

# Scoping Review of Prophylactic Treatments for Reducing Migraine Occurrences

Ethan Hopkins, William Nguyen, James F. Keane, Leonard B. Goldstein\*

Assistant Vice President for Clinical Education Development, A.T. Still University Mesa, Arizona, United States.

**\*Corresponding Author:** Leonard B. Goldstein, Assistant Vice President for Clinical Education Development, A.T. Still University Mesa, Arizona, United States.

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## Abstract

### Background:

Migraine is a prevalent neurological disorder with significant socioeconomic and quality-of-life burdens. While acute treatments exist, prophylactic therapies are essential to reducing monthly migraine days (MMDs). This scoping review evaluates pharmacologic, non-pharmacologic, and procedural interventions for migraine prevention, with an emphasis on osteopathic manipulative treatment (OMT), supplements, and emerging therapies.

### Methods:

A comprehensive literature search was conducted across PubMed, ClinicalTrials.gov, Cochrane Library, OSTMED.Dr, Still OneSearch, CINAHL, ClinicalKey, and Scopus using standardized keywords. Grey literature sources, including major headache organizations, were also reviewed. Studies were included if they examined prophylactic migraine treatments and reported changes in MMDs.

### Results:

Among pharmacologic interventions, onabotulinumtoxinA (Botox) and CGRP inhibitors demonstrated the greatest reductions in MMDs. Non-pharmacologic approaches, including OMT, acupuncture, and neuromodulation, showed varying effectiveness, often as adjunct therapies. Nutraceuticals, such as magnesium and riboflavin, provided modest benefits. Variability in study design, patient populations, and outcome measures impacted direct comparisons.

### Conclusion:

A range of prophylactic treatments exist for reducing MMDs, with efficacy varying by patient population. While pharmacologic options remain primary, non-pharmacologic and procedural therapies offer promising alternatives. Future research should standardize outcome measures and explore personalized treatment approaches.

**Keywords:** migraine; prophylactic treatment; osteopathic manipulative treatment; CGRP inhibitors; non-pharmacologic therapy; migraine prevention

## Introduction

Migraine is one of the most prevalent neurological disorders, and is a serious public health concern, affecting approximately 1 out of every 6 Americans. [1]. Although migraine is considered a benign disorder, the socioeconomic burden of migraine is substantial, with migraine-related lost productivity incurring extensive annual costs. [-4]

The clinical presentation of migraines is highly variable among individuals but commonly includes recurrent, intense unilateral throbbing headaches, often accompanied by anorexia, nausea, vomiting, phonophobia, and

photophobia. [5-6] Acute migraine attacks are typically divided into four phases—prodrome, aura, headache, and postdrome—that follow a sequential progression. However, the specific manifestation, overlap, duration, and intensity of these phases can vary significantly between individuals and even across episodes. [7]

The prodrome phase occurs hours to days before headache onset and is characterized by subtle warning signs like mood changes, neck stiffness, fatigue, increased urination and food cravings. [8] The aura phase, when

present, manifests as transient neurological symptoms such as visual, sensory, or motor disturbances that typically develop within an hour of headache onset. [9] The headache phase is the most debilitating, marked by severe pain and sensitivity to external stimuli. Finally, the postdrome phase, often referred to as the "migraine hangover," is associated with lingering symptoms, including fatigue, difficulty concentrating, mood disturbances, and residual head discomfort.[10] Migraine attacks can be triggered by a variety of factors, including stress, illness, emotions, and hormonal fluctuations, such as those occurring during the menstrual cycle.

Emerging research has advanced our understanding of migraine pathophysiology, shedding light on underlying mechanisms. Cortical spreading depression (CSD), a self-propagating wave of neuronal and glial depolarization across the cerebral cortex, has been implicated as a key driver of migraines. CSD is hypothesized to generate the aura phase, activate trigeminal nerve afferents, and disrupt the blood-brain barrier through matrix metalloproteinase activation and upregulation.[8] Additionally, while vasodilation of dural and extracranial vessels has long been considered central to migraine pain, recent findings challenge this theory, suggesting that other mechanisms may play a more pivotal role. [9]

The pathophysiology of migraines involves the activation of the trigeminal vascular system. While vasodilation of cranial blood vessels is no longer considered the primary or sole mechanism behind migraines, our current understanding suggests that blood vessels still play a role. The reason for this logic is that blood vessels release and respond to various mediators, such as growth factors, cytokines, ATP, and NO, and many of these mediators are also known to have actions in neurons that can lead to migraines. On the other hand, blood vessels are capable of facilitating bi-directional communication with the nervous system through the release of substances like norepinephrine and calcitonin gene-related peptide (CGRP), which directly impact the cells present in the vessels. This means that various normal and pathological processes taking place within and among vascular cells can serve as channels for interaction between the vascular system and the nervous system, without requiring alterations in vascular tone. [ ]

CGRP is a 37-amino acid neuropeptide that is produced as a consequence of alternative RNA processing of the calcitonin gene. It is known to have strong vasodilatory effects, and it is mainly released from C and A $\delta$  sensory fibers. [ ] CGRP receptors are located in various neuronal tissues, such as the trigeminal ganglion, cerebral and meningeal vasculature, trigeminal nucleus caudalis (located in the brainstem) and the thalamus. Activation of these receptors within the trigeminovascular system plays an important role in the events that ultimately lead to the experience of pain with migraines, as evidenced by the ability of IV administered exogenous CGRP to cause migraine-like headaches. [ - ] After nerve stimulation, the release of CGRP occurs through calcium-dependent exocytosis from its storage vesicles. Once released, it is hypothesized that CGRP binds to CGRP receptors, and relays migraine pain through the brainstem into the brain via the trigeminovascular system. [ ]

With this rather new discovery between the correlation of CGRP and migraines, many new studies have explored the efficacy of CGRP antagonists, specifically in comparison to other preventative medications. In fact, as of April 23, 2023, the FDA has approved expanding the indication of QULIPTA (atogepant) for the preventative treatment of migraine in adults. [ ] Atogepant has shown to significantly reduce monthly migraine days, monthly headache days, and monthly medication use days in comparison to a placebo, with no significant difference in adverse effects. [ ]

While CGRP antagonists as well as other medication classes like the serotonin receptor agonists (triptans) have demonstrated efficacy in the acute treatment of migraines, the focus of this scoping review is distinct. This review aims to explore and evaluate a broad range of preventive interventions aimed at reducing the frequency of migraine attacks. These interventions include pharmacological agents, such as beta-blockers,

antiepileptic drugs, and CGRP inhibitors, as well as non-pharmacological approaches, such as osteopathic manipulative treatment (OMT), acupuncture, and mindfulness-based therapies. Additionally, the review will assess the potential of nutraceuticals, including magnesium, riboflavin (vitamin B2), and coenzyme Q10, as well as dietary modifications and lifestyle interventions.

The effectiveness of these preventive strategies will be evaluated based on their ability to reduce monthly migraine days (MMDs). It is important to note that this review will not focus on interventions aimed at decreasing the intensity or severity of migraine symptoms, which are often measured using tools such as the Headache Impact Test-6 (HIT-6) or the Migraine Disability Assessment (MIDAS) scores. By concentrating on MMD reduction, this review seeks to provide a targeted analysis of diverse approaches to migraine prevention, contributing to a deeper understanding of their roles in long-term management.

## Methods

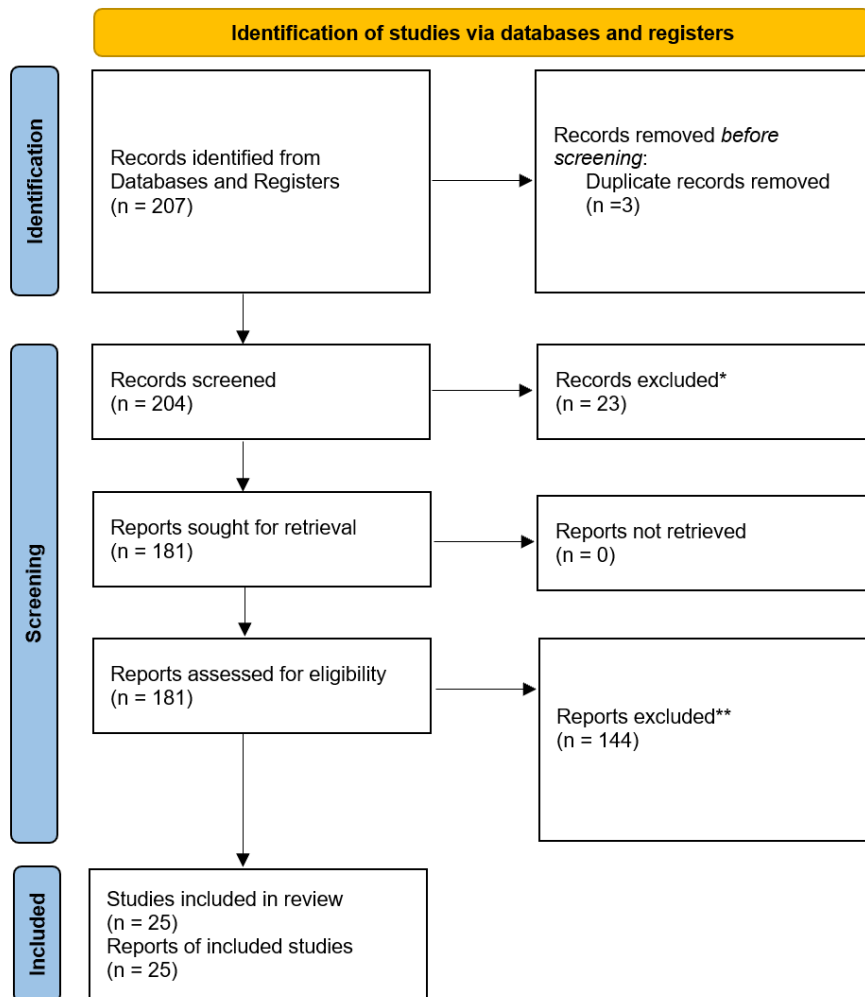
A comprehensive search strategy has been developed in consultation with a medical librarian (Leslie Golamb) to ensure breadth and relevance.

The search began with an exploration of grey literature sources to refine keyword selection and identify additional relevant studies. Google was used for preliminary searches to explore osteopathic treatments for chronic migraines, uncover relevant grey literature, and establish key search terms. Information was gathered from reputable organizations, including the American Migraine Foundation, the Association of Migraine Disorders, the National Headache Foundation, and the American Academy of Neurology. These sources provided insights into current best practices, research priorities, and established approaches to migraine prophylaxis, helping to inform the direction of the database search.

Following this preliminary investigation, systematic searches were conducted across multiple academic databases, including PubMed, ClinicalTrials.gov, Cochrane Library, OSTMED. Dr, Still One Search, CINAHL, Clinical Key, and Scopus. A standardized set of search terms was applied across databases to ensure consistency and comprehensive coverage. These included variations of "migraine," "migraine headache," "prophylactic treatment," "preventive treatment," "long-term treatment," "therapy," "intervention," "management," and "osteopathic manipulative treatment (OMT)." In PubMed, searches utilized Medical Subject Headings (MeSH) in combination with these keywords, while in other databases, similar Boolean strategies were employed to maximize relevant results. Filters were applied to restrict results to studies published from 2010 onward, with Scopus searches further refined to include only journal articles, conference proceedings, and trade journals from 2014 onward. ClinicalTrials.gov and the Cochrane Library were specifically searched for ongoing or completed clinical trials and systematic reviews evaluating OMT as a migraine prophylaxis. OSTMED. Dr, an osteopathic-focused database, was searched using the keyword "migraine headache." Broad searches in Still One Search, CINAHL, and Clinical Key incorporated the same standardized terms, with filters applied for peer-reviewed journal articles. By maintaining consistency in search terminology, the review ensured a systematic and reproducible approach to identifying relevant literature.

Our systematic search strategy ensured we captured a wide range of studies on prophylactic and preventive migraine treatments, with a specific emphasis on osteopathic interventions alongside supplements and medications. The inclusion criteria for this review were peer-reviewed articles published in English that addressed prophylactic treatments for chronic migraines, including pharmacological, non-pharmacological, or procedural interventions. Filters and date restrictions helped focus on the most recent and relevant research from 2010 onward. Studies that exclusively focused on acute treatment or did not provide evidence-based outcomes were excluded. This structured approach ensured a

comprehensive review of existing evidence on prophylactic migraine treatments and their impact on reducing MMDs.



**Figure 1:**

\* Reports were excluded at this stage if the study did not focus on either medications/ supplements/ or non-pharmacological modalities that can be used to prevent migraine occurrences

\*\* Reports were excluded at this stage if the reduction in monthly migraine days was not explicitly reported or if the evidence quality was deemed insufficient

Reference: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. doi:10.1136/bmj.n71.

## Results

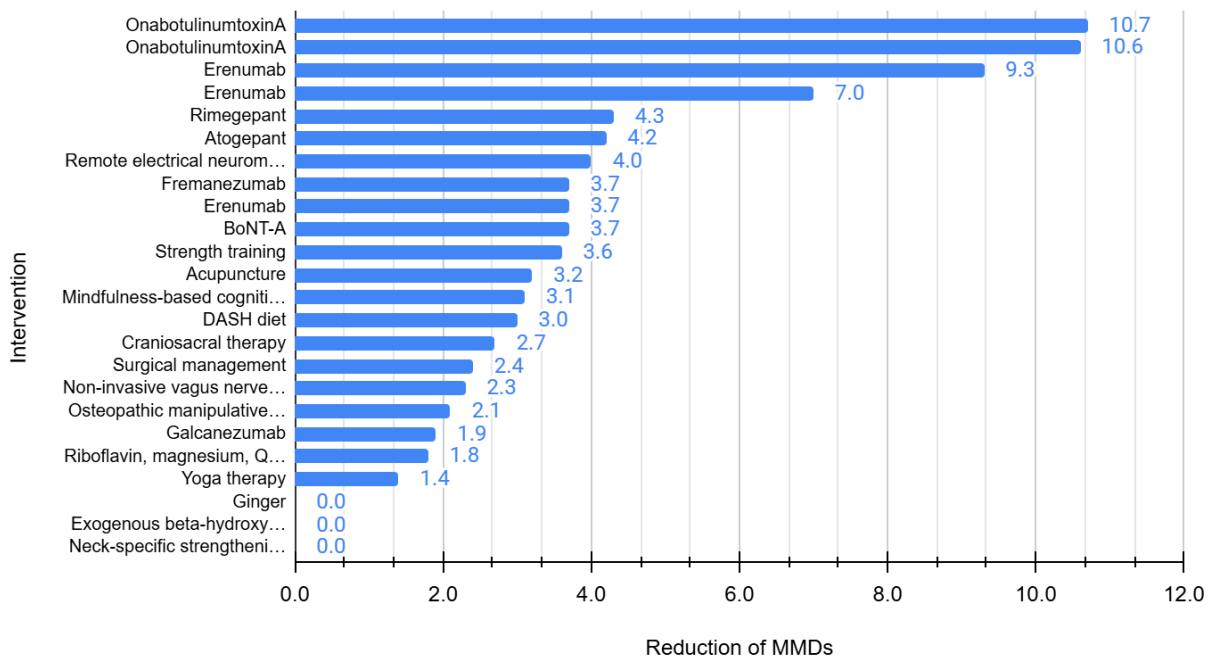
In our review, we included detailed information for each study, such as the population being studied, the intervention implemented, the outcomes measured, the study design, publication characteristics, quality of evidence, and the average reduction in monthly migraine days. Notably, all included articles provided a numerical value for the change in monthly migraine days, comparing the period before and after the intervention. However, it is important to highlight that several studies used the terms "migraine days" and "headache days" interchangeably, which may introduce variability in the reported outcomes.

The evidence quality for each article in the chart is assessed using established research appraisal criteria frequently applied in evidence-based practice. Articles are classified into three categories: high, moderate, and low evidence quality. High-quality evidence includes randomized controlled trials (RCTs), systematic reviews, or meta-analyses with rigorous methodologies, adequate sample sizes, proper blinding and randomization,

validated outcome measures, transparent and reproducible data, and publication in high-impact, peer-reviewed journals. Moderate-quality evidence encompasses cohort or observational studies and less robust systematic reviews, often with moderate sample sizes, limited blinding or randomization, and some methodological weaknesses, while still appearing in reputable peer-reviewed journals. Low-quality evidence involves case reports, case series, pilot studies, or poorly conducted observational studies, characterized by small sample sizes, lack of randomization or blinding, subjective outcome measures, and publication in lower-tier or non-peer-reviewed sources.

Additionally, relevance to migraine prevention or treatment, disclosure of conflicts of interest, and publication recency are considered to ensure the evidence aligns with current clinical practices. These criteria provide a consistent and transparent framework for evaluating the quality of evidence included in the chart.

Data was then charted and organized first on evidence quality, then on the reduction of monthly migraine days.



**Figure 2:** Chart of the included studies, looking at the intervention implemented in the study, and the mean reduction of monthly migraine days based on the intervention.

## Discussion

Based on our review process and results, we were able to discover a wide variety of interventions implemented to decrease monthly migraine days in comparison to a placebo. Botox injections in patients with severe chronic migraines showed the greatest reduction of MMDs, with two studies reporting decreases of 10.7 and 10.6 days. Of the studies focused on onabotulinumtoxinA injections, the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) injection protocol was followed, which consists of injecting 155 U–195 U to 31–39 sites every 12-weeks.<sup>1</sup> The longevity between trials changed between studies, although the results of effectiveness were similar between trials and studies. However, it is important to note that in several studies, more than 10% of patients dropped out due to adverse side effects.

Erenumab, a calcitonin gene-related peptide (CGRP) monoclonal antibody, demonstrated moderate efficacy, with reductions in MMDs ranging from 7.0 to 9.3 days. The variation in effectiveness across studies suggests that while erenumab provides a meaningful reduction in migraine burden, the response may depend on patient characteristics and baseline migraine severity. Notably, one study reported that the confidence interval for MMD reduction overlapped with zero, indicating that some patients may not experience a significant benefit. This highlights the need for individualized treatment approaches and further research to identify which subgroups may respond best to erenumab.

Rimegepant, an oral CGRP receptor antagonist, showed a more modest reduction in MMDs, with a reported decrease of 4.3 days. While this reduction is smaller than that observed with Botox and erenumab, it is still clinically meaningful, particularly for patients with episodic migraines who may not require as aggressive prophylactic treatment. Given that rimegepant

is an oral medication, it may offer a more convenient alternative to injectable treatments for some patients. However, the long-term effectiveness and adherence rates of rimegepant as a preventive option warrant further investigation.

## Study Design and Evidence Quality

The included studies encompassed a range of methodological approaches, including randomized controlled trials (RCTs), systematic reviews, meta-analyses, and real-world observational studies. Each study was assessed for evidence quality based on established appraisal criteria, with all included studies classified as high-quality evidence. The incorporation of systematic reviews and meta-analyses strengthens the reliability of the findings, as these studies aggregate data from multiple sources to provide a more comprehensive assessment of treatment efficacy.

One notable strength of this review is the inclusion of long-term safety and subgroup analyses, which provide valuable insights into the sustained benefits and tolerability of migraine prophylactic treatments. While RCTs remain the gold standard for evaluating treatment efficacy, real-world data from observational studies and meta-analyses of clinical practice data add an important layer of external validity, reflecting how these treatments perform outside of controlled trial settings. However, differences in study design, patient populations, and treatment protocols introduce some heterogeneity, which must be considered when interpreting the findings.

## Variability in Outcome Reporting

A major limitation identified in this review is the inconsistent use of terminology across studies, particularly regarding the distinction between migraine days (MMDs) and headache days (MHDs). While MMDs

specifically refer to days with migraine-level headache symptoms, MHDs encompass a broader range of headache types, including tension-type headaches and less severe headache episodes. Some studies used these terms interchangeably, complicating direct comparisons. This inconsistency highlights the need for standardized outcome reporting in migraine research to enhance clarity and comparability across studies.

Studies reporting a substantial reduction in MMDs often demonstrated statistically significant outcomes. However, placebo groups in these trials also exhibited notable reductions in MMDs, emphasizing the potential impact of placebo effects. This underscores the importance of carefully interpreting the net treatment benefit while accounting for the active placebo response in migraine prophylaxis trials. For example, in the study by on OnabotulinumtoxinA for migraine treatment, the placebo group experienced a 6.6-day reduction in MMDs compared to an 8.4-day reduction with Botox. Due to this significant placebo effect, the overall evidence quality was rated as “moderate” rather than “high,” highlighting the challenges in isolating true treatment effects in migraine prophylaxis research.

Additionally, variability in inclusion and exclusion criteria across the reviewed studies significantly affects result comparability. The baseline number of monthly migraine days (MMDs) varied widely, with some patient populations experiencing higher initial MMDs, making reductions appear more pronounced. These differences in study design and patient selection contribute to inconsistencies in treatment outcomes and reinforce the need for standardized baseline characteristics in migraine research to facilitate more reliable cross-study comparisons.

### Clinical Implications

The findings of this review reinforce the clinical utility of prophylactic migraine treatments, particularly for patients with chronic migraines who experience frequent and debilitating attacks. The substantial reduction in MMDs with onabotulinumtoxinA and erenumab suggests that these treatments may be highly beneficial for patients with a high migraine burden. However, treatment selection should consider not only efficacy but also factors such as tolerability, adherence, and patient preference. For example, Botox requires in-office injections every 12 weeks, which may be inconvenient for some patients, whereas erenumab and rimegepant offer self-administered options with different dosing schedules.

In addition to pharmacologic interventions, non-pharmacologic approaches may also play a role in migraine prevention, either as standalone options for patients seeking alternatives or as adjunct therapies to enhance treatment outcomes. Acupuncture, osteopathic manipulative treatment (OMT), and exercise have shown some efficacy in reducing headache frequency and intensity, potentially providing relief with fewer side effects. Similarly, certain supplements, such as magnesium, riboflavin, and CoQ [10] have been associated with reductions in migraine frequency and may be especially appealing to patients who prefer lifestyle or dietary approaches.

Additionally, the findings highlight the importance of individualized treatment approaches, as some patients may respond better to certain interventions than others. Given the variability in response rates and the presence of adverse effects, shared decision-making between patients and healthcare providers is essential to optimize treatment outcomes. Future studies should explore biomarkers or predictive factors that can help identify which patients are most likely to benefit from specific prophylactic treatments, while also investigating the potential long-term benefits of incorporating non-pharmacologic options into comprehensive migraine management plans.

### Limitations & Future Directions

While this review provides valuable insights into the effectiveness of prophylactic migraine treatments, several limitations should be

acknowledged. Variability in study design, patient populations, and outcome reporting introduces challenges in directly comparing results across studies. The interchangeable use of migraine days and headache days highlights the need for greater standardization in migraine research methodologies.

Additionally, while RCTs provide high-quality evidence, real-world data on long-term adherence, effectiveness, and patient satisfaction are still limited. Future studies should focus on long-term observational studies and real-world registries to better understand treatment persistence and patient-reported outcomes. Furthermore, continued head-to-head trials comparing different prophylactic treatments will help refine clinical decision-making by directly assessing their relative efficacy, tolerability, and patient preference.

### Conclusion

This scoping review underscores the effectiveness of onabotulinumtoxinA, erenumab, and rimegepant as prophylactic treatments for migraines, with Botox and CGRP inhibitors demonstrating the greatest reductions in MMDs. However, treatment tolerability, variability in response, and differences in outcome reporting highlight the need for an individualized approach to migraine prevention. Future research should prioritize long-term effectiveness, real-world adherence, and standardization of outcome measures to further guide evidence-based migraine management.

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