# Preventive and Acute Treatment of Migraine: New and Emerging Targeted Therapies

## Overview of Migraine

Migraine is a clinically complex, disabling neurological disease characterized by recurrent attacks of moderate to severe headache that are typically unilateral, pulsating, exacerbated by routine physical activity, and are associated with nausea, vomiting, phonophobia, photophobia,[1] and cutaneous allodynia.[2] Migraine diagnoses may be categorized based on the frequency of monthly migraine days (MMDs) and monthly headache days (MHDs). Patients with fewer than 15 MMDs or MHDs are diagnosed with episodic migraine, and those with at least 15 MHDs, of which at least 8 are MMDs, are considered to have chronic migraine.[1]

Migraine is very widespread; a 2017 meta-analysis involving over 6 million participants found that migraine affects one in ten people worldwide. The same study indicated that migraine prevalence is increasing throughout the global population.[3] While the disability it causes has likely been underestimated,[4] according to 2016 data, migraine is the most frequent cause of neurological disability, the sixth leading cause of disability worldwide, and the second leading cause of years lived with disability.[5] Migraine has many negative effects on patient quality of life including romantic and family relationships, work/career achievement, financial stability, and overall health.[6]

Migraine is responsible for a substantial economic burden. The costs associated with migraine include both direct costs (medical costs, including the cost of migraine-specific medications and the cost of managing conditions that are often comorbid with migraine, such as anxiety and depression) as well as indirect costs (decreased productivity due to absenteeism, short-term disability, and long-term disability). In 2016, the direct and indirect costs of migraine were estimated to amount to a total annual cost of $36 billion in the U.S.[7,8]

Because of its high prevalence and negative effects on the quality of life, migraine is one of the most common reasons for consulting a health care professional.[9] The medical professionals most likely to be consulted by patients with migraine are primary care providers (PCPs). Most headache patients remain in primary care; a minority are treated by specialists and even fewer at specialized headache centers.[10] Migraine pain and its accompanying symptoms, as well as its effects on patient quality of life, can be managed with preventive therapies, acute treatments, or a combination of both.[11,12]

To provide the appropriate standard of care for patients with migraine, clinicians, including PCPs, must remain current on all aspects of managing this condition. In the primary care setting, migraine is often inadequately treated.[13] Certain widely used treatments are contraindicated for a substantial number of patients. Adding to the complexity of current care options are recently developed classes of drugs for both preventive and acute treatment that may be unfamiliar to clinicians.[14] Therefore, it is critical to provide educational programs that outline the benefits and limitations of established migraine therapies, as well as the use of new and emerging therapies for preventive and acute treatment of migraine. The proposed educational activity would address current gaps in migraine care identified from published literature, including physician and patient surveys.

**Gap Analysis Table**

| Gap | Educational Objective | Outcome |
|---|---|---|
| Clinicians are not treating all patients with migraine to the appropriate treatment goals. | Summarize the benefits and limitations of established migraine treatments. | Clinicians will be able to summarize the benefits and limitations of established migraine treatments. |
| Clinicians may not be aware of current guidelines for using new targeted therapies to improve care for patients who do not experience complete symptom relief with established preventive treatments. | Discuss the advantages and limitations of new targeted agents as preventive therapies for migraine.<br><br>Review the current guidelines for integrating new targeted agents for migraine prevention into clinical practice. | Clinicians will be knowledgeable about the advantages and limitations of new targeted agents as preventive therapies for migraine.<br><br>Clinicians will be confident in applying current guidelines for using new targeted agents for migraine prevention for management of difficult-to-treat migraine. |
| Clinicians may not be familiar with new acute treatments for migraine that may be used when other therapies are contraindicated or do not provide complete symptom relief. | Describe the safety and efficacy data on new targeted agents for acute migraine treatment.<br><br>Outline clinical situations in which new acute therapies for migraine would be advantageous. | Clinicians will be able to describe the safety and efficacy data on new targeted agents for acute migraine treatment.<br><br>Clinicians will be adept at selecting patients with migraine who may benefit from new acute therapies. |

**Gap Analysis**

**Gap #1: Clinicians are not treating all patients with migraine to the appropriate treatment goals.**

A considerable percentage of patients with migraine remain undiagnosed and many others receive inadequate care, according to results from the Observational Survey of the Epidemiology, Treatment and Care of Migraine (OVERCOME) study, a web-based survey of 21,143 patients with migraine in the U.S.[15] One assessment of the survey found that 45% of those with 0–3 MHDs and 31% of those with ≥4 MHDs were undiagnosed. The authors of the study attributed this to both lack of consultation with health care providers and a lack of diagnosis among patients seeking care.[16]

While the majority of migraine patients are treated by PCPs,[16] management of migraine is often suboptimal in the primary care setting. Physician surveys conducted at a city hospital center indicated that while PCPs are aware of the prevalence of migraine and have some knowledge of available treatments, they are often uncertain about the details of management and have difficulty translating their knowledge into effective clinical practice.[13,17] In one survey, just 40% of PCPs were familiar with the recommendations of the Choosing Wisely Campaign[18] regarding migraine diagnosis and treatment.[13]

Preventive therapy is an important aspect of care for migraine patients; however, a large proportion of patients do not receive appropriate preventive treatment. The OVERCOME study determined that among patients considered eligible for preventive treatment (3.6% of those with 0–3 MHDs, 91.5% of

those with ≥4 MHDs), the number of patients using preventive medication was low (24% and 25%, respectively).[16] This deficiency in care leads to a greater number of headache days, higher morbidity, and increased costs.[14]

Clinicians are often not up to date on evidence-based guidelines for preventive treatment. According to one physician survey, 72% of PCPs reported being unaware of or only slightly aware of the American Academy of Neurology (AAN)/American Headache Society (AHS) guidelines for migraine prevention. Additionally, many PCPs described frequently referring patients for treatments that were not level A evidence-based; these included special diets (60%), acupuncture (50%), physical therapy (30%), and psychoanalysis (20%). Nearly one-fifth (19%) prescribed migraine preventive medications minimally or not at all. When asked about their reasons for not using preventive medications, responding clinicians expressed the belief that the drugs lack efficacy, as well as fears regarding potential side effects.[17] Additionally, a wide variety of medications in different drug classes may potentially be used to reduce headache frequency, which can be intimidating for those clinicians beginning to develop treatment plans for their patients.[14]

Acute treatment for migraine remains suboptimal, as well. Results from the OVERCOME study indicated that opioid use among patients with migraine was greater than that of triptan use. The proportion of patients who reported ever using opioids for migraine was 41% of those with 0–3 MHDs and 55% of those with ≥4 MHDs; 30% and 42%, respectively, reported ever using a triptan. The "preponderance of opioids relative to triptans continues to be a vexing problem,"[16] according to the study investigators.

As with preventive treatment, there is a need for education among clinicians with respect to acute migraine therapy. According to one physician survey, only 34% of the PCPs questioned recognized that opioids could lead to medication-overuse headache (MOH).[13] Another survey indicated low awareness among PCPs that triptans can cause MOH.[17]

Poor acute treatment is associated with worsening of the disease; low efficacy acute treatment of episodic migraine has been linked to a 2-fold increased risk of new onset chronic migraine (odds ratio [OR], 2.55; 95% confidence interval [CI], 1.42–4.61).[19] The resulting need for additional treatment and further loss of productivity leads to substantial direct and indirect costs.[8]

The AHS has issued a statement providing updated guidance on the treatment of migraine in adults.[20] For migraine prevention, according to the AHS guidelines (based on the AAN scheme for classification of evidence for efficacy), the following oral pharmacotherapies have established efficacy and should be offered: antiepileptic drugs (divalproex sodium, valproate sodium, topiramate); the beta-blockers metoprolol, propranolol, and timolol; and frovatriptan (for short-term prevention of menstrual migraine). The following prescription treatments are probably effective and should be considered for migraine prevention: tricyclic antidepressants (amitriptyline, venlafaxine); the beta-blockers atenolol and nadolol; and the angiotensin receptor blocker candesartan.[20] Additionally, the injectable botulinum toxin onabotulinumtoxinA is approved in the U.S. for prevention of chronic migraine.[20]

According to current AHS guidelines, acute treatment should be offered to all patients with migraine.[20] Evidence-based medications for acute treatment include both over-the-counter and prescription drugs. These can be grouped into 5 classes of agents: triptans, nonsteroidal anti-inflammatory drugs (NSAIDs), barbiturate-containing analgesics, opioids, and ergot alkaloids. Antiemetics, muscle relaxants, simple analgesics, and analgesic combinations may also be used for acute treatment.[10] The AHS guidelines recommend that NSAIDs (including aspirin), nonopioid analgesics, acetaminophen, or caffeinated

analgesic combinations (e.g., aspirin + acetaminophen + caffeine) should be used for mild-to-moderate attacks and migraine-specific agents (triptans, dihydroergotamine [DHE]) should be used for moderate or severe attacks, as well as for mild-to-moderate attacks that show poor response to NSAIDs or caffeine-containing combinations.[20]

Additionally, the AHS guidelines recommend that clinicians consider using nondrug therapy options such as neuromodulation and behavioral treatments, which have been shown to be effective for both preventive and acute treatment of migraine.[20] Neuromodulation treatments use noninvasive devices to modulate pain mechanisms involved in headache by stimulating the central or peripheral nervous system with a magnetic field or electric current.[21] Biobehavioral therapies for migraine include cognitive behavioral therapy, biofeedback, and relaxation therapies.[20] Patients who have not adequately responded to, have contraindications to, or demonstrate poor tolerance to pharmacotherapy, as well as those patients who prefer nondrug therapies, may benefit from nonpharmacologic treatments.[20]

**Gap #2: Clinicians may not be aware of current guidelines for using new targeted therapies to improve care for patients who do not experience complete symptom relief with established preventive treatments.**

There is a high level of unmet needs among patients receiving established preventive treatments for migraine, as a recent global cross-sectional survey demonstrates**.** The *My Migraine Voice* study was conducted worldwide in 31 countries across North and South America, Europe, the Middle East and Northern Africa, and the Asia-Pacific region, using an online survey to assess the disease burden among patients with migraine for whom preventive treatments had failed. The survey was administered to adults with migraine who reported ≥4 MMDs in the 3 months preceding the survey, with pre-specified criteria of 90% having used preventive migraine treatment, of which 80% had a history of one or more treatment failures. Preventive treatment failure was defined as a reported change in preventive medication by a patient with migraine at least once, for any reason.[22]

Of the 11,266 patients who participated in the survey, 85% reported negative aspects of living with migraine (e.g., feeling helpless, depressed, and/or not understood), 83% reported sleeping difficulties, 74% reported spending time in darkness/isolation due to migraine (an average of 19 hours per month), and 55% indicated fear of a subsequent attack. Feeling limited in daily activities throughout all migraine phases was reported by 49% percent of respondents. An effect of migraine on one or more professional, private, or social domains was reported by 87% of respondents (51% in all domains). Fifty-seven percent indicated one or more positive aspects of migraine, such as learning to cope or becoming a stronger person. In the previous 12 months, 38% of respondents reported visiting the emergency department, and 23% reported overnight hospital stays, because of migraine.[22]

The authors of the study noted that the subset of patients reporting ≥4 MMDs and prior preventive treatment failure is of particular interest "since new preventive migraine therapies have demonstrated efficacy and safety in this population."[22] This observation underscores the need for clinicians to integrate new preventive therapies into their treatment plans, particularly for patients with difficult-to-treat migraine.

Research into the pathophysiology of migraine has enabled researchers to identify novel therapeutic targets. Based on these discoveries, new classes of mechanism-based drug therapies have been developed to treat migraine.[23] Calcitonin gene-related peptide (CGRP) is one of the major neurotransmitters released during migraine;[14] investigation of the role of CGRP in migraine has led to

the recent development of specific agents that block CGRP activity. CGRP-targeted therapies include monoclonal antibodies (mAbs) directed against CGRP or its receptor, as well as a class of small molecule CGRP receptor antagonists known as gepants.[23] In 2018, three mAbs targeting CGRP were introduced into the U.S. market for preventive treatment of migraine;[23] a fourth is currently awaiting approval by the U.S. Food and Drug Administration (FDA).[24] Additionally, two gepants are in clinical development for migraine prevention, although none are yet approved for use.[23] Table 1 summarizes the targeted therapies currently available or under clinical investigation for preventive treatment of migraine.

**Table 1.** Targeted therapies for migraine prevention.[23]

| Drug | Mechanism of Action | Administration | Status |
|---|---|---|---|
| Erenumab | mAb targeting the CGRP receptor | Subcutaneous injection; 4-week interval between administrations | FDA approved |
| Fremanezumab | mAb targeting CGRP | Subcutaneous injection; 4- or 12-week interval | FDA approved |
| Galcanezumab | mAb targeting CGRP | Subcutaneous injection; 4-week interval | FDA approved |
| Eptinezumab | mAb targeting CGRP | Intravenous infusion; 12-week interval | Under FDA review[24] |
| Atogepant | CGRP receptor antagonist | Oral | Phase 3 clinical trials[25,26] |
| Rimegepant | CGRP receptor antagonist | Oral | Phase 2/3[27] clinical trials* |
| AMG-301 | mAb targeting the $PAC_1$ receptor | Subcutaneous injection; 4-week interval | Phase 2 clinical trials[28] |

CGRP, calcitonin gene-related peptide; mAb, monoclonal antibody; FDA, U.S. Food and Drug Administration; $PAC_1$, pituitary adenylate cyclase-activating polypeptide type I.
*Also currently awaiting FDA approval for acute migraine treatment.[29]

The recently issued AHS position statement provides clinicians with updated guidance on integrating CGRP-targeted mAb therapies into clinical practice as preventive treatments for migraine.[20] However, clinicians may not yet be familiar with these recent guidelines. A physician survey showed that just 28% of PCPs were familiar with earlier AAN/AHS guidelines for migraine prevention;[13] therefore, it is likely that many are not up to date on the most recent recommendations. Noting the higher costs of mAb treatment compared with generic oral preventive medications, the AHS statement points out that it is important that clinicians be able to implement the latest recommendations.[20] Educational initiatives, such as the one proposed, will help clinicians provide care that is both cost-effective and meets current treatment goals.

The AHS statement includes recommendations for clinicians regarding selecting which adult patients should receive CGRP-targeted mAb therapies. To initiate CGRP mAb treatment, the patient should have:

- Diagnosis of migraine (International Classification of Headache Disorders [ICHD]-3)[1], with or without aura, of 4–7 MHDs and have both (a) an inability to tolerate or inadequate response to a 6-week trial of at least two of the following: topiramate, divalproex sodium/valproate sodium, beta-blockers, tricyclic antidepressants, serotonin-norepinephrine reuptake inhibitors, or other Level A or B treatments according to the 2012 AAN/AHS guidelines,[12,30] and (b) at least

moderate disability (Migraine Disability Assessment [MIDAS]>11, Headache Impact Test [HIT]-6>50);
- Diagnosis of ICHD-3 migraine, with or without aura, of 8–14 MHDs and meet the criteria outlined in (a) above; or
- Diagnosis of ICHD-3 chronic migraine and meet either the criteria outlined in (a) above or demonstrate an inability to tolerate or inadequate response to a minimum of two quarterly injections of onabotulinumtoxinA.[20]

CGRP-targeted mAbs generally show efficacy in patients who have failed to respond to prior preventive treatment, as well as in patients receiving concurrent oral preventive therapy. Tolerability profiles are similar to placebo; the most common adverse effects are injection site reactions. These drugs may be added to or used in conjunction with other oral or injectable preventive therapies for migraine; their lack of hepatic metabolism or renal clearance helps to avoid interactions with concomitant medications.[20] One potential disadvantage of mAbs is the route of administration, which is either subcutaneous injection or intravenous infusion, although some patients may prefer the less frequent dosing required for injectable agents. Shared decision-making between patient and practitioner should guide choices regarding therapy selection and delivery.[20]

Clinicians should also be aware that small molecule CGRP receptor antagonists of the gepant class are currently under clinical investigation for use in migraine prevention. Atogepant has demonstrated safety and efficacy for preventing episodic migraine headaches in a phase 2/3, dose-ranging study. The primary endpoint was the reduction from baseline in average MMDs after 12 weeks of treatment.[25] The mean change from baseline in MMDs was statistically significant for all dosages of atogepant compared with placebo ($P < 0.05$ for all comparisons).[31] A phase 3 trial is in progress.[26] Additionally, rimegepant is currently being evaluated for migraine prevention in a phase 2/3 study.[27] If gepants reach FDA approval for migraine prevention, they may provide additional targeted options, particularly for patients who prefer oral treatments to injectable therapies.

Another neuropeptide, pituitary adenylate cyclase-activating polypeptide (PACAP), is currently being investigated for its potential role in in migraine pathophysiology.[23,32] Agents targeting a specific bioactive form of this peptide (PACAP38) and one of its receptors (pituitary adenylate cyclase-activating polypeptide type I ($PAC_1$) receptor) are being studied as migraine-specific drugs.[23] AMG-301, a mAb directed to the $PAC_1$ receptor, has recently undergone a phase 2 clinical trial to evaluate its efficacy and safety in migraine prevention.[23,28]

Successful clinical management of migraine requires that clinicians apply current guidelines, including recommendations for using new preventive therapies that are likely to improve care for patients with difficult-to-treat migraine. The proposed educational activity would address the use of recently approved therapies and those in late-stage clinical development for migraine prevention.

**Gap #3: Clinicians may not be familiar with new acute treatments for migraine that may be used when other therapies are contraindicated or do not provide complete symptom relief.**

Most patients with migraine treated with oral acute prescription migraine medication have unmet treatment needs, according to a global cross-sectional survey.[33] The data were obtained from the Migraine in America Symptoms and Treatment (MAST) Study, a longitudinal, internet-based panel study that assessed symptoms, approaches to disease management, and unmet medical needs among U.S. adults with migraine. The study included adults with migraine averaging one or more MHDs over the

previous 3 months. Respondents using acute oral migraine medications were included in the analysis; those using nasal or injectable treatments were excluded.[34]

Among 15,133 respondents, the majority reported at least 1 unmet need (95.8%). A high proportion had unmet needs related to demanding attack characteristics (89.5%), or had unmet needs related to inadequate treatment response (74.1). Additional unmet needs included rapid headache onset (65.3%), headache-related disability (55.6%), inadequate 2-hours of pain freedom (49%), and headache pain recurrence within 24 hours (38.6%).[33]

Acute migraine pharmacotherapy relies heavily on non-specific analgesic agents and triptans (serotonin [5-HT]$_{1B/1D}$ receptor agonists).[35] Because of their vasoactive properties, however, triptans are contraindicated in patients with vascular risk factors and disorders such as uncontrolled hypertension, a history of cerebrovascular accidents, ischemic heart disease, and myocardial infarction.[35] Thus, a substantial number of patients may not be eligible for triptan therapy. In particular, triptans may be contraindicated in many older patients due to cardiovascular and cerebrovascular risk factors.[14]

Additionally, there remain unmet treatment needs among patients receiving acute treatment with triptans,[36] as demonstrated by an Italian study involving a 2-year longitudinal analysis of adults with triptan-treated migraine.[37] Of the 10,270,683 patients considered, 8 out of 1000 were treated with triptans. Among those using triptans, 38.2% suffered from migraines and had unmet medical needs.[37]

Oral CGRP antagonists of the gepant class have demonstrated efficacy in the acute treatment of migraine. The small molecule selective serotonin (5-HT$_{1F}$) receptor agonists known as ditans have also shown efficacy as acute migraine treatments.[23] Unlike triptans, gepants and ditans do not cause vasoconstriction and thus may be particularly useful in patients with cardiovascular contraindications to triptans.[20]

The recently issued AHS position statement provides clinicians with updated guidance on integrating emerging acute treatments for migraine into clinical practice, including gepants and ditans.[20] However, as drugs in the gepant and ditan classes are still awaiting approval or have only recently been approved for the acute treatment of migraine, clinicians may not be up to date regarding their use. Physician surveys show that many PCPs were not aware of previous recommendations for managing migraine patients.[13] Additionally, new medications will most likely be more costly than, for example, oral triptans for which generic versions are available. Therefore, it is important that clinicians apply the most recent guidelines for use of new acute medications, to achieve care that is cost-effective and appropriate to patient needs.[20]

A recent survey indicates that approximately 30% of patients with migraine may qualify for novel medications for acute migraine therapy[15] according to the current AHS criteria.[20] The study included the migraine Treatment Optimization Questionnaire (mTOQ) as a measure of the efficacy of acute treatment. Overall, 27% of patients with 0–3 MHDs and 33% of those with ≥4 MHDs appeared to be eligible for new acute medications. Additionally, 30.4% of the eligible patients with 0–3 MHDs reported using an oral triptan, despite either it being contraindicated or showing poor or very poor treatment efficacy.[38] These data illustrate the need for awareness among clinicians regarding current guidelines for acute migraine treatment.

In October, 2019, lasmiditan was the first ditan to receive FDA approval for the acute treatment of migraine in adults.[39] In a phase 3 randomized study, lasmiditan (at doses of 200 mg and 100 mg) was

demonstrated to be efficacious and well-tolerated in the treatment of acute migraine in patients with a high level of cardiovascular risk factors. At 2 hours after dosing, more patients who received 200 mg lasmiditan were free of headache pain compared with those who received placebo (32.2% vs. 15.3%; OR, 2.6; 95% CI, 2.0–3.6; $P < 0.001$); patients who received 100 mg lasmiditan achieved similar results (28.2%; OR, 2.2; 95% CI, 1.6–3.0; $P < 0.001$).[40] Additionally, findings from the SAMURAI and SPARTAN phase 3 trials demonstrated that lasmiditan was more efficacious than placebo for the acute treatment of migraine in patients concurrently using medications for migraine prevention. Among patients using preventive medications, significantly more patients were free of pain at 2 hours, at all lasmiditan doses, compared with placebo ($P < 0.05$). The rates of adverse events were similar in patients using preventive therapies and those who were not.[41]

Two gepants, ubrogepant and rimegepant, are currently awaiting FDA approval[29] for use in the acute treatment of migraine. The efficacy and tolerability of ubrogepant compared with placebo for acute treatment of a single migraine attack was evaluated in a multicenter phase 3 clinical trial (ACHIEVE II). Results published in November, 2019, demonstrate that among adults with migraine, acute treatment with ubrogepant led to greater rates of pain freedom at 2 hours at doses of 50 mg and 25 mg compared with placebo (absolute difference for 50 mg vs. placebo, 7.5%; 95% CI, 2.6–12.5%; $P = 0.01$; 25 mg vs. placebo, 6.4%; 95% CI, 1.5–11.5%; $P = 0.03$), and absence of the most bothersome migraine-associated symptom at 2 hours at a dose of 50 mg (absolute difference for 50 mg vs. placebo, 11.5%; 95% CI, 5.4–17.5%; $P = 0.01$).[42]

Rimegepant has been evaluated for efficacy, safety, and tolerability in the acute treatment of migraine. In a phase 3 trial, a single 75 mg dose of rimegepant was shown to be more efficacious than placebo. At 2 hours after dosing, rimegepant was significantly more efficacious than placebo for freedom from pain (21% vs. 11%; $P < 0.0001$; risk difference 10; 95% CI, 6–14) and freedom from the most bothersome symptom (35% vs. 27%; $P = 0.0009$; risk difference 8; 95% CI, 3–13). Tolerability for rimegepant was similar to placebo. The most common adverse events were nausea (rimegepant, 2%; placebo, 1%) and urinary tract infection (rimegepant, 1%; placebo, 1%).[43]

Another gepant, vazegepant, is currently being evaluated in a phase 2/3 clinical trial for intranasal use in the acute treatment of migraine.[44]

According to the most recent AHS guidelines, patients are eligible for lasmiditan, ubrogepant, rimegepant, or a neuromodulation device if: (a) triptans are contraindicated; or (b) they have failed to respond to or tolerate at least 2 oral triptans, as determined by either a validated patient reported outcome questionnaire (e.g., mTOQ, Migraine Assessment of Current Therapy [Migraine-ACT], Patient Perception of Migraine Questionnaire-Revised [PPMQ-R], Functional Impairment Scale [FIS], or Patient Global Impression of Change [PGIC]), or attestation by a healthcare provider.[20]

Clinicians should design treatment plans to address the needs of individual patients; these may combine established and emerging treatments. To best manage disease, clinicians should apply evidence-based medicine, which requires that practitioners remain up to date on recent approvals and clinical trials.[20] The proposed educational activity would address therapies that are recently approved or in late-stage clinical development for acute migraine treatment.

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