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REVIEW

Safety evaluation of oral calcitonin-gene–related peptide receptor antagonists in patients with acute migraine: a systematic review and meta-analysis

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Abstract
Objective Calcitonin gene-related peptide (CGRP) receptor antagonists have been suggested as novel treatments for acute migraine. This study aimed to use meta-analysis to compare the safety and tolerability of five existing oral CGRP receptor antagonists (BI44370TA, MK-3207, rimegepant, telcagepant, and ubrogepant) with that of a placebo or triptans against acute migraine.
Methods Five prominent databases were searched to identify randomized controlled trials on this topic. The primary safety outcomes of interest were any adverse events (AEs) and treatment-related adverse events (TRAEs), and secondary outcomes were individual events, namely diarrhea, dizziness, dry mouth, fatigue, nausea, paresthesia, somnolence, upper abdominal pain, and vomiting.
Results Fifteen studies met the eligibility criteria and were examined in detail. Although, compared to placebo, oral CGRP receptor antagonists significantly increased the incidence of any AEs (risk ratio [RR] = 1.15; 95% confidence interval [CI] = 1.07–1.23), there was no difference in the incidence of TRAEs (RR = 1.18; 95% CI = 1.00–1.38). Moreover, CGRP receptor antagonists were safer than triptans with respect to primary safety outcomes, such as any AEs (RR = 0.78; 95% CI = 0.63–0.98) and TRAEs (RR = 0.68; 95% CI = 0.58–0.79).
Conclusion Despite oral CGRP receptor antagonists posing a significantly higher risk of AEs when compared to placebo, CGRP receptor antagonists have a favorable safety profile compared to triptans. Our findings inform strategies to enhance safety and tolerability in the treatment of acute migraine.

Keywords Migraine · Calcitonin gene-related peptide receptor antagonists · Meta-analysis · Safety · Triptan

Key points

- Oral CGRP receptor antagonists increase the risk of any adverse events compared to placebo, while no difference was found in the incidence of treatment-related adverse events between oral CGRP receptor antagonists and placebo.
- Oral CGRP receptor antagonists are safer than triptans in terms of any adverse events, treatment-related adverse events, dizziness, dry mouth, fatigue, paresthesia, and somnolence.
- Although the safety profile for ubrogepant is more favorable than that of triptans, more stringent safety monitoring is required in patients treated with 100 mg of ubrogepant.

Nayoung Han and In-hwan Baek contributed equally to this study.

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Introduction

Migraine is a chronic neurological disorder and a leading cause of suffering and disability at national and global levels [1]. It has been reported to have a prevalence rate of up to 15% in the adult population, and is largely concentrated in healthy young and middle-aged people, particularly women [2]. It is characterized by episodic and severe headaches associated with nausea, photophobia, and/or phonophobia [3–5]. Migraine remains an important public health problem that is more common and burdensome for women.

Analgesics and triptans (5-hydroxytryptamine$_{1B/1D}$ receptor agonists) are used as standard treatments for acute migraine [6]. Although triptans have been recognized as the current first-line prescribed therapy for acute migraine, their contraindication in an increasing number of patients with co-existing cardiovascular diseases is a major concern [7]. Triptans are

not always appropriate for management of acute migraine, they have a high incidence of adverse events (AEs), and more tolerable treatment is sometimes needed.

Calcitonin gene-related peptide (CGRP) receptor antagonists, also called gepants, are emerging as promising, new agents for the management of acute migraine [6]. To the best of our knowledge, five oral CGRP receptor antagonists (BI44370TA, MK-3207, rimegepant, telcagepant, and ubrogepant) have been studied. Ubrogepant (MK-1602) and rimegepant (BMS-927711; BHV-3000) were approved for the treatment of acute migraine by the Food and Drug Administration (FDA) in December 2019 and February 2020, respectively [8]. While rimegepant and atogepant were approved for the prevention of migraine by the FDA in 2021 [9].

Several randomized controlled trials (RCTs) have been undertaken to examine the clinical efficacy and/or safety of individual oral CGRP receptor antagonists. Based on these studies, a number of systematic reviews and meta-analyses of the efficacy and/or safety of oral CGRP receptor antagonists have been performed. To date, 13 meta-analyses have been published to assess the comparative efficacy and/or safety of oral CGRP receptor antagonists versus placebo or triptans in acute migraine treatment [10–22]. A previous meta-analysis demonstrated that oral CGRP receptor antagonists are more effective than placebo, but less effective than triptans against acute migraine [19]. With regard to safety, the incidence of AEs, such as nausea, somnolence, and dry mouth, have partially been reported in association with rimegepant, telcagepant, and ubrogepant [23–25]. However, the safety and tolerability of oral CGRP receptor antagonists has not been sufficiently compared with placebo or triptans. Although five meta-analyses have examined the safety of individual CGRP receptor antagonists, these have considered only one or two agents at a time, with none examining safety and tolerability across all available treatments. Furthermore, previous studies have not considered safety and tolerability data that has been reported very recently on the FDA-approved oral CGRP receptor antagonists, rimegepant and ubrogepant.

The aim of this study was to compare the safety and tolerability of all five oral CGRP receptor antagonists with that of a placebo and triptans against acute migraine. We considered all existing RCTs on five oral CGRP receptor antagonists (BI44370TA, MK-3207, rimegepant, telcagepant, and ubrogepant). In this comparative study, the primary outcomes of interest were AEs and treatment-related adverse events (TRAEs), and secondary outcomes were individual events, namely diarrhea, dizziness, dry mouth, fatigue, nausea, paresthesia, somnolence, upper abdominal pain, and vomiting. In addition, the clinical safety of each ubrogepant dose group (1, 10, 25, 50, and 100 mg) was compared with that of placebo.

Methods

Literature search

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature search was conducted to identify RCT that compared the clinical safety and tolerability of the aforementioned oral CGRP receptor antagonists to placebo or triptans in acute migraine treatment using the following databases: PubMed, Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform (WHO-ICTRP). Databases were searched from inception to August 20, 2021. The search query is presented in Supplemental Table S1.

Inclusion and exclusion criteria

Two independent investigators screened the studies identified and made decisions on their eligibility for inclusion in this research. Based on the PICO (participants, intervention, comparison, outcomes) framework, inclusion criteria were as follows: (a) adult patients aged 18 years or older, (b) patients diagnosed with migraine with or without aura, as defined by the International Headache Society criteria, (c) treatment intervention for acute migraine, and (d) comparisons of safety, tolerability, or AEs of oral CGRP receptor antagonist to placebo or triptan. A study was excluded if it was (a) for preventive treatment of migraine, (b) a phase I or open-label trial, (c) a clinical trial with incomplete or withdrawn data, (d) a clinical trial with no placebo or control group, and (e) a clinical trial with no results. Any disagreement between investigators on the eligibility of a study was resolved by discussion and, in cases of continued disagreement, by consulting a third party. The search strategy was used to extract titles and abstracts of relevant studies published in English, with no restrictions on publication dates. Duplicate records were removed following a review of the titles and abstracts, and full texts of the selected articles were then retrieved for further examination. Identified citations were tabulated in a Microsoft Excel 2019 spreadsheet, and full-text articles were retrieved. All articles were appraised for inclusion according to the pre-specified inclusion/exclusion criterion. The final set of articles qualified for meta-analysis were then subjected to quality scoring and data extraction by the primary investigators. A PRISMA flow chart was constructed to visually describe the selection process (Fig. 1).

Data extraction and risk of bias assessment

A standardized data extraction form was designed based on the Cochrane Handbook for Systematic Reviews of Interventions.

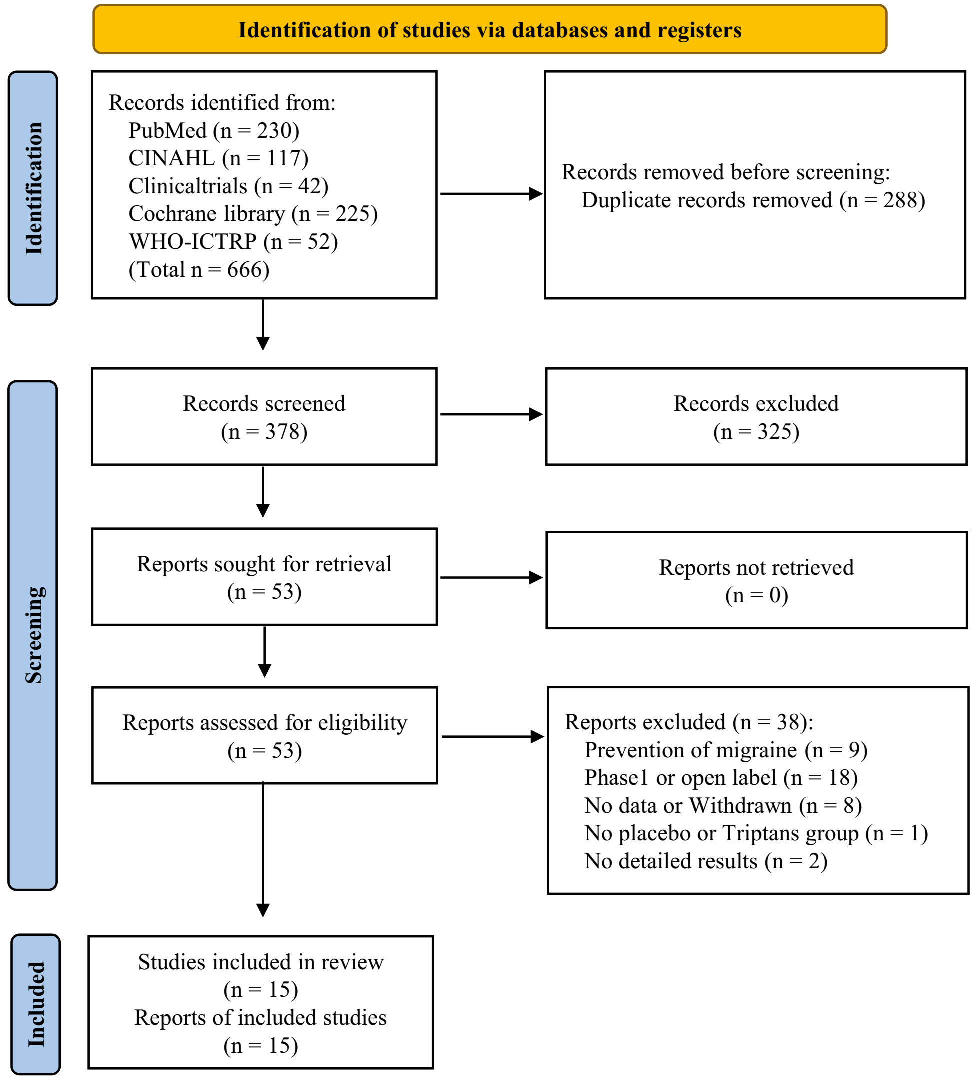


Fig. 1 Flow diagram of search strategy and study selection based on PRISMA

Information on patient demographics, study design, oral CGRP receptor antagonists used, type of comparator (placebo and/or triptans), and safety outcome measures was extracted for each study. Primary safety outcomes were AEs and TRAEs. Secondary safety outcomes were individual events, namely diarrhea, dizziness, dry mouth, fatigue, nausea, paresthesia, somnolence, upper abdominal pain, and vomiting. Data extraction was performed independently by two investigators with a third supervising the process.

Two reviewers independently assessed the risk of bias associated with each included study using the Cochrane Handbook's Risk of Bias assessment tool and resolved disagreements by discussion and further consultation if necessary. Studies were assessed based on the following six methodological aspects: random sequence generation and allocation concealment (to examine selection bias), blinding of participants and personnel (to examine performance bias), blinding of outcome assessment (to examine detection bias), outcome data completeness (to examine attrition bias), extent of selective reporting (to examine reporting bias), and other biases.

Data analysis and statistical assessment

The clinical safety and tolerability of oral CGRP receptor antagonists was compared to placebo across study participants. In addition, the clinical safety and tolerability of oral CGRP receptor antagonists was compared to triptans as active controls across study participants. Furthermore, the clinical safety and tolerability of the FDA-approved oral CGRP receptor antagonists, rimegepant and ubrogepant, was compared to placebo.

All dichotomous data were reported as the risk ratio (RR) with 95% confidence interval (CI), and p values were two-tailed, with statistical significance set at 0.05. The chi-square (χ^2) test was used to assess statistical heterogeneity among studies, including this meta-analysis, and I^2 statistics were used to quantify heterogeneity. A fixed-effects model was applied for all variables with $I^2 < 50\%$, which was defined as significant heterogeneity among the studies; otherwise, a random-effects model was used to calculate the pooled effect values in the presence of significant heterogeneity. All meta-analyses were conducted with Review Manager, version 5.4 (RevMan, The Nordic Cochrane Center, The Cochrane Collaboration, Copenhagen, Denmark), using a two-tailed test of significance ($p < 0.05$). The risk of bias (ROB) tool was used for quality assessment in each study with results plotted using Review Manager 5.4 software.

Results

Study selection

A total of 666 studies were initially identified from electronic databases. After removing 288 duplicates, screening against titles and abstracts excluded 302 references, as the content was unrelated to this review. The full text of the remaining 76 references was evaluated for eligibility, and 61 references were excluded. Finally, a total of 15 studies including 14 full-text publications and one unpublished study (ubrogepant, NCT01657370) were selected for the present meta-analysis [24–38]. Figure 1 presents a flow diagram of the literature search.

Study characteristics and risk of bias assessment

The characteristics of the included studies are summarized in Table 1. The included studies were published between 2007 and 2019. Seven studies were phase II trials, and the remaining eight were phase III trials. There were 13,270 patients involved across the 15 studies: the pooled oral CGRP receptor antagonist group included 8,240 patients, the pooled placebo group included 4,253 patients, and the pooled triptan group included 777 patients. One study examined BI44370TA treatment, one study examined MK-3207 treatment, three studies examined rimegepant treatment, six studies examined telcagepant treatment, and four studies examined ubrogepant treatment. The overall quality of the trials examined was good, and their designs were similar. The risk of bias across the trials is shown in Supplementary Fig. S1. Most studies had a low risk of bias, with one trial having an unclear risk of bias [34].

Oral CGRP receptor antagonists versus placebo

The CGRP receptor antagonist group, consisting of five oral CGRP receptor antagonists (BI44370TA, MK-3207, rimegepant, telcagepant, and ubrogepant), showed a significantly higher risk of any AEs and fatigue, nausea, and somnolence than the placebo group did. There was no significant difference between the oral CGRP receptor antagonists and placebo in the incidence of TRAEs, diarrhea, dizziness, dry mouth, paresthesia, upper abdominal pain, and vomiting.

Primary safety outcomes were reported in 12 studies for any AEs and in 8 studies for TRAEs. The results of any AEs and TRAEs associated with exposure to oral CGRP receptor antagonists versus placebo are presented in Fig. 2. The overall RR of any AEs was 1.15 (95% CI = 1.07–1.23, $p = 0.0001$), and heterogeneity was low ($\chi^2 = 4.99$; $I^2 = 0\%$; $p = 0.93$). The overall RR of TRAEs was 1.18 (95% CI = 1.00–1.38, $p = 0.05$), and heterogeneity was low ($\chi^2 = 5.31$; $I^2 = 0\%$; $p = 0.62$). Funnel plots were generated to assess for publication bias associated with primary safety outcomes when comparing oral CGPR receptor antagonists and placebo groups, but no apparent trend was observed (Supplementary Fig. S2). The result did not change during a sensitivity analysis, after omitting any individual study from the meta-analysis (Supplementary Fig. S3). Of the oral CGRP receptor antagonists, telcagepant was associated with the lowest risk of any AEs occurring (RR = 1.11, 95% CI = 1.02–1.21, $p = 0.02$), whereas MK-3207 was associated with the highest risk of any AEs occurring (RR = 1.41, 95% CI = 0.99–2.03, $p = 0.06$), although MK-3207 results were only informed by a single trial.

The results of secondary safety outcomes (diarrhea, dizziness, dry mouth, fatigue, nausea, paresthesia, somnolence, upper abdominal pain, and vomiting) associated with exposure to oral CGRP receptor antagonists versus placebo are presented in Supplementary Fig. S4. Overall, oral CGRP receptor antagonists were significantly associated with an increased risk of fatigue, nausea, and somnolence. The overall RR of fatigue from 9 studies was 1.52 (95% CI = 1.14–2.03, $p = 0.004$), and heterogeneity was low ($\chi^2 = 4.22$; $I^2 = 0\%$; $p = 0.84$). The overall RR of nausea in 14 studies was 1.27 (95% CI = 1.04–1.56, $p = 0.02$), and heterogeneity was low ($\chi^2 = 12.19$; $I^2 = 0\%$; $p = 0.51$). The overall RR of somnolence from 7 studies consisting of only telcagepant and ubrogepant was 1.59 (95% CI = 1.18–2.16, $p = 0.003$), and heterogeneity was low ($\chi^2 = 7.82$; $I^2 = 23\%$; $p = 0.25$). Funnel plots associated with secondary safety outcomes when comparing oral CGRP receptor antagonists and placebo groups were asymmetrical, indicating the presence of bias due to heterogeneity among the included studies (Supplementary Fig. S5).

Oral CGRP receptor antagonists versus triptans

The CGRP receptor antagonist group, consisting of five oral CGRP receptor antagonists (BI44370TA, MK-3207, rimegepant, telcagepant, and ubrogepant), showed a significantly lower risk of any AEs, TRAEs, dizziness, dry mouth, fatigue,

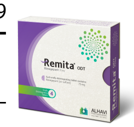


Table 1 Characteristics of studies included in the meta-analysis of oral CGRP antagonists for treatment of acute migraine

Author, year	Intervention		Control		Phase	Safety outcome
	Drug	Dose (mg)	Placebo	Active		
Diener et al. 2010	BI44370TA	50, 200, 400	pc	Eletriptan 40 mg	2	Any AEs, TRAEs Diarrhea, dizziness, fatigue, nausea, vomiting
Hewitt et al. 2011	MK-3207	2.5, 5, 10, 20, 50, 100, 200	pc	None	2	Any AEs, TRAEs Dizziness, dry mouth, fatigue, nausea, vomiting
Croop et al. 2019	Rimegepant	75	pc	None	3	Any AEs, TRAEs Dizziness, nausea
Lipton et al. 2019	Rimegepant	75	pc	None	3	Any AEs Nausea
Marcus et al. 2014	Rimegepant	10, 25, 75 150, 300, 600	pc	Sumatriptan 100 mg	2	Diarrhea, dizziness, nausea, paresthesia, vomiting
Connor et al. 2009	Telcagepant	50, 140 (150), 280 (300)	pc	None	3	Any AEs Dizziness, dry mouth, fatigue, nausea, paresthesia, somnolence, upper abdominal pain, vomiting
Connor et al. 2010	Telcagepant	280 (300)	None	Rizatriptan 10 mg	3	Any AEs, TRAEs Diarrhea, dizziness, dry mouth, fatigue, nausea, paresthesia, somnolence, upper abdominal pain, vomiting
Hewitt et al. 2011	Telcagepant	280 (300)	pc	None	2	Any AEs, TRAEs Dizziness, dry mouth, fatigue, nausea, somnolence
Ho et al. 2008 [NCT00246337]	Telcagepant	25, 50, 100, 200, 280 (300), 400, 600	pc	Rizatriptan 10 mg	2	Any AEs, TRAEs Dizziness, dry mouth, fatigue, nausea, paresthesia, somnolence
Ho et al. 2008 [NCT00442936]	Telcagepant	140 (150), 280 (300)	pc	Zolmitraiptan 5 mg	3	Any AEs Dizziness, dry mouth, fatigue, nausea, paresthesia, somnolence, vomiting
Ho et al. 2010	Telcagepant	140 (150), 280 (300)	pc	None	3	Any AEs Diarrhea, dizziness, dry mouth, fatigue, nausea, somnolence, upper abdominal pain, vomiting
Dodick et al. 2019	Ubrogepant	50, 100	pc	None	3	Any AEs, TRAEs, nausea, somnolence, dry mouth
Lipton et al. 2019	Ubrogepant	25, 50	pc	None	3	TRAEs Dizziness, nausea
Voss et al. 2016	Ubrogepant	1, 10, 25, 50, 100	pc	None	2	Any AEs, TRAEs Dizziness, dry mouth, fatigue, nausea, somnolence
Unknown, 2016[a]	Ubrogepant	1, 10, 25, 50, 100	pc	None	2	Any AEs Diarrhea, dizziness, dry mouth, fatigue, nausea, upper abdominal pain

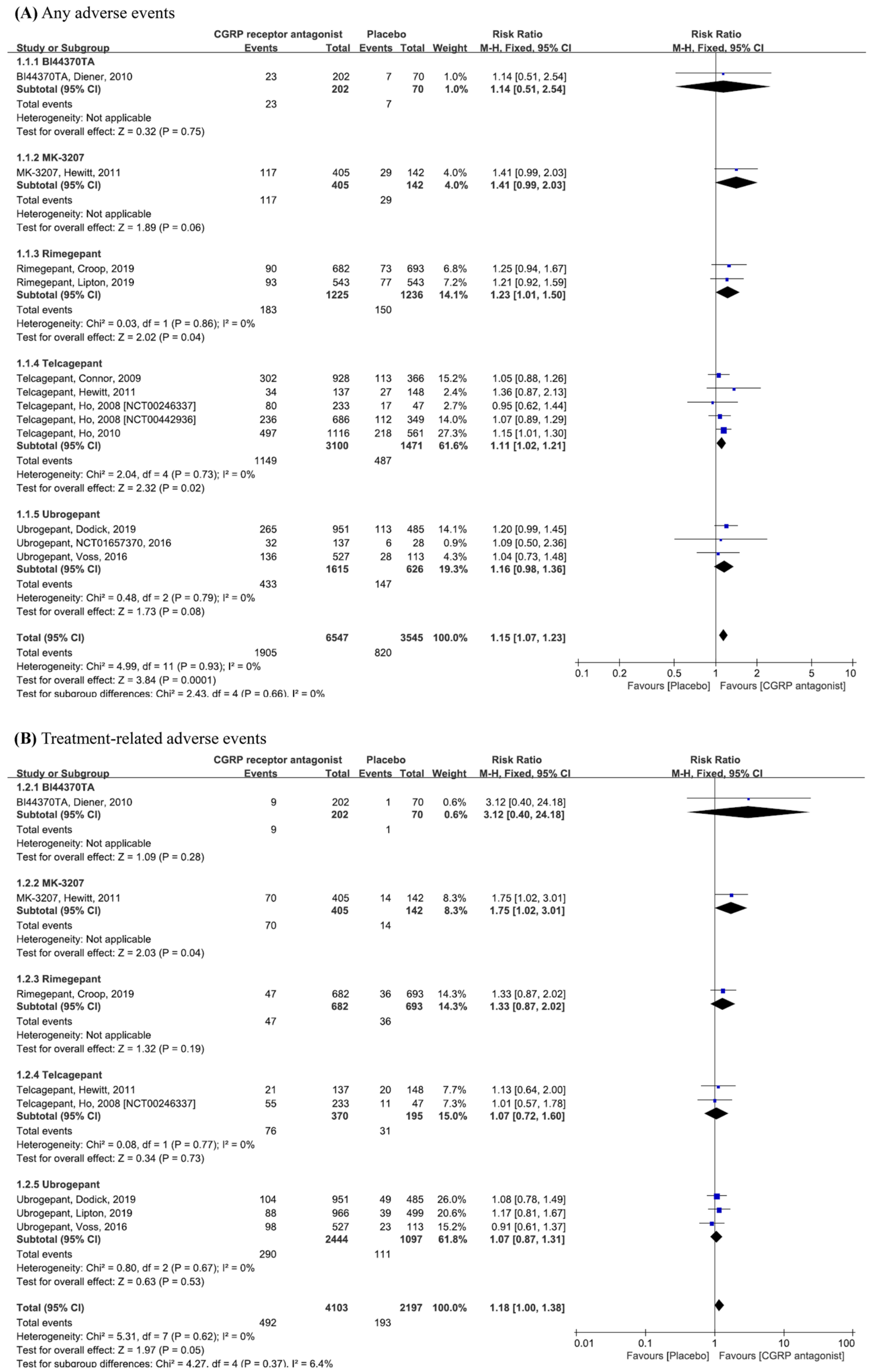
pc placebo, *AEs* adverse events, *TRAEs* treatment-related adverse event

[a]Unpublished study

paresthesia, and somnolence compared to that of the triptan group. There was no significant difference in the incidence of diarrhea, nausea, and vomiting between the oral CGRP receptor antagonists and triptans. No study had compared the incidence of upper abdominal pain between oral CGRP receptor antagonists and triptans.

Primary safety outcomes were reported in four studies (one study for BI44370TA and three studies for telcagepants)

Fig. 2 Forest plots for primary safety outcomes comparing oral CGRP receptor antagonist group and placebo group



for any AEs and in three studies (one study for BI44370TA and two studies for telcagepants) for any TRAEs. The results of any AEs and TRAEs associated with exposure to oral CGRP receptor antagonists versus triptans are presented in Fig. 3. The overall RR of any AEs was 0.78 (95% CI = 0.63–0.98, $p = 0.03$), and heterogeneity was high ($\chi^2 = 11.68$; $I^2 = 74\%$; $p = 0.009$); thus, a random-effects model was used. The overall RR of TRAEs was 0.68 (95% CI = 0.58–0.79, $p < 0.00001$), and heterogeneity was low ($\chi^2 = 1.09$; $I^2 = 0\%$; $p = 0.58$). Although BI44370TA results were only informed by a single trial, BI44370TA (any AEs RR = 0.65, 95% CI = 0.34–1.24, $p = 0.20$; TRAEs RR = 0.51,

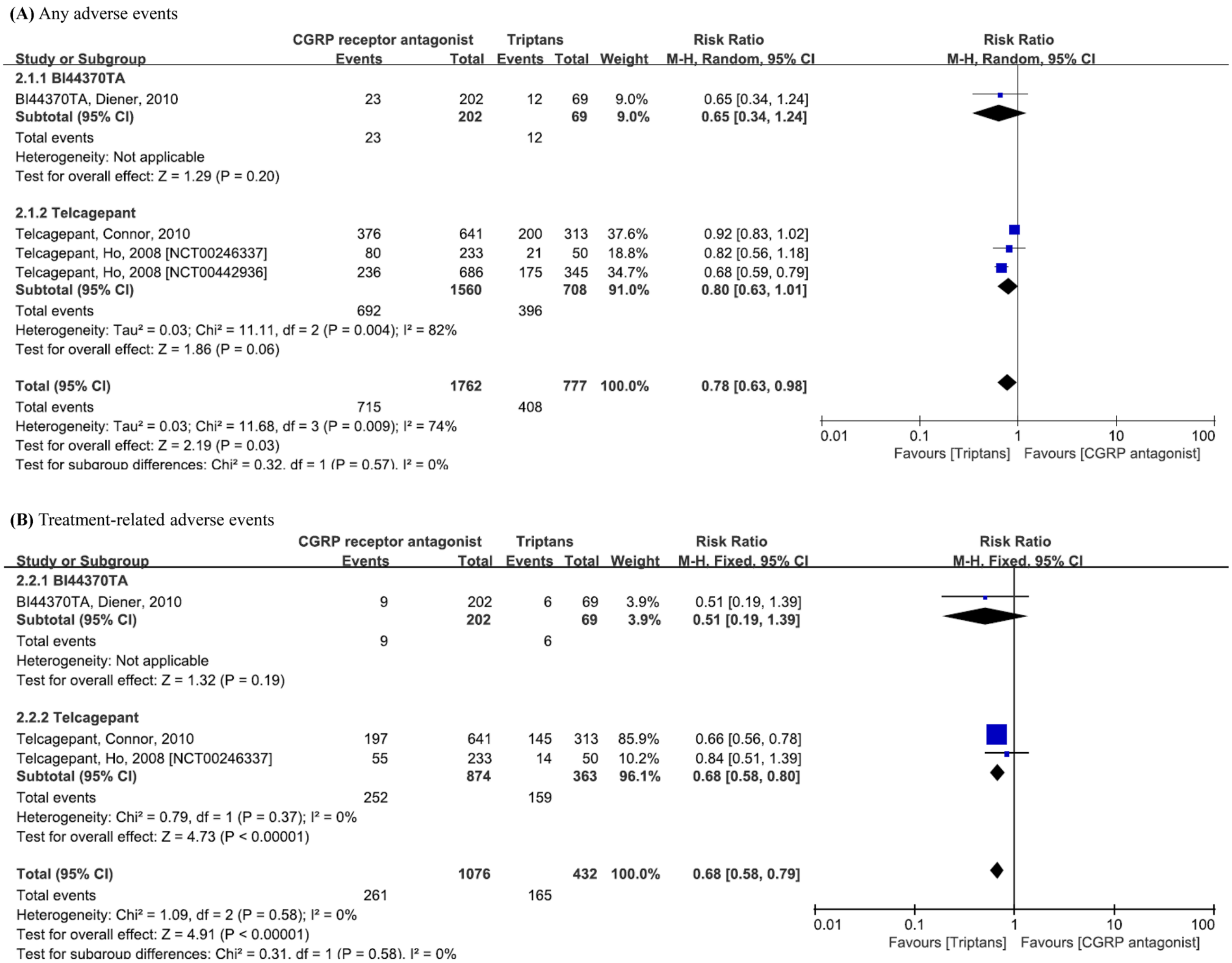


Fig. 3 Forest plots for primary safety outcomes comparing oral CGRP receptor antagonist group and triptan group

95% CI = 0.19–1.39, $p = 0.19$) was associated with a lower risk ratio of both AEs and TRAEs compared to telcagepant (any AEs RR = 0.80, 95% CI = 0.63–1.01, $p = 0.06$; TRAEs RR = 0.68, 95% CI = 0.58–0.80, $p < 0.00001$). Funnel plots associated with primary safety outcomes when comparing oral CGRP receptor antagonists with triptans were almost symmetric and indicated none of the publication bias (Supplementary Fig. S6). The results did not change during a sensitivity analysis, after omitting any individual study from the meta-analysis (Supplementary Figs. S7 and S8).

The results of secondary safety outcomes (diarrhea, dizziness, dry mouth, fatigue, nausea, paresthesia, somnolence, and vomiting) associated with exposure to oral CGRP receptor antagonists versus triptans are presented in Supplementary Fig. S9. Overall, oral CGRP receptor antagonists were significantly associated with a lower risk of dizziness, dry mouth, fatigue, paresthesia, and somnolence. The overall RR of dizziness from 5 studies was 0.69 (95% CI = 0.52–0.92, $p = 0.01$), and heterogeneity was moderate ($\chi^2 = 7.49$; $I^2 = 47\%$; $p = 0.11$). The overall RR of dry mouth from 3 studies consisting of only telcagepant was 0.72 (95% CI = 0.54–0.95, $p = 0.02$), and heterogeneity was low ($\chi^2 = 0.51$; $I^2 = 0\%$; $p = 0.78$). The overall RR of fatigue from 4 studies consisting of BI44370TA and telcagepant was 0.52 (95% CI = 0.37–0.73, $p = 0.001$), and heterogeneity was low ($\chi^2 = 1.55$; $I^2 = 0\%$; $p = 0.67$). The overall RR of paresthesia from 4 studies consisting of rimegepant and telcagepant was 0.34 (95% CI = 0.21–0.56, $p < 0.0001$), and heterogeneity was low ($\chi^2 = 3.64$; $I^2 = 18\%$; $p = 0.30$). The overall RR of somnolence from 3 studies consisting of only telcagepant was 0.65 (95% CI = 0.49–0.87, $p = 0.004$), and heterogeneity was low ($\chi^2 = 2.45$; $I^2 = 18\%$; $p = 0.29$). Funnel plots associated with secondary safety outcomes when comparing oral CGRP receptor antagonists with triptans were generated to assess for publication bias, but no apparent trend was observed (Supplementary Fig. S10).

Subgroup analysis of each ubrogepant dose group versus placebo

In terms of FDA-approved oral CGRP receptor antagonists, all 3 clinical studies for rimegepant were performed after a single dose (75 mg), whereas 4 clinical studies for ubrogepants were performed using different doses ranging from 1 to 100 mg. Therefore, a meta-analysis was conducted using data from four studies to compare any AEs between each ubrogepant dose group and the placebo group. The highest dose (100 mg) of ubrogepant showed a significantly higher risk of AEs compared to that of the placebo group. There was no significant difference between the other dose groups (1, 10, 25, 50 mg) of ubrogepant and placebo in the incidence of AEs.

The overall RR of any AEs for ubrogepant 1 mg from 2 studies was 1.20 (95% CI = 0.81–1.78, $p = 0.36$), and heterogeneity was low ($\chi^2 = 0.15$; $I^2 = 0\%$; $p = 0.69$). The overall RR of any AEs for 10 mg of ubrogepant from 2 studies was 0.96 (95% CI = 0.63–1.46, $p = 0.84$), and heterogeneity was moderate ($\chi^2 = 1.92$; $I^2 = 48\%$; $p = 0.17$). The overall RR of any AEs for ubrogepant 25 mg from 3 studies was 0.98 (95% CI = 0.80–1.20, $p = 0.84$), and heterogeneity was low ($\chi^2 = 1.92$; $I^2 = 0\%$; $p = 0.38$). The overall RR of any AEs for 50 mg of ubrogepant from 4 studies was 1.15 (95% CI = 1.00–1.33, $p = 0.06$), and heterogeneity was low ($\chi^2 = 1.55$; $I^2 = 0\%$; $p = 0.67$). Finally, the overall RR of any AEs for 100 mg of ubrogepant from 3 studies was 1.22 (95% CI = 1.01–1.47, $p = 0.04$), and heterogeneity was low ($\chi^2 = 0.02$; $I^2 = 0\%$; $p = 0.99$) (Fig. 4). Funnel plots associated with any adverse events when comparing ubrogepant (at different doses) with placebo were generated to access for publication bias, but no apparent trend was observed (Supplementary Fig. S11).

Discussions

The present meta-analysis was conducted to compare the clinical safety and tolerability of oral CGRP receptor antagonists and placebo or triptans in the treatment of acute migraine. Pooled data were extracted from 15 RCTs involving five oral CGRP receptor antagonists (BI44370TA, MK-3207, rimegepant, telcagepant, and ubrogepant). Our findings based on the primary outcomes indicate that oral CGRP receptor antagonists increase the risk of any AEs compared to placebo, while no difference was found in the incidence of TRAEs between oral CGRP receptor antagonists and placebo. Analysis of individual events as secondary outcomes demonstrated an increased risk of fatigue, nausea, and somnolence in the oral CGRP receptor antagonist group, but no increase in the rate of other commonly cited adverse events, including diarrhea, dizziness, dry mouth, paresthesia, upper abdominal pain, and vomiting.

Although the pathogenesis of migraine is multifactorial and has not yet been fully elucidated, CGRP is now considered a key element in its pathophysiology [39, 40]. Thus, recently, the focus for a novel target for acute migraine treatment has shifted to the development of CGRP receptor antagonists [6]. Nevertheless, uncertainties remain regarding the efficacy and safety of oral CGRP receptor antagonists compared with placebo or triptans as medications to treat acute migraine. Notably CGRP receptor antagonists MK-3207 and telcagepant were discontinued following phase II clinical trials due to safety concerns around liver toxicity in a migraine prevention study, with data on these two agents coming from relatively small numbers of patients. This study updates the current state of understanding around the clinical safety and tolerability of oral CGRP receptor antagonists and helps inform strategies to enhance safety and tolerability in the treatment of acute migraine.

Among the individual CGRP receptor antagonists, telcagepant was associated with the lowest risk of any AEs occurring, and the risk ratio increased in order from BI44370TA, ubrogepant, rimegepant, to MK-3207. In terms of TRAEs, telcagepant and ubrogepant were associated with the lowest risk, and the risk ratio increased in order, from rimegepant to MK-3207; BI44370TA was associated with the highest risk of TRAEs. Further studies are required to demonstrate significant differences in and ranking of clinical safety between individual CGRP receptor antagonists.

Triptans are the current standard of care for treating acute migraine, but their discontinuation rate is relatively high at 55.2–81.5% [41]. Frequent use of triptans may lead to headaches associated with medication overuse. Triptans are also contraindicated in patients with cardiovascular disease due to 5-hydroxytryptamine1B receptor–mediated vasoconstriction [7, 42]. Few studies have compared the incidence of cardiovascular events between CGRP receptor antagonists and triptans. No cardiovascular events were verified by electrocardiography in RCTs involving rimegepant. RCTs involving BI44370TA, MK-3207, and telcagepant did not report on the incidence of cardiovascular events. A previous meta-analysis suggested that the incidence of chest discomfort was not different between gepants and placebo [17]. Another previous study concluded that oral CGRP receptor antagonists with no or low likely cardiovascular risks might offer an alternative to current specific migraine treatments for patients with cardiovascular disease [43]. Our meta-analysis demonstrated that oral CGRP receptor antagonists were safer than triptans in terms of AEs, TRAEs, dizziness, dry mouth, fatigue, paresthesia, and somnolence. Therefore, CGRP receptor antagonists may be a safer and better tolerated treatment option not only in patients with cardiovascular disease, but also in those suffering from overall AEs due to triptans.

The current meta-analysis included ubrogepant and rimegepant, which received US FDA approval for the treatment of

Study or Subgroup	Ubrogepant Events	Ubrogepant Total	placebo Events	placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Ubrogepant 1mg						
Ubrogepant, NCT01657370, 2016	6	28	6	28	1.0%	1.00 [0.37, 2.73]
Ubrogepant, Voss, 2016	33	107	28	113	4.5%	1.24 [0.81, 1.91]
Subtotal (95% CI)		**135**		**141**	**5.5%**	**1.20 [0.81, 1.78]**
Total events	39		34			
Heterogeneity: Chi² = 0.15, df = 1 (P = 0.69); I² = 0%						
Test for overall effect: Z = 0.91 (P = 0.36)						
3.1.2 Ubrogepant 10mg						
Ubrogepant, NCT01657370, 2016	2	26	6	28	0.9%	0.36 [0.08, 1.62]
Ubrogepant, Voss, 2016	29	108	28	113	4.5%	1.08 [0.69, 1.69]
Subtotal (95% CI)		**134**		**141**	**5.4%**	**0.96 [0.63, 1.46]**
Total events	31		34			
Heterogeneity: Chi² = 1.92, df = 1 (P = 0.17); I² = 48%						
Test for overall effect: Z = 0.20 (P = 0.84)						
3.1.3 Ubrogepant 25mg						
Ubrogepant, Lipton, 2019	105	478	112	499	18.0%	0.98 [0.77, 1.24]
Ubrogepant, NCT01657370, 2016	10	28	6	28	1.0%	1.67 [0.70, 3.96]
Ubrogepant, Voss, 2016	21	103	28	113	4.4%	0.82 [0.50, 1.36]
Subtotal (95% CI)		**609**		**640**	**23.4%**	**0.98 [0.80, 1.20]**
Total events	136		146			
Heterogeneity: Chi² = 1.92, df = 2 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.21 (P = 0.84)						
3.1.4 Ubrogepant 50mg						
Ubrogepant, Dodick, 2019	126	466	113	485	18.2%	1.16 [0.93, 1.45]
Ubrogepant, Lipton, 2019	133	488	112	499	18.2%	1.21 [0.98, 1.51]
Ubrogepant, NCT01657370, 2016	7	28	6	28	1.0%	1.17 [0.45, 3.04]
Ubrogepant, Voss, 2016	23	107	28	113	4.5%	0.87 [0.53, 1.41]
Subtotal (95% CI)		**1089**		**1125**	**41.8%**	**1.15 [1.00, 1.33]**
Total events	289		259			
Heterogeneity: Chi² = 1.55, df = 3 (P = 0.67); I² = 0%						
Test for overall effect: Z = 1.91 (P = 0.06)						
3.1.5 Ubrogepant 100mg						
Ubrogepant, Dodick, 2019	139	485	113	485	18.6%	1.23 [0.99, 1.52]
Ubrogepant, NCT01657370, 2016	7	27	6	28	1.0%	1.21 [0.47, 3.14]
Ubrogepant, Voss, 2016	30	102	28	113	4.4%	1.19 [0.76, 1.84]
Subtotal (95% CI)		**614**		**626**	**23.9%**	**1.22 [1.01, 1.47]**
Total events	176		147			
Heterogeneity: Chi² = 0.02, df = 2 (P = 0.99); I² = 0%						
Test for overall effect: Z = 2.08 (P = 0.04)						
Total (95% CI)		**2581**		**2673**	**100.0%**	**1.12 [1.02, 1.23]**
Total events	671		620			
Heterogeneity: Chi² = 8.56, df = 13 (P = 0.80); I² = 0%						
Test for overall effect: Z = 2.35 (P = 0.02)						
Test for subgroup differences: Chi² = 3.26, df = 4 (P = 0.52), I² = 0%						

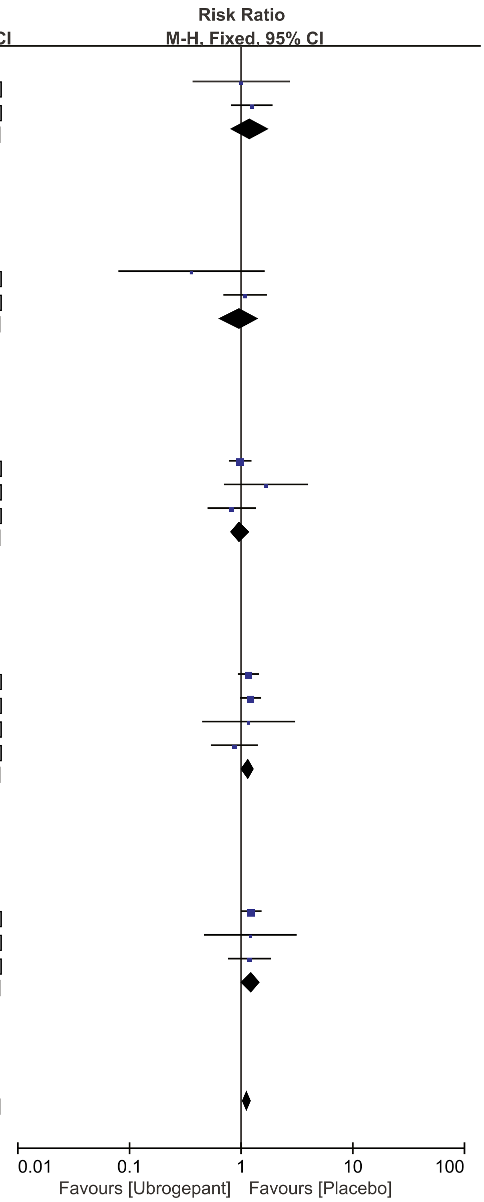


Fig. 4 Forest plots for any adverse event to compare ubrogepant across different dosages (range from 1 to 100 mg) and placebo

acute migraine in adults in December 2019 and February 2020, respectively. Rimegepant was administered orally at different dosages (ranging from 10 to 600 mg) in a phase 2b trial, while phase 3 clinical trials were performed with rimegepant 75 mg only. Ubrogepant has been studied at doses of 1, 10, 25, 50, and 100 mg. The highest dose group (100 mg of ubrogepant) showed a significantly greater risk of any AEs compared to that of the placebo group, while the incidence of any AEs in the other dose groups (1, 10, 25, and 50 mg) was not significantly different from that of placebo. In the dose group of 100 mg ubrogepant, analysis of individual events as a secondary outcome demonstrated an increased risk of nausea (RR = 1.87, 95% CI = 1.05–3.34, p = 0.03) and somnolence (RR = 3.74, 95% CI = 1.33–10.49, p = 0.01). Although the safety profile for ubrogepant is more favorable than that of triptans, it is likely more stringent safety monitoring is required in patients treated with 100 mg of ubrogepant.

This review has several limitations. First, the number of studies associated with some interventions was small, so we could not draw definite conclusions regarding these regimens. Although a minimum of two RCTs is considered adequate for performing meta-analyses, considering the average number of participants per group and anticipated high heterogeneity, more studies may be required to achieve a statistical power of 80% [44]. Moreover, according to Jackson and Turner, at least 5 studies are required to achieve power

from random-effects meta-analysis, which is greater than the number of studies that contributed to this review [45]. Second, there was significant heterogeneity among the studies. When comparing oral CGRP receptor antagonists and placebo, all eleven outcomes (any AEs, TRAEs, diarrhea, dizziness, dry mouth, fatigue, nausea, paresthesia, somnolence, upper abdominal pain, and vomiting) had low heterogeneity ($I^2 < 50\%$). When comparing oral CGRP receptor antagonists and triptans, nine outcomes (TRAEs, diarrhea, dizziness, dry mouth, fatigue, nausea, paresthesia, somnolence, and vomiting) had low heterogeneity ($I^2 < 50\%$), and one outcome (any AEs) had high heterogeneity ($\chi^2 = 11.68$; $I^2 = 74\%$; $p = 0.009$). This is probably a result of some differences in patient characteristics, clinical study design, and methodology between the studies. Importantly, triptans used in the enrolled trials were not identical. Studies by Diener et al. [27] and Marcus et al. [36] utilized eletriptan and sumatriptan, respectively. Studies by Connor et al. [33] and Hewitt et al. [28] used rizatriptan, and a study by Ho et al. [34] utilized zolmitriptan. The dosages of triptans were different. Finally, other possible confounders may exist across the different study methodologies. For example, patients were sometimes prescribed other analgesics such as acetaminophen or ibuprofen that may affect patient clinical status in individual subjects. We tried to adjust for such potential confounders where possible, but several studies failed to assess or exclude concomitant medications. Thus, high-quality prospective studies of strictly controlled variables are needed to validate the clinical safety of oral CGRP receptor antagonists on acute migraine.

Conclusion

The present meta-analysis demonstrated that oral CGRP receptor antagonists (BI44370TA, MK-3207, rimegepant, telcagepant, and ubrogepant) were associated with a significantly higher risk of any adverse event when compared to placebo. In particular, the incidence of fatigue, nausea, and somnolence with oral CGRP receptor antagonists was higher than that with placebo. However, oral CGRP receptor antagonists demonstrated a favorable safety profile compared to triptans in terms of any AEs, TRAEs, dizziness, dry mouth, fatigue, paresthesia, and somnolence. Our findings suggest that CGRP receptor antagonists may be a safer and better tolerated treatment option in the treatment of acute migraine, particularly in those suffering from overall AEs due to triptans. Study findings also inform strategies to enhance safety and tolerability in the treatment of acute migraine.

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Author contribution NH and IB conceived and designed the work. SL, NH, and IB collected the data. SL and IB performed the analysis. NH, CES, NH, and IB gave substantial contributions to data acquisition and interpretation for the work. SL and NH drafted the work. CES and IH revised it critically for important intellectual content. All the authors gave the final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors have read and agreed to the published version of the manuscript.

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Data availability The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Competing interests The authors declare no competing interests.

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