ABSTRACT

Preventive treatment of menstrually related migraine (MRM) is initiated when acute therapies fail to provide adequate relief of headache pain and other disabling symptoms associated with menstruation and migraine. Preventive treatment can be preemptive, short term or intermittent, or long term. Preemptive treatment is directed at known migraine triggers such as exercise; short-term prophylaxis is directed at time-limited headache triggers such as menstruation; and long-term treatment is indicated for women with ongoing susceptibility to MRM. This article reviews each of these 3 types of preventive treatment, the drugs and dosing schedules used, and special circumstances that may affect therapy. The article also takes a closer look at the use of sumatriptan, naratriptan, and frovatriptan as short-term prophylaxis and the approaches to hormonal manipulation in chronic treatment. (Adv Stud Med. 2005;5(9A):S790-S795)

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Address correspondence to: Stephen D. Silberstein, MD, Thomas Jefferson University, Jefferson Headache Center, 8130 Gibbon Building, 111 South 11th Street, Philadelphia, PA 19107. E-mail: Stephen.silberstein@jefferson.edu.
al activity. Pretreatment immediately before exposure to the triggering event with nonsteroidal anti-inflammatory drugs (NSAIDs) or triptans may avert the migraine attack.

**SHORT-TERM/INTERMITTENT PROPHYLAXIS**

Short-term or intermittent prevention is used for time-limited headache-triggering events such as menstruation. Here, the strategy is to medicate before and during the menses.

Ergotamine can be used during the perimenstrual period to prevent migraines that occur with the menses with little risk of producing a medication overuse headache. Dihydroergotamine (DHE) and methergine can be used perimenstrually to prevent migraines that occur with menses, and ergotamine with belladonna and phenobarbital can be used to treat symptoms of premenstrual syndrome (PMS) in addition to headache.

Although triptans were initially believed to be effective only if taken after headache onset, studies have shown that they are effective as short-term prophylaxis when taken over several days during the perimenstrual period.1-3 This was first demonstrated in 1998 by Newman et al in a small, open-label pilot study of oral sumatriptan.1 More recent double-blind placebo-controlled studies have shown that naratriptan and frovatriptan also are effective as short-term prophylaxis.2,3

**SUMATRIPTAN**

Low-dose oral sumatriptan was evaluated in an open-label study of 126 menstrual cycles in 20 women with menstrual migraine who took the medication for at least 1 cycle, beginning 2 to 3 days before expected headache onset and continuing for a total of 5 days.1 A low starting dose (25 mg 3 times per day) was chosen so that the women could be rescued with a higher dose if necessary. The proportions of cycles in which migraine attacks were absent (52%) and headache severity was reduced by ≥50% (42% of cycles overall) are shown in Figure 1. Only about 5% of patients in the study showed <50% benefit from treatment. Breakthrough headaches were rare, and were less severe than was baseline headache.1

**NARATRIPTAN**

A randomized, double-blind, placebo-controlled, parallel-group trial evaluating naratriptan for short-term prophylaxis in 206 women compared 2 doses of the drug—1 mg twice daily and 2.5 mg twice daily—with placebo.4 Treatment was started 2 days before the expected onset of a menstrually associated migraine attack and was continued for 5 days. As shown in Figure 2, a significantly higher proportion of women receiving naratriptan 1 mg were headache free compared with women receiving placebo, and a significantly higher proportion of women receiving the lower dose than women receiving naratriptan 2.5 mg or placebo reported having migraine attacks during ≤50% of their menstrual periods. Naratriptan 1 mg also produced a significant reduction in the number of menstrually associated migraine days, from 7 to 4 ($P = .001$). What was unusual about the study findings was the inverse dose response.

Two subsequent studies of naratriptan 1 mg vs placebo found that a higher mean percentage of women who received naratriptan were headache free during the perimenstrual period compared with women who received placebo (L. K. Mannix, MD, unpublished observations). However, the results were statistically significant in only 1 of these studies, and the results of both studies were nowhere near as robust as those seen in the parallel-group study.

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20 patients took study medication for at least 1 cycle.
126 treated menstrual cycles.
*Reprinted with permission from Newman et al.*
The study's primary efficacy variable was the incidence of MRM headache during the treated perimenstrual period. Secondary efficacy variables were severity and duration of MRM headaches, the incidence of MRM-associated symptoms, the severity of functional disability, the proportion of patients requiring rescue medication, and patient ratings of the study drug effectiveness.

The safety population consisted of all randomized patients (n = 546) who took at least 1 dose of study medication. The intent-to-treat (ITT) population consisted of all randomized patients who took at least 1 dose of study medication and provided efficacy data for at least 1 efficacy analysis (n = 506). A second ITT population (ITT2) consisted of patients in the ITT population who treated all 3 perimenstrual periods and provided efficacy data for each of these periods (n = 445).

With respect to the primary endpoint, both doses of frovatriptan were significantly more effective than placebo (P < .0001) in preventing MRM in both the ITT and ITT2 populations (Figure 3). Moreover, repeated daily use of frovatriptan did not delay the onset of MRM headaches.

**FROVATRIPTAN**

Frovatriptan was evaluated for the intermittent prevention of MRM in a double-blind, placebo-controlled, 3-way crossover study covering 3 perimenstrual periods in 546 women who met International Headache Society criteria for MRM (ie, migraine that occurs within 2 days before and 4 days after onset of menses). Inclusion criteria were age ≥ 18 years, a 12-month history of MRM, occurrence of MRM in at least 3 of 4 perimenstrual periods in the previous year, regular menstrual cycles (28 ± 4 days), and the ability to predict the onset of MRM headaches.

Dosing with frovatriptan 2.5 mg once daily, frovatriptan 2.5 mg twice daily, or placebo was begun 2 days before the anticipated onset of MRM—rather than onset of menses—for each of the 3 treated perimenstrual periods, and was continued for an additional 4 days, for a total of 6 days. That the starting point was 2 days before the onset of headache rather than onset of menses is an important distinction. Patients also were instructed to take a double dose on day 1 of the menstrual flow.
headache into the postdosing period, nor did it provoke rebound headache. Kaplan-Meier survival analysis revealed that the proportion of patients without migraine headache was similar to the proportion seen in the 5 days following the last frovatriptan dose.3

Both dosing regimens also led to significant reductions in headache severity compared with placebo in the ITT population (Figure 4), as well as to reductions in total headache duration, severity of functional disability, and incidence of MRM-associated symptoms.

The incidence of adverse events was similar in frovatriptan and placebo groups, and not essentially different from the incidence seen with acute use. Both dosing regimens were equally well tolerated, with a safety profile similar to that seen with acute use. Moreover, no new safety issues arose during the 6-day dosing period.

**LONG-TERM PREVENTIVE TREATMENT**

Long-term prevention of MRM is reserved for patients with ongoing susceptibility. It involves medicating on a regular basis with various hormonal regimens. Hysterectomy and oophorectomy, though advocated by some, more often exacerbate migraine. Hormonal intervention is indicated when simpler methods have failed and when more frequent and severe attacks are not relieved by triptans, DHE, opioids, neuroleptics, or corticosteroids.

Although diuretics and pyridoxine have been used for long-term prevention of MRM in the past, they are ineffective. Diuretics are helpful in relieving fluid retention, but are not effective in relieving headache. Pyridoxine is not effective for either PMS or MRM.

**HORMONAL MANIPULATION**

Various hormones and hormonal regimens are or have been used long term to create a stable hormonal environment and prevent MRM. Some regimens are more effective than others, some have limited data regarding their use in prevention, and some have more extensive data. For example, synthetic progesterone has not been proven to be effective, and there are virtually no data on whether natural progesterone would provide any benefit. By comparison, much more is known about the use of estrogens, with or without progesterone, in this regard.

Oral contraceptives, either estrogen + progestin or progestin alone, can be used to prevent MRM. When given cyclically they can, in some women, confine migraine attacks to the perimenstrual period only and prevent MRM headaches that occur at other times during the menstrual cycle. Moreover, they can lessen the severity of the migraine attacks that occur during menses. When given continuously (ie, for 3 months without a placebo) oral contraceptives can reduce the number of menstrual periods as well as the number of MRM attacks to 3 or 4 per year.

Estradiol can be given cyclically or continuously in various formulations, as a cream, a transdermal patch, or an implant. One study evaluating cyclic therapy with estradiol cream has shown that it is effective in preventing MRM.8 Another study found that an estradiol implant delivering continuous therapy was effective, as well.9

Transdermal patches delivering estradiol 15, 50, or 100 µg/day can be used during the perimenstrual period for prevention of MRM. However, reports in the literature indicate that patches are not always effective for this purpose. One study found that patches delivering 25 µg/day were not as effective as those delivering 100 µg/day,10 whereas another found that patches

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**Figure 4. Percentage of Patients (ITT) With Moderate and Severe Menstrually Related Migraine After Treatment With Frovatriptan vs Placebo**

<table>
<thead>
<tr>
<th>% of Patients</th>
<th>Placebo (n=487)</th>
<th>2.5 mg qd (n=488)</th>
<th>2.5 mg bid (n=492)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>24</td>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>Moderate</td>
<td>27</td>
<td>22</td>
<td>18</td>
</tr>
</tbody>
</table>

qd = every day; bid = twice a day.

*Reprinted with permission from Silberstein et al.1

1P < .0001

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qd = every day; bid = twice a day.

*Reprinted with permission from Silberstein et al.1
delivering 50 µg/day were not significantly better than placebo. This is because serum estradiol levels must be >60 pg/mL in order to be effective; patches delivering estradiol 50 µg/day result in serum levels of approximately 39 pg/mL.

Another reason for the inconsistent results seen with use of transdermal patches is the timing of their application. Applying a 100-µg patch and then taking it off after a week leads to a dip in recurrence. One alternative is to use 2 50-µg patches asynchronously (ie, applying a new patch before removing the old one) over a week to avoid the dip that occurs when a patch is taken off.

Transdermal estradiol, given as 2 100-µg patches on a constant basis, suppresses ovulation and eases symptoms of PMS. A double-blind study found that treatment with estradiol patches and cyclic norethisterone significantly reduced PMS symptoms. Thus, high-dose transdermal estradiol and cyclic norethisterone can be used for birth control or for treatment of PMS symptoms when estrogens are not contraindicated or when natural estrogens are preferred.

Other hormonal regimens that are or have been used to prevent MRM include estrogens and androgens, androgen derivatives, antiestrogens, dopaminergic agonists, and gonadotropin-releasing hormone (GnRH) analogues.

There is anecdotal evidence that the combination of ethinyl estradiol 0.05 mg and methyltestosterone 20 mg is effective when used during the perimenstrual period. Similarly, the androgen derivative danazol, at doses of 200 to 600 mg/day, suppresses the pituitary-ovarian axis and is helpful when used during the perimenstrual period.

Tamoxifen, a mixed agonist/antagonist antiestrogen, is effective in preventing MRM when taken at doses of 5 to 15 mg/day on days 7 to 14 of the luteal phase of the menstrual cycle. Raloxifene has estrogen antagonist effects on the uterus or breast and estrogen agonist effects on bone and serum lipids. However, it is not known whether it has beneficial effects on migraine headache.

Bromocriptine, a dopaminergic agonist, can be taken cyclically, at a dose of 2.5 to 5 mg/day during the luteal phase, or continuously, at a dose of 2.5 mg 3 times daily as add-on therapy. Cyclic dosing is helpful in relieving PMS symptoms, and also may help headache. Continuous therapy, which was assessed in several open-label studies, appears to be effective and superior to intermittent therapy, particularly in women with intractable MRM.

GnRH analogues suppress ovulation and produce a medical or pharmacologic oophorectomy, which is effective in reducing symptoms of PMS, including headache. Because GnRH analogues induce menopause, they should not be used for more than 6 months unless estrogen and progestin are added back.

One study found that GnRH analogues, with add-back therapy after 6 months, were effective for 10 months in women with severe MRM. Another study found that a combination of the GnRH analogue goserelin and transdermal estradiol was effective in MRM, but that goserelin alone was not.

**HYSTERECTOMY AND OOPHORECtOMY**

Hysterectomy with or without oophorectomy is a strategy that was used in the past in women who had both MRM and PMS, but that is used rarely today. In many cases, hysterectomy without oophorectomy only worsened the situation; women who underwent hysterectomy continued to experience PMS because neither a uterus nor menstruation is necessary for PMS symptoms to occur.

In unselected patients with MRM, hysterectomy is not effective. However, some advocate hysterectomy and oophorectomy for women with severe intractable PMS or MRM who first respond to medical oophorectomy induced by GnRH analogues. Although no controlled studies have proven the effectiveness of hysterectomy and oophorectomy in MRM, 2 small, flawed, retrospective studies have shown some benefit. In 1 of these studies, 14 women who responded to danazol underwent hysterectomy and were still showing improvement at 48-month follow-up. In the other, 14 women with intractable PMS underwent hysterectomy and oophorectomy and showed improvement at 6-month follow-up.

However, neither study was placebo controlled, an important limitation because many women with PMS are very sensitive to placebo. Moreover, patients in both studies received daily estrogen replacement therapy after surgery, which alone could have accounted for the positive results.

**CONCLUSION**

Preventive treatment of MRM is divided into 3 types of care: preemptive treatment, which is directed...
at known triggers such as exercise or sexual activity and involves pretreatment just prior to exposure; short-term treatment, which is directed at time-limited exposures such as menstruation and involves medicating before and during exposure; and chronic treatment, which targets patients with ongoing susceptibility and involves medicating on a regular basis.

Standard preventive drugs such as NSAIDs, ergotamine, DHE, methysergide, methergine, and triptans can be used preemptively or during the perimenstrual period as short-term prophylaxis. Triptans are especially useful in short-term prophylaxis.

Chronic therapy is largely based on hormonal manipulation with estrogens (with or without androgens or progestin), synthetic androgens, antiestrogens, GnRH analogues, and dopamine agonists.

REFERENCES


