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Brief Communication

# Concomitant cannabidiol does not impact safety and effectiveness of diazepam nasal spray for seizure clusters: Post hoc analysis of a phase 3 safety study

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ABSTRACT

People with epilepsy may experience episodes of frequent seizure activity (seizure clusters, acute repetitive seizures), and benzodiazepines are the cornerstone of rescue treatment. Cannabidiol (CBD) can be used as an adjunctive treatment for epilepsy, and it may interact with other antiseizure drugs, such as benzodiazepines. Here, we examined the safety and effectiveness of intermittent use of diazepam nasal spray in patients with seizure clusters who also received CBD treatment. This analysis included data from patients aged 6 to 65 years enrolled in a phase 3, long-term safety study of diazepam nasal spray. Age- and weight-based dosing of diazepam nasal spray were administered during a 12-month treatment period. Concomitant CBD use was recorded, and treatment-emergent adverse events (TEAEs) were collected. Of 163 treated patients, 119 (73.0%) did not receive CBD, 23 (14.1%) received the US Food and Drug Administration–approved highly purified CBD and 21 (12.9%) received another form of CBD. On average, patients receiving highly purified CBD were younger and more likely to have epileptic encephalopathies, including Dravet syndrome or Lennox-Gastaut syndrome, than patients who received another CBD preparation or no CBD. Rates of TEAEs and serious TEAEs were greater in patients who received any form of CBD (90.9% and 45.5%, respectively) compared with no CBD (79.0% and 26.1%, respectively). However, the lowest rates of TEAEs attributed to diazepam nasal spray were reported in patients who received highly purified CBD (13.0%), and this result was maintained in those who received concomitant clobazam. Use of second doses of diazepam nasal spray, a proxy for effectiveness, was lowest in the highly purified-CBD group (8.2%) compared with the no-CBD (11.6%) and other-CBD groups (20.3%). These results suggest that CBD does not alter the safety and effectiveness of diazepam nasal spray and supports concomitant use in appropriate patients.



## 1. Introduction

Patients with epilepsy may experience seizure clusters, which are intermittent increases in seizure activity that may occur despite treatment with daily antiseizure drugs (ASDs) [1]. Benzodiazepines, such as diazepam and midazolam, are the cornerstone of rescue therapies for seizure clusters [2]. Cannabidiol (CBD) is used as an ASD with multiple mechanisms of action that attenuate neuronal excitation. A highly purified oral solution of CBD (Epidiolex®) is approved by the US Food and Drug Administration (FDA) for the treatment of seizures in patients aged ≥1 year with Dravet syndrome, Lennox-Gastaut syndrome (LGS), or tuberous sclerosis complex [3].

Drug interactions between CBD and clobazam have been described, which may influence the effectiveness and safety of antiseizure treatment [4]. However, potential drug interactions between CBD and other benzodiazepines and any outcomes attributed to possible interactions are uncertain [4]. Diazepam nasal spray (Valtoco®) is approved by the FDA for the acute treatment

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of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy aged 6 years and older [5]. Here, we examined the safety and effectiveness of diazepam nasal spray in patients who also received CBD treatment.

## 2. Methods

This is a post hoc analysis from a phase 3, open-label, repeat-dose safety study of diazepam nasal spray conducted from April 2016 to July 2020 (ClinicalTrials.gov identifier: NCT02721069), for which full methods and results have been published [6]. The study protocol, informed consent form, and other documentation were approved by institutional review boards or ethics committees at each study site. The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP). Written informed consent was obtained from each participant or parent/-guardian prior to participation. Diazepam nasal spray was administered for the treatment of seizure clusters over 12 months, and patients could elect to remain on therapy after the treatment period.

### 2.1. Patients

Enrolled patients had a clinical diagnosis of epilepsy and, in the opinion of the investigator, might need benzodiazepine treatment for seizure control once every other month on average (i.e., 6 times a year) despite a stable ASD regimen. Key inclusion criteria consisted of the following: male or female patients aged 6 to 65 years; diagnosis of partial or generalized epilepsy with motor seizures or seizures with clear alteration of awareness; availability of a qualified caregiver or medical professional who could administer study medication in the event of a seizure; no clinically significant abnormal findings in the patient's medical history or on physical examination, electrocardiogram, or clinical laboratory results during screening; and female patients of childbearing potential agreed to use an approved method of birth control. History of status epilepticus or seasonal allergies/rhinitis was permitted, and no restriction was made on the concomitant use of benzodiazepines. Key exclusion criteria consisted of the following: history of a clinically significant medical condition that would jeopardize the safety of the patient, and major depression or a past suicide attempt or suicidal ideation.

### 2.2. Administration and dosing

Diazepam nasal spray was administered in doses of 5, 10, 15, or 20 mg, based on the patient's age and weight. If needed, a second dose could be administered 4 to 12 hours after the first dose. Investigators could adjust dose and timing for effectiveness or safety if there were no safety concerns associated with the change. Seizure timing and drug administration were recorded in a patient diary. The proportion of seizure clusters that received a second dose within 24 hours of the first dose was used as a proxy for effectiveness (ie, the proportion of clusters that continued following the initial dose, requiring a second dose). Concomitant use of CBD and clobazam (formulation, start and stop dates, dosage, route, frequency) was recorded, and treatment-emergent adverse events (TEAEs) were collected.

### 2.3. Data analysis

Data are expressed as proportions. The highly purified-CBD group comprised patients who received the FDA-approved highly purified CBD at any time during the trial, whereas patients who received any other form of CBD, including from unregulated sources, were also examined (other-CBD group). Patients in the highly purified-CBD group could have received other forms of CBD as well.

## 3. Results

Of the 175 patients enrolled in the long-term safety study, 163 were treated with ≥1 dose of diazepam nasal spray [6]. Of treated patients, 134 (82.2%) reported TEAEs, 50 (30.7%) reported serious TEAEs and 30 (18.4%) reported treatment-related TEAEs. No patients discontinued the study owing to a treatment-related TEAE, and no serious TEAE or death was attributed to treatment [6].

### 3.1. CBD analysis

Among treated patients, 119 (73.0%) did not receive CBD, 23 (14.1%) received the FDA-approved highly purified CBD, and 21 (12.9%) received another form of CBD (Table 1). Approximately twice as many patients who received any form of CBD had an epileptic encephalopathy diagnosis compared with patients who did not receive CBD (Fig. 1). Most patients with Dravet syndrome and LGS received highly purified CBD, whereas most patients with Rett syndrome received other CBD preparations.

Patients who received any form of CBD reported numerically greater rates of TEAEs and serious TEAEs compared with patients who did not receive CBD (Table 2). Other than seizure, the most common TEAEs in patients who received any form of CBD were upper respiratory tract infection (10 patients [22.7%]), nasopharyngitis (10 patients [22.7%]), and pyrexia (7 patients [15.9%]), which were the most common TEAEs reported in the overall study population [6]. The lowest rate of treatment-related TEAEs occurred in the group that received highly purified CBD (Fig. 2).

Second-dose use was lowest in the highly purified-CBD group (51 of 619 seizure clusters [8.2%]) compared with the no-CBD group (288 of 2492 seizure clusters [11.6%]) and the other-CBD group (147 of 725 seizure clusters [20.3%]) (Fig. 2). Notably, second-dose use of diazepam nasal spray was not associated with treatment-related TEAEs in the overall study population [7].

### 3.2. Concomitant clobazam

Twenty-nine patients (24.4%) in the no-CBD group, 12 (52.2%) in the highly purified-CBD group, and 5 (23.8%) in the other-CBD group received concomitant maintenance clobazam. Mean ages in the clobazam subgroups (no-CBD, 20.9 years; highly purified CBD, 10.9 years; other CBD, 15.0 years) were generally similar to

**Table 1**
Patient Characteristics.

| Characteristic | No CBD (n = 119) | Highly Purified CBD (n = 23) | Other CBD* (n = 21) |
|---|---|---|---|
| **Sex, n (%)** | | | |
| Female | 67 (56.3) | 12 (52.2) | 10 (47.6) |
| Male | 52 (43.7) | 11 (47.8) | 11 (52.4) |
| **Age, y** | | | |
| Mean (SD) | 26.4 (15.8) | 11.6 (4.8) | 16.7 (9.8) |
| 6–11, n (%) | 23 (19.3) | 12 (52.2) | 10 (47.6) |
| 12–17, n (%) | 21 (17.6) | 10 (43.5) | 2 (9.5) |
| ≥18, n (%) | 75 (63.0) | 1 (4.3) | 9 (42.9) |

CBD, cannabidiol.
* Other CBD includes any cannabidiol-containing product other than the highly purified CBD approved by the US Food and Drug Administration (eg, CBD oil, CBD gummies, cannabis sativa).

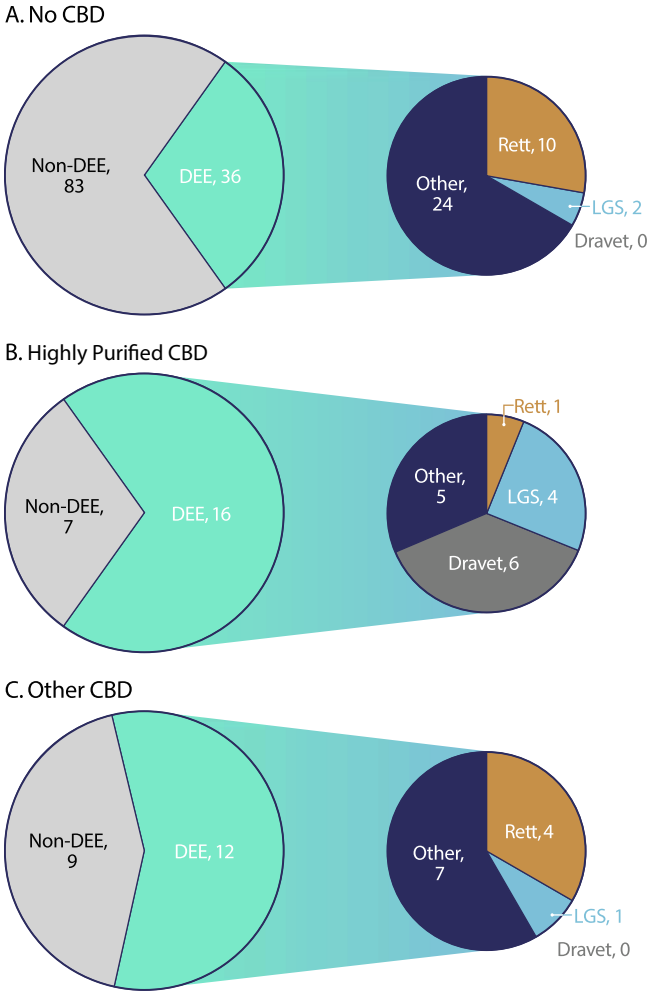


**Fig. 1. Epilepsy syndrome.** Numbers of patients with developmental and epileptic encephalopathies who received no CBD (A), highly purified CBD (B), and other CBD (C). Other developmental and epileptic encephalopathies primarily consisted of cerebral palsy, chromosomal/genetic disorders, and cortical dysplasia/malformation. CBD, cannabidiol; DEE, developmental and epileptic encephalopathies; LGS, Lennox-Gastaut syndrome.

the overall CBD groups. On average, rates of TEAEs and serious TEAEs were greater in patients who received clobazam, irrespective of CBD use (Table 2). Rates of treatment-related TEAEs in patients who received concomitant clobazam were lowest in the highly purified-CBD subgroup (Table 2).

**Table 2**
Safety Characteristics.

| Full Cohort | No CBD (n = 119) | Highly Purified CBD (n = 23) | Other CBD* (n = 21) |
|---|---|---|---|
| **Safety, n (%)** | | | |
| TEAEs | 94 (79.0) | 21 (91.3) | 19 (90.5) |
| Serious TEAEs | 31 (26.1) | 12 (52.2) | 8 (38.1) |
| Treatment-related TEAEs | 22 (18.5) | 3 (13.0) | 5 (23.8) |
| **Clobazam Subgroup** | **No CBD (n = 29)** | **Highly Purified CBD (n = 12)** | **Other CBD* (n = 5)** |
| **Safety, n (%)** | | | |
| TEAEs | 25 (86.2) | 11 (91.7) | 5 (100.0) |
| Serious TEAEs | 13 (44.8) | 8 (66.7) | 2 (40.0) |
| Treatment-related TEAEs | 6 (20.7) | 1 (8.3) | 2 (40.0) |

CBD, cannabidiol; TEAE, treatment-emergent adverse event.
* Other CBD includes any cannabidiol-containing product other than the highly purified CBD approved by the US Food and Drug Administration (eg, CBD oil, CBD gummies, cannabis sativa).

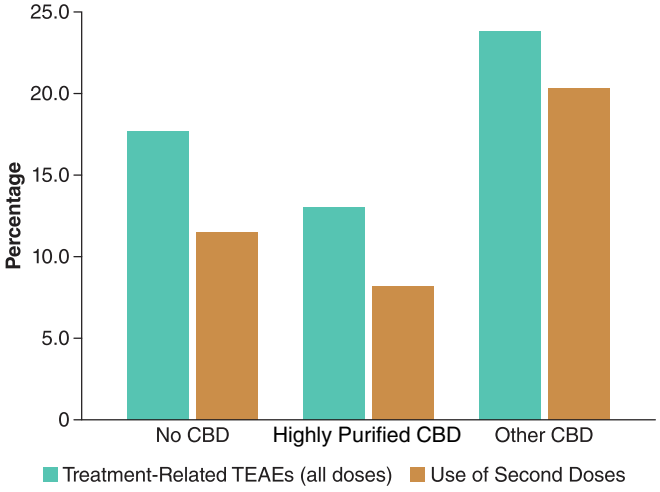


**Fig. 2. Safety and effectiveness profiles of diazepam nasal spray.** Proportion of patients who experienced a treatment-related TEAE and proportion of seizure clusters that received a second dose of diazepam nasal spray, expressed by CBD use. CBD, cannabidiol; TEAE, treatment-emergent adverse event.

Second-dose use in subgroups of patients who received concomitant clobazam and highly purified CBD (34 of 386 seizure clusters [8.8%]) or no CBD (70 of 611 seizure clusters [11.5%]) was similar to their respective overall groups. Second-dose use in the other-CBD subgroup of patients who received clobazam was much lower (19 of 201 seizure clusters [9.5%]) than in the overall other-CBD group.

## 4. Discussion

Patients with epilepsy may receive CBD as part of their daily ASD regimen [4], with an FDA-approved highly purified CBD available for the treatment of seizures associated with Dravet syndrome, LGS, and tuberous sclerosis complex [3]. Interactions have been reported between CBD and other ASDs, including clobazam [4,8], but the effectiveness and safety of intermittent use of diazepam nasal spray in patients who also received CBD had not been characterized. In this analysis, the rates of TEAEs were greater in patients who received any form of CBD. However, highly purified CBD did not lead to a greater rate of TEAEs attributed to intermittent use of diazepam nasal spray compared with no CBD, and this result was similar in patients who also received clobazam. Second-dose use, a proxy measure for effectiveness, was lowest in patients who received highly purified CBD. In all, highly purified CBD did not negatively influence the safety or effectiveness profile of diazepam nasal spray.

Cytochrome P450 (CYP) isoforms CYP2C19 and CYP3A4 are critical for the metabolism of diazepam and clobazam [9,10], and CBD is an inhibitor of both enzymes [11]. In healthy volunteers receiving daily administration of clobazam and highly purified CBD, N-desmethylclobazam, a clobazam metabolite and substrate for CYP2C19, was elevated by ~3.4-fold [11]. In a separate study that consisted of people with epilepsy, the metabolism of clonazepam, which shares similar metabolic pathways as clobazam, was not affected by highly purified CBD treatment, although blood levels of clonazepam metabolites were not measured [12]. The pharmacokinetics of diazepam administered intermittently as diazepam nasal spray in patients who use CBD has not been characterized.

In the present study population, patients who received CBD were more likely to have severe forms of epilepsy (ie, developmental and epileptic encephalopathies), which may have contributed to the overall rates of TEAEs and serious TEAEs. In a meta-analysis of 4 randomized controlled trials consisting of only patients with LGS and Dravet syndrome, highly purified CBD increased the rates of TEAEs, with slightly greater rates of TEAEs noted in those who also received clobazam [8]. The rates of TEAEs of sedation, somnolence, fatigue, and lethargy were more than 2 times higher in patients who received clobazam with CBD (CBD 10 mg/kg/d, 48%; CBD 20 mg/kg/d, 58%) than in patients who received clobazam without CBD (21%) [8]. Interestingly, in the present study, the lowest rate of treatment-related TEAEs was reported from patients who received highly purified CBD. A similarly low rate of treatment-related TEAEs was reported in the subgroup of patients who received concomitant clobazam in addition to highly purified CBD. In all, there was no evidence that CBD exacerbated TEAEs attributed to intermittent use of diazepam nasal spray (eg, somnolence), even in those patients who received clobazam treatment.

Cannabidiol with clobazam has been associated with higher proportions of patients who achieved a reduction in seizure frequency than with CBD alone [13,14]. In an open-label study of patients with treatment-resistant epilepsy, 51% who received highly purified CBD along with concomitant clobazam experienced a reduction of 50% or more in motor seizures compared with 27% without clobazam [13]. Similarly, in a study of patients with tuberous sclerosis complex, the responder rate (reduction of >50% in seizure frequency) with highly purified CBD was greater with clobazam than without (58.3% vs 33.3%, respectively) [14]. In the meta-analysis of 4 randomized controlled trials discussed above, CBD generally reduced the number of seizures and increased the responder rate compared with no CBD, independent of clobazam use [8]. Moreover, the magnitude of the treatment effect was numerically larger in patients who received CBD and clobazam, and the authors did not rule out the possibility of a synergistic effect [8]. In the present study, the rate of second-dose use was already low in the group that did not receive CBD; thus, the clinical relevance of the slightly lower rate of second-dose use in the highly purified-CBD group is unclear.

The disparity in the proportions of treatment-related TEAEs and second-dose use between the highly purified-CBD and other-CBD groups might be attributed, in part, to the uncertainty surrounding the quantity of CBD in the miscellaneous CBD products that constituted other CBD use. Many companies currently market CBD-containing products; however, the FDA has issued warnings over the lack of FDA approval and the questionable CBD content in these products [15]. Moreover, these products may contain tetrahydrocannabinol as well as other compounds that could potentially increase seizure activity. Given that the patients in the other-CBD group had relatively high rates of developmental and epileptic encephalopathies, it would be plausible that the high rates of treatment-related TEAEs and second-dose use were more reflective of epilepsy severity and less a product of negative interactions between CBD and diazepam nasal spray, especially given the low number of treatment-related TEAEs and second-dose use in patients who received highly purified CBD.

### 4.1. Limitations

There are limitations to this analysis. The number of patients who received highly purified CBD or other CBD was low, as were the subgroups of patients who also received clobazam, and the overall patterns of CBD use were variable (eg, duration of treatment, dose). This safety study was not powered to detect statistically significant differences between groups; as such, results should be interpreted with caution. As stated above, other CBD consisted of a wide variety of CBD-containing products (eg, CBD gummies, cannabis sativa), of which the actual concentrations and quality of CBD are poorly understood. An open-label safety study has less experimental control, and group heterogeneity may influence results (eg, TEAE rates in groups that primarily consist of patients with severe forms of epilepsy). Randomized studies controlling for age, number of ASDs, and other confounding variables might explore potential therapeutic interactions between CBD and intermittent use of diazepam nasal spray. However, the broad inclusion criteria of the current study resulted in a more generalizable sample of patients with epilepsy, which is a heterogeneous neurological disorder.

## 5. Conclusions

In this post hoc analysis from a long-term, repeat-dose safety study of diazepam nasal spray, the safety of intermittent use of diazepam nasal spray was maintained in patients who received concomitant CBD. Highly purified CBD did not increase the rate of TEAEs attributed to diazepam nasal spray. In contrast, it was associated with slightly fewer adverse events due to diazepam nasal spray, which was irrespective of clobazam use, compared with no CBD. The effectiveness of diazepam nasal spray was slightly improved in patients who received highly purified CBD compared with those who received no CBD. In this study, intermittent use of diazepam nasal spray remained safe and effective for those patients who also used CBD as part of their daily ASD regimen.

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## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Peters has served as a speaker and consultant for Greenwich Biosciences; Neurelis, Inc.; and Novartis. Dr. Puri is a speaker for Neurelis, Inc., and Eisai and is a consultant for Neurelis, Inc. Dr. Segal has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Eisai, Lundbeck, Nutricia, Novartis, Greenwich, Epitel, Encoded Therapeutics, and Q BioMed and is an advisor for Neurelis, Inc. Drs. Misra and Rabinowicz are employees of and have received stock options from Neurelis, Inc. Dr. Carrazana is an employee of and has received stock and stock options from Neurelis, Inc.

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