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Efficacy and safety of oral gepants for acute and preventive treatment of migraine: a systematic review of randomized placebo-controlled clinical trials

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Introduction
Migraine is a disabling neurological disorder affecting approximately 15% of the global population. Calcitonin gene-related peptide (CGRP) receptor antagonists (gepants) represent a novel oral therapeutic class developed specifically for migraine, offering efficacy without vasoconstrictive effects and with a potentially lower risk of medication-overuse headache. Despite growing evidence, a comprehensive synthesis of randomized placebo-controlled trials evaluating oral gepants for both acute and preventive treatment remains necessary.

Objective
To systematically evaluate the efficacy and safety of oral gepants in the acute and preventive treatment of migraine through randomized placebo-controlled clinical trials.

Methods
A systematic review was conducted following PRISMA guidelines. Databases including PubMed, Embase, Scopus, and Cochrane Library were searched for studies published between 2021 and 2025. Inclusion criteria were randomized placebo-controlled trials, adults with migraine diagnosis according to ICHD-3 criteria, oral gepant intervention (rimegepant or atogepant), and reporting of efficacy and/or safety outcomes. Filters applied included Clinical Trial and Randomized Controlled Trial. Two independent reviewers screened titles, abstracts, and full texts. Disagreements were resolved by consensus. A total of 758 records were identified; after removing 428 duplicates, 330 were screened. Following title and abstract screening, 307 were excluded, leaving 23 for full-text assessment, of which 17 were excluded, resulting in 6 studies included in the final analysis.

Results
Six randomized placebo-controlled trials were included, encompassing rimegepant for acute and preventive treatment and atogepant for preventive treatment. For preventive treatment, atogepant demonstrated significant reductions in monthly migraine days compared to placebo across all doses evaluated, accompanied by improvements in migraine-specific quality-of-life and activity-impairment measures. Rimegepant administered every other day also showed superior reduction in monthly migraine days versus placebo in Japanese adults, with consistent findings across subgroups. For acute treatment, rimegepant achieved significantly higher rates of pain freedom and freedom from the most bothersome symptom at two hours post-dose across distinct populations, including Japanese, Chinese, and triptan-unsuitable adults. Adverse events were mild to moderate across all trials, with no relevant hepatotoxicity signal reported in the included studies. Constipation was the most frequently reported adverse event with atogepant, while nasopharyngitis was most common with rimegepant.

Conclusion
Oral gepants, rimegepant and atogepant, demonstrated consistent efficacy and favorable safety profiles in both acute and preventive migraine treatment across diverse populations. These agents represent an important therapeutic option, particularly for patients unsuitable for triptans or conventional preventive therapies.

Keywords:
Migraine
Rimegepant
CGRP receptor antagonist
Gepants
Atogepant

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