The Journal of Headache and Pain

REVIEW

Open Access

The efficacy and safety of zavegepant nasal inhalation versus oral calcitonin-gene related peptide receptor antagonists in the acute treatment of migraine: a systematic review and network meta-analysis of the literature

Zixiang Zhu[1,2†], Yanbing Tang[1,2†], Longyuan Li[2†], Hanyu Ni[1,2], Meirong Liu[2*], Zhouqing Chen[2*] and Zhong Wang[2*]

Abstract

Background The latest randomized controlled trial (RCT) revealed that zavegepant, a new nasal inhalation calcitonin gene-related peptide (CGRP) receptor antagonist, has a clear efficacy in the acute treatment of migraine. However, whether the efficacy of this new nasal inhalation drug is better than other oral CGRP receptor antagonists remained to be confirmed. Therefore, we designed this network meta-analysis (NMA) to provide a reference for the clinical application of zavegepant.

Methods We systematically searched PubMed, EMBASE, The Cochrane Register of Controlled Trials, Scopus, and Web of Science up to December 1, 2024. RCTs using CGRP receptor antagonists (excluding non-randomized, non-English or no extractable data trials) to treat adult patients suffering from acute migraine were included. STATA 18.0 and R STUDIO were used for the statistical analysis.

Results A total of 15 randomized clinical trials with 11,179 patients were included. Compared with the placebo, zavegepant 10 mg demonstrated a significantly higher efficiency for pain freedom at 2 h (relative risk (RR) = 1.54, 95% CI: 1.28–1.82, $I^2 = 0.0\%$, $P < 0.001$) and most bothersome symptom (MBS) freedom at 2 h (RR = 1.26, 95% CI: 1.13–1.42, $I^2 = 0.0\%$, $P < 0.001$), but did not show significant superiority over oral CGRP receptor antagonists. In terms of safety, zavegepant 10 mg was significantly inferior to placebo but not inferior to oral CGRP receptor antagonists.

Conclusion Zavegepant 10 mg can quickly relieve symptoms and has no significant difference in safety compared with oral drugs, which can provide rapid and safe efficacy in the acute treatment of migraine. However, compared

†Zixiang Zhu, Yanbing Tang and Longyuan Li contributed equally to this work.

*Correspondence:
Meirong Liu
meizai26@163.com
Zhouqing Chen
zqchen6@163.com
Zhong Wang
wangzhong761@163.com
Full list of author information is available at the end of the article

with other oral CGRP receptor antagonists, zavegepant 10 mg by nasal inhalation has no obvious advantage in long-term symptom relief rate.

Keywords Migraine, Zavegepant, CGRP receptor antagonists, Acute treatment of migraine

Introduction

Migraine is a neurological disorder characterized by headache-related features and symptoms, such as recurrent unilateral or bilateral throbbing headache, which may be preceded by visual and somatosensory aura, with or without vomiting [1, 2]. Previous studies showed migraine was the second largest contributor to years lived with disability among neurological disorders [3], affecting an estimated one billion people worldwide [4]. The impact of migraine on patients is enormous, ranging from a loss of concentration to loss of labor [5]. Repeated headache attacks can affect the patient's mental health, which may lead to patients' irritability, anxiety and even depression [6].

Medications are often used as an acute treatment during migraine attacks [7], and triptans, agonists targeting 5-HT receptors, have already been widely used [8]. Several oral and non-oral triptans have been developed over the past few decades as acute treatments for migraine attacks [9]. Compared with oral therapies, non-oral therapies, such as nasal inhalation, can achieve maximum plasma concentration–time (T-max) earlier, thus achieving early relief of symptoms [10]. However, previous studies have suggested that long-term use of triptans may cause some cardiovascular system damage [11]. Thus, researchers are beginning to focus on other therapies, and calcitonin-gene related peptide (CGRP) receptor antagonists have gained widespread attention in recent years due to their safer properties for patients with cardiovascular disease [12]. The Food and Drug Administration (FDA) has approved several CGRP receptor antagonists to treat migraine [13]. Several previous clinical studies have demonstrated the effectiveness of oral formulations of CGRP receptor antagonists [14–16], but few trials have been done on non-oral drugs.

Zavegepant is the first CGRP receptor antagonist to be used via inhalation [17, 18], and previous clinical studies have reported its properties for rapid relief of migraine attacks [19, 20]. However, current clinical studies only compare the efficacy of zavegepant with placebo, and there is no clear comparison of efficacy and safety with oral CGRP receptor antagonists. We designed this study to evaluate the efficacy and safety of zavegepant and tried to use network meta-analysis (NMA) to compare with other oral CGRP receptor antagonists to provide evidence for the clinical application of zavegepant.

Methods

Study protocol

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards of quality [21]. The study has been registered on the website of INPLASY, with the registration number INPLASY202510064 (https://inplasy.com/inplasy-2025-1-0064/). Specific PRISMA checklists of the current meta-analysis are detailed in Supplementary Table 1.

Search strategy

We systematically conducted a search of PubMed, EMBASE, The Cochrane Register of Controlled Trials, Scopus, and Web of Science for eligible studies published up to December 1, 2024. Totally we selected 15 separate randomized controlled trials (RCTs). The following keywords (in the title/abstract) were used: "zavegepant" "CGRP" "calcitonin gene-related peptide" "acute migraine" and "RCT". The detailed search strategy was shown in Supplementary Table 2.

Eligibility criteria

A study was eligible if it met the following criteria: (1) was a RCT; (2) enrolled adult participants diagnosed with migraine; (3) included trials with at least one group evaluating the effect of oral or non-oral CGRP receptor antagonists in the acute treatment of migraine. (3) comparing one of the mentioned interventions with the placebo; (4) providing any accessible information on primary or secondary outcomes. We established the following exclusion criteria: (1) study type: non-randomized, included comment, letter, review, retrospective study, animal experiment, case report, or case series; (2) language: non-English articles; (3) data: no extractable data.

Study selection and data collection

Two authors (ZXZ and YBT) independently examined all entries queried from databases, RCTs, and relevant systematic reviews or meta-analyses, removing duplicates and abstract-only research papers respectively. Then they independently checked the titles and abstracts of all retrieved literature for initial screening, and obtained and screened the full text according to inclusion criteria. Conflicts between the authors were resolved by a third author (LYL). After evaluating the articles, HYN collected data in Table 1, including RCTs,

Table 1 Characteristics of the included studies and outcome events

Study	Publications	Countries	Study design	Centers	regimen	Treatment group (No. of participants)	Female (%)	Mean age (SD) (years)	Outcome Events
Lipton et al 2023 [22]	Lancet Neurol	USA	Randomized controlled trial	90	Zavegepant: 10 mg zavegepant; Control: 10 mg placebo	Zavegepant (*n* = 623) Control (*n* = 646)	Zavegepant: 81 Control: 85	Zavegepant: 40.9(13.19) Control: 40.7(13.46)	a; b; c; d; e; f; g; h; i; j; k
Croop et al 2022 [23]	Headache	USA	Randomized controlled trial	82	Zavegepant: 10 mg zavegepant; Control: 10 mg placebo	Zavegepant (*n* = 391) Control (*n* = 402)	Zavegepant: 85.2 Control: 84.3	Zavegepant: 41.4 (12.9) Control: 39.9 (12.0)	a; b; c; d; e; f; g; h; i; j; k
Cady et al 2022 [24]	The Journal of Headache and Pain	USA; Denmark	Randomized controlled trial	57	Eptinezumab: 100 mg eptinezumab; Control: 100 mg placebo	Eptinezumab (*n* = 238) Control (*n* = 242)	Eptinezumab: 84.9 Control: 83.1	Eptinezumab: 44.9(11.99) Control: 44.1(12.12)	a; b
Hutchinson et al. 2021 [25]	Neurology and Therapy	USA	Randomized controlled trial	188	Ubrogepant: 50 mg ubrogepant Control: 50 mg placebo	Ubrogepant (*n* = 887) Control (*n* = 912)	Ubrogepant: 90.5 Control: 88.7	Ubrogepant: 40.4 (12.1) Control: 41.1 (11.9)	a; b; c; d; e; f; g; h; i; j; k
Dodick et al 2019 [26]	The New England Journal of Medicine	USA	Randomized controlled trial	89	Ubrogepant: 50 mg ubrogepant Control: 50 mg placebo	Ubrogepant (*n* = 466) Control (*n* = 485)	Ubrogepant: 89.7 Control: 88.7	Ubrogepant: 40.1(11.7) Control: 40.9(11.7)	a; b; c; d; e; f; h; i; j; k
Lipton et al 2019 [27]	JAMA	USA	Randomized controlled trial	99	Ubrogepant: 50 mg ubrogepant Control: 50 mg placebo	Ubrogepant (*n* = 488) Control (*n* = 499)	Ubrogepant: 91.0 Control: 88.6	Ubrogepant: 41.2(12.5) Control: 41.7(12.1)	a; b; c; d; e; f; h; i; j; k
Croop et al 2019 [28]	The Lancet	USA	Randomized controlled trial	69	Rimegepant: 75 mg Rimegepant Control: 75 mg placebo	Rimegepant (*n* = 669) Control (*n* = 682)	Rimegepant: 85 Control: 85	Rimegepant: 40.3 (12.1) Control: 40.0 (11.9)	a; b; c; d; e; f; g; h; i; j; k
Lipton et al 2019 [29]	The New England Journal of Medicine	USA	Randomized controlled trial	49	Rimegepant: 75 mg Rimegepant Control: 75 mg placebo	Rimegepant (*n* = 537) Control (*n* = 535)	Rimegepant: 89.2 Control: 88.2	Rimegepant: 40.2 (11.9) Control: 40.9(12.1)	a; b; c; d; e; f; g; h; i; j; k
Voss et al 2016 [30]	Cephalalgia	USA	Randomized controlled trial	55	Ubrogepant: 50 mg ubrogepant Control: 50 mg placebo	Ubrogepant (*n* = 106) Control (*n* = 113)	Ubrogepant: 86.8 Control: 87.6	Ubrogepant: 40.7(12.3) Control: 40.5(11.7)	a; b; c; d; e; f; g; h; i; j; k
Marcus et al 2014 [31]	Cephalalgia	USA	Randomized controlled trial	41	Rimegepant: 75 mg Rimegepant Control: 75 mg placebo	Rimegepant (*n* = 91) Control (*n* = 229)	Rimegepant: 89 Control: 86	Rimegepant: 38.5 (11.87) Control: 37.9 (11.36)	a; b; c; d; e; f; g; h; i; j; k
Hewitt et al 2011 [32]	Cephalalgia	USA	Randomized controlled trial	47	MK-3207: 200 mg MK-3207 Control: 200 mg placebo	MK-3207(*n* = 63) Control (*n* = 140)	MK-3207: 85.7 Control: 89.3	MK-3207: 40.5 (10.7) Control: 42.1 (11.2)	a; c; d; e; j; k
Diener et al 2010 [33]	Cephalalgia	Europe	Randomized controlled trial	47	BI 44370 TA: 400 mg BI 44370 TA Control: 400 mg placebo	BI 44370 TA (*n* = 73) Control (*n* = 70)	BI 44370 TA: 75.3 Control: 87.1	BI 44370 TA: 41.1 (10.0) Control: 38.2 (10.3)	a; c; d; e; f; g; h; i; j

Table 1 (continued)

Study	Publications	Countries	Study design	Centers	regimen	Treatment group (No. of participants)	Female (%)	Mean age (SD) (years)	Outcome Events
Connor et al 2009 [34]	Neurology	USA	Randomized controlled trial	83	Telcagepant: 300 mg telcagepant Control: 300 mg placebo	Telcagepant ($n=371$) Control ($n=365$)	Telcagepant: 86.3 Control: 87.1	Telcagepant: 41.8 (11.6) Control: 41.9 (11.9)	a; c; d; h; i; j; k
Ho et al. 2008 [35]	The Lancet	USA; Europe	Randomized controlled trial	81	Telcagepant: 300 mg telcagepant Control: 300 mg placebo	Telcagepant ($n=354$) Control ($n=348$)	Telcagepant: 85 Control: 84	Telcagepant: 42.6 (11.4) Control: 42.3 (12)	a; c; d; h; i; j; k
Ho et al. 2007 [36]	Neurology	USA	Randomized controlled trial	20	Telcagepant: 300 mg telcagepant Control: 300 mg placebo	Telcagepant ($n=39$) Control ($n=115$)	Telcagepant: 87.2 Control: 90.4	Telcagepant: 40.5(NR) Control: 42.2 (NR)	a; c; d; h; i; j; k

SD Standard deviation (year), *NR* Not report, a: pain freedom at 2 h; b: freedom from the most bothersome symptom(MBS) at 2 h; c: pain relief at 2 h; d: sustained pain freedom from 2 to 24 h; e: sustained pain freedom from 2 to 48 h; f: sustained pain relief from 2 to 24 h; g: sustained pain relief from 2 to 48 h; h: phonophobia freedom at 2 h; i: photophobia freedom at 2 h; j: AEs(adverse events); k: nausea and vomiting

the name of the first author, year of publication, publications, authors' countries, study designs, the number of trial centers, interventions, the number of included patients, sex ratio, patient age, and outcome events.

Risk of bias

Studies were examined for risk of bias plots with Review Manager 5.3 software. The Cochrane Collaboration's consistent criteria for evaluating the risk of bias in RCTs were used, covering selection bias, performance bias, detection bias, attrition bias, reporting bias and other potential bias. The bias criteria were characterized as "low", "high" or "unclear".

Outcome measures

Primary outcomes of efficacy

Pain freedom at 2 **h** The degree of pain was assessed using a dichotomous scale (0 = none, 1 = mild, 2 = moderate, 3 = severe), in which pain freedom was determined as absent pain (0 = none).

Most bothersome symptom (MBS) freedom at 2 **h** The MBS was assessed using a dichotomous scale (0 = absent, 1 = present). MBS freedom was defined as the absence of the associated symptom described by participants as the MBS prior to the onset of medication treatment.

Secondary outcomes of efficacy

Pain relief at 2 hours Pain relief was measured as the percentage of participants who had pain levels of none (0) or mild (1) at 2 h post-dose.

Sustained pain freedom/relief from 2 to 24/48 h Sustained pain freedom/relief from 2 to 24 h and 2 to 48 h was assessed as the percentage of participants without taking rescue medication and maintained pain levels of none (0) or mild (1) during the time interval.

Freedom from phonophobia/photophobia at 2 h Freedom from phonophobia or photophobia at 2 h was determined by the percentage of participants with the absence of phonophobia or photophobia respectively at 2 h post-dose in the subset of participants with corresponding symptoms at the time of medication administration.

Safety outcomes

Safety outcomes refer primarily to adverse events (AEs), including dysgeusia, nausea, and vomiting. The AEs were evaluated by a binary scale (0 = absent, 1 = present).

Statistical analysis

The statistical analysis was performed using STATA 18.0 and R STUDIO (STATA Corp., College Station, Texas, USA) by two authors (ZXZ and YBT). A third author (LYL) solved the disputed data. We estimated and

generated the relative risk (RR) with the 95% confidence interval (CI) with random-effects models for the dichotomous outcomes. The I^2 statistic was used to measure heterogeneity; a value of less than 30% indicates "low heterogeneity," a value between 30 and 50% indicates "moderate heterogeneity," and a value of more than 50% indicates "severe heterogeneity." Sensitivity analysis was used to investigate the stability of the consolidated data. We used a two-tailed test for all analyses, and $P<0.05$ was deemed statistically significant.

Certainty assessment

We assessed the certainty of evidence for each outcome using the semi-automated web tool Certainty of Evidence in Network Meta-Analysis (CINeMA) [37, 38] (available at https://cinema.ispm.unibe.ch/). The tool evaluates six key dimensions: within-study bias (risk of bias), between-study bias (publication or reporting bias), indirectness, imprecision, heterogeneity, and incoherence. Each dimension was classified based on the severity of bias as "no concern" (no downgrading), "some concern" (one level of downgrading), or "major concern" (two levels of downgrading). Ultimately, the evidence for each comparison pair was rated as high, moderate, low, or very low, depending on the degree of downgrading [39].

Results

The study collectively involved a total of 1230 citations from PubMed ($n=534$), Embase ($n=438$), The Cochrane Register of Controlled Trials ($n=530$), Scopus (c199), and Web of Science ($n=201$). We used Endnote 20 to eliminate 1087 duplicate articles and 628 irrelevant articles based on their titles and abstracts. Except for 11 articles that were not retrieved, we then excluded 161 studies with different study types, including 58 reviews, 63 commentaries, 3 case report, 3 non-English articles, 14 retrospective studies, and 20 animal experiments. Finally, 15 studies with 11,179 patients were eligible and included in the final NMA (Table 1). Figure 1 shows the flowchart of the study selection process in detail.

Risk of bias, convergence, and heterogeneity analysis in included studies

The risk of bias of all included RCTs is illustrated in Fig. 2. Overall, articles are categorized with a low risk of allocation concealment bias. However, some articles are marked with a potential risk of random allocation bias because they did not specify whether patients were stratified based on the efficacy of corticosteroid drugs during randomization. Studies by Cady et al. [24] and Marcus et al. [31] are flagged with a high risk of bias in randomization because they did not provide detailed descriptions of their randomization methods. Furthermore, two studies [22, 23] on nasal inhalation formulations are labeled with a high risk of bias in blinding of participants and personnel because authors mentioned the difficulty of achieving double-blinding due to the nature of drug absorption. Additionally, the study by Hewitt et al. [32] is marked with a high risk of bias in incomplete outcome data and an unclear risk in selective reporting (reporting bias) because there were inconsistencies in participant involvement reported in the manuscript without explaining the reasons for exclusion or re-inclusion. Furthermore, the funnel plot demonstrates no potential reasons across different primary studies that could influence the NMA (Supplementary Fig. 1).

The convergence diagnostics for the computational model are presented in Supplement Figs. 3 to 19. Both the trace and density plots presented normal distributions, with all potential scaling factor values constrained to 1. Furthermore, no significant fluctuations were observed, indicating that our NMA has achieved satisfactory and excellent convergence.

In addition, we analysed the heterogeneity of the various results. The results showed low heterogeneity for most comparisons, with the exception of one study by Richard B et al. (NCT03237845) [29] (Supplementary Figs. 2020–28). Overall, the low level of heterogeneity in the comparison of different CGRP receptor antagonists suggests that our NMA results are robust.

Efficacy outcomes

Primary outcomes

Pain freedom at 2 h Based on the NMA, we compared all the included medications with placebo (Fig. 3). In our meta-analysis, a total of 15 RCTs and 7 intervention nodes were included for the outcome of pain freedom at 2 h post-dose (Fig. 3a). Compared with placebo, zavegepant 10 mg was significantly associated with increased pain freedom at 2 h (RR = 1.54, 95% CI: 1.28–1.84, $I^2=0.0\%$, $P<0.001$, Fig. 4a, Supplement Fig. 29a). All oral CGRP receptor antagonists were significantly superior to placebo (Supplement Fig. 32a) and not significantly inferior to zavegepant 10 mg in the primary outcomes of pain freedom at 2 h post-dose (Fig. 4c, Supplement Fig. 30, Supplement Fig. 33a), with telcagepant 300 mg and MK3207 200 mg showing significant advantages over zavegepant 10 mg in terms of pain freedom at 2 h (Fig. 4c, Supplement Fig. 33a). MK3207 100 mg had the highest SUCRA value for pain freedom at 2 h at 0.90, followed by BI_44370_TA 400 mg (SUCRA: 0.74), and telcagepant 300 mg (SUCRA: 0.75) (Supplement Fig. 42a).

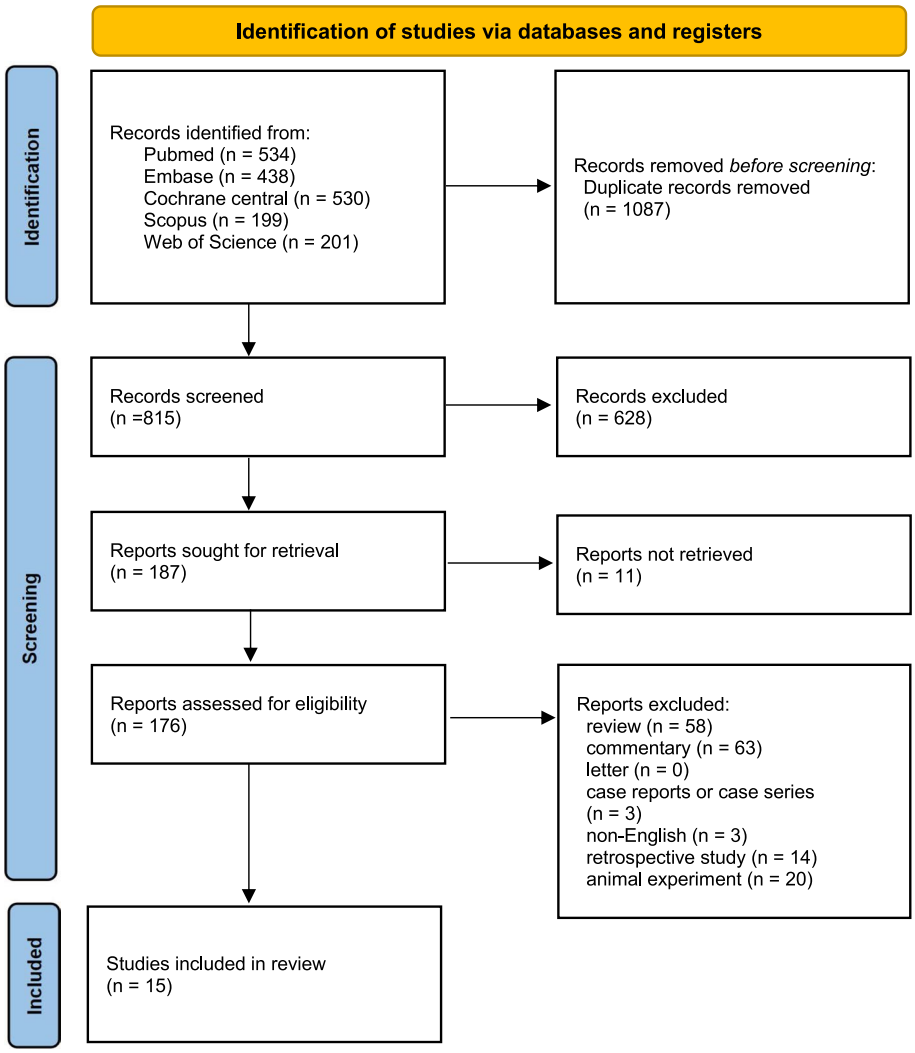

Fig. 1 PRISMA flow diagram of study selection

Most bothersome symptom (MBS) freedom at 2 h The network diagram for the primary outcome of MBS freedom at 2 h contained 10 RCTs and 4 intervention nodes (Fig. 3b). Zavegepant 10 mg showed significant advantages over placebo (RR = 1.26, 95% CI: 1.13–1.42, $I^2 = 0.0\%$, $P < 0.001$, Fig. 4b, Supplement Fig. 29b). Oral CGRP receptor antagonists including eptinezumab 100 mg, ubrogepant 50 mg, and rimegepant 75 mg all were significantly associated with higher RRs versus placebo (Supplement Fig. 32b). Compared with oral CGRP receptor antagonists, zavegepant 10 mg were not significantly superior in this specifc outcome (Fig. 4d, Supplement Fig. 31, Supplement Fig. 33b). Eptinezumab 100 mg had the highest SUCRA value for MBS freedom at 2 h at 0.87, followed by ubrogepant 50 mg (SUCRA: 0.66), and rimegepant 75 mg (SUCRA: 0.62) (Supplement Fig. 42b).

Secondary outcomes

Pain relief at 2 h A total of 14 RCTs and 6 intervention nodes were included for the outcome of pain relief at 2 h post-dose (Fig. 3c).In brief, zavegepant 10 mg showed statistically significant superiority to placebo (RR = 1.16, 95% CI: 1.07–1.25, $I^2 = 0.0\%$, $P < 0.001$ Supplement Fig. 29c). Telcagepant 300 mg, MK3207 200 mg, BI_44370_TA 400 mg, ubrogepant 50 mg, rimegepant 75 mg all were significantly more effective than placebo (Supplement Fig. 32c, Supplement Fig. 34). Compared with oral CGRP receptor antagonists, zavegepant 10 mg didn't demonstrate higher RRs (Supplement Fig. 33c). According to Supplement Fig. 43a, BI_44370_TA 400 mg showed the highest SUCRA value for this outcome, followed by MK3207 200 mg and telcagepant 300 mg.

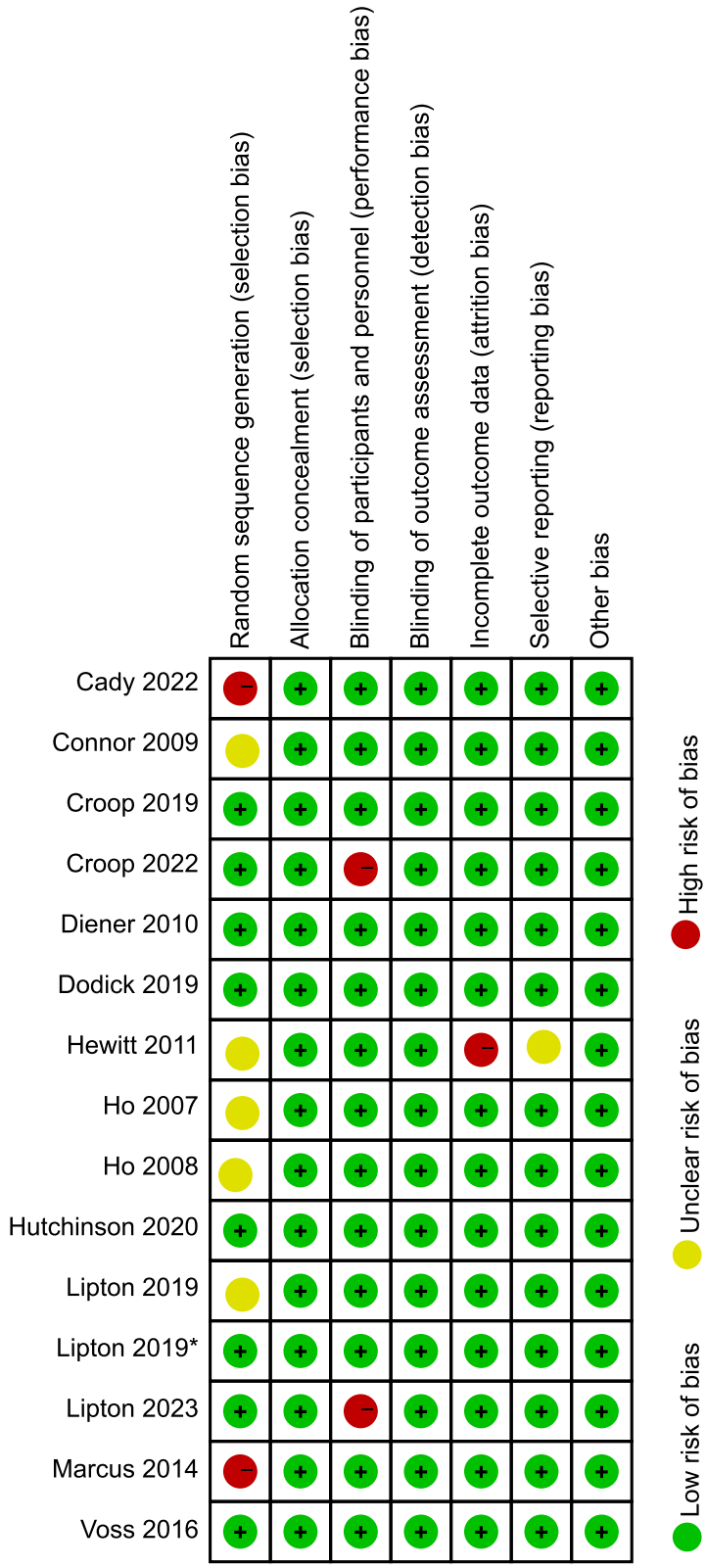

Fig. 2 Risk of bias summary of the included studies

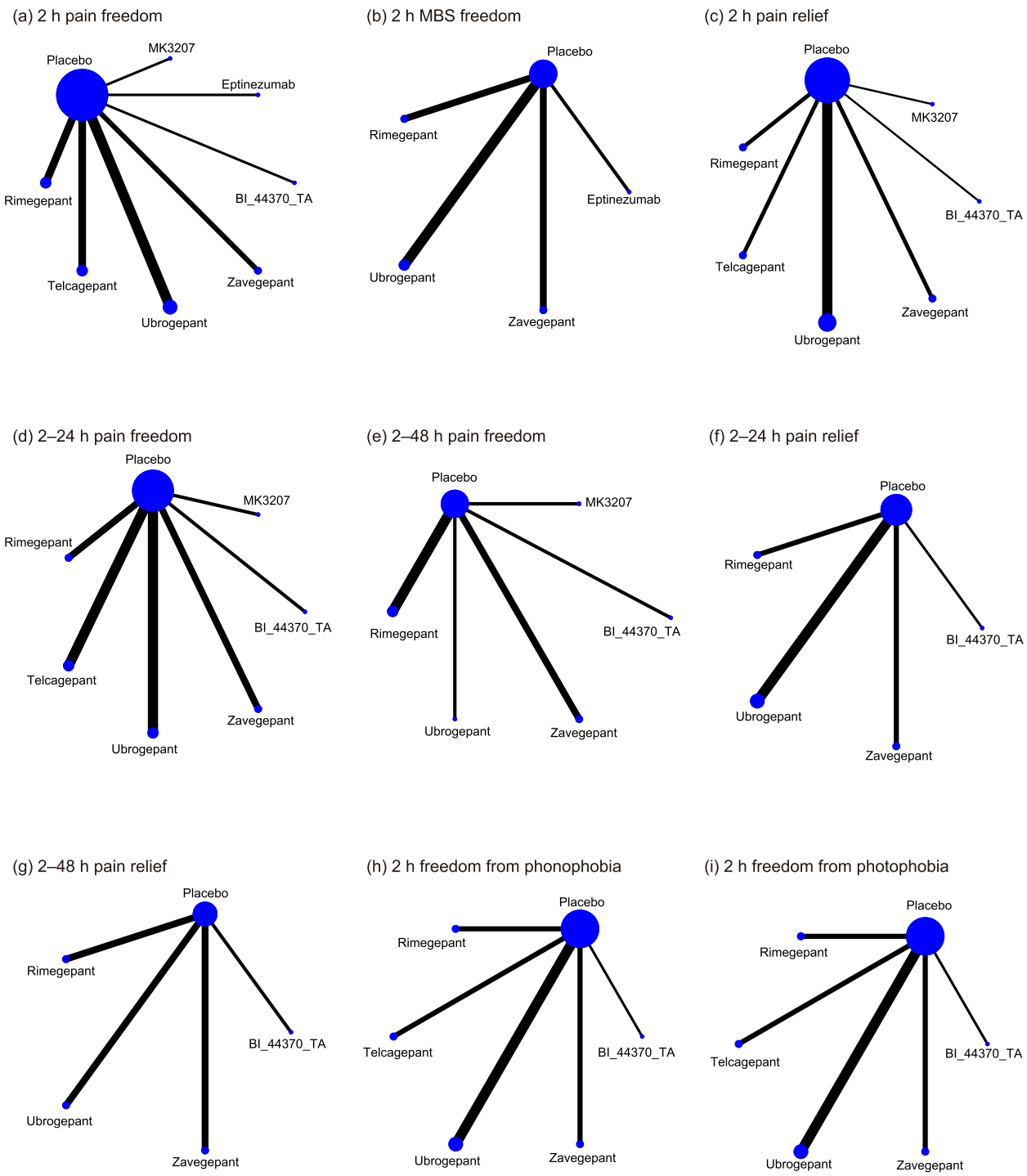

Fig. 3 Network structures of the outcomes. (a-b) Primary outcome: (a) pain freedom at 2 hours. (b) freedom from the most bothersome symptom (MBS) at 2 hours. (c-i) Secondary outcome: (c) pain relief at 2 hours. (d) sustained pain freedom from 2 to 24 hours. (e) sustained pain freedom from 2 to 48 hours. (f) sustained pain relief from 2 to 24 hours. (g) sustained pain relief from 2 to 48 hours. (h) phonophobia freedom at 2 hours. (i) photophobia freedom at 2 hours. The lines between the nodes indicate direct comparisons in different trials. The coarseness of the lines is proportional to the number of trials linked in the network

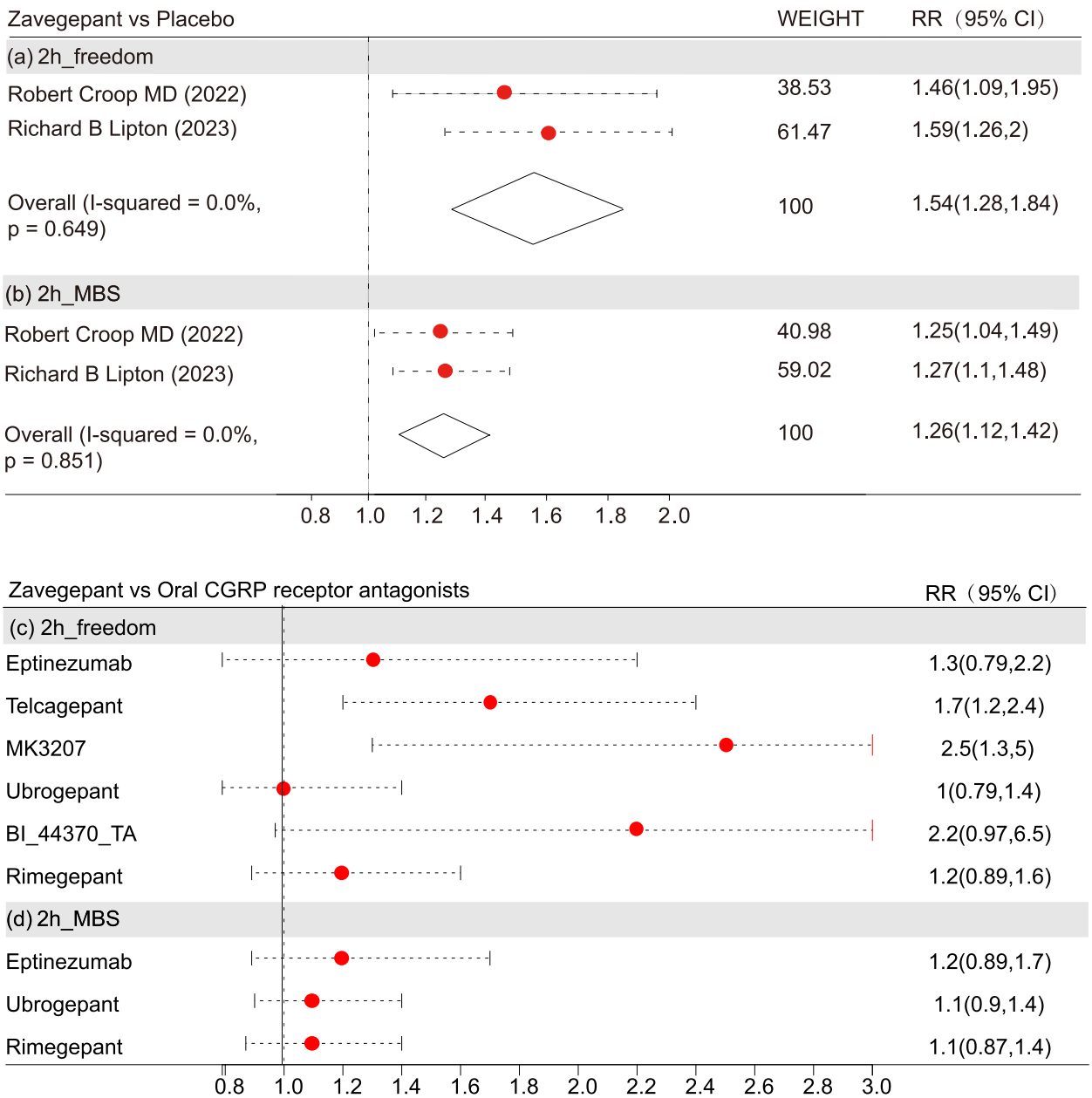

Fig. 4 Forest plots of the primary efficacy outcomes. (a) pain freedom at 2 hours between zavegepant and the placebo. (b) freedom from MBS at 2 hours between the zavegepant and the placebo. (c) pain freedom at 2 hours between the zavegepant and the oral calcitonin gene-related peptide (CGRP) receptor antagonists. (d) freedom from MBS at 2 hours between the zavegepant and the oral CGRP receptor antagonists

Sustained pain freedom from 2 to 24/48 h The network diagram for sustained pain freedom from 2 to 24 h included 14 RCTs and 6 intervention nodes (Fig. 3d), with zavegepant 10 mg demonstrating significant superiority over placebo (RR = 1.56, 95% CI: 1.23–1.99, $P < 0.001$, Supplement Fig. 29d). All treatments, except BI_44370_TA 400 mg with a null CI (0.99 to 8.90) (Supplement Fig. 32d, Supplement Fig. 35), showed statistically significant improvements compared to placebo. SUCRA results ranked MK3207 200 mg, telcagepant 300 mg, and rimegepant 75 mg as the top three treatments (Supplement Fig. 43b). For sustained pain freedom from 2 to 48 h, 11 RCTs and 5 intervention nodes were analyzed (Fig. 3e). Zavegepant 10 mg showed significant superiority (RR = 1.57, 95% CI: 1.21–2.04, P = 0.001, Supplement Fig. 29e), with MK3207 200 mg and rimegepant 75 mg also outperforming placebo. However, BI_44370_TA 400 mg and ubrogepant 50 mg did not show significant

improvements (Supplement Fig. 32e). There were no significant differences between zavegepant 10 mg and other oral CGRP receptor antagonists (Supplement Fig. 33e, Supplement Fig. 36). In SUCRA rankings, MK3207 200 mg had the highest value, followed by ubrogepant 50 mg and BI_44370_TA 400 mg (Supplement Fig. 43c).

Sustained pain relief from 2 to 24/48 h Regarding sustained pain relief, both from 2 to 24 h and from 2 to 48 h, zavegepant 10 mg and oral CGRP receptor antagonists demonstrated significantly greater efficacy compared to placebo (Supplement Fig. 32f, 32 g). For sustained pain relief from 2 to 24 h, data from 10 RCTs and 4 intervention nodes were analyzed (Fig. 3f) showed zavegepant 10 mg had a lower relative risk than other oral CGRP receptor antagonists (Supplement Fig. 33f, Supplement Fig.37). The top three interventions for sustained pain relief from 2 to 24 h were BI_44370_TA 400 mg, ubrogepant 50 mg, and rimegepant 75 mg (Supplement Fig. 43d). For sustained pain relief from 2 to 48 h, 7 RCTs and 4 intervention nodes were considered (Fig. 3g). Except for rimegepant 75 mg, oral CGRP receptor antagonists had a higher relative risk than zavegepant 10 mg (Supplement Fig. 3 g, Supplement Fig. 38). SUCRA rankings indicated BI_44370_TA 400 mg as the most effective treatment, followed by ubrogepant 50 mg and rimegepant 75 mg (Supplement Fig. 43e).

Freedom from phonophobia at 2 h For freedom from phonophobia at 2 h, the network diagram contained 13 RCTs and 5 intervention nodes (Fig. 3h). All pharmaceutical treatments showed higher odds of triggering freedom from photophobia at 2 h compared to placebo, including zavegepant 10 mg, telcagepant 300 mg, BI_44370_TA 400 mg, ubrogepant 50 mg, and rimegepant 75 mg (Supplement Fig. 32 h, Supplement Fig. 39). Among zavegepant 10 mg and these oral CGRP receptor antagonists, there were no statistically significant differences in terms of values of RR (Supplement Fig. 3 h). According to SUCRA, BI_44370_TA 400 mg was correlated with the best treatment, followed by telcagepant 300 mg and rimegepant 75 mg (Supplement Fig. 43f).

Freedom from photophobia at 2 h We incorporated 13 RCTs and 5 intervention nodes into the analysis for this outcome (Fig. 3i). Zavegepant 10 mg was significantly associated with higher rates of photophobia freedom at 2 h post-dose than placebo (RR = 1.25, 95% CI: 1.09–1.42, $P = 0.001$, Supplement Fig. 29i). Equivalently, oral CGRP receptor antagonists (containing telcagepant 300 mg, BI_44370_TA 400 mg, ubrogepant 50 mg, and rimegepant 75 mg) also exhibited statistically significant superiority over placebo (Supplement Fig. 32i, Supplement Fig. 40). The three top-ranked interventions for attaining freedom from photophobia at 2 h included BI_44370_TA 400 mg, telcagepant 300 mg, and rimegepant 75 mg (Supplement Fig. 43 g).

Safety outcomes

As for the safety outcomes, compared with placebo, dysgeusia was the most frequently reported AE in the treatment of zavegepant 10 mg (RR = 4.18, 95% CI: 3.05–5.72, $I^2 = 0.0\%$, $P < 0.001$, Supplement Fig. 41b). In addition, nausea, vomiting, and respiratory symptoms were relatively common in AEs (Supplement Fig. 41). In our NMA, zavegepant 10 mg was not associated with a lower rate of occurrence for any AEs compared with placebo. Furthermore, compared with oral CGRP receptor antagonists for migraine treatment, zavegepant 10 mg could not demonstrate statistically significant superiority in most drug-related AEs, especially nausea, and vomiting (Fig. 5).

Certainty of evidence

The GRADE evidence was detailed in Supplementary Table 3. Regarding the most comparisons, the quality evidence ranged from low to very low, which was mainly attributed to factors included imprecision, heterogeneity, and incoherence.

Discussion

In our systematic review and NMA, a total of 11,179 patients from 15 multicenter, double-blind, randomized clinical trials were pooled. According to the latest International Headache Society Guidelines (2019) (IHSG 2019) [40], we used pain freedom at 2 h and the absence of MBS at 2 h as the primary efficacy outcomes. Our study showed that zavegepant 10 mg was associated with better therapeutic efficacy in both primary outcomes, which could meet the patients' initial expectations to eliminate or relieve pain in the short term. In addition, zavegepant 10 mg was statistically significantly more effective than placebo in the secondary outcomes, including pain relief at 2 h, sustained pain freedom from 2 to 24 h, sustained pain freedom from 2 to 48 h, sustained pain relief from 2 to 24 h, sustained pain relief from 2 to 48 h, freedom from phonophobia at 2 h, and freedom from photophobia at 2 h. Additionally, compared with oral CGRP receptor antagonists, zavegegant 10 mg showed no significant advantages for the primary and secondary outcomes. Furthermore, zavegepant 10 mg was not observed to enhance the rate of any AEs compared to oral CGRP receptor antagonists. On balance, these findings indicate forcefully that zavegepant 10 mg might be an effective and safe therapeutic option for acute migraine in adults.

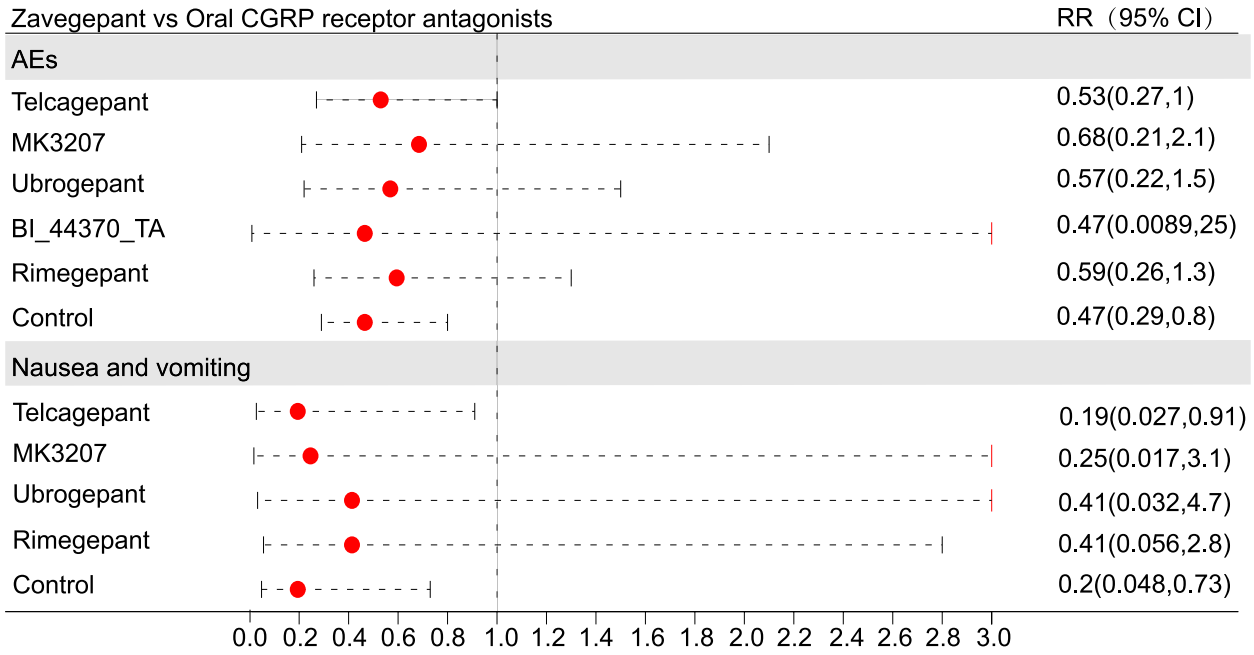

Fig. 5 Forest plot of the safety outcome: adverse events and nausea and vomiting, between zavegepant and the oral CGRP receptor antagonists

CGRP is widely expressed in the central nervous, peripheral, and cardiovascular systems [41]. CGRP promotes neuroinflammatory response and meningeal dural vasodilation, which is one of the critical factors leading to migraine [42]. CGRP receptor antagonists can effectively block the action of CGRP by inhibiting the binding of CGRP receptors, thus alleviating the occurrence and symptoms of migraine [43, 44]. Although triptan is currently the drug of choice in treating acute migraine [45], it still has some drawbacks. The most significant two points are that triptans should not be used in patients with cardiovascular disease or hypertension [46, 47], and that long-term use of triptans can lead to worsening of headache (medication-overuse headache) [48, 49]. The development of CGRP receptor antagonists is expected to avoid the above drawbacks through new therapeutic mechanisms to achieve better therapeutic effects.

Zavegepant, as the first CGRP receptor antagonist for intranasal administration for the acute treatment of migraine, has high affinity and good intranasal bioavailability and has proven its effectiveness in phase II/III clinical trials for the acute treatment of migraine [17]. Regarding the appropriate dose, the statistical results showed that zavegepant 10 mg and 20 mg were both effective in the treatment of acute migraine while zavegepant 10 mg was the optimal therapeutic dose [23]. There have been a few previous studies compared zavegepant with other medications for the treatment of migraine. Li et al. reviewed the efficacy and safety of zavegepant versus other intranasal-administered medications for the acute treatment of migraine. As they found, zavegepant 10 mg nasal spray had a better safety profile, although it may be less effective in pain freedom [50]. In addition, Dos Santos et al. investigated the efficacy of small molecule CGRP receptor antagonists for the prevention treatment of migraine. Since the phase 2/3 clinical trial of zavegepant for migraine prevention is still ongoing, no definitive conclusions are available [51].

To our knowledge, our article is the first NMA to evaluate the efficacy and safety of zavegepant 10 mg nasal spray versus oral CGRP receptor antagonists for the treatment of acute migraine. In the NMA, we selected six oral CGRP receptor antagonists (eptinezumab 100 mg [24], telcagepant 300 mg [34, 35], MK3207 200 mg [32], BI_44370_TA 400 mg [33], ubrogepant 50 mg [25–27, 30], rimegepant 75 mg [28, 29, 31]) to be analyzed with zavegepant 10 mg. Among them, telcagepant, MK3207, and BI_44370_TA [33] were discontinued due to liver toxicity or poor oral availability [9], and eptinezumab was mainly used for preventive treatment [52], which has been shown to be used for the optimization of acute medication effectiveness [24]. Ubrogepant and Rimegepant, as second-generation CGRP receptor antagonists, have received regulatory approval for the acute treatment of migraine in the USA [53]. Our NMA showed no significant advantage for zavegepant 10 mg over other drugs for the primary efficacy outcomes. This may be explained by the fact that during intranasal administration, a larger

portion of the drug is deposited in the anterior nasal cavity, after which it may be expelled from the nose. Only a limited portion penetrates into the bloodstream through the vascular mucosa in the posterior nasal cavity, resulting in a large deviation of the actual drug absorption from the theoretical value [54–58]. This deviation would not occur with oral administration, which may be an important factor in the lack of advantage of zavegepant over oral CGRP receptor antagonists.

In terms of safety, based on our NMA, zavegepant 10 mg was not associated with a lower rate of occurrence for any AEs compared with oral CGRP receptor antagonists and placebo, which is probably related to insufficient actual absorption of zavegepant, such that migraine-related symptoms are relieved to a lesser extent. Nausea and vomiting are the common AEs in the treatment of acute migraine [59], which were also more likely to occur in zavegepant treatment. In addition, as an intranasal formulation, zavegepant 10 mg might cause mild or moderate dysgeusia and nasal discomfort during clinical treatment [23]. However, relevant clinical trials have indicated that no serious adverse events were reported in treated participants [22], and most drug-related AEs were minor and resolved without intervention [23]. All in all, the safety profile of zavegepant 10 mg was favorable [22].

Zavegepant as an intranasal agent, has a shorter T-max [60, 61]. In phase III clinical trials (NCT04571060), it is worth mentioning that in the percentage of patients reporting pain relief within the first 2 h after treatment, the percentage of patients reporting pain relief in the zavegepant 10 mg group was higher than that in the placebo group at each measured time point, especially within 15 min [22]. The statistical result showed that zavegepant 10 mg took effect quickly [62]. The reason for this may be the fact zavegepant is administered intranasally, which facilitates rapid absorption via the nasal mucosa, thus achieving maximum plasma concentration in a shorter time [44, 63]. Relevant research results showed that the Tmax of 10 mg zavegepant was about 30 min [22], while oral CGRP receptor antagonists such as ubrogepant and rimegepant Tmax was about 1.5 h [64]. Shorter Tmax may be associated with a faster onset of therapeutic effects [65], which can help patients relieve pain in a short period of time and can be used for clinical emergency analgesia in the future. Moreover, due to the gastrointestinal symptoms that often occur during migraine attacks, including nausea, vomiting and gastroparesis, the absorption of oral CGRP receptor antagonists can be delayed or reduced [2, 66, 67]. Nevertheless, as nasal inhalation drugs are absorbed into the bloodstream through the submucosal blood vessels of the nose [54], the nasal spray is not going through the digestive tract and is not influenced by nausea or vomiting [22]. Our results provide references for clinicians to personalize the clinical management of acute migraine with CGRP receptor antagonists. In particular, zavegepant 10 mg would be a worthwhile option to consider for patients expecting rapid pain relief from migraine symptoms, as well as for patients who frequently suffer from nausea and vomiting leading to difficulty in administering oral medications.

Strengths of this review included the fact that our study was the first NMA to evaluate the efficacy and safety of zavegepant 10 mg nasal spray versus oral CGRP receptor antagonists for the treatment of acute migraine. Our study involved six oral CGRP receptor antagonists, resulting in two primary and seven secondary outcomes of efficacy, together with specific adverse effects. Furthermore, we emphasized the certainty of the evidence by using the CINeMA methodology to assess the level of evidence and presenting tables of results.

There are also some limitations in this study. Firstly, although our study included 15 multicenter randomized clinical trials at low risk of bias, we have to concede that the bound of our study is limited by the fact that all trials were conducted in the USA or Europe, with the conducted subjects predominantly white populations. Furthermore, due to the differences between the evaluation criteria of the RCTs assessing different oral CGRP receptor antagonists, we couldn't get the data on the efficacy of oral drugs in short periods like 15 min and 30 min. For this reason, we were unable to intuitively demonstrate the high efficiency of zavegepant 10 mg that takes effect in a short time. Lastly, the study placed its emphasis on efficacy and safety within hours, offering no information regarding the long-term safety and reliability of treatment response.

Future research could focus on several key areas to further optimize the clinical application of zavegepant 10 mg nasal spray in the acute treatment of migraine. Primarily, given the restricted number of RCTs of zavegepant 10 mg, there is an urgent necessity for additional clinical trials to comprehensively evaluate the safety and efficacy of zavegepant and other therapeutic modalities in the acute treatment of migraine, particularly in the shorter term of 15 min or 30 min. Secondly, since all included trials were conducted in the United States or Europe and were predominantly white, future research should explore racial and regional differences in medication response through diverse multicenter studies. Finally, in view of the low nasal medication absorption due to deposition and clearance [68], future studies would be appropriate to investigate formulation improvements or alternative delivery methods to enhance bioavailability and therapeutic

consistency. Filling these blanks will lead to a more comprehensive understanding of zavegepant.

Conclusion

Our studies suggested that nasal inhalation of zavegepant 10 mg showed significant efficacy compared to placebo. But when compared to other oral CGRP receptor antagonists, there was no significant superiority of zavegepant 10 mg for long-term symptom relief rate, and no significant difference in safety. However, in the acute treatment of migraine, zavegepant 10 mg had rapider and safer efficacy than other oral CGRP receptor antagonists. For patients with acute migraine attacks, zavegepant 10 mg can be effective in a short time to reach pain freedom or relief, which has a favorable clinical prospect.

Abbreviations

AEs	Adverse events
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CINeMA	Certainty of Evidence in Network Meta-Analysis
FDA	Food and Drug Administration
IHSG	International Headache Society Guidelines
MBS	Most bothersome symptom
NMA	Network meta-analysis
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
RR	Relative risk
SUCRA	Surface under the cumulative ranking curve
T-max	Maximum plasma concentration–time

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s10194-025-01984-7.

Supplementary Material 1. Table S1. PRISMA checklist of the current network meta-analysis. Table S2. Search strategies and results. Table S3. GRADE ratings for each network. eFig.1 Funnel plots of the efficacy outcomes. eFig.2 Trace and density of the network meta-analysis: pain freedom at 2 hours. eFig.3 Trace and density of the network meta-analysis: freedom from MBS at 2 hours.. eFig.4 Trace and density of the network meta-analysis: pain relief at 2 hours. eFig.5 Trace and density of the network meta-analysis: sustained pain freedom from 2 to 24 hours. eFig.6 Trace and density of the network meta-analysis: sustained pain freedom from 2 to 48 hours. eFig.7 Trace and density of the network meta-analysis: sustained pain relief from 2 to 24 hours. eFig.8 Trace and density of the network meta-analysis: sustained pain relief from 2 to 48 hours. eFig.9 Trace and density of the network meta-analysis: phonophobia freedom at 2 hours. eFig.10 Trace and density of the network meta-analysis: photophobia freedom at 2 hours. eFig.11 Convergence diagnostic charts of the network meta-analysis: pain freedom at 2 hours. eFig.12 Convergence diagnostic charts of the network meta-analysis: freedom from MBS at 2 hours. eFig.13 Convergence diagnostic charts of the network meta-analysis: pain relief at 2 hours. eFig.14 Convergence diagnostic charts of the network meta-analysis: sustained pain freedom from 2 to 24 hours. eFig.15 Convergence diagnostic charts of the network meta-analysis: sustained pain freedom from 2 to 48 hours. eFig.16 Convergence diagnostic charts of the network meta-analysis: sustained pain relief from 2 to 24 hours. eFig.17 Convergence diagnostic charts of the network meta-analysis: sustained pain relief from 2 to 48 hours. eFig.18 Convergence diagnostic charts of the network meta-analysis: phonophobia freedom at 2 hours. eFig.19 Convergence diagnostic charts of the network meta-analysis: photophobia freedom at 2 hours. eFig.20 Forest plots for the heterogeneity: pain freedom at 2 hours. eFig.21 Forest plots for the heterogeneity: freedom from MBS at 2 hours. eFig.22 Forest plots for the heterogeneity: pain relief at 2 hours. eFig.23 Forest plots for the heterogeneity: sustained pain freedom from 2 to 24 hours. eFig.24 Forest plots for the heterogeneity: sustained pain freedom from 2 to 48 hours. eFig.25 Forest plots for the heterogeneity: sustained pain relief from 2 to 24 hours. eFig.26 Forest plots for the heterogeneity: sustained pain relief from 2 to 48 hours. eFig.27 Forest plots for the heterogeneity: phonophobia freedom at 2 hours. eFig.28 Forest plots for the heterogeneity: photophobia freedom at 2 hours. eFig.29 Forest plots of the efficacy outcomes between zavegepant and the placebo. (a-b) Primary outcome: (a) pain freedom at 2 hours. (b) freedom from the most bothersome symptom (MBS) at 2 hours. (c-i) Secondary outcome: (c) pain relief at 2 hours. (d) sustained pain freedom from 2 to 24 hours. (e) sustained pain freedom from 2 to 4 hours. (f) sustained pain relief from 2 to 24 hours. (g) sustained pain relief from 2 to 4 hours. (h) phonophobia freedom at 2 hours. (i) photophobia freedom at 2 hours. eFig.30 Forest plots of the primary outcome: pain freedom at 2 hours. eFig.31 Forest plots of the primary outcome: freedom from MBS at 2 hours. eFig.32 Forest plots of the efficacy outcomes between the placebo and the CGRP receptor antagonists. eFig.33 Forest plots of the efficacy outcomes between zavegepant and the oral CGRP receptor antagonists. eFig.34 Forest plots of the secondary outcome: pain relief at 2 hours. eFig.35 Forest plots of the secondary outcome: sustained pain freedom from 2 to 24 hours. eFig.36 Forest plots of the secondary outcome: sustained pain freedom from 2 to 48 hours. eFig.37 Forest plots of the secondary outcome: sustained pain relief from 2 to 24 hours. eFig.38 Forest plots of the secondary outcome: sustained pain relief from 2 to 48 hours. eFig.39 Forest plots of the secondary outcome: phonophobia freedom at 2 hours. eFig.40 Forest plots of the secondary outcome: photophobia freedom at 2 hours. eFig.41 Forest plots of the safety outcomes between zavegepant and the placebo. (a) adverse events. (b) dysgeusia. (c) nasal discomfort. (d) nausea. (e) vomiting. eFig.42 The cumulative probability of obtaining a particular rank for the primary outcomes. The higher the surface under the cumulative ranking curve (SUCRA) value, the better the rank of the intervention. (a) pain freedom at 2 hours. (b) freedom from the most bothersome symptom (MBS) at 2 hours. eFig.43 The cumulative probability of obtaining a particular rank for the secondary outcomes. The higher the surface under the cumulative ranking curve (SUCRA) value, the better the rank of the intervention. (a) pain relief at 2 hours. (b) sustained pain freedom from 2 to 24 hours. (c) sustained pain freedom from 2 to 4 hours. (d) sustained pain relief from 2 to 24 hours. (e) sustained pain relief from 2 to 4 hours. (f) phonophobia freedom at 2 hours. (g) photophobia freedom at 2 hours.

Acknowledgements

We appreciate the valuable and constructive suggestions and assistance from our Team of Neurosurgical study.

Authors' contributions

ZXZ, YBT, and LYL were the principal investigator and contributed in writing of the article. ZXZ, LYL, and ZQC designed the study and developed the analysis plan. ZXZ, YBT, and HYN analyzed the data. MRL, ZQC and ZW supervised the project and polished the language. All authors read and approved the final submitted paper.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82171309 and No 82201445).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Present Address: Suzhou Medical College of Soochow University, Jiangsu Province, Suzhou, Jiangsu Province 215002, China. [2]Present Address: Department of Neurosurgery & Brain and Nerve Research Laboratory, The First Affiliated Hospital of Soochow University, Jiangsu Province, 188 Shizi Street, Suzhou 215006, China.

Received: 21 January 2025 Accepted: 22 February 2025
Published online: 10 March 2025

References

1. Ferrari MD et al (2022) Migraine. Nat Rev Dis Primers 8:2. https://doi.org/10.1038/s41572-021-00328-4
2. Silberstein SD (2004) Migraine. Lancet 363:381–391. https://doi.org/10.1016/s0140-6736(04)15440-8
3. GBD 2016 Neurology Collaborators (2019) Global, regional, and national burden of neurological disorders, 1990–2016: a systematic analysis for the global burden of disease study 2016. Lancet Neurol 18:459–480. https://doi.org/10.1016/s1474-4422(18)30499-x
4. Steiner TJ et al (2020) Migraine remains second among the world's causes of disability, and first among young women: findings from GBD2019. J Headache Pain 21:137. https://doi.org/10.1186/s10194-020-01208-0
5. Buse D et al (2012) Headache impact of chronic and episodic migraine: results from the American migraine prevalence and prevention study. Headache 52:3–17. https://doi.org/10.1111/j.1526-4610.2011.02046.x
6. Leonardi M, Raggi A (2019) A narrative review on the burden of migraine: when the burden is the impact on people's life. J Headache Pain 20:41. https://doi.org/10.1186/s10194-019-0993-0
7. Ashina M et al (2021) Migraine: epidemiology and systems of care. Lancet 397:1485–1495. https://doi.org/10.1016/s0140-6736(20)32160-7
8. Cameron C et al (2015) Triptans in the acute treatment of migraine: a systematic review and network meta-analysis. Headache 55(Suppl 4):221–235. https://doi.org/10.1111/head.12601
9. Yang CP et al (2021) Comparison of new pharmacologic agents with triptans for treatment of migraine: a systematic review and meta-analysis. JAMA Netw Open 4:e2128544. https://doi.org/10.1001/jamanetworkopen.2021.28544
10. Chokshi A et al (2019) Intranasal spray formulation containing rizatriptan benzoate for the treatment of migraine. Int J Pharm 571:118702. https://doi.org/10.1016/j.ijpharm.2019.118702
11. VanderPluym JH et al (2021) Acute treatments for episodic migraine in adults: a systematic review and meta-analysis. JAMA 325:2357–2369. https://doi.org/10.1001/jama.2021.7939
12. de Vries T, Villalón CM, MaassenVanDenBrink A (2020) Pharmacological treatment of migraine: CGRP and 5-HT beyond the triptans. Pharmacol Ther 211:107528. https://doi.org/10.1016/j.pharmthera.2020.107528
13. Bálint L et al (2023) Clinical potential of adrenomedullin signaling in the cardiovascular system. Circ Res 132:1185–1202. https://doi.org/10.1161/circresaha.123.321673
14. Ashina M et al (2021) Efficacy and safety of fremanezumab in patients with episodic and chronic migraine with documented inadequate response to 2 to 4 classes of migraine preventive medications over 6 months of treatment in the phase 3b FOCUS study. J Headache Pain 22:68. https://doi.org/10.1186/s10194-021-01279-7
15. McAllister P et al (2022) Eptinezumab treatment initiated during a migraine attack is associated with meaningful improvement in patient-reported outcome measures: secondary results from the randomized controlled RELIEF study. J Headache Pain 23:22. https://doi.org/10.1186/s10194-021-01376-7
16. Nahas SJ et al (2021) Efficacy and safety of fremanezumab in clinical trial participants aged ≥60 years with episodic or chronic migraine: pooled results from 3 randomized, double-blind, placebo-controlled phase 3 studies. J Headache Pain 22:141. https://doi.org/10.1186/s10194-021-01351-2
17. Mercer SE et al (2021) Azepino-indazoles as calcitonin gene-related peptide (CGRP) receptor antagonists. Bioorg Med Chem Lett 31:127624. https://doi.org/10.1016/j.bmcl.2020.127624
18. Mullin K et al (2024) Long-term safety of zavegepant nasal spray for the acute treatment of migraine: a phase 2/3 open-label study. Cephalalgia 44:3331024241259456. https://doi.org/10.1177/03331024241259456
19. Greco G, Monteith T (2024) Intranasal zavegepant for the acute treatment of migraine. Expert Rev Neurother 24:1131–1140. https://doi.org/10.1080/14737175.2024.2405741
20. Martirosov AL et al (2024) Zavegepant intranasal spray for migraines. Ann Pharmacother 58:827–833. https://doi.org/10.1177/10600280231209439
21. Page MJ et al (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372:n71. https://doi.org/10.1136/bmj.n71
22. Lipton RB et al (2023) 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. Lancet Neurol 22:209–217. https://doi.org/10.1016/s1474-4422(22)00517-8
23. Croop R et al (2022) Zavegepant nasal spray for the acute treatment of migraine: a phase 2/3 double-blind, randomized, placebo-controlled, dose-ranging trial. Headache 62:1153–1163. https://doi.org/10.1111/head.14389
24. Cady R et al (2022) Optimization of acute medication use following eptinezumab initiation during a migraine attack: post hoc analysis of the RELIEF study. J Headache Pain 23:91. https://doi.org/10.1186/s10194-022-01463-3
25. Hutchinson S et al (2021) Ubrogepant for the acute treatment of migraine: pooled efficacy, safety, and tolerability from the ACHIEVE I and ACHIEVE II phase 3 randomized trials. Neurol Ther 10:235–249. https://doi.org/10.1007/s40120-021-00234-7
26. Dodick DW et al (2019) Ubrogepant for the treatment of migraine. N Engl J Med 381:2230–2241. https://doi.org/10.1056/NEJMoa1813049
27. Lipton RB et al (2019) Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: the ACHIEVE II randomized clinical trial. JAMA 322:1887–1898. https://doi.org/10.1001/jama.2019.16711
28. Croop R et al (2019) Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. Lancet 394:737–745. https://doi.org/10.1016/s0140-6736(19)31606-x
29. Lipton RB et al (2019) Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. N Engl J Med 381:142–149. https://doi.org/10.1056/NEJMoa1811090
30. Voss T et al (2016) A phase IIb randomized, double-blind, placebo-controlled trial of ubrogepant for the acute treatment of migraine. Cephalalgia 36:887–898. https://doi.org/10.1177/0333102416653233
31. Marcus R et al (2014) BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. Cephalalgia 34:114–125. https://doi.org/10.1177/0333102413500727
32. Hewitt DJ et al (2011) Randomized controlled trial of the CGRP receptor antagonist MK-3207 in the acute treatment of migraine. Cephalalgia 31:712–722. https://doi.org/10.1177/0333102411398399
33. Diener HC et al (2011) BI 44370 TA, an oral CGRP antagonist for the treatment of acute migraine attacks: results from a phase II study. Cephalalgia 31:573–584. https://doi.org/10.1177/0333102410388435
34. Connor KM et al (2009) Randomized, controlled trial of telcagepant for the acute treatment of migraine. Neurology 73:970–977. https://doi.org/10.1212/WNL.0b013e3181b87942
35. Ho TW et al (2008) Efficacy and tolerability of MK-0974 (telcagepant), a new oral antagonist of calcitonin gene-related peptide receptor, compared with zolmitriptan for acute migraine: a randomised, placebo-controlled, parallel-treatment trial. Lancet 372:2115–2123. https://doi.org/10.1016/s0140-6736(08)61626-8
36. Ho TW et al (2008) Randomized controlled trial of an oral CGRP receptor antagonist MK-0974 in acute treatment of migraine Neurology 70(16) 1304–1312. https://doi.org/10.1212/01.WNL.0000286940.29755.61
37. Nikolakopoulou A et al (2020) CINeMA: an approach for assessing confidence in the results of a network meta-analysis. PLoS Med 17:e1003082. https://doi.org/10.1371/journal.pmed.1003082

38. Papakonstantinou T et al (2020) CINeMA: software for semiautomated assessment of the confidence in the results of network meta-analysis. Campbell Syst Rev 16:e1080. https://doi.org/10.1002/cl2.1080
39. Li X et al (2022) Evidence based social science in China paper 3: the quality of social science RCTs published from 2000–2020. J Clin Epidemiol 141:64–73. https://doi.org/10.1016/j.jclinepi.2021.09.014
40. Diener HC et al (2019) Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition. Cephalalgia 39:687–710. https://doi.org/10.1177/0333102419828967
41. Edvinsson L, Warfvinge K (2019) Recognizing the role of CGRP and CGRP receptors in migraine and its treatment. Cephalalgia 39:366–373. https://doi.org/10.1177/0333102417736900
42. Russo AF, Hay DL (2023) CGRP physiology, pharmacology, and therapeutic targets: migraine and beyond. Physiol Rev 103:1565–1644. https://doi.org/10.1152/physrev.00059.2021
43. Al-Hassany L et al (2022) Calcitonin gene-related peptide-targeting drugs for migraine: how pharmacology might inform treatment decisions. Lancet Neurol 21:284–294. https://doi.org/10.1016/s1474-4422(21)00409-9
44. Boucherie DM et al (2024) Comparison of gepant effects at therapeutic plasma concentrations: connecting pharmacodynamics and pharmacokinetics. J Headache Pain 25:141. https://doi.org/10.1186/s10194-024-01846-8
45. Ashina M (2020) Migraine. N Engl J Med 383:1866–1876. https://doi.org/10.1056/NEJMra1915327
46. Burch R (2024) Acute treatment of migraine. Continuum (Minneap Minn) 30:344–363. https://doi.org/10.1212/con.0000000000001402
47. Goadsby PJ, Lipton RB, Ferrari MD (2002) Migraine–current understanding and treatment. N Engl J Med 346:257–270. https://doi.org/10.1056/NEJMra010917
48. Diener HC et al (2016) Medication-overuse headache: risk factors, pathophysiology and management. Nat Rev Neurol 12:575–583. https://doi.org/10.1038/nrneurol.2016.124
49. Dodick D et al (2004) Consensus statement: cardiovascular safety profile of triptans (5-HT agonists) in the acute treatment of migraine. Headache 44:414–425. https://doi.org/10.1111/j.1526-4610.2004.04078.x
50. Li G et al (2023) Efficacy and safety of intranasal agents for the acute treatment of migraine: a systematic review and network meta-analysis. J Headache Pain 24:129. https://doi.org/10.1186/s10194-023-01662-6
51. Dos Santos JBR, da Silva MRR (2022) Small molecule CGRP receptor antagonists for the preventive treatment of migraine: a review. Eur J Pharmacol 922:174902. https://doi.org/10.1016/j.ejphar.2022.174902
52. Dhillon S (2020) Eptinezumab: first approval. Drugs 80:733–739. https://doi.org/10.1007/s40265-020-01300-4
53. Ashina H, Tfelt-Hansen P (2023) Zavegepant for the acute treatment of migraine: look before leaping. Nat Rev Neurol 19:329–330. https://doi.org/10.1038/s41582-023-00803-4
54. Silberstein S (2017) AVP-825: a novel intranasal delivery system for low-dose sumatriptan powder in the treatment of acute migraine. Expert Rev Clin Pharmacol 10:821–832. https://doi.org/10.1080/17512433.2017.1339600
55. Fuseau E et al (2002) Clinical pharmacokinetics of intranasal sumatriptan. Clin Pharmacokinet 41:801–811. https://doi.org/10.2165/00003088-200241110-00002
56. Lipton RB et al (2024) Real-world use of ubrogepant as acute treatment for migraine with an anti-calcitonin gene-related peptide monoclonal antibody: results from COURAGE. Neurol Ther 13:69–83. https://doi.org/10.1007/s40120-023-00556-8
57. Duquesnoy C et al (1998) Comparative clinical pharmacokinetics of single doses of sumatriptan following subcutaneous, oral, rectal and intranasal administration. Eur J Pharm Sci 6:99–104. https://doi.org/10.1016/s0928-0987(97)00073-0
58. Adams AM et al (2022) Real-world effectiveness of ubrogepant for the acute treatment of migraine when used in combination with an anti-calcitonin gene- related peptide monoclonal antibody preventive: results from the COURAGE study. Neurol Ther 13:69-83. https://doi.org/10.1007/s40120-023-00556-8
59. Pierce M (2013) Oral triptans and nausea: treatment considerations in migraine. Headache 53(Suppl 1):17–20. https://doi.org/10.1111/head.12110
60. Hughes JH et al (2024) Concentration-QTc and cardiac safety analysis of single and multiple zavegepant nasal spray doses in healthy participants to support approval. CPT Pharmacometrics Syst Pharmacol 13:1044–1054. https://doi.org/10.1002/psp4.13140
61. Sternieri E et al (2005) Pharmacokinetics of sumatriptan in non-respondent and in adverse drug reaction reporting migraine patients. J Headache Pain 6:319–321. https://doi.org/10.1007/s10194-005-0220-z
62. Powell L et al (2025) Reduction of pain and functional disability over time in patients treated with zavegepant: a post-hoc analysis of the BHV3500-301 phase 3 randomized controlled trial. J Headache Pain 26:1. https://doi.org/10.1186/s10194-024-01915-y
63. Schneider NG et al (1996) Clinical pharmacokinetics of nasal nicotine delivery. A review and comparison to other nicotine systems. Clin Pharmacokinet 31:65–80. https://doi.org/10.2165/00003088-199631010-00005
64. Altamura C et al (2022) Gepants - a long way to cure: a narrative review. Neurol Sci 43:5697–5708. https://doi.org/10.1007/s10072-022-06184-8
65. Noor N et al (2022) A comprehensive review of zavegepant as abortive treatment for migraine. Health Psychol Res 10:35506. https://doi.org/10.52965/001c.35506
66. Deng X et al (2024) Comparison of effectiveness and safety of lasmiditan and CGRP-antagonists for the acute treatment of migraine in adults: systematic review and network meta-analysis of randomised trials. J Headache Pain 25:16. https://doi.org/10.1186/s10194-024-01723-4
67. Goadsby PJ, Yates R (2006) Zolmitriptan intranasal: a review of the pharmacokinetics and clinical efficacy. Headache 46:138–149. https://doi.org/10.1111/j.1526-4610.2006.00301.x
68. Bhardwaj R et al (2025) Assessment of pharmacokinetic and pharmacodynamic interactions between zavegepant and sumatriptan: a phase 1, randomized, placebo-controlled study in healthy adults. Headache 65:315–325. https://doi.org/10.1111/head.14853

Publisher's Note