Evaluation and Management Issues in Migraine

Case Study and Commentary, Elizabeth Loder, MD
Migraine and Stroke, Gretchen E. Tietjen, MD
Diet and Headache, Dawn A. Marcus, MD (see Primer on page 70)

INSTRUCTIONS

The following case study, “Evaluation and Management Issues in Migraine,” is accompanied by a continuing medical education (CME) evaluation that consists of 5 multiple-choice questions. After reading the case study, carefully consider each of the questions in the CME evaluation on page 75. Then, circle your selected answer to each question on the CME evaluation form on page 76. In order to receive one CME credit, at least 3 of the 5 questions must be answered correctly. The estimated time for this CME activity is 1 hour.

OBJECTIVES

After participating in the CME activity, primary care physicians should be able to:
1. Describe the epidemiology of migraine
2. Know the International Headache Society criteria for diagnosis of migraine
3. Identify agents used for prophylaxis and acute treatment
4. Consider methods for evaluating the efficacy of the new specific, antimigraine agents (triptans)
5. Describe the evidence on migraine and psychiatric comorbidity

INTRODUCTION

Interest in migraine has increased dramatically over the past few years, largely as a result of the introduction of a number of new pharmacologic agents for the acute treatment of migraine. The unprecedented efficacy and specificity of these triptan drugs has improved our ability to manage migraine. At the same time, heightened recognition of the social, personal, and financial impact of migraine has made it more important than ever that migraine patients be identified and offered appropriate treatment. A significant additional benefit of the development of these drugs has been increased understanding of the underlying mechanisms, epidemiology, and natural history of migraine.

Well-done epidemiologic studies have demonstrated just how common migraine is: 1 widely quoted review found that 5.7% of males and 17.6% of females had 1 or more migraines over the course of a year [1]. Projecting these figures to the population of the United States as a whole produces an estimate of 2.6 million males and 8.7 million females with migraine who suffered moderate to severe disability as a result of the disorder. This same study showed that although prevalence varied by age, it was highest in mid-life, with the highest prevalence found in men and women between the ages of 35 and 45 years. This is in marked contrast to other chronic illnesses such as arthritis, in which severe forms of the disorder are more common in older age-groups. The peak prevalence of migraine thus occurs just when sufferers are otherwise healthy and in the most productive years of their lives. This tendency of the disorder to be most problematic in the economically important middle years makes it easy to see why the economic and social impact of migraine may seem to be disproportionately higher than that of other disorders with similar prevalence.

A variety of evidence suggests that the costs of migraine are substantial. It has been estimated that $6.5 to $17.2 billion of productivity losses each year are attributable to migraine. In addition to the costs of impaired productivity and lost work time, migraine accounts for a significant number of office visits, and migraineurs have been shown to have higher overall health care utilization and medication costs when compared with nonmigraineurs [2]. It is estimated that 4% of visits to physicians are related to headache [3].

Other important epidemiologic factors of note include the tendency for women with the disorder to suffer more frequent and more severe headaches than men with the disorder [4], suggesting, among other things, the impact of sex steroids on the expression of the disorder. Also, in contrast to commonly held views of migraine patients as affluent, the prevalence and frequency of migraine actually appears to be higher in lower socioeconomic groups, with 1 study showing migraine prevalence in the lowest income group more than 60% higher than in the 2 highest income groups.
For reasons that are not entirely clear, several sources have suggested an increase in migraine prevalence in the past decade [5].

CASE 1: MIGRAINE WITHOUT AURA
Initial Presentation
A 36-year-old woman with a 22-year history of episodic headaches presents to her newly assigned family physician complaining of increasing frequency and severity of headaches and inability to manage the headaches with over-the-counter (OTC) medications.

History
The patient recalls that headaches began shortly after menarche. Initially, they occurred only 3 to 4 times per year. Headaches were generalized, throbbing, and associated with nausea and sensitivity to light. Untreated, they could last up to a day, but if she was able to sleep or took aspirin she was generally able to function. The patient was evaluated for her headaches in college, when they occasionally failed to respond to treatment and caused her to miss classes and work. She was told she had “tension” headaches and was advised to “learn to relax.”

Approximately 2 years prior to this visit, the patient noted a gradual increase in both frequency and severity of her headaches. A previous physician prescribed 75 mg of amitriptyline daily. The patient discontinued the amitriptyline after a week because of lack of effect and unpleasant side effects of sedation and dry mouth. Lately, she has been using an OTC caffeine-containing combination analgesic. Initially it was effective in relieving her headaches, although it did not completely eliminate the pain and sometimes caused stomach irritation. Now that her headaches are more frequent (approximately 4 to 5 per month), she finds the medication seems to work less well. She worries that she is taking the medication too frequently.

Her father and siblings are well, but her mother had “sick headaches” and her 9-year-old son occasionally misses school because of severe vomiting, abdominal pain, and headache.

Physical and Neurologic Examinations
The patient’s physical and neurologic examination and the results of general primary care screening laboratory evaluations appropriate for her age are normal.

- How is the diagnosis of migraine made?

Diagnostic Criteria
In 1988 the International Headache Society (IHS) developed a system for diagnosis and classification of migraine that has achieved widespread acceptance [6]. As there is no “gold standard” for the diagnosis of migraine, the system relies on a system of inclusion and exclusion criteria similar to those of the various iterations of the Diagnostic and Statistical Manual of Mental Disorders published by the American Psychiatric Association. This patient clearly meets criteria for the diagnosis of migraine without aura (Table 1). Since the IHS criteria were initially developed to aid in patient selection for clinical trials of migraine drugs, they are highly specific but not particularly sensitive [7]. Thus, in clinical practice, a patient whose presentation does not strictly meet criteria for a diagnosis of migraine may still benefit from treatment for the disorder.

This patient’s story illustrates another troubling epidemiologic statistic: of women with migraine, only 41% have ever been diagnosed by a physician as having the disorder [4]. For men with migraine, the situation is even more dismal: only 29% have been told by a physician that they have migraine. It might be argued that these undiagnosed patients have mild, nondisabling forms of the illness, but studies do not bear this out. In fact, patients who have not been diagnosed by a physician have rates of disability fully as high as those of patients who have been diagnosed [8]. In the past, when treatment consisted largely of analgesic or sedative medications that simply covered up the pain of a headache, it might not have mattered whether an accurate diagnosis was made. Now that highly efficacious, migraine-specific drugs are available, a missed diagnosis can mean suboptimal treatment and unnecessary disability for a patient who might benefit from this treatment advance.

- What role do genetic factors play in migraine?

Role of Genetic Factors
This patient has a family history of migraine. Susceptibility to migraine very likely depends on genetic factors. Environmental factors, most as yet undefined, however, seem to play a more important role in determining expression of the disorder. This is demonstrated by twin studies, in which concordance for migraine in monozygotic twins is only 25% to 30% instead of the 100% that would be expected if genetic factors alone were operating. It therefore seems likely that a combination of genetic factors interact with environmental triggers to produce migraine in susceptible patients. Genetic factors likely account for only 30% of the risk, with environmental factors contributing a more important 70% of the risk [9].

What is the function of the genes involved in garden-variety migraine? In addition to speculation that the genes involved in many cases influence the function of the serotonin system, genes involved in the function of the
A number of investigators have proposed that dopamine hypersensitivity may be one of the driving forces in a migraine attack. This may explain why dopamine antagonists have been shown to be useful in treating migraine above and beyond their beneficial effects on migraine-associated symptoms such as nausea and vomiting. Genes regulating the entry of calcium into cells may also be involved, as illustrated by the finding that dopamine system may also play a role [10].

Table 1. International Headache Society Criteria for the Diagnosis of Migraine

<table>
<thead>
<tr>
<th>Migraine without aura</th>
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<tbody>
<tr>
<td><strong>Description</strong></td>
</tr>
<tr>
<td>Idiopathic, recurring headache disorder manifesting in attacks lasting 4–72 hours. Typical characteristics of headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea, photo- and phonophobia.</td>
</tr>
<tr>
<td><strong>Diagnostic criteria</strong></td>
</tr>
<tr>
<td>A. At least 5 attacks fulfilling B–D</td>
</tr>
<tr>
<td>B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)</td>
</tr>
<tr>
<td>C. Headache has at least 2 of the following characteristics:</td>
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<tr>
<td>1. Unilateral location</td>
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<tr>
<td>2. Pulsating quality</td>
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<tr>
<td>3. Moderate or severe intensity (inhibits or prohibits daily activities)</td>
</tr>
<tr>
<td>4. Aggravation by walking stairs or similar routine physical activity</td>
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<tr>
<td>D. During headache at least 1 of the following:</td>
</tr>
<tr>
<td>1. Nausea and/or vomiting</td>
</tr>
<tr>
<td>2. Photophobia and phonophobia</td>
</tr>
<tr>
<td>E. At least 1 of the following:</td>
</tr>
<tr>
<td>1. History and physical and neurologic examinations do not suggest other disease that might cause headache</td>
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<tr>
<td>2. History and/or physical and/or neurologic examinations do suggest such disorder, but it is ruled out by appropriate investigations</td>
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<tr>
<td>3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder</td>
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<table>
<thead>
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<th>Migraine with aura</th>
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<tbody>
<tr>
<td><strong>Description</strong></td>
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<tr>
<td>Idiopathic, recurring disorder manifesting with attacks of neurologic symptoms unequivocally localizable to cerebral cortex or brain stem, usually gradually developed over 5–20 minutes and usually lasting less than 60 minutes. Headache, nausea, and/or photophobia usually follow neurologic aura symptoms directly or after a free interval of less than an hour. The headache usually lasts 4–72 hours but may be completely absent.</td>
</tr>
<tr>
<td><strong>Diagnostic criteria</strong></td>
</tr>
<tr>
<td>A. At least 2 attacks fulfilling B</td>
</tr>
<tr>
<td>B. At least 3 of the following 4 characteristics:</td>
</tr>
<tr>
<td>1. One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction</td>
</tr>
<tr>
<td>2. At least 1 aura symptom develops gradually over more than 4 minutes, or 2 or more symptoms occur in succession</td>
</tr>
<tr>
<td>3. No aura symptom lasts more than 60 minutes. If more than 1 aura symptom is present, accepted duration is proportionally increased</td>
</tr>
<tr>
<td>4. Headache follows aura with a free interval of less than 60 minutes (It may also begin before or simultaneously with the aura)</td>
</tr>
<tr>
<td>C. At least 1 of the following:</td>
</tr>
<tr>
<td>1. History and physical and neurologic examinations do not suggest other disease that might cause headache</td>
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Adapted with permission from Classification and diagnostic criteria for headache disorders, cranial neuralgias and facial pain. Headache Classification Committee of the International Headache Society. Cephalalgia 1988;8 Suppl 7:1–96.
50% of cases of a rare subtype of migraine with aura, familial hemiplegic migraine, are associated with an alteration in a gene on chromosome 19. This particular gene appears to regulate the entry of calcium into cells [11].

- What factors can operate to worsen or transform migraine in a previously stable patient?

### Factors That Aggravate Migraine

In addition to environmental factors such as emotional upset, lack of sleep, skipping meals [12], and hormonal fluctuations, which are widely recognized to trigger or aggravate migraine in susceptible individuals, overuse of abortive medications may paradoxically worsen headache. In particular, the frequent use of ergotamine and caffeine-containing medications appears to be a potent cause of what has been termed “analgesic rebound headache,” although clinical observation suggests that even simple analgesics have been associated with the evolution of episodic into daily or nearly daily headache [13]. Despite the fact that caffeine in small, intermittent amounts is helpful in treating headache [14], caffeine withdrawal is known to precipitate a syndrome with headache among its features [15,16], and this has been shown to occur even in persons who consume low or moderate amounts of the substance [17].

The analogy with caffeine may hold true for other acute medications, and for this reason experienced headache experts usually limit the use of acute, symptomatic medications to no more than 2 to 3 times weekly. It is theorized that frequent use of symptomatic medications may somehow “reset” central pain control mechanisms in vulnerable individuals [18]. Overuse of triptans (a new class of specific antimigraine drugs) has been anecdotally reported to cause drug-induced rebound headache. It has been suggested that the dosages necessary to cause drug-induced headache may be lower than previously thought and time of onset shorter with new triptans with higher affinity for the 5-HT receptor site [19,20]. An alternative explanation, however, is that the underlying headache disorder worsened first, prompting the increased use of abortive medication. It is well to remember that considerable controversy remains about the cause-and-effect relationship of increased use of abortive medications and worsening of headache [21].

When analgesic rebound headache is present, detoxification from the offending agent must occur before other attempts at therapy will have maximum effectiveness [22]. The use of repetitive intravenous dihydroergotamine [23] or steroids can be very helpful in weaning patients from these drugs. In the case patient, it seems unlikely that overuse of medication has played a role in the worsening of her headaches. Although her headache frequency has increased, it is not at the minimum 2-to-3-headaches-per-week level where analgesic use becomes problematic.

### OUTCOMES AND THE PATIENT

- What nonpharmacologic treatment options exist for this patient?
- Is she a candidate for prophylactic therapy?

### Nonpharmacologic Therapy

Nonpharmacologic methods of therapy are the foundation of treatment for all patients. Such things as getting enough rest, eating regular meals, and a regular program of aerobic exercise have a beneficial impact on the course of the disorder. A well-done and careful review of the evidence in preparation for the development of guidelines for the treatment of migraine in Canada concluded that many forms of nonpharmacologic treatment for migraine are useful. Findings from randomized controlled trials support the use of biofeedback (which appeared similar in efficacy to preventive pharmacotherapy); relaxation strategies such as progressive muscle relaxation, breathing exercises, and imagery; and cognitive-behavioral therapy [24]. Given these data, and considering the substantial side-effect penalties of pharmacologic prophylaxis for migraine, it is disappointing that most insurance and managed care organizations still refuse to pay for these therapies. Nonpharmacologic therapies are especially valuable in a disorder such as migraine, which occurs in women of childbearing age and makes avoidance of unnecessary drug therapy particularly desirable.

Nonetheless, the majority of patients whose headaches are severe enough to consult a physician will require some form of pharmacologic treatment during the course of their illness. Drug treatment for headache can be divided into 2 categories: acute or abortive treatment, generally given at the onset of a headache in an effort to eliminate or modify the attack; and prophylactic or preventive treatment, which is given on a daily basis and for which the treatment goal is a reduction in frequency and intensity of the headache. As a general rule, a good response to prophylaxis is arbitrarily defined as a 50% reduction in frequency or severity of attacks [25].

### Use of Prophylactic Agents

Most authorities recommend consideration of prophylaxis when the patient has more than 2 or 3 headache attacks per month [26]. However, with the advent of newer, more efficacious abortive treatment, this number may reasonably be adjusted upwards: all of the currently available prophylactic agents can cause unpleasant side effects, and the efficacy of even the most effective seldom exceeds a 50% reduction in...
headache frequency for 50% of patients. Given this information, many patients will prefer abortive treatment of individual headaches rather than daily use of a medication with unpleasant side effects that is only partially effective. Other indications for prophylaxis include failure or unacceptability of abortive agents, aura that interferes with the patient’s ability to function, menstrual migraine, or the presence of a comorbid condition that might benefit from use of 1 of the prophylactic agents [27].

Most of the agents commonly employed for prophylaxis of migraine have not been studied rigorously, and only a few have a formal indication from the U.S. Food and Drug Administration (FDA) for the prophylaxis of migraine. While the case patient is clearly a candidate for prophylactic therapy based on a number of the criteria mentioned above, she has fallen prey to the most commonly made mistake in prophylactic treatment of migraine: failure to use an adequate dose of the medication for an adequate length of time. Most prophylactic medications take 4 to 6 weeks to show effectiveness, and the dose must be adjusted based on clinical response to treatment [28]. Noncompliance may also be a factor in apparently ineffective treatment, and drugs with tolerable side effects and once-daily regimens will likely improve treatment outcome in this chronic disorder [29].

Table 2 shows a list of typically employed preventive medications, with suggested dose ranges.

Little research exists to guide decisions about which prophylactic agents should be employed first and which reserved for more refractory patients. Common sense suggests that drugs with relatively benign side effect profiles, such as β blockers and tricyclic antidepressants, should probably be tried before such drugs as methysergide, with its small but real risk of retroperitoneal fibrosis. Similarly, sodium valproate is an excellent drug but one whose potential to cause neural tube defects in exposed fetuses makes its first-line use problematic in a disorder that predominantly affects women of childbearing years [30]. Finally, it should be noted that although newer classes of antidepressants, such as the serotonin reuptake inhibitors (SSRIs), are commonly used for migraine prevention, little evidence exists to show that they are effective for this indication.

The use of maintenance opioids for the prophylaxis of migraine has been advocated by some experts for patients with refractory headache. For obvious reasons, this is generally a treatment of last resort, but can be helpful in patients whose lack of response to conventional treatment methods leave few other options for treatment.

- What abortive agents are available for individual attacks of migraine?

### Acute Therapy

Abortive options for the treatment of acute migraine consist of medications that fall into 1 of 3 broad groups: analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, or tramadol; combination analgesics such as the commonly prescribed barbiturate/caffeine/ aspirin or acetaminophen combinations; and selective or semiselective serotonin agonists such as the ergotamines and triptans.

### Analgesics

Since the majority of migraine patients have never been told by a physician that they have migraine, it follows that most migraine patients resort to self-treatment, usually with OTC medications. While it might be assumed that these are patients who are not significantly disabled by migraine and for whom OTC preparations work well, this is not always the case. In addition, long-term use of OTC analgesics, particularly mixtures such as aspirin and acetaminophen, may cause serious health problems. An estimated 8% to 10% of new cases of chronic renal failure each year are related to heavy or long-term analgesic use, and a warning has been issued against habitual long-term use of OTC analgesics, especially those containing a mixture of analgesics such as aspirin and acetaminophen [31]. Thus, while OTC medications may be appropriate for patients with mild, infrequent headache [32], patients whose headaches are severe or frequent enough to come to medical attention should be urged to show restraint in their use of OTC analgesics. In cases where drug rebound headache has complicated the underlying migraine, the patient will need to be withdrawn from the analgesics before treatment responsiveness to other acute or prophylactic agents is restored [33].

Other nonspecific analgesic drugs such as tramadol, opioids, and NSAIDs are beneficial for some patients with migraine [34]. NSAIDs may play an important role in migraine associated with the menstrual period, in which prostaglandins may be a prominent factor in headache and associated symptoms. Drawbacks of this category of medications often limit their use, however: the risk of gastrointestinal ulceration or irritation with NSAIDs and sedation, habituation, and constipation from opioids are treatment-limiting factors for many patients. Finally, it should be remembered that these drugs merely cover up 1 of the symptoms of migraine (pain) and do little to address the underlying problem or treat other associated features such as nausea, vomiting, and photo- and phonophobia. Finally, the use of these drugs in injectable or nasal spray formulation, while fast-acting, may hasten the development of dependence or even addiction in susceptible individuals. This was a particular problem with a nasal spray formulation of butorphanol, in which the rapid development of apparent addiction to the drug in young patients with migraine was observed.
The use of antidopaminergic medications such as prochlorperazine, chlorpromazine, or metoclopramide has been advocated by some, based on trials showing efficacy in emergency department settings [35,36]. Given that dopaminergic pathways may play a role in migraine, this approach is a reasonable one in patients who do not benefit from or have contraindications to the newer nonsedating triptans and as “rescue” therapy in patients whose first-line treatments have failed. They are also useful as adjuncts to other therapies such as opioids or ergotamine preparations that may cause nausea. The gastric stasis that occurs in migraine also means that use of prokinetic agents such as metoclopramide can improve absorption of other drugs [22]. In fact, studies have suggested that the efficacy of aspirin-like compounds combined with metoclopramide is equivalent to that of oral sumatriptan. However, these studies lacked a control group, so the adequacy of study design cannot be evaluated.

However, the impairment of function that many of these medications cause is an unacceptable liability in the majority of

### Table 2. Some Medications for Migraine Prophylaxis

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dosage</th>
<th>Main Side Effects</th>
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</thead>
<tbody>
<tr>
<td><strong>β blockers</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>50–150 mg/d</td>
<td>Fatigue, bronchospasm, bradycardia, hypotension, congestive heart failure, depression, impotence, sleep disturbance</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>100–200 mg/d</td>
<td></td>
</tr>
<tr>
<td>Nadolol</td>
<td>20–160 mg/d</td>
<td></td>
</tr>
<tr>
<td>Propranolol</td>
<td>40–240 mg/d</td>
<td></td>
</tr>
<tr>
<td>Calcium-channel blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Flunarizine</td>
<td>5–10 mg/d</td>
<td>Fatigue, weight gain, depression (flunarizine), bradycardia, hypotension, constipation (verapamil), nausea, edema, headache, extrapyrimidal side effects</td>
</tr>
<tr>
<td>Verapamil</td>
<td>240–320 mg/d</td>
<td></td>
</tr>
<tr>
<td><strong>Serotonin receptor antagonists</strong></td>
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<td></td>
</tr>
<tr>
<td>Methysergide</td>
<td>2 mg every night, gradually increased to tid (maximum 8 mg/d if needed) (usual dose 4–8 mg/d)</td>
<td>Retroperitoneal, cardiac, and pulmonary fibrosis</td>
</tr>
<tr>
<td>Pizotyline (pizotifen)</td>
<td>0.5 mg every night, gradually increased to tid (maximum 3–6 mg/d if needed) (usual dose 1–6 mg/d); consider giving higher doses once every night</td>
<td>Weight gain, fatigue</td>
</tr>
<tr>
<td><strong>Tricyclic analgesics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>10–150 mg every night</td>
<td>Dry mouth, constipation, weight gain, drowsiness, reduced seizure threshold, cardiovascular effects</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>10–150 mg every night</td>
<td></td>
</tr>
<tr>
<td><strong>Antiepileptics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divalproex</td>
<td>500–1500 mg/d</td>
<td>Nausea, tremor, weight gain, alopecia, increased liver enzyme levels</td>
</tr>
<tr>
<td>Sodium valproate</td>
<td>500–1500 mg/d</td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>500–1500 mg/d</td>
<td></td>
</tr>
<tr>
<td><strong>NSAID</strong></td>
<td></td>
<td></td>
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<tr>
<td>Naproxen sodium*</td>
<td>550 mg bid, for no longer than 1 week per month</td>
<td>Gastrointestinal upset, ulceration, rebound headache, renal dysfunction</td>
</tr>
</tbody>
</table>

NSAID = nonsteroidal anti-inflammatory drug.

*As prophylaxis for perimenstrual migraine attacks only.

patients and renders them unsuitable for routine use. Reliance on sedating medications for acute treatment of a chronic, recurrent illness in otherwise healthy, busy adults is difficult to defend, even when taking into account the higher prices of the specific antimigraine agents. This view is reinforced by evidence that use of the newer medications, in addition to providing impressive relief of headache, also reduce productivity loss and improve return to normal performance in patients with migraine [37]. This is not an insignificant benefit, in view of the fact that one study from Canada suggested an annual loss of 7 million workdays due to migraine attacks [38].

Ergotamine
Ergotamine preparations have been in use for the treatment of migraine since the latter half of the 19th century [39]. They are available in rectal, sublingual, and oral formulations, often in combination with caffeine. A derivative of ergotamine, dihydroergotamine (DHE), is available in nasal spray and parenteral formulations. While ergotamine compounds have agonist activity at the serotonin 1B and 1D receptors important for antimigraine efficacy, they affect adrenergic and dopaminergic receptors as well, producing side effects such as intense vasoconstriction and nausea that are poorly tolerated by some patients. DHE has fewer side effects and appears less likely to induce rebound headache [40]. Ergotamine preparations and ampules of DHE are relatively inexpensive and can be tried before triptans in patients for whom simple or combination analgesics are ineffective or inappropriate. Side-effect liability will limit their usefulness for many patients, however, and in those cases the selective antimigraine drugs offer many benefits.

The Triptans
As a group, the triptans offer unprecedented efficacy, with 70% to 80% of patients obtaining relief of an acute attack within 2 hours of administration of parenteral sumatriptan [41]. Sumatriptan exerts its effects through stimulation of the 5-HT1 receptor, particularly the B and D subtypes. It is theorized that this causes cranial vasoconstriction [42], although inhibition of central pain transmission and reduction of neurogenic inflammation may also play a role in the effectiveness of some members of the triptan class of drugs [43]. Whether penetration of the central nervous system is important in efficacy of the triptans is unsettled: of currently available triptans, zolmitriptan, naratriptan, and rizatriptan have central effects while sumatriptan appears to cross the blood-brain barrier only when inflammation is present.

Until 1998, sumatriptan (Imitrex) was the only triptan available for clinical use. Subcutaneous, nasal spray, and oral formulations of the drug are marketed; the subcutaneous form is ideal for patients with rapid-onset attacks or those with prominent early nausea and vomiting. Side effects may be more marked with the subcutaneous form of the drug, however, reflecting the rapid rate of rise of plasma concentration. Clinical trials and accumulated experience suggest that the optimal oral starting dose of sumatriptan is 50 mg [44].

At the time of this writing, 3 other triptans are available for clinical use in the United States, all in oral formulations: zolmitriptan (Zomig); naratriptan (Amerge); and rizatriptan (Maxalt and Maxalt-MLT). The latter is available in both tablet and orally disintegrating wafer formulations. The wafer does not offer any advantages in speed of action, since it is dissolved in the saliva and absorbed through the gastrointestinal tract. However, it does offer a convenience factor since it can be used by patients unable to swallow tablets and taken without water by patients who are driving or in the middle of a meeting.

Initial Management and Follow-up
The primary care physician recognizes that the patient’s headaches meet IHS criteria for the diagnosis of migraine without aura. He reviews appropriate lifestyle changes such as instituting regular sleep and wake times and avoiding missed meals. He suggests that the patient begin a daily aerobic exercise program and keep a detailed headache calendar documenting not only the frequency of her headaches, but also their severity, length, association with possible trigger factors such as menstruation, and information about the amount and type of medication she uses for her headaches.

On her return visit 8 weeks later, review of her calendar indicates that headache frequency is approximately once to twice per week and headaches are more likely to occur prior to menstrual periods. According to the calendar, headaches generally last 12 to 18 hours and respond only partially to the OTC caffeine-containing analgesic she is taking. After discussion of the various treatment options available, the patient expresses an interest in avoiding the use of daily medication. The physician recommends that she consider learning biofeedback-assisted relaxation and provides her with the name of a local psychologist. Although biofeedback treatment is not generally covered by insurance reimbursement, the majority of patients with headache are able to learn the technique in 6 to 8 sessions, and the patient decides she is willing to pay out-of-pocket for this treatment.

The patient and physician also review options for improved abortive treatment of her headaches. As the patient had failed to obtain significant benefit from OTC anti-inflammatory medications, her physician decides she is an appropriate candidate for specific, prescription medications for migraine. The physician describes the side effects, efficacy, and characteristics of various ergotamine and triptan preparations available. As nausea is a troubling part of her headache already, the patient would prefer to avoid ergotamine and its derivatives. She also
expresses a strong preference for oral rather than injectable or nasal spray medications. Eventually, a standard dose of 1 of the new, oral triptan medications is prescribed. The physician emphasizes that it should be tried for several headaches before the patient draws conclusions about its effectiveness for her. The patient and physician also discuss the desirability of avoiding pregnancy while taking any regular medication, and the patient asks the physician whether or not oral contraceptives might worsen her migraines. At the conclusion of the visit, the patient is again asked to keep a headache calendar and to return in 8 to 12 weeks to evaluate her new regimen of treatment.

- Is there any reason to choose 1 triptan over another?
- Are there safety and tolerability concerns with the triptans?

**Comparative Benefits of the Triptans**

The traditional method of assessing efficacy in triptan trials has been headache response at 2 hours after dosing. “Response” is defined as reduction in headache from 2 (moderate) or 3 (severe) intensity at baseline to 0 (no headache) or 1 (mild headache) at 2 hours. Using this criterion, equivalent oral doses of currently available triptans look quite similar, with response rates around 60% [45]. The exception is naratriptan, with a response rate around 50%.[45] Subcutaneous sumatriptan is the gold standard, with a 2-hour response rate of 81% to 87%. Nasal spray formulations of sumatriptan and DHE produce response rates of around 60%.

It has been suggested that the criterion of percentage of patients who are pain-free at 2 hours is a more exacting way of judging the performance of the various triptans, and this is the recommended primary endpoint in acute attack studies [46]. Other suggestions for comparison among the triptans have been use of the concept of “number needed to treat” (NNT) and the related concept of “number needed to harm” (NNH) [47]. The NNT is the reciprocal of the absolute risk reduction and is gaining popularity as a method of comparing therapeutic interventions. It gives an idea of the number of patients who would need to be treated with the drug for 1 attack of migraine in order to obtain 1 true response to the drug. The NNH similarly gives an idea of the number of patients who would need to be treated with the drug for 1 attack of migraine before experiencing 1 adverse event related to the drug.

One way of choosing among the triptans would therefore be to select a drug with the lowest NNT and the highest NNH; this presumably would yield the best combination of efficacy and tolerability. As an example, the NNT for 50 mg of oral sumatriptan has been calculated to be 3.0, with an NNH of 14.3, whereas the NNT for 2.5 mg of oral naratriptan is 4.8 with an NNH of 1181 [46]. Similarly, the NNT for subcutaneous sumatriptan compared with placebo has been calculated to be around 2.0 [48]. For a physician and patient with clear therapeutic goals, such numbers offer useful information. Patients who are risk-averse and willing to accept lower efficacy for correspondingly low side-effect liability might wish to choose naratriptan rather than sumatriptan. Other patients, with severe headache and disability, might willingly tolerate a higher side-effect penalty in order to ensure efficacy. Intelligent use of NNT and NNH estimates offers a way of recognizing that patients have individual needs and preferences that vary dramatically depending on their circumstances.

Another method of drug comparison involves computing the “therapeutic gain” attributable to the drug. Therapeutic gain is calculated by subtracting the placebo response to a drug from the overall response rate, thus generating a number that allows comparison of different drugs with different placebo rates. Methodologically, this method suffers from the fact that comparison of results from different trials is not rigorous, since entry criteria to the trials and other factors may have varied. It does offer a method of correcting for placebo rates that is attractive to many clinicians, as the placebo rates in various trials have differed markedly [46].

Given this information, efforts can be made to individualize treatment depending on the patient’s presentation. For rapid-onset migraine associated with nausea and vomiting, subcutaneous sumatriptan offers the clearest benefit. Patients whose headaches build up slowly but last longer than 8 hours, or who are sensitive to the side effects of other triptans may benefit from naratriptan, with its relatively low recurrence rate of 27%. Patients who have difficulty swallowing tablets will find the rizatriptan rapidly dissolving tablet helpful. Zolmitriptan has been shown to be equally effective in migraine associated with menses and well-established migraine; its use can be considered in these situations. Nasal spray formulations may be preferred by patients who want faster results than those offered by tablets but in whom nausea or vomiting preclude the use of oral medications. Finally, patients who do not respond to 1 triptan still have a good likelihood of response to another, and several should be tried before concluding that a patient is a triptan nonresponder [49].

**Safety and Tolerability**

In general, the triptans appear to be safe and well-tolerated. The most common adverse events are “nuisance” side effects such as dizziness and somnolence. An important advantage of the triptans compared with earlier nonspecific treatments is the lack of significant sedation in most patients and early return to normal activities. Although it has been suggested that overuse of the triptans can cause rebound headache, clinical experience to date does not suggest this is...
a significant problem in most patients who use the drug. As is possible with any drug, there are patients who overuse the medication. They are more likely to have had previous problems with daily use of analgesics or rebound headache [20].

Despite being generally well-tolerated, the triptans as a group are capable of causing coronary vasoconstriction. Serious cardiac events, including myocardial infarction, have been reported in association with their use [50,51]. Most of the reports involve sumatriptan, but that likely reflects the fact that it was the first clinically available member of the triptan class. A recent review of the subject concluded that the drugs were unlikely to cause myocardial ischemia at typically used clinical doses, although all of them caused contraction of human coronary arteries in vitro [52]. It was noted that both ergotamine and DHE produced more sustained contraction than any of the triptan drugs, an important relative disadvantage of the older, less specific drugs.

Certainly the triptans should not be used in patients with established coronary artery disease (CAD). It also seems reasonable that these drugs should be used with caution in patients with risk factors for CAD. Fortunately, most patients seeking treatment for migraine are young, healthy women with few risk factors for CAD. Little guidance exists, however, on how to weigh the risks and benefits of triptan use in patients with 1 or 2 risk factors for CAD. Lacking data about the magnitude of various risk factors and their interaction with triptan use in increasing that risk, it seems reasonable that decisions should be individualized and made in collaboration with patients. For example, a migraine patient who has obtained benefit from sumatriptan and who is now entering her postmenopausal years for whom alternative treatments have not been effective might elect to continue using a triptan despite the fact that postmenopausal status puts her in a higher risk category.

What is the impact of sex steroids on the expression of migraine?

Impact of Sex Steroids

While men and women are probably equally likely to inherit a vulnerability to migraine, expression of the disorder is likely influenced by environmental factors such as hormonal fluctuations. In childhood, boys and girls are equally likely to suffer from migraine, but at the time of menarche, prevalence among girls increases. The gender discrepancy in prevalence peaks in middle age, but even after menopause female sufferers outnumber males [53]. Prevalence patterns thus suggest that the influence of hormonal factors somehow has a permanent effect on the central nervous system that persists even after inciting hormonal changes are no longer present. Additional evidence for the impact of sex hormones on migraine is the change in migraine patterns experienced by patients associated with normal menstrual cycles, pregnancy, menopause, and the use of exogenous hormonal preparations such as oral contraceptives and hormone replacement therapy (HRT).

Somerville demonstrated through a series of elegant experiments involving estrogen and progesterone supplements that it is likely that falling levels of estrogen are the trigger for headaches that occur around the menstrual period [54]. Although attention has been focused on hormonal manipulation in the treatment of menstrual associated migraine, most headache experts feel that hormonal levels in women with this problem are normal; what is abnormal is the way in which the migraine-prone central nervous system responds to normal fluctuations in hormonal levels. Thus, drastic interventions such as oophorectomy are not favored unless more traditional treatment of migraine has failed. In such cases, therapies such as estrogen add-back therapy around the time of the expected menstrual period or continuous use of oral contraceptives have been advocated [55].

What is the association between migraine and stroke?

Migraine and Stroke

Migraine may be linked to ischemia in a variety of ways. These may best be remembered as the “5 Cs.”

Coincidental

Given the high prevalence of migraine in the general population, up to one third of persons with stroke will have a history of migraine, even in the absence of further links between the 2 conditions [56].

Confusion

It is difficult to discern migraine from transient ischemic attacks: both are clinically defined and associated with headache and focal neurologic deficits. This further complicates the examination of migraine as an independent stroke risk factor.

Causal

Migrainous infarction (ie, an attack of migraine complicated by stroke) typically occurs in young persons with aura and involves the territory of the posterior cerebral artery [56,57]. The percentage of stroke in the young attributed to migrainous infarction ranges from 0% to 20%, with a mean of 7% [58–71], and the estimated annual incidence of this phenomenon in the United States is 1.7/100,000 [72]. The most commonly postulated mechanisms of migrainous infarction

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include vasospasm, cortical spreading depression with prolonged oligemia, and in situ thrombosis related to hypercoagulability [73]. Arterial dissection, a cause of stroke in the young, may be more common in migraineurs [74]. Large-scale epidemiologic studies of men [75], women [76], and mixed populations [77] suggest that a history of migraine doubles the risk for developing stroke remote from the migraine attack. Case-control studies suggest that the risk of stroke related to migraine may be especially high in young women and in those with aura [78–83].

Confounding Variables
In young women (< 45 years of age) with migraine, combined use of oral contraceptive pills and smoking may substantially increase relative risk for ischemic stroke, although the absolute risk remains low [76,79–81]. Antiphospholipid antibodies—a stroke risk factor—is not associated with migraine per se, but neuroimaging studies in neurologically normal migraineurs have shown more ischemic lesions in migraineurs with the antibodies than in those without [83].

Complex
Inherited conditions such as CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) are particularly complex, as both migraine and stroke characterize the disorder, although not in temporal association. Migraine with aura typically begins in the third decade, with strokes not occurring until age 40 years or older. White matter abnormalities on magnetic resonance imaging (MRI) often are apparent by age 30, predating stroke-like symptoms by many years [84]. Mutations in the notch 3 gene on chromosome 19 have been identified in CADASIL; this gene is near but not allelic to the gene for familial hemiplegic migraine [84]. In MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke), disordered mitochondrial metabolism may predispose to neuronal hyperexcitability and migraine, although a direct link to thrombotic stroke, which also occurs, is elusive [85].

Additional Follow-up
When the patient returns for her next scheduled office visit, she is excited to report that the oral triptan gave her complete relief in 2 out of 3 attacks. She noted no side effects from the medication. Occasionally, especially if she treated the headache after it was well-established, the triptan did not offer complete relief and she noticed that the headache tended to recur. Review of her headache calendar indicates she is using the triptan twice a week at most and that her headache frequency had declined by about 50%. The patient has begun biofeedback training and finds it is improving her ability to cope with the headaches when they do occur. She attributes the apparent reduction in headache frequency to the biofeedback training and the exercise program she has begun, as well as to paying more attention to her sleep habits.

The physician recommends that she continue to keep a headache calendar and plan to return every 6 months to review her headache situation. He also recommends that she consider treating her headaches before they are well-established to improve the chance of obtaining complete, rather than partial, relief with the triptan. He also gives the patient a prescription for a small quantity of an injectable triptan and a sedating antinausea medication in suppository form. He suggests that the patient keep this medication handy for use on occasions when headaches do not respond to the oral triptan or progress despite it. He tells the patient that in his experience, many migraine patients occasionally have very severe headaches with vomiting that do not respond to or cannot be treated with oral medications and require the use of an injectable medication or antinausea medication. He suggests that this would help the patient avoid disruptive and costly emergency room visits on those rare occasions.

CASE 2: MIGRAINE WITH AURA AND COMORBID DISORDERS

Initial Presentation
A 38-year-old man presents to his physician with complaints of increasing frequency of headache and disturbing visual phenomena.

History
The patient reports a history of intermittent headaches beginning in his early 20s. Initially the headaches were mild, and he paid more attention to the visual symptoms that preceded them. Prior to most of his headaches he develops what he refers to as “fuzzy” vision. A few minutes after the onset of these vague visual changes, he notes bright spots of light in the periphery of both visual fields. He then notices a sharp, jagged black line which grows in size, moves to the periphery of his visual field, and then fades away gradually after about half an hour. At this point his headache generally begins. The headache is generalized but severe enough to require bed rest. He notes sensitivity to loud noise but does not describe nausea or vomiting. Headaches do interfere with his ability to exercise, however, as his usual 2-mile run aggravates the pain.

For years this has occurred once or twice per year. Over the past year and a half, however, these episodes have increased in frequency to several times per month. The patient found he was increasingly anxious about their occurrence, and since he spends a great deal of time driving, he worries about what would happen if an episode occurred while he was on the road.

The patient reports a history of similar headaches in his mother. He has never sought specific treatment for his
headaches, because they were so infrequent. He has been using his mother’s prescription of a barbiturate-aspirin-caffeine-containing medication for his headaches and requests a prescription of his own. He would also like reassurance that he does not have a brain tumor and asks to have a computed tomography (CT) or MRI scan of his head. The patient says he has heard that headaches get better, not worse, as people age, and is worried that he has not followed this pattern. He also has questions about the use of vitamins and “natural” treatments for headache.

**Physical and Neurologic Examinations**

The patient has a normal physical examination, including funduscopic examination, visual fields, and visual acuity. The results of routine laboratory examinations are within normal limits. His physician notices, however, that the patient appears nervous and anxious during the office visit. Results of formal mental status testing are normal, but the patient admits that he has been feeling irritable recently and has lost interest in many of his usual activities. He has lost 10 lb without attempting to do so and is having difficulty sleeping at night. He also reports that for many years he has had episodes of extreme anxiety that occur spontaneously and for no apparent reason. These have been increasing in frequency, and he is becoming afraid of returning to places such as the grocery store where such episodes have previously occurred.

- **What is the state of current thinking on the relationship between migraine and psychiatric disorders?**

**Migraine and Psychiatric Disorders**

Evidence from recent epidemiologic studies suggests that there is significant comorbidity between migraine and certain psychiatric disorders, primarily affective disorders such as depression, anxiety, and panic [86]. Lifetime rates of affective and anxiety disorders are elevated in migraineurs, and in 1 study the odds ratios for development of particular psychiatric disorders in migraine were 4.5 for major depression, 6.0 for a manic episode, 3.2 for any anxiety disorder, and 6.6 for panic disorder. The risk appeared to be higher for patients who have migraine with aura than for those who have migraine without aura. Interestingly, patients suffering from migraine with aura may also be at heightened risk for suicide [87], again emphasizing that migraine with aura may be quite different from migraine without aura. The appearance of these comorbid disorders follows an orderly progression, with anxiety preceding migraine and major depression following it [88].

Far from being a simple cause-and-effect relationship, migraine and psychiatric comorbidities appear to be associated in a bidirectional way, suggesting that underlying factors, perhaps inherited central nervous system abnormalities in serotonergic transmission, are responsible for an increased risk of developing both disorders. This argues against older notions that one disorder somehow “causes” the other [89]. One study estimated the relative risk of depression developing in a migraine patient compared with controls as 4.1. The relative risk of migraine in a patient with depression was 3.3 [90].

This patient’s case illustrates these principles. It seems likely that in addition to migraine with aura he has major depression and a panic disorder. In selecting treatment for him, the presence of these comorbid disorders needs to be taken into account.

- **How does the presence of a comorbid condition affect the choice of migraine therapy?**

**Therapy Choice in the Setting of Comorbidities**

Current evidence suggests that patients with migraine should be periodically assessed for the presence of depression, and when treatment of 1 disorder is indicated, the possible effects of treatment on the other disorder should be taken into consideration. For example, in a patient with migraine who suffers from depression, one might want to avoid the use of β blockers, as some studies argue that they may aggravate or cause depression [91]. It is important to remember that other studies argue against such an association [92]; given the current state of the evidence, it is advisable to closely monitor migraine patients prescribed β blockers or consider therapeutic alternatives if available.

Similarly, in patients with documented panic disorder the use of combination barbiturate-containing medications should probably be avoided to minimize the risk that the medication may be inappropriately used to treat anxiety or panic attacks. Finally, the use of biofeedback or other relaxation strategies shown to be effective in migraine may also be useful in treating anxiety or panic disorders when present.

Disorders other than psychiatric illnesses have also been suggested as more common in patients with migraine. These include epilepsy, mitral valve prolapse, and hypertension.

- **Does migraine improve with age?**

**Course of Migraine**

Migraine is in most cases a chronic illness, as demonstrated by cohort studies showing that the majority of patients diagnosed with migraine in childhood continue to experience attacks for many years. One study showed that only 40% of
patients were migraine-free after 30 years [93]. However, the frequency and intensity of headaches often diminish with age [94]. Migraine attacks in children are often shorter than those in adults, and vomiting is much more prominent. In some cases, abdominal symptoms predominate, and headache itself is absent or mild, making accurate diagnosis difficult [95].

As this patient’s case illustrates, however, many patients with migraine do not find that headaches improve significantly as they get older, and it is important not to overlook the diagnosis of migraine in middle-aged or older patients. Patients who have migraine with aura may find that they begin to have more episodes of aura alone, without the subsequent headache.

Role of Imaging Studies

Very few patients who present to a physician with complaints of headache will turn out to have a serious underlying cause of headache. The diagnostic yield of neuroimaging studies in headache is extremely low. After study of the available evidence, the American Academy of Neurology has issued a practice parameter stating that neuroimaging is not recommended in patients whose headaches meet IHS criteria for migraine and whose neurologic examination is normal [96]. The Academy also discourages the use of electroencephalogram and thermography studies in this group of patients [97,98]. When imaging studies are obtained in patients with migraine, so-called “white, bright spots” on T-2 weighted images are common and of no significance [99] but can lead to significant anxiety on the part of the patient that is sometimes hard to dispel.

In clinical practice, patients whose headaches meet criteria for migraine and who have a normal neurologic examination can safely be treated empirically for migraine; if they do not respond to treatment as expected, decisions about imaging or further testing can be reevaluated. Other worrisome signs, which should prompt immediate consideration of a search for an underlying serious cause of headache, include headache occurring after trauma, a change in previously stable headache pattern, or headache in the context of fever or changing mental status.

Alternative Therapies

A landmark study on the use of alternative medicine in the United States produced evidence that 32.2% of patients with headache had used some type of alternative treatment in the prior 12 months, the most common being relaxation treatment and massage [100]. Even more important, the majority of patients who used alternative therapy did not discuss this with their treating physician.

Riboflavin 400 mg/day appeared in 1 study versus placebo to reduce frequency of migraine attacks, but the effect was not apparent until the 4th month of treatment [101]. These results need to be replicated before this treatment can be recommended with enthusiasm. Magnesium may also play a role in headache, and preliminary evidence suggests that magnesium infusion may benefit some patients [102].

The role of food triggers in the production of migraine is probably overemphasized (see Primer on page 70). A careful review of the evidence shows poor trial design in the majority of studies. Well-done studies have exonerated tyramine and chocolate as triggers for migraine, and aspartame has been shown to be a weak trigger only in doses much higher than those ingested by even the most fanatic diet soda drinker.

The role of feverfew in migraine prophylaxis is not well-established. Despite studies showing superiority to placebo, a recent meta-analysis suggested that the evidence for it is weak and that trial designs were poor. In addition, the demonstrated effects were modest [103].

Diagnosis and Treatment

After the initial history and physical examination, the physician discusses her impression that the most likely diagnosis is migraine with aura. She also discusses the possibility of a major depressive episode and panic disorder. She suggests that effective treatment for these conditions exists and that an imaging study is not warranted at this time. The patient accepts the physician’s advice that he replace his use of a barbiturate-containing medication with 1 of the newer triptans and accepts a next-day consultation with a psychiatrist for psychopharmacologic evaluation. He also agrees to keep a headache calendar and to return in 2 months for reevaluation.

Two months later he returns, stating that the psychiatrist started him on an antidepressant. He reports improvement in mood and reduction in the number of panic attacks. He has had a good response to the triptan prescribed for him, but is concerned because his health maintenance organization will allow him only 6 tablets of the medication per month. He states he is otherwise satisfied with current management of his headache problem and does not request further testing or evaluation. He also mentions that he has been able to attend work more regularly and has been able to resume his exercise program.
Food-Headache Hypothesis

Pharmacologic data point to the involvement of a variety of neurotransmitters in the pathogenesis of headache. Excess dopamine and deficient serotonin and norepinephrine can be measured in the bloodstream when headache occurs. Changes in the circulating levels of these chemicals cause the blood vessels surrounding the brain to dilate. As the blood vessels dilate, they stretch and activate nerves that send pain messages. Most medication therapies work by correcting these chemical imbalances. Acute care headache treatments like dihydroergotamine and the triptans correct serotonin imbalance, while antinausea medications affect dopamine. Headache preventive therapies, like the antidepressants, correct imbalances in both serotonin and norepinephrine. Nonmedication treatments, such as relaxation and biofeedback, have also been shown to change levels of these pain messengers within the brain [1].

A variety of foods contain chemicals that are the building blocks for or mimic the actions of neurotransmitters. These chemicals include tyramine (found in aged cheeses, alcohol, and sour cream), beta-phenylethylamine (in chocolate), nitrates (in hot dogs), and dopamine (in broad beans). Food additives, such as monosodium glutamate and aspartame, are also reported as headache triggers by 10% to 15% of sufferers [2]. Although the majority of headache sufferers cannot identify food triggers, headache patients are often given a broad recommendation to avoid eating any foods that may contain possible headache-triggering chemicals (Table). The most commonly reported food triggers are alcohol (33%) and chocolate (22%) [2].

Clinical Studies

It is unclear if eating foods potentially rich in triggering chemicals actually changes headache activity. One study revealed that eating foods rich in amines did not increase levels of tyramine or beta-phenylethylamine in blood or brain [3]. Therefore, although amines may indeed have the ability to change headache activity, eating foods containing these chemicals may not significantly change the amounts to which the brain is exposed. In addition, Medina and Diamond followed headache activity in 24 migraineurs while following different diets [4]. The authors recorded headache activity while subjects ate their regular diets and 2 restrictive diets for 6 weeks each. One restrictive diet restricted those foods believed to act as headache triggers, while the other diet required people to eat these possible trigger foods. Interestingly, headache activity improved equally on both diets compared to the baseline diet. Eating or avoiding trigger foods did not seem to make a difference. The only relationships that could be identified were the occurrence of headache in relation to fasting, alcohol, or chocolate consumption. A single study involving aspartame showed only a modest worsening of headache in subjects who consumed large amounts of aspartame (the equivalent of 12 cans of diet cola or 32 packets of sweetener daily) for 1 month [5]. A double-blind study evaluating chocolate as a headache trigger failed to show a relationship, even in subjects who believed chocolate was a headache trigger for them [6].

Patient Recommendations

These studies suggest that although there are theoretical reasons to believe that certain foods trigger headache,
most people will not find that their headaches are provoked by food ingestion. Belief that foods induce headache may be related to headache prodrome. Many headache sufferers notice changes or prodromes occurring for the day before their headache episodes, including irritability, yawning, and food cravings. Food ingestion to satisfy the cravings may be mistaken as a headache instigator rather than a headache symptom. Other commonly reported headache triggers are also associated with food and sweet cravings. These include fasting (49%), stress (72%), and premenstrual symptoms (66%) [2]. If someone has a stressful day at work, skips lunch, has a chocolate bar from the vending machine, and then gets a headache, which factor(s) caused the headache? Was it the stress, fasting, the chocolate bar, or something not obviously identified? Controlled studies would argue that the food is probably the least likely trigger.

To test whether foods may indeed trigger headaches in an individual patient, patients may follow a restrictive diet for 1 month. If during that month the headache activity does not change, patients can feel confident that foods are not an important trigger for them. They can then return to their normal diet without worry that they are exacerbating headaches by consuming certain foods. If headaches do improve on a restrictive diet, then foods should be added back into the diet 1 at a time to identify which foods are triggers for the patient. If a food triggers a headache, the headache should occur within 12 hours of ingestion. Sufferers should not follow a comprehensive restrictive diet indefinitely, as this may provide additional stress.

References
Studies such as these are a step toward assessing the true cost-effectiveness of treatment, which is especially important in attempting to show that the new, more specific anti-migraine agents and other technologies represent good value for money spent. One recent commentator has made the point that

Now, with price competition among health care plans and provider groups in the United States, the test of budget neutrality is starting to be used to restrict the flow of costly yet beneficial new medical technologies... Economic evaluation these days often takes the form of 'cost minimization' analysis (how much money can be saved?), rather than cost-effectiveness analysis (how much health improvement can be gained, dollar for dollar?) [107].

The advent of targeted, highly efficacious treatments for migraine, which has significant impact on productivity in otherwise healthy, young adults, promises real progress in improving clinical outcomes.

References

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EVALUATION FORM: Evaluation and Management Issues in Migraine

DIRECTIONS: Each of the questions or incomplete statements below is followed by four possible answers or completions of the statement. Select the ONE lettered answer that is BEST in each case and circle the corresponding letter on the answer sheet.

1. All of the following statements about migraine are true EXCEPT
   (A) Migraine is more common in females than males
   (B) The headache phase of migraine is always preceded by an aura
   (C) Estrogen withdrawal can precipitate migraine in susceptible individuals
   (D) Nausea and vomiting are frequent accompanying features of migraine

2. Which of the following disorders is NOT comorbid with migraine more often than expected by chance alone?
   (A) Epilepsy
   (B) Anxiety disorders
   (C) Panic attacks
   (D) Schizophrenia

3. Which of the following is likely to be most helpful in choosing appropriate therapy for a patient with migraine?
   (A) Headache calendar
   (B) History of previous response to sumatriptan therapy
   (C) Family history of medication allergies
   (D) Results of MRI scan

4. An MRI study should be most strongly considered in which of the following patients?
   (A) A young woman whose headaches are preceded by 30 minutes of visual distortion
   (B) An elderly man whose headaches began after a minor fall
   (C) A middle-aged female whose headaches increase in frequency after beginning the use of oral contraceptives
   (D) A middle-aged man whose headache responds to sumatriptan

5. Which of the following statements is TRUE?
   (A) Patients with migraine should not use oral contraceptives or hormone replacement therapy
   (B) 50% of patients with migraine have aura
   (C) Migraine worsens with age in half of patients
   (D) Prior to puberty, girls are as likely as boys to experience migraine
Evaluation Form: Evaluation and Management Issues in Migraine

To receive CME credit for this case study, read the case study and then answer the multiple-choice questions on page 75. Circle your answers below. Also, please respond to the four questions that follow. Then, detach the evaluation form and mail or FAX to:

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Circle your answer to the CME questions below:
1. A B C D
2. A B C D
3. A B C D
4. A B C D
5. A B C D

Please answer the following questions:
1. In general, how do you rate the information presented in the case study?
   - [ ] excellent  - [ ] good  - [ ] fair  - [ ] poor
2. Do you find the information presented in this case study to be fair, objective, and balanced?
   - [ ] yes  - [ ] no
3. Name three clinical conditions that, in your experience, lead to less than optimal patient outcomes:
   Condition 1: ___________________________
   Condition 2: ___________________________
   Condition 3: ___________________________
4. Name three clinical topics you would like explored in future JCOM® case studies:
   Topic 1: ___________________________
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Note: CME credit letter and correct responses will be sent to the above-named person.

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