ABSTRACT

Acute treatment of menstrually related migraine (MRM) focuses not only on prescribing a drug to abort an individual attack, but also on the patient’s treatment needs and the link between menstruation and migraine, other menstrually related symptoms and events, and the phases of a migraine attack. Because of its unique clinical characteristics, and because it is historically underdiagnosed and undertreated, MRM requires a unique treatment approach. This article reviews the components of such an approach, which include recognition of the contributions of the menstrual cycle and the migraine headache process, treatment dynamics, clinical aspects of acute treatment, and phase-based therapy. Central to the treatment approach is the premise that the clinical characteristics of MRM represent opportunities to integrate the predictability of the migraine attack into acute treatment, to explore new and potentially more effective treatment paradigms, and to help women with MRM achieve better control of their headaches. The importance of calendars and diaries in diagnosis and monitoring therapy and the special considerations involved in treating migraine during pregnancy and lactation also are addressed. (Adv Stud Med. 2005;5(9A):S783-S789)

ACUTE TREATMENT OF MENSTRUALLY RELATED MIGRAINE

Roger K. Cady, MD

Acute management of menstrually related migraine (MRM) goes beyond simply prescribing a drug to treat individual attacks. It also requires a philosophy that involves treating the patient and recognizing the connection between menstruation and migraine, other symptoms and events that occur during the menstrual cycle, the phases of a migraine attack, and the need to define treatment goals with each patient and construct an appropriate treatment paradigm.

WHY MENSTRUALLY RELATED MIGRAINE REQUIRES A UNIQUE APPROACH

The unique characteristics of MRM, particularly its association with the menses, its predictability, and its treatment dynamics, warrant a unique approach to acute treatment to optimize pain control and symptom relief.

CHARACTERISTICS OF MENSTRUALLY RELATED MIGRAINE

MRM headaches are commonly characterized by absence of aura, severe intensity, duration of up to 72 hours, a high rate of recurrence, greater work-related disability than non-menstrually related migraine (NMRM) headaches, and predictable timing. However, a review of treatment data indicates that there is relatively little evidence to support the generally accepted premise that MRM headaches are more severe and more difficult to treat for this reason.

The finding that migraine headaches occurring during menses are not more severe than migraine attacks occurring outside of the perimenstrual period suggests that MRM involves factors other than the menses alone. Evaluation is needed to determine the presence of neurologic pathology, systemic conditions,
or gynecologic comorbidities that could affect the choice of therapeutic options or otherwise interfere with treatment geared toward symptom relief or symptom prevention. That factors other than the menses are likely to be involved in MRM also raises an important series of questions: is MRM a more treatment-resistant form of migraine, or is it simply a more poorly recognized and more poorly treated form of migraine? Or, is it perhaps a combination of both?

In all probability, factors related to both the biology of MRM and its recognition and treatment are involved. Although there is evidence that MRM responds well to abortive therapies, it is historically undertreated, and although an MRM attack lasts longer than an NMRM attack, persisting up to 72 hours, clinical trials have not assessed MRM treatment beyond 24 hours, making it difficult to accurately determine the precise rate of recurrence.

There also are several barriers associated with MRM, particularly its underdiagnosis and a lack of awareness of the connection between menstruation and migraine. For example, many women with MRM assume that menses-associated headaches are simply part of the menstrual phenomenon. Unfortunately, the failure to connect menstruation and migraine is carried forward into the medical community.

Yet another barrier is the fact that migraine attacks occurring during the menstrual cycle tend to last longer and are less likely to respond to treatment than are migraine headaches occurring at other times of the month. This, in itself, discourages more aggressive treatment and in fact leads to undertreatment.

The clinical characteristics of MRM typically include lack of aura, a protracted period of development, a high incidence of vomiting, dysmenorrhea, and premenstrual syndrome (PMS) symptoms, and the association with onset of menses as 1 of many migraine risk factors. Of these, lack of aura and vomiting coincide with the International Headache Society (IHS) diagnostic criteria for MRM.

Typically, an MRM headache without aura develops slowly, with approximately 80% of affected women having a significant mild headache phase before progressing to the moderate-to-severe phase, compared with about 20% of women who have migraine with aura and whose headaches usually escalate more rapidly (R. K. Cady, MD, unpublished observations). Against this backdrop, a staged (step within attack) approach to MRM treatment often is used. This strategy may make good clinical sense for some women, provided second-tier therapy is utilized before the headache escalates if first-line intervention proves ineffective.

Stewart et al conducted a population-based diary study involving 81 women with migraine to determine the distribution of headaches related to the menstrual cycle. In the 98-day study, which covered 7219 diary days, a daily diary was used to record occurrence of menses, headache days, and headache features such as symptoms, quality of pain, attack duration, pain intensity, and disability. As shown in Figure 1 of the previous article in this issue, by Brandes et al, migraine without aura and tension-type headache are significantly more common than migraine with aura during the perimenstrual period. However, the relationship between the perimenstrual period and the increase in tension-type and migraine headache is ill defined; the study did not control for medication use/nonuse or its impact on perceived changes in headache symptomatology.

TREATMENT DYNAMICS IN MENSTRUALLY RELATED MIGRAINE

At the first sign of a headache, many women employ a “wait and see” approach before taking a migraine-specific or other medication—in an attempt to predict whether the headache will be a mild one or whether they think it might become severe. As a result, they often engage in a step-care process during the menstrual period. These women may initiate treatment for symptoms related to the menstrual cycle, such as menstrual cramps, or they may fail to recognize that many nonheadache symptoms occurring with the menses are in fact associated with the pathophysiologic process of migraine rather than with menses itself. These premonitory symptoms are the first phase of the migraine process and they foretell the occurrence of an impending headache rather than reflecting part of the premenstrual symptomatology.

This dynamic is amply illustrated in a recent study that examined the reasons for delaying medication and the impact of the timing of medication use on headache severity in men and women taking triptan therapy. Of the 49% of patients who reported delaying treatment, 69% said they did so because they were waiting to see if the headache really was a migraine attack, and 46% said they only wanted to take medication if the headache was severe. A much smaller percentage (9%) cited the cost of medication as the reason for delay, and 2.5% said they delayed medication use on the advice of a healthcare provider.
In the second part of this study, subjects were interviewed within 24 hours of treating a migraine attack and queried about the timing of acute treatment. In terms of medication timing, diary entries revealed that 53% of patients started medication before (that is, during aura) or at headache onset, 21% started within 1 hour of onset, 12% within 2 hours, and 15% after 2 hours. Of patients starting medication before or at onset, nearly half recorded their pain as moderate. A higher percentage of those starting medication within 1 hour of onset recorded their pain as moderate to severe, and virtually all patients who started medication after 2 hours recorded moderate to severe pain. Thus, the high predilection towards waiting for pain to be moderate to severe before taking medication substantially erodes any opportunity for early and more effective intervention.

This is particularly true in MRM, which often develops more slowly than NMRM. Many women become “caught” in the delayed treatment paradigm; in such cases headaches may appear to be resistant to treatment. Although there are physiologic factors that explain why MRM headaches can be more difficult to treat, issues related to treatment dynamics may play a role, as well.

**Clinical Trial Data**

There is a large body of particular retrospective data on the treatment and treatability of MRM. Clinical trials of various triptans have shown that they are superior to placebo and provide comparable pain relief in women with moderate to severe MRM or NMRM (Table 1).

A study examining early intervention (ie, during the mild pain phase) in women with MRM found that 61% of those receiving sumatriptan 100 mg were pain free at 2 hours, compared with 51% of those receiving sumatriptan 50 mg and 29% of those receiving placebo. These findings parallel those of most clinical trials assessing early intervention. However, virtually none of these trials has assessed efficacy beyond 24 hours, a crucial time period at which MRM headaches might recur.

**Clinical Approach to Acute Treatment**

The most important aspect of acute treatment of MRM is treatment of the patient and not necessarily of the individual episodes of headache. This includes ascertaining the headache pattern, its impact, and treatment needs. For example, did the headaches start as purely menstrually related, occurring only during menses? Have they become worse with perimenopause, or for any other reason? What impact does the headache have on overall functioning?

A strategic approach to acute intervention centers on the MRM phase during which the patient can first accurately predict the development of a high-impact headache, the time frame for each phase of MRM, and the identification of other symptoms associated with the menstrual cycle (eg, dysmenorrhea, PMS, mood disruption, sleep disturbances) that are consistently present during migraine attacks.

Accurate prediction of a high-impact headache by considering MRM phase—the premonitory period, mild headache, worsening headache with increased activity, moderate to severe headache—is important because treatment opportunities lie within each of these phases. The time frame is important because it determines which formulation of a medication is most appropriate. Menstrually related symptoms are important because they, too, may require pharmacologic interven-

<table>
<thead>
<tr>
<th>Triptan</th>
<th>Results MRM</th>
<th>Results NMRM</th>
<th>Endpoint(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eletriptan (40 mg)</td>
<td>63%</td>
<td>60%</td>
<td>Pain relief at 2 hours</td>
</tr>
<tr>
<td>Rizatriptan (10 mg)</td>
<td>68%</td>
<td>69%</td>
<td>Pain relief at 2 hours</td>
</tr>
<tr>
<td></td>
<td>42%</td>
<td>37%</td>
<td>Pain free at 2 hours</td>
</tr>
<tr>
<td></td>
<td>75%</td>
<td>77%</td>
<td>No nausea</td>
</tr>
<tr>
<td></td>
<td>53%</td>
<td>46%</td>
<td>No functional disability</td>
</tr>
<tr>
<td>Sumatriptan (po, 100 mg)</td>
<td>67%</td>
<td>79%</td>
<td>Pain relief at 4 hours</td>
</tr>
<tr>
<td>Zolmitriptan (2.5 mg)</td>
<td>56%</td>
<td>60%</td>
<td>Pain relief at 2 hours</td>
</tr>
<tr>
<td></td>
<td>27%</td>
<td>31%</td>
<td>Pain free at 2 hours</td>
</tr>
</tbody>
</table>

MRM = menstrually related migraine; NMRM = non-menstrually related migraine; po = by mouth; bid = twice a day; qd = every day.
tion. As a whole, this strategic approach is geared toward the whole patient, and is about treatment of acute migraine in general, not necessarily treatment of MRM in particular. This approach also underscores the opportunity for early intervention when the headache is mild, rather than waiting until the headache is more painful. This has the potential to significantly lessen the severity, duration, and impact of MRM.

Effective treatment of acute migraine is about outcome rather than a specific medication, and good outcome requires treatment goals and clearly articulated objective endpoints. It is not enough to prescribe a medication and ask a patient if it is working or if her headache is better. Rather, the goal of acute therapy is to terminate the pathophysiological process of migraine completely so the patient is pain free, there is restoration and preservation of function, and there is no headache recurrence. However, for women with MRM, instilling confidence that they can do something about a headache they know is coming also is an important outcome parameter.

**Acute Treatment of Menstrually Related Migraine**

Acute treatment of MRM begins before the attack, with education about MRM and its diagnosis; controllable risk factors; protective strategies such as getting enough sleep and following a healthful diet; positive self-talk and biofeedback; and use of a calendar and/or diary as well as temperature monitoring to document the connection between migraine and the menses and monitor the effectiveness of therapy. When providing such education, clinicians also should define and establish goals for each patient; draw up a treatment plan that is patient centered and balances the appropriateness of a staged (step within attack), stratified, or phased treatment interventional paradigm; and provide reassessment and continuity of care.

Medications that are commonly used for acute treatment of MRM include various over-the-counter pain relievers, which should be used at full doses, nonsteroidal anti-inflammatory drugs (NSAIDs), long–half-life or rapid-onset triptans, ergotamines, dihydroergotamine (DHE), neuroleptics/antidopaminergics, steroids, opioids, and possibly intravenous magnesium. Like other medications for acute treatment, triptans should be used early in the evolution of a potentially high-impact MRM.

Commonly used combination regimens for acute treatment include triptans and NSAIDs, triptans and neuroleptics/antidopaminergics, DHE and NSAIDs, and DHE and antidopaminergics. The use of antidopaminergics such as metoclopramide is especially helpful in controlling nausea and vomiting, both common in MRM.

**Phase-Based Approach**

The rationale for the phase-based approach to treatment of migraine and MRM is well illustrated by the evolution of migraine over a period of hours and the physiologic events that occur during the headache process (Figure). The premonitory phase is characterized by symptoms such as mood changes, irritability, fluid retention, and chocolate craving. Subsequent phases are characterized by the emergence of mild headache (often appearing as a tension-type headache) that progresses to moderate to severe headache with neurovascular symptoms such as throbbing and pounding, nausea, and sensory hypersensitivity and often culminating in severe headache and intense associated symptoms.

In the phase-based approach, treatment is aimed at targeting the headache severity during the various phases of the headache process with the most efficacious medication and/or formulation for each phase. Treatment options for preheadache, mild headache, moderate to severe headache, and protracted or intractable headache are summarized in Table 2. When triptans are used, their various formulations should be matched to treatment needs.

When a phase-based approach is not possible or is difficult to institute, other treatment strategies can be utilized, especially stratified care. In this model women with moderate to severe migraine-related disability (Migraine Disability Assessment scores >16) are provided triptan intervention to utilize with each migraine attack. This is a rational approach given the significant migraine-related disability in this patient population, but it lacks the sensitivity of individualizing treatment based on the unique presentations of different migraine attacks. A third option is step within attack (staged care) where treatment is initiated early and, if ineffective within 2 hours, rescue is provided with a high-end intervention. This is a rational approach if the first-line intervention has a high probability of success and if unsuccessful the rescue therapy provides a pain-free response. However, if these conditions are not met this strategy can result in prolonged disability.
IMPORTANCE OF CALENDARS AND DIARIES

A headache diary or calendar is useful as a diagnostic tool to record the relationship between the menstrual cycle and the migraine headache. The daily diary or calendar should include start and end dates of the menses, length of the menstrual cycle, menstrually related symptoms such as PMS, weight gain, and fluid retention; time and date of all headache episodes; severity of all migraine attacks on a scale of 1 to 10; and any changes in lifestyle, including changes in sleep patterns, food intake and cravings, illnesses, and all medications taken for migraine and other illnesses and/or symptoms.

Calendars and diaries also are useful for monitoring treatment efficacy and outcome and for helping patients understand the value of early intervention and overall treatment. When shared with healthcare providers, calendars and diaries provide an opportunity to monitor therapy, assess treatment goals, determine the optimal treatment paradigm for an individual patient, adjust medication, and educate. They also encourage increased communication between patient and provider.

MIGRAINE AND PREGNANCY

Although solid data on migraine during pregnancy are relatively scarce, most estimates suggest that headaches do, in fact, lessen in severity during this time. Various studies have found that:

- 50% of pregnancies are unplanned, which underscores the risk potential for women treating migraine early in pregnancy.
- 25% of women of childbearing age experience migraine.
- 60% to 70% of women with migraine experience attacks less frequently during pregnancy, particularly during the second and third trimesters.
- 4% to 8% of women experience worsening migraine (ie, increased frequency as well as intensity and/or other factors) during pregnancy.
- Approximately 10% of new cases of migraine begin during pregnancy.
- Prepregnancy headache patterns return almost immediately after delivery.

It is vital to discuss options for treating migraine during pregnancy before a woman becomes pregnant. Discussing and initiating nonpharmacologic options

![Diagram](image_url)
such as avoidance of migraine triggers, rest, ice and/or heat, massage, regular exercise, and biofeedback are especially appropriate at this time.

**MEDICATION USE DURING PREGNANCY**

Like menstruation, pregnancy is a symptom-producing event. In addition, general medication consumption during pregnancy is increased. A retrospective study of medication use during pregnancy in 8 health maintenance organizations from 1996 through 2000 found that medications were prescribed for 82% of pregnant women and drugs other than vitamins and minerals were prescribed for 64%.23 (The study did not assess use of over-the-counter medications during pregnancy.)

Medication during pregnancy, however, may be necessary for women with severe disabling migraine or chronic daily headache. In that case, the risks and benefits of treating migraine vs not treating migraine must be assessed, particularly with respect to self-medication, dehydration, exacerbation of comorbid conditions, maternal/fetal addiction, and overall safety.

The risk/benefit assessment for safety must weigh the likelihood of an abnormal pregnancy without treatment against the likelihood of a fetal abnormality induced by drug exposure. Several excellent resources are available for this purpose, including REPROTOX®24, the textbook *Drugs in Pregnancy and Lactation* by Briggs,25 and pregnancy registries that are maintained by all pharmaceutical companies that manufacture triptans. Healthcare providers with patients who have been exposed to triptans during pregnancy should consider submitting relevant data to the registries so the medical community can learn more about triptan exposure in pregnant women. (Pharmaceutical company representatives and pharmacists can provide the necessary information for submitting data to the registries.)

Food and Drug Administration pregnancy categories are a guide to drug risk, with Category A agents showing no risk in controlled clinical studies and Category B agents showing no evidence of risk in controlled clinical studies despite adverse findings in animals. Category C agents may place the mother or fetus at risk, but have not been assessed in adequate well-controlled human studies or in animal studies. Category D agents show positive evidence of risk in human studies or in postmarketing data, and Category X agents are contraindicated.

There are no Category A agents and a few Category B agents for acute and preventive treatment of migraine, but the latter are generally less effective than Category C agents, for which risk to mother or fetus cannot be ruled out.

Category B agents for acute treatment include acetaminophen, caffeine, NSAIDs (after implantation and before 32 weeks' gestation), butorphanol, metoclopramide, hydrocodone, and oxycodone. Category C agents include aspirin, butalbital, codeine, phenothiazines, and triptans. Ergot-containing medications are Category X and are contraindicated.

Category B agents for long-term preventive treatment include metoprolol. Category C agents include other β-blockers, calcium channel blockers, selective serotonin reuptake inhibitors (SSRIs), antiepileptics such as topiramate and gabapentin, and the tricyclic antidepressants protriptyline and doxepin. Category D agents include the tricyclics amitriptyline and nortriptyline and the antiepileptic divalproex sodium.

Emergency interventions that may be required during pregnancy in women with severe migraine include fluid resuscitation for both mother and fetus and intravenous therapy with metoclopramide, diphenhydramine, opioids, or magnesium sulfate for pain control. Occipital nerve blocks also can be considered for pain control. All of these options present minimal risk to the fetus.

If severe migraine episodes are recurrent, the use of preventive agents and more aggressive management should be considered.

**TREATING MIGRAINE DURING LACTATION**

The approach to managing migraine in women who choose to breast-feed centers on whether drug therapy really is needed. For cases in which it is necessary, the safest drug should be chosen, and it should be taken immediately after breast-feeding or before a lengthy sleep period for the baby—to minimize drug exposure to the infant.26 If there is a possibility of risk to the infant, a blood sample should be taken from the infant and tested for elevated levels of the mother's migraine drug.26

Other measures to minimize the infant's drug exposure include "pumping and dumping" breast milk shortly after taking medication, thus encouraging mothers and physicians to consider the half-lives of various medications and choose, whenever possible, those that have the shortest half-life and those least likely to be secreted in breast milk.
Drugs that are appropriate in this regard are codeine/hydrocodone, sumatriptan, zolmitriptan, and butorphanol for acute treatment, and β-blockers, tricyclics, and SSRIs for preventive treatment. Sumatriptan has been approved by the American Academy of Pediatrics for use in breast-feeding mothers,26 and both sumatriptan and zolmitriptan have been recommended for use in nursing mothers.27

CONCLUSION

Management of MRM goes beyond the specific migraine attack and should be considered in a broader context. The clinical characteristics of MRM represent opportunities to integrate predictability of the migraine attack into acute treatment and early intervention strategies, to explore new and potentially more effective acute treatment paradigms, and to help women establish more effective control of their headaches.

REFERENCES