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Emerging Role of Gepants in the Treatment of Migraine in the Emergency Department

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Abstract

Migraine is a disabling neurovascular disorder characterized by recurrent moderate-to-severe headaches accompanied by nausea, photophobia, and phonophobia. Calcitonin gene-related peptide (CGRP) plays a central role in trigeminovascular activation and neurogenic inflammation. Gepants, small-molecule CGRP receptor antagonists, have emerged as effective agents for acute and preventive migraine management.

Second- and third-generation gepants—including ubrogepant, rimegepant, atogepant, and zavegepant—demonstrate significant two-hour pain freedom, sustained symptom relief, and favorable tolerability without vasoconstrictive effects. These properties make them particularly relevant for emergency department (ED) patients with cardiovascular comorbidities, triptan intolerance, or inadequate response to conventional therapy.

This review examines migraine pathophysiology, pharmacologic mechanisms of gepants, clinical trial evidence, cardiovascular safety considerations, and practical integration into emergency migraine management pathways.

Keywords: Migraine; Gepants; CGRP receptor antagonists; Emergency department; Acute headache management

1. Introduction

Migraine affects over one billion individuals globally and remains one of the leading causes of years lived with disability. Emergency departments frequently encounter patients presenting with severe migraine requiring rapid symptom control. The pathophysiology involves cortical spreading depression, trigeminovascular activation, and the release of neuropeptides including CGRP. Traditional therapies such as triptans act via serotonin receptor agonism and induce vasoconstriction, limiting their use in patients with cardiovascular or cerebrovascular disease. The development of CGRP-targeted therapies has significantly reshaped migraine management strategies.

2. Pathophysiological Basis for CGRP Targeting

CGRP is a potent vasodilatory neuropeptide released from trigeminal sensory fibers during migraine attacks. Elevated CGRP levels are observed during acute migraine episodes, and infusion of CGRP can provoke migraine-like attacks in susceptible individuals. Blocking CGRP signaling interrupts the migraine cascade, reduces neurogenic inflammation, and attenuates central sensitization.

Unlike triptans, CGRP antagonism does not induce systemic vasoconstriction, providing a major therapeutic advantage.

3. Overview of Gepants

First-generation gepants demonstrated proof-of-concept but were limited by hepatotoxicity. Second-generation agents (ubrogepant, rimegepant, atogepant) and third-generation intranasal zavegepant demonstrate improved safety profiles and pharmacokinetic properties.Ubrogepant and rimegepant are approved for acute migraine treatment, while atogepant is approved for prevention. Zavegepant provides an intranasal option particularly valuable in patients with severe nausea or vomiting.

4. Pharmacokinetics and Drug Interactions

Ubrogepant achieves peak plasma concentrations within approximately 1.5 hours and has a half-life of 5–7 hours. Rimegepant has a half-life of approximately 11 hours and is available as an orally disintegrating tablet. Zavegepant is administered intranasally, allowing rapid systemic absorption. Gepants are primarily metabolized via CYP3A4; caution is warranted with strong inhibitors or inducers. Clinical trials report low hepatotoxicity and minimal cardiovascular adverse events.

5. Clinical Evidence in Acute Migraine

Phase 3 randomized controlled trials, including ACHIEVE I and II, demonstrated statistically significant two-hour pain freedom and improvement in the most bothersome symptom compared with placebo. Rimegepant and zavegepant similarly showed significant benefit in acute treatment trials. Network meta-analyses suggest efficacy comparable to triptans with improved cardiovascular safety profiles.
Real-world studies confirm sustained pain relief, reduced rescue medication use, and favorable tolerability.

6. Emergency Department Application

In the emergency setting, gepants are particularly suitable for patients with contraindications to triptans, including coronary artery disease, uncontrolled hypertension, or prior stroke. They may also benefit patients with inadequate response to NSAIDs or dopamine antagonists. Integration into ED migraine protocols may reduce opioid utilization and align with opioid-sparing strategies. Early administration is associated with improved therapeutic outcomes.

7. Limitations and Future Directions

Barriers to widespread ED adoption include higher acquisition costs, limited formulary availability, and scarcity of emergency-specific outcome studies evaluating length of stay and revisit rates.

Further prospective ED-focused research is warranted to clarify cost-effectiveness and long-term outcomes.

8. Conclusion

Gepants represent a significant advancement in migraine therapeutics. Their non-vasoconstrictive mechanism, favorable safety profile, and demonstrated efficacy support broader consideration in emergency migraine management. As evidence continues to evolve, integration into structured ED migraine pathways may enhance personalized,evidence-based, and opioid-sparing patient care.

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