

## Comparative Effectiveness of CGRP Antagonists Versus Traditional Prophylactic Agents in Migraine: A Comprehensive Review

Altaf Hussain<sup>1</sup>, Qasim Zia<sup>2\*</sup>, Muhammad Salman Khan<sup>2</sup>, Muhammad Usama Khalid<sup>2</sup>, Omer Ismail Khalid<sup>3</sup>, Muhammad Hamza Khan<sup>4</sup>, Ayesha Abbas<sup>5</sup>, Hajra Azmat<sup>6</sup>

<sup>1</sup>DHQ Hospital, Bhakkar

<sup>2</sup>Multan Medical & Dental College, Multan

<sup>3</sup>Arrahma Mental Hospital, Multan

<sup>4</sup>Nishtar Medical University, Multan

<sup>5</sup>Bahawal Victoria Hospital, Bahawalpur

<sup>6</sup>M.Islam Medical & Dental College, Gujranwala

---

**Citation:** Altaf Hussain, Qasim Zia, Muhammad Salman Khan, Muhammad Usama Khalid, Omer Ismail Khalid, Muhammad Hamza Khan, et al. Comparative Effectiveness of CGRP Antagonists Versus Traditional Prophylactic Agents in Migraine: A Comprehensive Review. *Anna Neur & Neurosci*. 2026;1(1):1-7.

**Received Date:** 16 April, 2026; **Accepted Date:** 19 April, 2026; **Published Date:** 20 April, 2026

\***Corresponding author:** Qasim Zia. Multan Medical & Dental College, Multan

**Copyright:** © Qasim Zia, Open Access 2022. This article, published in *Anna Neur & Neurosci (ANN)* (Attribution 4.0 International), as described by <http://creativecommons.org/licenses/by/4.0/>.

---

### ABSTRACT

Migraine is a highly prevalent and disabling neurovascular disorder with substantial socioeconomic impact worldwide. Preventive pharmacotherapy remains the cornerstone for reducing migraine frequency, severity, and associated disability. Traditional prophylactic agents — including beta-blockers, antiepileptics, antidepressants, and calcium channel blockers — have long been utilized despite limitations in efficacy, tolerability, and adherence. The emergence of calcitonin gene-related peptide (CGRP) antagonists, including monoclonal antibodies and small-molecule gepants, represents a paradigm shift in migraine prevention. These agents target migraine-specific pathophysiological pathways, offering improved efficacy and tolerability. This review critically examines and compares the effectiveness, safety, tolerability, and clinical utility of CGRP antagonists with conventional prophylactic therapies. Evidence from randomized controlled trials, systematic reviews, and meta-analyses suggests that CGRP-targeted therapies demonstrate superior efficacy in reducing monthly migraine days and exhibit a more favorable adverse effect profile. However, considerations such as cost, long-term safety, and accessibility remain challenges. This manuscript aims to provide a comprehensive and balanced evaluation to guide clinicians in evidence-based migraine management.

### INTRODUCTION

Migraine is a chronic neurological disorder affecting approximately one billion individuals globally,

ranking among the leading causes of disability, particularly in young and middle-aged adults.<sup>[1]</sup> Characterized by recurrent episodes of moderate-to-severe headache often accompanied by nausea, photophobia, and phonophobia, migraine significantly impairs quality of life and productivity.<sup>[2]</sup> Preventive therapy is indicated in patients with frequent attacks, significant disability, or inadequate response to acute treatments.

Historically, migraine prophylaxis has relied on medications developed for other indications, including cardiovascular and psychiatric disorders. These traditional agents, such as propranolol, topiramate, valproate, and amitriptyline, have demonstrated efficacy but are often limited by suboptimal tolerability and adherence.<sup>[3]</sup>

The discovery of calcitonin gene-related peptide (CGRP) as a key mediator in migraine pathophysiology has led to the development of targeted therapies, including monoclonal antibodies and small-molecule antagonists (gepants). CGRP is a neuropeptide widely distributed in the trigeminovascular system, playing a central role in vasodilation, neurogenic inflammation, and pain transmission.<sup>[4]</sup> Blocking CGRP or its receptor offers a mechanism-specific approach to migraine prevention.

This review explores the comparative effectiveness of CGRP antagonists versus traditional prophylactic agents, focusing on efficacy, safety, tolerability, and clinical applicability.

### **Pathophysiology of Migraine and Role of CGRP**

Migraine pathogenesis involves complex interactions between neuronal, vascular, and inflammatory pathways. Activation of the trigeminovascular system leads to the release of neuropeptides, including CGRP, substance P, and neurokinin A, resulting in vasodilation and neurogenic inflammation.<sup>[4]</sup>

CGRP, in particular, has been identified as a critical mediator in migraine attacks. Elevated levels of CGRP have been observed during migraine episodes, and infusion of CGRP can trigger migraine-like headaches in susceptible individuals.<sup>[5]</sup> CGRP receptors are widely expressed in both central and peripheral nervous systems, making them an attractive therapeutic target.

Blocking CGRP signaling can inhibit vasodilation and reduce nociceptive transmission, thereby preventing migraine attacks. This mechanism underpins the development of CGRP monoclonal antibodies and gepants.<sup>[6]</sup>

### **Traditional Migraine Prophylactic Agents**

Traditional prophylactic medications encompass several pharmacological classes: Beta-Blockers  
Beta-blockers such as propranolol and metoprolol are among the most commonly prescribed first-line agents. Their mechanism in migraine prevention is not fully understood but may involve modulation of adrenergic activity and cerebral blood flow.<sup>[7]</sup>

### **Antiepileptics**

Topiramate and valproate are effective in reducing migraine frequency. Topiramate modulates voltage-gated ion channels and enhances GABAergic activity, while valproate increases GABA levels and inhibits neuronal excitability.<sup>[8]</sup>

### **Antidepressants**

Tricyclic antidepressants, particularly amitriptyline, are widely used for migraine prevention due to their effects on serotonin and norepinephrine pathways.<sup>[9]</sup>

### **Calcium Channel Blockers**

Agents such as verapamil have been used, though evidence supporting their efficacy remains limited.<sup>[10]</sup>

Despite their efficacy, these medications are associated with significant adverse effects, including weight gain, sedation, cognitive impairment, and cardiovascular complications, leading to poor adherence.<sup>[3]</sup>

**CGRP Antagonists: Mechanisms and Classification** CGRP-targeted therapies are categorized into:

Monoclonal Antibodies

These include erenumab (CGRP receptor antagonist) and ligand-binding antibodies such as fremanezumab, galcanezumab, and eptinezumab. They are administered via subcutaneous or intravenous routes, typically on a monthly or quarterly basis.<sup>[11]</sup>

### **Gepants**

Small-molecule CGRP receptor antagonists, such as rimegepant and atogepant, are orally administered and can be used for both acute and preventive treatment.<sup>[12]</sup>

These agents specifically target migraine pathophysiology, distinguishing them from traditional therapies.

### **Comparative Efficacy**

Evidence from randomized controlled trials and meta-analyses demonstrates that CGRP antagonists are highly effective in migraine prevention.

A large network meta-analysis including over 32,000 patients found that CGRP monoclonal antibodies and gepants significantly increased the proportion of patients achieving at least a 50% reduction in monthly migraine days compared to placebo.<sup>[13]</sup> Furthermore, these agents demonstrated higher efficacy compared to traditional drugs such as beta-blockers, amitriptyline, and valproate, which showed only moderate-certainty evidence.<sup>[13]</sup>

CGRP-targeted therapies also exhibit rapid onset of action and sustained efficacy, with many patients experiencing improvement within the first month of treatment.<sup>[14]</sup>

In contrast, traditional agents often require several weeks to months for optimal effect and may not achieve comparable reductions in migraine frequency.

### **Safety and Tolerability**

Safety and tolerability are critical determinants of long-term adherence in migraine prophylaxis.

Traditional prophylactic agents are associated with a high incidence of adverse effects. For instance, valproate is linked to teratogenicity and weight gain, topiramate to cognitive impairment and paresthesia, and beta-blockers to fatigue and hypotension.<sup>[15]</sup>

In contrast, CGRP antagonists have demonstrated a favorable safety profile. Clinical trials and systematic reviews report minimal increases in adverse events compared to placebo.<sup>[13]</sup> Common side effects include mild injection-site reactions and constipation.

Importantly, CGRP-targeted therapies do not appear to increase treatment discontinuation rates due to adverse events, unlike traditional medications.<sup>[13]</sup>

However, long-term safety data remain limited, and theoretical concerns exist regarding cardiovascular risks due to CGRP's role in vasodilation.<sup>[6]</sup>

### **Adherence and Patient Satisfaction**

Adherence to migraine prophylaxis is often suboptimal, with discontinuation rates exceeding 50% within

six months for traditional therapies.<sup>[13]</sup>

Factors contributing to poor adherence include adverse effects, lack of efficacy, and complex dosing regimens.

CGRP antagonists offer advantages in this regard due to their favorable tolerability, convenient dosing schedules, and targeted mechanism of action. Studies indicate higher patient satisfaction and improved quality of life with CGRP-targeted therapies.<sup>[16]</sup>

### **Cost-Effectiveness and Accessibility**

Despite their clinical advantages, CGRP antagonists are significantly more expensive than traditional medications.

Cost-effectiveness analyses suggest that while CGRP-targeted therapies may be justified in patients with refractory migraine, their widespread use is limited by financial constraints.<sup>[17]</sup>

Insurance coverage and healthcare system policies play a crucial role in determining accessibility.

### **Special Populations**

The use of CGRP antagonists in special populations, such as pregnant women, elderly patients, and individuals with cardiovascular disease, requires careful consideration.

Traditional agents like valproate are contraindicated in pregnancy, while beta-blockers may be used with caution.<sup>[18]</sup>

Limited data exist on the safety of CGRP antagonists in pregnancy, and their use is generally not recommended.

### **Limitations of Current Evidence**

While the evidence supporting CGRP antagonists is robust, several limitations exist:

1. Lack of long-term safety data
2. Limited head-to-head trials comparing CGRP antagonists with traditional agents
3. Potential publication bias
4. High cost limiting real-world applicability

## Future Directions



Future research should focus on:

- Long-term safety and cardiovascular outcomes
- Comparative effectiveness in diverse populations
- Cost-reduction strategies
- Personalized medicine approaches

## CONCLUSION

CGRP antagonists represent a significant advancement in migraine prophylaxis, offering superior efficacy and tolerability compared to traditional agents. Evidence consistently demonstrates that these therapies achieve greater reductions in migraine frequency with fewer adverse effects. However, their high cost and limited long-term safety data remain challenges. Traditional prophylactic agents continue to play a role, particularly in resource-limited settings. A patient-centered approach, considering efficacy, safety, cost, and individual preferences, is essential in optimizing migraine management.

## REFERENCES

1. GBD 2019 Diseases and Injuries Collaborators. Lancet. 2020.
2. Steiner TJ, et al. J Headache Pain. 2020.
3. Silberstein SD. Neurology. 2012.
4. Edvinsson L. Lancet Neurol. 2018.
5. Goadsby PJ, et al. Brain. 2002.
6. Deen M, et al. J Headache Pain. 2017. 
7. Jackson JL, et al. BMJ. 2015.
8. Brandes JL. JAMA. 2004.
9. Couch JR. Headache. 2011.
10. Linde K, et al. Cochrane Database. 2013.
11. Dodick DW. N Engl J Med. 2018.
12. Croop R, et al. Lancet. 2019.
13. Sacco S, et al. J Headache Pain. 2023. 
14. Tepper SJ. Neurology. 2017.
15. Diener HC, et al. Lancet Neurol. 2004.
16. Lipton RB, et al. Headache. 2020.
17. ICER Report. 2021.
18. ACOG Guidelines. 2020.
19. Ferrari MD, et al. Lancet Neurol. 2015.
20. Ashina M, et al. Nat Rev Neurol. 2021.
21. Dodick DW, et al. Cephalalgia. 2014.

22. Bigal ME, et al. *Neurology*. 2015.
23. Olesen J. *Lancet*. 2018.
24. Raffaelli B, et al. *J Intern Med*. 2019.
25. Reuter U, et al. *N Engl J Med*. 2018.
26. Skljarevski V, et al. *Neurology*. 2018.
27. Goadsby PJ, et al. *Lancet Neurol*. 2017.
28. Lipton RB, et al. *JAMA*. 2019.
29. Dodick DW, et al. *Cephalalgia*. 2019.
30. Ashina H, et al. *JAMA Neurol*. 2021.
31. Charles A. *Lancet Neurol*. 2017.
32. Barbanti P, et al. *CNS Drugs*. 2019.
33. Negro A, et al. *Expert Opin Pharmacother*. 2020.
34. Tassorelli C, et al. *Eur J Neurol*. 2018.
35. Blumenfeld AM, et al. *Headache*. 2020.
36. Yuan H, et al. *Pain*. 2019.
37. Charles AC. *Neurology*. 2013.
38. Dodick DW, et al. *Headache*. 2020.
39. Rivera-Mancilla E, et al. *Expert Opin Drug Saf*. 2020.
40. Li J, et al. *J Transl Med*. 2025