# Nursing Insights for Seizure-Cluster Care in Epilepsy: Shorter Time to Treatment With Diazepam Nasal Spray Is Associated With Faster Time to Termination

## Abstract Description

• Nurses play a central role in medication management for people with epilepsy, and they require up-to-date information on rescue therapy for seizure clusters. This post-hoc analysis explored temporal patterns of seizure clusters treated with diazepam nasal spray, finding that treatment within 5 minutes was associated with faster seizure termination.

## Introduction

- More than one-third of people with epilepsy continue to have seizures despite a stable regimen of daily antiseizure medication (ASM)<sup>1</sup>
- Benzodiazepines are the cornerstone of rescue therapy (RT) for seizure clusters<sup>2</sup>
- Nurses play a central role in caring for patients with epilepsy, including educating patients and families on the appropriate use of RT<sup>3</sup>
- –Nurses also provide an important educational resource for other healthcare professionals on advances in epilepsy care<sup>4</sup>
- Delay in initiating treatment has been associated with longer times to achieve seizure control, lower effectiveness, more adverse events, and worse outcomes<sup>5,6</sup>
- Prompt treatment with rectal diazepam gel has been calculated to decrease emergency room visits<sup>7</sup>; the administration requires multiple steps, including partial disrobing of patient and preparation of the device,<sup>2</sup> which may delay treatment
- Intranasal formulations of midazolam<sup>8</sup> and diazepam<sup>9</sup> in prefilled delivery systems are easy to use and lend themselves to rapid administration,<sup>10</sup> including self-administration<sup>11</sup>
- Diazepam nasal spray (Valtoco<sup>®</sup>) is indicated for the acute treatment 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 6 years of age and older<sup>9</sup>
- Seizures typically stop spontaneously within 2 minutes,<sup>12</sup> and guidelines from the American Epilepsy Society for the treatment of status epilepticus recommend an initial 5-minute period of seizure first aid before initiating RT, preferably with a benzodiazepine<sup>13</sup>
- Little is known about the impact of timing of administration of RT during a seizure in a seizure cluster
- Seizure diary data collected during a long-term safety study of diazepam nasal spray provided an opportunity to explore temporal patterns of seizure clusters treated with diazepam nasal spray RT

## Objectives

- The research objective was to characterize temporal patterns of time to seizure-cluster treatment with diazepam nasal spray in relation to time to seizure termination
- The education objective is to provide nurses with new information about diazepam nasal spray showing that treatment of seizure clusters within 5 minutes of onset leads to shorter time to seizure-cluster termination

## Methods

- The results presented here are from the long-term, phase 3, open-label, repeat-dose safety study of diazepam nasal spray (ClinicalTrials.gov identifier: NCT02721069)<sup>14,15</sup>
- -Second doses for a seizure cluster used an operational definition of a dose of diazepam nasal spray given within a 24-hour period of the first dose
- -The study had a 12-month treatment period with study visits at days 30, 90, and every 90 days afterward; patients could elect to remain on therapy after the main treatment period ended
- -Each patient or care partner was provided with a diary to record seizure timing and drug administration
- At each visit, the seizure and dosing information from the diary, including the time when the seizure occurred, when it ended, and the time of dosing, were recorded on the case report form
- Seizure types were not specified in the diary; untreated seizures were not recorded

#### Patients

- Enrolled patients had a clinical diagnosis of epilepsy and, in the opinion of the investigator, might need benzodiazepine treatment for seizure control at least once every other month on average (ie,  $\geq 6$  times a year) despite a stable regimen of daily ASM
- Key inclusion criteria
- –Female or male patients aged 6–65 years
- seizures with clear alteration of awareness -Availability of a qualified care partner or medical professional who could
- administer study medication in the event of a seizure
- restriction was made on concomitant use of benzodiazepines (eg, clobazam)
- Key exclusion criteria
- -History of a clinically significant medical condition that would jeopardize the patient's safety
- –Major depression or a past suicide attempt or suicidal ideation

### Treatment

- Age- and weight-based doses of diazepam nasal spray were administered<sup>14,15</sup> -Care partners and patients were instructed to administer a second dose of diazepam nasal spray 4–12 hours after the first dose if needed to control a seizure cluster
- -Investigators could adjust doses or timing of second doses (eg, up to 24 hours) for effectiveness or safety if there were no safety concerns associated with the change
- Incidence and severity of treatment-emergent adverse events were collected, and relationship to therapy was assessed

### Seizure-Cluster Temporal Analysis

- Seizure clusters were identified from the seizure diaries of 163 patients in the safety population, and timing of seizure that prompted treatment, diazepam administration, and seizure termination were calculated
- Data preparation included removal of observations with missing date/time information, duplicate entries, seizures >24 hours in duration, and dose administration or seizure termination >1 minute before seizure start
- Descriptive statistics were calculated to describe temporal patterns and evaluate the impact of time of dose on seizure patterns
- An analysis was performed on data that excluded all observations with a seizure duration of <2 minutes; this reduced the possible confounding of seizures that may have terminated spontaneously without treatment<sup>12</sup>
- Analyses were also completed on observations from patients with  $\geq 20$  treated seizures and adult (aged ≥18 years) and pediatric (aged 6–17 years) patients

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–Diagnosis of partial (ie, focal) or generalized epilepsy with motor seizures or

History of status epilepticus or seasonal allergies/rhinitis was permitted; no

## Results

## **Overall Study**

- A total of 175 patients were enrolled in the phase 3 safety study, and 163 patients received  $\geq$ 1 dose of diazepam nasal spray and were included in the safety population (54.6% female; mean age, 23.1 years); overall safety and effectiveness results have been published<sup>14</sup>
- -A total of 3853 seizure clusters were treated with a total of 4390 doses -The mean number of doses per month per patient was 2.3
- -The majority of the patients (81.6%) had a duration of exposure  $\geq$ 12 months • The safety profile for diazepam nasal spray was consistent with that for
- rectal diazepam<sup>14</sup> (**Table 1**) • The proportion of clusters for which a second dose of diazepam nasal spray was administered was used as a proxy for effectiveness in the study
- -Overall, second doses were used in a low proportion of all seizure clusters (485 seizure clusters; 12.6%)

## Table 1. Safety Profile for the Overall Safety Population

Variable, n (%)	Overall Safety Populati (n=163)
Patients with TEAEs	134 (82.2)
Patients with serious TEAEs	50 (30.7)
Treatment related	0
Death	<b>1 (0.6)</b> <sup>a</sup>
Patients with treatment-related TEAEs	30 (18.4)
Discontinuation due to TEAE	<b>1 (0.6)</b> <sup>a</sup>

TEAE, treatment-emergent adverse event. <sup>a</sup>Sudden unexpected death in epilepsy, not deemed treatment related

## **Data Preparation**

- A total of 4466 observations were identified from seizure diaries
- After data preparation (Figure 1), 3225 observations were included in this analysis

#### Figure 1. Flowchart of Data Preparation for Analysis of Temporal Patterns of Treated Seizure Clusters



### Temporal Analysis

- Overall (n=3225 observations), median times (ranges) to dose administration, from administration to seizure termination, and total seizure duration were 2 (0–750), 3 (0–1440), and 7 (0–1440) minutes, respectively
- When grouped by median times from seizure start to dose administration, median time from administration to seizure termination was substantially faster for seizures treated 0 to <5 minutes after seizure start (2 min) compared with doses administered  $\geq 5$  minutes after seizure start (10 min) (Figure 2)
- -Similar results were obtained when all observations of treated seizures <2 minutes in duration were removed (not shown)
- Results were nearly identical for a subset of patients with  $\geq$ 20 observations (n=2484 total observations from 61 patients) (**Figure 3**)
- -Among those in this group treated in <5 minutes, median time to dose was 1 minute; dosing to seizure termination, 3 minutes; and total seizure duration, 4 minutes
- -For those treated in  $\geq 5$  minutes, median time to dose was 10 minutes; dosing to seizure termination, 11 minutes; and total seizure duration, 25 minutes

Figure 2. Time to Dose Administration, Time From Dose to Seizure Termination, and Total Seizure Duration by Time to Dose Administration (n=3225 Observations)<sup>a</sup>



necessarily sum to total seizure duration

#### Figure 3. Time to Dose Administration, Time From Dose to Seizure Termination, and Total Seizure Duration Among Patients With <a>20 Seizures (n=2484 Observations)</a>



results were comparable (**Figure 4**)



## **Conclusions and Nursing Implications**

- Time to seizure termination was substantially shorter in patients treated in <5 minutes after seizure onset than in patients with delayed treatment ( $\geq 5$  min)
- Seizure clusters are often readily recognizable<sup>16</sup> and provide an opportunity to treat quickly
- This post hoc analysis supports the applicability of these findings to multiple populations, including the overall study population, a group with a large number of treated seizure clusters, and adults and pediatric patients
- These data reinforce the value of prompt recognition and treatment intervention, which may help minimize risk of injury and additional healthcare utilization
- quality of life
- Nurses, who are central to patient care, can incorporate these findings, along with their own clinical expertise, into their knowledge and use of RTs in epilepsy
- This information can be translated and integrated appropriately into patient care and education and be shared with other healthcare professionals

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• When analyzed by age groups of adults (18–65 years; n=1567 observations) and pediatric patients (6–17 years; n=1658 observations),

Figure 4. Time to Dose Administration, Time From Dose to Seizure Termination, and Total Seizure Duration for *Pediatric Patients (n=1658 Observations) and Adult Patients (n=1567 Observations)* 

Time to Dose Administration

• In this long-term study of diazepam nasal spray as seizure-cluster RT, shorter time to treatment was associated with shorter time to seizure-cluster termination and overall shorter seizure duration in real-world settings

– Prompt treatment can potentially increase patients' and caregivers' sense of empowerment and enhance their

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