

A COMPARATIVE EXAMINATION OF VALTOCO AND NAYZILAM: INTRANASAL BENZODIAZEPINE SPRAYS FOR SEIZURE RESCUE

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ABSTRACT

Background: In order to avoid developing status epilepticus and other neurological problems, seizures particularly acute repetitive or cluster seizures-need to be treated right away. Benzodiazepine intranasal administration has become a non-invasive, quick, and successful rescue technique, especially in out-of-hospital situations.

Objective:

The purpose of this review is to compare the pharmacological profiles, efficacy, safety, usability, and clinical application of the two FDA-approved intranasal benzodiazepine sprays, Valtoco (diazepam) and Nayzilam (midazolam), in seizure rescue therapy. Both Valtoco and Nayzilam exhibit quick absorption and effective seizure cessation. While Valtoco has a longer duration of action, which is advantageous in managing seizure clusters, Nayzilam has a faster onset of action (~5 minutes), making it appropriate for immediate rescue. Although there are minor variations in dosing flexibility, age indications, and practical usability, safety profiles are generally similar. The WHO has also approved midazolam for wider worldwide use. Intranasal benzodiazepine sprays have revolutionized the treatment of seizures. Although Valtoco and Nayzilam are both effective, the choice of medication should be based on the patient's age, seizure pattern, clinical situation, and accessibility.

1. INTRODUCTION

Movement, behavior, emotions, and consciousness can all change during a seizure, which is an abrupt and uncontrollable electrical disruption in the brain¹. Seizures can be categorized as focal, general, or unknown onset according to the 2017 update to the International League Against Epilepsy's (ILAE) classification system. Where these seizures start in the brain determines how

they differ from one another. Seizures with focal onset may start in a single region, hemisphere, or cluster of brain cells. There are two types of focal seizures: aware and impaired awareness. When someone has focal onset aware seizures, they are conscious and awake at the time of the seizure^[1-2]. When someone is confused or has impaired awareness, they may experience focal onset impaired awareness seizures. Both motor and non-

motor symptoms may be present in focal onset seizures. Jerking, weak or limp muscles, and tense or rigid muscles are examples of motor symptoms^[3,4]. Changes in sensation, emotion, thought, and cognition, as well as gastrointestinal issues or a total lack of movement, are examples of non-motor symptoms. Both sides of the brain are affected by general onset seizures, or seizures that have both motor and non-motor symptoms. The motor symptoms resemble those of focal onset seizures. Staring fits or fleeting twitches that may only affect one area of the body (such as the eyelid) are examples of non-motor symptoms¹.

When the cause of a seizure is unknown, general onset seizures take place. As information is obtained from the patient or family members to determine how and why the seizure occurred, this category can typically be ruled out^[2,3,4]. Unknown onset seizures may manifest as epileptic motor spasms or tonic-clonic seizures, which are commonly defined as seizures in which the person loses consciousness or exhibits jerky movements and stiff muscles. Staring or lack of behavior are examples of non-motor seizures in this category. Seizures that begin and end in succession in groups are known as seizure clusters. Two or three seizures in a 24-hour period, with recovery in between, can also be regarded as a cluster⁵. Fast-acting "rescue therapies" that can be used right away, even outside of hospital settings, have been developed in response to the urgent need for emergency intervention. Intravenous benzodiazepines have long been the gold standard for stopping seizures, but they need hospital access and skilled staff. Intranasal benzodiazepine sprays, on the other hand, provide a simple, non-invasive substitute that patients, family members, or caregivers can use.

Because intranasal administration enables quicker therapeutic action and rapid drug absorption through the nasal mucosa, it has revolutionized emergency seizure care. In addition to reducing the length of seizures and neurological damage, early intervention also lowers hospitalization rates and enhances the general quality of life for individuals with epilepsy. Because of its speed, ease of use, and accessibility, the intranasal route has become the go-to way for administering emergency anticonvulsant therapy. Intranasal administration eliminates the need for invasive procedures, sterile equipment, and medical expertise that are required for intravenous or rectal routes. Because of the nasal cavity's highly vascularized surface, lipophilic medications, such as benzodiazepines, can be absorbed quickly, entering the bloodstream and taking effect in a matter of minutes. Similar to intravenous delivery, but without the logistical challenges, is this quick onset. Furthermore, the intranasal route circumvents the privacy issues and social discomfort that come with rectal formulations, particularly in public or educational settings. Because of its simplicity of use, it is perfect for paramedics, caregivers, and even patients themselves, especially in out-of-hospital seizures where every second matters. Because they provide a useful, quick, and efficient solution in both clinical and home settings, intranasal benzodiazepine sprays, such as Nayzilam and Valtoco, have consequently taken center stage in contemporary seizure rescue protocols^[6,7]. The comparison of Valtoco and Nayzilam in terms of pharmacology, clinical efficacy, safety, and usability in the treatment of acute seizures is the main objective of this review.

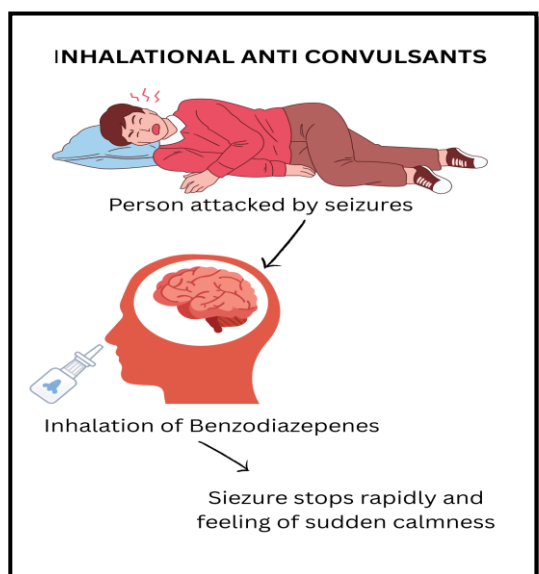


Fig (1)

Table 1: Drug overview ^[4]

Brand Name	Nayzilam	Valtoco
Drug	Midazolam	Diazepam
Drug Class	Benzodiazepine	Benzodiazepine
Dose(mg)	5.0	7.0
Cmax(ng/mL)	71	179
tmax(min)	14	42

3. Epidemiology:

Short-term use of benzodiazepines (BZDs) under medical supervision (MDPI) can quickly and effectively relieve anxiety, sleeplessness, muscular spasms, and seizures.

Clinical evaluations provide ample evidence of their good safety profile in acute care.

Although there are instances of misuse, benzodiazepines typically have a minimal potential for abuse in the general population. By using evidence-based prescribing, which has a limited duration and supervised tapering, therapeutic

benefits are maximized while hazards are reduced ^[4,5]

4. Pharmacology:

4.1 Mechanism of action:

4.1.1 Nayzilam:

Nayzilam is thought to function as a BZD, though its precise mode of action is not fully understood. A benzene ring and a diazepam ring are components of the BZD structure. BZDs have a strong affinity for the GABAA receptors, also known as the BZD receptor. On a single chloride channel of the neuron, these receptors subsequently couple with the GABA

receptors. As a result, the chloride channel opens more frequently, hyperpolarizing the neuron and resulting in neuronal inhibition. This occurs in neurons in the heart, limbic system, thalamus, and hypothalamus. Because Nayzilam is a nasal spray, its antiepileptic properties are attributed to its rapid neuronal inhibition in the brain and short-lived activity.

Because of the sedative effect of the excess GABA activity, BZDs can be used as muscle relaxants, anxiety medications, and sleep aids. Because of its low risk of drug abuse and physical dependence, nayzilam is classified as a schedule IV drug. Because of its inhibitory effects, other forms of midazolam that are administered by different routes (orally, rectally, intramuscularly, and intravenously) have been used as pre-anesthetics or adjunct anesthetics in

endoscopic procedures, dentistry, and cardiac surgery⁶.

4.1.2 Valtoco:

Chloride ions enter the cell upon activation of the GABAA receptor. This results in a general negative charge and hyperpolarization of the cell. They do not open the chloride channel directly because they are allosteric activators. The thalamus, hypothalamus, and limbic system are particularly affected by BZD. By blocking brainstem monoaminergic arousal pathways, BZD receptor agonists promote sedation via GABAA receptors. Sedation results from the facilitation of VLPO inhibitory GABAergic projections to arousal centers, including the brainstem arousal regions, the posterolateral hypothalamic hypocretin neurons, and the anterior hypothalamus TMN⁶.

Table 2: Comparative table (4.2) ¹⁰

Aspect	Nayzilam(midazolam)	Valtoco(diazepam)
Receptor target	GABAA receptor(BZD site)	GABAA receptor(BZD site)
Binding type	Binds with high affinity to BZD receptors(allosteric modulator)	Bind to BZD to receptor as an allosteric agent
Primary effect	Enhances GABA mediated inhibition by increasing frequency of chloride ion channel opening	Enhances GABA activity causing chloride influx, leading to hyperpolarization
Neuronal effect	Hyperpolarization and inhibition of neuronal firing	Hyperpolarization of neurons, suppressing arousal centers

Target Brain Areas	Cardiac neurons, limbic system, thalamus, hypothalamus	Limbic system, thalamus, hypothalamus, brainstem arousal centers
Clinical Effect	Rapid anticonvulsant effect, short duration	Anticonvulsant with additional strong sedative effects

4.3 Conclusion Based on the Comparative Table no:2 of Nayzilam (Midazolam) vs Valtoco (Diazepam):

The comparison of Valtoco (diazepam) and Nayzilam (midazolam) reveals that both medications function as allosteric modulators at the benzodiazepine (BZD) site of the GABA A receptor, enhancing GABA-mediated neuronal inhibition by increasing chloride ion influx and causing hyperpolarization. While diazepam targets

more extensive brain regions, including arousal centers, and has a longer-lasting action with additional sedative effects, midazolam binds with high affinity and produces a rapid, short-duration anticonvulsant effect, making it suitable for quick seizure control¹¹.

5. Table3: Clinical Use and Efficacy^(10,12)

Feature	Nayzilam(midazolam)	Valtoco(diazepam)
Indication	Acute treatment of intermittent, stereotypic episodes of seizure activity in patients > or = 12 years	Acute treatment of seizure cluster inpatients > or = 6 years
Type of benzodiazepine	Short acting	Long acting
Onset of action	Rapid (within 5-10 minutes)	Rapid (within 5-15 minutes)
Duration of action	Short (2-6 hours)	Longer (12+hours due to Diazepam half-life)

Frequency of use	Can be used once every three days	Can be used once every 5 days
Efficacy in seizure control	High Efficacy in stopping Cluster Seizures Quickly	Comparable efficacy; Longer duration may help prevent recurrence
Formulation strengths	5 mg per spray (single use unit)	5 mg, 7.5mg, 10mg depending on age and weight
FDA Approved Age	> or = 12 years	> or = 6 years
Clinical Trials outcome	Effective in stopping Seizures with minimum recurrence in Short-term	Demonstrated sustained seizures Control, especially with higher dose
Ideal for	Rapid, Short-term seizure control in teens and Adults	Long Lasting control in children, teens and adults

5.1 Comparative Discussion of table no:3

The comparison of Valtoco (diazepam) and Nayzilam (midazolam) demonstrates that both medications are useful in treating acute seizures. Valtoco is a long-acting medication that provides sustained seizure control, particularly in children older than six, while Nayzilam is a short-acting benzodiazepine that is best for quick, short-term control in patients 12 years of age and older. While Valtoco, while also

having a rapid onset, has longer-lasting effects because of the half-life of diazepam, making it useful for preventing recurrence, Nayzilam acts quickly (5–10 minutes) and lasts for 2–6 hours, making it suitable for immediate relief. In clinical trials, both have shown great efficacy; Valtoco has shown better sustained control with the right dosage, while Nayzilam has shown rapid action and little short-term recurrence^[10,12].

6. Table 4: Safety and tolerability) ^[13,14,15]

Parameter	Nayzilam(midazolam)	Valtoco(diazepam)
Age Approved for	Patients > or =12 Years	Patient > or =6 Years
Common Side Effects	Nasal Discomfort, Throat irritation, Sleepiness, Headache	Nasal Discomfort, Taste alteration, Fatigue, dizziness

Nasal Tolerability	Moderate-burning/stinging reported by nearly 30% Patients	Better Tolerated-Mild discomfort in fewer Patients
Sedation level	Higher Sedation reported	Mild to moderate sedation(less intense)
Rebound Seizures	Low risk (due to short duration)	Slightly High risk if Seizures not controlled fully
Systemic Tolerability	Well Tolerated, non serious long term toxicities reported	Well tolerated, systemic Exposure is minimal

6.1 Comparative discussion of table no:4

Regarding safety and tolerability, Nayzilam (midazolam) is authorized for use in patients 12 years of age and older. It is generally well tolerated, although approximately 30% of patients experience increased sedation and increased nasal irritation, including burning or stinging. Valtoco (diazepam), which is authorized for use in children as young as six years old, is preferred by sensitive populations due to its milder sedative effects, better nasal tolerability, and fewer complaints of discomfort. Valtoco has a marginally higher risk of rebound seizures if seizures are not completely controlled, whereas Nayzilam has a low risk because of its brief duration. Both are generally well tolerated systemically, but because Valtoco has fewer sedative and nasal side effects, it provides marginally greater overall patient comfort^[13,14,15].

7.OVERALL DISCUSSION

Particularly in actual clinical and residential settings, Valtoco (diazepam nasal spray) is the better treatment choice for emergency seizure situations when compared to Nayzilam (midazolam nasal

spray). Although Nayzilam has a somewhat quicker onset of action, its advantages are fleeting because of its short half-life and the inability to give a second dose during the same seizure episode. On the other hand, Valtoco reduces the risk of seizure recurrence, which is crucial in cluster scenarios, by offering both sufficiently quick seizure control and noticeably longer protection. A significant benefit in emergency situations is that Valtoco permits repeat dosing after 4 hours, providing clinicians and caregivers more flexibility in treating prolonged or recurrent seizures. Both pediatric and adult patients find it more acceptable due to its improved tolerability profile, which includes fewer complaints of nasal irritation and milder sedation. Valtoco is the more clinically feasible, adaptable, and efficient option for the emergency management of seizure clusters because of its longer duration of action and safer re-dosing potential, especially when both quick control and long-term protection are required^[20].

8.CONCLUSION

Intranasal benzodiazepine formulations Nayzilam (midazolam) and Valtoco (diazepam) are authorized for the acute treatment of intermittent, stereotypical seizure clusters in patients with epilepsy

aged 6 years and older. They provide a practical, non-invasive substitute for intravenous or rectal administration. Their primary application is in emergency and outpatient settings, where they offer quick seizure activity control to minimize hospital stays. Because of midazolam's greater lipid solubility and quick CNS penetration, nayzilam acts more quickly, which makes it particularly useful in situations where time is of the essence. Due to the pharmacokinetics of diazepam, valto, although effective, has a slower onset and longer duration, which may be appropriate for patients with persistent seizure tendencies but may also result in increased sedation. Clinical research and post-marketing data show that Nayzilam is generally more well-liked by patients and caregivers because of its easier single-dose form and is linked to fewer local side effects, such as nasal discomfort or irritation, than Valtoco. Although both medications work well to manage seizure clusters, the majority of the data points to Nayzilam as the better choice in emergency situations where quick onset, safety, tolerability, and ease of use are crucial considerations^[16].

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