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RESEARCH

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Efficacy of lasmiditan, rimegepant and ubrogepant for acute treatment of migraine in triptan insufficient responders: systematic review and network meta-analysis

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Abstract

Background Novel abortive treatments for migraine, ditans and gepants, have promising implications in triptan-insufficient responders with minimal existing comparative data. Our study aims to synthesize evidence through a systematic review and network meta-analysis to assess the comparative efficacy of lasmiditan, rimegepant and ubrogepant in triptan-insufficient responders.

Method We searched PubMed, Embase, CENTRAL, and EBSCO Open Dissertations up to May 2024. We included randomized controlled trials (RCTs) that compared novel abortive treatments, including lasmiditan, rimegepant, and ubrogepant, in migraine patients who self-reported insufficient response to triptans. Outcomes are represented using relative risks with corresponding 95% confidence intervals (CI). The surface under the cumulative ranking curve (SUCRA) was used to rank each medication.

Results A total of five phase 3 RCTs involving 3,004 patients were included in the analysis. All three agents were significantly superior to placebo for two-hour pain freedom (RR = 1.93, 95% CI [1.52, 2.46]), freedom from the most bothersome symptoms at two hours (RR = 1.55, 95% CI [1.37, 1.75]), and pain relief at two hours (RR = 1.46, 95% CI [1.35, 1.58]). No statistically significant differences in efficacy outcomes were observed among the three agents. However, lasmiditan 200 mg had the highest cumulative probability for two-hour pain freedom and relief (SUCRA 0.9, 0.8, respective), while rimegepant led in relieving the most bothersome symptoms (SUCRA 0.7).

Conclusion Lasmiditan, rimegepant, and ubrogepant are effective for acute treatment of migraine in triptan-insufficient responders, with high-dose lasmiditan showing the highest efficacy for pain control.

Keywords Triptan-Insufficient Responder, Gepant, Rimegepant, Ubrogepant, Lasmiditan, Abortive Treatment

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Introduction

Triptans are the standard of care for the acute treatment of migraine attacks [1]. However, approximately one-third of migraine patients may not achieve an initial response within two hours, may respond at two hours but relapse within 24 h of the initial dose, or may be intolerant to triptans due to side effects such as nausea, vomiting, tingling, and other symptoms [2]. According to the European Headache Federation (EHF) consensus, these patients are classified as patients with triptan-insufficient response (TIR) [3]. The impact of TIR is a burden at both individual and socioeconomic levels. These patients have a lower quality of life, as evidenced by higher disability rates, lower work productivity and overall activity impairment [4]. Moreover, TIR patients have higher rates of emergency care and inpatient care resulting in higher costs of treatment than their triptan-responder counterparts [5]. Triptan-insufficient response may stem from several factors, including low and inconsistent absorption, delayed use of the medication during an attack, unrecognized overuse of analgesics, insufficient dosing, and individual genetic variability related to serotonin transporters, metabolism of neurotransmitters, and 5-HT1 receptors [2, 6–10]. However, our understanding of the mechanisms contributing to triptan-insufficient response and this specific migraine population is still limited.

In recent years, novel abortive treatments for migraine, including ditans and gepants, have been implemented in clinical practice. These medications are designed to be highly specific to the pathophysiology of migraines without causing widespread systemic vasoconstriction, which is different from triptans. These drugs have demonstrated efficacy and tolerability for the acute treatment of migraines in phase 2 or phase 3 randomized clinical trials (RCTs) [11, 12]. Ditans, represented by lasmiditan, selectively targets the 5-HT_{1F} receptor and is notable for their ability to cross the blood–brain barrier. Thus, ditans primarily act as central pain inhibitors and are used as abortive medications. On the other hand, gepants, the calcitonin gene-related peptide (CGRP) receptor antagonists, including rimegepant and ubrogepant, respectively represent a distinct class of migraine treatments that act primarily on CGRP receptors outside the blood–brain barrier, i.e., the peripheral mechanism [13, 14]. Rimegepant is approved for both the acute and prevention treatment of migraine while ubrogepant is solely approved for the acute treatment of migraines.

These novel abortive therapies have demonstrated superior efficacy in the acute treatment of migraine, as shown in a systematic review and network meta-analysis [11]. However, in migraine patients who are insufficient responders to triptans—where the underlying mechanism may differ from that of general migraine patients—the collective data and comparisons between these agents remain limited. Given the varying efficacy profiles and mechanistic diversity of these treatments, they may offer potential benefits for patients with TIR. There is a compelling need to synthesize the available evidence through a systematic review and meta-analysis. Therefore, this study aims to assess the comparative efficacy of lasmiditan, rimegepant, and ubrogepant in migraine patients with TIR.

Methods

Approval and registration of standard protocols

We conducted this study in accordance with the Cochrane Collaboration Guidelines for systematic review of interventions [15] and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines (PRISMA) 2020 [16]. Our study protocol was registered in PROSPERO database (CRD42024544972).

Data source and search strategy

We searched the following databases: PubMed, EMBASE, and the Cochrane Central Register of Clinical Trials (CENTRAL). We also searched the grey literature using EBSCO Open Dissertation. We performed the database search from the inception date to May 2nd, 2024. Our search strategy comprised both free text and thesaurus to cover possible synonyms of the key domains. Following the PRISMA 2020 statement, we also performed other searching techniques in addition to the database search. Other searching techniques including snowballing and citation tracking in Scopus were also performed. The complete search strategy is provided in Appendix 1.

Selection criteria

We included RCTs and observational studies that met the following criteria:

1. Population: Patients aged 18 years or older with migraine, with or without aura, as defined by the International Classification of Headache Disorders (ICHD), 3rd Edition, beta version.
2. Triptan insufficiency: Participants had a history of insufficient response to at least one triptan. This was defined as a self-reported history of discontinuation of any medication in the triptan class (i.e., any formulation of almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan, or the combination of sumatriptan-naproxen) for any reason, including lack of efficacy and/or tolerability.
3. Intervention: The study compared the effects among novel abortive treatments and placebo.

4. Outcomes: The study measured at least one of the following outcomes: freedom from pain at 2 h, freedom from the most bothersome symptoms (MBS) at 2 h, or pain relief at 2 h.

Two reviewers (WL and PA) independently screened the titles and abstracts of the search results to determine whether the studies were likely to meet the inclusion criteria. Full-text articles that passed the title/abstract screening process were subsequently assessed independently by the two reviewers (WL and PA). Disagreements and uncertainties about inclusion were discussed and resolved by PJ if consensus could not be reached by the two reviewers.

Data extraction

PJ and PA independently extracted data using a data extraction form modified from the Cochrane Effective Practice and Organization of Care Group (EPOC) guidelines [17]. The following information was extracted from the included studies: patient demographics (age, gender, race), migraine history, history of insufficient response to triptans, study characteristics (study design, number of participants), intervention details (drug, dose), outcomes as defined above, and funding sources. Data extraction was randomly verified by WL.

Risk of bias assessment

Included trials were assessed for risk of bias using the Cochrane Risk of Bias (RoB) version 2 [18], which assesses the following five domains: 1) bias arising from the randomization process; 2) bias due to deviations from intended interventions; 3) bias due to missing outcome data; 4) bias in measurement of the outcome; and 5) bias in selection of the reported result. The overall risk of bias, based on the five domains was justified as low risk; some concerns; or high risk of bias. Risk assessment was performed independently by two reviewers (PJ and PA). Any disagreements were settled by consensus with the third reviewer (WL).

Analysis

We performed a meta-analysis comparing the novel abortive treatment versus placebo. Data from all studies were pooled using a random-effects model to determine the overall effect size with a 95% confidence interval (CI). A relative risk (RR) was used to determine the effect of lasmiditan, rimegepant and ubrogepant on pain freedom at 2 h, MBS freedom at 2 h, and pain relief at 2 h. Statistical heterogeneity between studies was assessed using the χ^2 test and I^2 statistic. Thresholds for I^2 were interpreted as follows: might not be important (0%-40%), moderate heterogeneity (30%-60%), substantial heterogeneity (50%-90%), and considerable heterogeneity (75%-100%). All analyses were performed using RevMan version 5.4.1, Cochrane's bespoke software.

We also conducted a network meta-analysis using random-effects models to compare the effects of different novel abortive treatments. We calculated pooled estimates of all efficacy outcomes as a RR, with effect estimates reported with 95% CIs.

We ranked novel abortive treatments using the surface under the cumulative ranking (SUCRA). Cochran's Q statistic and I^2 were used to assess statistical heterogeneity. We also assessed clinical heterogeneity based on variations that might affect outcomes across studies. We evaluated the transitivity of the network by considering the distribution of clinical variables across studies such as age, gender, preventive medication use, number of prior triptan uses, and comorbidities. A p-value of < 0.05 was considered statistically significant. All analyses were performed using STATA version 18.0, College Station, TX.

Assessment of certainty of evidence

We assessed the certainty of evidence of the primary outcome using the Confidence in Network Meta-Analysis (CINeMA) online platform by evaluating the following criteria: within-study bias, reporting bias, indirectness, imprecision, heterogeneity, and incoherence [19]. Judgments across these domains were summarized to obtain four levels of confidence for each relative treatment effect, namely very low, low, moderate, or high, aligning with the standard Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment [20].

Results

Search results

A total of 312 records were initially identified through the literature search (Fig. 1). After screening titles and abstracts, ten papers were selected for full-text review. Of these, four papers were excluded for lacking data on the population with insufficient response to triptans [21–24], and one paper was excluded for not reporting the outcome of interest [25] (Appendix 2). Consequently, five studies met the eligibility criteria and were included in the network meta-analysis.

Additionally, other search techniques, including snowballing and citation tracking, were employed, resulting in the screening of 188 records. Among these, 180 records were excluded due to duplication or because they did not meet the eligibility criteria based on titles and abstracts. The remaining eight studies were excluded upon full-text review for lacking data on the population with insufficient response to triptans [26–33], and none of these additional techniques met the criteria for inclusion in the

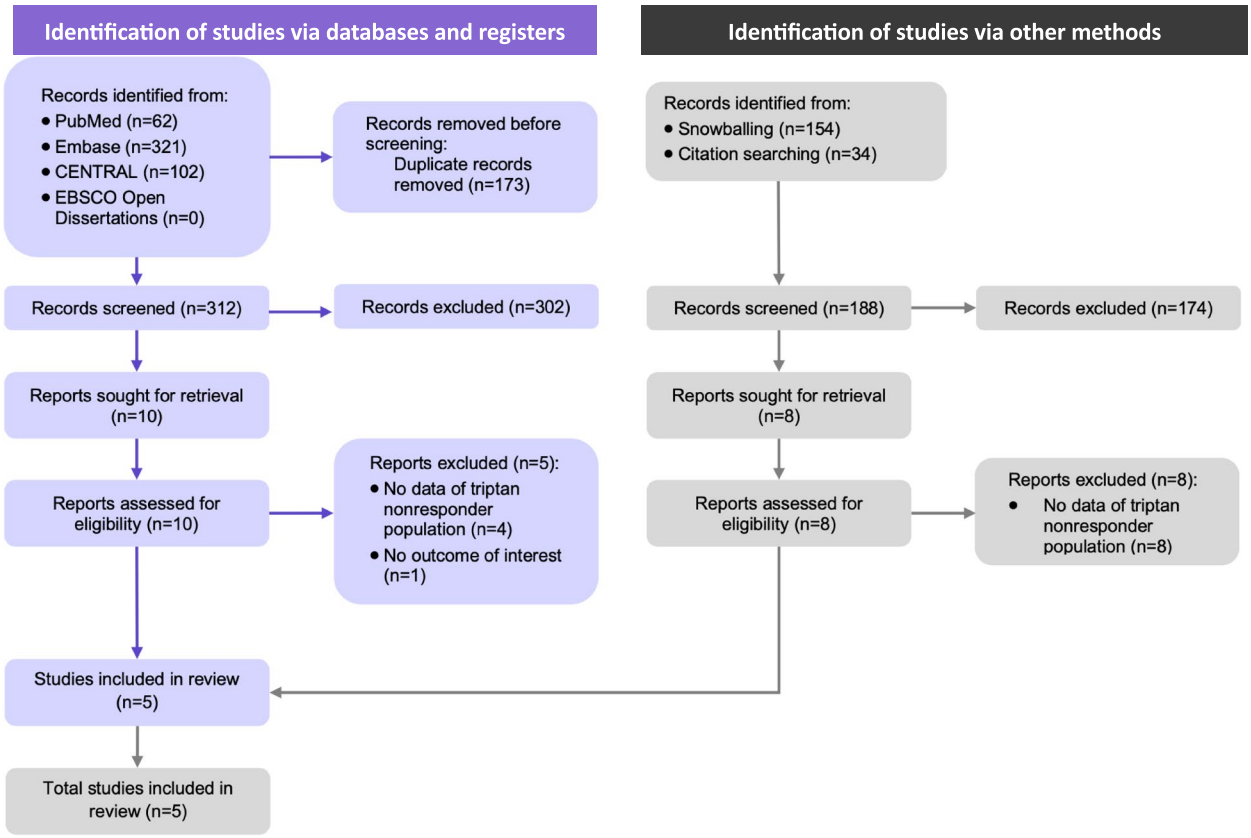


Fig. 1 PRISMA diagram

analysis (Appendix 2). Finally, a total of five studies were included in the network meta-analysis.

Included studies

The five included studies (total $n=3{,}004$ patients) consist of phase 3 RCTs assessing lasmiditan, ubrogepant, and rimegepant in individuals with TIR (Table 1). Lasmiditan was evaluated across three studies: Knievel et al. [34] investigated doses of 50, 100, and 200 mg from the SAMURAI and SPARTAN trials; Reuter et al. [35] examined 100 and 200 mg doses from the CENTURION trial; and Takeshima et al. [36] assessed doses of 50, 100, and 200 mg from the MONONOFU trial. Ubrogepant was studied by Blumenfeld et al. [37] at a dose of 50 mg in the ACHIEVE I and II trials, while rimegepant was evaluated by Lipton et al. [38] at a 75 mg dose in Studies 301, 302, and 303. All included studies targeted individuals who had discontinued triptans due to inefficacy, with some also considering participants who stopped due to side effects, intolerability, or contraindications.

Across these studies, participants with TIR were predominantly female (88%–93%), with a mean age ranging from 39 to 42.5 years. The proportion of Caucasian participants varied from 84 to 91%. Disease duration averaged between 19 and 23.1 years, and participants experienced a monthly average of 4.7 to 5.0 attacks.

Risk of bias assessment

The risk of bias for all trials in each study was assessed separately (Appendix 6). All trials were determined to have a low risk of bias across all domains, as well as overall.

Efficacy outcomes

A meta-analysis for the primary efficacy outcome of pain freedom at two hours demonstrated that the pooled estimates for the novel abortive —lasmiditan, rimegepant and ubrogepant— were significantly superior to placebo (RR 1.93, 95% CI [1.52, 2.46]), with no significant heterogeneity ($I^2=34\%$) (Fig. 2A). Secondary outcomes, including MBS freedom at two hours and pain relief at two hours, also favored the novel oral therapies (RR = 1.55, 95% CI [1.37, 1.75]; RR = 1.46, 95% CI [1.35, 1.58], respectively) with no observed heterogeneity ($I^2=0\%$) (Fig. 2B and C).

Table 1 Characteristics of included studies

Author (Year; Country)	Treatment, dose	Acronym and registration number	Definition of TIR	n of TIR patients	Mean age, year ± SD	Female, %	Caucasian, %	Mean disease duration, year ± SD	Mean attacks per month ± SD	History of aura, %	Preventive medication use, %	Exposed to 2 triptan, %
Knievel (2020; [34] USA, UK, Germany)	Lasmiditan, 50, 100, 200 mg vs placebo	SAMURAI, SPARTAN (NCT02439320, NCT02605174)	Poor/no response to recent triptan	554	42.2 ± 12.5[a]	83.9%[a]	78.8%[a]	18.8 ± 12.9[a]	5.3 ± 2.1[a]	34%[a]	19.1%[b]	NI
Reuter (2022; [35] Europe, North America, Asia)	Lasmiditan, 100, 200 mg vs placebo	CENTURION (NCT03670810)	Pain freedom failure in ≥ 2 of 3 attacks, low mTOQ-6 score, or triptan discontinuation	592	42 ± 12	88%	91%	19 ± 13	5.0 ± 1.6	NI	36%	34%
Takeshima (2022; [36] Japan)	Lasmiditan, 50, 100, 200 mg vs placebo	MONONOFU (NCT03962738)	Poor/no/inconsistent response to triptan, triptan discontinuation/contraindication	172	45.2 ± 9.6[a]	83.1%[a]	0%[a]	24.2 ± 12.0[a]	5.6 ± 1.6[a]	14.8%[a]	37.5%[a]	N/A
Blumenfeld (2021; [37] USA)	Ubrogepant, 50 mg vs placebo	ACHIEVE I, ACHIEVE II (NCT02828020, NCT02867709)	No pain freedom 2 hours post-dose on >50% occasions or triptan discontinuation due to lack of efficacy or side effects	451	39.2 ± 10.7	93%	84%	18.7 ± 12.4[c]	4.6 ± 1.8[c]	23.7%[c]	NI	NI
Lipton (2023; [38] USA)	Rimegepant 75 mg tablet, ODT vs placebo	Study 301, 302, 303 (NCT03235479, NCT03237845, NCT03461757)	Self-reported discontinuation of any triptan for lack of efficacy or tolerability	1235	42.5 ± 11.5	91%	85%	23.1 ± 11.9	4.7 ± 1.9	36%	26%	26.3%

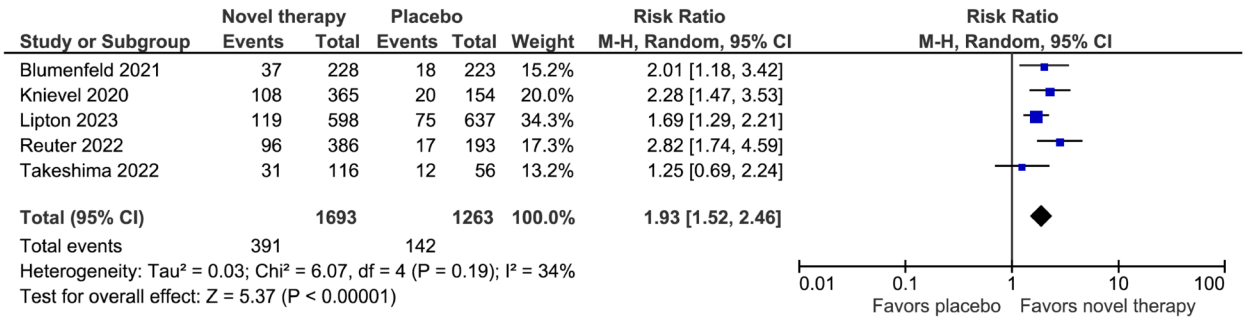
mTOQ Migraine Treatment Optimization Questionnaire, *ODT* Oral disintegrating tablet, *TIR* Triptan-insufficient response, *NI* No information

[a] The data is derived from the combination of the entire cohorts, which includes patients TIR as well as those who respond to triptans, as data specific to the TIR subgroup is unavailable

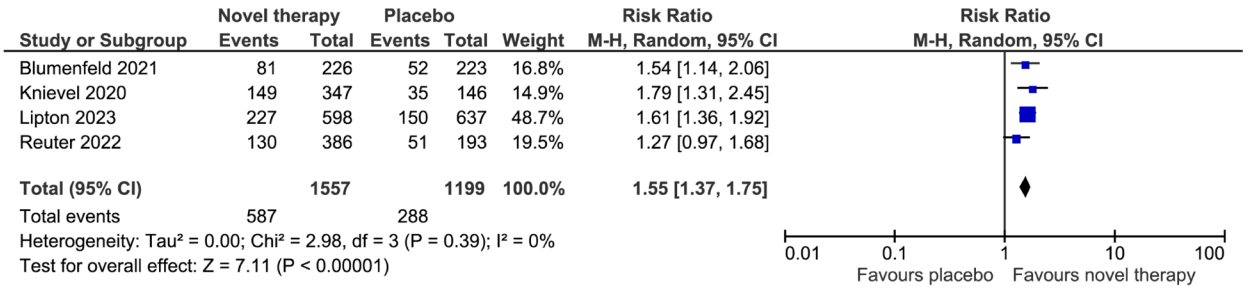
[b] The data is from the entire cohort of SPATAN due to unavailable data from TIR subgroup and data from SAMURAI trial

[c] The data is from the entire cohort of ACHIEVE II due to unavailable data from TIR subgroup and data from ACHIEVE I trial

A. Pain freedom at 2 hours.



B. Freedom of most bothersome symptoms at 2 hours.



C. Pain relief at 2 hours.

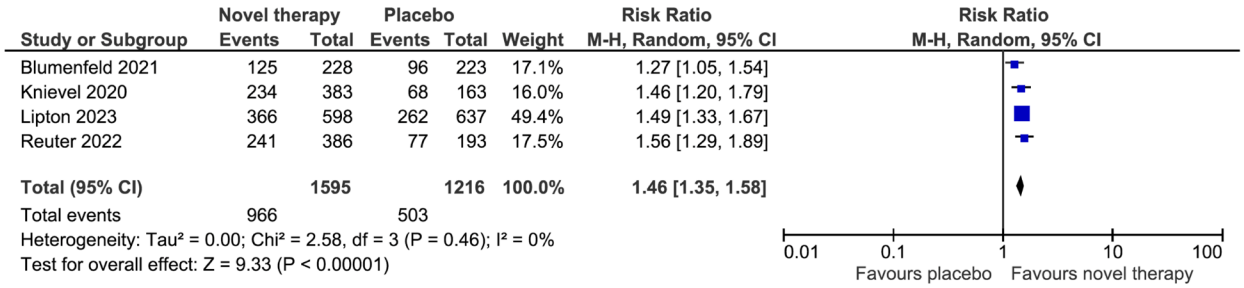


Fig. 2 Forest plot comparing the efficacy outcomes of novel abortive therapies versus placebo

Comparison of primary efficacy outcome

A network meta-analysis of the primary efficacy outcome, pain freedom at 2 h, demonstrated that all novel abortive therapies were significantly superior to placebo. Lasmiditan 200 mg showed the highest relative risk (RR 2.33 [95% CI: 1.71, 3.16), followed by lasmiditan 100 mg (RR 2.11 [95% CI: 1.55, 2.88]), ubrogepant 50 mg (RR 2.01 [95% CI: 1.18,3.42]), rimegepant 75 mg (RR 1.75 [95% CI: 1.34,2.28]), and lasmiditan 50 mg (RR 1.73 [95% CI: 1.11,2.69]) (Table 2A). However, there was no significant difference among these three agents.

Comparison of secondary efficacy outcomes

MBS freedom at 2 hours

Novel abortive therapies, including rimegepant 75 mg, lasmiditan 200 mg, and lasmiditan 100 mg, demonstrated efficacy superior to placebo in terms of MBS freedom at 2 h (RR 1.61 [95% CI: 1.07,2.43], RR 1.52 [95% CI: 1.07,2.16], RR 1.50 [95% CI: 1.05,2.13], (respectively). However, ubrogepant 50 mg and lasmiditan 50 mg was not superior to placebo (RR 1.54 [95% CI: 0.96,2.47], RR 1.49 [95% CI: 0.93,2.40], respectively) (Table 2B).

Table 2 League table comparing the efficacy outcomes among novel abortive therapies and placebo

A. League table comparing pain freedom at 2 hours.

Lasmiditan 200 mg					
1.10 (0.88,1.39)	**Lasmiditan 100 mg**				
1.16 (0.63,2.14)	1.05 (0.57,1.95)	**Ubrogepant 50 mg**			
1.33 (0.89,2.00)	1.21 (0.80,1.82)	1.15 (0.64,2.09)	**Rimegepant 75 mg**		
1.35 (0.91,2.00)	1.22 (0.83,1.81)	1.16 (0.58,2.33)	1.01 (0.60,1.69)	**Lasmiditan 50 mg**	
2.33 (1.71,3.16)	2.11 (1.55,2.88)	2.01 (1.18,3.42)	1.75 (1.34,2.28)	1.73 (1.11,2.69)	**Placebo**

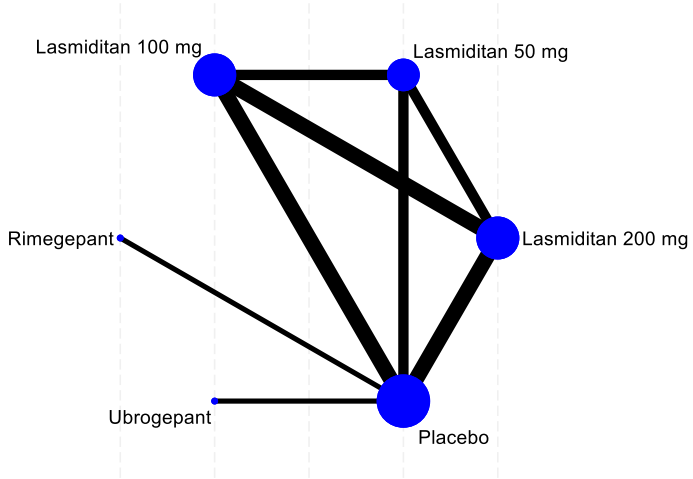
B. League table comparing freedom from the most bothersome symptoms at 2 hours.

Rimegepant 75 mg					
1.05 (0.56,1.96)	**Ubrogepant 50 mg**				
1.06 (0.62,1.82)	1.01 (0.56,1.83)	**Lasmiditan 200 mg**			
1.08 (0.63,1.85)	1.03 (0.57,1.85)	1.02 (0.73,1.41)	**Lasmiditan 100 mg**		
1.08 (0.58,2.03)	1.03 (0.53,2.02)	1.02 (0.65,1.61)	1.00 (0.64,1.58)	**Lasmiditan 50 mg**	
1.61 (1.07,2.43)	1.54 (0.96,2.47)	1.52 (1.07,2.16)	1.50 (1.05,2.13)	1.49 (0.93,2.40)	**Placebo**

C. League table comparing pain relief at 2 hours.

Lasmiditan 200 mg					
1.05 (0.93,1.18)	**Rimegepant 75 mg**				
1.06 (0.87,1.28)	1.00 (0.83,1.21)	**Lasmiditan 100 mg**			
1.05 (0.87,1.26)	1.01 (0.79,1.29)	1.01 (0.83,1.23)	**Lasmiditan 50 mg**		
1.22 (0.96,1.56)	1.17 (0.94,1.46)	1.17 (0.92,1.49)	1.16 (0.87,1.54)	**Ubrogepant 50 mg**	
1.56 (1.34,1.81)	1.49 (1.33,1.67)	1.49 (1.28,1.73)	1.47 (1.19,1.83)	1.27 (1.05,1.54)	**Placebo**

A. Primary outcome: pain freedom at 2 hours.



B. Secondary outcomes: freedom from the most bothersome symptoms at 2 hours and pain relief at 2 hours.

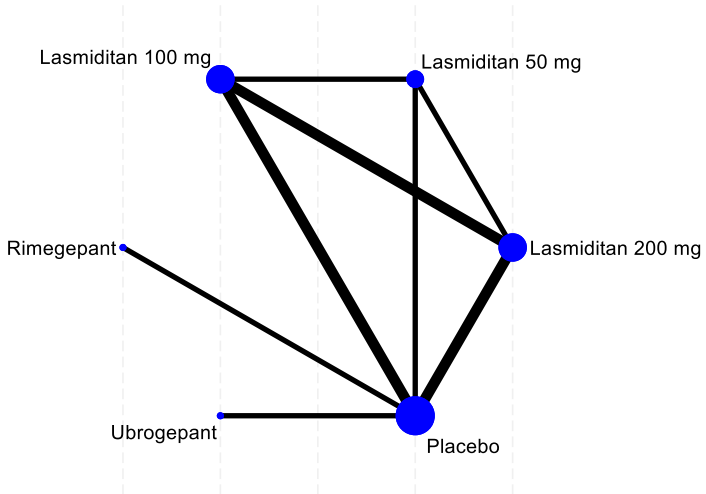


Fig. 3 Network map of the efficacy outcomes among novel abortive therapies and placebo

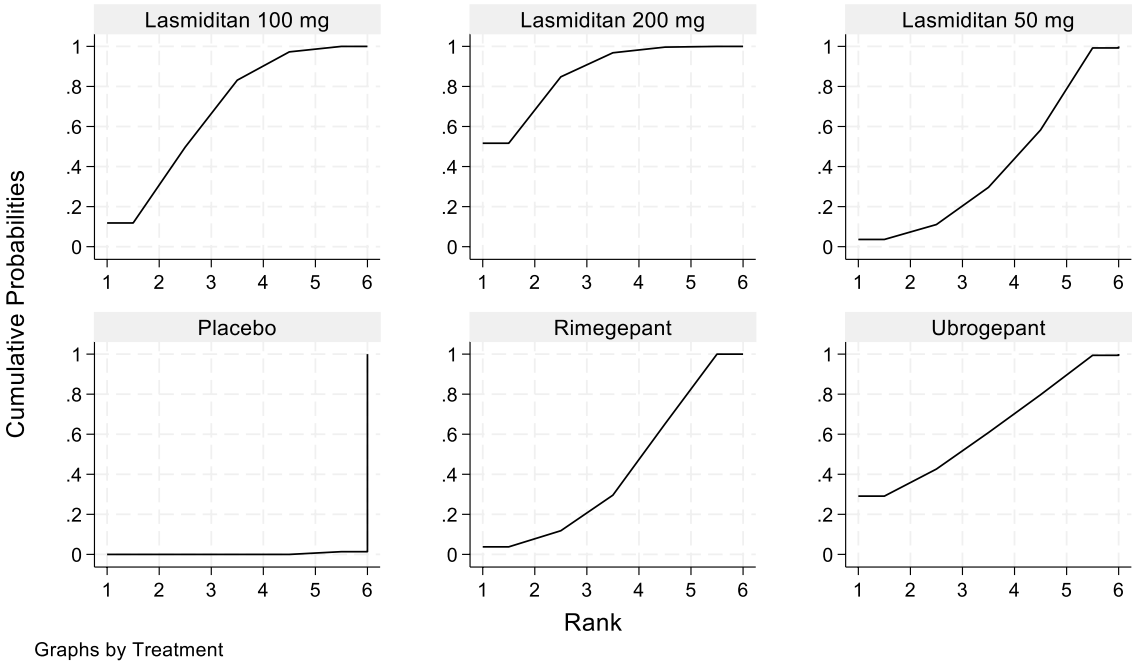
Pain relief at 2 hours

All novel abortive therapies were significantly superior to placebo in terms of pain relief at 2 h. Lasmiditan 200 mg exhibited the highest relative risk (RR 1.56 [95% CI: 1.34,1.81]), followed by rimegepant 75 mg (RR 1.49 [95% CI: 1.33,1.67]), lasmiditan 100 mg (RR 1.49 [95% CI: 1.28,1.73]), lasmiditan 50 mg (RR 1.47 [95% CI: 1.19,1.83]), and ubrogepant 50 mg (RR 1.27 [95% CI: 1.05,1.54]) (Table 2C).

Treatment ranking

By ranking all the novel abortive therapies in the network meta-analysis (Fig 3 and 4), Lasmiditan 200 mg showed the best cumulative probability on SUCRA in terms of pain freedom at 2 h, and pain relief at 2 h (SUCRA 0.9 and 0.8, respectively). Rimegepant showed the best cumulative probability on SUCRA in terms of MBS freedom at 2 h (SUCRA 0.7).

A. Pain freedom at 2 hours.



B. Freedom from the most bothersome symptoms at 2 hours.

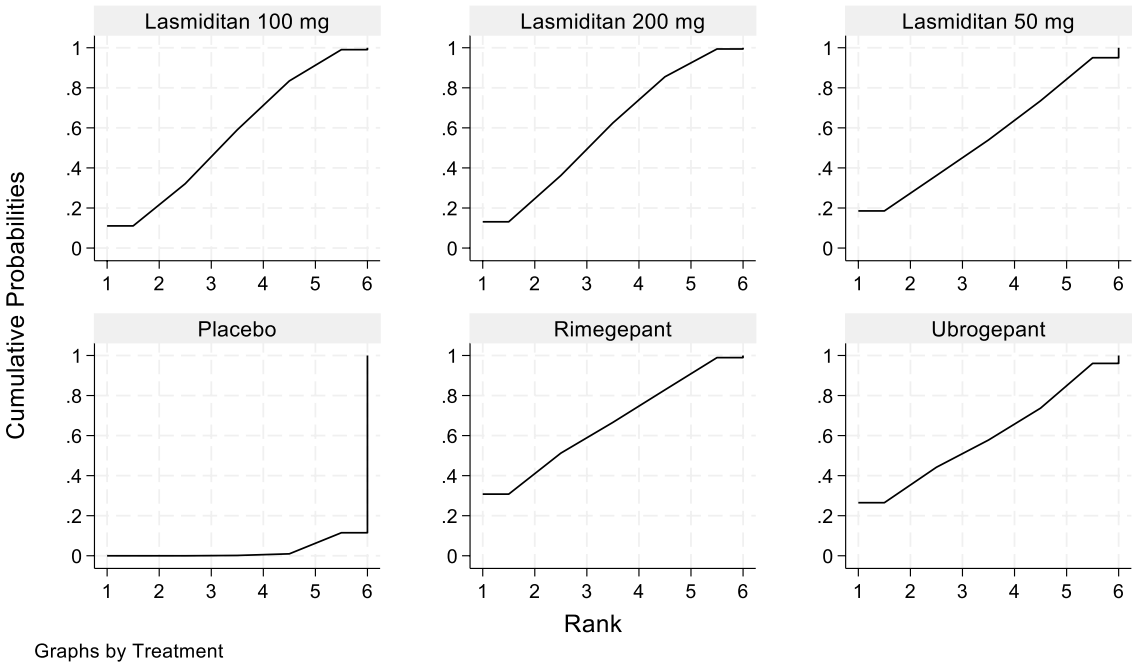


Fig. 4 Treatment ranking based on SUCRA of efficacy outcomes

Discussion

In this review, we assessed the efficacy of three novel oral drugs—lasmiditan, rimegepant, and ubrogepant—for the acute treatment of migraine in patients with TIR. We conducted a network meta-analysis using pooled data from phase 3 RCTs. All three drugs demonstrated greater efficacy than placebo in achieving pain freedom two hours after treatment, with lasmiditan 200 mg showing the numerically highest efficacy. Most interventions were superior to placebo for achieving freedom from MBS at two hours and for pain relief at two hours, except for lasmiditan 50 mg and ubrogepant 50 mg, which showed no significant difference in MBS freedom at two hours. Rimegepant tends to be the most effective for freedom from the MBS at two hours, while lasmiditan 200 mg likely has the highest efficacy for pain relief at two hours.

In patients with TIR, both pharmacodynamic and pharmacokinetic variations contribute to the variability in triptan efficacy. Pharmacodynamically, triptans target various serotonin (5-HT) receptors, including 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F}, depending on the specific medication used and the individual patient's receptor activity [39]. Triptans typically act as 5-$HT_{1B/1D}$ agonists, targeting peripheral neurons during migraine attacks, especially those marked by throbbing pain. However, in some patients, the trigeminal nucleus caudalis becomes sensitized, leading to allodynia (pain from normally non-painful stimuli). In these cases, triptans may only partially relieve pain and fail to fully address the allodynia. Additionally, genetic variability regards 5-HT1 receptors, serotonin transporters, and enzymes used to metabolize neurotransmitters has shown to result in variable response of triptans in migraine patients [8–10]. Therefore, triptan-insufficient responders may not be considered a subpopulation of general migraine patients but rather a distinct group with a specific pathophysiologic basis.

In contrast, novel migraine treatments offer distinct mechanisms of action [40]. For example, lasmiditan specifically acts on the 5-HT_{1F} receptor in the trigeminal nucleus caudalis, reducing c-fos expression and inhibiting the release of glutamate and CGRP [41]. Meanwhile, gepants block peripheral CGRP receptors to modulate pain and can also inhibit central sensitization of second-order neurons, working on both C-fibers and Aδ-fibers in the dura [42]. These different mechanisms of action may result in efficacy in patients with TIR.

Pharmacokinetically, triptans are metabolized by cytochrome P450 (CYP450) enzymes, which can vary between individuals due to genetic differences. In contrast, lasmiditan is metabolized by non-CYP450 pathways, minimizing this variability. Additionally, many migraine patients suffer from nausea and vomiting, which can impair the absorption of oral triptans. For these patients, alternative formulations like sublingual rimegepant orally disintegrating tablets (ODT), which has a high bioavailability of 64%, are valuable options as they bypass gastrointestinal issues and offer effective absorption despite nausea or vomiting [43].

Our network meta-analysis (NMA) demonstrated that lasmiditan 200 mg had the numerically highest efficacy in alleviating pain symptoms, including pain freedom and relief, two hours post-dose. Lasmiditan works by targeting 5-HT_{1F} receptors, which help control the release of glutamate and CGRP at nerve fibers. This mechanism is different from gepants, which only block CGRP receptors. This dual action of lasmiditan may make it more effective by reducing pain sensitivity in both the peripheral and central nervous systems [41, 44]. On the other hand, rimegepant was the most effective at relieving MBS symptoms, such as nausea, vomiting, and sensitivity to light (photophobia) and sound (phonophobia), at two hours based on SUCRA ranking. These symptoms are closely linked to CGRP. In animal studies, mice that were genetically engineered to overexpress a part of the CGRP receptor called RAMP1 showed light avoidance [45]. Additionally, when CGRP was injected into their brains, it increased light sensitivity, which was prevented by olcegepant, a CGRP receptor antagonist [46]. In clinical studies, patients treated with CGRP monoclonal antibodies experienced a greater reduction in days with photophobia and phonophobia compared to the reduction in headache days [47]. These findings highlight the distinct mechanisms of lasmiditan and rimegepant and their potential to address different aspects of migraine symptoms.

Although rimegepant demonstrated significant efficacy in achieving MBS freedom in our study, ubrogepant 50 mg did not show similar efficacy. This difference may be related to a dose-dependent response. In previous studies of the ACHIEVE II RCT, ubrogepant 25 mg did not lead to freedom from MBS at 2 h compared to placebo, while ubrogepant 50 mg did [29]. In our study, although ubrogepant 50 mg was included in the analysis, it is important to consider that our population consists of patients with TIR, who may be more difficult to treat. Therefore, responses to ubrogepant at a dose of 50 mg may not be sufficient. Higher doses of ubrogepant in this population need to be explored further.

This study has three primary limitations. First, the NMA included a small number of studies, and no direct head-to-head comparisons were available between different medications; only varying doses of lasmiditan were directly compared. The limited number of studies may constrain the conclusiveness of the findings.

Further validation of results should be made upon a well-designed study such as RCT. Second, safety profiles of the medications were not included in the analysis due to unavailable data. As a result, conclusions regarding the tolerability and safety of these treatments cannot be made, underscoring the need for further research in this area. Finally, although the European Headache Federation (EHF) introduced a formal definition of TIR in 2022 [3], most pooled RCTs included in this study were published between 2020 and 2023 and they defined TIR based on self-reported patient data. This may affect the accuracy of TIR determination. Additionally, varying definitions of TIR were used across studies. We suggest that future research should include TIR patients from prospective cohort studies to enable more rigorous documentation in alignment with the EHF definition.

Conclusion

Lasmiditan, rimegepant, and ubrogepant offer effective symptom management for patients with TIR, with high doses of lasmiditan demonstrating superior efficacy in terms of pain relief, while rimegepant shows greater efficacy for the most bothersome symptoms. These novel therapeutics hold significant promise for improving outcomes in TIR patients, potentially reducing the socioeconomic burden associated with challenging migraine cases.

Abbreviations

CGRP	Calcitonin gene-related peptide
CI	Confidence interval
MBS	Most bothersome symptoms
RCT	Randomized controlled trial
RR	Relative risk
TIR	Triptan-insufficient response

Supplementary Information

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Supplementary Material 1.

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NA.

Authors' contributions

WL and PA designed the meta-analysis and searched for relevant studies. PJ and PA selected the studies and extracted the relevant information. WL, PJ, and PA drafted the manuscript for intellectual content, created the tables and figures, analyzed data, and interpreted of data. All authors revised the manuscript and approved the final manuscript as submitted and agree to be accountable for all aspects of the work. WL and PJ contributed equally and qualified as co-first authors.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The ethical approval was not required for this type of study.

Competing interests

The authors declare no competing interests.

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