

Chapter 1

Migraine and Headache: General

Migraine Treatment: 2015–2016

Migraine is a very common and disabling illness. Choosing a therapeutic agent that is best for each individual patient requires consideration of the patient's history, lifestyle, comorbid conditions, and individual preferences.



Migraine headaches are a common cause of disability in the USA, affecting approximately 25 to 28 million American adults, or 18% of women and 7% of men [6]. To help define migraines better, the term classical migraine has been replaced with migraine with aura, and nonclassical migraine now is 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 h, 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 [4]. Current treatment for chronic migraine is divided into acute abortive agents (analgesics, triptans, ergots, etc.) and medications to prevent migraine onset.

This chapter highlights the current definition 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 4–72 h. Status migrainosus applies to migraine headaches that exceed 72 h. 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 1.1). Further characteristics include a positive relationship with menses, decreased frequency during pregnancy, increased pain with physical activity, and history of migraine in first-degree relatives. Between 70 and

Table 1.1 Characteristics of a migraine

Attacks last from 4–72 h
Patient history gives the diagnosis (not laboratory 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 years
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

75% of migraine patients report 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 these characteristics, there are certain diagnostic criteria that have been established by the International Headache Society for the definitive diagnosis of migraine [4]. 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.

Taking a History

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. 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 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 1–5 attacks in a month, but many patients average less than 1 (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 per month, with pain described as 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 1.2). 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 many patients experience vomiting as well. The nausea is often mild, and some patients are not bothered by it. Many patients state that the headache is lessened after they vomit. Diarrhea may occur and usually is mild to moderate. The presence of diarrhea renders the use of rectal suppositories impossible. Light-headedness often accompanies the migraine, and syncope may occur. Most patients become very sensitive to bright lights (photophobia), sounds (phonophobia), 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.

Table 1.2 Somatic symptoms

Accompanying migraine ^a
Sensitivity to light (photophobia)
Blurred vision
Nausea
Sensitivity to noise (phonophobia)
Scalp tenderness
Dizziness or light-headedness
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)

^aListed in order of frequency

Pallor of the face is common during a migraine; flushing may occur as well but is seen less often. Patients 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 actually may occur during the prodrome of the migraine. Both vascular and muscular factors contribute to the scalp tenderness. Autonomic disturbances, such as pupillary miosis or dilation, runny nose, eye tearing, and nasal stuffiness, are relatively common. These also are symptoms of cluster headache, including the sharp pain about one eye or temple.

Alterations of mood are seen in 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 an euphoric state occasionally is seen as a prodrome to the migraine. Rarely, euphoria or exhilaration may precede a migraine.

Weight gain due to fluid retention may occur prior to the onset of the migraine. The weight gain is usually less than 6 lb, and is transient.

At some point during the migraine, patients often experience polyuria.

Visual Disturbances

Approximately 25% of patients experience visual or other neurologic symptoms preceding or during the migraine; these auras may be as disturbing to the patient as the migraine pain itself. The visual symptoms usually last 15–20 min, 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 a 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 15–25 min, differentiating them from those with a more rapid pace that are seen in epilepsy.

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

Vertigo occasionally is experienced during migraine, and may be disabling.

“Migraine-associated vertigo” has become a common diagnosis. Ataxia may occur, but it is not common. Rarely, multiple symptoms of brain stem dysfunction occur, with the term migraine with brainstem aura (previously called 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 15–30 min 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 may not be necessary. Whether to do any testing at all depends on the physician's clinical suspicion of organic pathology. Sound clinical judgment, based on patient history and a physical exam, is crucial in deciding which exams a given patient needs.

In addition to the MRI and CT scan, tests that are generally 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 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.

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 preexisting headache pattern

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 rather 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. If a person 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, 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 min/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 neck pain. Physical therapy may help, and acupuncture or chiropractic treatments occasionally help as well. Certain physical therapists “specialize” in head and neck pain. Massage may be effective, but the relief often is short-lived. Temporomandibular disorder (TMD), with clenching and/or bruxing, may exacerbate migraine. For patients with TMD, physical therapy, a bite splint, and/or onabotulinum toxin A (Botox) injections may help. It often “takes a village” to help a person with pain, and we recruit other “villagers,” such as physical therapists and psychotherapists.

Caffeine Use

Although caffeine can help headaches, overuse may increase headaches. Patients must limit total caffeine intake from all sources (e.g., coffee, caffeine pills, or combination analgesics). 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/day (Table 1.3).

Foods to Avoid

As noted, multiple food sensitivities are not common. Patients tend to focus on food, because it is 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 h of eating that food. Table 1.4 provides a list of foods to avoid.

Table 1.3 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, Tired) 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)

^aLimit caffeine to 150 mg/day, or at most 200 mg/day

Table 1.4 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)

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 h, 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 (MOH).

Triptans are helpful for moderate as well as more severe migraines. Certain patients may tolerate one triptan better than others, and it is worthwhile for patients to try several. 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.

As noted, if patients do not do well with one triptan (lack of efficacy or side effects), it is usually worthwhile for them to try at least one or two other triptans. While they are all very similar, the minor chemical differences between them mean that some patients do well with one, and not another.

The usual triptan side effects may include pressure (or tightness) in the chest/neck (or other muscle areas), tingling, and fatigue. These are usually transient, lasting 10–30 min. If a patient experiences moderate to severe chest/throat/neck pressure (or pain), we usually discontinue the triptan or substitute a milder one (naratriptan/frovatriptan). The chest symptoms are rarely cardiac in nature, which is the primary concern with chest symptoms.

There are a number of triptan choices. Sumatriptan, zolmitriptan, rizatriptan, and naratriptan are available in generic formulations. Eletriptan (Relpax) is a very effective triptan and almotriptan (Axert) is useful for many patients (Fig. 1.1).

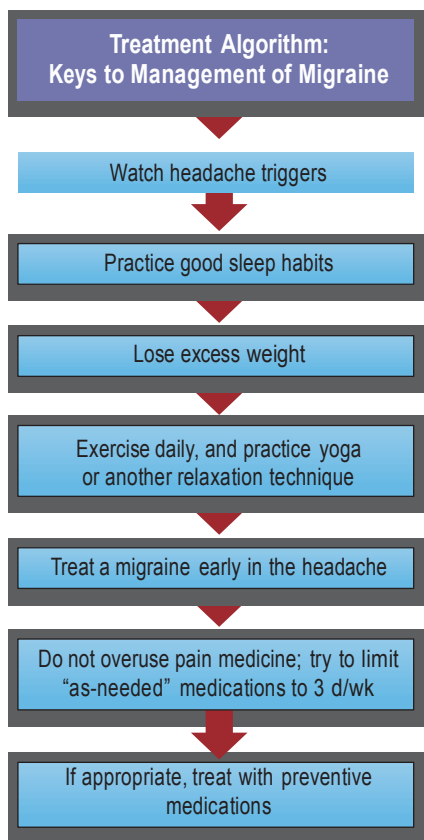
Treximet is a combination of sumatriptan and naproxen. Frovatriptan (Frova) is a “slow onset,” milder triptan, which has a longer half-life. Zolmitriptan (Zomig) nasal spray is not generic, but it is very effective, with a quick onset of action. The sumatriptan injections (available in various forms) remain the most effective migraine abortives.

For patients who cannot tolerate triptans, there are a number of other effective nontriptan first-line approaches, including diclofenac potassium powder (Cambia), Excedrin Migraine, naproxen, ketorolac, ibuprofen, and Prodrin (similar to Midrin, but without the sedative). We often combine two first-line approaches—for example, a triptan and a nonsteroidal anti-inflammatory drug (NSAID).

In general, drugs containing ergotamine (also called ergots) are effective second-line therapy for migraines. They were the first antimigraine 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. Intravenous DHE primarily is a “venoconstrictor” with few arterial effects. This renders it very unlikely to cause cardiac problems. Indeed, since its introduction in 1945, DHE has been remarkably safe. Intravenous DHE can be administered in the office or emergency room. Nasal (Migranal Nasal Spray) and inhaled forms of DHE (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, they should be used sparingly. For severe prolonged migraines, corticosteroids (oral, intravenous (IV), or intramuscular) often are effective. It is important to use low doses of steroids.

Fig. 1.1 Management tips for patients



Many patients use 3–6 abortives: a triptan, NSAID, Excedrin, an antinausea medication, and a painkiller (opioid/butalbital). Patients will use each medication in different situations, for different types and degrees of headache. Tables 1.5, 1.6, and 1.7 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 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 such as prochlorperazine (Compazine, others) or metoclopramide (Reglan) may be useful (Table 1.8). Certain preventive medications, such as valproic acid, or divalproex sodium (Depakote), topiramate (Topamax), and amitriptyline—in low doses every 4–6 h—may be useful on an as-needed basis. The antihistamine diphenhydr-

Table 1.5 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/day	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/day	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/day	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 per day	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 per day	Similar to sumatriptan (see below). Maxalt MLT (rapidly disintegrating tablets) is 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)	Oral tablet and nasal spray, a skin patch will be available Zecuity (for age 18 and up) is a unique sumatriptan skin patch, 6.5mg (low dose) over 4 hours; bypassing the GI tract, Zecuity has a good niche	Oral: 50 and 100 mg tablet every 2–3 h; maximum 200 mg/day 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

Table 1.5 (continued)

Drug name (brand)	Formulations	Usual dosage	Comments
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” 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/day 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, 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 1.6 First-line abortives for migraine: nontriptans

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 per day 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 is common Rebound headache may occur with overuse; 4 tablets per day (but not on a daily basis) should be maximum. Patients need to be educated about not exceeding acetaminophen’s upper daily limits

Table 1.6 (continued)

Drug name (brand)	FDA-approved for migraines	Formulations	Dosage	Comments
Prodrin	Yes	Oral tablet	Usual dose: 1 tablet every 2–3 h; limit to 2–3 doses per day 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 p.m. 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
<i>NSAIDs</i>				
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/day	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 2400 mg/day	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 3–4 h; maximum dose 1000 mg/day	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 1.7 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 per day Oral: 2 tablets per day, 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 per week due to possible nephrotoxicity. IV ketorolac is very effective There is a new 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 and an inhaled version will be available	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. Less likely to cause MOH than many other abortives
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 per day. Limit to 30 or 40 pills per month	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. MOH is always a concern with butalbital and opioids

Table 1.7 (continued)

Drug name (brand)	Formulations	Usual dosage	Comments
<i>Opioids</i>			
Hydrocodone and acetaminophen (Vicodin, Norco, generic) Hydrocodone and ibuprofen (Vicoprofen) Oxycodone (generic) Meprobendine (generic) Tramadol (Ultram)	Oral, IM	See individual PIs. These must be limited per day, and per month	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. Hydrocodone is now Schedule II, limiting access. Vicoprofen is more effective than the other hydrocodone preparations because of the addition of ibuprofen and, generally, is well tolerated.
<i>Corticosteroids</i>			
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/day. Limit to 12–16 mg/month, at most Prednisone: 20 mg (½ to 1 tablet) every 8–12 h as need. Maximum dose, 40 mg/day. Limit to 80 mg/month, 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.
<i>Ergot</i>			
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 1.8 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 3–4 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 gastrointestinal (GI) symptoms

amine occasionally is useful when administered intramuscularly. At times, patients may have injections for home use (ketorolac, orphenadrine, sumatriptan, diphenhydramine, promethazine, etc.). Transcranial magnetic stimulation (TMS) will soon be available. Patients will have a hand-held device, placed over the occiput, for only a minute. Several quick magnetic pulses are delivered, which are generally very safe. This may be effective for many people. TMS has been around for some time (for depression), in much higher doses, and has been fairly safe and well tolerated.

Medication Overuse Headache

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

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

Preventive Medications

There are no treatment algorithms to determine which migraine patient should be prescribed preventive headache medication. The choice of who qualifies for medication depends on the patient’s age, medical and psychiatric comorbidities, and frequency and severity of the patient’s migraine, as well as the patient’s preference. Patients have to be willing to take daily medication (many are not). 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.

Comorbidities often determine which preventive medications are used. If a patient has hypertension, a medication for blood pressure will be used. When patients concurrently suffer with anxiety or depression, various antidepressants are utilized to manage the headache and mood disorder. We want to minimize medications and treating two conditions with one medication is ideal.

In using medication, a realistic goal is to decrease the severity of headaches by 40–70%, not to completely eliminate the headaches. “Clinical meaningful pain relief” usually is around a 30% improvement. 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 3–6 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 remaining patients try various abortives.

As noted, patients should play an active role in medication choice. Preventive medications should be selected based on the patient’s comorbidities, GI system, medication sensitivities, and the like. Fatigue and/or weight gain are major reasons why patients abandon a preventive medication. Headache patients commonly complain of fatigue, and they 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 to achieve results. Table 1.9 provides a summary of first-line preventive medications.

First-Line Preventive Medications for Migraine

Onobotulinum toxin A has been studied extensively in patients with migraines. Nearly 4 million people have had onobotulinum toxin A injections for headache. Onobotulinum toxin A has been found to significantly improve quality of life and reduce headache impact [7].

Botox is the only onobotulinum toxin A that is FDA-approved for the treatment of chronic migraine. It is relatively safe and only takes a few minutes to inject. One set of injections can decrease headaches for 1–3 months. There also is a cumulative benefit, in which 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.

The anticonvulsant agents topiramate (Topamax) and valproate acid (Depakote) 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. This acidosis may lead to “tingling,” which sometimes may be counteracted by potassium (in foods or supplements).

Table 1.9 First-line preventive medications for migraine

Drug name (brand)	FDA-approved	Formulation	Usual dosage	Comments
Onabotulinum toxin A (Botox)	Yes	Injection	Dose: Varies (FDA official dose is 155 units, via 31 injections, every 3 months)	One set of injections can decrease headaches for 1–3 months. 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 year of Botox therapy
<i>Anticonvulsants</i>				
Topiramate (Topamax) Topiramate ER (Trokendi)	Yes	Oral	Total dose varies from 25 or 50 mg/day up to 400 mg/day	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: 500–1000 mg/day, in divided doses	Liver function levels need to be monitored in the beginning of treatment. Depakote needs 4–6 weeks 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
<i>β-blockers</i>				
Propranolol (Inderal, others)	Yes	Oral	60–120 mg/day	Side effects include dizziness, insomnia, fatigue, GI upset, respiratory distress, weight gain
Metoprolol (Toprol XL)	No	Oral	25–100 mg/day	Fewer respiratory effects than propranolol
Atenolol (Tenormin)	No	Oral	25–50 mg/day	Fewer respiratory effects than propranolol
Nebivolol (Bystolic)	No	Oral	2.5–10 mg/day	Better tolerated than the other β-blockers with the fewest respiratory effects

Table 1.9 (continued)

Drug name (brand)	FDA-approved	Formulation	Usual dosage	Comments
<i>Tricyclic antidepressants</i>				
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/day	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/day. Maximum dose: 150 mg/day	Similar to amitriptyline, with fewer side effects
Protriptyline	No	Oral	5–20 mg/day	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
<i>NSAIDs^a</i>				
Naproxen (Aleve, Anaprox, Naprelan, Naprosyn, others)	No	Oral	500–550 mg/day; maximum dose 1000–1100 mg/day	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
<i>Calcium channel blocker</i>				
Verapamil	No	Oral	120 mg/day slow-release tablet, titrate to 240 mg/day	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/day, 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

Natural Supplements and Herbs

Feverfew, Petadolex (butterbur), and magnesium oxide have all proven effective as migraine preventives in double-blind studies. Of these, Petadolex has been the most effective. Petadolex, a purified form of the herb butterbur, is made of extracted plant certified by the German Health Authority. This herb preparation is used commonly in Europe, and has been found to be successful in preventing migraines in several well-designed blind studies. The usual dose is 100 mg/day; many patients require an increase to 150 mg/day (all at once, or in two divided doses). 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 3 months or so. Petadolex is available by calling 1-888-301-1084 or through www.petadolex.com or Amazon.com.

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 is used as a supplement to maintain adequate magnesium in the body. A dose of 400 or 500 mg/day can be used as a preventive; tablets and powder versions are found in most pharmacies. However, mild GI side effects may limit use. There also are drug interactions that may occur; as always, advise your patients to consult with a physician before taking any supplements.

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 2 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 herbs than others. It is available in both capsule and liquid forms. The usual dose is two capsules each morning. 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 they are less effective than Petadolex (Table 1.10).

Medications: First Line

As noted, topiramate is an effective migraine preventive. While usually fairly well tolerated, topiramate commonly causes side effects including memory difficulties (“spaciness”) and tingling. Topiramate does decrease appetite, leading to weight loss for some patients. This anorexic effect tends to disappear after several months. The usual dose is 50–100 mg daily, but some patients do well on as little as 25 mg/day. The dose may be increased to 300 or 400 mg/day in the absence of significant side effects.

Table 1.10 Supplements, medicinal herbs, and teas for chronic migraine

Supplement	Dosage	Uses	Comment
Riboflavin (vitamin B2)	50–400 mg/day	Prevention	Occasionally helpful, but very mild effect. Higher dose found more effective in reducing number of headaches
Magnesium	200–700 mg/day	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/day	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)	6000 mg/day	Adjunctive therapy	May represent beneficial adjunctive therapy, but its efficacy as a preventive agent for chronic migraine has not been proven
<i>Medicinal herbs and teas</i>			
Botanical name (common name)	Dosage	Uses	Comment
Tanacetum parthenium (Feverfew)	50–143 mg/day	Treatment/prevention	Feverfew is well tolerated, but efficacy is very limited
Petasites Petadolex (Butterbur)	100–150 mg/day	Treatment	Petadolex is the branded, better form of butterbur (Petadolex limits the molecule that is worrisome in butterbur); of the natural supplements, this has the most solid evidence for efficacy Petadolex (Butterbur) is available online at: Petadolex.com or Amazon.com
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
Salix alba (white willow bark)	600 mg	Adjunctive therapy	Used for decades, but no true evidence of efficacy

Valproate, or divalproex sodium (Depakote), 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 4–6 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/day, and usually is kept between 60 and 120 mg/day. Lower doses, such as 20 mg twice per day of propranolol, sometimes are effective. Other β -blockers, such as metoprolol (Toprol XL) and atenolol, also are effective. 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 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, with the least amount of side effects.

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 anti-depressants, 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 it 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 NSAIDs similarly can be used for migraine prevention. As with all anti-inflammatories, GI side effects increase as people age, and, therefore, NSAIDs are used much more frequently in the younger population. Blood tests are needed to monitor liver and kidney function.

Second-Line Migraine: Preventive Therapy

There are a number of second-line migraine treatments (Table 1.11). 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

Table 1.11 Second-line migraine preventive therapy^a

Drug name (brand)	FDA approved	Formulation	Dosage	Comments
Antiepileptic medications				
Gabapentin (Neurotin, Gralise, others)	No	Oral	Usual dose: 600–2400 mg/day Some patients do well on low doses (100–300 mg/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. 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				
Cyclobenzaprime	No	Oral	5–10 mg/day	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/day	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 tablets
Antidepressants				
Desvenlafaxine (Pristiq)	No	Oral	50–100 mg/day	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/day	
Venlafaxine (Effexor XR)	No	Oral	75–225 mg/day	
Natural agent				
Petadolex (purified butterbur)	No	Oral	100–150 mg/day	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 (i.e., amitriptyline with propranolol, or amitriptyline with valproic acid)

2400 mg/day, but lower doses are usually prescribed [8]. Some patients do well with very low doses (200 or 300 mg/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. Pregabalin is fairly safe, but sedation and weight gain often occur.

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 it helps some patients with migraine and chronic daily headache. There have been a number of studies on using angiotensin receptor blockers (ARB) and 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.

Venlafaxine (Effexor XR) is an excellent antidepressant that is occasionally helpful for the prevention of migraine. At lower doses, venlafaxine functions primarily as an SSRI, but at higher doses (100–150 mg), it also increases norepinephrine. In fact, antidepressants with such dual mechanisms (serotonin and norepinephrine) are more effective for pain and headache. Another similar medication is duloxetine (Cymbalta, others), with typical doses being 30–60 mg daily. Duloxetine has several pain indications, but it is probably more effective for moods than for headache. For frontal, severe chronic migraine, sphenopalatine ganglion (SPG) blocks (Marcaine or Lidocaine sprayed up the nose, via a special device) have shown some efficacy, at least in the short term.

Polypharmacy

Polypharmacy is common in migraine prevention. Polypharmacy commonly is employed when significant comorbidities (anxiety, depression, hypertension, etc.) are present. Two first-line medications often are used together and the combination of two preventives can be more effective than a single drug alone [12]. For example, valproic acid (Depakote, or sodium 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” 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. Unfortunately, polypharmacy brings the risk of increased side effects.

Conclusion

Migraine is a very common and disabling illness. Outside of medications, 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 one algorithm for determining which medication is best for which patient. Each patient is unique, and comorbidities drive where we go with treatment. The goal is to decrease head pain while minimizing medications.

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Chronic Headache Management: Outpatient Strategies

A Guide to Treating Chronic Headache Patients

When we assess patients who seek medical treatment for headache pain, they usually suffer from migraine, tension, or chronic migraine (CM). Only about 5% of patients fall outside of that realm. Cluster headache is another type of primary headache, but cluster headache is relatively uncommon; it is only found in about one out of 250 men and one in 700 women [13]. In contrast, migraine is common; it occurs in 18% of women and 7% of men in the USA. Chronic daily headache (CDH), which is usually CM, often results in a markedly decreased quality of life. We have numerous medications for episodic migraine, but we have less that is effective for CM. The following discussion reviews what we currently know about the various types of headaches, comorbidities, triggers, and treatments.

Migraine

There are 25–28 million people in the USA with migraine, making it one of the most common of illnesses. Many migraine patients successfully alleviate their headaches with over-the-counter medicines, but most are disabled to one degree or another during the migraine. I look at migraine as an inherited, chronic illness. It is characterized by moderate to severe pain, often unilateral, although it certainly may be bilateral. Migraine is usually accompanied by associated features such as nausea, dizziness, photophobia, sonophobia, or osmophobia. Exacerbation of the headache from bending or other movement is common, as is neck pain. Aura is fairly common; up to 25% of migraineurs experience an aura, but not with every headache. It is common to have prodromal and/or postdromal fatigue and mood changes. Migraine may begin at any age and is surprisingly common in children and adolescents. At least 1% of 6-year-olds and 4% of 10-year-olds suffer from episodic migraine. Until age 12, boys and girls suffer from migraine in equal numbers.

During puberty, the familiar women to men ratio of 3:1 is reached, and that ratio is maintained throughout the rest of life [20].

In diagnosing migraine, it helps to look at consistent triggers—such as menses, weather, and under-sleeping. If weather changes bring on migraine, it is always confusing, since the migraineur is often told (and feels) that they have a sinus headache. To confuse the picture, the OTC sinus meds often help all types of headache. Most sinus headaches turn out to be migraines. There have been several large studies indicating that 95% of people presenting with chronic sinus headaches actually have migraines, not sinus headaches. So one must think “migraine first” regarding pain in the sinus area [2].

Workup

With a new onset headache—especially in a patient in middle or later life—more extensive workup is needed. This is also true for new neurological symptoms such as numbness, a change in mental status, or visual problems. The patient with CDHs warrants a magnetic resonance imaging (MRI) more often than the patient with sporadic migraines. Children with migraine may not need an MRI. If a 12-year-old presents with two migraines per month since age 6, an MRI is not absolutely necessary. However, when the kids are followed as far as college age, often there will be an incident where they will call and complain of a severe, prolonged headache and usually end up having a scan at some point. Most headache patients should undergo routine hematologic exams, primarily to assess liver and kidney function. Patients are often taking OTC medicines that they do not tell us about. They either do not remember or do not have a sense of how many OTCs they take for pain relief. It is not unusual for headache sufferers to consume eight to ten ibuprofen or Excedrin on a daily basis; the liver and kidneys may be affected.

Triggers

One of the primary things we can do is educate patients about triggers. Unfortunately, we cannot do very much about certain triggers, but when a patient has a headache every time the weather changes, or the first day of every menstrual period, we might be able to use medicine the day or night before as a preventative. The top triggers tend to be stress (daily hassles), menses, and weather. When they occur simultaneously is when patients get the worst, most prolonged migraines. Of course, missing meals, under- or oversleeping, bright lights, and certain foods also contribute, but the role of foods tends to be overemphasized. People are given a forbidden-food list and told, “Avoid these foods and you won’t have headaches,” and then they are disappointed. Many books concentrate on diet and foods, but these are low on the list of important triggers. Caffeine, however, is a major trigger. We need to limit the patient’s intake, although the limit varies. Some people can consume 800 mg a day of caffeine and not incur rebound headaches or withdrawal. Other people

get headaches from a small amount of caffeine in their diet. Caffeine is an adjunct for pain relief as it does help enhance analgesics. Small amounts often help people with their headaches. We have to watch out for the specialty coffeehouse effect. Starbucks coffee has approximately 23 mg of caffeine per ounce. In that oversized cup of Starbucks, you will ingest about 400 mg of caffeine, which is twice the daily maximum recommended. But most home-brewed coffees have manageable doses. Coffees such as Folgers or Hills Brothers have about 150 mg/cup, while instant coffee has half that amount. Tea, if it has caffeine, will generally have 30–60 mg/cup. Cola drinks have 40–60 mg and Mountain Dew has a little more. The new energy drinks may have 200 mg in 12 oz. Watch for accumulated caffeine from these and from OTC medication; each tablet of Excedrin has 65 mg of caffeine, while Anacin has only 33 mg. I attempt to limit a patient's daily caffeine intake to 150 mg—with 200 mg as the maximum [15].

Psychological Comorbidities

Comorbidities guide what we suggest for headache patients. Psychiatric comorbidities are relatively common in headache patients, primarily due to shared genetic susceptibilities. I tell patients that migraine is an inherited medical problem just like having asthma or diabetes. Similarly, in those with patients suffering anxiety and depression, a genetic tendency can make them susceptible—the same as with diabetes. So, refrain from telling patients that it is all in their heads since they have been told that their entire lives. If we “medicalize” these ailments and remove some of the stigma, patients will allow us to explore more of their psychological conditions. The psychological conditions often drive where we go with treatment.

Attention-Deficit Disorder

Attention-deficit disorder (ADD) is another important comorbidity. The ADD (in adults) often goes unrecognized and untreated. ADD is common and studies have shown that about 4.7% of adults have ADD. When someone comes into the office, we are not looking at a just a headache, we are assessing the whole person. If we are able to concurrently manage the comorbidities, the patient will have a better quality of life. The stakes increase with age for untreated ADD. At age 6, kids may not be doing well in school, but by age 26 they are losing their families and their jobs, with a much higher risk for addiction. The risk of addiction for older adolescent boys (8–20-year-olds) having untreated ADD is almost 75%, usually manifesting as an alcohol problem. If the ADD is treated, the addiction risk decreases to 20–25% [21]. The stimulants prescribed for ADD often help the headaches as well. Addictions are a comorbidity that complicate the treatment of a refractory patient. Treating pain patients in the face of addiction is complex and often requires a combined psychiatric and medical approach.

Anxiety

When the comorbidity is anxiety, it is usually generalized anxiety disorder (GAD). OCD is also common, and panic attacks are actually ten times more common in migraine patients than in the general population. Separation anxiety tends to begin early in childhood. We often see social anxiety in high school kids who miss days and even months of school, or are homebound. With these kids, simply prescribing meds is inadequate; we need to recruit psychotherapists in order to address the comorbid anxiety, depression, etc. Whether any adolescent should be homebound because of headaches is controversial. We usually take a nuanced approach to adolescents with severe headaches who miss school. Some do better with online schooling, homebound, or a combination. Certain adolescents require more of a “tough love” approach. If an adolescent has been homebound, it helps to ease them back into school, possibly with a lighter schedule for some period of time.

Depression

When the comorbidity is depression, it is usually major depression or dysthymia. Of course, many adults with depression are actually bipolar, or fit into the mild bipolar spectrum. Depression is often comorbid in headache patients, most likely due to shared inherited and environmental factors. Unipolar depression, whether it is major depression or dysthymia, is better recognized than bipolar depression. Up to 60% of adults with chronic depression fit into the bipolar spectrum. It is vital to treat both pain and depression, as they fuel one another. Patients do say, “Of course I am depressed. Wouldn’t anyone be with severe headaches?” My answer is, “Headaches do make the depression worse, but many people (60%) with chronic pain are not depressed. Depression is a separate, biological problem.”

Headache and the Bipolar Spectrum

The relationship between bipolar illness and migraine has not been as well studied as depression and migraine. However, in several studies, the bipolar spectrum has been found at an increased rate in migraineurs. Recent studies confirm that at least 8% of headache patients also are in the bipolar spectrum. Approximately 4.5% of the general population fits into the bipolar spectrum [16]. Studies of people with bipolar found that approximately 40% of bipolar patients also have migraines.

The clinical spectrum of bipolar disorders is an evolving concept. Historically, the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) has inherent biases against independently diagnosing bipolarity, and bipolar II is defined very conservatively in DSM-V. For example, in DSM-V, the important hypomanic reaction to an antidepressant is not included in helping determine bipolarity. The label “bipolar” is unfair and misleading and the associated stigma inhibits diagnosis. We need educational materials aimed at the milder end of the bipolar spectrum.

It is the milder end of the bipolar spectrum that tends to be missed. Look for patients with persistently agitated, angry personalities, with frequent depressions and/or, “too much energy,” and having a strong bipolar or depressive family history. Family history also may include substance abuse. Patients may not necessarily have had a clear hypomanic or manic episode. Soft bipolar signs include: early depression (beginning as teens), severe depression, quick onset depression, bipolar reaction to certain meds (up all night, thoughts racing, etc.), agitated and angry depression, very high anxiety and mood swings, poor response to medication, and moody personality. Sleep disorders are commonly seen. Cyclical depression, “for no reason,” along with high anxiety is common for bipolar depression. The therapeutic implications for recognizing bipolarity are enormous. These patients tend to bounce from antidepressant to antidepressant with predictably poor results. Mood stabilizers—lithium, lamotrigine, and atypicals such as quetiapine and aripiprazole—are much more effective.

Personality Disorders

It is crucial to recognize personality disorders (PDs) within your practice. Approximately 10% of people have strong features of a PD. Approximately 5% of migraineurs have one of the more severe PDs: borderline, narcissistic, antisocial, and paranoid. There are a number of PDs, some of which are more dangerous and difficult to deal with than others. In general, characteristics of PDs include: lack of insight; poor response to psychotherapy or other therapeutic interventions; difficulty with attachments and trust; a sense of entitlement; the creation of a great deal of chaos and distress in family, friends, and coworkers; etc.

PDs have a wide range of severity, from mild to very severe. These individuals often flip between victim, rescuer, and persecutor. When they turn persecutor, they can be dangerous to the person they have their sights set on. PD patients often create chaos and drama, and comorbid substance abuse is common. They also bring chaos and drama to the medical clinic. The more difficult PDs include paranoid, antisocial, borderline, and narcissistic behaviors. In general, therapy helps people with PDs only over long periods of time. Dialectical therapy is usually preferred for those with a PD. Seeing a therapist for 5–7 years may help to some degree. However, our goals and expectations are limited. The concept of plasticity of the brain is very important, as some people do improve naturally over time. One study of borderline PD in adolescents indicated that, by age 30, one third of the subjects no longer had borderline PD. Many people do not fit neatly into any of these categories, but have features of two or three PD types. Failure to identify those with PDs leads to increased risk for the provider and the patient. The small percentage of patients with moderate-to-severe PDs in a typical practice are the ones who create the majority of the drama, as well as legal and regulatory problems for the treating physicians [18].

Medical Comorbidities

As far as medical comorbidities in headache patients, the GI system is a common site—particularly irritable bowel syndrome (IBS). Most of one's serotonin is in the gut, and certain medicines that help IBS increase or decrease serotonin. IBS is frequently encountered in migraine patients, and very often we are trying to use medicines that help the GI symptoms as well as the headache. It is much easier to help patients who primarily have diarrhea since some of our medicines, such as the older tricyclics, slow the gut transit time. Constipation, on the other hand, is tougher to ameliorate. Some other comorbidities include hypertension, insomnia, fibromyalgia (or chronic pain syndrome), and fatigue.

Central sensitization syndromes include, among others: CM, IBS, fibromyalgia, and chronic pelvic pain. Many people suffer from more than one of these illnesses, which complicates the treatment. Comorbidities drive where we go with chronic pain patients.

Hypertension

A number of the antihypertensives do diminish migraine. Most β -blockers will help, as will the calcium channel blockers. More recently, the ARBs have been utilized.

Insomnia

Sleep disorders are frequently encountered with headache patients. Insomnia is common, but the available treatments are not ideal. Of course, we should institute sleep rules and behavioral treatments. For patients with comorbid insomnia and headache, sedating tricyclic antidepressants may be of benefit. Also, certain muscle relaxants, such as tizanidine or cyclobenzaprine, may help both conditions. Of course, we need more effective insomnia meds.

Fibromyalgia (or Chronic Pain Syndrome)

We do have a few drugs that are indicated for fibromyalgia. Many people with fibromyalgia also have CDHs and insomnia. These groups overlap, not only with the pain but the psychological comorbidities as well. Fibromyalgia patients share the allodynia commonly felt by headache patients. A number of medicines are used for both headache and fibromyalgia, such as tricyclics and muscle relaxants.

Fatigue

If you ask large groups of headache or migraine patients what their biggest problem is other than headache pain, it tends to be excessive daytime sleepiness. Fatigue is such a prevalent problem that we do not want to add medicines that fatigue people even more. There are no algorithms for headache patients since everyone is different. For example, suppose a woman comes in who is 45 years old and 25 lb overweight and is always tired. We do not want to prescribe amitriptyline or valproate, medicines that are going to make her more tired and gain more weight. Some medicines do not exacerbate fatigue, such as protriptyline (Vivactil) or ARBs, and, occasionally, we will use small doses of stimulants. Modafinil (Provigil) or Nuvigil may offset the fatigue, but do not help headaches. These are expensive medications. However, modafinil or Nuvigil do improve quality of life for many headache patients.

Outside of Medicine

It does take a village to treat a severe pain patient. We want to seek treatments outside of the pharmacy. We need to promote active coping. We must have other modalities involved. Pharmacotherapy may be important, but certainly we want to try everything else, whether it is physical therapy, yoga, biofeedback, etc. Psychotherapy is often important and I strongly recommend it as part of treatment. However, whether it is because of money or time, most people will not see a therapist. Cognitive-behavioral therapy is the usual approach, but with PDs one must take more of a dialectical tack. It is important to identify the best therapists in your area, as the skill levels of psychotherapists vary widely.

Acceptance

Acceptance of the pain as an illness is a very important concept. There are actually scales that measure acceptance. The road to acceptance of a chronic illness is often littered with many wrong turns along the way, looking for miracle cures. When people accept that they have a chronic illness, which may be managed but not cured, the inner angst decreases remarkably. Acceptance does not mean that patients are resigned to a lifetime of severe pain, it simply leads to management, not false hope.

Biofeedback

Biofeedback is a very useful tool. I think that the providers who have been trained in the past 5 or 10 years often do a better job with biofeedback. The home-based therapies involving relaxation techniques—where patients are taught by just giving them a booklet and tapes—can help but a good biofeedback therapist is much more

effective. When it is done well, biofeedback promotes an internal locus of control and helps promote self-efficacy. Exercise and yoga can have similar effects. We want people to feel that they can engender a positive outcome in their illness by doing something other than taking a pill. Meditation may also help.

Resilience

Resilience is an interesting concept. Resilience involves the early life experiences as well as genetics. In looking at resilience in individuals, the serotonin transporter gene is crucial. There are two arms on the gene, which can be either short or long. If a person has two long arms on the serotonin transporter gene, it turns out that he is going to be a lot more resilient. His childhood may be unhappy, but when the person has two long arms on the gene, he usually turns out very well. If the patient has an abusive childhood, and he has two short arms on the serotonin transporter gene, it is almost a certainty that he is going to have major problems in life, possibly borderline PD, or some other major psychiatric problem. So resilience is very important in terms of who can cope despite severe headaches, and who ends up disabled.

Exercise

We try to have patients average 15 or 20 min of any exercise. This includes light walking, treadmill, bike, elliptical, yoga, Pilates, etc. Even 5 or 10 min twice a day is sufficient. The idea with many chronic pain sufferers is to encourage any exercise. The old mantra of “you have to go to the gym, work out for an hour, get your heart rate up yada yada” actually has inhibited people from doing at least some exercise. Many headache patients suffer from “exercise-induced headaches.” The smoother, slower types of exercise minimize the headaches.

Disability and Catastrophizing

One might think that the pain level is the major predictor of disability. It has been shown, in well-done studies, that other factors are probably more important. Catastrophizing is one of these factors. For example, a patient who seems to think his headache is always a 14 on a scale of 1–10. Part of my job is to turn down the volume and limit the drama. We can talk to people about catastrophizing and work on the fear that underlies it. Catastrophizing by proxy also happens, where a parent thinks his child has the worst headaches on the planet and even says, “Have you ever seen such bad headaches in a kid before?” Fear of pain also plays a role in disability. Some people have more fear and anticipation of pain than others and, as with catastrophizing, fear of pain may be lessened through psychotherapy.

Neck and Occipital Pain

Physical therapy can be very helpful when there is associated pain in the neck and shoulders. At least half of headache patients have neck pain, particularly with their migraines. I often advocate physical therapy for the neck pain, posterior headaches, and jaw pain (many headache patients clench and brux). There are better medical doctors than others and there are better physical therapists than others. It is worthwhile to establish a relationship with the best “headache/neck pain” physical therapists in your area. Occipital pain may be originating in the cervical region; blocks or injections may help.

Dental, Massage, Acupuncture

Dental consultations may be beneficial for those who clench their jaw, and certainly if they are bruxing. For the associated clenching, bite splints may help, along with physical therapy. Massage can benefit a wide range of patients, but the benefits often are short-lasting. It has been difficult to prove in studies that acupuncture is more effective than sham treatment. After examining more than 500 randomized controlled trials of acupuncture for various conditions, nothing definite can be concluded as far as efficacy [5]. I think, with many pain studies, the outcome of the study can be predicted from how robust the placebo response is. Unfortunately, with acupuncture studies, when the sham acupuncture is performed along with the real acupuncture, there is going to be a robust placebo response. It has been difficult to prove efficacy over placebo. But, there are patients who do very well with acupuncture. Acupuncturists are another one of the “villagers” whom we recruit to help take care of pain patients.

Medications: Abortives

Most people with migraines do not need preventive medicines, particularly when they do not have comorbidities or not enough headaches. There is no good algorithm that applies to headache treatment. How many headaches a month are too many? With two headaches a month that are severe and prolonged and are not relieved by drugs, we might use preventive medicine. For another person with five headaches a month, who can take an Excedrin or a triptan and obtain relief, we may choose not to use preventive medicine, because all meds have their possible side effects.

For abortives, there are many choices among the triptans. Injections of sumatriptan are probably the most effective. The generic sumatriptan injections are available in several forms: an EpiPen, prefilled syringes, and the generic for the Stat Dose system. All of the triptans are effective, but they each have different clinical characteristics. The generic tablets include: sumatriptan, rizatriptan, naratriptan, and zolmitriptan. Sumatriptan, rizatriptan, zolmitriptan, and Relpax have slightly better efficacy than naratriptan and Frova. Naratriptan and Frova are slow-onset, longer-

acting meds. The triptan nasal sprays, particularly Zomig, are fast acting. Side effects of tingling and pressure may initially occur with the triptans. Since 1992, we have had more than 200 million people treated with the triptans. Safety has been well established. We have become more comfortable using triptans in higher-risk populations. If one triptan is ineffective, I usually will try one or two other triptans before giving up on the class. During pregnancy, particularly after the first trimester, triptans may be safer than many of the other migraine medications. The 16-year sumatriptan/naratriptan pregnancy registry demonstrated the relative safety during pregnancy. We use triptans cautiously, with informed consent.

Other than the triptans, most patients have tried over-the-counter products (ibuprofen, naproxen, aspirin, and caffeine combinations). Aspirin and metoclopramide combined may help. Prodrin is an interesting product, with a combination of a small amount (20 mg) of caffeine, acetaminophen, and a mild vasoconstrictor. For those intermediate headaches a reasonable choice, and is not addicting. Prodrin is similar to Midrin (generic Midrin is available), without the sedative in Midrin.

Transcranial magnetic stimulation (TMS) is a safe, noninvasive abortive treatment. Patients may use the stimulator at home; it only takes a few minutes. Over the coming few years, TMS will achieve a larger role as an abortive. There is a solid track record of TMS for depression, and it appears to be safe; for depression, thousands of pulses are given; for headache, only two pulses or so.

DHE is probably underutilized. DHE nasal spray (Migranal: generic available) is safe, but is not always effective. Migranal often leads to severe nasal congestion. DHE injections are much more effective, but are expensive, and often are not available. There is an inhaled version of DHE in the works, and should be available soon. It appears as if the inhaled DHE works better than the nasal spray, but not quite as effective as the injections. Since 1945, when DHE was introduced, there have been relatively few severe side effects reported. An inhaled version of DHE should be available soon. DHE is primarily a vasoconstrictor, so it actually safer than other ergotamines, which are arterial constrictors [11].

Antiemetics are important adjuncts for those with nausea. Ondansetron lets people get on with their day without sedation. We also use the other antiemetics, such as metoclopramide or prochlorperazine, which are somewhat sedating. The goal is to keep people out of the emergency room (ER), and the antiemetics help in this regard. I do use opioids and butalbital in selected patients. We limit their use, but nine out of ten patients do not overuse them. It is the 10% who create problems. Butalbital compounds are controversial, and are not used in Europe. Butalbital does result in rebound headaches more than with simple analgesics. Opioid and butalbital use in the headache patient has been found to be one source of transformation from episodic headache into daily pain.

Occasionally, we will use injectable opioids. Alternatively, as a last resort, other parenteral opioids may be of use. These include butorphanol nasal spray, or various forms of fentanyl oral preparations. Butorphanol and fentanyl are highly addicting, and frequently cause side effects. The quicker-onset medicines do tend to be over-used, and there are more withdrawal symptoms. These parenteral opioids should be used very sparingly in carefully selected patients. As a last resort, when sedation

is needed, we will occasionally use meds off-label, such as quetiapine (Seroquel), or benzodiazepines. When nothing works for refractory headaches, particularly for prolonged menstrual migraines, we do use corticosteroids, but in limited amounts. It is important to minimize the cortisone dose. We use dexamethasone, 4 mg, ½ or 1 every 12 h “as needed”; or prednisone, 20 mg, ½ or 1 every 12 h “as needed.” The cortisone “dose packs” deliver a higher dose than is usually necessary. I would usually limit these to three or four tablets a month, at most.

CM Meds

When it comes to preventives, each person is unique. While comorbidities guide how we proceed, patient preferences are also important. Patients have to be willing to put up with possible side effects. We tend to use more preventives in people with CDH (which is usually CM) than in semimonthly migraines. CM is basically defined as headaches occurring at least 15 days per month, of which at least eight fulfill probable migraine. About 3% of people, in almost every country that has been assessed, have CDH, or frequent headaches. CM greatly decreases one’s quality of life. It is a major problem, it is difficult to treat, and most analgesic overuse stems from CM. The severity of the daily headache is important. Some people will say, “My daily headaches don’t bother me, they’re mild; it’s the severe migraines that are important.” Other people say, “It’s these daily headaches that are the problem, the moderate or severe migraines are easily taken care of.” We aim our preventive meds at the predominant, more severe type of headache. With chronic headache, we need to limit the drugs prescribed as abortives. If patients are taking OTC medications and need to take more than two a day, we must consider daily preventive medicine. We might consider NSAIDs or Prodrin, neither of which are addicting. Triptans may be utilized, but overuse may lead to rebound. Tramadol is a mild opioid. Tramadol ER may be useful if patients can limit use to 200 mg/day, or less. Any medication used abortively for CDH should be strictly limited to two per day.

Abortives and Rebound Headache (Medication Overuse Headache)

The abortives for CM are basically the same as for episodic migraine. We do not want to use triptans on a daily basis, except in unusual circumstances. Rebound headache is always a consideration and is a remarkably complex subject. The term medication overuse headache has been overused. Many patients are labeled as having medication overuse headache, when in fact they simply have frequent migraines. The major question with rebound headache is which drugs, and how much of the drug, will trigger rebound. It appears that the butalbital and opioid meds, and the high caffeine drugs—such as Excedrin—may be more likely to cause rebound. It appears that in selected patients, NSAIDs may contribute to rebound, but in general they do not.

Preventives: Long-Term Results

The goal with preventives is to help reduce the headache by 25–75%. If patients believe that their headaches are going to be completely cured, they may return and state, “The medicines are not working because I still have some migraines.” They may be 50% improved, which is often the best that can be achieved. Headache diaries (or apps, such as ChronicPainTracker) may help, but we also need to convey realistic goals to the patient. In my experience, only 50% of people do well for the long-term on preventives. I have done two studies looking at usage over a year’s time, with a total of nearly 800 patients on preventives. Only 46% found any preventive that they could tolerate, and that remained effective for at least 9 months [19]. The remainder discontinued preventives for various reasons. We desperately need more effective preventives, with less side effects.

Natural Remedies

Natural remedies may help, without the common side effects seen with our usual preventives. Petadolex is an improved form of the herb butterbur, where the molecule that we worry about in butterbur is limited. Petadolex is effective, and held up well in randomized controlled trials. It was popular in a number of countries—for instance, in Germany where Petadolex was the number one preventive. I find it is more effective than feverfew, etc. In my years of experience with Petadolex, very few side effects have been reported. Occasionally, there is an upset stomach or a bad taste in the mouth. There is still a concern with carcinogenic properties, particularly with the parent compound of butterbur. We stop the Petadolex periodically for 1–2 months. Most people in the USA order Petadolex directly from the company (1–888-301-1084, Petadolex.com), or from Amazon. We also use magnesium oxide or citrate, 400–600 mg daily. I believe that the Petadolex and magnesium are the most consistently helpful of the natural supplements. Feverfew lags behind as far as efficacy, but it is fairly safe. I have not found vitamin B-2 (200–400 mg daily) to be very helpful in the long term, but occasionally it has been effective.

Tricyclics

Tricyclics remain a mainstay of headache treatment. With amitriptyline and nortriptyline, we do encounter weight gain, dry mouth, and constipation, but we use small-to-medium doses for most patients. I will start a patient on 5 mg (half of a 10 mg tablet of amitriptyline). The cost of medicine has increased but the generic tricyclics are very inexpensive. Some people remain on 10 mg or 20 mg/day of amitriptyline for years, doing very well. Amitriptyline is metabolized into nortriptyline; nortriptyline has fewer side effects. Protriptyline is one of the only tricyclics that does not cause weight gain, but it may cause anticholinergic side effects. With

protriptyline, patients experience dry mouth and constipation, but there is minimal sedation, without the weight gain.

Anticonvulsants

The primary anticonvulsants have been topiramate and sodium valproate (Topamax®, topiramate ER, generic topiramate, and Depakote® (generic available)). These are indicated for migraine. With topiramate, memory difficulties and mental fog are common. Depression or anxiety may occur as well. As the dose is increased, tingling of the extremities may be present due to carbonic anhydrase effects. Headache patients often quit the preventives due to annoying side effects, and so it is crucial to keep the dosage to a minimum. We try to start low and build up the dose. With topiramate, I will slowly increase to 50 mg and then, if needed, up to 100 mg; many patients do well on 25 or 50 mg. The generic topiramate ER is longer acting. While, the average dose of 500–1000 mg of sodium valproate (Depakote®) may lead to weight gain, topiramate may enhance weight loss. Unfortunately, the anorexic effects of topiramate do wane over a number of months. However, with sodium valproate, we see the weight gain often leading to discontinuation. Of course, we do never want a patient to become pregnant while on sodium valproate. We will start with 250 mg of sodium valproate and move up very slowly. Many other anticonvulsants have been used for headache, without solid studies to back up use. Oxcarbazepine (Trileptal®) has failed in several headache studies, though it probably is an effective mood stabilizer for some patients. Zonisamide (Zonegran®) has been used; it is a once-a-day, longer-acting, relatively safe anticonvulsant. Fatigue is the primary side effect. Zonisamide is usually started at 25 mg at night, and slowly titrated up to 100 mg. Zonisamide does not cause weight gain. Gabapentin has been widely utilized, as has pregabalin (Lyrica), but evidence is lacking for positive efficacy.

Antihypertensives and Muscle Relaxants

The antihypertensive meds are useful as preventives: β -blockers and calcium channel blockers are the ones most commonly prescribed. There have been studies on the angiotensin renin blockers (ARBs). We encounter fewer side effects with ARBs. Tiredness and weight gain are major problems in migraineurs, and β -blockers exacerbate fatigue and weight gain. So I often use one of the ARBs: Candesartan (Atacand) is the primary ARB that's been studied, but others have been utilized. Muscle relaxants certainly may help the associated neck pain and may aid sleeping. Tizanidine is nonaddicting and is fairly safe, but we use it mostly at night due to the sedation. Cyclobenzaprine is inexpensive, and the tablets can be cut in half. Sedation is often a problem with these muscle relaxants.

Refractory Headache: Botulinum Toxin Type A

Onabotulinumtoxin A (Botox) is Food and Drug Administration (FDA) indicated for CM (the only FDA-indicated preventive for CM). It has been daunting to prove that it works better than placebo, as the placebo response has been high in several of the Botox studies. In one major study, the placebo response was only about 21%, but in others, it has been higher. Placebo response in migraine preventive studies, across all trials, averages about 20–23%. For unknown reasons, the placebo response is lower in North America, by about 5%, than in Europe [1]. The placebo response also differs among countries in Europe. In a number of Botox studies, the placebo response led to failure in achieving the primary endpoint, but the Preempt Botox study in North America was positive [10]. Many patients do find that it works well for 10–14 weeks. They use considerably less medicine in the two to three months post-Botox, and they can feel the effects wearing off at 2.5–3.5 months. We now have had many years (since 1996) of Botox use for migraine, and one could make a strong case that it is probably safer than most of the other drugs that we use, with fewer side effects. The mechanism for why it works could be due to calcitonin gene-related peptide (CGRP) antagonism, or a similar anti-inflammatory effect. The usual dose, the FDA-indicated dose, is 155 units, distributed about the head in 31 injections. Botox usually takes 5 days to 2 weeks to become effective. There is evidence that Botox becomes more effective over time. Money is the primary concern with the use of Botox, but many insurances, and Medicare, provide reasonable coverage.

Long-Acting Opioids for Refractory Headache

What to do when nothing works? For refractory patients, long-acting opioids are a possibility. I previously assessed, over a period of 6 years, patients who used long-acting opioids [17]. We looked at comorbidities and predictors of overuse. The people who tend to overuse long-acting opioids are those who previously overused short-acting opioids. If they abused hydrocodone, they tended to overuse the long-acting Morphine ER (Kadian®), Oxycontin®, or methadone. I have not encountered many cases of pseudoaddiction. As a result, I am reluctant to prescribe the long-acting opioids to those individuals who previously overused the short-acting opioids.

We also assessed bipolar, ADD, depression and anxiety, and PDs. The other predictor for overuse of opioids is the presence of a PD. If people have more than a mild PD, opioids are not a good choice. However, for the right person, these drugs can be lifesavers, improving quality of life and functioning. The ideal candidate for long-acting opioids is one who: did well on short-acting opioids (without overuse), has no PD, is greater than 30 years of age, and does not develop tolerance to the analgesic effects. When nothing else works, taking long-acting morphine, buprenorphine, oxycodone, methadone, or hydrocodone in low doses may be effective. Not every doctor should prescribe opioids; there needs to be careful patient selection

and good psychiatric screening, and solid documentation with each visit. For certain select patients, opioids will lead to improved functioning, and if lucky they will not develop tolerance to the analgesic effects. Older patients, whose brains cannot do the “neuronal gymnastics” needed to become tolerant, may do well on the same low dose for many years. For a small group of refractory patients, the long-acting opioids may be worthwhile.

Frequent Triptans: Sumatriptan, Rizatriptan, etc.

There are many patients taking daily, or near-daily, triptans. Some are experiencing rebound headaches from the triptans, but they say, “If I don’t take my triptan, I have a severe headache and need to take 6 to 10 Excedrin!” We need more studies of people who need frequent triptans. I published one study of 100 patients, where we did cardiac echocardiograms and electrocardiograms (ECGs). In this particular study, no long-term adverse effects were found. The patients averaged near-daily triptans for almost 4 years [14]. I do not encourage frequent use, but many people do lapse into it. The physician must attempt to withdraw the person from frequent triptans for a period of time, and assess for MOH. There are CM sufferers who do well only with the triptans.

Refractory Patients: Stimulants

A case can be made for utilizing stimulants in selected patients. They may help with fatigue, concentration, and moods. In the right person, low doses of stimulants are remarkably useful. For some people, stimulants not only improve the quality of life, they also help alleviate the headache pain. There have been several stimulant studies in daily headache patients; I believe that stimulants are underutilized.

Refractory Patients: Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) have fallen out of favor, but occasionally they provide excellent relief for selected patients. Phenelzine is the usual MAOI for headache patients. Low doses are utilized, 15–45 mg daily; if used all at night, food interactions are minimized. For those with refractory headache and comorbid unipolar depression, MAOIs should be considered. Of course, drug interactions and dietary restrictions limit use.

Refractory Patients: Occipital Stimulators, TMS, and SPG Blocks

In refractory patients, the use of an occipital stimulator is controversial. The stimulator help for a period of time, but it is difficult to anchor the leads, and migration

away from the occipital nerve often occurs. Many patients require another surgery for a variety of reasons. Long-term efficacy and safety is questionable. TMS is much easier and is noninvasive, patients may do this at home, and will have a larger role in the next several years. SPG blocks, given once or twice weekly for several weeks, are safe and sometimes effective for daily frontal CM. The three devices on the market are: SphenoCath, Tianx360, and the AllevioSPG. Each device has its pluses and minuses. The SPG block is done in the office, is fairly quick, but there are a limited number of physicians who do this block.

Patent Foramen Ovale and Migraines

The jury is still out on the issue of patent foramen ovale (PFO; the hole in the heart that may contribute to headache). One recent trial did not reach its primary endpoint but the endpoint chosen was a very difficult one [9]. Several trials are still in progress, seeking to assess whether closure of a PFO will decrease migraines. It is likely that, in a select group of migraineurs with a sizable PFO, closure will significantly decrease the headache frequency.

Conclusion

Comorbidities often drive where we go with headache patients. It “takes a village” to help a severe headache or pain patient. We consider involving psychotherapists and physical therapists, among others. We want to achieve a balance between headaches and medication, and try to minimize drug usage. Most patients do well with the usual ministrations, but for the refractory patient we need to consider other approaches. When used appropriately, some of these “out of the box” therapies are the key to restoring a patient’s quality of life. Note: This is an updated version of an article that originally appeared in *Practical Pain Management*, vol 8, Nov 2008.

Clinical Pearls for Treating Headache Patients

These clinical tips for headache treatment run the gamut from medication and patient perception to broader health issues and strategies/procedures.

This is the latest in our series of clinical pearls for practical headache treatment. Headache patients often have complex medical and psychological issues, and these pearls hope to offer concise tidbits and suggestions regarding medications, how patients may perceive their condition, broader health options available, and strategies and protocols that may be beneficial.

Medication

- Start with low doses of medication, particularly with antidepressants and other preventives. Headache patients tend to be fairly somatic, and there is no need to push medicine very quickly.
- Stick with preventive medications for at least 4 weeks (or longer). If we abandon them too soon, we may not see the beneficial effect. However, few patients are willing to wait months for positive benefits from a medication.
- Consider newer abortive medications, such as Cambia (powdered diclofenac potassium; not sodium: The sodium version, such as Voltaren, will not work as a powder). Cambia, used in water or apple juice, achieves detectable blood levels in as little as 10 min. Prodrin (isometheptene/acetaminophen/caffeine) is a newer version of Midrin (isometheptene/dichloralphenazone/acetaminophen) with no sedative (Prodrin eliminates the dichloralphenazone) or caffeine. An inhaled version of dihydroergotamine (DHE) is expected to be approved by the Food and Drug Administration (FDA) and will be a better product than Migranal nasal spray, but not quite as effective as injections of DHE. Sphenopalatine ganglion (SPG) blocks, done in office, are usually considered treatments to stop a cycle of frontal migraines (or clusters), but may work abortively for one severe headache.
- Consider natural alternatives that work, such as Petadolex, the butterbur derivative. Petadolex is a highly regulated “adulterated herb,” and it had been the No. 1 preventive in Germany. I feel Petadolex is relatively safe, has a long successful track record, and is almost as effective as our mainstream preventives. We do stop the Petadolex for a month every so often. Magnesium and vitamin B2 are also used, but are not as effective as Petadolex. Turmeric and ginger may be an alternative for some patients.
- OnabotulinumtoxinA (Botox) should be considered early in the course of treatment. Botox is now FDA approved for chronic migraine (15 or more days per month). Botox has proven to be safe and effective (almost 60% of patients experience meaningful relief for 3 months). The cost is a concern. Botox is twice as effective as our usual daily preventive drugs, without the side effects.
- Previous sensitivities and allergies to medications often determine where we go with medications. If the patient has had severe reactions to two SSRIs, a third is not a good choice. However, those reactions may not be readily apparent in the chart. If they are extremely fatigued on one β -blocker, a second will probably not work for the long term.
- Weight gain is a major issue. Even though a drug may be more effective, choosing one that avoids weight gain (in those prone to it) is more likely to lead to long-term success. Fatigue is another major reason for patients abandoning a preventive medication. Headache patients commonly complain of fatigue. Many of our preventives (amitriptyline, β -blockers, valproate, etc.) may add to weight gain and/or fatigue.
- While most patients are honest about analgesic use, some are embarrassed to tell us how much they are utilizing. Between over-the-counter analgesics and herbal

preparations, many patients are consuming larger quantities of medications than we realize. That is one reason to regularly test liver and kidney functions (blood tests).

- Do not confuse addiction with dependency. When treating chronic daily headache, dependency has to be accepted. Dependency is acceptable, while addiction is not.
- When using opioids, you must be willing to say no and set limits. Refrain from using opioids in younger patients, so as to avoid “opioid hyperalgesia.” Once younger people are on frequent opioids for a period of time, they may be “sensitized,” and we have little choice but to use opioids.
- Heed red flags in your patients on opioids. While pervasive behaviors help to determine addiction, even one red flag early in treatment should be seriously considered. For instance: You see a new patient, begin Tylenol #3 (codeine/acetaminophen), and receive a call 4 days later from the patient stating, “I got the generic, but the regular works better. Can you call some in?” Or, “I left my codeine in the hotel room”.....If you discover the urine tox screen is abnormal, or that the patient is receiving addicting meds from other doctors, these must be addressed, not ignored.
- Using a medication to establish a diagnosis may not be accurate. For instance, DHE and triptans have also been effective for relieving the pain of nonaneurysmal subarachnoid hemorrhage and tumors.
- What to do when nothing works: Before “giving up” on a patient with severe, refractive chronic daily headache, consider “end of the line” strategies such as daily triptans in limited amounts, Botox injections, monoamine oxidase inhibitors, daily long-acting opioids, stimulants, or a combination of approaches. SPG blocks for frontal pain, using one of the newer devices (SphenoCath or Tx360), along with occipital injections for posterior pain, may help.

Patient Perceptions

- Legitimize the headache problem as a physical illness. Statements such as, “headaches are just like asthma, diabetes, or hypertension: a physical medical condition,” go a long way toward establishing trust between the patient and physician. When we mention that it is a medical condition—primarily inherited—and that there is too little serotonin in the brain in people with headaches, patients respond exceedingly well. Once we have established this, the patients are much more amenable to addressing anxiety, depression, etc., with therapy or other means. However, if we focus on the patient’s stress, anxiety, depression, and psychological comorbidities first, they are often turned off to the physician unless we also state that we are treating the headaches as a legitimate medical illness.
- When we place patients on antidepressants, we need to make it clear that we are trying to directly help their headache by increasing serotonin. We also state that

we certainly hope this helps anxiety, depression, etc. Patients are often confused as to the reason why they are given an antidepressant. It helps if we make it clear that we are not trying to treat their headache by treating depression, but rather trying to adjust serotonin levels. If the patient does report that the antidepressant made them feel “wired, racy, I was up all night”, consider the soft end of the bipolar spectrum.

- We must try to achieve a balance between medication and headache; we tell the patients that we are trying to improve the headaches by 50–90%, while minimizing medications. Many refractory patients are more than willing to accept 25% relief.
- Many patients are frustrated by the lack of efficacy and/or side effects of daily preventives. Tell them that only 50% of patients (at most) achieve long-term relief with preventives. This helps them to realize they are in a big boat, and that it is not their fault. Our current daily preventives often become ineffective over time, or patients cannot tolerate them.
- Patients with chronic daily headache may view the headache situation in black and white terms. They will come back for a return visit and state, “Well, I still have a headache every day.” They need to accept that if we have gone from moderate-to-severe headaches (7 on a scale of 1–10) to mild-to-moderate (4 on a scale of 1–10), then the situation is improved and we should not change all the medication. If the patients keep a headache chart or calendar, this may help. Patients need to be willing to accept 50–90% improvement in frequency and/or severity of headaches.
- Being aware that there are cultural and ethnic differences in the perception and experience of pain can aid treatment.
- Pain patients are often desperate and search the Internet for a cure or seek alternative practitioners. We should not castigate them for doing so; they are just looking for answers.
- Catastrophizing greatly inhibits patients from improving. Work with your patient on decreasing the level of catastrophizing and histrionics. This will improve the pain level and associated anxiety.
- When patients feel they can actively help their headaches (“self-efficacy”) through medication, biofeedback, or other means, it improves their sense of well being. Whether by taking a medication, watching triggers, exercising, or doing yoga, etc., increasing “self-efficacy” enhances outcomes.
- Acceptance of their chronic illness (headache) is a helpful state of mind for patients to achieve. Acceptance is different from resignation. Acceptance helps to ease anxiety (“Isn’t there a cure? These must be curable”). The road to acceptance may take years, and involve many doctors and alternatives. Lack of acceptance leads to frustration, and wasted time and money seeking the miracle “aha moment” cure. Lack of acceptance “by proxy” also occurs, as parents of children with headaches sometimes refuse to believe that kids can have daily headaches. They also will seek sudden “miracle” cures that almost never happen. The physician and psychotherapist can work on increasing acceptance.

Broader Health

- It can “take a village to help a person with severe pain.” Do not try to do it all by yourself; get other villagers involved, including psychotherapy, massage, physical therapy, pain specialists, acupuncture, etc. Direct the patient to whichever of these other professionals is appropriate.
- In choosing preventives, look at comorbidities, particularly anxiety, depression, insomnia, gastritis, gastroesophageal reflux disease, blood sugar, constipation, hypertension, asthma, and sensitivities or allergies to other drugs. These often determine which way to proceed with medication.
- Central sensitization is an important phenomenon that occurs in chronic headache, peripheral neuropathy, and probably also in irritable bowel syndrome (IBS) and fibromyalgia. Once this occurs, treatment is difficult.
- Virtually all patients should be on vitamin D, usually at least 2000 units. Vitamin D is almost “the last man standing” among supplements. Vitamin D helps skin and bones, prevents certain types of cancers, and may help to minimize depression and pain. Multivitamins have more negatives than positives for many patients, and the same is true for antioxidants. Both multivitamins and antioxidants have been associated with increased cancer rates. Even omega-3 fish oil capsules have failed to provide positive benefit in most studies, and (in one large European study) were associated with an increase in aggressive prostate cancer. Natural is better.
- For patients with IBS (primarily diarrhea) and frequent headaches, consider a low-gluten diet. I have the patients limit wheat-based bread, cereal, and pasta. There are many gluten-free products available.
- Aspartame may cause headaches in susceptible patients; aspartame is a commonly used sweetener in products such as diet sodas.
- Caffeine enhances the analgesic effects of aspirin (Excedrin) and of nonsteroidal anti-inflammatory drugs. However, overuse of caffeine may lead to medication-overuse headache. We limit caffeine to 150 or 200 mg/day, at most. The average home-brewed cup of coffee has 120–170 mg. Coffee from Starbucks has more caffeine: 23 mg/oz (approximately). Other specialty coffeehouses also serve coffee with a higher caffeine content. Soft drinks have 50–60 mg/cup, while tea has 0 (if herbal) to 50 mg/cup. Excedrin contains 65 mg of caffeine per tablet.
- Learn about, and recognize, personality disorders. Many medical clinics allow a small number of personality disorders to drain much of the clinic’s energy. Get others (psychiatrists, etc.) involved and set limits. It “takes a village” to help a person with pain and a personality disorder.
- For depression to improve, it is important to control pain. Likewise, to help pain, we must treat depression. They tend to “fuel” each other.
- Attention-deficit disorder (ADD) in adults is common (4.7% prevalence). Look for it since ADD decreases quality of life and is relatively easy to treat in adults.
- Watch for soft bipolar signs in headache patients who have anxiety and depression. Bipolar disorder tends to be underdiagnosed, and the clinical stakes for

missing it are enormous. Bipolar disorder, primarily mild and soft (bipolar 2 or 3), is seen in as many as 6–8% of migraineurs. While some of these patients will do well on an antidepressant, it is almost always necessary to add a mood stabilizer. Soft (milder end of the spectrum) bipolar patients with headache often are placed on antidepressants, with predictably poor results.

- We cannot promise patients that their headaches will improve with psychotherapy (as it often does not), but coping with headaches and the stresses that headaches produce is often improved with therapy. Unfortunately, because of stigma, time, and money, only a small minority of patients will actually go to a therapist. However, those who do go will usually benefit. Biofeedback is underutilized and should be offered more often.

Strategies and Procedures

- It helps to view chronic headache as a continuum or spectrum. The “in-between” headaches may not fall neatly into the current tension or migraine categories. Whether these are severe tension or milder migraines, they often respond to the same medications.
- Kindling of the brain is important in depression, seizures, and headache. It is crucial to treat depression to remission, control seizures, and treat headaches. Possibly, if we treat younger patients with frequent headaches fairly aggressively, we may prevent the progression into chronic daily headache.
- The initial history and physical is the best time to consider a differential list of medications, because at that point we have a good grasp of the patient’s comorbidities. If we list in the chart all other treatment possibilities (in case our initial medications do not work), later we, or our partners, do not have to reconstruct the entire history with the patients.
- Keep a drug-medication flow chart, which is easy to do with electronic medical records (EMR). Headache patients are constantly having medications stopped and restarted so that, over 10 years, a patient may have been on 50 different medications at various times. It is impossible to piece through 40 progress notes trying to determine what the next best course of action is. A drug-medication flow chart from the beginning would help immensely. For patients, “chronicpaintracker” is a nice app that is easy to use, tracking meds and triggers, along with pain.
- In treating pain patients, utilizing premade stamps or EMR software can be helpful for documenting that a discussion occurred about side effects, risk/benefits, limits, etc. Opioid stamps for each visit include level of pain and functioning, moods, overuse, and physical exam (pupils/gait/speech).
- When dismissing a patient from your practice (for abusive or drug-seeking behavior, or other reasons), do not abandon the patient. Instead, offer three other physicians’ names and phone numbers, suggest that you will transfer records, assist in any way to help obtain another physician, and give the patient 1–3 months to find another provider. It is common for dismissed patients to complain to departments of regulation about “abandonment.” Many physicians do not (or

cannot), for various reasons, dismiss patients. These physicians tend to be over-run with abusive personality disorder patients. This leads to legal and regulatory problems, as well as physician burnout. Burnout is a crucial concept, and many strategies need to be used to avoid it. These include in-office: limiting patients, dismissing abusive patients, utilizing staff for paperwork and difficult phone calls, etc. Outside of the office, there are a number of strategies to avoid burnout as well.

- While there is the official definition of pain, we prefer, “Pain is what the patient says it is, and it’s as bad as the patient says it is.”
- This is an updated version of an article that appeared in *Practical Pain Management*, vol 12, Sept 2012.

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