REVIEW

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Migraine prophylaxis: Who, why, and how

ABSTRACT

If a patient has frequent, severely debilitating migraine headaches, prophylactic treatment may help. Beta-blockers, tricyclic antidepressants, and anticonvulsants have the best evidence of efficacy; calcium channel blockers and nonsteroidal anti-inflammatory drugs are also popular because they are well tolerated and inexpensive. We review migraine treatment with emphasis on prophylaxis.

KEY POINTS

Migraine-aborting drugs must be taken promptly at the onset of the attack. In contrast, prophylactic drugs are taken every day on a regular schedule.

When choosing a prophylactic medication, one should consider the drug's efficacy and side effects and the patient's preferences and comorbid conditions.

Efficacy is not high: only about half of patients obtain a 50% or greater reduction in migraine attacks with prophylactic treatment.

One can try to stop prophylactic treatment after 6 to 12 months, depending on the baseline frequency of attacks and on whether the patient has another condition for which the drug may be beneficial.

WHEN IS A PREVENTIVE treatment worthwhile? In the case of migraine, the answer is highly individualized.

The drugs that are prescribed to prevent migraine attacks (as opposed to aborting attacks that occur) are not highly effective, and they have side effects. On the other hand, they have other indications, and if the patient has a concomitant condition for which one of these drugs is indicated, then the drug could have a two-for-one benefit. Further, pain is subjective, and a patient might well be glad to have fewer attacks, even if the treatment does not eliminate the attacks entirely.

In this article we discuss how to recognize patients who would benefit from preventive therapy and to tailor the treatment to the patient's needs.

MIGRAINE IS COMMON, UNDERTREATED

Migraine is a chronic disorder characterized by recurrent episodes of headache, autonomic dysfunction, gastrointestinal symptoms, and sometimes focal neurologic symptoms with or without aura (see below).[1] The frequency, intensity, and symptoms vary from patient to patient and even from attack to attack in a single patient.

In the United States, migraine affects 18% of women and 6% of men, or about 28 million people altogether.[2]

Migraine remains underdiagnosed and undertreated. The 1999 American Migraine Study II[3] found that, in the 10 years preceding the study, the percentage of people who met the clinical criteria for migraine as defined by the International Headache Society (see below) who actually received the diagnosis

TABLE 1

Common triggers of migraine headache

Alcohol
Anxiety
Change in sleep pattern
Depression
Flashing lights, visual stimulation
Foods and beverages containing nitrites, aspartate, glutamate, tyramine
High altitude
Medications—nitroglycerine, hydralazine, histamine, estrogen, reserpine, steroid withdrawal
Menstruation, ovulation
Organic solvents
Perfumes
Physical exertion
Sexual activity
Skipping meals
Smoke
Stress
Weather changes

Always ask the patient's preferences when deciding on migraine management

increased from 38% to a still-low 48%, and the percentage of migraine sufferers seeking medical attention increased from 16% to 47%. However, the use of prescription drugs to treat migraine increased only 4% during those 10 years.

DIAGNOSTIC CRITERIA

The International Headache Society[4,5] classifies migraine according to whether the patient experiences an aura.

Migraine without aura

Migraine without aura (previously called common migraine) is headache that, if untreated or unsuccessfully treated, lasts 4 to 72 hours and is at least two of the following:

- Unilateral
- Pulsating
- Moderate to severe in intensity
- Aggravated by usual physical activity.

In addition, the symptoms must not be attributable to another disorder, and at least one of the following must be present during the headache:

- Nausea or vomiting, or both
- Photophobia or phonophobia, or both.

Migraine with aura

Migraine with aura was previously called classic migraine.

An aura is a combination of focal neurologic symptoms that precede or accompany the migraine attack. The symptoms may affect vision (flickering lights, blurring or loss of vision), sensation ("pins and needles," numbness), and speech (dysphasia). Visual symptoms are the most common.

Auras typically develop gradually, last 5 minutes to 1 hour, and then completely go away.[4,5]

PATHOPHYSIOLOGY IS COMPLEX

Migraine is a complex neurovascular disorder, in which various triggering factors activate the trigeminal nerve and trigeminovascular system, leading to the release of several neurotransmitters (calcitonin gene-related peptide, substance P) that affect vasomotor tone, causing neurogenic inflammation of intracranial and extracranial cerebral vessels.[6] Before or during the onset of aura, the arteries of the brain first undergo vasoconstriction with decreased blood flow, followed by hyperemia and headache.[4]

Drugs for migraine target these mechanisms: ie, neuronal transmission, neurotransmitter release, neurogenic inflammation, and cerebrovascular tone.

PRINCIPLES OF MIGRAINE MANAGEMENT

The general principles of migraine management are to:

Establish the diagnosis (see above).

Educate patients about their condition and involve them in its management. Patients should be encouraged to keep a headache diary to help establish the frequency and severity of their attacks and to identify and avoid common headache triggers (TABLE 1). They should also be encouraged to keep to a daily routine and practice a healthy lifestyle.

Establish realistic expectations and goals of treatment, eg, controlling ongoing headaches and decreasing the frequency and intensity of recurring attacks.

Identify coexisting disorders that have higher prevalence in patients with migraine (TABLE 2).

Individualize therapy. The decision whether to use abortive therapy or abortive-plus-preventive therapy is based not only on the frequency of the attacks and the degree of disability, but also on the patient's personal preferences and on therapies already tried.

ABORTIVE TREATMENT

Abortive drugs should be taken early in the course of a migraine attack to stop or limit the symptoms and to restore the ability to function. The American Academy of Neurology has issued the following recommendations, based on available evidence[7]:

Triptans are recommended for patients with moderate to severe migraine attacks and for patients whose attacks do not respond to nonsteroidal anti-inflammatory drugs (NSAIDs) and combination analgesics (grade A evidence: multiple well-designed randomized clinical trials, directly relevant to the recommendation, yielded a consistent pattern of findings).

Ergot alkaloids and derivatives can be used to treat moderate to severe migraine in selected patients (grade B evidence: some evidence from randomized cliical trials supported the recommendation, but the scientific support was not optimal).

Oral NSAIDs and combination analgesics containing caffeine are recommended for initial treatment of mild to moderate migraine attacks or for the treatment of severe attacks that previously responded to similar treatment.

Antiemetics should be used promptly as adjunctive therapy; nausea and vomiting are the most debilitating symptoms associated with migraine attacks. For patients with severe nausea and vomiting, the abortive medications should be given by other than the oral route. For example, triptans can be given intranasally or subcutaneously.

Butalbital and opiates should be used only in the few patients who have intractable migraine headaches, with strict monitoring. Long-term use of these drugs should be avoided because they are highly habit-forming.

Corticosteroids (dexamethasone, hydrocortisone) are the treatment of choice for patients with status migrainosus (grade C evidence: the US Headache Consortium achieved consensus on the recommendation in the absence of relevant randomized controlled trials).

TABLE 2

Conditions often found in patients with migraine

Cardiac
- Mitral valve prolapse
- Myocardial infarction
- Patent foramen ovale

Immunologic
- Allergies

Neurologic
- Essential tremor
- Positional vertigo
- Seizure disorder

Psychologic
- Anxiety disorder
- Depression
- Manic disorder
- Panic disorder

Pulmonary
- Asthma

Vascular
- Hypertension
- Stroke

Other
- Fibromyalgia syndrome
- Irritable bowel syndrome
- Raynaud phenomenon

Abortive therapy should be started promptly at the onset of an attack

Educate patients to avoid drug-induced headache

Frequent use of abortive drugs may lead to medication-overuse headache (drug-induced headache, also called rebound headache). Patients need to be instructed not to use abortive therapy more than 2 days per week. Overuse of abortive treatment is one of the indications for preventive therapy.[7]

PRINCIPLES OF MIGRAINE PREVENTION

When to consider preventive therapy

The US Headache Consortium[7] of the American Academy of Neurology stated that prophylactic therapy should be considered if

the patient has one or more of the following:

- Recurring migraine attacks that cause severe debilitation and that significantly interfere with the patient's daily activities.
- Frequent migraine attacks. There is no set number of migraine attacks per month above which prophylaxis should be offered. We generally offer prophylactic therapy to patients who have two or more migraines per month, but the number given by different sources varies from more than two attacks to five attacks per month. Increasing frequency of the attacks is also an indication.
- Contraindications, failure, poor response, poor tolerance or overuse of abortive medications.
- Special situations such as rare types of migraine: hemiplegic migraine, basilar migraine, migraine with prolonged aura, and migrainous infarction.

Another factor to consider is patient preference. Patients should be informed about the effectiveness of preventive therapy, and realistic goals should be established. Currently available preventive pharmacologic therapies are nonspecific, moderately effective, and not without side effects.[1] Prophylactic medications reduce migraine frequency by about 50%. Patients should also be informed that it may take 1 to 2 months before preventive therapy will be fully effective.

If one beta-blocker does not work, another one may

General goals of preventive migraine therapy are to reduce the frequency, severity, and duration of attacks; improve the response to abortive medications and reduce their use; and improve the patient's ability to function and reduce his or her disability.[7]

How to select the right drug

Ideally, preventive therapy should be started with the drug that shows the highest efficacy based on the available evidence. Unfortunately, we as yet have no data to show that one drug class is better than another in migraine prevention, or that one drug within a class is better than another. Some general principles:

Start the drug at a low dose and then slowly increase the dose every 2 to 4 weeks until a therapeutic effect is achieved, until side effects are intolerable, or until the maximum effective dose is reached. Unfortunately, there is no standard recommended dosage yet for any of the drugs used to prevent migraine.[8]

Continue the preventive regimen long enough to judge if it is either clinically beneficial or ineffective (2 to 3 months).

Consider possible drug interactions in patients being treated for comorbid conditions, and avoid drugs that could exacerbate either migraine or the coexisting disease. If possible, select a drug that treats both conditions (eg, use a beta-blocker in a patient with coexisting hypertension, and avoid beta-blockers in a patient with coexisting asthma or depression).

Be especially careful when choosing a migraine prophylactic drug for a pregnant patient. Although few data are available on the adverse effects of these drugs, some prophylactic regimens may be teratogenic.[8] When migraine prophylaxis is absolutely necessary, the drug chosen must have the safest possible fetal side effect profile.

Discuss effective contraception options and pregnancy planning with any patient of childbearing age before starting prophylaxis. Some anticonvulsant drugs may alter the effectiveness of oral contraceptives.[9]

Monitor the effect of the therapy via regular follow-up visits.

Consider tapering and stopping the drug if the patient has had acceptable migraine control for 6 or 12 months. However, there is no consensus yet on when to discontinue preventive treatment. Preventive therapy can be restarted if symptoms worsen again.

DRUGS USED TO PREVENT MIGRAINE

Drugs currently used to prevent migraine include beta-blockers, anticonvulsants, antidepressants, calcium channel blockers, NSAIDs, and others (TABLE 3, TABLE 4).[10]

BETA-BLOCKERS IN MIGRAINE PREVENTION

Beta-blockers are commonly used as first-line drugs in migraine prophylaxis. They are among the most studied of drugs used for this indication, and clinical trials consistently showed them to decrease the frequency and severity of migraine headaches.[8,11,12]

Beta-blockers may be helpful in patients

TABLE 3

Drugs for migraine prevention: Current levels of evidence

Grade A evidence: Multiple randomized clinical trials with consistent findings to support efficacy

Anticonvulsants—divalproex, topiramate (was grade C in the 2000 US Headache Consortium consensus)
Beta-blockers—propranolol, timolol
Serotonin antagonists—pizotifen (not approved in the United States)
Tricyclic antidepressants—amitriptyline

Grade B evidence: Few randomized trials with some evidence supported by recommendation, suboptimal scientific support

Anticonvulsants—gabapentin
Beta-blockers—atenolol, metoprolol, nadolol
Calcium channel blockers—nimodipine, verapamil (cyclandelate and flunarizine not approved in the United States)
Neuromuscular blockers—botulinum toxin type A (not included in the 2000 US Headache Consortium consensus)
Nonsteroidal anti-inflammatory drugs (NSAIDs)—aspirin, fenoprofen, flurbiprofen, ketoprofen, mefenamic acid, naproxen
Selective serotonin reuptake inhibitors (SSRIs)—fluoxetine
Others—estradiol, feverfew, magnesium, vitamin B_2

Grade C evidence: US Headache Consortium consensus (published in 2000) in the absence of relevant controlled clinical trials

Calcium channel blockers—diltiazem
Monoamine oxidase inhibitors—bupropion, mirtazapine, phenelzine, trazodone, venlafaxine
NSAIDs—ibuprofen
Serotonin antagonists—cyproheptadine
SSRIs—fluvoxamine, paroxetine, sertraline
Tricyclic antidepressants—doxepin, imipramine, nortriptyline, protriptyline

with coexisting problems such as anxiety, essential tremor (for which propranolol is indicated), and hypertension. Their use is contraindicated in patients with coexisting asthma, cardiac conduction abnormalities, Raynaud disease, and brittle diabetes.

Exactly how beta-blockers prevent migraine attacks is unknown, although they are thought to inhibit beta-1-mediated mechanisms in the central catecholaminergic system.[13]

The only beta-blockers approved for migraine prophylaxis by the US Food and Drug Administration (FDA) are propranolol and timolol, but nadolol, atenolol, and metoprolol are also used.

Propranolol is the best-studied drug from this class and is proven to be more effective than placebo in short-term treatment of migraine.[14] In addition, multiple direct comparisons of propranolol showed it is at least as effective and safe as a variety of other drugs (other beta-blockers, calcium-channel antagonists, anticonvulsants) used in migraine prevention.[10,14]

However, there is no clear clinical evidence that one beta-blocker is more effective than another. The choice depends on the physician's preference and familiarity with the given drug. If one beta-blocker is not well tolerated or is ineffective, another can be tried: therapeutic failure of one beta-blocker does not predict that another will be ineffective.[8]

The dosages of beta-blockers vary widely, owing to differences in bioavailability.[8] To enhance patient compliance, twice-a-day or once-a-day dosing with extended-release preparations is recommended.

The most common adverse effects are fatigue, depression, nausea, dizziness, insomnia, decreased exercise tolerance, bradycardia, and orthostatic hypotension.

To avoid potential withdrawal symptoms (tachycardia, tremulousness) or increased headache, beta-blockers should be tapered over 2 weeks.[13]

ANTICONVULSANTS IN MIGRAINE PREVENTION

Anticonvulsants may be especially useful in patients who cannot tolerate beta-blockers or who have coexisting conditions prohibiting beta-blocker use. A review of 10 clinical trials

TABLE 4

Drugs to prevent migraine: Dosages and adverse effects

DRUG	DOSAGE*	SIDE EFFECTS
Beta-blockers		
Propranolol	80–240 mg/day	Tiredness, fatigue, nausea, depression, dizziness, decreased exercise tolerance, bradycardia, orthostatic hypotension
Timolol	20–30 mg/day	
Atenolol	100 mg/day	
Metoprolol	200 mg/day	
Nadolol	80–240 mg/day	
Anticonvulsants		
Divalproex sodium	500–1,500 mg/day	Weight gain, tremor, hair loss, teratogenic effect, hepatotoxicity
Gabapentin	900–2,400 mg/day	Tiredness, dizziness
Topiramate	100 mg/day	Paresthesias, fatigue, decreased appetite, nausea, diarrhea, cognitive dysfunction
Tricyclic antidepressants		
Amitriptyline	30–150 mg/day	Drowsiness, weight gain, anticholinergic side effects
Selective serotonin reuptake inhibitors		
Fluoxetine	20 mg every other day–40 mg/day	Insomnia, fatigue, tremor
Calcium channel blockers		
Nimodipine	120 mg/day	Abdominal discomfort
Verapamil	240 mg/day	Constipation, peripheral edema, atrioventricular conduction disturbances
Nonsteroidal anti-inflammatory drugs		
Aspirin	1,300 mg/day	Abdominal discomfort, gastritis, occult gastrointestinal bleeding
Ketoprofen	150 mg/day	
Naproxen	Not established	
Others		
Estradiol (percutaneous gel)	1.5 mg/day for 7 days perimenstrually	
Butterbur	50–75 mg twice daily	Gastrointestinal upset
Feverfew	50–82 mg/day	Inflammation of oral mucosa
Magnesium	400–600 mg/day	Diarrhea
Vitamin B_2	400 mg/day	Diarrhea, polyuria

*Dosages that were effective in clinical trials

showed that patients were more than twice as likely to have a 50% or greater reduction in migraine attack frequency if treated with anticonvulsants than with placebo.[15] Divalproex, topiramate, and gabapentin are used for migraine prevention, but only divalproex and topiramate are FDA-approved for this purpose.

Divalproex

Divalproex has been extensively studied. Multiple clinical trials found it to be highly effective when compared with placebo and similar in efficacy to propranolol.[16,17] Divalproex is effective for long-term migraine prophylaxis, and initial benefits are maintained for periods in excess of 3 years.[18] This drug is especially recommended for patients with prolonged or atypical migraine aura.[10]

Divalproex consists of sodium valproate and valproic acid. In the body, these molecules increase the gamma-aminobutyric acid (GABA) concentration and enhance its activity in the brain. Increased activation of GABA receptors, especially in the dorsal

raphe nucleus, causes decreased activity of serotoninergic neurons, which are involved in the pathogenesis of migraine.[8]

Dosage. Divalproex is available in short-acting and extended-release formulations. Both forms have similar clinical efficacy. Preventive therapy can start with 500 mg/day, which can be gradually increased to achieve clinical benefit.

Baseline liver function tests may be obtained before initiation of the therapy. Blood levels of valproic acid may be monitored to assess efficacy (the drug should achieve antiepileptic plasma concentrations before it is considered ineffective), toxicity, or compliance.

Adverse effects include nausea, weight gain, alopecia, tremor, asthenia, dyspepsia, and somnolence.

Contraindications. Divalproex is contraindicated in patients with liver disease and a history of pancreatitis. Rare cases of fulminant hepatitis and pancreatitis were reported when divalproex was used as an antiepileptic drug.[13] Divalproex is also contraindicated in patients with hematologic disorders, especially thrombocytopenia. Because of its teratogenic potential, it is absolutely contraindicated in pregnant patients and those considering pregnancy. Effective methods of contraception should be discussed with women of childbearing age before they start divalproex.

Divalproex is absolutely contraindicated in pregnancy

Topiramate

The FDA approved topiramate for migraine prophylaxis in 2004. Several randomized, placebo-controlled trials found that topiramate is an effective monotherapy for migraine prevention.[19–21] Treatment with topiramate 100 mg daily resulted in greater than a 50% reduction in migraine frequency in 49% to 54% of patients.[22] Compared with propranolol 160 mg daily as an active control, topiramate 100 mg daily showed similar efficacy.[23]

Dosage is 25 mg/day, increasing by 25 mg every week to a target dose of 100 mg/day. Efficacy was no better with 200 mg daily than with 100 mg, and the lower dose was better tolerated.[23] Clinical benefit is usually apparent within the first month of the therapy.

Adverse effects most often reported were paresthesias, fatigue, decreased appetite, nausea, diarrhea, cognitive dysfunction, and increased predisposition to kidney stones. Unlike several other prophylactic agents, topiramate is associated with weight loss.

Gabapentin

A few clinical trials found that gabapentin reduced the frequency of migraine headaches, but this drug needs further investigation. In a 4-week study, approximately 46% of patients receiving gabapentin 2,400 mg/day reported a 50% or higher reduction in migraine frequency, compared with 16% of patients receiving placebo.[24,25]

Gabapentin is also used for the treatment of neuropathic pain.

How gabapentin works is not fully understood, but it probably increases the concentration of GABA in the brain and interacts with calcium channels.[25]

Dosage is 900 to 2,400 mg/day in divided doses.

Adverse effects most often reported are somnolence and dizziness.

ANTIDEPRESSANTS IN MIGRAINE PREVENTION

Tricyclics

Of all the classes of antidepressants, only tricyclics have been proven effective in migraine prevention.

Amitriptyline is the tricyclic most extensively studied, and multiple clinical trials consistently support its efficacy in migraine prevention. Other tricyclics such as clomipramine, doxepin, imipramine, nortriptyline, and protriptyline are often used for migraine prevention in everyday practice, but we have insufficient data to support their efficacy—their use is based on uncontrolled studies and anecdotal reports.[9]

When choosing a tricyclic antidepressant for migraine prevention, consider its adverse effects. For patients with insomnia, agents that are more sedative (eg, amitriptyline, doxepin) should be used. For patients without sleep disturbances, nortriptyline, imipramine, or protriptyline are less sedating and may be of use.

Dosage. The initial dose of amitriptyline is 10 mg/day at bedtime. The dose can

be increased in 10-mg increments every 2 weeks to the target dose of 20 to 50 mg/day. The effective dose of amitriptyline varies among patients due to individual variations in bioavailability.

Because of their sedating effect, all tricyclics should be taken at bedtime except for protriptyline, which is nonsedating and should be taken in the morning.

Adverse effects are common with tricyclics and include sedation, dry mouth, blurred vision, constipation, urinary retention, orthostatic hypotension, palpitations, and weight gain. Tricyclics are often prescribed to patients with migraine who have coexisting tension-type headaches or depression. The migraine-preventing effect of tricyclics is independent of their antidepressant activity and occurs sooner than the antidepressant effect.

Selective serotonin reuptake inhibitors

Clinical trials of selective serotonin reuptake inhibitors (SSRIs) in migraine prevention have provided poor and conflicting data.[26,27] These drugs might be helpful in some patients with coexisting depression. Adverse effects include insomnia, anxiety, nervousness, fatigue, anorexia, nausea, and vomiting.

NSAIDs are considered generally less effective in preventing migraine

Serotonin-norepinephrine reuptake inhibitors

In a recent double-blind randomized study, venlafaxine was shown to be efficacious in migraine prophylaxis when compared with placebo. It is safe and well tolerated.[28]

Monoamine oxidase inhibitors

Because of numerous adverse effects and potentially serious interactions with drugs and certain foods, monoamine oxidase inhibitors should be used only in specialty headache clinics for patients with refractory headaches after multiple attempts at abortive and prophylactic treatment have failed. Adverse effects include insomnia, orthostatic hypotension, weight gain, constipation, peripheral edema, sexual dysfunction, and risk of hypertensive crisis.

CALCIUM CHANNEL BLOCKERS IN MIGRAINE PREVENTION

Calcium channel blockers are often used in migraine prophylaxis.

Verapamil is often the first-line prophylactic drug because it is well tolerated and safe. Two studies found verapamil to have a small but significant benefit, but the dropout rates were high. Verapamil is recommended in prolonged or atypical migraine aura.

Flunarizine has also shown strong evidence of efficacy in clinical trials of migraine prophylaxis. It is considered at least as effective as propranolol 160 mg/day.[29] However, flunarizine is currently not available in the United States.

Nimodipine gave mixed results in clinical trials, and trials involving nifedipine are difficult to interpret.[30] Data supporting the efficacy of diltiazem in migraine prophylaxis are insufficient.

The mechanism of action of calcium channel blockers in treating migraine is uncertain, but most likely they prevent brain hypoxia and release of serotonin, inhibiting neurovascular inflammation.

Dosage. The starting dose of verapamil is 240 mg/day. It may be gradually increased to a maximum dose of 640 mg/day. The optimal therapeutic dosage is probably 240 to 320 mg/day. Extended-release formulations may be used to improve compliance.

Adverse effects. Common adverse effects of verapamil include constipation, peripheral edema, cardiac conduction abnormalities, and dizziness. Verapamil is contraindicated in patients with bradycardia, second-degree and third-degree heart block, and sick sinus syndrome.

NSAIDs AND OTHER AGENTS IN MIGRAINE PREVENTION

NSAIDs

As a class, NSAIDs are considered to be generally less effective in migraine prophylaxis, and evidence supporting their use is limited. Adverse effects are mild to moderate. They are thought to act by inhibiting prostaglandin synthesis and platelet aggregation, which are thought to be involved in the etiology of migraine.

The NSAIDs most often studied and used in practice are aspirin, naproxen, fenoprofen, ketoprofen, flurbiprofen, and mefenamic acid. NSAIDs should be used with caution to avoid potential compromise of gastrointestinal and renal function.

Herbal and alternative medications

Butterbur (*Petasites hybridus*) is an herbal medicine, available in the United States as a food supplement. Two recent small clinical trials support the efficacy of butterbur as a preventive therapy for migraine headaches. The effective dosing range was 50 to 75 mg twice a day. Adverse effects most often reported were gastrointestinal events, predominantly burping. Overall the agent was well tolerated.[30,31] Some European preparations of butterbur had contaminants and were associated with an increased risk of cancer. The US preparation claims to be pure and claims not to cause cancer. These statements were not evaluated by the FDA since this is a nutritional supplement.

Melatonin. Since altered melatonin levels were found in patients with migraine headaches, this substance has been under investigation as a potential preventive agent. Only a few small studies found melatonin to be effective in reducing the number of migraine headaches per month when used at a daily dose of 3 mg at bedtime. This substance needs further study in larger clinical trials.[32]

Botulinum toxin type A has been gaining attention as a possible alternative treatment for migraine. Pericranial injections of botulinum toxin type A were evaluated in several clinical trials. The results of placebo-controlled trials have failed to consistently confirm the efficacy of this agent in reducing frequency, intensity, and disability associated with migraine headaches. Open-label studies suggest that botulinum toxin A is most useful for patients with migraine triggered by muscular stress, patients with concurrent chronic tension-type headache, patients with chronic migraine with more than 15 attacks per month for longer than 3 months, and patients in whom drug therapy failed or was intolerable.[33,34] No major complications of this treatment were reported; however, further clinical trials are needed to prove its efficacy in migraine prevention.

Others. The quality of evidence from clinical trials for feverfew (*Tanacetum parthenium*) 50 to 82 mg/day, magnesium 400 to 600 mg/day, and riboflavin (vitamin B_2) 400 mg/day falls into category B (some evidence from randomized clinical trials, but the scientific support is not optimal). Additional studies are needed to establish the clinical effectiveness of these agents.

SHORT-TERM PROPHYLAXIS FOR MENSTRUAL MIGRAINE

Menstrual migraine is defined as attacks occurring 2 days before menses until the second, third, or last day of menstruation. It is not officially included in the International Headache Society classification.

Estrogen withdrawal is a trigger of menstrual migraine. Several drug treatments have been proven to be effective as short-term prophylaxis for menstrual migraine: NSAIDs, triptans, and high-dose estradiol.[35] They may be useful in women with menstrual migraine and regular cycles. Preventive medication should be started 1 or 2 days before the expected onset and continued through the menstrual period.

High-dose estradiol 1.5 mg in a transdermal gel patch used for 7 days in the perimenstrual period has been effective in preventing menstrual migraine.[10]

NONPHARMACOLOGIC THERAPY

Consider alternative or nondrug therapy if the patient prefers it or if previous drug therapy has failed

Nonpharmacologic therapy in patients with migraine should be considered if any of the following is true:

- The migraine did not respond to multiple trials of drug treatment
- The patient could not tolerate the side effects of drug treatment
- The patient is pregnant, trying to get pregnant, or breast-feeding
- The patient has a history of frequent, excessive, or long-term use of analgesics or other abortive drugs, leading to worsening headaches
- The patient prefers nonpharmacologic treatment.

The American Academy of Neurology[7] has evaluated the evidence for nonpharmacologic treatment of migraine by itself or along with preventive drug therapy:

Grade A evidence: relaxation training, thermal biofeedback (hand-warming) combined with relaxation training, electromyographic biofeedback (feedback of electrical activity from the muscles of the scalp and

neck), and cognitive-behavioral therapy. The most commonly used relaxation techniques are progressive muscle relaxation, autogenic training, and meditation or passive relaxation. Cognitive-behavioral therapy involves psychotherapeutic intervention to teach the patient how to identify and control stress and minimize its effects.

Grade B evidence: behavioral therapy combined with preventive drug therapy.

Insufficient evidence: hypnosis, acupuncture, transcutaneous electrical nerve stimulation, chiropractic or osteopathic cervical manipulation, occlusal adjustment, or hyperbaric oxygen.

CLOSURE OF CARDIAC SHUNTS

Patients with migraine, especially migraine with aura, have a higher prevalence of patent foramen ovale and atrial septal defect, particularly with right-to-left cardiac shunting. Several retrospective studies suggested that migraine headaches may decline in frequency or even completely resolve after these defects are repaired: 29% to 84% of patients had complete resolution of symptoms, and 14% to 83% had improvement of symptoms.

Unfortunately, all the studies were small, retrospective, and nonrandomized, and most patients selected for surgical repair had a history of paradoxical embolism or cryptogenic stroke and were treated with clopidogrel and aspirin. Additional well-designed studies are needed to provide convincing clinical evidence that repair of these defects can ameliorate migraine headaches.[36]

SOME PRACTICAL ADVICE

Migraine is commonly encountered in outpatient practice. Be able to recognize patients who would benefit from preventive therapy, and be prepared to tailor the treatment to the patient's needs and preferences.

When choosing a drug for abortive or preventive treatment of migraine, first consider the risks and possible benefits,[8] and let clinical evidence of efficacy, migraine headache type, existing comorbidities, patient's preference, adverse effect profile, and cost effectiveness guide drug selection.

In pregnant patients and women of childbearing age, pay special attention to the drug's adverse effect profile.

Identify any coexisting medical conditions (eg, hypertension, depression, insomnia, seizure disorder) and use the opportunity to treat two conditions with one drug, while avoiding a drug that may worsen the coexisting illness.

For preventive therapy, consider a drug with the highest proven efficacy, ie, a beta-blocker, tricyclic antidepressant, or anticonvulsant. Calcium channel antagonists and NSAIDs are popular first-choice drugs because of their tolerability and low cost, but evidence of their effectiveness in migraine prevention is limited.

Consider using an alternative drug treatment or nonpharmacologic therapy in patients who prefer this approach or whose migraine has not responded to initial preventive treatment.

Consider discontinuing preventive therapy only after at least 6 months of effective treatment in patients who have a history of less-frequent attacks and fewer comorbid conditions. For patients with a long history of migraine headaches and multiple comorbidities, good control of migraine attacks with prophylaxis for at least 12 months is currently recommended.[37]

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