectal gel (83–170%), with rectal gel administered under ideal conditions (i.e., a fasted state, with enemas administered the night before testing and 1 h before testing) [43]. A single-dose pharmacokinetics and safety study of diazepam nasal spray conducted in patients with epilepsy [61] reported comparable pharmacokinetic characteristics during ictal/peri-ictal and

interictal periods, which were similar to those previously described in healthy volunteers [60, 61].

Diazepam Nasal Spray: Safety and Effectiveness Profile

The safety of diazepam nasal spray in patients with epilepsy was investigated in phase 1 and phase 3 clinical trials [61, 63]. Exploratory outcomes related to effectiveness and patient experiences were assessed in the phase 3 study [63]. There were no discontinuations, serious TEAEs, or deaths considered related to treatment in the clinical development program, which included 220 patients with epilepsy across studies [61, 63].

A phase 3, long-term, repeat-dose, open-label safety study of diazepam nasal spray (NCT02721069) was performed in 163 patients with epilepsy who received at least one dose of diazepam nasal spray [63]. A total of 82% of patients experienced TEAEs, 31% experienced serious adverse effects, and 18% experienced treatment-related TEAEs. Nasal discomfort was the most common treatment-related TEAE (6%), followed by headache (2%), dysgeusia (2%), epistaxis (2%), and somnolence (2%). There were no changes of clinical relevance in respiratory rate, laboratory tests, or vital signs with treatment [63]. In patients aged 6–11 years, rates of TEAEs, serious TEAEs, and treatment-related TEAEs were 91%, 40%, and 7%, respectively [64].

Administration of diazepam nasal spray was easily accomplished and rapidly effective. For example, the median time from seizure onset to administration was 2 min (range 1–750 min), whereas the median time from administration to seizure cessation was 4 min (range 1–1151 min) [65]. Consistency of effectiveness of diazepam nasal spray was shown by the low rate of a second dose used to treat seizure clusters (13%) over a 24-h period [63]. Seventy-nine patients (48%) received a second dose [66], and eight patients accounted for 50% of those who received a second dose (data on file). The safety and effectiveness of diazepam nasal spray were similar for the overall population and among patients who received concomitant benzodiazepines [63], pediatric patients with developmental and epileptic encephalopathies [67], and patients who averaged more than 2 to 5 doses per month [63].

Patient and Caregiver Perspectives on Diazepam Nasal Spray

In an exit survey from the phase 3 open-label safety study of diazepam nasal spray, 59% of patients indicated that they were back to baseline within an hour of administration, and 59% of caregivers were able to return to daily activities within an hour of administration [68]. Eighty-nine percent of patients said that it was extremely easy or very easy to train others on administration of diazepam nasal spray, and 79% were comfortable doing activities outside the home with diazepam nasal spray available [68]. In patients who self-administered diazepam nasal spray, 78% described administration as either very easy or extremely easy, and 67% were somewhat, very, or extremely comfortable administering in a public setting. In the caregiver survey, 100% responded that it was extremely easy or very easy to be trained to administer diazepam nasal spray, and 90% were extremely or very comfortable administering diazepam nasal spray in public [68].

Quality of Life Adult patient quality of life was assessed in the phase 3 open-label safety study of diazepam nasal spray using the Quality of Life in Epilepsy (QOLIE)-31-P instrument [69]. Overall scores using the QOLIE-31-P instrument to address quality of life in this patient sample with drug-resistant epilepsy were stable over time. Importantly, scores involving subscales of Seizure Worry and Social Functioning, which were hypothesized to be most relevant to use of rescue treatment, showed clinically meaningful improvements over the course of the study, indirectly suggesting a potential reduction in the burden of seizure clusters [69]. The peace of mind of having diazepam nasal spray on-hand also might contribute to these improvements in QOLIE-31-P subscale scores.

Exploring Long-Term Change in Interval Between Seizure Clusters

Conventional outcomes used to determine the effectiveness of treatment for seizure clusters typically include measures of frequency and recurrence [70]. Patterns of seizure clusters with long-term use of intermittent acute seizure rescue treatments are not well characterized. A post hoc analysis of data from the phase 3 open-label safety study of diazepam nasal spray examined the interval between treated seizure clusters (SEIVAL) over time in patients that received intermittent treatment with diazepam nasal spray. In patients with intervals between clusters in each of four 90-day periods, the mean interval between usage of diazepam nasal spray (excluding re-treatments for a single cluster) increased from 14 days during the initial period (days 1–90) to 27 days by the final period (days 271–360; $P \leq 0.001$ compared with period 1). A conservative analysis that included second doses for a seizure cluster resulted in a similar increase in intervals, from 12 days in the first 90 days to 26 days in the last 90 days ($P \leq 0.001$). Changes in concomitant ASMs (drug or dose) did not explain the changes over time [70]. Exploration of the cause for this pattern of increased duration between seizure clusters over time with intermittent therapy has allowed for hypothesis generation that was previously published [70].

INVESTIGATIONAL RESCUE MEDICATIONS

There are other benzodiazepine rescue medications that are being formally evaluated as treatments for seizure emergencies. Inhaled alprazolam suppressed photoepileptiform activity 2 min after administration in photosensitive subjects [71] and is being investigated as a potential treatment for stereotypical prolonged seizures (NCT05076617, NCT05077904) [72, 73]. Similar to other diazepam formulations, interim results of at least a 6-month-long safety study of diazepam buccal film (NCT03428360) is now complete [74]. This supports safety and tolerability in patients aged 4–62 years ($N = 118$) who were expected to use benzodiazepine treatment at least monthly, on average, for acute seizure rescue including seizure clusters [75]. Age- and weight-based dosing was modified from that of the rectal gel formulation. Treatment-related TEAEs occurred in 7.6% of patients, with fatigue and somnolence being the most common (1.7% of patients each); most were mild and no patients discontinued owing to a treatment-related TEAE, although one case of respiratory failure in a pediatric patient was deemed at least possibly related to treatment. Self-administration by adults, ease of use, and limited use of second doses were reported. There are challenges inherent to the buccal route of administration, including clenched jaw, aspiration, mechanical placement, and expulsion or ingestion of the film [75]. This formulation is being evaluated by regional regulatory agencies.

PRACTICAL GUIDANCE

Epilepsy can lead to fear and anxiety, which can influence the ability to engage in normal daily activities and affect quality of life [11, 76]. The availability of acute seizure rescue medications for use in the community provides a treatment option that does not require specialized medical training [27], allowing for self-care of seizure clusters by patients and caregivers. As such, rescue medications may empower patients and caregivers and reduce anxiety associated with these seizure emergencies [69].

Seizure clusters are unpredictable, and this is especially true for newly diagnosed patients, who may lack established seizure patterns. Despite the presence or absence of risk factors, it can be difficult for healthcare professionals to anticipate patients who are likely to develop seizure clusters or when clusters will occur. Treatment to be used as a rescue therapy could be considered for newly diagnosed patients or any other patient who could potentially experience seizure clusters (e.g., patients with a history of emergency department visits for seizures or status epilepticus), in addition to those with a history of seizure clusters (Table 2) [4]. Other considerations for prescribing a rescue medication might include patients with drug-resistant

Table 2 Characteristics of rescue medications for treatment of seizure clusters. Adapted from Cloyd et al., 2021 [25] with permission from John Wiley and Sons

Route	Drug(s)	Advantages	Disadvantages
Rectal	Diazepam [28] *Dose:* 2–5 years: 0.5 mg/kg 6–11 years: 0.3 mg/kg ≥ 12 years: 0.2 mg/kg	Can administer relatively large dose volume Relatively painless Safe [45] Patient cooperation not needed [28] Relatively fast absorption and onset of action [43, 80]	Inconsistent absorption and bioavailability Poor social acceptability Potential for leakage [81] Potential difficulty with administration (proper positioning, partial disrobing) [29]
Intranasal	Diazepam [54] *Dose:* 6–11 years: 0.3 mg/kg ≥ 12 years: 0.2 mg/kg Midazolam [40] *Dose:* 5 mg	Quick and easy administration Relatively fast absorption and onset of action Safe Patient cooperation not needed Relatively painless Avoids first-pass metabolism Socially acceptable vs rectal route Possible direct brain delivery of drug	Need for delivery device (e.g., atomizer) Possible CNS TEAEs Variable absorption and bioavailability depending on mucosal health and specific benzodiazepine Formulations require high drug concentration in a small volume Nasal/throat discomfort, inflammation, lacrimation, abnormal taste Need to enhance drug solubility

CNS central nervous system, *TEAE* treatment-emergent adverse event

epilepsy and those with an early age of seizure onset when seizures are likely to recur or be prolonged [30].

Some patients may experience recurrent seizures after treatment of their seizure cluster, and second doses of rescue medication may be needed. In the comparative phase of ARTEMIS-1, slightly more patients who received a second dose of midazolam nasal spray 10 min to 6 h after the first dose experienced a treatment-related TEAE than those who received a single dose (30% vs 22%) [49]. Greater rates of nasal discomfort were associated with two doses (16%) vs one dose (5%) of midazolam nasal spray; however, there were no reports of respiratory depression in the comparative phase (two cases of respiratory depression were reported in the test-dose phase) [49]. Similarly, slightly more patients in the open-label safety study of diazepam nasal spray who received a second dose of diazepam nasal spray within 24 h of the first dose had a treatment-related TEAE than the overall population (24% vs 18%) [66]. Nasal discomfort was reported more frequently in patients who received a second dose within 4 h of the first dose (8%) compared with those who received a second dose more than 4 h after the first dose (5%) with no reports of respiratory depression [77].

In addition to pediatric indication and route of administration, points of differentiation for the approved agents also include duration of effectiveness as well as differences in how the agents were evaluated. For example, seizure

control of acute repetitive seizures using a single dose or no second dose was measured in different time frames in noncomparative studies of midazolam nasal spray (61.5% at 6 h) [50], diazepam rectal gel (77.0% at 12 h) [45], and diazepam nasal spray (94.2%, 91.7%, and 87.4% at 6, 12, and 24 h, respectively) [78].

Acute seizure action plans (ASAPs) include detailed management strategies related to general seizure action plans (SAPs) for acute treatment of seizure emergencies [79]. SAPs provide a broad overview of seizure management in people with epilepsy. This includes information on seizure characteristics, ASMs including rescue treatments, and contact instructions, in addition to other medical and emergency support information relevant to the patient. An ASAP is a more concise, simplified document that describes usual seizure presentations of the patient as well as appropriate steps for treatment. Designed for use during a seizure, an ASAP should be easy to use, incorporating illustrations and simple directions to facilitate immediate treatment. These plans should be reviewed periodically, as needed. SAPs/ASAPs might improve self-management of seizures for all patients by providing education on treatments designed for in-home use, reducing anxiety associated with these types of emergencies [79].

CONCLUSION

Acute rescue medications can be used in a community setting to treat seizure clusters, which can potentially improve the time to treatment and quality of response. Although there are various formulations of benzodiazepines that have been used off-label for treatment of seizure clusters, each possesses drawbacks (e.g., qualified ease of use, inadequate absorption, risks to the patient) that limit their widespread use. In contrast, FDA-approved rescue medications for seizure clusters were designed to build upon the existing treatment paradigm at the time of their approval, with the intent of improving treatment practices and patient outcomes. Approved rescue medications have unique therapeutic profiles, and the latest intranasal medications have optimized their individual formulations with distinct characteristics to facilitate solubility and absorption via the nasal mucosa, leading to high bioavailability. Convenient delivery systems of intranasal medications allow for their rapid use in public settings.

Despite the approval of rescue medications that have the potential to improve patient care, there appear to be barriers that limit their use. Identifying patients that could benefit from rescue medication and providing materials that can support and direct patient care at the time of seizure emergency (i.e., SAPs) are areas that could be bolstered in clinical practice to potentially address these barriers with a goal of improving patient care and quality of life.

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