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Efficacy and safety of anti-calcitonin gene-related peptide monoclonal antibodies in episodic and chronic migraine prevention: A narrative review

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ABSTRACT

Migraine is a common neurological disorder associated with substantial disability. Advances in understanding its pathophysiology have led to the development of therapies, such as monoclonal antibodies directed against calcitonin gene-related peptide (CGRP) or its receptor. This review focused on the efficacy and safety of anti-CGRP monoclonal antibodies in preventing episodic and chronic migraine. A PubMed search was performed for studies published from January 2016 to January 2026. Anti-CGRP monoclonal antibodies reduce monthly migraine days. They also improve responder rates compared with placebo, and they maintain generally favorable safety profiles. However, the treatment effect is moderate, and a substantial placebo response has been consistently observed across trials. Indirect evidence suggests broadly comparable efficacy among available antibodies, whereas the main differences relate to route of administration, dosing schedule, and tolerability. Anti-CGRP monoclonal antibodies are an important option in migraine prevention, especially for patients who do not respond to or cannot tolerate other preventive therapies. Further research is needed to better define their long-term safety and effectiveness compared with other treatments, and their optimal role in individualized treatment strategies.

Keywords: migraine, CGRP, erenumab, fremanezumab, galcanezumab, and eptinezumab.

1. INTRODUCTION

Migraine is a neurological disorder involving repeated headache attacks lasting from 4 to 72 hours, which are often one-sided, pulsating, and commonly occur with nausea, photophobia, and phonophobia. It is one of the most common neurological diseases, affecting approximately 14% of the global population each year. Migraines

are also more common in women, who are more likely to experience migraine-related disability (Dong et al., 2025).

Migraines are classified into episodic migraine (EM) and chronic migraine (CM). Chronic migraine is defined as at least 15 headache days per month for more than 3 months, including at least 8 days meeting the criteria for migraine (Headache Classification Committee of the International Headache Society, 2018). Episodic migraine is characterized by fewer than 15 headache days per month. The differentiation between them is important because they differ in disease severity and treatment response. Therefore, the efficacy and safety should be assessed separately in these two groups.

Conventional migraine therapies are limited by variable efficacy, adverse effects, and contraindications. These limitations have driven the development of therapies targeting calcitonin gene-related peptide (CGRP) signaling. CGRP signaling is considered to play a key role in the pathophysiology of migraine (Wattiez et al., 2020). Monoclonal antibodies targeting the CGRP pathway are the first therapies specifically developed for migraine prevention. They include three antibodies that target the ligand of CGRP (eptinezumab, fremanezumab, and galcanezumab) and one antibody that targets the CGRP receptor (erenumab) (Cohen et al., 2022). Erenumab, fremanezumab, and galcanezumab were approved in 2018, and eptinezumab in 2020 (Aditya and Rattan, 2023).

Therefore, the aim of this narrative review is to evaluate the efficacy and safety of anti-CGRP monoclonal antibodies in the prevention of episodic and chronic migraine.

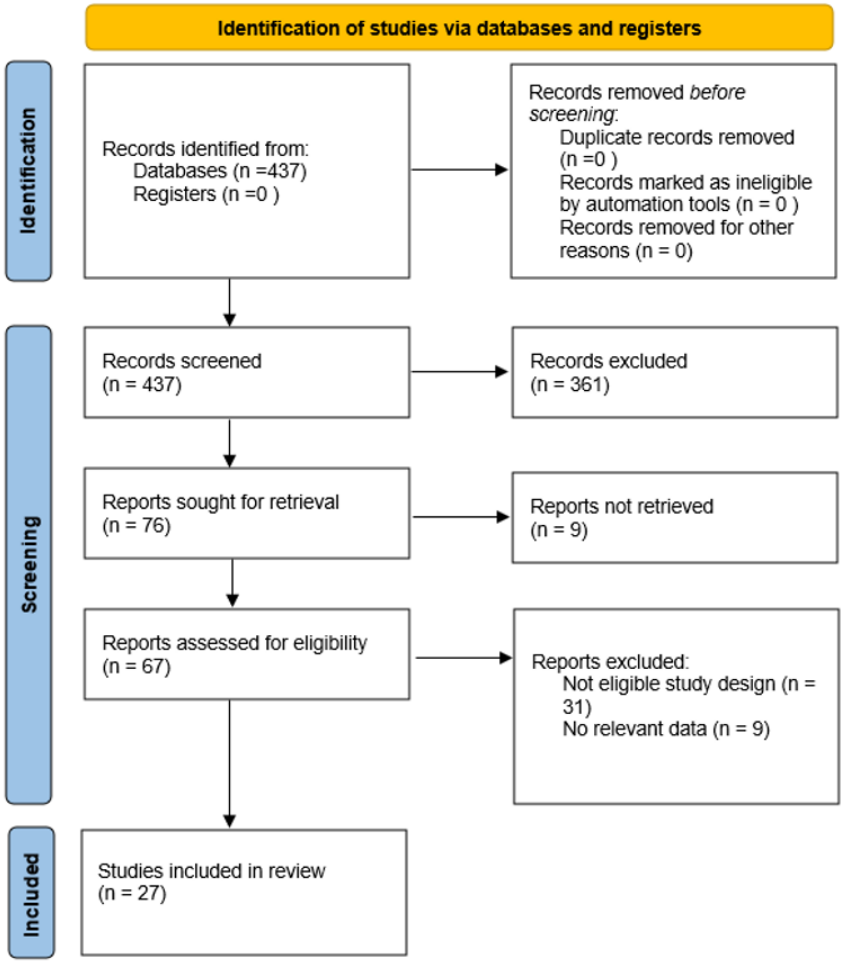

Figure 1. PRISMA flow diagram

2. REVIEW METHODS

A literature search was conducted in PubMed to identify studies evaluating the efficacy and safety of anti-CGRP monoclonal antibodies in the prevention of episodic and chronic migraine. The search included articles published between January 2016 and January 2026. The following keywords were used: “migraine”, “CGRP”, “erenumab”, “fremanezumab”, “galcanezumab”, and “eptinezumab”. Studies

were selected based on their relevance to the topic. Additional articles were identified through reference lists of selected publications when relevant.

Inclusion criteria were English-language studies involving human participants that reported efficacy or safety outcomes related to anti-CGRP monoclonal antibodies. Studies not focused on migraine, non-human studies, and articles lacking sufficient clinical data were excluded.

The selected studies were analyzed and narratively synthesized to provide an overview of the available evidence on anti-CGRP monoclonal antibodies for migraine prophylaxis. As this is a narrative review, no formal systematic review methodology, risk-of-bias assessment, or quantitative synthesis was performed. The literature search and study selection process are summarized in the PRISMA flow diagram (Figure 1).

3. RESULTS AND DISCUSSION

Mechanism of action

CGRP has a significant role in the pathophysiology of migraine, mainly by promoting vasodilation, neurogenic inflammation, and sensitization of trigeminal nociceptors (Wattiez et al., 2020). It is widely recognized as a key mediator in migraine, as its levels tend to increase during attacks and decrease after effective treatment. The way anti-CGRP monoclonal antibodies work depends on their target and pharmacokinetic characteristics. Because of their limited ability to cross the blood–brain barrier, these antibodies act mainly in the peripheral nervous system, although they can still reach structures such as the dura mater and trigeminal ganglia (Cohen et al., 2022).
By binding to the CGRP ligand or to its receptor, these agents block CGRP signaling. This results in reduced vascular dilation and reduced transmission of nociceptive signals (Cohen et al., 2022).

Clinical efficacy and safety of anti-CGRP monoclonal antibodies

Many randomized trials and meta-analyses have studied the efficacy and safety of anti-CGRP monoclonal antibodies. They reduce monthly migraine days (MMD) and improve treatment response compared with placebo. They also generally show a good safety profile. However, study results are variable, and a substantial placebo effect is consistently observed. Although there are some differences in their mechanisms of action, clinical outcomes appear to be largely similar between individual antibodies. The following section presents key findings regarding the efficacy and safety of specific agents used in migraine prevention.

Erenumab

Erenumab was the first monoclonal antibody targeting the CGRP receptor approved for migraine prevention (Pozo-Rosich et al., 2024). It is also the only fully human monoclonal antibody within this group (Yu et al., 2022).

In a phase 3 randomized trial in patients with episodic migraine, monthly migraine days (MMD) decreased by 3.2 days in the 70 mg group and 3.7 days in the 140 mg group, compared to 1.8 days in the placebo group ($P<0.001$ for both comparisons). Although these reductions were statistically significant, the difference compared to placebo remained relatively modest, which is consistent with the well-known placebo effect observed in migraine studies. The rate of adverse events was similar in all groups (Goadsby et al., 2017).

Table 1. Summary of the efficacy and safety of erenumab

Study	Population	Dose of erenumab	Comparator	Efficacy	Adverse events
Goadsby et al., 2017	955 patients with EM	70 mg or 140 mg	Placebo	MMD ↓ by 3.2-3.7 vs 1.8 days	Injection-site pain
HER-MES (Reuter et al., 2022)	777 patients with migraine	70 mg or 140 mg	Topiramate	≥50% MMD reduction: 55.4% vs 31.2%	Less frequent than in the topiramate group
APPRAISE (Pozo-Rosich et al., 2024)	621 patients with EM	70 mg or 140 mg	Oral preventive medications (OMPM)	MMD ↓ by 4.32 vs 2.65 days	Similar to OMPM

ARISE (Dodick et al., 2018a)	577 patients with EM	70 mg	Placebo	MMD ↓ by 2.9 vs 1.8 days	Similar to placebo
EMPOwER (Wang et al., 2021)	900 patients with EM	70 mg or 140 mg	Placebo	MMD ↓ by 4.2-4.8 vs 3.1 days	Similar to placebo
DRAGON (Yu et al., 2022)	557 patients with CM	70 mg	Placebo	MMD ↓ by 8.2 vs 6.6 days	Constipation
Sakai et al., 2019	475 patients with EM	28 mg or 70 mg or 140 mg	Placebo	MMD ↓ by 1.19-2.25 vs +0.06 days	Similar to placebo

Another important study, HER-MES, compared erenumab with topiramate. During the last 3 months of treatment, at least a 50% reduction in MMD was observed in 55.4% of patients receiving erenumab and in 31.2% of patients in the group of patients receiving topiramate (OR 2.76; 95% CI 2.06–3.71; RR 1.78; 95% CI 1.50–2.11). In addition, adverse effects were reported less frequently in the erenumab group (55.4%) than in the topiramate group (81.2%) (Reuter et al., 2022). These findings suggest that erenumab may be better tolerated than conventional oral preventive treatments.

Also, a recent meta-analysis did not show a significant difference in efficacy between episodic and chronic migraine. However, the 140 mg dose appeared more effective than the 70 mg dose (Haseeb et al., 2025). Taken together, these findings indicate that erenumab is an effective option for migraine prevention. At the same time, the magnitude of benefit varies and should be interpreted with consideration of the placebo effect and individual patient response. Key clinical trial data are summarized in Table 1.

Fremanezumab

Fremanezumab is a humanized monoclonal antibody that selectively binds to CGRP, targeting both α and β isoforms of the ligand. In a phase 3 randomized controlled trial in patients with chronic migraine, monthly migraine days (MMD) were reduced by 4.3 and 4.6 days in the treatment groups, compared with 2.5 days in the placebo group ($P<0.001$ for both of the comparisons). The improvement was statistically significant but only moderate compared with placebo. Adverse events were slightly more often in the fremanezumab groups (70–71%) than in the placebo group (64%), with injection-site pain being the most frequently reported. These events were generally mild and did not seem to significantly affect tolerability (Silberstein et al., 2017).

The efficacy of fremanezumab has also been confirmed in episodic migraine. After 12 weeks of treatment, MMD decreased from 9.2 to 5.3 days in one group and from 8.9 to 4.9 days in another, while in the placebo group it decreased from 9.1 to 6.5 days ($P<0.001$ for both comparisons). Similar to other studies, injection-site reactions were the most commonly reported adverse events (Dodick et al., 2018b).

Overall, fremanezumab appears to be an effective preventive option for both episodic and chronic migraine, with a generally favorable safety profile. As with other anti-CGRP therapies, the observed benefits should be interpreted with consideration of the placebo response and patient-to-patient variability. Key findings from clinical trials are summarized in Table 2.

Table 2. Summary of the efficacy and safety of fremanezumab

Study	Population	Dose of fremanezumab	Comparator	Efficacy	Adverse events
Silberstein et al., 2017	1130 patients with CM	Monthly (225 mg) or Quarterly (675 mg)	Placebo	MMD ↓ by 4.3-4.6 vs 2.5 days	Injection-site reactions
Dodick et al., 2018b	875 patients with EM	Monthly (225 mg) or Quarterly (675 mg)	Placebo	MMD ↓ by 3.9-4.0 vs 2.6 days	Injection-site reactions
Lipton et al., 2025	353 patients with comorbid major depressive disorder	Monthly (225 mg)	Placebo	MMD ↓ by 5.1 vs 2.9 days	No significant difference
Sakai et al., 2021a	571 patients with CM	Monthly (675 mg, 225 mg,	Placebo	MMD ↓ by 4.1	Injection-site

		225 mg) or Quarterly (675 mg)		vs 2.4 days	reactions
Sakai et al., 2021b	357 patients with EM	Monthly (225 mg) or Quarterly (675 mg)	Placebo	MMD ↓ by 4.0 vs 1.0 days	Injection-site reactions

Galcanezumab

Galcanezumab is a humanized monoclonal antibody that inhibits the biological activity of CGRP (Detke et al., 2018). Its efficacy in episodic migraine has been evaluated in two phase 3 randomized controlled trials, EVOLVE-1 and EVOLVE-2. In both studies, treatment with galcanezumab reduced monthly migraine days (MMD) compared with placebo ($p < 0.001$). The magnitude of effect was moderate and generally consistent with findings reported for other anti-CGRP monoclonal antibodies. The most common reported adverse events were injection-site reactions (Stauffer et al., 2018; Skljarevski et al., 2018a).

In patients with chronic migraine, efficacy was assessed in another phase 3 randomized trial. MMD was reduced by 4.8 days in the 120 mg group and by 4.6 days in the 240 mg group, compared to 2.7 days in the placebo group ($p < 0.001$ for both doses). As in other studies, the difference relative to placebo remained moderate. Injection-site reactions were reported more frequently in patients receiving galcanezumab, although they were typically mild and did not appear to significantly affect treatment tolerability (Detke et al., 2018).

Evidence from a meta-analysis of five clinical trials further supports the efficacy of galcanezumab, showing a significant reduction in MMD across a range of doses (120–300 mg) (Zhao et al., 2021). Overall, galcanezumab appears to be an effective preventive treatment for both episodic and chronic migraine, with a safety profile comparable to other agents in this class. As with other therapies targeting the CGRP pathway, the observed benefits should be interpreted due to the notable placebo effect and interindividual variability. Key results from clinical trials are summarized in Table 3.

Table 3. Summary of the efficacy and safety of galcanezumab

Study	Population	Dose of galcanezumab	Comparator	Efficacy	Adverse events
EVOLVE-1 (Stauffer et al., 2018)	858 patients with EM	120 mg or 240 mg	Placebo	MMD ↓ by 4.6-4.7 vs 2.8 days	Injection-site reactions
EVOLVE-2 (Skljarevski et al., 2018a)	915 patients with EM	120 mg or 240 mg	Placebo	MMD ↓ by 4.2-4.3 vs 2.3 days	Injection-site reactions
REGAIN (Detke et al., 2018)	1113 patients with CM	120 mg or 240 mg	Placebo	MMD ↓ by 4.6-4.8 vs 2.7 days	Injection-site reactions
Oakes et al., 2018	410 patients with EM	5 mg, 50 mg, 120 mg or 300 mg	Placebo	Efficacy not primary outcome	Injection-site pain
Skljarevski et al., 2018b	410 patients with EM	5 mg, 50 mg, 120 mg or 300 mg	Placebo	Significant reduction in headache days compared to placebo	Injection-site pain
PERSIST (Hu et al., 2022)	520 patients with EM	120 mg	Placebo	Significant reduction in headache days compared to placebo	Injection-site reactions

Eptinezumab

Eptinezumab is a humanized monoclonal antibody that binds selectively to CGRP (Dodick et al., 2019). Efficacy of eptinezumab in both episodic and chronic migraine has been evaluated in phase 3 randomized controlled trials, PROMISE-1 and PROMISE-2. In these studies, monthly migraine days (MMD) were reduced by 3.9–4.3 days compared to 3.2 days with placebo in episodic migraine, and by

7.7–8.2 days compared to 5.6 days with placebo in chronic migraine. Although these reductions were statistically significant, the difference relative to placebo remained moderate. Adverse events more frequent than in the placebo groups included upper respiratory tract infection and fatigue in PROMISE-1, and nasopharyngitis in PROMISE-2 (Ashina et al., 2020; Lipton et al., 2020). These events were generally mild and did not seem to substantially affect treatment tolerability.

Additional evidence comes from the SUNRISE trial. In this study, patients with chronic migraine experienced a notable reduction in monthly migraine days (MMD) (Yu et al., 2025). A meta-analysis of four randomized controlled trials also supported the effectiveness of eptinezumab. The study found that doses ranging from 30 mg to 1000 mg reduced MMD and were generally safe. The best results were seen with the 300 mg dose (Yan et al., 2021).

An important distinguishing feature of eptinezumab is its intravenous administration, which may allow a faster onset of action than subcutaneous therapies. Overall, eptinezumab appears to be an effective option for migraine prevention in episodic and chronic forms, with a safety profile similar to that of other agents targeting the CGRP pathway. As with other therapies in this class, the magnitude of benefit should be interpreted in the context of placebo response and patient-to-patient variability. Key clinical trial findings are summarized in Table 4.

Table 4. Summary of the efficacy and safety of eptinezumab

Study	Population	Dose of eptinezumab	Comparator	Efficacy	Adverse events
PROMISE-1 (Ashina et al., 2020)	888 patients with EM	100 mg or 300 mg	Placebo	MMD ↓ by 3.9-4.3 vs 3.2 days	≥2% more frequent: upper respiratory tract infection, fatigue
PROMISE-2 (Lipton et al., 2020)	1072 patients with CM	100 mg or 300 mg	Placebo	MMD ↓ by 7.7-8.2 vs 5.6 days	≥2% more frequent: nasopharyngitis
SUNRISE (Yu et al., 2025)	978 patients with CM	100 mg or 300 mg	Placebo	MMD ↓ by 7.2-7.5 vs 4.8 days	Similar to placebo
Dodick et al., 2019	616 patients with CM	10, 30, 100 or 300 mg	Placebo	Dose-dependent reduction in MMD	Similar to placebo

Comparison of anti-CGRP monoclonal antibodies

A meta-analysis of 19 studies showed that anti-CGRP monoclonal antibodies can help prevent migraines. The tested doses reduced the number of migraine days per month. The 30 mg dose of eptinezumab was less effective. More patients treated with these antibodies experienced at least a 50% reduction in migraine days than those who received a placebo (Haghdoost et al., 2023).

A network meta-analysis showed that these agents are generally safe and do not significantly increase the likelihood of serious adverse events. Among them, eptinezumab had the lowest risk of adverse events. Fremanezumab and galcanezumab were more often linked to treatment-emergent adverse events (TEAEs), which were mainly injection-site reactions. The highest rate of TEAEs was seen with galcanezumab at doses of 240 mg and 120 mg (Messina et al., 2023).

Taken together, current evidence suggests that anti-CGRP monoclonal antibodies have broadly similar efficacy, with no clear superiority of one agent over another. Differences in safety profiles appear to be relatively small and are mainly related to the type and frequency of adverse events rather than their severity. In clinical practice, the choice of a treatment is therefore more likely to depend on factors such as route of administration, dosing schedule, tolerability, and patient preference. Despite consistent results, the lack of direct comparisons makes it difficult to assess treatment differences. Further studies directly comparing individual therapies are needed to define potential differences between treatments.

Limitations

Although anti-CGRP monoclonal antibodies appear effective and safe, several limitations of the available evidence should be considered. Most data come from randomized controlled trials with relatively short follow-up periods, which makes it difficult to assess long-term outcomes, particularly with regard to safety and sustained effectiveness. In addition, there is a lack of direct comparisons between individual antibodies.

Trial populations are often highly selected, which may reduce the generalizability of the results to routine practice. Patients with comorbidities are underrepresented, and the way patients follow treatment may differ from that seen in trials. In addition, differences in study design, dosing, and outcome measures make comparisons between studies difficult.

Practical factors should also be taken into account. High treatment costs and limited accessibility may restrict the use of these therapies in everyday clinical practice. Overall, these limitations suggest that the current evidence should be interpreted with caution and indicate the need for further real-world studies as well as direct comparative trials.

Future perspectives

Further research is needed to better understand the long-term safety and effectiveness of anti-CGRP monoclonal antibodies. Most available data are based on studies with relatively short follow-up periods. Direct head-to-head comparisons between antibodies would also be valuable in defining potential differences in efficacy and tolerability. Further studies should focus on identifying predictors of treatment response to support a more personalized approach to migraine prevention.

The role of anti-CGRP monoclonal antibodies in relation to emerging therapies, such as gepants, and the potential for combination strategies is not yet fully understood. In addition, real-world data on long-term adherence, cost-effectiveness, and treatment access will be essential for determining their place in everyday clinical practice.

4. CONCLUSION

Anti-CGRP monoclonal antibodies are an effective and generally well-tolerated option for migraine prevention. Data from randomized controlled trials and meta-analyses show reductions in monthly migraine days in both episodic and chronic migraine. The efficacy of anti-CGRP monoclonal antibodies appears similar, but differences between studies make comparisons difficult. Treatment choice often depends on patient preference and tolerability.

In real-world settings, these therapies represent a great alternative for patients who do not respond to conventional preventive treatments or are unable to tolerate them. Their mechanism of action and relatively favorable safety profile further support their use in selected patient groups. Taken together, anti-CGRP monoclonal antibodies have clearly expanded the therapeutic options available for migraine prevention. However, several important questions remain unanswered.

Further research is needed to better define their long-term safety, comparative effectiveness, and cost-effectiveness, and to identify predictors of treatment response that could support a more individualized approach to therapy. Overall, while current evidence supports their clinical use, ongoing studies and real-world data will be essential to fully establish their role in the long-term management of migraine.

Abbreviations:

CGRP – calcitonin gene-related peptide
CM – chronic migraine
EM – episodic migraine
MMD – monthly migraine days
OMPM – oral migraine preventive medications
TEAEs – treatment-emergent adverse events

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Authors' Contributions

Zuzanna Irzyk - contributed to the study conception and design, conducted the literature search and data analysis, wrote the manuscript, approved the final version for publication
Dominika Ruszel - conducted the literature search and data analysis.
Emilia Goc - conducted the literature search and data analysis.
Julia Rogała - conducted the literature search and data analysis.
Katarzyna Markuszka – conducted the literature search and data analysis.

Kinga Polityńska – conducted the literature search and data analysis.
Klaudia Samuła - conducted the literature search and data analysis.
Martyna Sarzyńska – conducted the literature search and data analysis.
Mateusz Szabat – conducted the literature search and data analysis.
Sylwia Lepak - conducted the literature search and data analysis.

Informed consent
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Ethical approval
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Conflict of interest
The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability
All data associated with this study will be available based on the reasonable request to corresponding author.

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