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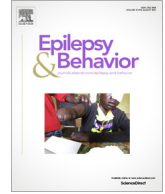
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Examining the patient and caregiver experience with diazepam nasal spray for seizure clusters: Results from an exit survey of a phase 3, open-label, repeat-dose safety study



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ABSTRACT

Background: Ideal rescue treatments for acute treatment of seizure clusters should be easy to administer, so it is important to assess user perceptions of these treatments. Diazepam nasal spray is designed to have a rapid, noninvasive, and socially acceptable route of administration. Patient and caregiver (including care partner) responses to surveys from a phase 3 safety study of diazepam nasal spray are reported. **Methods:** The study enrolled patients aged 6–65 years with seizure clusters. Surveys distributed to patients and caregivers at study end, completion, or discontinuation collected data on comfort using diazepam nasal spray outside the home, timing of administration and return to their usual selves, and comfort of use compared with rectal diazepam. Safety was assessed.

Results: Of 175 patients enrolled at the October 31, 2019, interim cutoff, 158 received diazepam nasal spray. Sixty-seven (42.4%) patients and 84 (53.2%) caregivers responded to the surveys (including 35 matched pairs). Most patients (78.8%, 52/66) responded that they were very comfortable doing activities outside the home with diazepam nasal spray available; 59.4% of patients returned to their usual selves within an hour of administration. Twenty-seven (40.3%) of these patients reported self-administration, 48% doing so at the first sign of a seizure. Administration of diazepam nasal spray was rated extremely or very easy by 93.8% of caregivers. Safety profile was consistent with diazepam rectal gel; no patient discontinued owing to treatment-emergent adverse events. Nasal discomfort was typically mild and transient. Among patients who had used diazepam rectal gel, most were not at all comfortable using it outside the home (86.7%) or at home (64.5%) compared with diazepam nasal spray, whereas caregivers reported that diazepam rectal gel was not at all easy to use compared with diazepam nasal spray.

Conclusions: This survey from the phase 3 safety study of diazepam nasal spray shows that patients and caregivers were satisfied with, and more comfortable using, diazepam nasal spray than rectal diazepam in public.

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1. Introduction

Seizure clusters are intermittent, recognizable stereotypic episodes of seizure activity that are distinct from a patient's usual seizures [1]. Rescue therapy for seizure clusters has generally relied

on benzodiazepines as first-line treatment [2,3]. Most seizure clusters occur outside the hospital environment [4]; therefore, ideal rescue treatments for patients with epilepsy experiencing seizure clusters should be easy for patients and caregivers (including care partners such as family members and school personnel) to access and administer in the community setting.

Although rectal diazepam has long been approved for treatment of seizure clusters outside the hospital, this route of administration may be considered socially unacceptable by some patients and

Abbreviations: TEAE, treatment-emergent adverse event.

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caregivers [2]. Without access to a more acceptable route of administration, patients who decline rectal therapy for seizure clusters may require admission to an emergency department. It is therefore important to assess user perceptions of rescue treatments to identify those that are more likely to be used, thereby reducing the potential for emergency department visits or hospitalization. Understanding the impact of seizure clusters on patients and caregivers may aid in enhancing management of the disease [5]. To promote self-management by patients, physicians should consider quality-of-life concerns when treating patients with refractory epilepsy [6].

Diazepam nasal spray (Valtoco[®]) is a proprietary intranasal formulation approved by the US Food and Drug Administration for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) in patients with epilepsy aged 6 years and older [7]. It is designed to provide a rapid, noninvasive, and socially acceptable route of administration. Diazepam nasal spray includes Intravail[®] A3 as an absorption enhancer and vitamin E to assist with solubility. For orphan drug exclusivity, the US Food and Drug Administration found that the intranasal route was clinically superior compared to rectal administration because it provides a major contribution to patient care by significantly improving ease of use and being more comfortable and easier to administer [8]. Diazepam nasal spray is designed to be portable and ready to use. The intranasal device provides a specified metered dose with ease of use in one hand and fitting easily inside a handbag or backpack, allowing for self-administration in patients who can participate in their own treatment. The safety and tolerability of diazepam nasal spray has been assessed in a phase 3, long-term, open-label safety study of patients with epilepsy.

A survey to understand patients' and caregivers' opinions of diazepam nasal spray as rescue therapy was included in the phase 3 study. The objective of the present analyses was to assess patient and caregiver responses to the survey regarding timing of administration of diazepam nasal spray, ease of administration, and comfort using this formulation outside of the home. Perceptions of diazepam nasal spray in subgroups who self-administered and who previously used diazepam rectal gel also were examined.

2. Methods

2.1. Study design and dosing

Diazepam nasal spray was evaluated in a phase 3, repeat-dose, open-label, long-term safety study (NCT02721069) of patients with epilepsy who have seizure clusters despite use of a stable regimen of antiseizure drugs. The study consisted of a screening phase, baseline, 12-month treatment period, and 28-day follow-up period; at the discretion of the investigator, patients could continue treatment beyond day 365. Patients received age- and weight-based doses of 5, 10, 15, or 20 mg of diazepam nasal spray. A second dose could be administered 4–12 h after the first dose if needed. Both patients and caregivers were trained in proper administration. Patient diaries were used to record seizures and diazepam nasal spray administration.

2.2. Patients

Patients aged 6–65 years with a diagnosis of either partial or generalized epilepsy with motor seizures or seizures with clear alteration of awareness were enrolled in the study. Additional key inclusion criteria were availability of a qualified caregiver or medical professional to administer study medication and no clinically significant abnormal findings in their medical history, or on

physical examination or electrocardiogram during screening. Female patients of childbearing potential were required to use an approved method of birth control. Patient history of status epilepticus or allergic rhinitis and current concomitant benzodiazepine use were permitted to best ensure an inclusive, relevant real-world population, which also allowed for evaluation of safety and effectiveness of diazepam nasal spray in these patients. Key exclusion criteria were history of major depression or a past suicide attempt or suicidal ideation; history of allergy or adverse response to diazepam; and history of a clinically significant medical condition that would jeopardize the safety of the patient. This trial was conducted in accordance with the principles outlined in the Declaration of Helsinki, and institutional review board approval (main board: Western Institutional Review Board, Puyallup, WA) was obtained before study initiation. All patients provided written informed consent to participate.

2.3. Study outcomes

The primary study objective was safety, including assessments of treatment-emergent adverse events (TEAEs; irrespective of relationship to study drug). All TEAEs were coded according to the Medical Dictionary for Regulatory Activities and graded according to the Common Terminology Criteria for Adverse Events v.4.03. Based on investigator assessment, TEAEs were categorized as unlikely, possibly, or probably treatment related. Serious TEAEs were reported per investigator assessment and defined as per International Council for Harmonisation Guidelines for Good Clinical Practice (i.e., those resulting in death or are life threatening, those requiring inpatient hospitalization or prolongation of hospitalization, those resulting in persistent or significant disability/incapacity, or those considered important medical events). Results are reported descriptively.

2.4. Patient and caregiver surveys

The surveys were provided to all patients enrolled in the study and their caregivers; caregivers and patients on the study at the time were given surveys at one time point toward the end of the study, to be returned at the next visit, and the surveys were mailed to those who had already completed or discontinued the study. Surveys were developed by the study investigators and an expert panel of epileptologists treating adult or pediatric patients to assess various facets of the patient and caregiver experiences, including comfort using diazepam nasal spray outside the home, timing of administration and return to their usual selves, and convenience of use compared with rectal diazepam (Supplemental Figs. 1 and 2) and received face validation prior to use but were not evaluated for construct validity. Surveys were provided in paper format with true/false or multiple-choice questions; responses were subsequently entered into the database. Patient and caregiver results were tabulated separately; cases in which both the patient and their caregiver responded to the survey were also evaluated as patient-caregiver matched pairs. Patients and caregivers were not required to answer every survey question. Responders received nominal compensation (\$50 gift card) for their time.

2.5. Statistical analysis

Statistical analysis was performed using Fisher's exact test on the patient and caregiver responses regarding satisfaction with diazepam nasal spray (Question 23, Suppl Fig. 1 and Question 26, Suppl Fig. 2, respectively) to determine overall impact of age group (<18 vs ≥18 years) and dose (5, 10, 15, and 20 mg) on the selected responses.

3. Results

3.1. Safety population

Overall, 175 patients had enrolled in the phase 3 study by the October 31, 2019, interim cutoff date; of these, 158 received a total of 3724 doses of diazepam nasal spray for 3370 reported clusters and were included in the safety population. The remaining 17 patients did not receive study drug. Approximately 53.8% of patients in the safety population were female, and the median age was 19.5 years. The majority of patients (73.4%) had 12 or more months of exposure to diazepam nasal spray (median, 13.0 months; range, <1–36.6 months). Treatment-related TEAEs were only reported in 26 patients (16.5%); there were no serious treatment-related TEAEs and no discontinuations due to TEAEs. The retention rate in this long-term study was 83% (i.e., 27 patients discontinued). At the time of the analysis, 47 patients had already completed the study, and surveys were mailed to their last known addresses as well as to patients who had discontinued. Not all questions were answered by all patients or all caregivers; thus, the denominators differ for some questions.

3.2. Patient survey

Sixty-seven patients responded to the survey; of these, 66 had safety data and were included in the safety set (Fig. 1). Of these patients, 47.0% were female, the median age was 24.5 years, and 78.8% had median diazepam nasal spray treatment duration of a year or more (Table 1). At the data cutoff, 22 patients had completed the study, 5 had discontinued, and 39 were ongoing.

Among the patients who responded, 19 trained another person to use diazepam nasal spray. In total, 48 individuals were trained by patients. People trained included both parents (n = 6), grandparents (n = 1), siblings (n = 5), friends (n = 8), and other (n = 28). Training others to use diazepam nasal spray was rated as either extremely easy or very easy by 42.1% (8/19) and 47.4% (9/19)

respondents, respectively. Only 1 patient (5.3%) reported that it was not at all easy to train others.

Among 53 patients who had had prior rescue medication protocols before starting this study, 32 (60.4%) reported prior administration of rectal diazepam. Of the 31 patients with safety data who reported prior use of rectal diazepam, the median age was 14 years (range, 7–51 years; 6–<12 years, n = 7; 12–18 years, n = 15; >18 years, n = 9). Compared with diazepam nasal spray, 86.7% of patients were not at all comfortable having rectal diazepam administered in public, and 64.5% were not at all comfortable having their caregiver administer rectal diazepam at home. When considering treatment convenience, 83.9% (26/31) would prefer using diazepam nasal spray exclusively going forward.

Among patient respondents, 87.9% reported they or their caregivers carried diazepam nasal spray outside the home; 84.5% of patients were extremely or very comfortable carrying it with them, and 78.8% of patients were very comfortable doing activities outside the home if they had diazepam nasal spray available. After the most recent time they administered diazepam nasal spray, the majority of patients returned to their usual selves within 1 h (59.4%; Fig. 2). The majority of patients (53/66; 80.3%) reported being very satisfied or satisfied with diazepam nasal spray, and were either extremely (39/64; 60.9%) or very (11/64; 17.2%) likely to ask the patient’s healthcare provider about continuing diazepam nasal spray.

Of the 66 patients who responded to the survey and had available safety data, 51 (77.3%) reported a TEAE. Seventeen patients (25.8%) had a serious TEAE, none of which was considered by the investigator to be treatment related (≥2 patients: seizure [13.6%], pneumonia [4.5%]). No patient discontinued because of a TEAE. Four mild and 1 moderate report of nasal discomfort were all assessed as treatment related.

3.2.1. Patient survey: patients self-administering diazepam nasal spray

A subset (n = 27) of the patients reported self-administering diazepam nasal spray. Of these patients, the median age was 34 (range, 11–65) years, 55.6% were female, and 96.3% had a treatment duration of a year or more (Table 2). Seizure types and subtypes were not consistently reported for these patients but included complex partial (focal onset impaired awareness), simple partial (focal onset aware), absence, generalized tonic-clonic, and myoclonic.

Doses administered were 10 mg (n = 2 [7.4%]), 15 mg (n = 10 [37.0%]), and 20 mg (n = 15 [55.6%]); no patient in this group received the 5-mg dose. Of the 3724 doses administered in the safety population, 994 (26.7%) doses were administered in this subgroup (10 mg, n = 61 [6.1%]; 15 mg, n = 180 [18.1%]; and 20 mg, n = 753 [75.8%]). Of the 27 patients, 3 (11.1%) used 1 to 2 doses, 4 (14.8%) each used 3 to 10 or 11 to 20 doses, and 8 (29.6%) each used 21 to 40 or >40 doses during the study. There was a low rate of dosing errors in the self-administering patient subgroup (11 [1.1%]), primarily missing the nostril and initially misunderstanding directions (e.g., missing half of a dose if 2 devices are required for dose), compared with 1.0% (27 errors in 2641 doses) among patients in the survey population who did not self-administer and 1.5% in safety population of the overall study.

Self-administering patients were asked when they primarily administered diazepam nasal spray (Fig. 3). The most common response was, “At the first signs that a seizure may be coming” (48.0%, n = 12). Twenty-one respondents (77.8%) reported that self-administration of diazepam nasal spray was either extremely easy (n = 11) or very easy (n = 10). The majority of patients (n = 18; 66.7%) reported that self-administering diazepam nasal spray in a public setting was either extremely (n = 5), very (n = 3), or somewhat (n = 10) comfortable.

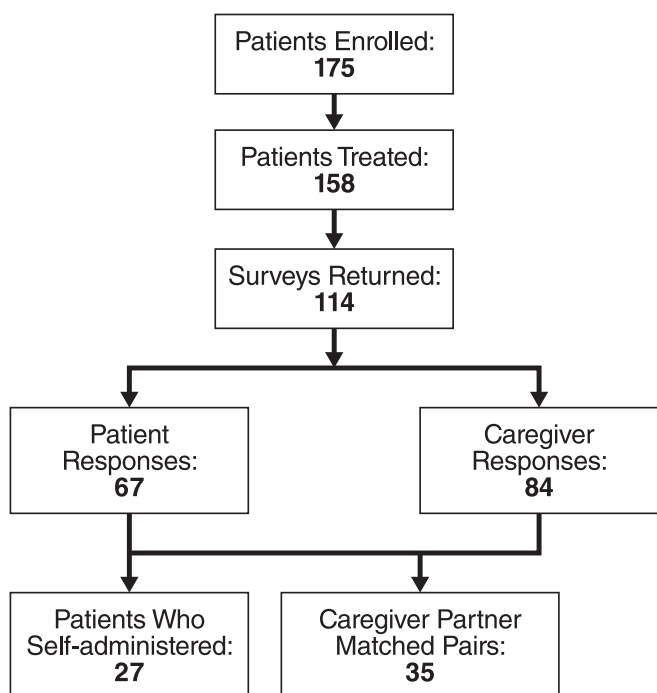


Fig. 1. Flowchart of responses to surveys.

Table 1
Baseline Characteristics of Patient Survey Respondents (Safety Population; n = 66).

Demographics n (%)	5 mg (n = 1)	10 mg (n = 18)	15 mg (n = 20)	20 mg (n = 27)	Total (n = 66)
Sex					
Male	0	11 (61.1)	9 (45.0)	15 (55.6)	35 (53.0)
Female	1 (100)	7 (38.9)	11 (55.0)	12 (44.4)	31 (47.0)
Race					
White	1 (100)	12 (66.7)	16 (80.0)	22 (81.5)	51 (77.3)
Black or African American	0	2 (11.1)	2 (10.0)	2 (7.4)	6 (9.1)
Asian	0	2 (11.1)	0	0	2 (3.0)
Native Hawaiian or other Pacific Islander	0	0	1 (5.0)	2 (7.4)	3 (4.5)
Other	0	2 (11.1)	1 (5.0)	1 (3.7)	4 (6.1)
Age, y					
Median	26.0	11.5	24.0	35.0	24.5
Range	26–26	7–65	12–54	11–59	7–65
Duration of exposure					
<6 mo	0	1 (5.6)	0	0	1 (1.5)
6–<12 mo	1 (100.0)	7 (38.9)	2 (10.0)	3 (11.1)	13 (19.7)
≥12 mo	0	10 (55.6)	18 (90.0)	24 (88.9)	52 (78.8)

Question: Thinking of the last time [diazepam nasal spray] was administered, how soon after the administration did you return back to your usual self? (n=64)

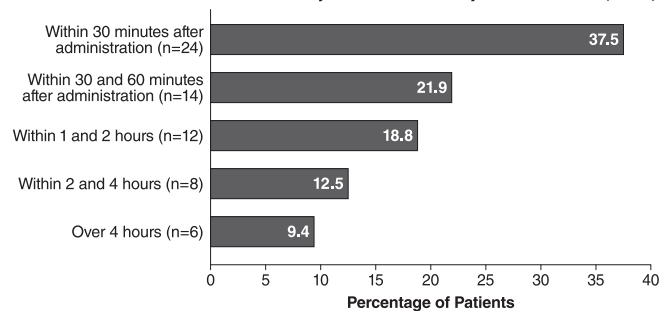


Fig. 2. Timing to return to usual for patients after the most recent administration of diazepam nasal spray. Sixty-four patients responded to the survey question. Bars represent percentage of patients who chose that answer.

The safety profile of the self-administering patients was similar to the full patient survey respondent population. In this subgroup, 20 patients (74.1%) had a TEAE. Six patients (22.2%) had TEAEs that were possibly treatment related. Only nasal discomfort (n = 4, 14.8% [3 mild, 1 moderate]) was reported in ≥2 patients. Six patients (22.2%) in this subgroup had a serious TEAE. However,

no serious TEAE was considered treatment related. No patient in this subgroup discontinued owing to a TEAE.

3.2.2. Caregiver survey

Eighty-four caregivers of enrolled patients responded to the survey (Fig. 1, Table 3). Of the 83 caregivers who responded to the question regarding their relationship to the patient, 100% were family members. Demographically, 85.2% (69/81) were female and 65.9% (54/82) were aged 31–50 years (median, 47 years; range, 29–73 years). Most caregivers (64/84; 76.2%) reported a post-high school education level (college, graduate school, or trade program). Of the 83 respondents to the question, 61 (73.5%) considered it extremely easy to be trained to administer diazepam nasal spray and 22 (26.5%) reported that it was very easy; no respondent considered it not at all easy. Sixty-eight caregivers trained another person to use diazepam nasal spray; 2 of the 68 caregivers did not answer this question, but did respond to the question of whom they trained. In total, 250 persons were trained by caregivers. The median (range) number of persons trained by an individual caregiver was 3 (1–15). Persons trained included both parents (n = 50), grandparents (n = 34), siblings (n = 26), friends (n = 29), teachers (n = 45), and other (n = 66). Training others to use diazepam nasal spray was rated as either extremely easy or very easy by 40 and 28 respondents, respectively.

Table 2
Baseline Characteristics of Patient Survey Respondents Who Reported Self-Administering of Diazepam Nasal Spray (Safety Population; n = 27).

Demographics* n (%)	10 mg (n = 2)	15 mg (n = 10)	20 mg (n = 15)	Total (n = 27)
Sex				
Male	1 (50.0)	5 (50.0)	6 (40.0)	12 (44.4)
Female	1 (50.0)	5 (50.0)	9 (60.0)	15 (55.6)
Race				
White	1 (50.0)	8 (80.0)	13 (86.7)	22 (81.5)
Black or African American	0	1 (10.0)	0	1 (3.7)
Asian	1 (50.0)	0	0	1 (3.7)
Native Hawaiian or other Pacific Islander	0	0	1 (6.7)	1 (3.7)
Other	0	1 (10.0)	1 (6.7)	2 (7.4)
Age, y				
Median	38.0	25.5	38.0	34.0
Range	11–65	16–54	22–59	11–65
Duration of exposure[†]				
6–<12 mo	0	1 (10.0)	0	1 (3.7)
≥12 mo	2 (100.0)	9 (90.0)	15 (100.0)	26 (96.3)
Number of doses[‡]	61	180	753	994

*None of the patients reporting self-administration were in the 5-mg dose group.

[†] None of the patients reporting self-administration had a duration of exposure <6 months.

[‡] This is the total number of self-administered doses in this group over the duration of the open-label study.

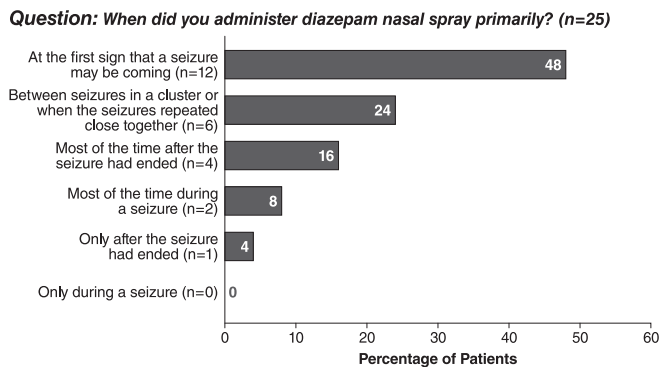


Fig. 3. Primary timing of administration of diazepam nasal spray by patients who self-administered doses. Twenty-five patients responded to the survey question. Bars represent percentage of patients who chose that answer.

Table 3
Caregiver Demographics (Survey Responders; n = 84).

Characteristic	n (%)
Caregiver type	
Family caregiver	83 (98.8)
Professional caregiver	0 (0)
No answer	1 (1.2)
Gender	
Male	12 (14.3)
Female	69 (82.1)
Nonbinary/third gender	0 (0)
No answer	3 (3.6)
Age, median, y (range)	47 (29–73)
18–30	2 (2.4)
31–40	24 (28.6)
41–50	30 (35.7)
51–60	14 (16.7)
61–70	10 (11.9)
71–80	2 (2.4)
No answer	2 (2.4)
Highest education level	
Elementary school	1 (1.2)
Less than high school (middle school)	3 (3.6)
High school	16 (19.0)
College	47 (56.0)
Graduate school	14 (16.7)
Trade program	3 (3.6)
Prior use of seizure rescue medications, yes	67 (79.8)
Diazepam rectal gel	57 (85.1)*
Patient age	
Child (6–11 y)	36 (42.9)
Adolescent (12–17 y)	26 (30.9)
Adult (≥18 y)	22 (26.2)
Number of doses administered to patients	2641

*Of the 67 caregivers who reported prior use of rescue medications.

The majority of caregivers (62/82; 75.6%) reported administering diazepam nasal spray to the patient either all (35/82; 42.7%) or two thirds of the time (27/82; 32.9%). Caregivers were asked when they primarily administered diazepam nasal spray to the patient. Caregiver-reported timing of primary administration of diazepam nasal spray was most commonly during a seizure cluster (Fig. 4A). Administration of diazepam nasal spray was rated extremely, very, or somewhat easy by 54.3% (44/81), 39.5% (32/81), and 4.9% (4/81) of caregivers, respectively, whereas 1 caregiver considered administration to be not at all easy. The majority of caregivers self-assessed that they (the caregivers themselves) could return to their own daily activities within an hour after the most recent administration of diazepam nasal spray to the patient (47/79; 59.5%; Fig. 4B).

The patients of these caregivers received 2641 doses of diazepam nasal spray. Most caregivers reported having administered a seizure rescue medication to the patient before this study

(67/83; 80.7%), primarily rectal diazepam (57/68; 83.8%). Although the vast majority of caregivers (76/81; 93.8%) considered administration of diazepam nasal spray to be extremely or very easy, use of diazepam rectal gel was rated not at all easy by 64.3% (36/56) in comparison to diazepam nasal spray. Only 4 (7.1%) caregivers rated diazepam rectal gel administration to be extremely easy or very easy. Most caregivers carried diazepam nasal spray outside the home (80/82; 97.6%) and considered it extremely or very comfortable to carry with them (76/81; 93.8%). The majority of caregivers were extremely or very comfortable (69/77; 89.6%) using diazepam nasal spray in a public setting. In contrast, 87.0% (47/54) of caregivers were not at all comfortable using rectal diazepam gel in a public setting. The majority of caregivers (77/83; 92.8%) reported being very satisfied or satisfied with diazepam nasal spray, and were either extremely (64/84; 76.2%) or very (13/84; 15.5%) likely to ask the patient’s healthcare provider about continuing diazepam nasal spray in the future.

Safety data were available for 76 patients (90.5%) whom these caregivers assisted; some of these patients (n = 35) were also included in the analysis of patient–caregiver matched pairs, below. Treatment-emergent adverse events occurred in 61 patients (80.3%). A total of 26 patients (34.2%) had a serious TEAE; none were treatment related. No patients discontinued owing to a TEAE.

3.2.3. Patient–caregiver matched pairs

There were 35 cases in which both the patient and caregiver individually responded to the survey (Fig. 1). Five (14.3%) of these patients were also included in the self-administration analysis described above. The majority of respondents said the caregiver previously administered rectal diazepam before use of diazepam nasal spray (patients, 77.4% [24/31]; caregivers, 81.5% [22/27]). When asked about the timing of administration of diazepam nasal spray, results were similar to the larger patient and caregiver groups for when diazepam nasal spray was primarily administered. The majority of patients who self-administered (3/5; 60.0%) reported administering diazepam nasal spray at the first sign of a seizure. The majority of caregivers (26/32; 81.3%) reported administering diazepam nasal spray either during a cluster of seizures or when they were repeating, only during a seizure, or most of the time during a seizure.

Both patients and caregivers reported on the ease of use of diazepam nasal spray. All patients reported that diazepam nasal spray was either extremely easy, very easy, or somewhat easy to self-administer, and the same was true for 97.1% (33/34) of the caregivers. Only 1 caregiver responded that diazepam nasal spray administration was not at all easy to use. Patients and caregivers were also asked about the ease of use of diazepam rectal gel versus diazepam nasal spray. Again, responses were similar for patients and caregivers. The majority of patients who previously received rectal diazepam responded that it was not at all easy (16/24; 66.7%) for their caregiver to administer versus diazepam nasal spray. Similarly, 59.1% (13/22) of caregivers who previously administered rectal diazepam responded that it was not at all easy to administer versus diazepam nasal spray. Compared with diazepam nasal spray, caregivers (16/20; 80.0%) reported that administration of diazepam rectal gel was not at all comfortable and patients (19/22; 86.4%) found it not at all comfortable to have diazepam rectal gel administered in public.

When asked about their treatment preference (vs rectal diazepam) based on treatment convenience, responses from patients and caregivers were again similar. The majority of both patients (21/24; 87.5%) and caregivers (29/33; 87.9%) responded that they would prefer to exclusively use diazepam nasal spray moving forward. Responses to the questions related to the time to return to usual self or usual activities after administering diazepam nasal spray were similar to the responses to these questions for the over-

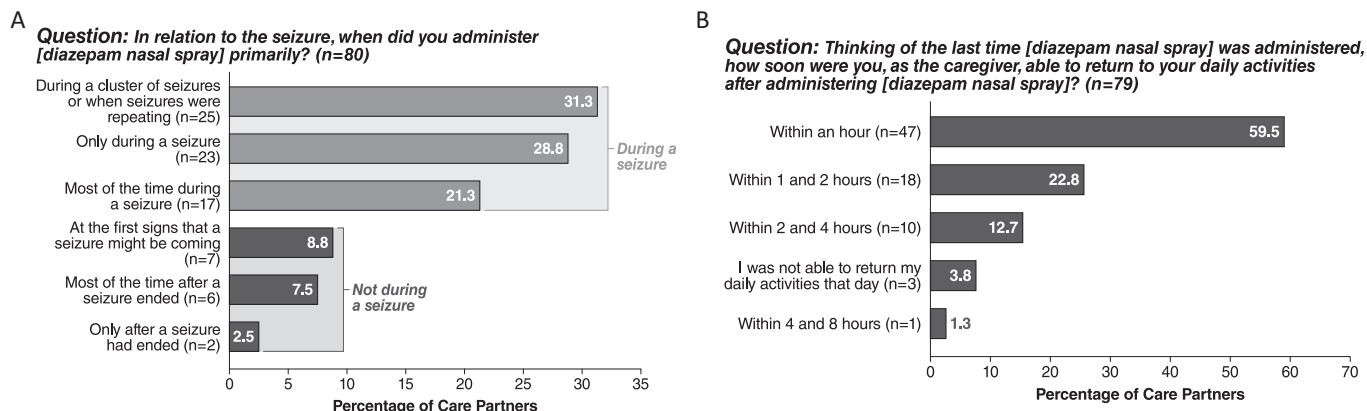


Fig. 4. Administration of diazepam nasal spray by caregivers. A, Timing of administration. B, Amount of time to return to daily activities after most recent administration. Of caregivers who responded to the survey question, the bars represent percentage who chose that answer.

all groups of patients and caregivers. Normal activities were able to be resumed in <1 h by 27.3% (9/33) of patients, in 1–2 h by 30.3% (10/33) of patients, and in >2 h by 42.4% (10/33) of patients. Normal activities were able to be resumed in <1 h by 48.5% (16/33) of caregivers, in 1–2 h by 30.3% of caregivers, and in >2 h by 21.2% of caregivers. Both patients (28/35, 80.0%) and caregivers (32/35, 91.4%) indicated that they were either very satisfied or satisfied with diazepam nasal spray.

Safety data were available for 33 of the patients in the matched pairs. Treatment-emergent adverse events occurred in 25 patients (75.8%). Eleven patients (33.3%) had a serious TEAE; none were treatment related. No patients discontinued owing to a TEAE.

3.3. Statistical analysis results

Patient and caregiver responses were analyzed regarding satisfaction with diazepam nasal spray by age and dose. Patient and caregiver age groups (<18 and ≥18 years) did not show statistical significance relative to the satisfaction responses (overall $P = 0.8135$ and $P = 0.4084$, respectively). The same was true for patient and caregiver dose groups of 5, 10, 15, and 20 mg (overall $P = 0.3450$ and $P = 0.5263$, respectively).

4. Discussion

Seizure clusters can place significant emotional and financial burdens on both patients with epilepsy and their caregivers [5]. Although diazepam rectal gel has been approved for decades for the treatment of seizure clusters, patients and caregivers report that it can be difficult to administer and socially unacceptable to use in public [2,3]. The availability of a rescue medication that is easy to use, convenient to carry, and socially acceptable to use in public may help patients and their caregivers choose to use rescue therapy instead of relying on hospitalization in the event of a seizure cluster. Thus, it is of great importance to assess patient and caregiver perceptions of treatment.

This analysis reports results from a survey of patients enrolled in the phase 3 safety study of diazepam nasal spray and their caregivers. Overall, both patients and caregivers had positive impressions of diazepam nasal spray. Patients and caregivers found diazepam nasal spray comfortable to carry and use outside the home; most were able to return to their usual self or daily activities in <1 h (patients, 59.4%; caregivers, 59.5%, respectively). A subgroup of self-treating patients reported that treatment was most commonly administered at the first sign of a seizure. Caregivers reported primarily administering diazepam nasal spray during a seizure cluster. Of the patients who were prescribed another sei-

zure rescue medication protocol before diazepam nasal spray study entry, most were prescribed diazepam rectal gel. Of note, caregivers reported that diazepam nasal spray was easier to administer than diazepam rectal gel, and both patients and caregivers were more comfortable with administration of diazepam nasal spray in public compared with rectal diazepam. These findings suggest that patients and their caregivers found that diazepam nasal spray was a beneficial treatment option.

A prior cross-sectional survey also investigated attitudes toward the use of intranasal midazolam and rectal diazepam as rescue therapy for seizure clusters in caregivers of young (ages 0–23 years) patients with epilepsy who received treatment at a tertiary level IV epilepsy center and large academic medical institution [9]. Of the caregivers who reported administering both formulations, the majority preferred intranasal midazolam to rectal diazepam: 87% considered it to be more effective, and 74% felt more comfortable with it [9]. Compared with rectal diazepam, intranasal midazolam was viewed as having fewer side effects, was easier to train others to use, and was more readily available at school [9]. That prior study had some differences from the present study: the patients were generally younger (average age, 10.5 years [range, 3–22] and 24.5 years [range, 7–65], respectively), and patient preferences were not assessed in the earlier study. Despite these differences, these findings complement those of the current study and provide further evidence of the preference of caregivers for intranasal versus rectal formulations of benzodiazepines to treat seizure clusters outside a hospital setting.

The results among patients who self-administered diazepam nasal spray support a potential benefit of this approach over other routes of administration that require a caregiver. Diazepam nasal spray is administered with a device similar to that used for some self-administered intranasal therapies, such as for migraine headaches [10]. The potential for self-administration of intranasal benzodiazepine rescue therapy for seizure clusters may provide patients with more control over their treatment. In the surveys, self-administering patients—some as young as 11 years old—reported ease of use of diazepam nasal spray, and their safety profile was consistent with the entire study population. Importantly, there were very few self-dosing errors. Overall, these findings support the use of self-administered diazepam nasal spray in a manner consistent with the prescribing information.

In cases in which both patient and caregiver responded to the survey ($n = 35$), paired responses tended to be similar overall. Both groups considered diazepam nasal spray to be convenient to carry and easy to use. Moreover, both groups preferred diazepam nasal spray to rectal diazepam gel, especially for use in a public setting. Both groups indicated that they were satisfied with diazepam nasal

spray and would prefer to use this formulation as rescue therapy in the future. These findings are important because they suggest that diazepam nasal spray would improve the quality of life and reduce burdens for both patients and their caregivers. Furthermore, the ease of use of diazepam nasal spray may result in increased use of rescue therapy during a seizure cluster, possibly reducing the need for emergency care.

For all survey groups, safety of the patients was consistent with that of the established profile of rectal diazepam, with no discontinuations due to TEAEs or unexpected TEAEs. No serious TEAEs were deemed treatment related for any of the subgroups of patients analyzed. Nasal discomfort was transient and typically mild.

This analysis is subject to some limitations. To our knowledge, this is one of the largest populations in a clinical study of rescue medication for seizure clusters, capturing the highest number of seizure events. These results are based on a subset of respondents, and the overall response rates for patients and caregivers of 48% compares favorably with response rates of about half to a quarter in other patient/caregiver surveys [11–13]. As such, they may be subject to self-selection, and responses may not be generalizable to the broad population of patients who experience seizure clusters in the real world or their caregivers. Because of the nature of surveys, verification of individual responses for internal consistency was not possible; however, the overall results show a high degree of consistency among patients and among caregivers as well as between patient and caregiver responses. Overall, there are few data on how patients and caregivers view rescue therapy for seizure clusters, and these results from a large open-label study provide novel information on this topic.

5. Conclusions

The responses from this survey demonstrate that patients and caregivers find diazepam nasal spray easy to administer and use outside the home. Moreover, a subgroup of patients, aged 11–65 years, were able to take an active role in their own treatment and reported ease of use with self-administration. Caregivers reported administration mainly during seizures. Of note, patients and caregivers who previously used rectal diazepam as a rescue therapy protocol strongly preferred the convenience of diazepam nasal spray. These results suggest that administration of diazepam nasal spray may provide patients and caregivers with more control of their treatment and daily routine.

6. Disclosures

Dr Penovich has served on speaker bureaus for GW Pharmaceuticals, Neurelis, Inc., SK Life Science, and UCB; and is an advisor to Engage Therapeutics; LVIS Corporation; Neurelis, Inc.; and SK Life Science. **Dr Wheless** has served as an advisor or consultant for: CombiMatrix; Eisai, Inc.; GW Pharmaceuticals; Lundbeck, Inc.; Neurelis, Inc.; NeuroPace, Inc.; Supernus Pharmaceuticals, Inc.; and Upsher-Smith Laboratories, Inc. Dr Wheless has served as a speaker or a member of a speakers bureau for Cyberonics, Inc.; Eisai, Inc.; Lundbeck, Inc.; Mallinckrodt; Neurelis, Inc.; Supernus Pharmaceuticals, Inc.; and Upsher-Smith Laboratories, Inc., and has received grants for clinical research from Acorda Therapeutics; GW Pharmaceuticals; Insys; Eisai, Inc.; Medtronic; Neurelis, Inc.; SK Life Science; Takeda; Sunovion; UCB Pharma; Xenon; and

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Appendix A. Supplementary data

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