Expert Review of Neurotherapeutics

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/iern20

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To cite this article: Lindsay M. Higdon & Michael R. Sperling (2021) A review of a diazepam nasal spray for the treatment of acute seizure clusters and prolonged seizures, Expert Review of Neurotherapeutics, 21:11, 1207-1212, DOI: 10.1080/14737175.2021.1965880

To link to this article: https://doi.org/10.1080/14737175.2021.1965880

Published online: 17 Aug 2021.

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NEURELIS, INC., EX2018, page 1
PADAGIS US LLC v. NEURELIS, INC.
IPR2025-00465, U.S. PATENT 11,241,414

EXPERT REVIEW OF NEUROTHERAPEUTICS
2021, VOL. 21, NO. 11, 1207–1212
https://doi.org/10.1080/14737175.2021.1965880

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A review of a diazepam nasal spray for the treatment of acute seizure clusters and prolonged seizures

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ABSTRACT

Introduction: Some people with epilepsy experience acute repetitive seizures (ARS), also termed seizure clusters, which have a negative impact on patient and caregiver quality of life, emotional wellbeing, daily function, and may pose risk of injury or death. In addition, these events increase healthcare utilization in emergency departments and hospitals, which might be avoided with use of an at-home rescue medication. Intranasal formulations of benzodiazepines used as rescue medications provide a means of delivering rescue medication that is socially acceptable and more easily administered than rectal drug.

Areas covered: This article provides a review of intranasal diazepam covering development, pharmacokinetics, dosing, safety, adverse effects, and efficacy. The authors compare it with rectal diazepam and intranasal midazolam.

Expert opinion: Intranasal rescue drugs are a valuable treatment modality for seizure clusters and prolonged seizures that are effective and well tolerated with the potential to enhance patient quality of life, reduce the incidence of seizure-related injury, and lessen the need for hospital visits. The literature does not provide evidence comparing the various rescue agents, and head-to-head comparison studies are needed. An inhaled benzodiazepine as a seizure rescue drug is currently undergoing clinical trials.

ARTICLE HISTORY
Received 24 May 2021
Accepted 5 August 2021

KEYWORDS
Intranasal; diazepam; rescue medication; acute repetitive seizures; seizure cluster

1. Introduction

Approximately one-third of people with epilepsy experience ongoing seizures, despite appropriate medical therapy [1]. Some of these individuals experience seizure clusters, also termed acute repetitive seizures (ARS) [2]. The International League Against Epilepsy (ILAE) lacks a formal definition of seizure clusters, and a variety of definitions have been suggested including three or more seizures in 24 hours with an interictal period of < 8 hours, two or more seizures in 24 hours, two to four seizures in 48 hours, or two generalized seizures or 3 complex partial seizures in 4 hours [2]. Acute repetitive seizures (ARS) or seizure clusters have a negative impact on patient and caregiver quality of life, emotional wellbeing, daily function, and productivity. In addition, clusters increase utilization of emergency departments, which might be avoided with use of an at-home rescue medication. Prolonged seizures are those that last longer than usual, defined by the treating physician, and this ambiguous term has been applied to seizures lasting several minutes or more. The treating neurologist should educate patients and their families or caregivers about the potentially dangerous implications of seizure clusters and prolonged seizures and plan an intervention that can abort these phenomena if prevention is not possible [3].

An ambiguous relationship exists between seizure clusters, prolonged seizures and status epilepticus. The International League Against Epilepsy published a definition that recognizes two aspects of prolonged seizures, one in which seizures are abnormally long possibly leading to continuous seizure activity, and another in which long-term consequences including neuronal injury or death, functional deficit, or alteration of neuronal networks becomes possible. Patients with habitual seizure clusters or prolonged seizures have an established pattern with spontaneous seizure termination; this provides comfort that an enduring seizure state is unlikely to occur, yet the adverse consequences of prolonged or repeated seizures might still occur. If a seizure cluster occurs outside of a medical setting, there is an inherent delay in treatment because of time needed for arrival of emergency medical services. For these reasons, rescue medication that can be administered safely at home, school, work, or play is needed. Such treatment may shorten the duration and severity of seizure clusters or prolonged seizures, avert transformation to status epilepticus, reduce risk of injury, improve recovery time, and avoid trips to the hospital.

Benzodiazepines, both on and off-label, have long been the reigning drug class for first-line emergency treatment of seizures. They are an ideal form of rescue therapy with a broad spectrum of activity and many desirable attributes (Table 1). Multiple routes of administration are available (Table 1), each carrying its own advantages and disadvantages that depend on patient and seizure characteristics.

Some methods of administration are preferred over oral or buccal routes due lack of first pass metabolism, choking hazard, and potential inability of a patient to swallow a pill

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Article highlights

- Patients with refractory epilepsy who experience seizure clusters benefit from having a rescue medication to abort subsequent seizures once a cluster has begun and avoid hospitalization.
- Until recently, rectal diazepam was the main formulation of rescue benzodiazepine that was not an oral pill.
- The FDA approved version nasal diazepam has demonstrated similar bioavailability as the rectal formulation.
- Nasal diazepam is overall well tolerated by patients and no serious adverse effects were reported.
- Direct comparisions in efficacy between nasal diazepam and midazolam have yet to occur, but a notable difference is nasal diazepam is approved for ages 6 and older compared to 12 and older for nasal midazolam.

Table 1. Benzodiazepine characteristics.

- Broad spectrum of activity
- Rapid suppression of seizures
- Attain reliable serum levels
- Intermediate duration of action
- Good safety profile
- Easy to use by patients, families, and caregivers via buccal, intramuscular, intranasal, oral, and rectal routes
- Long shelf life

or capsule [3–6]. The rectal route bypasses first pass hepatic metabolism and requires minimal patient cooperation (though patients must peacefully allow insertion of drug). Rectal diazepam was introduced in Europe in the 1970s and was approved for use in the United States in 1997. Difficulties with rectal forms of rescue medications center around ease of administration, variability of absorption as well as social concerns about administering medication in public places. Several studies performed prior to availability of other routes of administration (except oral) assessed attitudes toward rectal diazepam [7,8]. One retrospective questionnaire-based study focusing on rectal diazepam use in children reported that 58% of caregivers who used rectal diazepam felt increased comfort with managing their children's seizures at home, and 27% of caregivers who did not need to use rectal diazepam reported just having the medication gave them peace of mind [9]. Another study focusing on adult patients' perception of rectal diazepam found that most patients (63.6%) responded that rectal medications were a good option for early seizure management but that 33% were embarrassed by their use, 61.8% preferred a private setting if rectal drug was required and only 12.5% thought rectal medications were necessary despite a mean of 6.6 seizures per month (range 0–67.5). An overwhelming majority (93.3%) preferred rescue medication to a visit to the emergency department [7]. Hence, patients and families thought that rescue medications were desirable, but that rectal administration was less than ideal, potentially leading to underutilization or delay in treatment [4,7].

Intranasal formulations of benzodiazepines offer a more socially palatable and more easily administered form of rescue therapy than rectal drugs. Intranasal diazepam and midazolam have been used for many years, provided by compounding pharmacies using the intravenous form of these drugs as the active agent. However, these have not been rigorously designed or tested to ensure adequate absorption nor is duration of action known. The FDA recently approved intranasal forms of both diazepam and midazolam (Valtoco® and Nayzilam®, respectively,), both agents having undergone rigorous testing yielding knowledge about pharmacokinetics and efficacy. The remainder of this article will focus on intranasal diazepam, discussing it in detail and comparing it to rectal diazepam and intranasal midazolam.

2. Intranasal diazepam

All benzodiazepines have a similar chemical structure and mechanism of action and are differentiated by speed of onset and duration of action. Benzodiazepines bind to the $GABA_A$ receptor in neurons, thereby increasing inhibitory currents [10]. Electrophysiological studies demonstrate that benzodiazepines increased the amplitude of inhibitory post-synaptic potentials (IPSPs) by increasing the opening frequency of the GABA-gated chloride channel [11]. Duration of action is determined by the method of biotransformation and the extent of redistribution. Long-acting benzodiazepines, such as diazepam, are broken down into active metabolites, but diazepam is highly lipophilic with rapid redistribution into adipose tissue; this attribute leads to a shorter duration of action in the central nervous system than would be expected from its half-life [3,5,10].

2.1. Benefits of intranasal route

The intranasal (IN) route has several advantages. It is quick and easy to administer, has a good safety profile, and usually causes little discomfort. It allows for relatively fast drug absorption due to the rich vasculature network of nasal mucosa, resulting in a rapid onset of action with EEG changes noted in as little as 4 min after dosing [12]. Additional practical advantages are that the nose is easily accessible during a seizure, patient cooperation is not needed, and the IN route is more socially acceptable than rectal route. Lastly, absorption via nasal vasculature absorption avoids first pass hepatic metabolism. Hence, intranasal rescue drug administration offers a good treatment option.

2.2. Designing intranasal drugs

It is critical that any drug administered for rescue therapy be quickly and adequately absorbed. Lipophilic drugs, such as diazepam, dissolve poorly in water [3,4]. To enhance absorption, cell penetrating peptides could be added to the solution and to complement that viscosity increasing agents are added to increase residence time in nasal mucosa [13]. Organic cosolvents such as glycols or alcohol can be added but can lead to nasal irritation. Another alternative is to use a vitamin E-based formula, which increases the solubility of diazepam to 10 mg/100 µg [3,6,14] and facilitates absorption. In addition, a nonionic alkylglycoside surfactant (dodecyl-β-D-maltopyranoside [DDM]) can enhance absorption, working by altering electrical resistance values, mucosal viscosity, and

NEURELIS, INC., EX2018, page 3
PADAGIS US LLC v. NEURELIS, INC.
IPR2025-00465, U.S. PATENT 11,241,414

membrane fluidity to loosen cell-to-cell junctions thereby enhancing mucosal permeation [6].

2.3. Drug development

Rectal diazepam has been used for many years as a rescue therapy. It was evaluated in a multicenter, randomized, parallel double-blind study with administration of a single dose diazepam rectal gel. The drug was significantly more effective than placebo in reducing number of seizures after dosing during an episode of acute repetitive seizures (ARS) [15]. (Figure 1) Inasmuch as diazepam was known to be an effective agent, it was only necessary to show pharmacokinetic equivalence of the IN and rectal formulations to obtain FDA approval of IN diazepam; it was not necessary to demonstrate efficacy of the IN formulation. However, developing a commercial nasal formulation that reliably delivered an equivalent dose proved challenging despite demonstration of feasibility and tolerability in an early formulation of the drug [16].

One challenge, in addition to the aforementioned issues, relates to the small surface area (~160 cm^2) of the nasal cavity, which can accommodate only approximately 200 µL of solution. Ideally, any dose should have a lower volume. Any excess will drain into the nasopharynx and be swallowed or lost from leakage through the anterior nares [3,4,6]. A dropper or squeeze bottle may not disperse the drug evenly to deliver a specified dose and could cause drug leakage as well. Hence, a different approach must be used. The commercially approved IN diazepam formulation delivers 100 µL in a spray from a single-dose pump. This device has been used for other medications and has been proven to disperse nasal medication evenly. Moreover, it is easy to use with one hand by either patient or caregiver and is portable [4].

2.4. Pharmacokinetics and dosing of IN diazepam

An open-label study compared the bioavailability of the newer formulation of IN diazepam to oral and rectal diazepam in healthy controls [17]. The time to maximum plasma concentration (t_{max}) for the IN diazepam was comparable to PR diazepam under 'ideal conditions' for rectal absorption (fasting state, enema night prior and 1 hour prior to diazepam PR dose). (Figure 2) Variability in C_{max} and $AUC_{0-\infty}$ was lowest with oral diazepam, followed by diazepam nasal spray, and then rectal diazepam. Variability likely relates to both absorption characteristics and drug leakage, which appears greater with rectal administration than nasal dosing. Analysis revealed bioavailability of intranasal diazepam was similar to or greater than rectal diazepam at the 20 mg IN dose (used in 76–111 kg subjects) and that bioavailability was slightly lower for the 15 mg IN dose (used in 51–75 kg subjects) compared to rectal dosing, thought to be due to variability of rectal absorption. Nasal dosing has slightly less bioavailability than oral dosing [17]. (Figure 3) Plasma concentration of the IN formulation peaks approximately 1.5 hours after administration and absolute bioavailability is 97%. Metabolism is mainly hepatic (CYP2C19 and CYP3A4) as well as glucuronidation. Drug half-life is 49 hours, though effective antiseizure half-life is shorter because of distribution to adipose tissue [18].

A phase 1, open-label cross over study was performed in healthy volunteers to assess the effect on pharmacokinetics and dose proportionality of IN diazepam comparing single

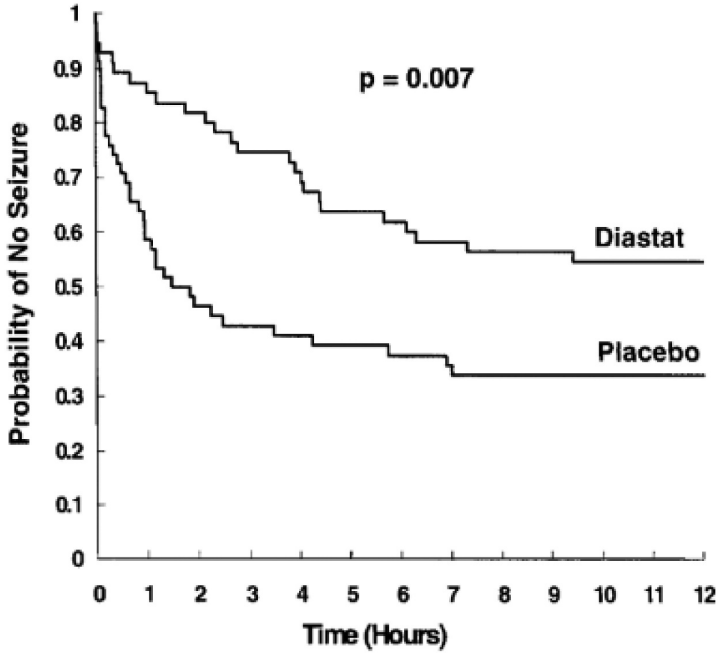

Figure 1. Kaplan-Meier survival analysis for time to next seizure comparing rectal diazepam (Diastat) to placebo. Reproduced with permission from Kriel *et al.* [9].

NEURELIS, INC., EX2018, page 4
PADAGIS US LLC v. NEURELIS, INC.
IPR2025-00465, U.S. PATENT 11,241,414

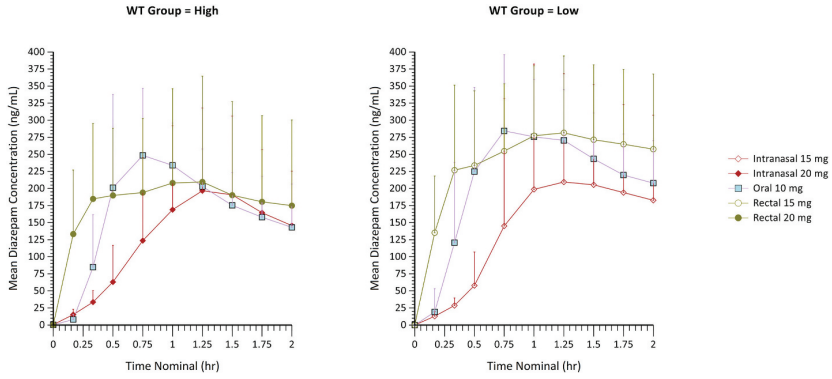

Figure 2. Mean plasma concentration-time profiles of diazepam (0-2 hours), mean ± SD. WT, weight High weight group (76-111 kg) Low weight group (51-75 kg). Reproduced with permission from Hogan *et al*. [17].

dosing (5 mg, 10 mg, and 20 mg) and giving two doses (2x 10 mg given 4 hours apart) [18]. A direct proportional relationship was observed between dose and plasma concentration-time profile [15]. Seasonal allergies do not appear to adversely affect absorption of the intranasally administered drug [11]. Also, absorption is not influenced by dosing IN diazepam in the ictal or immediate post-ictal state; C max and AUC are the same as when given in the interictal state [19].

The FDA-approved indication for IN diazepam is for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e. seizure clusters or acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older [20]. In practice, however, these clusters are typically part of the typical seizure pattern, as the periodic occurrence of clusters is a primary indication for use of the drug. IN diazepam is also commonly employed in clinical practice to treat prolonged seizures (but not approved for the treatment of status epilepticus). IN diazepam dose depends primarily on weight (and somewhat on age), and total dose then determines whether it must be given in one spray or two. Dose ranges from 5 mg to 20 mg depending upon weight (Table 2). The 5 mg and 10 mg doses can be administered as a single spray into one nostril; the 15 mg and 20 mg doses require splitting the dose into two sprays, half administered into each nostril to avoid delivery of excessive volume in a single nostril. If seizures have not satisfactorily responded, a repeat dose can be given 4 hours after the first. It is recommended to wait at least 5 days in between doses and to give no more than 5 treatments per month [20] to avoid tolerance; in practice, more closely spaced dosing may sometimes be needed.

2.5. Safety and Adverse effects

No severe adverse effects or deaths have been reported with IN diazepam and most (91.3%) adverse effects were mild [17]. In healthy volunteers, the rate of adverse effects was lower with nasal spray (60.9%) than rectal gel (93.5%) or the oral tablet (84.8%). The most common adverse effect was somnolence, more frequently seen with rectal and oral administration than nasal dosing. Many study participants have reported nasal irritation after receiving diazepam nasal spray, but this is typically modest and would rarely prevent use of the agent [17]. In another study, low rates of adverse effects were found related to nasal administration, with the most notable adverse effects consisting of dysgeusia (5.3%), nasal discomfort (3.5%), and burning sensation (1.8%) [19]. In a large study where diazepam nasal spray was administered 4390 times for 3853 seizure clusters, transient nasal irritation was noted in only 6.1% of subjects [21].

Many patients who suffer from seizure clusters take multiple antiseizure medications and some may take chronic benzodiazepine medication. While there is a theoretical risk of cardiorespiratory depression when employing IN diazepam in patients who take chronic daily benzodiazepine medication (e.g. clobazam, clonazepam), Segal et al. [22] found no instances of cardiorespiratory depression or serious adverse effects in patients who used rescue IN diazepam alongside concomitant chronic benzodiazepine use. In addition, this study showed a high retention rate after 12 months with no study discontinuations due to adverse reactions.

2.6. Efficacy

No formal efficacy studies have been performed contrasting IN diazepam with rectal diazepam for reasons noted above. However, one can get some sense of utility of the drug by looking at retention rates in long-term trials. Patients or their caregivers tend to continue using an intermittent rescue medication only if they perceive some benefit and long-term retention rates in outpatient studies were reasonably good. In a long-term study of 163 subjects who received at least one dose of medication [21], 81.6% stayed on drug for at least 12 months, and 71.8% completed the study with longest follow-up >3 years. A second dose was used 12.6% of times after administration of a first dose. In this study, a total of 3853 seizures clusters were treated with 4390 doses of IN diazepam

NEURELIS, INC., EX2018, page 5
PADAGIS US LLC v. NEURELIS, INC.
IPR2025-00465, U.S. PATENT 11,241,414

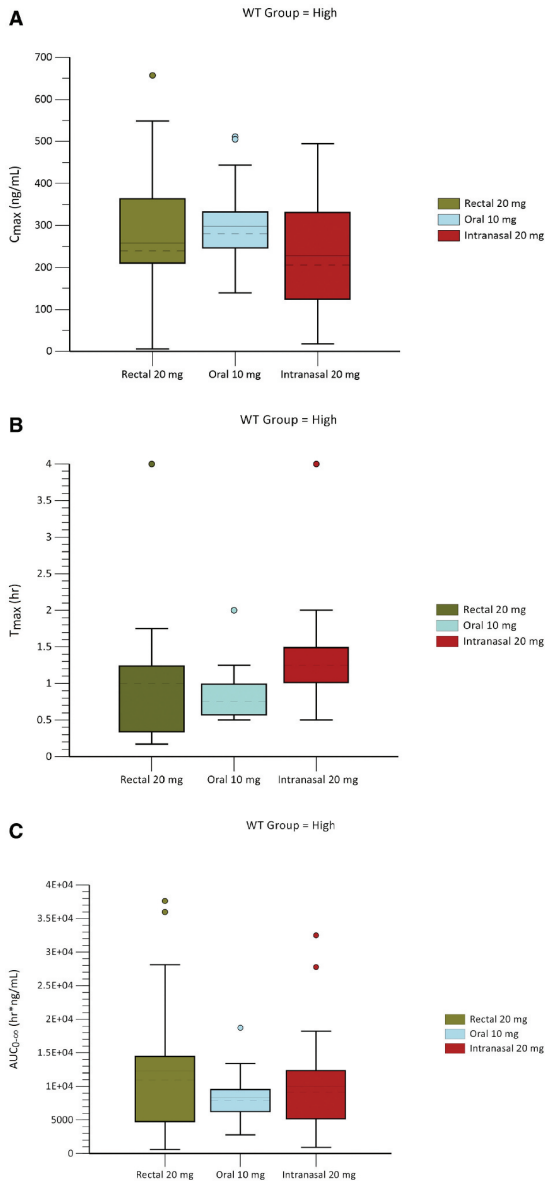

Figure 3. Comparative pharmacokinetic measures of rectal, oral and nasal diazepam: box and whiskers plots, mean ± SD. AUC, area under the curve; Cmax, peak plasma concentration; Tmax, time to reach maximum plasma concentration; WT, weight. Reproduced with permission from Hogan et al. [17].

spray. The high retention rate supports both efficacy and tolerability.

3. Comparison to other forms of rescue therapy

Other newer forms of rescue therapy, such as intranasal or buccal midazolam, have been approved by either the FDA or the EMA and are commercially available. Intranasal midazolam is reviewed elsewhere [23] for those who wish additional information. These drugs appear to be effective and well tolerated. However, no head-to-head comparisons have been performed for these drugs and the extant literature does not provide evidence to support claims of superiority of one agent over another.

Table 2. IN diazepam dose and weight.

Dose based on age and weight (kg)			Administration	
6 to 11 years of age (0.3 mg/kg)	12 years of age and older (0.2 mg/kg)	Dose (mg)	Number of nasal spray devices	Number of sprays
10–18 kg	14–27 kg	5	One 5 mg device	One spray in one nostril
19–37 kg	28–50 kg	10	One 10 mg device	One spray in one nostril
38–55 kg	51–75 kg	15	Two 7.5 mg devices	One spray in each nostril
56–74 kg	≥ 76 kg	20	Two 10 mg devices	One spray in each nostril

Adapted from Neurelis, Inc. Valtoco (diazepam nasal spray), Full prescribing information. San Diego, CA: Neurelis Inc.; 2021.

4. Conclusion

The development of new rescue therapies provides a welcome addition to the therapeutic arsenal against seizure clusters/ARS and prolonged seizures. Using routes other than rectal administration offers a significant advantage to patients and caregivers. Having several formulations provides multiple treatment options should any single agent or route of administration prove unsatisfactory. It is hoped that these treatments will increase the number of patients who are successfully treated, enhancing their quality of life, reducing the incidence of seizure-related injury, and lessening the need for hospital visits.

5. Expert opinion

Intranasal rescue drugs are a valuable treatment modality for patients with seizure clusters/ARS and prolonged seizures, potentially averting serious adverse consequences of seizures and reducing the need for emergency department visits and hospitalizations. The intranasal route of administration, which can be self-administered, is preferred over the rectal route because of reduced variability in serum levels and ease of administration, greater social palatability, and a less stigmatizing means of delivering drug in both public and private settings. The high retention rates observed in long-term studies of IN diazepam support utility of this treatment.

Studies are lacking that directly compare effectiveness and tolerability of IN midazolam, IN diazepam, and rectal diazepam. Therefore, choosing between these treatments is somewhat arbitrary, and physicians might reasonably switch from one therapy to another should treatment response drug or tolerability of one drug prove suboptimal. Head-to-head comparison studies might aid in therapeutic decision-making. Age may be another consideration when choosing a drug; IN midazolam has not been studied in children under 12 years of age (unlike buccal midazolam), whereas IN diazepam has been evaluated in children as young as 6 years of age.

An additional method of delivering rescue medication is presently under study. An inhaled formulation of alprazolam is being tested, and this offers more drug rapid delivery to the central nervous system. Should this agent prove effective and gain regulatory approval, comparison with existing therapies will be needed. Lastly, the authors strongly advocate for providing rescue antiseizure therapy to suitable patients. Having a rescue medication in hand provides a sense of empowerment and comfort to patients and their caregivers, and the psychological benefit cannot be underestimated.

Declaration of interest

M Sperling has received compensation for speaking at CME programs from Neurology Live, Medscape, Projects for Knowledge, international Medical Press, Eisai, and UCB pharma. He is an advisor for scientific publications for Neurelis. He consults for Medtronic with payments to Thomas Jefferson University. He has received research support from Eisai; Medtronic; Neurelis; SK Life Science; Takeda; Xenon; Cerevel; UCB pharma; and Engage Pharmaceuticals. He has received royalties from Oxford University press. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or conflict with the subject matter or materials discussed in this manuscript apart from those disclosed.

Reviewer disclosures

Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

Funding

This paper was not funded.

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