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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.

PRACTICE RECOMMENDATIONS

› *Consider small-molecule calcitonin gene-related peptide (CGRP) receptor antagonists (gepants) for acute migraine treatment after treatment failure of at least 2 non-CGRP first-line therapies.* (A)

› *Consider anti-CGRP monoclonal antibodies or gepants for migraine prevention if traditional therapies have proven ineffective or are contraindicated or intolerable to the patient.* (A)

› *Add an anti-CGRP monoclonal antibody or gepant to existing preventive treatment if the patient continues to experience migraine.* (B)

Strength of recommendation (SOR)

(A) Good-quality patient-oriented evidence

(B) Inconsistent or limited-quality patient-oriented evidence

(C) Consensus, usual practice, opinion, disease-oriented evidence, case series

Migraine is a headache disorder that often causes unilateral pain, photophobia, phonophobia, nausea, and vomiting. More than 70% of office visits for migraine are made to primary care physicians.[1] Recent data suggest migraine may be caused primarily by neuronal dysfunction and only secondarily by vasodilation.[2] Although there are numerous classes of drugs used for migraine prevention and treatment, their success has been limited by inadequate efficacy, tolerability, and patient adherence.[3] The discovery of pro-inflammatory markers such as calcitonin gene-related peptide (CGRP) has led to the development of new medications to prevent and treat migraine.[4]

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.[5] This results in increased cortical excitability, central trigeminal-thalamic sensitization, and defective descending pain modulatory activity.[6] 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.[5] 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.[7] 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-

It has been theorized that gepants bind to calcitonin gene-related peptide receptors, resulting in decreased blood flow to the brain, inhibition of neurogenic inflammation, and reduced pain signaling.

to-severe pain intensity, and (4) aggravated by or causing avoidance of routine physical activity.[7] The headache attacks also should have (1) associated nausea or vomiting or (2) photophobia and phonophobia.[7] 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 (**TABLE 1**).[8] 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.[8] Potential triggers for migraine can be found in **TABLE 2**.[9]

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.[7,10]

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**.[11] Lasmiditan (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.[11,12] In some placebo-controlled studies, acetaminophen was less effective than NSAIDs, but was safer because it did not cause gastric irritation or antiplatelet effects.[12]

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TABLE 1

SNNOOP10 red flags for secondary headache disorder[8]

Systemic symptoms including fever
Neoplasm in history
Neurologic deficit or dysfunction (including decreased consciousness)
Onset of headache is sudden or abrupt
Older age (> 65 years)
Pattern change or recent onset of headache
Positional headache
Precipitated by sneezing, coughing, or exercise
Papilledema
Progressive headache and atypical presentations
Pregnancy or puerperium
Painful eye with autonomic features
Posttraumatic onset of headache
Pathology of the immune system such as HIV
Painkiller overuse or new drug at onset of headache

TABLE 2

Migraine triggers[9]

Anxiety
Bright or flashing lights
Depression
Emotion
Hangover
Head trauma
Hormonal changes
Loud or sudden noises
Low blood sugar
Motion sickness
Overexertion
Skipped meals
Some medications
Stress
Strong odors or fumes
Sudden changes in weather or environment
Tobacco
Too much or not enough sleep

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-$HT_{1B/1D}$ 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.[13] Lasmiditan is a selective serotonin receptor (5-HT_{1F}) agonist that lacks vasoconstrictor activity. This is an option for patients with relative contraindications to triptans due to cardiovascular risk factors.[10]

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.[14] 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.[15]

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.[11] 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.[12] There is no high-quality evidence supporting the efficacy of barbiturates (ie, butalbital-containing compounds) for acute migraine treatment.[11] Moreover, use of these agents may increase the likelihood of progression from episodic to chronic migraine.[16]

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[a 11]

Medication	Dose[b]	Adverse effects	Comments
Acetaminophen	500-1000 mg once	Hepatotoxicity with excessive dosing	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.
NSAIDs			
Aspirin	325-650 mg once	**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	Highest risk for gastric and duodenal damage. Contraindicated during pregnancy and in patients with bleeding disorders.
Diclofenac	50-100 mg once		Available in a powdered form for dilution with water for oral solution.
Ibuprofen	200-600 mg once		Well tolerated. Shorter half-life compared to naproxen.
Naproxen	500-750 mg once		Well tolerated. Slower onset but can be dosed less frequently than ibuprofen. Available in a combination product with sumatriptan.
Triptans			
Almotriptan (Axert)	6.25-12.5 mg. May repeat after 2 h. Max dose, 25 mg/d.	**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	Dose adjustments in liver or severe renal disease. Potential drug interactions with potent CYP3A4 inhibitors.
Eletriptan (Relpax)	20-40 mg. May repeat after 2 h. Max dose, 80 mg/d.		Potential drug interactions with potent CYP3A4 inhibitors.
Frovatriptan (Frova)	2.5 mg. May repeat after 2 h. Max dose, 7.5 mg/d		Longest half-life of the triptans (~26 h).
Naratriptan (Amerge)	1-2.5 mg. May repeat once after 4 h. Max dose, 5 mg/d.		Dose adjustments in liver or severe renal disease.
Rizatriptan (Maxalt)	5-10 mg (5 mg with propranolol). May repeat after 2 h. Max dose, 30 mg/d.		Available in orally disintegrating tablets. Contraindicated if MAOI used in the past 2 weeks.
Sumatriptan (Imitrex)	**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.		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.
Zomitriptan (Zomig)	**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.		Available in orally disintegrating tablets. Contraindicated if MAOI used in the past 2 weeks.

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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.[17] 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

TABLE 3

Non-CGRP migraine treatment first-line therapies[a] [11] (*cont'd*)

Medication	Dose[b]	Adverse effects	Comments
Selective triptan			
Lasmiditan (Reyvow)	Oral tab: 50, 100, or 200 mg. Max 1 dose per day.	**Most common:** Dizziness, fatigue, sedation, paresthesia, nausea. May cause driving impairment (do not drive within 8 h of dose) **Rare/severe:** Serotonin syndrome	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).

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.

to the brain, inhibition of neurogenic inflammation, and reduced pain signaling.[17] 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),[18] rimegepant (Nurtec),[19] and zavegepant (Zavzpret)[20]—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**[18-24]).

Ubrogepant, in 2 Phase 3 trials (ACHIEVE I and ACHIEVE II) demonstrated effectiveness compared with placebo.[21,22] 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.[25]

Rimegepant was also superior to placebo (59% vs 43%) in pain relief at 2 hours post dose and other secondary endpoints.[23] Rimegepant also has potential drug interactions and dose adjustments (**TABLE 4**[18-24]).

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%).[24] Dosage modifications are not needed with mild-to-moderate renal or hepatic disease.[20]

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.[18,19]

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).[10] 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

TABLE 4

Small-molecule CGRP receptor antagonists (gepants): Phase 3 study data in acute treatment[18-24]

Medication, year approved	FDA-approved adult dose and frequency	Study participants[a]	Primary efficacy endpoints and outcomes[b]	Adverse events (> 2% reported)	Cost[c]
Rimegepant (Nurtec) 2020	75 mg, dissolve on or under the tongue. Max dose, 75 mg/d Avoid concomitant use with strong CYP3A4 inducers or inhibitors of CYP3A4, P-gp, or BCRP. Dose modification with moderate CYP3A4 inhibitors. Avoid use in patients with severe hepatic impairment or CrCl < 15 mL/min.	Migraine with or without aura	% free from pain at 2 h after initial dose[23]: • 75 mg: 21.2% • *Placebo*: 10.9% % without migraine-associated MBS identified at baseline at 2 h after initial dose[23]: • 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 Avoid concomitant use with strong CYP3A4 inducers. Dose modifications with CYP3A4 inhibitors, in severe hepatic impairment, and with CrCl of 15-29 mL/min. Avoid use with CrCl < 15 mL/min.	**ACHIEVE I, ACHIEVE II:** Migraine with or without aura	% free from pain at 2 h after initial dose: **ACHIEVE I**[21]: • 50 mg: 19.2% • 100 mg: 21.2% • *Placebo*: 11.8% **ACHIEVE II**[22]: • 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**[21]: • 50 mg: 38.6% • 100 mg: 37.7% • *Placebo*: 27.8% **ACHIEVE II**[22]: • 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 Avoid use in patients with severe hepatic impairment or CrCl < 30 mL/min.	Migraine with or without aura	% free from pain at 2 h after initial dose[24]: • 10 mg: 24% • *Placebo*: 15% % without migraine-associated MBS identified at baseline at 2 h after initial dose[24]: • 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).

TABLE 5

Adult migraine prophylaxis with established efficacy[a] [27-29]

Medication	Starting dose (dosage range)[b]	Adverse effects	Comments
Beta-blockers			
Metoprolol	25-100 mg bid (50-200 mg/d)	Fatigue, nausea, dizziness, depression, reduced exercise tolerance, orthostasis, decreased blood pressure	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
Propranolol[c]	20 mg bid (40-240 mg/d)		
Timolol[c]	5 mg daily (10-30 mg/d)		
Antiepileptic drugs			
Divalproex sodium[c]	250 mg bid (500-1500 mg/d)	Weight gain, dizziness, hepatotoxicity, bone marrow suppression, hair loss, pancreatitis, nausea, somnolence, tremor	Rarely used first line due to adverse effect profile; contraindicated during pregnancy
Valproate sodium			
Topiramate[c]	25 mg/d (50-200 mg/d)	Paresthesia, altered taste, fatigue, nausea, anorexia, diarrhea, memory impairment	First-line treatment for those needing weight loss; contraindicated during pregnancy
Others			
Frovatriptan	2.5 mg bid	Dizziness, headache, paresthesia, dry mouth, dyspepsia, fatigue	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
OnabotulinumtoxinA[a,c]	100 U SQ (155 U SQ every 12 wk)	Bladder dysfunction, urinary retention, dysphagia, neck pain	Approved only for chronic migraine

[a] 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).

[b] Adequate trial requires at least 2 months at target dose.

[c] Approved by the US Food and Drug Administration for migraine prevention.

headache disability.[26] 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[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[b] treatments.[10] 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

[a] ≥ 2 Class I randomized controlled trials incorporating 5 key study criteria and masked or objective outcome assessments.

[b] 1 Class I randomized controlled clinical trial, or 2 Class II randomized controlled trials lacking ≥ 1 key study criteria.

TABLE 6

CGRP inhibitors approved for migraine prevention in adults: Phase 3 study data[a 19,30-47]

Medication, year approved	Target	FDA-approved adult dose and frequency	Migraine subtype studied	Primary efficacy endpoints and outcomes[b]	Adverse events (> 2% in at least 1 treatment group)[c]	Cost per month[d]
Atogepant[e] (Qulipta) 2021	Small-molecule CGRP antagonist	10, 30, or 60 mg/d Dose modifications with strong CYP3A4 inhibitors, strong and moderate CYP3A4 inductors, OATP inhibitors severe renal impairment Avoid use in patients with severe hepatic impairment	**ADVANCE:** Episodic	**ADVANCE[46]:** Mean change in MMDs • 10 mg: –3.7 • 30 mg: –3.9 • 60 mg: –4.2 • *Placebo*: –2.5	Constipation, URTI, nausea, UTI, nasopharyngitis, fatigue, somnolence, increased blood creatine kinase level, sinusitis, gastroenteritis, increased ALT, influenza, sinus congestion, increased AST, anxiety	$1006
Eptinezumab (Vyepti)[f] 2020	Humanized mAb targeting CGRP ligand	100 mg IV every 3 mo; can increase to 300 mg IV every 3 mo	**PROMISE 1:** Episodic **PROMISE 2:** Chronic	**PROMISE 1[34]:** Change in MMDs • 30 mg: –4[b] • 100 mg: –3.9 • 300 mg: –4.3 • *Placebo*: –3.2 **PROMISE 2[35]:** Change in MMDs • 100 mg: –7.7 • 300 mg: –8.2 • *Placebo*: –5.6	**PROMISE 1:** URTI, nasopharyngitis, sinusitis, dizziness, nausea, bronchitis, cough, fatigue, back pain, influenza, diarrhea **PROMISE 2:** Nasopharyngitis, URTI, sinusitis, migraine, UTI, nausea, fatigue	100 mg: $598 300 mg: $1794
Erenumab (Aimovig)[f] 2018	Fully human mAb targeting CGRP receptor	70 mg SQ monthly; can increase to 140 mg SQ monthly	**ARISE:** Episodic **STRIVE:** Episodic **LIBERTY:** Refractory episodic	**ARISE[36]:** Change MMDs • 70 mg: –2.9 • *Placebo*: –1.8 **STRIVE[37]:** Mean change MMDs • 70 mg: –3.2 • 140 mg: –3.7 • *Placebo*: –1.8 **LIBERTY[38]:** Proportion of patients with ≥ 50% reduction in mean MMDs • 140 mg: 30% • *Placebo*: 14%	**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 **LIBERTY:** Injection-site pain, back pain, nasopharyngitis, dizziness, fatigue, injection-site erythema, neck pain, URTI	70 mg: $724 140 mg: $724

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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.[28] As noted in the Phase 3 studies

TABLE 6

CGRP inhibitors approved for migraine prevention in adults: Phase 3 study data[a] [19,30-47] (*cont'd*)

Medication, year approved	Target	FDA-approved adult dose and frequency	Migraine subtype studied	Primary efficacy endpoints and outcomes[b]	Adverse events (> 2% in at least 1 treatment group)[c]	Cost per month[d]
Fremanezumab (Ajovy)[f] 2018	Fully humanized mAb targeting CGRP peptide	225 mg SQ monthly, or 675 mg SQ every 3 mo[g]	**HALO CM:** Chronic **HALO EM:** Episodic	**HALO CM[39]:** Mean change in AHDs • Quarterly: –4.6 • Monthly: –4.3 • *Placebo*: –2.5 **HALO EM[40]:** Mean change in MMDs • Quarterly: –3.4[h] • Monthly: –3.7[h] • *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)[f,i] 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 period[j]	**EVOLVE 1:** Episodic **EVOLVE 2:** Episodic **REGAIN:** Chronic **EPISODIC CLUSTER:** Episodic cluster headache	**EVOLVE 1[41]:** Mean change in monthly MHDs • 120 mg: –4.7 • 240 mg: –4.6 • *Placebo*: –2.8 **EVOLVE 2[42]:** Mean change in monthly MHDs • 120 mg: –4.3 • 240 mg: –4.2 • *Placebo*: –2.3 **REGAIN[43]:** Mean change in monthly MHDs • 120 mg: –4.8 • 240 mg: –4.6 • *Placebo*: –2.7 **EPISODIC CLUSTER[44]:** 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, fatigue, back pain, UTI, abdominal pain, diarrhea, migraine, influenza, neck pain, oropharyngeal pain, sinusitis, arthralgia, pyrexia. **EPISODIC CLUSTER:** Vertigo, injection-site pain and swelling, nasopharyngitis, pyrexia, increased ALT and AST	Migraine: Load: $1332 Maintenance: $666 Cluster: $1538

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TABLE 6

CGRP inhibitors approved for migraine prevention in adults: Phase 3 study data[a] [19,30-47] (*cont'd*)

Medication, year approved	Target	FDA-approved adult dose and frequency	Migraine subtype studied	Primary efficacy endpoints and outcomes[b]	Adverse events (> 2% in at least 1 treatment group)[c]	Cost per month[d]
Rimegepant[e] (Nurtec ODT) 2021	Small molecule CGRP antagonist	75 mg orally every other day	**Phase 2/3 trial:** Episodic	**Phase 2/3 trial[45]:** 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; URTI, upper respiratory tract infection; 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.[49] 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.[10,28]

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.[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.[28,50]

Unlike triptans and ergotamine derivatives, gepants do not constrict blood vessels and may have a unique role in patients with contraindications to triptans.

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.[51] 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.[10] Consider combination therapy in those with refractory disease, partial responses, or intolerance to recommended doses.[52] Articles reporting on case study reviews have rationalized the combined use of onabotulinumtoxinA and anti-CGRP mAbs, noting better migraine control.[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.[10] Safety and efficacy also have been demonstrated with the combination of preventive anti-CGRP mAbs and acute treatment with gepants as needed.[54]

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. JFP

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Monoclonal antibodies are highly efficacious options for those who cannot tolerate or achieve only minimal efficacy with traditional preventive therapies.