REPORT

Migraine Overview and Summary of Current and Emerging Treatment Options

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Introduction to Migraine

The reach of migraine headaches spans the globe.[1] Migraine is sometimes confused with other types of headache, such as tension headache. Those with migraines may not receive the correct diagnosis, adequate treatment, or proper support from family, friends, or coworkers. Migraine treatment usually consists of acute or abortive medications, whereas preventive medications are used by a minority of individuals with migraine. The triptans, or selective serotonin 5-$HT_{1B/1D}$ receptor agonists, were approved for acute migraine therapy in the 1990s.[2] The calcitonin gene-related peptide (CGRP) antagonists approved in 2018 are the first class of medications specifically approved for migraine prevention, contrary to all the other migraine agents that are also used for other conditions. There are 3 newly approved CGRP monoclonal antibodies (mAbs) and a fourth mAb, a ditan, and 2 CGRP receptor antagonists (gepants) in development for migraine treatments. Erenumab, fremanezumab, and galcanezumab are newly approved CGRP mAbs for the prevention of migraines in adults. The emerging migraine treatments include the mAb eptinezumab, the ditan lasmiditan, and gepants ubrogepant and rimegepant.

Prevalence

Migraines are a leading cause of disability and suffering worldwide.[3] Migraine was ranked as the sixth cause of years lost due to disability globally in 2013.[3] Head pain or headache accounted for 3% of emergency department (ED) visits annually and was the fourth or fifth leading reason for patients to visit the ED.[1] In a review by Burch et al, various US government health surveys were analyzed to examine the prevalence and impact of migraines. According to the review, 1 in 6 individuals in the United States are affected by migraines. Contrary to most chronic conditions, people who are usually healthy and young or middle-aged are largely affected. In Americans aged 15 to 64 years, approximately 1 in 6 people and 1 in 5 women have reported either severe headaches or migraines in the past 3 months. The review also reported the highest migraine prevalence in people aged 18 to 44 years. Of this group, 17.9% experienced a migraine within the previous 3 months. The prevalence

ABSTRACT

Migraine is a leading cause of disability worldwide. Approximately 15% of Americans experience migraines. Most people who have migraines feel that people who do not have them often underestimate their condition. Migraines affect people's quality of life and ability to participate in work, family, and social events. A new class of medication, calcitonin gene-related peptide (CGRP) antagonists, has been approved for migraine prevention in adults. The newly approved CGRP antagonists are erenumab, fremanezumab, and galcanezumab, while eptinezumab looks to 2020 for approval. Lasmiditan, ubrogepant, and rimegepant are currently emerging acute migraine therapies that may be added to the arsenal of current migraine management.

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of migraines decreases as people age. For those aged 45 to 64 years, the prevalence was 15.9%, followed by 7.3% for those aged 65 to 74 years and 5.1% in individuals 75 years and older.[1]

When examining other factors, Burch et al discovered differences regarding gender, ethnicity, work status, income, and insurance type.[1] Women were more prone than men to experience migraines. In 1 of the government surveys examined, the 2015 National Health Interview Study reported the overall prevalence of migraines or severe headache to be 15.3%, with 20.7% prevalence in women and 9.7% prevalence in men. This has remained stable when compared with data from 2006 to 2015. In contrast to previous reports, 18.4% of native Americans (Alaskan natives or American Indians) were the most affected ethnicity compared with white, black, or Hispanic individuals.[4,5] People who worked full-time reported the least number of severe headaches or migraines (13.2%) compared with people working part-time (15.6%), those who were unemployed or had never worked (16.6%), and those who were unemployed but had previously worked (21.4%). Migraine prevalence was highest in those living below the poverty level (21.7%) and with an annual household income of less than $35,000 (19.9%). This may be explained by increased exposure to migraine triggers and decreased access to treatment and healthcare resources. Burch et al divided the findings relative to insurance by age in 2 groups, younger than 65 years and 65 years and older. In people younger than 65 years, those with Medicaid had the highest migraine prevalence (26.0%) as compared with those with no insurance (17.1%) and private insurance (15.1%). In those 65 years and older, participants with both Medicare and Medicaid coverage had the highest prevalence at 16.4% compared with those with Medicare Advantage (6.7%), Medicare only (5.8%), private insurance (4.4%), and other coverage (5.9%). The estimate for the uninsured patients in this age range was considered unreliable due to a relative standard error over 50% and therefore not reported.[3]

Headache Types

There are several headache classifications outlined by the International Headache Society Headache Classification Committee.[6] The more common headaches are outlined in **Table 1**.[6] Migraines are classified as with or without aura. Migraines with aura have fully reversible sensory, visual, or other symptoms related to the central nervous system. The aura usually begins before migraine onset but may occur with headache onset or after the headache has stopped. The most common type of aura in patients with migraine is visual aura, followed by sensory disturbances, and, less frequently, speech disturbances. Sensory disturbances may include a pins-and-needles sensation that slowly travels from a point of origin and affects 1 side of the tongue, body, and/or face. It may also be accompanied by numbness; however, numbness may also occur independently as the only symptom. Speech disturbances are usually aphasic and more difficult to categorize. The prodromal phase occurs hours to days before a headache and/or as a postdromal phase after the headache has resolved. Pro- and postdromal symptoms may include pain, fatigue, neck stiffness, hypo- or hyperactivity, food cravings, repetitive yawning, and/or depression. Prodromal symptoms may also include various combinations of pallor, blurred vision, fatigue, yawning, difficulty concentrating, nausea, and sensitivity to sound and/or light.[6]

Episodic migraines are defined as headaches occurring less than 15 days per month.[7] Chronic migraines are defined as headache occurring on 15 or more days per month for more than 3 months with at

TABLE 1. Headache Types[6]

Headache Type	Location	Type of Pain	Intensity	Duration	Aggravating Factors	Symptoms
Cluster	Unilateral	Orbital, supraorbital, and/or temporal	Severe to very severe	15-180 minutes	N/A	• Lacrimation • Nasal congestion • Rhinorrhea • Ptosis and/or eyelid edema • Restlessness/agitation
Migraine	Unilateral	Pulsating	Moderate to severe	4-72 hours	Physical activity	• Nausea • Vomiting • Photophobia • Phonophobia
Sinus	Paranasal sinuses, may be unilateral	Pulsating, pressing/tightening (nonpulsating)	Mild to severe	Resolves when rhinosinusitis resolves	• Rhinosinusitis onset • Applied pressure	• Purulent nasal discharge and/or other features diagnostic of acute rhinosinusitis
Tension-type	Bilateral	Pressing/tightening (nonpulsating)	Mild to moderate	30 minutes to 7 days	N/A	• No nausea or vomiting • No more than one of photophobia or phonophobia

Note: Clinical judgment is crucial when evaluating headache disorders; there are cases when headache types may overlap, making differentiating difficult.

least 8 days having migraine features.[6] Transformed migraines is an additional term used to describe chronic migraines because they evolve from episodic migraines.[7] Medication-overuse headaches are the most common cause of symptoms suggestive of chronic migraine.[6] It is defined as taking opioids, triptans, ergotamine, or combination analgesics for more than 9 days monthly, and aspirin, acetaminophen, or nonsteroidal anti-inflammatory drugs (NSAIDs) for more than 14 days monthly.[6] Since the use of combination butalbital products or opioids for fewer than 9 days monthly may increase migraine frequency, these medications should generally be avoided.[7,8] Once the medication is withdrawn, approximately 50% of patients return to episodic migraines, suggesting the patient was misdiagnosed with chronic migraines.[6]

Fewer than 10% of women experience migraines associated with their menstrual cycles. Most women with migraines do not have an aura with menstrual migraines. These attacks are usually coupled with more severe nausea and last longer than nonmenstrual cycle attacks.[6]

Risk Factors

There are several risk factors associated with migraine occurrence. Nonmodifiable factors include genetics, gender, and age. The probability of migraines is 40% in a person with 1 parent with migraines and 75% if both parents experience migraines. Adult women are 3 times more likely than men to have migraines. However, in preadolescents, migraines are more common in boys. Migraines usually have an onset in late childhood/early adolescence, and the prevalence peaks in individuals in their 50s, with notable decreases as people enter their 60s and 70s and rare occurrences in people 80 years and older.[9]

Ineffective acute treatment,[10] acute migraine medication overuse,[5,7,11-16] obesity,[17,18] and stressful life events[5,19] are modifiable risk factors that may increase the risk of progression from episodic to chronic migraines.[19] It is also important to note that patients who did not believe they could influence their headache or felt that their headache was due to fate or chance are more likely to insufficiently manage their headaches, resulting in poorer overall disability.[20,21] These factors highlight the need for education on methods to best manage and cope with migraines. Healthcare professionals should educate patients on protective factors that may increase the migraine threshold, including the use of migraine-preventive medication,[22] physical exercise, and stress management.[19]

Migraine triggers are patient specific. Examples include food additives, caffeine, artificial sweeteners, and delayed or missed meals. To determine the probability of an item being a trigger, patients should avoid the item for at least 4 weeks and then slowly reintroduce it, keeping in mind that migraines may start 24 to 48 hours before headache onset.[9]

Stigma and Impact on the Individual

In 2017, Neilsen conducted a survey sponsored by Eli Lilly, resulting in the Migraine Impact Report.[23,24] The report examined the economic, physical, and social impact of migraines. Of the 1018 US adult respondents, 518 were medically diagnosed with migraine, 200 respondents knew a person who experienced migraines, and 300 members of the community did not know anyone with migraines. Respondents who had given birth ranked the pain of their worst migraine higher than childbirth pain (8.6 vs 7.3 based on a scale of 1 to 10). Additionally, respondents with medically diagnosed migraines ranked their worst migraine pain (8.6) higher than pain associated with broken bones (7.0) and kidney stones (8.3). According to the report, people without migraines regularly underestimated the average migraine length (20.7 hours vs 31 hours) and pain. The average pain rating for a typical migraine determined by those without migraines was 6.2 compared with 7.1 by those with migraines. Among people with migraines, 91% indicated that people without migraines are not fully aware of the disease severity. Sixty-two percent also reported masking the full impact of their migraines when at school or work.

The reporting for those with migraine demonstrated their concerns with the effect of the condition on their lives. Some examples of this include the following[24]:

- 54%: "I worry that people think I'm lazy because of the impact migraines have on my life and ability to perform tasks."
- 40%: "I have been told to 'get over it' when I am experiencing a migraine attack."
- 29%: "I sometimes feel like my job is in jeopardy because of migraines."
- 28%: "I have been made fun of for having migraines."

Most people with migraines also indicated that their migraine attacks frequently interfere with work productivity and advancement, attending important events, and spending time with family and friends, resulting in the addition of more stress, which is a migraine trigger. These statistics highlight the stigma connected to and lack of awareness about migraines.

Migraine Pain Theories (vs Vascular Theory)

The exact mechanism for migraine generation is not completely understood. The vascular theory proposed that there was vasoconstriction of the intracerebral arterials, followed by extracranial vasodilation and then the associated pain with the migraine.[25] This hypothesis was debunked, and findings from Amin et al purported that the dilation of extracranial arterial was unlikely to play a role in migraines.[25] The now accepted mechanism for migraine headaches is the neurovascular hypothesis. This theory posits that migraine pain originates from the trigeminovascular system, which is the system that allows for nociceptive signals from the meningeal

blood vessels to transmit to higher centers of the central nervous system. When activated, the trigeminal sensory nerves trigger the release of vasoactive neuropeptides (eg, CGRP, neurokinin A, and substance P). The release of these vasoactive neuropeptides triggers vasodilation and dural plasma extravasation, leading to neurogenic inflammation. Pain impulses are then transmitted along the trigeminovascular system to the trigeminal nucleus caudalis, then to higher cortical pain centers of the brain.[26,27] Possessing a more enlightened view of the pathophysiology of migraine headache has allowed for new research into migraine treatment options. This greater understanding has led to the development of the new CGRP receptor antagonists and the serotonin 5-HT_{1F} agonists (ditans) for migraine treatment. There will be further discussion regarding the mechanisms these new agents play in migraine treatment.

TABLE 2. Migraine Prophylaxis Medications[28,31,32]

Medication	Dosage	Level of Evidence[a]
Divalproex/ sodium valproate	500-1500 mg/day PO	A
Metoprolol	50-200 mg/day PO	
Propranolol	80-240 mg/day PO	
Timolol	20-30 mg/day PO	
Topiramate	25-100 mg/day PO	
Amitriptyline	10-150 mg/day PO	B
Atenolol	50-200 mg/day PO	
Nadolol	40-240 mg/day PO	
Venlafaxine ER	37.5-150 mg/day PO	
Candesartan	Dosing varies	C
Carbamazepine		
Clonidine		
Cyproheptadine		
Guanfacine		
Lisinopril		
Nebivolol		
Pindolol		
Onabotulinum toxin A	Recommended total dose 155 units. Administer 5 units/0.1 mL per site at 31 total IM injection sites	U
Short-term Prevention Associated With Menstruation		
Frovatriptan	2.5 mg bid perimenstrually, loading dose was used	A
Naratriptan	1 mg bid for 5 days perimenstrually	B
Zolmitriptan	2.5 mg bid or tid perimenstrually	

bid indicates twice daily; ER, extended release; IM, intramuscular; PO, by mouth; tid, 3 times daily.
[a]Level of evidence: A = established as effective, B = probably effective, C = possibly effective, U = conflicting or inadequate evidence.
Adapted from Loder E, Burch R, Rizzoli P. The 2012 AHS/AAN guidelines for prevention of episodic migraine: a summary and comparison with other recent clinical practice guidelines. *Headache*. 2012;52(6):930-945. doi: 10.1111/j.1526-4610.2012.02185.x. © 2012 American Headache Society.

Overview of Guidelines and Current Treatment Options

Prophylaxis

Preventive migraine therapy is used daily to reduce the frequency, severity, and duration of migraine attacks.[28] Preventive therapy should be considered for patients with migraines who routinely have more than 6 headache-days per month, or in other special circumstances,[29] such as recurring migraines producing disability, acute therapies that are ineffective or contraindicated, when serious adverse reactions are produced, or even when it is the patient's preference.[30] Preventive migraine agents that are FDA approved include propranolol, timolol, divalproex sodium, and topiramate. Other agents possess established efficacy, but lack FDA approval. Current guidelines address which agents are effective in migraine prevention, but a lack of evidence prohibits the ability on how to choose 1 option over another. Preventive therapy is chosen based on adverse effect profiles and the patient's coexisting comorbidities (eg, comorbid hypertension can be treated with propranolol or timolol; comorbid depression or insomnia can be treated with tricyclic antidepressants; comorbid seizure disorders or bipolar disorder can be treated with anticonvulsants).[28,30] Full therapeutic effects take up to 6 months to be achieved. Selected medications used for migraine prophylaxis are included in **Table 2**.[28,31,32] This table does not include every agent that has been considered for use in migraine prevention. For this and additional tables, please refer to individual prescribing information or online clinical decision support resources for more complete dosing information.

Treatment of Acute Migraine

There are 2 types of acute treatment strategies: stratified and step. The treatment type is based on attack severity and patient-specific factors. Stratified treatment is preferred over step-care treatment.[7,32] A stratified treatment method is optimized when patients can discern their headache and which medication it is most likely to respond to. Patients should be prescribed medications for mild and moderate to severe migraines.[8] Stratified treatment was found to have reduced time to headache resolution, lowered headache attack treatment costs, significantly reduced disability time, and slightly lowered direct healthcare costs at 1 year.[33]

On the other hand, step therapy has the advantage of medication synergy. An example of medication synergy would be a patient who initially takes an NSAID before the migraine reaches its peak and then takes a triptan or dihydroergotamine (DHE) as soon as possible. However, step therapy may result in a delay in headache resolution.

The American Headache Society (AHS) developed guidance for the treatment of acute migraines.[34] Additionally, Pringsheim et al published recommendations illustrating how to apply the AHS guidelines to treat adult patients with acute migraines. For mild attacks, acetaminophen, aspirin, and NSAIDs are recommended.[8] The powdered form of diclofenac and effervescent aspirin have a faster onset than tablets.[8,35] Triptans or DHE are recommended for the treatment of a moderate to severe migraine.[7] Triptans are usually preferred over DHE because of the wider availability of dosage forms, tolerability, adverse effect profile, and better efficacy.[8] If a patient does not respond well to a triptan, another triptan should be tried for a future attack.[8] For migraines with maximum pain with rapid onset and migraines with nausea and vomiting, nasal and injectable DHE, intranasal and subcutaneous sumatriptan, and intranasal zolmitriptan may be more effective.[8] Lists of medications used to treat acute migraines are included in **Table 3**[36] and **Table 4**.[37]

Patients who initially took a triptan with relief and developed a recurrent migraine, defined as the return of a more severe headache within 24 hours, should take a second triptan dose. If patients have an inconsistent or incomplete response to triptans or suffer from frequent recurrent migraines, sumatriptan with an NSAID, such as naproxen, should be considered. There is some evidence that this may decrease headache recurrence and response.[8,38]

Contraindications

Patients with migraines may have coexisting conditions limiting the medications available for treatment. In patients with migraine with brainstem aura, coronary artery disease, hemiplegic migraine, peripheral vascular disease, and uncontrolled hypertension, the use of DHE and triptans is contraindicated. NSAIDs should not be used in patients with a history of gastrointestinal bleeding and peptic ulcer disease and should be used cautiously in those with cardiovascular disease (CVD) or an increased risk of CVD. Zolmitriptan, rizatriptan, and sumatriptan should not be used within 14 days of taking monoamine oxidase inhibitors.[8]

Gaps in Care and Shortcomings of Currently Available Treatments

The therapies addressed in the guidelines may not be effective in all patients, may have contraindications related to cardiovascular conditions in some patients, and may be nonspecific or poorly tolerated.[39] One study reported that 50% of patients were not

TABLE 3. Acute Migraine Treatment[36]

Medication	Dosage	Level of Evidence[b]
Acetaminophen (APAP)[a]	1000 mg PO	A
Almotriptan	12.5 mg PO	
APAP/Aspirin (ASA)/caffeine[a]	500/500/130 mg PO	
ASA[a]	500 mg PO	
Butorphanol[a]	1 mg nasal spray	
Diclofenac	50, 100 mg PO	
Dihydroergotamine (DHE)	• 2 mg nasal spray • 1 mg pulmonary inhaler	
Eletriptan	20, 40 mg PO	
Ibuprofen	200, 400 mg PO	
Naproxen[a]	500, 550 mg PO	
Naratriptan[a]	1, 2.5 mg PO	
Rizatriptan[a]	5, 10 mg PO	
Sumatriptan	• 25, 50, 100 mg PO[a] • 10, 20 mg nasal spray[a] • 6.5-mg patch • 4, 6 mg SC[a]	
Sumatriptan/naproxen	85/500 mg PO	
Zolmitriptan	• 2.5, 5 mg nasal spray • 2.5, 5 mg PO[a]	
Chlorpromazine IV[a]	12.5 mg IV	B
Codeine/APAP[a]	25/400 mg PO	
DHE[a]	1 mg IV, IM, SC	
Droperidol IV	2.75 mg IV	
Ergotamine/caffeine[a]	1/100 mg PO	
Flurbiprofen[a]	100 mg PO	
Isometheptene[a]	65 mg PO	
Ketoprofen	100 mg PO	
Ketorolac	30-60 mg IV/IM	
Metoclopramide IV[a]	10 mg IV	
$MgSO_4$ IV (migraine with aura)	1-2 g IV	
Prochlorperazine[a]	• 10 mg IV/IM • 25 mg PR	
Tramadol/APAP	75/650 mg PO	

IM indicates intramuscular; IV, intravenous; $MgSO_4$, magnesium sulfate; PO, by mouth; PR, per rectum; SC, subcutaneous.
[a]According to the 2000 American Academy of Neurology evidence review.
[b]Level of Evidence: A = Established as effective, B = Probably effective, C = Possibly effective.

(continued)

satisfied with how well their current therapy prevented the recurrence of pain and approximately 80% would consider another acute therapy.[7,39] Additionally, medication-overuse headaches rank in the top-20 disabling conditions globally.[40] Migraine experts have been discussing the need for new migraine treatment options for quite some time, specifcally due to contraindications, adverse effects, and tolerabilty of currently available migraine treatments. The new migraine preventive agents already approved may find a place in therapy by possessing more favorable safety and tolerability profiles. The emerging migraine agents yet to be approved may also fall into the category of more favorable safety and tolerability profiles, based on the mechanisms of action each agent is targeting.

TABLE 3. Acute Migraine Treatment[36] *(continued)*

Medication	Dosage	Level of Evidence[b]
Butalbital[a]	50 mg PO	C
Butalbital/APAP/caffeine[a]	50/325/40 mg PO	
Butalbital/APAP/caffeine/codeine[a]	50/325/40/30 mg PO	
Butorphanol IM[a]	2 mg IM	
Codeine[a]	30 mg PO	
Dexamethasone IV	4-16 mg IV	
Ergotamine[a]	1-2 mg PO	
Lidocaine[a]	4% intranasal	
Meperidine IM[a]	75 mg IM	
Methadone IM[a]	10 mg IM	
Phenazone	1000 mg PO	
Valproate IV	400-1000 mg IV	

IM indicates intramuscular; IV, intravenous; $MgSO_4$, magnesium sulfate; PO, by mouth; PR, per rectum; SC, subcutaneous.
[a]According to the 2000 American Academy of Neurology evidence review.
[b]Level of Evidence: A = Established as effective, B = Probably effective, C = Possibly effective.

TABLE 4. Treatment of Acute Migraine in the ED[37]

Medication	Dosage	Level of Evidence[a]
Metoclopramide IV	10-20 mg	B
Prochlorperazine IV	10 mg	
Sumatriptan SC	6 mg	
Acetaminophen IV	1 g	C
Chlorpromazine IV	0.1-25 mg	
Diclofenac IM	75 mg	
Droperidol IM	2.5-8.25 mg	
Haloperidol IV	5 mg	
Ketorolac IM, IV	30-60 mg	
Valproic acid IV	500-1000 mg	
Prevention of Recurrence in Adults Discharged From the ED		
Dexamethasone IV	8-24 mg	B

ED indicates emergency department; IM, intramuscular; IV, intravenous; SC, subcutaneous.
[a]Level of Evidence: A = Established as effective, B = Probably effective, C = Possibly effective.

Self-treatment and Diagnostic Delay

The CaMEO study reported that 41% of patients with chronic migraines were currently seeing a healthcare provider for their migraines.[41] Just 25% of patients in this group reported getting an accurate diagnosis of either transformed or chronic migraines. Additionally, 44% of those diagnosed with migraines received both acute and preventive medications. When considering all 3 barriers, 4.5% of patients reported actively seeing a healthcare provider for their migraines, being diagnosed with migraines, and receiving both acute and preventive therapy.[41] On the other hand, patients with episodic migraines had increased percentages of the 3 barriers. Forty-six percent of patients with episodic migraines reported actively seeing a healthcare provider, with 87% receiving a migraine diagnosis and 67% of the diagnosed patients receiving treatment.[42] This study emphasizes the need to overcome these barriers, particularly because early diagnosis and management improve long-term prognosis.[9]

New Therapies Based on Migraine Pathology

The physiologic method leading to the development of chronic migraines is not fully understood.[19] Descending pain-modulating network dysfunction and oxidative stress may be caused by more recurrent stimulation within the periaqueductal gray (PAG) area, leading to more frequent migraine attacks.[7] This may also cause increased sensitivity to environmental and physiologic factors that trigger migraines, thereby lowering the migraine threshold for subsequent migraines.[19] The trigeminovascular system is activated and sensitized, leading to pain[43] and elevated levels of cranial substance P, CGRP, and pituitary adenylate cyclase-activating peptide.[39,44-47] The biomarkers CGRP and vasoactive intestinal peptide have higher interictal levels in patients with chronic versus episodic migraines, implying changes in interictal activity in the cranial and trigeminal autonomic system in patients with chronic migraines.[19,48,49]

5-HT$_{1F}$ as a Treatment Target

Unlike 5-HT and 5-HT targeted by the triptans, 5-HT is a nonvascular serotonergic non-triptan receptor that does not have effects on cerebral microvascular smooth muscle.[50,51] This suggests that 5-HT has no role in vasoconstriction of the microcirculation of the human brain.[50,51] As a result, it may be an option for patients with CVD who are not able to take triptans.[50,51] Lasmiditan is highly selective for the 5-HT receptor agonist, targeting both peripheral and central 5-HT receptors.[52] By activating the 5-HT receptor, the activation of the trigeminal neurons is blocked, thus inhibiting the acute migraine pathway.[52] The ditan class differentiates itself from triptans by being highly selective for the 5-HT receptors and lacking vasoconstrictor properties.

CGRP as a Treatment Target

The CGRP receptor is found in both peripheral and central neurons. Exogenous CGRP can cause delayed migraine-like attacks and acute headaches in people with migraines.[53] Consequently, CGRP has become a major target of migraine therapeutics for both acute attacks and prevention. Thalamic activity in response to trigeminal nociceptive input is controlled by CGRP receptor antagonists.[19,54] One potential mechanism of the 5-HT receptor agonists, triptans, includes a decrease in the release of CGRP.[39,55,56] The gepants, ubrogepant and rimegepant, are small-molecule CGRP receptor antagonists, whereas CGRP mAbs are large-molecule CGRP receptor or ligand antagonists. CGRP antagonists inhibit vasodilation and neurogenic inflammation by blocking the release of CGRP at all locations within the migraine pathway, thus acting as a migraine preventive agent.[57]

Newly Approved and Emerging Treatment Options

In 2018, 3 CGRP mAbs were FDA approved for the prevention of migraines in adults: erenumab, fremanezumab, and galcanezumab. They are all administered subcutaneously (SC) monthly, with an additional quarterly dosing regimen for fremanezumab. The most common adverse effects are injection-site reactions due to the SC administration. The trials conducted with these medications showed a greater reduction compared with placebo in the average number of migraine-days monthly and in percentage of participants with at least a 50% reduction in migraine-days monthly in patients with both episodic and chronic migraines.[58-65] Several randomized trials, including several CGRP antagonists, have demonstrated promising results at migraine prevention; data from some of these trials are discussed below for each current/emerging agent.

Currently, there are 4 medications that have or are currently in phase 3 trials and may be submitted to the FDA for review in 2019. Lasmiditan is an orally administered 5-HT receptor agonist being investigated for the treatment of acute migraines. Eptinezumab is a fourth CGRP mAb being investigated for migraine prevention. The CGRP receptor antagonists, ubrogepant and rimegepant, are being studied for acute treatment in patients with migraines. Information about these newly approved and emerging treatments is available in **Table 5**.[60-82]

Newly Approved CGRP Monoclonal Antibodies

Erenumab-aooe (Aimovig)

On May 17, 2018, erenumab became the first FDA-approved CGRP antagonist approved for migraine prevention in adults.[66] It is an IgG2 CGRP receptor blocker. The recommended dose is 70 mg SC once monthly, although some patients may benefit from a 140-mg dose administered as 2 successive 70-mg doses. The white cap of the prefilled autoinjector and the gray needle cap contain the latex derivative dry natural rubber, which may cause an allergic reaction in patients with latex allergies. In addition to the injection-site reactions common with SC-administered CGRP antagonists, constipation is also a common adverse drug reaction.[67]

TABLE 5. New and Currently Emerging Migraine Therapies[60-82]

Medication	FDA Approved	Formulation	Indication	Dosing	Common AEs
Erenumab	Yes	SC	Prevention	70 mg monthly, some may benefit from 140 mg monthly	Infusion reaction and constipation
Fremanezumab				225 mg monthly or 675 mg every 3 months	Infusion reaction
Galcanezumab				240 mg loading dose (2 consecutive injections of 120 mg); followed by monthly dose of 120 mg	
Eptinezumab	No	IV	Prevention	No FDA-approved dosing	URI and UTI
Lasmiditan		Oral	Acute		Dizziness, somnolence, paresthesia, fatigue, and nausea
Rimegepant					Nausea and UTI
Ubrogepant					Nausea and dizziness

AE indicates adverse effect; IV, intravenous; SC, subcutaneous; URI, upper respiratory infection; UTI, urinary tract infection.

ARISE (EPISODIC MIGRAINE)

The placebo-controlled, randomized, double-blind phase 3 ARISE trial studied the effectiveness of erenumab as migraine prevention in 577 adults with episodic migraines over 12 weeks.[58] The primary end point was the change in average monthly migraine-days (MMDs) with a reduction of 2.9 days in the 70-mg group compared with 1.8 days in the placebo group (P <.001). There was a statistically significant difference in the percentage of participants with at least a 50% reduction of MMD, with 29.5% in the placebo group and 39.7% in the 70-mg group (P = .01). The most frequently reported adverse drug reactions were upper respiratory tract infection, injection-site pain, and nasopharyngitis, which were similar to placebo.[58]

STRIVE (EPISODIC MIGRAINE)

The STRIVE trial randomized 955 participants to erenumab 70 mg, 140 mg, or placebo to examine its effectiveness on prevention of episodic migraines.[61] The primary end point was the change from baseline to months 4 through 6 in the mean number of migraine-days monthly. A significant difference was reported on the primary end point, with a reduction of 3.2 days in the 70-mg group, 3.7 days in the 140-mg group, and 1.8 days in the placebo group (P <.001 for both groups when compared with placebo). The percentage of subjects with at least a 50% reduction in MMD was 43.3% in the 70-mg group, 50.0% in the 140-mg group, and 26.6% in the placebo group (P <.001) for both groups when compared with placebo). A similar rate of adverse drug events was observed between the erenumab groups and placebo.[61]

PHASE 2 TRIAL (CHRONIC MIGRAINE)

Tepper et al conducted a randomized, placebo-controlled, multicenter, double-blind trial to assess the safety and efficacy of erenumab for migraine prevention in subjects with chronic migraine.[65] Erenumab 70 mg and 140 mg were compared with placebo by assessing the change in the number of migraine-days monthly from baseline to treatment weeks 9 through 12 in 667 participants. The reduction in MMDs for both erenumab groups compared with placebo was statistically significant (6.6-day reduction in 70-mg and 140-mg groups compared with 4.2 days with placebo; P <.0001). The percentage of patients who had at least a 50% reduction in migraines was 40% in the 70-mg group, 41% in the 140-mg group, and 23% in the placebo group (70 mg, P = .0001; and 140 mg, P <.0001 when compared with placebo). The most commonly reported adverse drug events were injection-site pain, upper respiratory tract infection, and nausea.[65]

Fremanezumab-vfrm (Ajovy)

Fremanezumab was FDA approved on September 14, 2018.[66] It is a humanized IgG2 CGRP ligand antagonist administered SC as 225 mg monthly or 675 mg (3 consecutive 225-mg injections) every 3 months.[68] The Halo-CM and Halo-EM trials demonstrated its efficacy in preventing headaches in subjects with chronic and episodic migraines.

HALO-CM (CHRONIC MIGRAINE)

Halo-CM was a randomized, parallel-group, placebo-controlled, double-blind study that compared the mean change from baseline in the average number of headache-days monthly with fremanezumab 225 mg (F225) monthly or 675 mg (F675) quarterly with placebo in patients with chronic migraines.[62] A total of 1130 participants was studied for 12 weeks, beginning after the administration of the first dose. The average reduction in the number of headache-days monthly was 4.6 (±0.3) for F225, 4.3 (±0.3) for F675, and 2.5 (±0.3) for placebo (P <.001 when F225 and F675 were compared with placebo). The percentage of participants with a 50% or greater reduction in the average number of headache-days monthly was 41% in the F225 group, 38% in the F675 group, and 18% in the placebo group (P <.001 when F225 and F675 were compared with placebo). Injection-site reactions were the most common adverse effect.[62]

HALO-EM (EPISODIC MIGRAINE)

The effectiveness of fremanezumab in the prevention of episodic migraines was evaluated in the Halo-EM trial.[59] The study was similar to the Halo-CM trial in design. In the randomized, parallel-group, double-blind, placebo-controlled study, 875 participants were randomized to fremanezumab 225 mg (F225) monthly, fremanezumab 675 mg (F675) quarterly, or placebo. The primary end point was the average number of migraine-days per month from baseline to week 12 of treatment. The decrease in the average number of migraine-days per month was 4.0 in the F225 group, 3.9 in the F675 group, and 2.6 in the placebo group (P <.001 when F225 and F675 were compared with placebo). The percentage of participants with a 50% or greater reduction in the average number of headache-days monthly was 47.7% in the F225 group, 44.4% in the F675 group, and 27.9% in the placebo group (P <.001 when F225 and F675 were compared with placebo). Injection-site erythema, depression, injection-site induration, anxiety, and diarrhea were the most common adverse drug reactions that resulted in medication discontinuation.[59]

Galcanezumab-gnlm (Emgality)

On September 27, 2018, the humanized IgG4 CGRP ligand antagonist galcanezumab was approved by the FDA.[66] It is an SC injection administered as a 240-mg loading dose (2 consecutive 120-mg injections), followed by 120 mg injected monthly.[60]

REGAIN (CHRONIC MIGRAINE)

The global, double-blind, placebo-controlled, randomized REGAIN trial evaluated the efficacy and safety of galcanezumab for the prevention of chronic migraines.[69] Participants were randomized

(n = 1117) into treatment arms which included galcanezumab 240 mg, galcanezumab 120 mg, or placebo for 12 weeks. All doses were given subcutaneously. The average participant had a baseline average of 19.4 migraines per month. The average decrease in migraine headache-days monthly with acute medication use was 4.7 for the 120-mg group, 4.3 for the 240-mg group, and 2.2 in the placebo group (P <.001 for both groups when compared with placebo). The average percentage of participants with a 50% or greater reduction in headache-days monthly was 27.6% for the 120-mg group, 27.5% for the 240-mg group, and 15.4% for the placebo group (P <.001 for both groups when compared with placebo).[60,61,70] There was also a 9-month extension phase of REGAIN involving an open-label trial that further evaluated galcanezumab.[69]

EVOLVE-1 (EPISODIC MIGRAINE)

In the randomized, placebo-controlled, double-blind EVOLVE-1 trial, galcanezumab 120 mg and 240 mg were compared with placebo to assess effectiveness in the prevention of episodic migraines.[64] A total of 858 adults received at least 1 dose of study medication. The primary end point was the average number of headache-free days monthly. The average reduction in monthly headache-days was 4.7 in the 120-mg group, 4.6 in the 240-mg group, and 2.8 in the placebo group (P <.001 when both groups were compared with placebo). The percentage of participants with a 50% or greater decrease in monthly average headache-days was statistically significant, with 62.3% in the 120-mg group, 60.9% in the 240-mg group, and 38.6% in the placebo group (P <.001 when both were compared with placebo).[64]

EVOLVE-2 (EPISODIC MIGRAINE)

The EVOLVE-2 trial had a similar design to the EVOLVE-1 trial and compared galcanezumab for the prevention of episodic migraines.[63] The reduction of the average number of headache-days monthly was 4.3 in the 120-mg group, 4.2 in the 240-mg group, and 2.3 in the placebo group (P <.001 in both groups when compared with placebo), making the primary end point statistically significant. Both galcanezumab groups had significantly more injection-site pruritus than the placebo group (0%), with 2.7% in the 120-mg group and 3.1% in the 240-mg group (P = .001, 120-mg vs placebo; P <.001, 240-mg vs placebo) as well as reactions, with 3.1% in the 120-mg group, 7.9% in the 240-mg group, and 0% in the placebo group (P <.001 for both groups when compared with placebo). The 120-mg group had more swelling at the injection site (P = .004), and the 240-mg group had more erythema at the injection site (P = .048) when compared with placebo.[63]

Emerging Treatment Options

Eptinezumab

Eptinezumab, formerly ALD403, is a humanized IgG1 CGRP ligand antagonist.[70] If it is FDA approved, it will be the first CGRP antagonist administered intravenously (IV).

In a phase 2 trial, a 1-time dose of eptinezumab 1000 mg was studied against placebo for the prevention of frequent episodic migraines defined as 5 to 14 days per month.[70] The net reduction in migraine-free days was 1 day when compared with placebo. Upper respiratory tract infections followed by urinary tract infections were the most commonly reported adverse drug events.[71] The 6 serious adverse drug events reported by 3 patients were all determined to be unrelated to eptinezumab.

PROMISE-1

The PROMISE-1 trial is a parallel group, double-blind, randomized, placebo-controlled trial examining the effectiveness of eptinezumab for the prevention of frequent episodic migraines.[71-73] The primary end point is the frequency change of migraine-days over 12 weeks. When compared with placebo, eptinezumab 30 mg, 100 mg, and 300 mg significantly decreased the average number of migraine-days (placebo = –3.2; 30 mg = –4.0 [P = .0045]; 100 mg = –3.9 [P = .0179]; and 300 mg = –4.3 [P = .0001]). Adverse effects were similar to placebo.[72]

PROMISE-2

The PROMISE-2 trial has a design similar to the PROMISE-1 trial. It will evaluate the use of eptinezumab for the prevention of chronic migraines.[74,75] The primary end point of the trial was MMDs compared with baseline after the administration of IV eptinezumab 30 mg, 100 mg, 300 mg, or placebo at day 0 and week 12.[74] Results of efficacy were just shown for the 300-mg dose. The mean change in MMDs from baseline was –5.6 in the placebo group and –8.2 in the 300-mg group (P = .0001). Treatment-emergent adverse effects were similar in the groups. An open-label phase 3 trial investigating the safety of eptinezumab repeatedly dosed for the treatment of chronic migraines is also underway.[76]

Ubrogepant

Ubrogepant is an orally administered CGRP receptor antagonist being studied for the treatment of acute migraine.[80] The filing of a new drug application for FDA approval is anticipated in 2019.

ACHIEVE I

The phase 3 ACHIEVE I trial evaluated the efficacy of ubrogepant as an acute treatment option in patients with migraine attacks.[80] In this randomized, placebo-controlled trial, 1137 adult participants in the modified intent-to-treat population were randomized to either placebo or 50 mg or 100 mg of ubrogepant. The 50-mg and 100-mg doses both achieved statistical significance for the coprimary end point of the percentage of participants who were free from pain at 2 hours post dose (placebo = 11.8%; 50 mg = 19.2% [P = .0023]; 100 mg = 21.2% [P = .0003]). Both doses of ubrogepant were also found to be statistically significant at achieving the other coprimary

end point of the percentage of participants who were most bothersome associated symptom (MBS)-free at 2 hours post dose (50 mg = 38.6% and 100 mg = 37.7%; placebo = 27.8% [both with $P = .0023$ when compared with placebo]). The adverse effects were similar between the groups with somnolence, dry mouth, and nausea being the most common (<5%). There were 6 cases of participants with aminotransferases 3 times the upper limit of normal. According to the liver safety adjudication board, none were attributed to ubrogepant and there were no cases of Hy's law.

ACHIEVE II

The phase 3 ACHIEVE II parallel-group, multicenter, placebo-controlled, double-blind, randomized trial compared ubrogepant 25 mg and 50 mg to placebo in treating moderate to severe migraine. Freedom from pain 2 hours post dose was statistically significant when compared with placebo (25 mg, $P = .0285$; 50 mg, $P = 0.0129$ when compared with placebo). A statistical significance was also seen in MBS rate at 2 hours post dose, with the 50-mg dose ($P = .0129$), sustained relief of pain and freedom from pain from 2 to 24 hours ($P = .0129$), greater percentage of phonophobia ($P = .0440$) and photophobia ($P = .0167$) resolution at 2 hours post dose in the 50-mg group when compared with placebo. When the 25-mg dose was compared with placebo for these end points, statistical significance was not reached. Nausea and dizziness were the most commonly reported adverse drug events with a frequency of up to 2.5%. None of the 3 participants in the ubrogepant group with aminotransferases (AST/ALT) greater than 3 times the upper limit of normal were attributed to ubrogepant.[80]

Rimegepant

Rimegepant is another orally available CGRP receptor antagonist that is expected to be submitted to the FDA for review in 2019.[81] In 2 phase 3 studies, rimegepant reached its 2 primary end points of freedom from MBS at 2 hours post dose and freedom from pain. Without the use of rescue medications, 1 dose of rimegepant was superior to placebo for both primary end points and displayed improvement that increased through the first 8 hours that was maintained at 24 and 48 hours compared with placebo. In a 24-hour period, most rimegepant participants did not require a rescue medication. The rimegepant participants also exhibited improvements in functional disability with many participants reporting normal function. No single adverse effect was greater than 2%, including nausea (1.4% vs 1.1% for placebo) and urinary tract infections (1.0% vs 0.7% for placebo). Regarding patient preference, more than 3 times the number of participants would prefer rimegepant compared with prior migraine treatment options. The safety of rimegepant was similar when compared with placebo, including liver function measures. In addition to the phase 3 trials, there is an ongoing long-term, open-label trial assessing the safety of rimegepant administered up to once daily for up to a full year in patients with migraine. Another phase 3 clinical trial assessing rimegepant using a fast dissolving, orally disintegrating tablet preparation was being conducted.[82]

Lasmiditan

SAMURAI

The SAMURAI trial was a prospective, randomized, double-blind, placebo-controlled study examining the effectiveness of lasmiditan in the acute or abortive treatment of patients with moderate to severe migraine in an outpatient setting.[77] Participants were randomized to receive lasmiditan 100 mg, 200 mg, or placebo. Each participant was given a dosing card containing 2 doses, one for initial treatment and a second to be taken within 24 hours for migraine rescue or recurrence. The primary end point was the proportion of participants who were pain-free 2 hours post dose. The secondary end point was the proportion of participants where the MBS was absent 2 hours post dose. A certification or an extension request to delay the submission of the results was submitted on April 3, 2018, allowing for a delay of up to 2 years.[77]

SPARTAN

The SPARTAN trial evaluated the effectiveness of lasmiditan for the treatment of acute migraine with or without aura.[78] Participants were randomized to 1 of 7 groups: (1) lasmiditan 50 mg (L50) plus placebo, (2) lasmiditan 100 mg (L100) plus placebo, (3) lasmiditan 200 mg (L200) plus placebo, (4) 2 L50 doses, (5) 2 L100 doses, (6) 2 L200 doses, or (7) 2 placebo tablets. Similar to the SAMURAI trial, participants were given a dosing card with 2 doses, one for the initial migraine and a second as a rescue dose for recurrent migraine between 2 and 24 hours. Migraine relief was defined as mild, moderate, or severe pain decreasing to no pain no later than 2 hours post administration. Migraine recurrence was defined as a moderate to severe headache that resolved within 2 hours and increased in intensity within 2 to 48 hours post lasmiditan administration.

The analysis included 2583 participants. The primary end points of the percentage of headache-free participants 2 hours post dose were 28.6% L50, 31.4% L100, 38.8% L200, and 21.3% placebo. When compared with placebo, all 3 lasmiditan groups were found to contain a statistically higher percentage of headache-free participants, with L50 (OR, 1.5; 95% CI, 1.1-1.9; $P = .003$), L100 (OR, 1.7; 95% CI, 1.3-2.2; $P < .001$), and L200 (OR, 2.3; 95% CI, 1.8-3.1; $P < .001$). The second primary end point of the percentage MBS-free 2 hours post dose was 40.8% L50, 44.2% L100, 48.7% L200, and 33.5% placebo. When compared with placebo, all 3 lasmiditan groups were found to have statistically more participants with a resolution of MBS with L50 (OR, 1.4; 95% CI, 1.1-1.8; $P = .009$), L100 (OR, 1.6; 95% CI, 1.2-2.0; $P < .001$), and L200 (OR, 1.9; 95% CI, 1.4-2.4; $P < .001$). The participants were significantly photophobia- and phonophobia-free, but no statistical difference was seen for nausea.

Other end points included the evaluation of headache occurrence and usage of rescue medication. The numbers of participants with recurrent headache were 38, 44, 52, and 26 for L50, L100, L200, and placebo, respectively. The percentage of patients who used a rescue medication 2 hours post dose was 31.9% ($P = .002$), 26.4% ($P < .001$), 18.9% ($P < .001$) and 40.8%, respectively. No significant difference was found when L50, L100, and L200 were compared with placebo 2 to up to 24 hours post dose or 24 to 48 hours post dose. The most commonly reported adverse effects were dizziness, somnolence, paresthesia, fatigue, and nausea.[78]

GLADIATOR

Participants from the SAMURAI and SPARTAN trials were enrolled in the GLADIATOR trial to evaluate intermittent use and long-term efficacy.[79] Participants were to take either the 100-mg or 200-mg tablet with a second dose for reoccurrence or rescue of acute migraine. The estimated study completion date is August 1, 2019.[79]

Conclusions

With the approval of 3 new medications and 4 others in the pipeline, this is an exciting time for individuals with migraines and healthcare providers. The first class of migraine medications since the 1990s has emerged and may make an impact on individuals who currently experience migraines. However, time will tell if these options are as effective and tolerable as the current literature proclaims. Further information is needed regarding their place in therapy, cost, and efficacy compared with currently available options. ■

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