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REVIEW ARTICLE

Benzodiazepines for the Treatment of Seizure Clusters

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Abstract

Patients with epilepsy may experience seizure clusters, which are described by the US Food and Drug Administration (FDA) as intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern. Untreated seizure clusters may increase the risk for status epilepticus, as well as decrease quality of life and increase burden on patients and care partners. Benzodiazepine therapies are the mainstay for acute treatment of seizure clusters and are often administered by nonmedical care partners outside a healthcare facility. Three rescue therapies are currently FDA-approved for this indication, with diazepam rectal gel being the first in 1997, for patients aged ≥ 2 years. Limitations of rectal administration (e.g., positioning and disrobing the patient, which may affect ease of use and social acceptability; interpatient variation in bioavailability) led to the investigation of the potential for nasal administration as an alternative. Midazolam nasal spray (MDS) was approved by the FDA in 2019 for patients aged ≥ 12 years and diazepam nasal spray (DNS) in 2020 for patients aged ≥ 6 years; these two intranasal therapies have differences in their formulations [e.g., organic solvents (MDS) vs. Intravail and vitamin E for absorption and solubility (DNS)], effectiveness (e.g., proportion of seizure clusters requiring only one dose), and safety profiles. In clinical studies, the proportion of seizure clusters for which only one dose of medication was used varied between the three approved rescue therapies with the highest single-dose rate for any time period for DNS; however, although studies for all three preparations enrolled patients with highly intractable epilepsy, inclusion and exclusion criteria varied, so the three cannot be directly compared. Treatments that have been used off-label for seizure clusters in the USA include midazolam for injection as an intranasal spray (indicated for sedation/anxiolysis/amnesia and anesthesia) and tablet forms of clonazepam (indicated for treatment for seizure disorders) and lorazepam (indicated for anxiety). In the European Union, buccal and intranasal midazolam are used for treating the indication of prolonged, acute convulsive seizures and rectal diazepam solution for the indication of epileptic and febrile convulsions; duration of effectiveness for these medications for the treatment of seizure clusters has not been established. This paper examines the literature context for understanding seizure clusters and their treatment and provides effectiveness, safety, and administration details for the three FDA-approved rescue therapies. Additionally, other medications that are used for rescue therapy in the USA and globally are discussed. Finally, the potential benefits of seizure action plans and candidates for their use are addressed. This paper is intended to provide details about the unique characteristics of rescue therapies for seizure clusters to help clarify appropriate treatment for individual patients.

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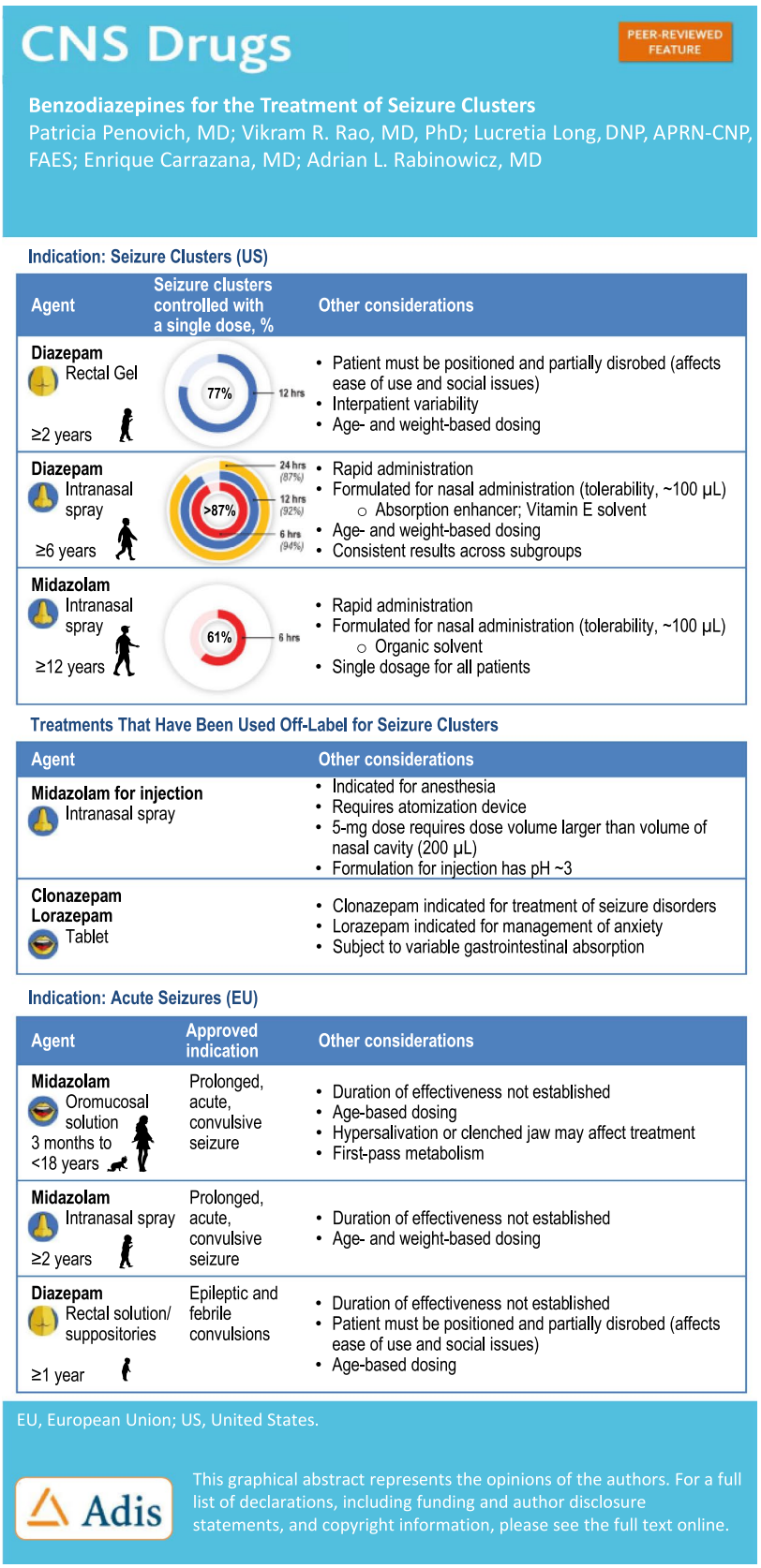
Graphical Abstract



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Key Points

Rectal diazepam gel was the first US Food and Drug Administration (FDA)-approved rescue therapy for seizure clusters; however, it has limitations for administration.

Recently two intranasal therapies were FDA-approved for seizure clusters, one with midazolam and the other with diazepam, which have important differences.

Midazolam nasal spray is FDA-approved for patients aged ≥ 12 years as a 5-mg dose regardless of age or weight; its formulation includes organic solvents for solubility and absorption.

Diazepam nasal spray is approved for patients aged ≥ 6 years with dosing based on patient age and weight; its formulation includes vitamin E for solubility and Intravail for absorption.

1 Introduction

Epilepsy affects 1.2% of the population in the USA (~ 3 million adults and 470,000 children) [1], with about 30–40% having drug-resistant epilepsy [2, 3]. Despite stable daily antiseizure medication (ASM), these patients may have seizure emergencies including status epilepticus, prolonged seizures, and seizure clusters (also known as acute repetitive seizures) [4–6]. Benzodiazepine rescue therapy is a cornerstone of seizure cluster treatment but has been underused by patients and caregivers [4]; historically, only 20% of adults with seizure clusters used rescue medications [6]. Among adults aged ≥ 18 years with focal-onset epilepsy in a retrospective study ($N = 46{,}474$), only 1948 (4.2%) had a documented rescue medication, and those adults who did use rescue medication at baseline had a reduced risk of failing treatment [7]. In another study, predictors of receiving rescue therapy included younger age, lower age at epilepsy onset, more frequent seizures, and a higher number of ASMs [8].

After its approval in 1997, rectal diazepam was the only rescue therapy approved by the US Food and Drug Administration (FDA) for seizure clusters until 2019, but patients may view rectal delivery as embarrassing and challenging in a public setting [9]. Preference by both patients and caregivers has been given to alternative forms of rescue therapy administration, with particular interest in newer intranasal options that are less invasive and potentially more likely to be used by caregivers [10, 11]. This review focuses on intranasal benzodiazepine rescue therapy for seizure clusters.

2 Seizure Clusters

At this time, there is no consensus definition of seizure clusters, with proposed definitions varying by seizure frequency and duration of the cluster [12] and patient-specific characteristics [3]. Although there is no standard definition of seizure clusters [12], untreated clusters are typically characterized by recurrent individual seizures within 6–24 h of the first seizure [13] and are typically recognizable by caregivers [14]. Differing empirical definitions have been proposed by studies in the literature (e.g., ≥ two or three seizures in a 24-h period; Table 1) [3]. The FDA recognizes seizure clusters as an orphan indication [15], defined as intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern [16–18]. Notably, because this definition is based on an individual patient's typical pattern, seizure clusters can include any seizure type.

Untreated seizure clusters may be associated with injury, increased rates of hospitalization [19–21], and risk of sudden, unexpected death in epilepsy [22]. Clusters may progress to status epilepticus [23], which can lead to neuronal damage [24] and be life threatening [19]. The ability of patients and caregivers to self-administer FDA-approved drugs may reduce burden to patients and families as well as decrease healthcare utilization and costs owing to the reduction in emergency department visits with associated transportation costs.

2.1 Recognizing Seizure Clusters

Because seizure clusters do not have a specific, accepted definition [12], identification of patients with seizure clusters presents a challenge. Seizure diaries can provide insight into the temporal relation between seizures that could be indicative of a cluster [13, 25].The number of seizures in a cluster, time between seizures in a cluster, duration of cluster, time between clusters, and experience and impact should all be taken into account [3]. Among risk factors for seizure clusters are high seizure frequency or prior status epilepticus and failure of multiple ASMs [26].

Not all patients may have these known risk factors. Newly diagnosed patients may not yet have established a clear pattern but may benefit from the availability of a rescue treatment. A Delphi consensus agreed that all people with epilepsy should be educated about rescue therapies, with a nearly unanimous agreement to provide rescue treatment to patients who have had prolonged seizures and/or prior status epilepticus, have needed rescue therapy in the past, or have a

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Table 1 Summaries of empirical definitions for seizure clusters and related terms in the literature (1998–2021)

Term used	Definition
Acute repetitive seizures [35]	Multiple complex partial or generalized (tonic, clonic, tonic–clonic, atypical absence, or myoclonic) seizures occurring within a 24-h period in adults or a 12-h period in children, with a pattern distinguishable from the patient's usual seizure pattern and with onset readily recognizable by a caregiver, such as a parent
Acute repetitive seizures [14]	A predictable component of a patient's seizure disorder historically distinct from the patient's other epileptic seizures in type, frequency, severity, or duration and with an onset easily recognized by family and physician
Seizure clustering [97]	≥ 3 seizures within a 24-h period
Acute repetitive seizures [98]	≥ 3 partial or generalized seizure episodes over a 24-h period
Seizure clusters [99]	≥ 3 or more complex partial seizures or generalized tonic–clonic seizures in a 4- or 24-h period
Perimenstrual seizure exacerbation [100]	Threefold or greater level of perimenstrual (days −3 to +3) seizure exacerbation
Seizure clusters [13]	≥ 2 seizures in a midnight-to-midnight calendar day
Seizure clusters [101]	≥ 2 seizures occurring within 2 days in a habitual pattern that was also distinguishable from more sporadic usual seizures
Seizure clusters [6]	≥ 2 seizures in 24 h outside a patient's typical seizure pattern
Seizure clusters [43]	≥ 2 seizures (focal or generalized) that lasted ≥ 10 min and had an observable, stereotyped, and recognizably different pattern from patients' noncluster seizure activity, with another seizure occurring within 6 h of cluster onset
Seizure clusters [102]	Individualized using a data-driven approach
Seizure clusters [46]	Intermittent increases of seizure activity
Repetitive seizures [103]	≥ 3 seizures within 1 h

Adapted with permission from Haut SR, Nabbout R. Recognizing seizure clusters in the community: The path to uniformity and individualization in nomenclature and definition. *Epilepsia*. Copyright 2022 International League Against Epilepsy; published by Wiley Periodicals LLC on behalf of the International League Against Epilepsy [3]

history of seizure clusters [12]. Additionally, seizure clusters are sometimes associated with catamenial epilepsy [27].

2.2 Patient and Caregiver Perspective

Seizure clusters can have a negative effect on quality of life for both patients and caregivers; three-quarters of adults who have seizure clusters report that they fear they will experience a seizure at any time [6]. They describe emotional, financial, and social concerns, including worrying about loss of independence and control of seizure clusters. In a 2017 study, a majority of patients (57%) stated that seizure clusters made their lives "miserable" [6]. A majority of patients and caregivers somewhat or strongly agreed that epilepsy prevents the patient from doing what other people do. The majority of patients worried about loss of seizure control in a public setting and being a burden to their caregiver [6]. Indeed, patients may under-report seizures to reduce the stress on caregivers [28].

Patients and caregivers felt that epilepsy limited participation in activities ranging from activities of daily life to travel and vacations [6]. Providing patients with knowledge and tools may empower their sense of control in these situations. Offering them education about treatments and tools could be an important initial step toward empowering patients.

3 Treating Seizure Clusters

The ideal acute treatment for seizures should allow for easy administration during a seizure by a nonmedical caregiver while providing consistent absorption, effectiveness, and safety [9]. In addition, because seizure clusters may last 24 h or more [13], a potential treatment would require an extended duration of action.

Currently, three agents are approved for this indication by the FDA (Table 1), and off-label oral and atomized intravenous treatments have also been used. Seizure clusters are not included in the International League Against Epilepsy classifications [29]. Different treatments may be used for different circumstances, such as different availability in different parts of the world. Many of these treatments were recently reviewed by Kienitz and colleagues [5].

Costs for rescue medications vary according to the needs of the individual patient, and should be taken into consideration along with the general cost burden for patients with epilepsy, including direct and indirect costs of epilepsy in general and seizure clusters specifically [30]. Rescue medication costs are based on such variables as the specific drug, route of administration, and how often the drug is administered, including the cost of repeat doses for a single seizure cluster or emergency services, if needed [30]. Additionally, coverage by private and public insurance plans may vary.

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For older adults, treatment for epilepsy in long-term care facilities is also an important consideration, as seizure disorders in that setting may be associated with increased comorbidity burden and mortality [31, 32]. For patients with seizure clusters, having rescue medication on hand in the facility may help to decrease seizure duration, onset of status epilepticus, and the need for emergency medical transport [33, 34].

3.1 Diazepam Rectal Gel

Diazepam rectal gel (Diastat®) was approved by the FDA in 1997 for the treatment of seizure clusters in patients aged ≥ 2 years based on two pivotal studies [14, 35]. This is a prefilled unit-delivery system with the dosing based on age and weight [16]. A second dose can be administered if needed 4–12 h after the initial dose [16]. Diazepam reduced seizure frequency per hour in the two placebo-controlled studies (Table 2) [14, 35]. In a study with 158 patients with seizure clusters (114 treated), outpatients or institutionalized patients 2 years or older were monitored, and their seizure episodes were treated with diazepam rectal gel or placebo [14]. The post-treatment median frequency of seizures within 6 h was 0 for diazepam rectal gel and 2.0 for placebo ($P = 0.029$). Kaplan-Meier survival curves showed that the rectal gel did not just delay but also prevented further seizures that would have been expected given their known seizure cluster patterns. More patients who took diazepam rectal gel were seizure-free for 12 h after treatment than those taking placebo (55% vs. 34%, respectively; $P = 0.031$) [14]. In the other pivotal trial in 125 patients (aged 2–60 years) with seizure clusters, more patients who used diazepam rectal gel were seizure-free 12 h after treatment than those who took placebo (median, 0 vs. 0.29 seizures per h, respectively; $P < 0.001$), and Kaplan-Meier survival was similar to that observed in the first study [35]. An open-label, long-term safety study of 149 patients (72 patients [48%] aged <12 years and 77 [52%] aged 12–76 years; 126 were enrolled after completing one of the double-blind studies mentioned above) investigated safety, efficacy, and tolerance over a period of 24 months [21]. In about a quarter of the patients (23%), further seizures occurred within 12 h of the initial dose. Tolerance for the 125 patients who experienced at least two episodes was not significantly different, suggesting no loss of efficacy (63% had no subsequent seizures after their first rectal gel administration, and 69% had no further seizures after their last administration) [21].

The most common adverse event was somnolence, occurring in 22% of patients in the rectal gel group and 7% in the placebo group [14, 35]. In the long-term study, treatment-related somnolence occurred in 9% of patients, although the authors commented that differentiating between medication-induced and post-ictal sleep was difficult [21]. Safety data from the studies observed no effect of diazepam rectal gel on respiration [14, 21, 35].

Administration of diazepam rectal gel involves positioning the person on his or her side, preparing the syringe by removing the cap and lubricating the tip, bending the person's leg forward and separating the buttocks to expose the rectum, inserting and slowly administering the dose, and then holding the buttocks together so that the gel does not leak [16]. It is important for prescribers to be confident that caregivers fully understand when and how to administer the treatment and when emergency medical attention is required [16].

Although the rectal epithelium can accommodate larger volumes than other mucosal routes of administration to allow rapid uptake compared to suppositories, this route presents barriers to use and presents unmet medical and social needs for an alternative route of administration. Rectal diazepam shows patient-patient variability in absorption and therefore plasma concentrations [36, 37]. Various studies have also shown that patients and caregivers much prefer to avoid rectal administration if there are alternatives available [4, 9, 36]. For example, in a survey conducted during a long-term study of diazepam nasal spray in children and adults, most patients (86.7%) stated that they were not at all comfortable using diazepam rectal gel outside the home, and a majority (64.5%) felt more uncomfortable using it at home compared with using diazepam nasal spray [10]. In a small study of atomized midazolam for injection given intranasally to adult patients, 76.2% of patients and caregivers preferred the midazolam nasal spray compared with diazepam rectal solution [38].

4 Role of Nasal Spray Formulations

Intranasal medication is simple, convenient, and socially acceptable to administer; does not need patient cooperation; requires minimal caregiver training; carries little risk of injury; and allows for rapid absorption of the drug through the nasal mucosa [9, 36, 39]. The National Association of School Nurses recommends using the least restrictive medication (e.g., buccal or nasal) [40], and the FDA states that the intranasal route of administration is less invasive and provides "significantly improved ease of use" compared with rectal administration [41]. The drug is sprayed into the nasal cavity, where it is deposited on the nasal mucosa, then transported across the nasal epithelium and absorbed into the systemic circulation via the vascular endothelia [42], avoiding first-pass metabolism. From there, the drug crosses the blood-brain barrier and reaches the central nervous system and the brain, where it exerts its effect [42]. However, drug volume is limited to ~ 100 μL to minimize leakage out of the nasal cavity from the back or the front [9]. This results in a

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Table 2 US Food and Drug Administration (FDA)-approved rescue therapies for seizure clusters

Drug	How supplied	Composition	Dose and dosing			Time to onset [104]	T_{max} [42]	Bioavailability [105]
			Dosing	Second dose	Max dose/ frequency			
Diazepam rectal gel (Diastat) [16]	Diazepam gel supplied in a prefilled, unit-dose (Acudial) rectal delivery system Unit doses: 2.5, 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20 mg in 0.1 mL	5 mg/mL diazepam, benzoic acid, benzyl alcohol (1.5%), ethyl alcohol (10%), hydroxypropyl methylcellulose, propylene glycol, sodium benzoate, purified water	***Patients ≥ 2 y of age*** Individualized by age and weight 0.2–0.5 mg/kg 2–5 y: 0.5 mg/kg 6–11 y: 0.3 mg/kg ≥ 12 y: 0.2 mg/kg	4–12 h after initial dose	No more than 1 episode every 5 d Max 5 episodes per mo	2–10 min	1.2 h[a]	90%
Diazepam nasal spray (Valtoco) [17]	Single-dose nasal spray unit (Aptar Pharma Unidose System) 5.0, 7.5 and 10 mg dose in 0.1 mL	Diazepam, benzyl alcohol (10.5 mg per 0.1 mL), dehydrated alcohol, n-dodecyl beta-D-maltoside (Intravail, absorption enhancer), vitamin E	***Patients ≥ 6 y of age*** Individualized by age and weight 0.3–0.5 mg/kg 6–11 y: 0.3 mg/kg ≥ 12 y: 0.2 mg/kg 5- and 10-mg doses given as 1 spray into 1 nostril 15- and 20-mg doses given as 2 spray devices, 1 spray each into each nostril	4 h after initial dose	Max 2 doses per episode No more than 1 episode every 3 d Max 5 episodes per mo	2–10 min	1.5 h[b]	97%
Midazolam nasal spray (Nayzilam) [18]	Single-dose nasal spray unit (Aptar Pharma Unidose System) 5 mg dose in 0.1 mL	5 mg midazolam in 0.1 mL, ethanol, PEG-6 methyl ether; polyethylene glycol 400 (absorption enhancer), propylene glycol, purified water	***Patients ≥ 12 y of age*** 5 mg into 1 nostril	10 min after initial dose (opposite nostril to initial dose)	Max 2 doses per episode ≤1 episode every 3 d Max 5 episodes per mo	3–10 min	17.3 min	~ 44%

d days, *mo* months, *y* years, t_{max} time to peak plasma concentration

[a]15-mg dose

[b]10-mg dose

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challenge for developing high-concentration formulations of benzodiazepines [9].

4.1 Midazolam Nasal Spray

Midazolam nasal spray (Nayzilam®) was approved by the FDA for the treatment of seizure clusters in 2019 for patients ≥ 12 years of age [18]. Midazolam nasal spray is provided in a single-dose spray unit containing 5 mg midazolam, irrespective of patient age and weight, and is sprayed into one nostril. A second dose can be administered into the other nostril after 10 min if the patient has not responded to the initial dose. The spray solution includes a number of organic solvents that improve midazolam's solubility and absorption by the nasal mucosa (ethanol, polyethylene glycol (PEG-6) methyl ether, PEG-400, propylene glycol) [9, 18].

Intranasal midazolam was studied in patients with seizure clusters in a phase 3, randomized, double-blind, placebo-controlled study and its open-label extension, which collected data for a median of 16.8 months and a total 1,998 seizure cluster episodes [43, 44]. In these studies, patients were ineligible if they had a seizure cluster progressing to status epilepticus within 2 years before the first study visit, and concomitant maintenance ASM with a benzodiazepine was not allowed [44].

In the initial phase of the placebo-controlled study, 292 patients (18 patients (6.2%) aged < 18 years; 274 patients (93.8%) aged ≥ 18 years) were given a test dose to assess safety; 5.5% discontinued owing to a treatment-emergent adverse event (TEAE), with two patients discontinuing owing to decreased oxygen saturation [44]. In the double-blind phase of the study, out of 262 randomized outpatients, 201 received double-blind treatment (134 patients randomized to intranasal midazolam (five aged <18 years) and 67 to placebo), and 53.7% who were taking intranasal midazolam achieved seizure treatment success (primary outcome), defined as seizure termination within 10 min and with no recurrence 10 min to 6 h after drug administration, compared to 34.4% of those treated with placebo ($P = 0.0124$). Seizure recurrence in the 10-min to 4-h period after the initial episode (secondary outcome) was significantly less frequent in the midazolam nasal spray group compared to placebo (38.1% vs. 59.7%, respectively; $P = 0.0043$). Nasal discomfort was the most common TEAE and was highest for patients who took two doses of intranasal midazolam to control their seizure episode (16.3%) compared with those who took placebo for the initial dose and midazolam for their second dose (7.3%); the comparative rates for those who took only one dose for an episode was similar (intranasal midazolam, 5.5%; placebo, 7.7%). Abnormal product taste was reported within 2 days of treatment in 5.8% of patients during the test dose phase and 4.4% in the midazolam arm during the comparative phase [44].

In the open-label extension, 55% of seizure clusters were successfully terminated after a single 5-mg dose and 80.2% were terminated after a first or second dose [43]. There were no discontinuations due to central respiratory depression and no treatment-related cases of acute respiratory depression during the study. Nasal discomfort was experienced by 12.4% overall, which was greater than the 9.3% of TEAEs for somnolence [43]. Abnormal product taste was noted for 2.5% of patients within 2 days and throughout the trial [43]. Quality of life was maintained during the study, and there were modest increases in the domains of the Short Form-12 Health Survey [11]. Treatment satisfaction was numerically increased during the study for the perceptions of effectiveness, side effects, convenience, and global satisfaction domains. Patient and caregiver anxiety was reduced and confidence to travel was increased [11].

Intranasal midazolam is packaged in a ready-to-use device that contains a 5-mg single dose [18]. Patient position is not specified in the directions for use. The device is held in one hand, inserted in the nose, and the plunger is depressed to give the dose. In patients with a risk of respiratory depression, healthcare providers should consider initial administration while the patient is under their supervision [18].

4.2 Diazepam Nasal Spray

Diazepam nasal spray (Valtoco®) was approved by the FDA in 2020 for the treatment of seizure clusters in patients with epilepsy aged 6 years and older [17]. This diazepam formulation was approved by the FDA 505(b)(2) pathway, which allows some safety and efficacy data for the same active molecule and indication to come from studies of a separate reference drug [45, 46]. Diazepam nasal spray uses the same weight-based dosing as diazepam rectal gel for patients aged 6–11 years (0.3 mg/kg) and ≥ 12 years (0.2 mg/kg) [17], facilitating transition between formulations for patients and caregivers who prefer the nasal route of administration. A second dose can be administered in ≥ 4 h if needed [17]. The spray solution includes Intravail® (also used in one of the nasal sprays for migraine, sumatriptan), an alkylsaccharide that improves the absorption of small molecules, peptides, and proteins by transiently loosening gap junctions in the nasal mucosa and facilitating rapid absorption and bioavailability of diazepam [47], with no evidence of a clinically relevant food effect observed in the clinical development program [48]. As sugar-based alkylsaccharides are nontoxic, the inclusion of this absorption enhancer and the solvent vitamin E in the diazepam nasal spray formulation may assist with the potential for nasal mucosal toxicity and associated nasal discomfort, which may be seen with some ASMs that include organic solvents [9, 47]. Vitamin E is included as the solubilizing agent [49].

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Support for the efficacy of diazepam nasal spray was determined based on similar bioavailability of the active compound in the rectal diazepam studies [37, 50]. The safety of diazepam nasal spray was demonstrated in a phase 3, long-term, open-label, repeat-dose safety study in 163 patients (45 patients (27.6%) aged 6–11 years; 118 patients aged ≥ 12 years (72.4%)) treated for 3,853 seizure clusters over a mean exposure of ~ 1.5 years [46]. In the study, if a second dose were needed, patients and caregivers were instructed to give it 4–12 h after the first; dosing could be adjusted by the investigator if there were no safety concerns. The primary finding was that the safety profile was consistent with the established profile of rectal diazepam. TEAEs considered related to treatment occurred in 18.4% of patients, with only nasal discomfort (6.1%) occurring in ≥ 5% of patients. No serious TEAEs were considered treatment related, and no cases of respiratory depression were reported. Dysgusia was reported in 1.8% of patients across the full study [46].

The use of second doses of diazepam nasal spray was evaluated in the phase 3 safety study as a proxy for effectiveness. Only 12.6% ($n = 485$) of seizure clusters were treated with a second dose within 24 h of the initial treatment [51]. The safety profile for those who used second doses was similar to those in the overall safety population, with TEAEs and treatment-related TEAEs occurring within 1 day after the second dose reported as 15.2% and 5.1%, respectively [51]. A further analysis of the phase 3 safety study and the addition of pharmacokinetic assessments from three phase 1 studies showed that there were similar TEAE rates for those patients who received a second dose ≤ 4 h after the initial treatment compared with those who received a second dose at > 4 h, and that pharmacokinetic modeling predicts that plasma diazepam levels would be comparable whether the dosing interval was 1 min or 4 h [52].

The results of this study appear to be broadly generalizable for patients with seizure clusters. Those with prior status epilepticus were allowed to enroll in this study, and daily concomitant benzodiazepine use as an ASM was also permitted. A subgroup analysis of children (age 6–11 years) and adolescents (age 12–17 years) provides support for the approved age-based dosing guidelines [53] (a study in children aged 2–5 years is underway (ClinicalTrials.gov identifier: NCT05076838)) [54]. Safety and effectiveness of diazepam nasal spray were also maintained among patients receiving highly purified oral cannabidiol [55]. Interim findings did not find evidence of effects on safety or effectiveness in subgroups with rhinitis/seasonal allergies, concomitant use of benzodiazepine maintenance therapy, or dosing frequency [56–58].

Other analyses included a patient/caregiver survey that was conducted at the end of the long-term safety study [10], which showed that patients and caregivers were substantially more comfortable using diazepam nasal spray than rectal diazepam in public and documented self-administration in patients as young as 11 years [10]. In addition, quality of life, as measured with the QOLIE-31-P tool for adults with epilepsy, showed improvement in the Seizure Worry and Social Functioning subscale scores, aspects of quality of life hypothesized to be most relevant to rescue therapy, while maintaining overall scores across 365 days [59].

Interestingly, an exploratory analysis of the phase 3 study found that the time between seizure clusters (SEIzure interVAL or SEIVAL) increased across four sequential 90-day periods (~ 12 mo) with diazepam nasal spray treatment, doubling from 12.2 days in the first period to 25.7 days in the fourth period [60]. This increase in SEIVAL occurred irrespective of age, change in concomitant medications, or treatment duration. Quality of life, as measured by the QOLIE-31-P, was unaffected. This is a novel hypothesis-generating finding that merits further exploration [60].

Diazepam nasal spray is packaged in ready-to-use devices, and each pack contains a weight- and age-based single dose [17]. For 15- and 20-mg doses, two spray devices are used, one in each nostril, to deliver the full dose. Patient position is not specified in the directions for use. The device is held in one hand, inserted in the nose, and the plunger is depressed to give the dose [17, 61].

5 Use of Other Treatments for Seizure Clusters

5.1 Antiseizure Medications (ASMs) Used Off-Label for Seizure Clusters in the USA

Although other treatments have not been assessed in clinical development programs for seizure clusters, some have been used as more socially acceptable and easier-to-use alternatives to diazepam rectal gel [62] and may be of use in resource-limited countries. Midazolam solution for injection has been administered intranasally via an atomizer or spray [38, 63] or dripped directly into the nostrils [64, 65], and has been studied in a number of open-label trials that have supported effectiveness in terminating acute seizures [38, 63, 66] or preventing the short-term recurrence of seizures [67]; however, durability of those effects has generally not been assessed. Further, atomized intravenous midazolam requires a high spray volume as each milliliter contains a maximum of 5 mg of midazolam and is therefore subject to leakage, swallowing, and gastric absorption. In addition, the IV formulation has a low pH (~ 3) [68], which may cause nasal discomfort [9].

Orally disintegrating clonazepam tablets (Klonopin®), indicated for seizure disorders and panic attacks [69], have been used for acute treatment of seizures [70]. In a

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single-center survey of patients (aged 2–25 years) with a prescription for clonazepam for acute treatment of seizures lasting > 5 min, 68% (38/56) of patients reported that > 50% of their seizures stopped within 10 min. Among 16 patients who had also been treated with diazepam rectal gel, 69% felt that clonazepam wafers were at least as effective as diazepam rectal gel in terminating an acute seizure [70]. Notably, oral treatments may be subject to variable gastric absorption and first-pass metabolism [9].

Lorazepam is available as tablets (0.5, 1, and 2 mg), an intravenous injection (2 and 4 mg/mL), an oral concentrate (2 mg/mL) [71–73], and a sublingual tablet, which is available in Europe and Canada. Two studies have shown that up to 4-mg doses of intravenous and a non-atomized intranasal solution of lorazepam (directly instilled into one nostril) produced remission of acute seizure within 10 min in pediatric populations (aged 5–14 years) in India [74, 75]. The effectiveness (time to onset, duration) of lorazepam for seizure clusters specifically has not been formally confirmed in large clinical trials [62].

5.2 Drugs Approved for Use in Europe

Buccal midazolam (Buccolam®), an oromucosal solution in prefilled syringes, was approved by the European Medicines Agency in 2011 to stop prolonged, acute (sudden) convulsive seizures in children and adolescents (from age 3 months to < 18 years) [76]. Additionally, use in adults was recommended in the National Institute for Health and Care Excellence (NICE, based in the UK) 2012 epilepsy clinical guideline and in Italy for those who initiated treatment prior to age 18 years [77, 78]. Pediatric-use marketing authorization of buccal midazolam was supported by four controlled studies using rectal diazepam as the active comparator as well as one study versus intravenous diazepam [76, 79]. Median ages in four of the studies were 1.4–1.5, 1.5, 3, and 15 years [80]. Oromucosal midazolam was effective in stopping a seizure within 10 min in 65–78% of children in the four studies with rectal diazepam as the comparator. The safety profile for patients administered oromucosal midazolam was similar to that of the patients administered rectal diazepam liquid [81]. Buccal administration in patients undergoing a seizure with a clenched jaw or clonic jaw movements or hypersalivation may present problems for caregivers or medical staff [9, 62, 82]. The potential for impaired swallowing of the midazolam as well as an unpleasant taste are other disadvantages [36]. Marketing authorization has now been granted in the EU for a midazolam nasal spray (Nasolam) as treatment for prolonged, acute, convulsive seizures [83]. It was granted marketing authorization in a single-dose container in doses ranging from 2.5 to 5 mg for adults and children weighing > 12 kg and aged 2 years and older [84]. Rectal diazepam solution has a substantial history of use in the European Union for the treatment of epileptic or febrile convulsions [85, 86].

6 Seizure Action Plans

For seizure clusters, benzodiazepines are the first line of rescue therapy [87]. Caregivers should understand when rescue treatment is indicated, how to administer it, and when it is imperative to call for immediate emergency medical services [88]. Written seizure action plans can provide patients and nonmedical caregivers with guidance on day-to-day care, tailored to the individual patient [88]. A related document, an *acute* seizure action plan, is a streamlined, easy-to-use document focusing on immediate care during a seizure [88]. The ability to recognize a seizure emergency and rapidly provide appropriate treatment may reduce the risk of seizure-related injury [89]. This is important because seizure clusters may become less responsive to treatment if left untreated [90–92].

Patients of all ages who are prescribed rescue therapy for seizure clusters, including adults who are unlikely to receive them [6], should have a written *acute* seizure action plan that can also be shared with other caregivers, schools, and workplaces as well as being a resource for other healthcare providers (e.g., in the emergency department). Pediatric treatment and emergency plans can have a role in the transition from adolescent to adult treatment, with the plan being updated in the process, which can allow for more open communication between adult patients and their clinicians [93, 94]. Links to plan templates are provided in Table 3. Acute seizure action plans are designed to empower patients and caregivers by providing a framework for care that may increase confidence in dealing with seizure emergencies, and thus facilitating independence. These plans may reduce emergency department visits, increase patient safety, and potentially reduce disease burden and costs [88]. Indeed, the cost of rescue medication for 10 years has been estimated to be roughly half that of a single hospitalization for epilepsy [30]. However, seizure action plans are underused. A poll from 2017 showed only 30% of patients have one [6, 88]. This gap is particularly substantial for adults who may not have had a caregiver with them at an appointment and may only have received verbal instructions about how care partners can help when a seizure occurs, rather than a written document that is easily referred to and followed step-by-step [95] (see Table 4).

7 Appropriate Candidates for Seizure Action Plans

Written seizure action plans and acute seizure action plans should be considered for all patients with epilepsy [88]. A written plan facilitates sharing the plan with others,

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Table 3 Seizure cluster rescue treatments: pivotal studies

	Study	Study type	Key selection criteria	Treatment and dose	Treated seizures, *n*	Outcomes efficacy/safety
	Diazepam rectal gel					
1	Efficacy/safety study (N = 91[a])[35]	Prospective, randomized, double-blind, placebo-controlled, parallel group	Children (2–14 y) and adults (15–60 y) Max 100 kg weight With SC (≥ 4 seizures in last year, 1 episode within 3 mo) Stable ASM regimen No BZPs allowed Ineligible if habitual progression to status epilepticus	DRG 2.5–20 mg 6–11 y: 0.3 mg/kg ≥ 12 y: 0.2 mg/kg Placebo	91	*Efficacy* DZG reduced seizure frequency vs. placebo (~ 0.08 vs. ~ 0.85 seizures per h; $P < 0.001$) Percentage of seizure-free patients: 78% (DRG) vs. 19% (placebo) Significant for both adults ($P < 0.001$) and children ($P < 0.02$) Caregiver's Global Assessment of Treatment Options superior for DRG vs. placebo ("better" ~ 37 vs. ~ 15, "same" ~ 6 vs. ~ 27; $P < 0.001$) Time to first seizure recurrence superior for DRG vs. placebo (chi-square test, 13.75; $P < 0.001$) *Safety* Most frequent TEAE: somnolence (DRG, 33%; placebo, 11%) No respiratory depression reported
2	Efficacy/safety study (N = 114[a])[14]	Multicenter, randomized, double-blind, placebo-controlled, parallel group	≥ 2 y with SC (≥ 2 seizures in last year, 1 episode within 6 mo of study entry) Stable ASM regimen Oral BZPs allowed at stable low doses Ineligible if habitual progression to status epilepticus	DRG 2.5–20 mg 2–5 y: 0.5 mg/kg 6– 11 y: 0.3 mg/kg ≥ 12 y: 0.2 mg/kg Placebo	114	*Efficacy* DRG reduced SC frequency vs. placebo (median 0 vs. 2 seizures; $P < 0.029$) Caregiver's Global Assessment of Treatment Options superior for DRG vs. placebo (mean, 6.73 vs. 5.60; $P < 0.018$) Kaplan-Meier time to next seizure favored DRG ($P < 0.007$) Post-treatment, more DRG patients seizure-free (55% vs. 34%; $P = 0.031$) *Safety* Most frequent treatment-related TEAE: somnolence (DRG, 13%; placebo, 3%) No respiratory depression reported
3	Safety study (N = 149)[21]	Multicenter, open-label, repeat-dose safety	≥ 2 y with seizure clusters or prolonged seizures Enrolled in prior placebo-controlled study or single-dose study	DRG 5–20 mg 2–5 y: 0.5 mg/kg 6– 11 y: 0.3 mg/kg ≥ 12 y: 0.2 mg/kg	1578	*Effectiveness* Open-label study with no control group 77% of clusters controlled at 12 h with a single dose [106] *Safety* Most frequent TEAE was somnolence (17% overall, 9% considered related to treatment) No serious TEAEs were considered treatment related No cardiorespiratory events reported 2 deaths considered unrelated to treatment

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Table 3 (continued)

	Study	Study type	Key selection criteria	Treatment and dose	Treated seizures, *n*	Outcomes efficacy/safety
	Diazepam Nasal Spray					
1	Bioavailability/safety study ($N = 48^b$)[37]	Single-center, open-label, randomized, single-dose, 3-treatment, 3-period, 6-sequence crossover study	Healthy subjects aged 18–55 y Exclusions included contraindication to diazepam, comorbid diseases, concomitant medications, and unlikeliness to be adherent to study procedures	DNS and DRG based on approved DRG doses and weight categories Oral diazepam comparator 10-mg tablet	Not applicable	*Bioavailability* Less variability of bioavailability with DNS (percent of geometric coefficient of variation of AUC 42–66%) than DRG (87–172%) (variability was lowest with oral diazepam taken after fasting) *Safety* Most common TEAE was somnolence: DNS, 56.5%; DRG, 89.1%; oral diazepam, 82.6%
2	Pharmacokinetics/safety study ($N = 57^b$)[50]	Multicenter, open-label, repeat-dose, pharmacokinetics study NCT02724423	6–65 y with clinical diagnosis of epilepsy Exclusions included pregnant/lactating, history of major depression, history of allergy to diazepam, and treatment with prescription medication in the past 14 d	DNS Individualized by age and weight	Not reported	*Pharmacokinetics* Rapid absorption with drug exposure similar between ictal/peri-ictal and interictal states *Safety* The most common TEAEs were dysgeusia (5.3%), seizure (3.5%), nasopharyngitis (3.5%), and nasal discomfort (3.5%) No reports of somnolence No evidence for respiratory depression No discontinuations due to a TEAE No serious TEAEs considered treatment related
3	Safety study ($N = 175^b$)[46]	Multicenter, open-label, repeat-dose safety NCT02721069	6–65 y with epilepsy and SC that might need BZP treatment on average 6 times per y History of status epilepticus permitted Concomitant use of BZPs permitted	DNS Individualized by age and weight 0.2–0.3 mg/kg *See* Table 1 *for detailed DNS dosing*	3853 (Mean duration of treatment 17.4 mo)	*Effectiveness* Open-label study with no control group 87.4% of clusters controlled at 24 h with a single dose (94.2% at 6 h) [106] *Safety* Most frequent nonseizure TEAEs: nasopharyngitis (12.3%) and upper respiratory tract infection (12.3%) No cardiorespiratory events reported 1 death due to epilepsy, considered unrelated to treatment

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Table 3 (continued)

	Study	Study type	Key selection criteria	Treatment and dose	Treated seizures, *n*	Outcomes efficacy/safety
	Midazolam Nasal Spray					
1	Efficacy/safety study (ARTEMIS-1) ($N = 262^{a}$) [44]	Multicenter, randomized, double-blind, placebo-controlled NCT01390220	≥ 12 y with epilepsy and history of SC (≥ 2 seizures, last ≥ 10 min and have recognizably different pattern for non-SC seizures) Stable ASM regimen BZPs allowed as rescue therapy Ineligible if have status epilepticus	*Test-dose stage (inpatient, open label)* Two 5-mg MNS doses 10 min apart in test-dose period *Comparative phase (outpatient, double-blind)* 5 mg MNS Placebo Second dose of 5 mg MNS allowed if SC not controlled	Not reported	*Efficacy* MNS increased treatment success (seizure terminations within 10 min and no recurrence in 10 min–6 h) vs. placebo (53.7% vs. 34.4%; $P < 0.0109$) MNS reduced seizure recurrence vs. placebo (38.1% vs. 59.7%; $P < 0.0043$) Kaplan-Meier time to next seizure favored MNS (21% effect size at 24 h; $P = 0.0124$) *Safety* Most frequent MNS TEAEs during test-dose phase: nasal discomfort (16.1%), somnolence (9.9%) Most frequent MNS TEAE during comparative phase: somnolence (9.9%) Respiratory depression (0.7%) reported in test-dose phase
2	Efficacy/safety study (ARTEMIS-2) ($N = 161$) [43]	Open-label extension of ARTEMIS-1 NCT01529034	Same as for ARTEMIS-1 Enrolled in prior placebo-controlled study	5 mg MNS Second dose of 5 mg MNS allowed if SC not controlled	1998 (Median treatment duration 16.8 mo)	*Effectiveness* Treatment success (seizure terminations within 10 min and no recurrence in 10 min–6 h) achieved for 55.5% of patients with first dose 61.5% of clusters controlled at 6 hours with a single dose [106] *Safety* Most common nonseizure TEAEs: nasal discomfort (12.4%), somnolence (9.3%) No treatment-related respiratory depression No TEAEs of abuse or dependence

ASM antiseizure medication, *AUC* area under the curve, *BZP* benzodiazepine, *DNS* diazepam nasal spray *DRG* diazepam rectal gel, *MNS* midazolam nasal spray, *SC* seizure cluster, *TEAE* treatment-emergent adverse event

[a]Randomized

[b]Enrolled

[c]Total enrollment $N = 175$

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Table 4 Seizure action plan templates

Templates	URL
Epilepsy Foundation	https://www.epilepsy.com/learn/managing-your-epilepsy/seizure-action-plans
Epilepsy Foundation Minnesota	https://epilepsyfoundationmn.org/wp-content/uploads/2019/04/Adult-Seizure-Action-Plan.pdf
Seizure Action Plan Coalition	https://seizureactionplans.org/wp-content/uploads/2021/01/Individualized-Seizure-Emergency-Plan-Template_fillable.docx
Epilepsy Foundation (Australia)	https://epilepsyfoundation.org.au/understanding-epilepsy/epilepsy-and-seizure-management-tools/epilepsy-plans/
Acute Seizure Action Plan	https://www.epilepsybehavior.com/article/S1525-5050(21)00525-4/fulltext

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including those at work and school as well as emergency medical personnel. In particular, seizure action plans may be especially beneficial to adult and pediatric patients with intractable epilepsy, those at risk of seizure clusters, those with limited local access to medical care (e.g., due to living in a remote location), those seeking to maintain independence, and during a transition in care (e.g., between pediatric and adult care or starting college) [88, 95]. Likewise, caregivers with limited experience or confidence in administering treatment (e.g., babysitters, co-workers) or those seeking guidance in determining whether to call emergency services may benefit from having an easy-to-use seizure action plan [88]. Further, written plans help ensure that patients understand the details of their plan, which is similar to the way that written titration plans function for patients and care partners. In addition, having a plan promotes empowerment and has been shown to increase caregiver confidence [88, 95, 96].

8 Conclusion

Seizure clusters require urgent care, and it is essential that rescue medications, designed for outpatient use, are available to nonmedical caregivers in the community and that appropriate use is understood. For approximately two decades, only diazepam rectal gel was approved by the FDA for this purpose, but its route of administration makes it less than ideal for home, office, public, or school situations. Other diazepam formulations (e.g., solution) are approved in other global regions to treat certain seizures. The newer intranasal formulations of diazepam and midazolam are specifically designed for ease of use and rapid administration, but each has unique characteristics based on factors including their chemistry, bioavailability, excipients, and dosing. Importantly, rescue treatment and an individualized seizure action plan can also be empowering for patients and caregivers. The individualized acute seizure action plan, which details the rescue treatment, increases sense of control and the ability to respond appropriately and quickly, which may provide patients and caregivers with greater comfort in public settings, leading to greater confidence to pursue activities outside the home. Together, *acute* seizure action plans along with nasal rescue treatment offer patients and caregivers new options for controlling seizure clusters in the community as well as the potential to reduce dependence on emergency services.

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Declarations

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Conflicts of Interest Dr Penovich has served on speakers' bureaus for Jazz, Neurelis, Inc., and UCB and is an advisor to Jazz, LVIS Corporation, and Neurelis, Inc. Dr Rao has served as a consultant for NeuroPace, Inc., manufacturer of the RNS System. Ms Long is a consultant for Neurelis, Inc., SK Life Science, and Supernus Pharmaceuticals and is a speaker for LivaNova. Dr Carrazana is an employee of and has received stock and stock options from Neurelis, Inc. Dr Rabinowicz is an employee and has received stock options from Neurelis, Inc.

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