Novel Migraine Treatments: A Review

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Aims: To present a review of the mechanisms of action, available clinical data, and safety profiles of novel migraine therapeutics to inform practice. **Methods:** PubMed, Medline, and Google Scholar were searched for randomized controlled trials (24 publications), review articles (15 publications), and other pertinent literature (16 publications) discussing the novel migraine therapeutics available between the years 2010 and 2021. All publications were reviewed to assess the mechanism of action, relevant clinical data, and side effect profile for each novel treatment. Therapeutic gain was also recorded in studies that included a placebo arm. **Results:** A total of 55 studies were included in the final analysis. In the preventive treatment of migraine, novel medications target calcitonin gene-related peptide (CGRP) and fall into either the monoclonal anti-CGRP or gepant class. For the acute treatment of migraine, novel medications fall into either the ditan or gepant class. Several medical devices have been developed for the acute and preventive treatment of migraine. **Conclusion:** Novel therapeutics are available for both the prevention and acute treatment of migraine headaches. These new medications and neuromodulatory devices appear overall to be safe and effective in the management of migraine headaches. *J Oral Facial Pain Headache 2023;37:25–32. doi: 10.11607/ofph.3163*

Migraine headache is characterized by severe unilateral head pain that is pulsating in quality, lasts 4 to 72 hours in duration, and is often accompanied by nausea, photophobia, and/or phonophobia.[1] These headaches affect 6% to 8% of men and 15% to 25% of women in the western world.[2] This highly prevalent disease leads to missed or impaired work days, resulting in an estimated $13 billion in lost wages and reduced productivity annually in the United States of America.[3] This demonstrates a definite need for effective migraine treatment options.

Migraine is thought to involve the trigeminovascular system, which is composed of the sensory neurons of the trigeminal ganglion, the upper cervical dorsal nerve roots, and the cerebral and dural blood vessels. The upper cervical nerve roots and the trigeminal ganglion meet within the trigeminal nucleus caudalis before traveling to the thalamus and subsequently to the sensory centers within the cortex. Activation within the trigeminal ganglion leads to a release of several neuropeptides, including calcitonin gene-related peptide (CGRP), substance P, pituitary adenylate cyclase activating polypeptide-38 (PACAP-38), and neurokinin A, each of which are thought to mediate vasodilation and neurogenic inflammation.[4]

The mainstays for migraine management have been nonspecific acute and preventive medications, and though they have been found to be effective, comorbidities and side effects make these options suboptimal for a large cohort of patients. Newer migraine treatment options with more disease specificity and less side effects have been developed as a result of this need.

In this review, the novel preventive and acute medication options for migraine will be discussed, as well as the new class of neuromodulatory devices that have achieved US Food and Drug Administration (FDA) clearance. Each medication or neuromodulatory device presented will have a description of its proposed mechanism of action, followed by its

Table 1 Preventive Migraine Medications

Medication	Target of action	Route of administration	Dosing frequency	Dose range, mg
Erenumab	CGRP receptor	Injectable	Monthly	70 or 140
Fremanezumab	CGRP ligand	Injectable	Monthly or quarterly	225 or 675
Galcanezumab	CGRP ligand	Injectable	Monthly	240 loading dose, then 120 monthly
Eptinezumab	CGRP ligand	Infusion	Quarterly	100 or 300
Atogepant	CGRP receptor	Oral	Daily	10, 30, or 60
Rimegepant	CGRP receptor	Oral	Every 48 hours	75

Summary table of novel preventive migraine medications. Erenumab, galcanezumab, and fremanezumab are once-monthly injectables, while eptinezumab is a quarterly infusion. Atogepant is a once-daily oral medication, while rimegepant is an oral medication taken every other day. Galcanezumab requires a loading dose in the first month, and fremanezumab offers a quarterly injectable option. Erenumab and eptinezumab have higher dose options available if the starting dose is not effective.

most significant published data, and conclude with its most common or notable side effects. All of the medications and devices presented in this review are used in clinical practice; however, they have only come to market after the latest American Headache Society (AHS) guidelines were published in 2012 and thus have not yet received a defined AHS grading.

Preventive Migraine Medications

The goal of preventive migraine medications is to reduce monthly headache frequency and severity by 50% or more. A general rule for each preventive medication is that it can take up to 3 months to take effect. Each novel preventive medication is summarized in Table 1.

Monoclonal Antibody Injectables/Infusions for Migraine

Erenumab.

Mechanism of action

CGRP, released by trigeminal neurons, plays a pivotal role in migraine pathophysiology. It has been demonstrated that serum levels are elevated during a migraine attack and fall interictally and after sumatriptan treatment.[5] CGRP is associated with an increase in middle meningeal artery circumference specific to the side of headache pain, likely reflecting activation of dural perivascular nociceptors.[6] Monoclonal antibodies (mAbs) target either the CGRP neuropeptide or the CGRP receptor to inhibit these processes. Erenumab is the only mAb that targets the extracellular domains of the CGRP receptor. Different targets (ie, CGRP binding vs CGRP receptor) might explain the slightly different mechanisms of action of the available mAbs. It is possible that migraines occurring under preventive treatment with an anti–CGRP receptor mAb might be caused by CGRP binding to other receptors with a structure similar to the CGRP receptor, while migraine occurring under prevention with an anti-CGRP mAb might be due to other peptides binding to the CGRP receptor. Erenumab is a fully human mAb CGRP receptor antagonist that is administered monthly via subcutaneous injection at doses of 70 mg and 140 mg for the prevention of migraine.[7]

Clinical trials

In a pivotal multinational, double-blinded, placebo-controlled 6-month trial including 955 patients with episodic migraine randomized to erenumab 70 mg, 140 mg, or placebo, patients experienced a mean monthly migraine day reduction of –3.2, –3.7, and –1.8 days, respectively.[8] In a randomized, double-blinded, placebo-controlled multicenter study with 667 patients with chronic migraine, erenumab at doses of 70 mg and 140 mg was found to reduce monthly migraine days by ~6 days, while each placebo reduced monthly migraine days by ~4.[9]

Adverse events

In a subgroup analysis of 2,443 patients from a compilation of double-blinded, placebo-controlled studies, risk of cerebrovascular or cardiovascular adverse events with erenumab doses of 70 mg or 140 mg was found to be comparable to placebo.[10] Adverse side effects are rare but include injection site reaction, constipation, viral upper respiratory tract infections, sinusitis, back pain, allergic reactions, alopecia, and, possibly, hypertension.[11,12]

Galcanezumab/fremanezumab/eptinezumab.

Mechanism of action

Galcanezumab, fremanezumab, and eptinezumab target migraine pathophysiology at the level of CGRP, similar to erenumab. However, these antibodies function differently in that they bind to the CGRP ligand on the peptide, preventing its subsequent binding to receptors.[13] The anti-CGRP monoclonal antibodies such as fremanezumab also inhibit afferent Aδ neurons and wide dynamic range neurons centrally.[14] All four reduce CGRP activity peripherally in the meninges, likely accounting for their anti-migraine effects.

Clinical trials

Galcanezumab is given as a monthly subcutaneous injection, fremanezumab can be given as a monthly or quarterly subcutaneous injection, and eptinezumab as

a quarterly intravenous infusion.[15] In a double-blinded, placebo-controlled 6-month trial with 915 patients with episodic migraine, galcanezumab at doses of 120 mg and 240 mg was effective in reducing mean monthly migraine days by −4.3 and −4.2 days, respectively, while placebo reduced mean monthly migraine days by −2.3 days.[16] In a double-blinded, placebo-controlled 3-month trial with a cohort of 1,113 patients with chronic migraine, galcanezumab at doses of 120 mg and 240 mg was effective in reducing mean monthly migraine days by −4.8 and −4.6 days, respectively, while placebo reduced mean monthly migraine days by −2.7 days.[17] As there was no difference between the 120-mg and the 240-mg doses, galcanezumab is FDA approved only as a 240-mg one-time loading dose followed by 120 mg monthly thereafter. As with all of the mAbs, it has approval in the US for prevention of all migraine, implying episodic and chronic, with and without aura, with and without acute medication use or overuse, and without restriction in hemiplegic and brainstem aura patients. Galcanezumab is also the only medication with FDA approval for the prevention of episodic cluster headache at a dose of 300 mg subcutaneously administered monthly during a cluster cycle.

Fremanezumab, in a randomized, double-blinded, placebo-controlled trial with a cohort of 875 patients with episodic migraine comparing monthly dosing of 225 mg, quarterly dosing of 675 mg, and placebo, mean monthly migraine days reduced by −4 days with monthly dosing, −3.9 days with quarterly dosing, and −2.6 days in the placebo group.[18] In a double-blinded, placebo-controlled trial including 1,130 patients with chronic migraine, patients treated with quarterly injections of 675 mg, monthly injections of 225 mg after a loading dose of 675 mg, and placebo showed reductions in mean monthly migraine days of −4.3 days, −4.6 days, and −2.5 days, respectively.[19]

Eptinezumab, in a randomized, double-blinded, placebo-controlled, 1-year trial including 888 patients with episodic migraine and quarterly infusions of 100 mg or 300 mg, reduced mean monthly migraine days by −3.9 days and −4.3 days, respectively, while only demonstrating a reduction of −3 days in the placebo group.[20] In a multicenter, randomized, double-blinded, placebo-controlled 6-month trial including 1,072 patients with chronic migraine, eptinezumab at quarterly infusion doses of 100 mg or 300 mg demonstrated a reduction of −7.7 and −8.2 mean monthly migraine days, respectively, in comparison to −5.6 days with placebo.[21]

Adverse events

CGRP ligand-targeting mAbs have been very well tolerated with minimal side effects, with adverse effects of injection site reaction, upper respiratory tract infection, urinary tract infection, fatigue, back pain, constipation, allergic reactions, and nausea.[22]

Gepants.

Mechanism of action

Both rimegepant and atogepant are small-molecule CGRP receptor antagonists that have demonstrated evidence for migraine prevention. Peripheral release of CGRP from trigeminal nerve fibers within the dura and from the cell body of trigeminal ganglion neurons likely contributes to the peripheral sensitization of the trigeminal nociceptors, while release of CGRP from the trigeminal nucleus caudalis facilitates activation of nociceptive second-order neurons and glial cells. It is through these processes that CGRP is likely involved in the development and maintenance of persistent pain, central sensitization, and allodynia associated with migraine.[23] As small molecules, gepants block the CGRP receptor and can terminate migraine acutely and prevent it when used regularly. Because they prevent CGRP-mediated vasodilation but do not cause vasoconstriction, there is no contraindication to their use in patients with vascular disease in the approved prescribing information.

Clinical trials

There are data from a randomized, double-blinded, placebo-controlled trial including 695 patients showing rimegepant 75 mg dosed every other day significantly reduced mean monthly migraine headache days by −4.3 days vs −3.5 days in the placebo cohort.[24] In 2021, the FDA approved rimegepant, with dosing every other day for prevention of episodic migraine only.

Atogepant was approved in 2021 for prevention of episodic migraine as well. In a double-blinded, placebo-controlled trial of 825 patients with episodic migraine treated with different doses of atogepant vs placebo, 10 mg daily reduced mean monthly migraines by −4 days, 30 mg daily reduced by −3.8 days, 60 mg daily reduced by −3.6 days, 30 mg twice daily reduced by −4.2 days, and 60 mg twice daily reduced by −4.1 days. These doses were statistically superior to placebo, which reduced mean monthly migraines by −2.9 days.[25] In the subsequent phase 3 pivotal trial including 873 patients with episodic migraine treated with different daily doses of atogepant vs placebo, atogepant 10 mg reduced mean monthly migraine days by −3.7, atogepant 30 mg reduced by −3.9, and atogepant 60 mg reduced by −4.2, while placebo only reduced mean monthly migraine days by −2.5.[26]

Adverse events

Gepants are quite well tolerated, with the most common adverse events being nausea, dry mouth, and drowsiness. Gepants are metabolized by the cytochrome P4503A4 (CYP3A4) liver enzyme systems, and the prescribing information for each gepant lists steps to be taken with concomitant use of other CYP3A4 substrates, inhibitors, or inducers.[27]

Table 2 Acute Migraine Medications

Medication	Target of action	Route of administration	Dose range, mg	Dose max in 24 h, mg
Lasmiditan	$5HT_{1F}$	Oral	50, 100, or 200	200
Rimegepant	CGRP receptor	Oral	75	75
Ubrogepant	CGRP receptor	Oral	50 or 100	200

Summary table of novel acute migraine medications. Rimegepant and ubrogepant target the CGRP receptor, while lasmiditan targets the $5HT_{1F}$ receptor. Ubrogepant can be re-dosed within a 24-hour period.

Constipation was the most common adverse event in the atogepant pivotal trial.[26]

Acute Migraine Medications

The goal of acute migraine medications is to abort a headache that is starting. These medications are most effective when used at the onset of a migraine headache. Table 2 provides a summary of the novel acute medications now available.

Ditans (Lasmiditan)

Mechanism of action.

Lasmiditan is a highly selective serotonin $(5\text{-HT})_{1F}$ receptor agonist that inhibits neurogenic inflammation in the dura via decreased c-Fos expression in the trigeminal nucleus caudalis after stimulation of the trigeminal ganglion.[28] Unlike triptans, which are agonists of $5HT_{1B}$, causing vasoconstriction and making them unsuitable medications for people with vascular disease and uncontrolled hypertension, the selectivity of lasmiditan for 5-HT_{1F} does not cause this vasoconstrictive effect, and thus it is thought to be safe in these patient populations.[29] 5-HT_{1F} receptors located peripherally and presynaptically inhibit CGRP release.[30] 5-HT_{1F} receptors located centrally probably interfere with central processing of migraine, but their activation is also likely a cause for central nervous system adverse events sometimes associated with lasmiditan use.[31,32]

Clinical trials and adverse events.

In a phase 3 double-blinded, randomized, placebo-controlled study with 2,583 patients, pain freedom at 2 hours was statistically superior for lasmitidan, as was demonstrated in 38.8% of patients treated with lasmiditan 200 mg, 31.4% of patients treated with lasmiditan 100 mg, and 28.6% of patients treated with lasmiditan 50 mg. Only 21.3% of patients treated with placebo had pain freedom at 2 hours.[33] Lasmiditan was demonstrated to show driving impairment at 50-mg, 100-mg, and 200-mg doses within 1.5 hours of medication administration vs placebo; however, there was no impairment at 8 hours post–medication administration, with the most common symptoms being dizziness, somnolence, and fatigue.[34] Patients should not drive or use heavy machinery for at least 8 hours after each dose of lasmiditan. Lasmiditan at all three doses is FDA approved for acute treatment of migraine.

Gepants

Ubrogepant/rimegepant.

Mechanism of action

Ubrogepant, rimegepant, and zavegepant are small-molecule CGRP receptor antagonists that are used in the treatment of acute migraine. Gepants block the CGRP receptor, thus limiting sensitization and nociceptor activation and thereby terminating an acute migraine.[23]

Clinical trials

In a randomized, double-blinded, placebo-controlled trial with 1,672 patients that investigated the efficacy of ubrogepant, the percentages of patients who had headache pain freedom at 2 hours for ubrogepant 50 mg, 100 mg, and placebo were 19.2% ($P = .002$), 21.2% ($P < .001$), and 11.8%, respectively, which was statistically significant for both doses.[35] In a randomized, double-blinded, placebo-controlled trial with 1,375 participants assigned to receive either rimegepant 75 mg or placebo for the acute treatment of migraine, rimegepant was found to be statistically superior to placebo at 2 hours post dose, with 21% of patients pain free vs only 11% in the placebo group ($P < .0001$).[36] Both ubrogepant and rimegepant are FDA approved for treatment of acute migraine.

Adverse events

As noted, gepants are quite well tolerated, with the most common adverse events being nausea, dry mouth, and drowsiness. Gepants are metabolized by the cytochrome P4503A4 (CYP3A4) liver enzyme systems, and, as previously stated, the prescribing information for each gepant lists steps to be taken with concomitant use of other CYP3A4 substrates, inhibitors, or inducers.[27]

Neuromodulation

External Trigeminal Stimulation/ Transcutaneous Supraorbital Nerve Stimulation

Mechanism of action.

The external trigeminal stimulation (eTNS) device is placed on the forehead and generates electrical impulses that are transmitted via a self-adhesive

supraorbital electrode to inhibit the supratrochlear and supraorbital branches of the ophthalmic division of cranial nerve V, subsequently reducing migraines as both an acute and prophylactic treatment.[37] The mechanism of action is likely inhibitory modulation of the trigeminal afferents, with resultant inhibitory modulation of the trigeminal cervical complex.

Clinical trials.

In a double-blinded, sham-controlled trial with 67 episodic migraine patients, the 50% responder rate after 3 months was significantly higher in the active group (38.2%) than in the sham group (12.1%), with a numeric, but not statistically significant, reduction in monthly headache attack frequency.[38] In a large survey with 2,313 eTNS users, 4.35% of subjects reported adverse effects, the most frequent being intolerance to the feeling of paresthesia and the most severe an allergic reaction to the electrode gel, all of which were fully reversible with discontinuation of the eTNS.[39] A pivotal sham-controlled study on eTNS for acute treatment of migraine was also positive.[40] The device is FDA cleared for both acute and preventive migraine treatment.

Noninvasive Vagus Nerve Stimulation

Mechanism of action.

Noninvasive vagal nerve stimulation (nVNS) is a noninvasive device that is held to the neck and stimulates the vagus nerve, subsequently modulating excess glutamate levels in the trigeminal nucleus caudalis, affecting the pain control centers and decreasing cortical excitability.[41] The nVNS device inhibits thalamic pain pathways and can interrupt cortical spreading depolarization (CSD).[42,43]

Clinical trials.

In a double-blinded, randomized, sham-controlled trial with 243 patients with episodic migraine, nVNS was significantly more effective in achieving pain freedom at 30 minutes and 60 minutes, but not at 120 minutes, and it failed to achieve the primary endpoint of pain freedom at 2 hours.[44] In a double-blinded, sham-controlled trial including 59 patients with chronic migraine, there was a mean reduction in the number of headache days of −1.4 in the active cohort vs −0.2 in the sham cohort (P = .56, not statistically significant) at 2 months. However, in the subsequent open label phase, of the 15 patients that underwent active treatments for 8 months, there was a reduction in baseline headache days of −7.9 (P < .01).[45] A sham-controlled trial of nVNS for prevention of episodic migraine also failed the primary endpoint.[46] However, based on the preponderance of evidence, the device is FDA cleared for both acute and preventive treatment of migraine in both adolescents and adults. nVNS is the only noninvasive neuromodulation device with FDA clearance for other headache indications, including acute treatment of episodic cluster headache, adjunctive preventive treatment of cluster headache, and treatment of hemicrania continua and paroxysmal hemicrania.

Adverse events.

The most common adverse events with nVNS are mild and transient rash, pain, erythema, discomfort at the application site, and dizziness. No serious adverse events have been described with the use of nVNS.[47]

Single-Pulse Transcranial Magnetic Stimulation

Mechanism of action.

Single-pulse transcranial magnetic stimulation (sTMS) is a neuromodulatory device held at the back of the head that delivers a magnetic pulse across the scalp, skull, meninges, and cerebrospinal fluid into the layers of the cortex, where it modulates the electrical environment of neurons.[48] In rodent animal models, sTMS inhibits cortical spreading depression, the ventral posteromedial nucleus of the thalamus, and C-fiber–mediated activity, each of which is thought to play a role in the pathophysiology of migraine, for greater than 90 minutes.[49]

Clinical trials.

In a randomized, double-blinded, sham-controlled, multicenter trial of 164 patients with migraine with aura, when sTMS was used for the acute treatment of migraine during the aura phase of attack, pain freedom at 2 hours was significantly higher in patients who used sTMS (32/82; 39%) vs sham stimulation (18/82; 22%).[50] A multicenter, prospective, open-label, observational study for migraine prevention with 217 patients was conducted using the sTMS device twice a day for prophylaxis, as well as when needed for acute treatment, and demonstrated a mean reduction of −2.75 days per month from baseline after 3 months of use, with 46% of patients having a greater than 50% reduction in monthly headache days.[51] The device is FDA cleared for both acute and preventive migraine treatment in adolescents and adults.

Adverse events.

With over 10,000 patients who have undergone sTMS therapy, there are no data to suggest that sTMS causes harm to humans or changes in neurophysiologic function.

Remote Electrical Neuromodulation

Mechanism of action.

The remote electrical neuromodulation (REN) device is worn held by a band around the upper arm, and it stimulates peripheral nerves to induce conditioned pain modulation, which in turn activates descending inhibition pathways that originate within the periaqueductal gray and the rostral ventromedial medulla, subsequently inhibiting remote pain via the release of serotonin and norepinephrine.[52]

Clinical trials.
In a randomized, double-blinded, sham-controlled, multicenter study with 252 adults with migraine, 66.7% of patients in the active arm vs 38.8% of patients in the sham arm achieved pain relief within 2 hours, and 37.4% achieved pain freedom after 2 hours in the active arm vs 18.4% in the sham arm. All comparisons were statistically significant for REN vs sham.[53] In an open-label trial with 42 participants, 73.7% achieved pain relief at 2 hours, of which 26.3% were pain free at 2 hours. Of these patients, 84.4% had sustained pain relief at 24 hours, again significant for active vs sham.[54] The device is FDA cleared for acute treatment of migraine in adolescents and adults.
Adverse events.
REN can cause a mild and transient warm sensation, temporary arm/hand numbness, redness, itching, tingling, muscle spasm, and pain in the arm, shoulders, or neck. There have not been any serious adverse events associated with REN use.

Combined Supraorbital, Supratrochlear (Trigeminal), and Greater Occipital Nerve Stimulation (Cervical)

Mechanism of action.
Combined supraorbital, supratrochlear, and greater occipital nerve stimulation (OS-TNS) is a lightweight device placed over the head that stimulates bilateral supraorbital, supratrochlear, and greater occipital nerves. The device inhibits both trigeminal and cervically derived occipital pathways, which together likely results in inhibitory effects in the trigeminal nucleus caudalis.[55]
Clinical trials.
In a randomized sham-controlled pivotal trial of 131 participants treated for 45 minutes, 2-hour pain relief was achieved in 60% of actively treated vs 37% treated with sham (P = .0018). Secondary and exploratory endpoints of 2-hour pain freedom, 2-hour freedom from most bothersome migraine symptom, and 2- to 24-hour sustained pain freedom were also positive. There were no serious adverse events related to device usage. Based on this study and smaller previous trials, in 2021, the FDA cleared the OS-TNS device for acute treatment of migraine in adults.[56]

Conclusions

This review serves as a reference to provide physicians with the tools necessary to optimize the treatment of their patient's migraines. Although the authors include notable literature published, it is important to note that the field of headache medicine is changing at a rapid pace. Changes in understanding of the pathophysiology of migraine and the development of new targets of medications/medical devices requires a commitment to continuing education. The therapies presented here can provide the foundation by which to initiate evidence-based treatment for patients.

Highlights/Clinical Implications

- Novel oral, subcutaneous, and intravenous medications that functionally inhibit calcitonin CGRP are available for use in migraine prophylaxis.
- Novel medications in the ditan and gepant classes provide safe options for the acute treatment of migraine.
- Neuromodulatory devices provide a nonpharmacologic option for both the prevention and acute treatment of migraine.

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