SUPPLEMENT TO
MANAGED Care

Expanding the Boundaries Of Migraine Management: A Focus on Menstrual Migraine

Based on a breakfast symposium held at the Academy of Managed Care Pharmacy 2007 Annual Meeting, San Diego

HIGHLIGHTS

- Prevalence and Burden of Migraine and The Impact on Managed Care
- Epidemiology and Pathophysiology of Migraine
- Treatment of Menstrual Migraine: Evidence-Based Review
- Panel Discussion

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SELF-STUDY CONTINUING EDUCATION ACTIVITY

Expanding the Boundaries of Migraine Management: A Focus on Menstrual Migraine

Continuing education credit is offered to pharmacists who read pages 2 through 17 of this publication, and submit the evaluation form on page 20. Estimated time to complete this activity is 2.0 hours.

Target Audience

This program is targeted to pharmacists and other health care decision makers in managed care organizations, health systems, academia, and industry.

Purpose and Overview

This publication is based on an Academy of Managed Care Pharmacy (AMCP) breakfast symposium held in San Diego on April 12, 2007.

Migraine poses a considerable clinical and economic challenge for health plans, employers, and patients. This extremely prevalent condition costs $13 to $17 billion annually in the United States. A significant proportion of migraine-related direct costs is spent on prescription drugs.

New insights and understanding of the pathophysiology of migraine are leading to a reclassification of migraine as a chronic condition with acute episodes. This new understanding has led to migraine being increasingly treated with preventive medications to decrease attack frequency, increase the effectiveness of acute medication, prevent progression, and minimize costs. Several treatment guidelines have outlined a consistent approach to migraine prophylaxis. Additionally, there is an emerging concept in the field of migraine prophylaxis: short-term prevention. One of the best examples of the role of short-term prevention is the management of menstrual migraine. Unlike acute treatment, however, the optimal approach to migraine prophylaxis has yet to be identified. Emerging evidence suggests that the preventive treatment approach may vary based on migraine characteristics and associated treatment needs.

To develop sound policies that are consistent with the evidence and the evolving understanding of migraine, managed care decision makers need to learn about new advances in migraine prophylaxis and the emerging models in preventive treatment. This program will explore opportunities to optimize the short-term prevention of migraines in patients with specific treatment needs.

Educational Objectives

After reading this publication, participants will be able to:

- Distinguish clinical characteristics and treatment needs associated with different types of migraine, including menstrual migraine
- Discuss the goals of preventive migraine treatment
- Identify limitations associated with the traditional approach to migraine prophylaxis
- Evaluate the evidence supporting the role of various agents in intermittent or chronic prevention

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This supplement is supported by an educational grant from Endo Pharmaceuticals. The material in this supplement has been independently peer reviewed. The grantor played no role in reviewer selection.

Prevalence and Burden of Migraine And the Impact on Managed Care

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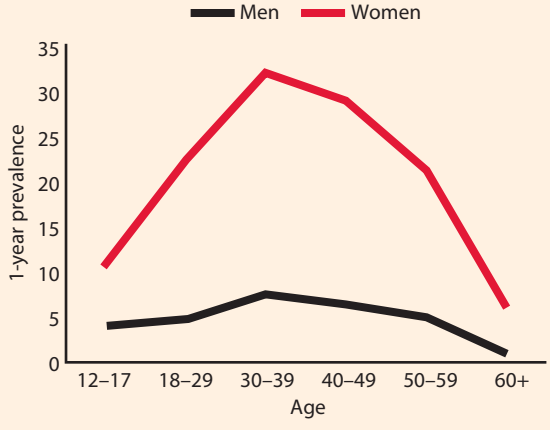
Migraine is a common disorder with a global impact. Its prevalence tends to be highest in North America and lowest in Africa and Asia (Lipton 2005). In virtually every locale, however, migraine is substantially more prevalent in women than in men. In the United States, overall prevalence is 11.7 percent, but the prevalence rates by sex are 17.1 percent and 5.6 percent for women and men, respectively (Lipton 2007). In this respect, migraine differs from many other chronic illnesses, such as diabetes, hypertension, and asthma, in which the gender imbalance is relatively slight. Migraine also differs from other chronic conditions in that its prevalence does not necessarily increase with age (Figure 1). Its prevalence is highest during the ages of peak productivity.

The prevalence of migraine has important economic implications. In the United States, the annual economic burden imposed by migraine has been estimated at $14 billion (Hu 1999). However, only 7 percent of that amount is attributed to direct medical costs (Figure 2). The remainder stems from indirect costs, in the form of missed workdays (59 percent) and reduced productivity (41 percent). This finding is of obvious importance to employers, and hence to managed care.

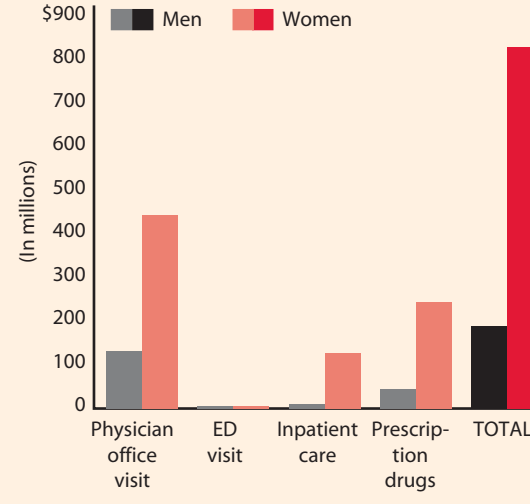
FIGURE 1
Prevalence of migraine in the United States



SOURCE: LIPTON 2007

These cost estimates fail to capture the full impact of migraine, however. First, they measure only migraine-related medical costs and migraine-related disability. If the costs of all the diseases and disorders associated with migraine were taken into account, the costs would probably rise exponentially. Second, the cost estimates fail to take into account the effect of migraine on families. In families with one or more migraineurs, total health care costs are substantially higher than in families with no migraineurs (Stang 2004). If a parent is a migraineur, mean total health care costs for the family are 70 percent higher than in families without migraineurs, and if both a parent and a child are migraineurs, the mean total health care costs are 90 percent higher. Third, measures of lost productivity do not include those individuals at home who do not work, children, and students. A Swedish study showed numerous negative effects of migraine on nonvocational aspects of life, with a negative effect on

FIGURE 2
Estimated direct annual costs associated with migraine attacks



ED=emergency department.
SOURCE: HU 1999

leisure time reported by 59 percent of respondents; on pursuing academic studies, 48 percent; sexual life, 43 percent; and love, 31 percent (Linde 2004). Because migraine is more prominent in women, migraine has a huge impact on child rearing.

In the following pages, Roger K. Cady, MD, reviews new scientific understanding of the pathophysiology of migraine. Stewart J. Tepper, MD, presents an evidence-based review of treatment of menstrual migraine, including recent studies evaluating the use of triptans for treating and preventing this disabling disorder.

References

Hu XL, Markson LE, Lipton RB, et al. Burden of migraine in the United States: disability and economic costs. *Arch Intern Med.* 1999;159:813–818.

Linde M, Dahlof C. Attitudes and burden of disease among self-considered migraineurs: a nation-wide population-based survey in Sweden. *Cephalalgia.* 2004;24:455–465.

Lipton RB, Bigal ME. Migraine: epidemiology, impact, and risk factors for progression. *Headache.* 2005;45[suppl 1]:S3–S13.

Lipton RB, Bigal ME, Diamond M, et al; AMPP Advisory Group. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology.* 2007;68:343–349.

Stang PE, Crown WH, Bizier R, et al. The family impact and costs of migraine. *Am J Manag Care.* 2004;10:313–320.

The Epidemiology and Pathophysiology Of Migraine

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Contemporary treatment of migraine is hindered by numerous myths. Migraine is considered to be a self-limited, episodic pain syndrome. For many people, that is undoubtedly true — but frequently, they are not the patients we see clinically. People seeking medical care for migraine live with a chronic condition that significantly affects multiple domains of their lives. Another myth, well ingrained, is that migraine is a vascular headache. In fact, it is nothing of the kind, and that terminology should be eliminated because it suggests blood vessels are behaving abnormally (May 1999). Migraine has been shown to be a neurological process. Even more devastating is the suggestion that, from a pathophysiologic perspective, migraine is just a stress disorder. To this way of thinking, people with migraine cannot cope with stress in the same way as other people do. Stress affects migraine much as it exacerbates hypertension or diabetes, but it is not the *cause* of migraine. Yet another myth is that migraine is just a component of the menstrual cycle. In this article, I wish to dispel old myths such as these and replace them with more recent scientific understanding about migraine.

One of the more recent concepts of migraine is that migraineurs have a nervous system that is physiologically and genetically unique from that of people without migraine (van de Ven 2007). This observation is borne out by a number of physiologic considerations. For example, the threshold for central nervous system activation by sensory stimuli is lower in migraineurs than in people without migraine. In addition, migraineurs have difficulty extinguishing sensory input to the nervous system as readily as individuals without migraine, who would just dismiss sensations after they are registered. This suggests that migraineurs have a unique nervous system.

Perhaps the most important fact about migraine is that it is not a vascular event but a neurological event — a *brain* disorder (Goadsby 2002). Also, uncontrolled migraine can progress into a chronic disease. Although chronic migraine lacks the catastrophic endpoint typically associated with chronic disease, it nevertheless can steal decades of a person's life. Those lost years often are the ones that otherwise would be the most productive in terms of vocation or child-rearing.

Migraine subtypes

Two classifications. The International Headache Society (IHS) divides migraine into two major subtypes, *migraine without aura* and *migraine with aura* (IHS 2004).

Migraine with aura sometimes is called *classic migraine*, but it is considerably less common than migraine without aura. The aura is a set of fully reversible, focal neurological symptoms that develop gradually over the course of 5 to 20 minutes and last no longer than 60 minutes. The most common types of aura are visual, sensory, and speech disturbances. Visual symptoms may be positive (flickering lights, spots, lines) or negative (vision loss). Sensory disturbances also may be positive (unilateral sensation of pins and needles, moving slowly away from a point of origin) or negative (numbness). Aura usually is followed by a headache with symptoms typical of migraine without aura.

For either subtype, the characteristics of the headache are unilateral location, a pulsating quality, pain of moderate or severe intensity, and aggravation by routine physical activity or causing the avoidance of routine physical activity. Two of these four characteristics are required for a diagnosis of migraine. In addition to the characteristic headache, the diagnosis of migraine requires that the patient experiences nausea, vomiting, or both, or sensitivity to light (photophobia) and sound (phonophobia). Untreated (or treated inadequately), the symptoms usually last 4 to 72 hours. Because migraine without aura can be confused with secondary headaches, the IHS requires at least five attacks with the preceding characteristics to diagnose migraine without aura. For a diagnosis of migraine with aura, only two attacks are required.

Menstrual migraine. In women, migraine without aura often has a strong menstrual component. The IHS describes two types of menstrual migraine, *pure menstrual migraine* and *menstrually-related migraine* (IHS 2004). Because of uncertainty over whether these are distinct entities, the IHS has assigned them to the appendix of its *International Classification of Headache Disorders,* second edition. This entry notes that to be diagnosed with pure menstrual migraine without aura, a menstru-

ating woman must meet the criteria for migraine without aura and her attacks must be perimenstrual — occurring in the 4-day interval starting 2 days prior to the first day of menstruation, and at no other time, during two of three menstrual cycles. The diagnostic criteria given by the IHS for menstrually-related migraine without aura are identical, except that attacks may also occur at other times during the cycle.

Pathophysiologic model of migraine

The balance between risk factors for migraine often are referred to as migraine triggers, and protective factors determine whether a given person crosses the migraine threshold and experiences a migraine attack. Thus far, more attention has been devoted to the risk factors than to the protective factors. The risk factors include alcohol, especially red wine; stress; skipped meals; weather changes and other alterations in the daily environment; food substances; medications; and menses. The protective factors include strategies people can use to stabilize and protect their nervous system from migraine. Simply put, protective factors are generally the things that are good for people's lives — regular sleep and wake patterns to keep the circadian clock properly set; regular meals, especially breakfast; regular exercise; and perhaps nutritional products, such as vitamins B2 and B12.

In a genetically sensitive nervous system, the various internal and external factors can increase the risk for migraine. In an environment conducive to migraine, changes in serotonin levels, norepinephrine levels, and other neurochemicals occur. As a result, many migraineurs experience premonitory symptoms. These often are referred to collectively as a *prodrome.*

Before the headache begins, migraineurs may notice mood changes. They may feel irritable, excited or energized, or perhaps depressed and anxious. They may experience changes in sensory perception, such that lights seem brighter and noises louder. They may feel fatigued. Often they notice changes in cognition, such as not thinking clearly and an inability to concentrate. They usually have food cravings, especially for things like chocolate. For years, we believed that chocolate is a major migraine trigger, but it is likely that for many it is just part of the food cravings that occur during the premonitory period.

Migraineurs often have muscle pain, which sometimes was attributed to stress and tension headaches. We now recognize muscle pain as a bona fide part of migraine. The same is true for nasal congestion, which often was associated with a sinus headache, but which we now recognize as autonomic symptomatology of migraine.

When a critical threshold is reached, activation in the brain stem or mid brain occurs. This has been called the *migraine generator,* but can be more accurately described as a migraine modulator.

In some (and possibly all) migraineurs, the next event is electrical instability, known as spreading cortical depression. It is known to occur in areas such as the visual cortex or the somatosensory cortex, producing the symptoms that we regard as aura, which precedes about 15 percent of migraine attacks (IHS 2004). Conceivably, spreading cortical depression could occur in a silent area of the brain, and there would be no clinical evidence of the event. This electrical instability may be a mechanism by which the trigeminal system is activated. Aura once was thought to be a consequence of blood vessel constriction, but now it is regarded as an electric event (spreading cortical depression) in the nervous system.

To understand migraine pain, we must consider how pain is processed in the head and face, which involves the trigeminal nerve. As its name implies, the trigeminal nerve has three branches. The ophthalmic branch goes to the forehead, cranial vault, the meninges, and the blood vessels. The maxillary branch extends to the midface and sinus cavities, and the mandibular branch to the lower jaw and the muscles of mastication, including the temporalis muscle. Inputs from each of these branches can contribute sensory inputs that occur as part of migraine symptomatology, but the ophthalmic branch probably is most critical. The ophthalmic branch innervates meningeal blood vessels. Activation of the trigeminal afferents innervating these vessels cause the release of a host of vasoactive peptides, such as substance P, neurokinin A, and a calcitonin gene-related peptide that cause the vessel to dilate (May 1999). Perhaps more importantly, the sensory threshold for the activation of the trigeminal nerve is lowered. Under these conditions, increased sensory input is transmitted along the trigeminal nerve and bombards second-order neurons in the nucleus caudalis in the brainstem. The nucleus caudalis under normal circumstances functions as a sensory filter but during migraine much of this inhibition is lost, thus more sensory information is brought into our conscious awareness.

Inputs from other divisions of the trigeminal nerve are important because of the sensory input they provide during migraine and the symptoms they produce. These symptoms are frequently causes of diagnostic confusion for patients and clinicians. Because of the autonomic symptomatology associated with migraine, if blood vessels in the nose become inflamed, the patient experiences mucosal swelling, edema, rhinorrhea, facial pressure, and eventually, pain. Based on the location of the symptoms, it is easy to understand why people might conclude that the pathology is in the sinuses. In one study, 88 percent of patients with a history of physician-diagnosed or self-described "sinus" headache, but with no history of migraine and no evidence of infection, met the IHS criteria for a migraine-type headache (Schreiber 2004).

Integration of trigeminal input and sensory input in the C2 and C3 dermatomes can give rise to symptoms of muscle pain, producing the sore, stiff muscles in the back of the neck that are commonly observed during an attack of migraine.

As the process of migraine progresses, the abundant sensory input begins to sensitize second-order neurons in the brainstem. This is followed by sensitization of third-order neurons in the thalamus and, eventually, sensitization of the nervous system itself, which is referred to as *central sensitization.* At its zenith, migraine is a centrally mediated allodynic pain syndrome, such that normal sensation becomes a signal of pain. Patients complain that their skin hurts and they do not want to be touched; doing so even lightly is painful to the migraineur. Not every migraine attack, however, progresses through all phases.

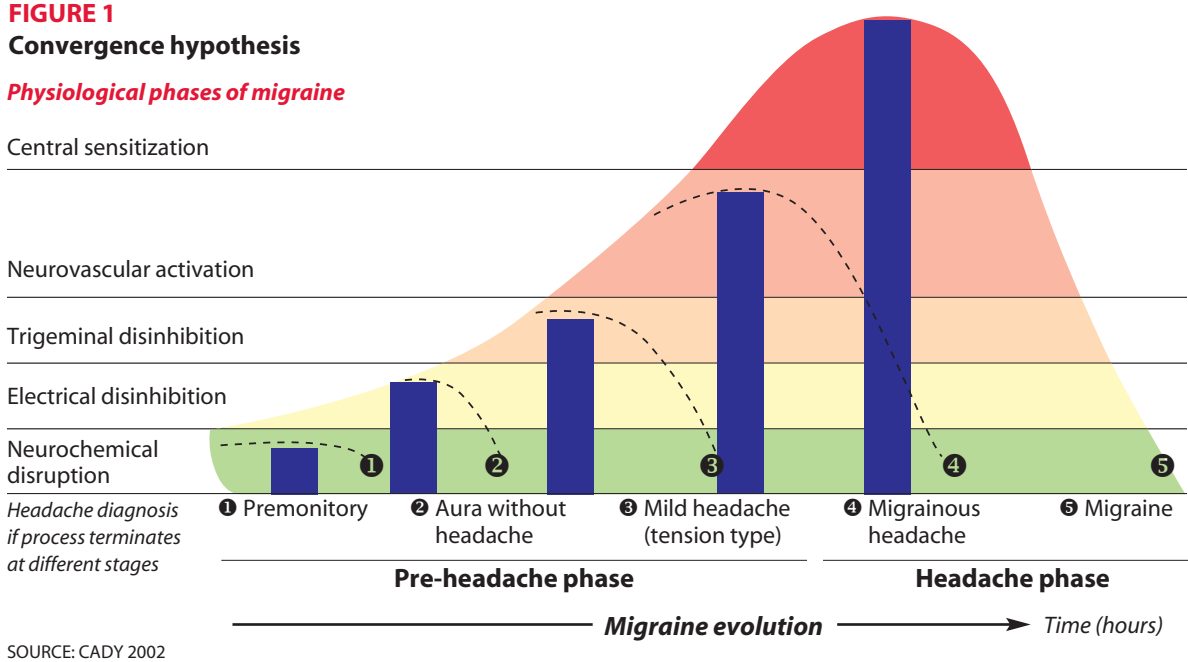
The majority of people with migraine experience a spectrum of headaches stemming from a common pathophysiologic mechanism (Figure 1). A symptom biopsy conducted after central sensitization has developed would likely show all the symptoms included in the IHS criteria for migraine, and the diagnosis of migraine would be obvious. But if the process leading to a fully developed attack of migraine is terminated prematurely, all of the classic symptoms might not be evident. A symptom biopsy earlier in the migraine process might suggest a migraine-like headache, or what has been called *probable migraine* or a *migrainous* headache, with one cardinal feature of migraine being absent. If the process has not advanced beyond the point of trigeminal disinhibition, the person might experience mild pain without any of the accompanying migraine symptoms. This headache would look like a tension headache, or what might be called a *tension headache of migraine.* If the process is terminated after spreading cortical depression has occurred, the patient might experience only the aura, and if the migraine is terminated during the premonitory period, only those symptoms of prodrome would be experienced. Premature termination of the migraine process can be due to treatment or it can be part of the natural history. It is important to understand that the patients we see often are managing multiple expressions of migraine.

The best definition of migraine simply may be a stable pattern of recurrent disabling headache without any evidence of underlying disease. When I was in medical school, we were taught that migraine was an episodic pain syndrome that would resolve. People would return to feeling normal even without treatment. In clinical practice, however, we see patients for whom this is not true. Between attacks of migraine, they do not return to normal, but instead are living on the verge of their next headache, or in a state of chronic headache.

Using the IHS criteria for migraine without aura, episodic migraine can be defined as 5 or more headache attacks, lasting 4 to 72 hours each, that include at least two of the following characteristics: (1) unilateral location; (2) moderate or severe pain intensity; (3) pulsation; and (4) aggravated by activity or causing the avoidance of routine activity. Attacks are also accompanied by at least one of the following: (a) nausea, vomiting, or both; or (b) photophobia and phonophobia (IHS 2004).

FIGURE 1
Convergence hypothesis

Physiological phases of migraine



SOURCE: CADY 2002

Effects of chronic migraine

Chronic migraine has been differentiated from episodic migraine on the basis of frequency — a migraine occurring 15 or more days per month for 3 or more months in the absence of medication overuse. With episodic migraine, sufferers return to normal function after the headache ends. Most of the time, the migraine resolves when the person goes to sleep; the nervous system fully recovers and returns to a state of normal function. For this population, headaches are self-limited, well defined, and meet the criteria of IHS migraine. Realistically, the diagnosis is often self-evident. As a consequence, this population of migraine sufferers will self-diagnose and self-treat their migraines.

Physicians often evaluate a different population of people with migraine — those who lose the pattern of returning to normal function between headaches. They have migraine, they sleep, and they awaken with more migraine. Even when the headache resolves, these patients often are not fully recovered. They often continue to have a low-grade headache, or they stay on the verge of their next headache. Their migraines are frequent. During more severe episodes of headache, they experience nausea, vomiting, and photophobia, but they also display many other symptoms, particularly psychological and myofascial symptomatology. These are the people who commonly become patients with migraine. When migraine becomes chronic, it is no longer just a headache. The population with chronic migraine has a group of comorbidities, many of which may be related to the neurologic disruption observed during migraine, although this contention is not easy to prove. In our clinic, these patients experience sleep disorders, gastrointestinal complaints, muscle complaints, and often psychological complaints, such as anxiety and depression. This population requires more than acute treatment for migraine. These are the individuals on antidepressants, anticonvulsants, and other preventive medications, and they often are being treated for other migraine comorbidities. This population of migraine suffers consume a tremendous amount of health care resources (Lipton 2001).

That migraine and depression are bidirectional supports the idea that the disorders are related neurochemically. Compared with controls over 2 years, subjects with migraine were 5.8 times more likely to develop depression, and subjects with major depression were 3.4 times more likely to develop migraine (Breslau 2003). If the depression were a consequence of living with recurrent pain, a unilateral association would be expected, such that the burden of pain would lead to depression.

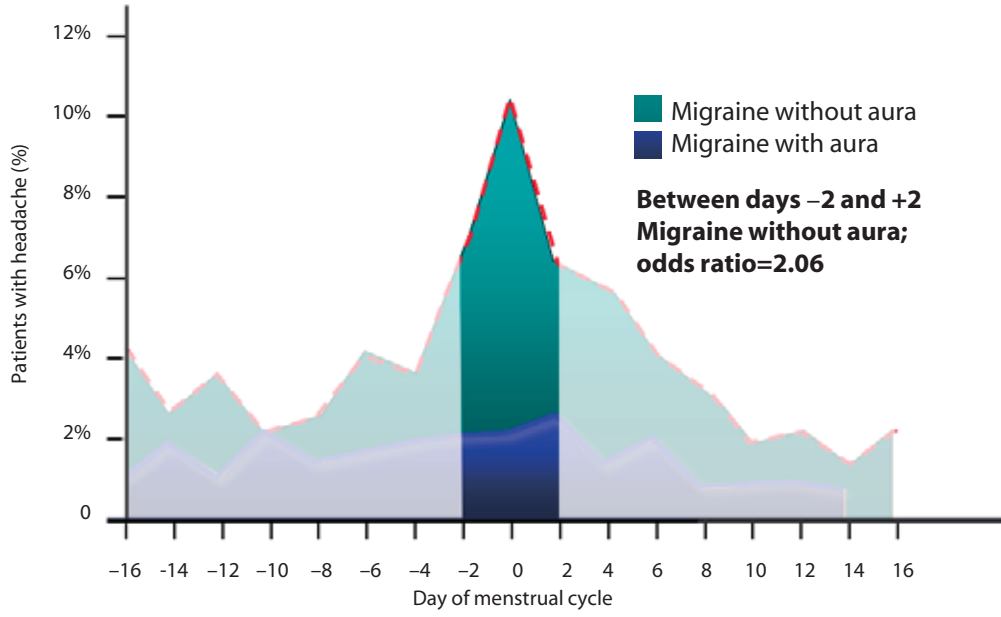
Menstrual migraine

Overall, migraine is about 3 times more prevalent in women than in men (Lipton 2007). For the group between 25 and 40 years of age, however, the gender bias is much greater, at least from a clinical perspective; the female-to-male ratio of migraineurs in this age group approaches 7 to 1. The most probable reason relates to changes in neurosteroid levels in the brain, which is supported by numerous observations. In children, migraine is more common in boys than in girls, but in women becomes more prevalent after menarche. During the reproductive cycle, migraine associated with the menses is very common. During pregnancy, however, when the hormonal environment is stabilized, the frequency of migraine tends to decrease. In contrast, during menopause, the hormonal environment is disrupted, and an increase in migraine often occurs. In the postmenopausal period, the prevalence of migraine declines. It would appear that estrogen acts as a protective factor against menstrual migraine. When estrogen levels decline, women with a genetic predisposition for migraine develop headaches. The basis for this belief was an experiment showing that migraine could be postponed by giving women estradiol, but not by giving them progesterone (Somerville 1971, Somerville 1972).

About 60 percent of female migraineurs have an association between migraine without aura and menses (Mannix 2004). A peak in the frequency of migraine without aura is seen in the 4-day interval encompassing the 2 days before and after the onset of menses (Figure 2, page 8). In 14 percent of these migraineurs, migraine occurs only at this time and not at any other during the menstrual cycle. These women are described by the IHS as having pure menstrual migraine (IHS 2004). It is possible, however, that if these women were followed long enough, they probably would be found to have migraine at other times, too. The other 46 percent are described as having menstrually-related migraine. There also is a spike in tension-type headache around the onset of menses. It is possible that many of these apparent tension-type headaches share the same pathophysiology as the menstrual headaches, but without displaying all of the symptoms of migraine, perhaps because treatment blocks the emergence of symptoms.

In the general population, menstrual migraine does not appear to differ from migraines occurring at other times during the menstrual cycle (Stewart 2000). However, in women referred to headache clinics, those who had menstrually-related migraine report them to be more frequent, more severe, and more often associated with vomiting than their nonmenstrual migraines (MacGregor 2004). In clinic populations, menstrual migraines also have been found to more likely cause work-related disability and are more likely to recur (Couturier 2003, Granella 2004). One study also reported that perimenstrual attacks were less responsive to acute therapy than nonmenstrual attacks (Granella 2004), but the authors observed that this finding may have been due to the fact that the patients used nonsteroidal anti-inflammatory

FIGURE 2
Migraine and the menstrual cycle



REPRODUCED WITH PERMISSION FROM: STEWART WF, LIPTON RB, CHEE E, ET AL. MENSTRUAL CYCLE AND HEADACHE IN A POPULATION SAMPLE OF MIGRAINEURS. *NEUROLOGY*. 2000;55(10):1517–1523

drugs far more often than triptans (74 percent versus 26 percent).

One of the barriers to the treatment of menstrual migraine is underrecognition of the condition. At first glance, it might seem a simple matter to discern the association between migraine and menses, but in practice, it is more difficult, particularly because migraines often occur before the onset of menses. If a woman is having migraines at other times during her menstrual cycle, sometimes the association is not made at all.

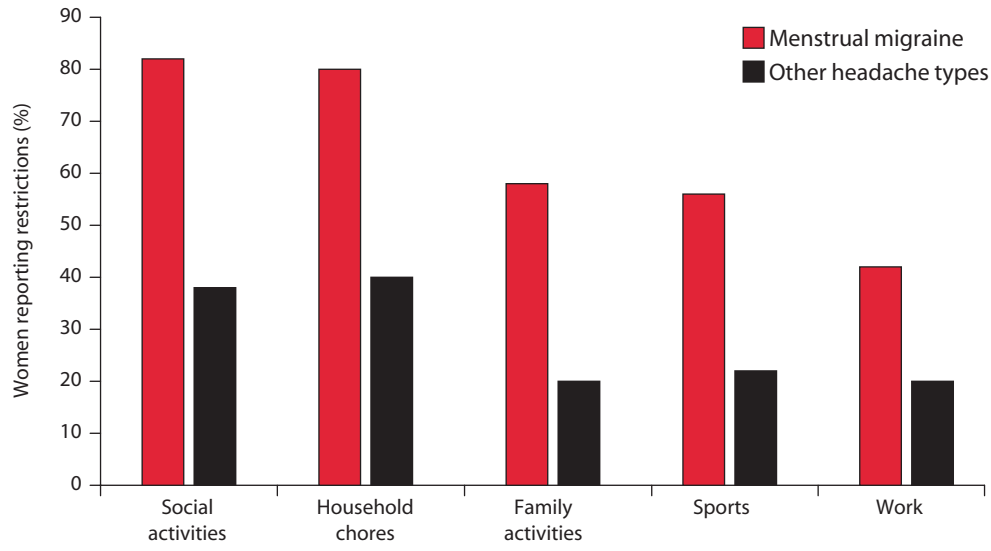
For some women, knowing that a migraine is likely to happen is an advantage, but for many of the patients I see in my practice, it is not. They postpone social events and plan vocational and family activities in frantic anticipation of a migraine attack. Compared with other headache types, menstrual migraines result in far greater restrictions in daily activities (Figure 3). When you consider the overall impact of this kind of headache, it becomes more than just migraine, and instead becomes an event that life must be planned around.

It is important to remember that menstruation itself often is a symptom-producing event. Compared with women without migraine, migraineurs have reported a higher frequency of menorrhagia (adjusted odds ratio [OR], 2.8) and endometriosis (adjusted OR, 6.2) along with a greater amount of interference in their lives during their menstrual periods (adjusted OR, 3.3) (Tietjen 2006). Premenstrual exacerbation of symptoms may be seen with many other disorders, including anxiety disorders, substance abuse, seizures, rheumatoid arthritis, irritable bowel syndrome, pain disorders, and asthma (Endicott 1993, Hendrick 1996, Case 1998). In a population seeking evaluation for premenstrual syndrome, about 40 percent met the criteria for anxiety disorder (7 percent), mood disorder (23 percent), or both (8 percent) (Bailey 1999). In such women, a migraine attack during or associated with menses will only exacerbate their overall burden.

Conclusion

No longer regarded as a vascular disorder, migraine now is regarded as a brain disorder. Its pathophysiology often produces symptoms that cause it to be mistaken for a sinus headache or a tension-type headache by patients and health care providers alike. Many people with migraine never seek medical care, because their attacks are episodic and respond to acute treatment, such that the person regains normal functioning. In contrast, many migraineurs who seek out medical evaluation for migraine have a chronic condition characterized by frequent, severe headaches, and they often fail to return to normal neurological function between attacks of definable migraine. It is important to prevent episodic migraine from progressing to chronic migraine, because the chronic disorder is associated with comorbidities that greatly increase the disease burden, complicate treat-

FIGURE 3
Headache-related restrictions in daily activities



SOURCE: COUTURIER 2003

ment, and increase health care costs. This is the rationale for early identification of migraine patients and for providing them with effective management skills and treatment.

References

Bailey JW, Cohen LS. Prevalence of mood and anxiety disorders in women who seek treatment for premenstrual syndrome. *J Womens Health Gend Based Med.* 1999;8:1181–1184.

Breslau N, Lipton RB, Stewart WF, et al. Comorbidity of migraine and depression: investigating potential etiology and prognosis. *Neurology.* 2003;60:1308–1312.

Cady R, Schreiber C, Farmer K, Sheftell F. Primary headaches: a convergence hypothesis. *Headache.* 2002;42:204–216.

Case AM, Reid RL. Effects of the menstrual cycle on medical disorders. *Arch Intern Med.* 1998;158:1405–1412.

Couturier EG, Bomhof MA, Neven AK, van Duijn NP. Menstrual migraine in a representative Dutch population sample: prevalence, disability and treatment. *Cephalalgia.* 2003;23:302–308.

Endicott J. The menstrual cycle and mood disorders. *J Affect Disord.* 1993;29:193–200.

Goadsby PJ, Lipton RB, Ferrari MD. Migraine – current understanding and treatment. *N Engl J Med.* 2002;346:257–270.

Granella F, Sances G, Allais G, et al. Characteristics of menstrual and nonmenstrual attacks in women with menstrually related migraine referred to headache centres. *Cephalalgia.* 2004;24:707–716.

Hendrick V, Altshuler LL, Burt VK. Course of psychiatric disorders across the menstrual cycle. *Harv Rev Psychiatry.* 1996;4:200–207.

IHS (International Heada

Lipton RB, Bigal ME, Diamond M, et al; AMPP Advisory Group. Migraine prevalence, disease burden, and the need for preventive therapy. *Neurology.* 2007;68:343–349.

Lipton RB, Stewart WF, Diamond S, et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. *Headache.* 2001; 41: 646–657.

Mannix LK, Calhoun AH. Menstrual migraine. *Curr Treat Options Neurol.* 2004;6:489–498.

May A, Goadsby PJ. The trigeminovascular system in humans: pathophysiologic implications for primary headache syndromes of the neural influences on the cerebral circulation. *J Cereb Blood Flow Metab.* 1999;19:115–127.

MacGregor EA, Hackshaw A. Prevalence of migraine on each day of the natural menstrual cycle. *Neurology.* 2004;63: 351–353.

Schreiber CP, Hutchinson S, Webster CJ, et al. Prevalence of migraine in patients with a history of self-reported or physician-diagnosed "sinus" headache. *Arch Intern Med.* 2004;164:1769–1772.

Stewart WF, Lipton RB, Chee E, et al. Menstrual cycle and headache in a population sample of migraineurs. *Neurology.* 2000;55:1517–1523.

Somerville BW. The role of progesterone in menstrual migraine. *Neurology.* 1971;21:853–859.

Somerville BW. The role of estradiol withdrawal in the etiology of menstrual migraine. *Neurology.* 1972;22:355–365.

Tietjen GE, Conway A, Utley C, et al. Migraine is associated with menorrhagia and endometriosis. *Headache.* 2006;46: 422–428. Erratum in: *Headache.* 2006;46:548.

van de Ven RC, Kaja S, Plomp JJ, et al. Genetic models of migraine. *Arch Neurol.* 2007:64:643–646.

Treatment of Menstrual Migraine: Evidence-Based Review

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Most physicians regard migraine as a disorder for which acute treatment is the appropriate (and sometimes the only) therapy. Acute treatment alone, without preventive therapy, is warranted when migraine attacks are infrequent. Even if a patient experiences disabling migraines, a migraine-specific medication (e.g., a triptan) taken during the early stage of the attack can result in the patient being pain-free within a few hours and often without recurrence. If a patient has frequent migraines or responds poorly to therapy, two concerns arise. The first is the extent of the disability caused by the migraines, and the second is that episodic migraine might transform into chronic daily headache, which is far more difficult to treat. If the migraines are predictable, for example occurring at menses, short-term preventive strategies can be considered to reduce the severity and duration of menstrual migraines, if not eliminate them completely (Figure).

The theoretical advantages of short-term prophylactic treatment are that the patient would be exposed to fewer days of drug treatment, and direct and indirect costs would be lower because disability would be reduced. Short-term prevention is not suitable for a woman whose menses are irregular, but it would be an option for a woman with regular periods who is reasonably certain when a menstrual migraine is likely.

A headache diary is a critical tool for the management of any patient with migraine. The diary eliminates recall bias with respect to the timing and characteristics of menses and headaches, and it enables the clinician to assess the reliability of the occurrence of migraine with respect to a particular day of flow, as well as to gauge the effects of treatment. The diary also cements the therapeutic alliance between patient and caregiver, and it dramatically improves the quality of care.

For acute treatment of menstrual migraines, triptans work quite well, as menstrual migraines are still migraines. The efficacy of triptans as acute treatment has been demonstrated in numerous placebo-controlled trials.*

When evaluated using conventional endpoints, there appears to be little difference in the efficacy of triptans for acute treatment of menstrual migraine compared with their efficacy in nonmenstrual migraines. For example, in one study patients received placebo or an injection of sumatriptan, which was shown to provide equivalent headache relief after one hour for menstrually-related migraines and nonmenstrually-related migraines alike (Solbach 1993). This study, however, provided no details about what happened to the subjects later that day or the next day, nor did it provide any information about consistency across menstrual migraine attacks. Similarly, a study of rizatriptan demonstrated that it provided relief from moderate to severe pain in menstrually-related migraine after 2 hours (Silberstein 2000), but was silent on the question of whether headaches recurred later in the day, or what happened on subsequent days, or if rescue medication was needed. A recent study of zolmitriptan 2.5 mg for acute treatment of menstrual migraine showed that it was efficacious in reducing pain 2 hours posttreatment as well as in reducing the likelihood of recurrence (Tuchman 2006). A 2-hour headache response was reported by 66 percent of the zolmitriptan group versus 33 percent of the placebo group ($P<.0001$), and recurrence was reported in 29 percent of zolmitriptan-treated attacks versus 45 percent of placebo-treated attacks ($P=.0009$).

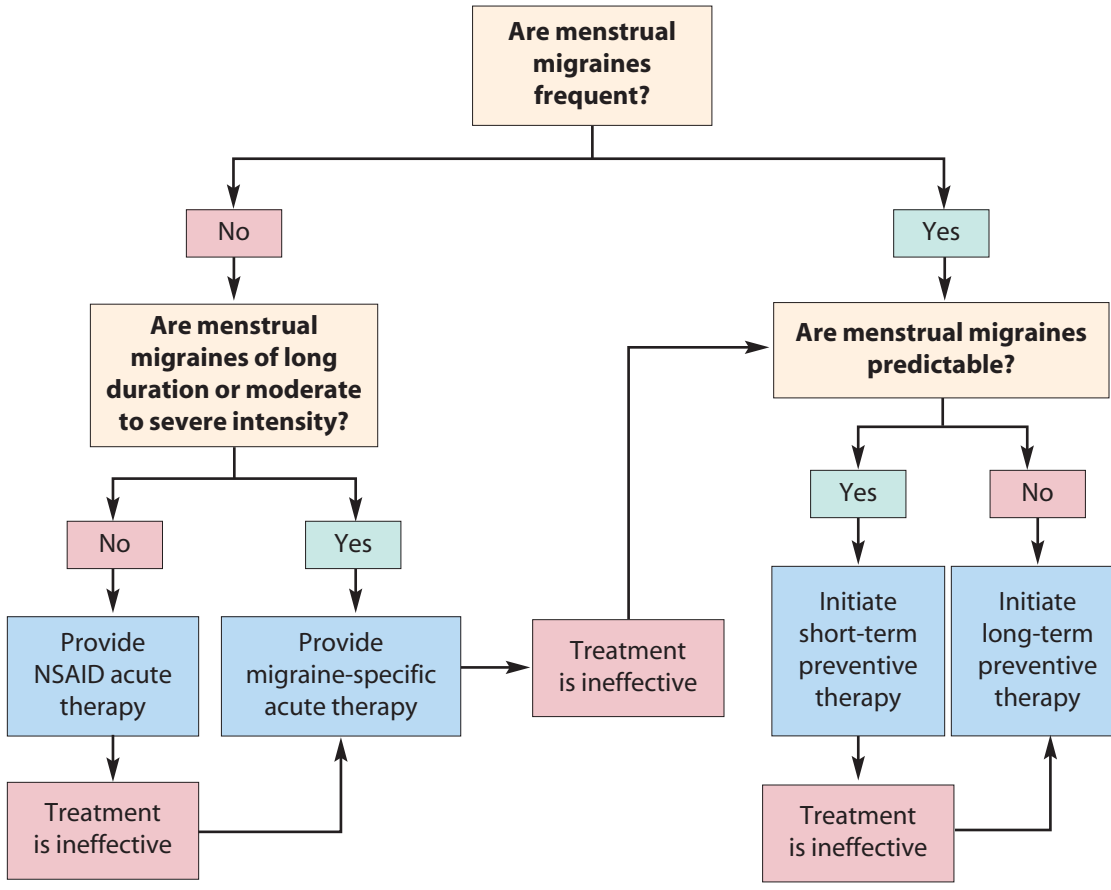
Many women think that acute treatment is all they need, because it makes them pain-free, reduces the risk of recurrence, and enables them to function. In some respects, the recent zolmitriptan study supports that notion. Another way of looking at these results, however, is to note that headache recurred in 29 percent of the zolmitriptan-treated patients. They represent the group that will have difficulty controlling their menstrual migraines over time, which raises the question of whether short-term preventive strategies provide a model for managing this group of patients.

Prevention using agents other than triptans

Several agents for short-term prevention of menstrual migraine have been tested in randomized clinical trials. Some of these trials reported negative findings, some

* Solbach 1993, Silberstein 2000, MacGregor 2000, Loder 2004, Massiou 2005.

FIGURE
Menstrual migraine pharmacologic treatment decision tree



NSAID=nonsteroidal anti-inflammatory drug.
SOURCES: TEPPER 2006, SNOW 2002

used questionable methodologies, and most enrolled only a small number of subjects.

Magnesium. Magnesium is postulated to affect the pain threshold, and magnesium supplements can prevent migraine in some patients. This was demonstrated in a small study (N=24, with efficacy data for 20) in which magnesium was provided from the start of ovulation (day 15) until the beginning of menses (Facchinetti 1991). Patients were randomized to placebo or magnesium pyrrolidone carboxylic acid (equivalent to a daily dose of 360 mg of magnesium) from the 15th day of the menstrual cycle until the next menstrual flow. During the next two cycles, both groups received magnesium. In the magnesium-treated group, a statistically significant reduction was observed in the number of days with headache (from 4.7 days in the first month to 2.4 days in the second month; $P<.01$) and the total pain index ($P<.03$). In comparison with 15 migraine-free controls, the migraineurs were found to have intracellular magnesium deficiencies that were restored after treatment, supporting the hypothesis that a magnesium deficiency may play a role in the pathophysiology of some women with menstrual migraine. Given that the subjects received magnesium for 2 weeks, this protocol does not quite fit the description of "short-term" prophylaxis, and it has not been repeated.

Naproxen sodium. Nonsteroid anti-inflammatory drugs are commonly used for short-term prevention of menstrual migraine, but only one randomized controlled trial supports their use (Sances 1990). This was a small, double-blind, placebo-controlled study (N=40; completers=35) in which women with menstrual migraine received treatment with naproxen or placebo from the 7th day before the expected onset of menstruation through the 6th day of menstrual flow for three menstrual cycles. In months 4 through 6, the study was opened and the women who had been receiving placebo were switched to naproxen. During the blinded portion,

migraine-free months were experienced by 17 percent, 33 percent, and 33 percent of naproxen-treated patients in months 1, 2, and 3, respectively, but no patients who received placebo were migraine-free. Moreover, statistically significant improvement in several other headache measures was seen in patients who received intermittent naproxen for all 6 months in comparison with the placebo group.

Estrogen. Estrogen is commonly prescribed to prevent menstrual migraine, but the results of clinical trials have been equivocal. Initial studies of estrogen patches and gels were conducted in the 1980s. The first showed positive results; patients treated with estradiol gel experienced migraine attacks less frequently than patients who received placebo, and the attacks that did occur when estradiol was administered were of short duration and less severity than those occurring when placebo was applied (de Lignieres 1986). This study employed a double-blind, placebo-controlled, crossover design enrolling 20 women with menstrual migraine and regular menstrual cycles. The patients applied either 2.5 g of gel containing estradiol 1.5 mg or placebo (gel only) for 7 consecutive days, starting 48 hours before the expected onset of migraine. This was done for three consecutive cycles in the pattern of estradiol-placebo-estradiol or placebo-estradiol-placebo. Eighteen women completed the trial, resulting in 26 cycles in which estradiol was applied (one cycle was missed because of amenorrhea) and 27 in which placebo was applied. Menstrual migraine attacks occurred during 97 percent (26 of 27) of the placebo cycles, but only 31 percent (8 of 26) of the estradiol cycles. In addition, all of the migraine attacks during placebo cycles lasted at least 24 hours, and 92 percent (24 out of 26) were rated as severe. In contrast, only one attack during estradiol cycles lasted more than 12 hours and was rated as moderate. One patient reported a migraine attack 3 days after stopping estradiol treatment, but no breast soreness or mood changes were reported.

Another study employing a double-blind, placebo-controlled, crossover design (N=22) showed a reduction in the occurrence of moderate or severe migraine in women receiving estradiol 1.5 mg in 2.5 g of gel (Dennerstein 1988). The medication was administered for 7 days encompassing menstruation, starting two days before the expected onset of migraine, for four cycles.

In studies of transdermal estrogen patches for short-term prophylaxis, dosage appears to be a factor in determining efficacy. A placebo-controlled study enrolling 20 women with pure menstrual migraine showed no benefit from a patch delivering 50 mcg of 17-β estradiol per day, in terms of reductions in the number, duration, or frequency of attacks (Smits 1994). A second, open-label study, in which patients received either 100 mcg or 25 mcg doses, suggested that use of rescue medication could be reduced with the higher dose ($P<.05$), but not the lower one.

More recently, however, another trial of short-term prevention with estradiol gel found that the benefits seen in the estradiol group were offset by the emergence of postdosing migraines (MacGregor 2006). This study was a double-blind, placebo-controlled, crossover study that enrolled 35 women. Participants applied a placebo gel or gel containing estradiol 0.5 mg 3 times daily, starting 9 days after their surge in luteinizing hormone as determined by a home fertility monitor (about 6 days before the first full day of menses) and continuing through the second full day of bleeding. For six cycles, the women alternated between placebo and estradiol treatment during this interval. Compared with placebo, estradiol was associated with a 22 percent reduction in the number of migraine days ($P=.04$) and reductions in headache severity and nausea, but these benefits were offset by a 40 percent increase in migraine during the 5 days after estradiol cessation. Beyond this 5-day window, there was no increased risk of postdosing migraine.

Prevention trials with triptans

Seven triptans are indicated in the United States for the acute treatment of migraine attacks. Three triptans (naratriptan, zolmitriptan, and frovatriptan) have been evaluated in randomized, double-blind, placebo-controlled trials for short-term prophylaxis of menstrual migraine, but thus far only two of these trials have been published in full peer-reviewed form (Newman 2001, Silberstein 2004).

The first trial of a triptan as short-term prophylaxis for menstrual migraine was an open-label study enrolling 20 patients who were refractory to other treatments (Newman 1998). They received oral sumatriptan 25 mg, 3 times daily for 5 days, starting 2 days before the expected onset of migraine. Headache was found to be absent in 52 percent of patients and migraine severity was reduced by 50 percent or greater in 42 percent of patients.

Naratriptan. The encouraging results achieved with sumatriptan prompted double-blind, placebo-controlled trials of naratriptan, which was selected for study because of its tolerability and longer half life (Newman 2001). Patients were randomized to placebo (n=66) or naratriptan 1 mg (n=70) or 2.5 mg (n=70) twice daily for 5 days, starting 2 days before the expected onset of migraine, for four cycles. The primary efficacy endpoint was the number of migraines occurring during four perimenstrual periods, defined as the 6-day interval beginning 2 days before the onset of menses. In the naratriptan 1 mg twice daily group, 61 percent of patients experienced migraines during 50 percent or more of their perimenstrual periods, compared with 38 percent of the patients in the placebo group ($P<.01$). Compared with the placebo group, patients receiving naratriptan 1 mg twice daily also had a lower median frequency of migraines (4 versus 2; $P<.01$) and a lower median number of migraine

days (7 versus 4; $P<.01$). However, the differences between the naratriptan 2.5 mg group and the placebo group for these measures did not reach statistical significance.

Two additional studies of naratriptan 1 mg showed similar results. In the first, 365 women were randomized to placebo or naratriptan 1 mg twice daily for a 6-day interval, starting 3 days before the expected onset of migraine, for four cycles (Savani 2002). The primary endpoint was the number of perimenstrual periods without migraine, which was achieved by 34 percent of the naratriptan group versus 24 percent of the placebo group ($P=.002$).

The other trial was an open-label, noncomparative pilot study enrolling 61 women with pure menstrual migraine (Moschiano 2005). During a 3-month observation period prior to naratriptan administration, the patients were required to have at least one migraine attack during the five-day perimenstrual period, starting two days before the onset of menses, and no migraine attacks at other times during the menstrual cycle. During the 3-month treatment period, the women took naratriptan 1 mg twice daily for a 6-day period. The intent-to-treat population consisted of the 59 women who took at least 1 dose of naratriptan and completed at least two headache diaries during the observation period and two diaries during the treatment period. During the observation period, the mean number of menstrual migraine attacks was 3.5, but during the treatment period it was reduced to 1.6 attacks. A decrease of 50 percent or more in the mean number of attacks occurred in 61 percent of the subjects. Additionally, during the observation period, the women were free of migraine during only 14 percent (24/177) of their cycles, but during the treatment period they were migraine-free during 54 percent (87/162) of cycles.

Frovatriptan. Another trial that examined the use of a triptan for short-term prophylaxis of menstrual migraine was a placebo-controlled, cross-over study evaluating frovatriptan 2.5 mg once- or twice-daily (Silberstein 2004). Patients received placebo or frovatriptan for 6 days, starting 2 days before the expected onset of menstrually-related migraine,[1] over the course of three menstrual cycles. Six different dosing sequences were utilized, such that each patient who completed the study would receive each of the three regimens once in a crossover design: placebo (n=505), once-daily frovatriptan (n=501), and twice-daily frovatriptan (n=501). On the first day of frovatriptan administration, patients received a double loading dose (i.e., 5 mg once daily or 5 mg twice daily) to achieve a therapeutic blood level quickly.

[1] The terminology used in this study was *menstrually associated migraine,* the definition of which is equivalent to the IHS terminology for *menstrually-related migraine,* as used in this publication.

The primary endpoint was the incidence of menstrual migraine during the 6-day treatment period. Compared with the incidence of migraine in the placebo group (67 percent), migraine incidence was significantly lower in the once-daily frovatriptan group (52 percent; $P<.0001$) and the twice-daily group (41 percent; $P<.0001$). In addition, the difference between the two frovatriptan groups was statistically significant ($P<.001$), and 51 percent of the patients receiving twice-daily frovatriptan experienced no menstrually-related migraines.

The incidence of moderate or severe migraine also was significantly lower in both frovatriptan groups (once-daily, 37 percent; twice-daily, 28 percent) in comparison with the placebo group, in which 51 percent of patients experienced moderate or severe migraine ($P<.0001$). The difference between the frovatriptan groups was statistically significant as well ($P<.01$).

The size of the study and the level of statistical significance made for very robust results. One potential limitation in the interpretation of the results could stem from errors in the timing of the dosing of study medication in relation to the expected onset of migraine, due to natural variation in cycle length.

As a result of the positive study outcomes, a subsequent regulatory trial of frovatriptan was completed, which has not yet been published. In May 2006, full data from this study were submitted to the U.S. Food and Drug Administration to request a new indication for frovatriptan, for short-term prophylaxis of menstrual migraine.

Once- and twice-daily frovatriptan 2.5 mg also have been evaluated in a study population including both patients on oral contraceptives (n=166) and patients not using oral contraceptives (n=284) (Singer 2003). Treatment began with a 10-mg loading dose on the first day of the 6-day treatment interval, starting 2 days before expected onset of migraine. Compared with placebo, the frovatriptan regimen reduced the frequency and severity of menstrual migraines, and there was no increase in adverse events or difference in efficacy in the oral contraceptive users.

Zolmitriptan. Most recently, zolmitriptan has been evaluated for short-term prevention of menstrual migraine. Participants (N=244) were randomized to either receive zolmitriptan 2.5 mg 2 or 3 times daily or placebo for 7 days, beginning on the second day before the expected start of menses (Tuchman 2005). The primary endpoint was the percentage of patients with a 50 percent or greater reduction in frequency and mean number of headaches. In this study, twice-daily dosing appeared to be about as effective as thrice-daily dosing, as 55 percent and 59 percent of the patients in these groups, respectively, had a greater than 50 percent reduction in perimenstrual periods with headache.

In summary, randomized controlled trials have suggested that three triptans — naratriptan, frovatriptan, and zolmitriptan — have demonstrated efficacy as short-term prophylaxis for reducing the incidence of menstrual migraine. They appear to be well-tolerated,[2] but long-term safety data have not yet been published. Thus far, no triptan has been FDA approved for short-term prevention of menstrual migraine, but regulators are evaluating data for one (frovatriptan) and a decision on that application is expected this year.

Conclusion

What is the optimal strategy for preventing migraines during the menstrual and perimenstrual periods? Some physicians favor boosting the dosage of conventional preventive drugs during these times, but no data support this practice, which has been clinically disappointing. Continuous dosing of oral contraceptives may suppress menstrual migraines, and this practice is commonly employed in primary care and gynecology offices, in which patients with severe menstrual migraines are put on continuous oral contraceptives for three or four months at a time. The long-term safety of this practice for migraine control has not been established, and some caution may be warranted, especially in those patients with migraine with aura. In most migraineurs, oral contraceptives are not contraindicated, even though both migraine and oral contraceptives are associated with an increased risk of ischemic stroke, but patients who have migraine with aura are at twice the risk of ischemic stroke as patients who have migraine without aura (Massiou 2000).

If patients experience frequent severe attacks throughout the month, long-term preventive strategies are required. In carefully selected patients, however, the predictability of menstrual migraines facilitates short-term prophylaxis as a strategy for dealing with these disabling headaches.

References

de Lignieres B, Vincens M, Mauvais-Jarvis P, et al. Prevention of menstrual migraine by percutaneous oestradiol. *Br Med J (Clin Res Ed)*. 1986;293:1540.

Dennerstein L, Morse C, Burrows G, et al. Menstrual migraine: a double-blind trial of percutaneous estradiol. *Gynecol Endocrinol.* 1988;2:113–120.

Facchinetti F, Sances G, Borella P, et al. Magnesium prophylaxis of menstrual migraine: effects on intracellular magnesium. *Headache.* 1991;31:298–301.

Frovatriptan (Frova) prescribing information. Chadds Ford, Pa.; Endo Pharmaceuticals. April 2007.

Loder E, Silberstein SD, Abu-Shakra S, et al. Efficacy and tolerability of oral zolmitriptan in menstrually associated migraine: a randomized, prospective, parallel-group, double-blind, placebo-controlled study. *Headache.* 2004;44:120–130.

[2] Major side effects for triptans include head, jaw, chest or arm discomfort, tightening, or tingling, throat discomfort, muscle cramps, or flushing. See product inserts for additional information

MacGregor EA, Frith A, Ellis J, et al. Prevention of menstrual attacks of migraine: a double-blind placebo-controlled crossover study. *Neurology*. 2006;67:2159–2163.

MacGregor EA, Keywood C. Frovatriptan is effective in menstrually associated migraine [abstract 196]. *Cephalalgia.* 2000;20:345.

Massiou H, Jamin C, Hinzelin G, Bidaut-Mazel C; The French Naramig Collaborative Study Group. Efficacy of oral naratriptan in the treatment of menstrually related migraine. *Eur J Neurol.* 2005;12:774–781.

Massiou H, MacGregor EA. Evolution and treatment of migraine with oral contraceptives. *Cephalalgia.* 2000;20:170–174.

Moschiano F, Allais G, Grazzi L, et al. Naratriptan in the short-term prophylaxis of pure menstrual migraine. *Neurol Sci.* 2005;26(suppl 2):S162–S166.

Naratriptan (Amerge) prescribing information. Research Triangle Park, N.C.: GlaxoSmithKline. June 2006.

Newman LC, Lipton RB, Lay S, Solomon S. A pilot study of sumatriptan as intermittent prophylaxis of menstruation-related migraine. *Neurology*. 1998;51:307–309.

Newman LC, Mannix LK, Landy S, et al. Naratriptan as short-term prophylaxis of menstrually associated migraine: a randomized, double-blind, placebo-controlled study. *Headache* 2001;41:248–256.

Sances G, Martignoni E, Fioroni L, et al. Naproxen sodium in menstrual migraine prophylaxis: a double-blind placebo controlled study. *Headache.* 1990;30:705–709.

Savani N, Loftus J, Mansbach H, Scott A. A randomized, double-blind, placebo-controlled, parallel group evaluation of oral naratriptan 1 mg twice daily as prophylactic treatment for menstrually associated migraine [abstract P-45]. *Cephalalgia.* 2002;22:25.

Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. *Neurology*. 2004;63:261–269.

Silberstein SD, Massiou H, Le Jeunne C, et al. Rizatriptan in the treatment of menstrual migraine. *Obstet Gynecol.* 2000;96:237–242.

Singer R, Schim J. Frovatriptan for prophylaxis of menstrually associated migraine: efficacy and tolerability in patients using oral contraceptives compared to nonusers [abstract S168]. *Headache.* 2003;43:587.

Smits MG, van der Meer YG, Pfeil JP, et al. Perimenstrual migraine: effect of Estraderm TTS and the value of contingent negative variation and exteroceptive temporalis muscle suppression test. *Headache.* 1994;34:103–106.

Snow V, Weiss K, Wall EM, Mottur-Pilson C; American Academy of Family Physicians; American College of Physicians-American Society of Internal Medicine. Pharmacologic management of acute attacks of migraine and prevention of migraine headache. *Ann Intern Med.* 2002;137:840–849.

Solbach MP, Waymer RS. Treatment of menstruation-associated migraine headache with subcutaneous sumatriptan. *Obstet Gynecol.* 1993;82:769–772.

Tepper SJ. Tailoring management strategies for the patient with menstrual migraine: focus on prevention and treatment. *Headache.* 2006;46(suppl 2):S61–S68.

Tuchman M, Hee A, Emeribe U. Oral zolmitriptan 2.5 mg demonstrates high efficacy and good tolerability in the prophylactic treatment of menstrual migraine headaches [abstract OR13]. *Headache.* 2005;45:771–772.

Tuchman M, Hee A, Emeribe U, Silberstein S. Efficacy and tolerability of zolmitriptan oral tablet in the acute treatment of menstrual migraine. *CNS Drugs.* 2006;20:1019–1026.

Zolmitriptan (Zomig) prescribing information. Wilmington, Del.: AstraZeneca Pharmaceuticals LP. 2007.

PANEL DISCUSSION

Optimal Patient Management

PANELISTS

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The opening presentations at "Expanding the Boundaries of Migraine Management: A Focus on Menstrual Migraine" generated a robust panel discussion among the presenters. Topics covered included early identification of migraine patients through the use of headache diaries, the role of several agents for short-term prevention, and the need for pharmacoeconomic data on both the direct and indirect costs of migraine. Excerpts from this discussion are presented below.

DIANA I. BRIXNER, PhD, RPh: From a managed care perspective, how cost-effective is it to start treatment when aura appears to prevent a menstrual migraine? Or is it better to treat a predictable menstrual migraine? If we see the potential for managing a predictable migraine in women, does that challenge our thinking on quantity limits in that population? Can we show whether there is a benefit in allowing access to these drugs in that capacity? For example, what is the impact of a 50 percent reduction in menstrual migraine in terms of time and productivity at work?

STEWART J. TEPPER, MD: One of the mistakes we see clinically is physicians recommending that triptans be given at the beginning of aura. Several prospective, randomized controlled trials have shown that triptans are effective only when the aura is over and the pain is beginning. So an appropriate recommendation is to have patients wait until the aura is over. Every so often, someone will swear they can take a triptan at the beginning of aura and prevent the pain. But it is not proven in randomized controlled trials. In those few patients who have predictable aura linked to migraine headache, the triptan should be administered at the onset of pain.

BRIXNER: We need pharmacoeconomic data on women who consume large amounts of medications during their periods [but] end up in emergency rooms. One trip to the ER... is more than $1,000, and one can pay for an awful lot of triptan for $1,000.

ROGER K. CADY, MD: This underscores the need to keep headache diaries and look for predictability. Sometimes people have aura with no headache or a mild headache. If this is a pattern you see, it certainly shapes your treatment recommendations for that person. On the other hand, if the aura means that 95 percent of the time this individual will go on to a disabling migraine, then of course you will want to start treatment as soon as that headache begins.

TEPPER: With a disease as variable as migraine, a headache diary lets patients look at their headaches with their caregiver and come up with a strategy that makes sense for the frequency, severity, and characteristics of their attacks.

BRIXNER: What is the role of drugs like topiramate, selective serotonin reuptake inhibitors (SSRIs), or serotonin norepinephrine reuptake inhibitors (SNRIs) in short-term prevention of predictable migraines?

TEPPER: You cannot use topiramate for short-term prevention because its titration sequence has to be slow. The faster the titration regimen, the greater the risk of significant psychiatric and neurologic adverse effects. You cannot put somebody on topiramate 100 mg 3 days before menstruation. The half-life of topiramate is 24 hours, so it would take 4 days to achieve a steady state, even if you could put them on 100 milligrams a day in one fell swoop. It cannot be used that way.

As far as SSRIs are concerned, fluoxetine is approved for premenstrual dysphoric disorder, so you can, theoretically, put people on fluoxetine for those kinds of symptoms. There are no randomized controlled trials using conventional endpoints that show efficacy for any SSRI in the prevention of episodic migraine. As for SNRIs, there are two positive studies for daily venlafaxine 150 mg in the long-term prevention of episodic migraine (Ozyalcin 2005); you cannot, how-

ever, establish 150 mg of venlafaxine in 2 days for the prevention of menstrual migraine. You cannot use those drugs in that manner in short-term prevention.

CADY: I agree wholeheartedly. Taking 100 mg of topiramate initially would be difficult for almost anybody, but it is even more difficult if you have a genetically sensitive nervous system. And it does not matter what we use in terms of long-term prevention — we are almost invariably starting at very low doses and titrating upward because of those issues. Triptans seem to be the exception. They seem to be well tolerated, even in the loading doses used with frovatriptan.

TEPPER: With daily long-term prevention, starting low, working up gradually, and knowing what the effective dose is for prophylaxis is very important, as is keeping a headache diary to see whether the patient has achieved at least a 50 percent reduction in migraine frequency. That is what you are trying to do with prevention. But I do not think it is clinically possible to use conventional daily preventive agents, other than nonsteroidal anti-inflammatory drugs or magnesium, in short-term prevention.

BRIXNER: I would anticipate that this is particularly complex in the patient with depression who also experiences menstrual migraines, somehow striking a balance between using an SSRI or SNRI versus a triptan.

CADY: I think we often make clinical errors around this idea of going for a "two-fer." That is, if a woman is depressed, we will put her on an antidepressant, and the idea is we are going to prevent migraine and treat depression. The reality is that the dosing rarely lines up well. Very often, it is better to treat depression and migraine separately, or at least have that awareness when you are monitoring patients. I see a lot of patients who are on woefully low doses of a tricyclic antidepressant and are still depressed, but it is being given as some kind of a two-fer for them, and efforts to go higher with that particular patient end up producing adverse events. So sometimes it is better to keep them on a different preventive treatment and treat their depression as a coexisting disorder.

CADY: We are witnessing a significant shift in thinking ... about the pathophysiology of migraine. Migraine is becoming understood as a chronic disease with episodic manifestations.

TEPPER: The dichotomy in tricyclics is particularly true. Lower-dose tricyclics work very well for migraine prevention, and they may help with sleep, but they really do not work as primary antidepressant strategies unless you get into the therapeutic range of the tricyclic, which is above 100 milligrams or more of most of the major tricyclics. On the other hand, in the venlafaxine study, which was a three-arm study of placebo, venlafaxine 75 mg, and venlafaxine 150 mg, there was efficacy for migraine prevention with 150 mg, but not 75 mg (Ozyalcin 2005). So, with at least one antidepressant, the antidepressant dose and the antimigraine dose actually do line up. In monoamine oxidase (MAO) inhibitors, which we use by consensus for migraine depression, the antidepressant effects and the antimigraine effects sometime line up. But who uses MAO inhibitors for migraine except tertiary centers?

BRIXNER: Are there concerns about adverse events if any of the triptans are used for 2-week periods?

TEPPER: Well, triptans are not used for 2-week periods. The maximum daily use in the frovatriptan short-term prevention study was 6 days (Silberstein 2004). And the blood levels were very carefully monitored in these trials. So it looks like the therapeutic window in terms of adverse event versus efficacy is satisfactory. The only data we have in the public domain on monthly short-term prevention is a study by Tobin, presented at the 2005 American Neurological Association meeting (Tobin 2005). In that study, patients received a loading dose and then frovatriptan 2.5 mg for 5 days, for a total of 6 days, and then they were followed for 6 months using it for every period. During those 6 months, there were no serious adverse events that would have raised concerns. We need the placebo-controlled trials and the extension trials to be published in peer-review form before we rest easy, but so far it looks like the ratio between adverse events and efficacy doses on the short-term prevention has been fine.

BRIXNER: Are there any economic studies looking at the use of triptans in short-term prevention? That would help us understand the benefits of short-term prevention.

CADY: They are not completed yet. This is not a strategy for all women. For some, the acute treatment strategy works extremely well, and that is probably the starting point for most. For others, if they are on birth control pills, it might make sense to go with a continuous oral contraceptives, and see if stabilizing estrogen levels with a fixed combination pill prevents migraine. We are really talking about women who have significant disability — the women who end up in the emergency room, who are frequently absent from work and family. They feel a significant impact. I think it would be satisfying and gratifying if we could not only stop the migraine, but also have a strategy to prevent the disability in many of these women.

TEPPER: We need pharmacoeconomic data on women who are disabled and consuming large amounts of medications during their periods, such as those who are ending up in the emergency rooms and in acute care treatment centers. We need to look at both the direct and indirect costs and whether this strategy of short-term prevention works. My assump-

tion is that one trip to an emergency room in the New York area is more than $1,000, and one can pay for an awful lot of triptan for $1,000.

BRIXNER: And a day away from work …

TEPPER: It is not just work, as Dr. Cady just said. It is work, home, school, and recreational activities. It is the whole package.

CADY: We have tried to look at the gender bias of migraine in clinical practice, not in the population. If you look at clinical trials, one of the first things you notice is that the gender distribution is always about 8 or 9 to 1, and it does not matter what study. If you start looking at clinic-based studies, that ratio of women to men stays strongly biased toward women; more than the 3:1 ratio seen in the American adult population. Once a person makes migraine a medical problem and once they are seeing a physician, migraine has even a greater bias toward women. This suggests that migraine is typically more disabling for women than it is for men, in terms of frequency, duration, and overall impact. Hopefully, we will have some solid data soon. When you consider that menstruation probably is the most consistent trigger for women, particularly women who are patients, this bias becomes even more of an issue.

TEPPER: It is exciting [to] see this gradual movement toward understanding how we might tailor treatment for the severity of predictable migraines.

TEPPER: It is exciting, because we see this gradual movement toward understanding how we might tailor treatment for the severity of the disability of predictable migraines.

CADY: We are witnessing a significant shift in thinking not only about treatment, but also about the pathophysiology of migraine. Migraine is becoming understood as a chronic disease with episodic manifestations — that people live with this sensitive nervous system all the time and then there are manifestations of nervous system, disruption that, clinically, are attacks of migraine. In some people, the potential is for migraine to become a chronic disorder that can literally last years and decades. This model of disease has been well accepted for asthma, but I think there are important parallels, and I think that the paradigm is starting to shift. Inherent in this model is that education and self-management skills should be the cornerstone of medical management.

BRIXNER: Based on the data available, does any triptan stand out for short-term prophylaxis of menstrual migraine?

TEPPER: If the regulatory trials for frovatriptan are published in peer-reviewed form and are positive, and if the extension trials on frovatriptan are positive, then frovatriptan may be the one that stands out. But at this point, what has been made public are randomized, controlled trials for multiple triptans, and without that, effective short-term prevention looks like a class effect. It would be useful to have an FDA imprimatur saying, yes, this particular triptan is both safe and effective in preventing disabling menstrual migraines. That would help us explain the selection of a particular triptan to our patients, formularies, and colleagues.

References

Ozyalcin SN, Talu GK, Kiziltan E, et al. The efficacy and safety of venlafaxine in the prophylaxis of migraine. *Headache.* 2005;45:144–152.

Silberstein SD, Elkind AH, Schreiber C, Keywood C. A randomized trial of frovatriptan for the intermittent prevention of menstrual migraine. *Neurology.* 2004;63:261–269.

Tobin J, Hutchinson J, MacGregor EA. Interim safety and tolerability of frovatriptan during long-term intermittent treatment for prevention of menstrually related migraine headaches. American Neurological Association 130th annual meeting, September 25-28, 2005. San Diego, Calif. Abstract #58.

CONTINUING EDUCATION POST-TEST

Expanding the Boundaries of Migraine Management: A Focus on Menstrual Migraine

Please refer to the combined answer sheet/evaluation form on page 20. On the answer sheet, place an X through the box of the letter corresponding with the correct response for each questions. There is only one correct answer to each question.

1. **Which branch of the trigeminal nerve is most important in the pathophysiology of migraine?**
   a. Mandibular.
   b. Maxillary.
   c. Ophthalmic.
   d. Each branch is of equal importance.

2. **Treatment with magnesium supplementation has not been shown to be efficacious as short-term prophylaxis for menstrual migraine.**
   a. True.
   b. False.

3. **In the United States, the prevalence of migraine in the general population is:**
   a. About the same in men and women.
   b. Higher in men, by a ratio of about 3:1.
   c. Higher in men, by a ratio of about 10:1.
   d. Higher in women, by a ratio of about 3:1.
   e. Higher in women, by a ratio of about 10:1.

4. **Migraine is best understood as a vascular headache.**
   a. True.
   b. False.

5. **In studies of estrogen patches for short-term prophylaxis of menstrual migraine, which doses have been found to be ineffective?**
   a. 25 mcg.
   b. 50 mcg.
   c. 100 mcg.
   d. All the above.
   e. Both (a) and (b).
   f. Both (b) and (c).

6. **Compared with families with no migraineurs, families with a migraineur incur annual mean total health care costs that are:**
   a. Higher.
   b. Lower.
   c. About the same.
   d. Undetermined.

7. **Which triptans have been evaluated in randomized controlled trials for short-term prevention of menstrual migraine?**
   a. Almotriptan, eletriptan, and frovatriptan.
   b. Frovatriptan only.
   c. Frovatriptan, naratriptan, and zolmitriptan.
   d. Frovatriptan, naratriptan, sumatriptan, and zolmitriptan.
   e. Naratriptan, sumatriptan, and zolmitriptan.

8. **Which hormone(s) appear(s) to act as a protective factor against menstrual migraine?**
   a. Estrogen.
   b. Estrogen and progesterone .
   c. Progesterone.
   d. Testosterone.

9. **Migraine is most prevalent during which decades of life?**
   a. Teens.
   b. Teens and 20s.
   c. 30s and 40s.
   d. 50s and 60s.
   e. 70s and 80s.

10. **A loading dose has been employed in clinical trials of which triptan?**
    a. Frovatriptan.
    b. Naratriptan.
    c. Sumatriptan.
    d. Zolmitriptan.
    e. None of the above.

11. **The prevalence of migraine reaches its peak during which days of the menstrual cycle?**
    a. The 4 days before the onset of menses.
    b. The 4 days after the onset of menses.
    c. The 2 days before and the 2 days after the onset of menses.
    d. The 2 days after the cessation of bleeding.
    e. The 4 days after the cessation of bleeding.

12. **According to a study by Hu (1999), which component accounts for the greatest percentage of direct costs associated with migraine?**
    a. Emergency department visits.
    b. Inpatient care.
    c. Physician office visits.
    d. Prescription drugs.

13. In a trial by MacGregor (2006) of estradiol gel for short-term prophylaxis of menstrual migraine, the benefit of a 22 percent reduction in number of headache days was offset by:
a. A 40 percent increase in the relative risk of migraine during the 5 days after cessation of estradiol treatment.
b. A 40 percent increase in the relative risk of tension-type headache during the 5 days after cessation of estradiol treatment.
c. A 10 percent increase in the relative risk of ischemic stroke.
d. A 10 percent increase in the relative risk of hemorrhagic stroke.

14. In the United States, the indirect costs of migraine, in terms of time lost from work and reduced productivity, are estimated to be:
a. More than 10 times higher than the direct costs of migraine.
b. More than 5 times higher than the direct costs.
c. About the same as the direct costs of migraine.
d. More than 5 times lower than the direct costs.
e. More than 10 times lower than the direct costs.

15. The only nonsteroidal anti-inflammatory drug that has been shown to be efficacious for short-term prophylaxis of menstrual migraine is:
a. Celecoxib.
b. Diclofenac.
c. Ibuprofen.
d. Naproxen.
e. Rofecoxib.

16. In comparison with their headaches at other times of their cycle, women referred to headache clinics experience menstrual migraines that are:
a. More frequent.
b. More severe.
c. More often associated with vomiting.
d. All the above.
e. None of the above.

17. According to a study by Breslau (2003), subjects with migraine are how many times more likely than control to develop depression over the course of 2 years?
a. 2.8.
b. 3.8.
c. 4.8.
d. 5.8.

18. The symptoms of migraine can resemble those of sinus headache, to the extent that the latter often is mistaken for the former.
a. True.
b. False.

19. The titration schedule precludes the use of which drug(s) in the short-term prevention of menstrual migraine?
a. Fluoxetine.
b. Topiramate.
c. Venlafaxine.
d. All the above.
e. Only (a) and (b).
f. Only (b) and (c).

20. Which tool(s) is/are critical for developing a treatment strategy for menstrual migraine?
a. Estrogen assay.
b. Headache diary.
c. Progesterone assay.
d. Thermometer.
e. All the above.

CONTINUING EDUCATION ASSESSMENT/EVALUATION/CERTIFICATE REQUEST

Expanding the Boundaries of Migraine Management: A Focus on Menstrual Migraine

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I certify that I have completed this education activity and post-test and claim 2.0 pharmacist contact hours.

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T7E14-MG

EXAMINATION: Place an X through the box of the letter that represents the best answer to each question on pages 18–19. There is only ONE correct answer per question. Place all answers on this form.

	A	B	C	D	E	F
1.	☐	☐	☐	☐		
2.	☐	☐				
3.	☐	☐	☐	☐	☐	
4.	☐	☐				
5.	☐	☐	☐	☐	☐	☐
6.	☐	☐	☐	☐		
7.	☐	☐	☐	☐	☐	
8.	☐	☐	☐	☐		
9.	☐	☐	☐	☐	☐	
10.	☐	☐	☐	☐	☐	
11.	☐	☐	☐	☐	☐	
12.	☐	☐	☐	☐		
13.	☐	☐	☐	☐		
14.	☐	☐	☐	☐	☐	
15.	☐	☐	☐	☐	☐	
16.	☐	☐	☐	☐	☐	
17.	☐	☐	☐	☐		
18.	☐	☐				
19.	☐	☐	☐	☐	☐	☐
20.	☐	☐	☐	☐	☐	

PROGRAM EVALUATION
So that we may assess the value of this self-study program, we ask that you fill out this evaluation form.

Have the activity's objectives, listed below, been meet?

1. Distinguish clinical characteristics and treatment needs associated with different types of migraine, including menstrual migraine.
☐ Yes ☐ No

2. Discuss the goals of preventive migraine treatment.
☐ Yes ☐ No

3. Identify limitations associated with the traditional approach to migraine prophylaxis.
☐ Yes ☐ No

4. Evaluate the evidence supporting the role of various agents in intermittent or chronic prevention.
☐ Yes ☐ No

Was this publication fair, balanced, and free of commercial bias?
☐ Yes ☐ No

If no, please explain: _____

_____

_____

_____

_____

Did this educational activity meet your needs and contribute to your personal effectiveness? Please indicate your level of agreement:

Strongly agree.....5
Agree.....4
Neutral.....3
Disagree.....2
Strongly disagree.....1

Did it improve your ability to:

Treat/manage/support patients?
5 4 3 2 1 N/A

Communicate with patients?
5 4 3 2 1 N/A

Manage your pharmacy practice?
5 4 3 2 1 N/A

Other _____
5 4 3 2 1 N/A

Effectiveness of this method of presentation:

Excellent	*Very good*	*Good*	*Fair*	*Poor*
5	4	3	2	1

What other topics would you like to see addressed? _____

_____

_____

_____

Comments: _____

_____

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_____