Migraine Treatment From A to Z

Migraine is a very common and disabling illness. Picking an agent that is best for each individual patient requires considering the patient's history, lifestyle, comorbid conditions, and individual preferences.

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Migraine headaches are a common cause of disability in the United States, affecting approximately 60 million American adults, or 17.1% of women and 5.6% of men.[1] To help better define migraines, the term *classical migraine* has been replaced with *migraine with aura* and *nonclassical migraine* is now referred to as *migraine without aura*. Chronic migraine, which affects 3.2 million Americans (2%), is defined as having migraine symptoms for at least 15 days per month, lasting at least 4 hours and for longer than 3 months in duration. This is in contrast to episodic migraine, which causes symptoms on fewer than 15 days per month.[2] Current treatment for chronic migraine is divided into acute abortive agents (analgesics, triptans, ergots, etc) and medications that will prevent migraine onset.

This review will highlight the current definitions of migraines as well as treatment options.

Migraine Characteristics

A recurring headache that is of moderate or severe intensity and is triggered by migraine-precipitating factors usually is considered to be migraine. Precipitating factors can include stress, certain foods, weather changes, smoke, hunger, fatigue, and hormones. Migraine without aura is a chronic idiopathic headache disorder with attacks lasting 4 to 72 hours. Status migrainosis applies to migraine headaches that exceed 72 hours. Migraine features often include a unilateral location and a throbbing or pulsating nature

to the pain. There may be associated nausea, photophobia, or phonophobia (Table 1). Further characteristics include a positive relationship with menses, decreased frequency during pregnancy, increase of the pain with physical activity, and history of migraine in first-degree relatives. Seventy to 75% of migraine patients report a first-degree relative with a history of migraines.[3]

Patients who suffer from migraines often have colder hands and feet compared with controls, and the prevalence of motion sickness is much higher in migraine patients. Although most patients will not have all of these characteristics, there are certain diagnostic criteria that have been established by the International Headache Society for the definite diagnosis of migraine.[2] Distinguishing a milder migraine without aura from a moderate or severe tension headache may be difficult, and I am not surprised when "pure" migraine medications are effective for severe tension-type headaches.

I generally regard recurrent, repeated attacks of throbbing or severely aching headache as migraine, whether or not the patient has nausea, photophobia, or phonophobia. The patient's history is used to make the diagnosis of migraine. Physical examination and magnetic resonance imaging (MRI) or computed tomography (CT) scans are helpful only in ruling out organic pathology—recent-onset headaches need to be investigated with an MRI scan to rule out other organic disorders, particularly brain tumors. In addition to physical exam and imaging, a check of intraocular pressure (IOP) may be warranted.

Although the pain is unilateral in 50% of migraine patients, the entire head often becomes involved. The pain may be in the facial or the cervical areas, and often will shift sides from one occurrence to another. Most patients, however, suffer the severe pain on one favored side from attack to attack.

Table 1. Characteristics of a Migraine

- Attacks last from 4 to 72 h
- Patient history gives the diagnosis (not lab tests)
- Often occur in early morning (but may be anytime)
- Unilateral location in approximately 50% of patients
- One to five migraines per month is typical
- Gradual onset of pain is followed by a peak for hours, then slow decline
- Moderate or moderate to severe pain; pain is throbbing, pounding, pulsating, or deeply aching
- Sharp "ice-pick" jabs are common
- Peak ages are between 20 and 35 y
- 18% of women and 7% of men will experience a migraine in their lifetime; female ratio is 3:1
- Family history often is positive for migraine
- Associated nausea, photophobia, blurred vision, phonophobia, or dizziness are common; however, these may be absent
- In women, there often is a positive relationship with menses
- Cold hands and feet and motion sickness are common

The typical migraine patient suffers one to five attacks in a month, but many patients average less than one (episodic) or more than 15 per month (chronic). The attack frequency varies with the seasons, and many patients can identify a time of year when their headaches increase significantly.

The pain of the migraine often follows a bell-shaped curve, with a gradual ascent, a peak for a number of hours, and then a slow decline (Table 2, page 68). Occasionally, the pain may be at its peak within minutes of onset. Most patients with migraine suffer some degree of nausea during the attack, and many patients experience vomiting as well. The nausea often is mild, and some patients are not bothered by it. Many patients state that the headache is lessened after they vomit. Diarrhea occurs in some patients, and is usually mild to moderate. The presence of diarrhea renders the use of rectal suppositories very difficult.

Lightheadedness often accompanies the migraine, and syncope may occur. Most patients become very sensitive to bright lights, sounds, and odors. Between migraine attacks, many patients retain the photophobia, and it is common for migraine patients to wear sunglasses most of the time. Sensitivity to bright lights is a distinctive migraine characteristic.

Pallor of the face is common during a migraine; flushing may occur as well, but is seen less often. Patients do complain of feeling excessively hot or cold during an attack, and the skin temperature may increase or decrease on the side with pain. Patients with migraines often experience tenderness of the scalp that may linger for hours or days after the migraine pain has ceased. This tenderness may actually occur during the prodrome of the migraine. Both vascular and muscular factors contribute to the scalp tenderness. Autonomic disturbances are relatively common, such as pupillary miosis or dilation, rhinorrhea, eye tearing, and nasal stuffiness. These also are symptoms of cluster headache, including the sharp pain about one eye or temple.

Table 2. Somatic Symptoms Accompanying Migraine[a]

- Sensitivity to light
- Blurred vision
- Nausea
- Sensitivity to noise
- Tenderness about the scalp
- Dizziness or lightheadedness
- Lethargy
- Vomiting
- Sensitivity to odors
- Retention of fluid, with weight gain
- Photopsia
- Vertigo
- Anxiety
- Paresthesias
- Diarrhea
- Fortification spectra
- Nasal stuffiness
- Mild aphasia
- Syncope or near syncope
- Severe confusion
- Seizures
- Fever
- Hemiparesis or hemiplegia
- Ataxia or dysarthria (brainstem dysfunction)

[a] Listed in order of frequency

Alterations of mood are seen with many patients before, during, and after migraine attacks. Patients are usually anxious, tired, or depressed. They often feel "washed out," after an attack, but a calm or euphoric state occasionally is seen as a postdrome to the migraine. Rarely, euphoria or exhilaration may precede a migraine.

Weight gain due to fluid retention may occur, and begins prior to the onset of the migraine. At some point during the migraine, patients often experience polyuria. The weight gain is usually less than 6 lbs, and is transient.

Visual Disturbances

Approximately 20% of patients experience visual neurologic disturbances preceding or during the migraine; these auras may be as disturbing to the patient as the migraine pain itself. The visual symptoms usually last 15 to 20 minutes, and most often will be followed by the migraine headache. Most migraine sufferers experience the same aura with each migraine, but occasionally one person may have several types of auras. "The light of a flashbulb going off," is the description many patients give to describe their aura. The visual hallucinations seen most often consist of spots, stars, lines (often wavy), color splashes, and waves resembling heat waves. The images may seem to shimmer, sparkle, or flicker. These visual occurrences are referred to as *photopsia*.

Fortification spectra are seen much less often than photopsia. They usually begin with a decrease in vision and visual hallucinations that are unformed. Within minutes, a paracentral scotoma becomes evident and this assumes a crescent shape, usually with zigzags. There often is associated shimmering, sparkling, or flickering at the edges of the scotoma.

Patients may experience a "graying out" of their vision, or a "white out" may occur. Some patients suffer complete visual loss, usually for some minutes. Photopsia may be experienced at the same time as the gray out, white out, or visual loss.

Miscellaneous Neurologic Symptoms

Numbness or tingling (paresthesias) commonly are experienced by patients as part of the migraine. These are experienced most often in one hand and forearm, but may be felt in the face, periorally, or in both arms and legs. Like the visual disturbances, they often last only minutes preceding the pain, but the numbness may continue for hours, and at times the paresthesias are severe. The sensory disturbances usually increase slowly over 15 to 25 minutes, differentiating them from the more rapid pace seen in epilepsy.

Paralysis of the limbs may occur, but this is rare. This is occasionally seen as a familial autosomal dominant trait, and the term *familial hemiplegic migraine* is applied to this form. With the weakness, aphasia or slurred speech may also occur, and sensory disturbances are seen ipsilateral to the weakness.

Vertigo is occasionally experienced during migraine, and may be disabling. Ataxia may occur, but is not common. Rarely, multiple symptoms of brain stem dysfunction occur, with the term *basilar migraine* being applied to this type of syndrome. The attack usually begins with visual disturbances (most often photopsia), followed by ataxia, vertigo, paresthesias, and other brain stem symptoms. These severe neurologic symptoms usually abate after 15 to 30 minutes, and are followed by a headache. This type of migraine often stops over months or years, and the patient is simply left with migraine headaches without neurologic dysfunction.

Workup for Migraine

As noted, when patients present with a long history of typical migraine attacks, and the headaches are essentially unchanged, scans of the head usually are not absolutely necessary. Whether to do any testing at all depends on the physician's clinical suspicion of organic pathology (see Box). Sound clinical judgment, based on patient history and a physical exam, is crucial in deciding who needs which exam.

In addition to the MRI and CT scan, tests that are generally useful for diagnosis of headache include lumbar

Situations that raise concern about organic pathology include:

- Progressive headaches over days or weeks, increasing in intensity
- New-onset headaches, particularly in patients who "never" get headaches, or new-onset exertional headaches
- Neurologic symptoms or signs, stiff neck, papilledema, and changes in level of consciousness
- A fever that is not explained
- Radical increase or change in a pre-existing headache pattern

puncture, IOP testing, CT scan of the sinuses, and blood tests. The current ability to noninvasively obtain a magnetic resonance angiogram allows the detection of most intracranial aneurysms.

The problems that need to be excluded in a patient with new-onset migraine include sinus disease, meningitis, glaucoma, brain tumor, arteritis, subarachnoid hemorrhage, idiopathic intracranial hypertension, hydrocephalus, pheochromocytoma, stroke or transient ischemic attack, internal carotid artery dissection, and systemic illness.

Headache Triggers

With migraine and chronic daily headache sufferers, avoidance of triggers should be emphasized. The most common triggers are stress (both during and after stress), weather changes, perimenstruation, missing meals, bright lights or sunlight, under- and oversleeping, food sensitivity, perfume, cigarette smoke, exercise, and sexual activity. Some foods can be headache triggers, but foods tend to be overemphasized. In general, headache patients do better with regular schedules, eating three or more meals per day, and going to bed and awaking at the same time every day.

Regarding stress as a trigger, it is not so much extreme stress, but daily hassles that increase headaches. When patients are faced with overwhelming daily stress, particularly when they are not sleeping well at night, headaches can be much worse the next day.

Psychotherapy is extremely useful for many headache patients with regard to stress management, coping, life issues, family of origin issues, and so on. Although psychotherapy may be recommended, it is crucial to legitimize the headaches as a physical condition; headaches are not a "psychological" problem, but rather a physical one that stress may exacerbate.

Managing stress with exercise, yoga, and Pilates, often will reduce the frequency of headaches. The ideal would be for the patient to take a class weekly, then do the stretches and breathing for 10 minutes per day. Relaxation techniques such as biofeedback, deep breathing, and imaging also can be helpful for daily headache patients, particularly when stress is a factor.

Many migraine patients have accompanying back or neck pain and physical therapy or chiropractic treatment may help. Acupuncture occasionally is helpful. Massage can be effective, but the relief is short-lived. Temporomandibular disorder (TMD) may exacerbate migraine; with TMD, a bite splint often is useful.

Caffeine Use

Although caffeine can help headaches, overuse may increase headaches. Whether in coffee, caffeine pills, or combination analgesics, patients must limit total caffeine intake. The maximum amount of caffeine taken each day varies from person to person, depending on sleep patterns, presence of anxiety, and sensitivity to possible rebound headaches. In general, caffeine should be limited to no more than 150 or 200 mg per day (Table 3).

Table 3. Common Caffeine Sources[a]

- Coffee, brewed, 8 oz cup: 75-150 mg. Drip is the strongest form, percolated is weaker. Specialty coffee brewers such as Starbucks may be up to 50% stronger than home-brewed. A small latte has 70-90 mg
- Instant: 40-150 mg/cup, usually closer to 40 mg. Decaf: about 5 mg/cup, but may be higher
- Tea, 8 oz: 30-50 mg
- Soft drinks: approximately 40 mg/cup; energy drinks may have more than 200 mg/8 oz
- Chocolate: 1-15 mg/oz
- Cocoa: 20-50 mg/8 oz
- Caffeine tablets: (NoDoz, Vivarin, Tirend) contain 100 mg of caffeine
- Caffeine also is present in many analgesic medications, such as Excedrin Migraine (65 mg), Anacin (32 mg), and Vanquish (33 mg)

[a] Limit caffeine to 150 mg/d, or at most, 200 mg/d

Table 4. Foods to Avoid

- Monosodium glutamate (MSG)—also labeled as autolyzed yeast extract, hydrolyzed vegetable protein, or natural flavoring. Possible sources of MSG include broths or soup stocks; seasonings; whey protein; soy extract; malt extract; caseinate; barley extract; textured soy protein; chicken, pork, or beef flavoring; meat tenderizer; smoke flavor; spices, carrageenan; seasoned salt; TV dinners; instant gravies; and some potato chips and dry-roasted nuts
- Alcohol. All alcohol can trigger a headache; beer and red wine are the worst offenders. White wine is not as likely to trigger a headache
- Cheese. Ripened, aged cheeses (Colby, brick, cheddar, Roquefort, brie, gruyere, bleu, Boursault, mozzarella, parmesan, Romano) and processed cheese are the worst. Less likely to trigger a headache: cottage cheese, cream cheese, and American cheese
- Chocolate
- Citrus fruits
- Meat that has been cured or processed, such as bacon, bologna, ham, hot dogs, pepperoni, salami, sausage; canned, aged, or marinated meats
- Nuts, peanut butter
- Yogurt, sour cream
- Large amounts of aspartame (Nutrasweet)

Foods to Avoid

As noted, multiple food sensitivities are not that common. However, most people are sensitive to two or three types of food in the diet. If a particular food is going to cause a headache, it usually will occur within 3 hours of eating. Table 4 provides a list of foods to avoid.

Keys to treatment management are outlined in the Figure.

Medications: Abortives

The most common first-line treatment for migraines includes triptans. More than 200 million patients worldwide have used triptans. The most effective way to use triptans is to take them early in the headache—the earlier a patient takes these agents the better the effect. Sumatriptan is an extremely effective migraine-abortive medication with minimal side effects. It is effective for approximately 70% of patients and has become the gold standard in abortive headache treatment. The usual dose is one tablet every 3 hours, as needed; maximum dose, two tablets per day. However, clinicians do need to limit triptan use (ideally, 3 days per week) to avoid rebound headaches or medication overuse headaches.

Triptans are helpful for moderate as well as more severe migraines. Certain patients may tolerate one triptan better than others and it is worthwhile to try several in an individual patient. Triptans are an excellent choice for migraine patients who are not at risk for coronary artery disease (CAD). Patients in their 50s or 60s can use these drugs, but they should be prescribed cautiously, and only in those patients who have been screened for CAD.

For patients who cannot tolerate triptans, there are a number of other effective non-triptan first-line approaches, including diclofenac (Cambia), Excedrin Migraine, naproxen, ibuprofen, and prodrin.

In general, drugs containing ergotamine (also called ergots) are effective second-line therapy for migraines. They were the first anti-migraine drugs available, but they have many side effects, and at most, should be used only 2 days per week. Dihydroergotamine (DHE) is an ergot derivative. Intravenous DHE is a very effective migraine-abortive agent administered in the office or emergency room. Nasal and inhaled forms of DHE have been found to be safe and effective as well. Barbiturates and opioids have been studied and are effective, but because of the risk for addiction, should be used sparingly. For severe prolonged migraines, corticosteroids (oral, IV, or intramuscular) often are effective. However, patients need to be informed of, and accept, possible adverse events.

Tables 5 to 7 review all the first- and

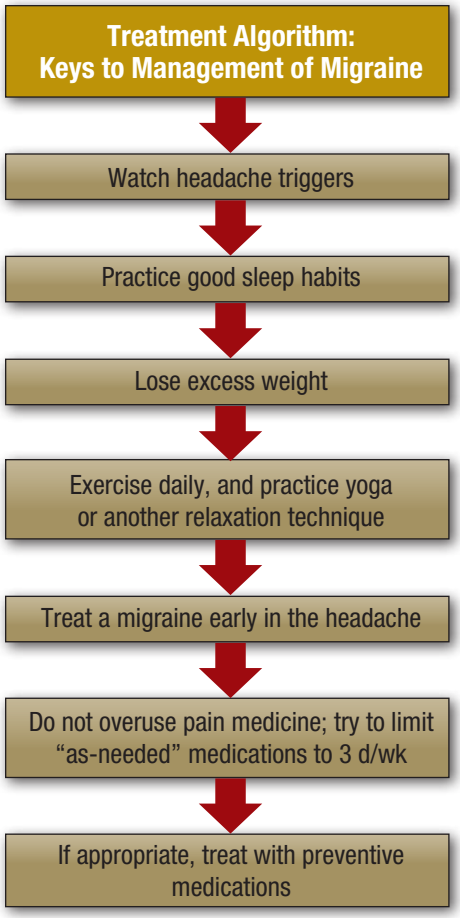

Figure. Management tips for patients.

second-line migraine-abortive medications (pages 72-75).

Miscellaneous Approaches

Muscle relaxants (carisoprodol, diazepam) or tranquilizers (clonazepam, alprazolam) occasionally are useful, primarily to aid in sleeping. Intravenous valproate sodium (Depacon) is safe and can be effective. The atypical antipsychotics, such as olanzapine (Zyprexa) or quetiapine (Seroquel), occasionally may be useful on an as-needed basis. In the emergency room, IV administration of antiemetic agents like prochlorperazine (Compazine, others) or metoclopramide (Reglan) may be useful. Certain preventive medications, such as valproic acid, or divalproex sodium (Depakote), topiramate (Topamax), and amitriptyline, may be useful on an as-needed basis, utilizing low doses every 4 to 6 hours. The antihistamine Benadryl is occasionally useful when administered intramuscularly.

Antiemetic Medications

Table 8, page 75, outlines commonly prescribed antiemetic agents for the management of nausea and other gastrointestinal (GI) symptoms.

Preventive Medications

Two of the main concerns in headache treatment are deciding which migraine patient should be given preventive medicines and determining how many headaches are too many. There is no absolute rule that applies to headache treatment. For a patient with two headaches per month that are severe, prolonged, and not relieved by drugs, preventive medicine might be used. On the other hand, for the person who has five headaches per month, but can obtain relief from Excedrin or a triptan, preventive medicine may not be optimal. The choice of who qualifies for medication depends on the patient's age, medical and psychiatric comorbidities, and frequency and severity of the migraine, as well as the patient's preference.

In using medication, a realistic goal is to decrease the frequency and/or severity of headaches by 40% to 70%, not to completely eliminate the headaches. It is wonderful when the headaches are 90% improved, but the idea is to minimize medication. Most patients need to be willing to settle for moderate improvement. Preventives may take 3 to 6 weeks to work and trial and error often is used to find the best approach for each patient. In the long run, preventive medications are effective for approximately 50% of patients.

As noted, patients should play an active role in medication choice. Preventive medications should be selected depending on the patient's comorbidities, GI system, medication sensitivities, and the like. Fatigue is a major reason why patients abandon a preventive medication. Headache patients commonly complain of fatigue, and tend to give up on medications that increase tiredness. A patient's occupation also may guide the caregiver away from certain medications; for example, an accountant may not be able to tolerate the memory problems associated with topiramate.

Side effects are possible with any medication; the patient must be prepared to endure mild side effects in order to achieve results.

First-line Preventive Medications for Migraine

Table 9, pages 76-77, provides a summary of first-line preventive medications.

Botulinum Toxin A

Botulinum toxin A (Botox) has been studied extensively in patients with migraines. Nearly 3 million people have had botulinum toxin A injections for headache. Botulinum toxin A has been found to significantly improve quality of life and reduce headache impact.[4] Botox is the only botulinum toxin A FDA-approved for treatment of chronic migraine. It is relatively safe and only takes a few minutes to inject. One set of injections can decrease headaches for 1 to 3 months. There also is a cumulative benefit, where the headaches continue to improve over 1 year of injections. Botox may be safer than many of the medications that are used for headache.

Natural Supplements and Herbs

Feverfew, Petadolex (butterbur), and magnesium oxide have all proven effective in double-blind studies as migraine preventives. Of these, Petadolex has been the most effective. Omega-3 fatty acids may help headaches, and are an excellent supplement for general good health.

Petadolex is a purified form of the herb butterbur and is made of extracted plant certified by the German Health Authority. This herb preparation is commonly used in Europe, and has been found to be successful in preventing migraines in several well-designed blind studies. The usual dose is 50 mg twice per day. Earlier concerns about carcinogenesis with this family of herbs have decreased with the use of Petadolex. Patients have occasionally experienced GI upset or a bad taste in the mouth, but Petadolex is usually well tolerated. It is prudent to stop it every three months or so. Petadolex is available by calling 1-888-301-1084 or through www.petadolex.com and other Web sites.

Magnesium is a naturally occurring mineral that helps many systems in the body to function, especially the muscles and nerves. It has been shown that magnesium levels in the brain of migraine patients tend to be lower than normal. Magnesium oxide

Text continued on Page 77 ››

Table 5. First-line Abortive Medications: Triptans[a]

Drug Name (Brand)	Formulation	Usual Dosage	Comments
Almotriptan (Axert)	Oral tablet	12.5 mg every 3-4 h; limit to 25 mg/d	Similar to other triptans, almotriptan combines good efficacy with excellent tolerability. In 2009, almotriptan gained an official FDA indication for use in adolescents with migraine.
Eletriptan (Relpax)	Oral tablet	40 mg every 4 h; limit to 80 mg/d	Effective and well tolerated; minimal side effects include nausea, pressure in the throat, dizziness, and tiredness or weakness.
Frovatriptan (Frova)	Oral tablet	2.5 mg every 4 h; limit to 5 mg/d	Useful for slower-onset moderate or moderate to severe migraines; effective for preventing menstrual migraines. Long (26 h) half-life advantageous for patients with prolonged migraines. Mean maximal blood concentrations are seen approximately 2-4 h after a dose.
Naratriptan (Amerge, generic)	Oral tablet	2.5 mg every 3-4 h; maximum 2 doses/d	Milder, longer-acting triptan. A generic form is now available.
Rizatriptan (Maxalt)	Oral tablet and rapidly disintegrating tablet	10 mg every 4 h; maximum 3 doses/d	Similar to sumatriptan (see below). Maxalt MLT (rapidly disintegrating tablets) are placed on the tongue; tablets have a pleasant taste and may be taken without water. Approved in children and adolescents. Side effects are similar to those of sumatriptan. It will be available as a generic in 2012.
Sumatriptan (Imitrex)	Oral tablet or nasal spray	Oral: 50 and 100 mg tablet every 2-3 h; maximum 200 mg/d Nasal spray: maximum daily dose 40 mg	Sumatriptan is the most effective migraine abortive for severe, faster-onset migraines. More than 100 million people have used it over the past 20 years. The addition of an NSAID to a triptan may enhance efficacy and prevent recurrence.
Sumatriptan (Imitrex STATdose, Sumavel DosePro, Alsuma, or generic prefilled syringes)	Subcutaneous injection	Injection: 4 and 6 mg every 3-4 h as needed; maximum dosing: twice daily	Although the usual dose had been 6 mg, the 4 mg STAT dose often is effective. Sumavel is a good “needle-free” option. Alsuma is a new “epi-pen” device containing 6 mg/0.5 mL of sumatriptan. There are also generic, easy-to-use prefilled syringes of 6 mg sumatriptan.
Sumatriptan plus naproxen (Treximet)	Oral tablet	85 mg sumatriptan and 500 mg naproxen sodium. Dosage: 1 tablet every 3-4 h; maximum daily dose: 2 tablets	Treximet is an excellent combination drug that helps prevent recurrence of headache. The addition of naproxen may cause stomach pain or nausea.
Zolmitriptan (Zomig)	Dissolvable tablet	2.5 or 5 mg; usual dose 5 mg every 3-4 h as needed; maximum 10 mg/d	Zolmitriptan ZMT, 5 mg, is a pleasant-tasting, dissolvable tablet. Like Maxalt MLT, it provides an alternative to the oral tablets.

FDA, Food and Drug Administration
[a] All FDA-approved for migraine

Table 6. First-line Abortives for Migraine: Non-triptans

Drug Name (Brand)	FDA-Approved for Migraines	Formulation	Usual Dosage	Comments
Acetaminophen-containing Products				
Excedrin Migraine or E.S. Excedrin	Yes	Oral tablet	Tablets contain 250 mg aspirin, 65 mg caffeine, and 250 mg acetaminophen. Usual dosing 1-2 tablets every 3 h; maximum of 4 tablets/d	Useful as OTC for patients with mild or moderate migraines. Anxiety from the caffeine or nausea from the aspirin is common. Rebound headache may occur with overuse; 4/d (but not on a daily basis) should be maximum. Patients need to be educated about not exceeding acetaminophen's upper daily limits.
Prodrin	Yes	Oral tablet	Tablets contain 20 mg caffeine, 65 mg isometheptene, and 325 mg acetaminophen. Usual dose 1 tablet every 2-3 h; limit to 2-3 doses/d	Nonsedating and nonaddictive. Caffeine may cause nervousness or a faster heartbeat—limit dosing to 2-3 times per day. Patients with insomnia should not use it after 3 PM. Patients with hypertension should use with caution, and only if blood pressure is controlled. If not available, generic Midrin, which has a sedative and no caffeine, is usually used along with additional caffeine. Patients need to be educated about not exceeding acetaminophen's upper daily limits.
NSAIDs				
Diclofenac potassium (Cambia)	Yes	Packets dissolved in water. Available in boxes of 3 or 9 packets	50-mg packet every 2-4 h, maximum dose 150 mg/d	Excellent new migraine abortive. Useful in younger patients and in older individuals who can tolerate NSAIDs. Typical side effects of NSAIDs, primarily GI, may occur. May be combined with triptans; caffeine may be added to increase efficacy.
Ibuprofen (Advil, Motrin, generic)	No	Liquid or oral tablet/capsule	400-800 mg every 3 h; maximum dose 2,400 mg/d	Available OTC and approved for children; occasionally useful in treating menstrual migraine. GI side effects are common. May be used with triptans; caffeine increases efficacy.
Naproxen (Anaprox, Aleve, generic)	No	Oral tablet or capsule	220 mg; usual dose, 500 mg, repeated in 1 h and again 3-4 h; maximum dose 1,000 mg/d	Useful in younger patients; occasionally helpful for menstrual migraine. Nonsedating, but patients frequently report GI upset. First/usual dose is taken with food or a Tums; may be repeated in 1 h if no severe nausea is present, and again in 3-4 h. May be used with triptans; caffeine increases efficacy.

GI, gastrointestinal; NSAID, non-steroidal anti-inflammatory drug; OTC, over the counter

Table 7. Second-line Abortive Medications for Migraine

Drug Name (Brand)	Formulation	Usual Dosage	Comments
NSAIDs			
Ketorolac (Toradol, generic)	Oral, nasal spray, injection	Injection: 60 mg/2 mL; repeat in 4 h if needed. Maximum dose, 2 injections/d Oral: 2 tablets/d, at most	Ketorolac injections, which can be done at home, are much more effective than tablets. Nausea or GI pain may occur. Ketorolac is nonaddicting and does not usually cause sedation. Limit to 3/wk due to possible nephrotoxicity. IV Ketorolac is very effective. There is a new nasal spray form of Toradol, "Sprix," which may produce a burning feeling in the throat.
DHE			
Dihydroergotamine (Migranal, generic DHE, Levadex)	IV, IM, nasal spray, inhaled	1 mg IM or IV, but may be titrated up or down. If it is the first time a patient has used DHE, start with 0.33 or 0.50 mL only. Inhaled (Levadex) dosage is pending	Effective as an IV or IM injection, and occasionally as a nasal spray. Migranal is the brand name of DHE nasal spray; inhaled form of DHE (Levadex) is awaiting FDA approval. All forms of DHE are safe and well tolerated. Nausea, leg cramps, and burning at the injection side are common. IV DHE is very effective in the office or emergency room.
Butalbital			
Butalbital (Phrenilin) **Butalbital, ASA, and caffeine (Fiorinal)** **Butalbital, acetaminophen, and caffeine (Fioricet, Esgic)** **Butalbital, acetaminophen or ASA, caffeine, and 30 mg codeine (Fiorinal #3, Fioricet with codeine)**	Oral tablets or capsules	Dosage is 1-2 tablets or capsules every 3 h; maximum dose, 4 tablets/d. Limit to 30 or 40 pills/mo	Barbiturate medications are addicting, but very effective for many patients. Generics of these compounds may not work as well. Fiorinal #3 is more effective than plain Fiorinal or Fioricet. Esgic Plus adds additional acetaminophen to Esgic. Phrenilin contains no aspirin or caffeine, and is very useful at night, or in those with GI upset. Short-lasting tiredness and spacey or euphoric feelings are common side effects. Butalbital must be used sparingly in younger people.
Opioids			
Codeine and butalbital (Fiorinal #3) **Fentanyl (Actiq, others)** **Hydrocodone and acetaminophen (Vicodin, generic)** **Hydrocodone and ibuprofen (Vicoprofen)** **Oxycodone (generic)** **Meperidine (generic)** **Tramadol (Ultram)**	Oral, IM	See individual PIs. These must be limited per d, and per mo	By mouth or IM, opioids are often the best of the "last resort" approaches. When given IM, they usually are combined with an antiemetic. Although addiction is a potential problem, the difference between dependency and addiction is crucial to understand. Tramadol is milder, with relatively few side effects. Vicoprofen is more effective than the other hydrocodone preparations because of the addition of ibuprofen, and generally is well tolerated. Actiq (Fentanyl oral) has been used in several small studies, but is not indicated for this use. Opioids should be used sparingly.

Table 7. Second-line Abortive Medications for Migraine (continued)

Drug Name (Brand)	Formulation	Usual Dosage	Comments
Corticosteroids			
Cortisone (generic) **Dexamethasone (Decadron)** **Prednisone (generic)**	Oral, IV, and IM	Dexamethasone: 4 mg, ½ to 1 tablet every 8-12 h as needed. Maximum 8 mg/d. Limit to 12 to 16 mg/mo, at most Prednisone: 20 mg, ½ to 1 tablet every 8-12 h as need. Maximum dose, 40 mg/d. Limit to 80 mg/mo, at most	Most effective therapy for severe, prolonged migraine; dexamethasone and prednisone are very helpful for menstrual migraine. The small doses limit side effects, but nausea, anxiety, a "wired" feeling, and insomnia are seen. IV or IM steroids are very effective as well. Patients need to be informed of, and accept, the possible adverse events.
Ergots			
Ergotamine (Ergomar, generics) **Ergotamine and caffeine (Cafergot)**	Sublingual tablets, suppositories	Varies with preparation Tablets: ½ or 1 tablet once or twice per day as needed	Oldest therapy for migraines. Often effective, but side effects, including nausea and anxiety, are common. Only compounded Cafergot PB is available. The suppositories are more effective than the tablets. Rebound headaches are common with overuse of ergots. Use with caution after age 40, particularly with cardiac risk factors. Ergomar SL tablets are back on the market; contains no caffeine. The Ergomar dose is ½ or 1 tablet once or twice per day as needed.

ASA, aspirin; DHE, dihydroergotamine; GI, gastrointestinal; IM, intramuscular; IV, intravenous; NSAID, non-steroidal anti-inflammatory drug; PI, prescribing information

Table 8. Antiemetic Medications[a]

Drug Name (Brand)	Formulation/Dosage	Comments
Promethazine (Phenergan)	Available as tablets, suppositories, and oral lozenges (which are formulated by compounding pharmacists)	Mild but effective for most patients. Very sedating, but with a low incidence of serious side effects. Used for children and adults.
Prochlorperazine (Compazine)	IV, tablets, long-acting spansules, and suppositories	Very effective but there is a high incidence of extrapyramidal side effects. Anxiety, sedation, and agitation are common. When given IV, it may stop the migraine pain as well as the nausea.
Metoclopramide (Reglan)	Oral, IM, and IV; dose 5-10 mg	Mild, but well tolerated; commonly used prior to IV DHE. Fatigue or anxiety do occur, but usually are not severe. It is Pregnancy Category B (relatively safe).
Trimethobenzamide (Tigan)	Tablets, oral lozenges, suppositories	Well tolerated, useful in children and adults. Oral lozenges are formulated by compounding pharmacists.
Ondansetron (Zofran, generic)	Oral tablets or disintegrating tablets; dose 4 or 8 mg	A very effective antiemetic with few side effects, but expensive. It is not sedating. Zofran is extremely useful for patients who need to keep functioning and not be sedated with an antiemetic. It is Pregnancy Category B (relatively safe).

DHE, dihydroergotamine; IM, intramuscular; IV intravenously

[a] These are commonly prescribed for nausea and other GI symptoms.

Table 9. First-line Preventive Medications for Migraine				
Drug Name (Brand)	**FDA-Approved**	**Formulation**	**Usual Dosage**	**Comments**
Botulinum toxin A (Botox)	Yes	Injection	Dose: Varies	One set of injections can decrease headaches for 1-3 mo. Botox may be safer than many of the medications that are used for headache. There is also a cumulative benefit, where the headaches continue to improve over 1 y of injections.
Anticonvulsants				
Topiramate (Topamax)	Yes	Oral	25 mg once or twice daily; may be increased to 100 mg once or twice per day	Sedation and cognitive side effects, such as confusion or memory problems, may limit its use; GI upset may occur. The risk for kidney stones is increased by the use of topiramate. Bicarbonate levels should be monitored, as topiramate may cause dose-related metabolic acidosis.
Valproic acid (Depakote)	Yes	Oral	Available in 125, 250, and 500 mg tablets. Usual dose: 500 to 1,000 mg/d, in divided doses	Liver function levels need to be monitored in the beginning of treatment. Depakote needs 4-6 wks to become effective. Side effects include lethargy, GI upset, depression, memory difficulties, weight gain, and alopecia. Depakote should not be used during pregnancy.
β-blockers				
Propranolol (Inderal, others)	Yes	Oral	60-120 mg/d	Side effects include dizziness, insomnia, fatique, GI upset, respiratory distress, weight gain.
Metoprolol (Toprol XL)	No	Oral	25-100 mg/d	Has fewer respiratory effects than propranolol.
Atenolol (Tenormin)	No	Oral	25-50 mg/d	Has fewer respiratory effects than propranolol.
Nebivolol (Bystolic)	No	Oral	2.5-10 mg/d	Has fewest respiratory effects.
Tricyclic Antidepressants				
Amitriptyline (Elavil)	No	Oral	Starting dose: 10 mg at bedtime; titrate up to 25-50 mg/d. Maximum dose: 150 mg/d	Effective, inexpensive, and also useful for daily headaches and insomnia. Sedation, weight gain, dry mouth, and constipation are common.
Doxepin (Sinequan)	No	Oral	Starting dose: 10 mg at bedtime; titrate up to 25-50 mg/d. Maximum dose: 150 mg/d	Similar to amitriptyline, but fewer side effects.
Protriptyline (Vivactil)	No	Oral	5-20 mg/d	Protriptyline is one of the older antidepressants that does not cause weight gain. However, anticholinergic side effects are increased with protriptyline.

Table 9. First-line Preventive Medications for Migraine (continued)

Drug Name (Brand)	FDA-Approved	Formulation	Usual Dosage	Comments
NSAIDs				
Naproxen (Aleve, Anaprox, Naprelan, Naprosyn, other)	No	Oral	500-550 mg/d; maximum dose 1,000-1,100 mg/d	OTC option. Because of frequent GI side effects, more useful in younger patients—particularly menstrual migraine. With daily NSAIDs, blood tests are needed to monitor liver and kidney function.
Calcium Channel Blocker				
Verapamil	No	Oral	120 mg/d slow-release tablet, titrating to 240 mg/d	Reasonably effective for migraine. Usually nonsedating; weight gain is uncommon. May be combined with other first-line medications, particularly amitriptyline or naproxen. With doses higher than 240 mg/d an ECG needs to be performed. Constipation is common.
Natural Agent				
Petadolex (purified butterbur)	No	Oral	100-150 mg/d	Petadolex is very effective; it is a safer form of butterbur. Minimal side effects.

ECG, electrocardiogram; GI, gastrointestinal; NSAIDs, non-steroidal anti-inflammatory drugs; OTC, over the counter

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is used as a supplement to maintain adequate magnesium in the body. A dose of 400 or 500 mg per day can be used as a preventive; tablets are found in most pharmacies. However, mild GI side effects may limit use. There are also complications from drug interactions, and kidney and other diseases.

Feverfew has been demonstrated to be mildly effective in some patients for prevention of migraine headache. Feverfew can cause a mild increased tendency toward bleeding, and should be discontinued two weeks prior to any surgery. The problem with many herbal supplements is quality control. The amount of parthenolide (the active ingredient in feverfew) varies widely from farm to farm; certain farms consistently have better quality than others. Eclectic Institute uses a process that freeze-dries the herbs, making the product highly reliable. It is available in health food stores and at Whole Foods. The usual dose is 2 capsules each morning. Patients occasionally will be allergic to feverfew, and it should not be used during pregnancy.

Medications

The anticonvulsant agents topiramate and valproic acid are FDA-approved as migraine preventives. Topiramate is used to manage migraine, chronic daily headaches, and cluster headache; however, sedation and cognitive side effects, such as confusion or memory problems, may limit its use. Topiramate often decreases appetite, which leads to weight loss; this is unusual among headache preventives. The use of topiramate increases the risk for kidney stones. Bicarbonate levels should be monitored because this agent may cause dose-related metabolic acidosis.

Valproic acid is a long-time staple, popular for migraine prevention. It is usually well tolerated in the lower doses used for headaches; however, the generic may not be as effective. Liver functions need to be monitored in the beginning of treatment. Valproate also is one of the primary mood stabilizers for bipolar disorder. Oral Depakote ER (500 mg) is an excellent once-daily, long-acting agent. As with most preventives, valproate needs 4 to 6 weeks to become effective.

The -blocker propranolol also is FDA-approved as a preventive agent for migraines. Long-acting oral propranolol (Inderal), for example, is very useful in combination with the tricyclic antidepressant amitriptyline. Dosage begins with the long-acting agent given at 60 mg per day, and is usually kept between 60 and 120 mg per day. Lower doses are sometimes effective, such as 20 mg twice per day of propranolol. Other -blockers also are effective, such as metoprolol (Toprol XL) and atenolol. Some of

Table 10. Second-line Migraine Preventive Therapy[a]

Drug Name (Brand)	FDA-Approved	Formulation	Usual Dosage	Comments
Antiseizure Medications				
Gabapentin (Neurotin, Gralise, others)	No	Oral	Available in 100, 300, 400, 600, and 800 mg doses; usual dosage: 600-2,400 mg/d	Sedation and dizziness may be a problem; however, gabapentin does not appear to cause end-organ damage, and weight gain is relatively minimal. Gabapentin can be used as an adjunct to other first-line preventive medications.
Pregabalin (Lyrica)	No	Oral	25 mg bid to 150 mg tid	Side effects similar to those of gabapentin.
Muscle Relaxants				
Cyclobenzaprine	No	Oral	10 mg/d; patients can use ½ tablet	Sedation is a common side effect; helpful for sleeping.
Tizanidine	No	Oral	Available in 2 and 4 mg tablet. Usual dose: 2-4 mg every night; patients start with ¼ to ½ tablet. May be increased to 12 mg/d	Safe, nonaddicting agent. Sedation and dry mouth are common. Tizanidine may be used on an as-needed basis for milder headaches, or for neck or back pain.
Antidepressants				
Desvenlafaxine (Pristiq)	No	Oral	50-100 mg/d	The antidepressants with dual mechanisms (serotonin and norepinephrine) are more effective for pain and headache than the SSRIs.
Duloxetine (Cymbalta)	No	Oral	30-60 mg/d	
Venlafaxine (Effexor XR)	No	Oral	75-225 mg/d	

bid, twice daily; SSRIs, selective serotonin reuptake inhibitors; tid, thrice daily

[a] Polypharmacy is also commonly used as second-line treatment of migraine (ie, amitriptyline with propranolol, or amitriptyline with valproic acid).

these are easier to work with than propranolol because they are scored tablets, and metoprolol and atenolol have fewer respiratory effects. Depression may occur. Beta-blockers are useful for those migraine patients with concurrent hypertension, tachycardia, mitral valve prolapse, and panic/anxiety disorders. Bystolic (Nebivolol) is another -blocker that may be helpful for the prevention of headaches, and has fewer respiratory side effects than other agents.

As noted, amitriptyline is an effective, inexpensive agent that is useful for the prevention of daily headaches and insomnia. As a preventive agent, amitriptyline is prescribed at low doses and taken at night. Sedation, weight gain, dry mouth, and constipation are common side effects. Other tricyclic antidepressants such as doxepin and protriptyline can be effective for migraine. Nortriptyline is similar to amitriptyline, with somewhat fewer side effects. These also are used for daily tension-type headaches. Protriptyline is one of the few older antidepressants that does not cause weight gain. However, anticholinergic

side effects are increased with protriptyline. Although selective serotonin reuptake inhibitors (SSRIs) are used, they are more effective for anxiety and depression than for migraine.

Once-daily naproxen is a very useful agent for the treatment of daily headaches, as well as for younger women suffering from menstrual migraine. Naproxen is nonsedating, but frequently causes GI upset that increases as a person ages. Effective as an abortive, it may be combined with other first-line preventive medications. Other nonsteroidal anti-inflammatory drugs (NSAIDs) can be used for migraine prevention. As with all anti-inflammatories, GI side effects increase as people age, and so NSAIDs are used much more in the younger population. With once-daily NSAIDs, blood tests are needed to monitor liver and kidney function. Verapamil is reasonably effective for migraine; it may be combined with other first-line medications, particularly amitriptyline or naproxen.

Second-line Migraine Preventive Therapy

There are a number of second-line migraine treatments. The antiseizure medication gabapentin has been demonstrated to be useful in migraine and tension headache prophylaxis. In a large study on migraine, doses averaged approximately 2,400 mg per day, but lower doses are usually prescribed.[5] Some patients do well with very low doses (200 or 300 mg per day). Sedation and dizziness may be a problem; however, gabapentin does not appear to cause end-organ damage, and weight gain is relatively minimal. Gabapentin can be used as an adjunct to other first-line preventive medications. A newer drug, pregabalin (Lyrica), has a similar mechanism of action to gabapentin.

A safe, nonaddicting muscle relaxant, tizanidine, is useful for migraine and chronic daily headache. Tizanidine may be used on an as-needed basis for milder headaches, or for neck or back pain. Cyclobenzaprine (10 mg) is helpful for sleeping, and helps some with migraine and chronic daily headache.

There have been a number of studies on using angiotensin receptor blockers (ARB) and the angiotensin-converting enzyme inhibitors (ACEIs) for the prevention of migraine. ARBs are preferred because of minimal side effects. Examples include losartan (Cozaar), olmesartan (Benicar), and candesartan (Atacand). These may be useful for the patient with hypertension and migraine. Side effects include dizziness, among others, but they are usually well tolerated, with no sedation or weight gain.

Polypharmacy is common in migraine prevention. Two first-line medications often are used together and the combination of two preventives can be more effective than a single drug alone. For example, valproic acid often is combined with an antidepressant. Amitriptyline may be combined with propranolol, particularly if the tachycardia of the amitriptyline needs to be offset by a -blocker; this combination is commonly used for "mixed" headaches (migraine plus chronic daily headache). NSAIDs may be combined with most of the other first-line preventive medications. Thus, naproxen often is given with amitriptyline, propranolol, or verapamil. Naproxen is employed simultaneously as preventive and abortive medication. Polypharmacy commonly is employed when significant comorbidities (anxiety, depression, hypertension, etc) are present.

Venlafaxine (Effexor XR) is good antidepressant for the prevention of migraine. It is used primarily as an SSRI at lower doses; at higher doses (100-150 mg) norepinephrine also is increased. In fact, antidepressants with dual mechanisms (serotonin and norepinephrine) are more effective for pain and headache. These include duloxetine (Cymbalta) and desvenlafaxine (Prestiq). A review of second-line treatment can be found in Table 10.

Conclusion

Migraine is a very common and disabling illness. Deciding which patient would benefit from preventive therapy, and how best to treat acute attacks, can be difficult for the primary care physician. A wide variety of abortive and preventative treatments have been presented to help guide the physician.[6] Remember that picking an agent that is best for each individual patient requires considering the patient's history, lifestyle, comorbid conditions, and individual preferences.

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