Migraine Preventive Therapies

With new—and first-in-class—migraine-specific treatments, preventive treatment of migraine is changing quickly.

By Charisse Litchman, MD, FAHS and Sirisha Sanamandra, MBBS

Introduction
Migraine preventive therapy is indicated for patients with 4 or more migraine headache days per month, significant disability associated with individual attacks, or frequent acute medication use. Other indications for preventive therapy are unusual migraine type at any frequency, (eg, brainstem aura or hemiplegic migraines), and previous migrainous infarction.1-4 Unfortunately, available preventive therapy has been inadequate even when delivered optimally, with more than 80% of patients discontinuing preventive treatment within a year of initiation.5 Reasons for discontinuation include daily dosing, lack of efficacy, safety concerns, intolerance, drug–drug interactions, cost, and the development of medication overuse headache (MOH) in patients reaching too often for abortive medications for symptomatic relief.

With the development, approval, and recent release of monoclonal antibodies (MAb) to calcitonin gene-related peptide (CGRP) or the CGRP receptor for prevention of migraine, the field of headache medicine has the first treatment specifically designed for migraine prevention. CGRP is a main inflammatory mediator in migraine pathophysiology and therefore provides a useful target for therapy (Table 1).6-12

Oral Preventive Medications
When considering migraine preventive treatment, it is important to distinguish between episodic migraine (fewer than 15 headache days monthly) (EM) and chronic migraine (15 or more headache days monthly) (CM). Of the oral preventives listed in Tables 2 and 3, topiramate has the most evi-

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<th>Theory</th>
<th>Overview</th>
<th>Current evidence</th>
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<tr>
<td>CGRP theory</td>
<td>Increases in the level of CGRP have been measured in the nerves involved in nociception when migraine attacks occur</td>
<td>CGRP levels rise during a migraine and fall after symptoms resolve. Migraine can be triggered by infusing patients with CGRP. Triptans and onabotulinumtoxinA prevent CGRP release and are also effective for aborting and preventing headaches, respectively.</td>
</tr>
<tr>
<td>Cortical spreading depression (CSD)</td>
<td>Propagated waves of cortical activity, blood flow, metabolism, and MRI signal during migraine attacks mirrored aura</td>
<td>Many patients with migraine do not experience aura and premonitory symptoms such as confusion and yawning occur hours before the aura in different brain areas. Some abortive medications stop aura only; others stop only pain.</td>
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<tr>
<td>Serotonergic changes</td>
<td>Increased serotonin metabolites in urine collected during migraine suggested changing levels of serotonin could be involved</td>
<td>Triptans that block serotonergic receptors are effective for some people with migraine.</td>
</tr>
<tr>
<td>Dural neurogenic inflammation</td>
<td>Neurogenic inflammation in dura initiates migraine</td>
<td>Multiple drugs known to block dural protein extravasation in animal models of neurogenic inflammation have failed to yield clinical benefit in clinical migraine trials.</td>
</tr>
<tr>
<td>Vascular theory</td>
<td>Stimulating dural trigeminal afferents causes headaches, suggesting that intracranial blood vessel dilation initiates headache</td>
<td>Intracranial vessel dilation is not detectable with MRI or MRA during migraine.</td>
</tr>
</tbody>
</table>
# Table 2: Oral Medications for Migraine Prevention

<table>
<thead>
<tr>
<th>Drug/(Evidence level)</th>
<th>Dose</th>
<th>Adverse reactions</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antiepileptic drugs</strong></td>
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<tr>
<td>Topiramate(^{13-15}$/ (Level A)</td>
<td>25-200 mg/day</td>
<td>Cognitive changes, glaucoma, hyperchloremic acidosis, nephrolithiasis, paresthesias</td>
<td>Inhibits excitatory activity (glutamate) and enhances inhibitory activity (GABA)</td>
</tr>
<tr>
<td>Divalproex, sodium valproate(^{15,16}$/ (Level A)</td>
<td>400-1,000 mg/day</td>
<td>Alopecia/hair thinning, bone marrow dysfunction, drowsiness, hepatitis, neural tube defects, pancreatitis, teratogenicity, tremor, weight gain</td>
<td>Increases GABA to attenuate nociceptive neurotransmission; modulates serotonin</td>
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<tr>
<td><strong>Beta-blockers</strong></td>
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<tr>
<td>Propranolol(^{17}$/ (Level A)</td>
<td>40-240 mg/day</td>
<td>Bradycardia, bronchospasm, depression, dizziness, fatigue, impotence</td>
<td>Reduces adrenergic tone, norepinephrine release, and synthesis, and inhibits (\beta)-adrenergic receptors</td>
</tr>
<tr>
<td>Metoprolol(^{18}$/ (Level A)</td>
<td>100-200 mg/day</td>
<td></td>
<td></td>
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<tr>
<td>Timolol(^{19}$/ (Level A)</td>
<td>20-60 mg/day</td>
<td></td>
<td></td>
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<tr>
<td>Atenolol(^{20}$/ (Level B)</td>
<td>50-200 mg/day</td>
<td></td>
<td></td>
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<tr>
<td><strong>Antidepressants and tricyclic antidepressants</strong></td>
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<tr>
<td>Venlafaxine(^{21,22}$/ (Level B)</td>
<td>70-225 mg/day</td>
<td>Drowsiness, nausea</td>
<td>Inhibits serotonin/norepinephrine reuptake</td>
</tr>
<tr>
<td>Tricyclic antidepressant, amitriptyline(^{23}$/ (Level B)</td>
<td>10-300 mg/day</td>
<td>Agitation, anticholinergic effects (dry mouth, constipation, blurred vision), postural hypotension, sedation, seizures, sexual dysfunction, tremor, weight gain</td>
<td>Inhibits norepinephrine and serotonin high-affinity uptake; downregulates (\beta)-adrenergic receptors to decrease excitatory activity</td>
</tr>
<tr>
<td><strong>Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Lisinopril/ (Level C)</td>
<td>10-40 mg/day</td>
<td>Cough, dizziness, fatigue, hypotension</td>
<td>Blocks conversion of angiotensin I to angiotensin II and degradation of bradykinin, encephalin, and substance (P); increases prostacyclin</td>
</tr>
<tr>
<td>Candesartan/ (Level C)</td>
<td>16-32 mg/day</td>
<td>Cough, dizziness, fatigue, hypotension</td>
<td>Angiotensin receptor blockade, unknown mechanism for migraine</td>
</tr>
<tr>
<td><strong>Nonsteroidal anti-inflammatory agents (NSAIDS)</strong></td>
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<td></td>
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<tr>
<td>Naproxen/naproxen sodium(^{18,24}$/ (Level B)</td>
<td>500-1100 mg/day</td>
<td>Diarrhea, heartburn, gastric bleeding, stomach pain; use with caution in patients with gastrointestinal problems, hypertension, cardiovascular risk factors, or renal insufficiency</td>
<td>Inhibits prostaglandin biosynthesis and platelet aggregation</td>
</tr>
<tr>
<td>Histamine(^{25}$/ (Level B)</td>
<td>1-10 ng subcutaneous twice/week</td>
<td>Itching, injection reaction (burning sensation)</td>
<td>Inhibits mast cell degranulation and neuropeptide release at C-fiber endings and may modulate C-fibers and mast cell communication to control neurogenic inflammation</td>
</tr>
<tr>
<td>Cyproheptadine(^{26}$/</td>
<td>4 mg/day</td>
<td>Dry mouth, edema (ankle), light-headedness, nausea, sedation, weight gain; may inhibit growth in children</td>
<td>Serotonin, histamine, and muscarinic cholinergic receptor antagonist</td>
</tr>
</tbody>
</table>

\(^a\text{Level A = at least 2 high-quality randomized, controlled trials (RCTs) demonstrating efficacy. Level B = only 1 high-quality RCT, or 2 or more less rigorous studies suggesting efficacy. Level C = single less rigorous study indicating efficacy.}\)
dence for treatment of CM. Use of topiramate is limited, however, by cognitive side effects and contraindications in pregnancy. In contrast, topiramate can be helpful for people with comorbid epilepsy or idiopathic intracranial hypertension.

It is helpful to obtain a detailed history to identify potential triggers and identify comorbidities, such as depression and anxiety. Effectively identifying common comorbidities can guide medication choices for migraine prevention. For example, if a patient is hypertensive, a beta-blocker may be considered, or, if a patient has comorbid depression, a tricyclic antidepressant or venlafaxine may be considered. Pregnancy and pregnancy planning are also important factors to consider; for example, topiramate may interfere with the metabolism of oral contraceptives and render them ineffective. (See Migraine During Pregnancy in this issue.)

If a patient with CM does not respond to at least 1 medication from at least 2 classes of oral medications, botulinum toxin is an option. It is important to note that MAb CGRP antagonists have changed the treatment landscape significantly. With this migraine-specific preventive treatment available as a monthly injection, many patients choose to use it as a first option.

It is not necessary for the nonmigraine specialist to be familiar with all preventive treatment options available. Each practitioner should become comfortable with offering 1 option from each class of oral medication and at least 1 therapeutic MAb. More important than being able to deliver preventive treatments is being able to recognize when prevention is needed and refer appropriately.

### Injectable Preventive Medications

**OnabotulinumtoxinA**

OnabotulinumtoxinA is approved by the Food and Drug Administration (FDA) for prevention of CM (Table 4). It would be an understatement to say that its entry into the arsenal for migraine was short of revolutionary (See Procedural Treatments for Headache Disorders in this issue). OnabotulinumtoxinA does not cross the blood-brain barrier, and it is thought to prevent CM by blocking CGRP release from peripheral C fibers.\(^\text{12,30}\)

#### The CGRP Monoclonal Antibodies

In 2018, the FDA approved 3 MAb CGRP antagonists for prevention of EM and CM (ie, erenumab, fremanezumab, and galcanezumab) (see Table 4). In clinical trials, all 3 MAbs show clinical improvement through reduced headache frequency compared with placebo for patients with EM and CM. The profiles of these 3 medications are similar, with rapid onset of action, minimal side effects, ability to initiate at therapeutic doses without titration, and parenteral administration monthly or quarterly via self-administered subcutaneous injection. These attributes will likely increase patient adherence.

The MAb CGRP antagonists are approved to prevent both episodic and CM, whereas onabotulinumtoxinA is approved to prevent CM only. There are no head-to-head trials comparing the MAbs to onabotulinumtoxinA. Ease of administration and rapid onset of action are 2 benefits of using the MAbs. They are packaged in disposable prefilled autoinjectors or disposable prefilled syringes.

The MAbs have a serum half-life of 20 to 50 days,\(^\text{27}\) allowing monthly or quarterly injections, which translates to increased patient adherence vs oral prophylactic medications. The parenteral delivery route bypasses the decreased gastrointestinal absorption that often accompanies migraine, resulting in greater bioavailability than oral agents. As with most subcutaneous injections, the bioavailability of the CGRP antagonists ranges from 40% to 74%.\(^\text{28,29}\) In contrast to oral preventive medications, which require up to 3 months to reach therapeutic doses and maximal efficacy and onabotulinumtoxinA, which can take 2 to 3 cycles to demonstrate benefit, the MAbs are effective as early as 1 week, and produce meaningful reduction in migraine days per month within 1 month.\(^\text{30}\)

The safety profile of all 3 MAbs is close to that of placebo. Treatment-related adverse effects in clinical trials were injection site reactions for all 3 MAbs plus constipation for erenumab; postmarketing data suggest that constipation may be a side effect of all 3. Because CGRP is involved in cardiovascular homeostasis, glomerular filtration, bone metabolism, and the gastrointestinal mucosa,\(^\text{31-33}\) there needs to be close monitoring for adverse effects postmarketing. Whether chronic

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</tr>
</thead>
<tbody>
<tr>
<td>Riboflavin/(Level B)</td>
<td>400 mg/day</td>
<td>Abdominal pain, diarrhea, possible photosensitization</td>
<td>Unknown</td>
</tr>
<tr>
<td>CoQ10/(Level C)</td>
<td>100 mg 3 times daily</td>
<td>Abdominal pain/discomfort, elevated liver enzymes (mild), nausea, vomiting</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**Herbal**

- **Petasites**\(^b\)/(Level A) 50-75 mg twice daily: Burping

\(^a\) Level B = 1 high-quality RCT, or 2 or more less rigorous studies suggesting efficacy. Level C = single less rigorous study indicating efficacy.\(^9\)

\(^b\) Only if certified free of pyrrolizidine alkaloids and with liver function monitoring.
blockade of CGRP, a potent vasodilatory agent, results in hypertension and cardiac dysfunction and impedes its safeguard action in the face of cardiac and cerebral ischemia is of particular concern.\textsuperscript{34,35} Patients who received 140 mg of erenumab intravenously had no change from baseline in exercise duration, time to onset of ST segment depression, or time to onset of exercise-induced angina compared with those who took placebo; this was interpreted as a 97.6\% likelihood of cardiovascular safety.\textsuperscript{36} A low percentage of patients using the MAb CGRP antagonists develop antidrug antibodies (1\%-18\%), which may explain why no immunologically adverse reactions have been seen to date.\textsuperscript{37,38} The significance of antidrug antibodies remains unclear, and longitudinal monitoring will be necessary to determine if they reduce therapeutic effectiveness. A possible explanation for why there have been no serious immune-mediated adverse interactions is that these MAbs are human or fully humanized with few to no nonhuman amino acids. Because these MAbs are eliminated by the reticuloendothelial system and not metabolized by the liver or the kidney, there are fewer potential drug-drug interactions.\textsuperscript{11} Without breakdown into peptides and amino acids, no toxic metabolites are produced.\textsuperscript{39}

Differences among erenumab, fremanezumab, and galcanezumab are in dosages and intervals of administration (Table 4) and whether the antibody binds to CGRP or the CGRP receptor. Erenumab has been shown to work equally well in persons with CM who have or who do not have concomitant MOH\textsuperscript{40,41} compared with topiramate, which did not perform as well in patients with migraine plus MOH.\textsuperscript{30} Erenumab may resolve medication overuse in patients with CM.\textsuperscript{40}

\textit{Erenumab.} Because a less selective monoclonal antibody could be more likely to cause adverse side effects,\textsuperscript{42} it is notable that erenumab is highly selective for the CGRP receptor. Evaluated in patients whose migraine was not prevented by 2 or more prophylactic agents,\textsuperscript{30} erenumab proved beneficial in those patients with more refractory migraine. Erenumab is the only 1 of the 3 MAb\s that is fully human and is administered in 1 or 2 doses of 70 mg monthly via an autoinjector.\textsuperscript{42,43} The response is dose-dependent with a 10.5 day decrease in migraine days per month at 52 weeks with the 140-mg dose and an 8.5 day decrease in migraine days per month at 52 weeks with the 70-mg dose compared to baseline.\textsuperscript{44} In the open-label extension trial for erenumab, 65\% of patients experienced a 50\% or greater reduction in headache days, 42\% experienced a 75\% or greater reduction in headache days, and 26\% experienced a 100\% reduction in headache days.\textsuperscript{45} In the pivotal trial of erenumab for CM, after 1 year in the open-label extension, patients had 10.5 fewer migraines per month, which translates to a 4-month drop in migraines per year.\textsuperscript{46}

\textit{Fremanezumab.} A 95\% fully humanized MAb (remaining 5\% is murine) that binds CGRP, fremanezumab was also studied in patients with migraine refractory to treatment.\textsuperscript{47} Fremanezumab is administered monthly via a prefilled 225-mg syringe or quarterly with the injection of 3 syringes (total 675 mg). This flexibility may be desirable for patients who have difficulty adhering to monthly injections because the quarterly injections can are administered in the physician’s office. In a placebo-controlled add-on trial for both EM and CM, use of fremanezumab in combination with other migraine prophylactic agents (eg, anticonvulsants, antidepressants, and beta-blockers), patients had close to a 50\% reduction in headache days.\textsuperscript{47} In an open-label extension trial, Migraine Disability Assessment Scale (MIDAS) scores continued to drop over 6 months in patients who had monthly injections.\textsuperscript{48,49}

\textit{Galcanezumab.} A 90\% fully humanized MAb (the remaining 10\% is murine), galcanezumab binds to CGRP and is administered with a loading dose of 2 injections of 120 mg followed by monthly 120-mg injections. In clinical trials, 62\% of patients treated with 120 mg of galcanezumab had a 50\% or more reduction in the number of migraine days per month, 39\%
had more than a 75% reduction. For those with EM treated with galcanezumab, 16% had an average of 1 month of headache freedom during the 6-month study. 50

Access. Insurance coverage may drive how these drugs fit into our treatment paradigm. Given the safety and efficacy of the MAbs, they could be used as first-line treatment; however, they are expensive, and many insurance companies require documentation of patients’ migraine being refractory to treatment with 2 or 3 different oral prophylactic agents before approving the MAbs. Further, some insurance companies will not approve this therapy for 4 months for the last set of onabotulinumtoxinA injections—a requirement can increase patient disability while patients await treatment approval.

Conclusion

The field of headache medicine and the therapeutic options available to patients and physicians have expanded dramatically in just the last year. Several of the oral preventative medications and onabotulinumtoxinA continue to offer excellent migraine prevention to many patients. The addition of the anti-CGRP and anti-CGRP receptor MAbs to the physician’s armamentarium has revolutionized migraine treatment. Our focus now must include ascertaining the long-term safety profile of these agents, encouraging untreated patients to seek treatment, and overcoming insurance barriers to make these advances available to all patients with migraine.


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