Migraine Treatment: What's Old, What's New

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. There are a few new treatment options, including TMS and Ketamine.

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Migraine headaches are a common cause of disability in the United States, affecting approximately 27 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 non-classical 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, hormones, and so on. 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, phonophobia, or dizziness. (Table 1, page 34). Further characteristics include a positive relationship with menses,

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 5 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

Table 2. Somatic Symptoms Accompanying Migraine[a]

- Sensitivity to light (photophobia)
- Blurred vision
- Nausea
- Sensitivity to noise (phonophobia)
- Scalp tenderness
- Dizziness or lightheadedness
- Lethargy
- Vomiting
- Sensitivity to odors
- Retention of fluid, with weight gain
- Photopsia (light flashes/flickers)
- Vertigo
- Anxiety
- Paresthesias (numbness/tingling)
- Diarrhea
- Fortification spectra
- Nasal stuffiness
- Mild aphasia (slurred speech)
- Syncope or near syncope
- Severe confusion
- Seizures
- Fever
- Hemiparesis or hemiplegia
- Ataxia or dysarthria (brainstem dysfunction)

[a] Listed in order of frequency

decreased frequency during pregnancy, increased pain with physical activity, and history of migraine in first-degree relatives. It has been reported by 70% to 75% of migraine patients that they have 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 the 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 it is not surprising when "pure" migraine medications are effective for severe tension-type headaches.

Recurrent, repeated attacks of throbbing or severely aching headache are generally regarded as migraine, whether or not the patient has nausea, dizziness, 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 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. With new-onset headaches, an eye exam is always 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 (neck) 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.

The typical migraine patient suffers one to five attacks in a month, but many patients average less than one (episodic) or more than 10 per month (chronic). The attack frequency varies with the seasons, and many patients can identify a time of year when their headaches increase significantly. Patients with chronic migraine may have 15 days a month of headache, and many even have 30 days/month, 24/7.

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). Occasionally, the pain may be at its peak within minutes of onset. Many patients with migraine suffer some degree of nausea during the attack, and some 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 may occur, and is usually mild to moderate. The presence of diarrhea renders the use of rectal suppositories impossible.

Lightheadedness often accompanies the migraine, and syncope may occur. Most patients become sensitive to bright lights, sounds, and/or 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 around one eye or temple.

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 even 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 may experience polyuria. The weight gain is usually less than 4 lb., 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 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 and/or dizziness are often experienced during migraine, and may be disabling. "Migraine associated vertigo" has become a common diagnosis. At times, the dizziness is more disabling to patients than the other symptoms. 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 sometimes useful for diagnosis of headache include lumbar puncture, IOP testing, CT scan of the sinuses, and blood tests. A magnetic resonance angiogram (MRA) allows the detection of most intracranial aneurysms.

The problems that need to be

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

excluded in a patient with new-onset migraine include sinus disease, meningitis, glaucoma, brain tumor, arteritis, subarachnoid hemorrhage, low pressure headache, 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. Many patients state that "I can tell the weather with my head." Barometric changes and storms are typical weather culprits, but some patients do poorly on bright "sun-glare" days.

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. Once one inherits the brain chemistry for headache, these triggers come into play; without the inherited genetics, most people may have stress/weather changes/hormonal changes, but not experience a headache.

Managing stress with exercise, yoga/Pilates/meditation, etc., 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 a day. Patients may experience some relief from associated neck or back pain. Relaxation techniques such as biofeedback, deep breathing, and imaging also may be helpful for daily headache patients, particularly when stress is a factor.

Many migraine patients have accompanying neck pain and physical therapy may help; acupuncture or chiropractic treatments occasionally help. Certain physical therapists "specialize" in head and neck pain. Massage may be effective, but the relief is often short-lived. Temporomandibular disorder (TMD), with clenching and/or bruxing, may exacerbate migraine; with TMD, physical therapy, a bite splint, and/or Botox may help. It often "takes a village" to help a person with pain, and we recruit other "villagers", such as physical therapists or psychotherapists.

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 a day (Table 3).

Foods to Avoid

As noted, food sensitivities are not that common. Patients tend to focus on the foods, as they are a tangible trigger that one can control (as opposed to weather, for example). However, most people are sensitive to only 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.

Migraine Treatments

Keys to treatment management are outlined in the Figure, page 42.

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 is 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 headache (MOH). See section on rebound/MOH.

Triptans are helpful for moderate as well as more severe migraines. Certain patients tolerate one of the triptans better than another, 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. Over the 23 years that triptans have been available, serious side effects have been few; they appear to be much safer than was previously thought in 1993. Most of the triptans are now available as generics.

For patients who cannot tolerate triptans, there are a number of other effective non-triptan first-line approaches, including diclofenac potassium powder (Cambia), Excedrin Migraine, naproxen, ketorolac (po/IM/nasal: Sprix nasal spray), ibuprofen, and Prodrin (similar to Midrin, but without the sedative). We often combine 2 first-line approaches (a triptan and a non-steroidal anti-inflammatory drug [NSAID] combination, for instance).

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 the safest ergot derivative. DHE is primarily a "venoconstrictor," with little arterial effects. This renders it very unlikely to cause cardiac problems. Indeed, since its introduction in 1945, DHE has been remarkably safe. Intravenous DHE is a very effective migraine-abortive agent administered in the office or emergency room. Nasal (Migranal Nasal Spray) and inhaled forms of DHE (hopefully soon to be released) 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. It is important to use low doses of steroids.

Many patients have 3 to 6 abortives: triptan, NSAIDs, Excedrin, an anti-nausea medication, and a pain-killer (opioid/butalbital). They use

Table 3. Common Caffeine Sources and Content[a]

- Brewed coffee: 75-150 mg/8 oz (cup). Drip is the strongest form, percolated is weaker. Coffee from specialty brewers, such as Starbucks, may be up to 50% stronger than home-brewed. A small latte has 70-90 mg of caffeine
- Instant coffee: 40-150 mg/8 oz, usually closer to 40 mg
- Decaf coffee: about 5 mg/8 oz, but may be higher
- Tea: 30-50 mg/8 oz
- Soft drinks: approximately 40 mg/8 oz; 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, 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)

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

Drug Name (Brand)	Formulations	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	1 tablet every 3-4 h; maximum 2 doses/d	Milder, longer-acting triptan. A generic form is available.
Rizatriptan (Maxalt, generic)	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 for use in children and adolescents. Side effects are similar to those of sumatriptan. A generic form is available.
Sumatriptan (Imitrex, generic; Onzetra Xsail nasal spray)	Oral tablet and nasal spray	Oral: 50 and 100 mg tablet every 2-3 h; maximum 200 mg/d Nasal spray: maximum daily dose 40 mg	More than 100 million people have used sumatriptan over the past 20 years. The generic form of sumatriptan is the least expensive triptan available.
Sumatriptan (Imitrex STAT dose, 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. A generic STAT form is available. Sumavel is a good "needle-free" option. Alsuma is a new EpiPen-type device containing 6 mg/0.5 mL of sumatriptan. A generic form is available. 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, generic tablets; Zomig 5 mg nasal spray)	Dissolvable tablet and nasal spray	Oral: 2.5 or 5 mg; usual dose 5 mg every 3-4 h as needed; maximum 10 mg/d Nasal spray: 2.5 or 5 mg	Zolmitriptan ZMT, 5 mg, is a pleasant-tasting, dissolvable tablet. Like Maxalt MLT, it provides an alternative to the oral tablets. A generic ZMT form is available. The nasal spray is very effective and works quickly.

FDA, Food and Drug Administration; **NSAID**, nonsteroidal anti-inflammatory drug

[a] All FDA-approved for migraine. The addition of an NSAID to a triptan may enhance efficacy and prevent recurrence.

Table 6. First-Line Abortives for Migraine: Non-Triptans

Drug Name (Brand)	FDA Approved for Migraines	Formulations	Dosage	Comments
Acetaminophen-containing Products				
Excedrin Migraine	Yes	Oral tablet	Usual dose: 1-2 tablets every 3 h; maximum of 4 tablets/d Tablets contain 250 mg aspirin, 65 mg caffeine, and 250 mg acetaminophen	Useful OTC for patients with mild or moderate migraines. Anxiety from the caffeine and nausea from the aspirin are common. Rebound headache may occur with overuse; 4 tablets/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	Usual dose: 1 tablet every 2-3 h; limit to 2-3 doses/d Tablets contain 20 mg caffeine, 65 mg isometheptene, and 325 mg acetaminophen	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 Prodrin 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, usually is used, along with additional caffeine. Patients need to be educated about not exceeding acetaminophen's upper daily limits.
NSAIDs				
Diclofenac potassium powder (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 and 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 and capsule	220 mg; usual dose, 500 mg, repeated in 1 h and again in 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**, nonsteroidal anti-inflammatory drug; **OTC**, over the counter

Table 7. Second-Line Abortive Medications for Migraine

Drug Name (Brand)	Formulations	Usual Dosage	Comments
NSAIDs			
Ketorolac (Toradol, generic; Sprix nasal spray)	Oral, IM, nasal spray	Injection: 60 mg/2 mL; repeat in 4 h if needed. Maximum dose, 2 injections/d Oral: 2 tablets/d, at most	Ketorolac intramuscular (IM) injections, which can be administered 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 injections/wk due to possible nephrotoxicity. IV ketorolac is very effective. There is a nasal spray form of ketorolac (Sprix), which may produce a burning feeling in the throat. Sprix is more effective than tablets but not as effective as IM.
DHE			
Dihydroergotamine (Migranal nasal spray, generic DHE)	IV, IM, nasal spray	1 mg IM or IV; 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.	Effective as an IV or IM injection, and may be effective as a nasal spray. Migranal is the brand name of DHE nasal spray; inhaled form of DHE is awaiting FDA approval. All forms of DHE are safe and well tolerated. Nausea, leg cramps, and burning at the injection site are common. IV DHE is very effective in the office or emergency room.
Butalbital			
Butalbital (Phrenilin) **Butalbital, aspirin and caffeine (Fiorinal)** **Butalbital, acetaminophen, and caffeine (Fioricet, Esgic)** **Butalbital, acetaminophen, caffeine, and 30 mg codeine (Fiorinal #3)**	Oral tablets and capsules	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. Phrenilin contains no aspirin or caffeine and is very useful at night and in those with GI upset. Brief fatigue and "spacey" or euphoric feelings are common side effects. Butalbital must be used sparingly in younger people.
Opioids			
Hydrocodone and acetaminophen (Vicodin, Norco, 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 often are the best of the "last resort" approaches. When given IM, they usually are combined with an antiemetic. Although addiction is a potential problem, it is crucial to understand the difference between dependency and addiction. 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.

Table 7. Second-Line Abortive Medications for Migraine

Drug Name (Brand)	Formulations	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	Often very 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 only in younger patients. 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**, nonsteroidal anti-inflammatory drug; **PI**, prescribing information

Table 8. Antiemetic Medications[a]

Drug Name (Brand)	Formulations/Dosage	Comments
Promethazine (Phenergan)	Available as tablets, suppositories, and oral lozenges	Mild but effective for most patients. Very sedating with a low incidence of serious side effects. Used for children and adults. Oral lozenges are formulated by compounding pharmacists.
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, and suppositories	Well tolerated, useful in children and adults. Oral lozenges are formulated by compounding pharmacists.
Ondansetron (Zofran, generic)	Oral tablets and disintegrating tablets; dose: 4 or 8 mg (usually 8 mg every 3 to 4 h prn)	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; **prn**, as required
[a] These are commonly prescribed for nausea and other GI symptoms.

each in different situations, for different types and degrees of headache.

Tables 5 to 7 review all the first- and second-line migraine-abortive medications.

Miscellaneous Approaches

Muscle relaxants (carisoprodol, diazepam) or tranquilizers (clonazepam, alprazolam) occasionally are useful, primarily to aid in sleeping. Intravenous sodium valproate (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 such as prochlorperazine (Compazine, others) or metoclopramide (Reglan) may be useful. Certain preventive medications, such as valproic acid (Depakote), topiramate (Topamax), and amitriptyline, may be useful on an as-needed basis, utilizing low doses every 4 to 6 hours. The antihistamine diphenhydramine is occasionally useful when administered intramuscularly. At times, patients may have injections for home use: ketorolac, orphenadrine, sumatriptan, diphenhydramine, promethazine, etc.

Antiemetic Medications

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

Medication Overuse Headache (MOH)

Much is written about MOH, with many patients diagnosed with this condition. Often a patient will be overusing abortive medications (medication overuse), but not be suffering "rebound/withdrawal" headaches (medication overuse, but NOT medication overuse headache). Up until recently, all NSAIDS were lumped under "meds that cause MOH," and this simply is not true. For some patients, opioids, butalbital, and high-caffeine containing meds cause MOH. Triptans are occasionally implicated as well. However, for most patients with chronic migraine, they have daily (or near-daily) headaches, the preventives may not be effective, and they use abortives in an attempt to get through the day.

There are more questions in the area of MOH than we have answers. The pathophysiology of MOH is unclear. Some patients will have MOH from 2 Excedrin daily, while others do not suffer from MOH consuming 8 per day. When patients are using frequent abortives, we often withdraw them from that abortive, push preventives, and attempt to minimize analgesics. However, for many chronic migraine sufferers, the preventives are not very effective. For those sufferers, abortives allow them to live with a reasonable quality of life.

Treatment Algorithm: Keys to Management of Migraine

- Watch headache triggers
- Practice good sleep habits
- Lose excess weight
- Exercise daily, and practice yoga or another relaxation technique
- Treat a migraine early in the headache
- Do not overuse pain medicine; try to limit "as-needed" medications to 3 d/wk
- If appropriate, treat with preventive medications

Figure. Management tips for patients.

Preventive Medications

There is no algorithm to determine who is to go on preventive headache medication. The number of monthly headaches is one factor, along with comorbidities. Patients have to be willing to take daily medication (many do not want any daily meds). There is no absolute rule that applies to headache treatment. For a patient with two headaches a 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 a 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. Comorbidities often determine which preventive meds are used. If a patient has HTN, a med for blood pressure will be used. When patients concurrently suffer with anxiety or depression, various antidepressants are utilized for the headache and mood disorder. We want to minimize meds, and treating 2 conditions with one medication is ideal.

In using medication, a realistic goal is to decrease the headache severity by 40% to 70%, not to completely eliminate the headaches. It is wonderful when the headaches are 90% improved, but the idea is also to minimize medication. "Clinical meaningful pain relief" is usually around a 30% improvement. Most patients need to be willing to settle for moderate improvement. Preventives may take 3 to 6 weeks to work, and "educated guesswork" often is used to find the best approach for each patient. In the long run, preventive medications are effective for approximately 50% of patients. The other 50% scramble with various abortives.

As noted, patients should play an active role in medication choice. Preventive medications should be selected depending on the patient's medical and psychological comorbidities, GI system, medication sensitivities, weight, sleep, family history of reaction to medications, finances, willingness to take daily meds, and many other factors. Fatigue and/or weight gain are major reasons 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

Botulinum Toxin A

Botulinum toxin A (Botox) has been studied extensively in patients with migraines. Nearly 8 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. Botox is the only botulinum toxin A that is FDA-approved for treatment of chronic migraine. It is relatively safe and only takes a few minutes to inject. One set of injections may 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. Botox does not cause the "annoying" side effects that are commonly encountered with preventives. Except for the cost, the experience with Botox has been very positive.

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.

Petadolex is a purified form of the herb butterbur and is made of extracted plant certified by the German Health Authority. The 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 100 mg per day, and many increase this to 150 mg daily (all at once, or in 2 divided doses). Earlier concerns about carcinogenesis with this family of herbs have decreased with the use of Petadolex. However, there are lingering concerns as to hepatotoxicity. 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 six months or so. Petadolex is available by calling 1-888-301-1084, through www.petadolex.com, or at Amazon.com.

Magnesium helps many systems in the body to function, especially the muscles and nerves. It has been shown that magnesium levels in the brains of migraine patients tend to be lower than normal. Magnesium oxide 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 drug interactions that may occur; as always, consult your physician. There are tablets, as well as powdered versions available.

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. The usual dose is 2 capsules each morning; there is a liquid form available. Patients occasionally will be allergic to feverfew, and it should not be used during pregnancy.

Miscellaneous herbs/supplements have been used, particularly vitamin B2. CoQ10 and fish oil have also been studied. These occasionally help, but are less effective than Petadolex. MigreLief has been a reliable combination of magnesium, riboflavin, and feverfew. The usual dose is 2 capsules per day, as a preventive. Most people order from MigreLief.com.

Medications: First-Line

Topiramate is an effective migraine preventive, without the weight gain commonly encountered with the other meds. While usually fairly well tolerated, common side effects include memory difficulties ("spaciness"), and tingling. In higher doses, topiramate increases the risk for kidney stones. Topiramate does decrease appetite, leading to weight loss for some patients. This anorexic effect tends to disappear after several months. The usual dose is 50 mg to 100 mg daily, but some do well on as little as 25 mg. The dose may be pushed to 300 or 400 mg per day, in the absence of significant side effects. Topiramate is primarily used for migraine prevention, but has also been utilized for cluster and tension headache as well. Topiramate may cause a metabolic acidosis, with lower bicarbonate levels (and increased chloride). The acidosis may lead to the tingling, which sometimes is alleviated by increasing potassium-containing fruits/vegetables (or adding potassium). Trokendi XR is an excellent long-acting form of topiramate, approved

for migraine prophylaxis.

Valproate, or divalproex sodium (Depakote), is a longtime 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 β-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 a day of propranolol. Other β-blockers also are effective, such as metoprolol (Toprol XL) and atenolol. Some of these are easier to work with than propranolol because they are scored tablets, and metoprolol and atenolol have fewer respiratory effects. Depression may occur. β-blockers are useful for those migraine patients with concurrent hypertension, tachycardia, mitral valve prolapse, and panic/anxiety disorders. Bystolic (nebivolol) is another β-blocker that may be helpful for the prevention of headaches, and has fewer respiratory side effects than other agents. Bystolic probably has the fewest side effects among the β-blockers.

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; protriptyline is more effective for tension headache than for migraine. Although selective serotonin reuptake inhibitors (SSRIs) are used, they are more effective for anxiety and depression than for migraine.

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 or pain. Effective as an abortive, it may be combined with other first-line preventive medications. Other NSAIDs can similarly be used for migraine prevention. It is crucial to use low doses. As with all anti-inflammatories, GI side effects increase as people age, and therefore NSAIDs are used more often in the younger population. Blood tests are needed to monitor liver and kidney function.

Table 9 reviews first-line migraine preventive therapy.

Second-line Migraine Preventive Therapy

There are a number of second-line migraine treatments. The anti-seizure medication gabapentin has been demonstrated to be mildly 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. Pregabalin (Lyrica) has a similar mechanism of action to gabapentin. Lyrica is fairly safe, but sedation and weight gain often occur.

A safe, non-addicting 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 the efficacy of using angiotensin receptor blockers (ARBs) and the angiotensin-converting enzyme inhibitors (ACEs) for the prevention of migraine. ARBs are preferred because of minimal side effects. Examples include losartan (Cozaar) 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.

Similar to the ARBs, the calcium channel antagonists have been utilized for migraine prevention. Verapamil ER (extended release) is the most commonly used form, with doses ranging from 120 mg daily up to 360 mg per day. Verapamil is probably more effective as a cluster headache preventive.

Polypharmacy is common in migraine prevention. Two first-line medications often are used together, and the combination of 2 preventives can be more effective than a single drug alone. For example, valproate often is combined with an antidepressant. Amitriptyline may be combined with propranolol (or other β-blockers), particularly if the tachycardia of the amitriptyline needs to be offset by a β-blocker; this combination is commonly used for "mixed"

Migraine Treatment: What's Old, What's New

Table 9. First-Line Preventive Medications for Migraine

Drug Name (Brand)	FDA Approved	Formulation	Usual Dosage	Comments
Onobotulinum toxin A (Botox)	Yes	Injection	Dose: Varies (FDA official dose is 155 units, via 31 injections, every 3 mo)	One set of injections can decrease headaches for 1-3 mo. Botox is most likely safer than the other medications used for headache. There also is a cumulative benefit, in which the headaches continue to improve over 1 y of Botox therapy.
Anticonvulsants				
Topiramate (Topamax) **Topiramate ER (Trokendi)**	Yes	Oral	Total dose varies from 25 or 50 mg/d up to 400 mg/d.	Sedation and cognitive side effects, such as confusion or memory problems, may limit its use; GI upset may occur. Topiramate increases the risk for kidney stones. Bicarbonate levels should be monitored because topiramate may cause dose-related metabolic acidosis.
Valproic or Divalproex sodium (Depakote)	Yes	Oral	Usual dose: 500-1,000 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. Available in 125, 250-ER, and 500-ER mg tablets.
β-blockers				
Propranolol (Inderal, others)	Yes	Oral	60-120 mg/d	Side effects include dizziness, insomnia, fatigue, GI upset, respiratory distress, weight gain.
Metoprolol (Toprol XL)	No	Oral	25-100 mg/d	Fewer respiratory effects than propranolol.
Atenolol (Tenormin)	No	Oral	25-50 mg/d	Fewer respiratory effects than propranolol.
Nebivolol (Bystolic)	No	Oral	2.5-10 mg/d	Better tolerated than the other β-blockers with the fewest respiratory effects.
Tricyclic Antidepressants				
Amitriptyline (Elavil, others) **Nortriptyline (Pamelor)**	No	Oral	Starting dose: 10 mg at bedtime; titrate up to 25-50 mg at night. Maximum dose: 150 mg/d	Effective, inexpensive, and also useful for daily headaches and insomnia. Sedation, weight gain, dry mouth, and constipation are common. Nortriptyline, a metabolite of amitriptyline, is somewhat better tolerated (milder).
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, with fewer side effects.
Protriptyline	No	Oral	5-20 mg/d	Protriptyline is one of the only older antidepressants that does not cause weight gain. However, its anticholinergic side effects are more pronounced. More effective for tension than migraine.

Table 9. First-Line Preventive Medications for Migraine

Drug Name (Brand)	FDA Approved	Formulation	Usual Dosage	Comments
NSAIDs[a]				
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, Naproxen is more useful in younger patients, particularly for 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, titrate 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.

ECG, electrocardiogram; **GI**, gastrointestinal; **NSAIDs**, nonsteroidal anti-inflammatory drugs; **OTC**, over the counter
[a] Other NSAIDs are useful as well.

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. Unfortunately, polypharmacy brings the risk of increased side effects.

Venlafaxine (Effexor XR) is an excellent antidepressant, occasionally helpful 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. Another similar medication is duloxetine (Cymbalta), with typical doses being 30 mg to 60 mg daily. Cymbalta has several pain indications, but is probably more effective for moods than for headache.

A review of second-line treatment can be found in Table 10.

What's New in Headache

Transcranial magnetic stimulation (TMS) has been the primary new therapy to emerge. In addition to TMS, ketamine is (occasionally) being utilized for refractory headaches. Calcitonin gene-related peptide (CGRP) inhibitors are in the late stages of development for the prevention of migraine; however, if they are approved, CGRP inhibitors will not be available until mid-2018 (at the earliest).

Transcranial Magnetic Stimulation (TMS)

TMS has primarily been utilized for depression. The repetitive TMS units give thousands of pulses in an hour. The SpringTMS (from eNeura) handheld system imparts only a single pulse. There have been a number of well done studies on TMS for headache and depression. The patient uses a handheld TMS device, 4 pulses twice daily (as a preventive). This takes about 5 to 10 minutes for the 4 pulses. TMS may be used abortively as well. Long-term efficacy is not well established. However, early results are promising, at least for a subset of refractory chronic migraineurs. TMS has been safe, although some patients do not like the "thump" that each pulse imparts. The cost is $450 for the first 3 months (the company rents the machine to the user).

Ketamine

Ketamine has been used to treat refractory pain or depression for the past several years. Ketamine is an NMDA receptor glutamate antagonist. In addition, ketamine affects several other receptors as well. Ketamine has been used for treatment-resistant depression, primarily as the IV formulation. Ketamine has been a drug of abuse, and has major addiction potential. There have been a number of successful trials utilizing ketamine, either intravenously or as a nasal spray. A nasal spray form of Ketamine may be marketed for severe depression in 2019.

Table 10. Supplements for Chronic Migraine

Supplement	Dosage	Uses	Comment
Riboflavin (vitamin B2)	50-400 mg/d	Prevention	Occasionally helpful, but very mild effect. Higher dose found more effective in reducing number of headaches.
Magnesium	200-700 mg/d	Prevention	Magnesium (usually magnesium oxide or citrate) is available in capsule or powder forms. Safe for pregnant women. Not as effective as Petadolex, but occasionally helpful.
Coenzyme Q10 (CoQ10)	300-500 mg/d	Prevention	CoQ10 is primarily used to offset side effects of statins, occasionally helpful for migraine. No solid controlled trial data proving efficacy.
Fish oil (omega-3 fatty acids)	6,000 mg/d	Adjunctive therapy	May represent beneficial adjunctive therapy, but its efficacy as a preventive agent for chronic migraine has not been proven.
Medicinal Herbs and Teas			
Botanical Name (Common Name)	**Dosage**	**Uses**	**Comment**
***Aromatherapy:* lavender/peppermint, and others**	Unknown	Symptomatic treatment	Lavender oil (as well as peppermint, and others) applied topically may help reduce sympathetic outflow, reducing pulse and blood pressure, while having a calming effect; aromatherapy Is safe and occasionally helpful.
MigreLief (magnesium, riboflavin, and feverfew)	2 capsule/d	Migraine prevention	Reliable formulation. MigreLief is available online at MigreLief.com.
***Petasites* Petadolex (Butterbur)**	100-150 mg/d	Treatment	Petadolex is the branded, better form of butterbur (Petadolex limits the molecule that is worrisome in butterbur); of the natural supplements, it has the most solid evidence for efficacy. Petadolex (Butterbur) is available online at Petadolex.com or Amazon.com.
***Salix alba* (white willow bark)**	600 mg	Adjunctive therapy	Used for decades, but no true evidence of efficacy.
***Tanacetum parthenium* (Feverfew)**	50-143 mg/d	Treatment/prevention	Feverfew is well tolerated, but efficacy is very limited.

Table 11. Second-Line Migraine Preventive Therapy[a]

Drug Name (Brand)	FDA Approved	Formulation	Dosage	Comments
Antiseizure Medications				
Gabapentin (Neurotin, Gralise, others)	No	Oral	Usual dose: 600-2,400 mg/d Some patients do well on low doses (100-300 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. Available in 100, 300, 400, 600, and 800 mg doses Gralise is a once-daily, long-acting version of gabapentin.
Pregabalin (Lyrica)	No	Oral	25 mg bid to 150 mg tid	Side effects similar to those of gabapentin; possibly causes more weight gain
Muscle Relaxants				
Cyclobenzaprine	No	Oral	5-10 mg/d	Sedation is a common side effect; helpful for sleeping.
Tizanidine	No	Oral	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. Available in 2 and 4 mg tablet.
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, generic)	No	Oral	30-60 mg/d	
Venlafaxine (Effexor XR)	No	Oral	75-225 mg/d	
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.

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

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

The intravenous treatment may be more effective than using ketamine as a nasal spray. However, this author has found that the nasal spray is exceedingly well tolerated, with few side effects. The usual side effects include feeling euphoric, sleepy, dizzy, and (with the IV form) hallucinations.

This author has utilized ketamine for 42 refractory headache patients, some of whom also suffered from severe depression. Our results indicated that ketamine is more helpful for the depression than the pain. The decrease in headache tends to be short-lived. However, certain patients do well with both depression and headache. We have used only the nasal spray. It is formulated as a liquid, 10 mg ketamine per 0.1 mL. The patient does the treatment in our office once per week. The usual dose is 10 mg (one spray) every 10 to 15 minutes. Usually the total dose for the treatment ranges from 50 mg to 100 mg. We check vitals after every 2 sprays (occasionally blood pressure will rise with ketamine).

New Formulations

Several newer formulations of older migraine medications have emerged. Onzetra nasal powder is a new form of sumatriptan nasal spray. Onzetra uses a unique "breath powered" delivery system. Onzetra delivers 11 mg of sumatriptan powder per breath; the usual dose is 22 mg at one time. This places the sumatriptan powder posteriorly, where there is respiratory epithelium. This epithelium is more conducive for absorption of medication than is the anterior squamous epithelium. Onzetra has excellent efficacy, and is well tolerated.

Trokendi XR is a long-acting formulation of topiramate. Trokendi has the indication for migraine prophylaxis. In our (anecdotal) experience, approximately 70% of patients prefer the Trokendi XR, versus the generic topiramate.

Medical cannabis has been used for about 5,000 years. Cannabis has multiple active ingredients—tetrahydrocannabinol (THC) is the main cannabinoid for analgesia and also produces the euphoric effect. Cannabidiol (CBD), the other important compound, is an anti-inflammatory. CBD also may enhance analgesia. One advantage of medical marijuana is that the dispensary is able to manipulate the percentage of THC vs. CBD. It often takes weeks to months in order to achieve optimum results. Vaporized inhalation is the most commonly employed route. Marijuana may help with anxiety as well as the pain.

Vagal Nerve Stimulation

Non-invasive vagal nerve stimulation (VNS)—the gammaCore VNS system from the company electroCore—was approved in April 2017 for use in episodic cluster headache (not yet approved for migraine) in adults. VNS may suppress glutamate levels in the trigeminal nucleus caudalis, resulting in decreased head pain. The portable gammaCore VNS has demonstrated efficacy for cluster headache. The long-term results in migraineurs has yet to be established. This form of VNS has minimal side effects or dose limitations. The device is not indicated for patients with an active implantable medical device, such as a pacemaker or hearing aid; those with carotid atherosclerosis, or who have had a cervical vagotomy. Also patients with hyper- or hypotension, bradycardia, or tachycardia are not candidates for the device.

Conclusion

Migraine is a common and disabling illness. Outside of meds, it is important for migraineurs to watch their headache triggers, and exercise regularly. Physical therapy and/or psychotherapy may be of help ("it takes a village"). There is no good algorithm for determining which medication is best. Each patient is unique, and comorbidities drive where we go with treatment. The goal is to decrease head pain, while minimizing medications.

Author's Bio: *Lawrence Robbins, MD, recently published a new book,* Advanced Headache Therapy: Outpatient Strategies. *He was awarded the 2008 Janet Travell Clinical Pain Management Award by the American Academy of Pain Management. He has been chosen as on of "America's Top Doctors" every year since 2002. He has certificates in pain management and psychopharmacology. He has previously published 3 headache books—one for patients,* Headache Help*; one for physicians,* Management of Headache and Headache Medications*; and an eBook* Headache 2013-2014. *Dr. Robbins has authored (or co-authored) 250 articles and abstracts. He has served his patients in his headache clinic since 1986. Dr. Robbins also was an assistant professor of neurology at Rush Medical College, in Chicago, and at the University of Illinois at Chicago. Dr. Robbins is a member of the* Practical Pain Management *Editorial Board.*

References

1. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology.* 2007;68(5):343-349.
2. Headache Classification Subcommittee of the International Headache Society. *The International Classification of Headache Disorders.* 2nd ed. Oxford, England: Blackwell Publishing; 2003.
3. Gardner KL. Genetics of migraine: an update. *Headache.* 2006;46 Suppl 1:S19-S24.
4. Lipton RB, Varon SF, Grosberg B, et al. OnabotulinumtoxinA improves quality of life and reduces impact of chronic migraine. *Neurology.* 2011;77(15):1465-1472.
5. Mathew NT, Rapoport A, Saper J, et al. Efficacy of gabapentin in migraine prophylaxis. *Headache.* 2001;41(2):119-128.
6. Robbins Headache Clinic. Robbins Headache Clinic. Available at: www.chicagoheadacheclinic.com. Accessed May 18, 2017.