**Emerging Therapies for Patients With Difficult-to-Treat Migraine**

Troy Kish, PharmD, BCPS

Migraine is a debilitating neurological disorder that affects over one billion individuals worldwide and is the second most common condition when ranked by years living with disability. In the United States, data from the National Health Interview Survey in 2015 show that 20% of women and 9.7% of men over the age of 18 experienced a severe headache or migraine in the previous three months. Rates of severe headache or migraine are highest among individuals aged 18–44 years and subsequently decline with advancing age in both men and women.

Diagnosis of migraine requires patients to have at least five headache attacks that meet the following criteria: lasting 4–72 hours; the presence of nausea and/or vomiting or photophobia and phonophobia; they must be present in a unilateral location, accompanied by moderate to severe pain, possess a pulsating quality, or be aggravated by or cause

---

**Table 1 Common Therapies Used for Acute and Preventative Management of Migraine**

<table>
<thead>
<tr>
<th>Medication Class</th>
<th>Available Products</th>
<th>How Supplied</th>
<th>Limitations of Medication Class</th>
<th>Generic Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Therapies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonsteroidal Anti-inflammatory Drugs (NSAIDs)</td>
<td>• Aspirin • Diclofenac • Naproxen • Ibuprofen</td>
<td>• Tablet, suppository, caplet • Tablet, oral solution, capsule • Tablet, capsule, ER and DR tablet • Tablet, capsule</td>
<td>May increase risk of bleeding or formation of gastric ulcers, concerns with renal disease</td>
<td>Generics available</td>
</tr>
<tr>
<td>Triptans</td>
<td>• Almotriptan (Axert) • Eletriptan (Relpax) • Frovatriptan (Frova) • Naratriptan (Amerge) • Rizatriptan (Maxalt) • Sumatriptan (Imitrex) • Zolmitriptan (Zomig)</td>
<td>• Tablet • Tablet • Tablet • Tablet, OD, DT • Tablet, SQ injection, NS • Tablet, OD, NS</td>
<td>Cannot be used in patients with history of ischemic cardiovascular disease or cerebrovascular disease</td>
<td>Generics available</td>
</tr>
<tr>
<td>Ergot Alkaloids</td>
<td>• Ergotamine • Ergotamine with caffeine • Dihydroergotamine</td>
<td>• Sublingual tablet • Tablet, suppository • NS, SQ or IM injection</td>
<td>Cannot be used in patients with history of cardiovascular disease</td>
<td>Generics available</td>
</tr>
<tr>
<td><strong>Preventative Therapies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botulinum Toxin Type A</td>
<td>• Onabotulinum toxin A (Botox)</td>
<td>IM injection by physician</td>
<td>Cost, need for injections</td>
<td>No generic available</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>• Atenolol (Tenormin) • Metoprolol (Toprol) • Propranolol (Inderal) • Timolol (Blocadren)</td>
<td>• Tablet • Tablet • Tablet, oral solution, ER capsule • Tablet</td>
<td>Bradycardia, bronchospasm, increased fatigue or lethargy</td>
<td>Generics available</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>• Amitriptyline (Elavil) • Venlafaxine (Effexor)</td>
<td>• Tablet • Tablet, ER tablet, ER capsule</td>
<td>• Anticholinergic effects, orthostatic hypotension • Insomnia, dizziness, drowsiness</td>
<td>Generics available</td>
</tr>
<tr>
<td>Calcium-channel Blockers</td>
<td>• Verapamil (Calan; Verelan)</td>
<td>• Tablet, ER tablet, ER capsule</td>
<td>• Constipation, potential drug–drug interactions</td>
<td>Generics available</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>• Valproic acid (Depakote) • Topiramate (Topamax)</td>
<td>• ER and DR tablet, oral solution, capsule, DR sprinkle capsule • Tablet, ER tablet, ER capsule, sprinkle capsule</td>
<td>• Avoid in pregnancy, nausea, drowsiness, insomnia, alopecia • Cognitive dysfunction, sedation, taste disturbances</td>
<td>Generics available</td>
</tr>
</tbody>
</table>

DR= delayed release; ER= extended release; IM= intramuscular; NS= nasal spray; ODT= orally dissolving tablet; SQ= subcutaneous.

* Not a comprehensive listing.
Most patients experience emergent medications. Patients with migraine need and use for acute or prophylactic and specialists, as well as an increased primary care offices, emergency rooms, resources through increased visits to when compared to patients with EM, migraines, monthly for three months. Some patients ing at least 15 headaches, with eight being migraines (CMs), defined as experiencing aura symptoms may also occur. Most patients experience emergent migraines (EMs) that occur periodically, with eight being migraines, monthly for three months. When compared to patients with EM, patients with CM utilize more health care resources through increased visits to primary care offices, emergency rooms, and specialists, as well as an increased need and use for acute or prophylactic medications. Patients with migraine also suffer from reduced productivity and higher absenteeism, leading to higher indirect costs associated with this condition.

Knowledge of the complex pathophysiology involved in migraine development is constantly growing. The once-held theory that vasodilation was responsible for migraines has largely been debunked. Two key targets that are the focus of new drug development are serotonin and calcitonin-gene-related peptide (CGRP). Serotonin has been well documented to contribute to the development of migraines; however, the exact mechanism(s) through which it does so remains unclear. Triptans, which work by stimulating the 5HT1B/D receptor, are the most effective acute treatment while medications inhibiting serotonin reuptake, such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), have proven efficacy in migraine prevention. CGRP is the most abundant neuropeptide found in the trigeminal nerve and is involved in promoting vasodilation and neurogenic inflammation. Circulating levels of CGRP are increased during episodes of migraine and an injection of CGRP can induce migraine headaches in patients with a history of migraine but not in healthy volunteers. Emergent migraines are treated with a variety of medications from differing classes ranging from simple over-the-counter analgesics to prescription agents. Patients with CM may regularly take prophylactic medications to reduce their frequency of attacks. Table 1 provides an overview of common medications used in the acute treatment as well as chronic prevention of migraines.

Despite the variety of agents available, there are still limitations in the ability to treat some patients. Areas of unmet need are medications that are safe for patients with cardiovascular disease as well as agents with novel and more targeted mechanisms of action for both prevention and treatment of acute episodes. This article will highlight, in no particular order, medications recently approved by the FDA or those in late-stage development that are intended to fill those treatment gaps. A summary of these medications can also be found in Table 2.

<table>
<thead>
<tr>
<th>Medication Developers</th>
<th>Mechanism of Action</th>
<th>Targeted Indication/Population</th>
<th>Route and Dose*</th>
<th>Current or Expected Pricing Strategy</th>
<th>FDA Approval or Anticipated Launch Date (United States)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lasmiditan Eli Lilly &amp; Company</td>
<td>5-HT1 receptor agonist</td>
<td>Patients with CV disease or those who are unresponsive to triptans</td>
<td>50-mg, 100-mg, or 200-mg oral tablets</td>
<td>10% premium to Imitrex tablets</td>
<td>2019</td>
</tr>
<tr>
<td>Erenumab-aooe (Aimovig) Amgen Novartis</td>
<td>Monoclonal antibody against CGRP</td>
<td>Preventative therapy for patients with chronic migraine</td>
<td>70 mg or 140 mg subcutaneously monthly</td>
<td>AWP: $690 for 70-mg or 140-mg dose</td>
<td>Approved May 2018</td>
</tr>
<tr>
<td>Fremanezumab Teva Pharmaceutical Industries</td>
<td>Monoclonal antibody against CGRP</td>
<td>Preventative therapy for patients with chronic migraine</td>
<td>225 mg or 675 mg intravenously or subcutaneously monthly or every 12 weeks</td>
<td>20% premium to Praluent</td>
<td>2018</td>
</tr>
<tr>
<td>Galcanezumab Eli Lilly &amp; Company</td>
<td>Monoclonal antibody against CGRP</td>
<td>Preventative therapy for patients with chronic migraine</td>
<td>120 mg subcutaneously monthly</td>
<td>20% premium to Praluent</td>
<td>2018</td>
</tr>
<tr>
<td>Eptinezumab Alder Biopharmaceuticals</td>
<td>Monoclonal antibody against CGRP</td>
<td>Preventative therapy for patients with chronic migraine</td>
<td>100 mg or 300 mg intravenously every 12 weeks</td>
<td>20% premium to Praluent</td>
<td>2019</td>
</tr>
<tr>
<td>Ubrogepant Allergan</td>
<td>CGRP antagonist</td>
<td>Acute treatment of episodic migraine</td>
<td>25-mg, 50-mg tablets at migraine onset</td>
<td>20% premium to Imitrex tablets</td>
<td>2020</td>
</tr>
<tr>
<td>Atogepant Allergan</td>
<td>CGRP antagonist</td>
<td>Preventative therapy for patients with episodic migraine</td>
<td>10-mg, 30-mg, or 60-mg capsule once or twice daily</td>
<td>30% premium to Topamax tablets</td>
<td>2022</td>
</tr>
</tbody>
</table>

* Doses listed reflect those evaluated in clinical trials. FDA-approved doses and routes may change.

AWP= Average wholesale price; CV= cardiovascular.
Erenumab

Erenumab is a monoclonal antibody (mAb) that binds to and inhibits CGRP, and which was recently approved by the FDA in May, 2018 for the prevention of episodic migraines. It is available as an auto-injector, which patients can self-administer at doses of 70 or 140 mg subcutaneously monthly.\textsuperscript{13}

STRIVE was a randomized, 24-week, double-blind placebo-controlled trial that enrolled 995 patients suffering from episodic migraines to receive monthly subcutaneous injections of 70 mg or 140 mg of erenumab or placebo. At baseline, enrolled patients experienced an average of 8.3 migraines per month. Results of this trial showed a decrease of 3.2 and 3.7 migraines per month in the 70-mg and 140-mg arms, respectively, as compared to a decrease of 1.8 migraines in the placebo arm. The secondary endpoint evaluating a 50% or greater reduction in monthly migraine days (MMD) was observed in 43.3% and 50% of patients receiving 70 or 140 mg, respectively, as compared to 26.6% of placebo patients.\textsuperscript{14}

The ARISE trial was a phase 3, randomized, double-blind, placebo-controlled trial to evaluate the use of erenumab for the prevention of episodic migraine. Five-hundred seventy-seven patients were randomized to 70 mg of erenumab or placebo and followed for three months. Patients receiving erenumab noted a reduction of 2.9 MMD while placebo patients reported a 1.9 MMD decrease. Nearly 40% of treatment patients experienced a 50% reduction in MMD, and 29.5% of placebo patients reported the same.\textsuperscript{15}

A third trial enrolled patients with chronic migraine to assess erenumab as a preventative medication. A total of 667 patients were divided into groups receiving subcutaneous injections of 70 mg or 140 mg of erenumab or placebo monthly for three months. At baseline, patients reported an average of 18 MMD and patients in both treatment groups reported a decline of 6.6 MMD while placebo patients reported a decrease of 4.2 MMD. Similar to the other trials, 39–41% of treatment patients achieved a 50% reduction in MMD; this was seen in only 23.5% of placebo patients.\textsuperscript{16} Patients who completed this trial were eligible to enroll in a 52-week, open-label follow-up study to assess long-term safety and efficacy. Twenty-four out of the 609 patients who continued in the study experienced a severe adverse effect, and ultimately 16 patients discontinued treatment following an adverse reaction. Non-serious adverse effects included viral upper respiratory tract infection (15.8%), upper respiratory tract infection (7.4%), and sinusitis (7.2%). Evaluation of efficacy at Week 52 showed a 9.3-day reduction in the mean number of MMD in participants who continued treatment.\textsuperscript{17}

During these trials, patients were permitted to continue using other therapies such as nonsteroidal anti-inflammatory drugs (NSAIDs), triptans, or ergotamine products. In addition, patients with a major cardiovascular event or procedure (myocardial infarction, unstable angina, transient ischemic attack, revascularization procedures) in the preceding 12 months were excluded. The compiled adverse effects from these 3 trials show erenumab to be well tolerated with the most commonly reported adverse effects being injection-site reactions (5–6%), including injection-site pain or erythema, constipation (1–3%), or cramps or muscle spasms (<1–2%) for both the 70-mg and 140-mg doses.\textsuperscript{13}

Fremenezumab

Fremenezumab is a CGRP mAb under development from Teva Pharmaceuticals. In clinical trials, patients received subcutaneous injections of either 675 mg quarterly or 225 mg monthly following a 675-mg initial dose. The possibility of quarterly dosing helps to set fremenezumab apart from other CGRP mAbs in development. Results of two large clinical trials involving fremenezumab have been published, with one focusing on prevention of episodic migraine and the other on prevention of chronic migraine.\textsuperscript{18,19}

The phase 3 clinical trial focusing on prevention of episodic migraine enrolled patients experiencing 6–14 MMD with at least four days being categorized as migraine days. Ultimately, 875 patients were randomized to receive either a single 675-mg injection followed by placebo injections at weeks 4 and 8, a 675-mg injection followed by 225-mg injections at weeks 4 and 8, or placebo. Overall, patients receiving monthly active treatment demonstrated a 3.7-day reduction in least-squares mean MMD, patients receiving quarterly fremenezumab reported a 3.4-day reduction, and placebo patients reported a 2.2-day reduction. Among patients who experienced a 50% reduction in MMD, 47.7% of patients were receiving monthly fremenezumab, 44.4% were receiving quarterly fremenezumab, and 27.9% received placebo.\textsuperscript{18}

A separate clinical trial evaluating patients with chronic migraine was also conducted with 1,130 patients receiving the same dosing protocol as in the previous trial. The primary outcome was a reduction in the mean number of headache days per month, which was defined as any headache lasting at least four consecutive hours and reaching moderate pain levels, or a headache for which a migraine-specific medication (triptan or ergot derivative) was used for treatment. The number of headache days at baseline was ~13 across all groups. At 12 weeks, the least-square mean change from baseline was a reduction of 4.3 days and 4.6 days for patients receiving quarterly and monthly fremenezumab, respectively, while placebo patients reported a 2.5-day reduction. Only 18% of placebo patients reported a 50% reduction in average headache days per month as compared to 38–41% of fremenezumab patients.\textsuperscript{19}

Rates of adverse effects in both of the above trials were similar between the patients receiving fremenezumab and placebo. The most commonly reported events in the fremenezumab groups included: injection-site reactions (26–30%) such as pain, induration, erythema, or hemorrhage; infections (1–5%) such as nasopharyngitis, upper respiratory tract infections, or sinusitis; dizziness (2–3%) or nausea (1–2%).\textsuperscript{18,19}

Galcanezumab

Galcanezumab is another CGRP mAb in development for the prevention of episodic migraines; its efficacy has been supported by two large trials. EVOLVE-1 was a randomized, double-blind, placebo-controlled trial that enrolled 1,671 participants who experienced 4–14 migraines or probable migraine headaches per month and two migraine attacks in the baseline evaluation. Patients in the active treatment arms received a loading dose of 240 mg, followed by either 120 mg or 240 mg monthly via subcutaneous injection. Patients receiving 120 mg and 240 mg reported a 4.7-day and 4.6-day reduction, respectively, in the number of monthly headaches while placebo...
patients reported a 2.8-day reduction. Rates of serious adverse effects were similar in both treatment and placebo groups, and none were attributed to galcanezumab. Adverse effects seen more frequently in the galcanezumab groups included injection-site pruritus (4.4–4.6%), injection-site reactions (3.4–5.5%), and generalized pruritus (1–2.7%). The EVOLVE-2 trial had the same inclusion criteria and treatment doses as EVOLVE-1 and enrolled 1,696 patients. Galcanezumab-treated patients saw a similar reduction of 4.3 and 4.2 migraine days for 120 mg and 240 mg, respectively, while placebo patients reported a 2.3-day reduction. Again, injection-site reactions (3.1–7.9% vs. 0%) and injection-site pruritus (2.7 – 3.1% vs. 0%) were the only adverse effects reported at a higher frequency than placebo.

The REGAIN trial followed 1,117 patients with chronic migraine who received either 120 mg or 240 mg of galcanezumab monthly or placebo. At the 3-month follow-up, patients in the 120-mg and 240-mg groups reported a 4.8 and 4.6 least-squares mean decrease in the number of MMD, respectively, while placebo patients noted a 2.7-day decrease. Twenty-seven percent of patients receiving either dose of galcanezumab experienced a 50% reduction in MMD as compared to 15% of placebo patients. The only adverse effects to occur more frequently in the treatment groups were injection-site reactions (4.1%) and injection-site erythema (3.1%), while other common adverse effects such as nasopharyngitis (4.7%), upper respiratory tract infection (3.2%), and sinusitis (2.2%) were at a rate similar to that seen in the placebo arm.

**Eptinezumab**

Eptinezumab is a CGRP mAb under development from Alder Biopharmaceuticals. Eptinezumab will provide a convenient dosing schedule, as it can be administered every 12 weeks; it can be administered every 12 weeks; as compared to placebo and treatment arms. Allergan’s second CGRP antagonist, atogepant, is being evaluated for use in the prevention of migraine, as it possesses a longer half-life and is more potent than ubrogepant. Recent results from a phase 2b/3 clinical trial provided initial efficacy and safety information for atogepant in migraine prevention. This trial evaluated multiple doses and regimens in 834 patients with episodic migraines over a 12-week period. Patients were randomized to receive either daily doses of 10, 30, or 60 mg or twice daily doses of 30 or 60 mg, or placebo. All atogepant treatment groups noted a significant decrease in their mean monthly migraine/probable migraine headache days when compared to placebo. The most commonly observed adverse effects included nausea, fatigue, constipation, nasopharyngitis, and urinary tract infection. In addition, the frequency of liver enzyme elevation was similar in both the placebo and treatment arms.

When compared to CGRP mAbs, these agents have the advantage of being orally administered and will likely have a lower price point. Drugs in this class do not carry any cardiovascular warnings, which
may make them an option in patients for whom triptans are contraindicated. Long-term safety may be a concern, as a previous CGRP receptor antagonist, telcagepant, stopped early clinical trials following concerns about liver damage. Atogepant and ubrogepant belong to a different chemical series than telcagepant and have thus far not demonstrated increased liver toxicity, but data from larger and long-term clinical studies is still desired.

**Lasmiditan**

Lasmiditan is a novel migraine therapy that works upon the 5-HT	extsubscript{1F} receptors along the trigeminal nerve, ultimately blocking the transmission of migraine pain sensations. Some advantages of lasmiditan over the triptan class include its lack of cardiovascular effects and the ability to target receptors both within the periphery and the brain. The phase 3 SAMURAI trial evaluated the ability of lasmiditan oral tablets to reduce migraine pain at two hours compared to placebo. There were 630 and 609 patients in the lasmiditan 100-mg and 200-mg groups, respectively, while 617 patients received a placebo. Patients enrolled were mostly Caucasian females with a mean migraine history of 19 years, an average age of 41.6 years, and an average Migraine Disability Assessment (MIDAS) score of 31. Cardiovascular risk factors were present in 82% of enrollees, and patients with established cardiovascular disease were also included. At two hours, 28.2% and 32.2% of patients receiving lasmiditan 100 mg and 200 mg, respectively, reported being pain-free as compared to 15.3% of placebo patients. In addition, 40–41% of patients receiving lasmiditan reported resolution of their MBS as compared to 29.5% of placebo patients. Adverse effects were similar to those described in SAMURAI; however, their frequency was not reported. An ongoing, open-label trial known as GLADIATOR is designed to evaluate the long-term safety and efficacy of lasmiditan 100 mg and 200 mg for acute migraine treatment with an anticipated completion date of August 2019. Lasmiditan will be the first medication from the ditan class to enter the market and will serve as an option for patients in whom triptans are either ineffective or contraindicated. A current lack of head-to-head comparative trials and long-term safety data along with prohibitive medication pricing may serve as barriers for lasmiditan.

**CONCLUSION**

The landscape of migraine therapy is set to change with these new classes of medications that are poised to enter the market soon. These therapies will provide options for patients who previously did not respond to or were contraindicated to receive existing medications; however, given the comparatively low-cost generic status of most existing migraine therapies, the pricing of these novel agents will likely be a key determinant in the extent of their use in clinical practice.

**REFERENCES**


2. QuickStats: percentage of adults aged ≥18 years who reported having a severe headache or migraine in the past 3 months, by sex and age group—National Health Interview Survey, United States: 2013. MMWR Morb Mortal Wkly Rep 2017;66:654. DOI: http://dx.doi.org/10.15585/mmwr.mm6624a8.


