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General

Midazolam nasal spray to treat intermittent, stereotypic episodes of frequent seizure activity: pharmacology and clinical role, a comprehensive review

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An intranasal formulation of midazolam, Nayzilam, has been FDA-approved to treat intermittent, stereotypic episodes of frequent seizure activity. Nayzilam is easy to administer and can quickly treat seizures that occur outside of the hospital. The intra-nasal route of administration allows non-medical personal to administer the drug which makes it more accessible and user-friendly in the event of a seizure. Many studies have indicated quick cessation of seizures with Nayzilam compared to rectal diazepam, which has been the standard of care treatment. Nayzilam has been proven to be safe and effective for acute seizures in children, deeming it a revolutionary alternative in times where intravenous administration is not possible.

INTRODUCTION

Seizures commonly occur in the pediatric population, increasing the likelihood of significant neurological deficits if not properly rescued.[1] Benzodiazepines (BZD) have been the standard of care to treat seizures for decades due to their ability to facilitate the inhibitory neurotransmitter, gamma-amino-butyric acid (GABA), in the brain. Benzodiazepines are positive allosteric modulators of GABA, inducing inhibition on excitatory neurons, causing a calm and soothing effect on the nervous system.[2] Benzodiazepines have an increased therapeutic index and varying durations of action, deeming them more efficacious than barbiturates, which were more commonly used in the past.[2] Midazolam, which is commonly used as an induction agent for anesthesia, has recently been tested as an intranasal alternative, Nayzilam, which can effectively treat status epilepticus (a single seizure lasting more than five minutes or two or more seizures within a five-minute period without the person returning to normal between them).[3] In the hospital, seizure medications are typically administered intravenously or rectally (diazepam). However, many seizure-related emergencies occur outside the hospital, therefore, the development of a more cost-effective and convenient route of administration was essential. Nayzilam (Midazolam) allows non-medical personal and caregivers to administer this medicine to patients with seizures that occur outside of their typical seizure patterns. The intra-nasal route of administration and fast onset of action are beneficial especially when intravenous access is not feasible.[4] Furthermore, intranasal Nayzilam absorption is more rapid compared to intravenous or rectal (diazepam) administration. This review discusses the current literature available regarding Nayzillam, and evaluate the mechanism of action, pharmacodynamics, safety, efficacy, and clinical uses of Nayzilam in hopes of providing a greater understanding of this new line therapy for status epilepticus.

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NAYZILAM (MIDAZOLAM) WITHDRAWAL EPIDEMIOLOGY/PATHOPHYSIOLOGY/RISK FACTORS/PRESENTATION

EPIDEMIOLOGY

Aside from their indications as anxiolytics and anticonvulsants, BZDs are also commonly prescribed as hypnotics to induce sleep, muscle-relaxants, and at one time, were widely prescribed for anxiety.[5] However, BZDs are associated with a serious risk of abuse potential.[5,6] From 1996 - 2013, BZD-related overdose deaths increased by 400%. Moreover, there has been a 300% increase in BZD related emergency department visits from 2004 – 2011.[5] This can be attributed to the number of medications that have been prescribed in the past decade, which has increased by 67% from the 1990s to 2013.[7] One of the major concerns of BZD misuse are the associated withdrawal symptoms that start with abrupt cessation of the medication. Patients who have taken BZDs for longer than 3-4 weeks commonly experience withdrawal symptoms upon medication cessation. The recent indications for Nayzilam in pediatric populations with intermittent, stereotypic episodes of frequent seizure activity predisposes these populations to potential withdrawal risks with significant presentations.

PATHOPHYSIOLOGY

There are a wide range of withdrawal symptoms associated with BZD dependence and abrupt cessation. Although the mechanism of withdrawal remains to be elusive, certain studies suggest that it is largely due to its connection with the mesolimbic reward system.[8] Midazolam has been found to cause disinhibition of dopamine (DA) neurons in the brain and trigger synaptic plasticity in the ventral tegmental area (VTA).[8] It is proposed that BZDs rely on $GABA_A$ receptor subsets, specifically the α1subunit of $GABA_A$Rs, to illicit their addictive potential. When a BZD binds to $GABA_A$Rs, the release of GABA onto dopamine neurons is decreased. Consequently, the inhibitory effect of GABA interneurons on dopamine neurons diminishes, which leads to increased dopamine transmission, a phenomenon referred to as disinhibition.[9,10]

Although elevated mesolimbic dopamine plays a significant role in the pathogenesis of addiction, studies indicate that elevated dopamine alone is not sufficient to explain the complete basis of addiction to BZDs.[8] Addiction may also be explained by long-lasting changes to the reward system that occur through synaptic plasticity, or changes in neuronal connections in the brain. Long periods of elevated DA in the brain, induced by BZDs, can cause changes in neuronal connections. Furthermore, BZDs also induce changes in alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors, which are sensitive to the neurotransmitter glutamate, an excitatory neurotransmitter in the brain.[11] The AMPA receptors migrate from the interior portion of DA neurons out to the surface of the neuron. This transformation increases the susceptibility of the DA neurons to be stimulated by glutamate. All of these effects contribute to the addictive potential of BZDs.[11]

RISK FACTORS

The common risk factors that predispose patients to develop dependence and, consequently, withdrawal if abruptly weaned can be divided into three categories based on the patient, process, and system-level factors.[12] Many of the factors are based on the patient-level, which includes age, ethnicity, duration of therapy, and cumulative dosage of the medication(s) the patient received.[12] Numerous studies indicate that younger age, increased severity of illness, longer duration of therapy, and higher dosages of BZDs are associated with increased withdrawal syndromes. Some retrospective studies indicate that younger patients who experienced abrupt cessation of midazolam infusions experienced more of the neurologic symptoms associated with withdrawal in comparison to other age distributions.[13] The severity of illness also contributes significantly to withdrawal experienced by midazolam overuse, particularly illnesses involving the brain result in increased levels of withdrawal. Children with pre-existing seizure disorders have an increased chance of experiencing withdrawal.[12,13] Furthermore, the duration of therapy with BZDs highly correlated to symptoms experienced as well; the longer the duration, the more likely patients were to experience withdrawal. Those who stayed in hospital settings and with longer ventilator days were observed to experience more withdrawal. Longer stays corresponded to subjects receiving BZD therapy for at least ten days.[12,14] For patient-factors, higher cumulative doses were associated with increased withdrawal. Strong predictors of withdrawal syndromes were observed in children receiving mean cumulative doses of midazolam greater than the standard averages.[12] In addition to the patient level, and process-level factors such as sedation protocol also contribute strongly to whether or not patients experience withdrawal. Sedation protocols include drug choice, mode of administration, and weaning. Although there are not many articles explaining these factors in-depth, the lack of a sedation management protocol is a considerable risk factor in developing withdrawal syndrome from BZD overuse. Lastly, weaning sedation is also considered a system-level factor, which requires time-sensitive titration plans to limit patient withdrawal.[12]

PRESENTATION

The symptoms experienced with BZD withdrawal vary depending on the duration of action of the medication. Given that midazolam is an ultra-short acting BZD, symptoms are considerably less severe in comparison to longer-acting BZD's.[15] Common symptoms include rebound anxiety with insomnia, restlessness, agitation, poor concentration and memory, and muscle tension and aches man.[16]

CURRENT TREATMENT OF NAYZILAM (MIDAZOLAM) WITHDRAWAL

TREATMENT OF ADULTS

Chronic use of BZDs may result in dependence, and in the case of sudden cessation, prolonged sedation, and high

dosage, withdrawal may occur. Symptoms of midazolam withdrawal may include sympathetic hyperactivity, visual hallucinations, combative behavior, agitation, hyperpyrexia, emesis, and an increase in frequency and severity of tonic-clonic seizures.[17] Chronic users of BZDs are more likely to overdose on the drug, which could be fatal without treatment. The treatment of BZD overdose includes the administration of a specific BZD-receptor antagonist, flumazenil. Flumazenil can lead to withdrawal and increased frequency and severity of seizures. So, the use of flumazenil in patients with epilepsy is contraindicated.[18]

Treatment inludes restarting midazolam at a tapering dose.[17] The first step in general BZD withdrawal management is to find an appropriate initial dose to stabilize the patient. This dose should be given to the patient intermittently throughout a 24-hour period for 4-7 days. Once the patient is considered stabilized, begin tapering the dose. The total amount of time spent tapering the dose will depend on the patient and the dose they used while physically dependent.[19]

TREATMENT DURING INFANCY

Infants whose mothers take BZDs or opioids during late-stage pregnancy can experience withdrawal resulting in neonatal abstinence syndrome. The symptoms of withdrawal may include hypertonia, hyperreflexia, hypoventilation, irritability, tremors, diarrhea, and vomiting. These symptoms start from birth and last up to three weeks of life. The persistence of the symptoms varies from several hours to months, depending on the dependency of the child on BZDs. The treatment of these symptoms has not yet been defined.[18]

Supportive care includes intravenous fluids, replacement electrolytes, and gavage feedings as a treatment in the acute stages of withdrawal may stabilize the infant's condition, obviating the need for pharmacologic treatment. If the symptoms persist treatment includes drugs that promote a depressive state, like opioids, barbiturates, and BZDs.[17]

When comparing supportive care and pharmacologic treatment, the treatment failure rates, defined as "the inability of the treatment to maintain abstinence scores within a preset "safe" level and/or the need to add another drug therapy," are not significantly different. Pharmacologic treatment decreases the amount of time needed for the infant to remain on supportive care and to regain a healthy weight, but the treatment increases the duration of hospitalization for the infant. One study found that infants may be discharged from the hospital after concluding phenobarbital treatment, which was an average duration of 3.5 months.[20] Another study found significant reductions in the duration of hospitalization in those treated with supportive care (average 38 days of hospitalization) versus the maximal daily dosage in the phenobarbital-treated infants (average 79 days of hospitalization).[19]

Studies have compared treatment with opioids (morphine), barbiturates (phenobarbital), and BZDs (diazepam) with varied results. Morphine and phenobarbital treatment show no significant difference in treatment failure rates. Treatment with morphine and phenobarbital have lower treatment failure rates than treatment with diazepam.[19]

NAYZILAM (MIDAZOLAM) DRUG INFO

Nayzilam (midazolam) is a nasal spray used for immediate, short-term treatment of seizure clusters, or acute repetitive seizures, in patients 12 years old and older. Nayzilam is considered a rescue therapy option for seizure clusters, but not an approved seizure medicine to be used on a daily basis.[21]

Nayzilam is usually given as a single spray into one nostril during or after experiencing a seizure or more than one seizure within 10 minutes. Patients experiencing seizures 10 minutes after using one spray should administer a second spray in the opposite nostril. No more than two sprays of Nayzilam should be used to treat a seizure cluster. Nayzilam should not be used to treat more than one seizure cluster every three days, or more than five seizure clusters in one month, or 30 days.[22] If the seizures do not stop after Nayzilm is used then emergency medical help should be sought immediately.

Nayzilam is contraindicated in patients that are allergic to Nayzilam (midazolam) and those with narrow-angle glaucoma, also called closed-angle glaucoma. Pregnancy and breastfeeding may not be safe while taking Nayzilam. Taking opioid medicines, drinking alcohol, or taking any other drugs that cause drowsiness or slow your breathing, such as sleeping pills, muscle relaxers, or medicine for anxiety, could significantly slow breathing and become fatal. Some herbal substances and vitamins may interact with Nayzilam.[22]

Nayzilam could cause an allergic reaction, potentially causing hives, difficult breathing, swelling of the face, lips, tongue, or throat. Some patients experience depression, anxiety, and suicidal thoughts while using Nayzilam. Common adverse effects include drowsiness, headache, runny nose, discomfort in the nose, throat irritation, hiccoughs, cough, nausea, and vomiting. If Nayzilam is used more often than indicated, physical dependence can occur. This could lead to Nayzilam addiction, withdrawal symptoms when suddenly stopping Nayzilam, or potentially a fatality due to overdose.[22]

MECHANISM OF ACTION

Although Nayzilam's exact mechanism of action is not completely understood, it is presumed to act as a BZD. The BZD structure includes a benzene ring and a diazepine ring. BZDs bind to the $GABA_A$ receptors, also called the BZD receptor, with high affinity. These receptors then couple with the GABA receptors on a single chloride channel of the neuron. This increases the frequency of the chloride channel opening, thus hyperpolarizing the neuron and causing neuronal inhibition. This happens in cardiac, limbic, thalamus, and hypothalamus neurons. Nayzilam is administered as a nasal spray, allowing the neuronal inhibition in the brain to occur quickly, but its activity is short-lived; these factors give Nayzilam its antiepileptic property.[23,24]

The excess GABA activity also results in a sedative state, making BZDs useful as anxiety drugs, muscle relaxers, insomnia treatment.[23] Nayzilam is considered a schedule IV drug due to its low potential for drug abuse and physical dependence. Other forms of midazolam that are delivered by differing routes (orally, rectally, intramuscularly, and intravenously) have been used in as pre-anesthetic or adjunct anesthetic in dentistry, cardiac surgery, and endoscopic procedures due to its inhibitory effects.[24]

NAYZILAM (MIDAZOLAM) ORIGINAL USE

Midazolam became available for medical use in 1982, as the first-ever water-soluble BZD. Its water-soluble properties allow it to exhibit fast absorption rates and rapid excretion.[25] Given these properties, it differed from other BZD in that it had the ability to diffuse through capillary walls and go into the central nervous system.[26] Its ability to mix with saline and glucose solutions has also made it a preferred drug for numerous procedures.

Before the discovery of the anti-seizure activity of midazolam, it was indicated as a hypnotic for insomnia patients and a sedative-anxiolytic for patients undergoing anesthesia.

As a hypnotic, midazolam has beneficial effects for insomniac patients who have difficulty falling asleep or those who have pathologic disrupted sleep patterns.[25] This observation in midazolam administration is highly advantageous. Manu studies report significant decreases in the onset of sleep and increases in duration of sleep.[25,27] There are also no remarkable hangover effects experienced in patients, as it normally is with other BZDs.[25,27]

In anesthesiology, midazolam's water-soluble property is advantageous over other induction medications due to its rapid onset of action. It is also used as an adjunct in regional and local anesthesia.[28]

In the early 1990s, midazolam was indicated for the treatment of status epilepticus.[29] Although drugs such as diazepam and phenytoin sodium were sufficient for most patients, others required further modalities like general anesthesia. The dual effect of midazolam as a pre-anesthetic agent and an anticonvulsant deemed it a viable treatment option in status epilepticus.[26] It has been used as an intravenous medication in aborting the ongoing activity of seizures to avoid the long-term complications of prolonged status epilepticus.[29]

PHARMACOKINETICS AND PHARMACODYNAMICS

Nayzilam is a fast-acting, but short-lived BZD, which has inhibitory effects on the central nervous system. Nayzilam is absorbed by intranasal administration, with the average peak plasma concentrations reached within 10.2 to 12.6 minutes.[21] The volume of distribution of Nayzilam will increase in geriatric, female, and obese patients, and their dosages should be decreased.[30]

Once Nayzilam is active, it causes sedation which can affect memory. Studies have shown that 73% of the adult patients who were administered midazolam intramuscularly had no recollection of memory cards shown 30 minutes following drug administration, and 40% had no recollection of the memory cards shown 60 minutes after drug administration.[23] Nayzilam may also have an anesthetic effect, with the peak plasma concentrations reached within 1.5 to 2.5 minutes after administration.[21]

Nayzilam is metabolized in the liver by the CYP3A4 enzyme, resulting in the active metabolite alpha-hydroxymidazolam, or 1-hydroxy-midazolam, which is responsible for the pharmacological effects of the drug. The active metabolite is filtered by the kidneys and excreted in the urine. The half-life and clearance of intranasal administered Nayzilam is unknown.[31]

Because Nayzilam travels in the blood, transplacental transfer of the drug from the pregnant patient to the developing fetus is likely if the patient is pregnant. This may result in the infant experiencing physical dependence and withdrawal symptoms soon after birth.[17] There are no adequate data to determine if Nayzilam causes developmental abnormalities in the growing fetus. Nayzilam can be passed to the infant through breast milk. A patient should not breastfeed their infant for up to 4 hours after taking Nayzilam. Breastfed infants with mothers taking BZDs may experience lethargy, somnolence, and poor sucking. There are no adequate data to determine if Nayzilam causes developmental abnormalities in the infants with BZD metabolites present in the breast milk they ingest.[30]

Physical dependence, withdrawal, and overdose of Nayzilam is possible if taken incorrectly, and could potentially be fatal. Addiction and tolerance occur by an adaptive mechanism when Nayzilam is chronically used because the $GABA_A$ receptors that are activated during Nayzilam also trigger the nearby dopamine neurons.[8,32] This is an example of neuroplasticity that reinforces Nayzilam use. An overdose could occur by administering too much of the drug too quickly or by using other depressants with Nayzilam. The combined use of alcohol and/or other CNS depressants like opioids can lead to additive CNS depression and could be fatal. Alcohol taken with CNS depressants also can lead to additive respiratory depression, hypotension, profound sedation, or coma.[30] Signs of overdose include, but are not limited to, sedation, confusion, impaired coordination, coma, and deleterious effects on vital signs, such as hypotension.[8,32]

Those that are considered high-risk patients that may need a lower dosage include adults over 60 years of age, chronically ill or debilitated patients, chronic respiratory insufficiency patients, patients with chronic renal failure, impaired hepatic function or with impaired cardiac function, pediatric patients, especially those with cardiovascular comorbidities. For young patients without any comorbidities, the therapeutic index for Nayzilam is high, as the common adverse effects mentioned previously are mild.[31]

CLINICAL STUDIES: SAFETY AND EFFICACY

The treatment of episodic seizure activity with intranasal midazolam is generally well-tolerated and effective. The clinical trials described below demonstrate rare occurrences of only minor treatment-emergent adverse events (TEAEs).

CLINICAL TRIALS

A 2019 randomized, double-blind, placebo-controlled trial evaluated the safety and efficacy of midazolam nasal spray in the outpatient treatment of patients with seizure clusters.[33] In the comparative phase of this study, a sample size of 262 patients was randomly assigned into two groups: placebo and midazolam nasal spray 5 mg. The total number of patients analyzed after accounting for discontinuation of subjects during the comparative phase was 201. Either the placebo or the midazolam nasal spray was administered by a caregiver when the patient experienced a seizure cluster. The primary outcome measured was the proportion of patients achieving seizure termination within 10 minutes of administration, with no seizure recurrence 10 minutes to 6 hours after. Patients receiving midazolam nasal spray experienced significantly greater treatment success (53.7%) compared to patients receiving placebo (34.3%).[33] Further, a greater number of patients receiving midazolam nasal spray did not experience recurrent seizure activity 10 minutes to 6 hours following administration (58.2%) compared to placebo (37.3%). The rate of adverse events was the same in both the treatment group receiving double-blind midazolam nasal spray and the double-blind placebo treatment, at 23.1% for both groups.[33] The two primary adverse events described were nasal discomfort and somnolence. Of the 88 patients receiving the placebo treatment, 21 discontinued. Of the 174 patients receiving midazolam nasal spray, 40 discontinued. The majority of patients discontinuing the study in both the placebo and midazolam nasal spray groups did so for one of the following reasons: the patient did not experience seizure clusters according to trial criteria, the caregiver was no longer available, the trial drug was unavailable at the site, the trial was terminated, the patient/caregiver was unable to comply with trial procedures/visits, or the site was closed.

A 2012 randomized clinical trial compared intranasal midazolam with intravenous diazepam in patients suffering from acute seizure.[34] The primary focus of this study was to measure the difference in time needed to control seizure attacks with intranasal midazolam versus intravenous diazepam, the common treatment. The study included 60 patients ranging from 2 months old to 15 years old, divided randomly into two groups of 30. The patients were administered either intranasal midazolam 0.2 mg/kg or intravenous diazepam 0.3 mg/kg and monitored for time to seizure cessation. The time needed for seizure control was significantly less with administration of intranasal midazolam (3.26±1.24 minutes) than with intravenous diazepam (6.42±2.59 minutes), taking into account the time needed to establish IV access ($p<0.001$).[34] The pulse rate and oxygen saturation were also measured at 5 minutes and 10 minutes following drug administration, but these findings did not indicate a statistically significant difference.[34] There were no cases of treatment failure in this study.

A 2017 phase 1, randomized, double-blind, 2-way crossover study examined the pharmacokinetics, pharmacodynamics, and tolerability of midazolam nasal spray in healthy geriatric and non-geriatric adults.[35] The study included 18 geriatric patients (⩾ 65 years) and 12 non-geriatric patients (18-40 years) administered single doses (2.5 mg and 5.0 mg) of midazolam intranasally.[35] Treatment-emergent adverse events (TEAEs) were summarized by dose, severity, and relationship to treatment in either group. Safety was assessed using laboratory values, vital signs, pulse oximetry, the Columbia Suicidality Severity Rating Scale, and other parameters. The percentage of subjects experiencing one or more TEAE was 89% in the geriatric group and 83% in the non-geriatric group, with all TEAEs (115 total) being either mild (109) or moderate (6) in severity.[35] Increased lacrimation (n=12, 67%) and throat irritation (n=10, 56%) were the two most common TEAEs in the geriatric group.[35] Nasal congestion (n=5, 42%) was the most common TEAE in the non-geriatric group, followed by increased lacrimation and dysgeusia (n=4, 33%).[35] Laboratory values and vital signs remained within reference ranges for all study participants.

A 2020 study assessed the efficacy, tolerability, and safety of intranasal midazolam spray as emergency medication in epilepsy patients during video-EEG monitoring.[36] The primary factor examined in the study was the timespan until the occurrence of another seizure in patients administered intranasal midazolam 5 mg compared with those not receiving intranasal midazolam. The median time span of seizure recurrence was found to be 10.67 hours (range .03-24 hours, 95% CI 7.28-14.77) following the application of intranasal midazolam, compared with 5.00 hours (range .02-24 hours, 95% CI 4.12-6.55) in patients not receiving intranasal midazolam.[36] Intranasal midazolam also had a significant effect on seizure recurrence within the same 24-hour period, with 29.2 % of patients not experiencing another seizure in the following 24 hours, compared with only 14% of patients who did not receive intranasal midazolam not experiencing another seizure. The study included 243 patients with a mean age of 35.5 years. Treatment emergent adverse events were seen in 108 (44.4%) patients, with the most common events being nasal irritation (n=32 patients, 13.2%) and prolonged sedation (n=22 patients, 9.1%).[36] **See Table 1.**

COMPARISON STUDIES

A 2019 study compared intranasal midazolam with intravenous lorazepam for seizure termination and prevention of seizure clusters in adults.[39] While the previous study examined the effectiveness of intranasal midazolam in a pediatric population, this retrospective cohort study selectively included only patients with epilepsy who were 18 years of age or older. The primary outcome measured was the effectiveness of intranasal midazolam and intravenous lorazepam for termination of seizure activity. There was a total of 50 patients included in the study, 27 receiving in-

Table 1. Clinical Efficacy and Safety

Study and Author (year)	Groups Studied and Intervention	Results and Findings	Conclusions
Safety and Efficacy of midazolam nasal spray in the outpatient treatment of patients with seizure clusters: Detyniecki et al. (2019)[33]	201 patients, 12 years old to 65 years old, median age of 33.0 (SD:11.96) administered intranasal midazolam (134 patients) or placebo (67 patients).	**Seizure Cessation within 10 minutes of drug administration**: Intranasal midazolam: 53.7 % of patients Placebo group: 34.4% of patients	Intranasal midazolam has shown rapid and persistent seizure control, with minimal safety risks, in patients greater than 12 years old, making it the preferred treatment choice for seizure control in a prehospital setting.
Pharmacokinetics, pharmacodynamics, and tolerability of USL261, midazolam nasal spray: Berg et al. (2017)[35]	30 patients, 18 geriatric (range: 65-78 y/o) and 12 non-geriatric (range: 20-40 y/o) administered intranasal midazolam 2.5 mg and 5.0 mg.	**Intranasal midazolam 2.5 mg**: 12 patients (40%) experienced increased lacrimation, 9 patients (30%) experienced throat irritation. **Intranasal midazolam 5.0 mg**: 12 patients (40%) experienced increased lacrimation, 9 patients (30%) experienced dysgeusia. No serious adverse events were seen.	Intranasal midazolam 2.5 mg and 5.0 mg showed only mild treatment emergent adverse events (TEAEs) in both geriatric and non-geriatric populations, making this drug a safe choice for patients of all ages.
Efficacy, tolerability, and safety of concentrated intranasal midazolam spray as emergency medication in epilepsy patients during video-EEG monitoring: von Blomberg et al. (2020)[36]	243 patients with epilepsy, mean age of 35.5 years (range: 5-76 years), receiving intranasal midazolam 5.0 mg or not receiving intranasal midazolam (controls) for seizure treatment.	**Median seizure-free timespan after treatment**: 10.67 hours following intranasal midazolam 5.00 hours in controls **Side Effects**: irritation of nasal mucosa [37 cases (8.1%)], prolonged sedation [26 cases (5.7%)], nausea and vomiting [12 cases (2.6%)].	Intranasal midazolam is both safe and efficient in the treatment and short-term prevention of seizure activity. Administration can be accomplished quickly, and severe adverse events are rare.
Intranasal midazolam as first-line in hospital treatment for status epilepticus: a pharmaco-EEG cohort study: Kay et al. (2019)[37]	42 patients experiencing status epilepticus (SE), mean age of 52.7 ± 22.7 years, treated with a median dose of 5 mg of intranasal midazolam.	**Cessation of SE following administration of intranasal midazolam**: 24 patients (57.1%) **Time to SE cessation on EEG**: 5:05 (minutes:seconds) on average (median: 04:56; range: 00:29 – 14:53) **Adverse events**: Nasal irritations (5 patients, 11.9%), prolonged sedation (1 patient, 2.6%)	Intranasal midazolam is an effective treatment for patients experiencing status epilepticus. Adverse events are rarely seen with intranasal midazolam use, and they are mild when present. The intranasal route of administration provides rapid relief of status epilepticus.

Study and Author (year)	Groups Studied and Intervention	Results and Findings	Conclusions
Intranasal midazolam for the treatment of seizures in children in rural India: Babbar et al. (2020)[38]	50 pediatric patients experiencing seizure activity for > 3 minutes, age range of 6 months to 14 years, administered intranasal midazolam by a caregiver.	**Average duration of seizure abortion**: Before administration of intranasal midazolam: 16.22 min After administration of intranasal midazolam: 4.66 min Seizures aborted in 45/50 children (90%) within 10 minutes.	Intranasal midazolam represents a quick and efficacious method of seizure termination in the pediatric population. The intranasal administration provides an easy option for caregivers who are not medically trained.

travenous lorazepam and 23 receiving intranasal midazolam.[39] The study showed no significant difference with regards to median time to seizure cessation for intravenous lorazepam (3.3 minutes) compared with intranasal midazolam (3.2 minutes).[39] There was also no significant difference seen in the duration of index seizure with intravenous lorazepam versus intranasal midazolam (1.7 minutes vs. 2.0 minutes, p=0.20).[39] The results indicate that while each drug is comparable in efficacy, intranasal midazolam may be preferred due to easier, faster, and safer route of administration. The rate of adverse events was comparable in each group, with the most common adverse event following intravenous lorazepam being confusion (n=10, 37%) and the most common adverse event following intranasal midazolam being fatigue (n=7, 30.4%).[39]

A 2010 prospective randomized study compared intranasal midazolam with rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy.[40] A total of 358 pediatric patients were included in this study, with caretakers randomized to administer either 0.2 mg/kg of intranasal midazolam or 0.3 to 0.5 mg/kg of rectal diazepam.[40] 179 patients were allocated to the intranasal midazolam group, with 50 patients in this group included in the data analysis. 179 patients were allocated to the rectal diazepam group, with 42 patients in this group included in the data analysis. The primary outcome measured was the total seizure time following medication administration. The median time to seizure cessation following intranasal midazolam was 3.0 minutes, while the median time to seizure cessation following rectal diazepam was 4.3 minutes, a difference of 1.3 minutes (95% CI, 0.0-3.5; P=0.09).[40] The study also showed identical time-to-medication administration in both groups, the median time being 5.0 minutes.[40] The total seizure time observed for the intranasal midazolam group was a median of 10.5 minutes (IQR 7.0-18.0), compared with a median of 12.5 minutes (IQR 7.0-30.0) in the rectal diazepam group, a difference of 2.0 minutes (95% CI, -1.0-5.7; p=0.25).[40] The results of this study are further supported by a prior study by Holsti et al., which found that prehospital administration of intranasal midazolam resulted in significantly shorter seizure time (median 11 minutes) when compared with rectal diazepam (median 30 minutes, P=0.003).[41] **See Table 2.**

OTHER STUDIES

A 2019 pharmaco-EEG cohort study examined the efficacy and tolerability of intranasal midazolam as a first-line in-hospital treatment for status epilepticus.[37] A total of 42 patients were initially treated with intranasal midazolam for status epilepticus with continuous EEG monitoring, with the mean age of the patients being 52.7 years old (range: 5-92 years; SD: 22.7).[37] Of the patients included in the study, 25 (59.5%) had a known diagnosis of epilepsy prior to their hospitalization, with 17 patients (40.5%) having no history of seizures prior to hospitalization. In 15 patients (35.7%), the onset of seizure activity was recorded on EEG. In these patients, status epilepticus was shown to last an average of 46 minutes before intranasal midazolam was given (mean: 46:15; median:18:48; range: 00:05:49-02:30:00; SD:55:35).[37] An average of 6.4 mg of intranasal midazolam was administered. Of the 42 patients treated, status epilepticus was successfully terminated following only administration of intranasal midazolam in 24 patients, while 18 patients did not achieve termination of status epilepticus following intranasal midazolam.[37] In the 24 patients responding to intranasal midazolam, EEG monitoring showed cessation of status epilepticus after an average of 5:05 following intranasal midazolam (median: 4:56; range: 00:29–14:53; SD: 3:10).[37] Treatment-emergent adverse events were noted in 6 patients (14.3%), with 5 patients (11.9%) experiencing nasal irritation and one patient (2.6%) experiencing prolonged sedation.[37] No respiratory, circulatory, or ECG irregularities were observed following intranasal midazolam administration.

A 2020 study assessed the use of intranasal midazolam for the treatment of seizures in children in rural India.[38] This study examined the effectiveness of intranasal midazolam for seizure cessation when given by caregivers in the home setting. A total of 50 children ranging from 6 months of age to 14 years old were included in the study. Intranasal midazolam was administered by the caregiver at a dose of 0.2 mg/kg, with instructions to wait 3 minutes after seizure initiation to give the drug.[38] The 50 patients were divided into three groups, separated by age: group A included patients aged 6 months-4 years (13 patients), group B included patients aged 4-9 years (18 patients), and group C included patients aged 9-14 years (19 patients). Between all three groups, the average time to seizure cessation was 4.66 minutes.[38] Intranasal midazolam was successful in controlling seizures within 5 minutes in 37 patients and between 5-10 minutes in 13 patients.[38] In 13 patients requiring repeat doses, 8 patients responded successfully. The most common seizure type seen in the 50 patients included in the study was generalized tonic-clonic (46%), followed by complex partial seizures (32%).[38] There were no significant side effects due to administration of intranasal midazolam, but some difficulties were experienced by caregivers, including excessive nasal secretions and head movements.

A 2013 review article examined the viability of intranasal midazolam in the treatment of acute seizures.[1] This article reviewed data regarding the safety and efficacy of intranasal midazolam alone, as well as comparing intranasal midazolam to rectal diazepam for treatment of pediatric acute seizures in the prehospital, home, and emergency department settings. One study by Lahat and colleagues found that intranasal midazolam successfully treated seizures in 19 of 20 patients, with a mean time to seizure control of 3.5 minutes (range, 2.5-5 minutes).[42] Another study by Kutlu et al. examined the efficacy of intranasal midazolam in 9 pediatric patients with seizures lasting greater than 10 minutes but fewer than 30 minutes. The mean time to seizure cessation in this study was 139.6 seconds, with all 9 patients experiencing treatment success.[43] In a study 2006 by Bhattacharyya and colleagues, it was found that, in 46 children presenting to the emergency department, intranasal midazolam successfully terminated febrile or afebrile seizures in a mean time of 1.95 minutes, compared with a mean time of 2.97 minutes with rectal di-

Table 2. Comparative Studies

Study and Author (year)	Groups Studied and Intervention	Results and Findings	Conclusions
Intranasal midazolam compared with intravenous diazepam in patients suffering from acute seizure: Javadzadeh et al. (2012)[34]	60 patients, ranging from 2 months to 15 years old, experiencing an acute seizure episode and administered either intranasal midazolam 0.2mg/kg or IV diazepam 0.3mg/kg.	**Time needed to control seizure**: Intranasal midazolam: 3.16 ± 1.24 minutes IV diazepam: 6.42 ± 2.59 minutes	Intranasal midazolam has shown superiority in regard to time needed for seizure cessation compared with IV diazepam. This, along with ease of use by non-medical caregivers, makes intranasal midazolam the preferred drug of choice for pediatric seizure rescue.
Comparison of intranasal midazolam versus intravenous lorazepam for seizure termination and prevention of seizure clusters in the adult epilepsy monitoring unit: Owusu et al. (2019)[39]	50 patients ≥ 18 years old experiencing epileptic seizures requiring rescue therapy. 27 patients received IV lorazepam, and 23 patients received intranasal midazolam.	**Median duration of index seizure**: 1.7 min (IQR 1.1-2.7) with IV lorazepam 2.0 min (IQR1.5-2.6) with intranasal midazolam **Number of subjects requiring repeat BZD administration**: 8/27 (29.6%) with IV lorazepam 7/23 (30.4%) with intranasal midazolam	Intranasal midazolam is comparable with IV lorazepam for seizure termination and seizure cluster prevention. The benefit of bypassing the need for IV access makes intranasal midazolam the preferred choice for seizure control over IV lorazepam.
Intranasal midazolam vs. rectal diazepam for the home treatment of acute seizures in pediatric patients with epilepsy: Holsti et al. (2010)[40]	92 pediatric patients experiencing seizure activity were given either intranasal midazolam (50 patients) or rectal diazepam (42 patients) by a caregiver.	**Median time to seizure cessation following drug administration**: 3.0 min with intranasal midazolam 4.3 min with rectal diazepam **Median seizure time**: 10.5 min with intranasal midazolam 12.5 min with rectal diazepam No differences were seen in regard to adverse effects due to drug administration.	Intranasal midazolam is more effective than rectal diazepam regarding the time needed for seizure control in pediatric patients in the home setting. Caregivers reported that intranasal midazolam was easier to administer than rectal diazepam, making this the drug of choice for seizure control in the home setting.

azepam (p=0.005).[44] Furthermore, the same study found that seizures ceased within 10 minutes in 88.5% of patients administered rectal diazepam, compared to 96.7% of patients administered intranasal midazolam (p=0.06).[44] Regarding the safety of intranasal midazolam compared with rectal diazepam, a comparative study by Fişgin and colleagues found that only 2 of 45 patients experienced adverse events of tachypnea and tachycardia after intranasal midazolam administration.[45] It was believed that these effects were due to pain caused by nasal irritation, rather than a direct effect of intranasal midazolam. Neither of these events was found to be statistically different from the group receiving rectal diazepam (p>0.05).[45]

CONCLUSION

Benzodiazepines have been the standard of care to treat seizures for decades due to their ability to facilitate the inhibitory neurotransmitter, gamma-amino-butyric acid (GABA), in the brain. Midazolam, a BZD which is commonly used as an induction agent for anesthesia, has recently been tested as an intranasal alternative, Nayzilam, which can effectively treat status epilepticus in patients 12 years old and older. Nayzilam is considered a rescue therapy option for seizure clusters, but not an approved seizure medicine to be used on a daily basis. Nayzilam is usually given as a single spray into one nostril during or after experiencing a seizure or more than one seizure within 10 minutes. Although Nayzilam's exact mechanism of action is not completely understood, it is presumed to act as a BZD and BZDs are associated with a serious risk of abuse potential and withdrawal. Given that midazolam is an ultrashort acting BZD, withdrawal symptoms are considerably less severe in comparison to longer-acting BZD's. That being said, the treatment of episodic seizure activity with Nayzilam is generally well-tolerated and effective. The clinical trials described in this paper demonstrate rare occurrences of only minor treatment-emergent adverse events. Overall, Nayzilam will make seizure treatment easier and more accessible to individuals who need help fast in emergency situations.

ETHICAL CONSIDERATIONS

HCA Centralized Algorithms for Research Rules on IRB Exemptions (CARRIE)/ IRB manager issued study exemption # 2022-752.

CONFLICTS OF INTEREST

None of the authors report any conflicts of interest.

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