

Zavegepant Nasal Spray for Treatment of Acute Migraine: A Systematic Review

Abstract

Background: Migraine is a widespread neurological disorder that can impair quality of life. Current treatments are often insufficient, with side effects causing some patients to seek alternative options. Zavegepant nasal spray, a new treatment being developed for acute migraine, shows promise in blocking the CGRP receptor and providing several potential advantages, such as faster onset of action and higher bioavailability. This systematic review aimed to assess the efficacy and safety of Zavegepant nasal spray in treating acute migraine attacks and identify adverse events.

Methods: Adult patients diagnosed with acute migraine who were treated with Zavegepant nasal spray in randomized controlled trials (RCTs) or non-randomized clinical trials were included. A comprehensive search was conducted in PubMed, Embase, Cochrane Library, and ClinicalTrials.gov until March 2023. The following keywords were employed: "Zavegepant nasal spray", "migraine", "calcitonin gene-related peptide receptor antagonist." A narrative synthesis was conducted to summarize and analyze the extracted data from the included studies, with a focus on the efficacy and safety of Zavegepant nasal spray for the treatment of acute migraine.

Results: This systematic review included three clinical trials, of which two were RCTs, and one was an open-label trial. The total number of participants was 3681, and all of them were in phase 2/3 of testing. The inclusion criteria for these trials were broadly based on individuals who had a history of migraines with or without aura lasting for over a year, which is consistent with the third edition of the International Classification of Headache Disorder. The findings were tabulated and discussed.

Conclusion: Zavegepant nasal spray is an effective and well-tolerated treatment for acute migraines. Further research is needed to confirm its safety and efficacy, optimal dosing and administration, and effectiveness in different populations. The cost-effectiveness, patient satisfaction, and long-term effects on migraine burden ought to be investigated.

Keywords: Zavegepant; Nasal Spray; Acute Migraine; Neurological Disorder

Introduction

Migraine is a life-debilitating neurological disorder that affects an estimated 12% of the global population. The symptoms of migraine include recurrent and intense headaches, nausea, vomiting, and sensitivity to light and sound, which can significantly impact a person's quality of life [1]. The current treatment options for acute migraine include nonsteroidal anti-inflammatory

drugs (NSAIDs), ergots, triptans, and antiemetics [2]. However, these treatments are not always effective, and some patients may experience side effects such as nausea, dizziness, and rebound headaches [3].

Zavegepant nasal spray is a novel medication being developed for the treatment of acute migraine [4]. It is a small molecule antagonist of the CGRP receptor, which is believed to play a key role in the pathophysiology of migraine [5]. By blocking the CGRP receptor, Zavegepant can reduce the activity of the trigeminal nerve and alleviate migraine symptoms. The nasal spray formulation of Zavegepant offers several potential advantages over other forms of medication delivery [6]. Nasal sprays can provide faster onset of action and higher bioavailability compared to oral formulations, as they bypass the digestive system and are absorbed directly into the bloodstream [6]. Additionally, nasal sprays may be more convenient and easier to use compared to other forms of medication, as they do not require water or food and can be self-administered [6].

The development of the Zavegepant nasal spray represents an important advance in the treatment of acute migraine. The U.S. FDA approved the first CGRP receptor antagonist nasal spray for the acute treatment of migraine with or without aura in adults on 10th March 2023 [7]. The ability to deliver the medication via nasal spray offers several potential advantages, including a faster onset of action and higher bioavailability. These advantages may translate into improved efficacy and patient satisfaction with treatment. Furthermore, the targeting of the CGRP receptor represents a novel approach to the treatment of migraine. The current treatments for migraine, such as NSAIDs and triptans, do not target the underlying pathophysiology of the condition [8]. By blocking the CGRP receptor, Zavegepant may offer a more targeted and effective approach to the treatment of acute migraine [9].

CGRP is a neuropeptide widely distributed in both the central and peripheral nervous systems. It is primarily synthesized in the cell bodies of sensory neurons and released upon nerve stimulation [10]. CGRP plays a crucial role in vasodilation, nociception (the perception of pain), and neurogenic inflammation, which are key processes involved in migraine pathophysiology. The pathophysiology of migraine is thought to involve the activation and sensitization of the trigeminovascular system, a network of neurons innervating the cranial blood vessels and dura mater. Activation of these neurons results in the release of multiple vasoactive peptides, including CGRP, which leads to vasodilation of the cranial blood vessels and increased blood flow. This, in turn, contributes to the neurogenic inflammation, sensitization of pain pathways, and the perception of migraine pain [11]. CGRP levels have been found to be elevated during a migraine attack and return to normal following headache resolution. Additionally, intravenous administration of CGRP has been shown to induce migraine-like headaches in migraine sufferers but not in healthy individuals, further supporting the role of CGRP in migraine pathophysiology. The connection between CGRP and migraine has led to the development of a new class of migraine-specific drugs, known as CGRP receptor antagonists or "gepants." These drugs work by blocking the CGRP receptor, thereby preventing the binding of CGRP and inhibiting its downstream effects on vasodilation, inflammation, and pain signaling [12]. Several gepants, such

as ubrogepant and rimegepant, have shown promising results in clinical trials, offering rapid and effective relief for migraine sufferers with minimal side effects.

The objective of this systematic review is to provide a comprehensive analysis of the available evidence on the use of Zavegepant nasal spray for the treatment of acute migraine. Specifically, the aim is to assess the efficacy and safety of Zavegepant nasal spray in reducing the pain of acute migraine attacks, as well as its impact on any other migraine-related symptoms. Identification of any potential adverse events associated with the use of Zavegepant nasal spray was also attempted. By synthesizing the available evidence, clinicians and patients will have a clearer understanding of the potential benefits and risks of Zavegepant nasal spray as a treatment option for acute migraine.

Methods

Eligibility Criteria

- **Participants:** Studies involving adult patients (18 years or older) diagnosed with acute migraine were included.
- **Intervention:** Studies investigating the use of Zavegepant nasal spray for the treatment of acute migraine were included.
- **Study Design:** Randomized controlled trials (RCTs) and/or non-randomized clinical trials were included.
- **Outcome Measures:** Studies reporting outcomes related to the efficacy and safety of Zavegepant nasal spray for the treatment of acute migraine were included.

Information Sources

An electronic search was conducted of the following databases and registers: PubMed, Embase, Cochrane Library, and ClinicalTrials.gov. A manual search of relevant journals and conference proceedings was also conducted to ensure a comprehensive search. The search was limited to studies published in English and conducted on human subjects.

Search Strategy

Our search strategy included relevant keywords such as "Zavegepant nasal spray", "migraine", "calcitonin gene-related peptide receptor antagonist", and other related terms. We used a combination of Medical Subject Headings (MeSH) and free-text terms to ensure a comprehensive search. The search was conducted until March 2023.

Study Selection

Two independent reviewers screened the titles and abstracts of the identified studies for eligibility. Full-text articles were then screened for inclusion based on the eligibility criteria. Studies were included if they involved adult patients (18 years or older) diagnosed with acute migraine, investigated the use of Zavegepant nasal spray for the treatment of acute migraine, reported outcomes related to the efficacy and safety of Zavegepant nasal spray, and were

conducted using RCTs/non-randomized clinical trials. Studies that did not meet these criteria were excluded.

Data Extraction and Synthesis

A narrative synthesis was conducted. The extracted data from the included studies were summarized and analyzed to determine the efficacy and safety of Zavegepant nasal spray for the treatment of acute migraine. The results of the studies were reported descriptively, and the strengths and weaknesses of the included studies were discussed. Finally, the findings of the included studies were summarized, and the implications for clinical practice and future research were discussed.

Results

Of 125 studies identified, seven duplicates were removed before screening. A total of 118 studies were screened for titles and abstracts, of which 12 were excluded as they did not meet the inclusion criteria; 106 studies were fully reviewed. A final of three studies were included in the review.

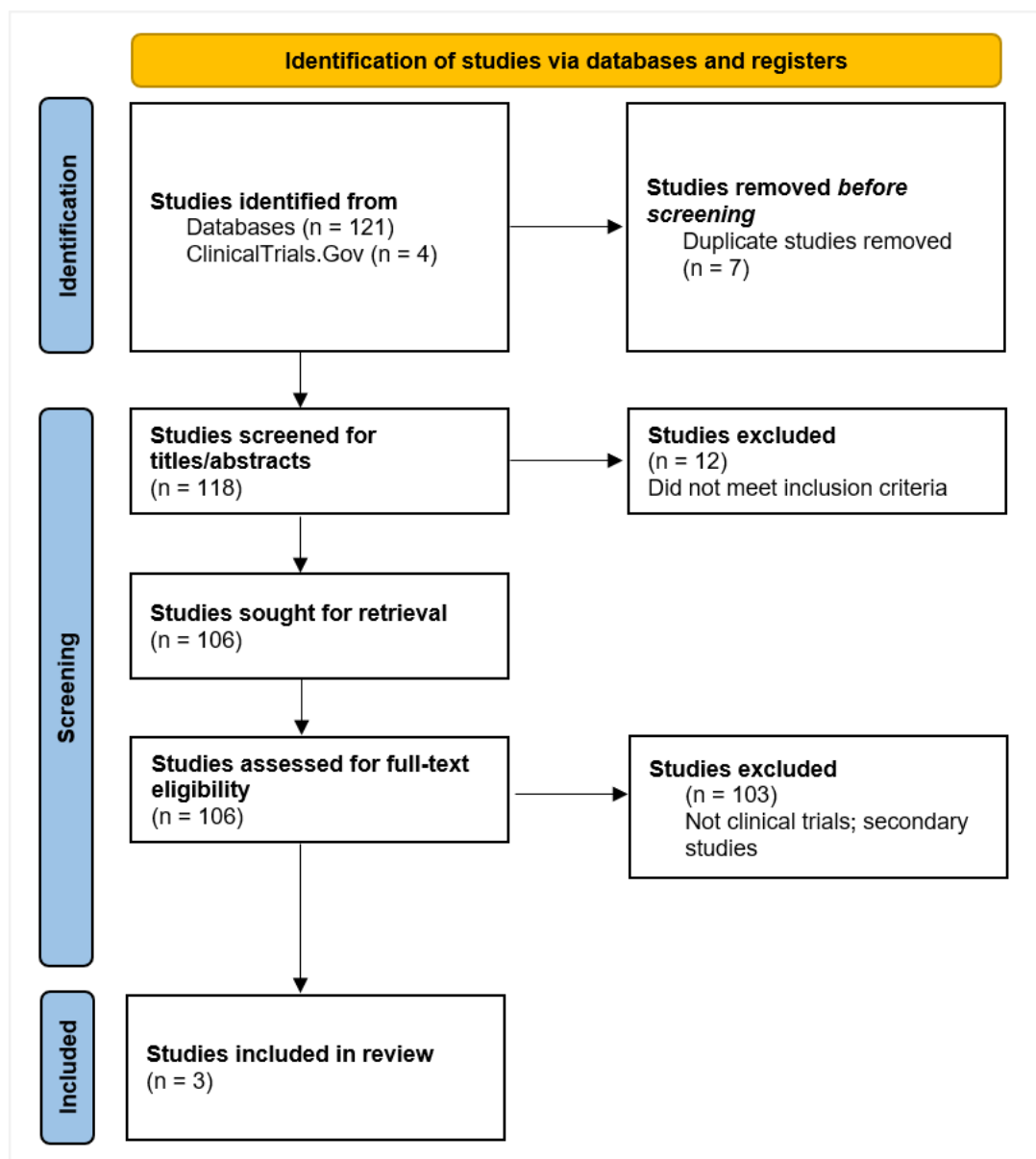


Figure 1. PRISMA flowchart depicting the study selection process.

In total, three clinical trials were included in this systematic review of which 2 were RCTs and one was an open-label trial. The total participant count was 3681. The trials were in phase 2/3 of testing. The inclusion criteria broadly comprised over one-year histories of migraines with or without aura, in line with the third edition of the International Classification of Headache Disorder. The characteristics of the included studies are depicted in **Table 1**.

Table 1. Characteristics of the included studies.

Identifier	Title	Study Type	Intervention	Inclusion Criteria	Primary Outcomes	N	Findings	Adverse Events
Croop, 2022 [13]	Zavegepant nasal spray for the acute treatment of migraine: A Phase	RCT; Phase 2, 3	Zavegepant (BHV3500) was given as	Over 1-year history of migraines (with	Percentage of participants with freedom from	1673 (N=387, 5 mg;	Zavegepant at 10 mg and 20 mg dosage	Treatment-emergent AEs were

	2/3 doubleblind, randomized, placebocontrolled, doseranging trial		a single intranasal dose of 5 mg, 10 mg, and 20 mg using an Aptar UDS liquid spray device	or without aura), consistent with the 3rd Edition of the International Classification of Headache Disorder	pain and MBS at 2 hours	N=391, 10 mg; N=402, 20 mg; N=401, placebo)	was more effective than placebo for pain freedom (15.5% and 22.5%, respectively) and MBS (33.7% and 42.5%) at 2h-postdose (P<0.05); findings for 5 mg dose were insignificant	mostly mild or moderate: primarily-nausea (2.6-4.1%), nasal discomfort (1.3-5.2%), and dysgeusia (13.5-16.1%); no hepatotoxic effects were observed
Lipton, 2023 [14]	Safety, tolerability, and efficacy of zavegepant 10 mg nasal spray for the acute treatment of migraine in the USA: a phase 3, double-blind, randomised, placebo-controlled multicentre trial	RCT; Phase 3	Zavegepant (BHV3500) given as a single intranasal dose of zavegepant 10 mg on the occurrence of migraine with moderate or severe intensity using an Aptar UDS liquid spray device	At least 1-year history of migraines (with or without aura), consistent with the 3rd edition of the International Classification of Headache Disorder; male and female adult (≥18 years old) participants	Percentage of participants with freedom from pain and MBS at 2 hours	1405 (N=703, zavegepant group; N=702, placebo)	Zavegepant compared to the placebo group depicted pain freedom at a 24% rate versus 15%, respectively (P<0.0001); freedom from MBS was 40% vs. 31% respectively (P=0.0012)	The most common reports were for dysgeusia (21%), nasal discomfort (4%), and nausea (3%)
NCT04408794, 2023 [15]	Long-term Safety study of BHV-3500 (Zavegepant) for the Acute Treatment of Migraine	Open-label Safety Trial; Phase 2, 3	Zavegepant (10 mg) given intranasally for a maximum of 8 times per month up to 1 year	Migraine attacks present for over 1 year; 2-8 moderate to severe migraines/month lasting between 4-72 hours; adult participants	Number of participants with adverse events (severe and/or leading to discontinuation) and with clinically significant laboratory abnormalities immediately and 52 weeks post-treatment	603	Laboratory abnormalities were seen as changes in LDL (N=15), CK (N=13), AST, and ALT (N=8); no mortality was reported for any cause	A large majority reported AEs (N=460); only seven experienced serious AEs. 41 participants withdrew from the study due to AEs

Table 1. Characteristics of the included studies. Abbreviations: AEs: Adverse Events; AST: Aspartate Aminotransferase; ALT: Alanine Transaminase; CK: Creatine Kinase; LDL: Low-Density Lipoprotein; RCTs: Randomized Controlled Trials; MBS: Most Bothersome Symptom; UDS: Unidose.

Croop et al. (2022) conducted a Phase 2/3 double-blind, randomized, placebo-controlled, dose-ranging trial to evaluate the efficacy and safety of Zavegepant nasal spray for the acute treatment of migraine [13]. The study included 1673 participants who had a history of migraines with or without aura consistent with the 3rd Edition of the International Classification of Headache Disorders. Participants were randomly assigned to receive a single intranasal dose of Zavegepant at 5 mg, 10 mg, or 20 mg using the Aptar Unidose (UDS) liquid spray device, or a placebo. The primary outcomes assessed were the percentage of participants with freedom from pain and from the most bothersome symptom (MBS) at 2 hours post-dose. The study found that

Zavegepant at 10 mg and 20 mg dosage was more effective than placebo for pain freedom (15.5% and 22.5%, respectively) and MBS (33.7% and 42.5%) at 2 hours post-dose ($P < 0.05$). The findings for the 5 mg dose were insignificant. The study also reported the adverse events (AEs) associated with Zavegepant nasal spray. Treatment-emergent AEs were mostly mild or moderate, and the most common were nausea (2.6-4.1%), nasal discomfort (1.3-5.2%), and dysgeusia (13.5-16.1%). No hepatotoxic effects were observed. Overall, the study suggests that Zavegepant nasal spray may be an effective treatment option for acute migraine.

Lipton et al. (2023) conducted a Phase 3, double-blind, randomized, placebo-controlled multicenter trial to evaluate the safety, tolerability, and efficacy of Zavegepant nasal spray for the acute treatment of migraine in the United States [14]. The study included 1405 male and female adults (≥ 18 years old) who had at least a one-year history of migraines with or without aura consistent with the 3rd edition of the International Classification of Headache Disorders. Participants were randomly assigned to receive a single intranasal dose of Zavegepant 10 mg using the Aptar UDS liquid spray device on the occurrence of migraine with moderate or severe intensity or a placebo. The primary outcome assessed was the percentage of participants with freedom from pain and from the most bothersome symptom (MBS) at 2 hours post-dose. The study found that Zavegepant compared to the placebo group depicted pain freedom at a 24% rate versus 15%, respectively ($P < 0.0001$); freedom from MBS was 40% vs. 31%, respectively ($P = 0.0012$). The most common adverse events (AEs) were for dysgeusia (21%), nasal discomfort (4%), and nausea (3%). Overall, the study suggests that Zavegepant nasal spray at a 10 mg dose is a safe and effective treatment option for acute migraine in the United States. The study's strengths include its large sample size and randomized, placebo-controlled design. However, the study was limited by its short follow-up period and lack of long-term safety data.

In an open-label safety trial, BHV-3500 (Zavegepant) was evaluated for its long-term safety and efficacy for the acute treatment of migraine attacks that have been present for over one year. The study included adult participants who experienced 2-8 moderate to severe migraines per month, lasting between 4-72 hours. Participants were given a maximum of 8 intranasal doses of Zavegepant (10 mg) per month, for up to one year. The primary outcomes assessed in the study were the number of participants with adverse events (AEs), severe AEs, and clinically significant laboratory abnormalities immediately and 52 weeks post-treatment. The study included 603 participants. The study found that laboratory abnormalities were seen as changes in LDL (N=15), CK (N=13), AST, and ALT (N=8). However, no mortality was reported for any cause. A large majority of participants reported AEs (N=460), but only seven experienced serious AEs. Furthermore, 41 participants withdrew from the study due to AEs. Overall, the study suggests that Zavegepant (10 mg) may be a safe and well-tolerated treatment option for the acute treatment of migraine attacks over an extended period. The study's strengths include its long-term follow-up period and the evaluation of clinically significant laboratory abnormalities. However, the study was limited by its lack of a control group and the potential for bias due to the open-label design.

Discussion

This systematic review aimed to provide a comprehensive analysis of the available evidence on the use of Zavegepant nasal spray for the treatment of acute migraine. We included three clinical trials, two RCTs, and one open-label trial with a total of 3681 participants, in phase 2/3 of testing. The inclusion criteria broadly comprised over one-year histories of migraines with or without aura, in line with the third edition of the International Classification of Headache Disorder. The review found that Zavegepant nasal spray may be an effective and safe treatment option for acute migraine attacks.

The RCT by Croop et al. (2022) found that Zavegepant at 10 mg and 20 mg doses were more effective than placebo for pain freedom and most bothersome symptom relief at 2 hours post-dose, while the 5 mg dose was insignificant. The adverse events associated with Zavegepant nasal spray were mostly mild or moderate, with no hepatotoxic effects observed [13]. Similarly, the RCT by Lipton et al. (2023) found that Zavegepant at a 10 mg dose was a safe and effective treatment option for acute migraine in the United States, with dysgeusia, nasal discomfort, and nausea being the most common adverse events [14]. The long-term safety trial of BHV-3500 (Zavegepant) found that it may be a safe and well-tolerated treatment option for the acute treatment of migraine attacks over an extended period [15]. The study included a long follow-up period and evaluated clinically significant laboratory abnormalities. However, the lack of a control group and the open-label design limited the study's validity.

The use of nasal spray Zavegepant has been shown to provide effective pain relief and most bothersome symptom relief for patients experiencing acute migraine attacks. Clinical trials have demonstrated the safety and efficacy of Zavegepant, particularly at the 10 mg and 20 mg doses, which are more effective than a placebo. Furthermore, Zavegepant is well-tolerated, with treatment-emergent adverse events being mostly mild or moderate. The benefits of Zavegepant in the acute treatment of migraine attacks are particularly noteworthy given the limitations and drawbacks of current treatment guidelines. For example, the use of triptans, a commonly prescribed medication for acute migraine attacks, is limited by the occurrence of cardiovascular events in certain patients [16, 17]. Additionally, triptans are contraindicated in patients with uncontrolled hypertension and those with a history of stroke or ischemic heart disease [18, 19]. On the other hand, NSAIDs are not effective in all patients and can have adverse gastrointestinal effects, particularly in the long term [20, 21].

Zavegepant nasal spray, however, is effective and well-tolerated and it does not have the same cardiovascular contraindications as triptans [22, 23]. While more research is needed to confirm the long-term safety and efficacy of Zavegepant, the current evidence suggests that it may be a valuable addition to current treatment guidelines for acute migraine. Overall, the use of Zavegepant nasal spray offers a promising treatment option for patients experiencing acute migraine attacks. Given the burden of migraine on individuals and society, the development of new and effective treatment options like Zavegepant is a notable development that can help improve patient outcomes and quality of life [24, 25].

It ought to be stated that the studies included in this systematic review had some limitations. The sample sizes of the studies were relatively small, and the follow-up periods were short. Additionally, the open-label trial lacked a control group, which may have introduced bias into the results. Despite these limitations, the results of this systematic review provide valuable insights into the potential use of Zavegepant nasal spray for the treatment of acute migraine. The targeting of the CGRP receptor with Zavegepant represents a novel and promising approach to the treatment of migraine, and the results of the included studies suggest that Zavegepant nasal spray may offer a safe and effective treatment option for patients with acute migraine.

Further research is needed to confirm the safety and efficacy of Zavegepant nasal spray for the treatment of acute migraine [26]. Future studies should be designed with larger sample sizes, longer follow-up periods, and appropriate control groups to provide more robust evidence of the effectiveness of Zavegepant nasal spray. Additionally, studies evaluating the comparative effectiveness of Zavegepant nasal spray to existing treatments for acute migraine would be valuable to help inform treatment decisions.

Conclusion

In conclusion, this systematic review provides evidence for the safety and efficacy of Zavegepant nasal spray as a treatment option for acute migraine attacks. The trials included in this review demonstrated that Zavegepant is effective in providing pain relief and most bothersome symptom relief for patients with a history of migraines, particularly at the 10 mg and 20 mg doses. The adverse events associated with Zavegepant were mostly mild or moderate, indicating that it is well-tolerated. The results of this review suggest that Zavegepant nasal spray may offer a promising treatment option for patients with acute migraines, particularly in cases where current treatment guidelines are not effective or are contraindicated. However, further research is needed to confirm the long-term safety and efficacy of Zavegepant, as well as to explore potential benefits and drawbacks in comparison to other treatments for acute migraine.

Future primary research in this area should focus on the long-term safety and efficacy of Zavegepant, particularly concerning its potential to replace or augment existing treatments for acute migraine. Additionally, further research could investigate the optimal dosing and administration of Zavegepant, as well as its effectiveness and safety in different populations, such as pregnant women and elderly patients. Secondary research could explore the cost-effectiveness of Zavegepant compared to current treatment options, as well as patient satisfaction and quality of life outcomes. Furthermore, additional research is needed to investigate the potential long-term effects of Zavegepant on overall migraine burden and frequency of attacks. Overall, the findings of this systematic review suggest that Zavegepant nasal spray has the potential to be a valuable addition to current treatment guidelines for acute migraine attacks. Further research is needed to confirm its safety and efficacy, as well as to explore potential benefits and drawbacks in comparison to existing treatments.

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