Management of primary headache: Serendipity and science

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ABSTRACT

Most patients find some relief with current agents, even though a poor understanding of the causes of chronic primary headache limits prophylaxis and treatment. The author reviews current preventive and treatment strategies for migraine, chronic tension headache, cluster headache, and substance withdrawal headache.

We can reduce attack frequency by 50% in two thirds of patients

WE CAN OFFER some degree of relief for most patients with chronic headache, even though we cannot offer definitive prophylaxis and treatment.

While we wait for research to shed more light on the causes of migraine, chronic tension headache, cluster headache, and substance withdrawal headache, we need to rely on what both serendipity and science have provided. This article capsulizes current management of the main types of primary headache (TABLE 1).

MIGRAINE

Migraine is the most common type of chronic primary headache. It most often strikes in the peak productive years, with significant economic impact. Researchers are looking into new pathophysiological areas (see "Migraine pathophysiology: the search for new therapeutic targets," page 908).

*The author discusses therapies that are either investigative or not yet labeled for the use under discussion.

Prevention

Of the various agents we now use to prevent migraine attacks, most have similar efficacy: we can offer about two thirds of our patients a 50% reduction in frequency, which is not bad, but neither is it great.

Beta-blockers. Propranolol and timolol are the only beta-blockers currently approved by the US Food and Drug Administration (FDA) for migraine prophylaxis, but all beta-blockers—except those with intrinsic sympathomimetic activity, such as pindolol—work essentially the same way. They differ in convenience, cost, and tolerability. I prefer once-daily formulations.

Calcium channel blockers. Verapamil is probably the most used calcium channel blocker for migraine. The others have not been well studied. Flunarizine is used in Europe, but parkinsonism is a potential side effect.[1]

Nonsteroidal anti-inflammatory drugs (NSAIDs) can also be effective, with aspirin probably the least so.

Anticonvulsants. Valproic acid was recently approved by the FDA for migraine prophylaxis. It is a teratogen, which limits its usefulness in women of childbearing age.[2] Other anticonvulsants under study are more expensive and may be less well tolerated.[3]

Alternative prophylaxis

Vitamin B_2. A Belgian study of high-dose vitamin B_2 (riboflavin, 400 mg/day)[4] showed effective frequency reduction after 3 months.

Intravenous magnesium has shown modest efficacy.[5]

Botulinum toxin. Patients are asking about botulinum toxin. Plastic surgeons reported that after chemical face-lifts many patients noticed less frequent migraines.

TABLE 1

Comparison of clinical features of primary headaches

	MIGRAINE	CHRONIC TENSION HEADACHE	CLUSTER HEADACHE
Prevalence	6% of men 18% of women Female-male ratio is lower before puberty and after menopause Peak prevalence ages 25 to 55	3%–4% of the general population Onset in teens to 30s	0.1% of men 2 to 6 times more common in men Onset during 20s to 50s Tall, slender smokers with leonine facies
Frequency	Intermittent, 1–4 times per month	Daily or nearly daily	1–4 times daily over 4–16 weeks Remission for 6–12 months
Duration	4–72 hours	Constant	15 minutes to 2 hours
Intensity	Moderate to severe, increases with exertion	Mild to moderate	Severe
Character	Pounding or throbbing, typically unilateral	All over the head Swelling Weight-like or vise-like pressure	Always unilateral and orbital Excruciating burning or stabbing pain
Symptoms	Photophobia in 90% Phonophobia Gastrointestinal upset ranging from anorexia to vomiting "Aura" in 10%–20%, lasting about 20 minutes, with brain dysfunction manifesting as vertigo, dysarthria, visual disturbances; headache usually follows within 1 hour	Neurovegetative labile moods Appetite or weight change Fatigue Sleep disturbance Disturbed memory or concentration	Parasympathetic overactivity, all ipsilateral: lacrimation, red conjunctiva, scleral injection, nasal congestion and drainage, ptosis and miosis of the eye
Triggers	Letdown after a stressful event Food (chocolate, aged cheeses, red wine) Changes in sleep Skipping meals Hormone fluctuations Changes in weather	Stress Lack of sleep	Typically strikes 90 minutes after falling asleep

Clinical trials have shown, however, that it does not work much better than placebo,[6] and insurers are not likely to cover the $1,000 treatment.

Feverfew is an herb used for prophylaxis in England, but the plant grown in the United States has much less active agent than its British cousin, so I do not recommend it.

Treatment of acute migraine

An important caveat when interpreting studies of the treatment of acute migraine is that the term "pain relief" means that pain has gone from severe or moderate to mild or none. We should keep in mind, however, that the "70% pain relief" used in many studies is an arbitrary and artificial measure that does not

Migraine pathophysiology: The search for new therapeutic targets

WE DO NOT KNOW what actually happens during a migraine attack, but several theories have now been backed up with research.

In a German study (Weiller C, May A, Limmroth V, et al. Brain stem activation in spontaneous human migraine attacks. Nat Med 1995; 1:658–660), positron emission tomographic scans taken during an attack in nine patients with right-sided migraine showed pain activation in two areas: the anterior cingulate cortex and the serotonin-rich brain stem areas of the raphe nuclei, locus ceruleus, and periaqueductal gray matter. After medication, when the migraine pain had stopped, the brain stem areas remained activated while the anterior cingulate was no longer "lit up." This led researchers to believe that the serotonergic neurons in the brain stem are where migraine is generated.

Once the migraine train is rolling, the cause of pain is dilation of the meningeal blood vessels outside the brain. This dilation activates branches of the trigeminal nerve surrounding the dural blood vessels. This causes release of neuropeptides. The trigeminal nerve signal travels through the trigeminal nucleus caudalis to the thalamus, resulting in pain sensation. These pain pathways may provide a basis for new therapies, such as stopping dural dilation by using vasoconstrictors.

Try triptans first in migraine patients unable to work

take into account nausea, light sensitivity, functionality, or other symptoms.

Serotonin receptor agonists (5-hydroxytryptamine 1B/1D agonists, or triptans) relieve migraine pain within 2 hours in up to 70% of patients. However, these drugs are vasoconstrictors and so must be used with caution in patients with vascular or coronary artery disease. The Holy Grail of acute migraine therapies is a drug that targets pain transmission without vasoconstriction. The triptans studied so far have not shown these characteristics.

Keeping the above caveat in mind, comparisons of the oral triptans rizatriptan, sumatriptan, and zolmitriptan do not show much difference in pain relief at 2 hours. Rizatriptan seems to outperform the other two in terms of the number of patients pain-free at 2 hours. Naratriptan has a longer half-life, a slower onset of action, and lower efficacy rates (in pain relief) at 2 hours compared with the other triptans.

Fiorinal and Fioricet, which contain butalbital, caffeine, and aspirin or acetaminophen, are commonly prescribed for migraine, but no controlled studies support their use in migraine.

In patients moderately disabled by migraine, start with high-dose NSAIDs, isometheptene, or an oral triptan. If the patient has had success with ergots, I see no need to prescribe a new agent. For infrequent attacks that respond well to analgesics, codeine-containing preparations should not pose a problem.

It might be worth informing patients that some FDA-approved over-the-counter analgesics (eg, Excedrin Migraine, Motrin Migraine) are exactly the same as the regular product, but with new packaging and a higher price. Because of their lower doses, they probably are not as effective as generic high-dose NSAIDs.

In patients significantly disabled by migraine (unable to work), triptans should be the first-line treatment, orally, intranasally, or subcutaneously. Dihydroergotamine, with or without an antiemetic, can also be effective. For patients who have not been able to sleep for 1 or 2 days, intravenous prochlorperazine will reduce nausea and induce sleep; however, patients cannot function after receiving the drug.

Prolonged attacks. Corticosteroids are useful on rare occasions of prolonged migraine. Their effectiveness is probably related to neurogenic inflammation. Intranasal lidocaine has not been found to be effective clinically.

CHRONIC TENSION HEADACHE

Chronic tension headache is very difficult to treat because we do not yet understand its pathophysiology. Some experts believe that it is a central nervous system manifestation of what started as an episodic tension headache of musculoskeletal origin, and that minor nonnociceptive stimuli can trigger pain.

We use NSAIDs, antidepressants, and, to a much lesser extent, muscle relaxants, but we have few clinical studies to back up therapies.[7] A sedating or nonsedating antidepressant can be selected on the basis of how well the patient is sleeping.

No treatments are very effective in aborting acute attacks. However, we should avoid giving habituating drugs in patients with daily attacks; therefore, NSAIDs and muscle relaxants are the best of poor options.

Nonpharmacologic treatments

Biofeedback, guided imagery, relaxation training, and perhaps physical therapy can be useful,[8] especially as adjuncts to drug therapy. We should not consider them merely as a last resort after drugs have failed.

Biofeedback and relaxation training are not just last-resort therapies

CLUSTER HEADACHE

Cluster headache is a severe and devastating disorder. About 80% of patients are middle-aged men who smoke. These unilateral, cyclic headaches produce severe stabbing or burning pain.

Because symptoms also include ocular changes and unilateral nasal congestion and discharge, cluster headache is often mistaken for sinus infection: patients go through courses of antibiotics, with the second or third course "working" when the cycle subsides naturally.

The few clinical studies of this disease do little to illuminate it. It is difficult to know if a therapy is effective or if the patient simply reaches the end of a cycle.

Preventing attacks

Verapamil is the drug of choice for prophylaxis of cluster headache. Methysergide, an ergot derivative and vasoconstrictor, has a variety of adverse effects.

Acute therapy

Oxygen is by far the drug of choice for the treatment of acute attacks: 10 L/minute by face mask for 10 minutes, with the patient sitting up, is the usual regimen. It aborts 70% to 80% of attacks and is the safest therapy, with one important caveat: we need to warn patients not to store oxygen where they smoke. Because of the large volumes required, portable oxygen is not practical.

Corticosteroids (40 to 60 mg, tapered over 4 weeks) can bring relief in 1 or 2 days[9] but are less effective and more dangerous for the 10% of patients who have attacks every day for years, rather than a cyclic pattern. As steroids are tapered, attacks can recur; combining prednisone with verapamil may provide long-term benefit.

Valproate. Only a few small studies have found valproate beneficial in cluster headache.[10] Adverse effects include drowsiness, tremor, weight gain, gastrointestinal upset, and perhaps liver dysfunction.

Lithium. For chronic cluster headache that either partially responds or does not respond to verapamil, lithium alone or in combination with verapamil can be helpful, although the combination increases the risk of lithium toxicity.

Baclofen. Based on a small pilot study that showed relief in six of nine patients,[11] I have given baclofen in chronic cases that have not responded to any other drugs.

Subcutaneous sumatriptan brings relief within 15 minutes for about 50% of patients. But this is a vasoconstrictor and costs $45 per injection, which limit its long-term use and its use in patients at risk for vascular and coronary artery disease. When oxygen is unwieldy, such as during travel, injectable sumatriptan or sublingual ergotamine are alternatives.

Intranasal lidocaine works very well in a small percentage of patients and is not vasoconstrictive.

Smoking cessation may reduce pain intensity in migraine; however, no similar study has been done in cluster headache. Still, we should encourage our patients to quit on the grounds of lowering other health risks.

Surgery a last resort

Sadly, for some patients, drugs are ineffective,

and surgical treatment needs to be considered.

Dr. Peter Jannetta, a University of Pittsburgh neurosurgeon, claims 73% of his patients experience at least a 50% reduction in frequency of cluster headache attacks after microvascular decompression of the trigeminal nerve.[12] However, patients who have undergone craniotomy may not consider two cluster headache attacks a day instead of four a good outcome. And if headaches recur, repeating the procedure is not effective. Patients in whom this procedure fails are miserable.

Radiofrequency lesions of the sphenopalatine ganglia bring modest relief in intractable cases.[13] At the Cleveland Clinic, we had success with glycerol injections instead of radiofrequency.[14] But both procedures can cause facial hemianesthesia, especially of the cornea.

A small study[15] claimed relief in five of six patients within 1 week after gamma knife surgery. The Cleveland Clinic's success rates are closer to 50%, which is still a good result in patients with pharmacologically intractable disease, and this is the surgical option I would recommend first.

SUBSTANCE WITHDRAWAL HEADACHE

Quitting caffeine gradually helps to avert withdrawal headache

Withdrawal syndrome and rebound headache can accompany withdrawal from any addictive drug or substance, the most common being caffeine. For example, people who drink an average of three cups of coffee a day will likely develop a moderate to severe headache if they skip coffee for 48 hours. In this case, caffeine is the treatment of choice. The message is to encourage patients who want to quit to do so gradually.

Patients who are instructed to take nothing by mouth for 24 hours before surgery often have severe headache by the end of the procedure. We can help them avoid this problem by advising them to withdraw gradually from caffeine and certain drugs over a few weeks, or by allowing them to drink black tea or coffee on the day of the procedure. If substance withdrawal is the suspected cause of headache during recovery, coffee is better therapy than narcotics or opiates.

RISKS OF ANALGESIC OVERUSE

Patients taking barbiturates, sedatives, ergots, or narcotics are at risk for analgesic overuse syndrome. Overuse may trigger more headaches, and stopping the medicine most certainly will. This feedback loop is a common cause of chronic headache. Appropriate use of preventive medications and strict limits on the use of habituating acute therapies should reduce the likelihood of analgesic overuse.

Patients should not use any abortive medicines more than twice a week. Those requiring more frequent abortive medications should be re-evaluated for prophylactic therapy. Additionally, these patients should be evaluated for the appropriateness of the diagnosis: ie, Does the patient have more than one headache disorder? Research should focus more on prophylactic approaches.

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