REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

Preventive Therapy of Migraine

By Todd J. Schwedt, MD, FAAN

CITE AS:
CONTINUUM (MINNEAP MINN) 2018;24(4, HEADACHE):1052–1065.

Address correspondence to Dr Todd J. Schwedt, Mayo Clinic, 5777 East Mayo Blvd, Phoenix, AZ 85054, *Schwedt.todd@mayo.edu*.

RELATIONSHIP DISCLOSURE:
Dr Schwedt serves on the board of directors for the American Headache Society and the International Headache Society; receives personal compensation as associate editor for *Cephalalgia*, *Headache*, and *Pain Medicine*; and receives personal compensation as a consultant for Alder BioPharmaceuticals, Inc; Allergan; Amgen Inc; Autonomic Technologies, Inc; Avanir Pharmaceuticals, Inc; Dr. Reddy's Laboratories Ltd; Eli Lilly and Company; Ipsen Bioscience, Inc; Nocira, LLC; Novartis AG; and Teva Pharmaceutical Industries Ltd. He has stock options in Aural Analytics; Nocira, LLC; and Second Opinion.
Continued on page 1065

UNLABELED USE OF PRODUCTS/INVESTIGATIONAL USE DISCLOSURE:
Dr Schwedt discusses the unlabeled/investigational use of numerous medications for the treatment of migraine; none of the therapies discussed are approved by the US Food and Drug Administration except for caloric vestibular stimulation, divalproex sodium, erenumab, propranolol, timolol, topiramate, transcranial magnetic stimulation, and transcutaneous supraorbital nerve stimulation for the treatment of migraine and the use of onabotulinumtoxinA for the treatment of chronic migraine.

ABSTRACT

PURPOSE OF REVIEW: This article reviews the preventive therapy of migraine, including indications, strategies for use, and available treatments.

RECENT FINDINGS: Lifestyle modifications and migraine trigger avoidance are recommended as preventive measures for all individuals with migraine. The decision to recommend additional migraine preventive therapy should consider the frequency of migraine attacks and headaches, extent of migraine-associated disability, frequency of using acute migraine treatments and the responsiveness to such treatments, and patient preferences. Additional therapies include prescription medications, nutraceuticals, neurostimulation, and behavioral therapy. Considering evidence for efficacy and the risk of potential side effects and adverse events, treatments with the most favorable profiles include (in alphabetical order): amitriptyline, beta-blockers (several), biofeedback, candesartan, coenzyme Q10, cognitive-behavioral therapy, magnesium citrate, onabotulinumtoxinA (for chronic migraine only), relaxation therapy, riboflavin, and topiramate. In addition, erenumab, a calcitonin gene-related peptide (CGRP) receptor monoclonal antibody, received approval from the US Food and Drug Administration (FDA) for the prevention of migraine in May 2018.

SUMMARY: Successful migraine preventive therapy reduces the frequency and burden of attacks while causing limited side effects. Individual treatment recommendations are determined based upon evidence for efficacy, side effect and adverse event profiles, medication interactions, patient comorbidity, costs, and patient preferences. Patients must be counseled on reasonable expectations for their preventive therapy and the importance of adhering to the recommended treatment plan for a period of time that is sufficient to determine outcomes.

INTRODUCTION

Migraine prevention is multifaceted and includes lifestyle modifications, migraine attack trigger identification and avoidance, avoidance of risk factors for developing more frequent migraine attacks, and, when indicated, medications, nutraceuticals, neurostimulation, and behavioral therapies. The goal of preventive therapy is to reduce the frequency of migraine attacks, days with migraine and headache, severity of symptoms, frequency of taking acute

migraine therapy, and migraine-related disability. Commonly used measures of efficacy in clinical trials of migraine preventive therapies include reductions in the number of migraine days, reductions in the number of headache days, and responder rate, typically defined as at least a 50% reduction in headache frequency. However, in the clinical setting, measures of success and failure are often more subjective and individualized according to the specific patient. For example, the patient who has substantial reductions in migraine symptom severity and migraine-related disability with minimal side effects might find a preventive therapy successful even if headache frequency is only modestly reduced. On the other hand, a preventive therapy that is very effective in reducing migraine frequency would be considered a failure if it causes intolerable side effects.

When formulating recommendations for specific preventive therapies, clinicians must consider the likelihood for effectiveness and side effects as well as other factors such as potential interactions with other therapies that the patient uses, the patient's comorbidities, the cost of the therapy, and the patient's ability to adhere to the recommended treatment schedule. The clinician-patient conversation about preventive therapies must set realistic expectations regarding the likely magnitude of benefit, realizing that reductions but not elimination of migraine burden is expected. It is also essential to discuss the timing by which a patient is expected to note the benefits from a preventive therapy. For example, with the most commonly prescribed oral migraine preventive medications, the patient may need to take the medication at the target dose for 2 to 3 months before realizing substantial benefits.

In this article, the following migraine preventive therapy topics are discussed: (1) lifestyle modifications and avoidance of migraine attack triggers; (2) avoiding factors associated with development of more frequent headaches; (3) indications for medications, nutraceuticals, neurostimulation, and behavioral therapies; (4) currently available therapies and those in the pipeline; and (5) adherence and persistence with therapy.

LIFESTYLE MODIFICATION AND TRIGGER AVOIDANCE

Lifestyle modifications and migraine attack trigger identification and avoidance should be discussed with all patients with migraine. Although limited published data support the notion that lifestyle modifications and avoidance of triggers are effective in reducing migraine burden, they are commonly recommended and are associated with little risk to the patient.[1]

It is generally believed that fluctuations/changes in a person's usual daily routine can trigger migraine attacks. Thus, individuals with migraine are likely to do better if they maintain a stable daily schedule that includes going to sleep the same time each night, waking at the same time each day, eating regular meals, exercising, and maintaining a consistently low-stress lifestyle. Although such a lifestyle is not easy to maintain, or is not possible in some situations, patients are counseled to adhere to such a lifestyle as closely as possible.

Although the evidence strength is low, several studies and systematic reviews of the literature have concluded that aerobic exercise can provide benefits to headache patterns.[2,3] Aerobic exercise as monotherapy and multicomponent behavioral headache interventions that include aerobic exercise are associated with reductions in headache frequency and severity as well as with improvements in health-related quality of life.[2–7] Although the exercise protocols used in these studies are varied, based on these studies and recommendations from the Office

KEY POINTS

- Migraine prevention is multifaceted and includes lifestyle modifications, migraine attack trigger identification and avoidance, avoidance of risk factors for developing more frequent migraine attacks, and, when indicated, medications, nutraceuticals, neurostimulation, and behavioral therapies.
- The goal of preventive therapy is to reduce the frequency of migraine attacks, days with migraine and headache, severity of symptoms, frequency of taking acute migraine therapy, and migraine-related disability.
- When formulating recommendations for specific preventive therapies, clinicians must consider the likelihood for effectiveness and side effects as well as other factors such as potential interactions with other therapies that the patient uses, the patient's comorbidities, the cost of the therapy, and the patient's ability to adhere to the recommended treatment schedule.
- Lifestyle modifications and migraine attack trigger identification and avoidance should be discussed with all patients with migraine.
- Moderate-intensity aerobic exercise (150 minutes per week, generally divided among three to five sessions) should be considered for migraine prevention in adults.

of Disease Prevention and Health Promotion (*health.gov*), 150 minutes per week of moderate-intensity aerobic exercise (generally divided among three to five sessions) should be considered for migraine prevention in adults.[8]

Maintenance of a daily headache diary is recommended to obtain an accounting of migraine frequency, treatment patterns, and potential migraine attack triggers. Identification of triggers can be a complicated process since several triggers might need to be present simultaneously for them to actually trigger a migraine attack and because a causal relationship between trigger exposure and an individual migraine attack is very difficult to prove. Despite

CASE 5-1

A 35-year-old woman presented for evaluation and management of frequent headaches. She reported having onset of headaches approximately 20 years ago. Initially, she had two to three episodes per month, during which she experienced moderate or severe, unilateral, throbbing headaches associated with sensitivity to light, sound, and nausea. Typically, to avoid exacerbation of her symptoms, she would lie in bed for several hours with each attack. Less severe attacks were treated with an over-the-counter nonsteroidal anti-inflammatory drug (NSAID)/acetaminophen/caffeine combination pill, while more severe attacks were treated with a triptan.

Over the years, she had a slow increase in the frequency of her attacks. Since she was treating all episodes with medication, the frequency of medication use also increased. Over the past few years, she noted that between her full-blown attacks, she had a constant mild to moderate headache that would partially respond to the NSAID/acetaminophen/caffeine combination pill. At the time of presentation, she reported taking the NSAID/acetaminophen/caffeine combination pill several times each day and a triptan for full-blown attacks approximately 10 days per month.

COMMENT

This patient was diagnosed with chronic migraine with medication overuse. Chronic migraine was diagnosed since she experienced 15 or more days with headache each month, including at least 8 days on which she had full-blown migraine attacks. The patient also met criteria for overuse of triptans and for overuse of combination analgesics, each being used on 10 or more days per month. It is likely that the frequent use of migraine acute medications led to medication-overuse headache.

The treatment of chronic migraine with medication overuse includes the use of migraine preventive therapy and reductions in the frequency of using acute treatments. Since many patients are not familiar with medication-overuse headache, education about this secondary headache disorder and the risks of taking frequent acute medications must be discussed. Typically, the patient with medication overuse is switched from the overused medication(s) to an acute therapy that is from a different medication class and is instructed to limit use of the new medication to 2 to 3 days per week.

these limitations, commonly cited triggers include: high stress, stress let down (moving from high-stress to low-stress environments, such as might occur during a vacation), weather changes, sex hormone fluctuations in women, not eating, alcohol, sleep disturbance, odors, light, smoke, heat, and certain foods.

Foods that are commonly cited as triggers include those with monosodium glutamate, those with nitrates/nitrites (eg, processed meats), aged cheeses, and artificial sweeteners. Caffeine overuse and caffeine withdrawal are both associated with headaches and migraine.

Avoiding Factors That Increase Risk of Developing More Frequent Migraine

Several factors are associated with increased risk for developing more frequent headaches (eg, transitioning from episodic migraine to chronic migraine), including obesity, sleep disorders, excessive caffeine intake, psychiatric disease, higher baseline headache frequency, the frequent use of abortive migraine medications, female sex, lower socioeconomic status, comorbid pain disorders, major life events, history of head or neck injury, ineffective acute treatment of migraine attacks, and presence of cutaneous allodynia.[9–11] It is presumed that avoiding these risk factors, when possible, reduces the risk of developing more frequent headaches. Among these risk factors, caffeine, obesity, certain sleep disorders, and medication overuse are avoidable or modifiable.

CAFFEINE. A complex relationship exists between caffeine and migraine: caffeine can be an effective treatment for migraine attacks, likely via its action as an adenosine receptor antagonist; withdrawal from caffeine can cause headaches, perhaps due to upregulation of the adenosine receptors; and regular caffeine use is a risk factor for developing more frequent headaches.[12,13] Caffeine cessation among frequent users will improve migraine burden for some individuals.[14] Thus, a period of caffeine cessation lasting at least 2 to 3 months is recommended for individuals with frequent migraines to determine if caffeine avoidance results in reduced frequency of migraine attacks/headaches. Individuals with a regular intake of large amounts of caffeine should slowly taper their caffeine intake to avoid an initial headache exacerbation due to caffeine withdrawal.

OVERUSE OF ACUTE HEADACHE MEDICATIONS. The term *medication overuse* refers to taking migraine-abortive medications too frequently. Medication overuse is a risk factor for developing more frequent headaches and can lead to medication-overuse headache (**CASE 5-1**). The definition of medication overuse differs according to the medication(s) being used. Simple analgesics are overused if taken on 15 or more days per month (regardless of the reason for taking the medication), whereas triptans, dihydroergotamine, combination analgesics, opiates, and combinations of medications from different medication classes are overused when taken on 10 or more days per month.[15] Despite these definitions, it is likely that intake of butalbital-containing medications or opiates on fewer than 10 days per month still increases the risk of developing more frequent headaches, and thus their use should be severely limited or avoided altogether.

SLEEP. Sleep is an effective treatment for migraine attacks. Sleep disturbances are common among individuals with migraine, and poor sleep is positively associated with the occurrence and frequency of migraine attacks. Common sleep disturbances among individuals with migraine include: insomnia, poor quality sleep, short sleep duration, snoring, sleep-related breathing disorders, and restless

KEY POINTS

- Maintenance of a daily headache diary is recommended to obtain an accounting of migraine frequency, treatment patterns, and potential migraine attack triggers.
- Commonly cited migraine triggers include: high stress, stress let down (moving from high-stress to low-stress environments, such as might occur during a vacation), weather changes, sex hormone fluctuations in women, not eating, alcohol, sleep disturbance, odors, light, smoke, heat, and certain foods.
- Caffeine overuse and caffeine withdrawal are both associated with headaches and migraine.
- Several factors are associated with increased risk for developing more frequent headaches (eg, transitioning from episodic migraine to chronic migraine), including obesity, sleep disorders, excessive caffeine intake, psychiatric disease, higher baseline headache frequency, the frequent use of abortive migraine medications, female sex, lower socioeconomic status, comorbid pain disorders, major life events, history of head or neck injury, ineffective acute treatment of migraine attacks, and presence of cutaneous allodynia.
- A period of caffeine cessation lasting at least 2 to 3 months is recommended for individuals with frequent migraine.

legs syndrome.[16–19] In addition to being comorbid with migraine, sleep disturbances can be associated with greater migraine burden, such as higher headache frequency.[20] Effective treatment of sleep disturbances may lead to improved migraine patterns. For example, behavioral treatment of insomnia and continuous positive airway pressure (CPAP) therapy for sleep apnea have been associated with reductions in migraine burden such as reduced headache frequency.[21,22] Identification and treatment of sleep disturbances is recommended as part of a comprehensive preventive treatment plan for patients with migraine.

OBESITY. Obesity is associated with a moderately higher risk of migraine and with an increasing number of headache days among those with migraine.[23,24]

CASE 5-2

A 40-year-old woman presented for evaluation and management of migraine. She had a 20-year history of migraine without aura. For many years, she had migraine attacks 1 to 2 times per month, each lasting no longer than 1 day, which were often triggered by menstruation and typically relieved by an oral triptan. However, over the last 8 to 10 years, she had a slow increase in the frequency of her headaches, which progressed to her current pattern of full-blown migraine attacks 4 times per month, each lasting 1 to 2 days, and milder headaches on an additional 2 days per week. Overall, she estimated having a headache of some severity on about 14 days per month, with complete headache freedom on the remaining days. She reported that her migraine attacks felt the same as they had for many years, but they were more frequent, of a longer duration, and were less responsive to her usual triptan. She had severe migraine-related disability requiring bedrest 3 days per month.

Her past medical history was notable for kidney stones (calcium phosphate), obesity, and borderline hypertension. Her medications included a daily multivitamin, sumatriptan 100 mg tablet that she took for each migraine attack, and ibuprofen that she took for her milder headaches. She had never tried other treatments for her migraine. Her mother, sister, and daughter all had migraine.

On examination, her body mass index was 32 kg/m^2, her blood pressure was 145/88 mm Hg, and her heart rate was 85 beats/min. General physical, neurologic, and funduscopic examinations were normal.

COMMENT

This patient was clearly a candidate for migraine preventive therapy given the frequency and duration of her migraine attacks and headaches, their relative lack of response to acute medication, and her migraine-related disability. Since she had not previously been treated with migraine preventive therapy, a first-line agent such as a beta-blocker, topiramate, or amitriptyline should be considered. Her history of calcium phosphate kidney stones is a contraindication to the use of topiramate, and her obesity is a relative contraindication to amitriptyline. Given these contraindications and the presence of borderline hypertension, propranolol would be a good choice.

Although further studies are needed to confirm findings, weight loss may be associated with reductions in headache frequency and severity.[25] Monitoring of a patient's weight, including the effects of migraine preventive treatment on a patient's weight, and treatment of obesity should be considered part of a comprehensive migraine preventive therapy plan.

INDICATIONS FOR ADDITIONAL MIGRAINE PREVENTION

The decision to recommend further migraine preventive therapy to a patient is based upon headache frequency, migraine attack frequency and duration, the severity of symptoms, the frequency of taking migraine acute therapies, the patient's responsiveness to migraine acute therapies, extent of migraine-related disability, and patient preference.

For example, a patient who has four migraine attacks per month, each of which responds completely to a single dose of abortive therapy, lasts only for 2 hours, and causes limited disability, might not warrant preventive therapy. However, the patient who has four migraine attacks per month, most of which do not respond to abortive therapy, continue for 2 days, and cause substantial disability, is likely to desire preventive therapy.

Guidelines regarding when to offer migraine preventive therapy are available from the American Academy of Neurology (AAN), the American Headache Society, the Canadian Headache Society, and an expert panel of the American Migraine Prevalence and Prevention Study.[26–28] Although the guidelines have slightly differing recommendations, taken together they suggest that migraine preventive therapy should be considered when one or more of the following are present:

- Three or more moderate or severe headache days per month causing functional impairment and that are not consistently responsive to acute treatments
- At least 6 to 8 headache days per month even if acute medications are effective
- Contraindications to acute migraine treatments
- Particularly bothersome symptoms even if infrequent attacks (eg, migraine with brainstem aura, hemiplegic migraine)
- Migraine has a significant impact on patient's life despite lifestyle modifications, trigger avoidance, and use of acute treatment
- Patient is at risk of developing medication-overuse headache

Migraine Preventive Treatments

Currently, our knowledge is insufficient to accurately predict which individual patient is most likely to benefit from a particular preventive therapy. Thus, the decision of which preventive therapy or therapies to recommend is based on the level of evidence that a specific therapy is effective, the likelihood of a patient tolerating the therapy, its safety profile and cost, patient comorbidities, potential interactions with other therapies that the patient uses, the patient's prior experiences with similar or related therapies (eg, choose a medication that works differently than medications that were previously ineffective or not tolerated), and patient preferences (CASE 5-2).

For most patients, a treatment's effectiveness and side effects are the most important qualities in determining their satisfaction with the treatment. Although

KEY POINTS

- Medication overuse is a risk factor for developing more frequent headaches and can lead to medication-overuse headache.
- Sleep is an effective treatment for migraine attacks. Sleep disturbances are common among individuals with migraine, and poor sleep is positively associated with the occurrence and frequency of migraine attacks.
- Identification and treatment of sleep disturbances is recommended as part of a comprehensive preventive treatment plan for patients with migraine.
- Obesity is associated with a moderately higher risk of migraine and with an increasing number of headache days among those with migraine.
- Weight loss may be associated with reductions in headache frequency and severity.
- The decision to recommend migraine preventive therapy to a patient is based upon headache frequency, migraine attack frequency and duration, the severity of symptoms, the frequency of taking migraine acute therapies, a patient's responsiveness to migraine acute therapies, extent of migraine-related disability, and patient preference.

the majority of preventive therapies have been studied in episodic migraine populations, medications used for episodic migraine are also used for prevention of chronic migraine (ie, headaches on at least 15 days per month including at least 8 days on which symptoms meet diagnostic criteria for migraine or are treated with a migraine-specific acute medication). OnabotulinumtoxinA is effective for prevention of chronic migraine but not episodic migraine. The discussion of individual therapies herein includes only those medications, nutraceuticals, neurostimulation devices, and behavioral therapies that are commonly available at the time of writing this article. This section ends, however, with a brief description of migraine preventive therapies that are in late stages of clinical development.

Medications and Nutraceuticals

Most prescription medications currently used for the prevention of migraine were developed for other purposes such as epilepsy, hypertension, and depression. To reduce the risk of a patient feeling uncertain about the prescriber's recommendation for one of these medications and, as a result, never filling the initial prescription, the clinician should acknowledge this fact when discussing treatment plans with the patient.

Guidelines from the American Headache Society, AAN, and Canadian Headache Society help to define which medications and nutraceuticals should be considered for migraine prevention.[27,29–31] Medications and nutraceuticals recommended for use from at least one of these guidelines include: topiramate, propranolol, nadolol, metoprolol, timolol, amitriptyline, gabapentin, candesartan, divalproex sodium, sodium valproate, flunarizine, pizotifen, venlafaxine, verapamil, lisinopril, coenzyme Q10, magnesium citrate, riboflavin, and feverfew (flunarizine and pizotifen are not approved by the US Food and Drug Administration [FDA] for use in the United States). OnabotulinumtoxinA is recommended for prevention of chronic migraine. In addition, erenumab, a calcitonin gene-related peptide (CGRP) receptor monoclonal antibody, received FDA approval for the prevention of migraine in May 2018. [32–34]

TABLE 5-1 includes recommended daily doses of medications, the AAN's and American Headache Society's evidence levels for efficacy of medications, and the Canadian Headache Society's overall recommendation and evidence levels for efficacy of medications.[27,29–37] It must be noted that the rating of evidence level for efficacy does not take into account other factors such as tolerability, side effects, toxicities, ease of administration, cost, or patient preferences. However, these factors must be considered when making treatment recommendations, and these factors have been considered in the Canadian Headache Society's "recommendation" level. For example, although divalproex sodium/sodium valproate received a level A rating for level of evidence from the AAN and a "high" rating for evidence of efficacy from the Canadian Headache Society, it was given a "weak" recommendation from the Canadian Headache Society, presumably because of its potential for being associated with serious adverse events such as fetal malformations and liver toxicity. Furthermore, the 2000 AAN guideline[28] has since been replaced by the 2012 AAN guideline,[30] and the 2012 AAN guideline "NSAIDs and Other Complementary Treatments for Episodic Migraine Prevention in Adults"[29] has been retired because of concerns about the safety of butterbur related to changes in its manufacturing that occurred after these guidelines were developed. TABLE 5-2 lists contraindications, precautions, and the most common adverse effects associated with each medication and nutraceutical.

Neurostimulation

Several modalities of invasive and noninvasive neurostimulation have been studied or are currently being studied for the prevention of migraine, including transcranial magnetic stimulation, transcutaneous supraorbital nerve stimulation, sphenopalatine ganglion stimulation, occipital and supraorbital nerve stimulation via implanted stimulators, transcutaneous vagal nerve stimulation, percutaneous mastoid electric stimulation, and caloric vestibular stimulation.[38–40] Transcutaneous supraorbital nerve stimulation, transcranial magnetic stimulation, and caloric vestibular stimulation (not yet commercially available) have received clearance from the FDA for migraine prevention. These devices are used on a daily basis for the prevention of migraine. Additional studies are needed to determine if other forms of noninvasive neurostimulation are effective for the primary or adjunctive prevention of migraine. Invasive neurostimulation might play a limited role for migraine prevention in those patients with very severe migraine who are refractory to other treatments; studies are needed to determine which subsets of these patients are most likely to benefit from and tolerate invasive neurostimulation.

Behavioral Therapy

Behavioral therapies for migraine are used with the intent of reducing the frequency of migraine attacks and the impact of such attacks on the individual, such as headache-related disability, quality of life, and psychological comorbidity.[41] Although behavioral therapies should be considered for all patients significantly impacted by migraine, special consideration should be given when a patient prefers nonpharmacologic therapy; does not tolerate, respond well, or has contraindications to pharmacologic therapy; and when patient behaviors and stress are triggers for migraine attacks or add significantly to migraine-related disability.[42] The 2000 AAN practice parameter gave Grade A recommendations for using relaxation training, thermal biofeedback combined with relaxation training, electromyographic biofeedback, and cognitive-behavioral therapy for the treatment of migraine.[28] Each of these therapies has been shown in randomized clinical trials to result in substantial improvements in migraine.[41] Furthermore, combining pharmacologic treatment with behavioral therapies is likely to provide greater benefits than either therapy alone, as has been shown in a study of combined therapy with propranolol and cognitive-behavioral therapy.[43]

Combination Therapy

A combination of treatments can be used for migraine prevention when a patient has inadequate response to a single therapy. Although limited data support the idea that therapy with a combination of medications can be superior to monotherapy, it is a common practice in the clinical setting. When done, it is recommended that the medications work via complementary but different mechanisms of action. Of note, however, one study demonstrated that a combination of topiramate and propranolol is no more effective than topiramate alone for chronic migraine treatment.[44] Clinicians must ensure that combination medication therapy is being used with the intent of obtaining greater effectiveness, as opposed to prescribing one medication to treat the side effects of another migraine medication, a practice that is discouraged. In addition to therapy with combinations of prescription medications, combination therapy that includes combining a medication with a nutraceutical or neurobehavioral therapy or

KEY POINTS

- **Transcutaneous supraorbital nerve stimulation, transcranial magnetic stimulation, and caloric vestibular stimulation have received clearance from the US Food and Drug Administration for migraine prevention.**
- **Behavioral therapies for migraine are used with the intent of reducing the frequency of migraine attacks and the impact of such attacks on the individual, such as headache-related disability, quality of life, and psychological comorbidity.**
- **Although behavioral therapies should be considered for all patients significantly impacted by migraine, special consideration should be given when a patient prefers nonpharmacologic therapy; does not tolerate, respond well, or has contraindications to pharmacologic therapy; and when patient behaviors and stress are triggers for migraine attacks or add significantly to migraine-related disability.**
- **A combination of treatments can be used for migraine prevention when a patient has inadequate response to a single therapy.**
- **In addition to therapy with combinations of prescription medications, combination therapy that includes combining a medication with a nutraceutical or neurobehavioral therapy or noninvasive neurostimulation can be considered and may be necessary for the effective treatment of patients who are refractory to single treatments.**

noninvasive neurostimulation can be considered and may be necessary for the effective treatment of patients who are refractory to single treatments.

Therapies in the Pipeline

In addition to several modes of noninvasive neurostimulation briefly discussed above, several other migraine preventive therapies are in the pipeline including CGRP monoclonal antibodies that target the CGRP ligand. Results from Phase 2 and Phase 3 clinical trials of CGRP monoclonal antibodies demonstrate their efficacy, tolerability, and safety for prevention of episodic migraine and chronic migraine.[32–34,45–50] The CGRP monoclonal antibodies are the only class of medication specifically designed for the prevention of migraine. Erenumab has recently received FDA approval for the prevention of migraine.[32–34] Beyond

TABLE 5-1 **Medications and Nutraceuticals With Evidence for Efficacy in Preventing Migraine**

	Daily Dose[a]	American Academy of Neurology Evidence Level for Efficacy[29–31,b,c]	Canadian Headache Society Recommendation[27,d]	Canadian Headache Society Evidence Level for Efficacy[27,d]
Medication				
Metoprolol	100–200 mg	A	Strong	High
Propranolol	80–240 mg	A	Strong	High
Topiramate	50–200 mg	A	Strong	High
Amitriptyline	10–200 mg	B	Strong	High
Timolol	20–60 mg	A	N/A	N/A
Nadolol	20–160 mg	B	Strong	Moderate
Divalproex sodium/ sodium valproate	500–2000 mg	A	Weak	High
Venlafaxine	75–225 mg	B	Weak	Low
Atenolol	50–200 mg	B	N/A	N/A
Gabapentin[e]	600–3600 mg	U	Strong	Moderate
Candesartan[f]	16–32 mg	C	Strong	Moderate
Lisinopril	10–40 mg	C	Weak	Low
Flunarizine[g]	5–10 mg	N/A	Weak	High
Pizotifen[g]	1.5–4 mg	N/A	Weak	High
Verapamil	120–480 mg	U	Weak	Low
OnabotulinumtoxinA (chronic migraine only)	155 units every 12 weeks	A	N/A	N/A
Erenumab[h]	70 mg or 140 mg each month	N/A	N/A	N/A

CONTINUED ON PAGE 1061

CGRP monoclonal antibodies, other migraine preventive therapies that are under investigation include small-molecule CGRP antagonists and therapies that target pituitary adenylate cyclase-activating polypeptide, kappa opioid receptors, nitric oxide synthase, orexins, and glutamate.[51,52]

Adherence and Persistence With Preventive Therapy

Rates of adherence and persistence with migraine preventive therapies are low. Even among individuals with chronic migraine (ie, those with the most severe disease), adherence to oral migraine preventive medications ranges from only 26% to 29% at 6 months and 17% to 20% at 12 months.[53] Although the reasons for low adherence vary, side effects and lack of efficacy are commonly cited. Thus, it is important to educate patients that persistence with a medication will, in

CONTINUED FROM PAGE 1060

	Daily Dose[a]	American Academy of Neurology Evidence Level for Efficacy[29–31,b,c]	Canadian Headache Society Recommendation[27,d]	Canadian Headache Society Evidence Level for Efficacy[27,d]
Nutraceuticals				
Coenzyme Q10	300 mg	C	Strong	Low
Magnesium citrate	400–600 mg	B	Strong	Low
Riboflavin	400 mg	B	Strong	Low
Feverfew	50–300 mg	B	Strong against	Moderate

N/A = not applicable.

[a] Daily dose refers to the recommended total daily dose for migraine prevention.

[b] The American Academy of Neurology's ratings for level of evidence that each medication is effective for migraine prevention include the following: A = medication with established efficacy (at least two Class 1 trials); B = medication probably effective (one Class 1 or two Class 2 studies); C = medication possibly effective (one Class 2 study); U = inadequate or conflicting data to support or refute medication efficacy.

[c] The 2012 American Academy of Neurology guideline has been retired because of concerns about the safety of butterbur related to changes in its manufacturing.[29]

[d] The Canadian Headache Society's guidelines provide a level of evidence and recommendation based upon the principles of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group system (high = confident that the true effect lies close to the estimate; moderate = moderately confident in the effect estimate; low = confidence in the effect estimate is limited; very low = little confidence in the effect estimate), and a recommendation that considers the balance between desirable and undesirable consequences of therapy, and the quality of the evidence on which judgments of the magnitude of benefit and harm are based (strong = benefits clearly outweigh risks and burdens for most patients; weak = benefits are more closely balanced with risks and burdens for many patients).

[e] Although the Canadian Headache Society gives gabapentin a strong recommendation and moderate evidence rating, publication bias and selective reporting of clinical trial results suggest that lower ratings might be appropriate.[35,36]

[f] Since the publication of the American Academy of Neurology and Canadian Headache Society treatment guidelines, there has been an additional positive randomized, placebo-controlled trial with candesartan, a study that might strengthen its rating for an efficacy evidence level.[37]

[g] Flunarizine and pizotifen are not approved by the US Food and Drug Administration for use in the United States.

[h] Erenumab trials were completed after publication of the American Academy of Neurology's and Canadian Headache Society's guidelines.[32–34]

TABLE 5-2 **Contraindications and Precautions to Migraine Preventive Therapies[a]**

	Contraindications/Precautions	Most Common Adverse Effects
Medications		
Beta-blockers (metoprolol, propranolol, timolol, nadolol, atenolol)	Bradycardia, hypotension, asthma, heart failure, may mask signs and symptoms of hypoglycemia	Orthostatic intolerance, exercise intolerance, fatigue, dizziness
Topiramate	Nephrolithiasis, renal impairment, metabolic acidosis	Paresthesia, weight loss, memory impairment, word-finding difficulties
Amitriptyline	Suicidal thinking/behavior, cardiac conduction abnormalities/arrhythmia	Weight gain, dry mouth, fatigue, blurred vision, constipation
Divalproex sodium/sodium valproate	Liver impairment, pancreatitis, certain hematologic disorders, childbearing potential	Weight gain, tremor, nausea, alopecia, fatigue
Venlafaxine	Suicidal thinking/behavior, renal impairment, hepatic impairment	Nausea, dizziness, insomnia, diaphoresis, sexual dysfunction
Gabapentin	Renal impairment	Dizziness, fatigue, peripheral edema
Candesartan	Hyperkalemia	Hypotension, dizziness
Lisinopril	Hyperkalemia, renal impairment	Hypotension, dizziness, cough
Flunarizine[b]	Hepatic impairment, extrapyramidal symptoms	Weight gain, fatigue, blurred vision
Pizotifen[b]	Hepatic impairment, renal impairment, visual disturbances	Weight gain, fatigue, dizziness
Verapamil	Cardiac conduction disorders, renal impairment, hepatic impairment, heart failure	Gingival hyperplasia, constipation, dizziness, hypotension, bradycardia
OnabotulinumtoxinA (chronic migraine only)	Neuromuscular/neuromuscular junction disease	Injection site pain, muscle pain, muscle weakness
Erenumab	None (according to US Food and Drug Administration label)	Injection site reactions, constipation
Nutraceuticals		
Coenzyme Q10	Biliary obstruction, hepatic insufficiency	Nausea, diarrhea
Magnesium citrate	Neuromuscular/neuromuscular junction disease, renal impairment	Diarrhea
Riboflavin	N/A	Urine discoloration, polyuria
Feverfew	Anticoagulant use	Nausea, diarrhea, mouth ulcers

N/A = not applicable.

[a] This table includes a partial listing of contraindications, precautions, and more common side effects associated with each therapy. Clinicians should refer to appropriate sources for comprehensive information. Pregnancy and breast-feeding are relative or absolute contraindications for many migraine preventive medications and nutraceuticals, but are not included within the contraindications/precautions column in this table. To determine the estimated risk of using these medications and nutraceuticals during pregnancy and breast-feeding, please refer to appropriate sources.

[b] Flunarizine and pizotifen are not approved by the US Food and Drug Administration for use in the United States.

some cases, result in waning side effects and improved effectiveness. Furthermore, when assessing response to migraine preventive therapy, it is essential to determine the patient's level of adherence with the treatment before determining that the therapy was ineffective.

Few data exist to help determine the optimal timing for stopping preventive therapy. When oral preventive therapy administered at a target therapeutic dose is ineffective after 2 to 3 months, it should be discontinued or the dose should be increased, if appropriate. At least two to three treatments with onabotulinumtoxinA are suggested prior to determining its efficacy for treatment of chronic migraine. Effective preventive therapy should be continued for at least 3 to 6 months before tapering the dose or discontinuing the treatment. The decision to lower doses or discontinue therapy should be individualized according to a patient's migraine pattern and personal preferences. For example, a patient with episodic migraine who has a reduction in migraine attack frequency down to one attack per month on their first migraine preventive therapy trial should be considered for dose reduction with the aim of discontinuation at the 3- to 6-month follow-up. However, the patient with many decades of chronic migraine who has had numerous treatment failures is not likely to desire preventive medication discontinuation if they finally find an effective migraine preventive approach. For such patients, it can be reasonable to maintain the preventive therapy for periods much longer than 3 to 6 months, all the while assessing for continued need, side effects, and tolerability and utilizing the lowest necessary dose.

KEY POINTS

- **Rates of adherence and persistence with migraine preventive therapies are low.**
- **When assessing response to migraine preventive therapy, it is essential to determine the patient's level of adherence with the treatment before determining that the therapy was ineffective.**

CONCLUSION

Migraine prevention requires a comprehensive approach that should include trigger identification and avoidance and lifestyle modifications that reduce the risk of migraine attacks. Further migraine preventive interventions are required when migraine attacks are frequent, unresponsive to acute therapy, associated with substantial disability, accompanied by particularly bothersome symptoms (eg, brainstem aura, intractable vomiting), or when a patient is at risk of developing overuse of acute migraine medications. Further interventions can include one or a combination of medications, nutraceuticals, behavioral therapies, and neurostimulation. When making migraine preventive recommendations, it is essential that the patient be educated on the expected outcomes and the duration of time that might be required to realize the benefits. Finally, since rates of adherence and persistence with migraine preventive medications are low, patient compliance with the recommended treatment plan must be considered when assessing outcomes.

REFERENCES

1 Woldeamanuel YW, Cowan RP. The impact of regular lifestyle behavior in migraine: a prevalence case-referent study. J Neurol 2016; 263(4):669–676. doi:10.1007/s00415-016-8031-5.

2 Irby MB, Bond DS, Lipton RB, et al. Aerobic exercise for reducing migraine burden: mechanisms, markers, and models of change processes. Headache 2016;56(2):357–369. doi:10.1111/head.12738.

3 Varkey E, Cider A, Carlsson J, Linde M. Exercise as migraine prophylaxis: a randomized study using relaxation and topiramate as controls. Cephalalgia 2011;31(14):1428–1438. doi:10.1177/0333102411419681.

4 Baillie LE, Gabriele JM, Penzien DB. A systematic review of behavioral headache interventions with an aerobic exercise component. Headache 2014;54(1):40–53. doi:10.1111/head.12204.

5 Busch V, Gaul C. Exercise in migraine therapy–is there any evidence for efficacy? A critical review. Headache 2008;48(6):890–899. doi:10.1111/j.1526-4610.2007.01045.x.

6 Darabaneanu S, Overath CH, Rubin D, et al. Aerobic exercise as a therapy option for migraine: a pilot study. Int J Sports Med 2011; 32(6):455–460. doi:10.1055/s-0030-1269928.

7 Varkey E, Cider A, Carlsson J, Linde M. A study to evaluate the feasibility of an aerobic exercise program in patients with migraine. Headache 2009; 49(4):563–570. doi:10.1111/j.1526-4610.2008.01231.x.

8 Office of Disease Prevention and Health Promotion. Physical activity guidelines for adults. *health.gov/paguidelines/guidelines/adults.aspx*. Accessed June 7, 2018.

9 Bigal ME, Lipton RB. Obesity is a risk factor for transformed migraine but not chronic tension-type headache. Neurology 2006;67(2):252–257. doi:10.1212/01.wnl.0000225052.35019.f9.

10 Louter MA, Bosker JE, van Oosterhout WP, et al. Cutaneous allodynia as a predictor of migraine chronification. Brain 2013;136(pt 11):3489–3496. doi:10.1093/brain/awt251.

11 May A, Schulte LH. Chronic migraine: risk factors, mechanisms and treatment. Nat Rev Neurol 2016; 12(8):455–464. doi:10.1038/nrneurol.2016.93.

12 Fried NT, Elliott MB, Oshinsky ML. The role of adenosine signaling in headache: a review. Brain Sci 2017;7(3). pii:E30. doi:10.3390/brainsci7030030.

13 Zaeem Z, Zhou L, Dilli E. Headaches: a review of the role of dietary factors. Curr Neurol Neurosci Rep 2016;16(11):101. doi:10.1007/s11910-016-0702-1.

14 Lee MJ, Choi HA, Choi H, Chung CS. Caffeine discontinuation improves acute migraine treatment: a prospective clinic-based study. J Headache Pain 2016;17(1):71. doi:10.1186/s10194-016-0662-5.

15 Headache Classification Committee of the International Headache Society. International classification of headache disorders, 3rd edition (beta version). Cephalalgia 2013;33(9):629–808. doi:10.1177/0333102413485658.

16 Harnod T, Wang YC, Kao CH. Association of migraine and sleep-related breathing disorder: a population-based cohort study. Medicine (Baltimore) 2015;94(36):e1506. doi:10.1097/MD.0000000000001506.

17 Kim J, Cho SJ, Kim WJ, et al. Insomnia in probable migraine: a population-based study. J Headache Pain 2016;17(1):92. doi:10.1186/s10194-016-0681-2.

18 Kim J, Cho SJ, Kim WJ, et al. Insufficient sleep is prevalent among migraineurs: a population-based study. J Headache Pain 2017;18(1):50. doi:10.1186/s10194-017-0756-8.

19 van Oosterhout WP, van Someren EJ, Louter MA, et al. Restless legs syndrome in migraine patients: prevalence and severity. Eur J Neurol 2016;23(6):1110–1116. doi:10.1111/ene.12993.

20 Song TJ, Yun CH, Cho SJ, et al. Short sleep duration and poor sleep quality among migraineurs: a population-based study. Cephalalgia 2018;38(5):855–864. doi:10.1177/0333102417716936.

21 Johnson KG, Ziemba AM, Garb JL. Improvement in headaches with continuous positive airway pressure for obstructive sleep apnea: a retrospective analysis. Headache 2013;53(2): 333–343. doi:10.1111/j.1526-4610.2012.02251.x.

22 Smitherman TA, Walters AB, Davis RE, et al. Randomized controlled pilot trial of behavioral insomnia treatment for chronic migraine with comorbid insomnia. Headache 2016;56(2): 276–291. doi:10.1111/head.12760.

23 Gelaye B, Sacco S, Brown WJ, et al. Body composition status and the risk of migraine: a meta-analysis. Neurology 2017;88(19):1795–1804. doi:10.1212/WNL.0000000000003919.

24 Ornello R, Ripa P, Pistoia F, et al. Migraine and body mass index categories: a systematic review and meta-analysis of observational studies. J Headache Pain 2015;16:27. doi:10.1186/s10194-015-0510-z.

25 Cervoni C, Bond DS, Seng EK. Behavioral weight loss treatments for individuals with migraine and obesity. Curr Pain Headache Rep 2016;20(2):13. doi:10.1007/s11916-016-0540-5.

26 Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology 2007;68(5): 343–349. doi:10.1212/01.wnl.0000252808.97649.21.

27 Pringsheim T, Davenport W, Mackie G, et al. Canadian Headache Society guideline for migraine prophylaxis. Can J Neurol Sci 2012; 39(2 suppl 2):S1–S59.

28 Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology 2000;55(6):754–762. doi:10.1212/WNL.55.6.754.

29 Holland S, Silberstein SD, Freitag F, et al. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults. Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78(17): 1346–1353. doi:10.1212/WNL.0b013e3182535d0c.

30 Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. Neurology 2012;78(17): 1337–1345. doi:10.1212/WNL.0b013e3182535d20.

31 Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016;86(19):1818–1826. doi:10.1212/WNL.0000000000002560.

32 Dodick DW, Ashina M, Brandes JL, et al. ARISE: a phase 3 randomized trial of erenumab for episodic migraine. Cephalalgia 2018;38(6): 1026–1037. doi:10.1177/0333102418759786.

33 Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab for episodic migraine. N Engl J Med 2017;377(22):2123–2132. doi:10.1056/NEJMoa1705848.

34 Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol 2017; 16(6):425–434. doi:10.1016/S1474-4422(17)30083-2.

35 Vedula SS, Bero L, Scherer RW, Dickersin K. Outcome reporting in industry-sponsored trials of gabapentin for off-label use. N Engl J Med 2009; 361(20):1963–1971. doi:10.1056/NEJMsa0906126.

36 Vedula SS, Goldman PS, Rona IJ, et al. Implementation of a publication strategy in the context of reporting biases. A case study based on new documents from Neurontin litigation. Trials 2012;13:136. doi:10.1186/1745-6215-13-136.

37 Stovner LJ, Linde M, Gravdahl GB, et al. A comparative study of candesartan versus propranolol for migraine prophylaxis: a randomised, triple-blind, placebo-controlled, double cross-over study. Cephalalgia 2014;34(7): 523–532. doi:10.1177/0333102413515348.

38 Miller S, Matharu M. Non-invasive neuromodulation in primary headaches. Curr Pain Headache Rep 2017;21(3):14. doi:10.1007/s11916-017-0608-x.

39 Puledda F, Goadsby PJ. An update on non-pharmacological neuromodulation for the acute and preventive treatment of migraine. Headache 2017;57(4):685–691. doi:10.1111/head.13069.

40 Schwedt TJ, Vargas B. Neurostimulation for treatment of migraine and cluster headache. Pain Med 2015;16(9):1827–1834. doi:10.1111/pme.12792.

41 Singer AB, Buse DC, Seng EK. Behavioral treatments for migraine management: useful at each step of migraine care. Curr Neurol Neurosci Rep 2015;15(4):14. doi:10.1007/s11910-015-0533-5.

42 Penzien DB, Irby MB, Smitherman TA, et al. Well-established and empirically supported behavioral treatments for migraine. Curr Pain Headache Rep 2015;19(7):34. doi:10.1007/s11916-015-0500-5.

43 Holroyd KA, Cottrell CK, O'Donnell FJ, et al. Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine: randomised controlled trial. BMJ 2010;341:c4871. doi:10.1136/bmj.c4871.c.

44 Silberstein SD, Dodick DW, Lindblad AS, et al. Randomized, placebo-controlled trial of propranolol added to topiramate in chronic migraine. Neurology 2012;78(13):976–984. doi:10.1212/WNL.0b013e31824d5846.

45 Tso AR, Goadsby PJ. Anti-CGRP monoclonal antibodies: the next era of migraine prevention? Curr Treat Options Neurol 2017;19(8):27. doi:10.1007/s11940-017-0463-4.

46 Skljarevski V, Matharu M, Millen BA, et al. Efficacy and safety of galcanezumab for the prevention of episodic migraine: results of the EVOLVE-2 phase 3 randomized controlled clinical trial [published online ahead of print January 1, 2018]. Cephalalgia. doi:10.1177/0333102418779543.

47 Stauffer VL, Dodick DW, Zhang Q, et al. Evaluation of galcanezumab for the prevention of episodic migraine: the EVOLVE-1 randomized clinical trial [published online ahead of print May 29, 2018]. JAMA Neurol. doi:10.1001/jamaneurol.2018.1212.

48 Dodick DW, Silberstein SD, Bigal ME, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial. JAMA 2018;319(19):1999–2008. doi: 10.1001/jama.2018.4853.

49 Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine. N Engl J Med 2017;377(22): 2113–2122. doi:10.1056/NEJMoa1709038.

50 Dodick DW, Goadsby PJ, Silberstein SD, et al; ALD403 Study Investigators. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: a randomised, double-blind, placebo-controlled, exploratory phase 2 trial. Lancet Neurol 2014;13(11): 1100–1107. doi:10.1016/S1474-4422(14)70209-1.

51 Akerman S, Romero-Reyes M, Holland PR. Current and novel insights into the neurophysiology of migraine and its implications for therapeutics. Pharmacol Ther 2017;172: 151–170. doi:10.1016/j.pharmthera.2016.12.005.

52 Schuster NM, Rapoport AM. New strategies for the treatment and prevention of primary headache disorders. Nat Rev Neurol 2016;12(11): 635–650. doi:10.1038/nrneurol.2016.143.

53 Hepp Z, Dodick DW, Varon SF, et al. Adherence to oral migraine-preventive medications among patients with chronic migraine. Cephalalgia 2015; 35(6):478–488. doi:10.1177/0333102414547138.

DISCLOSURE

Continued from page 1052

Dr Schwedt has received research/grant support from the American Migraine Foundation, the National Institutes of Health, Patient-Centered Outcomes Research Institute, and the United States Department of Defense. Dr Schwedt has received publishing royalties from UpToDate, Inc.