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MIGRAINE: NEW THERAPEUTIC PERSPECTIVES. A NARRATIVE REVIEW

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ABSTRACT

Migraine remains a major cause of disability despite the expanding range of acute and preventive treatments. This narrative review examines established and emerging pharmacological therapies alongside procedural and non-pharmacological interventions, with emphasis on clinical efficacy, tolerability and implications for individualised care. A defined collection of 64 publications, including randomised controlled trials, systematic reviews, meta-analyses and observational studies, was synthesised qualitatively without generating pooled estimates. Triptans remain effective acute treatments, whereas gepants and lasmiditan broaden the therapeutic options for patients with an insufficient response, poor tolerability or contraindications to vasoconstrictive agents. Their clinical utility depends on differences in administration, adverse effects and functional outcomes, including the central nervous system effects of lasmiditan. Calcitonin gene-related peptide pathway-targeting monoclonal antibodies and preventive gepants reduce migraine frequency, while onabotulinumtoxinA provides an established preventive option for chronic migraine. Targeting pituitary adenylate cyclase-activating polypeptide offers a biologically plausible additional strategy, although clinical findings remain heterogeneous and require confirmation. Neuromodulation, greater occipital nerve block, exercise, acupuncture and myofascial interventions may contribute to multimodal management, but the certainty and applicability of evidence vary substantially. Treatment selection should integrate migraine phenotype, comorbidities, previous treatment response and patient preferences. Further comparative trials and longer follow-up are needed to define optimal treatment sequencing, sustained effectiveness and the role of emerging approaches.

KEYWORDS

Migraine, Acute Treatment, Preventive Treatment, Calcitonin Gene-Related Peptide, Pituitary Adenylate Cyclase-Activating Polypeptide, Neuromodulation

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1. Introduction

Migraine is a primary neurological disorder characterised by recurrent attacks of moderate to severe headache, often accompanied by nausea, vomiting, photophobia, and phonophobia. A typical attack lasts from 4 to 72 hours and is usually manifested as unilateral, pulsating pain that worsens with physical activity (Eigenbrodt et al., 2021). According to the third edition of the International Classification of Headache Disorders (ICHD-3), migraine is primarily classified into migraine without aura, migraine with aura, and chronic migraine. The latter is characterised by the occurrence of headache on at least 15 days per month for a duration of more than three months, with criteria for migraine being met on a minimum of eight days per month (Eigenbrodt et al., 2021). A migraine attack may involve four partially overlapping phases: prodromal, aura, headache, and postdromal (Puledda et al., 2023).

Migraine constitutes a significant public health problem. According to epidemiological data cited by Lu et al. (2026), in 2021, approximately 1.6 billion people lived with migraine, while the age-standardized global prevalence in 2023 was 14.1% (95% UI: 12.1-15.9%). Despite the increase in the absolute number of affected individuals from 1990 to 2023, the prevalence of the disorder, when age-standardised, remained relatively stable, indicating a significant impact of demographic changes and case identification methods. Migraine occurs about two to three times more frequently in women than in men, reaching its highest prevalence during working age. It is also one of the leading causes of years lived with disability (YLD) among reproductive-age women.

Understanding the pathophysiology of migraine has significantly evolved, from the initial vascular concept to the contemporary model of a multifactorial neurological disorder. Currently, there is an emphasis on the importance of genetic predisposition, hormonal and environmental factors, and dysfunctions of neural networks involving the cerebral cortex, hypothalamus, brainstem, and trigeminovascular system (Puledda et al., 2023; Lu et al., 2026). Activation of the latter leads to the release of neuropeptides, including calcitonin

gene-related peptide (CGRP) and pituitary adenylate cyclase-activating polypeptide (PACAP), which are involved in nociceptive transmission (Puledda et al., 2023). The primary neurophysiological mechanism of aura is considered to be cortical spreading depolarisation (CSD) (Dai et al., 2021). Furthermore, hyperexcitability of trigeminal nerve fibres, descending pain inhibition disturbances, and central sensitisation may play a significant role in the process of migraine chronicity (Atraszkiewicz et al., 2021).

Despite advances in understanding the pathophysiological mechanisms of migraine, its treatment remains a substantial clinical challenge. The consensus by Eigenbrodt et al. (2021) indicates that in analysed European population studies, only 2-14% of patients qualifying for preventive treatment actually received it. However, the development of knowledge regarding the neuronal and molecular mechanisms of migraine has enabled the establishment of new therapeutic strategies, encompassing both pharmacotherapy targeting specific receptors and neuropeptides, as well as non-pharmacological methods (Puledda et al., 2023; Deng et al., 2020).

The aim of this work is to review the available treatment options for migraine, with particular emphasis on modern pharmacological and non-pharmacological methods, their mechanisms of action, clinical efficacy, and safety profile.

2. Methods

This paper is a narrative review. PubMed/MEDLINE, Scopus, and Web of Science were searched for publications available up to November 2026, using combinations of search terms related for the migraine (migraine treatment, gepants, onabotulinumtoxinA, ergotamine, anti-PACAP, CGRP), the clinical entities under review, and preventive strategies. It is based on a defined set of 64 full-text publications selected for their relevance to new methods of migraine treatment. No separate systematic database search was conducted specifically for this review, and no protocol was registered. Publications were eligible if they addressed migraine treatment with preference given to meta-analyses, randomized controlled trials, systematic reviews and cohort studies. The resulting evidence base comprised 64 publications dating from 2003 to 2026. Estimates are presented as reported by the original authors, and where discrepancies between sources were identified, the reported range is provided instead of a pooled estimate.

3. Results

3.1. Gepants

Gepants are calcitonin gene-related peptide (CGRP) receptor antagonists that interrupt neurogenic inflammation within the meninges. An important characteristic of these drugs is their lack of vasoconstrictive effects, which are observed with triptans. This is particularly relevant for patients with cardiovascular disease, in whom the use of triptans is contraindicated (Ashina et al., 2025; Ikeda et al., 2025).

Rimegepant is an orally administered medication used both for the acute treatment and prevention of migraine with and without aura. Studies have shown that patients taking rimegepant for acute treatment are less likely to require additional acute medication within 24 hours of migraine symptom onset. They also experience a reduction in headache severity and an improvement in daily functioning. It has been demonstrated that acute administration of rimegepant at a dose of 75 mg results in headache relief in 32.4–55.9% of patients within two hours, compared with 13.0–32.7% in the placebo group. A return to normal functioning two hours after administration was reported in 45.5% of patients, compared with 26.9% in the placebo group. Preventive treatment with rimegepant at a dose of 75 mg in patients with migraine resulted in a reduction of 6.2 monthly migraine days compared with baseline. Adverse effects include constipation, respiratory tract infections, nausea, increased alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity, and weight gain (Ashina et al., 2025; Ikeda et al., 2025; Kudrow et al., 2026).

Zavegepant is administered intranasally (as a spray or by inhalation) and is used for the acute treatment of migraine with and without aura. Studies have demonstrated that patients receiving zavegepant experience rapid symptom relief, improved daily functioning and reduced headache severity. Administration of a 10 mg dose results in complete pain freedom within two hours in 22.5% of patients, compared with 15.5% in the placebo group. Freedom from the most bothersome symptom (MBS) at two hours was achieved by 41.9% of patients receiving zavegepant at a dose of 10 mg, compared with 33.7% in the placebo group. The most common adverse effects include taste disturbances, nausea, nasal discomfort, throat irritation and vomiting (Croop et al., 2022; Deng et al., 2024; Zhu et al., 2025).

Atogepant is a CGRP receptor antagonist used for the preventive treatment of migraine in adults. Studies have shown that daily administration of atogepant at a dose of 60 mg leads to a significant and sustained reduction in the number of monthly migraine days. From a baseline of 7.3 days per month, the number decreased by 3.8 days after four months of treatment and by 5.2 days per month after one year of treatment. Atogepant also reduces the frequency of acute medication use. It is generally well tolerated; the most common adverse effects include respiratory tract infections, constipation, nausea, urinary tract infections, fatigue and weight loss (Ashina et al., 2023; Ailani et al., 2025).

3.2. Calcitonin gene-related peptide pathway-targeting monoclonal antibodies (CGRP mAbs)

Calcitonin gene-related peptide (CGRP) pathway-targeting monoclonal antibodies (CGRP mAbs) represent one of the newer preventive treatment options for patients with migraine. These agents can be divided into those targeting the CGRP ligand, namely fremanezumab, galcanezumab and eptinezumab, and those targeting the CGRP receptor, namely erenumab (Messina et al., 2023).

These drugs have demonstrated statistically significant efficacy compared with placebo, as evidenced by a substantial reduction in monthly migraine days (MMD) and a higher proportion of treatment responders. For example, clinical trials investigating eptinezumab have shown that 12 weeks of treatment results in a reduction of 7.2 to 7.5 MMD (compared with a reduction of 4.8 days in the placebo group). Depending on the agent and dosage, the proportion of patients with chronic migraine achieving at least a 50% reduction in MMD ranges from approximately 37.8% to 42.9%, compared with approximately 21.8% in the placebo group (Messina et al., 2023; Yu et al., 2025; Huang et al., 2020; Han et al., 2019; Zhao et al., 2021).

An advantage of parenterally administered medications is their improved treatment effectiveness, associated with a lower risk of missed doses compared with orally administered drugs. Furthermore, these medications are characterised by a rapid onset of action, with a significant reduction in the number of monthly migraine days observed as early as the first day following injection (Messina et al., 2023; Yu et al., 2025).

Studies have demonstrated that, in terms of their safety profile, CGRP mAbs are considered safe and well tolerated, with the incidence of adverse events not differing significantly from that observed in the placebo group. In the multicentre phase III SUNRISE trial, the proportion of patients reporting any adverse events during treatment ranged from 32.2% to 37.6% in the eptinezumab group, which was comparable to that observed in the placebo group (33.5%). It is also noteworthy that the incidence of serious adverse events in the study group remained below 2% (Yu et al., 2025; Huang et al., 2020; Han et al., 2019).

For subcutaneously administered agents (erenumab, fremanezumab and galcanezumab), the most commonly observed adverse events were local injection-site reactions, including pain, erythema, pruritus, swelling and bruising. Among systemic adverse events reported during treatment, upper respiratory tract infections and sinusitis were the most frequent. The incidence of these events was comparable to that observed in the placebo groups. For example, nasopharyngitis occurred in 3.4% of patients treated with eptinezumab and in 4.9% of patients in the placebo group (Messina et al., 2023; Yu et al., 2025; Huang et al., 2020; Han et al., 2019; Zhao et al., 2021).

3.3. Lasmiditan

Lasmiditan is a medication belonging to the ditan class. It is a highly selective agonist of the serotonin 5-HT1F receptor. Unlike triptans (5-HT1B/1D receptor agonists), lasmiditan exhibits low affinity for 5-HT1B receptors and therefore does not induce vasoconstriction, while maintaining its ability to inhibit pain signal transmission. The drug is also characterised by its high ability to cross the blood–brain barrier (Deng et al., 2024; Puledda et al., 2023; Laohapiboolarattana et al., 2024).

Clinical trials have demonstrated the statistically significant superiority of lasmiditan over placebo. The overall relative risk of achieving complete pain freedom two hours after administration was 1.71 (95% CI: 1.55–1.87) compared with placebo. Treatment efficacy was found to increase with the administered dose, as illustrated in Table 1 (Deng et al., 2024; Puledda et al., 2023; Laohapiboolarattana et al., 2024; Hou et al., 2020).

Table 1. Efficacy of lasmiditan according to dose.

dose of the medicine	the number of patients whose pain subsided after 2 hours
placebo	15,3-21,3%
50 mg	28,2%
100 mg	28,7%
200 mg	34,5%

Note. Adapted from Deng et al., 2024; Puledda et al., 2023; Laohapiboolarattana et al., 2024; Hou et al., 2020

The main limitations of lasmiditan include the high incidence of central nervous system-related adverse events, which is attributable to its lipophilic structure. These events occur significantly more frequently than in the placebo group (RR = 2.77; CI: 2.53–3.03) and are dose-dependent. The most commonly reported adverse events include dizziness, nausea, fatigue/tiredness, paraesthesia and somnolence. Given its effects on the central nervous system and the potential to impair driving ability, patients are advised to refrain from driving for at least 8 hours following administration of the medication (Deng et al., 2024; Puledda et al., 2023; Laohapiboolarattana et al., 2024; Hou et al., 2020).

3.4. Triptans

Triptans, which are selective agonists of 5-HT1B/1D receptors, represent one of the main classes of drugs used in the acute treatment of migraine attacks. Their mechanism of action involves inhibiting the release of pro-inflammatory neuropeptides involved in pain transmission and inducing vasoconstriction. Consequently, they are contraindicated in patients with cardiovascular diseases, including atrial fibrillation (AF), a history of myocardial infarction, and a history of stroke (Ashina et al., 2025; Karlsson et al., 2024; Yang et al., 2021).

Studies conducted by Karlsson et al. (2024) confirm the efficacy of this class of drugs in the acute treatment of migraine. The meta-analysis included 137 randomised clinical trials involving 89,445 patients. The efficacy of triptans is presented in Table 2.

Table 2. Efficacy of triptans.

Drug	Percentage of patient achieving complete headache pain relief at 2 hours	Percentages of patients with sustained pain freedom from 2 to 24 hours
Eletriptan	37%	26%
Rizatriptan	33%	21%
Sumatriptan	29%	20%
Zolmitriptan	28%	19%

Note. Adapted from Karlsson et al., 2024

Despite their documented efficacy, triptans do not provide adequate symptom control in all patients. Studies have shown that approximately 10–44% of patients experience an insufficient response to triptan treatment. Factors associated with an inadequate treatment response include high baseline headache intensity, photophobia, phonophobia, nausea, and comorbid depression (Leroux et al., 2020; Lipton et al., 2025).

In summary, triptans remain a highly effective option for the acute treatment of migraine attacks. The development of new antimigraine medications is necessary because triptans are contraindicated in patients with cardiovascular diseases. However, such advances should focus not only on improving analgesic efficacy but also on expanding opportunities for individualised treatment through the use of agents with different mechanisms of action and safety profiles. Novel therapeutic strategies are particularly important for patients in whom existing treatments are contraindicated, ineffective, or poorly tolerated (Karlsson et al., 2024; Yang et al., 2021; Leroux et al., 2020; Lipton et al., 2025).

3.5. Ergotamine and its derivatives

Ergot alkaloids derived from *Claviceps purpurea*, represented primarily by ergotamine tartrate, along with their semisynthetic derivatives such as dihydroergotamine (DHE), exhibit a complex, multireceptor pharmacological profile. Ergotamine and DHE act as potent agonists at vascular serotonin 5-HT1B receptors (Whealy et al., 2024). Activation of these receptors on cranial vascular smooth muscle induces selective vasoconstriction of extracranial carotid artery branches and meningeal blood vessels dilated during a migraine attack, attenuating pulsatile plasma extravasation and reducing mechanical stimulation of meningeal nociceptors (Bigal et al., 2003; Mitsikostas et al., 2024).

These compounds also exert neurogenic anti-nociceptive effects via high-affinity agonism at presynaptic 5-HT1D receptors located on both peripheral and central terminals of trigeminal sensory afferents within the trigeminovascular system. Stimulation of 5-HT1D receptors inhibits the release of pro-inflammatory vasoactive neuropeptides—predominantly calcitonin gene-related peptide (CGRP) and substance P—thereby preventing meningeal neurogenic inflammation and blocking nociceptive transmission to brainstem sensory nuclei (Whealy et al., 2024; Bigal et al., 2003; Mitsikostas et al., 2024).

Additionally, ergot alkaloids interact with dopaminergic (D2) and alpha-adrenergic (α_1 and α_2) receptors. Compared with ergotamine tartrate, DHE displays markedly lower affinity for α-adrenergic receptors, translating into a substantially reduced potential for peripheral vasoconstriction and superior cardiovascular tolerability (Whealy et al., 2024; Bigal et al., 2003).

The clinical efficacy of ergotamine and its derivatives depends heavily on their route of administration and pharmacokinetic characteristics. Orally administered ergotamine exhibits exceedingly low systemic bioavailability (less than 1%), resulting from poor gastrointestinal absorption and extensive hepatic first-pass metabolism. To improve its absorption profile, ergotamine has traditionally been co-formulated with caffeine, which increases peak plasma concentration (C_{max}) and area under the concentration–time curve (AUC) by enhancing gastric absorption (Ngo et al., 2026). Rectal administration partially bypasses hepatic first-pass metabolism, yielding higher and more predictable bioavailability—a particularly advantageous option for patients presenting with severe migraine-associated nausea and vomiting (Terpening et al., 2025). Owing to its negligible oral bioavailability, DHE is formulated for parenteral administration (intramuscular, subcutaneous, or intravenous injection) as well as advanced intranasal delivery systems. Currently, two intranasal DHE formulations are clinically available: a liquid nasal spray and an intranasal dry powder. While the liquid nasal spray offers a more rapid onset of action than oral ergot formulations, it exhibits considerable interindividual variability in systemic absorption. Conversely, the novel intranasal dry powder formulation of DHE provides a more consistent pharmacokinetic profile, achieving a C_{max} of 1,870–2,230 pg/mL at a T_{max} of approximately 0.5 hours, with an elimination half-life ($t_{1/2}$) of roughly 12 hours (Terpening et al., 2025; Silvestro et al., 2024; Cooper et al., 2022).

Despite high clinical efficacy in selected patient subgroups, the therapeutic use of ergotamine and its derivatives is subject to strict safety limitations. Chronic or overly frequent administration of ergotamine predisposes patients to medication-overuse headache (MOH) and pharmacological tolerance. Furthermore, their propensity to provoke potent peripheral and coronary vasoconstriction—potentially culminating in clinical ergotism—precludes their use in patients with ischaemic heart disease, uncontrolled hypertension, or peripheral vascular disease. Prolonged exposure to ergot alkaloids, mediated via concomitant 5-HT2B receptor agonism, also carries the risk of fibrotic complications, including pleuropulmonary fibrosis, cardiac valvulopathy, and fibrosing pachymeningitis. Consequently, contemporary clinical guidelines designate ergotamine and DHE as second-line acute therapies, reserved primarily for patients experiencing prolonged, recurrent migraine attacks or those refractory to newer-generation 5-HT1B/1D receptor agonists (triptans) (Tynan et al., 2018).

3.6. Anti-PACAP Monoclonal Antibodies

Drugs targeting the pituitary adenylate cyclase-activating polypeptide (PACAP) pathway, a neuropeptide with potent vasodilatory properties that induces migraine attacks in approximately 68–72% of patients, represent a novel class of therapeutic agents currently under investigation for migraine prevention (Rubio-Beltran et al., 2018).

Their mechanism of action involves either direct neutralisation of the ligand (PACAP38) or blockade of the PAC1 receptor. PACAP signalling has been shown to operate independently of, and in parallel with, the CGRP pathway. This was demonstrated, among others, in a study involving eptinezumab (an anti-CGRP

monoclonal antibody), in which treatment did not prevent migraine attacks induced by PACAP38 infusion (migraine occurred in 53% of patients receiving eptinezumab and 63% of those receiving placebo) (Rubio-Beltran et al., 2018; Al-Karagholi et al., 2025).

Clinical trial results for drugs targeting this pathway have been mixed. The monoclonal antibody targeting the PAC1 receptor (AMG 301) failed to meet its efficacy endpoints. In contrast, a phase II trial investigating the anti-PACAP antibody LY3451838 in patients with treatment-resistant migraine demonstrated a reduction in the mean number of monthly migraine days of 4.7 days in patients with chronic migraine (vs 3.0 days with placebo) and 1.7 days in those with episodic migraine (vs 1.2 days with placebo), although these differences did not reach statistical significance. Nevertheless, the positive results of a phase II trial involving another anti-PACAP antibody, Lu AG09222 (a reduction of 6.2 days vs 4.2 days with placebo), provide evidence supporting the therapeutic potential of targeting this pathway. Regarding safety, anti-PACAP antibodies demonstrated a tolerability profile comparable to that of placebo (the incidence of adverse events was 57.9% for LY3451838 vs 68.4% for placebo), with no significant haemodynamic disturbances. These findings suggest that anti-PACAP therapies may represent a promising treatment option for patients with an inadequate response to CGRP-targeted therapies. Table 3 summarises the characteristics of drugs targeting the PACAP pathway (Rubio-Beltran et al., 2018; Kuburas and Russo, 2023; Al-Karaghali et al., 2025; Johnson et al., 2025).

Table 3. Targets, mechanisms of action and efficacy of drugs targeting the PACAP pathway.

Drug	Target	Mechanism of action	Efficacy (reduction in monthly migraine days)
Lu AG09222	PACAP (ligand)	Monoclonal antibody neutralising PACAP	Reduction of 6.2 days per month compared with 4.2 days in the placebo group
LY3451838	PACAP (ligand)	Anti-PACAP monoclonal antibody	Chronic migraine: reduction of 4.7 days per month compared with 3.0 days in the placebo group. Episodic migraine: reduction of 1.7 days per month compared with 1.2 days in the placebo group.
AMG 301	Receptor PAC1	Monoclonal antibody blocking the PAC1 receptor	Reduction of 2.2 days per month compared with 2.5 days in the placebo group; the primary efficacy endpoint was not met.

Note. Adapted from Rubio-Beltran et al., 2018; Kuburas and Russo, 2023; Al-Karaghali et al., 2025; Johnson et al., 2025

In summary, the development of therapies targeting the PACAP pathway represents an important step towards the individualisation of migraine treatment. Given the independence of the PACAP pathway from CGRP signalling, these therapies may provide a novel therapeutic alternative for patients who have not achieved a satisfactory response to existing preventive treatments (Rubio-Beltran et al., 2018; Kuburas and Russo, 2023; Al-Karaghali et al., 2025; Johnson et al., 2025).

3.7. OnabotulinumtoxinA

Botulinum toxin is an inhibitor of acetylcholine release and an agent that blocks neuromuscular transmission. Furthermore, it inhibits mast cell degranulation and the secretion of pro-inflammatory cytokines. In the context of migraine, the mechanism of action of botulinum toxin type A (BoNT-A) involves the peripheral inhibition of the exocytosis of pain and inflammatory mediators – including CGRP, substance P and glutamate – from the presynaptic nerve terminals of the trigeminal system. This action prevents peripheral nociceptor sensitisation, thereby indirectly reducing the transmission of pain signals to the central nervous

system and preventing the development of a migraine attack. BoNT-A therapy has demonstrated clinical benefits not only in chronic migraine (CM), but also in treatment-resistant migraine (CRM) and vestibular migraine (VM) (Shaterian et al., 2022; Turkel et al., 2023; Lanteri-Minet et al., 2022).

The European Headache Federation (EHF) guidelines recommend the administration of 155–195 units (U) of BoNT-A by intramuscular injection at 31–39 anatomical sites across the head and neck, with treatment repeated at 12-week intervals. The use of BoNT-A in patients with chronic migraine results in a significant reduction in the monthly frequency of attacks, pain severity, the frequency of psychiatric disorders, the use of acute medication, the number of visits to hospital emergency departments, and disease-related disability (Shaterian et al., 2022; Turkel et al., 2023; Lanteri-Minet et al., 2022).

A meta-analysis of 10-year observational data demonstrated that treatment with botulinum toxin reduces the mean number of headache days per month by 10.64 days after 24 weeks and by 10.32 days after 52 weeks of treatment. After 24 weeks of therapy, the number of days on which acute analgesic medication is required decreases by 7.40 days per month, while the proportion of patients achieving at least a 50% reduction in the number of migraine days is 46.57%. Significant improvements were also demonstrated in standardised clinical outcome measures: the HIT-6 (Headache Impact Test-6) score decreased by 11.70 points at 24 weeks and 11.80 points at 52 weeks, while the MSQ v2.1 (Migraine-Specific Quality-of-Life) score increased by 23.60 points at 24 weeks and 30.90 points at 52 weeks, alongside a reduction in MIDAS (Migraine Disability Assessment) scores (Lanteri-Minet et al., 2022).

The use of botulinum toxin type A (BoNT-A) for migraine prevention is characterised by a favourable safety profile and very good patient tolerability. Any adverse events – which are predominantly limited to mild-to-moderate neck pain, localised tenderness or muscle weakness – tend to resolve spontaneously over subsequent treatment cycles. This therapy represents a safe and beneficial treatment option for adult patients, including those with concomitant medication-overuse headache. The main limitations of BoNT-A use in migraine prevention are the lack of a satisfactory treatment response in some patients and the invasive nature of the procedure. Furthermore, this approach is considered a second-line treatment and is recommended following the failure of previous standard preventive treatment trials (Shaterian et al., 2022; Turkel et al., 2023; Lanteri-Minet et al., 2022).

3.8. Neuromodulation, Greater Occipital Nerve Block and Vagus Nerve Stimulation

3.8.1. Neuromodulation

Non-invasive neuromodulation is currently one of the most rapidly developing non-pharmacological approaches to migraine treatment, representing a promising alternative to or adjunct to conventional therapy. Neuromodulation involves the application of physical stimuli (electrical, magnetic, oscillatory or thermal) to the body surface in order to modify the activity of nervous system structures involved in the generation and transmission of pain (Yuan et al., 2025; Reuter et al., 2019).

Neuromodulation employs a variety of neurobiological mechanisms, depending on the technology used. Devices based on transcranial magnetic stimulation have demonstrated the ability to inhibit cortical spreading depression and modulate thalamocortical pathways. By contrast, transcutaneous trigeminal nerve stimulation utilises the peripheral pain gate-control mechanism and exerts central effects on the anterior cingulate cortex and thalamus. Vagus nerve stimulation also plays an important role, including both non-invasive cervical stimulation (nT-VNS, e.g. gammaCore) and auricular stimulation (at-VNS), as well as auricular electroacupuncture (EA). These methods target the auricular branch of the vagus nerve (ABVN), modulating the activity of brainstem nuclei, including the nucleus tractus solitarius (NTS) and the spinal trigeminal nucleus (Sp5), while also activating descending pain inhibitory pathways. These approaches are complemented by remote electrical neuromodulation, which induces descending inhibition of nociception through the pain-inhibits-pain phenomenon (Yuan et al., 2025; Fernández-Hernando et al., 2023).

Meta-analyses involving patients with chronic migraine have demonstrated that auricular vagus nerve stimulation (at-VNS) results in a statistically significant reduction in the monthly number of migraine days (MMD), decreased pain intensity as assessed using the VAS/NPRS scales, and improved quality of life, as measured by HIT-6 and MIDAS scores (Fernández-Hernando et al., 2023).

The principal clinical advantage of neuromodulation is its exceptionally favourable safety profile. These devices are not associated with systemic adverse effects or drug interactions and do not induce medication-overuse headache (MOH). This makes neuromodulation a particularly suitable treatment option for specific patient populations in whom pharmacotherapy is strictly contraindicated, ineffective or poorly tolerated, including pregnant women, children and adolescents, and patients with concomitant MOH (Yuan et al., 2025; Reuter et al., 2019).

3.8.2. Greater Occipital Nerve Blocks (GONB)

Greater occipital nerve block (GONB) is a non-pharmacological approach to the treatment of migraine headache. Its neurophysiological basis lies in the anatomical and functional convergence of cervical sensory fibres and trigeminal nerve branches within the trigeminocervical complex (TCC), resulting in central desensitisation. The procedure is based on the neuromodulation of functionally interconnected trigeminocervical afferents involved in the transmission of headache pain signals. Injection in the vicinity of the nerve reduces the influx of nociceptive signals reaching TCC neurons. Both clinical studies and review analyses confirm that the administration of a local anaesthetic by means of GONB provides benefits in acute settings, reducing pain severity (Atraszkiewicz et al., 2025; Tamayo de León et al., 2025).

In the emergency department (ED) setting, the evaluation of GONB as an adjunct to a three-drug intravenous treatment regimen (ketorolac, paracetamol and metoclopramide) in patients with severe or refractory migraine attacks demonstrated that as many as 95.2% of patients in the intervention group achieved a reduction in pain intensity of more than 50% on the VAS after two hours, compared with 47.6% in the control group. Furthermore, the 30-day follow-up revealed a significant reduction in the number of migraine days among these patients (median 3.0 vs 7.0 days), an increase in the number of pain-free days (14.0 vs 5.0 days), and a tendency towards lower rates of repeat hospitalisation, irrespective of the preventive treatment previously administered (Tamayo de León et al., 2025).

In contrast, research conducted by Atraszkiewicz et al. (2025) demonstrated that existing systematic reviews in the literature are characterised by numerous methodological limitations, including the unjustified pooling of populations with episodic and chronic migraine. Using the GRADE assessment framework, the authors concluded, with low certainty of evidence, that weekly bilateral injections of local anaesthetic reduce pain severity and the monthly number of migraine days in patients with chronic migraine after one month of treatment, although the long-term durability of these effects remains unclear.

A meta-analysis of ultrasound-guided greater occipital nerve blocks (US-GONB) in chronic migraine demonstrated that this technique provides significant clinical benefits compared with sham procedures. US-GONB significantly reduces pain intensity (mean difference: –3.57 points), decreases the monthly number of migraine days (by approximately 12.12 days) and reduces analgesic consumption. The findings also suggest a potential synergistic effect when US-GONB is combined with pulsed radiofrequency (PRF) (Sabet et al., 2025).

The GONB procedure is characterised by very good patient tolerability, with reported adverse events being exclusively mild, transient and localised in nature. These include, among others, injection-site pain, minor bleeding and temporary paraesthesia, with no severe systemic complications reported (Atraszkiewicz et al., 2025; Tamayo de León et al., 2025; Sabet et al., 2025).

3.8.3. Vagus nerve stimulation

Vagus nerve stimulation (VNS) is a modern bioelectronic neuromodulation technique involving the delivery of controlled electrical impulses to branches of the vagus nerve (cranial nerve X). The vagus nerve constitutes the principal parasympathetic pathway connecting peripheral organs and brainstem structures with higher centres of the central nervous system. In migraine research, non-invasive techniques are employed, namely non-invasive cervical vagus nerve stimulation (nVNS) and transcutaneous auricular vagus nerve stimulation (taVNS). Non-invasive cervical vagus nerve stimulation (nVNS) involves applying a portable electrostimulation device directly to the skin of the neck, overlying the common carotid artery, where the neurovascular bundle containing the vagus nerve is located. Transcutaneous auricular vagus nerve stimulation (taVNS) employs auricular stimulation, with electrodes placed on the surface of the pinna, where the vagus nerve's only cutaneous sensory branch is located (Nasir et al., 2026; Farahani et al., 2026; Diener et al., 2019).

The analgesic and preventive effects of vagus nerve stimulation are based on the modulation of central pain transmission pathways. This intervention acts on the trigeminovascular system through projections originating from the nucleus tractus solitarius (NTS), exerting analgesic effects and attenuating inflammatory responses. Furthermore, central suppression of cortical spreading depolarisation (CSD) plays a key role in migraine prevention, which may explain the particularly favourable clinical response observed in patients with migraine with aura. In vestibular migraine, the combination of taVNS and vestibular rehabilitation produces synergistic effects by promoting neuroplasticity within the brainstem and cerebellar structures, thereby improving sensory integration and central vestibular compensation (Diener et al., 2019; Farahani et al., 2026).

The use of non-invasive vagus nerve stimulation has demonstrated significant efficacy in reducing migraine attack frequency in adults. In the per-protocol population, the study by Diener et al. (2019) showed that nVNS resulted in a mean reduction of 2.26 migraine days per month, compared with a reduction of 1.37

days in the sham-stimulation control group. Moreover, a significantly higher proportion of patients in the nVNS group achieved a treatment response, defined as a reduction of at least 50% in the number of monthly migraine days (30.3% vs 17.6%). This effect was particularly pronounced in patients with migraine with aura. Additionally, nVNS resulted in a significant reduction in the number of days per month on which patients required acute analgesic medication or triptans. Significant improvements in pain intensity, monthly attack frequency and quality-of-life measures among patients with chronic migraine following four weeks of active stimulation have also been confirmed by research conducted by Nasir et al. (2026)].

In patients with vestibular migraine, the addition of taVNS to standard vestibular rehabilitation (VR) results in greater clinical efficacy than rehabilitation alone. Significantly greater reductions were observed in monthly headache frequency, as well as more pronounced improvements in disability, as measured by the HIT-6 questionnaire, and in dizziness severity, as assessed using the DHI scale. Greater improvements were also observed in postural stability parameters assessed using a stabilometric platform (Farahani et al., 2026).

Non-pharmacological methods of vagus nerve stimulation are characterised by an exceptionally favourable safety profile and very good patient tolerability. No serious adverse events associated with the use of stimulation devices were identified in the clinical trials analysed. Reported adverse effects were exclusively mild, localised and transient, with the most frequently reported symptoms including minor skin irritation, erythema and a tingling sensation at the electrode application site. In a long-term study involving children and adolescents, three years of follow-up revealed no long-term complications or delayed safety signals associated with the previous short-term preventive pharmacotherapy (Nasir et al., 2026; Farahani et al., 2026; Diener et al., 2019).

The main methodological challenge in studies investigating electrostimulation devices for migraine is the pronounced placebo effect (response in the sham group). Additional limitations include substantial heterogeneity in study protocols, differences in electrical stimulation parameters and the short duration of some studies, which preclude conclusions regarding the persistence of therapeutic effects following discontinuation of treatment (Nasir et al., 2026; Diener et al., 2019).

3.9. Myofascial Release and Therapeutic Exercise

3.9.1. Myofascial Release Therapy in the Non-Pharmacological Management of Migraine

Activation of the trigeminovascular system plays a central role in migraine pathophysiology. Although migraine is a primary neurobiological disorder, the clinical conceptualisation of myofascial trigger points (MTrPs) located within the pericranial, cervical, and nuchal musculature—including the trapezius, suboccipital, and sternocleidomastoid muscles—has evolved from an incidental epiphenomenon to a clinically relevant disease modifier. Chronic irritation of myofascial nociceptors generates sustained afferent nociceptive input into the trigeminal nucleus caudalis (TNC). Through trigeminocervical convergence, peripheral nociceptive signals originating from upper cervical segments lower the central nervous system (CNS) excitability threshold, thereby amplifying central sensitisation and increasing headache attack frequency (Rezaeian et al., 2021; Jara Silva et al., 2022).

Myofascial release (MFR) therapy involves the application of sustained, targeted, low-load mechanical pressure to restricted fascial tissues and active MTrPs. The physiological response to MFR encompasses two complementary pathways. First, at the local biomechanical level, MFR restores inter-fascial gliding properties, alleviates focal tissue ischaemia secondary to sustained muscle contraction, and reduces local concentrations of vasoactive pro-inflammatory mediators, including bradykinin and substance P. Second, at the neurophysiological level, mechanical stimulation of fascial mechanoreceptors (Ruffini endings and Pacinian corpuscles) modulates sympathetic nervous system tone, eliciting a local vasomotor response and inhibiting descending pain facilitation pathways (Rezaeian et al., 2021; Pillai et al., 2023). Clinical studies indicate that manual suboccipital soft-tissue inhibition and stretching combined with MFR significantly improve cervical range of motion (CROM), reduce Neck Disability Index (NDI) scores, and decrease pain intensity in individuals with migraine (Rezaeian et al., 2021).

A systematic review and meta-analysis by Lu et al. (2024) evaluated the clinical efficacy of MFR interventions across primary and secondary headache disorders. In migraine, the adjunctive utility of MFR—particularly in alleviating ictal and interictal suboccipital and cervical myofascial tension—is underpinned by a sound anatomical and neurophysiological rationale; however, larger, methodologically rigorous randomised trials remain necessary to definitively quantify its effect size. Furthermore, systematic reviews in

musculoskeletal medicine consistently confirm that MFR exhibits a favourable safety profile devoid of serious adverse events, supporting its integration as a low-risk adjuvant therapy (Lv and Yin, 2024).

Incorporating MFR into multimodal migraine care is clinically justified in patients presenting with comorbid cervicobrachial musculoskeletal dysfunction and active MTrPs. While MFR does not replace targeted acute pharmacotherapy (e.g., triptans or gepants), it serves as an effective complementary intervention that attenuates peripheral nociceptive input contributing to attack initiation (Lu et al., 2024; Lv and Yin, 2024).

3.9.2. Aerobic Exercise and Migraine Course Modification

Regular moderate-to-vigorous aerobic exercise exerts a significant beneficial effect on overall disease burden in migraine. As demonstrated in a systematic review and meta-analysis by Lemmens et al. (2019), structured aerobic training produces statistically significant reductions in monthly migraine days, attack duration, and pain severity.

The physiological mechanisms underlying exercise-induced analgesia include enhanced endogenous opioid release (notably β-endorphins), modulation of central serotonergic pathways, and downregulation of neurogenic inflammatory mediators such as CGRP. Moreover, a comparative network meta-analysis by Woldeamanuel and Oliveira (2022) indicates that structured physical exercise interventions—encompassing both aerobic and resistance training—may achieve prophylactic efficacy comparable to established oral preventives (e.g., topiramate), while concurrently improving cardiometabolic health and alleviating comorbid anxiety.

3.10. Akupunktura

Akupunktura wywodzi się z medycyny chińskiej i jest stosowana od tysięcy lat. Współcześnie w EBM stosuje się ją według ustandaryzowanych protokołów, obejmujących ilość sesji, czas sesji oraz miejsca wkłucia. Akupunktura manualna polega na wprowadzeniu sterylnych, jednorazowych igieł w określone punkty akupunkturowe oraz manipulacja nimi w celu uzyskania efektu Deqi. Deqi to odczucie określane jako bolesność, drętwienie, rozpieranie lub uczucie ciężkości, uznawane za wskaźnik prawidłowej stymulacji punktu akupunturowego. Głównym mechanizmem działania akupunktury jest modulacja funkcjonalnej łączności sieci neuronalnych mózgu. obniżenie łączności z DMN-SC odpowiada z redukcję bólu, wzmocnienie Łączności SC-motor za obniżenie poziomu niepełnosprawności. Zmiany te umożliwiają predykcję efektu terapeutycznego u poszczególnych pacjentów na podstawie wyjściowych wzorców łączności neuronalnej (Liu et al., 2024,Lu et al., 2025; Zhang et al., 2026).

Wyniki przeglądów systematycznych z metaanalizami jednoznacznie wskazują na wysoką wartość kliniczną akupunktury w profilaktyce oraz terapii migreny. Metoda ta wykazuje wyższą skuteczność w profilaktycznym leczeniu migreny w bezpośrednim porównaniu ze standardową opieką medyczną (*standard medical care*). Ponadto stosowanie akupunktury prowadzi do istotnej klinicznie poprawy ogólnego stanu zdrowia pacjentów oraz znacząco podnosi ich jakość życia (QoL). Dane te wskazują na zasadność włączania akupunktury jako niefarmakologicznej alternatywy lub wsparcia w profilaktyce migrenowej (Lu et al., 2025; Pistoia et al., 2025).

Zastosowanie zaawansowanych technik funkcjonalnego rezonansu magnetycznego (fMRI) oraz modelowania predykcyjnego opartego na konektomie (Connectome-Based Predictive Modeling, CPM) umożliwiło zidentyfikowanie centralnych mechanizmów odpowiadających za efekty akupunktury w OUN. Wykazano, że wyjściowa połączalność funkcjonalna mózgu w stanie spoczynku determinuje odpowiedź na leczenie. Akupunktura prowadzi do obniżenia natężenia bólu w skali VAS, redukcji wskaźnika niepełnosprawności (HIT-6, MIDAS) oraz poprawy funkcjonowania w kwestionariuszach jakości życia (MSQ / MSQOL). (Zhang et al., 2026).

Główna zaletą Akupunktury jest jej bezpieczeństwo stosowania. Powikłania Po akupunkturze były łagodne, miejscowe i przemijające (podskórny krwiak, niewielka bolesność w miejscu wkłucia, drętwienie). Nie powodowały rezygnacji z leczenia w przeciwieństwie do niektórych powikłań metod farmakologicznych. Dlatego akupunktura może stanowić dobrą alternatywę dla osób nietolerujących metod farmakologicznych lub kobiet w czasie ciąży czy laktacji.Autorzy badań podkreślają konieczność dalszego prowadzenia na szeroką skalę badań, trudności związane z prowadzeniem badań (w szczególności ograniczenia populacyjne badań oraz trudności w projektowaniu grup kontrolnych) oraz ryzykiem popełnienia biasu (Liu et al., 2024; Lu et al., 2025; Zhang et al., 2026; Pistoia et al., 2025).

4. Discussion

4.1 Interpretation of the Findings

The evidence reviewed supports a broader, mechanism-informed approach to migraine care, in which the availability of additional therapeutic targets increases the scope for individualisation. Clinical benefit should nevertheless be assessed in relation to the purpose of treatment: rapid and sustained symptom resolution during an attack, or reduction of migraine frequency and associated disability over time. These outcomes are complementary but cannot be compared interchangeably. The continuing gap between eligibility for preventive treatment and its actual use also indicates that therapeutic innovation must be accompanied by improved recognition of treatment needs and regular assessment of outcomes (Eigenbrodt et al., 2021; Puledda et al., 2023).

For acute treatment, the comparative literature does not support assuming that newer agents are uniformly more effective than established triptans. Network meta-analyses identify several triptans among the most effective oral options for achieving pain freedom, while also demonstrating differences between individual agents. Gepants and lasmiditan therefore extend the range of clinically useful choices, particularly when triptans are ineffective, poorly tolerated or unsuitable. However, indirect comparisons depend on the comparability of trial populations, doses and outcome definitions, and should inform rather than determine treatment selection. Pain relief, complete pain freedom and freedom from the most bothersome symptom represent distinct endpoints and should remain clearly differentiated when interpreting efficacy estimates (Deng et al., 2024; Puledda et al., 2023; Laohapiboolrattona et al., 2024; Karlsson et al., 2024; Yang et al., 2021; Leroux et al., 2020; Lipton et al., 2025).

The absence of a vasoconstrictive mechanism is an important pharmacological distinction for gepants and lasmiditan. Nevertheless, this property should not be interpreted as proof of unrestricted safety in every patient with cardiovascular disease. The characteristics and exclusions of the studied populations remain relevant. Practical differences also influence clinical value: intranasal zavegepant offers an alternative route when oral administration is difficult, whereas the central nervous system adverse effects of lasmiditan, including dizziness and somnolence, may limit its suitability for patients who need to drive or maintain unimpaired alertness. Thus, an appropriate acute treatment must balance symptom control with the patient's ability to resume normal activities (Ashina et al., 2025; Croop et al., 2022; Deng et al., 2024; Zhu et al., 2025; Puledda et al., 2023; Laohapiboolrattona et al., 2024; Hou et al., 2020).

In prevention, CGRP pathway-targeting monoclonal antibodies and gepants provide evidence that targeting a defined component of migraine biology can reduce disease burden. Their value extends beyond average changes in monthly migraine days to responder rates, acute medication use and daily functioning. However, substantial improvements from baseline in an open-label extension cannot be equated with the treatment effect observed against placebo in a blinded trial. Longer-term findings for rimegepant and atogepant support sustained benefit among participants who remain under observation, but treatment persistence and the absence of a concurrent placebo group constrain causal interpretation. Similarly, the generally favourable tolerability observed in monoclonal antibody trials does not establish equivalence between agents or exclude uncommon adverse effects (Kudrow et al., 2026; Ashina et al., 2023; Messina et al., 2023; Yu et al., 2025; Huang et al., 2020; Han et al., 2019; Zhao et al., 2021).

OnabotulinumtoxinA retains a distinct role in chronic migraine. Its long-term observational evidence is particularly relevant to clinical practice because it describes outcomes across repeated treatment cycles and includes disability and quality-of-life measures. The meta-analysis of real-world data reported reductions of approximately ten monthly headache days at 24 and 52 weeks. These changes represent within-patient improvement rather than placebo-adjusted effects and should not be used to infer superiority over CGRP-targeted treatments. Differences in baseline headache frequency, study design and follow-up further preclude such comparisons. Treatment burden also differs: oral dosing, subcutaneous injection, intravenous infusion and repeated multisite injections offer different practical advantages and constraints (Ashina et al., 2023; Yu et al., 2026; Shaterian et al., 2022; Turkel et al., 2023; Lanteri-Minet et al., 2022).

Ergot derivatives illustrate how improvements in drug delivery can renew interest in an established treatment without removing its pharmacological limitations. Intranasal dihydroergotamine formulations may offer practical advantages over poorly absorbed oral preparations, but their place in care must still account for vasoconstrictive effects and treatment-specific contraindications. Accordingly, novel delivery systems and novel molecular targets address different clinical problems; neither alone establishes a universally preferable

acute treatment (Whealy et al., 2024; Bigal et al., 2003; Mitsikostas et al., 2024; Terpening et al., 2025; Silvestro et al., 2024; Cooper et al., 2022; Tynan et al., 2018).

The PACAP pathway is an important emerging target, but mechanistic plausibility and clinical efficacy require separate interpretation. The persistence of PACAP38-induced attacks despite CGRP ligand blockade supports a component of migraine provocation that is not prevented by that intervention. It does not establish that anti-PACAP treatment will benefit all patients who have not responded to CGRP-targeted prevention. Clinical results are also inconsistent: a positive phase II signal has been reported for Lu AG09222, whereas LY3451838 did not demonstrate a statistically significant benefit over placebo and the PAC1 receptor antibody AMG 301 failed to show efficacy. The LY3451838 study enrolled only 38 participants, limiting precision. Ligand neutralisation and selective receptor blockade should therefore not be treated as interchangeable strategies, and the identification of responsive patient subgroups remains a research priority (Rubio-Beltran et al., 2018; Kuburas and Russo, 2023; Al-Karagholi et al., 2025; Johnson et al., 2025).

The evidence for non-invasive neuromodulation supports a device-specific assessment. Distinct stimulation sites, treatment schedules and mechanisms make general claims about a single class effect inappropriate. Interpretation is further complicated by the credibility and possible physiological activity of sham stimulation, adherence requirements and inconsistent endpoints. Positive findings from adherent or per-protocol populations should be distinguished from results in the full randomised population. These considerations are particularly relevant when translating vagus nerve stimulation findings into routine practice. Although local and transient adverse effects predominate in the reviewed studies, favourable tolerability alone does not establish effectiveness or justify extrapolation to populations inadequately represented in trials (Yuan et al., 2025; Reuter et al., 2019; Fernandez-Hernando et al., 2023; Canales-Rodriguez et al., 2026; Nasir et al., 2026; Farahani et al., 2026; Diener et al., 2019).

Greater occipital nerve block may offer short-term benefit in selected acute and preventive settings, but these indications require separate evaluation. A randomised emergency-treatment study found benefit when the procedure was added to an intravenous regimen; this does not establish equivalent effectiveness as a standalone intervention. Reviews of preventive use identify limitations in certainty, protocol consistency and the durability of benefit. Further trials should distinguish episodic from chronic migraine and standardise injection technique, comparator treatment and follow-up (Atraszkiewicz et al., 2025; Tamayo de Leon et al., 2025; Sabet et al., 2025).

Exercise, acupuncture and manual interventions broaden the possibilities for multimodal care, although their evidential foundations differ. Exercise studies support a preventive benefit, but estimates from indirect comparisons do not establish equivalence to a particular medicine. Acupuncture trials and meta-analyses report improvements in migraine outcomes, while interpretation depends on comparator selection, blinding and treatment expectations. Findings linking functional connectivity to response remain exploratory and do not yet justify routine imaging-based treatment selection. Myofascial release may be relevant when cervical symptoms coexist, but evidence derived from mixed headache populations should not be assumed to establish migraine-specific efficacy. These interventions should be discussed with patients in proportion to the certainty of their supporting evidence (Rezaeian et al., 2021; Jara Silva et al., 2022; Pillai et al., 2023; Lu et al., 2024; Lv and Yin, 2024; Lemmens et al., 2019; Woldeamanuel et al., 2022; Liu et al., 2024; Lu et al., 2025; Zhang et al., 2026; Pistoia et al., 2025).

4.2. Limitations

This review has methodological limitations inherent in its narrative design. It synthesises a predefined collection of 64 publications rather than an independently reproducible systematic evidence set, and no protocol was registered. No formal review-wide risk-of-bias assessment or quantitative synthesis is reported. Publication selection may therefore have influenced the balance of evidence, and the present discussion should not be interpreted as an exhaustive comparison or a definitive hierarchy of treatments. The inclusion of both primary studies and meta-analyses also creates potential overlap in the underlying trial populations; their findings should not be treated as independent replications.

Comparability is further limited by differences in episodic and chronic migraine populations, baseline attack frequency, previous preventive treatment failures, doses, administration routes and follow-up duration. Acute pain freedom, headache relief, monthly migraine days and monthly headache days measure different aspects of disease burden. Likewise, reductions from baseline in open-label studies and observational cohorts cannot be interpreted as placebo-adjusted treatment effects. These distinctions are particularly important when comparing long-term gepant and onabotulinumtoxinA findings with randomised preventive trials. Indirect

network comparisons also depend on assumptions of comparability across studies and do not replace direct randomised comparisons (Kudrow et al., 2026; Deng et al., 2024; Ashina et al., 2023; Puledda et al., 2023; Karlsson et al., 2024; Yang et al., 2021; Lanteri-Minet et al., 2022).

The emerging and non-pharmacological evidence introduces additional uncertainty. In the LY3451838 phase II study, recruitment was lower than planned and only 38 participants were randomised, limiting power to detect a modest treatment effect. Neuromodulation studies differ in device characteristics, adherence and sham procedures, while procedural and manual therapy studies frequently have small samples, short follow-up or heterogeneous headache populations. These limitations constrain conclusions about sustained benefit and generalisability. The favourable tolerability reported in individual studies also provides limited information about uncommon adverse events or populations insufficiently represented in those studies (Johnson et al., 2025; Yuan et al., 2025; Reuter et al., 2019; Fernandez-Hernando et al., 2023; Canales-Rodriguez et al., 2026; Atraszkiewicz et al., 2025; Tamayo de Leon et al., 2025; Sabet et al., 2025; Rezaeian et al., 2021; Jara Silva et al., 2022; Pillai et al., 2023; Lu et al., 2024.

4.3. Directions for Future Research

Future comparative trials should evaluate clinically relevant treatment choices directly, using consistent definitions of acute and preventive outcomes. Stratification by migraine phenotype, prior treatment response and baseline disease burden would help distinguish average efficacy from benefit in particular patient groups. In addition to attack frequency and two-hour pain freedom, studies should assess sustained response, acute medication use, disability, daily functioning and quality of life. Longer follow-up is needed to clarify persistence of benefit, treatment discontinuation and uncommon adverse effects, particularly for newer preventive therapies. The comparative literature and long-term studies reviewed here provide a rationale for these priorities (Kudrow et al., 2026; Ashina et al., 2023; Messina et al., 2023; Puledda et al., 2023; Laohapiboolrattana et al., 2024; Karlsson et al., 2024; Yang et al., 2021; Leroux et al., 2020; Lipton et al., 2025; Lanteri-Minet et al., 2022).

PACAP-targeted therapies require adequately powered confirmatory studies that distinguish ligand neutralisation from selective PAC1 receptor blockade. The persistence of PACAP38-induced attacks despite eptinezumab treatment provides a mechanistic rationale for further investigation, but does not establish that patients who do not respond to CGRP-targeted therapies will respond to PACAP inhibition. Trials specifically characterising previous preventive failures and prospectively evaluating response in relevant subgroups are therefore needed. The contrasting findings for Lu AG09222, LY3451838 and AMG 301 also support further investigation of the receptor pathways responsible for clinical benefit (Rubio-Beltran et al., 2018; Kuburas and Russo, 2023; Al-Karagholi et al., 2025; Johnson et al., 2025).

For neuromodulation, greater occipital nerve block and rehabilitative interventions, priorities include credible control procedures, standardised treatment protocols and assessment after treatment has ended. Procedural studies should distinguish acute adjunctive use from prevention and report episodic and chronic migraine outcomes separately. Exercise and manual therapy trials should define intervention intensity, adherence and relevant musculoskeletal features, while acupuncture studies should address comparator choice and the reproducibility of proposed response predictors. Functional connectivity findings warrant independent prospective validation before they can inform routine treatment selection. Finally, studies of multimodal care should determine whether combining interventions provides additional benefit over their individual components, rather than assuming additive efficacy (Yuan et al., 2025, Reuter et al., 2019; Fernandez-Hernando et al., 2023; Canales-Rodriguez et al., 2026; Atraszkiewicz et al., 2025; Tamayo de Leon et al., 2025; Sabet et al., 2025; Farahani et al., 2026; Rezaeian et al., 2021; Jara Silva et al., 2022; Pillai et al., 2023; Lu et al., 2024; Lv and Yin, 2024; Lemmens et al., 2019; Woldeamanuel et al., 2022; Liu et al., 2024; Lu et al., 2025; Zhang et al., 2026; Pistoia et al., 2025).

5. Conclusions

Migraine treatment increasingly permits selection according to the clinical needs of the individual patient. Triptans remain important acute therapies, while gepants and lasmiditan provide additional options when response, tolerability or contraindications limit their use. CGRP-targeted preventive treatments and onabotulinumtoxinA for chronic migraine expand opportunities to reduce attack burden and disability. Anti-PACAP strategies offer a promising additional direction, but their clinical role remains to be established. Procedural interventions, neuromodulation, exercise, acupuncture and selected manual therapies may complement care, with treatment decisions reflecting the variable certainty of evidence. The most useful measure of progress is sustained improvement in symptoms, functioning and quality of life. Future studies should clarify comparative effectiveness, treatment sequencing and predictors of response.

REFERENCES

1. Eigenbrodt, A. K., Ashina, H., Khan, S., Diener, H., Mitsikostas, D. D., Sinclair, A. J., Pozo-Rosich, P., Martelletti, P., Ducros, A., Lantéri-Minet, M., Braschinsky, M., Del Rio, M. S., Daniel, O., Özge, A., Mammadbayli, A., Arons, M., Skorobogatykh, K., Romanenko, V., Terwindt, G. M.,... Ashina, M. (2021). Diagnosis and management of migraine in ten steps. *Nature Reviews Neurology, 17*(8), 501–514. https://doi.org/10.1038/s41582-021-00509-5
2. Puledda, F., Silva, E. M., Suwanlaong, K., & Goadsby, P. J. (2023). Migraine: From pathophysiology to treatment. *Journal of Neurology, 270*(7), 3654–3666. https://doi.org/10.1007/s00415-023-11706-1
3. Lu, W., Zhang, Y., Shi, C., et al. (2026). Migraine: Epidemiology, risk factors, pathophysiology, and treatment. *MedComm, 7*, e70933. https://doi.org/10.1002/mco2.70933
4. Dai, W., Liu, R., Qiu, E., Liu, Y., Chen, Z., Chen, X., Ao, R., Zhuo, M., & Yu, S. (2021). Cortical mechanisms in migraine. *Molecular Pain, 17*, 17448069211050246. https://doi.org/10.1177/17448069211050246
5. Atraszkiewicz, D. (2021). The processes underlying chronic migraine pathophysiology and its treatment with botulinum toxin type A. *Neurology and Clinical Neuroscience, 9*(6), 421–429. https://doi.org/10.1111/ncn3.12551
6. Deng, H., Li, G., Nie, H., Feng, Y., Guo, G., Guo, W., & Tang, Z. (2020). Efficacy and safety of calcitonin-gene-related peptide binding monoclonal antibodies for the preventive treatment of episodic migraine – an updated systematic review and meta-analysis. *BMC Neurology, 20*(1), 57. https://doi.org/10.1186/s12883-020-01633-3
7. Ashina, M., McAllister, P., Gaul, C., Leyva-Rendon, A., Ramirez, L. M., Nalpas, C., Thiry, A., Abraham, L., Fountaine, R. J., & Fullerton, T. (2025). Rimegepant for acute treatment of migraine in triptan-unsuitable adults: A randomized, double-blind, placebo-controlled phase 4 trial. *Cephalalgia, 45*(11), 3331024251395298. https://doi.org/10.1177/03331024251395298
8. Ikeda, K., Matsumori, Y., Kudo, M., Ishikawa, T., Hoshino, Y., Yoshimatsu, H., Thiry, A., Arakawa, A., Croop, R., Fullerton, T., Sakai, F., & Takeshima, T. (2025). Efficacy and safety of rimegepant for the acute treatment of migraine in japan: A dose-ranging, double-blind, randomized controlled trial. *Headache the Journal of Head and Face Pain, 65*(10), 1811–1820. https://doi.org/10.1111/head.14994
9. Kudrow, D., Croop, R. S., Thiry, A., & Lipton, R. B. (2025). A 52-week open-label extension study to evaluate the safety and efficacy of oral rimegepant for the preventive treatment of migraine. *Headache the Journal of Head and Face Pain, 66*(2), 407–416. https://doi.org/10.1111/head.15002
10. Croop, R., Madonia, J., Stock, D. A., Thiry, A., Forshaw, M., Murphy, A., Coric, V., & Lipton, R. B. (2022). Zavegepant nasal spray for the acute treatment of migraine: A phase 2/3 double-blind, randomized, placebo-controlled, dose-ranging trial. *Headache the Journal of Head and Face Pain, 62*(9), 1153–1163. https://doi.org/10.1111/head.14389
11. Deng, X., Zhou, L., Liang, C., Shang, X., Hui, X., Liu, W., Liang, S., Wang, Y., Xu, M., Guo, K., Yang, K., & Li, X. (2024). Comparison of effectiveness and safety of lasmiditan and CGRP-antagonists for the acute treatment of migraine in adults: Systematic review and network meta-analysis of randomised trials. *The Journal of Headache and Pain, 25*(1), 16. https://doi.org/10.1186/s10194-024-01723-4
12. Zhu, Z., Tang, Y., Li, L., Ni, H., Liu, M., Chen, Z., & Wang, Z. (2025). The efficacy and safety of zavegepant nasal inhalation versus oral calcitonin-gene related peptide receptor antagonists in the acute treatment of migraine: A systematic review and network meta-analysis of the literature. *The Journal of Headache and Pain, 26*(1), 48. https://doi.org/10.1186/s10194-025-01984-7
13. Ashina, M., Tepper, S. J., Reuter, U., Blumenfeld, A. M., Hutchinson, S., Xia, J., Miceli, R., Severt, L., Finnegan, M., & Trugman, J. M. (2023). Once-daily oral atogepant for the long-term preventive treatment of migraine: Findings from a multicenter, randomized, open-label, phase 3 trial. *Headache the Journal of Head and Face Pain, 63*(1), 79–88. https://doi.org/10.1111/head.14439
14. Ailani, J., Lipton, R. B., Blumenfeld, A. M., Mechtler, L., Klein, B. C., He, M. Y., Smith, J. H., Trugman, J. M., De Abreu Ferreira, R., & Brand-Schieber, E. (2024). Safety and tolerability of ubrogepant for the acute treatment of migraine in participants taking atogepant for the preventive treatment of episodic migraine: Results from the tandem study. *Headache the Journal of Head and Face Pain, 65*(6), 1005–1014. https://doi.org/10.1111/head.14871
15. Messina, R., Huessler, E., Puledda, F., Haghdoost, F., Lebedeva, E. R., & Diener, H. (2023). Safety and tolerability of monoclonal antibodies targeting the CGRP pathway and gepants in migraine prevention: A systematic review and network meta-analysis. *Cephalalgia, 43*(3), 3331024231152169. https://doi.org/10.1177/03331024231152169

16. Yu, S., Matsumori, Y., Kim, B., Gryglas-Dworak, A., Giorgadze, G., Pozo-Rosich, P., Josiassen, M. K., Ranc, K., Ettrup, A., Mittoux, A., Sperling, B., & Takeshima, T. (2025). Efficacy and safety of eptinezumab in a predominantly asian population with chronic migraine: Results of the randomized, double-blind, placebo-controlled sunrise trial. *Cephalalgia, 45*(10), 3331024251386095. https://doi.org/10.1177/03331024251386095

17. Huang, I., Wu, P., Lee, Y., & Kang, Y. (2020). Optimal treatment strategy of fremanezumab in migraine prevention: A systematic review with network meta-analysis of randomized clinical trials. *Scientific Reports, 10*(1), 18609. https://doi.org/10.1038/s41598-020-75602-8

18. Han, L., Liu, Y., Xiong, H., & Hong, P. (2019). CGRP monoclonal antibody for preventive treatment of chronic migraine: An update of meta-analysis. *Brain and Behavior, 9*(2), e01215. https://doi.org/10.1002/brb3.1215

19. Zhao, X., Xu, X., & Li, Q. (2020). Efficacy and safety of galcanezumab for preventive treatment of migraine: A systematic review and meta-analysis. *Journal of Neurology, 268*(7), 2364–2376. https://doi.org/10.1007/s00415-020-09707-5

20. Puledda, F., Younis, S., Huessler, E., Haghdoost, F., Lisicki, M., Goadsby, P. J., & Tassorelli, C. (2023). Efficacy, safety and indirect comparisons of lasmiditan, rimegepant, and ubrogepant for the acute treatment of migraine: A systematic review and network meta-analysis of the literature. *Cephalalgia, 43*(3), 3331024231151419. https://doi.org/10.1177/03331024231151419

21. Laohapiboolrattana, W., Jansem, P., Anukoolwittaya, P., Roongpiboonsopit, D., Hiransuthikul, A., Pongpitakmetha, T., Thanprasertsuk, S., & Rattanawong, W. (2024). Efficacy of lasmiditan, rimegepant and ubrogepant for acute treatment of migraine in triptan insufficient responders: Systematic review and network meta-analysis. *The Journal of Headache and Pain, 25*(1), 194. https://doi.org/10.1186/s10194-024-01904-1

22. Hou, M., Xing, H., Li, C., Wang, X., Deng, D., Li, J., Zhang, P., & Chen, J. (2020). Short-term efficacy and safety of lasmiditan, a novel 5-HT1F receptor agonist, for the acute treatment of migraine: A systematic review and meta-analysis. *The Journal of Headache and Pain, 21*(1), 66. https://doi.org/10.1186/s10194-020-01138-x

23. Karlsson, W. K., Ostinelli, E. G., Zhuang, Z. A., Kokoti, L., Christensen, R. H., Al-Khazali, H. M., Deligianni, C. I., Tomlinson, A., Ashina, H., De La Torre, E. R., Diener, H., Cipriani, A., & Ashina, M. (2024). Comparative effects of drug interventions for the acute management of migraine episodes in adults: Systematic review and network meta-analysis. *BMJ, 386*, e080107. https://doi.org/10.1136/bmj-2024-080107

24. Yang, C., Liang, C., Chang, C., Yang, C., Shih, P., Yau, Y., Tang, K., & Wang, S. (2021). Comparison of new pharmacologic agents with triptans for treatment of migraine. *JAMA Network Open, 4*(10), e2128544. https://doi.org/10.1001/jamanetworkopen.2021.28544

25. Leroux, E., Buchanan, A., Lombard, L., Loo, L. S., Bridge, D., Rousseau, B., Hopwood, N., Matthews, B. R., & Reuter, U. (2020). Evaluation of patients with insufficient efficacy and/or tolerability to triptans for the acute treatment of migraine: A systematic literature review. *Advances in Therapy, 37*(12), 4765–4796. https://doi.org/10.1007/s12325-020-01494-9

26. Lipton, R. B., Gendolla, A., Abraham, L., Jenkins, A., Telfort, J., Blakeman, K. H., Saccone, P. A., Pustulka, I., Fotheringham, I., & Engh, A. (2024). Relative frequency, characteristics, and disease burden of patients with migraine unsuitable for triptan treatment: A systematic literature review. *Headache the Journal of Head and Face Pain, 65*(1), 164–179. https://doi.org/10.1111/head.14854

27. Whealy, M., & Becker, W. J. (2024). The 5-HT1B and 5-HT1D agonists in acute migraine therapy: Ergotamine, dihydroergotamine, and the triptans. *Handb Clin Neurol, 199*, 17-42. https://doi.org/10.1016/B978-0-12-823357-3.00008-2

28. Bigal, M. E., & Tepper, S. J. (2003). Ergotamine and dihydroergotamine: A review. *Current Pain and Headache Reports, 7*(1), 55–62.

29. Mitsikostas, D. D., & Ward, T. N. (2024). Evidence-based symptomatic treatment of migraine. *Handb Clin Neurol, 199*, 203-218. https://doi.org/10.1016/B978-0-12-823357-3.00004-5

30. Koehler, P. J., & Boes, C. J. (2023). History of migraine. *Handb Clin Neurol, 198*, 3-21. https://doi.org/10.1016/B978-0-12-823356-6.00002-0

31. Ngo, M., & Patel, P. (2026, June 8). Ergotamine/caffeine. In StatPearls. StatPearls Publishing.

32. Terpening, C. M., & Wietholter, J. P. (2025). Dihydroergotamine intranasal powder for acute migraine treatment. Annals of Pharmacotherapy, Advance online publication.

33. Silvestro, M., Orologio, I., Tessitore, A., Trojsi, F., Tedeschi, G., & Russo, A. (2024). Dihydroergotamine mesylate nasal spray: An acute treatment option for migraine in adults. *Expert Rev Neurother, 24*(6), 555-564. https://doi.org/10.1080/14737175.2024.2342446

34. Cooper, W., Ray, S., Aurora, S. K., Shrewsbury, S. B., Fuller, C., Davies, G., & Hoekman, J. (2022). Delivery of dihydroergotamine mesylate to the upper nasal space for the acute treatment of migraine: Technology in action. *J Aerosol Med Pulm Drug Deliv, 35*(6), 321-332. https://doi.org/10.1089/jamp.2022.0005

35. Tynan, D., Ahmad, K., & Thieben, M. (2018). Long-term ergotamine derivative therapy for migraine associated with pachymeningitis and sixth cranial nerve palsy. *Neuro-Ophthalmology, 44*(2), 117–121.

36. Rubio-Beltrán, E., Correnti, E., Deen, M., Kamm, K., Kelderman, T., Papetti, L., Vigneri, S., MaassenVanDenBrink, A., & Edvinsson, L. (2018). PACAP38 and PAC1 receptor blockade: A new target for headache? The journal of headache and pain, 19(1), 64. https://doi.org/10.1186/s10194-018-0893-8

37. Kuburas, A., & Russo, A. F. (2023). Shared and independent roles of CGRP and PACAP in migraine pathophysiology. *The Journal of Headache and Pain, 24*(1), 34. https://doi.org/10.1186/s10194-023-01569-2

38. Al-Karagholi, M. A., Zhuang, Z. A., Beich, S., Ashina, H., & Ashina, M. (2025). PACAP38-induced migraine attacks are independent of CGRP signaling: A randomized controlled trial. *The Journal of Headache and Pain, 26*(1), 79. https://doi.org/10.1186/s10194-025-02022-2

39. Johnson, M. P., Krikke-Workel, J., Patel, C. N., Morin, S. M., Turner, P. K., Clark, K. A., Donley, D., Jin, Y., Johnson, K. W., Vincent, M., Stille, J. R., Broad, L. M., & Patel, A. (2025). Preclinical and clinical evaluation of LY3451838, a PACAP-neutralizing monoclonal antibody, in randomized, double-blind, placebo-controlled phase 1 and phase 2 studies involving healthy adults and adults with treatment-resistant migraine. *Cephalalgia, 45*(8), 3331024251368757. https://doi.org/10.1177/03331024251368757

40. Shaterian, N., Shaterian, N., Ghanaatpisheh, A., Abbasi, F., Daniali, S., Jahromi, M. J., Sanie, M. S., & Abdoli, A. (2022). Botox (onabotulinumtoxinA) for treatment of migraine symptoms: A systematic review. *Pain research & management, 2022*, 3284446. https://doi.org/10.1155/2022/3284446

41. Turkel, C. C., Aurora, S., Diener, H. C., Dodick, D. W., Lipton, R. B., Silberstein, S. D., & Brin, M. F. (2023). Treatment of chronic migraine with Botox (onabotulinumtoxinA): Development, insights, and impact. *Medicine, 102*(S1), e32600. https://doi.org/10.1097/MD.0000000000032600

42. Lanteri-Minet, M., Ducros, A., Francois, C., Olewinska, E., Nikodem, M., & Dupont-Benjamin, L. (2022). Effectiveness of onabotulinumtoxinA (Botox®) for the preventive treatment of chronic migraine: A meta-analysis on 10 years of real-world data. *Cephalalgia: an international journal of headache, 42*(14), 1543–1564. https://doi.org/10.1177/03331024221123058

43. Yuan, H., Orr, S. L., Al-Karagholi, M. A. M., Ashina, M., Cohen, F., Diener, H. C., Dodick, D. W., Jensen, R. H., Marmura, M. J., Martinelli, D., Matharu, M. S., Petersen, A. S., Pozo-Rosich, P., Sacco, S., Simmonds, L., Tassorelli, C., Tepper, S. J., Terwindt, G. M., Wang, S. J., Yeh, J. T., … Silberstein, S. D. (2025). International headache society evidence-based guidelines on the use of non-invasive neuromodulation devices for the acute and preventive treatment of migraine. *Cephalalgia: an international journal of headache, 45*(10), 3331024251388377. https://doi.org/10.1177/03331024251388377

44. Reuter, U., McClure, C., Liebler, E., & Pozo-Rosich, P. (2019). Non-invasive neuromodulation for migraine and cluster headache: A systematic review of clinical trials. *Journal of neurology, neurosurgery, and psychiatry, 90*(7), 796–804. https://doi.org/10.1136/jnnp-2018-320113

45. Fernández-Hernando, D., Fernández-de-Las-Peñas, C., Pareja-Grande, J. A., García-Esteo, F. J., & Mesa-Jiménez, J. A. (2023). Management of auricular transcutaneous neuromodulation and electro-acupuncture of the vagus nerve for chronic migraine: A systematic review. *Frontiers in neuroscience, 17*, 1151892. https://doi.org/10.3389/fnins.2023.1151892

46. Canales-Rodríguez, J., Angerhöfer, C., Caronna, E., Raffaelli, B., Overeem, L. H., Pozo-Rosich, P., & Reuter, U. (2026). Efficacy, IHS guideline adherence, and methodological quality of noninvasive neuromodulation clinical trials in migraine and cluster headache: A systematic review. *European journal of neurology, 33*(6), e70559. https://doi.org/10.1111/ene.70559

47. Atraszkiewicz, D., Ünal, E., Bassett, P., Morell-Ducos, F., & Bahra, A. (2025). Greater occipital nerve block for the treatment of migraine: An umbrella review, systematic review, and meta-analysis. *Cephalalgia: an international journal of headache, 45*(12), 3331024251398390. https://doi.org/10.1177/03331024251398390

48. Tamayo de Leon, C. D., Gama-Reyes, E. G., Paredes Moreno, F. A., & Galnares-Olalde, J. A. (2025). Adjunctive occipital nerve block for emergency treatment of acute migraine: A randomized, controlled trial. *Cephalalgia: an international journal of headache, 45*(10), 3331024251381764. https://doi.org/10.1177/03331024251381764

49. Sabet, H., Abbas, A., Abouelmagd, M. E., Samir, A., Helal, M. M., El-Moslemani, M., Younis, A. F., Yousef, O., Rouby, R. A., & Abd-Elsayed, A. (2025). Ultrasound-guided greater occipital nerve block for chronic migraine: A systematic review and meta-analysis. *Head & face medicine, 21*(1), 81. https://doi.org/10.1186/s13005-025-00554-1

50. Nasir, R., Baig, M. O., Abualait, T., Obaid, S., Jadoon, I. J., Al-Hussain, F., & Bashir, S. (2026). Effects of vagal nerve stimulation on pain frequency and intensity in chronic migraine in adults: A randomized controlled trial. *Physiological reports, 14*(7), e70843. https://doi.org/10.14814/phy2.70843

51. Farahani, A., Adel Ghahraman, M., Togha, M., Malmir, K., & Jalaie, S. (2026). Effects of adding transcutaneous vagus nerve stimulation to vestibular rehabilitation on dizziness and postural control in vestibular migraine: A randomized clinical trial. *Scientific reports, 16*(1), 8133. https://doi.org/10.1038/s41598-026-39697-9

52. Diener, H. C., Goadsby, P. J., Ashina, M., Al-Karagholi, M. A., Sinclair, A., Mitsikostas, D., Magis, D., Pozo-Rosich, P., Irimia Sieira, P., Làinez, M. J., Gaul, C., Silver, N., Hoffmann, J., Marin, J., Liebler, E., & Ferrari, M. D. (2019). Non-invasive vagus nerve stimulation (nvns) for the preventive treatment of episodic migraine: The multicentre, double-blind, randomised, sham-controlled premium trial. *Cephalalgia: an international journal of headache, 39*(12), 1475–1487. https://doi.org/10.1177/0333102419876920

53. VanderPluym, J. H., Halker Singh, R. B., Urtecho, M., Morrow, A. S., Nayfeh, T., Torres Roldan, V. D., Farah, M. H., Hasan, B., Saadi, S., Shah, S., Abd-Rabu, R., Daraz, L., Prokop, L. J., Murad, M. H., & Wang, Z. (2021). Acute treatments for episodic migraine in adults: A systematic review and Meta-analysis. *JAMA, 325*(23), 2357–2369. https://doi.org/10.1001/jama.2021.7939

54. Rezaeian, T., Ahmadi, M., Mosallanezhad, Z., & Nourbakhsh, M. R. (2021). The impact of myofascial release and stretching techniques on the clinical outcomes of migraine headache. *Journal of Research in Medical Sciences, 26*, 45.

55. Jara Silva, C. E., Joseph, A. M., Khatib, M., Knafo, J., Karas, M., Krupa, K., Rivera, B., Macia, A., Madhu, B., McMillan, M., Burtch, J., Quinonez, J., Albert, T., & Khanna, D. (2022). Osteopathic manipulative treatment and the management of headaches: A scoping review. *Cureus, 14*(8), e27830. https://doi.org/10.7759/cureus.27830

56. Pillai, S., & Zhang, N. (2023). The role of manual therapies in the treatment of headache disorders. *Curr Neurol Neurosci Rep, 23*(8), 399-405. https://doi.org/10.1007/s11910-023-01279-x

57. Lu, Z., Zou, H., Zhao, P., Wang, J., & Wang, R. (2024). Myofascial release for the treatment of tension-type, cervicogenic headache or migraine: A systematic review and Meta-Analysis. *Pain Research and Management, 2024*, 2042069.

58. Lv, Y., & Yin, Y. (2024). A review of the application of myofascial release therapy in the treatment of diseases. *Journal of Multidisciplinary Healthcare, 17*, 4507–4517.

59. Lemmens, J., De Pauw, J., Van Soom, T., et al. (2019). The effect of aerobic exercise on the number of migraine days, duration and pain intensity in migraine: A systematic literature review and meta-analysis. *J Headache Pain, 20*(1), 16. https://doi.org/10.1186/s10194-019-0961-8

60. Woldeamanuel, Y. W., & Oliveira, A. B. D. (2022). What is the efficacy of aerobic exercise versus strength training in the treatment of migraine? A systematic review and network meta-analysis of clinical trials. *J Headache Pain, 23*(1), 134. https://doi.org/10.1186/s10194-022-01503-y

61. Liu, L., Chen, Q., Zhao, L., Lyu, T., Nie, L., Miao, Q., Liu, Y., Zheng, L., Fu, F., Luo, Y., Zeng, C., Zhang, C., Peng, P., Zhang, Y., & Li, B. (2024). Acupuncture plus topiramate placebo versus topiramate plus sham acupuncture for the preventive treatment of chronic migraine: A single-blind, double-dummy, randomized controlled trial. *Cephalalgia: an international journal of headache, 44*(6), 3331024241261080. https://doi.org/10.1177/03331024241261080

62. Lu, T., Yang, Y., Li, J., Lu, L., & Liu, J. (2025). Acupuncture improves migraine and quality of life in patients with migraine: A systematic review with meta-analysis. *Systematic reviews, 14*(1), 220. https://doi.org/10.1186/s13643-025-02977-y

63. Zhang, X., Chen, Q., Liu, Y., Li, J., Nie, L., Miao, Q., Fu, F., Lyu, T., Tan, Z., Kong, Y., Li, B., & Liu, L. (2026). Acupuncture for migraine without aura and connection-based efficacy prediction: A randomized clinical trial. *JAMA network open, 9*(1), e2555454. https://doi.org/10.1001/jamanetworkopen.2025.55454

64. Pistoia, F., Cesarano, S., Saporito, G., Albanese, M., Lucenti, C., Scarsella, S., Liguori, A., & Ronchi, F. U. (2025). Acupuncture versus standard medical care in the prophylactic treatment of migraine: A systematic review and Meta-Analysis. *European journal of neurology, 32*(4), e70160. https://doi.org/10.1111/ene.70160