Migraine headache: When to consider these newer agents

These agents are as effective as traditional acute and preventive treatments, cause fewer adverse effects, and can simplify regimens.

**Pathophysiology, Dx and triggers, indications for pharmacotherapy**

- **Pathophysiology.** A migraine is thought to be caused by cortical spreading depression (CSD), a depolarization of glial and neuronal cell membranes. This results in increased cortical excitability, central trigeminal-thalamic sensitization, and defective descending pain modulatory activity. The activation of the trigeminal sensory pathways, primarily the ophthalmic branch, sends nociceptive signals to second-order neurons mediated by the release of neurotransmitters, such as CGRPs. This activation explains in part the primary location for a migraine, which is around the eye and the neighboring cranial regions. The pain perceived by the patient is caused by these second-order neurons.

- **Dx and triggers.** In 2018, the International Headache Society revised its guidelines for the diagnosis of migraine. According to the 3rd edition of The International Classification of Headache Disorders (ICHD-3), the diagnosis of migraine is made when a patient has at least 5 headache attacks that last 4 to 72 hours and have at least 2 of the following characteristics: (1) unilateral location, (2) pulsating quality, (3) moderate-...
to-severe pain intensity, and (4) aggravated by or causing avoidance of routine physical activity. The headache attacks also should have (1) associated nausea or vomiting or (2) photophobia and phonophobia. The presence of atypical signs or symptoms as indicated by the SNNOOP10 mnemonic raises concerns for secondary headaches and the need for further investigation into the cause of the headache. It is not possible to detect every secondary headache with standard neuroimaging, but the SNNOOP10 red flags can help determine when imaging may be indicated. Potential triggers for migraine can be found in Table 2.

**Indications for pharmacotherapy.** All patients receiving a diagnosis of migraine should be offered acute pharmacologic treatment. Consider preventive therapy anytime there are ≥ 4 headache days per month, debilitating attacks despite acute therapy, overuse of acute medication (> 2 d/wk), difficulty tolerating acute medication, patient preference, or presence of certain migraine subtypes.

**Acute treatments**
Abortive therapies for migraine include analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, and ergot alkaloids, triptans, or small-molecule CGRP receptor antagonists (gepants). Prompt administration increases the chance of success with acute therapy. Medications with the highest levels of efficacy based on the 2015 guidelines from the American Headache Society (AHS) are given in Table 3. Lamotrigine (Reyvow) is not included in the 2015 guidelines, as it was approved after publication of the guidelines.

**Non-CGRP first-line therapies**
- **NSAIDs and acetaminophen.** NSAIDs such as aspirin, diclofenac, ibuprofen, and naproxen have a high level of evidence to support their use as first-line treatments for mild-to-moderate migraine attacks. Trials consistently demonstrate their superiority to placebo in headache relief and complete pain relief at 2 hours. There is no recommendation for selecting one NSAID over another; however, consider their frequency of dosing and adverse effect profiles. The number needed to treat for complete pain relief at 2 hours ranges from 7 to 10 for most NSAIDs. In some placebo-controlled studies, acetaminophen was less effective than NSAIDs, but was safer because it did not cause gastric irritation or antiplatelet effects.
A meta-analysis found that triptans at standard doses provided pain relief within 2 hours in 42% to 76% of patients, and sustained freedom from pain for 2 hours in 18% to 50% of patients.

**Triptans** inhibit 5-HT<sub>1B/1D</sub> receptors. Consider formulation, route of administration, cost, and pharmacokinetics when selecting a triptan. Patients who do not respond well to one triptan may respond favorably to another. A meta-analysis of the effectiveness of the 7 available agents found that triptans at standard doses provided pain relief within 2 hours in 42% to 76% of patients, and sustained freedom from pain for 2 hours in 18% to 50% of patients. Lasmiditan is a selective serotonin receptor (5-HT<sub>1F</sub>) agonist that lacks vasoconstrictor activity. This is an option for patients with relative contraindications to triptans due to cardiovascular risk factors.

**Second-line therapies**

Intranasal dihydroergotamine has a favorable adverse event profile and greater evidence for efficacy compared with ergotamine. Compared with triptans, intranasal dihydroergotamine has a high level of efficacy but causes more adverse effects. Severe nausea is common, and dihydroergotamine often is used in combination with an antiemetic drug. Dihydroergotamine should not be used within 24 hours of taking a triptan, and it is contraindicated for patients who have hypertension or ischemic heart disease or who are pregnant or breastfeeding. There is also the potential for adverse drug interactions.

Antiemetics may be helpful for migraine associated with severe nausea or vomiting. The dopamine antagonists metoclopramide, prochlorperazine, and chlorpromazine have demonstrated benefit in randomized placebo-controlled trials. Ondansetron has not been studied extensively, but sometimes is used in clinical practice. Nonoral routes of administration may be useful in patients having trouble swallowing medications or in those experiencing significant nausea or vomiting early during migraine attacks.

Due to the high potential for abuse, opioids should not be used routinely for the treatment of migraine. There is no high-quality evidence supporting the efficacy of barbiturates (ie, butalbital-containing compounds) for acute migraine treatment. Moreover, use of these agents may increase the likelihood of progression from episodic to chronic migraine.

**Gepants for acute migraine treatment**

Neuropeptide CGRP is released from trigeminal nerves and is a potent dilator of ce-
TABLE 3
Non-CGRP migraine treatment first-line therapies

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosea</th>
<th>Adverse effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>500-1000 mg once</td>
<td>Hepatotoxicity with excessive dosing</td>
<td>Use with caution with hepatic impairment or active liver disease. Do not use with other products containing acetaminophen. The combination of aspirin-acetaminophen-caffeine has strong evidence of effectiveness.</td>
</tr>
<tr>
<td>NSAIDs</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>325-650 mg once</td>
<td>Most common: Nausea, gastritis, abdominal cramps, GI ulcers, peripheral edema, hypertension, diarrhea Rare/severe: GI perforation and bleeding, renal toxicity, acute renal failure, angioedema, bronchoconstriction, asthma, rash, tinnitus, hearing loss</td>
<td>Highest risk for gastric and duodenal damage. Contraindicated during pregnancy and in patients with bleeding disorders.</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>50-100 mg once</td>
<td></td>
<td>Available in a powdered form for dilution with water for oral solution.</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>200-600 mg once</td>
<td></td>
<td>Well tolerated. Shorter half-life compared to naproxen.</td>
</tr>
<tr>
<td>Naproxen</td>
<td>500-750 mg once</td>
<td></td>
<td>Well tolerated. Slower onset but can be dosed less frequently than ibuprofen. Available in a combination product with sumatriptan.</td>
</tr>
<tr>
<td>Triptans</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Almotriptan (Axert)</td>
<td>6.25-12.5 mg. May repeat after 2 h. Max dose, 25 mg/d.</td>
<td>Most common: Nausea, asthenia, dizziness, somnolence, fatigue Contraindicated in patients with coronary artery disease, peripheral vascular disease, history of stroke or TIA, uncontrolled hypertension, and other vascular risk factors and disorders</td>
<td>Dose adjustments in liver or severe renal disease. Potential drug interactions with potent CYP3A4 inhibitors.</td>
</tr>
<tr>
<td>Eletriptan (Relpax)</td>
<td>20-40 mg. May repeat after 2 h. Max dose, 80 mg/d.</td>
<td></td>
<td>Potential drug interactions with potent CYP3A4 inhibitors.</td>
</tr>
<tr>
<td>Frovatriptan (Frova)</td>
<td>2.5 mg. May repeat after 2 h. Max dose, 7.5 mg/d</td>
<td></td>
<td>Longest half-life of the triptans (~26 h).</td>
</tr>
<tr>
<td>Naratriptan (Amerge)</td>
<td>1-2.5 mg. May repeat once after 4 h. Max dose, 5 mg/d.</td>
<td></td>
<td>Dose adjustments in liver or severe renal disease.</td>
</tr>
<tr>
<td>Rizatriptan (Maxalt)</td>
<td>5-10 mg (5 mg with propranolol). May repeat after 2 h. Max dose, 30 mg/d.</td>
<td></td>
<td>Available in orally disintegrating tablets. Contraindicated if MAOI used in the past 2 weeks.</td>
</tr>
<tr>
<td>Sumatriptan (Imitrex)</td>
<td>Oral tab: 25, 50, or 100 mg. May repeat after 2 h. Max dose, 200 mg/d (100 mg if used after injection). Injection: 1-6 mg. May repeat after 1 h. Max dose, 12 mg/d. Nasal spray: 5, 10, or 20 mg. May repeat once after 2 h. Max dose, 40 mg/d.</td>
<td>Subcutaneous injection: Fastest and most effective treatment but a higher rate of adverse effects than oral and nasal formulations. Contraindicated if MAOI used in the past 2 weeks.</td>
<td></td>
</tr>
<tr>
<td>Zolmitriptan (Zomig)</td>
<td>Oral tab: 1.25, 2.5, or 5 mg. May repeat after 2 h. Max dose, 10 mg/d. Nasal spray: 2.5, 5 mg. May repeat after 2 h. Max dose, 10 mg/d.</td>
<td></td>
<td>Available in orally disintegrating tablets. Contraindicated if MAOI used in the past 2 weeks.</td>
</tr>
</tbody>
</table>

rebral and dural vessels, playing a key role in regulating blood flow to the brain. Other roles of CGRP include the release of inflammatory agents from mast cells and the transmission of painful stimuli from intracranial vessels. The CGRP receptor or ligand can be targeted by small-molecule receptor antagonists for acute and preventive migraine treatment (and by monoclonal antibodies solely for prevention, discussed later). It has been theorized that gepants bind to CGRP receptors, resulting in decreased blood flow...
to the brain, inhibition of neurogenic inflammation, and reduced pain signaling. Unlike triptans and ergotamine derivatives, these novel treatments do not constrict blood vessels and may have a unique role in patients with contraindications to triptans.

The 3 gepants approved for acute treatment—ubrogepant (Ubrelvy), rimegepant (Nurtec), and zavegepant (Zavzpret)—were compared with placebo in clinical trials and were shown to increase the number of patients who were completely pain free at 2 hours, were free of the most bothersome associated symptom (photophobia, phonophobia, or nausea) at 2 hours, and remained pain free at 24 hours (TABLE 4).

- **Ubrogepant**, in 2 Phase 3 trials (ACHIEVE I and ACHIEVE II) demonstrated effectiveness compared with placebo. The most common adverse effects reported were nausea and somnolence at very low rates. Pain-relief rates at 2 hours post dose (> 60% of participants) were higher than pain-free rates, and a significantly higher percentage (> 40%) of ubrogepant-treated participants reported ability to function normally on the Functional Disability Scale.

- **Rimegepant** was also superior to placebo (59% vs 43%) in pain relief at 2 hours post dose and other secondary endpoints. Rimegepant also has potential drug interactions and dose adjustments (TABLE 4).

- **Zavegepant**, approved in March 2023, is administered once daily as a 10-mg nasal spray. In its Phase 3 trial, zavegepant was significantly superior to placebo at 2 hours post dose in freedom from pain (24% v 15%), and in freedom from the most bothersome symptom (40% v 31%). Dosage modifications are not needed with mild-to-moderate renal or hepatic disease.

- **Worth noting.** The safety of using ubrogepant to treat more than 8 migraine episodes in a 30-day period has not been established. The safety of using more than 18 doses of zavegepant in a 30-day period also has not been established. With ubrogepant and rimegepant, there are dosing modifications for concomitant use with specific drugs (CYP3A4 inhibitors and inducers) due to potential interactions and in patients with hepatic or renal impairment.

There are no trials comparing efficacy of CGRP antagonists to triptans. Recognizing that these newer medications would be costly, the AHS position statement released in 2019 recommends that gepants be considered for those with contraindications to triptans or for whom at least 2 oral triptans have failed (as determined by a validated patient outcome questionnaire). Step therapy with documentation of previous trials and therapy failures is often required by insurance companies prior to gepant coverage.

### Preventive therapies

Preventive migraine therapies are used to reduce duration, frequency, and severity of attacks, the need for acute treatment, and overall

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**TABLE 3**

<table>
<thead>
<tr>
<th>Non-CGRP migraine treatment first-line therapies$^{11}(cont’d)</th>
<th>Dose$^b$</th>
<th>Adverse effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selective triptan</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lasmiditan (Reyvow)</td>
<td>Oral tab: 50, 100, or 200 mg. Max 1 dose per day.</td>
<td><strong>Most common:</strong> Dizziness, fatigue, sedation, paresthesia, nausea. May cause driving impairment (do not drive within 8 h of dose)</td>
<td>Do not take second dose within 24 h; no benefit for same migraine attack. Dizziness is dose dependent. Potential drug interactions with CNS depressants, serotonergic agents, heart rate–lowering agents (propranolol).</td>
</tr>
</tbody>
</table>

CGRP, calcitonin gene-related peptide; CNS, central nervous system; GI, gastrointestinal; MAOI, monoamine oxidase inhibitors; NSAIDs, nonsteroidal anti-inflammatory drugs; TIA, transient ischemic attack.

$^a$ All medications listed here (except lasmiditan) are established as effective (American Academy of Neurology and American Headache Society Level A: ≥ 2 Class I randomized controlled trials incorporating 5 key study criteria and masked or objective outcome assessments) for acute migraine treatment based on available evidence.

$^b$ Information taken from medication package labeling.
<table>
<thead>
<tr>
<th>Medication, year approved</th>
<th>FDA-approved adult dose and frequency</th>
<th>Study participantsa</th>
<th>Primary efficacy endpoints and outcomesb</th>
<th>Adverse events (&gt; 2% reported)</th>
<th>Costc</th>
</tr>
</thead>
</table>
| **Rimegepant (Nurtec) 2020** | 75 mg, dissolve on or under the tongue. Max dose, 75 mg/d | Migraine with or without aura | % free from pain at 2 h after initial dose:  
- 75 mg: 21.2%  
- Placebo: 10.9%  
% without migraine-associated MBS identified at baseline at 2 h after initial dose:  
- 75 mg: 35.1%  
- Placebo: 26.8% | Nausea | 8 ODT, 75 mg tablets: $934 |
| **Ubrogepant (Ubrelvy) 2019** | 50 or 100 mg tab; may repeat in 2 h. Max dose, 200 mg/d | ACHIEVE I, ACHIEVE II: Migraine with or without aura | % free from pain at 2 h after initial dose:  
ACHIEVE I:  
- 50 mg: 19.2%  
- 100 mg: 21.2%  
- Placebo: 11.8%  
ACHIEVE II:  
- 25 mg: 20.7%  
- 50 mg: 21.8%  
- Placebo: 14.3%  
% without migraine-associated MBS identified at baseline at 2 h after initial dose:  
ACHIEVE I:  
- 50 mg: 38.6%  
- 100 mg: 37.7%  
- Placebo: 27.8%  
ACHIEVE II:  
- 25 mg: 34.1%  
- 50 mg: 38.9%  
- Placebo: 27.4% | Nausea, somnolence, dry mouth | 8 tablets, 50 mg: $711  
8 tablets, 100 mg: $711 |
| **Zavegepant (Zavzpret) 2023** | Single spray (10 mg)/d | Migraine with or without aura | % free from pain at 2 h after initial dose:  
- 10 mg: 24%  
- Placebo: 15%  
% without migraine-associated MBS identified at baseline at 2 h after initial dose:  
- 10 mg: 40%  
- Placebo: 31% | Dysgeusia, nasal discomfort, nausea | 1 carton (6 nasal sprays): $1063 |

*BCRP, breast cancer resistance protein; CGRP, calcitonin gene-related peptide; CrCl, creatinine clearance; FDA, US Food and Drug Administration; MBS, most bothersome symptom; ODT, oral disintegrating tablet; P-gp, P-glycoprotein.

*a All trials were multicenter, randomized, double-blinded, and placebo-controlled.

b Statistically significant vs placebo.

c Estimated cost based on lowest retail price listed on GoodRX (www.goodrx.com).
headache disability. Medications typically are chosen based on efficacy, adverse effect profile, and patient comorbidities. Barriers to successful use include poor patient adherence and tolerability, the need for slow dose titration, and long-term use (minimum of 2 months) at maximum tolerated or minimum effective doses. Medications with established efficacy (Level A) based on the 2012 guidelines from the American Academy of Neurology (AAN) and the AHS are given in TABLE 5.27-29

Drugs having received the strongest level of evidence for migraine prevention are metoprolol, propranolol, timolol, topiramate, valproate sodium, divalproex sodium, and onabotulinumtoxinA (Botox), and frovatriptan for menstrual migraine prevention. Because these guidelines were last updated in 2012, they did not cover gepants (which will be discussed shortly). The AHS released a position statement in 2019 supporting the use of anti-CGRP monoclonal antibodies (mAbs) in those who cannot tolerate or have had an inadequate response to a 6-week trial of at least 2 AAN/AHA Level A or B treatments.8 No head-to-head trials exist between non-CGRP preventive therapies and the CGRP antagonists.

### CGRP-targeted prevention

Four anti-CGRP mAbs and 2 gepants have been approved for the prevention of chronic migraine.

### TABLE 5

<table>
<thead>
<tr>
<th>Medication</th>
<th>Starting dose (dosage range)</th>
<th>Adverse effects</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Beta-blockers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>25-100 mg bid (50-200 mg/d)</td>
<td>Fatigue, nausea, dizziness, depression, reduced exercise tolerance, orthostasis, decreased blood pressure</td>
<td>First-line treatment for those with high blood pressure; use with caution in those with diabetes, bradycardia, low blood pressure, asthma, depression, or age older than 60 y. Propranolol safest in pregnancy</td>
</tr>
<tr>
<td>Propranolol</td>
<td>20 mg bid (40-240 mg/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Timolol</td>
<td>5 mg daily (10-30 mg/d)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Antiepileptic drugs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divalproex sodium</td>
<td>250 mg bid (500-1500 mg/d)</td>
<td>Weight gain, dizziness, hepatotoxicity, bone marrow suppression, hair loss, pancreatitis, nausea, somnolence, tremor</td>
<td>Rarely used first line due to adverse effect profile; contraindicated during pregnancy</td>
</tr>
<tr>
<td>Valproate sodium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>25 mg/d (50-200 mg/d)</td>
<td>Paresthesia, altered taste, fatigue, nausea, anorexia, diarrhea, memory impairment</td>
<td>First-line treatment for those needing weight loss; contraindicated during pregnancy</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frovatriptan</td>
<td>2.5 mg bid</td>
<td>Dizziness, headache, paresthesia, dry mouth, dyspepsia, fatigue</td>
<td>Only for short-term prevention of menstrual migraine; contraindicated in those with stroke, coronary artery disease, peripheral vascular disease, uncontrolled hypertension, or ischemic bowel disease</td>
</tr>
<tr>
<td>OnabotulinumtoxinA</td>
<td>100 U SQ (155 U SQ every 12 wk)</td>
<td>Bladder dysfunction, urinary retention, dysphagia, neck pain</td>
<td>Approved only for chronic migraine</td>
</tr>
</tbody>
</table>

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8. Based on the 2012 Guidelines from the American Academy of Neurology and American Headache Society (AAN and AHS Level A ≥ 2 Class I randomized controlled trials incorporating 5 key study criteria and masked or objective outcome assessments).

9. Adequate trial requires at least 2 months at target dose.

10. Approved by the US Food and Drug Administration for migraine prevention.
<table>
<thead>
<tr>
<th>Medication, year approved</th>
<th>Target</th>
<th>FDA-approved adult dose and frequency</th>
<th>Migraine subtype studied</th>
<th>Primary efficacy endpoints and outcomes&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Adverse events (&gt; 2% in at least 1 treatment group)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Cost per month&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atogepant&lt;sup&gt;e&lt;/sup&gt; (Qulipta) 2021</td>
<td>Small-molecule CGRP antagonist</td>
<td>10, 30, or 60 mg/d Dose modifications with strong CYP3A4 inhibitors, strong and moderate CYP3A4 inducers, OATP inhibitors severe renal impairment Avoid use in patients with severe hepatic impairment</td>
<td>ADVANCE: Episodic ADVANCE&lt;sup&gt;bc&lt;/sup&gt;: Mean change in MMDs • 10 mg: -3.7 • 30 mg: -3.9 • 60 mg: -4.2 • Placebo: -2.5</td>
<td>Constipation, URTI, nausea, UTI, nasopharyngitis, fatigue, somnolence, increased blood creatine kinase level, sinusitis, gastroenteritis, increased ALT, influenza, sinus congestion, increased AST, anxiety</td>
<td>$1006</td>
<td></td>
</tr>
<tr>
<td>Eptinezumab (Vyepi)&lt;sup&gt;f&lt;/sup&gt; 2020</td>
<td>Humanized mAb targeting CGRP ligand</td>
<td>100 mg IV every 3 mo; can increase to 300 mg IV every 3 mo</td>
<td>PROMISE 1: Episodic PROMISE 1&lt;sup&gt;1c&lt;/sup&gt;: Change in MMDs • 30 mg: -4&lt;sup&gt;b&lt;/sup&gt; • 100 mg: -3.9 • 300 mg: -4.3 • Placebo: -3.2</td>
<td>PROMISE 1: URTI, nasopharyngitis, sinusitis, dizziness, nausea, bronchitis, cough, fatigue, back pain, influenza, diarrhea</td>
<td>100 mg: $598 300 mg: $1794</td>
<td></td>
</tr>
<tr>
<td>Erenumab (Aimovig)&lt;sup&gt;f&lt;/sup&gt; 2018</td>
<td>Fully human mAb targeting CGRP receptor</td>
<td>70 mg SQ monthly; can increase to 1 40 mg SQ monthly</td>
<td>ARISE: Episodic ARISE&lt;sup&gt;1a&lt;/sup&gt;: Change MMDs • 70 mg: -2.9 • Placebo: -1.8</td>
<td>ARISE: URTI, injection-site pain, nasopharyngitis, influenza, fatigue, nausea, migraine, sinusitis, constipation STRIVE: Nasopharyngitis, URTI, sinusitis, constipation, arthralgia, fatigue, nausea, influenza, UTI, back pain, injection-site pain, migraine, hypertension</td>
<td>70 mg: $724 140 mg: $724</td>
<td></td>
</tr>
</tbody>
</table>

been approved for migraine prevention in the United States. Differences between products include targets (ligand vs receptor), antibody IgG subtype, bioavailability, route of administration, and frequency of administration. As noted in the Phase 3 studies
TABLE 6  
CGRP inhibitors approved for migraine prevention in adults:  
Phase 3 study data¹ 19,30-47 (cont’d)

<table>
<thead>
<tr>
<th>Medication, year approved</th>
<th>Target</th>
<th>FDA-approved adult dose and frequency</th>
<th>Migraine subtype studied</th>
<th>Primary efficacy endpoints and outcomesb</th>
<th>Adverse events (&gt; 2% in at least 1 treatment group)c</th>
<th>Cost per monthd</th>
</tr>
</thead>
</table>
| Fremanezumab (Ajovy)² 2018 | Fully humanized mAb targeting CGRP peptide | 225 mg SQ monthly, or 675 mg SQ every 3 mo³ | HALO CM: Chronic  
HALO EM: Episodic | HALO CM³: Mean change in AHDs  
• Quarterly: –4.6  
• Monthly: –4.3  
• Placebo: –2.5  
HALO EM³: Mean change in MMDs  
• Quarterly: –3.4h  
• Monthly: –3.7h  
• Placebo: –2.2 | HALO CM: Injection-site reaction (pain, induration, erythema, hemorrhage), nasopharyngitis, URTI, sinusitis, dizziness, nausea  
HALO EM: Injection-site reaction (pain, induration, erythema, hemorrhage), fatigue, URTI, nasopharyngitis, UTI, bronchitis | $742 |

| Galcanezumab (Emgality)³ 2018 | Humanized mAb targeting CGRP peptide or ligand | Migraine: Load: 240 mg SQ  
Maintenance: 120 mg SQ  
Episodic cluster headaches: 300 mg SQ at onset of cluster headache and then monthly until end of cluster periodd | EVOLVE 1: Episodic  
EVOLVE 2: Episodic  
REGAIN: Chronic EPISODIC CLUSTER: Episodic cluster headache | EVOLVE 1³: Mean change in monthly MHDs  
• 120 mg: –4.7  
• 240 mg: –4.6  
• Placebo: –2.8  
EVOLVE 2³: Mean change in monthly MHDs  
• 120 mg: –4.3  
• 240 mg: –4.2  
• Placebo: –2.3  
REGAIN³: Mean change in monthly MHDs  
• 120 mg: –4.8  
• 240 mg: –4.6  
• Placebo: –2.7  
EPISODIC CLUSTER³: Mean change in weekly frequency of cluster headache attacks  
• 300 mg: –8.7  
• Placebo: –5.2 | EVOLVE 1: Injection site (pain, erythema, pruritus, reaction), nasopharyngitis, UTI, sinusitis, nausea, back pain, dizziness, bronchitis, cough, influenza, pruritus, migraine  
EVOLVE 2: Injection site (pain, reaction, erythema, pruritus, swelling), nasopharyngitis, URTI, dizziness, influenza, fatigue, diarrhea  
REGAIN: Injection site (pain, reaction, erythema, pruritus), nasopharyngitis, URTI, sinusitis, back pain, dizziness, cough, bronchitis, fatigue, URTI, migrainae, influenza, neck pain, oropharyngeal pain, pyrexia  
EPISODIC CLUSTER: Vertigo, injection-site pain and swelling, nasopharyngitis, pyrexia, increased ALT and AST | Migraine: Load: $1332  
Maintenance: $666  
Cluster: $1538 |

CONTINUED
### TABLE 6
**CGRP inhibitors approved for migraine prevention in adults:**
**Phase 3 study data** $^{19,30-47}$ (cont’d)

<table>
<thead>
<tr>
<th>Medication, year approved</th>
<th>Target FDA-approved adult dose and frequency</th>
<th>Migraine subtype studied</th>
<th>Primary efficacy endpoints and outcomes$^a$</th>
<th>Adverse events (&gt; 2% in at least 1 treatment group)$^c$</th>
<th>Cost per month$^d$</th>
</tr>
</thead>
</table>
| Rimegepant* (Nurtec ODT) 2021 | Small molecule CGRP antagonist 75 mg orally every other day | Phase 2/3 trial: Episodic | Phase 2/3 trial$^{19}$:
- Change in MMDs
  - 75 mg every other day: –4.3
  - Placebo: –3.5 | Nasopharyngitis, nausea, UTI, URTI | $2044$ (16 pills) |

**AHDs, average headache days; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FDA, US Food and Drug Administration; mAb, monoclonal antibody; MHD, migraine headache days; MMDs, monthly migraine days; OATP, organic anion transporting polypeptide; UTI, urinary tract infection.**

$^a$ All were Phase 3 trials except LIBERTY, which was Phase 3b; the rimegepant was a Phase 2/3 trial. All trials were multicenter, randomized, double-blinded, and placebo-controlled.

$^b$ With the exception of eptinezumab 30 mg, all products/doses were statistically superior to placebo.

$^c$ Listed in descending order of occurrence.

$^d$ Estimated cost based on lowest retail price listed on GoodRX (www.goodrx.com). Infusion fees would need to be applied.

$^e$ FDA approved for preventive treatment of episodic migraine.

$^f$ FDA approved for preventive treatment of migraine.

$^g$ Administered as 3 consecutive injections of 225 mg each.

$^h$ Representing least-square mean differences.

$^i$ FDA approved for preventive treatment of episodic cluster headaches.

$^j$ Administer as 3 consecutive injections of 100 mg each.

*TABLE 6* $^{19,30-47}$, these therapies are highly efficacious, safe, and tolerable.

**Gepants.** Rimegepant, discussed earlier for migraine treatment, is one of the CGRP receptor antagonists approved for prevention. The other is atogepant (Qulipta), approved only for prevention. Ubrogepant is not approved for prevention.

**Anti-CGRP mAb** is the only medication class specifically created for migraine prevention.$^{10,26}$ As already noted, several efficacious non-CGRP treatment options are available for migraine prevention. However, higher doses of those agents, if needed, can lead to intolerable adverse effects for some patients, thereby limiting overall efficacy. Anti-CGRP mAbs, a targeted, highly efficacious treatment option, offer efficacy comparable to non-CGRP agents with a more favorable adverse effect profile for those who cannot tolerate or achieve only minimal efficacy with traditional preventive therapies.$^{10}$

The targeted anti-CGRP approach, which can be used by patients with liver or kidney disease, results in decreased toxicity and minimal drug interactions. Long half-lives allow for monthly or quarterly injections, possibly resulting in increased compliance.$^{28}$ Dose titration is not needed, allowing for more rapid symptom management. The large molecular size of a mAb limits its transfer across the blood-brain barrier, making central nervous system adverse effects unlikely.$^{28}$ Despite the compelling mAb pharmacologic properties, their use may be limited by a lack of long-term safety data and the need for parenteral administration. Although immunogenicity—the development of neutralizing antibodies—can limit long-term tolerability or efficacy of mAbs generally,$^{26,28}$ anti-CGRP mAbs were engineered to minimally activate the immune system and have not been associated with immune suppression, opportunistic infections, malignancies, or decreased efficacy.$^{28}$

A pooled meta-analysis including 4 trials (3166 patients) found that CGRP mAbs compared with placebo significantly improved patient response rates, defined as at least a 50% and 75% reduction in monthly headache/migraine days from baseline to Weeks 9 to 12.$^{48}$ Another meta-analysis including 8 trials (2292 patients) found a significant reduction from baseline in monthly migraine days and...
monthly acute migraine medication consumption among patients taking CGRP mAbs compared with those taking placebo. Open-label extension studies have shown progressive and cumulative benefits in individuals who respond to anti-CGRP mAbs. Therefore, several treatment cycles may be necessary to determine overall efficacy of therapy.\textsuperscript{10,20}

\textbf{Cost initially can be a barrier.} Insurance companies often require step therapy before agreeing to cover mAb therapy, which aligns with the 2019 AHS position statement.\textsuperscript{10} Due to differences in insurance coverage, out-of-pocket expenses can vary greatly. However, options are available through online manufacturer assistance to reduce cost, making it comparable to other migraine treatments. Safety and efficacy studies of anti-CGRP mAbs use in pregnant individuals are limited. At this time, they should not be prescribed for those who are pregnant, planning to become pregnant, or breastfeeding. Counsel nonpregnant patients on appropriate contraception while using a mAb due to possible teratogenicity and negative pregnancy outcomes.\textsuperscript{20,25}

\textbf{When combination treatment may be appropriate}  
Monotherapy is the usual approach to preventing migraine due to advantages of efficacy, simplified regimens, lower cost, and reduced adverse effects.\textsuperscript{31} However, if a patient does not benefit from monotherapy even after trying dose titrations as tolerated or switching therapies, trying complementary combination therapy is appropriate. Despite a shortage of clinical trials supporting the use of 2 or more preventive medications with different mechanisms of action, this strategy is used clinically.\textsuperscript{16} Consider combination therapy in those with refractory disease, partial responses, or intolerance to recommended doses.\textsuperscript{52} Articles reporting on case study reviews have rationalized the combined use of onabotulinumtoxinA and anti-CGRP mAbs, noting better migraine control.\textsuperscript{51,53} The 2019 AHS position statement recommends adding a mAb to an existing preventive treatment regimen with no other changes until mAb effectiveness is determined, as the risk for drug interactions on dual therapy is low.\textsuperscript{10}

Safety and efficacy also have been demonstrated with the combination of preventive anti-CGRP mAbs and acute treatment with gepants as needed.\textsuperscript{34}

Overall, gepants and mAbs are as effective as traditional acute and preventive treatments for migraine, and they cause fewer adverse effects and often allow a more simplified regimen. Gepants and mAbs are viable options in the primary care setting. Due to limited long-term data and high cost, however, they routinely are used for refractory migraine rather than as first-line agents. These therapies are especially favorable options for patients when traditional migraine therapies yield inadequate efficacy, cause intolerable adverse effects, are contraindicated, or introduce the risk for medication interactions.

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References