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CLINICAL EFFICACY AND SAFETY OF TRIPTANS VERSUS GEPANTS IN MIGRAINE MANAGEMENT: IMPLICATIONS FOR PHYSICAL ACTIVITY AND QUALITY OF LIFE

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ABSTRACT

Introduction: Migraine is a chronic and disabling neurological disorder that substantially impairs daily functioning and limits participation in physical activity. Pharmacological management must therefore consider not only symptom relief but also safety, tolerability, and the ability to maintain functional and exercise capacity. Triptans have been the standard for acute migraine treatment, whereas calcitonin gene-related peptide (CGRP) receptor antagonists (gepants) have emerged as a newer therapeutic class without vasoconstrictive effects, potentially offering advantages for physically active individuals.
Aim of the study: The aim of this article was to review and compare current evidence on the clinical efficacy, safety, cardiovascular considerations, and functional outcomes associated with triptans and gepants, with particular attention to implications for physically active individuals and sport participation.
Methods and Materials: This narrative review was based exclusively on peer-reviewed full-text scientific articles provided by the author, including randomized controlled trials, long-term safety studies, meta-analyses, and mechanistic investigations related to triptans and CGRP receptor antagonists. Data were synthesized qualitatively with a focus on acute and preventive efficacy, adverse events, cardiovascular and exercise-related findings, and functional or quality-of-life outcomes.
Conclusion: Triptans demonstrate superior acute efficacy in achieving pain freedom and pain relief; however, their vasoconstrictive properties, safety limitations, and low long-term adherence may restrict their suitability for some physically active individuals. Gepants provide clinically meaningful efficacy with a more favorable safety and tolerability profile, preserved exercise capacity, and improved functional outcomes, particularly in preventive treatment settings. These findings support gepants as a valuable therapeutic option for migraine management in patients for whom cardiovascular safety, exercise compatibility, and sustained functional performance are key considerations.

KEYWORDS

Migraine, Triptans, Gepants, CGRP Receptor Antagonists, Physical Activity, Sport Performance

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1. Introduction

Migraine is a prevalent and disabling neurological disorder affecting more than one billion individuals worldwide and is a leading cause of functional limitation in adults (Ali et al., 2023). Characterized by recurrent attacks of moderate to severe headache, sensory hypersensitivity, nausea, and impaired concentration, migraine significantly disrupts daily functioning and limits participation in physical activity (Villar-Martinez & Goadsby, 2022; Yalın et al., 2016). For physically active individuals, including recreational exercisers and competitive athletes, migraine poses unique challenges: exercise may precipitate attacks in susceptible individuals, exacerbate symptoms during an ongoing episode, or, conversely, reduce attack frequency in some patients (La Touche et al., 2023; Amin et al., 2018). These heterogeneous responses highlight the importance of selecting pharmacological treatments that not only offer effective symptom control but also support safe return to activity and minimize exercise-related risk (Reina-Varona et al., 2024).

Triptans, selective serotonin 5-HT1B/1D receptor agonists, have been the cornerstone of acute migraine therapy for over three decades (Huang et al., 2020; Mitsikostas & Tfelt-Hansen, 2012). Their mechanism of action involves cranial vasoconstriction, inhibition of neurogenic inflammation, and suppression of trigeminovascular transmission (de Vries et al., 2020). While triptans offer robust clinical efficacy with well-documented reductions in pain intensity and migraine-associated symptoms, their vasoconstrictive properties impose important safety limitations. These include contraindications in patients with cardiovascular disease, caution during high-intensity physical exertion, and the potential for performance-impairing adverse effects (Wang et al., 2024; Robbins 2021). As a result, triptans may not be ideal for individuals regularly engaging in strenuous exercise or competitive sports, especially when rapid and complete functional recovery is required.

In recent years, gepants - oral antagonists of the calcitonin gene-related peptide (CGRP) receptor have emerged as a novel therapeutic class for both acute and preventive migraine treatment (Lipton et al., 2019). Unlike triptans, gepants do not induce vasoconstriction and exhibit a more favorable cardiovascular safety profile, making them an appealing option for active individuals and those with contraindications to traditional therapies (Karsan & Goadsby, 2015). Clinical trials of rimegepant and ubrogepant have demonstrated significant efficacy in achieving pain freedom, reducing associated symptoms, and improving functional outcomes (Dong et al., 2023). Long-term safety studies further support their use, revealing stable tolerability without hepatotoxicity or cardiovascular complications (Jakubowska & Sowa-Kućma, 2025).

Functional recovery is central to migraine management in sport. Treatments that can restore cognitive clarity, physical capability, and participation readiness are particularly valuable for individuals whose daily routines or athletic performance depend on maintaining high physical standards. Measures such as return to normal activity rates, quality of life scores, and patient-reported functional outcomes therefore play a critical role in evaluating therapeutic suitability for active populations. This review synthesizes the available clinical evidence regarding the efficacy, safety, tolerability, functional outcomes, and exercise-related implications of both medication classes. The goal is to elucidate their relative advantages and limitations in the context of physical activity, thereby informing optimal therapeutic strategies for active individuals living with migraine.

2. Methods and materials

This narrative review was based exclusively on peer-reviewed full-text scientific articles provided by the author. No additional database searches, grey literature, or unpublished sources were included. The analyzed materials comprised randomized controlled trials, phase II and III clinical studies, long-term safety extensions, real-world observational and pharmacovigilance analyses, systematic reviews and meta-analyses, and mechanistic studies relevant to the use of triptans and calcitonin gene-related peptide (CGRP) receptor antagonists in migraine treatment.

All articles were reviewed in full, and data were extracted qualitatively with a focus on clinical efficacy, safety and tolerability, cardiovascular and exercise-related findings, and functional or quality-of-life outcomes. Acute and preventive treatment effects were analyzed separately. Functional and exercise-related measures were included only when explicitly reported in the original studies.

Comparative statements between triptans and gepants were limited to results reported within individual studies or existing meta-analyses. Interpretation was strictly confined to the evidence contained in the supplied articles, and no head-to-head comparisons were inferred where direct comparative data were unavailable.

3. Results

Randomized controlled trials and network meta-analyses consistently demonstrated that both triptans and CGRP receptor antagonists are effective in the acute treatment of migraine compared with placebo. However, comparative analyses showed higher rates of pain freedom and pain relief at 2 hours for most triptans relative to gepants. In a large network meta-analysis including 64 randomized controlled trials and more than 46,000 participants, most triptans were associated with significantly higher odds ratios (ORs) for pain freedom at 2 hours compared with rimegepant and ubrogepant (Yang et al., 2021). Similar superiority of triptans was observed for pain relief at 2 hours, while comparisons between individual gepants did not reach statistical significance (Yang et al., 2021). Despite lower relative efficacy compared with triptans, second-generation gepants demonstrated clinically meaningful acute benefits. Phase III trials of rimegepant and ubrogepant reported significantly higher rates of pain freedom and freedom from the most bothersome symptom at 2 hours compared with placebo (Tepper, 2018; Chiang & Schwedt, 2020). Absolute response rates were lower than those observed with most triptans but were consistent across studies and endpoints.

The study by Tepper et al. demonstrated that first-generation gepants also showed efficacy in acute migraine. Intravenous olcegepant achieved 2-hour pain freedom in approximately 44% of treated patients compared with 2% in the placebo group. Oral telcagepant demonstrated efficacy comparable to zolmitriptan in phase II and III trials, with 2-hour pain freedom rates of approximately 23% for telcagepant, 31% for zolmitriptan, and 10% for placebo (Tepper, 2018).

Preventive efficacy of gepants was demonstrated in multiple randomized controlled trials, whereas triptans are not indicated for migraine prevention. In a phase 2/3 randomized trial, rimegepant administered every other day resulted in a statistically significant reduction in monthly migraine days compared with placebo during weeks 9–12 of treatment (Croop et al., 2021). The mean reduction from baseline was −4.3 days in the rimegepant group compared with −3.5 days in the placebo group.

Preventive efficacy was further confirmed for atogepant in the ADVANCE phase III trial. Once-daily atogepant at doses of 10 mg, 30 mg, and 60 mg significantly reduced mean monthly migraine days over 12 weeks compared with placebo, with dose-dependent effects observed (Ailani et al., 2021). Mean reductions ranged from −3.7 to −4.2 days across active treatment groups versus −2.5 days with placebo.

Triptans were consistently associated with safety considerations related to their vasoconstrictive mechanism of action. Clinical trials and post-marketing data identified adverse events affecting multiple organ systems, including nervous, cardiovascular, gastrointestinal, and respiratory systems (Chen et al., 2014; Liu et al., 2024). Real-world pharmacovigilance analyses based on the FDA Adverse Event Reporting System identified reports of reversible cerebral vasoconstriction syndrome and cardiovascular-related adverse events across several triptans, with variability between individual agents (Liu et al., 2024).

Long-term adherence to triptans was low in real-world settings. In a large cohort study, only 34% of new users refilled their first prescription, and the 2-year retention rate was approximately 4% (Chen et al., 2014).

In contrast, second-generation gepants demonstrated favorable tolerability profiles. Across randomized trials of rimegepant, ubrogepant, and atogepant, the incidence of treatment-emergent adverse events was comparable to placebo, and discontinuation due to adverse events was uncommon (Tepper, 2018; Croop et al., 2021; Ailani et al., 2021). The most frequently reported adverse events included nausea and constipation, with low rates of serious adverse events.

First-generation gepants were associated with elevations in liver transaminases during preventive dosing regimens, which led to termination of their development. These hepatotoxicity signals were not observed in trials evaluating gepants exclusively for acute treatment (Tepper, 2018). Cardiovascular safety represents a key differentiating feature between triptans and gepants. Triptans exert vasoconstrictive effects through 5-HT1B receptor activation, which underlies contraindications in patients with cardiovascular disease and warrants caution during physical exertion (Yang et al., 2021). Mechanistic and clinical studies consistently showed that gepants do not induce direct vasoconstriction. Ex vivo studies demonstrated that rimegepant, ubrogepant, and related compounds did not constrict human coronary or cerebral arteries at therapeutic concentrations, although they inhibited CGRP-mediated vasodilation (Chiang & Schwedt, 2020; Juhasz et al., 2023).

Exercise tolerance was directly assessed in a randomized, placebo-controlled crossover study evaluating telcagepant in patients with stable angina. No significant differences were observed between telcagepant and placebo in treadmill exercise duration, time to ischemic electrocardiographic changes, or maximal heart rate, indicating preserved exercise capacity during CGRP receptor blockade (Tepper, 2018).

Functional recovery was assessed as a secondary outcome in several gepant trials. Acute treatment studies reported improved ability to resume normal activities and reduced functional impairment compared

with placebo (Chiang & Schwedt, 2020). Preventive treatment with atogepant resulted in significant improvements in patient-reported activity impairment and quality-of-life measures, with dose-dependent effects observed across most functional domains (Ailani et al., 2021). Preventive rimegepant treatment was also associated with stable functional outcomes and low discontinuation rates over the study period (Croop et al., 2021).

In contrast, real-world triptan studies highlighted challenges in sustained functional benefit, reflected by high discontinuation rates and frequent switching to non-triptan acute therapies (Chen et al., 2014).

4. Discussion and Conclusions

This narrative review synthesized current evidence comparing triptans and calcitonin gene-related peptide (CGRP) receptor antagonists in the treatment of migraine, with particular emphasis on efficacy, safety, cardiovascular considerations, and functional outcomes relevant to physically active individuals. Consistent with previous meta-analyses, triptans demonstrated superior acute efficacy, achieving higher rates of pain freedom and pain relief at 2 hours compared with gepants. These results confirm their established role as highly effective abortive agents for acute migraine attacks. However, this efficacy advantage is accompanied by clinically relevant limitations related to their vasoconstrictive mechanism of action. Contraindications in patients with cardiovascular disease, the need for caution during physical exertion, and the occurrence of adverse events affecting multiple organ systems may restrict their suitability for some individuals, particularly those engaging in regular or high-intensity physical activity. Moreover, real-world data indicate low long-term adherence to triptan therapy, suggesting that sustained clinical and functional benefit may be difficult to achieve in a substantial proportion of patients.

In contrast, gepants demonstrated a more favorable safety and tolerability profile across both acute and preventive treatment settings. Although their acute efficacy was generally lower than that of triptans, gepants consistently provided clinically meaningful benefits compared with placebo. Importantly, preventive trials of rimegepant and atogepant showed significant reductions in monthly migraine days accompanied by improvements in functional and quality-of-life measures. These findings suggest that gepants may offer advantages in long-term disease management, particularly for patients requiring stable symptom control without compromising daily activities or exercise capacity.

Cardiovascular and exercise-related considerations further differentiate these therapeutic classes. Triptans exert vasoconstrictive effects through 5-HT1B receptor activation, which underlies established cardiovascular precautions. In contrast, mechanistic and clinical evidence indicates that CGRP receptor antagonists do not induce direct vasoconstriction and do not impair exercise tolerance, even in populations with underlying cardiovascular disease. Preservation of exercise capacity observed in controlled studies supports the potential suitability of gepants for physically active individuals and those engaged in sport.

Functional recovery emerged as a clinically relevant outcome in the analyzed studies. Improvements in activity impairment and quality-of-life measures were more consistently reported in gepant trials, particularly in preventive treatment settings. Given the central role of functional performance, cognitive clarity, and participation readiness in physically active populations, such outcomes may be as important as short-term pain relief when selecting migraine therapies.

Several limitations should be acknowledged. The available evidence does not include direct head-to-head trials comparing triptans and gepants specifically in athletic or highly active populations. Functional and exercise-related outcomes were generally secondary endpoints, and long-term real-world data for gepants remain limited relative to the extensive post-marketing experience with triptans. Additionally, most clinical trials excluded patients with significant cardiovascular comorbidities, which may limit generalizability.

In conclusion, triptans remain highly effective agents for the acute treatment of migraine, while gepants represent a valuable therapeutic alternative characterized by improved safety, better tolerability, and favorable functional outcomes. For physically active individuals and those engaged in sport, CGRP receptor antagonists may be particularly advantageous when cardiovascular safety, exercise compatibility, and sustained functional performance are key treatment priorities. Further studies focusing on active and athletic populations are warranted to refine evidence-based migraine management strategies in this context.

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