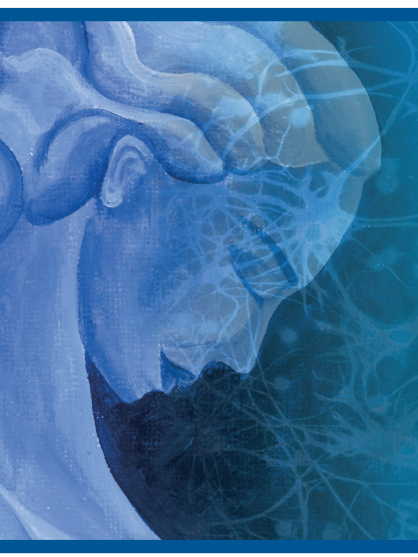

Breakthroughs and Challenges in the Management of Common Chronic Pain Conditions:

A Focus on

Menstrual Migraine

Presented by

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"Breakthroughs and Challenges in the Management of Common Chronic Pain Conditions: A Focus on Menstrual Migraine" is a self-study newsletter designed for neurologists, primary care clinicians, obstetricians/gynecologists, women's health nurse practitioners, and other healthcare professionals who treat patients with menstrual migraine. CME credit will be awarded to physicians who successfully complete this activity. Participation should take approximately 1.5 hours. To complete this activity and receive credit, the participant should:

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TARGET AUDIENCES

Neurologists, primary care clinicians, obstetricians/gynecologists, women's health nurse practitioners, and other healthcare professionals who treat patients with menstrual migraine.

STATEMENT OF NEED

Migraine affects the functional ability and quality of life of millions of Americans, especially during their productive years. Management of the disorder is particularly challenging in women, who outnumber male migraineurs by a ratio of 3:1.[1] Unlike men, women are subject to hormonal triggers and fluctuations that increase the risk of migraine during each stage of their reproductive lives. Approximately 75% of all migraine sufferers are female, and it has been estimated that as many as 70% of those female migraineurs will describe a relationship between their headaches and their menstrual periods (menstrual migraine).[2] The prevalence of migraine in women rises dramatically after puberty.[3] In addition, 51% experience 6 or more workdays lost per year.[4] An understanding of the relationship between the reproductive endocrinology and migraine is essential to the selection of optimal preventive and acute therapies.[5] There are few well-controlled clinical trials regarding the prevention of menstrual migraine; however, recent data regarding the prevention and management of menstrual migraine are showing positive results.[6,7] Primary care clinicians, obstetricians/gynecologists, and neurologists see many patients suffering from migraines. The information provided in this publication will assist them in the identification of patients with menstrual migraine, and in understanding the treatment and management options for the menstrual migraine patient.

EDUCATIONAL OBJECTIVES

After reviewing this publication, the reader should be able to:

- Review the incidence and prevalence of menstrual migraine and describe its impact on patient quality of life and functionality
- Describe the associated comorbidities/risks related to migraine
- Describe the pathophysiology of menstrual migraine, including the relationship of hormonal fluctuations to menstrual migraine
- List strategies to identify and assess patients with menstrual migraine
- Reiterate the 2004 International Classification of Headache Disorders subclassifications of menstrually-related migraines
- Discuss the risks and benefits of various modalities for treatment/prevention of menstrual migraine, including triptans, hormone therapy, and other options
- Describe advances in the management of menstrual migraine

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Frovatriptan, naratriptan, sumatriptan, naproxen, mefenamic acid	Short-term prevention
Amitriptyline, atenolol, bromocriptine, doxepin, gabapentin, metoprolol, nadolol, nortriptyline, oral contraceptives, protriptyline, verapamil	Long-term prevention

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BREAKTHROUGHS AND CHALLENGES IN THE MANAGEMENT OF COMMON CHRONIC PAIN CONDITIONS: A FOCUS ON MENSTRUAL MIGRAINE

INTRODUCTION

Migraine is a chronic, progressive disorder that significantly reduces quality of life and imposes a substantial societal and personal health-care burden. Migraineurs experience decreased family and leisure time, reduced productivity, and frequent absence from work or school. Many experience headaches of sufficient severity to require bed rest. Migraine also imposes a financial burden, with an average cost of healthcare that is 70% higher for families with a migraineur than for families with no migraineur.[8] Prevalence data show that women between puberty and menopause are at a 3 times greater risk for migraine than men. Of the 28 million migraineurs in the United States, approximately 21 million are women, 60% of whom have migraine that is menstrually-related (ie, associated with menstruation).[1,9]

Migraine can be triggered by hormonal fluctuations associated with neurochemical dysregulation during the menses, and menstrual migraine is underdiagnosed and undertreated. The 2004 International Classification of Headache Disorders defines 2 subclassifications of menstrually-related migraines: pure menstrual migraine and menstrually-related migraine (Table 1). Pure menstrual migraine occurs exclusively between days –2 to +3 of the cycle, while menstrually-related migraine was defined as occurring during that same perimenstrual window as well as at other times in the cycle.[10] Aura is not present during pure menstrual migraine, but may occur during episodes outside the perimenstrual window in women with menstrually-related migraine. For the purposes of this discussion, the term "menstrual migraine" will be used to denote both pure menstrual migraine and menstrually-related migraine.

The accurate diagnosis and appropriate treatment of menstrual migraine will decrease the societal and economic burdens of migraine for a large number of migraineurs and their families.

TABLE 1

INTERNATIONAL CLASSIFICATION OF HEADACHE DISORDERS PROPOSED DEFINITION OF MENSTRUAL MIGRAINE[10]

Pure menstrual migraine without aura

- Occurring exclusively during 5-day perimenstrual period—2 days before to 3 days after onset of menstruation in at least 2 of 3 menstrual cycles

Menstrually-related migraine without aura

- Occurring during perimenstrual period and at other times of the month

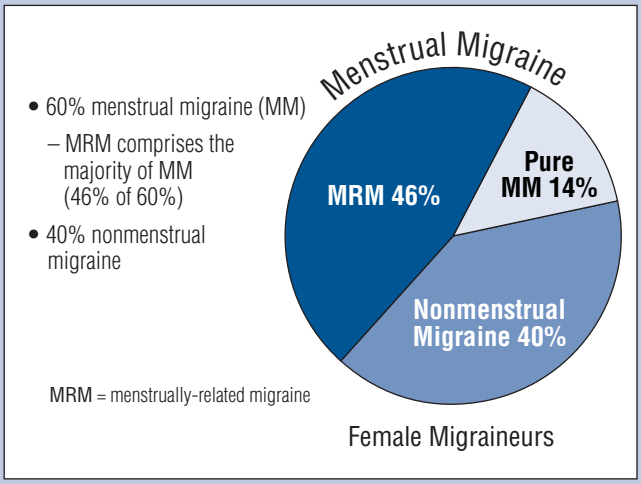
EPIDEMIOLOGY

Prevalence

Migraine is a chronic, debilitating disorder that affects approximately 28 million individuals in the United States, approximately 21 million of whom are women.[1] Prevalence estimates from the Second American Migraine Study, a population-based study of 30,000 individuals in the United States, demonstrate that women are 3 times more likely to be affected by migraine than men. The study found an overall migraine prevalence of 18% among women versus 6% among men.[1] Primary triggers of migraine in women include the hormonal and neurochemical fluctuations associated with menstruation. Epidemiologic studies show that, among women with migraine, approximately 60% have menstrual migraines.[9] Forty-six percent have menstrually-related migraine (IHS classification)—typically occurring during the peri-menstrual period and occasionally at other times in the menstrual cycle—and 14% have pure menstrual migraine—occurring only during the perimenstrual period (Figure 1, page 2).[11] Indeed, the majority of females do not experience migraine until the onset of menstruation, and the increased prevalence of migraine among women after puberty is due, in part, to changes in hormonal levels.[12] Prior to puberty, the prevalence of migraine does not differ significantly between males and females: 5.2% versus 7.1%, respectively.[1] However, in the years following puberty, migraine prevalence triples in women (21.5%) while rising gradually in men (7.2%) (Figure 2, page 2).[13] Both sexes experience a peak in migraine prevalence between ages 25 and 55, followed by a decline to preadolescent levels in women after age 60 (7.5%), and declining even further in men after age 60 (2.5%).[1,13]

FIGURE 1

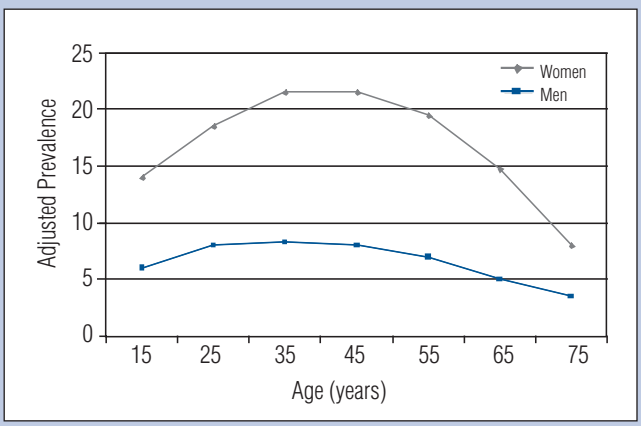
MIGRAINE TYPES IN WOMEN[11]



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

FIGURE 2

PREVALENCE OF MIGRAINE PEAKS IN REPRODUCTIVE YEARS[13]



Reprinted from Scher AI, et al. Migraine and headache: a meta-analytic approach. In: Crombie IK, ed. *Epidemiology of Pain.* Seattle, Wash: IASP Press; 1999:159-170 with permission from the International Association for the Study of Pain.

During the monthly menstrual cycle, migraine occurs most frequently during the days immediately preceding menstruation and the initial days of the menstrual cycle.[14] In a study by MacGregor and Hackshaw, diary data were collected from 155 migraineurs to determine migraine frequency, severity, and timing. The investigators found that migraine was 1.7 times more likely to occur in the 2 days prior to menstruation (and 2.1 times more likely to be severe), and 2.5 times more likely to occur during first 3 days of menstruation (and 3.4 times more likely to be severe).[14] While the highest prevalence rates of migraine in women are found between menarche and menopause, women continue to have a disproportionately higher rate of migraine prevalence following menopause, reflecting the presence of causative factors other than altered hormonal levels.[1,15]

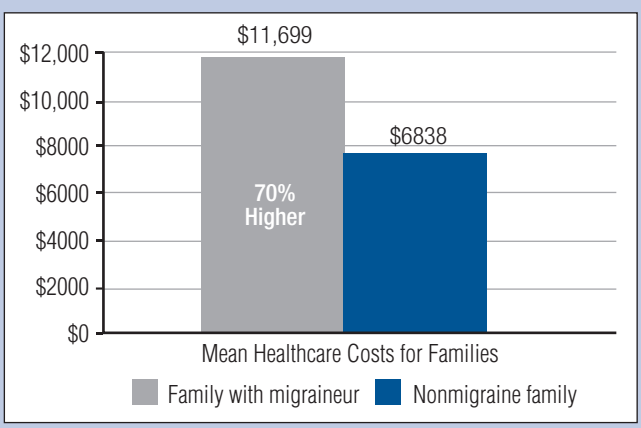
Societal Impact

Because migraine prevalence peaks during the most productive years, it has a substantial effect on productivity and causes a significant economic burden on families and society. The debilitating effects of migraine include decreased family and leisure time, as well as reduced productivity and absence from work and school. The majority of migraineurs (53%) responding to the Second American Migraine Study reported headaches of sufficient severity to result in substantial impairment in daily activities, often requiring bed rest.[1] Nearly one third of respondents reported missing a day of work in the previous 3 months due to migraine-related disability, and half had a substantial decline in work- or school-related productivity.[1] Severe episodes of migraine leading to bed rest result in an average of 3.8 bedridden days for men and 5.6 bedridden days for women each year. Overall, migraine causes a collective 112 million days of bed rest for American migraineurs annually.[16]

Men and women have similar rates of migraine frequency. On average, one third of migraineurs experience 1 to 3 severe migraines per month, and 14% experience 2 to 6 severe migraines per week.[1] The missed work and impaired productivity associated with migraine costs American employers approximately $13 billion per year, a substantial health-related burden to the economy.[16] Migraine-related costs place a substantial economic burden on families as well. A retrospective study of pharmacy claims data evaluated healthcare costs for families with individuals who have migraine versus those without migraineurs.[8] Over 73,000 families were identified with at least 1 migraineur. The average healthcare costs for such families were 70% higher than for families with no migraineurs ($11,669 vs $6838), with most of the difference due to outpatient care and pharmacy costs (Figure 3).[8] The total cost of healthcare for each family depended on which family member had migraine. The average cost for a family with a child migraineur was $600 higher than for the nonmigraineur family and $2500 higher when both a parent and a child had migraine.[8]

FIGURE 3

HIGHER HEALTHCARE COSTS FOR FAMILIES WITH MIGRAINEURS[8]

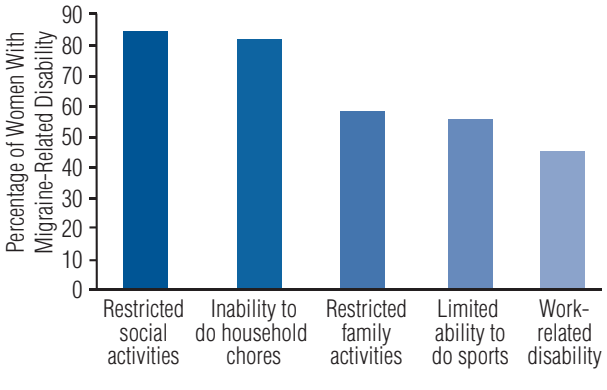


Stang PE et al. *Am J Manag Care.* 2004;10:313-320.

Because women are often caregivers for their families, an acute menstrual migraine attack, resulting in the need for bed rest, can significantly disrupt the flow of family life. Women who experience menstrual migraine average approximately 10 menstrual migraines per year, substantially increasing their rate of disability.[17] Couturier et al conducted a population-based study of over 1000 Dutch women that demonstrated the extent to which menstrual migraine affects daily activities.[17] Restrictions in social activities were reported by 84% of women with menstrual migraine; 81% were often unable to perform household chores; 58% reported restricted family activities; 55% were limited in their ability to participate in sports; and work-related disability was reported by 45% of respondents (Figure 4).[17]

FIGURE 4

EFFECTS OF MENSTRUAL MIGRAINE ON DAILY ACTIVITIES[17]



Couturier EG et al. *Cephalalgia.* 2003;23:302-308.

Barriers to Treatment

For many reasons, menstrual migraine often goes undiagnosed and untreated. Fewer than half of all migraine sufferers contact their physician when they experience a headache and use medication to relieve their pain.[12,18] Among migraineurs who do seek medical help, women with menstrual migraine are more likely to visit their primary care physician than are women with other types of headache, yet medication is often not prescribed.[17] This may be due to the misperception that migraine is "part of the menses," or it may represent an underestimation of the severity of the disorder.[17,19] When physicians do not recognize the extent of disability caused by menstrual migraine, they may be less likely to recognize and treat the disorder. Similarly, patients may not recognize the cyclical pattern of their headaches and may attribute them to other causes or self-medicate with over-the-counter (OTC) medication.[19] Even when a diagnosis of menstrual migraine is made, many women receive suboptimal treatment and are not aware that therapeutic alternatives are available that offer effective headache relief.[19]

A number of studies have concluded that menstrual migraine attacks are more severe, longer in duration, and more resistant to treatment than migraine attacks occurring during nonmenstrual times of the month.[14,17,20,21]

Migraine-Associated Comorbidity

In recent years, an independent association has been found between migraine and increased risk for ischemic stroke. A meta-analysis of 14 studies conducted by Etminan et al found an increased risk for ischemic stroke among individuals with all types of migraine (relative risk 2.16, 95% confidence interval [CI] 1.89 to 2.48).[22] When migraine without aura was assessed, a relative risk of 1.83 was found (95% CI 1.06 to 3.15). The risk among women taking oral contraceptives was 8-fold higher than for others. Young women with migraine are at particular risk for ischemic stroke.[23,24] A study by Tzourio et al showed that women below age 45 with migraine with aura have an almost 4-fold greater risk for stroke than their counterparts without migraine.[24] When women below 45 years of age who had suffered ischemic stroke were evaluated, 60% had concurrent migraine, while 30% of the control group (without stroke) had migraines.[24] While the effects of this finding are still unclear, it may suggest that treatment of migraine in women is strongly advised. It is also suggestive that smoking and oral contraceptive use, which further increase the risk for stroke in young women, should be avoided by them.[24]

ETIOLOGY & PATHOPHYSIOLOGY

Triggers of Menstrual Migraine

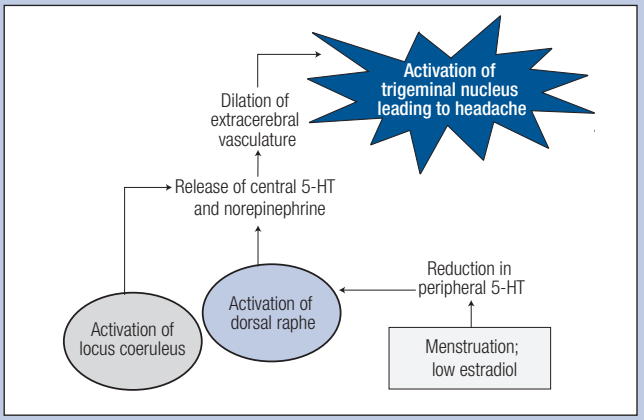
In general, migraine is triggered by exercise, bright lights, anxiety, stress, loud noise, oral contraceptives, lack of sleep, weather, skipped meals, certain foods, or alcohol. One of the primary triggers of menstrual migraine is fluctuation in levels of hormones and neurochemicals.[19,25] The relationship between hormones and the development of the migraine headache was explained through the neurovascular model of chronic headache developed by Moskowitz.[26] Moskowitz postulated that migraine headaches are triggered by numerous chemical factors (food, alcohol, serotonin, hormones, etc), as well as mechanical, ionic, and neurovascular mechanisms.[26] These triggers activate the dorsal raphe nucleus and locus coeruleus, causing a central release of serotonin.[5,27] As a result, dilation of intracranial extracerebral vessels occurs, activating the trigeminal nucleus and causing the sensations of a headache. When peripheral serotonin levels are high, they have an inhibitory effect on the dorsal raphe nucleus, reducing the susceptibility to headache triggers. However, when peripheral serotonin levels are low, headache risk increases.[5] A relationship has been found between peripheral levels of serotonin and estradiol.[5] When blood levels of serotonin increase, there is a corresponding increase in estradiol. Similarly, decreased levels of estradiol, which occur during menstruation, correspond with a decline in peripheral serotonin levels and an increase in migraine susceptibility (Figure 5, page 4).[5]

Role of Hormones in Menstrual Migraine

One of the primary triggers of menstrual migraine is a decline in estrogen levels during the luteal phase of the menstrual cycle.[19,28] The role of hormones in migraine was initially explored by Somerville, who administered both progesterone and estrogen to women with menstrual migraine.[28,29] He found that premenstrual administration of high levels of estrogen caused migraine when estrogen was withdrawn. This suggests that estrogen withdrawal associated with the onset of

FIGURE 5

NEUROVASCULAR PROGRESSION OF MENSTRUAL MIGRAINE[5]



Adapted from Marcus DA. Focus on Primary Care Diagnosis and Management of Headache in Women. *Obstet Gynecol Surv.* 1999;54:395-402 with permission from Lippincott Williams & Wilkins.

menstruation may be a trigger for menstrual migraine. This finding corresponds with the clinical observation that migraines often occur during the hormone-free week among patients taking oral contraceptives.[25] Since the work of Somerville in the 1970s, many different mechanisms have been proposed to explain the pathogenesis of menstrual migraine, including impaired central serotonergic metabolism, dysregulated prostaglandin production, platelet dysfunction, abnormal opioid regulation, and decreased melatonin secretion.[25,30,31] It is likely that many of these mechanisms act together to form a cascade leading to the onset of an acute migraine attack.

Fluctuations in hormone levels associated with migraine are also implicated in the increased incidence of stroke seen among women with migraine. Li et al studied the levels of estrogen and progesterone in cerebral vascular smooth muscle cells.[32] They found that at normal physiologic levels, estrogen and progesterone either maintain or increase magnesium levels in cerebral arterial muscle. However, high levels of estrogen and progesterone significantly deplete magnesium, possibly resulting in cerebrovasospasms and reduced cerebral blood flow. Depleted levels of magnesium are typically found during the late luteal phase of the menstrual cycle when menstrual migraine tends to occur. This may suggest a potential explanation for the increased risk of stroke among women with migraine.[23,24]

DIAGNOSIS OF MENSTRUAL MIGRAINE

Migraine is typically a one-sided or bifrontal throbbing headache, worsened by routine activity and associated with photo/phonophobia and often nausea. As described above, menstrual migraines typically occur from 2 days prior to and through the first 3 days of menses. Therefore, in making a diagnosis of menstrual migraine, it is important to obtain a clear record of the timing of each acute attack in relation to the menstrual cycle, because patients can be poor predictors of their own migraine attacks and often make incorrect estimations of their menstrual patterns. The recommended approach is to have patients keep a daily diary in which they record: 1) length of the menstrual cycle; 2) start and end of each menstrual period; 3) time and date of each headache episode; 4) a severity rating of each migraine attack on a scale of 1 to 10; and 5) lifestyle changes including sleeping patterns, foods eaten, illnesses, and medications.[11] The diary should be kept for at least 3 months to determine the causes of the migraine attacks and potential triggers. Examination of the correlation between the menstrual cycle and the migraine attacks will determine whether the patient has menstrual migraine, or migraine unrelated to menstruation. An accurate diagnosis will help determine an appropriate management strategy for the patient.

TREATMENT OPTIONS

Migraine is a progressive disorder that worsens over time if left untreated or treated ineffectively.[33] The goals of menstrual migraine treatment are to reduce migraine symptoms, shorten migraine duration, and reduce migraine-related disability. Several options are available for treatment of menstrual migraine, including nonpharmacologic approaches, acute (abortive) agents, short-term preventive therapy, and long-term preventive therapy. Lifestyle modification decreases migraine triggers; use of acute agents at the outset of an unpredicted attack helps to abort the attack; short-term preventive therapy for predictable migraines seeks to prevent attacks before they occur without continual treatment; and long-term preventive therapy for recurrent headaches can be used in patients with concomitant medical conditions for whom the migraine therapy could serve a dual purpose.

When migraine is predictable, as it is in menstrual migraine, fear of migraine onset can be as disabling as the headache itself. Use of acute therapy can cause apprehension for migraineurs as they await migraine onset before treatment. Evidence-based proposals for treating the patient with menstrual migraine take advantage of the therapeutic window when patients are at greatest risk for migraine attack—2 days prior to 3 days following the onset of the menses. This offers protection during the days when patients are at greatest risk for menstrual migraine. As data from clinical trials show, short-term prevention with triptan therapy effectively increases the percentage of pain-free days for patients with menstrual migraine.[6,7,34,35]

Nonpharmacologic Approaches to Menstrual Migraine

Some of the nonpharmacologic approaches to the treatment of migraine were investigated by the U.S. Headache Consortium, a group of 7 professional organizations that have an interest in improving migraine quality of care.[36] The group assessed the efficacy of behavioral and physical treatments for migraine through a review of the published literature. The Consortium gave a Grade A recommendation to the following nonpharmacologic techniques for treatment of migraine: relaxation training, thermal biofeedback combined with relaxation training, electromyographic (EMG) biofeedback, and cognitive-behavioral therapy. Grade A indicates support from well-designed, randomized clinical trials. The group gave a Grade B recommendation to behavioral therapies such as relaxation and biofeedback, when used in combination with prophylactic pharmacologic therapy such as propranolol or amitriptyline. A Grade B recom-

mendation indicated some evidence was available from randomized trials but that it was not optimal. The Consortium could not make evidence-based treatment recommendations for hypnosis, acupuncture, transcutaneous electric nerve stimulation (TENS), cervical manipulation, occlusal adjustment, or hyperbaric oxygen. These methods lacked adequate randomized controlled trials to support their use.

The mainstay of nonpharmacologic therapy for menstrual migraine is for patients to make lifestyle changes that minimize or eliminate known migraine triggers (Table 2).[11,37] Patients should maintain regular routines for eating, sleep, and exercise. It is important to establish a consistent schedule for wakefulness and sleep, as migraines can occur when patients go to bed late, sleep in, or experience sleep deprivation. Regular meals and good hydration minimize the onset of migraine attacks. In selecting foods and beverages, patients should avoid well-known migraine triggers. These include caffeinated drinks, alcoholic beverages, aged cheeses, salty foods, chocolate, and simple carbohydrates. Low blood sugar typically occurs within several hours of eating simple carbohydrates and is a trigger for migraine attacks. These changes should be accompanied by participation in a regular aerobic exercise routine.

TABLE 2

NONPHARMACOLOGIC THERAPY FOR MENSTRUAL MIGRAINE: LIFESTYLE CHANGES[11,37]

- Establish regular schedule for going to sleep and awaking
  - Avoid late nights, oversleeping, and sleep deprivation
- Avoid well-known migraine triggers such as wine, beer, or other alcoholic beverages; chocolate and other sweets; caffeine; aged cheeses such as cheddar or Brie; and salty foods—especially during week before menses
- Participate in regular aerobic exercise

Acute Treatment of Menstrual Migraine

Early treatment of menstrual migraine attacks with acute agents can terminate or abbreviate a migraine episode, allowing patients to resume daily activities without missing school, work, or other necessary events.[11] The triptans are generally considered first-line therapy in the acute treatment of moderate to severe migraine.[19,31] In the event triptans are contraindicated or cannot be taken, other therapies for treatment of acute migraine include nonsteroidal anti-inflammatory drugs (NSAIDs), ergot derivatives, analgesics, antiemetics, and as a last resort, opioids (Table 3). Overuse of acute agents, however, can lead to rebound headache—the development of headache resulting from the excessive use of a drug.

NSAIDs

The U.S. Headache Consortium Guidelines recommend that treatment of acute migraine attacks be based on severity.[38] NSAIDs are typically used in the treatment of acute migraine attacks that are infrequent or of low intensity, whereas triptans are recommended for acute attacks of moderate to severe intensity.[38,39] The NSAIDs with proven efficacy in the treatment of migraine include diclofenac, naproxen sodium, piroxicam, and mefenamic acid; however, these drugs are not indicated for this use.[39-41] Because of the risk for rebound headache and other side effects associated with NSAIDs, these agents should not be taken more than 3 days per week.[39]

TABLE 3

ACUTE THERAPIES FOR TREATMENT OF MENSTRUAL MIGRAINE[11,38-40]

Triptans
- Almotriptan
- Eletriptan
- Frovatriptan
- Naratriptan
- Rizatriptan
- Sumatriptan
- Zolmitriptan

NSAIDs
- Diclofenac
- Naproxen sodium
- Piroxicam
- Mefenamic acid

Ergot Derivatives
- Dihydroergotamine
- Ergotamine

Analgesics
- Acetaminophen
- Aspirin
- Aspirin-acetaminophen-caffeine combination

Antiemetics
- Metoclopramide
- Prochlorperazine

Opioids
- Meperidine
- Butorphanol

Triptans

The triptans are selective 5-hydroxytriptamine (5-HT) agonists at 5-HT_{1D} and 5-HT_{1B} receptor sites on trigeminal nerves and intracranial arteries, respectively.[11] Seven triptans are currently available for acute treatment of migraine: almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan. All are associated with significant efficacy for the following parameters: pain relief at 2 hours, pain-free status, reduction of migraine recurrence, control of nausea and vomiting, and reduction in functional disability.[11,19] Yet, the triptans have different formulations and pharmacokinetic properties that lead to distinctions among their effects (Table 4, page 6). Adverse events are mostly mild and transient among the triptans, especially with almotriptan, frovatriptan, and naratriptan.[39] The different routes of administration of triptan therapy affect the medications' speed of delivery, efficacy, and side-effect profile. Subcutaneous delivery is the most rapid and effective for pain relief, with an onset of pain relief at 10 to 15 minutes. Yet, this formulation has a higher incidence of adverse events than oral administration.[39] Triptan delivery through a nasal spray also offers rapid relief of migraine attacks. While sumatriptan nasal spray is not as effective as oral therapy, zolmitriptan nasal spray has shown better efficacy rates.[39] The primary drawback to the nasal spray is the common experience of taste disturbance following administration. A recently developed route of administration for triptans consists of an orally disintegrating tablet. This route offers triptans in a form that is easy to take and convenient.[39] Duration of therapy differs between the triptans. The drugs with the longest half-lives are naratriptan (6 hours) and frovatriptan (26 hours).[42,43]

TABLE 4

ACUTE THERAPY WITH TRIPTANS

Generic name/ Brand name	Dosage forms	Tmax (h)	Half life (h)
Almotriptan/(Axert®)	12.5-mg oral tablet	1.4-3.8	3.2-3.7
Eletriptan/(Relpax®)	20-, 40-mg oral tablet	1-2	3.6-5.5
Frovatriptan/(Frova®)	2.5-mg oral tablet	2-4	26
Naratriptan/(Amerge®)	1-, 2.5-mg oral tablet	2-3	5-6.3
Rizatriptan/(Maxalt®)	10-mg oral tablet 10-mg ODT	1.2 1.6-2.5	2 2
Sumatriptan/(Imitrex®)	50-, 100-mg oral tablet 6-mg SC injection 20-mg nasal spray	2.5 0.16-0.2 1	2 2 2
Zolmitriptan/(Zomig®)	2.5-, 5-mg oral tablet 2.5-, 5-mg ODT 5-mg nasal spray	2 3.3 4	3 2.5-3 2.8

ODT = orally disintegrating tablets; SC = subcutaneous.

Adapted with permission from Mannix LK, Calhoun AH. Menstrual migraine. *Curr Treat Options Neurol.* 2004;6:489-498 © 2004 Current Medicine.

An evidence-based review of therapeutic options for menstrual migraine shows treatment efficacy with the following triptans: eletriptan[44]; frovatriptan[6,34]; naratriptan[7]; rizatriptan[45-47]; sumatriptan[35,48]; and zolmitriptan.[49]

Ergotamines

Ergotamine and dihydroergotamine have been used for a long time in the treatment of migraine and are considered safe. However, compared with the triptans, they show lower efficacy.[39] These medications, which exert their effects through vasoconstrictive activity, are associated with several limitations including medication overuse and rebound headaches.[39] They are also associated with nausea and may require coadministration with an antiemetic.[50]

Other therapies that have been used as abortive treatment for menstrual migraine include analgesics and prokinetic antiemetics, which may be used in combination with other therapies. Opiates should be considered as a last resort and OTC medications should be avoided to reduce risk of rebound headache.[50]

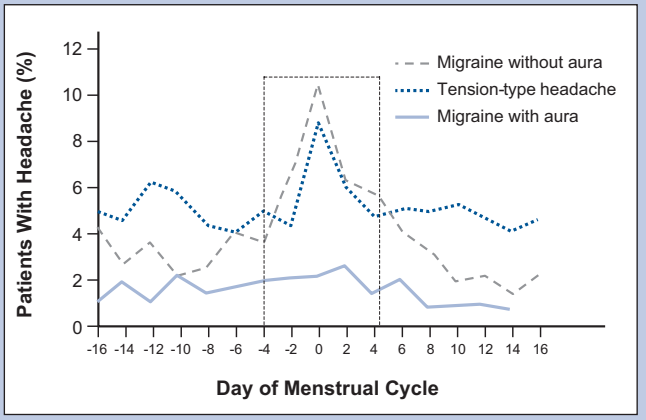
Short-term Preventive Therapy

Short-term prevention is a treatment approach that targets the predictability of menstrual migraine by providing preventive therapy within the period of time that menstrual migraine is most likely to occur. When migraine without aura—the type of migraine typically associated with menstrual migraine—is compared with migraine with aura and tension-type headache, it is clear that there is a treatment window (typically several days before to several days after the onset of menstruation) when administration of therapy for menstrual migraine is optimal (Figure 6).

NSAIDs have been successfully used in the short-term prevention of menstrual migraine. Naproxen sodium, 500 mg bid, was studied in a double-blind treatment protocol involving 40 women with menstrual

FIGURE 6

HEADACHES AND MENSTRUAL CYCLE[3]



Adapted from Stewart WF, Lipton RB, Chee E, Sawyer J, Silberstein SD. Menstrual cycle and headache in a population sample of migraineurs. *Neurology.* 2000;55:1517-1523 with permission from Lippincott Williams & Wilkins.

migraine. The therapy was initiated on day –7 and continued through day +6 for a 3-month study period. Compared with placebo, naproxen was more effective in reducing headache intensity and duration as well as the number of days with headache.[41] In another study, the NSAID mefenamic acid, 500 mg tid, was compared with placebo in the treatment of 24 women with menstrual migraine. Therapy was administered for 1 menstrual cycle. Among the women who received mefanamic acid, 79% had significant pain relief versus 17% with placebo.[40]

Triptans, while indicated for abortive migraine therapy, also have been found effective for short-term prevention of menstrual migraine. Clinical trials for short-term prevention of menstrual migraine have been conducted with sumatriptan,[35] naratriptan,[7] and frovatriptan.[34] In a small, open-label pilot study, sumatriptan was evaluated for short-term prophylaxis of menstrually-related migraine.[35] When treated for 5 days with sumatriptan, 25 mg tid, patients were headache free in 52% of treated attacks and had reduced severity in 42%. Naratriptan also proved successful for short-term prophylaxis of menstrual migraine.[7] Researchers found that significantly more perimenstrual periods per patient treated with naratriptan 1 mg bid for 5 days were headache free, compared with placebo. More patients in the naratriptan-treated group were headache free (23%) across all treated perimenstrual periods than those receiving placebo (8%). A study of frovatriptan as a short-term preventative in 546 women with menstrually-related migraine also demonstrated efficacy in this population.[6] The incidence of menstrually-related migraine was 67% among placebo-treated patients, 52% among patients receiving frovatriptan 2.5 mg qd, and 41% for patients given frovatriptan 2.5 mg bid ($P<.0001$ vs placebo). Frovatriptan also reduced migraine severity ($P<.0001$), duration ($P<.0001$), and use of rescue medication ($P<.0001$).[6] One of the advantages of using frovatriptan for short-term prophylaxis of menstrual migraine is a half-life of 26 hours, which is substantially longer than that of the other triptans.[51]

Short-term prevention of menstrual migraine requires the ability to predict when such migraines will occur, but may protect the patient during the at-risk period. It can be challenging to determine when the

high-risk time period for migraine will occur in each individual patient. One approach, suggested by MacGregor et al, is the use of a fertility monitor at home to identify when ovulation occurs, and thereby predict the appropriate timing for short-term prophylaxis of migraine.[52] Many women have poor recall of their menstrual cycles, and natural variations in cycle length make estimation of the beginning of the menses difficult for many women. Use of the home fertility monitor in 27 women accurately predicted ovulation in more than 90% of subjects, which allowed for a more precise prediction of the onset of menses and the timing of migraine prophylaxis. Another advantage of short-term preventive therapy versus long-term preventive therapy is the utilization of smaller amounts of medication, since therapy is administered only during the 5-day period surrounding the first menstrual day.

Long-term Migraine Preventive Therapy and Comorbidities

The U.S. Headache Consortium Guidelines suggest prophylactic (preventive) treatment of migraine in the following circumstances: 1) when migraine is recurrent and disabling despite acute therapy (ie, 2 or more attacks per month producing disability lasting ≥ 3 days); 2) when acute therapy results in failure, is contraindicated, or results in adverse events; 3) when overuse of acute medication occurs; 4) when migraine attacks put the patient at risk for permanent injury; 5) when migraine headaches are very frequent (> 2 per week); and 5) when the patient requests preventive treatment to have fewer attacks.[53]

Long-term preventive therapy may be optimal for patients with concomitant medical conditions for whom migraine therapy would serve a dual purpose.[19,39] Some of the therapies used for long-term preventive therapy in migraine include beta-blockers, calcium channel blockers, anticonvulsants, tricyclic antidepressants, riboflavin, coenzyme Q-10, magnesium, oral contraceptives and other hormonal therapies, and ergots.[51] Tricyclic antidepressants can be administered for patients with frequent migraine who also suffer from depression and beta-blockers may be useful in patients with recurring migraine and hypertension, as are calcium channel blockers. Anticonvulsants are beneficial to patients with migraine who have concurrent epilepsy, anxiety disorder, or bipolar disorder. Oral contraceptives can be given to women with menstrual disorders and frequent migraine; however, in some cases oral contraceptives can cause migraine, so the patient must be evaluated for reactions to oral contraceptives before long-term therapy is begun. In addition, oral contraceptives are associated with an increased risk for stroke in migraine with aura which, when added to the increased risk for stroke associated with migraine, may make this therapeutic option undesirable.[24]

Few clinical trials have been performed to support the use of agents discussed in this section for treatment of menstrual migraine.[51] The beta-blockers propranolol, nadolol, atenolol, metoprolol, and timolol have demonstrated efficacy in the treatment of migraine; however, side effects limit their use in patients with asthma, congestive heart failure, Raynaud disease, and insulin-dependent diabetes.[39] Of the calcium channel blockers, verapamil is the most widely used in migraine.[39] It is especially useful in patients with hypertension or contraindications to beta-blockers. Anticonvulsants including valproate, divalproex, topiramate, and gabapentin are effective in the treatment of migraine.[39] Valproate and most recently, topiramate are the only antiepileptic drugs approved for migraine prevention. Supplemental magnesium has been studied in patients with menstrual migraine for whom magnesium depletion is a common problem. When administered for 15 days premenstrually, it has been shown to reduce the number of days with headache.[11]

The tricyclic antidepressants most often used for treatment of migraine include amitriptyline, nortriptyline, doxepin, and protriptyline.[39] Amitriptyline is commonly used for migraine prophylaxis; however, due to amitriptyline's poor side-effect profile, nortriptyline is often a better choice. Side effects of tricyclics include dry mouth, sedation, increased appetite, cardiac toxicity, and orthostatic hypotension.[39]

Hormonal preventive therapy has been used to prevent migraines in patients with resistant menstrual migraine.[50] The goal of hormonal therapy is a reduction in the decline of estradiol typically associated with the onset of menstruation.[11] Some of the hormonal therapies used for the prevention of menstrual migraine include combined oral contraceptives containing 20-μg ethinyl estradiol or the 20-mg patch or vaginal ring administered for the first 3 weeks of the cycle, followed by estrogen supplementation during the fourth week.[11] This limits the decline in estrogen to a 10-μg equivalent in the premenstrual time period. Another approach is the continuous use of either 20 μg monophasic oral contraceptive pill (OCP) or the new 3-month OCP for 11 weeks with the effect of limiting ovulation and menses—and, as a consequence, menstrual migraine—to 4 times per year.[11] Administration of hormonal therapy via estradiol gel or transdermal patches containing 100-μg estradiol have also been used in the prevention of menstrual migraine.[11,51] The FDA has issued a warning that women who use the transdermal patch are exposed to about 60% more total estrogen in their blood than if they were taking a typical birth control pill containing 35 mg of estrogen.[54] A woman may be at higher risk for serious side effects than if she is using a typical birth control pill.[55] The effectiveness of these approaches is still being investigated; however, it has been shown that use of oral contraceptives can cause menstrual migraine as well as prevent it. In addition, as noted, oral contraceptives are a risk factor for stroke.[24] When prescribing estrogens, use of the lowest possible dose is recommended. Other hormonal therapies that have been used in menstrual migraine include estradiol implants, gonadotropin-releasing hormone (GnRH) agonists, danazol, and phytoestrogen.[51] The ergot therapy bromocriptine, which blocks release of prolactin, has been used successfully in menstrual migraine if given continuously.[51]

Duration of Preventive Therapy

When administering long-term preventive therapy for menstrual migraine, a trial of at least several menstrual cycles is recommended, as maximal efficacy is typically not achieved for several weeks. Therapy should be initiated at a low dose and increased over the ensuing weeks and months.[39] Patient expectations should be managed by establishing long-term goals rather than immediate clinical benefit. Regular office visits are essential to ensure adherence to therapy and to monitor for potential side effects of therapy.

CONCLUSIONS

Menstrual migraine is a common problem among women migraineurs; however, it often goes unrecognized. Proper diagnosis is the key to initiating effective treatment. Because it is triggered by hormonal fluctuations and neurochemical changes, the optimal treatment approach differs from nonmenstrual migraine. Acute therapy is initiated first; however, the predictability of menstrual migraine allows clinicians to target periods of high-risk by providing short-term preventive therapy within a narrow treatment window. Menstrual migraine is predictable in nature, typically occurring 2 days before to 3 days after onset of the menses. By providing preventive therapy during this period, migraine-headache frequency and severity can be reduced. For breakthrough migraine headaches, acute therapy is still administered. Long-term preventive therapy may be recommended for women with severe migraine outside the menstrual cycle. As investigators better understand the pathophysiology of menstrual migraine, treatment strategies to optimize migraine management can be developed to target the individual needs of migraineurs.

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BREAKTHROUGHS AND CHALLENGES IN THE MANAGEMENT OF COMMON CHRONIC PAIN CONDITIONS: A FOCUS ON MENSTRUAL MIGRAINE

PENNSTATE
Milton S. Hershey Medical Center
College of Medicine

ANSWER SHEET, PROGRAM EVALUATION, AND CME CREDIT REQUEST

POSTTEST

Instructions: To receive CME credit, complete the posttest and evaluation. Participants must receive a score of 80% or better to receive credit.

1. On average, migraine occurs more frequently in women than men, affecting:
   a. 4% of women and 1.5% of men
   b. 6% of women and 3% of men
   c. 18% of women and 6% of men
   d. 18% of women and 12% of men
2. Risk for stroke in women with migraine with aura is increased by:
   a. 2-fold
   b. 4-fold
   c. 5-fold
   d. 6-fold
3. Menstrual migraine is associated with which of the following etiologic factors:
   a. Reduced estrogen levels
   b. Altered serotonin metabolism
   c. Reduced magnesium in the brain
   d. All of the above
4. Definition of pure menstrual migraine is:
   a. Migraine without aura occurring exclusively from 2 days before through 3 days after onset of menstruation in at least 2 of 3 menstrual cycles
   b. Migraine without aura occurring exclusively from 2 days before through 2 days after onset of menstruation in at least 2 of 3 menstrual cycles
   c. Migraine without aura occurring exclusively from 3 days before through 2 days after onset of menstruation in at least 2 of 3 menstrual cycles
   d. Migraine without aura occurring exclusively from 3 days before through 3 days after onset of menstruation in at least 2 of 3 menstrual cycles
5. Barriers to menstrually-related migraine therapy include:
   a. Underdiagnosis
   b. Belief that migraine is 'part of the menses'
   c. Lack of recognition of the cyclical nature of the disorder
   d. All of the above
6. The elimination of migraine triggers involves which of the following:
   a. Getting regular exercise
   b. Eliminating certain foods from the diet
   c. Making up for lost sleep
   d. a and b
7. First-line abortive therapy for moderate to severe menstrual migraine is:
   a. Triptans
   b. Over-the-counter analgesics
   c. Low-dose oral contraceptives
   d. Ergotamine
8. Short-term prophylaxis for menstrual migraine:
   a. Prevents migraine during the time when the patient is at greatest risk
   b. Uses less drug than conventional prophylaxis
   c. Is enhanced by triptans with long half-lives
   d. All of the above
9. If not appropriately treated, over a period of years, migraine is likely to:
   a. Become less severe
   b. Worsen
   c. Occur with decreased frequency
   d. Cease
10. Long-term migraine prophylaxis is appropriate in which of the following circumstances:
    a. Recurrent disabling migraine despite acute therapy
    b. Occurrence of disabling headaches more than twice a month
    c. For patients with concomitant medical disorders
    d. All of the above

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2. Extent to which you are satisfied with the overall quality of the newsletter	O	O	O	O	O
3. To what extent did the newsletter present scientifically rigorous, unbiased, and balanced information?	O	O	O	O	O
4. To what extent was the newsletter free of commercial bias?	O	O	O	O	O
5. To what extent did this newsletter change your knowledge/attitudes?	O	O	O	O	O
6. To what extent did this educational activity change your skills?	O	O	O	O	O
7. To what extent will you make a change in your practice as a result of your participation in this educational activity?	O	O	O	O	O

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   O This activity will not change my behavior because I do not agree with the information presented.
   O I need more information before I can change my practice behavior.
   O I will immediately implement the information in my practice.

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Breakthroughs and Challenges in the Management of Common Chronic Pain Conditions: A Focus on Menstrual Migraine

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