Evaluation of diazepam nasal spray in patients with epilepsy concomitantly using maintenance benzodiazepines

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.

Welcome to the Neurelis Medical Affairs podcast series. These podcasts offer an opportunity to learn directly from the authors about recently published articles discussing strategies for the treatment of seizure clusters in patients with epilepsy. The series can be accessed at neurelismedicalaffairs.com or through a Neurelis Medical Science Liaison.

[2:37] In this episode, we hear from Dr. Eric Segal from the Northeast Regional Epilepsy Group, from Hackensack, New Jersey. The podcast features the discussion of the findings on an interim subgroup analysis of the safety of diazepam nasal spray in patients who use concomitant benzodiazepine maintenance therapy. The findings were published in 2021 by Segal and colleagues in the paper titled, "Evaluation of diazepam nasal spray in patients with epilepsy concomitantly using maintenance benzodiazepines: an interim subgroup analysis from a phase 3, long-term, open-label safety study," in the journal *Epilepsia*.

An important note, this paper provides an in-depth, but interim analysis of patients receiving concomitant benzodiazepines in this study. At the end of this podcast, we will

discuss how these results fit into the context of the final report from the study. Welcome, Dr. Segal, thanks for joining us.

Segal: [3:34] Sure, thanks for having me.

Narrator: [3:35] To start us off, perhaps some context. Benzodiazepines have played an important role in the management of epilepsy since the 1960s. In particular, they play a central role as a rescue therapy for seizure clusters, but there are also some potential considerations around safety and effectiveness associated with their use. Can you describe some of those?

Segal: [3:55] Benzodiazepines can modulate the $GABA_A$ receptor and produce sedative, anxiolytic, and anticonvulsive effects, with potential dose-related effects on both respiratory and hemodynamic parameters. So, in other indications and doses, the use of benzodiazepines has sometimes been associated with either cardiorespiratory suppression or even development of reduced effectiveness or tolerance. So, for example, cardiorespiratory adverse effects have been reported with the use of intravenous anticonvulsants that treat status epilepticus. Therefore, it is clinically relevant to understand how rescue with diazepam nasal spray for seizure clusters may be affected by concomitant use of other benzodiazepines as chronic or intermittent therapy.

Narrator: [4:40] Thank you. For many years, the only FDA-approved rescue medication for seizure clusters was diazepam rectal gel, and that therapy is invasive and has social limitations. More recently, two intranasal formulations have been approved for this indication. Diazepam nasal spray is designed to provide a rapid, noninvasive, and socially acceptable route of administration. And it's indicated in patients six years of age and older with epilepsy for acute treatment of intermittent, stereotypical episodes of frequent seizure

activity, i.e. seizure clusters or acute repetitive seizures, that are distinct from a patient's usual seizure pattern.

Studies have shown that diazepam nasal spray has comparable bioavailability with less pharmacokinetic interpatient variability than rectal diazepam, and its safety profile was consistent with the established safety profile of rectal diazepam. Final results of the phase 3, long-term, open-label safety study of diazepam nasal spray was published in *Epilepsia* in 2021 and we discuss them with Dr. James Wheless in another Neurelis Medical Affairs podcast.

The study included many patients receiving concomitant benzodiazepine maintenance therapy. And today, we're focusing on findings from that group of participants. Dr. Segal, I understand that the overall study is following real-world experience of patients using diazepam nasal spray. Can you explain the particular value of studying the concomitant use of benzodiazepines within the context of the overall study?

Segal: [6:13] Sure. The 05 study of diazepam nasal spray evaluated the safety of diazepam nasal spray as rescue therapy in patients with epilepsy who have seizure clusters, despite the use of a stable regimen of antiseizure medications.

In the final analysis, 163 patients were treated and more than 80% had at least a year of exposure to diazepam nasal spray. Of note, the inclusion criteria were pretty broad. Patients were aged from six to 65 years. A history of status epilepticus was permitted. There was no restriction on concomitant use of benzodiazepines as maintenance therapy. And patients with a history of seasonal allergies or rhinitis were not excluded.

Safety was the main outcome of interest. And the study also explored effectiveness and potential for development of tolerance. The proxy marker for effectiveness was the

proportion of seizure clusters during which a second dose of diazepam nasal spray was given within 24 hours of the initial dose among all patients in the study.

Two markers explored as potential signals of benzodiazepine tolerance were either the use of second doses within 24 hours specifically among patients also taking concomitant benzodiazepines, as well as the need for a second dose in patients using diazepam nasal spray on a more frequent basis, like two to five times per month, regardless of concomitant benzodiazepine use. The concomitant benzodiazepine analysis was based on data from an interim cutoff. The objective of this interim analysis was to evaluate whether effectiveness and safety were affected by concomitant use of benzodiazepines as a part of a patient's antiseizure therapy.

Narrator: [8:06] Thank you. Before discussing the main findings, perhaps you can tell us about the study patients and their use of concomitant benzodiazepines?

Segal: [8:13] So, at the interim analysis cutoff date, 158 patients received diazepam nasal spray and were included in the safety analysis. The majority were female, a little bit over 50%. And the mean age was around 23–24 years. Patients were divided into three mutually exclusive groups, a group with chronic concomitant use, a group with intermittent use, and a group who did not use a concomitant benzodiazepine. Now, within the concomitant benzodiazepine groups, there was 119 patients that received concomitant benzodiazepines. About 40% had chronic use and that mean age was about 19 years old. And then about 37% had intermittent use and their mean age was about 28.

In addition to the concomitant benzodiazepine group, there was about 25% of patients who had no concomitant use. And the mean age there was about 24 years old. So, the most common concomitant benzodiazepines by group—within that chronic group, about

40 patients were using clobazam; about 19, clonazepam. Within the intermittent group, about 44 patients were using diazepam, 32, lorazepam and also 32 with clonazepam. So, there was a possibility of patients in either group receiving two or more concomitant benzodiazepines during the study period.

Narrator: [9:35] Thank you. And what were the findings around the use of the study drug, diazepam nasal spray, for each of the three groups?

Segal: [9:42] At least two thirds of patients in each subgroup had at least 12 months of exposure to diazepam nasal spray. A total of about 3,300 treated seizure clusters were included in this interim analysis. About 1,300 seizure clusters treated among 60 patients using chronic benzodiazepines. About 1,600 clusters were treated among 59 patients using benzodiazepines intermittently. Now, comparing usage among groups, there was a similar percentage of patients averaging two to five doses of diazepam nasal spray per month, as well as there was a similar mean doses per month, about two to three doses per month.

Narrator: [10:21] Dr. Segal, while the study was not designed to test efficacy of diazepam nasal spray, proxy measures of effectiveness were explored. What can you tell us about the effectiveness in groups taking concomitant benzodiazepines?

Segal: [10:35] Effectiveness was defined by proxy as the percentage of seizure clusters for which a second dose was used within 24 hours of the initial dose. The chronic concomitant group used a second dose in about 11% of seizure clusters. Patients using no concomitant benzodiazepines used the second dose in about 10% of seizure clusters. Now, patients in the chronic concomitant benzodiazepine group may be hypothesized to

have a more severe disease than those not using concomitant benzodiazepines. That's supported by the higher number of doses in the chronic use group.

But all the same, the rates of the second dose use were similar between the chronic use and the no use groups, suggesting that diazepam nasal spray maintained effectiveness. So, within the chronic use group, about 9.6% of clusters were treated with the second dose. Within the intermittent use group, about 14% of clusters were treated with the second dose. And in the no use group, about 15% of clusters were treated with a second dose.

Narrator: [11:31] Let's turn our attention to issues of safety. What was the safety profile of diazepam nasal spray among these different groups?

Segal: [11:40] The proportion of patients with any treatment-emergent adverse event, which is a TEAE, irrespective of causality, differed between groups: 80% in the group with chronic use concomitant benzodiazepines; about 79.7% in intermittent use of concomitant benzodiazepines; and then about 62% in the group without concomitant benzodiazepines. Now, the most common treatment-emergent adverse event in all groups was seizure. So, other TEAEs occurring greater than 10% of patients were pneumonia, about 13%; pyrexia, about 12% in the chronic concomitant group; nasopharyngitis in 10% of the intermittent group; and upper respiratory infections in about 10% in the no-concomitant use group.

Similarly, serious TEAEs also differed. So, 35% in the group with chronic use of concomitant benzodiazepines; about 25% in the group with intermittent use of concomitant benzodiazepines; and about 23% in the group without concomitant benzodiazepines. TEAEs deemed possibly related to treatment varied by group and were

primarily related to nasal discomfort. And that was seen in about 17% in the chronic use group, about 20% in the intermittent use group, and about 10% in the group who did not use any concomitant benzodiazepines. I think what's important to note here is that there is no occurrence of cardiorespiratory depression, hypotension, or sedation in any group, and no serious TEAEs were deemed related to treatment in any group.

Narrator: [13:18] Finally, Dr. Segal, you and the research team also analyzed the data for the subset of patients taking clobazam, which is an important part of the daily treatment algorithm for refractory childhood epilepsies and has proven efficacy as monotherapy and adjunctive therapy for adults. In your study, clobazam was the only concomitant benzodiazepine used primarily as chronic treatment. What were the outcomes of the analysis?

Segal: [13:46] Out of 119 patients receiving any concomitant benzodiazepines, about 37% were taking clobazam. In terms of the patient characteristics, the mean age was younger in the clobazam group, about 17 years old in the clobazam, compared to 27 years old in the group not taking clobazam. The proportion of patients who were female were similar, about 55% in the clobazam group, compared to about 49% in the non-clobazam group.

In terms of the usage of the diazepam nasal spray, so the monthly usage of two or more doses of diazepam nasal spray was higher in the clobazam group, 66% versus 55% in the group not taking clobazam. But the proportion of seizure clusters for which a second dose was used was numerically lower in the clobazam group, about 9.6% of seizure clusters in the clobazam group, compared to about 15% of seizure clusters in the non-clobazam group.

While no statistical analysis of this difference was undertaken, the findings indicate that the safety and effectiveness profiles of patients taking clobazam are similar to the established profile of diazepam nasal spray.

From a safety perspective, the proportion of patients with any TEAEs was similar, about 82% in the clobazam group, 79% in the non-clobazam group. The proportion of serious TEAEs were higher in the clobazam group, about 41% in clobazam group, as opposed to 24% of the non-clobazam group. Now, the proportion of TEAEs that were deemed possibly treatment related were similar between the groups—about 18% of the clobazam group compared to 19% of the non-clobazam group. And the treatment-related TEAEs affecting two or more patients were nasal discomfort, changes in smell, headache, and rhinalgia.

Narrator: [15:30] Thank you, Dr. Segal for summarizing the study findings for us. Perhaps we can now turn to their clinical implications?

Segal: [15:37] Yeah. So, this was the first analysis from a long-term safety study of the use of intranasal benzodiazepine rescue therapy for seizure clusters and people with epilepsy who also receive concomitant benzodiazepines. The studies of other rescue therapies, such as intranasal midazolam, have used concomitant benzodiazepines for use as an exclusion criteria. Benzodiazepines are generally used to treat refractory or difficult-to-treat epilepsy. So, we might expect patients with concomitant benzodiazepine use to have more severe disease, and they did have higher seizure burden and also receive more doses of diazepam nasal spray.

However, the rates of second-dose use were similar between those using chronic concomitant therapy and those not using concomitant therapy, suggesting that diazepam

nasal spray maintained effectiveness. Now, diazepam nasal spray also showed good safety. The most common treatment-related TEAEs were related to nasal discomfort, and they were mild and transient. No serious TEAEs were related to treatment, and there was no discontinuations due to TEAEs in this interim analysis. There are also no reported cases of respiratory depression or hypotension.

Narrator: [16:53] Before we close, Dr. Segal, do you have any final thoughts to share with our listeners about the use of diazepam nasal spray and its use among people with epilepsy who are taking concomitant benzodiazepine therapy?

Segal: [17:05] The interim results were consistent with the final analysis of 163 treated patients. Now, those final results I think are discussed by Dr. James Wheless in another Neurelis Medical Affairs podcast. Overall, the 125 patients receiving any concomitant benzodiazepines had similar TEAE profile as the 38 patients not receiving another benzodiazepine. There was a numerically greater proportion of TEAEs considered related to diazepam nasal spray in the concomitant benzodiazepine group, however (20% versus 11%), but no clinically relevant difference in the second doses between the concomitant benzodiazepine and the no other benzodiazepine group.

Results from this long-term study support the use of intranasal diazepam nasal spray in patients with and without concomitant benzodiazepine. It is a potentially valuable treatment option for pediatric patients with epilepsy six years and older, as well as adults.

Narrator: [18:05] Thank you, Dr. Segal, for speaking with us today and sharing your expertise. We very much appreciate it. And thank you to our audience for joining this conversation. Before we conclude, here is some additional important safety information about Valtoco.

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: [20:18] To close, we would like to say thanks again, Dr. Segal. 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.