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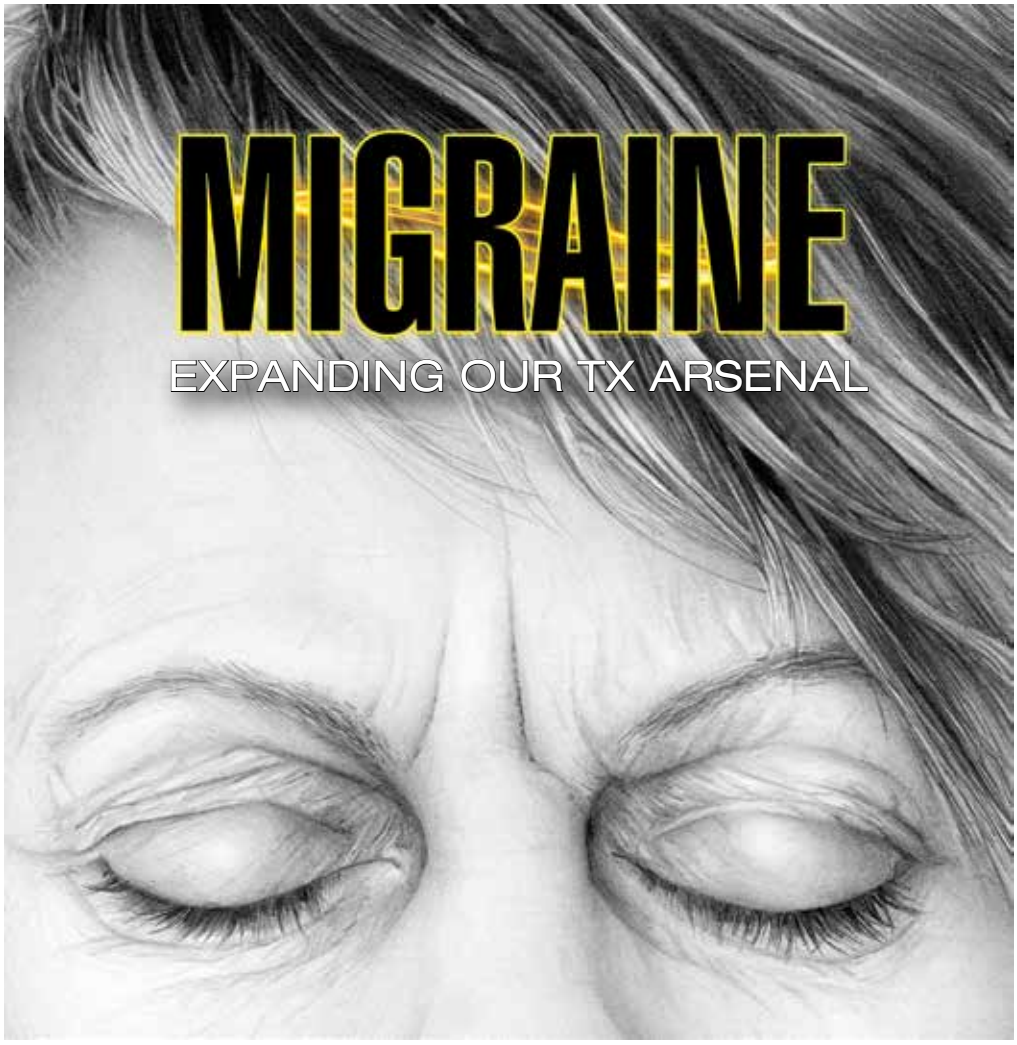

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Beyond tried-and-true therapies are new therapeutic targets on the horizon—giving you a bigger toolbox to help patients abort and prevent migraine episodes.

Migraine is a highly disabling primary headache disorder that affects more than 44 million Americans annually.[1] The disorder causes pain, photophobia, phonophobia, and nausea that can last for hours, even days. Migraine headaches are 2 times more common in women than in men; although migraine is most common in people 30 to 39 years of age, all ages are affected.[2,3] Frequency of migraine headache is variable; chronic migraineurs experience more than 15 headache days a month.

Recent estimates indicate that the cost of acute and chronic migraine headaches reaches approximately $78 million a year in the United States.[4] This high burden of disease has made effective migraine treatment options absolutely essential. Recent

advances in our understanding of migraine pathophysiology have led to new therapeutic targets; there are now many novel treatment approaches on the horizon.

In this article, we review the diagnosis and management of migraine in detail. Our emphasis is on evidence-based approaches to acute and prophylactic treatment, including tried-and-true options and newly emerging therapies.

Neuronal dysfunction and a genetic predisposition

Although migraine was once thought to be caused by abnormalities of vasodilation, current research suggests that the disorder has its origins in primary neuronal dysfunction. There appears to be a genetic predisposition toward widespread neuronal hyperexcitability in migraineurs.[5] In addition, hypothalamic neurons are thought to initiate migraine by responding to changes in brain homeostasis. Increased parasympathetic tone might activate meningeal pain receptors or lower the threshold for transmitting pain signals from the thalamus to the cortex.[6]

Prodromal symptoms and aura appear to originate from multiple areas across the brain, including the hypothalamus, cortex, limbic system, and brainstem. This widespread brain involvement might explain why some headache sufferers concurrently experience a variety of symptoms, including fatigue, depression, muscle pain, and an abnormal sensitivity to light, sound, and smell.[6,7]

Although the exact mechanisms behind each of these symptoms have yet to be defined precisely, waves of neuronal depolarization—known as cortical spreading depression—are suspected to cause migraine aura.[8-10] Cortical spreading depression activates the trigeminal pain pathway and leads to the release of pro-inflammatory markers such as calcitonin gene-related protein (CGRP).[6] A better understanding of these complex signaling pathways has helped provide potential therapeutic targets for new migraine drugs.

Diagnosis: Close patient inquiry is most helpful

The International Headache Society (IHS) criteria for primary headache disorders serve as the basis for the diagnosis of migraine and its subtypes, which include migraine without aura and migraine with aura. Due to variability of presentation, migraine with aura is further subdivided into migraine with typical aura (with and without headache), migraine with brainstem aura, hemiplegic migraine, and retinal migraine.[11]

How is migraine defined? Simply, migraine is classically defined as a unilateral, pulsating headache of moderate to severe intensity lasting 4 to 72 hours, associated with photophobia and phonophobia or nausea and vomiting, or both.[11] Often visual in nature, aura is a set of neurologic symptoms that lasts for minutes and precedes the onset of the headache. The visual aura is often described as a scintillating scotoma that begins near the point of visual fixation and then spreads left or right. Other aura symptoms include tingling or numbness (second most common), speech disturbance (aphasia), motor changes and, in rare cases, a combination of these in succession. By definition, all of these symptoms fully resolve between attacks.[11]

Validated valuable questionnaires. To help with accurate and timely diagnosis, researchers have developed and validated simplified questionnaires that can be completed independently by patients presenting to primary care (**TABLE 1**[12,13]):

- **ID Migraine** is a set of 3 questions that scores positive when a patient endorses at least 2 of the 3 symptoms.[12]
- **MS-Q** is similar to the ID Migraine but includes 5 items. A score of ≥4 is a positive screen.[13]

The sensitivity and specificity of MS-Q (0.93 and 0.81, respectively)

PRACTICE RECOMMENDATIONS

› *Offer treatment with a triptan to adult patients with moderate-to-severe episodic migraine.* (A)

› *Consider prescribing topiramate, divalproex sodium, metoprolol, propranolol, or the herbal,* Petasites hybridum*, for the prevention of recurrent episodic migraine that has not responded to a reduction in headache triggers.* (A)

› *Add onabotulinumtoxinA injection to your therapeutic toolbox as an effective preventive treatment for chronic migraine (≥15 headache days a month for 3 months).* (B)

› *Recommend magnesium and feverfew as adjunctive preventive treatments for 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

TABLE 1

2 Helpful questionnaires for pursuing a migraine diagnosis*[12,13]

ID Migraine[12]	
During the last 3 months, did you have the following with your headaches?	
Felt nauseated or sick to your stomach	Yes/No
Light bothered you a lot (or a lot more than when you do not have headaches)	Yes/No
Your headaches limited your ability to work, study, or do what you needed to do for at least 1 day	Yes/No

MS-Q[13]	
Instructions: The questions below refer to the headaches or migraine episodes without headache that you may have experienced in your lifetime. Answer each question as indicated. If you are not sure how to answer a given question, please answer what you believe is most correct.	
Do you have frequent or intense headaches?	Yes/No
Do your headaches usually last more than 4 hours?	Yes/No
Do you usually suffer from nausea when you have a headache?	Yes/No
Does light or noise bother you when you have a headache?	Yes/No
Does headache limit any of your physical or intellectual activities?	Yes/No

*A score of ≥2 on the ID Migraine and ≥4 on MS-Q is a positive screen for migraine.

After taking the initial history (headache onset, location, duration, associated symptoms), focus attention on assessing the risk of intracranial pathology.

are slightly higher than those of ID Migraine (0.81 and 0.75).[13]

Remember POUND. This mnemonic device can also be used during history-taking to aid in diagnostic accuracy. Migraine is highly likely (92%) in patients who endorse 4 of the following 5 symptoms and unlikely (17%) in those who endorse ≤2 symptoms[14]: **P**ulsatile quality of headache 4 to 72 h**O**urs in duration, **U**nilateral location, **N**ausea or vomiting, and **D**isabling intensity.

Differential Dx. Although the differential diagnosis of headache is broad (**TABLE 2**[14,15]), the history alone can often guide clinicians towards the correct assessment. After taking the initial history (headache onset, location, duration, and associated symptoms), focus your attention on assessing the risk of intracranial pathology. This is best accomplished by assessing specific details of the history (**TABLE 3**[14]) and findings on physical examination[15]:

- blood pressure measurement (seated, legs uncrossed, feet flat on the floor; having rested for 5 minutes; arm well supported)
- cranial nerve exam
- extremity strength testing
- eye exam (vision, extra-ocular muscles, visual fields, pupillary reactivity, and funduscopic exam)
- gait (tandem walk)
- reflexes.

Further testing needed? Neuroimaging should be considered only in patients with an abnormal neurologic exam, atypical headache features, or certain risk factors, such as an immune deficiency. There is no role for electroencephalography or other diagnostic testing in migraine.[16]

Take a multipronged approach to treatment

As with other complex, chronic conditions, the treatment of migraine should take a multifaceted approach, including management of acute symptoms as well as prevention of future headaches. In 2015, the American Headache Society published a systematic review that specified particular treatment goals for migraine sufferers.[17] These goals include:

- headache reduction

TABLE 2
Establishing the differential diagnosis of headache[14,15]

Cause of headache	Triggers
Primary headache syndrome	Cluster headache
	Tension-type headache
Autoimmune	Autoimmune thyroiditis
	Systemic lupus erythematosus
	Temporal arteritis
Congenital	Arachnoid cyst
	Arnold–Chiari malformation
	Pineal cyst
Degenerative	Cervical spondylosis
	Osteoarthritis
	Temporomandibular joint disorder
Endocrine or metabolic	Estrogen withdrawal
	Growth hormone imbalance
	Hypoglycemia
	Hypothyroidism and hyperthyroidism
	Parathyroid disease
Iatrogenic or intoxication	Nonsteroidal anti-inflammatory drug–induced headache
	Substance intoxication (eg, alcohol, carbon monoxide)
	Substance withdrawal (eg, alcohol, medications)
Infectious	Acute and chronic sinusitis
	Meningitis
Neoplastic	Lymphoma
	Metastases
	Primary brain tumor
Trauma	Concussion
	Skull fracture
Vascular	Acute hypertension
	Carotid dissection
	Intracerebral hypertension
	Subarachnoid hemorrhage
	Subdural hematoma

- headache relief
- decreased disability from headache
- elimination of nausea and vomiting
- elimination of photophobia and phonophobia.

Our review, which follows, of therapeutic options focuses on the management of migraine in adults. Approaches in special populations (older adults, pregnant women, and children) are discussed afterward.

Pharmacotherapy for acute migraine

Acute migraine should be treated with an abortive medication at the onset of headache.

Electroencephalography and other diagnostic testing have no role in the workup of migraine.

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TABLE 3

Risk factors for intracranial pathology[14]

Acute headache
Abnormal neurologic exam
Acute "thunderclap" headache
Age >55 years
History of human immunodeficiency virus infection, cancer, or other type of immunosuppression
Occipitonuchal location
Systemic illness (eg, fever, stiff neck, rash)
Non-acute headache
Associated with exertion (eg, exercise, sex) or Valsalva maneuver
Lack of coordination
Leads to awakening from sleep
Localized neurologic findings
Rapidly increasing frequency

Treat migraine with a multifaceted approach, including management of acute symptoms and prevention of future headaches.

The immediate goal is to relieve pain within 2 hours and prevent its recurrence within the subsequent 48 hours (**TABLE 4**[12,18-20]).

In the general population, mild, infrequent migraines can be managed with acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs).[21]

For moderate-to-severe migraine, triptans, which target serotonin receptors, are the drug of choice for most patients.[21] Triptans are superior to placebo in achieving a pain-free state at 2 and 24 hours after administration; eletriptan has the most desirable outcome, with 68% of patients pain free at 2 hours and 54% pain free at 24 hours.[22] Triptans are available as sublingual tablets and nasal sprays, as well as subcutaneous injections for patients with significant associated nausea and vomiting. Avoid prescribing triptans for patients with known vascular disease (eg, history of stroke, myocardial infarction, peripheral vascular disease, uncontrolled hypertension, or signs and symptoms of these conditions), as well as for patients with severe hepatic impairment.

Importantly, although triptans all have a similar mechanism of action, patients might respond differently to different drugs within the class. If a patient does not get adequate headache relief from an appropriate dosage of a given triptan during a particular migraine episode, a different triptan can be tried during the next migraine.[22] Additionally, if a patient experiences an adverse effect from one triptan, this does not necessarily mean that a trial of another triptan at a later time is contraindicated.

For patients who have an incomplete response to migraine treatment or for those with frequent recurrence, the combination formulation of sumatriptan, 85 mg, and naproxen, 500 mg, showed the highest rate of resolution of headache within 2 hours compared with either drug alone.[23] A similar result might be found by combining a triptan known to be effective for a patient and an NSAID other than naproxen. If migraine persists despite initial treatment of an attack, a different class of medication should be tried during the course of that attack to attain relief of symptoms of that migraine.[21]

When a patient is seen in an acute care setting (eg, emergency department, urgent care center) while suffering a migraine, additional treatment options are available. Intravenous (IV) anti-emetics are useful for relieving the pain of migraine and nausea, and can be used in combination with an IV NSAID (eg, ketorolac).[21] The most effective anti-emetics are dopamine receptor type-2 blockers, including chlorpromazine, droperidol, metoclopramide, and prochlorperazine, which has the highest level of efficacy.[24] Note that these medications do present the risk of a dystonic reaction; diphenhydramine is therefore often used in tandem to mitigate such a response.

Looking ahead. Although triptans are the current first-line therapy for acute migraine, their effectiveness is limited. Only 20% of patients report sustained relief of pain in the 2 to 24 hours after treatment, and the response can vary from episode to episode.[25]

With better understanding of the pathophysiology of migraine, a host of novel anti-migraine drugs are on the horizon.

CGRP receptor antagonists. The neuropeptide CGRP, which mediates central and peripheral nervous system pain signaling, has been noted to be elevated during acute migraine attacks[26]; clinical trials are therefore

TABLE 4

Migraine therapy: Options[a] and promising approaches[12,18-20]

Drug class or device	Medications/treatment	Important considerations
Available for acute migraine		
Over-the-counter analgesics	Acetaminophen, ibuprofen, naproxen	For mild, infrequent migraine only Frequent use can lead to medication overuse headache
Barbiturates	Amobarbitol, butalbital–acetaminophen–caffeine, pentobarbital	For moderate-to-severe migraine For symptom control, but *only* during an acute episode Can cause central nervous system depression and medication overuse headache High addictive potential Recommend *against* prescribing as first-line treatment in recurrent headache disorders
Dihydroergotamine	—	For moderate-to-severe migraine Vasoconstrictive Does not prevent headache or reduce number of migraine attacks
Triptans	Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, zolmitriptan	For moderate-to-severe migraines Taken at onset of headache Avoid in patients with history of atherosclerotic vascular disease FDA warning about potential for serotonin syndrome with concomitant use of triptans and SSRIs or SNRIs[12]
Triptan-NSAID combination	Sumatriptan and naproxen sodium (tablet)	For moderate-to-severe migraine Consider when use of a single drug fails to provide adequate control
On the horizon		
Calcitonin gene-related peptide receptor antagonist	Ubrogepant	Awaiting FDA approval Better tolerated than triptans; fewer central nervous system adverse effects[18] Concerns for liver toxicity[19]
Selective serotonin 5-HT_{1f} receptor agonist	Lasmiditan[20]	Investigational Not vasoconstrictive Potentially safe for patients with cardiovascular disease
Therapeutic devices		
sTMS mini	Single pulses to the back of the head	Appproved in 2013 for acute migraine with aura Hand-held device Potentially high out-of-pocket costs

TABLE 4

Migraine therapy: Options[a] and promising approaches[12,18-20] *(cont'd)*

Drug class or device	Medications/treatment	Important considerations
gammaCore	Transcutaneous vagal nerve stimulation	For acute migraine and migraine prophylaxis Thought to suppress high levels of glutamate in the trigeminal nucleus Held against the neck; requires 2 minutes to administer
Spring TMS	TMS uses single pulses to the back of the head; used during acute headache Being studied for migraine prophylaxis (approved for this use in the European Union)	Approved in 2014 for acute migraine with aura Effective for headache cessation at 2 hours in 40% of patients Avoid in patients with an implanted metal device or history of seizures

FDA, Food and Drug Administration; NSAID, nonsteroidal anti-inflammatory drug; SNRIs, serotonin–norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors; TMS, transcranial magnetic stimulation.

[a]Examples; not an exhaustive list.

underway to evaluate the safety and efficacy of CGRP receptor antagonists.[18] These agents appear to be better tolerated than triptans, have fewer vascular and central nervous system adverse effects, and present less of a risk of medication overuse headache.[18] Liver toxicity has been seen with some medications in this class and remains an important concern in their development.[19]

Phase 3 clinical trials for 1 drug in this class, ubrogepant, were completed in late 2017; full analysis of the data is not yet available. Primary outcomes being evaluated include relief of pain at 2 hours and relief from the most bothersome symptoms again at 2 hours.[27]

Selective serotonin-HT$_{1f}$ receptor agonists, such as lasmiditan, offer another potential approach. Although the exact mechanism of action of these agents is not entirely clear, clinical trials have supported their efficacy and safety.[20] Importantly, ongoing trials are specifically targeting patients with known cardiovascular risk factors because they are most likely to benefit from the nonvasoconstrictive mechanism of action.[28,29] Adverse effects reported primarily include dizziness, fatigue, and vertigo.

Strategies for managing recurrent episodic migraine

Because of the risk of medication overuse headache with acute treatment, daily preventive therapy for migraine is indicated for any patient with[30]:

- ≥6 headache days a month
- ≥4 headache days a month with some impairment
- ≥3 headache days a month with severe impairment.

Treatment begins by having patients identify, and then avoid, migraine triggers (**TABLE 5**). This can be accomplished by having patients keep a headache diary, in which they can enter notations about personal and environmental situations that precede a headache.

For the individual patient, some triggers are modifiable; others are not. Helping a patient develop strategies for coping with triggers, rather than aiming for complete avoidance, might help her (him) manage those that are inescapable (eg stress, menstruation, etc).[31] For many patients, however, this is not an adequate intervention and other approaches must be explored. When considering which therapy might be best for a given patient, evaluate her (his) comorbidities and assess that particular treatment for potential secondary benefits and the possibility of adverse effects. Pay attention to the choice of preventive therapy in women who are considering pregnancy because many available treatments are potentially teratogenic.

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TABLE 5

Common migraine triggers

Alcohol
Anxiety
Caffeine (or caffeine withdrawal in regular users)
Dehydration
Diet
Excessive head movement
Eye strain
Fatigue
Hunger
Menstruation
Noise
Sleep deprivation
Stress

Oral medications. Oral agents from several classes of drugs can be used for migraine prophylaxis, including anti-epileptics, antidepressants, and antihypertensives (**TABLE 6**[20,29,30,32-41]). Selected anti-epileptics (divalproex sodium, sodium valproate, topiramate) and beta-blockers (metoprolol, propranolol, and timolol) have the strongest evidence to support their use.[32] Overall, regular use of prophylactic medications can reduce headache frequency by 50% for approximately 40% to 45% of patients who take them.[29] However, adherence may be limited by adverse effects or perceived lack of efficacy, thus reducing their potential for benefit.[42]

OnabotulinumtoxinA. In patients with chronic migraine (≥15 headache days a month for at least 3 months) who have failed oral medications, the American Academy of Neurology (AAN) recommends the use of onabotulinumtoxinA.[30] The treatment regimen comprises 31 injections at various sites on the head, neck, and shoulders every 3 months.[33]

A 2010 large randomized controlled trial showed a decrease in the frequency of headache days for patients receiving onabotulinumtoxinA compared to placebo after a 24-week treatment period (7.8 fewer headache days a month, compared to 6.4 fewer in the placebo group).[33] A recent systematic review also noted a reduction of 2 headache days a month compared with placebo; the authors cautioned, however, that data with which to evaluate onabotulinumtoxinA in comparison to other prophylactic agents are limited.[43]

In both studies, the risk of adverse drug events due to onabotulinumtoxinA was high and led to a significant rate of discontinuation.[33,43] Despite this, onabotulinumtoxinA remains the only Food and Drug Administration (FDA)–approved treatment for chronic migraine, making it reasonable to consider for appropriate patients.

Acupuncture. A 2016 Cochrane review found benefit for patients using acupuncture compared with sham acupuncture.[34] When acupuncture was compared with prophylactic agents such as beta-blockers, calcium-channel blockers, and anti-epileptics, however, there was no significant difference between the procedure and pharmacotherapy. Patients willing and able to try acupuncture might see a reduction in the overall number of headaches. Acupuncture has few adverse effects; however, long-term data are lacking.[34]

Exercise is not supported by robust data for its role as a prophylactic treatment. It is generally considered safe in most populations, however, and can be pursued with little out-of-pocket cost.[35]

Cognitive behavioral therapy (CBT). The AAN recommends CBT, relaxation therapy, and biofeedback therapy. Accessibility of these services remains limited for many patients, and cost can be prohibitive.[16]

Supplements used to help prevent migraine include the root of *Petasites hybridus* (butterbur), magnesium, vitamin B2 (riboflavin), *Tanacetum parthenium* (feverfew), and coenzyme Q10.[16] Although the strength of evidence for these therapies is limited by small trials, their overall risk of adverse effects is low, and they might be easier for patients to obtain than acupuncture or CBT.

Butterbur, in particular, has been found to be beneficial for migraine prevention in 2 small placebo-controlled trials. In a randomized controlled study of 245 patients *P hybridus*, (specifically, the German formulation, Petadolex), 75 mg BID, reduced the frequency of migraine attack by 48% at 4 months, compared to placebo (number

TABLE 6

Migraine prophylaxis: What's available? What's being studied?[20,29,30,32-41]

Available medications		
Drug class or device	**Examples; description of intervention**	**Important considerations**
Allergy medications	Cyproheptadine (serotonin and histamine antagonist)[32]; subcutaneous histamine	Off-label use; awaiting FDA approval for this indication Sedating side effects may limit use
Antidepressants	Amitriptyline (25-150 mg/d)[32]; venlafaxine	Amitriptyline is the only tricyclic antidepressant with proven efficacy[32]
Anti-epileptics	Divalproex sodium, sodium valproate, topiramate (25-200 mg/d)[32]	Topiramate has high-quality evidence supporting its use[32] Lamotrigine is ineffective and should be avoided[32]
Beta-blockers	*AHS/AAN Level-A evidence*[32a] Metoprolol Propranolol Timolol *AHSD/AAN Level-B evidence*[32a] Atenolol Nadalol *AHS/AAN Level-C evidence*[32a] Nebivolol Pindolol	Use with caution in patients >60 years of age (risk of bradycardia)
Calcitonin gene-related peptide (CGRP) monoclonal antibodies	Eptinezumab, erenumab, fremanezumab, galcanezumab	Eptinezumab trials are still being completed; approval pending Erenumab was recently approved by the FDA CGRP monoclonal antibodies are well-tolerated; no severe adverse effects noted[39,40] Reduce the number of headache days per month, compared to placebo[39,40]
Other antihypertensives	Candesartan, clonidine, lisinopril	Level-C evidencea for these agents (AHS/AAN review)[32] Insufficient evidence for calcium-channel blockers Telmisartan is ineffective[32]
Triptans	*AHS/AAN Level-A evidence*[32a] Frovatriptan *AHS/AAN Level-B evidence*[32a] Naratriptan Zolmitriptan	Menstruation-related migraine (given before onset of menses)
Alternative therapies		
Acupuncture	—	Mildly better than sham, may be less effective than prophylactic oral agents[34] Low risk of adverse events

CONTINUED

TABLE 6

Migraine prophylaxis: What's available? What's being studied?[20,29,30,32-41] *(cont'd)*

Drug class or device	Examples; description of intervention	Important considerations
Alternative therapies		
OnabotulinumtoxinA	Administered every 12 weeks[30,33]; 31 injections in 7 areas of the head and neck	May be effective at reducing number of headache days for patients with >15 headache days a month (chronic migraine)[30,33]
Cefaly (transcutaneous electrical nerve stimulator)	Targets the trigeminal nerve specifically; applied to the forehead and turned on daily for 20 minutes	Safe, well tolerated; approved by the FDA in 2014[38] No serious adverse events noted after short-term use For migraine prophylaxis in patients unable to tolerate medications
Dietary supplements and herbal preparations	*AHS/AAN Level-A evidence*[32a] Butterbur (*Petasites hybridus*), 50-300 mg BID[32] *AHS/AAN Level-B evidence*[32a] Magnesium, 600 mg/d as trimagnesium dicitrate[20] Riboflavin, 400 mg/d[32] *Tanacetum parthenium* (feverfew), 50-75 mg BID[29] *AHS/AAN Level-C evidence*[32a] Coenzyme Q10, 100 mg TID[32]	Low risk of harm (except see comment below regarding butterbur) Avoid butterbur in patients with hepatic disease; use caution with unknown formulations for all patients because of the potential for exposure to hepatotoxic compounds in unpurified formulations[41] Weakest evidence for coenzyme Q10[32] New combination products are in early clinical trials[36,37]
Exercise	Cardiovascular exercise, yoga	Small RCT showed no significant difference (P = .95) between exercise and relaxation or topiramate[35] Low risk of harm if no prohibiting comorbidities
Under investigation		
Occipital nerve stimulators	Inserted in the back of the head; have wires and batteries	Limited tolerability; not approved in EU because of adverse effects[38]
Sphenopalatine nerve stimulators	Invasive insertion procedure	Being studied in the United States; in use in the EU Being studied for migraine prophylaxis Effective for cluster headache prophylaxis[38]

AAN, American Academy of Neurology; AHS, American Headache Society; CNS, central nervous system; EU, European Union; FDA, Food and Drug Administration; RCT, randomized controlled trial.

[a]Level A AHS/AAN ranking indicates "established" effectiveness; "Level B," "probably" effective; and Level C, "possibly" effective.[32]

needed to treat, 5.3).[44] No difference was found at lower dosages. The most common reported adverse effect was burping.

Regrettably, unpurified butterbur extract contains pyrrolizidine alkaloids, potentially hepatotoxic and carcinogenic compounds. Because of variations in purification in production facilities in the United States, butterbur supplements might not have all of these compounds removed—and so should be used with caution.[41]

Magnesium. Studies evaluating the use of magnesium have demonstrated varied results; differences in methods and dosing have

limited broad application of findings. As with most supplements considered for prophylactic treatment, magnesium dosing is poorly understood, and bioavailability varies in its different forms. Oral supplementation can be given as magnesium dicitrate, 600 mg/d.[45]

Recently, products containing various combinations of feverfew, coenzyme Q10, riboflavin, magnesium, and other supplements have shown benefit in early clinical trials.[36,37]

Neural stimulation. Over the past few years, a variety of transcutaneous nerve stimulator devices have gained FDA approval for use in migraine prophylaxis. The long-term safety and efficacy of these devices is not yet well understood, but they appear to provide headache relief in the short term and decrease the frequency of headache.[38] Use of the noninvasive stimulators is limited today by high cost and poor coverage by US health care insurers.

Newly available medical therapy. The FDA recently approved erenumab, a fully human monoclonal antibody for prevention of migraine in adults. This is the first drug in the CGRP antagonist class to be approved for this indication. Trials of this once-monthly, self-injectable drug show promising results for patients whose migraines have been refractory to other therapies.

A recent large trial evaluated 955 adults with migraine, randomizing them to receive erenumab, 70 mg; erenumab, 140 mg; or placebo over 28 weeks.[39] The groups receiving erenumab had a nearly 2-fold higher odds of having their migraine reduced by 50%, compared with placebo (number needed to treat with the 140-mg dose, 4.27). Similar numbers of participants from all groups discontinued the study.[39] Phase 3 trials that are not yet formally published have produced similarly beneficial results.[40,46] The FDA has listed injection site reaction and constipation as the most reported adverse effects.[40]

Three other anti-CGRP antibodies are likely to be approved in the near future: fremanezumab, galcanezumab, and eptinezumab.

The approach to migraine in special populations

Management of acute and chronic migraine in children, pregnant women, and older adults requires special attention: Treatment approaches are different than they are for adults 19 to 65 years of age.

Pediatric patients. Migraine is the most common acute and recurrent headache syndrome in children. Headaches differ from those of adult migraine as a result of variations in brain maturation, plasticity, and cognitive development.[47] Migraine attacks are often of shorter duration in children, lasting 1 to 2 hours, but can still be preceded by visual aura.[48] Just as with adults, imaging, electroencephalography, lumbar puncture, and routine labs should be considered only if a child has an abnormal neurological exam or other concerning features (**TABLE 2**[14,15]).

The general approach to migraine treatment in the pediatric population includes education of the child and family about symptom management. Acetaminophen, NSAIDs, and triptans are approved for abortive therapy in children and should be used for acute headache relief in the same way that they are used in adults. Oral rizatriptan, the most well studied triptan in the pediatric population, is approved for use in children as young as 6 years[49]; the pediatric dosage is 5 mg/d for patients weighing 20 to 39 kg and 10 mg/d for patients weighing more than 40 kg (same as the adult dosage).

Oral almotriptan and zolmitriptan are also approved for use in children 12 to 17 years of age. Usual dosages are: almotriptan, 12.5 mg at onset, can repeat in 2 hours as needed (maximum dosage, 25 mg/d); and zolmitriptan, 2.5 mg at onset, can repeat in 2 hours as needed (maximum dosage, 10 mg/d).[50]

For children who are unable to swallow pills or who are vomiting, a non-oral route of administration is preferable. Rizatriptan is available as an orally disintegrating tablet. Zolmitriptan is available in a nasal spray at a dose of 5 mg for children 12 years and older. Sumatriptan is not approved for use in patients younger than 18 years; however, recent studies have shown that it might have good efficacy and tolerability.[50]

Daily prophylactic treatment for recurrent migraine in the pediatric population is an evolving subject; published guidelines do

Don't prescribe triptans for patients with known vascular disease or severe hepatic impairment.

not exist. It is reasonable to consider treatment using the same guidelines as those in place for adults.[51] Topiramate, 1 to 2 mg/kg/d, is the only therapy approved by the FDA for episodic migraine preventive therapy in adolescents.[50]

Notably, a nonpharmacotherapeutic approach may be more effective for pediatric prevention. In 2017, a large double-blind, placebo-controlled trial investigated the use of amitriptyline, topiramate, and placebo for the treatment of recurrent migraine in children 8 to 17 years of age. An interim analysis of the 328 children enrolled found no significant differences in reduction of headache frequency with treatment compared with placebo over a 24-week period; the trial was stopped early due to futility.[52]

The study did show, however, that reducing migraine triggers provided a high level of benefit to study participants. Stress is one of the most common migraine triggers in children; lack of sleep, exposure to a warm climate, and exposure to video games are also notable triggers.[53] CBT may augment the efficacy of standard migraine medications in the pediatric population and may help prevent recurrence of episodes.[54]

Pregnancy. The treatment of migraine is different in pregnant women than it is in nonpregnant adults because of a concern over adverse effects on fetal development. For acute headache treatment, first-line therapies include trigger avoidance and acetaminophen, 1000 mg (maximum dosage, 4000 mg/d).[55] If this is ineffective, a 10-mg dose of metoclopramide, as often as every 6 hours (not an FDA-approved indication), can be considered. During the second trimester, NSAIDs can be considered second-line therapy.

Triptans—specifically, sumatriptan and rizatriptan—can also be considered if first-line therapies fail.[56] Triptan-exposed pregnant women with migraine have a rate of congenital malformations, spontaneous abortions, and prematurity that is similar to what is seen in pregnant women with migraine who have not been exposed to triptans. However, when triptan-exposed women are compared with healthy, non-migraine-suffering women, the rate of spontaneous abortion appears to be increased in the triptan-exposed population.[57]

Ergotamine is contraindicated during pregnancy because of its potential to induce uterine contractions and vasospasm, which can be detrimental to the fetus.[56]

Nonpharmacotherapeutic interventions such as heat, ice, massage, rest, and avoidance of triggers are as successful in the pregnant population as in the nonpregnant population. For migraine prevention, coenzyme Q10, vitamins B2 and B6 (pyridoxine), and oral magnesium can be considered. Feverfew and butterbur should be avoided because of concerns about fetal malformation and preterm labor.[58]

Older adults. Choosing appropriate migraine therapy for older adults requires special consideration because of changes in drug metabolism and risks associated with drug adverse effects. Additionally, few studies of migraine drugs have included large populations of adults older than 65 years; medications should therefore be prescribed cautiously in this population, with particular attention to drug–drug interactions.

Just as for younger adults, mild symptoms can be managed effectively with acetaminophen. NSAIDs may be used as well, but carry increased risks of gastric bleeding and elevation in blood pressure.[59] The use of triptans is acceptable for the appropriate patient, but should be avoided in patients with known vascular disease.[60] Antiemetics present an increased risk of extrapyramidal adverse effects in the elderly and should be used with caution at the lowest effective dosage.[59] Novel mechanisms of action make some of the newer agents potentially safer for use in older adults when treating acute migraine.

For migraine prevention in older adults, particular attention should be paid to reducing triggers and minimizing polypharmacy.

If a patient doesn't get adequate headache relief from an appropriate dosage of a given triptan, try a different triptan during the next migraine.

More and more, successful treatment is within reach

With many clinical trials evaluating novel drugs underway, and additional studies contributing to our understanding of nonpharmacotherapeutic approaches to migraine treatment, improved headache

control may become increasingly common over the next few years. JFP

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