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SPECIAL ISSUE ARTICLE

Rescue therapies for seizure clusters: Pharmacology and target of treatments

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Abstract

The primary goal of treatment for seizure clusters is cessation of the cluster to avoid progression to more severe conditions, such as prolonged seizures and status epilepticus. Rescue therapies are key components of treatment plans for patients with seizure clusters. Three rescue therapies are approved in the United States for the treatment of seizure clusters: diazepam rectal gel, midazolam nasal spray, and diazepam nasal spray. This review characterizes the pharmacological function of rescue therapies for seizure clusters, as well as describing γ-aminobutyric acid A ($GABA_A$) receptor functions. $GABA_A$ receptors are heteropentamers, consisting primarily of α1-6, β1-3, γ2, and δ subunits in the central nervous system. These subunits can traffic to and from the membrane to regulate membrane potential. Benzodiazepines, such as diazepam and midazolam, are positive allosteric modulators of $GABA_A$ receptors, the activation of which leads to an increase in intracellular chloride, hyperpolarization of the cell membrane, and a reduction in excitation. $GABA_A$ receptor subunit mutations, dysregulation of trafficking, and degradation are associated with epilepsy. Although benzodiazepines are effective $GABA_A$ receptor modulators, individual formulations have unique profiles in practice. Diazepam rectal gel is an effective rescue therapy for seizure clusters; however, adults and adolescents may have social reservations regarding its administration. Intranasal delivery of midazolam or diazepam is a promising alternative to rectal administration because these formulations offer easy, socially acceptable administration and exhibit a rapid onset. Off-label benzodiazepines, such as orally disintegrating lorazepam and intranasal use of an intravenous formulation of midazolam via nasal atomizer, are less well characterized regarding bioavailability and tolerability compared with approved agents.

KEYWORDS
acute repetitive seizures, epilepsy, seizure emergency

1 | INTRODUCTION

Rescue therapy is a critical component of seizure cluster management, both to reduce the risks of prolonged seizures and to prevent the progression to status epilepticus.[1–3] Moreover, effective rescue therapy is important to reduce the need for emergency services as well as the clinical and quality-of-life burdens of seizure clusters for patients, family members, and caregivers/care partners (please see Kapur et al, *Consequences: Bench to Home*[4] for further discussion on the impact of seizure clusters). Ideal rescue therapies should be easy and safe to administer, be effective at small doses (with a large therapeutic index), and exhibit rapid onset of action that can be sustained for several hours.[5]

Three rescue therapies are approved by the US Food and Drug Administration (FDA) for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from the usual seizure pattern in patients with epilepsy (Table 1)[6–8] (please see Haut and Nabbout, *Recognizing Seizure Clusters in the Community: The Path to Uniformity and Individualization in Nomenclature and Definition*[9] for further discussion on seizure cluster definitions in this issue). Diazepam rectal gel (Diastat) was approved for patients ≥2 years of age in 1997.[6] Midazolam nasal spray (Nayzilam) was approved in May 2019 for patients ≥12 years of age.[7] Most recently, diazepam nasal spray (Valtoco) was approved in January 2020 for patients ≥6 years of age.[8]

Key Points

- Benzodiazepines are the key rescue therapies used to terminate seizure clusters
- Benzodiazepines increase chloride conductance of γ-aminobutyric acid A ($GABA_A$) receptors, resulting in neuronal hyperpolarization and a reduction in excitation
- Rescue therapy formulations and route of administration differ by agent, which can influence the onset of action

Before FDA approval of diazepam rectal gel, parenteral diazepam, which was intended for use in emergency medical settings, may have been offered to caregivers for outpatient rectal administration, posing risks of dosing errors and safety concerns.[10–12] The efficacy and safety of diazepam rectal gel for the treatment of seizure clusters were later established in pivotal clinical trials with randomized, double-blind, placebo-controlled designs collectively demonstrating significant reduction in seizure frequency along with acceptable safety and tolerability (with somnolence as the most common adverse event but without respiratory depression).[12,13]

TABLE 1 Approved treatments for seizure clusters

Treatment	Age- and weight-based dosing		
Diazepam rectal gel[6]	**Age 2–5 years (0.5 mg/kg)**	**Age 6–11 years (0.3 mg/kg)**	**Age 12+ years (0.2 mg/kg)**
	6–10 kg, 5 mg	10–16 kg, 5 mg	14–25 kg, 5 mg
	11–15 kg, 7.5 mg	17–25 kg, 7.5 mg	26–37 kg, 7.5 mg
	16–20 kg, 10 mg	26–33 kg, 10 mg	38–50 kg, 10 mg
	21–25 kg, 12.5 mg	34–41 kg, 12.5 mg	51–62 kg, 12.5 mg
	26–30 kg, 15 mg	42–50 kg, 15 mg	63–75 kg, 15 mg
	31–35 kg, 17.5 mg	51–58 kg, 17.5 mg	76–87 kg, 17.5 mg
	36–44 kg, 20 mg	59–74 kg, 20 mg	88–111 kg, 20 mg
Diazepam nasal spray[8]		**Age 6–11 years (0.3 mg/kg)**	**Age 12+ years (0.2 mg/kg)**
10–18 kg, 5 mg		10–18 kg, 5 mg	14–27 kg, 5 mg
		19–37 kg, 10 mg	28–50 kg, 10 mg
		38–55 kg, 15 mg[a]	51–75 kg, 15 mg[a]
		56–74 kg, 20 mg[a]	76+ kg, 20 mg[a]
Midazolam nasal spray[7]			**Age 12+ years**
			All weights, 5 mg

[a]Administered using two sprayers from a single blister pack (i.e., two sprays of 7.5 mg for 15 mg total dose or two sprays of 10 mg for 20 mg total dose, one in each nostril).

Despite their ability to improve outcomes, including decreasing risk of progression to prolonged seizures and potential avoidance of emergency room admissions, rescue therapies designed for use by nonmedical caregivers have been historically underused in patients with seizure clusters, particularly in the adult population.[2,14] Social and institutional constraints or perceptions regarding patient willingness to receive rectal administration may be barriers to the use of diazepam rectal gel.[14,15] Research efforts to develop intranasal formulations faced challenges related to pharmacology, solubility, and bioavailability, thus delaying the introduction of such formulations.[16] Agents using other routes of administration have been used off-label for nonmedical caregiver use (e.g., oral or buccal benzodiazepines, such as midazolam syrup). Lorazepam tablets or liquid and clonazepam orally disintegrating tablets may have been prescribed to adolescents and adults to minimize social concerns in the period when the only approved treatment was rectal diazepam[2]; however, these have not been formally established to be effective specifically for the treatment of seizure clusters in large, well-designed clinical trials. Moreover, oral benzodiazepines possess other challenges, such as the potential for aspiration and biting injury.[3,16]

2 | IMPACT OF BENZODIAZEPINE EXPOSURE ON GABA RECEPTOR BINDING AND TIME TO EFFECTIVENESS IN SEIZURE CLUSTERS

γ-Aminobutyric acid A ($GABA_A$) receptors are heteropentameric chloride channels, of which eight subunits have been identified (α, β, γ, δ, ε, π, θ, and ρ).[17] $GABA_A$ receptor activation leads to chloride influx, hyperpolarization of the neuronal cell membrane, and a reduction in excitation. Repetitive seizures can attenuate physiological function of $GABA_A$ receptors through altered subunit localization and trafficking, as well as through disruptions to intracellular chloride homeostasis.[18–20] Benzodiazepines, positive allosteric modulators of $GABA_A$ receptors, are used therapeutically to attenuate the high levels of neuronal excitation that occur during a seizure. Physiological function of the $GABA_A$ receptor is dependent on subunit subtype (e.g., α1, α2, and so on), whereas benzodiazepine-induced modulation of $GABA_A$ can occur with receptors containing α1, α2, α3, or α5 subunits, along with β and γ2 subunits (Figure 1).[21] The type of γ2 isoform expressed (long [γ2L] vs. short [γ2S] forms) and its characteristics (e.g., phosphorylation status) can modulate $GABA_A$ receptor currents, synaptic clustering and dispersion, internalization, trafficking, and degradation.[22] Anxiolytic-like effects

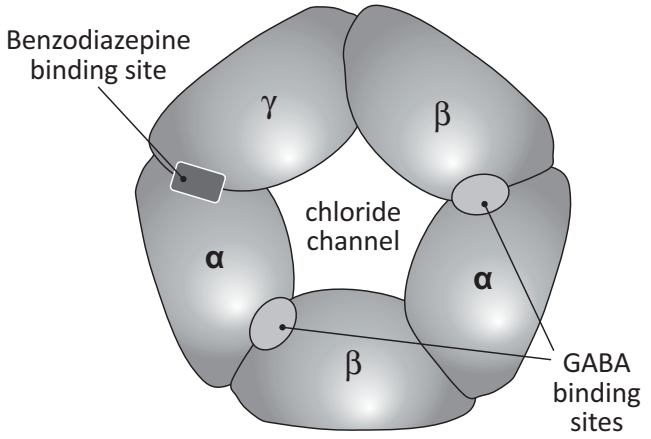

FIGURE 1 Structure of a γ-aminobutyric acid A ($GABA_A$) receptor consisting of α, β, and γ subunits. Benzodiazepines bind at the α/γ junction of the receptor complex, whereas GABA binds at an α/β junction. Reprinted from Howard P, Twycross R, Shuster J, Mihalyo M, Wilcock A. Benzodiazepines. *J Pain Symptom Manage*. 2014;47(5):955–64, with permission from Elsevier.

are mediated through $GABA_A$ receptors that contain α2, α3, and/or α5 subunits but not α1 subunits.[23] In contrast, locomotor function is attenuated and sedation induced through $GABA_A$ receptor activation when the α1 subunit is present in the receptor complex; however, activation of α2, α3, and/or α5 does not affect locomotor function or sedation.

The majority of benzodiazepines in clinical use are characterized by nitrogen bound to the first and fourth carbons of the diazepine ring (1,4-benzodiazepine, Figure 2A).[24] An exception is the 1,5-benzodiazepine clobazam (Figure 2B), commonly prescribed for Lennox–Gastaut and Dravet syndromes.[24] Although 1,4- and 1,5-benzodiazepines are both positive allosteric modulators of $GABA_A$ receptors, the benzodiazepine chemical structure and $GABA_A$ receptor subunit expression may influence the physiological function of $GABA_A$ receptors. For example, diazepam, a 1,4-benzodiazepine, elicited similar or marginally higher functional responses in recombinantly expressed human $GABA_A$ receptors compared with clobazam and its metabolite *N*-desmethylclobazam.[25] The small difference between benzodiazepines to potentiate GABA-induced $GABA_A$ currents was attributed to the type of α subunit expressed, with receptors containing α1 or α2 subunits exhibiting slightly lower $GABA_A$ currents in response to clobazam and *N*-desmethylclobazam.[25]

The anticonvulsant mechanism of action for benzodiazepines, although not fully elucidated, involves binding at the benzodiazepine site of the $GABA_A$ receptor and resultant potentiation of GABAergic neurotransmission.[26] Several factors are known to influence the central nervous system effects of benzodiazepines, including dosing, route of administration, and the presence or absence of other

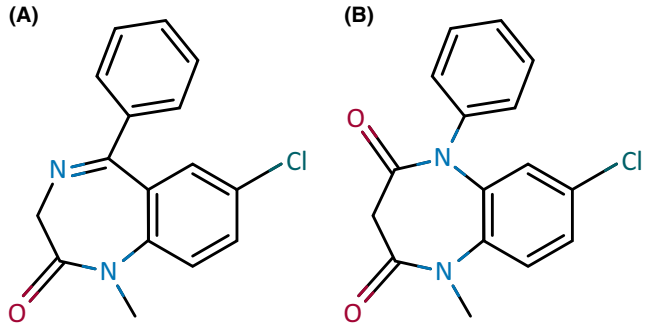

FIGURE 2 Chemical structures of (A) a 1,4-benzodiazepine (diazepam) and (B) a 1,5-benzodiazepine (clobazam).

therapies.[6–8,27] Evidence derived from animal models and human studies collectively suggest that epilepsy as a condition (both acute and chronic states) can invoke changes in $GABA_A$ receptor composition and function, which may contribute to tolerance or adverse effects to treatment.[26] Benzodiazepine administration over time has also been associated with reductions in $GABA_A$ receptor subunit expression in animal models,[28,29] which could contribute to tolerance. However, in a post hoc analysis that examined tolerance effects of clobazam use in patients with Lennox–Gastaut syndrome over a 2-year period, only 12% of patients exhibited tolerance to treatment, as determined by an increase in dose ≥40% in combination with an increase in seizure rates.[30] In addition, evidence suggests that tolerance to intermittent benzodiazepine exposure in patients with seizure clusters is infrequent.[31–33]

3 | DEVELOPMENT OF APPROVED RESCUE MEDICATIONS

3.1 | Diazepam rectal gel

Diazepam rectal gel (Diastat, Bausch Health US, LLC) was the first rescue therapy approved by the FDA for acute treatment of seizure clusters in patients with epilepsy ≥2 years of age.[6] This formulation is packaged as a prefilled, unit-dose delivery system. Doses range from 5 to 20 mg based on age and weight, with target doses of 0.5 mg/kg (patients ages 2–5 years), 0.3 mg/kg (6–11 years), and 0.2 mg/kg (≥12 years). If needed, a second dose can be administered after 4 h.

Two randomized, double-blind, placebo-controlled studies, including a total of 239 treated patients, showed reduced seizure frequency per hour ($p < .001$) with diazepam rectal gel. Four patients discontinued treatment owing to an adverse event (AE) in one study; two patients in the diazepam arm (lethargy, rash) and two patients in the placebo arm (sedation, seizure).[13] There were no discontinuations owing to an AE in the other study,[12] and no cases of respiratory depression were reported in either study.

In a long-term safety study ($N = 149$ treated; 48.3% were ≤11 years of age), 1578 seizure clusters were treated and ~48% of patients participated for ≥2 years.[34] In 23% of treated seizure clusters, further seizures occurred within 12 h of dosing. There was limited provision for a second dose in this study. Somnolence was the most common AE (occurred in 17% of patients and was considered treatment related in 9% of patients), but the investigators noted that it was difficult to distinguish from postictal somnolence. No respiratory compromise or serious AEs were attributed to diazepam rectal gel, and three patients (2%) withdrew owing to AEs possibly related to treatment.[34,35] When compared to treatment before enrollment in the study, caregivers and investigators were satisfied with diazepam rectal gel treatment at 12- and 24-month follow-up visits.[34] However, despite the efficacy and safety of this rectal formulation, this route of administration is associated with social considerations, and alternative routes of administration were an unmet need, particularly for adolescents and adults.[5]

3.2 | Midazolam nasal spray

Midazolam nasal spray (Nayzilam, UCB, Inc.) is approved by the FDA for the treatment of seizure clusters in patients ≥12 years of age.[7] The drug is packaged in a single-use sprayer with a premeasured 5-mg dose (used for patients of all ages and weights). If needed to control an ongoing cluster, a second dose of midazolam nasal spray can be administered 10 min after the initial dose. For patients at risk of respiratory depression, a test dose is recommended, given under the supervision of a health care professional. The formulation includes the organic solvents ethanol, polyethylene glycol (PEG)-6, methyl ether, PEG-400, and propylene glycol to achieve solubility of the midazolam.

In a double-blind study, 292 patients received an open-label test dose (total of 10 mg of midazolam nasal spray) to assess safety, and 262 patients were subsequently randomized to receive midazolam or placebo, with 201 proceeding with the study drug.[36] During the randomized comparative phase, the primary, composite end point of seizure termination within 10 min of dosing and no further seizures between 10 min and 6 h after treatment was significantly higher in the active drug group compared with placebo (53.7% vs. 34.4%; $p = .0109$). Thirteen patients discontinued the test dose phase owing to a drug-related treatment-emergent AE (eight owing to sedation-type AEs), including three patients with serious AEs. Two of these three patients had clinically meaningful respiratory depression. During the comparative phase, no patients discontinued owing to an AE, and none had respiratory depression.

In the long-term safety study (N = 161 treated, 5.0% were <18 years of age), 1998 seizure clusters were treated across a median of 16.8 months.[32] Second doses were used in 38.5% of clusters to treat seizures that did not terminate within 10 min or to treat other seizures that occurred 10 min to 6 h following the first dose. Fifty-seven patients (35.4%) experienced ≥1 treatment-related AE over the course of the trial (≥12 months). The most common AEs were nasal discomfort (12.4%) and somnolence (9.3%), and there were no reports of respiratory depression in the long-term safety study. Four patients (2.5%) experienced ≥1 serious AE, which was categorized as potentially treatment related (all classified as "unlikely related"), and two patients (1.2%) discontinued owing to treatment-related AEs (one case each of nasal discomfort and somnolence, both nonserious).[32] Patient satisfaction and anxiety as assessed with questionnaires improved over time in patients who received midazolam nasal spray.[37]

3.3 | Diazepam nasal spray

Diazepam nasal spray (Valtoco, Neurelis, Inc.) is approved by the FDA for the treatment of seizure clusters in patients ≥6 years of age.[8] Diazepam nasal spray is provided in premeasured, single-use sprayers. Dose strengths are available in 5, 10, 15, and 20 mg based on patient age and weight, with target doses of 0.3 mg/kg for patients 6–11 years of age and 0.2 mg/kg for patients ≥12 years of age.[8] The 15- and 20-mg doses both require use of two sprayers in a single blister pack to provide the full dose (i.e., two sprays of 7.5 or 10 mg; one in each nostril). A second dose may be administered if needed at least 4 h after the first dose, which would require a new blister pack. The formulation includes benzyl alcohol, dehydrated alcohol, *n*-dodecyl beta-D-maltoside (DDM), and vitamin E. The excipient DDM increases absorption across the mucosa.[38] Vitamin E is used to promote the nonaqueous solubility of diazepam.[39]

In a pharmacokinetic study, intrapatient variability was found to be lower for patients receiving diazepam nasal spray compared with diazepam rectal gel (% geometric coefficient of variation of area under the curve, 42%–66% compared with 87%–172%).[27] Respiratory depression was not reported in a pharmacokinetic study of patients with epilepsy who were treated with diazepam nasal spray, and it was not observed in previous studies of healthy subjects.[39]

The long-term safety study for diazepam nasal spray was published recently.[40] A total of 163 patients (27.6% ≤12 years of age) were treated for 3853 seizure clusters, and a second dose was used for 12.6% of clusters within 24 h of the first dose. Of the second doses, 31.3% were administered 0–4 h after the first dose, with 46.2% occurring 0–6 h and 65.6% occurring 0–12 h after the first dose. Thirty patients (18.4%) experienced ≥1 treatment-related AE; among these, treatment-related nasal discomfort occurred in 6.1% of patients, whereas treatment-related somnolence occurred in 1.8% of patients. No patients withdrew owing to a treatment-related AE, there were no treatment-related serious AEs, and no cases of respiratory depression were observed.[40] Analyses in subpopulations of this study based on frequency of use,[41] use of concomitant benzodiazepines,[42] and history or concomitant treatment of seasonal allergies or rhinitis[43] reported results that were similar to those reported in the overall study. A survey conducted as part of the study found that patients and caregivers were satisfied with diazepam nasal spray and were more comfortable using it in public situations compared with diazepam rectal gel, and some patients (as young as 11 years) reported self-administration of diazepam nasal spray.[44]

4 | OTHER THERAPIES FOR SEIZURE CLUSTER TREATMENT

4.1 | European Medicines Agency–approved treatments for prolonged acute convulsive seizures

Reflecting differences across geographic and regulatory jurisdictions, available agents are somewhat different in the European Union and are not approved specifically for the treatment of "seizure clusters" per se. For example, in the European Union, diazepam for rectal administration is formulated as a solution and is indicated for the treatment of epileptic convulsions when a rapid effect is required but when intravenous injection is impracticable or undesirable in patients ≥1 year of age.[45–47] Another European Union option, buccal midazolam, is approved for the treatment of prolonged acute convulsive seizures in pediatric patients ages 3 months to <18 years, with age-based doses of 2.5, 5, 7.5, and 10 mg.[48] In a randomized in-hospital study comparing rectal diazepam and buccal midazolam in children ages 7 months to 15 years, there were 219 episodes in 177 patients. Cessation of seizures between 10 min and 1 h without respiratory depression (primary end point) was higher for buccal midazolam (56% vs. 27%) than for rectal diazepam. Rates of respiratory depression were 5% and 6%, respectively.[49]

4.2 | Medications used off-label

Other agents that have been prescribed in the past include off-label oral benzodiazepines, such as orally

disintegrating lorazepam. This route of administration may affect absorption/bioavailability, and safety considerations include the potential for aspiration and a requirement that caregivers take precautions to reduce risk of biting injury.[3,16] Midazolam for injection also has been administered with an atomizer as a nasal spray.[2,50] The pH of the solution is ~3 (compared with a more neutral 5–9 pH for the approved midazolam intranasal formulation), so it may lead to substantial patient discomfort.[16] Agents designed for intravenous use are not optimal for nasal administration because of the relatively low concentrations used in intravenous formulations requiring large volumes in addition to the small surface area of the nasal cavity.[16]

5 | CHARACTERISTICS OF RESCUE THERAPIES

5.1 | Routes of administration: Advantages and limitations

The different routes of administration for rescue therapy have potential advantages and disadvantages (Table 2).[16] The recently approved intranasal formulations offer the opportunity for rapid administration relative to intravenous and rectal formulations, as well as improved patient/caregiver satisfaction and resultant usage relative to rectal formulations, without compromising efficacy or safety.[51] The approved intranasal midazolam formulation uses several organic solvents to increase the solubility of midazolam while maintaining the pH in the range of 5–9.[7] However, organic solvents may cause nasal irritation.[52,53] The approved diazepam nasal spray formulation contains DDM (Intravail A3; 0.25% weight/volume concentration) to enhance nasal absorption and vitamin E as a solvent (organic solvents are not included).[16] Vitamin E has also been shown to promote healing of nasal mucosal damage.[54]

Although the intent of intranasal administration of any drug is to provide rapid systemic and/or direct nose-to-brain exposure, the potential role of mucociliary clearance needs to be considered. This system's physiologic role is to remove foreign particles from the nasal cavity to prevent them from reaching the lungs. From a drug-delivery perspective, this ciliary action may result in a certain fraction of drug reaching the gastrointestinal (GI) tract.[55–57] Indeed, it has been suggested that a certain fraction of intranasally administered midazolam is absorbed via the GI tract, in that there is a 3.7%–6.8% higher ratio of the metabolite 1-OH-midazolam to midazolam after intranasal administration compared with intravenous administration,[58] which is suggestive of presystemic metabolism. GI absorption of structurally dissimilar drugs, such as sumatriptan, has also been suggested following intranasal administration.[59,60] Currently, it is unknown if this process is clinically relevant or whether the benzodiazepine rate or extent of absorption would be impacted if intranasal agents were administered to patients in the fed versus fasting state.

TABLE 2 Advantages and disadvantages of types of rescue therapies for seizure clusters[16]

Route of adminstration	Advantages	Disadvantages
Rectal	• Can administer relatively large dose volume • Relatively painless	• Inconsistent absorption and bioavailability • Limited medications can be delivered by this route • Poor social acceptability
Intranasal	• Quick and easy administration • Relatively fast absorption and onset of action • Patient cooperation not needed • Relatively painless • Avoids first-pass metabolism • Socially acceptable versus rectal route • Possible direct brain delivery of drug	• Need for delivery device (e.g., atomizer) • Possible CNS treatment-emergent adverse events • 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
Buccal	• Easy to use • Can administer a relatively large dose volume • Painless • Avoids first-pass metabolism	• Limited medications can be delivered by this route • Potentially distasteful • Inconsistent absorption • Swallowing reduces buccal delivery • Difficult when patient is experiencing a seizure • Precautions to reduce risk of biting

Note: Adapted from Cloyd J, Haut S, Carrazana E, Rabinowicz AL. Overcoming the challenges of developing an intranasal diazepam rescue therapy for the treatment of seizure clusters. *Epilepsia* 2021;62 (4):846–56.

Abbreviation: CNS, central nervous system.

5.2 | Time to onset of action and duration

The timing for onset of action of rescue therapies for seizure clusters may be determined by the drug plasma level associated with a reduction in spike counts,[61] rather than the time to maximum plasma concentration (t_{max}) or other pharmacokinetic parameters (Table 3). Early efforts to develop a rectal formulation of diazepam had detected a reduction in spike–wave activity after 10–20 min (per electroencephalography [EEG]) despite peak serum levels being achieved after 15–90 min, suggesting that the EEG response occurs much earlier than t_{max}.[61] A subsequent study of oral diazepam conducted in healthy volunteers noted a similar response, with EEG effects (fraction of total EEG amplitude within 13–31 Hz) detected 15 min following administration, whereas t_{max} occurred ~1 h after administration.[62] In a rodent model that utilized continuous diazepam infusion, an elevation in seizure threshold was associated with relatively low plasma levels (≈74 ng/ml) of diazepam.[63] Although brain electrical activity can exhibit responsiveness to low plasma concentrations of benzodiazepines before achieving maximal concentrations, the clinical efficacy of low concentrations to terminate or prevent seizures in humans is difficult to characterize owing to patient heterogeneity. Plasma concentrations of diazepam in excess of 200 ng/ml have been associated with successful termination of seizure clusters (serial seizures) in adult patients,[64] as well as seizures and malaria-induced convulsions in pediatric patients.[65,66]

In a phase 1 open-label crossover study of an intranasal midazolam formulation dosed at 2.5, 5.0, or 7.5 mg compared with midazolam intravenous solution (given intranasally or intravenously) in 25 healthy adults, t_{max} was rapid with midazolam nasal spray at 10–12 min across the three doses, with maximum plasma concentration (C_{max}) values of 59, 73, and 93 ng/mL for the 2.5-, 5.0-, and 7.5-mg doses, respectively (Figure 3A).[67]

The pharmacokinetics of the approved diazepam nasal spray have been assessed across several studies. In a randomized phase 1 crossover study comparing diazepam nasal spray (10-mg solution, the approved formulation) and an intranasal suspension versus intravenous (IV) diazepam in 24 healthy adults,[68] pharmacokinetic parameters for the nasal solution included a C_{max} of 272 ng/mL and a t_{max} of 1.5 h (Figure 3B). Similarly, in a dose-ranging crossover pharmacokinetic study of single nasal spray doses (5, 10, and 20 mg) and a two-dose regimen (2 ×10 mg, 4 h apart) of diazepam nasal spray in 33 healthy adults,[69] single-dose median t_{max} was 1.4–1.5 h and mean C_{max} values were 85.6, 133.6, and 235.3 ng/ml, respectively, for the 5-, 10-, and 20-mg doses. When the bioavailability and safety of diazepam nasal spray (15 or

TABLE 3 Phamacokinetic and pharmacodymanic characteristics of agents used to treat seizure clusters[77]

Agent	Maximum dose	Route	Bioavailability (%)	Volume of distribution (L/kg)	Metabolism	Excretion	$t_{1/2}$ (h)
Lorazepam (Ativan Intensol)	0.1 mg/kg (4 mg)	Sublingual	90	1.3	Liver to inactive metabolites	Hepatic metabolism to inactive metabolites	12
Lorazepam (Ativan Sublingual tablets)[a]		Sublingual	>90				
Midazolam (Nayzilam)	0.2 mg/kg (15 mg)	Intranasal	44	1–3	CYP3A4 to active metabolite	Renal	2–6
Midazolam		IV given intranasally	44–83				2–4
Midazolam (Buccolam, Epistatus)[a]	0.5 mg/kg (15 mg)	Buccal	75–87				3–4
Diazepam (Diastat)	0.2 mg/kg (20 mg)	Rectal	97	0.8–1.2	CYP2C19 and CYP3A4 to active metabolites	Renal	~49
Diazepam (Valtoco)		Intranasal	90				~46

Note: Adapted from Almohaish S, Sandler M, Brophy GM. Time is brain: acute control of repetitive seizures and status epilepticus using alternative routes of administration of benzodiazepines. *J Clin Med.* 2021;10(8):1754.

Abbreviations: CYP, cytochrome P450; IV, intravenous.

[a]Not available in the United States; IV injectable solution is used for buccal administration in the United States.

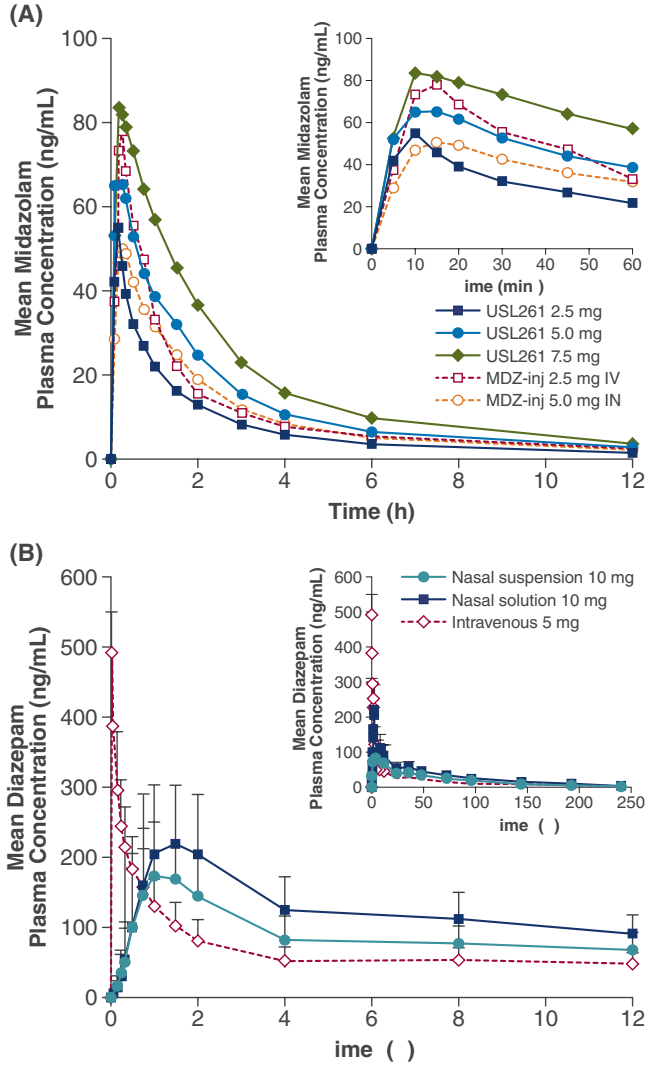

FIGURE 3 Mean plasma concentrations in pharmacokinetic evaluations with (A) intranasal midazolam and (B) diazepam nasal spray. Panel A reprinted from Bancke LL, Dworak HA, Rodvold KA, Halvorsen MB, Gidal BE. Pharmacokinetics, pharmacodynamics, and safety of USL261, a midazolam formulation optimized for intranasal delivery, in a randomized study with healthy volunteers. *Epilepsia* 2015;56 (11):1723–31, Wiley Periodicals, Inc. © 2015 International League Against Epilepsy. Panel B reprinted from Agarwal SK, Kriel RL, Brundage RC, Ivaturi VD, Cloyd JC. A pilot study assessing the bioavailability and pharmacokinetics of diazepam after intranasal and intravenous administration in healthy volunteers. *Epilepsy Res.* 2013;105(3):362–7, with permission from Elsevier.

20 mg) were compared with those for diazepam rectal gel and oral diazepam (reference formulation) in 48 healthy adults,[27] the median t_{max} was 1.25 h for both doses of diazepam nasal spray. Geometric mean C_{max} values were 226 and 186 ng/ml, respectively, for diazepam nasal spray at 15- and 20-mg doses.

In a long-term safety study of diazepam nasal spray, a second dose was given for 12.6% of clusters within 24 h.[40] In this trial, only 5.8% of clusters received a second dose in <6 h. Of note, this study design allowed for inclusion of patients who were receiving concomitant, chronic oral benzodiazepines, such as clobazam. Patients who received chronic concomitant benzodiazepines used a second dose of diazepam nasal spray to treat 12.5% of clusters.[40] In an interim analysis, the use of second doses was generally similar between patients who received concomitant clobazam and those who did not.[42] These data suggest that chronic exposure to a 1,5-benzodiazepine, such as clobazam, does not seem to result in an impaired response to diazepam nasal spray.

Onset and duration of action for the three FDA-approved rescue therapies have not been compared formally in a controlled study. Although pharmacokinetic characteristics of rescue therapies differ in individual studies (Table 3), the meaningfulness of these differences for control of seizure clusters is unclear. This remains an area for future investigation.

6 | FUTURE RESCUE THERAPIES

Prospective rescue therapies with different routes of administration and associated formulations are currently being investigated. Buccal diazepam film can be applied to the inner cheek, whereby the film dissolves and the diazepam is absorbed through the buccal mucosa. Buccal diazepam includes some of the same beneficial characteristics as nasal spray benzodiazepines (e.g., avoids first-pass metabolism), while possessing some unique challenges in the mode of delivery (e.g., clenching of the jaw, drooling, swallowing the drug/film).[70] Moreover, the portion of diazepam that is swallowed is not absorbed as efficiently through the digestive system as it is through the buccal mucosa.[71] Potential benefits include portability (can fit in a wallet), which is preferred by some patients.

Another investigational therapy, inhaled alprazolam, uses a route of administration that capitalizes on the pulmonary architecture (large surface area, extensive blood supply) for drug delivery and exhibits a high rate of absorption. In a proof-of-concept study, inhaled alprazolam reduced epileptiform activity in photosensitive patients, with effectiveness recorded at 2 min following administration,[72] which is similar to IV administration of benzodiazepines, and can potentially be used to abort an ongoing seizure.[73] In a phase 2b study,[74] a greater proportion of patients with predictable seizure patterns who were treated with inhaled alprazolam experienced seizure cessation within 2 min of treatment as compared to those who received placebo control. Alprazolam is approved for use in anxiety disorders but has no indication in epilepsy at this time.[75]

7 | CONCLUSIONS

Benzodiazepines are effective at reducing seizure activity through $GABA_A$ receptor activation, resulting in an increase in chloride conductance of the receptor and hyperpolarization of the neuronal cell membrane. Although the primary mechanism of action for benzodiazepines is well characterized, outcomes related to specific therapies can vary in real-world practice. Effective rescue therapies should exhibit high potency, rapid and extensive absorption, and consistent bioavailability, as well as a large therapeutic index. The route of administration and drug formulation largely affect the effectiveness of drug delivery, with key differences across rescue therapies. In addition to optimal formulations, the effectiveness of rescue therapies is dependent on the immediate actions of patients, family members, and caregivers, supported by education and an acute seizure action plan (please see Patel and Becker, *Introduction to Use of an Acute Seizure Action Plan for Seizure Clusters and Guidance for Implementation*[76] in this issue). Future studies are needed that examine new drug formulations and routes of administration, as well as drugs that have been used successfully off-label for the treatment of seizure clusters. Other outcomes that examine rescue therapy efficacy to address a broader range of patient challenges, such as the ability to stop an ongoing seizure or to treat status epilepticus, have not been studied.

AUTHOR CONTRIBUTIONS

Writing—Original Draft Preparation: all authors developed the initial content outline for the manuscript. Writing—Review and editing: all authors provided critical review and revision. All authors approved the final version of this manuscript for submission to *Epilepsia*.

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CONFLICT OF INTEREST

Dr Gidal is a consultant for Aquestive, Eisai Inc., Greenwich, Neurelis, Inc., and SK Life Science; is a member of the End Point Review Committee for Sunovion Pharmaceuticals Inc; and has a grant/contract with UCB, Inc. Dr Detyniecki is a consultant for Aquestive; Neurelis, Inc.; UCB; and Greenwich Biosciences. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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