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About Robbins Headache Clinic

For more than 25 years, the clinic has given headache sufferers relief from their pain, with our cutting-edge treatment based on the latest advancements in the field. We are known as one of the nation's best headache treatment centers, providing care that is more aggressive and comprehensive than many chronic headache sufferers have ever encountered. Each patient receives individual attention and personalized treatments selected from a wide range of remedies. Care is coordinated with other specialties, such as physical therapy and psychotherapy.

Visit www.chicagoheadacheclinic.com for helpful information about headaches, including more than 200 articles and a popular blog with more than 700 posts that is updated daily. The website includes info about a longer ebook version of this book that has more comprehensive information.

Dr. Lawrence Robbins

Lawrence Robbins, M.D., is one of the top 10 experts in the country on management of headache medication. He is a leader in the field on "refractory" headaches: those that are difficult to treat. He has spearheaded cutting edge research, ranging from the immune system in headache patients to Botox for headache.

Dr. Robbins repeatedly has been named one of America's Top Doctors since 2001, and also was named one of Chicago's Top Doctors by Chicago Magazine. He received the 2008 Clinical Pain Management Award, which is given by the American Academy of Pain Management to one physician per year.

Dr. Robbins has written more than 200 articles and abstracts, as well as three books.

Certified Nurse Practitioner Brooke Phenicie

Brooke Phenicie, NP-C, works with Dr. Robbins managing headache patients. She previously worked in a family practice and has experience treating a wide variety of medical conditions.

Brooke is a member of the American Headache Society and the Neuroscience Education Institute. Through the NEI, she holds a certificate as a master psychopharmacologist. She is certified by the American Academy of Nurse Practitioners.

Brooke is the co-author of a number of headache articles.

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Disclaimer: This guide is the author's opinion. Medications must be individually prescribed and used only in conjunction with treatment by a physician. Side effects, as listed in the PDR, must be accepted and understood. Some medications and treatments listed do not have an official FDA indication for the condition discussed. This guide is not a prescription, and it does not represent a standard consensus of treatment.

Migraine Treatment from A to Z

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

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

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

Migraine Characteristics
A recurring headache that is of moderate or severe intensity and is triggered by migraine-precipitating factors usually is considered to be migraine. Precipitating factors can include stress, certain foods, weather changes, smoke, hunger, fatigue, and hormones. Migraine without aura is a chronic idiopathic headache disorder with attacks lasting 4 to 72 hours. Status migrainosis applies to migraine headaches that exceed 72 hours. Migraine features often include a unilateral location and a throbbing or pulsating nature to the pain. There may be associated nausea, photophobia, or phonophobia (Table 1). Further characteristics include a positive relationship with menses, decreased frequency during pregnancy, increase of the pain with physical activity, and history of migraine in first-degree relatives. Seventy to 75% of migraine patients report a first-degree relative with a history of migraines.[3]

Table 1. Characteristics of a Migraine

- Attacks last from 4 to 72 h
- Patient history gives the diagnosis (not lab tests)
- Often occur in early morning (but may be any time)
- Unilateral location in approximately 50% of patients
- One to five migraines per month is typical
- Gradual onset of pain is followed by a peak for hours, then slow decline
- Moderate or moderate to severe pain; pain is throbbing, pounding, pulsating, or deeply aching
- Sharp "ice-pick" jabs are common
- Peak ages are between 20 and 35 y
- 18% of women and 7% of men will experience a migraine in their lifetime;
- female ratio is 3:1

- Family history often is positive for migraine
- Associated nausea, photophobia, blurred vision, phonophobia, or dizziness are common; however, these may be absent
- In women, there often is a positive relationship with menses
- Cold hands and feet and motion sickness are common

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

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

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

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

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

Table 2. Somatic Symptoms Accompanying Migraine (in order of frequency)

- Sensitivity to light
- Blurred vision
- Nausea
- Sensitivity to noise
- Tenderness about the scalp
- Dizziness or lightheadedness
- Lethargy

- Vomiting
- Sensitivity to odors
- Retention of fluid, with weight gain
- Photopsia
- Vertigo
- Anxiety
- Paresthesias
- Diarrhea
- Fortification spectra
- Nasal stuffiness
- Mild aphasia
- Syncope or near syncope
- Severe confusion
- Seizures
- Fever
- Hemiparesis or hemiplegia
- Ataxia or dysarthria (brainstem dysfunction)

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

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

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

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

Visual Disturbances

Approximately 20% of patients experience visual neurologic disturbances preceding or during the migraine; these auras may be as disturbing to the patient as the migraine pain itself. The visual symptoms usually last 15 to 20 minutes, and most often will be followed by the migraine headache. Most migraine sufferers experience the same aura with each migraine, but occasionally one person may have several

types of auras. "The light of a flashbulb going off," is the description many patients give to describe their aura. The visual hallucinations seen most often consist of spots, stars, lines (often wavy), color splashes, and waves resembling heat waves. The images may seem to shimmer, sparkle, or flicker. These visual occurrences are referred to as photopsia.

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

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

Miscellaneous Neurologic Symptoms

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

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

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

Workup for Migraine

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

Situations that raise concern about organic pathology include:

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

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. The current ability to noninvasively obtain a magnetic resonance angiogram allows the detection of most intracranial aneurysms.

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

Headache Triggers

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

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

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

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

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

Caffeine Use

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

Table 3. Common Caffeine Sources

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

Foods to Avoid

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

Table 4. Foods to Avoid

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

Keys to Management of Migraine

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

Medications: Abortives

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

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

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

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

Miscellaneous Approaches

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

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

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

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

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

First Line Preventive Medications for Migraine

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

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

Petadolex is a purified form of the herb butterbur and is made of extracted plant certified by the German Health Authority. This herb preparation is commonly used in Europe, and has been found to be successful in preventing migraines in several well-designed blind studies. The usual dose is 50 mg twice per day. Earlier concerns about carcinogenesis with this family of herbs have decreased with the use of Petadolex. Patients have occasionally experienced GI upset or a bad taste in the mouth, but Petadolex is usually well

tolerated. It is prudent to stop it every three months or so. Petadolex is available by calling 1-888-301-1084 or through www.petadolex.com and other Web sites.

Magnesium is a naturally occurring mineral that helps many systems in the body to function, especially the muscles and nerves. It has been shown that magnesium levels in the brain of migraine patients tend to be lower than normal. Magnesium oxide is used as a supplement to maintain adequate magnesium in the body. A dose of 400 or 500 mg per day can be used as a preventive; tablets are found in most pharmacies. However, mild GI side effects may limit use. There are also complications from drug interactions, and kidney and other diseases.

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

Medications

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

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

The b-blocker propranolol also is FDA-approved as a preventive agent for migraines. Long-acting oral propranolol (Inderal), for example, is very useful in combination with the tricyclic antidepressant amitriptyline. Dosage begins with the long-acting agent given at 60 mg per day, and is usually kept between 60 and 120 mg per day. Lower doses are sometimes effective, such as 20 mg twice per day of propranolol. Other b-blockers also are effective, such as metoprolol (Toprol XL) and atenolol. Some of these are easier to work with than propranolol because they are scored tablets, and metoprolol and atenolol have fewer respiratory effects. Depression may occur. Beta-blockers are useful for those migraine patients with concurrent hypertension, tachycardia, mitral valve prolapse, and panic/anxiety disorders. Bystolic (Nebivolol) is another b-blocker that may be helpful for the prevention of headaches, and has fewer respiratory side effects than other agents.

As noted, amitriptyline is an effective, inexpensive agent that is useful for the prevention of daily headaches and insomnia. As a preventive agent, amitriptyline is prescribed at low doses and taken at night. Sedation, weight gain, dry mouth, and constipation are common side effects. Other tricyclic antidepressants such as doxepin and protriptyline can be effective for migraine. Nortriptyline is similar to amitriptyline, with somewhat fewer side effects. These also are used for daily tension-type headaches.

Protriptyline is one of the few older antidepressants that does not cause weight gain. However, anticholinergic side effects are increased with protriptyline. Although selective serotonin reuptake inhibitors (SSRIs) are used, they are more effective for anxiety and depression than for migraine.

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

Second-line Migraine Preventive Therapy

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

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

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

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

Venlafaxine (Effexor XR) is good antidepressant for the prevention of migraine. It is used primarily as an SSRI at lower doses; at higher doses (100-150 mg) norepinephrine also is increased. In fact, antidepressants with dual mechanisms (serotonin and norepinephrine) are more effective for pain and headache. These include duloxetine (Cymbalta) and desvenlafaxine (Pristiq).

Conclusion

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

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Refractory Chronic Migraine

RCM is often a disabling, debilitating and challenging illness; patients who have medication overuse headache or psychological comorbidities require a combination of therapeutic approaches.

By Lawrence Robbins, MD
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Refractory Chronic Migraine (RCM) results in a great deal of disability for patients and has a huge impact on their quality of life. In order to provide a framework for other physicians and health care providers, this author initiated the Refractory Headache Special Interest Section of the American Headache Society. This committee of headache specialists seeks to define a standard of diagnosis for health practitioners and raise awareness of improved treatments for headache. Since its inception, the committee has primarily focused on the critical area of RCM definition. Chronic migraine (CM) is outlined in Table 1. Chronic migraine occurs in approximately 2% of the population; we do not yet know the epidemiology or rate of occurrence of RCM. The current proposed criteria for RCM are summarized in Table 2.[1,2]

Table 1. Appendix Criteria for A.1.5.1 Chronic Migraine (Headache Classification Committee 2006)

A. Headache (tension-type and/or migraine) on 15 days per month for at least 3 months
B. Occurring in a patient who has had at least 5 attacks fulfilling criteria for 1.1 Migraine without aura
C. On 8 days per month for at least 3 months, headache has fulfilled C1 and/or C2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura

1. Has at least two of ‘a’ through ‘d’
    a) Unilateral location
    b) Pulsating quality
    c) Moderate or severe pain intensity
    d) Aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs) And at least one of ‘e’ or ‘f’
    e) Nausea and/or vomiting
    f) Photophobia and phonophobia
2. Treated and relieved by triptan(s) or ergot before the expected development of C1 above

D. No medication overuse and not attributed to another causative disorder.

The definition of RCM is a work in progress; the final version may be quite different than that cited in Table 2. We may want to add modifiers as to the degree of refractoriness (mild, moderate or severe). In some patients, RCM improves or resolves over time, while others worsen. These situations need to be addressed in the definition. [3]

Challenges of Refractory Migraine[3]

There are a number of major challenges in dealing with RCM with each category requiring a different approach. These include:

1) What does the role of disability play, and should disability help to define RCM?
2) How resistant to the myriad of treatments does one have to be?
3) There is no accepted, identifiable biological marker for RCM.
4) The degree of refractoriness can change over time, improving or worsening. What role does this varying severity play?
5) There are various subsets of RCM— post-traumatic headache, RCM with or without Medication Overuse Headache (MOH), with or without major psychiatric comorbidities, etc.

Pathophysiology

We are just beginning to look beneath the surface as to what causes RCM. Some of the issues are:

1) What is the role of genetics in drug resistance and inheritance of chronic headaches?
2) What structural changes (in white matter or iron deposition) play a role?
3) What part does central sensitization and plasticity have?
4) How much involvement is peripheral vs. brainstem vs. cortical?
5) How does MOH affect the structure and function of the nervous system?
6) What is the physiologic impact of psychiatric comorbidities? Do depression and/or anxiety fuel the headaches?

Continuing research is critical in order to answer these questions. We do know several risk factors that may drive the development of RCM. These include lifestyle issues such as medication overuse, sleep habits, caffeine overuse and obesity.[5] While pharmacotherapy may be the cornerstone of treatment, other modalities are no less important. The patient must manage his or her triggers with regards to sleep, food and caffeine. Exercise and weight reduction are encouraged. Stress, another major trigger, may be relieved by practicing biofeedback and/or yoga. Depending on the origin of the pain, physical therapy and massage may help. Problems with the teeth, jaw, eyes or neck should be addressed.

Medication Overuse Headache

Table 1, Part D, refers to the overriding condition of MOH. MOH is a critical issue that must be addressed early in the treatment of any form of headache.[6] Abortive medication overuse is a major risk factor for the progression of migraine into RCM. Some patients have medication overuse without an increase in headache. In others, overuse of abortives is the principal cause for the headaches. The criteria for MOH are listed in Table 3. Note that the headache progresses instead of subsides over time, and the calls for prescription refills will become more frequent with the progression. When treating patients with MOH, the offending drugs will need to be withdrawn or limited. While we do not know with any certainty the percentage of RCM patients where MOH is a major contributor, we do know that MOH should be one of the first considerations when a patient presents with worsening headaches.

Psychiatric Comorbidities

Significant abuse in childhood, whether sexual, physical or emotional, may predispose one to develop RCM, separately or in conjunction with other central sensitization syndromes such as fibromyalgia, irritable bowel syndrome, chronic pelvis pain or TMD. Important comorbidities include anxiety, depression, the bipolar spectrum, personality disorders, somatization and post-traumatic stress disorder.7 The author has published several articles on the bipolar spectrum and personality disorders and how they relate to migraine patients; a brief synopsis will be discussed here.

Bipolar Spectrum. The bipolar spectrum is seen relatively often in headache patients and particularly among migraineurs.[8] The depression and hypo-mania of the bipolar spectrum complicate treatment; in RCM patients, these issues must be recognized. Bipolar disorder is not an easy condition to have or to deal with in a patient or family member. The clinical spectrum of bipolar is an evolving concept: mania is better recognized than is hypomania with milder bipolar features. Symptoms of mania include euphoric mood, distractibility, flight of ideas, grandiosity, thoughtlessness, risk-taking, increase in general activity, excessive involvement in pleasurable activities (sex, spending, gambling), pressured speech, excited or irritable mood, and insomnia. Hypomanias, with milder versions of these symptoms, can be missed if a doctor relies solely on the patient's own history; it is important to talk with a family member or significant other to get a complete history. In addition, brooding or irritable pessimism may be a manifestation of hypomania. During these periods, many people will lose jobs or damage relationships.

The prevalence of bipolar disorder is at least 4% in the general population, but bipolar illness is seen with increased frequency in the migraine population.[9] Studies have indicated that from 7.2% to 8.6% of migraine patients fit the bipolar spectrum.[9,10] Conversely, in assessing patients with bipolar spectrum disorders for migraine, several studies have indicated an increased risk. One study indicated that, in bipolar patients, 14.9% of the men and 34.7% of the women had a lifetime occurrence of migraine.[11] Additional studies of the bipolar population resulted in a lifetime migraine prevalence of 39.8% (men) and 44% (women).[12] Recognizing bipolarity in headache patients has a significant impact. When not diagnosed, these patients often are given antidepressants alone, with predictably poor results. While of some benefit, these medications generally are not effective for the bipolar spectrum and may trigger mania or hypomania. The presence of bipolar illness complicates treatment of RCM. Mood stabilizers that help both conditions, such as lamotrigine or sodium valproate, are important. Psychotherapy plays a vital role with these patients.

Personality Disorders and Migraine. In patients with certain personality disorders, failure on the part of the physician to recognize Axis II pathology puts both doctor and patient at risk. Patients with antisocial, borderline or paranoid personality disorders may wreak havoc on an unsuspecting medical practice.

Table 2. Proposed Criteria for Definition of Refractory Migraine and Refractory Chronic Migraine (From the Refractory Headache Special Interest Section: Elliott A. Schulman, MD; Alvin E. Lake III, PhD; Peter J. Goadsby, MD, PhD; B. Lee Peterlin, DO; Sherry Siegel, MD; Herbert J. Markley, MD; Richard B. Lipton, MD)

Criteria	Definition	
Primary Diagnosis	A.	ICHD-II migraine or chronic migraine
Refractory	B.	Headaches cause significant interference with function or quality of life despite modification of triggers, lifestyle factors, and adequate trials of acute and preventive medicines with established efficacy. 1. Failed adequate trails of preventive medicines, alone or in combination from at least 2 of 4 drug classes: a. Beta-blockers b. Anticonvulsants c. Tricyclics d. Calcium channel blockers 2. Failed adequate trials of abortive medicines from the following classes, unless contraindicated: a. Both a triptan and DHE intranasal or injectable formulation b. Either nonsteroidal anti-inflammatory drugs or combination analgesics
Adequate trial	Period of time during which an appropriate dose of medicine is administered, typically at least 2 months at optimal or maximum-tolerated doses, unless terminated early due to adverse effects	
Modifiers	With or without medication overuse, as defined by ICHD-2 With significant disability, as defined by MIDAS > 11	

DHE = dihydroergotamine; ICHD = International Classification of Headache Disorders; MIDAS = Migraine Disability Assessment

Table 3. Appendix Criteria for A8.2 Medication Overuse Headache (Headache Classification Committee 2006)

a) Headache present on > 15 days/month.
b) Regular overuse (>10 days/month or > 15 days/ month, depending on the medication) for > 3 months of one or more acute/symptomatic treatment drugs as defined under sub forms of 8.2.
c) Headache has developed or markedly worsened during medication overuse.

Approximately 10-15% of people have features of a personality disorder.[13] There are a number of personality disorders, and some exhibit more dangerous and difficult behavior than others. The general characteristics of personality disorders include lack of insight, poor response to psychotherapy and other therapeutic interventions, difficulty with attachments and trust, a sense of entitlement and the creation of chaos and distress among family, friends and co-workers. Comorbid substance abuse is common. Personality disorders range from the mild to the very severe. Patients with personality disorders will take on various roles: victim, rescuer or persecutor. When they turn persecutor, they can be dangerous to the person they have their sights set on. Seeing a therapist for a long time helps to some degree. However, goals and expectations must be limited. The plasticity of the brain is important, as some people improve naturally over time. The following are disorders that may be seen in RCM patients:

Antisocial Personality Disorder. These people have no regard for the rights of others. They tend to be irritable and impulsive in demeanor. They are exploitative, often see themselves as superior, and can be very opportunistic in getting what they want. Antisocials are deceitful, may steal from those around them, and often have trouble with the law. They rarely show remorse.[13]

Borderline Personality Disorder. This type of personality shows instability of mood, poor self-image and pervasive abandonment fears. There is an identity disturbance and major boundary issues. Borderlines usually demonstrate impulsiveness, and quick shifts of depression to anxiety to irritability. There are chronic feelings of emptiness or severe loneliness, plus anger and even suicidal behavior. Under stress, they can become paranoid. Problems with drug abuse or other addictive behaviors may coexist, as well as sleep disturbances with insomnia. Severe borderlines will react with high drama and create chaos for everyone around them. They tend to have a split view, seeing people as wonderful or terrible, with nothing in between. Suicide becomes more likely as patients age into their upper twenties and thirties. Suicide is also more common within a week of discharge from a psychiatric unit.[14]

There are other personality disorders which are not as dangerous for the people around them. Although PD characteristics seem extreme, they are often overlooked, and health care providers may react by treating these patients in a dysfunctional manner. The problem begins with not recognizing the personality disorder.

One previous study on borderline personality (BPD) concluded that BPD comorbidity with migraine is associated with increased disability from the headaches.[15] In addition, among those with BPD, there was an increase in medication overuse headache, and headaches were more severe. There was a higher degree of depression among those with BPD, more unscheduled visits for acute headache treatment, and a lesser chance of adequate response to headache medications. Those with BPD were more severely affected by headaches, and more inclined to be refractory to treatment.[15]

Another study indicated that the incidence of BPD was increased in migraineurs.15 The author's recent study of 1,000 migraineurs indicated that 5.5% of patients had a moderate or severe personality disorder.[16] There is ample evidence that transformed migraine is associated with more prevalent psycho-pathology, including PD, than is episodic migraine. BPD itself is the mental health equivalent of chronic pain. These patients suffer constantly with feelings of depression, anxiety and loneliness.

In my experience, the two most important prognostic indicators for those with PD are impulsivity and substance abuse. Treatment for those with PD necessitates a caring, but stern, approach. Limits must be set on physician contact, including telephone calls, and no abuse of staff should be tolerated. Referral to mental health professionals should be emphasized. Psychotherapists and psychiatrists who are experienced with this population are vital to the adequate management of the patient. Many PD patients

do not do well with traditional, insight-oriented therapy treatment, but are better managed long-term with a dialectical behavioral approach. For a therapy to be beneficial, it must be consistent and long-term. A psychoeducational approach may also help. Unfortunately, many PD patients will not continue in therapy, even with encouragement and support. Our therapeutic goals for the PD patient are relatively modest.

Medications, though limited, may be beneficial for the impulsivity, aggression, self-mutilation, anxiety and depression components of PD.[17] While there are no specific medications indicated for those with PD, the Axis I symptoms are more amenable to pharmacotherapy. Antidepressants, mood stabilizers, and antipsychotics may ameliorate symptoms. Some of these medications may lessen headache pain as well. PD patients with severe, chronic pain present additional challenges for treatment. It is important to limit and closely monitor addicting medications: opioids and benzodiaze-pines are best avoided, particularly with BPD. The diagnosis of a moderate or severe personality disorder alters both our goal and approach, and greatly complicates the treatment for chronic migraine.

Outpatient Treatments for RCM

New Technologies and Pharmacotherapies

There are a number of therapeutic options for RCM, including inpatient treatment. New approaches, such as transcranial brain stimulation (TMS), are in various stages of development and will come along. TMS has the potential to alleviate RCM without side effects. There is currently one newer type of TMS machine in use in the US, the Neurostar machine. It is FDA- indicated for the treatment of depression. There is another type of TMS unit in development by the company Neuralieve, which will be primarily used as a migraine abortive. It has the advantage of being readily available in a patient's home.

Occipital nerve stimulation has been beneficial for a small number of RCM patients. Techniques of implantation have improved but the technical challenges need to be overcome; the leads tend to migrate away from the occipital nerve, for example. Other implantable stimulators are being studied, such as the Bion microstimulator and the Precision Implantable Stimulator for Migraine. It is too early to know what, if any, role these will play.

In pharmacotherapy, there are a number of emerging compounds that may eventually come to market. These include newer abortives, such as 5-HTIF drugs. These work on the 5-HT F receptor, while the current triptans target B and D. CGRP antagonists, such as olcagepant and telcagepant, may be very useful. Gap junction blockers at the neural-glial level are being assessed. Finally, glutamate receptor antagonists are currently in Phase III trials.

Five Approaches to RCM

It is crucial to resolve medication overuse, and eliminate rebound in all RCM patients. For the remainder of this article, the author has highlighted five possible approaches (opioids, botulinum toxin, daily or frequent triptans, stimulants, and monamine oxidase inhibitors), some of which may be combined. For a RCM patient, the choice of therapy depends on a number of variables. These include age, psychiatric comorbidities, tendency towards addiction, sleep, medical conditions, etc. Comorbidities often steer where we go with medications: conditions such as IBS, fatigue or psychiatric conditions have to be considered. Of course, the familiarity and confidence with a particular therapy on the part of the treating physician plays a major role in selection. There is no algorithm for migraine treatment. The choices of medication will vary for each patient depending on headache severity and comorbidities.

Long-acting Opioids

In my practice, long-acting opioids are the most commonly utilized approach for RCM. The best candidate for LAOs is the person who has done well on short-acting opioids (SAO) and who does not have characteristics of a personality disorder. The following summarizes certain LAO studies and describes guidelines for using LAOs in chronic migraineurs.

In a 2007 study, we assessed 115 patients with refractory chronic migraine who were treated with long-acting opioids during a six-year period. This was a select group of patients who had all done well previously with short-acting opioids. Avoidance of opioid-induced hyperalgesia is important in chronic patients; however, all of the patients in this study had already been on short-acting opioids for at least a year.[18]

Sixty-five percent of the patients did well for at least nine months on the opioid; the average duration of use of the opioid was 4.5 years. Forty-four percent of the patients reported adverse events. Patients with an increased chance of success included younger patients, high copers, and those without previous opioid abuse. Predicators of failure were those with personality disorders, older patients, and, in particular, those with previous abuse of the short-acting opioids. In this study, anxiety, depression, bipolar depression, ADD, exercise, working, disability, fatigue or cigarette smoking did not significantly change the long-term outcome. In one of our previous studies (1999),[19] a significantly lower rate of success (13%) was obtained compared to the 2007 study (65%). This was, in part, due to an altered standard of success utilized in the more recent study.

In 1997, Saper and associates assessed refractory chronic daily headache with scheduled long-acting opioids, particularly methadone.[20] There was a small subset of patients who did well. Similar results were obtained from Rothrock[21] and from Robbins.[18] Subsequently, Saper and his associates soured on the use of the opioids. An unpublished study from Rothrock indicated that in the chronic migraine patients who were responsive at two months to the methadone treatment, over 70% continued to maintain a response at one year.[22] Rothrock found that patients tend to either respond to relatively low doses, or not respond at all. His studies also indicated that virtually all of the positive responders, when tapered off of the methadone, did relapse into their frequent headache patterns.[22]

Short-acting (SAO) versus Long-acting (LAO) Opioids

Short-acting generally refers not only to how long a drug carries the desired effect, but the speed of the onset of the drug and how fast it drops off toward the end of the dose. Quick onsets and fast dropoffs are major determinants for abuse.[23] SAOs are not necessarily quick-onset medications. Most oral SAO tablets are slow to take effect. A short duration of action then leads to frequent administration by the patient, and overuse may occur. However, it has not been proven conclusively that SAOs lead to more abuse than LAOs. Although certain drugs are easily abused, such as oxycodone CR, it is the person, not the drug, who governs abuse. While some abusers have only one drug of choice, many will tend to abuse a succession of drugs.

Several previous studies have evaluated daily opioids for severe chronic daily headache.[20,21,24] While success rates have been relatively low, they represent patients who have failed the usual ministrations, and who have few options available.

The advantages of long-acting opioids include:

1. avoidance of the "end-of-the-dose" phenomenon, with mini-withdrawals throughout the day;
2. consistent dosing one or two times daily, which decreases the obsession with the next dose;
3. maintenance of stable blood levels;
4. avoidance of acetaminophen, aspirin and NSAIDs that are included in many short-acting preparations;
5. probable diminished risk of significant abuse; and
6. better compliance, with less psychological dependency on the drug.

Disadvantages of long-acting opioids include:

1. social stigma;
2. fatigue and constipation;
3. difficulty in obtaining scripts, with no refills available;
4. need for frequent office visits and monitoring;
5. risk of opioid-induced hyperalgesia;
6. risk of abuse, although probably less than the SAOs;
7. interactions with other sedating drugs and alcohol; and
8. risk of overdose.

Opioid Abuse

Opioid abuse is much more common than true addiction. In general, using opioids for therapeutic reasons other than pain constitutes abuse. In a headache practice, the most common reasons for abuse are using the opioids to alleviate moods, anxiety or depression.

Patients in our previous study were assessed for behaviors typical of opioid abuse or overuse. The criteria that we used included: early refill requests, dose escalations, insistence on increasing doses, abusive treatment of the staff regarding refills, false reports of stolen or lost medications, utilizing the opioid for depression or anxiety, using the opioid for other pains not discussed with the physician, receiving similar medication from other physicians, unexpected or abnormal urine screening test results, using illicit drugs or alcohol, missing, canceling, or refusing appointments, selling the drugs, obtaining opioids from non-medical arenas, frequent ER visits for opioids, hoarding, forging or altering scripts, borrowing or stealing similar medications from family and friends, physical signs of overuse or addiction, and calls to the physician from family members with concerns about patient overuse.[25,26]

There is a range of abuse, from the person who samples his spouse's codeine prescription once in a while to the addict who obtains hundreds of opioid tabs from the internet. We cannot paint all abusers with one broad brush. Some situations need watching, such as the patient who took her mom's pills because she had excess pain; this behavior is a red flag and the patient may be an abuser. For a different patient, one who has already been prescribed low dose, long-acting morphine, the discovery of undisclosed opioid prescriptions from other sources must be regarded as severe abuse; in this situation, discontinuation of the opioids is necessary.

It is not always clear how serious the abuse is. Minor aberrant behaviors are often overlooked. It is not as if any one aberrant behavior warrants immediate discontinuation of an opioid, but most of the serious overuse situations have previously had a number of minor abuse occurrences. Physicians must pay attention to red flags, particularly those that arise early in the relationship with the patient. In my experience, pain patients who raise objections to urine tests usually have a drug problem. Specimen collections should be random and not scheduled. Urine testing serves two purposes: one is to identify

other substances that are present but should not be. Another is to measure the levels of the prescribed substance for compliance. When there is no opioid present, there is sometimes a lab error or test insensitivity, but it may be that the patient has been binging early on and has run out of drugs before the visit.[27] Another possibility is that the patient is selling the drugs.

In those who self-medicate, a drug is used for a purpose other than the intended one, such as using an opioid as a mood stabilizer or enhancer. Opioids can be both calming and stimulating, often giving a brief burst of energy followed by a tranquil period. Chemical coping is all too common, but is poorly understood and under-researched.[28] All addicts are chemical copers to some degree, but not all people who cope chemically are addicts. The person who utilizes one or two pills of hydrocodone a day for stress and anxiety is not an addict by definition, but is certainly using chemicals to cope. The severe patients basically live for the drug; their lives are controlled by procurement of the drug, and they have few coping skills outside of using the drug.[29] They will self-escalate their drug use, particularly during periods of high stress.

As much as 35% of patients with chronic pain may fall under the definition of chemical copers.[30] There are gender differences, with women using the substances primarily for anxiety, stress and depression. Women are at somewhat of an increased risk for chemically coping than are men.[29] Men may utilize the drugs for anxiety and depression, but also use them out of boredom, particularly when they are disabled by their pain. For some men, there is a strong relationship between substance abuse and sensation seeking.[29]

While physical dependence and tolerance are to be expected with long-term opioid use, addiction is not. Addiction constitutes a biologic and behavioral disease. Most abusers can stop using the drug when harm occurs, but an addict cannot. Whether a patient with previous addictions should be treated with long-acting opioids is a complicated issue. It should be approached on a case-by-case basis and is dependent on a number of factors. Among the considerations:

1. What substances were abused?
2. How many years has the patient been clean?
3. Whether the patient successfully completed treatment.
4. The quality of the support system.
5. Any comorbid psychiatric conditions.31
6. Assessment of risk factors.

Previous studies have indicated that risk factors for opioid abuse include cigarette smoking, previous drug abuse, a strong family history of drug abuse, stress, young age, early sexual abuse, poor support, low level of functioning due to headache or other pain, pain embellishment, and certain psychiatric conditions.[32-34]

An NIMH analysis identified certain problems that carried an increased risk for substance abuse. Of those with anxiety, 25% had a substance use problem, as did 33% of those with OCD and 61% in the Bipolar I category. Unipolar depression also carried a higher risk, but not as much as bipolar. Among PD patients, 84% of those with antisocial personality disorders were substance abusers.35 Also, patients with somatization are probably at a higher risk. Untreated ADHD in older adolescent boys carried a 75% risk of substance abuse, while treated ADHD in this category falls to a 25% risk. The boys without ADHD had an 18% overall abuse rate.36 Our study indicated that those with personality disorders were at increased risk for abuse, but that other psychiatric conditions did not lead to more abuse.

Successful Management of Long-Acting Opioids

The physician must have knowledge and experience in the use of these drugs. The patient has to be reliable and well known to the practitioner. Many of the problems occur with new patients; it is prudent to wait several visits before prescribing the long-acting opioids—after the physician can establish that there has been little or no previous abuse.

Patients must have demonstrated an adequate response to short-acting opioids. To avoid opioid-induced hyperalgesia, we restrict use to patients who have received SAOs for one year or more. The patient must truly be refractory to the typical ministrations, with multiple adequate trials of the usual preventive medications. Previous abuse of opioids should exclude patients. In this author's view, previous abuse of SAOs almost always leads to abuse of the LAOs. Pseudoaddiction is certainly encountered, but seems to be rare in headache patients. Be wary of the patient who claims he or she can tolerate almost no medications except for the opioids.

The use of opioids in patients under thirty should be restricted. Younger patients are more likely to develop tolerance; in older patients, particularly after age 65-70, the brain has lost the ability to do the "neuronal gymnastics" necessary in the development of tolerance. Therefore, older patients may remain on the same low dose for a number of years. If a younger patient fulfills all the requirements, such as truly being refractory, is normal psychologically and at low risk for addiction, he or she may be the exception to the age rule. Management of those with chronic migraine involves a biopsychosocial approach. Patients must not rely simply on the drug in order to function. While medications may be a mainstay of therapy, other interventions must be employed. Active coping should be strongly encouraged with each visit, and may involve a variety of approaches. These may include seeing a psychotherapist, physical therapist or other practitioner, or using self-help approaches such as exercise or biofeedback. Passive coping is a major predictor of disability in chronic pain patients. Those patients who rely only on opioids have less chance of sustaining long-term relief. Even though pharmacotherapy is the cornerstone of treatment, it is only part of a more comprehensive plan.

There are three distinct phases in the use of opioids. The first phase is the initiation of treatment. This includes the initial screening and risk assessment, the doctor's decision as to which opioid to utilize, and the doctor-patient discussion and signing of an opioid agreement. Prior to initiation of LAOs, an assessment of the following should be done: pain level, moods, social and family functioning, work status, physical functioning, and activities of daily living.[37]

The intermediate phase is comprised of the diligent monitoring of the patient while on the opioid. This must include ongoing assessment of the patient's pain level and overall functioning, with a watchful eye for signs of abuse. The physical exam on a return visit needs to assess for slurring of words, abnormal gait, and pupillary abnormalities. Do not assume that low risk patients will never abuse the opioids. During the maintenance phase of opioid prescribing, it is remarkable how many seemingly low-risk patients do misuse the drugs.

Patients usually respond fairly quickly to an opioid; if they have not responded by two to four weeks on a low dose, there usually will not be an adequate response.[22] If patients do not report an improvement in functioning, or if functioning declines, consideration should be given for withdrawal from the opioid. Some patients have an improvement in pain but a decline in activity, possibly due to sedation or other opioid-related side effects.

The third phase is switching or withdrawing the opioids when abuse has occurred, or there is lack of efficacy. Withdrawing or switching an opioid may be exceedingly difficult in some patients. Each of these phases involves a learning curve on the part of the practitioner and proper documentation by staff members.

In my experience, using higher doses of the opioid rarely works out in the long term. They place the patient at increased risk of addiction and abuse, and complications from withdrawal. It may be thought that, given the great variation in individual responses, the opioid should be increased or "pushed" to whatever level is beneficial. However, medical and regulatory considerations should be limiting factors in keeping the opioid dose at a low level. The choice of opioid may be key; some have been shown to have less abuse potential. The long-acting fentanyl patch is subject to less abuse than oxycodone CR. The once or twice daily, long-acting morphine preparations have not been subjected to widespread abuse.

Methadone may be more effective than some of the other medications, but has a litany of problems associated with it. Besides the social stigma, high protein binding is a risk, which may lead to irregular drug levels, difficulty with withdrawal, and an increased risk for sudden death.[38] If methadone is used, it should be started at a very low dose of no more than 5-10mg a day, and titrated slowly. Patients placed on methadone require close monitoring, and other sedatives must be reduced or discontinued. The usual dosing range in my practice is:

- methadone, 5 to 40mg per day
- morphine, 20 to 90mg per day
- oxycodone, 20 to 60mg per day
- Fentanyl patch, 12.5 to 50mcg per day

Some type of written opioid agreement should be part of the doctor-patient alliance, although there is a lack of evidence that these agreements do much good for the majority of the patients. There is no standard opioid contract; practices should adapt one for their own purposes. There are several resources on opioid agreements, such as the AAPM website, www.painmed.org, the American Pain Society website, www.ampainsoc.org, the Federation of State Medical Boards, Inc., www.fsmb.org, and the US DEA, www.usdoj.gov/dea. In addition there is an excellent article on agreement contracts by Fishman, 1999.[39]

The treatment of breakthrough pain is controversial. Most of the breakthrough studies have been concerned with cancer pain, where the average number of breakthroughs is 4 per 24 hours.[40] For patients with non-cancer breakthrough pain, such as chronic daily headache, I tend to minimize the total opioid and avoid layering pain medicines on top of each other. Prescribing short-acting medications, such as hydrocodone, for chronic headaches greatly increases the abuse rate. The occasional patient can remain on a low dose of the long-acting opioid, with one or two SAOs such as hydrocodone per day, but, in general, try to avoid these SAOs.

Botulinum Toxin Injections (BoNT-A)

Botulinum toxin type A (US trade names: Botox® and Dysport®) has been utilized as a migraine and chronic daily headache preventive since the 1990s.[41] The results of studies have varied widely. Two Phase III studies (PREEMPT 1 and 2) with 1,384 CM patients, found Botox useful for improving functioning and reducing disablility. One of the studies was very positive in reducing headache days.[42] The preponderance of evidence points to BoNT-A as being safe and efficacious and this author concurs.

There are a number of possible explanations as to why BoNT-A may alleviate pain. One of BoNT-A actions is as an anti-inflammatory at the neuronal level. BoNT-A may block the release of substance P. More importantly, it may also inhibit the level of secretion of calcitonin gene-related peptide (CGRP).[41] CGRP has now been recognized as a key inflammatory mediator, a vital cog in the cascade leading to headache. Efforts are underway to develop drugs that are CGRP antagonists. BoNT-A may also block the release of certain other neuropeptides that contribute to the "inflammatory soup." This neuropeptide blockage, along with BoNT-A inhibitory effects on the excitatory neurotransmitter glutamate, results in a lessening of peripheral sensitization. With the use of BoNT-A, there is also a decrease in central sensitization.[43] Relatively few other compounds have an effect on central sensitization, which is so vital to the pathophysiology of chronic migraine.

As with a number of migraine treatments, the results of BoNT-A studies do vary. A number of variables may explain some of the differences, including:[41]

1) headache severity, chronicity and degree of refractoriness
2) medication overuse
3) patients with differing types of pain ("imploding" vs. "exploding")
4) different methods of assessing outcomes and
5) differences in the number of units of BoNT-A used, and the location of injections.

In a number of BoNT-A studies, the high placebo response rate has been difficult to overcome in proving efficacy. The optimal mechanics of BoNT-A administration are still a work in progress.[44] I usually average 50 units per treatment, but 100 or 200 may be more effective. The injections are most often administered frontally and temporally, with 9 to 12 total injections. There are some patients who do well with as little as 25 units,45 while, at the other end of the range, some outliers respond only to 250 (or more) units.

For some patients, we "chase the pain" and administer additional injections around the area of pain. For those with occipital pain, posterior injections may be very helpful. If patients do not respond to the first treatment, it is worthwhile to repeat BoNT-A at least once more. BoNT-A is expensive but relatively safe. Of course, BoNT-A may be combined with various medication approaches.

Side effects to BoNT-A tend to be minimal; occasionally patients experience a mild droop of one eye. Some have reported numbness or other sensations around the areas of injection. Generalized weakness should not occur with the low doses that are used. On occasion, patients experience an increase in headaches for one to two weeks.

Daily or Frequent Triptans

Some patients respond only to triptan medications (sumatriptan, naratriptan, rizatriptan, almotriptan, zolmitriptan, frovatriptan, eletriptan). Several studies have described the use of daily triptans for the preventive treatment of CDH.[46,47]

Short-lasting adverse events are often encountered with triptan use. These include paresthesias, fatigue, chest heaviness, jaw or neck discomfort, etc.[48] Chest symptoms are, with rare exceptions, not of cardiovascular origin. Cardiac ischemia due to triptan use is rare.[48] Triptans do constrict coronary vessels, but this is a mild and short-lived effect. Despite widespread triptan use, the number of adverse cardiac events has been limited. Echocardiography and electrocardiography generally have been normal after triptan uses, even in the presence of chest symptoms.

The primary issue with frequent triptan use, assuming rebound headache is not present, is long-term adverse events. The cardiovascular system would be the most likely for possible long-term sequelae. Chronic ischemic changes, valvular abnormalities, or fibrosis are theoretical considerations. To date, there is no evidence of long-term triptan use producing any of these adverse events. This has not been systematically studied, however. The number of patients throughout the world who have utilized triptans on a near-daily basis is unknown. Until these patients have been studied, it is reasonable and prudent to do cardiac monitoring, as well as hematologic tests.

The following describes a study that we did on frequent triptan use.[46] The patients in this study were never instructed to use triptans on a daily basis. They self-discovered that a dose of triptans would alleviate headache for most or all of the day. Most patients in this study had a long history of headache refractory to usual medications. They finally had found a medication (a triptan) that would alleviate the headache for some time. Most of the patients had been using frequent triptans through their primary care physician. A minority of our patients had increased the amount of triptans prescribed. Patients were withdrawn from triptans in order to determine if rebound headache was present. The only patients who continued on triptans were those who: 1) had been determined to truly be refractory to other approaches, 2) experienced no or minimal side effects, 3) had rebound headaches excluded, and 4) signed a "Frequent Triptan Informed Consent" form. Many patients did not meet these criteria and the triptans were discontinued.

One goal of this retrospective study of a large group of patients was to evaluate the cardiac safety of triptans. A secondary objective was to assess the hematologic tests that were performed in these patients.

For most of the treatment course, most patients (97 of 118) averaged 1 tablet daily (50mg sumatriptan, 2.5mg naratriptan, 10mg rizatriptan, 5mg zolmitriptan). Eight patients used only ½ tablet daily, while 8 others used 1.5 tablets on a daily basis. Five patients consumed 2 tablets daily. Ninety patients used the triptan every day, while 28 patients averaged 4 to 5 days a week. All of the patients would occasionally go for several days without a triptan, or occasionally take a drug holiday for a week or more.

Forty patients had taken a triptan for six months to a year, 37 for two to four years. Forty-one patients had taken daily triptans for 4 or more years: 29 for four to six years, and 12 for more than six years.

The patients were monitored for several years. Routine laboratory (hematologic) tests were done, including complete blood counts and chemistries. No abnormality was felt to be due to the triptans. Electrocardiograms were performed on all of the 118 patients, and no abnormality was determined to be from the triptan. Eight patients did have abnormal electrocardiograms. Echocardiograms (with Doppler) were done on 57/118 patients, and 10 were abnormal. The attending cardiologist did not feel that any of these abnormalities were due to triptan use. Twenty patients underwent stress tests, and all were normal.

Nine patients felt that the triptans contributed to fatigue. Five patients had mild chest tightness at times, possibly due to the triptans; cardiac disease was ruled out. Three patients felt that the triptans contributed to nausea.

Because these patients decided on their own to use triptans on a daily basis, adverse events would be expected to be low. If patients were not tolerating the medication well or were having significant adverse effects, they would not choose to continue the triptan on a frequent basis. There were no adverse consequences from frequent triptan use over a prolonged period.

Stimulants

When prescribed for headache patients, stimulants may be beneficial for various comorbidities, such as attention deficit hyperactivity disorder (ADHD), depression, and fatigue. In addition, stimulants do not cause the weight gain that is seen with a number of other current headache preventives. Amphetamines have been shown to possess intrinsic analgesic properties, primarily through brain catecholamine activity. They also intensify the analgesic effects of certain opioids.[49] Stimulants have been utilized to counteract the sedation encountered by opioids. An excellent review article on stimulants as adjuncts for opioids concluded that, "The evidence suggests that amphetamine drugs may enhance the effect of opioids and, at the same time, decrease somnolence and increase cognitive performance."[50]

As a group, central nervous system (CNS) stimulants cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity.[51] Caffeine, the most widely consumed stimulant in the world, is believed to act by several mechanisms of action in the pre-frontal cortex and other areas of the brain. These include translocation of extracellular calcium, inhibition of phosphodiesterase, and adenosine receptor antagonism, resulting in decreased fatigue and increased mental alertness.[51]

Nicotine, the active ingredient in tobacco, specifically stimulates nicotinic receptors in the autonomic ganglia, resulting in euphoria, arousal, relaxation, and improved attention, learning, problem solving, and reaction time.[51] However, in very high doses, nicotine causes blockade of autonomic ganglia, resulting in respiratory depression and severe hypotension.

Amphetamine and its derivatives, such as methylphenidate, demonstrate indirect CNS and PNS effects similar to cocaine. Like cocaine, they initially increase levels of catecholamines. However, amphetamines do this by a different mechanism of action. They accomplish this effect by causing the release of intracellular stores of catecholamines and inhibiting monamine oxidase (MAO).[51] The major cause of the behavioral effects of amphetamines is thought to be due more to release of dopamine rather than norepinephrine.[51] This ultimately results in increased alertness, decreased fatigue, decreased appetite, and insomnia as well as the usual "fight or flight" response characteristic of adrenergic stimulation in the PNS.

Amphetamines have been known to possess independent analgesic activity, possibly due to release of norepinephrine. The effect was felt to be about the same as that of ibuprofen. Also, stimulants may potentiate the analgesic actions of opioids.[50] The most commonly studied combination has been dextroamphetamine and morphine. Methylphenidate has also been studied as an opioid adjunctive medication. In one small study, the use of dextroamphetamine for patients with tension and migraine headache was assessed. It concluded that dextroamphetamine was viable as a preventive medication for chronic tension and migraine headaches in some subjects.[52] In another case report, a man was successfully treated with methylphenidate for his refractory episodic cluster headaches.[53]

One of our previous studies assessed 73 chronic migraineurs who had been prescribed stimulants in addition to their other medications. While the stimulants were primarily prescribed for certain comorbidities, their effect on headaches was also assessed. Seventy-five percent of the patients who were placed on the stimulants remained on them for at least 9 months. Thirty-four percent of the 73 patients both remained on the stimulants and reported positive efficacy with regard to headache. Forty-one percent of the patients suffered at least one adverse event, while only two patients abused the stimulant.[54]

Stimulants have proven utility for certain conditions, such as ADHD. For patients with these comorbidities the stimulants may also be beneficial for a minority of patients with chronic migraine.

Advantages of stimulants include enhanced cognition and alertness, with no weight gain. Disadvantages primarily revolve around the side effects, such as anxiety or insomnia. Abuse may certainly occur, but it is uncommon in adults. Stimulants should be considered in patients with certain comorbidities. The few studies to date have indicated a positive role for stimulants, but further studies on stimulants for headache would help to clarify that role.

Table 4. Sunnybrook Health Center MAOI Diet57

Food Group	Food to Avoid	Food Allowed
Cheese	Mature or aged cheese, casseroles made with these cheeses; all others except listed in 'allowed' column	Fresh cottage, cream, and ricotta cheese and processed cheese slices; all fresh milk products
Meat, fish, poultry	Fermented/dry sausage, pepperoni, salami, mortadella, improperly stored meat, fish or poultry	All fresh packaged or processed meat, fish or poultry; stored in refrigerator and eaten as soon as as possible
Fruits and vegetables	Fava or broad bean pods, banana peel	Banana pulp, all others except listed in 'avoid' column
Alcoholic beverages	All tap beer	Alcohol: no more than 2 domestic or canned beers or 4 oz. wine a day
Miscellaneous foods	Marmite yeast concentrate, sauerkraut, soy sauce and soy condiments	Other yeast extracts, soy milk

Monoamine Oxidase Inhibitors (MAOIs)

For those with RCM and unipolar depression, MAOIs may be of help. MAOIs are sometimes effective for treatment-resistant depression.[55] They are also effective for alleviating anxiety. MAOIs were commonly prescribed in the 1980s, but with the advent of SSRIs and triptans, they fell out of favor. The available literature on MAOIs for headache treatment dates to the 1970s and 80s. For a select group of RCM patients, the MAOIs greatly enhance quality of life. At this point, I believe that MAOIs are under-utilized.

The traditional, classical MAOIs form an irreversible complex with the enzyme monamine oxidase. Monamine oxidase is located in a number of tissues, including the brain. The mechanism of action is most likely receptor-mediated pre- and post-synaptic events, not simply an increase in serotonin.55 Phenelzine, a traditional MAOI, has been the one most commonly used for headache.

One non-traditional reversible MAOI is moclobemide, which is not available in the USA. Moclobemide has fewer dietary and medication restriction than the classic MAOIs. The transdermal selegiline patch is a selective MAO-B inhibitor that does not require the tyramine-restricted diet. The efficacy of these non-traditional MAOIs is not as clearly established as the more traditional MAOIs (phenelzine).[56]

Careful patient selection is crucial when using the MAOIs. Patients need to carefully observe the restrictions on diet and medications. I usually prescribe low doses of phenelzine, 15mg tablets, and start with one tablet at night, increasing after one week to two at night. If no response is noted after three to four weeks, I usually push the dose to 3 tablets at night. By always using the MAOI at night, the patient is less likely to encounter a food interaction. Five tablets a day (75mg) is the usual maximum. Side effects include insomnia, weight gain, sedation, and orthostatic hypotension. The MAOIs have a reputation as being somewhat dangerous and difficult to use. Despite this reputation, MAOIs are usually well-tolerated.

The previous MAOI diets were overly restrictive. The listed risk of most foods was based on anecdotal cases. Newer evidence-based diets are easier to follow. See Table 4 for the MAOI diet.

The hypertensive crisis that may occur with a food interaction is due to a number of factors, primarily the amount of tyramine absorbed into the bloodstream. The tyramine content of food has been difficult to accurately establish. When patients consume the phenelzine at night, in low doses, while avoiding the major tyramine-rich foods, interactions are less likely. The reversible MAOI moclobemide is much less likely to trigger any adverse reaction.

The serotonin syndrome may occur due to the administration of serotonergic drugs and MAOIs. SSRIs should not be concurrently used. Other drugs that should be avoided include amphetamines, sympathomimetics, pseudoephedrine, certain opioids (meperidine), dextromethorphan, and others. Most triptans are not utilized with MAOIs, but low doses of frovatriptan may be used with caution.

For those patients suffering from both refractory chronic headache and treatment-resistant depression, MAOIs may offer some measure of hope. They also alleviate anxiety. When cautiously used, the MAOIs are not as dangerous as their reputation might imply.

Conclusion

Refractory chronic migraine is often a disabling and debilitating illness. We face major challenges in attempting to define RCM. The definition must allow for severity of illness; also, degrees of refractoriness may change over time.

Other major areas of study within RCM include pathophysiologic mechanisms, the role of medication overuse, search for biomarkers, psychological comorbidities, non-medication approaches, and pharmacotherapy.

Patients with RCM who have medication overuse headache or psychological comorbidities require a combination of approaches. It “takes a village” to help those with severe, refractory headaches, and we need to guide the patient into comprehensive treatments. There are a number of viable therapeutic approaches, five of which are presented in this article. However, we desperately need breakthrough medications and technologies that can prevent headache pain.

Disclosure

Dr. Robbins is a partner in Brain Stimulation Chicago North Shore, which provides TMS therapy for depression.

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Clinical Pearls for Treating Headache Patients

By Lawrence Robbins, MD, Fred Ludwig and Brooke Phenicie, NP-C

Headache patients often have complex medical and psychological issues. The following "pearls" reflect the author's philosophy in treating these patients.

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 four 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. Cambia is 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 minutes. Prodrin is a newer version of Midrin, with no sedative (Prodrin eliminates the dichloralphenazone), and 20mg of caffeine. Levadex (from Map Pharmaceuticals) is an inhaled version of DHE, expected to be approved by the FDA. Levadex will be a better product than Migranal Nasal Spray, but not quite as effective as injections of DHE.
- Consider natural alternatives that work, such as the butterbur derivative, Petadolex. Petadolex is a highly regulated "adulterated herb," and it is the #1 preventive in Germany. I feel Petadolex is safe, has a long successful track record, and is almost as effective as our mainstream preventives.
- 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 high cost is a concern.
- Previous sensitivities and allergies to medications often determine where we go with meds. If the patient has had severe reactions to two selective serotonin reuptake inhibitors (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 beta-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, beta 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.

- Do not confuse addiction with dependency. When treating chronic daily headache, dependency has to be accepted. Dependency is acceptable, while addiction is not.
- In using opioids, you must be willing to say NO and set LIMITS. Avoid 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 may have little choice but to utilize 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, and receive a call four days later from the patient stating "I got the generic, the regular works better, can you call some in?"
- Using a medication to establish a diagnosis may not be accurate. For instance, dihydroergotamine (DHE) and triptans have also been effective for relieving the pain of non-aneurysmal subarachnoid hemorrhage (SAH) 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 (MAOIs), daily long-acting opioids, stimulants, or a combination of approaches.

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.
- We must try to achieve a balance between medication and headache; we tell the patients that we are trying to improve the headaches 50% to 90%, while minimizing medications.
- Many patients are frustrated by the lack of efficacy and/or side effects of daily preventives. Tell them that only 50% (at most) of patients achieve long-term relief with preventives. This helps them to realize they are in a big boat, and that it is not their fault.
- 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 1-1 0), 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% to 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 that they can actively help their headaches ("self-efficacy"), by medication or 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 than 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.

Broader health

- It can "take a village to help a person with severe pain." Don't 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 (GERD), 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 2,000 units. Vitamin D is almost "the last man standing" among supplements. Multivitamins have more negatives than positives for many patients, and the same is true for antioxidants. Vitamin D helps many conditions, among them pain and depression.
- 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.
- Aspartame may cause headaches in susceptible patients; aspartame is a commonly used sweetener in products such as Diet Coke and Diet Pepsi.
- Caffeine enhances the analgesic effects of aspirin (such as Excedrin) and of NSAIDS. However, overuse of caffeine may lead to medication-overuse headache. We limit caffeine to 150 or 200mg per day. The average home-brewed cup of coffee has 120 to 170mg. Coffee from Starbucks and other specialty stores has more caffeine: 23mg per ounce. Soft drinks have 50 to 60mg per cup, while tea has 0 (if herbal) to 50mg per cup. Excedrin contains 65mg of caffeine per tablet.

- Learn about, and recognize, personality disorders (Axis 2). 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.
- For depression to improve, it is important to control pain. Likewise, to help pain, we must treat depression.
- 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 under-diagnosed, 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% to 8% of migraineurs. While some of these patients will do well on an antidepressant, it is almost always necessary to add a mood stabilizer.
- 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 that do go will usually benefit. Biofeedback is under-utilized 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 re-started so that, over ten 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.
- In treating pain patients, utilizing pre-made 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, 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 one to three months to find another provider. It is common for dismissed patients to complain to departments of regulation about “abandonment.”

- 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.”

Management of Chronic Headache

A review of assessment and treatment of outpatient chronic headache patients, along with a commentary on aggravating and mitigating factors.

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When we assess patients who seek medical treatment for headache pain, they usually suffer from migraine, tension, or chronic daily headache. 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 out of 700 women.[1] In contrast, migraine is common; it occurs in 18% of women and 7% of men in the U.S. Chronic daily headache (CDH) often results in a markedly decreased quality of life for patients. Including triptans and other new preventives, we have numerous medications for migraine, but we don't have much that is new or effective for chronic daily headache. The following discussion reviews what we currently know about the various types of headaches, comorbidities triggers, and treatments.

Migraine

Migraine, of course, is the more severe type of headache. There are twenty-five to twenty-eight million people in the U.S. with migraine, making it one of the most common of illnesses. Many migraine patients can successfully take care of their headaches with over-the-counter medicines, but most are disabled to one degree or another during their 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 have them, increasing to 4% by age 10. Until the age 12, boys and girls suffer from migraine in equal numbers but, during puberty, the familiar women-to-men ratio of 3:1 is reached and that ratio is maintained throughout the rest of life.[2]

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 told (and feels) that they have a sinus headache and so they take an OTC sinus medicine, which often helps. Most sinus headaches turn out to be migraines.

There have been several large studies on this and 95% of people presenting with chronic sinus headaches are found to have migraines, not sinus headaches. So one must think "migraine first" regarding pain in the sinus area.[3]

Work-up

With a new onset headache—especially in a patient in middle or later life—more extensive work-up is needed. This is also true for new neurological symptoms such as numbness, a change in mental status, or

visual problems. The patient with chronic daily headaches warrants an 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 don't tell us about. Either they don't remember or don't have a sense of how many OTCs they take for pain relief. It is not unusual for headache sufferers to consume 8 to 10 ibuprofen or Excedrin on a daily basis and so the liver and kidneys may be affected.

Triggers

One of the primary things we can do is educate patients about triggers. Unfortunately, we can't 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 800mg 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 23 mg. of caffeine per ounce so that, in that oversized cup of Starbucks, you are going to get 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 50 mg. per cup, while instant coffee has half that amount. Tea, if it has caffeine, will generally have 30-60 mg per cup. Cola drinks have 40- 60 mg. and Mountain Dew has a little more. The new energy drinks may have 200 mg. in 12 ounces. Watch for accumulated caffeine from these and from OTC medication; each tab 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.[4]

Psychological Comorbidities

Comorbidities guide where we go with 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. 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's all in their heads since they've 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

ADD is another important comorbidity. Often, in adults, the ADD goes unrecognized and untreated. ADD is common and studies have shown that about 4.7% of adults have it. 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. At age 6, kids may not be doing well in school, but by age 26 they are losing their families and their jobs and they are at a much higher risk for addiction.

The risk of addiction for older adolescent boys (8-20 year olds) having ADD is almost 75% and usually manifests as an alcohol problem. If the ADD is treated, the addiction risk decreases to 20- 25%.[5] The stimulants prescribed for ADD often help the headaches. Addictions are a comorbidity that complicate the treatment of a refractory patient. Ten to fifteen percent of the general population has an addiction problem. Treating pain patients in the face of addiction is complex and often requires several professionals, both medical and psychological.

Anxiety

When the comorbidity is anxiety, it is usually generalized anxiety disorder. OCD is also common, and panic attacks are actually ten times more common in migraine patients than in the regular population. Separation or social 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. 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 that we are talking about. Of course, many adults with depression are actually bipolar, or fit into the mild bipolar spectrum. Depression is often seen 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 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 7% of headache patients fit onto the bipolar spectrum, whereas about 4.5% of the general population fits into the bipolar spectrum.[6] Studies which looked at the bipolar population found that 40 to 50% of bipolar patients have migraines, so there is a definite correlation. The clinical spectrum of bipolar disorders is an evolving concept. Historically, the DSM has inherent biases against independently diagnosing bipolarity, and bipolar II is defined very conservatively in DSM-IV. For example, in DSM-IV, the important hypomanic reaction to an antidepressant is not included in helping determine bipolarity. Some authors feel DSM-IV has an inherent bias towards diagnosing personality disorders rather than bipolar disorders. These biases lead to bipolar disorders being missed and underdiagnosed. 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. They may not 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—are much more effective.

Personality Disorders

It is crucial to recognize personality disorders within your practice. Approximately 10-15% of people have strong features of a personality disorder. There are a number of personality disorders, some of which are more dangerous and difficult to deal with than others. In general, characteristics of personality disorders 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 co-workers, etc. Personality disorders 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. Personality disorder patients often create chaos and drama, and comorbid substance abuse is common. The more difficult personality disorders include paranoid, antisocial, borderline, and narcissistic behaviors. In general, therapy helps people with personality disorders only over long periods of time. 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 personality disorder in adolescence indicated that, by age 30, one third of the subjects no longer had borderline personality. Many people do not fit neatly into any of these categories, but have features of two or three personality disorder types. Failure to identify those with personality disorders leads to increased risk for the provider and the patient. The small percentage of patients with moderate-to-severe personality disorders 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.[7]

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 seen in migraine patients, and very often we're 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.

Hypertension. A number of the antihypertensives do help decrease migraine. Most beta blockers will help, as will the calcium channel blockers. More recently, the angiotensin receptor blockers (ARB's) have been utilized.

Insomnia. Sleep disorders are frequently seen in 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 better meds for insomnia to be developed.

Fibromyalgia (or Chronic Pain Syndrome). We do have a few drugs that are indicated for fibromyalgia. Many people with fibromyalgia also have chronic daily headaches 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 don't 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 pounds overweight and is always tired. We don't 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 ARB's, and, occasionally, we will use small doses of stimulants.

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's 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 don't go. Cognitive-behavioral therapy is the usual approach, but with personality disorders 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 can be littered with many wrong turns along the way in looking for sudden cures. But at the end, when people accept that they have a chronic illness, when they know they don't have to simply give up and suffer, when they know the situation is bad but there is quite a bit that they can do, they can accept that the pain is chronic and needs to be managed, and there is no cure. This relieves a lot of the inner angst in which patients feel that there must be a cure. So we do promote acceptance but that does not mean resignation. People need to realize that much can be done about their headaches.

Biofeedback. Biofeedback is a very useful tool. I think that the providers who have been trained in the last 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.

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 personality disorder, 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.

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 to 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?" Studies of disability have shown that some of this is the result of the fear of pain. Some people have more fear and anticipation of pain than others and, as with catastrophizing, fear of pain can be worked on through therapy.

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 and chiropractic treatment can also be very helpful. It depends, of course, on the individual practitioner. 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 chiropractor in your area—one who is good with headaches and neck pain. Occipital pain may be derived from the cervical region and doing blocks or injections may help. Always think about treating the whole person and so any treatment should include all their pain conditions.

Dental, Massage, Acupuncture

Dental consultations may help when people are clenching their jaws and certainly if they are bruxing. Massage can benefit a wide range of patients, as can acupuncture. It's been difficult to prove in studies that acupuncture is more effective than sham treatment. After examining over 500 randomized controlled trials of acupuncture for various conditions, nothing definite can be concluded as far as efficacy.[8] 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 don't 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. A newer tablet, Treximet, combines sumatriptan (Imitrex) with naproxen. It is reasonably effective at keeping the headache from returning. All of the triptans do work but, unfortunately, they are all expensive and have annoying side effects. The triptan nasal sprays, particularly Zomig, can be very effective and bypasses the GI tract. Side effects of tingling and pressure may initially occur with the triptans followed by the headache lifting away. Since 1992, we have had over 85 million people treated with the triptans. I think safety has been well established. We have become more comfortable using triptans in higher risk populations. I am not saying that we want to use them in someone at high risk for cardiovascular problems, but we will use them more than we did 10 or 15 years ago. If one triptan is ineffective, I usually will try one or two other triptans before giving up on the class.

Outside of the triptans, most patients have tried over-the-counter products. Aspirin and metoclopramide combined sometimes help. MigraTen is an interesting product and was available in the 1980s as Migralam. For those intermediate headaches it is pretty good and MigraTen is not addicting. I advise patients to avoid other caffeine on the day they take MigraTen. We do want to limit the caffeine as there is a considerable amount (100mg) in MigraTen. While it has a vasoconstrictor, it doesn't contain aspirin and so it is better than Excedrin. It is a good product that fits the bill for many headaches but, as with any caffeine-containing medication, MigraTen should be limited to one or two per day.

DHE is probably underutilized. Migranal nasal spray is safe, but is not always effective; the DHE injections work better. Since 1945, when DHE was introduced, there have been relatively few bad side effects reported. It is primarily a venoconstrictor, so it actually safer than other ergotamines, which are arterial constrictors.[9]

Antiemetics, such as ondansetron, can work wonders. Ondansetron lets people go on with their day without sedating them. We also use the other antiemetics, such as metaclopromide or prochlorperazine. The goal is to keep people out of the ER, and the antiemetics can help in this regard. I do use opioids and butalbital in some patients. We limit their use as they may lead to more problems, but 9 out of 10 patients do not overuse them. It's the one patient out of 10 who can create a lot of problems, of course.

Butalbital, on the other hand, is controversial and is not used in Europe. It does lead to more rebound headaches than analgesics, and rebound is always a concern. Opioid and butalbital use in the headache patient has been found to be a major source of transformation of episodic headache into daily pain.

Occasionally we will use injectable opioids, or fentanyl oral suckers. In my experience, the problem with fentanyl oral (Actiq), which is now out in generic form, has been that many people will abuse the fentanyl. The quicker-onset medicines do tend to be overused, and there are more withdrawal symptoms. Actiq does work quickly, and there have been a couple of small headache studies involving Actiq. Again, to keep people out of the emergency room, we will occasionally use parenteral opioids. The antiemetics can also keep people out of the emergency room. As a last resort, when sedation is needed, we will occasionally use some meds off-label, such as quetiapine (Seroquel) or benzodiazepines. When nothing works for refractory headaches, particularly prolonged menstrual migraines, we do use corticosteroids, but in limited amounts. It is important to minimize the cortisone dose. We use dexamethesone, 4mg, ½ or 1 every 12 hours; or prednisone, 20mg, ½ or 1 every 12 hours. I would usually limit these to three or four tabs a month, at most.

Chronic Daily Headache Meds

When it comes to preventives, each person is different of course. 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 chronic daily headache than in semi-monthly migraines. Chronic daily headache is basically defined as headaches occurring at least 15 days per month. About 3% of people, in almost every country that has been assessed, have chronic daily headache. Chronic daily headache greatly decreases one's quality of life. It is a major problem, it is difficult to treat, and most analgesic overuse stems from chronic daily headache. 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 migraines are easily taken care of." We aim our preventive meds at the predominant, more severe type of headache. With chronic daily 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 Norgesic forte, which is orphenadrine, aspirin and caffeine, or MigraTen. Neither of these is addicting. The problem is that all abortives for daily headaches have their own side effects. There is a longer-acting form of tramadol, but tramadol is a mild opioid agonist and is somewhat addicting itself. Whatever is used abortively for CDH should be strictly limited to two per day.

Abortives and Rebound Headache

The abortives for chronic migraine are basically the same as for episodic migraine. We don't want to use triptans every day, except in unusual circumstances. Rebound headache is always a consideration and is remarkably complex as it involves a complicated pathophysiology at the brainstem level. The major question with a rebound headache is which drugs, and how much of the drugs, will trigger it. It appears that the butalbital and opioid meds, and the high caffeine drugs—such as Excedrin—may be more likely to cause rebound. Rebound does tend to be somewhat overdiagnosed, however. The situation with NSAIDs and rebound is interesting. It appears that in patients with 10 days or less of headache per month, certain NSAIDs may trigger rebound. However, for those with CDH, NSAIDs are less likely to cause rebound.

Preventives: Long-term Results

The goal with preventives is to help reduce the headache by 25 to 75%. If patients think their headaches are going to be completely cured, they may come back and say, "The medicines are not working because I still have some migraines." They may be 50% better, which is often as good as we can achieve. Headache diaries can help, but we also need to convey realistic goals to the patient. In my experience, only 50% of people do well on long-term preventives.

I've done two long-term studies looking at usage over a year's time, with a total of nearly 800 patients on preventives. Only 46% found any preventive they could tolerate and that worked for at least nine months.[10] The remainder discontinued preventives for various reasons. We have a ways to go as we need much better preventives.

Natural Remedies

Natural remedies can be useful. Petadolex is an improved form of the herb butterbur, where the molecule that we worry about in butterbur is limited. Petadolex is effective, and holds up well in randomized controlled trials (RCTs). It is popular in a number of countries—for instance, in Germany where

Petadolex is 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. Most people in the U.S. order Petadolex directly from the company (1- 888-301-1084). We also use feverfew, magnesium, vitamin B-2, omega-3s, and others. I think the Petadolex and magnesium are the most consistent. Feverfew lags behind as far as efficacy, but it is fairly safe. I have not found vitamin B-2 to be very helpful in the long term.

Tricyclics

As the prescription drugs go, the tricyclics are important. With amitriptyline and nortriptyline, we do see weight gain, dry mouth and constipation, but we use small to medium doses for most patients. I will start a patient at 5 mg. (half of a 10 mg. tablet of amitriptyline) and it is very inexpensive. The cost of medicine has increased but the generic tricyclics are very inexpensive. Some people remain on 10 mg. or 20 mg. a day of amitriptyline for years and do very well. Amitriptyline is metabolized into nortriptyline and so by using capsules of nortriptyline we see fewer side effects. Protriptyline is the only tricyclic that does not cause weight gain, but it does have increased anticholinergic side effects. With protriptyline, patients experience dry mouth and constipation, but it can help chronic daily headache with minimal sedation and without the weight gain.

Anticonvulsants

The primary anticonvulsants have been topiramate (Topamax®) and sodium valproate (Depakote®). These are indicated for migraine. With topiramate, we often see memory problems and spaciness and, occasionally, depression as well. As the dose is increased, tingling will occur due to carbonic anhydrase effects. Headache patients often quit the preventives due to annoying side effects, 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 towards 50mg and then, if needed, towards 100mg but many people do well at 25 or 50mg. While the average dose of 100mg sodium valproate (Depakote®) will cause more weight gain, topiramate may cause 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 contributing to discontinuation. Of course, we do not want a patient to become pregnant while on sodium valproate. We will start with 250mg of sodium valproate and move up the dosage very slowly. Many other anticonvulsants have been used with less solid evidence. Oxcarbazepine (Trileptal®) has failed in several headache studies, though it has been positive in some bipolar studies. Sometimes it does help moods and, if a patient is at the mild end of the bipolar spectrum and has daily headaches but cannot tolerate the other drugs, oxcarbazepine may be useful. Zonisamide (Zonegran®) has been used; it's a once-a -day, longer-acting, relatively safe anticonvulsant. Fatigue is the primary side effect. Zonisamide is usually started at 25mg at night, and slowly titrated up to 100mg.

Antihypertensives and Muscle Relaxants

The antihypertension meds are useful as preventives: beta 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. Remember, tiredness and weight gain are major problems in migraineurs, and beta blockers exacerbate fatigue and weight gain. So I often use one of the ARBs: Atacand is the main ARB that's been studied, but others have been utilized. Muscle relaxants certainly can help the associated neck pain and may aid sleeping. Tizanidine is non-addicting and is fairly safe, but we use it mostly at night due to the sedation. Cyclobenzaprine now has a longer-acting version called

Amrix® but the generic 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

Botulinum toxin type A (Botox) has been an interesting compound. It's 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% although, for some reason, it is lower in North America than in Europe.[11] The placebo response also differs among countries in Europe. Placebo response is about 5% lower in North America, on average, than in Europe. In the Botox studies, the placebo response has led to failure in achieving the primary endpoint, which is unfortunate. Many patients do find that it works. They use considerably less medicine in the two to three months post-Botox, and they can feel the effects wearing off at two and a half months. We now have had many years of Botox use, and one could make the 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. Results of a large, multicenter RCT from 2007-08 on Botox for chronic migraine are positive and fulfill the primary endpoints. This study could lead to an FDA indication.[12]

Long-acting Opioids for Refractory Headache

What to do when nothing works? For refractory patients, long-acting opioids are a possibility. In my new study, I assessed patients using long-acting opioids over a period of six years.[13] We looked at comorbidities and predictors of overuse. The people who tend to overuse are those who also overused short-acting opioids. If they overused hydrocodone, they tended to overuse the long-acting Kadian®, Oxycontin®, and methadone. I didn't find many cases of pseudoaddiction in this study, but I did find true addiction. 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 personality disorders.

The other predictor for overuse is the presence of a personality disorder. If people have more than a mild personality disorder, it does not usually work out well with the opioids. However, for the right person, these drugs can be lifesavers, improving quality of life and functioning. When nothing else works, taking morphine once a day, or twice a day in a low dose can 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. In many patients, opioids will lead to much better functioning, and they may not develop tolerance to the drug. 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!" I do think that we need more studies of people who have taken frequent triptans. I published one study of 100 patients, where we did cardiac echocardiograms and ECGs. In this particular study, no long-term adverse effects were found. The patients averaged near daily triptans for almost 4

years.[14] I don't advocate such frequent use, but many people do lapse into it. The physician must make sure that the headaches are not rebounds.

Refractory Patients: Stimulants

I do think there is a case for using stimulants in selected patients. They may help with fatigue, concentration, and moods. In the right person, they are remarkably useful. For some people, stimulants improve the quality of life, and can help the headaches. There have been some validating studies and I believe that stimulants are underutilized.

Refractory Patients: MAO Inhibitors

We tended to use MAO inhibitors frequently in the '80s, but do so much less now. The right patient, who is refractory and sometimes with a difficult depression, may respond to MAOIs. Of course, drug interactions and dietary restrictions limit use.

Refractory Patients: Occipital Stimulators

In refractory patients, the use of an occipital stimulator is controversial. I think it can help for a period of time, depending on the skill of the neurosurgeon. It is difficult to anchor the leads, and migration away from the occipital nerve often occurs. Neural implants and stimulators are coming along, but there may be better treatments under development, such as magnetic stimulation.

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.[15] Several trials are still in progress, seeking to assess whether closure of a PFO will decrease migraines.

Conclusion

Treating headache patients involves assessing the headache frequency and severity and also the comorbidities. The psychiatric and medical comorbidities help determine the direction we should take. It "takes a village" to help a severe headache or pain patient and so consider involving psychotherapists, physical therapists, chiropractors, etc. 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 do more. It requires a regimen that also includes botulinum toxin injections, or opioids. When used appropriately, some of these "out of the box" therapies are the key to restoring a patient's quality of life.

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Headache in Children and Adolescents

A multidisciplinary approach—a balance of medication with therapy and lifestyle changes—is the most helpful for children with severe headaches to help them return to normal functioning in home, school and social life.

By Joseph Maides, DO and Lawrence Robbins, MD
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Headache is a common complaint among children and adolescents. The prevalence of migraine in those with headache varies by age and gender throughout childhood and adolescence. Migraine begins earlier in boys than in girls and, until the age of seven, migraine occurs slightly more often among boys. By menarche, the prevalence of migraine in boys and girls is roughly equal. However, after menarche, migraine begins to predominate among females and this gender separation increases even further in late adolescence.

Headaches, especially migraines, have a significant impact on the lives of young people. Approximately 65-80% of children with migraine headaches will experience disruption of their normal daily activities at home, in school and other social settings. The burden of migraine may also result in the development or worsening of anxiety or depression. Because of quality of life issues, early recognition and management of headaches in children and adolescents is crucial.

Headache disorders can be categorized as either primary or secondary. As with adults, the vast majority of headaches in children and adolescents are primary headache disorders: migraine (with or without aura), tension-type headache and chronic daily headache.

Secondary headache disorders, although much less common, may be due to various organic etiologies which can range from the relatively benign to the serious. Such underlying organic conditions include:

- bacterial causes: acute febrile illness, rhinosinusitis, dental abscess, intracranial and extracranial infections;
- systemic illness: hypertension, diabetic ketoacidosis;
- miscellaneous: head or neck trauma, vascular malformations, subarachnoid hemorrhage, intracranial mass lesions, etc.

Diagnostic Approach

Although headache can be a presenting symptom of underlying organic pathology, accurate information from the patient and family is often enough to identify or rule out the most serious etiologies. The overwhelming majority of headache disorders are diagnosed by a thorough history and physical examination. A complete medical and psychiatric history, family history, medication history (including prescription, over-the-counter, and vitamins/herbs), allergy history, and social history should also be obtained.

Migraine tends to be under-diagnosed; patients and their parents often attribute headaches and nausea to "the flu" or dismiss them as "sinus headaches." Careful attention must be paid to the patient's description

of headache onset, timing, frequency, duration, severity, quality, location, precipitating factors, and aggravating or alleviating factors. Associated symptoms—especially nausea, vomiting, photophobia and phonophobia—are often the key to an accurate diagnosis of migraine.

Potential indicators of organic pathology can include severe vomiting, a headache which awakens a child from sleep, and the absence of a family history of migraine. Also, progressive, unremitting daily pain, neurologic symptoms and fevers are important. If any of these red flags are present, the appropriate laboratory and imaging investigations should be performed.

In a patient with an unremarkable history, where a primary headache disorder is suspected, laboratory investigation is usually not warranted beyond baseline labs. These usually include, but are not limited to, a complete blood count and metabolic panel.

Neuroimaging studies are usually not indicated in children with a normal neurologic examination and a history consistent with a primary headache disorder, especially migraine or tension-type headache. These children will not usually have significantly abnormal findings on head CT scans or intracranial MRIs. A small percentage may have incidental and/or unrelated findings, but routine neuro-imaging is not absolutely indicated in children with typical primary headaches.

Usually, electroencephalography (EEG) is not helpful in the routine diagnostic assessment of pediatric headache patients. However, an EEG should be performed on patients with an atypical migraine aura, episodic loss of consciousness, or symptoms suggestive of a seizure disorder. Background slowing may be seen during some migraine attacks, but the EEG results are usually normal.

Lumbar puncture (LP) is indicated if meningitis, encephalitis, subarachnoid hemorrhage, or high-low pressure syndromes are suspected. Cerebrospinal fluid and pressure measurement should also be performed. In those patients where increased intracranial pressure is suspected—or in those with focal neurologic deficits—a head CT scan or similar neurologic imaging modality should be performed prior to a lumbar puncture. We attempt to avoid the LP unless absolutely indicated. However, if meningitis or encephalitis is suspected in a toxic-appearing patient, treatment should not be delayed in order to perform the head CT scan first.

Biopsychosocial Approach

For those with more severe or frequent headaches, a comprehensive biopsychosocial approach is needed. This approach requires the collaboration of medical and behavioral specialists working together to improve a patient's overall functioning and quality of life. The combination of both pharmacologic and nonpharmacologic treatments is ideal for those with frequent headaches. Nonpharmacologic treatments are particularly important as they are typically more effective in children and help to minimize medications and side effects.

Non-pharmacologic Treatments

Non-pharmacologic modalities consist of patient education, lifestyle strategies, behavioral interventions, physical therapy, etc. Patient education should be the first step taken. Legitimizing the headache as a physiological disorder is of primary importance. It helps to say "…Migraines are a genetic medical condition, like asthma or diabetes…"

Children and their parents usually want to hear three things from the physician: (1) the cause of the headache (including triggers), (2) the treatment and prognosis, and (3) reassurance that a primary headache disorder is not serious. It is important that realistic goals and expectations are set. Children and their parents should understand that there are no miracle cures for headaches.

It is usually helpful to introduce the use of a headache diary as a means to identify specific triggers. Of course, some triggers (e.g., weather changes, stress, hormonal influences) cannot be avoided, but certainly many—such as missing meals, bright lights/sunlight, undersleeping/ oversleeping, foods, perfume, cigarette smoke and certain types of physical exertion—can be managed. Headache diaries should record the frequency and severity of headaches as well as document the efficacy and side effects of treatments. Using a diary will improve the patient's or parents' recall of the headaches and make office visits more productive. They can also help persuade children and adolescents of the need for lifestyle changes.

Lifestyle strategies should include an emphasis on proper diet, exercise, and sleep habits. Headache patients do better with regular schedules, eating three or more meals per day, and going to bed and awakening at the same time every day, including weekends. Daily exercise can be particularly helpful; patients should strive for at least 30 minutes of exercise per day. Generally, headache patients do better with low impact exercise such as swimming, walking, biking, and yoga.

Behavioral interventions—such as psychotherapy, counseling and relaxation techniques—may be helpful for many adolescents who experience significant stress in their lives. Overscheduling adds to the usual adolescent stressors. The incidence of hard-driving perfectionistic behavior and depression is increased in adolescents with severe headache. Children and adolescents who miss substantial blocks of time in school or social activities need to be assessed for depression, school phobia, and secondary gains. Counseling for children, as well as family-centered therapy for children and their parents, are often helpful in promoting active coping and is an indispensable augmentation to medical therapy.

Relaxation techniques such as biofeedback, deep breathing, and imaging should be encouraged. Most adolescents can learn relaxation techniques from books or audiovisual aids that are readily available. However, seeing a therapist who teaches biofeedback is much more effective. Most children under the age of 10 cannot learn and apply biofeedback, but some as young as seven can learn simple breathing and imaging techniques.

Pharmacologic Treatment

There are two types of pharmacologic treatment for headaches: abortive and preventive. Decisions on medication will depend upon the frequency and severity of the headaches and how much they bother the patient. Some children are not overly bothered by their daily headaches and tend to ignore them. Others may be incapacitated and miss an entire year of school.

As with adult headaches, abortive medication is used in the overwhelming majority of cases without daily preventive medication. Patients should be encouraged to use their abortive medication early, while their headaches are mild. Early intervention is a key step in successful use of migraine abortives. See Table 1 for a list of first line abortive medications.

Table 1. First Line Abortive Medications for Migraine and Tension-Type Headaches in Children and Adolescents

Under 12 years of age:

- Ibuprofen. Effective, and available as a liquid, but GI upset is relatively common.
- Acetaminophen. Well tolerated, safe, but not as effective as ibuprofen. Chewable tablets and liquid are available. Due to its relative safety, acetaminophen is the usual primary abortive used in young children.
- Naproxen. (Naprosyn, Aleve). Effective abortive that is non-sedating and is available as a liquid. However, GI side effects are common. (Aleve = OTC = 220mg).
- Midrin. Capsules (acetaminophen 325mg/dichloralphenazone 100mg/isometheptene 65mg): ½ or 1 capsule PO q 4 hours prn. These are very large capsules, but may be taken apart and sprinkled into apple sauce or juice. Sedation is common, as is lightheadedness. GI upset, although not common, occurs at times.
- Caffeine. Either used by itself, or with an analgesic, caffeine is useful for tension and migraine headache. In children, soft drinks containing caffeine are helpful. Side effects are minimal when caffeine is used in very limited amounts.
- Triptans. Off-label, but are occasionally used in low doses at ages 10-11.

Over 12 years of age (includes the above plus the following):

- Triptans. Almotriptan (Axert tablets) is the only one FDA-indicated in adolescents. Triptans are generally more effective than analgesics. Contraindicated in complicated migraine and in those with cardiovascular risk factors. Potential side effects include flushing, chest tightness, paresthesias, nausea, and somnolence. More effective when taken early. May be combined with NSAIDs (ibuprofen, naproxen).
- MigraTen. (Generic available.) Acetaminophen, isometheptene, caffeine. Similar to Midrin, but non-sedating.

It is always reasonable to try biofeedback together with simple abortive medications as the first step and attempt to avoid daily preventive medication, if possible. However, with frequent migraines, or for moderate to severe daily headaches, daily preventive medication may be necessary. In order to minimize medications, start at a low dose of a daily preventive and slowly titrate up to reasonable efficacy. Table 2 has a more complete list of criteria for the use of preventive medication. Table 3 lists first line preventive medications.

Table 2. Criteria for the Use of Prevention Medication

- The headaches interfere significantly with the child's functioning socially or at school. The extent of how much the headaches bother the child is a major consideration.
- Failure of non-pharmacological approaches (watching triggers, biofeedback, etc.).
- The child's and parent's willingness to utilize daily medication with possible side effects.
- Willingness of the child and parents to change medication, if necessary.
- Failure of abortive medication to effectively treat the headaches; continued frequency of headaches, daily or near-daily.

Table 3. First Line Preventive Medications for Migraine, Tension-Type, and Chronic Daily Headaches in Children and Adolescents

Under 12 years of age:

- Cyproheptadine. Safe, but efficacy is questionable. It is usually well-tolerated but fatigue and weight gain may be a problem. Not as useful in children over the age of 11. It may be dosed once a day and is available in liquid form.
- NSAIDs. (Ibuprofen, naproxen.) Ibuprofen and naproxen may be utilized as daily preventives or as abortive for both tension and migraine headaches. The lack of sedation renders these very helpful for daily use. GI side effects are relatively common, and when these are used on a long-term basis, regular blood tests for hepatic enzymes and renal function need to be done.
- Petadolex. (Age 9+.) A form of the herb butterbur. Good evidence for efficacy in migraine. Widely used in Europe; available for over 35 years and regarded as safe. One tablet (50mg) daily; may increase to two. Occasional mild GI upset. May be ordered through www.petadolex.com, 1-888-301-1084.
- Magnesium oxide. Available OTC as "Kid Calm." Mild, but effective for some. Safe in this age range. Usual dose is 100–200mg a day.
- Over 12 years of age:
- Petadolex. See above.
- Topiramate. Useful for both migraine and CDH, lower doses (e.g., 25-50mg qHS) are often effective; may be pushed to 100-150mg daily. Potential side effects include cognitive slowing, paresthesias, decreased appetite/weight loss, and rarely acute glaucoma, renal stones, and acidosis. Cognitive side effects often limit use.
- Divalproex. Useful for both migraine and chronic daily headache (CDH), lower doses (e.g., 250mg) are usually used with some efficacy. May be pushed to 750-1000mg daily. Potential side effects include GI upset, sedation, weight gain, tremor, dizziness, and alopecia. Blood tests should be performed periodically for hepatic enzymes.
- Gabapentin. Useful for both migraine and CDH, lower doses (e.g., 100-300mg BID to TID) are often effective. Potential side effects include dizziness and weight gain, although it is usually very well tolerated by most people, especially at the lower doses recommended.
- Tricyclic Antidepressants. Effective for migraine and CDH. Nortriptyline and amitriptyline are commonly used. Usually well tolerated in low doses and safe for long term use. Cognitive side effects, dry mouth, drowsiness, dizziness, and weight gain are common. Usual dose of amitriptyline is 10-50mg daily. Protriptyline does not cause weight gain, but is somewhat less effective. Blood tests should be performed periodically for hepatic enzymes and renal function.

- Propranolol. Generally well tolerated. Fatigue and decreased exercise tolerance may be a problem. Usual dose is 20-80mg daily. With doses less than 60mg qd, BID dosing is required which is inconvenient for children.
- Verapamil. A calcium channel blocker that is effective for migraine and occasionally CDH. Generally well tolerated, with constipation common. Convenient once per day dosing with the sustained release formulations. Usual dose ranges from 80mg once a day up to 240mg ER q day.

Realistic goals and expectations for medications need to be discussed. For abortive medications, the goal is to achieve significant relief (>70%) as quickly as possible. When preventive medications are used, the goal is to reduce headache frequency and severity by 30% or more and to improve functioning. Patients may note that the efficacy of their abortive medications improves with the use of a daily preventive.

When preventive medications are used in children and adolescents, it is prudent to periodically attempt to discontinue the daily preventive in an effort to minimize medications. As with adults, the idea is to see if the patient may return to simply using abortive medication. However, if an adolescent has had headaches for a number of years and has found a preventive that works, the usual practice is to continue it long-term.

Conclusion

Many children and adolescents have episodic migraines that respond easily to abortive medications. The challenge is in dealing with those who have frequent and debilitating headaches. A multidisciplinary approach is the most helpful for patients with severe headaches: a balance of medication with therapy and lifestyle changes. Management of headache disorders is a trial and error process; there is no "cookie cutter" approach. Although decreasing the frequency and severity of headaches is important, success is ultimately measured by how much we help the child return to normal functioning in home, school and social life.

The Homebound Adolescent Headache Patient

By Lawrence Robbins, MD
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I have an adolescent headache center north of Chicago. Years ago, I would take a simplistic, tough-love approach: "…My job is to come to work; yours is to go to school, no excuses." I have evolved toward a more nuanced approach, individualized to each child's situation.

In the case of chronic refractory headache patients, we are not simply treating one child in isolation; we are also dealing with the parents, siblings, and the school. Long-term outcomes with these children somewhat depend upon the psychiatric health of the parent. The primary "caretaker" parent (usually the mother) can range from psychiatrically normal to those with a severe personality disorder (PD). The child's psychiatric status is also a crucial variable. It "takes a village" to raise some of these children, and we recruit "other villagers." These include psychotherapists, physical therapists, biofeedback specialists, etc.

Role of Therapist Is Key

Adolescent psychotherapists are invaluable in treating these patients. They often provide the most useful treatment for the child. Many therapists will take a family therapy approach. Family dynamics play a crucial role in perpetuating refractory headaches. Also, the patient's severe headaches adversely affect the rest of the family. Many of the kids are not ready for high school, and have tremendous fears and anxieties. After a number of sessions, the therapist often has a good grasp on why the child has severe headaches, along with school avoidance. For some kids, the long-term relationship with the psychotherapist may be the most important element of treatment.

Mental Health of Parent Is Important

The psychiatric health of the parent (usually mom) is also important. The most difficult case is when the mother has a PD, most often borderline personality disorder (BPD), and the child has a PD. Except in severe cases, we reserve diagnosing an adolescent as having a PD until their later teens or early 20s. With plasticity of the brain, children diagnosed with BPD may significantly improve by age 25 or 30. I have followed a number of patients into their 20s, and when both mother and child are psychiatrically ill, the result is not good. These patients often under function as young adults, never leaving home or finishing school.

When mom has a BPD, she may perpetuate a mild factitious disorder by proxy (Munchausen by proxy). I published an article on this situation, where we evolved into taking a dialectical approach with both mom and adolescent.[1] Dialectical therapy is used with BPD, and with these mothers I call it "dialectical by proxy." Basically, this means we are nonconfrontational, "go with the flow," trying to minimize medical interventions, and maximize psychotherapy. Confronting the BPD parent leads to an angry scene, with the parent (and child in tow) stomping out of the office, never to be seen again. With the milder approach, I have had several children actually separate from the mother after high school, and do reasonably well. Separation is vital if the child is to mature into a relatively healthy adult.

Ease into a School Program

Many children need a tough-love approach and must be pushed to go to school. Others do best with home schooling or when homebound, online education, modified school (limited hours in class), or a hybrid. Home-schooled kids may do reasonably well academically, but they risk ending up being socially isolated. Homebound-schooled adolescents often experience severe anxiety, and not attending school may help exacerbate their social anxiety. Each child's needs differ. Not all schools are flexible, and alternative programs may not be available.

When a homebound child returns to school, it is helpful to ease back into school. I will usually write letters recommending late starts, early release, no gym, etc.—whatever helps. If the adolescent is at least willing to go back to school part time, I will do my part and help facilitate the return to school. This works for some of the children.

The idea is to go from point A (9th grade) to point B (graduating high school). Some children accomplish this by taking the General Educational Development exam. It may take part home schooling, part regular high school, going for two classes in summer—whatever works. If we can help these children progress through high school, and separate them from mom, they usually function better into their late teens and 20s.

Somatizing Disorders

Many children with refractory headaches are somatizers—that is, patients with frequent physical complaints for which no organic basis is found. They tend to visit multiple physicians and other providers. I minimize testing with these patients, and almost never hospitalize them. It is important to move away from the medications and medical establishment, and help these children see themselves as healthy, not chronically ill.

As with adults, active coping (taking responsibility for one's illness) is a key. Pain level itself is not the only predictor of disability in these children. Other predictors include catastrophizing (thinking illness is worse than it actually is), fear of pain, passive (versus active) coping, depression, and anxiety.[2-4] We can work on "dialing down the volume" on catastrophizing, both in the child and parent. I see "catastrophizing by proxy," where a parent may say: "These headaches are the worst anybody has ever had. They are a 12 on a scale of 1 to 10. It is a nightmare. You have to cure them!" Encouraging active coping is a major challenge. We need to have the parent, teacher, therapist, etc., on the same page. If the parent (and child) state: "When you give enough drugs to stop the pain, then he will go back to school," that never works out well.

Summary

My approach to the refractory headache patient has evolved over the years toward a flexible case-by-case approach. I encourage active coping, and always minimize use of medications. I attempt to work with other health care providers ("villagers"), particularly psychotherapists. One goal, outside of helping to decrease the pain, is to gently facilitate a separation of adolescent from parent. Each adolescent with refractory headaches is unique, and requires an individualized approach.

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Case Studies in NDPH: New Daily Persistent Headache

Lawrence Robbins, M.D., and Brooke Phenicie, NP-C

Case history #1, adult: Jack is a 42 y.o. male with no prior history of headaches or migraines and is in good overall health. Two years ago, he awoke with a mild headache, which became severe as the day progressed. He had been experiencing cold type symptoms for about a week, had been under severe stress, and was not sleeping well. Jack now suffers from a moderate daily headache that is continuous, 24/7.

A workup by his GP was completely normal. He visited a succession of doctors: his chiropractor, acupuncturist, physical therapist, dentist, and psychotherapist, all to no avail. He was prescribed various analgesics and headache preventives over the next two years, but found nothing that helped. After two years, a neurologist diagnosed Jack with NDPH. Jack has lost his job due to the head pain, and his marriage is suffering. The next step is to try onabotulinumtoxinA (Botox) injections.

Case history #2, adolescent: Rose is a 17 y.o. female with no history of headaches. She presented with a severe headache that began suddenly three months prior, during finals of her junior year. A perfectionist, Rose is a straight A student who puts enormous pressure on herself. Rose has moderate anxiety, but no depression. She has a history of IBS that worsens under stress. Prior to visiting a headache specialist, she had not had a recent work-up, nor had she seen an ophthalmologist. Her continuous headaches have interfered with school, and she is now homebound.

Her workup, consisting of labs, MRI and an ophthalmological exam, was normal. Topiramate was titrated to 150mg, but it did not help, and produced intolerable side effects. Amitriptyline did help, but Rose gained weight and was very tired. Various abortives were utilized, but none was particularly helpful. A psychologist trained Rose in biofeedback, which was somewhat helpful for her head pain and IBS. Botox injections are being considered.

Introduction

New daily persistent headache (NDPH) is one type of chronic daily headache, along with chronic migraine, chronic tension headache, and hemicrania continua. NDPH is being increasingly recognized as an important type of headache, both because of the frequency and also the refractory nature of the head pain.

Onset and Symptoms

NDPH develops quickly, usually within hours or one day, but within three days the headache must be constant. Many patients remember exactly what they were doing when the headaches began. The pain is usually bilateral, with aching pressure and/or throbbing. The intensity may vary from mild to severe, but tends to be mild to moderate. The headache is usually constant. At least half of patients describe migraine-associated features, such as nausea, phonophobia, lightheadedness, photophobia, etc. Allodynia, often seen in chronic migraine, is present in approximately a quarter of patients. Autonomic symptoms (nasal stuffiness, conjunctival injection, etc.) may occur.

Diagnosis

NDPH is somewhat a diagnosis of exclusion. Infection (including meningitis and sinusitis), mass lesions, subdural hematomas, cerebral venous thrombosis, low or high CSF pressure headaches, arteritis, arterial dissection, post-traumatic, etc., all need to be excluded. Usually the history, along with MRI/MRA, will exclude these entities. There are several newer proposed diagnostic classifications; generally, diagnosis includes:

- at least three months of sudden-onset headache
- no significant remission
- exclusion of other disorders

NDPH is unilateral in a small number of patients, and if this occurs with autonomic symptoms, it may represent a variant of hemicrania continua.

Pathophysiology

While we do not know the pathophysiology of NDPH, CNS inflammation is one possibility. Tumor necrosis factor alpha (TNF alpha) has been implicated in neuro-inflammation. TNF alpha is a cytokine that enhances inflammation. In one study, CSF evaluations of NDPH patients resulted in almost all samples showing an increase in CSF TNF alpha.

Glial cell disruption may play a role; glial cells manufacture CNS cytokines. Glial cells are very sensitive to viral infection and stress; surgery may impact glials as well. Cervical joint hypermobility, along with hypermobility of other joints, may play a role. Patients with NDPH often are tall and thin, with long necks.

Epidemiology

CDH occurs in approximately 3.5% of the population, but the prevalence of NDPH is not known. One study from a headache center concluded that 10.8% of 638 CDH patients had NDPH. A similar study in the pediatric population revealed that, among those with CDH, 13% had NDPH. NDPH may well be more prevalent among adolescents than in adults. Females outnumber males with NDPH by approximately 2.5 to 1.3 Most patients do not have a previous history of headache. A prior history of anxiety or depression is seen in about half of the NDPH patients. 3 After the onset of NDPH, many patients experience depression.

Triggering Events

Approximately 50% of patients have an identifiable trigger. Stress may be a trigger in some patients. Infection, particularly viral, is often cited as a trigger. 1 In one study, Epstein-Barr virus was implicated as an initiating culprit. Exposure to certain toxins may also precede the onset of NDPH. Surgical procedures have occasionally triggered the onset of NDPH. Head injury, even when mild, may be an initial event. Cervical trauma or other pathology, particularly in those who have thin necks with cervical hypermobility, may initiate the onset of NDPH.

Treatment

NDPH is more resistant to treatment than is chronic migraine, which is usually transformed migraine (slow-onset over years). The usual daily preventive migraine medications are given, as they may be helpful for some NDPH patients. These include tricyclic antidepressants (amitriptyline, protriptyline, etc.), anticonvulsants (valproate, topiramate, etc.), anti-hypertensives (beta blockers, calcium channel blockers, etc.), Petadolex (natural butterbur), SSRI's (fluoxetine, sertraline, etc.), SNRI's (duloxetine, venlafaxine, etc.) and muscle relaxants (tizanidine, etc.) OnabotulinumtoxinA (Botox) may be helpful as well; there are no published controlled trials of treatment. Benzodiazepines, particularly clonazepam, have had some limited success. IV DHE is more likely to be of help with chronic migraine. A course of high dose IV corticosteroids, followed by oral steroids, has shown some promise, but the high doses can predispose to serious side effects. IV magnesium may provide short-term relief. Doxycycline, given over several months, may help some patients with NDPH. Greater occipital nerve blocks sometimes are useful, particularly with unilateral headaches.

Outside of medication, psychotherapy is worthwhile for those with anxiety or depression. Biofeedback is helpful for some headache patients. Exercise is always encouraged, as is yoga and Pilates. Acupuncture, physical therapy, or chiropractic may help for some patients.

While the results of treatment may be discouraging, it is crucial to stick with the patient, continue to try different medications or modalities, and not to give up on the NDPH sufferer.

Long-Term Prognosis

Several studies have evaluated long-term outcomes. One study revealed that, after two years with NDPH, about 25% of the patients were free of headache, and 66% had at least a 50% reduction in pain levels. Another study reported that 76% of patients continued to have headaches over time, while 15% remitted; median time to remission was 21 months. 8% had a cyclic form, with a relapsing-remitting pattern. A small study of children and adolescents discovered that 8 out of 28 patients were free of headache within one to two years, while most (20) continued to suffer long-term from head pain.

Conclusion

NDPH is an important category of headache, as it is often difficult to treat, and results in considerable disability. It is unique in that over 50% of patients have an identifiable trigger, although these range from infection to surgery to head trauma. We are just beginning to identify the pathophysiology that leads to NDPH. Treatment of NDPH is scattershot and varied at present; further studies will undoubtedly lead to more effective therapies.

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Heather's Chronic Migraine: an Interactive Case History, Part 1

This column will take you, step by step, through the diagnosis of a complex headache patient with the pseudonym of "Heather."

By Lawrence Robbins, M.D.

New patient "Heather" is a 24-year-old hairdresser with migraines since age 12, which have been slowly increasing. In the last three years she has endured daily headaches. Her mom and sister also have migraines. Her usual daily headache is an aching, throbbing moderate headache, with photophobia. About six times per month Heather has a moderate to severe migraine, lasting one day, with nausea. She has been diagnosed with chronic migraine (CM). Triggers for her more severe migraines include weather changes, stress, and menstrual (1 day prior to her menses).

Heather has also struggled with Irritable Bowel Syndrome (IBS) for much of her life; she has occasional constipation, but diarrhea and cramps are her usual symptoms. She has not been treated for this. She is 5'5", weighs 128, and has, at times, struggled with weight gain. She does not smoke cigarettes.

Besides the daily headache, Heather has associated neck pain, with tenderness in her neck and shoulder muscles. She clenches her teeth, and grinds them, particularly at night while sleeping. She was prescribed diazepam, but says, "I became wired and had a bad reaction on it…"

Heather has not been on daily preventives. She consumes four Extra Strength Excedrin daily, and, for her migraine uses hydrocodone. This dampens the pain but does not help more than 30%.

Psychological Aspects

Heather also has been diagnosed with generalized anxiety disorder and depression. She first became depressed at age 14, and has had mild to moderate chronic depression since age 18. There is a strong family history of anxiety and depression. Her grandmother was hospitalized for possible depression, and an uncle committed suicide. Heather's mom suffers from lifelong depression, and has struggled with alcoholism.

Heather is chronically irritable and somewhat angry; she is prone to bouts of road rage. She has several spells a year which she describes as, "too much energy, where I don't sleep much." In certain seasons, she seems to cycle into worsening depression.

Heather was placed on fluoxetine, and she "was up all night, my mind was going too fast." She was then prescribed Cymbalta, and the same thing happened. Heather also becomes "wired" from certain meds, such as pseudephedrine.

In summary, Heather has: moderate daily headache, with migraines six times a month, plus anxiety and depression, IBS, and neck pain.

QUESTION: Outside of medication, what would you suggest for Heather?

We need to teach Heather about regular sleep habits, not missing meals, avoiding too much caffeine, identifying stresses that may contribute to her headaches, exercise and posture, etc.

In addition, a referral to a good psychotherapist would be beneficial, as would biofeedback by a skilled therapist. Psychiatric referral would be a reasonable choice as well.

For the neck pain, physical therapy may be helpful, at least as far as teaching about exercise and posture. Heather's profession as a hairdresser often will exacerbate neck pain and the headaches, due to the constant arm movements. A dentist who is adept at evaluating TMD may be beneficial for Heather as well.

We do not expect Heather to rush off to the psychologist, psychiatrist, physical therapist and dentist all at once. Because of money and time, most patients carefully select which healthcare professionals they visit. However, it 'takes a village' to treat a complicated pain patient, and I try to send the patient to 'other villagers'.

QUESTION: What type of depression does Heather suffer from?

We need to think about the mild end of the bipolar spectrum. Some 8.6% of migraineurs fit into the bipolar spectrum, according to one study. Heather has a number of features of bipolar, including early depression (age 14), and a family history of depression, suicide and substance abuse. Other indicators are her irritable/angry personality, cyclical depression, spells of too much energy, and poor (bipolar) reaction to certain meds (antidepressants, pseudoephedrine, diazepam). The clinical stakes for missing bipolar are enormous; people like this tend to bounce from antidepressant to antidepressant, with predictably poor results.

QUESTION: What are the initial choices of preventive medication for Heather?

Comorbidities, along with the headache characteristics, guide where we go with the headache meds. Along with the CDH and migraines, Heather fits the mild end of the bipolar spectrum, has IBS (primarily diarrhea), neck pain, and has struggled with weight gain. All of these characteristics figure into our medication choices.

As a headache preventive, topiramate may be a good choice. It will not cause weight gain, and may decrease appetite for some period of time. It may act as a mild mood stabilizer, although studies have been both positive and negative on topiramate as a bipolar medication, and topiramate may certainly exacerbate depression. We would begin with a low dose because headache patients tend to be somatic, and will not tolerate large initial doses, which leads to them quitting the medicine prematurely. My recommendation would be: topiramate, 25mg., one at night for the first 6 nights, then, if tolerated, increasing to 50mg at night. Utilizing the topiramate at night may minimize cognitive side effects and fatigue. Some patients cannot tolerate more than 25mg of topiramate. The usual dose is 50mg to 100mg, although some patients do well on 25mg, while others require 300 or 400mg. per day. The cognitive side effects of spacey feelings and memory problems often limit topiramate's use, as does the tingling sensation in fingers and toes. Primarily due to carbonic anhydrase activity, the tingling is sometimes offset via the use of potassium, either natural or in tablets/powder.

QUESTION: Which abortive meds would you consider?

Most daily headache patients have 2 or 3 abortives; they may have something for milder daily headaches, a migraine medication, and an 'escape' analgesic for the severe migraine. With Heather, we do not want to go down the road of overused daily analgesics, but most patients want and need something for the daily headaches, as well as for the migraine. In Heather's case, we need to emphasize that we do not want to constantly chase the headache all day, but rather use the preventive meds, and non-medication techniques, to decrease the severity.

For Heather's migraines, my recommendation would be sumatriptan, 100mg. tabs. If patients have never used a triptan before, I start with a low dose the first time, such as half of a tablet. Many patients are frightened by the muscle pressure, tingling, and other side effects of the triptans, and we need to test them on a low initial dose. This will improve compliance. With the triptans and other antimigraine abortives, early intervention is crucial; there is an enormous difference between using the triptan in the first half hour, and waiting an hour or more.

For Heather's nausea, we prescribe ondansentron, 8mg., as this is the only antiemetic that is non-sedating. We stop the hydrocodone, except as an "escape" medication, used on a very limited basis.

For Heather's daily headaches, we discontinue the Excedrin, and have her use naproxen, with limited amounts of caffeine. I try and limit caffeine intake to 150mg., or at most 200 mg. a day. She was taking 250 mg. just in her daily dose of four Excedrin, with more in coffee, tea and colas. The idea with daily abortives is to limit caffeine, use the longer acting NSAIDs such as naproxen, and avoid addicting meds.

Initial Prescription

Heather has started on topiramate as a preventive, and sumatriptan as the primary abortive, with naproxen, ondansentron and limited hydrocodone.

QUESTION: What other preventive medicines are possibilities?

When we initially see a complicated headache patient, our list of possible meds takes into account a number of factors, including all of the comorbidities: psychiatric, medical and GI. It is helpful to note these other medicine possibilities in the chart; headache patients call often, as the meds may be ineffective or have side effects. We need to be able to easily switch meds. If you work with other physicians, they should be able to scan the chart and select another appropriate med.

With Heather, other preventive possibilities would be noted in her chart, as follows:

- Petadolex, an excellent evidence-based natural preventive
- lamotrigine, which may be helpful for her mild bipolar depression, although there is less evidence for helping the headaches
- verapamil, which may help the headache, and also the diarrhea with IBS
- gabapentin, which is safe, inexpensive, and easy to use
- sodium valproate could help her bipolar depression, but weight gain is a drawback, and we would need to warn her about risks of pregnancy
- oxcarbazepine, an anticonvulsant with more efficacy for her bipolar than headaches
- ARB's such as Atacand or Benicar. These would avoid the weight gain of the beta blockers.

- muscle relaxants such as tizanidine, etc.

It should be noted in Heather's chart that lithium is a possibility, not for the headaches but for the bipolar issues. Lithium is underused, and many mildly bipolar patients state that they "finally feel normal" once lithium is given. In addition, the atypicals, such as quetiapine (Seroquel), may be useful, not only for Heather's moods, but for the headaches as well.

Drugs that we want to avoid include the tricyclics (amitriptyline, nortriptyline, etc.), as they may exacerbate the bipolar illness and cause weight gain.

If Heather is on adequate mood stabilizing medication, we may be able to utilize antidepressants. The use of antidepressants in bipolar patients is still controversial; for some, they help the depression with no side effects, and in others, even a small dose will trigger hypomania. If Heather is on mood stabilizers, we may be able to add a small dose of an SSRI, or similar med.

Beta blockers are also to be avoided, as we do not want to incur weight gain, and these may exacerbate Heather's depression. If a patient's headaches are improved, but she gains 20 lbs. and is tired from the medicine, it is not the answer in the long run.

QUESTION: What about other abortive possibilities?

For other abortive possibilities, we would note in the chart the following:

1. Other triptans; if sumatriptan does not work out, it is worthwhile to use another triptan. Since these are far superior to our other choices, it is worthwhile to try at least three before giving up on the class.
2. Other NSAIDS (she is on naproxen); NSAIDS are not addicting, and do not cause fatigue.
3. MigraTen; this is a good combination of a mild vasoconstrictor, 100mg caffeine, and acetaminophen. MigraTen fits the bill as a non-addicting or sedating milder medicine, useful for moderate headaches. We need to be careful with the amount of caffeine, however.
4. Dihydroergotamine (DHE) is primarily a venoconstrictor, not arterial, rendering it safer than other ergots.
5. We would also consider other antiemetic meds, such as prochlorperazine. We did prescribe ondansentron, one of the antiemetics that does not cause sedation.

Heather's Second Visit, Six Weeks Later

Heather reports that the topiramate has lessened the frequency of the migraines, and the daily headaches are not quite as severe. However, she is having a difficult time with her memory, and does not feel that she can increase the dose past 50mg. The depression is possibly worse on the topiramate, but she wishes to continue with it, as it 'is the first drug that has decreased how severe my headaches are.'

OTC naproxen helps her to some degree, and she is limiting her caffeine to 150 mg. daily. For the migraines, the sumatriptan helps only 25%, but the ondansentron is effective for her nausea.

Heather has begun to see a psychotherapist, who is teaching her to do biofeedback. She feels that this is helpful. She is exercising 20 minutes daily, on average.

QUESTION: What would you consider as far as Heather's daily preventive meds at this time?

We choose to continue with the topiramate, as it has helped. We cannot increase the dose, due to the cognitive side effects. Because of the depression, which is probably mild bipolar, we add quetiapine (Seroquel). It is important to begin with low doses of quetiapine, as many patients will quit the drug due to sedation. We start with 25mg. at night, and increase to 50mg. after 1 week. The atypicals carry the warning of an increased risk of developing diabetes, and of course, this must be communicated through informed consent. For most patients, I try to utilize as low a dose as is effective. Naturally, we warn Heather about possible sedation and weight gain. Some bipolar patients will have a paradoxical reaction to certain atypicals, and actually experience hypomania, usually mild. For the bipolar, lithium carbonate is a strong consideration.

QUESTION: For Heather's abortives, the sumatriptan was only mildly effective; what would you consider?

I do not want to quit the triptan class, as these are the most likely meds to stop the migraine, with minimal side effects. I would substitute rizatriptan, 1 tab every 3 hours prn, 3 in a day at most. The naproxen, limited to one or two OTC tabs per day, has been useful for her daily headaches, and ondansentron helps her nausea. She has only used 3 tabs of hydrocodone as an "escape" analgesic.

Summary

Heather is currently on: topiramate, 50mg. qhs, quetiapine, slowly increasing to 50mg qhs, and prn she uses: OTC naproxen, rizatriptan, and ondansentron, with occasional hydrocodone as a back-up.

In addition, Heather is watching triggers (regular meals, sleeping on time, etc.), exercising 20 min. per day, and seeing a psychotherapist for therapy and biofeedback.

Two Weeks Later: a Call from Heather

She reports that the quetiapine seems to help her mood the next day, but is sedating, and she cannot take more than 25mg. at night. Rizatriptan has not been helpful, and she had to resort to the hydrocodone for her last migraine.

QUESTION: Would you change meds on the phone at this point, and if so what would you consider?

Since Heather seems to tolerate the low dose of quetiapine fairly well, and it may be starting to help her moods, we would continue this drug. On a mood stabilizer, such as lithium, lamotrigine, or quetiapine, Heather may be able to tolerate a low dose antidepressant.

As far as her abortive medicines, the sumatriptan and rizatriptan have not been particularly effective. At this point, it is worthwhile to try one more triptan, either sumatriptan injections, the most effective form, or zolmitriptan nasal spray. Since she does not want to give herself an injection, we would prescribe the zolmitriptan nasal spray. As usual, the instructions will be to use this early in the headache. This is a very effective triptan that bypasses the GI tract, and has a relatively quick onset of action.

Weight Loss and Exercise

By Lawrence Robbins, MD, and Brooke Phenicie, NP-C

Although weight loss and exercise take considerable effort, there are ways to make it a little easier. And when you make these healthy habits easier, they are more likely to become part of your life for the rest of your life.

Different approaches work for different people, but all require strong commitment. Permanent weight loss is difficult. It takes psychological readiness, and changes in lifestyle and behavior. It never comes about through wishfully thinking, "I need to lose a few pounds and exercise." It comes about via a concerted effort in which exercise and weight control become an important project in your life. You need to get up every morning committed to your program, focusing on how to get your needed exercise and arranging for healthy meals each day.

Key steps to maintaining weight loss are:

- Grazing (eating small meals throughout the day while reducing portions at mealtime).
- Portion control (measure or weigh your food) PORTION CONTROL IS CRUCIAL!
- Count calories or points. (Weight Watchers is a good program, as is the www.sparkpeople.com website.)
- Weigh yourself often.
- Eat foods that are low in fat, sugar and salt, and high in fiber.
- Do NOT diet. Severely restricting food is related to the yo-yo syndrome, in which weight is frequently lost but quickly regained. When you fall off the wagon, get right back on your diet/exercise program; it is crucial to NOT let bad days turn into weeks and months.
- Motivation is a key; dietitians/nutritionists can help. Fitness/health magazines are motivating. One good newsletter is the Nutrition Action Newsletter (www.cspinet.org). Apps such as myfitnesspal are helpful.
- The old Weight Watchers motto to "Move more and eat less" is still relevant.
- Exercise regularly.

Exercise: Just do something

Exercising may decrease headaches. It is certainly crucial for weight loss. To get most of the benefits of exercise, you only need to think of exercising in small chunks of time, even 10 or 15 minutes. Most people are able to fit exercise more easily into their lives when thinking this way. We are looking for a total of 30 daily minutes on average. The more the merrier. Some people do well counting total minutes of exercise from Monday to Sunday, including everything (walking, etc.).

It helps to have a routine, whether it is regular walks, classes or equipment to use at home. A stationary bike is easy to use; you can read or watch TV while riding, and even five or ten minutes at a time will add up. Studies have shown that short intervals of exercise throughout the day can be as effective as doing one prolonged session. I think that the old mantra of getting your heart rate up to a target number, for an intense hour, actually kept people from exercising; the idea is to just do something, anything, for any period of time.

Health clubs are great, and the classes are motivating. Pilates is core work, and is crucial for preventing back pain, and falls, as we age. The Pilates classes, without equipment, are offered at the health clubs, and some park districts. There are also DVD and Cable TV Pilates, but live classes are best. Yoga is also very good, and can help with stress and headaches. Even 5 or 10 minutes of yoga posing is beneficial.

Remaining active throughout the day is also important. People who are moving throughout the day instead of sitting are in better shape than those who sit all day and exercise only at night. Standing at the computer may help the core, and taking frequent breaks from sitting is important.

Many people get into diet and exercise, for a period of time, and then get out of it. Getting back into exercise takes some inertia, such as just walking (or a stationary bike) for 5 minutes. Just do something for a few days, and you will get back into it. Don't worry about going to the club and getting your heart rate up and exercising hard for an hour. Just dive back in with baby steps.

Anxiety in a Headache Patient: Case Challenge

In headache patients, anxiety may increase pain while pain may fuel anxiety.

By Lawrence Robbins, MD, and Brooke Phenicie, NP-C
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History: Caitlin is a 27-year-old woman with a history of migraines and anxiety. She began having separation anxiety at age 5. The patient can remember hanging onto her mother's leg "for dear life" on the first day of kindergarten. Later, at 9 years of age, symptoms of obsessive-compulsive disorder (OCD) began; these included intrusive thoughts, an aversion to germs, and the compulsion to touch everything "equally on both sides." These symptoms waxed and waned over time. By age 15, Caitlin suffered from generalized anxiety disorder (GAD), with intense worrying and feeling "keyed up." The anxiety would, at times, trigger a migraine. Additionally, when Caitlin's headaches were worse, her anxiety also increased.

Over the years, Caitlin found yoga, Pilates, and exercise to be helpful in managing her anxiety. She also noted that cognitive-behavioral psychotherapy was very useful. Biofeedback was "not for her," but she was able to use breathing techniques to calm herself down. As far as medications, she was prescribed fluoxetine (Prozac) and later switched to escitalopram (Lexapro). The selective serotonin reuptake inhibitor (SSRI) helped her anxiety, but not the migraines. She did take alprazolam (Xanax) for acute, severe anxiety.

She was switched to serotonin norepinephrine reuptake inhibitors (SNRIs), starting with duloxetine (Cymbalta) and then desvenlafaxine (Pristiq). These agents helped to treat the anxiety and, to a lesser extent, the migraines. A course of gabapentin did not help the anxiety or the headaches. Caitlin feels that with therapy and medications, she remains anxious but is significantly improved.

Caitlin's history is fairly typical; anxiety may change over time, both in form and in severity. The search for effective medications may take time, as there is no accurate predictor of who will do well with what medication.

What Is Anxiety?

Anxiety is a necessary and universal emotion. With anxiety that originates from a real or perceived threat of danger, one experiences an increase in heart rate, blood pressure, diaphoresis, and other physical accompaniments to anxiety. At times, anxiety comes across as excessive worrying, and this leads to avoidant behavior. Hypervigilance is an excessive focusing of one's attention on a possible danger or perceived danger.

When we think of anxiety, it is usually revolving around a problem or threat in the future. Fear, on the other hand, can be a very intense emotional reaction to a danger or threat that is in the present. We react to immediate dangers with the "fight-or-flight" response. Fear and anxiety, to some extent, are crucial for our existence. Fear allows us to escape from imminent threats; anxiety allows us to prepare for future problems. Anxiety, at least in low or moderate amounts, helps motivate many people to achieve. When someone crosses from moderate to high anxiety, it usually will interfere with the ability to perform.

The triggers for fear and anxiety may be internal or external. With internal triggers, one may have panic attacks that accelerate, feeding on themselves, in part because the associated tachycardia can convey the message that a serious physical problem is imminent. External triggers involve situations that may trigger phobias, or severe anxiety. These may include social situations, crowded or closed-in spaces, tests or other performances, etc. This leads to avoidant behavior, as anxious patients will tend to avoid those situations.

Types of Anxiety

Separation Anxiety Disorder

Patients with separation anxiety disorder have a fear of leaving a close relationship, such as the parent or home situation. Separation anxiety begins in childhood, and may or may not continue later on in life. It may manifest itself for the first time in kindergarten, with the child hanging onto the mother. Approximately 5% of the adult population has had the symptoms of separation anxiety. Separation anxiety may morph into a panic disorder or GAD.

Panic Disorder

Panic attacks occur with a number of physical symptoms that may include feelings of choking, trembling, diaphoresis, racing heart, shortness of breath, chest pain, fears of losing control or dying, numbness, chills or flushing, dizziness, lightheadedness, or fainting. Panic attacks usually reach their peak quickly, and last minutes to 1 or 2 hours. While they may be triggered by situations such as having to speak in public, they often occur without any obvious external trigger. Panic attacks may occur with agoraphobia, which involves a fear of situations where escape is not easy. These include public places and crowds, public transportation, highway driving, being on a bridge, or in an elevator or other enclosed space, being far from home or alone, or being stuck at a party. Agoraphobia such as this may occur without panic disorder.

Generalized Anxiety Disorder

GAD involves excessive worrying, which may be about school, work, family, health, finances, or the outside world. With GAD, most people worry on a daily basis, not just occasionally. To diagnose GAD, the worrying must have been present for at least 6 months. People with GAD don't worry about just one facet of life, but many things. The worry becomes completely out of proportion to the significance of the problems. They also feel the physical aspects of anxiety, such as feeling "keyed up," having concentration problems, insomnia, irritability, anger, or fatigue. Approximately 5% to 6% of the population suffers from GAD. It is more common in women than in men.

Social Anxiety Disorder

Social anxiety disorder, also known as SAD, is common during adolescence, particularly with the onset of dating, parties, and other social events. It may persist into the adult years. Public speaking is difficult for those with SAD, and this and other triggers can lead to avoidant behavior. Approximately 12% of the population experiences SAD at some point.

Obsessive-Compulsive Disorder

OCD often has an onset in early adolescence. The obsessions are intrusive, and distressing thoughts become focused on one or more concerns: germs or other contaminants, a need to have things arranged perfectly, a fear of hurting someone close, somatic (body) obsessions, hoarding, or sexual or religious obsessions. Compulsions are actions that reduce the person's anxiety somewhat, and are triggered by the obsessions. Compulsions can take the form of obsessive checking (particularly things like locks or a stove), repeated cleaning routines, repetition of words, prayers or actions, counting, or arranging objects over and over. As with most anxiety symptoms, OCD may wax and wane over time.

Post-traumatic Stress Disorder
This occurs following one or repeated traumas, such as abuse of various types, a serious accident, combat, being in a fire, etc. Symptoms of post-traumatic stress disorder (PTSD) include reliving the trauma through flashbacks or nightmares, and subsequent avoidance of certain situations. PTSD may lead to feeling detached, or having amnesia for certain parts of the trauma. Hypervigilance may occur, with increased arousal and insomnia, concentration problems, anger, and a marked startle response. Approximately 6% to 7% of the population has had PTSD.

The Limbic System
A propensity to anxiety is a physical, inherited illness, as is migraine. It is not psychological! By viewing certain key structures in the brain, such as the amygdala, one can almost predict who has anxiety. Even at age 5, in a child with separation anxiety, the amygdala is larger than normal and fires more often. Anxiety could almost be termed "the overactive amygdala syndrome."

The amygdala is part of the larger limbic system, which includes the thalamus, hippocampus, hypothalamus, along with the anterior cingulate gyrus and the orbitofrontal cortex. The amygdala warns of incoming dangers, after processing multiple incoming sensory inputs. Amygdala connections are vast, with direct connections to:

1. The hypothalamus, triggering fight-or-flight responses
2. The locus ceruleus (in the pons), increasing the output of norepinephrine, with a resulting rise in blood pressure, heightened response to fear, and level of alertness
3. Various other structures, such as the periaqueductal gray matter, modulating aspects of our fear response. The amygdala regulates the tone of our emotions, and is hyperreactive in anxious patients

The hypothalamus initiates our fear response; when it overreacts, the resultant anxiety is out of proportion to the actual threat. The hypothalamus may trigger an overproduction of corticotrophin release factor, adding to the anxiety response. The thalamus is our integrating relay station, with a vital direct connection to the amygdala. The thalamus controls many brain functions, and its amygdala connection initiates our stress response. The thalamus plays a vital role in regulating sleep and eating patterns, which often are disrupted in anxious patients. The hippocampus is crucial for memory, and it holds the memories that trigger the fear response. The hippocampus is important in the development of PTSD by holding onto the traumatic memories.

Treatments of Anxiety in Pain Patients

Non-pharmaceutical Approaches
Pharmacotherapy is important in treating anxiety, but it is by no means the only treatment. For those with severe pain and psychological comorbidities, "it takes a village" to treat a patient, which may include psychotherapists, yoga or Pilates instructors, biofeedback specialists, etc.

Taking medicine alone is considered passive coping and is not sufficient for those with severe anxiety. People are best off when they exercise regularly, and learn relaxation techniques, whether they are based in yoga, Pilates, tai chi, deep breathing, biofeedback, or meditation. We need to promote this "active coping" as a vital component of treating chronic pain and anxiety. The addition of psychotherapy, primarily cognitive/behavioral, is also important. It is vital to locate an excellent therapist, and for the patient to stick with that therapist for at least 4 to 6 months. While short-term therapy is better than no therapy, we believe that the ideal time frame is 1 or more years. It takes some time to integrate the ideas

of therapy into our lives. Self-help books, while somewhat useful, do not replace a great therapist; neither does talking to a close friend or relative. A great therapist can be life-changing.

Medications for Anxiety

Benzodiazepines

Benzodiazepines are a well-recognized treatment for anxiety, and are best used for acute anxiety, or a panic attack. Alprazolam is the most effective benzodiazepine for panic attacks, and is best used on an "as needed" basis. The lowest effective dose should be used; usual doses are 0.25 mg to 1 mg (start with ½ or 1 of the 0.25 mg tablets) as needed. Alprazolam should be limited and the patient closely monitored for overuse. Limited quantities should be prescribed.

At times, in a minority of patients, daily benzodiazepines are warranted. The usual situation is when the patient cannot tolerate non-addicting approaches, such as the antidepressants. For insomnia, the occasional patient will only do well with a benzodiazepine, such as clonazepam (Klonopin). Diazepam (Valium) has anti-anxiety and muscle-relaxant properties. Patients must be warned of the dangers of overuse and of combining these agents with alcohol or opioids, as well as the difficulty patients may encounter on withdrawal. For some highly anxious patients, the only medication tolerated is a benzodiazepine.

Antidepressants: Tricyclics

The older tricyclic antidepressants (TCAs) are more useful for certain types of pain (particularly headaches) than are the SSRIs or SNRIs. We will often use a TCA in anxious pain patients in an attempt to treat both their anxiety and migraine in order to minimize medication use. The prototype tricyclic is amitriptyline (Elavil). Amitriptyline is inexpensive, and is useful for chronic daily headache, migraine, neuropathy, fibromyalgia, etc. We recommend that clinicians start with very low doses of amitriptyline, taken at night, 5 mg (½ of a 10 mg tablet), slowly increasing to 20 or 25 mg per day. Doses may be increased to 100 mg (or more), but side effects may limit its usefulness. These include sedation, dry mouth, constipation, dizziness, weight gain, and urinary retention. Other TCAs include nortriptyline, a milder form of amitriptyline; doxepin, which has fewer side effects and is helpful for insomnia; and protriptyline (Vivactil). Protriptyline is one of the few TCAs that does not cause weight gain, but anticholinergic effects limit its use.

Antidepressants: SSRIs and SNRIs

Because of the potential for adverse events, the newer SSRIs and SNRIs are often favored over the older TCAs. The major SSRIs differ somewhat in their side effect profile. Some patients do extremely well with one SSRI, but not with another. The most common side effects include nausea, spaciness, drowsiness or fatigue, dry mouth, anxiety, insomnia, decreased libido, impotence, asthenia, sweating, constipation, tremor, diarrhea, and anorexia. In addition, weight gain may be a major problem. In fact, weight gain and sexual side effects are the most common reason to discontinue an SSRI. Any of the SSRIs can decrease motivation.

Since many of the adverse events are dose related, one key to minimizing side effects is to begin with low doses—"start low and go slow" (Table 1). Minimizing the dose can, for instance, decrease the sedation or sexual side effects. Compliance is enhanced when the SSRIs are slowly titrated. The initial anxiety seen with SSRIs often abates if low enough doses are used.

Table 1. Keys to Using Antidepressants in Comorbid Anxiety and Pain Patients

- Start with very low doses. This minimizes sedation and anxiety and increases compliance. If the patient is bipolar, SSRIs are best avoided.
- If patients are warned about the initial anxiety that may occur with SSRIs, they are more likely to be compliant and stay on the medication.
- For most headache patients, lower doses are utilized than for severe depression.
- If one SSRI does not help or causes side effects, it is often worthwhile to try another. Patients have widely differing responses to these medications.
- Slowly withdraw patients in order to avoid withdrawal syndrome.
- If the headaches are exacerbated, discontinue the SSRI.
- Paroxetine (Paxil), fluoxetine (Prozac), and duloxetine (Cymbalta) have more drug interactions than the others. These are all cytochrome P450 2D6 inhibitors.

At times, we will use a combination of older TCAs (usually at night) and SSRIs in the morning. One of the SNRIs, duloxetine, has several pain and GAD indications, making it a useful tool for treating the comorbid migraine patient. Table 2 highlights the more effective SSRIs and SNRIs for mood and headaches listed below.

Table 2. Major SSRIs and SNRIs for Anxiety in Pain Patients

SSRIs

Drug Name (Brand)	Formulation	Usual Dosage	Comments
Citalopram (Celexa, generic)	Oral tablet	1/2 of a 20 mg tablet/d for 4-6 d (initial dose); may go up to 40 mg/d	Effective and well tolerated antidepressant. Mean terminal half-life is ≈35 h; has a clean drug–drug interaction profile (ie, cytochrome P450 enzymes).Side effect profile similar to other SSRIs.
Escitalopram (Lexapro)	Oral tablet	1/2 of a 10 mg tablet/d for 4-6 d (initial dose); limit to 30 mg/d	Well tolerated with a favorable side effect profile similar to other SSRIs. Fairly clean drug–drug interaction profile.
Fluoxetine (Prozac, others)	Oral tablet, oral pulvule, oral liquid	5 or 10 mg/d for 4-10 d (initial dose); limit to 80 mg/d	Well-established, long-acting SSRI; half-life is 4-6 d— an advantage in avoiding SSRI withdrawal syndrome. Important to start with low doses so patients are less likely to discontinue the medication.
Paroxetine (Paxil, generic)	Oral tablet and oral CR tablet	Oral tablet: 1/2 of a 10 mg tablet/d (initial dose); limit to 30 mg/d Oral CR tablet: 12.5 mg tablet/d (initial dose); limit to 25 mg/d	Well tolerated with no active metabolite and a shorter half-life of 21 h. Discontinue slowly to minimize withdrawal symptoms, which can include flu-like symptoms, malaise, dizziness, and asthenia. Adding fluoxetine may help wean patient off.
Sertraline (Zoloft, generic)	Oral tablet	1/2 of a 25 mg tablet/d (initial dose) Average dose for antidepressant: 75 to 150 mg/d Average dose for headache: 50 mg/d	Shorter half-life (26 h). Patients can usually stop sertraline for 1-2 d and alleviate sexual side effects. Due to short halflife, withdrawal syndrome is occasionally seen.

Vilazodone (Viibryd)	Oral tablet	5 or 10 mg tablet/d (initial dose); up to 40 mg/d	Newer SSRI with dual mechanism of action. Is well tolerated, and may have lower incidence of weight gain and sexual side effects.

SNRIs

Desvenlafaxine (Pristiq)	Oral capsule	50 mg capsule/d (initial dose); up to 100 mg/d	Highly effective and tolerable antidepressant. Useful in headache patients who have concurrent anxiety/depression. Side effects include nausea, constipation, somnolence, dry mouth, dizziness, insomnia, and agitation. At lower doses, is classified as an SSRI.
Duloxetine (Cymbalta)	Oral capsule	20 or 30 mg capsule/d (initial dose); 60 mg/d is usual dose for depression	Very effective antidepressant and has 3 FDA pain indications. May benefit both headache and anxiety/depression. Side effects include nausea, dry mouth, anxiety, fatigue, lethargy, sexual effects, and weight gain. Use with caution in patients with glaucoma.
Venlafaxine (Effexor XR, generic)	Oral capsule	37.5 mg capsule/d (initial dose); 75 or 150 mg/d is usual dose for depression	Highly effective and tolerable antidepressant. Useful in headache patients who have concurrent anxiety/depression. Side effects include nausea, constipation, somnolence, dry mouth, dizziness, insomnia, and agitation. At lower doses, is classified as an SSRI.

The Major SSRIs
These are more effective for moods than for headaches.

Fluoxetine (Prozac, generic) is available in 10, 20, and 40 mg pulvules; 10 mg scored tablets; or liquid (20 mg/5 mL). Prozac Weekly is a once per week capsule, equal to 20 mg daily. Fluoxetine is the prototype SSRI, having been used in tens of millions of people. Fluoxetine is a long-acting SSRI with a well-established track record. Its elimination half-life is 4 to 6 days, but the active metabolite, norfluoxetine, has an elimination half-life of 4 to 16 days. The long half-life is generally an advantage in avoiding the SSRI withdrawal syndrome. It is important to start with low doses of SSRIs; 5 or 10 mg of fluoxetine is a good starting point. Many patients report initial anxiety (or even panic) from SSRIs, and if they are on a low enough dose, they are less likely to discontinue the medication. Patients can begin with ½ a tablet of 10 mg fluoxetine. Over 4 to 10 days, the dose may be raised to 10 or 20 mg. The effective dose for migraine or tension headache varies widely, from 5 mg per day to 60 mg (or more). Formal studies on fluoxetine for headache prevention have yielded mediocre results. Most patients are on 20 mg daily. Milder tension-type headache often responds to low doses (10 or 20 mg). As is true with TCAs, lower doses of SSRIs are used for headache than for major depression. In some patients, SSRIs actually exacerbate headaches. Fluoxetine is an inhibitor of the cytochrome P450 (CYP450) 2D6 system, and to a lesser extent, CYP450 3A4.

Sertraline (Zoloft, generic) is available in 25, 50, and 100 mg scored tablets. Sertraline is somewhat shorter-acting; elimination half-life is 26 hours of the parent drug and 62 to 104 hours of the active metabolite. Because the half-life is shorter than with fluoxetine, patients are occasionally able to stop sertraline for 1 or 2 days and alleviate the sexual side effects. However, with the shorter half-life, withdrawal syndrome is occasionally seen with sertraline. I usually start with 25 mg, or ½ of a 25 mg tablet, and slowly increase; the average antidepressant dose is 75 to 150 mg, but the usual headache dose is approximately 50 mg. While many patients are on 100 mg or more for headaches, most patients are maintained on lower doses. The cost of the 50 mg and 100 mg tablets is approximately the same. In higher doses, sertraline is a CYP450 2D6 and 3A4 inhibitor.

Paroxetine (Paxil, generic) is available in 10, 20, 30, and 40 mg tablets. Paxil CR (controlled release) is available in 12.5 and 25 mg doses. The elimination half-life is 21 hours, with no active metabolite. Paroxetine is generally very well tolerated. I usually begin with ½ of a 10 mg tablet and slowly increase to 10 or 20 mg; many patients need 30 to 60 mg for depression. Another option is starting with 12.5 mg CR and titrate as needed to 25 mg CR. It is important to stop paroxetine slowly in order to minimize withdrawal. Paroxetine (SSRI) withdrawal consists of one to several days (and occasionally longer) of flu-like symptoms, malaise, dizziness, and asthenia. This often goes unreported to the physician. Managing the withdrawal can be difficult; at times, the addition of fluoxetine may help in weaning off of the short-acting SSRI. Paroxetine is a potent inhibitor of the CYP450 2D6 system and, to a lesser extent, 3A4.

Citalopram (Celexa, generic) is available in 20 and 40 mg tablets, which are scored. The mean terminal half-life is about 35 hours. Citalopram has a clean profile with regard to CYP450 enzymes. It has been an outstanding antidepressant with a very good track record, and is well tolerated. Side effects are similar to the other SSRIs. As always, we start with low doses, half of a 20 mg tablet for 4 to 6 days, then progress to 20 mg per day. Withdrawal symptoms have been unusual with citalopram. Its use has mostly given way to escitalopram, but, due to its lower cost, citalopram is useful.

Vilazodone (Viibryd) is a newer SSRI with a dual mechanism of action. Vilazodone is well tolerated, and patients may have fewer problems with weight gain and sexual side effects. It is available in 10, 20, and 40 mg tablets. We start with ½ or one of a 10 mg tablet, and slowly increase to 20 or 40 mg.

Escitalopram (Lexapro) is a newer, more selective version of citalopram and has been fairly well tolerated. It is metabolized primarily by the liver. Escitalopram has a favorable side effect profile, but side effects are similar to the other SSRIs. Escitalopram is available in 10 and 20 mg tablets. We start with ½ of the 10 mg tablet for 4 to 6 days, and then increase to 10 mg daily. Withdrawal symptoms are relatively unusual with escitalopram; it is fairly clean as far as drug interactions. Escitalopram has risen to be one of the most prescribed antidepressants in the United States.

The Major SNRIs

Venlafaxine (Effexor XR) and Desvenlafaxine (Pristiq) are major SNRIs. The long-acting venlafaxine is available in 37.5, 75, and 150 mg doses. Venlafaxine has been an outstanding antidepressant because of efficacy and tolerability. A generic is available, but does not consistently work as well. Desvenlafaxine is a newer form of venlafaxine, which is very well tolerated. It is available in 50 and 100 mg doses, and is usually started at 50 mg; the final dose ranges from 50 to 100 mg per day.

Basically, venlafaxine and desvenlafaxine are SSRIs at low doses; at higher doses, levels of norepinephrine, rather than dopamine, are affected. They are very well tolerated, with less weight gain and sexual side effects than some of the other antidepressants. Venlafaxine has few interactions with CYP450 enzymes, rendering it a fairly clean medication. We usually begin with 37.5 mg and progress to 75 mg, with a typical dose in headache patients being 75 mg or 150 mg. Effexor XR is particularly well tolerated. It is very useful in headache patients who have concurrent anxiety and depression. Sustained elevation in blood pressure may occur at higher doses, particularly 250 mg or more per day. The lower doses have not increased blood pressure. While headache is a potential side effect of venlafaxine and desvenlafaxine, it has been no more so than the rate of placebo in studies. Nausea, constipation, somnolence, dry mouth, dizziness, insomnia, and agitation are seen more than in placebo. However, if doses remain low, venlafaxine and desvenlafaxine are well tolerated. While venlafaxine and desvenlafaxine are less effective than TCAs for pain or headache, their efficacy in anxiety and depression, and their tolerability, render them extremely useful medications.

Duloxetine (Cymbalta) has three FDA pain indications, and is a very effective antidepressant. Duloxetine increases both serotonin and norepinephrine. It is available in 20, 30, and 60 mg capsules. Duloxetine may be helpful for headache, as well as for anxiety/depression. The usual dose is 60 mg daily for depression; starting dose is 20 or 30 mg, increasing over several days to weeks. Side effects include, among others, nausea, dry mouth, anxiety, fatigue, lethargy, sexual effects, and weight gain. Use with caution in patients with glaucoma. Duloxetine is a moderate CYP450 2D6 inhibitor. It has been much more effective for moods (including anxiety and depression) than for pain.

Miscellaneous Medications

In addition to antidepressants and benzodiazepines, various other medications are useful on occasion. For those migraine patients on the bipolar spectrum, antipsychotic medications, such as quetiapine (Seroquel) and aripiprazole (Abilify), are often used. These two medications can be particularly helpful for the management of anxiety and depression.

Certain anticonvulsant agents may be of benefit. Gabapentin increases the neurotransmitter γ-aminobutyric acid (GABA), which calms the brain. Gabapentin may decrease certain types of pain, and

some patients find it helpful for anxiety or insomnia. Pregabalin (Lyrica) is a newer form of gabapentin, and may be beneficial.

Muscle relaxants are useful in some anxious patients. Preference is given to the non-addicting muscle relaxants, such as cyclobenzaprine. These may be helpful for associated insomnia.

Conclusion

Anxiety is commonly encountered in pain and headache patients. Like migraine, anxiety is an inherited physical condition. In headache patients, pain may fuel anxiety, and anxiety may increase the pain. With medications, the antidepressants remain the mainstay of preventive treatment; the benzodiazepines are used sparingly. A variety of non-medicine approaches should also be used in treatment, such as psychotherapy, yoga, exercise, etc. For quality of life, it is crucial to treat anxiety and other psychiatric comorbidities in addition to treating the pain.

Attention Deficit Hyperactivity Disorder and Patients with Pain

A growing number of patients with chronic pain are presenting with ADHD. Clinicians need to understand how the disorder is diagnosed in adults, as well as how to balance various medications required to treat both ADHD and pain.

By Lawrence Robbins, MD, and Brooke Phenicie, NP-C

Along with anxiety and depression, attention deficit hyperactivity disorder (ADHD) is a common comorbidity among patients with chronic pain. Although most commonly diagnosed in childhood, ADHD is seen in approximately 4.8% of adults.[1]

ADHD has become a well-recognized and validated syndrome, known for the havoc it can create in patients' lives. The public is increasingly aware of ADHD, and more of our patients arrive at the clinic with that diagnosis. *The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* criteria for ADHD will be amended in the upcoming *DSM-V*; the current criteria relate primarily to children and adolescents and are not entirely applicable to an adult population. Because more patients carry the diagnosis and are on ADHD medications (primarily stimulants), it is important for pain physicians to be aware of the consequences of the disorder. In addition, it is helpful to be aware of interactions between ADHD and pain medications.

Diagnosis of ADHD in Adults

The diagnosis of ADHD includes the patient's history along with corroborating evidence: educational records and history, input from family or significant other, and so forth. In my experience, most patients who carry the diagnosis of ADHD from childhood have been correctly diagnosed; although there is occasional overdiagnosis of ADHD, underdiagnosis remains more prevalent.

The *DSM-IV* criteria for the diagnosis of ADHD require that the symptoms have lasted for at least 6 months.[2] As noted, the current criteria do not always reflect the adult patient with ADHD. For example, the three primary features of ADHD (attention, hyperactivity, and impulsivity) change over time. Many children and adolescents "lose" the "H" (hyperactive) portion of ADHD as they approach adulthood, and present as the inattentive type. Therefore, using hyperactivity as a measure of ADHD may not be valid in adults.

In addition, ADHD adversely affects adults in their family and work lives; these effects are not addressed by the current criteria. The age of onset, usually listed as before 7 years of age in the *DSM-IV*, may not be accurate when assessing adults, and adults' recall of the exact age of onset is often inaccurate. In the *DSM-V*, it is possible that the age of onset criterion for adult ADHD may either be dropped or amended to state that symptoms must have begun by age 15 or so.

In children, input from parents and teachers is crucial. In adults, we often use patient recall for assessment, in addition to speaking with others who know the person well. There are pitfalls in assessing adults; for example, we must not compare the patient with a high-functioning, high-IQ peer group, but

rather with average individuals. In addition, particularly in college students, the desire to excel on examinations or improve scores does not qualify as a diagnosis of ADHD.

Mood disorders may cause an attention/concentration problem in adults, leading to an inappropriate diagnosis of ADHD. However, most patients with ADHD do have associated psychiatric comorbidities, such as anxiety or depression. Many individuals who fit on the bipolar spectrum can have concurrent ADHD. It is important to assess patients for all of these conditions.

One objective test that we have found useful is the Adult Self-Report Scale (ASRS),[3] which is an 18-item questionnaire. The first nine questions relate to attention, the remaining nine to hyperactivity. Using the first nine questions gives the clinician an easy screen for ADHD and requires only minutes to administer. The attention portion of the ASRS gives a score of 0 to 36, with 36 being the most severe. This scale or similar ones, along with the clinical and educational histories, helps to determine the diagnosis.

An important question to ask the patient is, "How difficult is it for you to do boring tasks?" People with ADHD have great difficulty with boring material. To aid the diagnosis, I often have the patient read books or other materials on adult ADHD so that they can provide better-informed input into the diagnosis.

ADHD and Impairment

Adult patients with ADHD often are impaired in several categories. They may have done poorly in school, leading to problems with their work and career. Home life is adversely affected, with problems fulfilling daily responsibilities. Relationships are negatively affected by ADHD, and family life often falls apart as a result. The severity of childhood/adolescent ADHD is an accurate predictor of impairment as an adult. Young children who are constantly restless and cannot wait their turn in line, for example, often show more impairment as young adults. ADHD increases the likelihood of driving accidents and also of drug or alcohol abuse. It is probably not true that ADHD allows one to excel in certain areas; the evidence speaks more for impairment than for any positive outcome for those with ADHD, particularly if it is not treated.

The associated psychiatric comorbidities add to impairment, particularly if they are not treated. These include anxiety, depression, bipolar depression, and substance abuse.

The evidence is strong for treating ADHD. Compared with treated patients, those who remain untreated are at greater risk, at age 20 to 25, for drug abuse, accidents, joblessness, and jail. The clinical stakes for underrecognizing and undertreating ADHD are enormous. If impulsivity does not improve by the early 20s, it is a poor prognostic indicator for how the patient will do over time.

ADHD and the Patient with Pain

ADHD complicates the lives of patients with pain. The patient struggles with functional impairment due to pain, and ADHD adds to this dysfunction. Education often suffers because of pain; students take longer to complete their degree, and the addition of the negative impact of ADHD can make completion impossible. Family life is adversely affected, as spouses may tire of the burden of pain complaints, along with the various ADHD symptoms. Chronic pain often leads to performance issues at work or joblessness; ADHD only accentuates this problem. It is not uncommon for patients with chronic pain and ADHD, in combination with anxiety and depression, to be underfunctioning in a number of areas.

ADHD Medications

"First-line" medications for ADHD are stimulants.[4-6] The most commonly used stimulants include methylphenidate (Concerta, Ritalin, others), dextroamphetamine (Dexedrine, others), amphetamine and

dextroamphetamine (Adderall), and lisdexamfetamine (Vyvanse). The longer-acting forms are Adderall XR, Vyvanse, Ritalin LA, Focalin XR, Daytrana, and Concerta. Side effects of these agents include, among others, anxiety, insomnia, tachycardia, and, occasionally, increased headache. The stimulants have mild analgesic effects and in some patients may be an adjunct for the pain. In addition, some patients with depression find that the stimulants act as an adjunct for the depression, whereas in others they may actually exacerbate depression. Fatigue is a common comorbidity encountered in patients with pain, and stimulants may help their energy level during the day. In addition, the anorexiant effects are beneficial for some patients with pain, as obesity and weight gain are commonly encountered among this population.

The stimulants may improve attention, energy level, pain, and depression, as well as decrease appetite. However, many patients cannot tolerate the adverse effects of stimulants. In addition, patients with pain are usually on various medications, with possible interactions. For instance, these patients often take antidepressants, with resulting tachycardia when combined with stimulants. When patients with pain are taking daily opioids, adding a stimulant contributes another potentially addicting medication. Fortunately, addiction to stimulants among adults with ADHD is uncommon.

When stimulants are not appropriate or are not tolerated, various "second-line" medications can be tried for ADHD. The α2-adrenergic agonists (guanfacine ER [Intuniv], clonidine [Kapvay]) are primarily used in children and adolescents. Various antidepressants have been successfully used for ADHD. These include the older tricyclics (desipramine, nortriptyline), as well as bupropion. These may be appropriate with concurrent anxiety or depression. Atomoxetine (Strattera), a selective norepinephrine reuptake inhibitor, is used as a second-line medication for ADHD and is very similar to the tricyclic desipramine, which also increases norepinephrine. Although these medications are not as effective as the stimulants, they offer several benefits, including the advantage of being nonaddictive, and, when used as once-daily medications, being long acting.

Nonmedication Treatments

In addition to medications, we often refer patients to psychotherapy. Although therapy does not improve attention itself, the patient benefits in a number of ways. These include receiving help with associated anxiety/depression, family life, relationships, organization, and work life. A good therapist who is acquainted with pain and ADHD can play a crucial role in improving a patient's functioning and quality of life.

It is important to work on sleep issues and diet. In addition, as with almost all patients, we supplement with at least 2,000 units of vitamin D3. We stress the role of exercise, advising patients to try to build up to 20 to 30 minutes daily on average.

Conclusion

ADHD is commonly encountered, and is seen in 4.8% of adults. The various symptoms complicate the lives of patients with pain. The clinical stakes for not recognizing ADHD are enormous; patients often underperform at work, have poor family relationships, and are at increased risk for substance abuse. Treatment with medications, primarily stimulants, improves quality of life and functioning. In addition, psychotherapy plays a role, as does stressing the role of sleep, nutrition, and exercise.

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