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BEYOND TRIPTANS: SYSTEMATIC REVIEW FOCUSING ON THE EFFICACY AND SAFETY PROFILE OF CGRP RECEPTOR ANTAGONISTS IN MIGRAINE MANAGEMENT

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ABSTRACT

Background: Despite the availability of traditional pharmacotherapies, including triptans and nonsteroidal anti-inflammatory drugs (NSAIDs), clinical value is often limited by suboptimal efficacy, significant cardiovascular contraindications, and the risk of medication-overuse headache (MOH). This study aims to evaluate the clinical efficacy and safety of rapidly developing calcitonin gene-related peptide (CGRP) receptor antagonists named 'gepants'.
Material and methods: A systematic review of scientific literature was performed to evaluate the efficacy of novel antimigraine agents. A structured search of the PubMed database was conducted using keywords including "migraine", "gepant", and "CGRP receptor antagonists." Emphasis was placed on clinical trials, RCTs, and meta-analyses, supplemented by references to neurological textbooks to provide clinical context.
Results: Analysis of clinical data indicates that daily administered gepants reduce mean monthly migraine days (MMDs) compared to placebo in preventive treatment model. Furthermore, gepants proved their efficacy in acute migraine treatment, providing pain relief and the absence of the most bothersome symptoms (MBS). Multiple studies evaluating novel gepants have reported safety profiles comparable to placebo. In addition, gepants do not exert vasoconstrictive effects, making them a viable candidate for triptan-unsuitable patients or those who had documented adverse events (AEs) of traditional oral preventive medications (OPMs).
Conclusions: Novel CGRP receptor antagonists represent a significant advancement in migraine therapy. By providing high tolerability and efficacy without the risk of MOH, hepatotoxicity or cardiovascular events, gepants emerge as a transformative option for both acute relief and prophylaxis in adult triptan-unsuitable patients suffering from migraine.

KEYWORDS

Migraine, CGRP Receptor Antagonists, Rimegepant, Gepants, Atogepant, Zavegepant

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1. Introduction

Migraine is recognized as the second leading neurological cause of disability worldwide (calculated in 2016 using DALY) and is a primary contributor to the loss of Healthy Life Years (HLY). As of 2021, migraine affected approximately 1.16 billion people globally, representing a 58.15% increase in prevalence since 1990 (Dong et al., 2025). In the majority of patients, migraine does not cause permanent, irreversible brain alterations; however, scientific literature has reported instances of structural changes in brain tissue among migraine sufferers compared to healthy individuals (Bashir et al., 2013). Furthermore, episodes of migraine headache significantly restrict patients' daily activities, often for a duration of 24 to 72 hours. Given that the prevalence of migraine peaks within the 30–50 age demographic, the limitation of daily functioning during an attack also carries social significance, as these episodes substantially impede occupational productivity for a significant proportion of the workforce.

Current antimigraine pharmacotherapies enable millions of individuals worldwide to mitigate symptoms to a degree that permits daily activity. Unfortunately, these medications carry risks of frequent AEs and are contraindicated for many patients. The most commonly prescribed drugs include triptans (e.g. sumatriptan, zolmitriptan, eletriptan), NSAIDs (e.g. ibuprofen, naproxen, diclofenac, metamizole), as well as paracetamol, acetylsalicylic acid (ASA), and ergotamine. These agents have been associated either with suboptimal efficacy (primarily NSAIDs, ASA, and paracetamol) or a high risk of AEs and an extensive list of contraindications (triptans, ergotamine) (de Vries et al., 2020; Dodick et al., 2020). Many patients also develop MOH, a condition particularly associated with chronic migraine or tension-type headaches (de Vries et al., 2020; Vandenbussche et al., 2018). In these individuals, recurrent headaches occur despite, or as a consequence of, the use of medications such as ergotamine, triptans, paracetamol, ASA, or NSAIDs. Naturally, MOH introduces further

complications into already challenging antimigraine therapeutic regimens. Consequently, the search for superior first-line candidates for migraine treatment continues. In recent years, prominence has been gained by gepants (CGRP receptor antagonists), lasmiditan (a 5-HT1F receptor agonist), and the rapidly advancing class of monoclonal antibodies targeting CGRP or its receptor, such as eptinezumab, fremanezumab, and galcanezumab.

The objective of this study is to conduct a systematic review of contemporary scientific literature and randomized controlled trials (RCTs) was performed to evaluate the therapeutic efficacy of novel antimigraine agents. A structured search of the PubMed database was conducted between November and December 2025 using keywords including "migraine", "rimegepant", "atogepant", "ubrogepant", "zavegepant", and "CGRP receptor antagonists." Primary emphasis was placed on clinical trials, RCTs, and meta-analyses, supplemented by secondary references to authoritative neurological textbooks to provide clinical context.

1.1 The role of CGRP in pain signaling and the therapeutic mechanism of CGRP receptor antagonists

A typical migraine episode is characterized by a severe, unilateral, pulsating headache lasting from several hours up to 72 hours. During an episode, patients frequently experience symptoms such as photophobia, phonophobia, nausea, vomiting, and cutaneous allodynia (Blair, 2023). The presence of a migraine aura is a significant factor in the management of migraine attacks. This characteristic neurological disturbance occurs in approximately 10–33% of patients, preceding the onset of headache and thus serving as a warning of the impending episode (de Vries et al., 2020). Aura most commonly manifests as visual disturbances, often described as flashes or other moving shapes within the field of vision. Administration of medication at the onset of the aura is recommended, as it often allows for the cessation of the headache before it fully develops (Lucas, 2021).

The new wave of antimigraine pharmacotherapies involves substances related to CGRP. In the human body, this peptide is produced in both the central and peripheral nervous systems and is responsible for potent vasodilation of the intracranial arteries (Messlinger, 2018; Russell et al., 2014),. Studies have demonstrated elevated CGRP concentrations in patients during migraine episodes, as well as in individuals with cluster headaches, trigeminal neuralgia, and even rhinosinusitis. CGRP was discovered by researchers conducting studies on rats, in which alternative mRNA splicing of the calcitonin gene led to the increased production of CGRP. Subsequently, researchers established a link between capsaicin consumption and the release of CGRP and substance P from capsaicin-sensitive afferent nerves (Gibbins et al., 1985; Lundberg et al., 1985). Initial experiments suggested the potential for CGRP-based drugs in the therapy of cardiovascular diseases. However, research in this direction was eventually ended, when the peptide's significant association with headaches became evident, and pharmacologists successfully developed CGRP antagonists that effectively alleviated migraine pain.

Gepants are an oral CGRP receptor antagonist in humans. Numerous randomized clinical trials have demonstrated the safety and efficacy of rimegepant, a leading representative of gepants, which has been approved for administration at a dose of 75 mg (Croop et al., 2021). The exact antimigraine mechanism of rimegepant has not been fully discovered. However, it is known that rimegepant, much like ubrogepant and lasmiditan, does not exert a vasoconstrictive effect, which was a significant concern in triptan therapy. Vasoconstriction posed a serious risk to patients with chronic cardiovascular diseases, and for these patients, triptans were classified as contraindicated. Consequently, rimegepant is a first-choice treatment for patients with the aforementioned contraindications to triptans. Furthermore, rimegepant and ubrogepant have shown no association with MOH (Ailani, Burch, et al., 2021).

2. Discussion

2.1 Analysis of clinical efficacy and safety - rimegepant vs placebo

The study by Robert Croop et al. (Croop et al., 2021) aimed to evaluate the efficacy of rimegepant compared to placebo in the prophylactic treatment of migraine. A total of 1,591 participants were assessed for eligibility, of whom 695, following a 4-week observation period, were recruited and subsequently randomized into the research (n=348) and control (n=347) groups using an interactive web-based randomization system. The primary endpoint of the study was a significant change in the mean number of MMD after an additional 4 weeks of observation. At the end of the observation phase, each participant was provided with 30 tablets of oral rimegepant and instructed to administer one tablet daily for 30 days, regardless of migraine status on any given day. Additionally, each participant was required to use an electronic diary to record each migraine episode, focusing on its severity. The use of one concurrent migraine prevention medication was permitted, provided the dosage had remained stable for at least 3 months prior to the observation period. The findings were as follows: the change from the observation phase to the treatment phase in MMD was -4.3 days (95% CI –4.8 to –3.9) in the rimegepant group and -3.5 days in the placebo group. An equal number of participants reported AEs in both the rimegepant and placebo groups (n=133). The authors concluded that a daily dose of 75 mg of rimegepant was effective in reducing the mean number of migraine episodes per month compared to placebo, and that the tolerability of rimegepant was statistically similar to that of the placebo.

Another study by Messoud Ashina et al. (Ashina et al., 2025) evaluated the efficacy and tolerability of rimegepant in patients with documented triptan intolerance, insufficient therapeutic response, or contraindications to triptans. Participants were categorized into two cohorts: Group A, comprising individuals with a history of intolerance and/or lack of efficacy to triptans, and Group B, including those with contraindications to triptan therapy. Participants were subsequently randomized (1:1) to receive either rimegepant 75 mg or a placebo. The primary endpoint was the percentage of patients reporting pain relief at 2 hours post-dose during a migraine attack. Pain relief was defined as either the complete absence of pain or significant alleviation. Secondary endpoints included: migraine pain freedom at 2 hours, use of rescue medication within 24 hours, return to normal function at 2 hours, sustained return to normal function (2–24 hours and 2–48 hours), sustained pain relief (2–24 hours and 2–48 hours), sustained pain freedom (2–24 hours and 2–48 hours), and freedom from MBS at 2 hours. Furthermore, safety was assessed through comprehensive laboratory testing and the monitoring of AEs. Of the 585 participants, 295 received rimegepant and 290 received the placebo. The primary endpoint was achieved by 55.9% of the rimegepant group compared to 32.7 % in the placebo group (difference [95% CI]: 23.2% [15.3–31.1%]). Statistically significant differences favoring rimegepant were also observed across all secondary endpoints, including pain freedom at 2 hours (15.3% [9.6–21.1%]), reduction in rescue medication use (–28.2% [–35.6 to –20.8%]), and MBS freedom at 2 hours (12.5% [5.4–19.5%]). Adverse events occurred in 12.5% of the rimegepant group and 12.1% of the placebo group. Rimegepant 75 mg demonstrated not only superiority over placebo regarding both primary and secondary endpoints but also a safety profile comparable to placebo. These findings suggest that rimegepant is an effective and well-tolerated treatment option for migraine, particularly in the triptan-unsuitable adult population.

Pozo-Rosich et al. evaluated the efficacy and tolerability of rimegepant for the preventive treatment of episodic migraine in adults with a history of inadequate response to traditional oral preventive medications (OPMs)(Pozo-Rosich et al., 2025). The study included patients previously treated with valproic acid, gabapentin, topiramate, beta-blockers (e.g., atenolol, bisoprolol, metoprolol, nadolol, propranolol, or timolol), tricyclic antidepressants (specifically amitriptyline), SNRIs (desvenlafaxine or venlafaxine), calcium channel blockers (flunarizine or verapamil), angiotensin blockers (candesartan or lisinopril), or other locally approved preventive therapies.

Following a methodology similar to Croop et al., participants underwent a 28-day baseline observation period, followed by a 12-week double-blind treatment phase. Eligible participants had a history of 4–14 MMDs, fewer than 15 monthly headache days (of which <7 were non-migraine), and documented inadequate response to 2–4 traditional OPMs. Patients were randomized to receive either rimegepant 75 mg (n=328) or a placebo (n=324). The rimegepant group demonstrated a statistically significant reduction in MMDs compared to the placebo group (–2.1 vs. –0.5 days; difference = –1.6 days; 95% CI: –2.1 to –1.2;). Furthermore, all key secondary endpoints significantly favored rimegepant. The safety and tolerability profile of rimegepant was comparable to placebo, with AEs incidences of 56.7% and 54.9%, respectively. These findings further substantiate the efficacy of rimegepant in migraine prophylaxis. Recent academic findings provide increasing evidence that rimegepant 75 mg should be considered a first-line therapy for both the acute treatment of migraine attacks and potentially for migraine prevention. The safety profile and the low incidence of AEs are comparable to placebo, which represents a significant clinical advantage for patients with triptan intolerance or contraindications.

2.2Analysis of clinical efficacy and safety of other gepants.

One of rimegepant's sibling drugs is atogepant, an oral CGRP receptor antagonist, which design was primarily migraine prophylaxis. A study by Goadsby et al. (Goadsby et al., 2020) evaluated the efficacy and safety of various oral doses of atogepant for the preventive treatment of migraine. A total of 834 participants were randomized into six cohorts: placebo, atogepant 10mg once daily, atogepant 30mg once daily, atogepant 60mg once daily, atogepant 30mg twice daily and atogepant 60mg twice daily. The primary endpoint was the change from baseline in mean MMDs over a 12-week treatment period.

All atogepant groups demonstrated a significant reduction in mean MMDs compared to placebo. The change from baseline was as follows - atogepant 10 mg once daily −4.0 days (0.3; p=0.024), 30 mg once daily −3.8 days (0.2; p=0.039), 60 mg once daily −3.6 days (0.2; p=0.039), 30 mg twice daily −4.2 days (0.4; p=0.0034), and 60 mg twice daily −4.1 days (0.3; p=0.0031); placebo −2.9 days (0.2). The most frequently reported AEs was nausea, occurring in 5% (5/93) for 10 mg once daily and up to 12% (22/186) for 60 mg once daily *vs* 5% (9/186) for placebo.

Building upon these findings, Ailani et al. (2021) (Ailani, Lipton, et al., 2021) conducted a subsequent double-blind trial involving 873 participants. The efficacy analysis included groups receiving 10 mg (n=214), 30 mg (n=223), and 60 mg (n=222) of atogepant, alongside a placebo group (n=214). Consistent with previous results, all atogepant doses significantly reduced MMDs over 12 weeks: –3.7 days (10 mg), –3.9 days (30 mg), and –4.2 days (60 mg), compared to –2.5 days for placebo. The mean differences were as follows: −1.2 days with 10mg atogepant (95% confidence interval [CI], −1.8 to −0.6), −1.4 days with 30mg atogepant (95% CI, −1.9 to −0.8), and −1.7 days with 60mg atogepant (95% CI, −2.3 to −1.2) (P<0.001 for all comparisons with placebo). The most common AEs identified were constipation and nausea. Serious AEs were rare, though one case of asthma and one case of optic neuritis were reported in the 10 mg group.

Dodick et al. (Dodick et al., 2019) analyzed the safety and efficacy of ubrogepant in a multicenter, double-blind, randomized controlled trial. A total of 1,327 adults with migraine were randomized into three cohorts: Group A received two placebo tablets; Group B received 50 mg of ubrogepant and one placebo tablet; and Group C received two 50-mg tablets of ubrogepant (100 mg total). In cases of persistent headache, participants were permitted to take an additional dose of received- medication or use their own rescue medication. The co-primary endpoints were pain freedom at 2 hours after the initial dose and the absence of MBS at 2 hours. Secondary endpoints included pain reduction at 2 hours post-dose, sustained pain relief for up to 24 hours, and the absence of photophobia, phonophobia, or nausea at 2 hours post-dose. Pain freedom at 2 hours was achieved by 54 of 456 participants (11.8%) in the placebo group, compared to 81 of 422 (19.2%) in the 50-mg group (P=0.002) and 95 of 448 (21.2%) in the 100-mg group (P<0.001). Absence of the MBS at 2 hours was reported by 27.8% (126 of 454) of the placebo group, 38.6% (162 of 420) of the 50-mg group (P=0.002), and 37.7% (169 of 448) of the 100-mg group (P=0.002). Regarding secondary endpoints, ubrogepant demonstrated significant advantages over placebo; however, no statistically significant difference was observed for sustained pain freedom between the 50-mg dose and placebo. Furthermore, the 100-mg dose did not significantly differ from placebo regarding the absence of phonophobia at 2 hours. The most common AEs were nausea, somnolence, and xerostomia, which occurred more frequently in the 100-mg ubrogepant group. In summary, this study demonstrated that ubrogepant achieved higher rates of pain freedom at 2 hours (approximately 20% vs. 12%) and a higher percentage of MBS absence (38% vs. 28%) compared to placebo.

Yang et al. (Yang et al., 2020) conducted a large-scale meta-analysis of three multicenter, randomized clinical trials involving 3,326 patients diagnosed with episodic migraine who were treated with ubrogepant. Overall, participants that administered ubrogepant reported a significantly higher rate of pain freedom at 2 hours post-dose compared to those receiving a placebo (20.8% vs. 12.6%; relative risk [RR] 1.65; 95% CI, 1.38–1.98). Furthermore, the ubrogepant group showed a higher percentage of absence of migraine-associated symptoms at 2 hours compared to the placebo group (37.3% vs. 27.6%; RR 1.35; 95% CI, 1.20–1.53). The incidence of AEs was found to be similar between the ubrogepant and placebo cohorts, indicating a favorable safety profile.

Zavegepant is a novel CGRP receptor antagonist; its intranasal administration may provide a vital alternative for patients who cannot tolerate oral medications due to gastrointestinal symptoms, such as nausea or vomiting.

Lipton et al. (Lipton et al., 2023) conducted a double-blind, randomized, multicenter trial across 90 academic medical centers and clinics, recruiting adults with a documented history of 2 to 8 migraine episodes per month. Participants were randomized (1:1) to receive either zavegepant 10 mg or a placebo, with instructions to self-administer a single intranasal dose during a migraine attack. The two co-primary endpoints

were pain freedom and freedom from MBS at 2 hours post-dose. In the efficacy analysis of 1,269 patients (zavegepant: n=623; placebo: n=646), a significantly higher percentage of the zavegepant group achieved pain relief (24% vs. 15%; risk difference: 8.8 percentage points; 95% CI: 4.5–13.1) and MBS freedom (40% vs. 31%; risk difference: 8.7 percentage points; 95% CI: 3.4–13.9). The most common AEs included dysgeusia, nasal discomfort, and nausea (3% vs. 1% in placebo). While this study confirms the acute efficacy of intranasal zavegepant, further research is required to evaluate its long-term safety and role in clinical practice.

A randomized, double-blind trial conducted by Croop et al. (Croop et al., 2022) evaluated the efficacy of zavegepant by comparing various dosages against a placebo. The co-primary endpoints were pain freedom and freedom from MBS at 2 hours post-dose. Participants were instructed to treat a single migraine attack with one intranasal dose of zavegepant and record pain severity 2 hours later. A total of 1,588 patients were randomized into four cohorts: Group A (5 mg zavegepant), Group B (10 mg zavegepant), Group C (20 mg zavegepant), and Group D (placebo). While findings for the 5-mg group were not statistically significant, both the 10-mg and 20-mg groups reported significantly higher rates of pain freedom at 2 hours compared to placebo (placebo: 15.5%; 10 mg: 22.5%; 20 mg: 23.1%). Similarly, freedom from the MBS at 2 hours was significantly higher in the active treatment groups (placebo: 33.7%; 10 mg: 41.9%; 20 mg: 42.5%). The most frequently reported AEs were dysgeusia (13.5%-16.1% for zavegepant vs. 3.5% for placebo), nausea, and nasal discomfort. These AEs were generally mild to moderate in severity and resolved without intervention. In conclusion, this study demonstrated the efficacy and favorable safety profile of intranasal zavegepant in the acute treatment of migraine.

2.3 Analysis of hepatotoxicity (comparison to gepants I gen.) and cardiovascular risk

The first generation of gepants was clinically discontinued due to unfavorable administration routes (e.g. intravenous olcegepant) or a high risk of hepatotoxicity (e.g. telcagepant). A pivotal study by Ho et al. (Ho et al., 2014) demonstrated that telcagepant induced significant elevations in serum aminotransferase levels. These findings led to the cessation of further clinical development of telcagepant and catalyzed the search for next-generation gepants devoid of hepatotoxic effects.

In contrast, recent clinical trials have reported no significant hepatotoxicity for rimegepant (Ashina et al., 2025; Croop et al., 2024; Pozo-Rosich et al., 2025), ubrogepant (Ankrom et al., 2020; Dodick et al., 2019; Goadsby et al., 2019), atogepant (Boinpally, Jakate, et al., 2021; Boinpally, McNamee, et al., 2021; Min et al., 2021), and zavegepant (Bertz et al., 2025; Bhardwaj et al., 2024). This data suggests that the safety concerns associated with early CGRP receptor antagonists have been successfully addressed in newer generations of gepants. Furthermore, the studies cited in this review found no evidence of increased cardiovascular risk associated with gepant use. Unlike triptans, gepants do not interact with 5-HT_{1F} receptors, thereby avoiding the vasoconstrictive mechanisms linked to cardiovascular AEs.

3. Conclusions

These clinical findings suggest that atogepant, rimegepant, ubrogepant, and zavegepant represent safe and effective pharmacological options for migraine management. Specifically, atogepant serves as a vital tool for prophylaxis, whereas Rimegepant, ubrogepant and zavegepant offer flexible solutions for acute treatment. Research into gepants has further elucidated that vasoconstriction is not the only mechanism underlying migraine pathophysiology; CGRP receptor antagonists provide relief from migraine pain without inducing vasoconstrictive effects.

While all gepants demonstrate superior efficacy compared to placebo, there is currently insufficient evidence to support their clinical superiority over triptans. Nevertheless, in patients with contraindications or those experiencing intolerable AEs from triptans, gepants emerge as a primary therapeutic alternative. Current data continues to accumulate, suggesting a highly promising future for this drug class in personalized migraine therapy. Atogepant, rimegepant, ubrogepant, and zavegepant have been approved for clinical use in various countries, which indicates substantial influx of important data in the following years, which will determine gepants' place in further migraine therapy.

Disclosure:

Author's contribution

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