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REVIEW

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Combining treatments for migraine prophylaxis: the state-of-the-art

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Abstract

Combination treatments for migraine prophylaxis present a promising approach to addressing the diverse and complex mechanisms underlying migraine. This review explores the potential of combining oral conventional prophylactics, onabotulinumtoxin A, monoclonal antibodies (mAbs) targeting the calcitonin gene-related peptide (CGRP) pathway, and small molecule CGRP receptor antagonists (gepants). Among the most promising strategies, dual CGRP inhibition through mAbs and gepants may enhance efficacy by targeting both the CGRP peptide and its receptor, while the combination of onabotulinumtoxin A with CGRP treatments offers synergistic pain relief. Oral non-CGRP treatments, which are accessible and often prescribed for patients with comorbid conditions, provide an affordable and practical option in combination regimens. Despite the potential of these combinations, there is a lack of evidence to support their widespread inclusion in clinical guidelines. The high cost of certain combinations, such as onabotulinumtoxin A with a CGRP mAb or dual anti-CGRP mAbs, presents feasibility challenges. Further large-scale trials are needed to establish safe and effective combination protocols and solidify their role in clinical practice, particularly for treatment-resistant patients.

Keywords CGRP, Gepants, Onabotulinumtoxin A, Propranolol, Rational polytherapy, Topiramate

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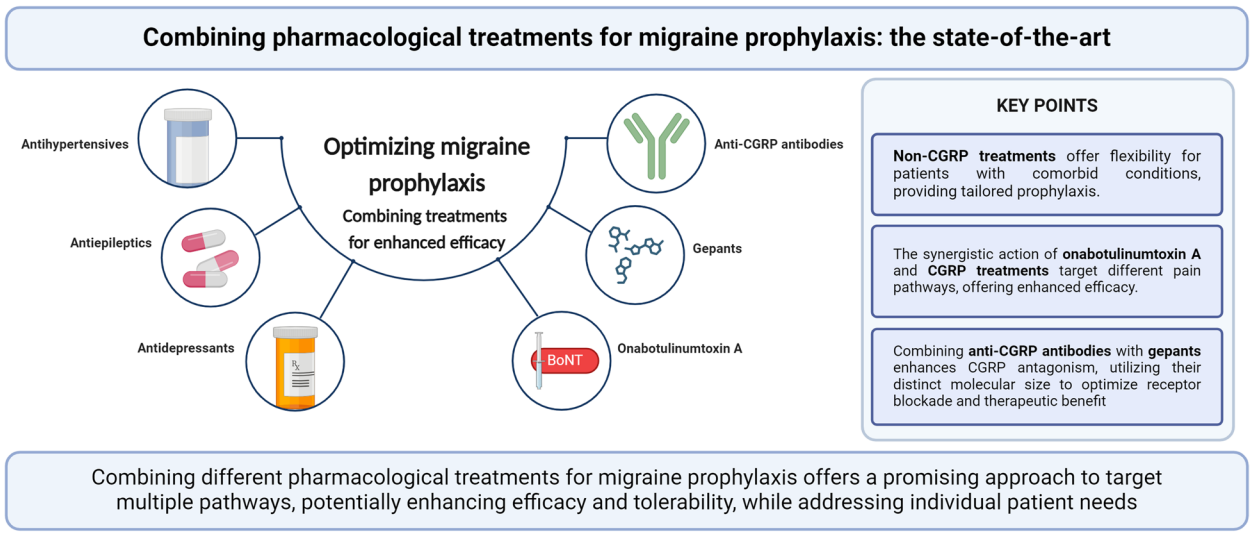
Graphical Abstract



Background

Migraine prophylaxis aims to reduce the frequency, severity, and duration of migraine attacks, offering relief to patients who suffer from frequent or disabling headaches. Over the years, treatment options have expanded from non-specific medications developed for other conditions to more targeted therapies [1]. Traditional treatments, including antihypertensives, antiepileptics, and antidepressants, are highly available, affordable in cost, and widely used in clinical practice. These treatments have been used for decades but are limited by non-specific mechanisms of action and variable effectiveness, along with side effects that can restrict their use. A significant advancement has been the introduction of treatments with effects on calcitonin gene-related peptide (CGRP). Onabotulinumtoxin A (BoNT-A), which works by blocking the release of CGRP and other pain-modulating transmitters from meningeal and extracranial afferents, was initially approved for migraine prophylaxis [2, 3]. More recently, selective therapies such as monoclonal antibodies targeting CGRP or its receptor, and small-molecule CGRP antagonists (gepants), have broadened the range of therapeutic options available. Despite these advancements, treatment failures are observed in up to 30–40% of patients [4]. Combining treatments with different pharmacodynamic profiles presents a potential strategy to enhance outcomes by targeting multiple pathways involved in migraine. Although current guidelines largely overlook combination therapy, exploring the balance between potential benefits and risks is relevant for developing more effective, individualized treatment approaches. This review aims to summarize existing knowledge on combining different therapies, providing a foundation for future research and informing updated guidelines on migraine prophylaxis.

Methods

This is a narrative review with a specific focus on combination therapies for migraine prophylaxis. The aim was to provide a comprehensive overview of existing treatments and explore the rationale for combining various therapeutic approaches. To achieve this, we conducted a broad literature search using databases such as PubMed, Scopus, and Google Scholar. The search terms included combinations of keywords such as "migraine prophylaxis", "combination therapy", "preventive treatments", and "pharmacological and non-pharmacological approaches". In addition, the search terms included the names of specific drugs commonly used for migraine prophylaxis, such as propranolol, amitriptyline, topiramate, valproate, erenumab, fremanezumab, and others. Relevant studies were also identified based on the personal knowledge and expertise of the authors, reflecting their extensive experience in migraine research and treatment. Studies were selected with priority given to those that discussed the efficacy and safety of combination treatments for migraine prophylaxis in individuals with migraine. As this is a narrative review, no formal systematic review methodology – such as predefined eligibility criteria,

structured data extraction, or critical appraisal of individual studies – was employed.

Treatments non targeting the CGRP pathway

Treatment non targeting the CGRP pathway, including antihypertensives, antiepileptics, and antidepressants, have long been the cornerstone of migraine prophylaxis. These therapies, though not specifically developed for migraine, offer broad therapeutic benefits and are widely accessible and affordable, making them essential options in clinical practice.

Antihypertensives

Several antihypertensive drugs are used for migraine prophylaxis. Current guidelines recommend beta-blockers such as propranolol and metoprolol, supported with moderate to high level of evidence [5, 6]. The exact mechanisms behind their antimigraine effects are not fully understood. The hypothesized mechanisms involve the inhibition of nitric oxide (NO) synthesis, the impairment of thalamic relay neurons, the enhancement of specific serotonergic pathways and the reduction of central sensitization [7]. A daily dose of 80 mg of propranolol is as effective as a higher dose of 160 mg in reducing the number of monthly migraine days and the intensity of pain [8]. While bisoprolol, timolol, nebivolol and atenolol may also be effective, the evidence for these is less robust compared to propranolol and metoprolol [5]. Beta-blockers are well tolerated at therapeutic dosages, with the most common side effects being tiredness, sleepiness, cough, constipation, trouble sleeping and cold limbs. A history of cardiac disorders and/or rhythm abnormalities should be investigated before prescribing these drugs. Other antihypertensives used for migraine prophylaxis includes angiotensin II receptor antagonists and angiotensin-converting enzyme (ACE) inhibitors. Two randomized controlled trials and three retrospective cohort studies demonstrated that candesartan effectively prevents migraine attacks, with efficacy similar to propranolol and good tolerability [9–13]. Common side effects associated with daily use of candesartan include tiredness, flu-like symptoms and back pain. In a placebo-controlled crossover study, the ACE inhibitor lisinopril was more effective than placebo in reducing the number of monthly migraine days and headache severity [14]. Common side effects of ACE inhibitors include cough, tiredness, headache, palpitations, and fatigue.

Antiseizure medications

There is high level of evidence supporting the use of two broad-spectrum anti-seizure medications, topiramate and sodium valproate, for migraine prevention [15]. The mechanisms by which anti-seizure medications work to prevent migraine are still unclear. Topiramate and sodium valproate target pathways that reduce excitatory neurotransmission, which in turn decreases neuronal excitability [16, 17]. This involves modulating glutamate activity, blocking voltage-gated sodium (Na^+) and calcium (Ca^{2+}) channels, and enhancing inhibitory neurotransmission through γ-aminobutyric acid (GABA). In animal studies, topiramate reduced nociceptive neuronal firing in the trigeminocervical complex [18]. Additionally, anti-seizure medications could prevent the release of CGRP by inhibiting voltage-gated Ca^{2+} channels at trigeminal nerve endings [19]. In 2023, the European Headache Federation published a review confirming the efficacy and tolerability of topiramate for migraine prevention. The analysis included 8 randomized controlled trials involving 2610 adults who received topiramate doses ranging from 50 to 200 mg [20]. The pooled data showed that topiramate significantly increased the percentage of patients achieving a 50% reduction in monthly migraine days compared to placebo. On average, patients taking topiramate experienced 0.99 fewer monthly migraine days than those on placebo. About 20% of patients discontinued topiramate due to side effects [20]. The effectiveness of sodium valproate (500–1000 mg/day) has been confirmed in both randomized controlled trials and open-label studies [21–25]. A pooled analysis found that patients taking sodium valproate were three times as likely, to achieve a 50% reduction in headache frequency compared to placebo [24]. Other anti-seizure medications, such as lamotrigine, gabapentin, pregabalin, levetiracetam, zonisamide, and carbamazepine, have shown some benefit in treating migraine, but are not recommended due to insufficient evidence [26–28]. No benefits were observed with clonazepam, oxcarbazepine, perampanel, lacosamide, tiagabine, carisbamate, or vigabatrin [29, 30]. Both topiramate and valproate require careful monitoring for side effects, such as cognitive and language impairment. In the case of topiramate, patients should be observed for behavioral disturbances, including the risk of suicidal thoughts, weight loss, and kidney stones. Valproate and topiramate are contraindicated during pregnancy due to the high risk of neurodevelopmental disorders and congenital malformations. Both the Food and Drug Administration and the European Medicines Agency recommend avoiding the use of topiramate and valproate in women of childbearing potential [31, 32].

Antidepressants

Tricyclic antidepressants (TCAs) are commonly used for migraine prevention, with amitriptyline being the most extensively studied TCA for this purpose. Amitriptyline works by inhibiting serotonin and noradrenaline

reuptake in the synaptic cleft. Its antimigraine effects may be linked to its influence on serotonergic transmission and activation of α2-adrenoceptors [33]. Additionally, amitriptyline has anticholinergic and antihistaminergic properties and may impact sodium, calcium, and potassium channels, as well as α1-adrenoceptors, N-methyl-D-aspartate (NMDA) receptors, and opioid receptors [34–36]. The European Headache Federation, American Headache Society, and American Academy of Neurology classify amitriptyline as a level B treatment, meaning it is probably effective for preventing migraine [37, 38]. Moderate-certainty evidence suggests that amitriptyline increases the proportion of patients achieving a ≥ 50% reduction in monthly migraine days [37]. Amitriptyline is also associated with a higher incidence of adverse events compared to placebo, often leading to treatment discontinuation [37]. A meta-analysis of nine clinical trials comparing TCAs to placebo found that patients on TCAs were more likely to experience a ≥ 50% reduction in headache burden compared to placebo [39]. Most of the studies evaluating amitriptyline for migraine prevention are old and involve small sample sizes [37], highlighting the need for high-quality trials to further validate amitriptyline's role in migraine prevention. Serotonin and norepinephrine reuptake inhibitors (SNRIs) are other antidepressants that modulate pain pathways through increased norepinephrine levels [40]. SNRIs including venlafaxine and duloxetine have evidence for efficacy and may be the most effective treatments in patients with comorbid depression and migraine [41]. A recent meta-analysis supports that SNRIs are clinically safe and effective for migraine prevention, showing they outperform placebo and are comparable to other active medications [42]. Patients with higher pain sensitivity identified through psychophysical testing may benefit from SNRI-based prevention strategies [43]. A single-center, randomized, double-blind trial comparing venlafaxine and nortriptyline in migraine prevention found both drugs to be similarly effective in reducing headache intensity, frequency, and duration [44]. Venlafaxine had a lower incidence of adverse effects, making it a potentially better option than nortriptyline [44]. Other two trials comparing venlafaxine and amitriptyline showed similar effectiveness in reducing the severity and number of migraine attacks [45, 46]. Amitriptyline had more side effects, suggesting that venlafaxine might be the preferred choice for migraine prophylaxis [45, 46].

Treatments targeting the CGRP pathway

For the purpose of this review, BoNT-A is included alongside treatments targeting the CGRP pathway due to its ability to inhibits the release of CGRP from trigeminal nerve endings [2, 3].

Onabotulinumtoxin A

BoNT-A has shown efficacy for chronic migraine prevention with and without medication overuse [47]. The mechanisms of BoNT-A are not fully understood [48]. Dural nociceptive fibers have branches that extend outside the skull via the sutures, making them accessible for BoNT-A injections. BoNT-A is taken up and transported along nerve fibers, including collaterals and the trigeminal or cervical ganglia [49]. BoNT-A is a metalloprotease that exerts its effects by cleaving synaptosomal-associated protein 25 (SNAP-25), thereby inhibiting exocytosis, which is responsible for the release of neurotransmitters and peptides such as glutamate, CGRP, and pituitary adenylate cyclase activating peptide-38 (PACAP-38). In addition to its inhibition of neurotransmitter release, BoNT-A prevents the insertion of nociceptive receptors, such as transient receptor potential cation channel subfamily V member 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1), into the cell membrane [49, 50]. BoNT-A primarily acts on C-fibers rather than Aδ-fibers, with its main effect being the reduction of CGRP release and other mechanisms [51]. The pivotal trials included a total of 1384 patients that were treated every 12 weeks with 155 units of BoNT-A at 31 defined pericranial injection points, with optional addition of 40 units (8 points) [52]. A significant effect was observed starting at 4 weeks and amounting to −8.4 headache days per month (placebo −6.6 days, $p < 0.001$) at 24 weeks [52]. Reduction of headache-related disability was also significant after 24 weeks of BoNT-A treatment. In patients with medication overuse, 53% of them stopped overuse after two BoNT-A cycles [53]. The trials have shown an increasing effect over the first year [54], with 49% of patients responding after the first treatment cycle, and an additional 11% and 10% responding after the second and third treatment cycle, respectively [55]. This led to the recommendation of completing up to three treatment cycles before assessing efficacy [56]. One advantage of BoNT-A is that its side effects are mild and rarely interfere with therapy. These side effects include temporary ptosis, neck weakness, hematomas, and pain at the injection sites [57]. Additionally, BoNT-A has no known interactions with other medications. In a randomized open-label study with 282 participants, BoNT-A demonstrated better tolerability and efficacy than topiramate, although the study had methodological limitations [58]. Discontinuing effective BoNT-A treatment can be challenging. In a study of 108 patients who had completed five or more treatment cycles, 40% of them were able to extend their injection interval to four months, while 45% had to return to the standard three-month intervals [58]. Health insurance data indicates that most patients who undergo a year of BoNT-A treatment either continue or resume regular

therapy after a pause or reduced treatment [59]. Only super-responders – those experiencing fewer than five headache days per month – had an 80% chance of needing no further treatment within six months of stopping BoNT-A [60]. Recent advancements include the "follow the sutures" paradigm [61] and ongoing studies on the efficacy of BoNT-A in preventing high-frequency episodic migraine (NCT05028569 and NCT06047457).

Monoclonal antibodies targeting the CGRP pathway

Four monoclonal antibodies (mAbs) targeting the CGRP pathway are currently available for migraine prevention [62]. Erenumab is a fully human mAb that targets the CGRP receptor, while fremanezumab, galcanezumab, and eptinezumab are humanized mAbs that target the CGRP molecule itself [63]. All four mAbs have a high affinity for their targets with minimal cross-reactivity and an elimination half-life of about four weeks. CGRP(-receptor) mAbs are administered parenterally (either subcutaneously or intravenously) and enter the systemic circulation. Their bioavailability ranges from 50 to 100%, and they are eliminated through the reticuloendothelial system, bypassing renal and hepatic pathways [64]. The efficacy and safety of CGRP(-receptor) mAbs have been assessed in extensive clinical trial programs. All four mAbs demonstrated superior efficacy compared to placebo, with no major differences in performance observed among the different antibodies and were well-tolerated [65–69]. Common adverse events included injection-site reactions, constipation, and upper respiratory infections, with serious adverse events and discontinuations occurring in less than 2% of patients [70]. Multiple indirect comparisons have shown that CGRP(-receptor) mAbs are superior to traditional oral preventives for migraine, such as topiramate, beta-blockers, valproate, or amitriptyline [71–73]. A randomised, double-blind, active-controlled phase 4 trial compared erenumab with topiramate. Erenumab outperformed topiramate in efficacy, achieving a ≥ 50% reduction in monthly migraine days in 55% of participants compared to 31% with topiramate [74]. Erenumab showed superior tolerability, with a 39% discontinuation rate due to adverse events for topiramate versus 11% for erenumab.

Gepants

Gepants are small molecules that antagonize CGRP receptors with high affinity and the amylin 1 (AMY_1) receptor to a lesser extent [75]. Despite their lower molecular weight compared to CGRP(-receptor) mAbs (approximately 250-fold difference), gepants exhibit limited penetration of the blood-brain barrier [76]. Gepants prevent migraine attacks through different peripheral mechanisms, including the attenuation of CGRP-induced neurogenic inflammation, and nociceptive transmission, thus modulating central sensitization [77]. Rimegepant and atogepant have demonstrated efficacy, tolerability, and safety as preventive treatments for migraine [78, 79]. Rimegepant is currently the only gepant approved for both acute and preventive migraine therapy. For prevention, it is taken as a 75 mg orally disintegrating tablet every 48 h. A phase 2/3 trial evaluated rimegepant in 695 migraine patients experiencing 4–18 monthly migraine days [80]. Compared to placebo, rimegepant demonstrated a significant reduction in monthly migraine days (−4.3 vs. −3.5) over 12 weeks. Nausea was the most common adverse event (3% rimegepant vs. 1% placebo). A further evaluation showed that the preventive effect of rimegepant was durable and associated with improved quality of life up to 64 weeks [81]. A direct comparison with galcanezumab showed comparable efficacy in reducing monthly migraine days by ≥ 50% (61% rimegepant vs. 62% galcanezumab) [82]. Two double-blind, randomized, placebo-controlled trials assessed atogepant efficacy and safety in approximately 900 episodic migraine patients [83, 84]. Both studies demonstrated that atogepant was superior to placebo in reducing monthly migraine days after 12 weeks. A sustained efficacy was observed in approximately 85% of patients achieving an initial ≥ 50% reduction in monthly migraine days after 52 weeks of treatment [85]. The efficacy of atogepant was confirmed in difficult-to-treat episodic migraine patients, who had failed two to four conventional non-CGRP treatments [86]. Additionally, atogepant-treated patients reported improved quality of life and reduced headache impact [87, 88]. A dose-response relationship has been established for atogepant, with evidence supporting 60 mg as the optimal daily dosage. A reduced 10 mg daily dose is recommended for patients using strong inhibitors of hepatic cytochrome P450 family 3 subfamily A member 4 (CYP3A4), or those with severe renal impairment or end-stage kidney disease [79]. A phase 3 trial involving approximately 700 chronic migraine patients confirmed the superiority of atogepant 60 mg to placebo, showing a significantly greater reduction in monthly migraine days (−6.9 vs. −5.1) over 12 weeks [89]. Post-hoc analysis confirmed the efficacy of atogepant in both patients with and without medication overuse, demonstrating a 52–62% reduction in the proportion of participants with medication overuse over 12 weeks [90]. Atogepant demonstrated a favorable safety profile and was well tolerated over one year of treatment. The most common adverse events were nausea, fatigue, and constipation, and no serious treatment-related adverse events emerged [91].

Combining two oral non-CGRP treatments

Many migraine patients achieve partial relief with conventional oral prophylactics, but combining non-CGRP treatments may offer enhanced benefits, especially in those with comorbid conditions such as tremor, insomnia, epilepsy, arterial hypertension or depression [92–94]. By leveraging different mechanisms of action, combination therapy could better address the complexity of migraine. Evidence supporting this approach, while still emerging, shows promise, as outlined in Table 1, which summarizes key studies [95–107]. These studies encompass diverse patient populations, ranging from low-frequency episodic migraine to treatment-resistant chronic migraine. Frequently tested combinations include antihypertensives, antidepressants, and antiepileptics, with propranolol and topiramate often used as part of dual therapy. In 62% of studies, combination therapy resulted in improved outcomes compared to monotherapy. Moreover, 90% of studies found no significant increase in adverse effects with combination therapy, suggesting that this approach may offer enhanced efficacy without compromising tolerability. Some trials did not observe superior benefits compared to monotherapy, highlighting the need for further research to better understand which patients and drug combinations may respond best. In epilepsy, rational polytherapy is a well-established strategy for balancing efficacy and side effects by using lower doses of multiple drugs [108, 109]. A similar approach in migraine prophylaxis holds potential to optimize treatment outcomes, though specific guidelines for combination therapy in migraine are still lacking. The available evidence suggests that carefully selected combinations of non-CGRP treatments could offer an important avenue for individualized, effective migraine management.

Combining an oral non-CGRP treatment with BoNT-A or a CGRP treatment

The combination of non-CGRP and CGRP-targeted treatments is an opportunity to address multiple pathways involved in migraine [110, 111]. While BoNT-A and CGRP(-receptor) mAbs primarily modulate peripheral mechanisms, oral conventional prophylactics affect both central and peripheral pathways, suggesting the potential for complementary therapeutic effects [16, 33, 60, 110–113]. In clinical practice, combining conventional prophylactics with BoNT-A is a common practice that did not raise tolerability issues [114]. Concerns regarding safety primarily revolve around drug-drug interactions, particularly when combining CGRP-targeted small molecules, such as gepants, with other medications. Gepants are metabolized by cytochrome P450 enzymes, mainly CYP3A4, which could lead to interactions with drugs that share this metabolic pathway [115, 116]. CGRP(-receptor) mAbs represent an alternative due to their minimal risk for such interactions, as they are not dependent on hepatic metabolism or renal clearance [117]. Emerging evidence supports the potential efficacy of combining non-CGRP and CGRP-targeted treatments. For example, a post-hoc analysis of two studies evaluated fremanezumab as an add-on to various oral prophylactics, including beta-blockers, calcium channel blockers, antiepileptics, and antidepressants [118]. In this analysis, patients receiving fremanezumab alongside these treatments experienced a significant reduction in monthly migraine days and acute medication use compared to those on placebo, with no increase in adverse events. A retrospective real-world study from the United Arab Emirates showed that adding erenumab to oral prophylactics provided similar benefits to erenumab monotherapy over six months, with a consistent safety profile [119]. Though current data are still limited, the combined use of non-CGRP and CGRP-targeted treatments appears promising. Importantly, some trials evaluating the safety and efficacy of CGRP mAbs did not contraindicate oral prophylactics [120–123]. While these combinations were not the primary focus of analyses, post-hoc evaluations could provide further insights.

Combining a CGRP treatment with BoNT-A or two CGRP treatments

Combining BoNT-A with a CGRP-targeted treatment may offer significant benefits for patients, particularly the approximately 50% who do not experience sufficient clinical improvement from CGRP medications alone [124, 125]. BoNT-A works by inhibiting the release of CGRP from C-fibers [60, 126], while gepants and CGRP(-receptor) mAbs target Aδ-fibers, which are two nerve fibers that mediate nociceptive transmission in the trigeminovascular system [127, 128]. By inhibiting different components of this system, concomitant use of BoNT-A and a CGRP treatment could provide a more comprehensive therapeutic effect [129]. Although no randomized clinical trials have yet been conducted, 15 studies, most of which were retrospective, evaluated the effects of this combination in 1,428 patients with chronic migraine (Table 2) [130–144]. Of these, 11 studies (73%) reported superior outcomes with dual therapy compared to monotherapy (either BoNT-A or a CGRP-targeted treatment alone). A pooled analysis revealed that this combination therapy led to a ≥ 50% reduction in monthly headache days in up to 58.8% of patients [145]. Moreover, the dual therapy was safe and well-tolerated, with no significant safety concerns reported. Another promising strategy involves combining two CGRP-targeted therapies, such as a CGRP(-receptor) mAb and a gepant. This approach

Table 1 Clinical studies evaluating the combination of non-CGRP treatments for migraine prophylaxis. Treatment A and treatment B represent the therapies used in combination for migraine prophylaxis

Study design	Number of patients	Type of migraine	Treatment A	Treatment B	Efficacy results	Safety results
Unclear [94]	Not reported	Unclear	Magnesium	Cinnarizine	Better than magnesium	Not registered
Randomized, double-blind trial [95]	45	2–6 attacks per month	Propranolol	Flunarizine	Comparable to propranolol and flunarizine	Similar to monotherapies
Randomized, double-blind trial [96]	39	Transformed migraine	Amitriptyline	Fluoxetine	Comparable to amitriptyline	Similar to amitriptyline
Open-label study [97]	52	Episodic migraine with and without aura unresponsive to monotherapies	Propranolol/nadolol	Valproate	29 cases (59%) showed a > 50% reduction in migraine days. Nine cases (17%) showed an optimal response	Eight (15%) patients discontinued due to adverse events
Open-label-study [98]	36	> 3 attacks per month	Propranolol, flunarizine or other treatments	Topiramate	Improvement in frequency and severity of migraine was observed in 83% of patients	Tolerability was good in 30 patients
Open-label study [99]	58	Episodic and chronic migraine	Propranolol/nadolol	Topiramate	36 patients (62%) showed a positive response	Ten patients (17%) discontinued due to adverse events
Randomized, double-blind trial [100]	73	3–12 attacks per month	Topiramate	Amitriptyline	Higher satisfaction and better depression scores compared with monotherapies	Fewer side effects than monotherapies
Randomized, double-blind trial [101]	76	Episodic and chronic migraine	Propranolol	Nortriptyline	Comparable to propranolol and better than nortriptyline	Similar to monotherapies
Randomized, double-blind trial [102]	80	4–12 headache days per month	Topiramate	Nortriptyline	Reduced headache frequency compared with monotherapies	More side effects than monotherapies
Randomized, double-blind trial [103]	191	Chronic migraine	Topiramate	Propranolol	Similar to topiramate	Similar to topiramate
Randomized trial [104]	150	Chronic migraine	Topiramate	Flunarizine	Similar to topiramate and flunarizine	Similar to monotherapies
Randomized, double-blind trial [105]	222	> 4 attacks per month	Magnesium	Sodium valproate	Significant reduction in headache severity, duration and use of painkillers than sodium valproate	Not reported
Randomized, controlled trial [106]	120	2–8 attacks per month	Propranolol	Cinnarizine	The drug combination had an additional effect on reducing acute migraine attacks compared to propranolol	Not reported

Table 2 Clinical studies evaluating the combination of onabotulinumtoxin A and CGRP treatments for migraine prophylaxis

Study type	Number of patients	Type of migraine	CGRP treatment	Efficacy results	Safety results
Real world, prospective, observational study [129]	69	Chronic migraine	Erenumab (70 or 140 mg)	Dual treatment reduced monthly migraine days in 45 out of 69 patients (65%)	No relevant side effects were reported
Retrospective, observational study [130]	43	Chronic migraine	Erenumab (70 or 140 mg)	No difference was detected between dual treatment and erenumab alone	No relevant side effects were reported
Case series [131]	36	Chronic migraine	Erenumab, fremanezumab or galcanezumab	Half of the patients demonstrated an improvement in their headache burden after the addition of an anti-CGRP antibody	Not analyzed
Retrospective chart review [132]	257	Chronic migraine	Erenumab, fremanezumab or galcanezumab	Compared with onabotulinumtoxinA alone, adding an anti-CGRP antibody yielded meaningful reductions in monthly headache days	The safety of combination treatment was similar to that observed in each treatment alone
Case series [133]	17	Chronic migraine	Erenumab, fremanezumab or galcanezumab	Monthly headache days and headache severity were further reduced after the addition of an anti-CGRP antibody	Not analyzed
Retrospective chart review [134]	153	Chronic migraine	Erenumab, fremanezumab or galcanezumab	After the addition of an anti-CGRP mAb, CM patients experienced a further decrease of 5.7 monthly headache days	The safety of combination treatment was similar to that observed in each treatment alone
Retrospective chart review [135]	78	Chronic migraine	Erenumab (70 or 140 mg)	Dual treatment determined a further reduction of monthly migraine days and monthly headache days	Not analyzed
Real world, prospective, observational study [136]	45	Chronic migraine	Anti-CGRP monoclonal antibodies	No significant differences were found in clinical parameters between dual therapy and anti-CGRP antibodies alone	Not analyzed
Case series [137]	10	Chronic migraine and medication overuse headache	Erenumab (140 mg)	Dual treatment further reduced monthly headache days, headache severity, symptomatic drug intake and disability	No relevant side effects were reported
Retrospective, longitudinal study [138]	148	Chronic migraine	Erenumab, fremanezumab or galcanezumab	After 12 months of dual treatment, monthly headache days were reduced by 4.6 days/month from baseline	Safety was consistent with that observed in prior analyses of each treatment alone
Multicenter, retrospective chart review [139]	19	Chronic migraine	Erenumab or fremanezumab	Dual therapy was effective and was associated with clinically meaningful improvement in 14 out of 19 patients	Safety was consistent with that observed in prior analyses of each treatment alone

Table 2 (continued)

Study type	Number of patients	Type of migraine	CGRP treatment	Efficacy results	Safety results
Retrospective, cohort study [140]	50	Chronic migraine	Erenumab (70 or 140 mg)	Combining erenumab with onabotulinumtoxin A reduced monthly migraine days and monthly headache days	Safety was consistent with that observed in prior analyses of each treatment alone
Retrospective, cohort study [141]	187	Chronic migraine	Erenumab (70 or 140 mg)	Dual therapy with erenumab was more effective than onabotulinumtoxin A alone	No relevant side effects were reported
Prospective, multiple attack, observational study [142]	122	Chronic migraine	Ubrogepant (50 or 100 mg)	Ubrogepant was effective and safe when used in combination with onabotulinumtoxinA	No relevant side effects were reported
Retrospective chart review [143]	194	Chronic migraine	Erenumab, fremanezumab or galcanezumab	Dual treatment showed significant improvement in monthly migraine days compared with monotherapy of either treatment	Not analyzed

could provide both direct inhibition of the CGRP receptor and a reduction in free CGRP peptide available to bind to receptors. Due to their smaller molecular size, gepants may penetrate areas where CGRP(-receptor) mAbs, which are larger, have limited access [146]. Furthermore, both gepants and erenumab target the AMY_1 receptor, a promising additional pathway in migraine treatment [147–149]. Combining these treatments could yield synergistic effects, addressing both CGRP and AMY1 pathways for enhanced efficacy. So far, questions remain about whether such combinations would lead to complete inhibition of the CGRP pathway in patients with a suboptimal response to monotherapy, or if the risk of adverse events might increase without providing significant therapeutic benefit. Evidence from a phase I trial showed no change in ubrogepant plasma concentrations when combined with either erenumab or galcanezumab [150]. Table 3 summarizes the existing published reports on combining CGRP(-receptor) mAbs with gepants [151–154]. They include one case series, one case report, and two retrospective studies involving 494 patients with migraine, with no safety issues being identified. At present, there is a lack of studies evaluating combinations of two CGRP(-receptor) mAbs or two gepants. A phase I trial assessing the pharmacokinetics of atogepant and ubrogepant, when the former was prescribed daily, did not identify any significant drug interactions [155]. Such combinations may be feasible, though more robust clinical studies are needed to fully assess their efficacy and safety.

Practical considerations

The existing literature on combination treatments for migraine prophylaxis is limited by methodological shortcomings, including small sample sizes, geographical constraints, and variability in study designs, all of which reduce the generalizability of findings. Moreover, critical practical aspects of combination therapy, such as dose adjustments and treatment duration, remain insufficiently explored, despite their impact on both efficacy and safety. One promising approach is the use of dose-sparing strategies, which aim to maintain therapeutic efficacy while minimizing adverse effects by using lower doses of each medication. Evidence from other fields, such as epilepsy, demonstrates that combining drugs with complementary mechanisms of action can reduce the required doses of individual agents, thereby decreasing the risk of cumulative side effects [156]. Dose-sparing strategies may be particularly useful when combining non-CGRP-targeting medications with CGRP-targeting therapies. However, in the context of migraine prophylaxis, data supporting dose-sparing effects are scarce, emphasizing the need for further investigation.

Additionally, unlike monotherapy, where treatment durations are typically standardized, combination therapies may benefit from a tailored approach to duration. For instance, one medication could be administered for a shorter period to achieve rapid symptom relief, while another is continued longer to provide sustained prophylaxis. This staggered strategy could help prevent cumulative side effects and optimize therapeutic outcomes. Despite the potential benefits, most current studies fail to address this aspect, leaving clinicians without clear guidance. Future research should prioritize investigating the optimal dosing and treatment durations for combination therapies in migraine prophylaxis (Fig. 1).

Safety and potential risks

Combination therapies for migraine prophylaxis, while promising, come with potential limitations and risks. A major concern is the risk of drug-drug interactions, particularly when medications share similar metabolic pathways. For example, rimegepant and atogepant are metabolized by the CYP3A4 enzyme, and combining them together or with drugs that inhibit or induce this enzyme can increase the likelihood of adverse effects or compromise therapeutic efficacy [157]. Topiramate, a mild inducer of CYP3A4, may alter the metabolism of rimegepant or atogepant, further complicating treatment [158]. Medications with overlapping mechanisms of action may exacerbate side effects. For instance, combining CGRP(-receptor) mAbs with gepants could amplify adverse effects, such as constipation or cardiovascular issues, due to their shared influence on CGRP-related pathways [159]. The long-term safety profiles of CGRP(-receptor) mAbs with gepants are still under investigation, raising concerns about the prolonged use in combination therapies. Patient adherence presents another critical challenge; complex regimens involving multiple drugs can reduce compliance, particularly among patients who experience side effects or find such regimens burdensome. Furthermore, not all patients respond well to combination therapies [160]. Variability in genetic factors affecting drug metabolism, the presence of comorbidities, and individual differences in migraine pathophysiology may attenuate the benefits of certain combinations, potentially leading to diminished efficacy. Economic barriers and limited guideline support also pose significant hurdles [161]. The high costs associated with certain combinations, such as pairing CGRP(-receptor) mAbs with BoNT-A, can make these therapies financially inaccessible for many patients. There is a high need for further research to evaluate their cost-effectiveness and establish clearer clinical guidelines to support their use.

Table 3 Clinical studies evaluating the combination of CGRP treatments for migraine prophylaxis. Treatment A and treatment B represent the therapies used in combination for migraine prophylaxis

Study design	Number of patients	Type of migraine	Treatment A	Treatment B	Study results
Case report [150]	2	Episodic migraine	Erenumab (70 or 140 mg)	Rimegepant (75 mg)	No reported adverse events
Case series [151]	13	Episodic migraine	Erenumab, fremanezumab or galcanezumab	Rimegepant (75 mg)	No safety issues were identified
Prospective, multiple-attack, observational study [152]	245	Episodic and chronic migraine	Erenumab, galcanezumab, fremanezumab or eptinezumab	Ubrogepant (50 or 100 mg)	Ubrogepant use with an anti-CGRP antibody was associated with meaningful pain relief and satisfaction
Retrospective study [153]	234	Episodic and chronic migraine	Erenumab, fremanezumab or galcanezumab	Rimegepant or ubrogepant	Combining CGRP antibodies with gepants was safe and well-tolerated

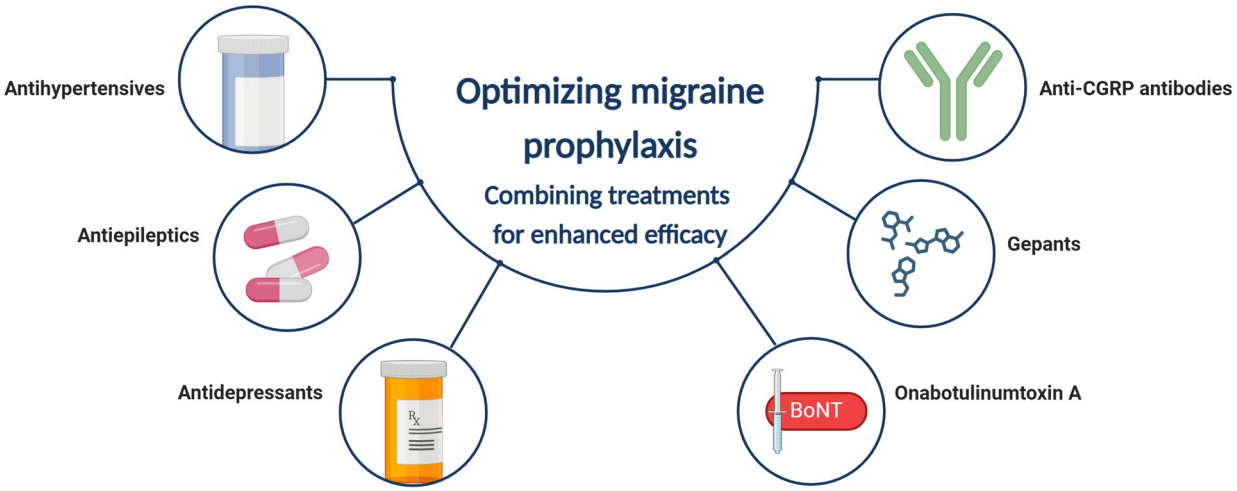


Fig. 1 Overview of pharmacological treatments which can be used in combination for migraine prophylaxis. CGRP: calcitonin gene-related peptide

Final remarks

Monotherapy remains the first-line approach for migraine prophylaxis, with combination treatments being considered in patients who do not sufficiently respond to a single therapy. Combination treatments represent a rational and feasible approach that target multiple therapeutic pathways and could significantly improve patient outcomes, particularly for those with treatment-resistant migraine. Several promising combinations have emerged, drawing parallels to rational polytherapy used in epilepsy, though scientific evidence remains limited to establish their role in clinical guidelines. Oral treatments that do not target the CGRP pathway, due to their accessibility and affordability, are practical options for combination regimens with BoNT-A or CGRP-targeted therapies and could be easily incorporated into reimbursement frameworks. However, the high costs of combining treatments such as BoNT-A with a monoclonal antibody targeting the CGRP pathway, or two CGRP-targeted therapies (e.g., an antibody with a gepant), pose challenges to widespread adoption. Despite these challenges, such strategies may offer substantial benefits to patients who have not responded to monotherapy. Large-scale clinical trials are essential to refine combination therapy protocols and provide the robust evidence needed to support structured guidelines in clinical practice. Future research directions should include identifying subgroups of patients most likely to benefit from combination therapies and investigating strategies to optimize their safety and efficacy. Beyond traditional clinical trials, alternative research approaches may offer valuable insights into combination therapy. Testing every potential combination through clinical trials is time-consuming and costly. Computational modeling and simulation could

serve as a valuable preliminary step in narrowing down the most promising and safest combinations for further study [162, 163]. These models can predict effective dose ranges, potentially identifying dose-sparing effects while avoiding cumulative toxicity. Additionally, computational tools can approximate the impact of sustained drug exposure in combination regimens, helping to estimate long-term safety and efficacy. Preclinical studies, informed by such models, could provide further insights into the pharmacological interactions between treatments, guiding the design of future clinical trials. The limited range of combinations tested to date likely reflects the cost and complexity of clinical trials, as well as challenges related to administration requirements. Leveraging alternative research tools could address these barriers by streamlining the development of evidence-based combination regimens. As research advances, clinicians will need to tailor combination treatments to individual patient characteristics, considering factors such as potential drug-drug interactions, comorbidities, and patient preferences. Addressing these questions will not only enhance clinical practice but also ensure that combination therapies are accessible, effective, and safe for a broader range of patients.

Abbreviations

ACE	angiotensin-converting enzyme
AMY_1	amylin 1
BoNT-A	onabotulinumtoxin A
Ca^{2+}	calcium
CGRP	calcitonin gene-related peptide
CYP3A4	cytochrome P450 family 3 subfamily A member 4
GABA	γ-aminobutyric acid
mAbs	monoclonal antibodies
Na^{+}	sodium
NMDA	N-methyl-D-aspartate
NO	nitric oxide
PACAP-38	pituitary adenylate cyclase activating peptide-38
SNRIs	serotonin and norepinephrine reuptake inhibitors
TCAs	tricyclic antidepressants
TRPV1	transient receptor potential cation channel subfamily V member 1
TRPA1	transient receptor potential ankyrin 1

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Competing interests
LP has been employed by Lundbeck in the past two years. DGA has received honoraria for lectures and presentations from AbbVie/Allergan, Eli Lilly, Teva, Lundbeck, and Novartis and has participated in clinical trials as the principal investigator for Pfizer, BioHaven, and Lundbeck. DGA has also received honoraria from the World Health Organization as a subject matter expert. RM reports personal fees from AbbVie, Eli Lilly, Lundbeck, Pfizer, Teva, and Biomedia, outside the submitted work. IP serves as Head of Imaging Section of SN Comprehensive Clinical Medicine. BR reports research grants from Lundbeck, Novartis, the German Research Foundation, the German Migraine and Headache Society, and Else Kröner-Fresenius Stiftung, as well as personal fees from AbbVie/Allergan, Lilly, Lundbeck, Novartis, Perfood, and Teva. RR has received travel grants and/or honoraria from Allergan/AbbVie, Lilly, Lundbeck, Novartis, Pfizer, and Teva. WW serves as Section Editor of SN Comprehensive Clinical Medicine. All authors serve as junior editors of The Journal of Headache and Pain.

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References

1. Ha H, Gonzalez A (2019) Migraine headache prophylaxis. Am Fam Physician 99(1):17–24
2. Burstein R, Zhang X, Levy D, Aoki KR, Brin MF (2014) Selective inhibition of meningeal nociceptors by botulinum neurotoxin type A: therapeutic implications for migraine and other pains. Cephalalgia 34:853–869. https://doi.org/10.1177/0333102414527648

3. Zhang X, Strassman AM, Novack V, Brin MF, Burstein R (2016) Extracranial injections of botulinum neurotoxin type A inhibit intracranial meningeal nociceptors' responses to stimulation of TRPV1 and TRPA1 channels: are we getting closer to solving this puzzle? Cephalalgia 36:875–886. https://doi.org/10.1177/0333102416636843
4. Waliszewska-Prosół M, Vuralli D, Martelletti P (2023) What to do with non-responders to CGRP(r) monoclonal antibodies: switch to another or move to gepants? J Headache Pain 24(1):163. https://doi.org/10.1186/s10194-023-01698-8
5. Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A et al (2009) European Federation of Neurological Societies. EFNS guideline on the drug treatment of migraine–revised report of an EFNS task force. Eur J Neurol 16(9):968–981. https://doi.org/10.1111/j.1468-1331.2009.02748.x
6. Versijpt J, Deligianni C, Hussain M, Amin F, Reuter U, Sanchez-Del-Rio M et al (2024) European Headache Federation (EHF) critical re-appraisal and meta-analysis of oral drugs in migraine prevention - part 4: propranolol. J Headache Pain 25(1):119. https://doi.org/10.1186/s10194-023-01573-6
7. Sprenger T, Viana M, Tassorelli C (2018) Current prophylactic medications for migraine and their potential mechanisms of action. Neurotherapeutics 15(2):313–323. https://doi.org/10.1007/s13311-018-0621-8
8. al-Qassab HK, Findley LJ (1993) Comparison of propranolol LA 80 mg and propranolol LA 160 mg in migraine prophylaxis: a placebo controlled study. Cephalalgia 13(2):128–131. https://doi.org/10.1046/j.1468-2982.1993.1302128.x
9. Tronvik E, Stovner LJ, Helde G, Sand T, Bovim G (2003) Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. JAMA 289(1):65–69. https://doi.org/10.1001/jama.289.1.65
10. Stovner LJ, Linde M, Gravdahl GB, Tronvik E, Aamodt AH, Sand T et al (2014) A comparative study of candesartan versus propranolol for migraine prophylaxis: a randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia 34(7):523–532. https://doi.org/10.1177/0333102413515348
11. Messina R, Lastarria Perez CP, Filippi M, Goadsby PJ (2020) Candesartan in migraine prevention: results from a retrospective real-world study. J Neurol 267(11):3243–3247. https://doi.org/10.1007/s00415-020-09989-9
12. Sánchez-Rodríguez C, Sierra Á, Planchuelo-Gómez Á, Martínez-Pías E, Guerrero ÁL, García-Azorín D (2021) Real world effectiveness and tolerability of candesartan in the treatment of migraine: a retrospective cohort study. Sci Rep 11(1):3846. https://doi.org/10.1038/s41598-021-83508-2
13. García-Azorín D, Martínez-Badillo C, Camiña Muñiz J, Gago-Veiga AB, Morollón Sánchez N, González-Quintanilla V et al (2024) CandeSpartan Study: Candesartan Spanish response-prediction and tolerability study in migraine. Cephalalgia 44(4):3331024241248833. https://doi.org/10.1177/03331024241248833
14. Schrader H, Stovner LJ, Helde G, Sand T, Bovim G (2001) Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. BMJ 322(7277):19–22. https://doi.org/10.1136/bmj.322.7277.19
15. Eigenbrodt AK, Ashina H, Khan S, Diener HC, Mitsikostas DD, Sinclair AJ et al (2021) Diagnosis and management of migraine in ten steps. Nat Rev Neurol 17(8):501–514. https://doi.org/10.1038/s41582-021-00509-5
16. Calabresi P, Galletti F, Rossi C, Sarchielli P, Cupini LM (2007) Antiepileptic drugs in migraine: from clinical aspects to cellular mechanisms. Trends Pharmacol Sci 28:188–195. https://doi.org/10.1016/j.tips.2007.02.005
17. Rogawski MA, Löscher W (2004) The neurobiology of antiepileptic drugs. Nat Rev Neurosci 5:553–564. https://doi.org/10.1038/nrn1430
18. Storer RJ, Goadsby PJ (2004) Topiramate inhibits trigeminovascular neurons in the cat. Cephalalgia 24:1049–1056. https://doi.org/10.1111/j.1468-2982.2004.00767.x
19. Hoffmann J, Akerman S, Goadsby PJ (2014) Efficacy and mechanism of anticonvulsant drugs in migraine. Expert Rev Clin Pharmacol 7:191–201. https://doi.org/10.1586/17512433.2014.885835
20. Raffaelli B, García-Azorín D, Boucherie DM, Amin FM, Deligianni CI, Gil-Gouveia R et al (2023) European Headache Federation (EHF) critical reappraisal and meta-analysis of oral drugs in migraine prevention – part 3: topiramate. J Headache Pain 24(1):134. https://doi.org/10.1186/s10194-023-01671-5
21. Sørensen KV (1988) Valproate: a new drug in migraine prophylaxis. Acta Neurol Scand 78(4):346–348. https://doi.org/10.1111/j.1600-0404.1988.tb03667.x
22. Silberstein SD, Collins SD (1999) Safety of divalproex sodium in migraine prophylaxis: an open-label, long-term study. Long-term safety of Depakote in Headache Prophylaxis Study Group. Headache 39(9):633–643. https://doi.org/10.1046/j.1526-4610.1999.3909633.x
23. Linde M, Mulleners WM, Chronicle EP, McCrory DC (2013) Valproate (valproic acid or sodium valproate or a combination of the two) for the prophylaxis of episodic migraine in adults. Cochrane Libr 2013(6):CD010611. https://doi.org/10.1002/14651858.CD010611
24. Sarchielli P, Messina P, Cupini LM, Tedeschi G, Di Piero V, Livrea P et al (2014) Sodium valproate in migraine without aura and medication overuse headache: a randomized controlled trial. Eur Neuropsychopharmacol 24(8):1289–1297. https://doi.org/10.1016/j.euroneuro.2014.03.010
25. Cui XY, Sun SM, Liu J, Wu QY, Zhang JF, Li X (2020) The efficacy and safety of valproate medications for migraine in adults: a meta-analysis. Eur Rev Med Pharmacol Sci 24(10):5734–5741. https://doi.org/10.26355/eurrev_202005_21365
26. Marmura MJ, Kumpinsky AS (2018) Refining the Benefit/Risk Profile of anti-epileptic drugs in Headache disorders. CNS Drugs 32(8):735–746. https://doi.org/10.1007/s40263-018-0555-z
27. Kanner AM, Bicchi MM (2022) Antiseizure medications for adults with epilepsy. JAMA 327(13):1269–1281. https://doi.org/10.1001/jama.2022.3880
28. Rollo E, Romozzi M, Vollono C, Calabresi P, Geppetti P, Iannone LF (2023) Antiseizure medications for the Prophylaxis of Migraine during the Anti- CGRP drugs era. Curr Neuropharmacol 21(8):1767–1785. https://doi.org/10.2174/1570159X21666221228095256
29. Mulleners WM, McCrory DC, Linde M (2015) Antiepileptics in migraine prophylaxis: an updated Cochrane review. Cephalalgia 35(1):51–62. https://doi.org/10.1177/0333102414534325
30. Parikh SK, Silberstein SD (2019) Current status of antiepileptic drugs as preventive migraine therapy. Curr Treat Options Neurol 21(4):16. https://doi.org/10.1007/s11940-019-0558-1
31. Bjørk MH, Zoega H, Leinonen MK, Cohen JM, Dreier JW, Furu K et al (2022) Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. JAMA Neurol 79(7):672–681. https://doi.org/10.1001/jamaneurol.2022.1269
32. Wells-Gatnik W, Martelletti P (2023) Antiseizure medications as migraine preventatives: a call for action for a teratogenic and neurodevelopmental risk removal. Expert Opin Drug Saf 22(9):777–781. https://doi.org/10.1080/14740338.2023.2247963
33. Gray AM, Pache DM, Sewell RD (1999) Do alpha2-adrenoceptors play an integral role in the antinociceptive mechanism of action of antidepressant compounds? Eur J Pharmacol 378(2):161–168. https://doi.org/10.1016/s0014-2999(99)00464-1
34. Joshi PG, Singh A, Ravichandra B (1999) High concentrations of tricyclic antidepressants increase intracellular Ca2 + in cultured neural cells. Neurochem Res 24(3):391–398. https://doi.org/10.1023/a:1020937717260
35. Galeotti N, Ghelardini C, Bartolini A (2001) Involvement of potassium channels in Amitriptyline and clomipramine analgesia. Neuropharmacology 40(1):75–84. https://doi.org/10.1016/s0028-3908(00)00097-6
36. Dharmshaktu P, Tayal V, Kalra BS (2012) Efficacy of antidepressants as analgesics: a review. J Clin Pharmacol 52(1):6–17. https://doi.org/10.1177/0091270010394852
37. Lampl C, Versijpt J, Amin FM, Deligianni CI, Gil-Gouveia R, Jassal T et al (2023) European Headache Federation (EHF) critical re-appraisal and meta-analysis of oral drugs in migraine prevention - part 1: Amitriptyline. J Headache Pain 24(1):39. https://doi.org/10.1186/s10194-023-01573-6
38. Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E (2012) Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 78(17):1337–1345. https://doi.org/10.1212/WNL.0b013e3182535d20

39. Xu XM, Liu Y, Dong MX, Zou DZ, Wei YD (2017) Tricyclic antidepressants for preventing migraine in adults. Med (Baltim) 96(22):e6989. https://doi.org/10.1097/MD.0000000000006989
40. Marks DM, Shah MJ, Patkar AA, Masand PS, Park GY, Pae CU (2009) Serotonin-norepinephrine reuptake inhibitors for pain control: premise and promise. Curr Neuropharmacol 7(4):331–336. https://doi.org/10.2174/157015909790031201
41. Burch R (2019) Antidepressants for preventive treatment of migraine. Curr Treat Options Neurol 21(4):18. https://doi.org/10.1007/s11940-019-0557-2
42. Wang F, Wang J, Cao Y, Xu Z (2020) Serotonin-norepinephrine reuptake inhibitors for the prevention of migraine and vestibular migraine: a systematic review and meta-analysis. Reg Anesth Pain Med 45(5):323–330. https://doi.org/10.1136/rapm-2019-101207
43. Kisler LB, Weissman-Fogel I, Coghill RC, Sprecher E, Yarnitsky D, Granovsky Y (2019) Individualization of migraine prevention: a randomized controlled trial of psychophysical-based prediction of Duloxetine Efficacy. Clin J Pain 35(9):753–765. https://doi.org/10.1097/AJP.0000000000000739
44. Roghani M, Ghaedi G, Iranzadeh S, Golezar MH, Afshinmajd S (2024) Efficacy and safety of venlafaxine versus nortriptyline for the preventive treatment of migraine: a double-blind randomized clinical trial. Clin Neurol Neurosurg 243:108400. https://doi.org/10.1016/j.clineuro.2024.108400
45. Bulut S, Berilgen MS, Baran A, Tekatas A, Atmaca M, Mungen B (2004) Venlafaxine versus Amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study. Clin Neurol Neurosurg 107(1):44–48. https://doi.org/10.1016/j.clineuro.2004.03.004
46. Hedayat M, Nazarbaghi S, Heidari M, Sharifi H (2022) Venlafaxine can reduce the migraine attacks as well as Amitriptyline: a noninferiority randomized trial. Clin Neurol Neurosurg 214:107151. https://doi.org/10.1016/j.clineuro.2022.107151
47. Baraldi C, Lo Castro F, Ornello R, Sacco S, Pani L, Guerzoni S (2023) OnabotulinumtoxinA: still the Present for Chronic Migraine. Toxins (Basel) 15(1):59. https://doi.org/10.3390/toxins15010059
48. Ramachandran R, Yaksh TL (2014) Therapeutic use of botulinum toxin in migraine: mechanisms of action. Br J Pharmacol 171(18):4177–4192. https://doi.org/10.1111/ejn.13261
49. Burstein R, Blumenfeld AM, Silberstein SD, Manack Adams A, Brin MF (2020) Mechanism of action of OnabotulinumtoxinA in chronic migraine: a narrative review. Headache 60(7):1259–1272. https://doi.org/10.1111/head.13849
50. Shimizu T, Shibata M, Toriumi H, Iwashita T, Funakubo M, Sato H et al (2012) Reduction of TRPV1 expression in the trigeminal system by botulinum neurotoxin type-A. Neurobiol Dis 48(3):367–378. https://doi.org/10.1016/j.nbd.2012.07.010
51. Pellesi L, Do TP, Ashina H, Ashina M, Burstein R (2020) Dual therapy with Anti-CGRP monoclonal antibodies and Botulinum Toxin for Migraine Prevention: is there a Rationale? Headache 60(6):1056–1065. https://doi.org/10.1111/head.13843
52. Dodick DW, Turkel CC, DeGryse RE, Aurora SK, Silberstein SD, Lipton RB et al (2010) OnabotulinumtoxinA for treatment of chronic migraine: pooled results from the double-blind, randomized, placebo-controlled phases of the PREEMPT clinical program. Headache 50(6):921–936. https://doi.org/10.1111/j.1526-4610.2010.01678.x
53. Silberstein SD, Blumenfeld AM, Cady RK, Turner IM, Lipton RB, Diener HC et al (2013) OnabotulinumtoxinA for treatment of chronic migraine: PREEMPT 24-week pooled subgroup analysis of patients who had acute headache medication overuse at baseline. J Neurol Sci 331(1–2):48–56. https://doi.org/10.1016/j.jns.2013.05.003
54. Aurora SK, Winner P, Freeman MC, Spierings EL, Heiring JO, DeGryse RE et al (2011) OnabotulinumtoxinA for treatment of chronic migraine: pooled analyses of the 56-week PREEMPT clinical program. Headache 51(9):1358–1373. https://doi.org/10.1111/j.1526-4610.2011.01990.x
55. Silberstein SD, Dodick DW, Aurora SK, Diener HC, DeGryse RE, Lipton RB et al (2015) Per cent of patients with chronic migraine who responded per onabotulinumtoxinA treatment cycle: PREEMPT. J Neurol Neurosurg Psychiatry 86(9):996–1001. https://doi.org/10.1136/jnnp-2013-307149
56. Bendtsen L, Sacco S, Ashina M, Mitsikostas D, Ahmed F, Pozo-Rosich P et al (2018) Guideline on the use of onabotulinumtoxinA in chronic migraine: a consensus statement from the European Headache Federation. J Headache Pain 19(1):91. https://doi.org/10.1186/s10194-018-0921-8
57. Rothrock JF, Adams AM, Lipton RB, Silberstein SD, Jo E, Zhao X et al (2019) FORWARD Study: evaluating the comparative effectiveness of OnabotulinumtoxinA and topiramate for Headache Prevention in adults with chronic migraine. Headache 59(10):1700–1713. https://doi.org/10.1111/head.13653
58. Cernuda-Morollón E, Ramón C, Larrosa D, Alvarez R, Riesco N, Pascual J (2015) Long-term experience with onabotulinumtoxinA in the treatment of chronic migraine: what happens after one. year? Cephalalgia 35(10):864–868. https://doi.org/10.1177/0333102414561873
59. Richer L, Luu H, Martins KJB, Vu K, Guigue A, Wong KO et al (2023) Trajectory of health care resources among adults stopping or reducing treatment frequency of botulinum toxin for chronic migraine treatment in Alberta, Canada. Headache 63(9):1285–1294. https://doi.org/10.1111/head.14613
60. Ching J, Tinsley A, Rothrock J (2019) Prognosis following discontinuation of OnabotulinumA therapy in super-responding. Chronic Migraine Patients Headache 59(8):1279–1285. https://doi.org/10.1111/head.13630
61. Stovner LJ, Hagen K, Tronvik E, Bruvik Gravdahl G, Burstein R, Dodick DW (2022) FollowTheSutures: piloting a new way to administer onabotulinumtoxinA for chronic migraine. Cephalalgia 42(7):590–597. https://doi.org/10.1177/03331024211067775
62. Raffaelli B, Neeb L, Reuter U (2019) Monoclonal antibodies for the prevention of migraine. Expert Opin Biol Ther 19(12):1307–1317. https://doi.org/10.1080/14712598.2019.1671350
63. Labastida-Ramírez A, Caronna E, Gollion C, Stanyer E, Dapkute A, Braniste D et al (2023) Mode and site of action of therapies targeting CGRP signaling. J Headache Pain 24(1):125. https://doi.org/10.1186/s10194-023-01644-8
64. Kielbasa W, Helton DL (2019) A new era for migraine: pharmacokinetic and pharmacodynamic insights into monoclonal antibodies with a focus on galcanezumab, an anti-CGRP antibody. Cephalalgia 39(10):1284–1297. https://doi.org/10.1177/0333102419840780
65. Haghdoost F, Puledda F, Garcia-Azorin D, Huessler EM, Messina R, Pozo-Rosich P (2023) Evaluating the efficacy of CGRP mAbs and gepants for the preventive treatment of migraine: a systematic review and network meta-analysis of phase 3 randomised controlled trials. Cephalalgia 43(4):3331024231159366. https://doi.org/10.1177/03331024231159366
66. Ashina M, Kudrow D, Reuter U, Dolezil D, Silberstein S, Tepper SJ et al (2019) Long-term tolerability and nonvascular safety of erenumab, a novel calcitonin gene-related peptide receptor antagonist for prevention of migraine: a pooled analysis of four placebo-controlled trials with long-term extensions. Cephalalgia 39(14):1798–1808. https://doi.org/10.1177/0333102419888222
67. Diener HC, McAllister P, Jürgens TP, Kessler Y, Ning X, Cohen JM et al (2022) Safety and tolerability of fremanezumab in patients with episodic and chronic migraine: a pooled analysis of phase 3 studies. Cephalalgia 42(8):769–780. https://doi.org/10.1177/03331024221076485
68. Bangs ME, Kudrow D, Wang S, Oakes TM, Terwindt GM, Magis D et al (2020) Safety and tolerability of monthly galcanezumab injections in patients with migraine: integrated results from migraine clinical studies. BMC Neurol 20(1):25. https://doi.org/10.1186/s12883-020-1609-7
69. Smith TR, Spierings ELH, Cady R, Hirman J, Schaeffler B, Shen V et al (2021) Safety and tolerability of eptinezumab in patients with migraine: a pooled analysis of 5 clinical trials. J Headache Pain 22(1):16. https://doi.org/10.1186/s10194-021-01227-5
70. Messina R, Huessler EM, Puledda F, Haghdoost F, Lebedeva ER, Diener HC (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
71. Vandervorst F, Van Deun L, Van Dycke A, Paemeleire K, Reuter U, Schoenen J et al (2021) CGRP monoclonal antibodies in migraine: an efficacy and tolerability comparison with standard prophylactic drugs. J Headache Pain 22(1):128. https://doi.org/10.1186/s10194-021-01335-2
72. Naghdi S, Underwood M, Madan J, Brown A, Duncan C, Matharu M et al (2023) Clinical effectiveness of pharmacological interventions for managing chronic migraine in adults: a systematic review and network

meta-analysis. J Headache Pain 24(1):164. https://doi.org/10.1186/s10194-023-01696-w
73. Lampl C, MaassenVanDenBrink A, Deligianni CI, Gil-Gouveia R, Jassal T, Sanchez-Del-Rio M et al (2023) The comparative effectiveness of migraine preventive drugs: a systematic review and network meta-analysis. J Headache Pain 24(1):56. https://doi.org/10.1186/s10194-023-01594-1
74. Reuter U, Ehrlich M, Gendolla A, Heinze A, Klatt J, Wen S et al (2022) Erenumab versus topiramate for the prevention of migraine - a randomised, double-blind, active-controlled phase 4 trial. Cephalalgia 42(2):108–118. https://doi.org/10.1177/03331024211053571
75. Russo AF, Hay DL (2023) CGRP physiology, pharmacology, and therapeutic targets: migraine and beyond. Physiol Rev 103(2):1565–1644. https://doi.org/10.1152/physrev.00059.2021
76. Altamura C, Brunelli N, Marcosano M, Fofi L, Vernieri F (2022) Gepants - a long way to cure: a narrative review. Neurol Sci 43(9):5697–5708. https://doi.org/10.1007/s10072-022-06184-8
77. Boinpally R, Shebley M, Trugman JM (2024) Atogepant: mechanism of action, clinical and translational science. Clin Transl Sci 17(1):e13707. https://doi.org/10.1111/cts.13707
78. Lo Castro F, Guerzoni S, Pellesi L (2021) Safety and risk of medication overuse headache in lasmiditan and second-generation gepants: a rapid review. Drug Healthc Patient Saf 13:233–240. https://doi.org/10.2147/DHPS.S304373
79. Baraldi C, Beier D, Martelletti P, Pellesi L (2024) The preclinical discovery and development of atogepant for migraine prophylaxis. Expert Opin Drug Discov 19(7):783–788. https://doi.org/10.1080/17460441.2024.2365379
80. Croop R, Lipton RB, Kudrow D, Stock DA, Kamen L, Conway CM et al (2021) Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. Lancet 397(10268):51–60. https://doi.org/10.1016/S0140-6736(20)32544-7
81. Powell LC, L'Italien G, Popoff E, Johnston K, O´Sullivan F, Harris L et al Health state utility mapping of rimegepant for the preventive treatment of migraine: double-blind treatment phase and open label extension (BHV3000-305). Adv Ther 40(2):585–600. https://doi.org/10.1007/s12325-022-02369-x
82. Schwedt TJ, Myers Oakes TM, Martinez JM, Vargas BB, Pandey H, Pearlman EM et al (2024) Comparing the efficacy and safety of Galcanezumab versus Rimegepant for prevention of episodic migraine: results from a randomized, controlled clinical trial. Neurol Ther 13(1):85–105. https://doi.org/10.1007/s40120-023-00562-w
83. Goadsby PJ, Dodick DW, Ailani J, Trugman JM, Finnegan M, Lu K et al (2020) Safety, tolerability, and efficacy of orally administered atogepant for the prevention of episodic migraine in adults: a double-blind, randomised phase 2b/3 trial. Lancet Neurol 19(9):727–737. https://doi.org/10.1016/S1474-4422(20)30234-9
84. Ailani J, Lipton RB, Goadsby PJ, Guo H, Miceli R, Severt L et al (2021) Atogepant for the preventive treatment of migraine. N Engl J Med 385(8):695–706. https://doi.org/10.1056/NEJMoa2035908
85. Lipton RB, Nahas SJ, Pozo-Rosich P, Bilchik T, McAllister P, Finnegan M et al (2024) Sustained response to atogepant in episodic migraine: post hoc analyses of a 12-week randomized trial and a 52-week long-term safety trial. J Headache Pain 25(1):83. https://doi.org/10.1186/s10194-024-01783-6
86. Tassorelli C, Nagy K, Pozo-Rosich P, Lanteri-Minet M, Sacco S, Nežádal T et al (2024) Safety and efficacy of atogepant for the preventive treatment of episodic migraine in adults for whom conventional oral preventive treatments have failed (ELEVATE): a randomised, placebo-controlled, phase 3b trial. Lancet Neurol 23(4):382–392. https://doi.org/10.1016/S1474-4422(24)00025-5
87. Lipton RB, Pozo-Rosich P, Blumenfeld AM, Li Y, Severt L, Stokes JT et al (2023) Effect of atogepant for preventive migraine treatment on patient-reported outcomes in the Randomized, Double-blind, phase 3 ADVANCE trial. Neurology 100(8):e764–e777. https://doi.org/10.1212/WNL.0000000000201568
88. Lipton RB, Halker Singh RB, Mechtler L, McVige J, Ma J, Yu SY et al (2023) Patient-reported migraine-specific quality of life, activity impairment and headache impact with once-daily atogepant for preventive treatment of migraine in a randomized, 52-week trial. Cephalalgia 51(8):3331024231190296. https://doi.org/10.1177/03331024231190296
89. Pozo-Rosich P, Ailani J, Ashina M, Goadsby PJ, Lipton RB, Reuter U et al (2023) Atogepant for the preventive treatment of chronic migraine (PROGRESS): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 402(10404):775–785. https://doi.org/10.1016/S0140-6736(23)01049-8
90. Goadsby PJ, Friedman DI, Holle-Lee D, Demarquay D, Ashina S, Sakai F et al (2024) Efficacy of atogepant in chronic migraine with and without acute medication overuse in the randomized, double-blind, phase 3 PROGRESS trial. Neurology 103(2):e209584. https://doi.org/10.1212/WNL.0000000000209584
91. Ashina M, Tepper SJ, Reuter U, Blumenfeld AM, Hutchinson S, Xia J et al (2023) Once-daily oral atogepant for the long-term preventive treatment of migraine: findings from a multicenter, randomized, open-label, phase 3 trial. Headache 63(1):79–88. https://doi.org/10.1111/head.14439
92. McCracken HT, Thaxter LY, Smitherman TA (2024) Psychiatric comorbidities of migraine. Handb Clin Neurol 199:505–516. https://doi.org/10.1016/B978-0-12-823357-3.00013-6
93. Nesbitt AD (2024) Comorbidities of migraine: sleep disorders. Handb Clin Neurol 199:525–534. https://doi.org/10.1016/B978-0-12-823357-3.00020-3
94. Pelzer N, de Boer I, van den Maagdenberg AMJM, Terwindt GM (2023) Neurological and psychiatric comorbidities of migraine: concepts and future perspectives. Cephalalgia 43(6):3331024231180564. https://doi.org/10.1177/03331024231180564
95. Opavský J (1992) Magnesium and its combination with cinnarizine in the long-term treatment of headache. Acta Univ Palacki Olomuc Fac Med 131:157–164
96. Bordini CA, Arruda MA, Ciciarelli MC, Speciali JG (1997) Propranolol vs flunarizine vs flunarizine plus propranolol in migraine without aura prophylaxis. A double-blind trial. Arq Neuropsiquiatr 55(3B):536–541. https://doi.org/10.1590/s0004-282x1997000400003
97. Krymchantowski AV, Silva MT, Barbosa JS, Alves LA (2002) Amitriptyline versus Amitriptyline combined with fluoxetine in the preventative treatment of transformed migraine: a double-blind study. Headache 42(6):510–514. https://doi.org/10.1046/j.1526-4610.2002.02125.x
98. Pascual J, Leira R, Láinez JM (2003) Combined therapy for migraine prevention? Clinical experience with a beta-blocker plus sodium valproate in 52 resistant migraine patients. Cephalalgia 23(10):961–962. https://doi.org/10.1046/j.1468-2982.2003.00615.x
99. Martínez HR, Londoño O, Cantú-Martínez L, del Carmen Tarín L, Castillo CD (2003) Topiramate as an adjunctive treatment in migraine prophylaxis. Headache 43(10):1080–1084. https://doi.org/10.1046/j.1526-4610.2003.03209.x
100. Pascual J, Rivas MT, Leira R (2007) Testing the combination beta-blocker plus topiramate in refractory migraine. Acta Neurol Scand 115(2):81–83. https://doi.org/10.1111/j.1600-0404.2006.00772.x
101. Keskinbora K, Aydinli I (2008) A double-blind randomized controlled trial of Topiramate and Amitriptyline either alone or in combination for the prevention of migraine. Clin Neurol Neurosurg 110(10):979–984. https://doi.org/10.1016/j.clineuro.2008.05.025
102. Domingues RB, Silva AL, Domingues SA, Aquino CC, Kuster GW (2009) A double-blind randomized controlled trial of low doses of propranolol, nortriptyline, and the combination of propranolol and nortriptyline for the preventive treatment of migraine. Arq Neuropsiquiatr 67(4):973–977. https://doi.org/10.1590/s0004-282x2009000600002
103. Krymchantowski AV, da Cunha Jevoux C, Bigal ME (2012) Topiramate plus Nortriptyline in the preventive treatment of migraine: a controlled study for nonresponders. J Headache Pain 13(1):53–59. https://doi.org/10.1007/s10194-011-0395-4
104. Silberstein SD, Dodick DW, Lindblad AS, Holroyd K, Harrington M, Mathew NT et al (2012) Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine. Neurology 78(13):976–984. https://doi.org/10.1212/WNL.0b013e31824d5846
105. Luo N, Di W, Zhang A, Wang Y, Ding M, Qi W et al (2012) A randomized, one-year clinical trial comparing the efficacy of topiramate, flunarizine, and a combination of flunarizine and topiramate in migraine prophylaxis. Pain Med 13(1):80–86. https://doi.org/10.1111/j.1526-4637.2011.01295.x
106. Khani S, Hejazi SA, Yaghoubi M, Sharifipour E (2021) Comparative study of magnesium, sodium valproate, and concurrent magnesium-sodium

valproate therapy in the prevention of migraine headaches: a randomized controlled double-blind trial. J Headache Pain 22(1):21. https://doi.org/10.1186/s10194-021-01234-6
107. Adeeb Sheet D, Bibani RH, Kheder AH (2022) Comparison of the effect of propranolol combination with cinnarizine and propranolol in the prevention of acute migraine attacks. Cell Mol Biol (Noisy-le-grand) 68(11):37–42. https://doi.org/10.14715/cmb/2022.68.11.7
108. Giussani G, Beghi E (2013) Does mechanism of drug action matter to inform rational polytherapy in epilepsy? CNS Neurol Disord Drug Targets 12(3):426–435. https://doi.org/10.2174/18715273113120300015
109. Verrotti A, Tambucci R, Di Francesco L, Pavone P, Iapadre G, Altobelli E et al (2020) The role of polytherapy in the management of epilepsy: suggestions for rational antiepileptic drug selection. Expert Rev Neurother 20(2):167–173. https://doi.org/10.1080/14737175.2020
110. Lee MJ, Al-Karagholi MA-M, Reuter U (2023) New migraine prophylactic drugs: current evidence and practical suggestions for non-responders to prior therapy. Cephalalgia 43(2):03331024221146315. https://doi.org/10.1177/03331024221146315
111. Zobdeh F, Ben Kraiem A, Attwood MM, Chubarev VN, Tarasov VV, Schiöth HB et al (2021) Pharmacological treatment of migraine: drug classes, mechanisms of action, clinical trials and new treatments. Br J Pharmacol 178(23):4588–4607. https://doi.org/10.1111/bph.15657
112. Deligianni CI, Sacco S, Ekizoglu E, Uluduz D, Gil-Gouveia R, MaassenVanDenBrink A et al (2023) European Headache Federation (EHF) critical re-appraisal and meta-analysis of oral drugs in migraine prevention – part 2: flunarizine. J Headache Pain 24(1):128. https://doi.org/10.1186/s10194-023-01657-3
113. Nguyen JL, Munshi K, Peasah SK, Swart ECS, Kohli M, Henderson R et al (2022) Trends in utilization and costs of migraine medications, 2017–2020. J Headache Pain 23(1):111. https://doi.org/10.1186/s10194-022-01476-y
114. Overeem LH, Ornello R, Pocora MM, Reuter U, Sacco S, Tassorelli C et al (2023) A retrospective real-life multicenter study on concurrent oral preventive treatments in patients with chronic migraine treated with OnabotulinumtoxinA. CNS Drugs 37(5):453–465. https://doi.org/10.1007/s40263-023-01001-y
115. Szkutnik-Fiedler D (2020) Pharmacokinetics, pharmacodynamics and drug-drug interactions of new anti-migraine drugs-lasmiditan, gepants, and calcitonin-gene-related peptide (CGRP) receptor monoclonal antibodies. Pharmaceutics 12(12):1180. https://doi.org/10.3390/pharmaceutics12121180
116. Bruijn N, van Lohuizen R, Boron M, Fitzek M, Gabriele F, Giuliani G et al (2024) Influence of metabolic state and body composition on the action of pharmacological treatment of migraine. J Headache Pain 25(1):20. https://doi.org/10.1186/s10194-024-01724-3
117. Joshi S, Tepper SJ, Lucas S, Rasmussen S, Nelson R (2021) A narrative review of the importance of pharmacokinetics and drug-drug interactions of preventive therapies in migraine management. Headache 61(6):838–853. https://doi.org/10.1111/head.14135
118. Cohen JM, Dodick DW, Yang R, Newman LC, Li T, Aycardi E et al (2017) Fremanezumab as add-on treatment for patients treated with other migraine preventive medicines. Headache 57(9):1375–1384. https://doi.org/10.1111/head.13156
119. Alsaadi T, Noori S, Varakian R, Youssef S, Almadani A (2022) Real-world experience of erenumab in patients with chronic or episodic migraine in the UAE. BMC Neurol 22(1):221. https://doi.org/10.1186/s12883-022-02710-5
120. Goadsby PJ, Reuter U, Hallström Y, Broessner G, Bonner JH, Zhang F et al (2017) A controlled trial of Erenumab for episodic migraine. N Engl J Med 377(22):2123–2132. https://doi.org/10.1056/NEJMoa1705848
121. Silberstein SD, Dodick DW, Bigal ME, Yeung PP, Goadsby PJ, Blankenbiller T et al (2017) Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med 377(22):2113–2122. https://doi.org/10.1056/NEJMoa1709038
122. Detke HC, Goadsby PJ, Wang S, Friedman DI, Selzler KJ, Aurora SK (2018) Galcanezumab in chronic migraine: the randomized, double-blind, placebo-controlled REGAIN study. Neurology 91(24):e2211–e2221. https://doi.org/10.1212/WNL.0000000000006640
123. Lipton RB, Goadsby PJ, Smith J, Schaeffler BA, Biondi DM, Hirman J et al (2020) Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. Neurology 94(13):e1365–e1377. https://doi.org/10.1212/WNL.0000000000009169
124. Raffaelli B, Fitzek M, Overeem LH, Storch E, Terhart M, Reuter U (2023) Clinical evaluation of super-responders vs. non-responders to CGRP(-receptor) monoclonal antibodies: a real-world experience. J Headache Pain 24(1):16. https://doi.org/10.1186/s10194-023-01552-x
125. Lipton RB, Pozo-Rosich P, Blumenfeld AM, Dodick DW, McAllister P, Li Y et al (2022) Rates of response to atogepant for migraine prophylaxis among adults: a secondary analysis of a randomized clinical trial. JAMA Netw Open 5(6):e2215499. https://doi.org/10.1001/jamanetworkopen.2022.15499
126. Cernuda-Morollón E, Ramón C, Martínez-Camblor P, Serrano-Pertierra E, Larrosa D, Pascual J (2015) OnabotulinumtoxinA decreases interictal CGRP plasma levels in patients with chronic migraine. Pain. 156(5):820–824. https://doi.org/10.1097/j.pain.0000000000000119
127. Melo-Carrillo A, Strassman AM, Nir RR, Schain AJ, Noseda R, Stratton J et al (2017) Fremanezumab-A humanized monoclonal anti-CGRP antibody-inhibits thinly myelinated (Aδ) but not unmyelinated (C) meningeal nociceptors. J Neurosci 37(44):10587–10596. https://doi.org/10.1523/JNEUROSCI.2211-17.2017
128. Melo-Carrillo A, Noseda R, Nir RR, Schain AJ, Stratton J, Strassman AM (2017) Selective inhibition of trigeminovascular neurons by fremanezumab: a humanized monoclonal Anti-CGRP antibody. J Neurosci 37(30):7149–7163. https://doi.org/10.1523/JNEUROSCI.0576-17.2017
129. Pellesi L (2023) Combining onabotulinumtoxin A with a CGRP antagonist for chronic migraine prophylaxis: where do we stand? Front Pain Res (Lausanne) 4:1292994. https://doi.org/10.3389/fpain.2023.1292994
130. Boudreau GP (2020) Treatment of chronic migraine with erenumab alone or as an add on therapy: a real-world observational study. Anesth Pain Res 4(1):1–4
131. Robblee J, Devick KL, Mendez N, Potter J, Slonaker J, Starling AJ (2020) Real-world patient experience with erenumab for the preventive treatment of migraine. Headache 60(9):2014–2025. https://doi.org/10.1111/head.13951
132. Ozudogru SN, Bartell JW, Yuan H, Digre KB, Baggaley SK (2020) The effect of adding calcitonin gene-related peptide monoclonal antibodies to onabotulinum toxin A therapy on headache burden: a retrospective observational case series. Headache 60(7):1442–1443. https://doi.org/10.1111/head.13839
133. Blumenfeld AM, Frishberg BM, Schim JD, Iannone A, Schneider G, Yedigarova L et al (2021) Real-world evidence for control of chronic migraine patients receiving CGRP monoclonal antibody therapy added to onabotulinumtoxinA: a retrospective chart review. Pain Ther 10(2):809–826. https://doi.org/10.1007/s40122-021-00264-x
134. Toni T, Tamanaha R, Newman B, Liang Y, Lee J, Carrazana E et al (2021) Effectiveness of dual migraine therapy with CGRP inhibitors and onabotulinumtoxinA injections: case series. Neurol Sci 42(12):5373–5376. https://doi.org/10.1007/s10072-021-05547-x
135. Cohen F, Armand C, Lipton RB, Vollbracht S (2021) Efficacy and tolerability of calcitonin gene-related peptide-targeted monoclonal antibody medications as add-on therapy to onabotulinumtoxinA in patients with chronic migraine. Pain Med 22(8):1857–1863. https://doi.org/10.1093/pm/pnab093
136. Armanious M, Khalil N, Lu Y, Jimenez-Sanders R (2021) Erenumab and onabotulinumtoxinA combination therapy for the prevention of intractable chronic migraine without aura: a retrospective analysis. J Pain Palliat Care Pharmacother 35(1):1–6. https://doi.org/10.1080/15360288.2020.1829249
137. Alpuente A, Gallardo VJ, Caronna E, Torres-Ferrús M, Pozo-Rosich P (2021) Partial and nonresponders to onabotulinumtoxinA can benefit from anti-CGRP monoclonal antibodies preventive treatment: a real-world evidence study. Eur J Neurol 28(7):2378–2382. https://doi.org/10.1111/ene.14828
138. Silvestro M, Tessitore A, Scotto di Clemente F, Battista G, Tedeschi G, Russo A (2021) Additive interaction between onabotulinumtoxin-A and erenumab in patients with refractory migraine. Front Neurol 12:656294. https://doi.org/10.3389/fneur.2021.656294
139. Mechtler L, Saikali N, McVige J, Hughes O, Traut A, Adams AM (2022) Real-world evidence for the safety and efficacy of CGRP monoclonal antibody therapy added to onabotulinumtoxinA treatment for

migraine prevention in adult patients with chronic migraine. Front Neurol 12:788159. https://doi.org/10.3389/fneur.2021.788159
140. Argyriou AA, Dermitzakis EV, Xiromerisiou G, Vikelis M (2022) OnabotulinumtoxinA Add-On to monoclonal Anti-CGRP antibodies in treatment-refractory chronic migraine. Toxins (Basel) 14(12):847. https://doi.org/10.3390/toxins14120847
141. Nandyala AS, Suri H, Dougherty CO, Ailani J (2022) A retrospective evaluation of the combination of erenumab and onabotulinum toxin A for the prevention of chronic migraine. Clin Neurol Neurosurg 215:107200. https://doi.org/10.1016/j.clineuro.2022.107200
142. Jaimes A, Gómez A, Pajares O, Rodríguez-Vico J (2023) Dual therapy with Erenumab and onabotulinumtoxinA: no synergistic effect in chronic migraine: a retrospective cohort study. Pain Pract 23(4):349–358. https://doi.org/10.1111/papr.13196
143. Manack Adams A, Hutchinson S, Engstrom E, Ayasse ND, Serrano D, Davis L et al (2023) Real-world effectiveness, satisfaction, and optimization of ubrogepant for the acute treatment of migraine in combination with onabotulinumtoxinA: results from the COURAGE study. J Headache Pain 24(1):102. https://doi.org/10.1186/s10194-023-01622-0
144. Salim A, Hennessy E, Sonneborn C, Hogue O, Biswas S, Mays M et al (2024) Synergism of Anti-CGRP monoclonal antibodies and OnabotulinumtoxinA in the treatment of chronic migraine: a real-world retrospective Chart Review. CNS Drugs 38(6):481–491. https://doi.org/10.1007/s40263-024-01086-z
145. Scuteri D, Tonin P, Nicotera P, Vulnera M, Altieri GC, Tarsitano A et al (2022) Pooled analysis of real-world evidence supports Anti-CGRP mAbs and OnabotulinumtoxinA combined trial in chronic migraine. Toxins (Basel) 14(8):529. https://doi.org/10.3390/toxins14080529
146. de Vries T, Rubio-Beltrán E, van den Bogaerdt A, Dammers R, Danser AHJ, Snellman J et al (2024) Pharmacology of erenumab in human isolated coronary and meningeal arteries: additional effect of gepants on top of a maximum effect of erenumab. Br J Pharmacol 181(12):1720–1733. https://doi.org/10.1111/bph.16322
147. Pan KS, Siow A, Hay DL, Walker CS (2020) Antagonism of CGRP Signaling by Rimegepant at two receptors. Front Pharmacol 11:1240. https://doi.org/10.3389/fphar.2020.01240
148. Ghanizada H, Al-Karagholi MA, Walker CS, Arngrim N, Rees T, Petersen J et al (2021) Amylin analog pramlintide induces migraine-like attacks in patients. Ann Neurol 89(6):1157–1171. https://doi.org/10.1002/ana.26072.8
149. Bhakta M, Vuong T, Taura T, Wilson DS, Stratton JR, Mackenzie KD (2021) Migraine therapeutics differentially modulate the CGRP pathway. Cephalalgia 41(5):499–514. https://doi.org/10.1177/0333102420983282
150. Jakate A, Blumenfeld AM, Boinpally R, Butler M, Borbridge L, Contreras-De Lama J et al (2021) Pharmacokinetics and safety of ubrogepant when coadministered with calcitonin gene-related peptide-targeted monoclonal antibody migraine preventives in participants with migraine: a randomized phase 1b drug-drug interaction study. Headache 61(4):642–652. https://doi.org/10.1111/head.14095
151. Mullin K, Kudrow D, Croop R, Lovegren M, Conway CM, Coric V et al (2020) Potential for treatment benefit of small molecule CGRP receptor antagonist plus monoclonal antibody in migraine therapy. Neurology 94(20):e2121–e2125. https://doi.org/10.1212/WNL.0000000000008944
152. Berman G, Croop R, Kudrow D, Halverson P, Lovegren M, Thiry AC et al (2020) Safety of rimegepant, an oral CGRP receptor antagonist, plus CGRP monoclonal antibodies for migraine. Headache 60(8):1734–1742. https://doi.org/10.1111/head.13930
153. Lipton RB, Contreras-De Lama J, Serrano D, Engstrom E, Ayasse ND, Poh W et al (2024) Real-world use of Ubrogepant as acute treatment for migraine with an anti-calcitonin gene-related peptide monoclonal antibody: results from COURAGE. Neurol Ther 13(1):69–83. https://doi.org/10.1007/s40120-023-00556-8
154. Alsaadi T, Suliman R, Santos V, Al Qaisi I, Carmina P, Aldaher B et al (2024) Safety and tolerability of combining CGRP monoclonal antibodies with gepants in patients with migraine: a retrospective study. Neurol Ther 13(2):465–473. https://doi.org/10.1007/s40120-024-00586-w
155. Blumenfeld AM, Boinpally R, De Abreu Ferreira R, Trugman JM, Dabruzzo B, Ailani J et al (2023) Phase ib, open-label, fixed-sequence, drug-drug interaction, safety, and tolerability study between atogepant and ubrogepant in participants with a history of migraine. Headache 63(3):322–332. https://doi.org/10.1111/head.14433
156. Pong AW, Xu KJ, Klein P (2023) Recent advances in pharmacotherapy for epilepsy. Curr Opin Neurol 36(2):77–85. https://doi.org/10.1097/WCO.0000000000001144
157. Wells-Gatnik WD, Pellesi L, Martelletti P (2024) Rimegepant and atogepant: novel drugs providing innovative opportunities in the management of migraine. Expert Rev Neurother 24(11):1107–1117. https://doi.org/10.1080/14737175.2024.2401558
158. Nallani SC, Glauser TA, Hariparsad N, Setchell K, Buckley DJ, Buckley AR et al (2003) Dose-dependent induction of cytochrome P450 (CYP) 3A4 and activation of pregnane X receptor by topiramate. Epilepsia 44(12):1521–1258. https://doi.org/10.1111/j.0013-9580.2003.06203.x
159. Deen M, Correnti E, Kamm K, Kelderman T, Papetti L, Rubio-Beltrán E et al (2017) Blocking CGRP in migraine patients - a review of pros and cons. J Headache Pain 18(1):96. https://doi.org/10.1186/s10194-017-0807-1
160. Martelletti P (2020) Combination therapy in migraine: asset or issue? Expert Rev Neurother 20(10):995–996. https://doi.org/10.1080/14737175.2020.1821655
161. Mistry H, Naghdi S, Underwood M, Duncan C, Madan J, Matharu M (2023) Competing treatments for migraine: a headache for decision-makers. J Headache Pain 24(1):162. https://doi.org/10.1186/s10194-023-01686-y
162. Sheng Z, Sun Y, Yin Z, Tang K, Cao Z (2018) Advances in computational approaches in identifying synergistic drug combinations. Brief Bioinform 19(6):1172–1182. https://doi.org/10.1093/bib/bbx047
163. Kong W, Midena G, Chen Y, Athanasiadis P, Wang T, Rousu J et al (2022) Systematic review of computational methods for drug combination prediction. Comput Struct Biotechnol J 20:2807–2814. https://doi.org/10.1016/j.csbj.2022.05.055

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