

Evaluation and Management Issues in Migraine

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Introduction

The burden of migraine. Migraine headaches are relatively common in the United States: 5.7% of men and 17.6% of women are affected by migraine symptoms at least once yearly.¹ These percentages represent approximately 23.6 million patients in the United States; half of these patients experience moderately to severely debilitating symptoms² that significantly affect their quality of life.³ It has been reported that migraine results in an average of 3.8 bedridden days for men and 5.6 bedridden days for women annually—an average of 112 million bedridden days yearly in the United States alone.⁴ The economic costs are equally staggering. It has been estimated that United States businesses lose \$13 to \$50 billion yearly due to absenteeism, reduced employee productivity, and medical expenses caused by headache.^{4,5}

The costs of migraine are most likely underestimated. Most migraine sufferers self-treat their symptoms, thus reflecting a lower medical cost than if they sought professional care.^{4,6} It has been estimated that the overall cost of migraine to society is similar to other chronic diseases, such as diabetes and asthma.⁴ Studies indicate that migraine is one of the top 10 causes for outpatient physician visits in the United States⁷ and that migraine sufferers have greater morbidity and medical resource use than patients without migraine.⁸

Diagnosis and clinical picture. The onset of symptoms makes migraine headaches a severe and dramatic presentation, but diagnosis may be difficult because of its potential to mimic other serious disorders (eg, stroke, transient ischemic attack,⁹ subarachnoid hemorrhage,¹⁰ idiopathic occipital epilepsy,¹¹ tumor, acute intracranial bleed, meningeal irritation, vasculitis, encephalitis, increased intracranial pressure, cerebral

edema, systemic processes^{12,13}). Also, migraine is associated with several psychiatric and neurological conditions, which may also make diagnosis difficult.⁴

The significant association in women between migraine and stroke complicates the clinical picture. There has been much debate about whether the odds of ischemic stroke in younger women is correlated with migraine with aura (classical migraine) and migraine without aura (simple migraine), leading to conflicting recommendations regarding oral contraceptive use.^{14–19} Similarly, migraine with aura has been associated with patent foramen ovale, which may also complicate the clinical presentation and implicating oral contraceptive use in these patients.²⁰

Treatment issues. Migraine headaches are often debilitating. Therefore, treatment in the acute phase requires rapid relief and, if possible, a reduction of future recurrence.²¹ Migraine sufferers access and use pharmacotherapy as a major source to alleviate symptoms; roughly 95% of patients take some form of medication in an effort to treat their headaches.²²

The associated symptoms of migraines (ie, those in addition to the headache) exacerbate the problems of this condition. Up to 92% of patients experience nausea and 50% to 68% report vomiting,^{21,23} precluding wide use of oral agents. Unfortunately, patients are exceedingly reluctant to self-administer injections of

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pain medication.^{24,25} However, current intranasal migraine medications (eg, sumatriptan) have been reported to be as effective as subcutaneous injection forms and address patient delivery considerations.¹ There has been limited success with alternative therapies (eg, feverfew leaves,²⁶ riboflavin²⁷) for migraine prophylaxis when taken orally. Also, acupuncture has been reported to have a positive effect on the symptoms of migraine.^{28,29}

All avenues of treatment should be encouraged. It has been shown that even the less preferable subcutaneous triptan derivative treatment is effective in improving workplace productivity and reducing labor costs for migraine sufferers.^{30,31}

Summary. Migraine is a significant social issue that is costly both to patients and the health care system. Also, physicians may be seeing only “the tip of the iceberg,” because most migraine sufferers have not been officially diagnosed by a physician (as noted by the authors in this case study). Therefore, many patients are lacking the medical guidance to effectively address their migraine attacks.

With the successful advent of triptan derivatives for treatment, the costs of migraine can at least be ameliorated; and with more tolerable delivery mechanisms, additional savings may be realized. As the following case studies highlight, migraine can be effectively treated but is a lifelong disease that has severe symptoms and costs and requires significant attention. As additional treatment modalities are recognized, costs to patients (and their employers) will be reduced; yet it should be noted that countervailing these savings may be the higher short-term costs associated with newer pharmacotherapeutic agents and increased diagnosis of the disease by primary care physicians. Therefore, physicians and policymakers must take a broader viewpoint in assessing effective treatment of this debilitating disease through a long-term perspective focused on the benefits associated with reduced work loss and increased productivity in symptom-free migraine patients.

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 her headaches began shortly after menarche. Initially, they occurred only 3 to 4 times

per year. Her headaches were generalized, throbbing, and associated with nausea and sensitivity to light. Untreated, they could last up to 24 hours. However, if she was able to sleep or took aspirin, she was generally able to function. The patient was evaluated for her headaches in college, because the headaches were occasionally unresponsive 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 before this visit, the patient noted a gradual increase in both the frequency and severity of her headaches. A previous physician prescribed amitriptyline (75 mg/day). The patient discontinued the amitriptyline after 1 week because of lack of effect and the unpleasant side effects of sedation and dry mouth.

The patient 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.

QUESTION

- **How is the diagnosis of migraine made?**

DISCUSSION

Diagnostic Criteria

In 1988, the International Headache Society (IHS) developed a system for diagnosis and classification of migraine that has achieved widespread acceptance.³² Because there is no “gold standard” for the diagnosis of migraine, the IHS diagnostic and classification system relies on 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. Patient 1 clearly meets criteria for the diagnosis of migraine without aura (**Table 1**). Because the IHS criteria were initially developed to aid in patient selection for clinical trials of migraine drugs,

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

Migraine without aura

Description

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.

Diagnostic criteria

- A. At least 5 attacks fulfilling B–D
- B. Headache attacks lasting 4–72 hours (untreated or unsuccessfully treated)
- C. Headache has at least 2 of the following characteristics:
 - 1. Unilateral location
 - 2. Pulsating quality
 - 3. Moderate or severe intensity (inhibits or prohibits daily activities)
 - 4. Aggravation by walking stairs or similar routine physical activity
- D. During headache at least 1 of the following:
 - 1. Nausea and/or vomiting
 - 2. Photophobia and phonophobia
- E. At least 1 of the following:
 - 1. History and physical and neurologic examinations do not suggest other disease that might cause headache
 - 2. History and/or physical and/or neurologic examinations do suggest such disorder, but it is ruled out by appropriate investigations
 - 3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder

Migraine with aura

Description

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

Diagnostic criteria

- A. At least 2 attacks fulfilling B
- B. At least 3 of the following 4 characteristics:
 - 1. One or more fully reversible aura symptoms indicating focal cerebral cortical and/or brain stem dysfunction
 - 2. At least 1 aura symptom develops gradually over more than 4 minutes, or 2 or more symptoms occur in succession
 - 3. No aura symptom lasts more than 60 minutes. If more than 1 aura symptom is present, accepted duration is proportionally increased
 - 4. Headache follows aura with a free interval of less than 60 minutes (it may also begin before or simultaneously with the aura)
- C. At least 1 of the following:
 - 1. History and physical and neurologic examinations do not suggest other disease that might cause headache
 - 2. History and/or physical and/or neurologic examinations do suggest such disorder, but it is ruled out by appropriate investigations
 - 3. Such disorder is present, but migraine attacks do not occur for the first time in close temporal relation to the disorder

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.

they are highly specific but not particularly sensitive.³³ 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.

Patient 1's story illustrates another troubling epidemiologic statistic: only 41% of women with migraine have ever been diagnosed by a physician as having the disorder.³⁴ The situation is even more dismal for men: only 29% of men with migraine 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.³⁵ 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.

QUESTIONS

- **What role do genetic factors play in migraine?**
- **What is the function of genes involved in "garden-variety" migraine?**

DISCUSSION

Role of Genetic Factors

Patient 1 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. Therefore, it 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.³⁶

Function of Genes 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 dopamine system may also play a role.³⁷ 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 (eg, nausea, vomiting).

Genes regulating the entry of calcium into cells may also be involved. For example, 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.³⁸

QUESTION

- **What factors may worsen or transform migraine in a previously stable patient?**

DISCUSSION

Factors That Aggravate Migraine

In addition to environmental factors (eg, emotional upset, lack of sleep, skipping meals,³⁹ 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 near-daily headache.⁴⁰ Despite the fact that caffeine in small, intermittent amounts is helpful in treating headache,⁴¹ caffeine withdrawal is known to precipitate a syndrome with headache among its features;^{42,43} this syndrome has been shown to occur even in persons who consume low or moderate amounts of the substance.⁴⁴

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.⁴⁵ 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.^{46,47} An alternative explanation, however, is that the underlying headache disorder

worsened first, prompting the increased use of abortive medication. Considerable controversy remains about the cause-and-effect relationship of increased use of abortive medications and worsening of headache.⁴⁸

When analgesic rebound headache is present, detoxification from the offending agent must occur before other attempts at therapy will have maximum effectiveness.⁴⁹ The use of repetitive intravenous dihydroergotamine⁵⁰ or steroids can be very helpful in weaning patients from these drugs. In the patient 1, 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 in which analgesic use becomes problematic.

QUESTIONS

- **What nonpharmacologic treatment options exist for patient 1?**
- **Is patient 1 a candidate for prophylactic therapy?**

DISCUSSION

Nonpharmacologic Therapy

Nonpharmacologic methods of therapy are the foundation of treatment for all patients. Factors such as getting adequate 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.⁵¹ Given these data, and considering the substantial side effect profile 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 migraine, which occurs in women of child-bearing 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, which is 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.⁵²

Use of Prophylactic Agents

Most authorities recommend consideration of prophylaxis when the patient has more than 2 or 3 headache attacks per month.⁵³ However, with the advent of newer, more efficacious abortive treatment, this number may reasonably be adjusted upward: 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 a partially effective daily medication with unpleasant side effects. 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.⁵⁴

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 United States Food and Drug Administration (FDA) for the prophylaxis of migraine. Although patient 1 is clearly a candidate for prophylactic therapy based on a number of the criteria mentioned, she is an example of 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.⁵⁵ 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.⁵⁶ **Table 2** shows a list of typically employed preventive medications with suggested dose ranges.

Choosing a prophylactic agent. 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 attempted before a drug such as methysergide

Table 2. Some Medications for Migraine Prophylaxis

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

NSAID = nonsteroidal anti-inflammatory drug.

*As prophylaxis for perimenstrual migraine attacks only.

Adapted from Pryse-Phillips WE, Dodick DW, Edmeads JG, et al: Guidelines for the diagnosis and management of migraine in clinical practice. *Can Med Assoc J* 1997;156:1273–1287. By permission of the publisher. ©1997 Canadian Medical Association.

(which has a 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.⁵⁷ 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 unresponsiveness to conventional treatment methods leave few other options for treatment.

QUESTION

- **What abortive agents are available for acute attacks of migraine?**

DISCUSSION

Acute Therapy

Abortive options for the treatment of acute migraine consist of three broad groups of medications: 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. Because the majority of migraine patients have never been told by a physician that they have migraine, most migraine patients resort to self-treatment, usually with OTC medications. Although 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 yearly are associated with 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.⁵⁸ Thus, although OTC medications may be appropriate for patients with mild, infrequent headache,⁵⁹ patients whose headaches are severe or frequent enough to present to a physician should be urged to show restraint in their use of OTC analgesics. In cases in which 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.⁶⁰

Other nonspecific analgesic drugs—such as tramadol, opioids, and NSAIDs—are beneficial for some patients with migraine.⁶¹ 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 only one symptom of migraine (ie, pain) and do little to address the underlying problem or treat other associated features (eg, nausea, vomiting, photo- and phonophobia). Finally, the use of these drugs in injectable or nasal spray formulation, although fast-acting, may hasten the development of dependence or even addiction in sus-

ceptible 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.

Antidopaminergics. The use of antidopaminergic medications (eg, prochlorperazine, chlorpromazine, or metoclopramide) has been advocated by some, based on trials showing efficacy in emergency department settings.^{62,63} Given that dopaminergic pathways may play a role in migraine, these medications are reasonable for patients who do not benefit from or have contraindications to the newer non-sedating triptans and as “rescue” therapy in patients whose first-line treatments have failed. Antidopaminergic medications 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 (eg, metoclopramide) can improve absorption of other drugs.⁴⁹ 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 functional impairment caused by many of these medications is an unacceptable liability in most 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 accounting for 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 reduces productivity loss and improves return to normal performance in patients with migraine.³⁰ This benefit is not insignificant: one study from Canada suggested an annual loss of 7 million workdays due to migraine attacks.⁶⁴

Ergotamine. Ergotamine preparations have been in use for the treatment of migraine since the latter half of the 19th century.⁶⁵ 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. Although ergotamine compounds have agonist activity at the serotonin 1B and 1D receptors important for antimigraine efficacy, they affect adrenergic and dopamine 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.³³ 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.²⁴ 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,⁶⁶ 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.⁶⁷ Whether penetration of the central nervous system is important in efficacy of the triptans is unsettled: of currently available triptans, zolmitriptan, rizatriptan, and naratriptan have central effects, whereas 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 increase of plasma concentration. Clinical trials and accumulated experience suggest that the optimal oral starting dose of sumatriptan is 50 mg.⁶⁸

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, because it is dissolved in the saliva and absorbed through the gastrointestinal tract. However, it is convenient because 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 patient 1'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 patient 1 begin a daily aerobic exercise program and keep a detailed headache calendar: he advises

her to document the frequency, severity, and length of her headaches; association with possible trigger factors, such as menstruation; and information about the amount and type of medication she uses for her headaches.

She returns to the primary care physician 8 weeks later. Review of her headache 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. Patient 1 decides she is willing to pay out-of-pocket for this treatment.

Patient 1 and her physician also review options for improved abortive treatment of her headaches. Because patient 1 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. Because nausea is already a troubling part of her headache, patient 1 prefers to avoid ergotamine and its derivatives. She also expresses a strong preference for oral rather than injectable or nasal spray medications. A standard dose of one 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 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.

QUESTIONS

- **Is there any reason to choose one triptan over another?**
- **What are the safety and tolerability concerns with the triptans?**

DISCUSSION

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 appear similar, with response rates around 60%.⁶⁹ (The exception is naratriptan, with a response rate around 50%.) 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.⁷⁰ 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).⁷¹ 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 one attack of migraine in order to obtain one 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 one attack of migraine before experiencing one adverse event related to the drug.

Therefore, a method of choosing among the triptans is to select a drug with the lowest NNT and the highest NNH; this presumably would yield the best combination of efficacy and tolerability. For 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 1181.⁷⁰ Similarly, the NNT for subcutaneous sumatriptan compared with placebo has been calculated to be around 2.0.⁷² For a physician and patient with clear therapeutic goals, these numbers offer useful information. Patients who are risk-averse and willing to accept lower efficacy for correspondingly low side-effect liability may wish to choose naratriptan rather than sumatriptan. Other patients, with severe headache and disability, may willingly tolerate a higher side-effect penalty to ensure efficacy. Intelligent use of NNT and NNH estimates offers a method 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, because 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, because the placebo rates in various trials have differed markedly.⁷⁰

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 one triptan still have a good likelihood of response to another, and several should be tried before concluding that a patient is a triptan nonresponder.⁷³

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.⁴⁷

Despite being generally well-tolerated, the triptans as a group are capable of causing coronary vasoconstriction. Serious cardiac events, including myocardial

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infarction, have been reported in association with their use.^{74,75} 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.⁷⁶ 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 one or two 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.

QUESTION

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

DISCUSSION

Impact of Sex Steroids

Although men and women are probably equally likely to inherit a vulnerability to migraine, expression of the disorder is likely influenced by environmental factors (eg, 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.⁷⁷ 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.

Somerville demonstrated through a series of elegant experiments involving estrogen and progesterone supplements that it is likely that decreasing levels of estrogen are the trigger for headaches that occur around the menstrual period.⁷⁸ 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.⁷⁹

QUESTION

- **What is the association between migraine and stroke?**

DISCUSSION

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, as many as 33% of individuals with stroke will have a history of migraine, even in the absence of further links between the two conditions.⁸⁰

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.^{80,81} The percentage of stroke in the young attributed to migrainous infarction ranges from 0% to 20%, with a mean of 7%,⁸²⁻⁹⁵ and the estimated annual incidence of this phenomenon in the United States is 1.7/100,000.⁹⁶ The most commonly postulated mechanisms of migrainous infarction include vasospasm, cortical spreading depression

with prolonged oligemia, and in situ thrombosis related to hypercoagulability.⁹⁷ Arterial dissection, a cause of stroke in the young, may be more common in migraineurs.⁹⁸ Large-scale epidemiologic studies of men,⁹⁹ women,¹⁰⁰ and mixed populations¹⁵ 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.^{16,18,101–104}

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.^{16,18,100,102} 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.¹⁰⁴

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.¹⁰⁵ 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.¹⁰⁵ 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.¹⁰⁶

ADDITIONAL FOLLOW-UP

When patient 1 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 decreased by approximately 50%. Patient 1 has begun biofeedback training and finds it is improving her ability to cope with the head-

aches 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 anti-nausea 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 anti-nausea 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

Patient 2 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; his usual 2-mile run aggravates the pain.

For years, these headaches have occurred once or twice per year. However, over the past 18 months, these episodes have increased in frequency to several times per month. Patient 2 states that he is increasingly

anxious about their occurrence and, because he spends a great deal of time driving, he worries about what would happen if an episode occurred while he was on the road.

Patient 2 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. Patient 2 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

Patient 2 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 episodes have previously occurred.

QUESTION

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

DISCUSSION

Migraine and Psychiatric Disorders

Evidence from recent epidemiologic studies suggests there is significant comorbidity between migraine and certain psychiatric disorders, primarily affective disorders such as depression, anxiety, and panic.¹⁰⁷ Lifetime rates of affective and anxiety disorders are elevated in migraineurs, and in one 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,¹⁰⁸ 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.¹⁰⁹

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.¹¹⁰ 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 3.3.¹¹¹

Patient 2's case illustrates these principles. It seems likely that in addition to migraine with aura he has major depression and a panic disorder. The presence of these comorbid disorders needs to be accounted for when selecting treatment for patient 2.

QUESTION

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

DISCUSSION

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 one 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, because some studies argue that they may aggravate or cause depression.¹¹² It is important to remember that other studies argue against such an association;¹¹³ given the current state of the evidence, it is advisable to closely monitor migraine patients prescribed beta 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.

QUESTION

- **Does migraine improve with age?**

DISCUSSION

Course of Migraine

Migraine is, in most cases, a chronic illness. Cohort studies show 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.¹¹⁴ However, the frequency and intensity of headaches often diminish with age.¹¹⁵ 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.¹¹⁶

As patient 2'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.

QUESTION

- **What is the role of neuroimaging or specialized testing in the diagnosis of migraine?**

DISCUSSION

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.¹¹⁷ The Academy also discourages the use of electroencephalogram and thermography studies in this group

of patients.^{118,119} When imaging studies are obtained in patients with migraine, so-called *white, bright spots* on T-2 weighted images are common and of no significance¹²⁰ 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.

QUESTIONS

- **What evidence exists regarding the safety and efficacy of nonstandard, alternative treatments for migraine?**
- **What is the role of food triggers in migraine?**

DISCUSSION

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.¹²¹ Even more important, the majority of patients who used alternative therapy did not discuss this with their treating physician.

In one study of riboflavin (400 mg/day) versus placebo, riboflavin appeared to reduce frequency of migraine attacks, but the effect was not apparent until the fourth month of treatment.²⁷ 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.¹²²

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.¹²³

The role of food triggers in the production of migraine is probably overemphasized. 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. 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.

DIAGNOSIS AND TREATMENT

After the initial history and physical examination, the physician discusses her impression that the most likely diagnosis for patient 2 is migraine with aura. The physician 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. Patient 2 accepts the physician's advice that he replace his use of a barbiturate-containing medication with one of the newer triptans, and he also accepts a next-day consultation with a psychiatrist for psychopharmacologic evaluation. Patient 2 also agrees to keep a headache calendar and to return in 2 months for re-evaluation.

Two months later, patient 2 returns to his primary care physician. He tells her 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. Patient 2 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.

QUESTION

- **What information do we have about the costs and benefits of migraine therapy for individual patients and society in general?**

DISCUSSION

Costs and Benefits of Treatment

The cost of migraine therapy must always be weighed against the cost of untreated or inadequately treated migraine. One recent article reported the cost of migraine to American employers is around \$13 billion a year, with \$8 billion attributable to missed workdays. This study also pointed out that the average female migraineur required 5.6 bed rest days yearly, and that male sufferers requires an average 3.8 bed rest days yearly.⁴ Although the benefits of early identification of migraine patients and aggressive treatment for migraine have yet to be demonstrated prospectively, information

available suggests that both indirect and direct costs increase as headache grade increases. Thus, a subgroup of severely affected patients account for much of the burden of migraine.¹²⁴

It seems likely that early, targeted intervention in these patients could be highly cost-effective. An example that this may be possible can be seen in one recent study, which was able to show that the use of one of the new triptans substantially reduced lost work time and productivity.¹²⁵ In this study, patients treated with sumatriptan were followed for 6 months and information obtained about use of health care resources as well as time lost from both workplace and nonworkplace activity. Health-related quality of life and satisfaction measures were also monitored. Improvements in all of these parameters were shown. The number of workdays lost to migraine decreased by 0.5 days in the 3 months after triptan therapy was initiated and continued to decrease over the 6-month period.

Studies such as this are a step toward assessing the true cost-effectiveness of treatment, which is especially important in attempting to show that the new, more specific antimigraine 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?).¹²⁶

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. HP

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