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CURRENT PERSPECTIVES

# Seizure Rescue Therapies: Comparing Approved and Commonly Used Benzodiazepine Formulations

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**Abstract**
Acute seizure therapies given out of the hospital are important for interrupting acute repetitive and prolonged seizures and preventing hospitalization. These vary in their administration routes, indications for children and adults, pharmacologic profiles, and efficacy. We reviewed and compared the uses of current formulations available to treat acute seizures, including newly released intranasal (IN) benzodiazepines and older formulations which are widely used for interrupting seizures.

**Keywords** Acute repetitive seizures · Seizure clusters · Antiseizure medications · Midazolam · Diazepam

## Introduction

Seizure rescue therapies given outside the hospital are valuable for treating acute repetitive seizures (ARS) (also called "seizure clusters") and are frequently used to interrupt prolonged seizures. Seizure rescue therapies often prevent the need for ED visits and hospitalizations and are helpful as safety or preventive treatments in patients at risk for seizures. They can support safe conversion between chronic antiseizure medications (ASMs) and may be used in low, non-sedating doses to prevent seizures during limited-risk periods such as menses or during special events such as weddings or long flights [1]. A large number of new and older seizure rescue therapies—mostly benzodiazepine drugs—are available to treat acute seizures. These formulations vary in routes of delivery—oral, buccal/sublingual, rectal, and intranasal—and in their pharmacologic properties and antiseizure effects. Different formulations of seizure rescue medications may match specific treatment needs, e.g., prolonged convulsions require rapidly delivered, highly effective acute treatments [2]. Spaced-out clusters of catamenial seizures occurring over several days may be suppressed with repeated low doses of oral benzodiazepines [1]. Older benzodiazepine formulations, such as clonazepam oral disintegrating tablet (ODT) and lorazepam Intensol solution, were approved to treat anxiety but are widely used to treat ARS. Availability of formulations varies across countries—acute seizures in children are routinely treated with buccal midazolam in Europe; however, only an intranasal midazolam formulation is approved in the USA. Clinicians need to match these formulations to individual seizure patterns and needs. In this review, we compare the pharmacology and possible clinical uses of seizure rescue therapies, including recently approved nasal formulations.

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### Prevalence of Acute Seizures—Both ARS and Prolonged Seizures

Seizure rescue therapies are helpful for treating both prolonged and ARS; however, the prevalence of patients with these seizure patterns vary across pediatric, adult, and elderly age ranges, and across population and referral groups of patients [3]. Many studies define ARS as 3 or more seizures occurring in 24 h; while other define ARS as > 2 seizures in 6 h. Some patients have high baseline seizure frequencies; consequently, many treatment series use statistical definitions of ARS as an increase in background frequency of seizures [4]. ARS are very common: 43% of patients with epilepsy have ARS if defined as having a history of 3 or more seizures in 24 h; 29% are reported to have ARS defined as > 2 seizures in 6 h [5] and when defined as an increase in seizure frequencies, approximately 22% of patients with epilepsy are reported to have ARS [4]. Patients with ARS are reported to have approximately 10 × increased frequencies of seizures compared to those without ARS [4].

Acute prolonged seizures (incipient status epilepticus with duration > 5 min) are common in patients with treatment-resistant epilepsy and may evolve from ARS with rapid seizures without recovery between seizures [6].

These various acute seizure patterns—e.g., prolonged or rapid ARS with tonic clonic seizures versus spaced out and less severe seizure types—match up with preferred routes of administration: rectal or nasal therapies for active convulsions that interfere with administration of oral therapies; sublingual/buccal/rectal formulations for moderately severe ARS; and oral formulations for spaced out ARS or preventive use. Randomized trials in the UK comparing compounded formulations of buccal midazolam and rectal diazepam found both were effective for treating acute seizures though response rates were slightly higher with buccal midazolam in several studies [7, 8]. There are limited numbers of similar studies comparing various seizure rescue therapies. In this review "acute repetitive seizures" (ARS) and "seizure clusters" are used interchangeably.

## Formulations Approved for Anxiety Treatment Often Used for Treating Acute Seizures

### Clonazepam Orally Disintegrating Tablets (Clonazepam ODT)

Clonazepam ODT is available in generic formulations as dissolving tablets that disintegrate rapidly in saliva and are then ingested [9]. The formulation is approved by the FDA to treat anxiety and seizures associated with Lennox Gastaut syndrome, absence seizures, akinetic seizures, and myoclonic seizures. Clonazepam ODT is widely used as an oral rescue therapy to treat seizure clusters [2]. Peak plasma concentrations (6.5–13.5 ng/mL after 2 mg doses) are usually reached within 1–2 h. Clonazepam ODT has rapid CNS penetration and an elimination half-life of 19–60 h. There are no controlled trials evaluating clonazepam ODT for treating seizure clusters. It was safe and well tolerated in large, controlled trials for treating anxiety ($N = 574$) [9]. Somnolence (37%) was the only adverse event increased compared to PBO (10%): 26% had somnolence with < 1 mg dose; 35% with 1 to < 2 mg dose; 50% with 2 to < 3 mg doses. In a retrospective series, Troester et al. reported favorable efficacy for treating acute seizures in children, most of whom had intellectual disability [10]. Caregivers reported seizures stopped within 10 min in > 50% of seizures in 68% of patients with acute seizures. Treatment doses ranged from 0.25 (babies or young infants) to 2 mg (full sized adults). All seizure types responded to treatment. Most caregivers who had also administered rectal diazepam for acute seizures thought clonazepam ODT was more effective than rectal diazepam (31% favored rectal diazepam).

In a 2019 survey, pediatric epileptologists ($N = 36$) viewed clonazepam ODT as a first-line treatment for treating seizure clusters for most children [2]. Rectal diazepam was preferred for developmentally delayed 9-month- to 3-year-old children. The survey was completed prior to the release of commercial nasal benzodiazepine therapies. Many patients are treated with a moderate dose, e.g., clonazepam ODT 0.5 mg for children, 1 mg for adults, with a second dose given if seizures recur after 5 to 10 min. Advantages of clonazepam ODT are that it is an inexpensive, stable, easily transported wafer formulation that rapidly disintegrates in saliva. This permits it to also be used as preventive treatment, e.g., low doses can be taken to avoid seizures on long flights. Disadvantages are that—despite its wide use—acute seizure treatment is "off label," and mucosal absorption (versus gastric) has not been measured.

### Lorazepam Intensol Solution for Sublingual Use

Concentrated oral lorazepam solution (2 mg/mL) was developed to be administered from a dropper in food or liquids but is often administered sublingually to treat repetitive seizures. Lorazepam is a first-line treatment for status epilepticus [11]. Peak plasma levels from lorazepam 2 mg are approximately 20 ng/mL; mean half-life is about 12 h. The solution must be refrigerated, and patients often store the solution in picnic coolers when out. Kwok et al. surveyed 103 patients and caregivers prescribed lorazepam Intensol [12]; 41 used it to treat acute seizures. Caregivers reported prolonged or repetitive seizures ceased in 68% of patients for > 24 h. This is comparable to other acute rescue therapies, though controlled prospective studies have not been done. No serious treatment-emergent adverse symptoms were reported for the 41 patients—24% had brief moderate to severe sedation. Caregivers reported minimal difficulty administering the lorazepam solution with droppers.

## Diazepam Rectal and Intranasal Formulations

### Rectal Diazepam Gel

Rectal diazepam gel (Diastat®) was approved as a rescue therapy for acute, repetitive seizures (ARS) by the FDA in 1997. Until 2019, this was the only formulation approved by the FDA for this use; however, various benzodiazepine formulations have been used for many years to treat acute seizures "off-label," and buccal midazolam has been approved for use in children with acute seizures in the European Union [13, 14].

Two pivotal clinical trials for rectal diazepam gel were the first randomized, parallel, placebo-controlled investigations

into out-of-hospital ARS rescue medication administered by non-medical caregivers. These trials enrolled patients aged 2 and older and used weight-based dosing targeting diazepam levels known to reduce interictal EEG spikes [15, 16]. In an initial study, children received rectal diazepam at the onset of individually defined ARS with a second dose given 4 h later; adults received a third dose 12 h after seizure onset. Primary outcomes were proportions of patients with ARS who were seizure-free for 12 h (children) or 24 h (adults). Time to next seizure was also a primary outcome [15]. Diazepam rectal gel markedly increased seizure freedom after initial doses in both children and adults compared to placebo ($P < 0.00$, $P = 0.02$); time to next seizure was also increased in the treatment group ($P < 0.001$) [15].

In a second pivotal trial, patients with ARS received single doses of rectal diazepam treatment based on individualized definitions of subjects' ARS. Table 1 shows examples of individual acute seizure treatment plans used in this trial. Twelve hours after administration, 55% of diazepam patients remained seizure-free, compared to 34% of placebo-treated patients ($P = 0.031$) [16]. Rectal diazepam markedly reduced the need for ED admissions—13% of patients who received placebo required ED admission, compared to 5% of patients treated with diazepam [16]. Rectal diazepam treatment was also well tolerated: 13% reported somnolence in the second single-dose study compared to 33% in the multiple dose initial study (somnolence in the respective placebo groups was 3% and 11%) [15, 16].

Diazepam rectal gel was approved for treating ARS in patients aged 2 and older and is currently the only seizure rescue therapy approved by the FDA for children aged 2–5 [17]. There were no reports of respiratory depression in the trials, and subsequent studies suggested that diazepam treatment posed a lower risk for cardio-respiratory complications compared to untreated ARS [11, 15, 16]. The maximum recommended dosing for diazepam rectal gel is at 5-day intervals or 5 times per month [17].

Despite its effectiveness, diazepam rectal gel treatment has poor social acceptability, particularly in public settings. School nurses surveyed in the USA cited student privacy (26%), legal concerns (16%), and staff hesitation (13%) as barriers to administration of rectal diazepam. This is consistent with a 2019 survey of pediatric epileptologists: they generally preferred other options such as clonazepam ODT for treating most patient groups; but preferred rectal diazepam to treat acute seizures in children with intellectual disability who did not participate in public activities [2]. In a separate survey, adults with ARS strongly preferred receiving out-of-hospital rectal diazepam rescue treatment over visiting emergency rooms (93.3% and 6.7%, respectively), and they preferred receiving rectal rescue medication in private settings even if seizures lasted longer as a result (61.8%) [18].

## Intranasal (IN) Diazepam

IN diazepam was developed to provide a more convenient and socially acceptable treatment for ARS than rectal diazepam. During convulsive seizures or very rapid ARS, caregivers often find IN benzodiazepines (midazolam or diazepam) easier to administer than oral or rectal formulations [19]. IN formulations also avoid first-pass hepatic metabolism and—similar to rectal tissue—the nasal mucosa's high vascularity and vascular permeability permit rapid drug absorption.

**Table 1** Individual administration criteria for treating ARS with rectal diazepam gel. Reproduced with permission from Cereghino et al., "Treating repetitive seizures with a rectal diazepam formulation." [16]

| ARS definition | Criteria to treat |
|---|---|
| More than three GTC seizures in 2 h | After the fourth GTC seizure in 2 h |
| Head turns, face flushed, snorting respirations, jerking of upper extremities, pupils dilated; will continue to have seizures a few seconds to several minutes apart | After the second seizure in 2 h |
| Cries out, stiffens, may extend one arm, face gets red, then circumoral cyanosis; gets limp and begins clonic jerks in right arm, then left; lasts approximately 5 min; will have three or more per hour for several hours or days | Treat after the second 5-min seizure |
| Hard tonic seizure (knees buckle, head and trunk jerk forward, patient falls to ground, stiffens, arms draw up on chest); clusters of tonic seizures continue every 5 to 10 min for as long as 90 min; episodes occur 2 times per week | Treat after second hard tonic seizure |
| In and out of seizures (repetitive mouth smacking, hand clapping, vocalizations, repetitive words [e.g., mom, mom]); lack of response for 20 min to 8 h | If patient is in and out of seizures for more than 2 h |
| Tonic seizures lasting only a few seconds; patient always falls, usually forward; occurs at any time of day | If patient has two seizures, he or she will have more; caregiver to treat after two tonic seizures |
| Falls forward and to left; occurs repetitively; typically has seven to eight seizures per cluster; sometimes has jerking movements | Treat after the third seizure |
| Patient asleep; during last third of night, GTC seizures occur; as many as 15 seizures; seizures are 10 to 45 min apart; never have just one per night | Treat after the first sleep-related GTC seizure |

Development of an early diazepam nasal spray formulation (PLUMIAZ™) stopped due to lack of bioequivalence with rectal diazepam gel. This was due to poor nasal absorption, rectal leakage of the Diastat comparator, and high rates of nasal irritation and lacrimation [20].

Another IN diazepam spray formulation (Valtoco) was developed and approved in the USA based on relative bioavailability to rectal diazepam gel [21] and a long-term safety study. The Valtoco formulation added dodecyl maltoside (DDM) and vitamin E to improve nasal mucosal absorption of diazepam. DDM is a surfactant that transiently loosens tight junctions between cells and increases cell membrane permeability; vitamin E helps solubilize diazepam and may improve tissue tolerability [21]. In the bioequivalence and safety studies, patients 6 years and older were administered IN diazepam 0.3 mg/kg (ages 6–11 years) and 0.2 mg/kg (12 + years) with doses ranging from 5 to 20 mg. The IN diazepam (Valtoco) did not meet traditional BE standards with Diastat. The Diastat reference formulation, however, had very broad variability in concentrations compared to IN diazepam and relative bioavailability was judged comparable. The $C_{max}$ ratio of IN diazepam and Diastat was 85% for lower weight subjects and 118% for higher weight subjects, with broad 90% confidence intervals (Fig. 1) [22]. The $AUC_{0-\infty}$ ratio for IN diazepam versus reference Diastat for low weight subjects was 74% and 100% for high weight subjects, also with broad 90% CIs [16, 21, 23].

The safety and use of IN diazepam (Valtoco) were evaluated in 175 subjects with histories of seizure clusters; a total of 163 received treatment. Most subjects were evaluated for > 12 months and study retention was high (71.8%). Subjects typically used IN diazepam one to five times per month [24]. Rates of seizure recurrence were low over the 24-h monitoring periods following treatment [25]. Nearly half of subjects (48.5%) required second IN diazepam treatments during the study; however, only 12.6% of ARS episodes required a second IN diazepam dose [25]. The monthly use of IN diazepam was stable in patients requiring infrequent and frequent ARS treatment, with no increased use of second treatments during ARS over time. These are signs that they had not developed tolerance with exposure to Valtoco [26]. None of the patients with epilepsy reported respiratory depression or treatment-related serious adverse events in the safety study. Although many healthy volunteers (56.8%) had somnolence with IN diazepam, only 6.7% of subjects with epilepsy in the safety trial reported somnolence [21, 24]. The most common adverse events were nasopharyngitis and URI (12.3% each). Patients in the IN diazepam open-label trial listed ease of use (93.8%) and comfort with public use (86.7%) as advantages of IN diazepam over the rectal diazepam gel formulation [19, 27].

Recently, a fed/fasting PK study showed a strong food effect with IN diazepam administration [28]. IN-delivered diazepam concentrations increased similarly in the first 30 min in the fed/fasting studies. There was a subsequent food effect: $C_{max}$ decreased by an average of 48% in the fed compared to fasting state and the partial AUC (0–4 h) decreased by 57% in the fed compared to the fasting state

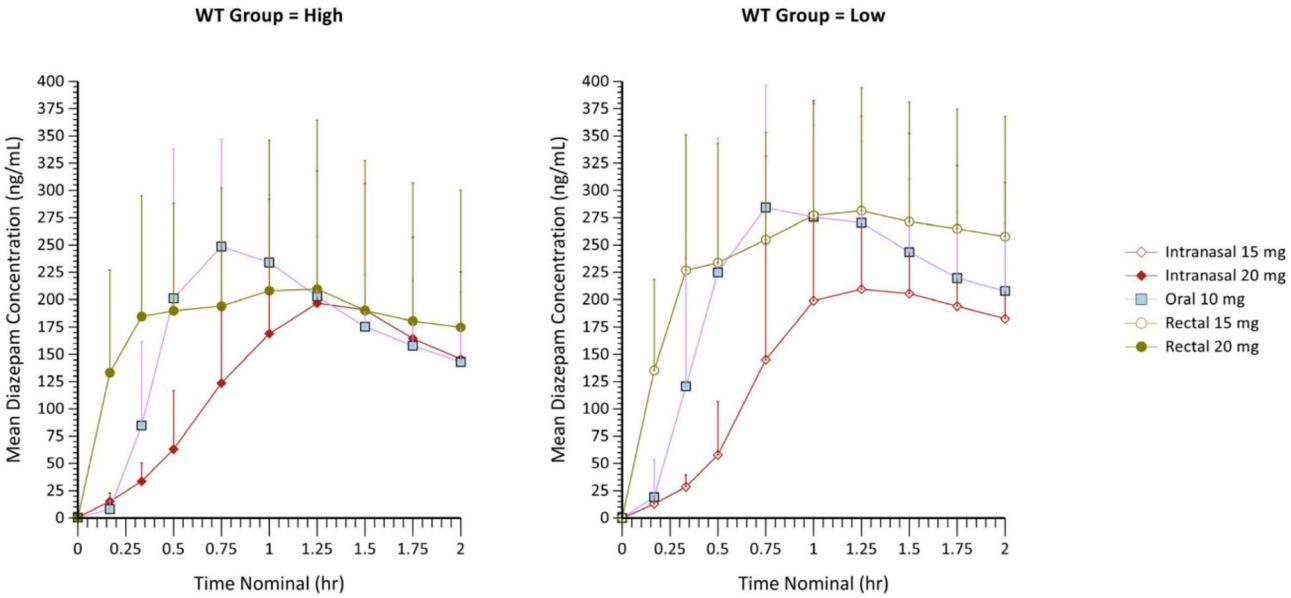


**Fig. 1** IN diazepam (Valtoco), diazepam rectal gel (Diastat), and oral diazepam: plasma concentrations compared in high weight subjects (left panel) and low weight subjects (right panel). Reproduced from Fig. 1 in Hogan et al., "Bioavailability and safety of diazepam intranasal solution compared to oral and rectal diazepam in healthy volunteers." [21]

(Fig. 2) [28]. This suggests that the IN formulation initially delivers diazepam via trans-nasal absorption and subsequently is absorbed enterically, with 70 to 120 ng/mL diazepam concentrations rapidly attained in the fasted state only [28].

The FDA approved Valtoco IN diazepam in 2020, shortly after approving Nayzilam IN midazolam in 2019 [29]. The effectiveness of the two formulations have not been compared. IN diazepam is the only intranasal seizure rescue therapy in the USA approved for treating children aged 6–11.

### Other Diazepam Formulations Used to Treat Acute Seizures

Diazepam Intensol solution (5 mg or 25 mg/mL) is frequently used to treat ARS in children and adults, with a dropper for diazepam sublingual administration [30]. Unlike lorazepam Intensol solution, diazepam Intensol does not require refrigeration. A diazepam buccal film is discussed further in the "Pipeline formulations" section.

## Midazolam: Buccal, Intramuscular, and Intranasal Formulations

### Buccal Midazolam

Buccal (oromucosal) midazolam (Buccolam) is an approved and commonly used rescue therapy for treating acute seizures in children in the EU (ages infants to < 18 years); however, the formulation has not been approved and released in the USA. The buccal route provides rapid absorption without the first-pass metabolism associated with gastric administration. Buccal midazolam was equal or more effective than rectal diazepam for treating acute seizures in children and some adults in several randomized trials comparing the formulations.

The pharmacokinetics of buccal versus intravenous midazolam were compared in 8 healthy volunteers [31]: 5 mg doses of both formulations caused sedation or sleep in all subjects. The mean buccal bioavailability was 78% in children, and the half-life was 143 min. $C_{max}$ was 55.9 ng/mL and $T_{max}$ was 30 min.

In a randomized trial of children in a residential home with prolonged seizures (> 5 min), buccal midazolam was only slightly more effective than rectal diazepam but was easier to administer and socially preferred. Children predominantly not only had tonic–clonic seizures but also had multiple other seizure types. Buccal midazolam was effective in ending 75% of seizures compared to 59% with rectal diazepam ($P = 0.16$). Neither group had significant respiratory depression [32].

In a randomized trial comparing buccal midazolam to rectal diazepam for treating prolonged tonic clonic seizures in children presenting to EDs, 56% of seizures ceased with buccal midazolam treatment compared to 27% with rectal diazepam [7]. The formulations were associated with a similar incidence (5–6%) of mild respiratory depression. Dosing was 0.5 mg/kg for both treatments. Seizures ceased much earlier with buccal midazolam treatment compared to rectal diazepam and only 33% required a second rescue treatment with intravenous lorazepam compared to 57% with rectal diazepam.

Rectal diazepam gel, though more variable in absorption, often has a more rapid initial delivery than IN diazepam. Given these results and the UK comparator study results for compounded formulations, IN midazolam may be more appropriate for treating acute convulsive seizures or very rapid ARS in children ≥ 12 years of age than rectal and IN diazepam [7, 33].

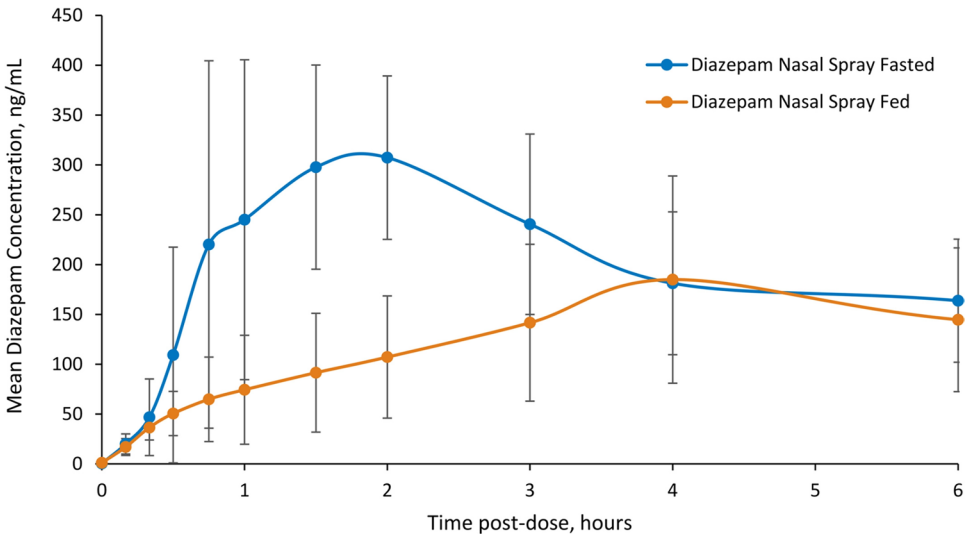


**Fig. 2** Mean plasma diazepam concentrations in fed and fasted subjects for a 6-h period after administration of IN diazepam. Reproduced from Rogawski and Slatko, "A randomized, open-label, two-treatment crossover study to evaluate the effect of food on the pharmacokinetics of diazepam nasal spray in healthy adults" [28]

### Intramuscular (IM) Midazolam (Seizalam)

IM midazolam solution (Seizalam) 10 mg was approved in the USA in 2018 with an IM autoinjector approved in 2022 for treatment of status epilepticus in adults [34]. IM midazolam treatment was only approved for administration by healthcare workers trained in treating status epilepticus and was not approved for out-of-hospital consumer use. The $T_{max}$ in healthy subjects was approximately 0.5 h for IM midazolam 10 mg solution; $C_{max}$ after 10 mg IM injections was 114 ng/mL. Midazolam is metabolized by CYP3A4, with concentrations reduced by CYP3A4 inducers such as cenobamate and increased by inhibitors (e.g., erythromycin, diltiazem, and saquinavir).

A large multicenter study compared pre-hospital treatment for status epilepticus by paramedics with randomized IM midazolam 10 mg or intravenous lorazepam 4 mg [35]. Status epilepticus was defined as continuous clinical or electrographic activity that lasted 5 min or more or multiple seizures occurring without recovery in between seizures. A total of 893 subjects were randomized to the treatments: seizures ceased prior to arrival of the ambulance to emergency departments in 73% with IM midazolam treatment and 63% with intravenous lorazepam treatment (difference $P=0.002$). Adverse events were similar for the two treatments with upper airway obstruction reported in 5% after IM midazolam treatment. Four percent had pyrexia and 4% had agitation, which may have been linked to seizure activity. This is the first midazolam formulation approved in the USA for treating seizures, though compounded midazolam sprays have been used for "off-label" treatment for many years.

### Intranasal Midazolam (IN)

Compounded forms of IN midazolam solution delivered via a spay or droplets have been used to treat acute seizures in children for many years. Comparison studies have reported successful treatment of acute seizures in home and residential settings using IN midazolam. IN midazolam 10 mg spray (two puffs of 5 mg) was compared to diazepam 10 mg rectal solution for treating acute seizures in a residential program in the UK [36]. Efficacy was defined as seizures ceasing within 15 min and not recurring in 2 h. Both treatments were effective, with seizures ceasing in 82% treated with midazolam and 89% of those treated with rectal diazepam solution. Over one half of both groups of children had drowsiness with treatment. Caregivers and patients felt IN midazolam was easier to give than rectal diazepam.

A commercial intranasal delivery system of midazolam (Nayzilam) was approved by the FDA for treating repetitive seizures in children > 12 years and adults in 2019 [37]. With a shelf life of 24 months, it can be available for rescue therapy for patients at risk for repetitive seizures, e.g., patients switching antiseizure therapies and patients with histories of repetitive seizures or intermittent severe acute seizures.

The IN midazolam formulation (Nayzilam) has relatively straightforward pharmacokinetics with an absolute bioavailability of 44% compared to intravenous delivery and with a moderate 21% to 45% increase in PK parameters in patients > 65 years old. Strong CYP3A4 enzyme inhibitors increase Nayzilam concentrations, e.g., diltiazem increases oral midazolam over twofold, while cenobamate induces CYP3A4 and decreases midazolam approximately 50%. IN midazolam 5 mg reaches maximum concentrations ($T_{max}$) at approximately 15 min with a geometric mean $C_{max}$ of 56 ng/L. It has a mean half-life of 3.6 h for a single dose and 3.9 h for two doses. The range of elimination half-life is approximately 2.1 to 2.7 h; with a 6 to 7 h elimination half-life for the major 1-OH-midazolam metabolite [38].

IN midazolam (Nayzilam) was tested and approved based on a randomized double-blind, placebo-controlled study in patients aged 12 years and older [39]. Patients with focal and generalized onset seizures were enrolled. Patients ($N=292$) had baseline ARS with > 2 stereotyped seizures over a minimum of 10 min and had individualized patient management plans. They received treatment for ARS with 2:1 randomization to IN midazolam 5 mg or placebo. If seizures did not cease after 10 min of initial study treatment, IN midazolam 5 mg treatment could be given. The treatment efficacy endpoint was seizure termination within 10 min of treatment and no recurrence for 6 h. Most ($N=201$; 77%) randomized patients had seizure clusters and received study treatment [39].

Seizures ceased in 53.7% treated with IN midazolam (Nayzilam) treatment compared to 34.3% treated with placebo ($P<0.01$). Only 31% of patients treated with IN midazolam required the second open-treatment dose compared to 61% of placebo-treated patients. Nayzilam significantly reduced proportions of patients having additional seizures over 24 h compared to placebo treatment (Fig. 3). The most common TEAEs with treatment were nasal discomfort (16%) and somnolence (9%). Only one patient had a SAE of sedation; 8 discontinued due to sedation/somnolence with test doses [39].

## Pipeline Formulations

### Diazepam buccal film

Diazepam buccal film (Libervant) was tentatively approved, but not released for marketing in the USA by the FDA, due to orphan drug exclusivity granted to diazepam nasal spray. It is being reviewed for marketing and use outside the USA. It was tested in children ages 2 to 16 during ictal periods and interictally in older children. In a safety study, 67 adults and children had treatment with diazepam 5 to 17.5 mg (based on age and size) during 471 seizure episodes. Only

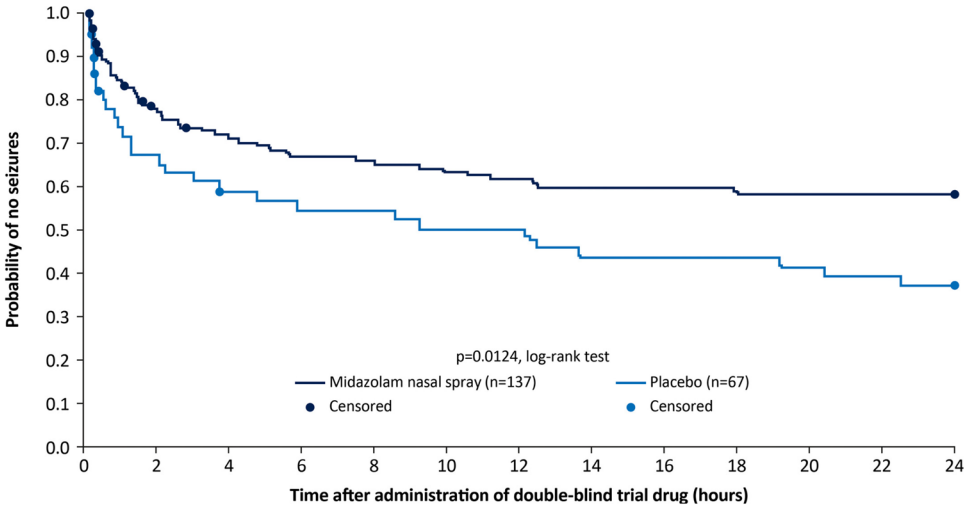


**Fig. 3** Kaplan–Meier survival curves for time to next seizure. Proportions of subjects with seizure recurrence within 24 h were significantly reduced with IN midazolam treatment compared to placebo. Reproduced from Detyniecki et al., "Safety and efficacy of midazolam nasal spray in the outpatient treatment of patients with seizure clusters—a randomized, double-blind, placebo-controlled trial" [39]

4% reported somnolence, and several patients had difficulty with buccal administration due to jaw clenching, drooling/spitting, or rapid swallowing [40]. Diazepam buccal film had similar bioavailability to Diastat in a fed subject study with relatively rapid and linear dose-dependent increases in diazepam concentrations [41].

### Inhaled Alprazolam (Staccato) to Interrupt Seizures

Current treatments for ARS do not interrupt the first seizure and may require 5 min or more to be effective in treating prolonged seizures or seizure clusters. Abortive seizure treatment may target evolving seizure activity, such as a cluster of brief myoclonic seizures preceding a generalized tonic clonic seizure or an aura or focal aware seizure evolving into focal seizures with altered awareness or tonic clonic seizures.

Inhaled alprazolam (Staccato) is being developed to interrupt seizures. Alprazolam is effective in reducing seizures in several animal models, such as audiogenic seizures, and its antiseizure effects are believed to be via activity as a $GABA_A$ agonist. Inhaled alprazolam (Staccato) aerosolizes alprazolam and delivers it into the lung for rapid systemic exposure. Peak concentrations are achieved within minutes. The formulation rapidly suppressed epileptiform activity in photosensitive subjects and is being tested as treatment to interrupt evolving seizures. In the phase IIa screening study, inhaled midazolam at three doses (0.5, 1, and 2 mg) was compared to two placebo doses in a 5-way crossover study [42]. Inhaled alprazolam in 5 subjects reduced photoparoxysmal EEG responses at 2 min with sustained effects for 4 to 6 h. Alprazolam plasma levels were proportionate to dose. The most common AEs were cough, dysgeusia, and somnolence. Subjects had dose-related sleepiness, reported beginning at 2 min with maximum symptoms around 60 min. A phase I safety and PK study in children is being done and a phase 3 study in adolescents and adults to interrupt seizures is underway.

## Discussion

Acute seizure rescue therapies are designed to interrupt ARS and provide important emergency out-of-hospital treatment for patients with acute seizures. Regulatory study design requirements, though, have hampered the development of therapies for status epilepticus. Despite this, there are a large number of formulations available to treat ARS for a number of clinical subgroups and many of these are routinely used for out of hospital treatment of status epilepticus.

Buccal midazolam is used extensively in Europe to interrupt acute seizures, predominantly in children (< 18 years). Rectal diazepam is effective for treating repetitive seizures in adults and children 2 years and older. Three randomized studies (two comparator trials with rectal diazepam) in children in UK showed buccal midazolam was effective in treating acute seizures in children and adolescence, with more rapid seizure cessation compared to diazepam solution administered rectally. IN midazolam (Nayzilam) and IN diazepam (Valtoco) are newer formulations, with IN midazolam showing effectiveness for interrupting repetitive seizures in a placebo-controlled trial in patients 12 years and older. IN diazepam has total bioavailability comparable to rectal diazepam gel, with efficacy assumed to be similar.

Several inexpensive benzodiazepine formulations originally released for anxiety treatment have been reported in open series to have similar efficacy to commercial formulations approved for treating ARS. Several rescue therapies such as lorazepam tablets or clonazepam ODT are often used at low, repeated doses to treat ARS with low frequency patterns of seizures, e.g., catamenial seizures occurring over

several days. Preventive treatment with low doses of seizure rescue therapies also helps patients avoid seizures in special circumstances, such as during important events or long flights.

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## Declarations

**Conflict of interest** The authors declare no competing interests.

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