Patient and caregiver experiences with diazepam nasal spray for seizures

Narrator: [0:00] This podcast is presented and supported by Neurelis, Inc. It is provided for informational purposes only and is not intended to replace a discussion with a healthcare provider. All decisions regarding patient care must be made with a healthcare provider and consider the unique characteristics of each patient. This podcast discusses Valtoco® (diazepam nasal spray). Valtoco is indicated for the acute treatment of intermittent of stereotypic episodes of frequent seizure activity, also known as 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.

Here is some important safety information for Valtoco

Warning: Risks from Concomitant Use with Opioids; Abuse, Misuse, and Addiction, and Dependence and Withdrawal reactions. Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation.

The use of benzodiazepines, including Valtoco, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing Valtoco and throughout treatment, assess each patient's risk for abuse, misuse, and addiction.

The continued use of benzodiazepines may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Although Valtoco is indicated only for intermittent use, if used more frequently than recommended, abrupt discontinuation or rapid dosage reduction of Valtoco may precipitate acute withdrawal reactions, which can be life-threatening. For patients using Valtoco more frequently than recommended, to reduce the risk of withdrawal reactions, use a gradual taper to discontinue Valtoco.

Please listen to additional important safety information for Valtoco presented at the end of this podcast.

[2:19] Welcome to the Neurelis Medical Affairs podcast series. These podcasts offer an opportunity to learn about recently published articles, discussing strategies for the treatment of seizure clusters in patients with epilepsy, directly from the authors. The series can be accessed at neurelismedicalaffairs.com or through a Neurelis Medical Science Liaison. In this episode, we hear from Dr. Patricia Penovich from the Minnesota Epilepsy Group in St. Paul and from Dr. Joseph Sirven from the Mayo Clinic, Jacksonville, Florida. Dr. Sirven, an expert on epilepsy and psychosocial issues, will lead a conversation with Dr. Penovich about the results of a survey on patient and caregiver experiences, as part of the long-term safety study of diazepam nasal spray. Both of our invited experts will provide insights into the significance of the findings. The full survey results were published in 2021 by Penovich and colleagues in the open-access paper, "Examining the patient and caregiver experience with diazepam nasal spray for seizure clusters: Results from an exit survey for phase 3, open-label, repeat-dose safety study" in the August 2021 issue of *Epilepsy and Behavior*.

[3:35] Welcome, Dr. Penovich and Dr. Sirven. Thank you for joining us today. I understand that you are going to discuss the patient and caregiver survey administered in the DIAZ.001.05 study, a phase 3, repeat-dose, open-label, long-term safety study of diazepam nasal spray in patients with epilepsy who have seizure clusters, despite use of a stable regimen of anti-seizure medication. We discuss the final study results with Dr. James Wheless in another podcast, but perhaps we can start with a brief summary of the study and its main findings. Dr. Penovich, would you start us off?

Penovich: [4:12] I'd be delighted to do that. This study involved 163 patients who actually completed the study, and the primary objective was to evaluate the safety. 80% of those patients had at least one year of exposure to diazepam nasal spray, and they were between the ages of six to 65. The final study results were published in *Epilepsia* in 2021 by Dr. Wheless and others, and they reported that treatment-emergent adverse events *[TEAEs]* were possibly or probably related to the medication in 30 of 163 patients, or 18%. There were no serious TEAEs that were related to the treatment itself. The safety profile of diazepam nasal spray was consistent with the known established profile of rectal diazepam. As part of the study, an exit survey was conducted that involved both the patients who had epilepsy, as well as caregivers of patients with epilepsy, with respect to their experience with diazepam nasal spray. Joe, that’s the background of the study overall.

Sirven: [5:25] Pat, regarding the survey, would you start by telling me a little bit about the survey methodology and the respondents?

Penovich: [5:31]Well, the patients who were enrolled in this study, as I said, were between six to 65 years, so it covered both pediatric and adults. And they had a diagnosis of either partial or generalized epilepsy with motor seizures or seizures that had a clear alteration of

awareness. Also, seizures had to occur on an average of once every two months, despite being on a stable anti-seizure medication regimen. The exit survey of the patient and caregiver experience was actually developed in tandem with the research team and an expert panel of epileptologists who treated both adult and pediatric patients, and that methodology is reported in our paper in 2021. The survey was provided to all people with epilepsy enrolled in the study and their care partners, including all those who had completed the study, as well as those who discontinued from the study. The people who did respond did have a nominal honorarium given to them for their time.

So, among those 163 patients, we had 66 responses that were included in the safety set, which translated to a 40% response rate. 47% of them were female with a median age of 24.5 years. The median duration of treatment of at least one year was accomplished in 78.8% of those patients. The majority of the patients, or 80%, had prior experience using a rescue medication. 58% of that group had actually previously used rectal diazepam. In the group who had used the prior rectal diazepam, the median age was 14 years, and it was distributed through children, adults, and adolescents, with 31 of those patients having that exposure.

A subset of the 66 patients, or about 40% of them, actually self-administered diazepam nasal spray at least once during the study. That group was generally older than the overall group and had a median age of 34 years, although the youngest patient was 11 years of age. Almost all had at least one year of treatment duration in the study. 84 caregivers responded; they were all family members of patients. 85% were female and their median age was 47 years. The majority of the caregivers had experienced administering rescue therapies previously and of those rescue therapies, primarily, that rescue was rectal diazepam in 83%.

Sirven: [8:26] I understand that the survey first asked about training on the use of diazepam nasal spray. What was the respondents' impressions of being trained or training others to use the therapy? Was it easy to be trained and who did the training?

Penovich: [8:44] Among the patients, nearly 30% of them trained another person to administer the nasal diazepam and these people included parents, grandparents, siblings, friends, and even other people who were not related. Almost 90% stated that it was extremely easy or very easy to train someone else. Among the 83 caregivers who responded, 100% of them considered it extremely or very easy to be trained on the diazepam nasal spray. And interestingly, most of the caregivers also trained additional people to administer the medication. In fact, they actually trained a median number of three other people, and all of the training was rated as extremely easy or very easy by all of those respondents.

Sirven: [9:36] Pat, did the survey also ask about what people with epilepsy or care partners use diazepam nasal spray during a seizure cluster? I mean, who actually administered the diazepam nasal spray and when did patients receive it? And what did you learn from it?

Penovich: [9:54] We asked the patients who self-administered the medication. About half of them replied that they did so at the first sign that their seizure might be coming. So, in what they identified as an aura. Another quarter of them replied that they did that between seizures in a cluster or when the seizures were repeating at very close intervals. The caregivers' response to timing of administration was slightly different. 81% of them reported giving the diazepam nasal spray actually during a seizure, 31% of them gave it during a cluster of seizures or when seizures were repeating. Another 50% reported that they gave it only during a seizure or most of the time during a seizure. A small percentage did at the first sign a seizure might be coming and 10% administered either most of the time after the seizure had actually ended.

Sirven: [10:56] Pat, after administration, how were patients affected? What was the post-administration period like for the caregiver?

Penovich: [11:02] Among the patients, 59% of them stated that they returned back to their normal self within one hour. 37.5% stated they were back to their normal selves within 30 minutes of administration and another 22% returned within 30 to 60 minutes. Almost 19% returned to normal within one to two hours and only a very few or 9.4% took over four hours to return to normal. With respect to the caregivers, almost 60% reported they were able to return to their normal activities within an hour after administering nasal spray. Another 35% were able to return to normal within one to four hours. And again, only a small number, 3.8%, stated that they were unable to return to normal daily activities that day. So, for both the patients and the caregivers, the return to functional self happened fairly quickly.

Sirven: [12:04] Pat, since seizure clusters can occur suddenly without warning and may occur outside the home, rescue therapies may need to be given or administered in public. How did the study participants feel about carrying and using diazepam nasal spray outside of the home?

Penovich: [12:23] When the patients were surveyed about their comfort using the diazepam nasal spray, 88% reported that they or their caregiver carried the nasal spray outside of their home, and 85% were extremely or very comfortable carrying it outside the home. 79% were very comfortable doing activities outside the home if they had the diazepam nasal spray available. The caregivers who were surveyed stated that 98% of them carried it outside of the home, and 94% considered it extremely or very comfortable to carry with them. So, I think that ability to have that comfort level was something that can certainly improve a patient with epilepsy and their caregiver's quality of life.

Sirven: [13:15] Pat, did the participants have prior experience with rescue therapies and in particular diazepam rectal gel, and what were the impressions of the ease of administration of the diazepam nasal spray?

Penovich: [13:31] As mentioned, a majority of the patients, or 80%, had prior experience with rescue medications. 58% of this group had used rectal diazepam previously. The majority of the caregivers, or 81%, had experienced administering rescue therapies, primarily rectal diazepam, in the past. Among the patients who self-administered diazepam nasal spray, 78% reported that it was extremely easy or very easy to use. 67% reported that administering the nasal spray in public was extremely, very or somewhat comfortable. A very important point was that dosing errors were very similar between this group and the group who did not administer. Each group had basically about 1% dosing errors. Among patients asked about the administration of different rescue therapies, 87% were not at all comfortable using rectal diazepam in public compared to diazepam nasal spray. 65% were not at all comfortable having their caregiver administer the rectal diazepam at home. 84% would prefer using the diazepam nasal spray exclusively, going forward. All but one of the 81 caregivers responded that the diazepam nasal spray was easy to administer, and nearly 90% of the caregivers were extremely or very comfortable using the diazepam nasal spray in public.

When caregivers were asked about administering the rectal gel, 64% stated it was not at all easy to use, compared to the nasal spray. And 87% were not at all comfortable administering rectal diazepam gel in a public setting. So, I think they were certain as well as the patients felt that the nasal spray was a more comfortable and easy way to go.

Sirven: [15:37] Pat, overall, what were the impressions of nasal diazepam spray among the patients and caregivers who responded? Was this a treatment that they wish to continue to use and ask their provider to prescribe it?

Penovich: [15:49] Joe, that's a really important question, isn't it? Their overall satisfaction was quite good. Among the patients, 80% were very satisfied or satisfied with the diazepam nasal spray, and among the caregivers, 93% were very satisfied or satisfied with the nasal spray. With respect to continuing the diazepam nasal spray, the patients were extremely likely or very likely to ask their healthcare provider about staying on diazepam nasal spray in 78%. Among the caregivers, 92% were extremely or very likely to ask to continue to use the diazepam nasal spray. Finally, there was another interesting evaluation where we looked at 35 matched pairs where both the patient and the caregiver responded to the survey.

Sirven: [16:42] Among the 35 matched pairs was a group of five patients who also self-administered diazepam nasal spray. Were there any notable differences between self-treating patients and their caregivers, in when they chose to administer the diazepam nasal spray?

Penovich: [17:00] The only notable difference was the timing of administration of the diazepam nasal spray. There were five patients who self-administered and the majority, or three of those patients, did so at the first sign of a seizure. The majority of the caregivers, there were 32 who responded and 26 of them did so either during a cluster of seizures, when the seizures were repeating, only during a seizure, or most of the time during a seizure. So, they tended to be a little bit later in their dosing of the medication than the patients were.

Sirven: [17:39] Pat, what do you think are the take-home points and significance of these findings for diazepam nasal spray as a rescue therapy for seizure clusters?

Penovich: [17:46] Joe, I think this boils down to some very easy things to remember from this study: that diazepam nasal spray is a rescue medication that is easy to administer, convenient to carry, and socially acceptable to use. Joe, what do you think the results of this survey may mean to the larger group of people with epilepsy and care partners who potentially may use nasal spray diazepam?

Sirven: [18:13] It may help patients and caregivers to use a rescue medication instead of relying on emergency health services in the event of a seizure cluster, which can delay treatment and potentially lead to negative health outcomes. Rectal diazepam has been available for decades, but patients and caregivers report it can be difficult to administer and can be socially unacceptable to use in public. My adult patients have asked, sometimes begged, for a non-stigmatizing rescue treatment. This is the promise that this delivery system provides.

Pat, let's focus on the idea of self-administration for a moment as self-administration may not always be considered by clinicians caring for patients with epilepsy. What insights can we draw from this group and their impressions of diazepam nasal spray?

Penovich: [19:13] So, Joe, this device is not a new device, it's been around for a while and has been used to administer other medications intranasally, such as for migraine headache. Patients who self-administered this medication commonly did so at the first sign of a seizure, compared to caregivers who administered it primarily during a seizure or repeated seizures. Self-administration of the intranasal benzodiazepine rescue for seizure clusters

may give patients more control over their treatment. And as we know, the sense of self-control helps with a sense of self-worth and a better quality of life.

There was a patient as young as 11 years of age who reported self-administering in this survey. So, this is an indication that we are providing our younger patients with the ability to have some sense of control at a younger age—again, an important developmental process. Self-dosing errors were very infrequent. That's important because if an error is made in dosing a medicine, it may not necessarily work. So, the fact that there were only 1% dosing errors is a really important fact. Taken together, this study supports the self-administration of diazepam nasal spray in a way that is consistent with the prescribing information.

Sirven: [20:41] Pat, do you have any final thoughts about the results of this survey of people with epilepsy and their care partners using diazepam nasal spray to treat seizure clusters?

Penovich: [20:50] So the study showed that diazepam nasal spray has a safety profile that is completely consistent with the established safety profile of the rectal diazepam gel. Through the survey, we found that patients and caregivers find diazepam nasal spray both easy to administer and use outside the home. Those who had used rectal diazepam rescue previously strongly preferred diazepam nasal spray.

Joe, what do you think this means for your patient management?

Sirven: [21:23] Pat, I think that the fact that some patients can self-administer the therapy may provide a patient with increased control over their disease. It may increase their degree of self-management. It may increase their ability to manage seizure clusters at home. It might even lead to a decreased need to call emergency services or visit the emergency

department. Putting it all together, these benefits could lead to improved quality of life for people with epilepsy and their care partners.

Narrator: [22:00] Thank you, Dr. Penovich and Dr. Sirven, for speaking with us today and sharing your expertise for this installment of the Neurelis Medical Affairs podcast series. We very much appreciate it. Before we conclude, here is some additional important safety information about Valtoco.

Narrator: [22:15] Valtoco is contraindicated in patients with:

- Hypersensitivity to diazepam and
- Acute narrow-angle glaucoma

Benzodiazepines, including Valtoco, may produce Central Nervous System (CNS) depression. Caution patients against engaging in hazardous activities requiring mental alertness, such as operating machinery, driving a motor vehicle, or riding a bicycle, until the effects of the drug, such as drowsiness, have subsided, and as their medical condition permits.

The potential for a synergistic CNS-depressant effect when Valtoco is used with alcohol or other CNS depressants must be considered, and appropriate recommendations made to the patient and/or care partner.

Antiepileptic drugs (AEDs), including Valtoco, increase the risk of suicidal ideation and behavior. Patients treated with any AED for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or unusual changes in mood or behavior.

Benzodiazepines, including Valtoco, can increase intraocular pressure in patients with glaucoma. Valtoco may only be used in patients with open-angle glaucoma only if they are receiving appropriate therapy. Valtoco is contraindicated in patients with narrow-angle glaucoma.

Valtoco is not approved for use in neonates or infants. Serious and fatal adverse reactions, including "gasping syndrome", can occur in neonates and low-birth-weight infants treated with benzyl alcohol-preserved drugs, including Valtoco. The "gasping syndrome" is characterized by central nervous system depression, metabolic acidosis, and gasping respirations. The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known.

The most common adverse reactions (at least 4%) were somnolence, headache, and nasal discomfort.

Diazepam, the active ingredient in Valtoco, is a Schedule IV controlled substance.

Please read full Prescribing Information, including Boxed Warning, for additional important safety information—available at www.valtoco.com.

Narrator: [24:13] To close, we would like to say thanks again, Dr. Penovich and Dr. Sirven. We would also like to say thank you to our audience for joining this conversation. For more information on this particular article, please contact your Neurelis Medical Science Liaison directly or the Neurelis Medical Affairs team at medinfo@neurelis.com.

This podcast is one of a series. To access the series, as well as other resources for your patients with seizure clusters, visit NeurelisMedicalAffairs.com.