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Systematic Review

Novel Pharmacotherapies for Migraine Prevention: A Systematic Review

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Abstract:

Background: Migraine is a prevalent neurological disorder associated with substantial disability and reduced quality of life. Recent advances in migraine pathophysiology have led to the development of novel preventive pharmacotherapies, including calcitonin gene-related peptide (CGRP)-targeted monoclonal antibodies, gepants, and other emerging mechanism-based therapies. This systematic review aimed to evaluate the efficacy, safety, and clinical utility of these novel agents in migraine prevention.

Material and Methods: A systematic search of PubMed/MEDLINE, Scopus, Web of Science, Embase, and Google Scholar was conducted for studies published between January 2020 and December 2025. Eligible studies included randomized controlled trials, systematic reviews, meta-analyses, narrative reviews, and real-world observational studies evaluating novel pharmacotherapies for episodic or chronic migraine prevention. Nineteen studies meeting predefined eligibility criteria were included in the qualitative synthesis.

Results: The included studies consistently demonstrated that novel preventive therapies significantly reduced monthly migraine days, headache frequency, and migraine-related disability. CGRP-targeted monoclonal antibodies and gepants showed favorable efficacy across episodic and chronic migraine populations, including patients with prior preventive treatment failures. Long-term extension studies and real-world investigations reported sustained effectiveness, high treatment adherence, and low discontinuation rates. Safety analyses revealed predominantly mild adverse events, most commonly gastrointestinal symptoms and injection-site reactions. Emerging evidence also supported individualized treatment strategies, combination approaches in refractory migraine, and exploration of alternative molecular targets beyond CGRP signaling.

Conclusion: Novel pharmacotherapies have transformed migraine prevention by providing effective, well-tolerated, and targeted treatment options. Continued research into long-term outcomes, comparative effectiveness, and emerging therapeutic pathways is essential to further optimize individualized migraine management.

Keywords: Migraine; CGRP; Gepants; Atogepant; Rimegepant; Erenumab; Fremanezumab; Eptinezumab.

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Introduction

Migraine is a prevalent and debilitating neurological disorder that poses a considerable public health burden worldwide. It affects nearly one in seven individuals globally and remains a leading contributor to years lived with disability, particularly among women of working and reproductive age [1]. The recurrent nature of migraine attacks, characterized by moderate-to-severe headache accompanied by symptoms such as nausea, photophobia, and phonophobia, significantly disrupts daily functioning, occupational productivity, and social engagement. In addition to its clinical manifestations, migraine is associated with substantial psychosocial consequences, including reduced quality of life, emotional distress, and social stigma, further amplifying its overall disease burden [2].

The pathogenesis of migraine is complex and involves interactions between neuronal, vascular, and inflammatory mechanisms. Current evidence highlights the pivotal role of the trigeminovascular system, in which activation of trigeminal sensory pathways leads to the release of vasoactive neuropeptides and transmission of nociceptive signals within central pain-processing networks [3]. Among these mediators, calcitonin gene-related peptide (CGRP) has emerged as a key factor in migraine pathophysiology. CGRP contributes to vasodilation, neurogenic inflammation, and sensitization of pain pathways, thereby facilitating

both the initiation and persistence of migraine attacks [4].

For many years, preventive migraine management relied largely on medications originally developed for other conditions, including antihypertensive agents, antidepressants, and antiepileptic drugs. Although these therapies provided benefit for some patients, their use was frequently limited by modest efficacy, poor tolerability, and suboptimal adherence. Advances in the understanding of migraine biology have led to the development of targeted therapies specifically designed to interfere with the CGRP signaling pathway, representing a major advancement in preventive treatment strategies [5].

The introduction of CGRP monoclonal antibodies and small-molecule CGRP receptor antagonists (gepants) has transformed the therapeutic landscape of migraine prevention. These agents offer mechanism-based treatment approaches with demonstrated efficacy and favorable safety profiles across diverse patient populations. As evidence supporting these novel pharmacotherapies continues to expand, a comprehensive evaluation of their clinical effectiveness, safety, tolerability, and role in contemporary migraine management is warranted [6]. Therefore, the present systematic review aims to synthesize current evidence regarding novel pharmacological interventions for migraine prevention.

Materials and Methods

Study Design: This systematic review was conducted to evaluate the efficacy, safety, tolerability, and long-term effectiveness of novel pharmacological agents developed for migraine prevention. The review methodology was designed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [7].

Literature Search Strategy: A comprehensive literature search was performed across multiple electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, Embase, and Google Scholar. The search covered studies published between January 2020 and December 2025. Additional records were identified through manual screening of reference lists from relevant articles.

The search strategy incorporated combinations of Medical Subject Headings (MeSH) terms and free-text keywords related to migraine prevention and emerging therapeutic agents. Keywords included “migraine,” “migraine prevention,” “migraine prophylaxis,” “calcitonin gene-related peptide,” “CGRP,” “monoclonal antibody,” “gepant,” “atogepant,” “rimegepant,” “erenumab,” “fremanezumab,” “eptinezumab,” “galcanezumab,” “preventive treatment,” and “novel pharmacotherapy.” Boolean operators (AND, OR) were applied to optimize retrieval of relevant studies.

Eligibility Criteria: Studies were selected according to predefined inclusion and exclusion criteria.

Inclusion Criteria

1. Studies evaluating novel pharmacological agents for migraine prevention.
2. Randomized controlled trials, prospective studies, observational studies, real-world evidence studies, systematic reviews, and meta-analyses.
3. Studies involving adult patients diagnosed with episodic or chronic migraine.
4. Studies reporting efficacy, safety, tolerability, adherence, or long-term treatment outcomes.
5. Articles published in English between January 2020 and December 2025.

Exclusion Criteria

1. Studies focusing exclusively on acute migraine treatment.
2. Animal studies, laboratory investigations, and preclinical studies.
3. Case reports, conference abstracts, editorials lacking relevant clinical data, and expert opinions.
4. Articles with insufficient outcome data.
5. Duplicate publications or studies with substantially overlapping datasets.

Study Selection: All retrieved records were screened independently through title and abstract evaluation. Potentially eligible studies underwent full-text assessment. Articles that met the predefined eligibility criteria were included in the final review. Any discrepancies during study selection were resolved through discussion and consensus.

Data Extraction: Data extraction was performed using a standardized data collection form. Extracted information was reviewed for consistency and accuracy prior to inclusion in the evidence synthesis.

Outcome Measures: The primary outcomes of interest included reduction in monthly migraine days, reduction in monthly headache days, responder rates, and overall effectiveness of preventive treatment. Secondary outcomes included treatment-emergent adverse events, serious adverse events, treatment discontinuation rates, medication adherence, patient-reported outcomes, and long-term safety and tolerability.

Data Synthesis: A qualitative synthesis of the included studies was conducted. Studies were categorized according to therapeutic class, including calcitonin gene-related peptide (CGRP) monoclonal antibodies and CGRP receptor antagonists

(gepants). Findings were summarized descriptively with emphasis on efficacy, safety, tolerability, and real-world clinical effectiveness. Due to heterogeneity in study designs, interventions, and reported outcomes, a narrative synthesis approach was adopted.

Risk of Bias Assessment: The methodological quality of included studies was evaluated according to study design. Randomized controlled trials were assessed using established risk-of-bias domains, while systematic reviews and observational studies were appraised using appropriate quality assessment frameworks. Potential sources of selection, performance, detection, attrition, and reporting bias were considered during evidence interpretation.

PRISMA Flow Diagram Description: A systematic search of PubMed/MEDLINE, Scopus, Web of Science, Embase, and Google Scholar was conducted to identify studies on novel pharmacotherapies for migraine prevention published between January 2020 and December 2025. A total of 1,285 records were identified, including 38 records from manual searches. After removal of 312 duplicates, 973 records underwent title and abstract screening. Subsequently, 886 records were excluded, and 87 full-text articles were assessed for eligibility. Of these, 68 studies were excluded due to irrelevant outcomes, insufficient data, duplicate datasets, non-migraine populations, or failure to meet the inclusion criteria. Ultimately, 19 studies were included in the qualitative synthesis. The study selection process was performed according to PRISMA guidelines and is illustrated in the PRISMA flow diagram.

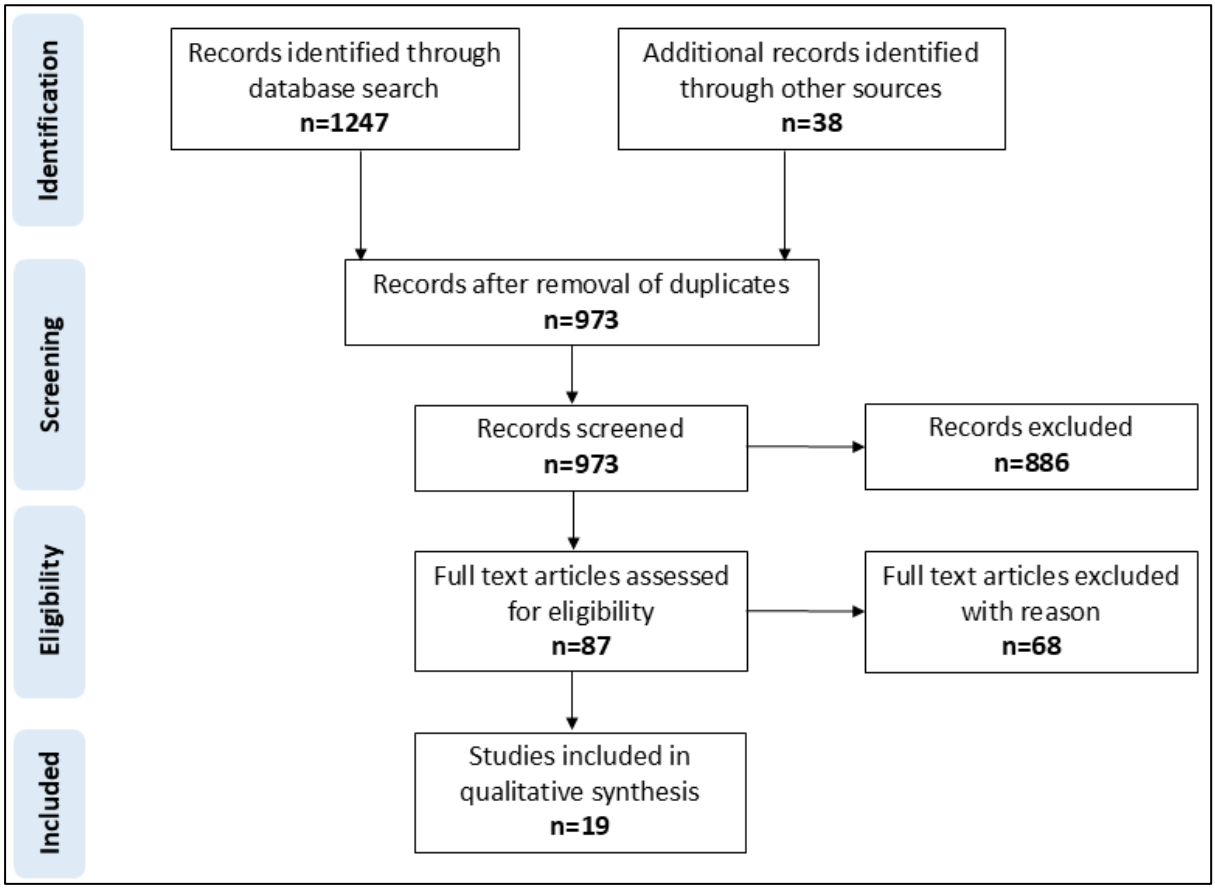

Figure 1: PRISMA flow diagram

Results

Randomized controlled trials consistently demonstrated the efficacy of CGRP-targeted therapies in reducing migraine frequency and improving patient-reported outcomes. The RELEASE trial reported that daily oral atogepant was effective and well tolerated for episodic migraine prevention, with sustained benefits during long-term treatment. Similarly, the PROGRESS trial showed significant reductions in monthly migraine days (MMDs) with atogepant 30 mg twice daily and 60 mg once daily compared with placebo. Rimegepant also demonstrated superior efficacy over placebo in reducing MMDs while maintaining an excellent long-term safety profile. In patients with multiple prior preventive treatment failures, fremanezumab administered either monthly or quarterly achieved significantly greater reductions in migraine days compared with placebo,

highlighting its effectiveness in refractory populations (Table 1).

Systematic reviews and meta-analyses further reinforced these findings. A comprehensive meta-analysis involving more than 15,000 patients demonstrated that both CGRP monoclonal antibodies and gepants consistently reduced MMDs while exhibiting superior tolerability compared with conventional oral preventive medications. Additional pooled analyses confirmed that atogepant significantly decreased monthly migraine days, monthly headache days, and acute medication use while improving quality-of-life measures. Among the evaluated doses, atogepant 60 mg once daily was associated with the greatest reduction in migraine frequency (Table 2).

Real-world evidence supported the effectiveness observed in clinical trials. Registry and cohort studies demonstrated that anti-CGRP monoclonal antibodies remained effective and safe across diverse patient populations, including individuals with comorbid autoimmune diseases. Clinical response was influenced by baseline disease burden, with higher migraine frequency and disability associated with lower odds of achieving excellent outcomes. Eptinezumab showed substantial effectiveness in patients who had failed multiple previous preventive therapies, with high responder rates observed at six months. Furthermore, increasing numbers of treatment failures were associated with greater healthcare utilization, higher costs, and increased disability, while fremanezumab demonstrated comparable efficacy and safety with both monthly and quarterly dosing schedules (Table 3).

Guideline recommendations and consensus statements reflected the growing role of CGRP-targeted therapies in migraine management. Recent evidence-based guidelines endorsed CGRP-targeted treatments as viable preventive options alongside established agents such as topiramate, valproate, magnesium, and angiotensin receptor blockers. Consensus statements emphasized the need to move beyond traditional percentage-based response criteria toward patient-centered outcomes such as complete migraine freedom. Additional recommendations focused on optimizing treatment selection across different healthcare settings while ensuring continued access to essential therapies in resource-limited environments (Table 4).

Clinical overviews and management reviews highlighted the integration of pharmacological and non-pharmacological approaches for comprehensive migraine care. Contemporary reviews supported personalized management strategies incorporating lifestyle modification frameworks such as SEEDS (Sleep, Exercise, Eat, Diary, and Stress management), nutraceutical supplementation, and evidence-based preventive medications. CGRP-targeted therapies were consistently identified as a major advancement in migraine prophylaxis due to their favorable efficacy, safety, and adherence profiles. Atogepant was specifically recognized as the first oral CGRP receptor antagonist approved for chronic migraine prevention, representing an important addition to the preventive treatment landscape (Table 5).

Table 1: Randomized Controlled Trials (Clinical Efficacy and Safety)

Citation	Study Design	Outcome Measures	Key Findings
Matsumori et al. [8]	RELEASE trial; Phase II/III randomized, double-blind, placebo-controlled trial with active-treatment extension in Japanese participants.	Change from baseline in mean Monthly Migraine Days (MMDs), safety, tolerability, and long-term maintenance.	Daily oral atogepant is highly effective and safe for episodic migraine prevention, with a safety profile consistent with multinational trials.
Pozo-Rosich et al. [9]	Phase III PROGRESS trial; randomized, double-blind, placebo-controlled multicenter study of 773 chronic migraine patients.	Mean MMD change at 12 weeks, MSQ RFR scores, AIM-D scores, and incidence of adverse events.	Both atogepant 30 mg BID and 60 mg QD achieved significant MMD reductions (-7.5 and -6.9 days vs. -5.1 for placebo).
Croop et al. [10]	Phase II/III randomized, double-blind, placebo-controlled trial of 747 patients, followed by a 52-week open-label extension.	MMD reduction at weeks 9–12, clinical responder rates, long-term safety, and hepatotoxicity parameters.	Rimegepant 75 mg EOD significantly reduced MMDs vs. placebo (-4.3 vs. -3.5 days) and showed excellent long-term safety.
Ferrari et al. [11]	Phase IIIb FOCUS trial; randomized, double-blind, placebo-controlled trial of 838 patients with 2–4 prior class failures.	Mean change in monthly average migraine days during the 12-week double-blind period and safety.	Both quarterly and monthly fremanezumab regimens demonstrated superior efficacy over placebo in highly refractory migraine.

Table 2: Systematic Reviews and Meta-Analyses

Citation	Study Design	Outcome Measures	Key Findings
Vélez-Jiménez et al. [12]	Systematic review and meta-analysis of 39 RCTs involving over 15,000 patients with episodic migraine.	Post-treatment MMD changes, incidence of adverse events, and comparative efficacy/safety of diverse interventions.	CGRP mAbs and gepants demonstrated consistent MMD reductions (-3.2 to -4.4 days) and superior tolerability over traditional oral agents.
Ladhwani et al. [13]	Systematic review and meta-analysis of 6 RCTs comprising 4,052 patients evaluating atogepant.	MMD and MHD changes at 12 weeks, ≥50% responder rates, acute medication days, and MSQ RFR scores.	Confirms atogepant significantly reduces MMDs, MHDs, and acute drug use at all doses (10, 30, 60 mg) while improving quality of life.
Alrasheed et al. [14]	Systematic review and meta-analysis of randomized trials (up to June 2024) for episodic migraine.	Baseline to 12-week changes in MMDs, MHDs, acute medication days, and 50% responder rates.	Oral atogepant (all doses) significantly reduces migraine frequency, with the 60 mg QD dose showing the most pronounced reduction.

Table 3: Real-World Evidence and Cohort Studies

Citation	Study Design	Outcome Measures	Key Findings
Ashina et al. [15]	Multicenter cohort study and OVERCOME (US) registry analysis of anti-CGRP mAb use.	Prescription patterns, long-term adherence, healthcare barriers, and safety in patients with comorbidities.	Anti-CGRP mAbs are effective and safe regardless of comorbid autoimmune diseases; minimizing access barriers correlates with superior clinical outcomes.
Caronna et al. [16]	Real-world, prospectively collected cohort study analyzing clinical predictive factors via GLMMs.	Achievement of ≥50% (good) and ≥75% (excellent) reductions in monthly headache days (MHD) at 6 months.	Higher baseline migraine frequency and disability significantly decrease the odds of excellent responses, supporting earlier preventive intervention.
Dermitzakis et al. [17]	Multicenter, real-world, prospective 6-month study of 142 patients failing ≥3 prior preventives.	Reductions in MMDs/MHDs, ≥50% and ≥75% responder rates at 3 and 6 months, and quality-of-life changes.	Eptinezumab 100 mg IV quarterly achieved ≥50% MMD response in 73.5% of HFEM and 57.6% of CM patients at 6 months.
Oliveira et al. [18]	Cross-sectional, real-world clinical study of patients with ≥4 MHDs and multiple historical treatment failures.	Frequency of treatment failure, healthcare resource utilization (HCU), direct/indirect costs, and functional disability.	Treatment failures are directly correlated with exponential increases in HCU and cost; CGRP mAbs showed greatest efficacy in refractory cases.
Zanandrea et al. [19]	Italian multicenter, prospective real-world cohort study of 95 patients receiving fremanezumab.	Changes in MMDs, MHDs, acute medication days (AMD), disability scores (HIT-6, MIDAS), and safety.	Both monthly and quarterly regimens significantly reduced all clinical endpoints, establishing therapeutic equivalence in long-term safety and efficacy.

Table 4: Evidence-Based Guidelines and Position Statements

Citation	Study Design	Outcome Measures	Key Findings
Robblee J et al. [20]	Systematic review and clinical guideline update by an AHS/AAN panel for acute treatment in the ED.	6-hour acute pain relief, pain freedom, reduction in recurrence, and incidence of adverse events.	Upgraded IV prochlorperazine and GONB to Level A ("Must Offer") recommendations; establishes IV hydromorphone as Level A ("Must NOT Offer").
Shaukat et al. [21]	Consensus position statement developed by the	Residual disease burden, quality of life, and percentage-based vs.	Recommends a paradigm shift from percentage-based metrics (e.g., ≥50% response) to absolute

	IHS outlining clinical practice priorities.	absolute clinical treatment goals.	treatment goals like "Migraine Freedom" (0 days).
VA/DoD guidelines [22]	Structured evidence synthesis and guideline development by a VA/DoD multidisciplinary panel using GRADE.	Evaluation of preventives, neuromodulatory devices, nerve blocks, and non-pharmacological therapies.	Recommends ARBs, magnesium, topiramate, valproate, and CGRP-targeted therapies as viable options for episodic migraine prevention.
Puledda et al. [23]	Consensus practice guidelines developed by Italian/IHS experts across diverse economic settings.	Categorization of pharmacological options into "optimal" and "essential" tiers based on drug access.	Establishes a global framework for optimizing treatment selection while identifying "essential" options to maintain care in resource-limited settings.

Table 5: Clinical Overviews and Management Reviews

Citation	Study Design	Outcome Measures	Key Findings
Ray et al. [24]	Evidence-based practice review of contemporary, personalized multimodal migraine management.	Assessment of modifiable risk factors, pharmacological preventives, and nutraceutical supplements.	Emphasizes the SEEDS framework and validates the benefits of daily magnesium, riboflavin, and CoQ10 in preventing attacks.
Haanes et al. [25]	Systematic review and clinical evidence synthesis of articles regarding migraine prophylaxis.	Efficacy, dosing, mechanism of action, and safety of traditional and CGRP-targeted therapies.	Categorizes CGRP-targeted preventives as a revolutionary clinical advance and highlights atogepant as the first oral preventive for chronic migraine.
Ashina et al. [26]	Comprehensive clinical review and modified GRADE evidence synthesis published in *The Lancet*.	Route, dose range, NNT, AAN/EAN recommendation level, and drug safety of modern therapies.	Highlights that mechanism-based CGRP-targeted preventives offer significantly greater real-world adherence and safety compared to traditional options

Discussion

The findings of the present systematic review highlight the substantial evolution of migraine prophylaxis over the past decade, driven by the emergence of mechanism-based therapies and a growing emphasis on individualized treatment strategies. While conventional preventive agents such as beta-blockers, antiepileptic drugs, and antidepressants have historically formed the cornerstone of migraine management, their effectiveness has often been limited by suboptimal tolerability, poor adherence, and variable clinical response. The studies included in this review demonstrate that newer preventive pharmacotherapies provide improved efficacy and safety profiles, thereby reshaping contemporary approaches to migraine prevention [27].

A major theme emerging from the evidence is the increasing role of targeted therapies in reducing migraine burden. Clinical trials and pooled analyses consistently reported significant reductions in monthly migraine days, headache frequency, and disability scores among patients receiving novel preventive treatments. Although CGRP-targeted monoclonal antibodies and gepants constitute the most extensively studied agents, the broader significance of these findings lies in the transition toward disease-specific interventions that directly address key neurobiological mechanisms involved in migraine pathogenesis. Compared with traditional oral preventives, these therapies generally exhibit superior tolerability and lower discontinuation rates, contributing to improved treatment adherence and long-term clinical outcomes [27,28].

The review also underscores the importance of patient characteristics in determining treatment success. Real-world studies revealed that individuals with lower baseline disease burden, fewer monthly migraine days, and less severe disability were more likely to achieve substantial clinical improvement following preventive therapy [29]. These observations support the growing movement toward personalized treatment goals and early therapeutic intervention. Rather than relying solely on conventional responder thresholds, contemporary migraine management increasingly emphasizes clinically meaningful outcomes such as optimal disease control, restoration of daily functioning, and improvement in quality of life [30]. Furthermore, long-term follow-up data suggest that sustained treatment benefits can be achieved when preventive therapies are initiated before the establishment of chronic migraine-related neuroplastic changes, highlighting the potential value of early and proactive management strategies [31].

Management of refractory migraine remains a significant clinical challenge. Evidence included in this review indicates that patients with previous failure of multiple preventive medications can still derive meaningful benefit from newer pharmacological approaches. Intravenous therapies and alternative targeted agents have demonstrated effectiveness in difficult-to-treat populations, while emerging evidence supports combination treatment strategies for selected patients with persistent symptoms despite monotherapy [32]. Such approaches reflect a broader shift toward precision medicine, where therapeutic decisions are increasingly guided by disease severity, prior treatment response, patient preferences, and comorbid conditions.

Long-term safety and treatment persistence emerged as key strengths of novel migraine preventive therapies. Across randomized trials, extension studies, and real-world investigations, adverse events were generally mild to moderate and rarely resulted in treatment discontinuation. This favorable safety profile contrasts with many traditional preventive medications, which are frequently associated with cognitive impairment, weight changes, fatigue, cardiovascular effects, or mood disturbances that limit long-term adherence [33]. Improved tolerability may therefore contribute substantially to the superior persistence rates observed with newer preventive therapies and ultimately enhance their real-world effectiveness.

The findings of this review also highlight the continuing expansion of therapeutic targets beyond CGRP modulation. Although CGRP-based interventions currently dominate the preventive treatment landscape, ongoing research into alternative pathways, including pituitary adenylate cyclase-activating polypeptide (PACAP) signaling and other neuropeptide-mediated mechanisms, may provide additional options for patients who fail to respond adequately to existing therapies. The development of such treatments has the potential to further broaden the scope of precision-based migraine care and address important unmet clinical needs.

This review possesses several strengths. It provides a contemporary synthesis of evidence from randomized controlled trials, systematic reviews, meta-analyses, narrative reviews, and real-world studies evaluating novel pharmacotherapies for migraine prevention. The inclusion of both efficacy and safety outcomes offers a comprehensive overview of current therapeutic developments, while the incorporation of long-term and real-world data enhances the clinical applicability of the findings.

Nevertheless, certain limitations should be acknowledged. The included studies exhibited heterogeneity in design, patient populations, outcome measures, treatment duration, and definitions of treatment response, which limited direct comparisons across studies. Several included articles were narrative reviews and observational investigations, which may be subject to publication bias and confounding. In addition, the rapidly evolving nature of migraine therapeutics means that newer agents and emerging targets may not yet be adequately represented in the available literature. Finally, the predominance of studies evaluating CGRP-targeted therapies reflects the current evidence base and may have limited the assessment of other emerging pharmacological approaches.

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