Acute treatment and prevention of menstrually related migraine headache

Evidence-based review

Tamara Pringsheim, MD
William Jeptha Davenport, MD
David Dodick, MD

Address correspondence and reprint requests to Dr. Tamara Pringsheim, Movement Disorders Centre, Toronto Western Hospital, 399 Bathurst Street, Toronto ON M5T 2S8 Canada
tamara.pringsheim@utoronto.ca

ABSTRACT

Menstrually related migraine (MRM) headache is common in women and associated with substantial disability. Compared to nonmenstrual migraine, MRM attacks are more severe, longer in duration, and have a poorer response to analgesics. The purpose of this guideline is to provide a systematic review and meta-analysis of the existing therapy trials for MRM and evidence-based recommendations for acute and short-term preventive treatment of MRM headache. Prospective, double-blind, randomized controlled trials of any pharmacologic agent for the symptomatic relief or prevention of MRM headache were included in the guideline. The main outcomes considered were the pain response and pain-free response at 2 hours for acute treatment trials, and the incidence of MRM or the number of days on which MRM attacks occurred for short-term prevention trials. Nineteen trials were included in the analysis. The US Preventive Services Task Force quality criteria were used to assess trial quality and to grade recommendations. Based on the evidence, grade B recommendations can be made for the use of sumatriptan 50 and 100 mg, mefenamic acid 500 mg, and rizatriptan 10 mg for the acute treatment of MRM. For the preventive treatment of MRM, there are grade B recommendations for the perimenstrual use of transcutaneous estrogen 1.5 mg, frovatriptan 2.5 mg twice daily, and naratriptan 1 mg twice daily. Choosing among treatment strategies must be based on clinical considerations.

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GLOSSARY

AAN = American Academy of Neurology; **AE** = adverse event; **AHS** = American Headache Society; **ANA** = American Neurological Association; **ARR** = absolute risk reduction; **IHS** = International Headache Society; **ITT** = intent-to-treat; **MAOI** = monoamine oxidase inhibitor; **MC** = menstrual cycles; **MRM** = menstrually related migraine; **PMM** = pure menstrual migraine; **RCT** = randomized controlled trial; **RD** = risk differences; **USPSTF** = US Preventive Services Task Force.

Migraine headache is common. While the prevalence of migraine is equal in prepubertal boys and girls, migraine prevalence is three times higher in women. A population-based study revealed a 1-year prevalence of migraine of 25% in women, compared to 7.5% in men.[1]

The International Classification of Headache Disorders, 2nd edition,[2] defines menstrually related migraine (MRM) as attacks that occur on day −2 to +3 of menstruation in at least two of three menstrual cycles (MC) and additionally at other times in the cycle. The first day of the MC is defined as day 1, and the day preceding menstruation is day −1. Pure menstrual migraine (PMM) is defined as attacks occurring exclusively on days −2 to +3 of menstruation in at least two of three MC and at no other times of the month.

Population-based studies reveal that 8% of women have MRM.[3] In headache clinics, 50% of women report MRM.[4] MacGregor and Hackshaw found that compared with all other times of the cycle, migraine was 1.7 times more likely to occur during the 2 days before menstruation and 2.1 times more likely to be severe, and 2.5 times more likely to occur during the first 3 days of menstruation and 3.4 times more likely to be severe.[5]

Supplemental data at www.neurology.org

From the Division of Neurology (T.P.), University of Toronto; private practice (W.J.D.), Toronto, Ontario, Canada; and Department of Neurology (D.D.), Mayo Clinic College of Medicine, Scottsdale, AZ.

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Granella et al. found that perimenstrual attacks are significantly longer in duration, have greater work-related disability, and respond less well to acute treatment.[6]

Natural changes in levels of estrogen during the MC are associated with MRM.[7] In a study by MacGregor et al.,[7] women with normal MC who had migraine kept a daily migraine dairy, and used a fertility monitor to identify ovulation. There was a significantly higher number of migraines during the late luteal/early follicular phase of falling estrogen and lower number of attacks during rising phases of estrogen, supporting the hypothesis of estrogen withdrawal triggering migraine.

The treatment of MRM is divided into two strategies: symptomatic therapy taken at the time of the migraine, and short-term prevention taken perimenstrually. While migraine is not a life-threatening condition, it is associated with substantial disability.[8,9] Information regarding the most effective treatment options is important for clinicians. The purpose of this guideline is to provide a systematic review and meta-analysis of treatment trials for MRM and evidence-based recommendations for acute and short-term preventive treatment of MRM.

OBJECTIVES/CLINICAL QUESTIONS This review was performed to specifically address the following three questions:

- Which acute treatments for MRM are effective in reducing pain?
- Which short-term preventive treatments are effective for MRM?
- How should clinicians choose between management strategies for MRM?

CRITERIA FOR CONSIDERING STUDIES Studies were required to be prospective, double-blind, randomized controlled trials (RCTs) of any pharmacologic agent vs placebo or another drug, for the symptomatic relief or prevention of MRM. Both parallel group and crossover studies of at least 20 patients were included. Study participants were required to be women (18 or older) with MRM or PMM. Participants had to fulfill International Headache Society criteria for the diagnosis of migraine and have MRM in at least two of three cycles.

For efficacy analysis, the following main outcomes were considered:

1. Pain-free response at 2 hours (symptomatic trials)
2. Pain response at 2 hours (symptomatic trials)
3. Incidence of MRM (preventive trials)
4. Number of days on which a MRM occurred (preventive trials)

The analysis of data reported on adverse events (AEs) considered the overall number of patients reporting AEs.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES The review was performed by three neurologists with expertise in headache and clinical epidemiology. MEDLINE (1966 to present) and EMBASE (1980 to present) databases and the Cochrane Collaboration library were searched for double-blind RCTs relating to the clinical questions. The search was repeated prior to final revision of the manuscript. Search terms included migraine, menstrual disturbances, menstrual cycle, and menstruation, as well as terms describing specific types of clinical studies. Additionally, the references of review articles on MRM were searched. Finally, all abstracts presented at the 2007 meetings of the International Headache Society (IHS), American Headache Society (AHS), American Academy of Neurology (AAN), and American Neurological Association (ANA) meetings were reviewed for RCTs conducted in the past year. An attempt was made to contact the senior author on each abstract to request full data sets.

METHODS OF REVIEW Two reviewers (T.P. and W.J.D.) independently screened titles and abstracts for trials fulfilling inclusion criteria. A data abstraction instrument was used to summarize the findings of the studies used in the development of this guideline. Data were abstracted independently by two reviewers and confirmed for accuracy (T.P. and W.J.D.). Discrepancies between reviewers were resolved by discussion.

The studies were evaluated using quality criteria developed by the US Preventive Services Task Force (USPSTF).[10] Studies are rated "good" if all of the following criteria are met: assembly of comparable groups, adequate randomization, allocation concealment, confounders distributed equally, maintenance of comparable groups, absence of overall high or important differential loss to follow-up, mea-

Table 1 Summary of results: The effect of acute treatment of menstrually related migraine

Ref. no.	No.	Quality assessment	Intervention	Primary outcome	Results	*p* Value	Quality criteria unfulfilled
26	260	Poor	Sumatriptan 6 mg SC vs placebo, up to 2 attacks assessed	2 hour pain response	Attack 1: 73 vs 31%; Attack 2: 81 vs 29%	<0.001	ITT analysis not used; inadequate attention to confounders
27	24	Fair	Mefenamic acid 500 mg TID vs placebo perimenstrually, 2 cycles assessed	2 hour pain-free response	Mefenamic acid 66.6%; placebo 8.3%	<0.05	No statement on allocation concealment
28	417	Good	Sumatriptan 50 or 100 mg tab vs placebo; 1 attack	2 hour pain-free response	Pain-free: 100 mg 61%; 50 mg 50%; placebo 29%	<0.001	
29	447	Poor	Sumatriptan 50 or 100 mg tab vs placebo; 1 attack	2 hour pain-free response	Pain-free: 100 mg 58%; 50 mg 51%; placebo 22%	<0.001	No statement on allocation concealment; no attention to confounders
30	579	Poor	Zolmitriptan 1.25, 2, or 5 mg tab vs placebo; 1 attack	Headache response at 2 hours	Headache response: zolmitriptan 48%; placebo 27%; OR 2.8; CI (2.09, 3.75)	<0.0001	No statement on allocation concealment; no attention to confounders
31	115	Poor	Sumatriptan 100 mg tab vs placebo	4 hour pain response	Headache response: sumatriptan 67%; placebo 33%	0.0072	ITT analysis not used; no statement on allocation concealment; unacceptable measures used
32	275	Poor	Naratriptan 2.5 mg tab vs placebo; 1 attack	4 hour pain-free response	Pain-free: naratriptan 58%; placebo 30%	<0.001	No statement on allocation concealment; ITT analysis not used; unacceptable measures used
33	336	Fair	Zolmitriptan 2.5 mg tab vs placebo; 1 attack	Headache response at 2 hours	Headache response: zolmitriptan 65.7%; placebo 32.8%	<0.0001	No statement on allocation concealment
34	Study 1: 403; Study 2: 399	Good	Rizatriptan 10 mg vs placebo; 1 attack	Headache response at 2 hours	Headache response at 2 hours: Study 1: rizatriptan 70%, placebo 53%; Study 2: rizatriptan 73%, placebo 50%	Study 1: 0.001; Study 2: <0.001	

ITT = intent-to-treat.

surement instruments are acceptable and applied equally, masking of outcome assessment, clear definition of interventions, all important outcomes considered, and intention to treat analysis performed. A "fair" study does not meet all criteria but has no fatal flaw that invalidates its results. A "poor" study contains a fatal flaw. Fatal flaws include the assembly of noncomparable groups, the use of unacceptable or unequally applied measurements, lack of blinding of outcome assessment, failure to address key confounders, and lack of intention to treat analysis. Recommendations were made according to the USPSTF grades (appendix). Substantial net benefit is defined as a therapeutic gain (drug response minus placebo response) or absolute risk reduction (ARR) of greater than 50%, and a moderate net benefit is defined as a therapeutic gain or ARR of 20 to 50%. Recommendations were not made for medications for which only abstracts were available at the time of final revision.

SUMMARIZING THE RESULTS Meta-analysis was performed by treatment type if more than one trial was performed. ORs and risk differences (RD) were calculated with 95% CIs. For efficacy data, the RD represents the therapeutic gain. OR and RD from multiple studies were tested for homogeneity using the χ^2 test and by calculating the I^2 statistic. If study estimates were homogenous, they were combined using a fixed-effects model. When studies with heterogeneous results were clinically similar, the study estimates were combined using a random-effects model. Clinical heterogeneity was assessed by looking at trial and patient characteristics, and outcome measures. Clinically heterogeneous studies were not statistically combined. Meta-analysis was performed for sumatriptan, zolmitriptan, and rizatriptan. Results for the remaining trials were summarized individually for studies of "good" or "fair" quality.

Table 2 Summary of results: The effect of short-term prevention on menstrually related migraine

Ref. no.	No.	Quality assessment	Intervention	Primary outcome	Results	*p* Value	Quality criteria unfulfilled
16	20	Fair	Percutaneous estradiol 1.5 mg for 7 days vs placebo, 3 cycles assessed	Presence of menstrual migraine attack	Menstrual migraine attack: Estradiol 30.8%; Placebo 96.3%	<0.01	No statement on allocation concealment; some, but not all confounders discussed
17	22	Fair	Estradiol gel 1.5 mg for 7 days vs placebo, 4 cycles assessed	No. of migraine days occurring over 7 perimenstrual days	Migraine days: Estradiol gel: 48 days; Placebo: 86 days	<0.05	No statement on allocation concealment; some, but not all confounders discussed
18	40	Poor	Naproxen 550 mg BID for 13 days vs placebo, 3 cycles assessed	Pain Total Index (no. headaches + [duration × severity])	Cycle 1: 51.2 vs 48.5; Cycle 2: 57.2 vs 66.5; Cycle 3: 49.4 vs 69.1	NS	No statement on allocation concealment; some, but not all possible confounders discussed; inadequate power
19	24	Poor	Magnesium 120 mg TID for last 2 weeks of menstrual cycle vs placebo, 2 cycles assessed	Pain Total Index	Magnesium 33; placebo 77	<0.03	No statement on allocation concealment; no attention to confounders
20	20	Poor	Percutaneous estradiol 50 μg vs placebo, 3 cycles assessed	Presence of menstrual migraine attack	Menstrual migraine attack: estradiol 59%, placebo 69%	NS	No statement on allocation concealment; intervention not clearly stated; inadequate power
21	30	Poor	Nimesulide 100 mg TID for 10 days vs placebo, 3 cycles assessed	Hourly pain intensity and duration of pain in hours	Pain intensity: 19 vs 150.3; pain duration: 13.7 vs 63.2	<0.0001	No statement on allocation concealment; unacceptable measurements used
22	220	Fair	Naratriptan 1 or 2.5 mg BID for 5 days vs placebo, 4 cycles assessed	Median no. of menstrual migraines over 4 cycles	Naratriptan 1 mg: 2; naratriptan 2.5 mg: 3; placebo: 4	<0.01 for Naratriptan 1 mg vs placebo	No statement on allocation concealment
23	49	Poor	Phytoestrogen: 60 mg soy isoflavones, 100 mg dong quai, 50 mg black cohosh vs placebo, for 24 weeks	No. of menstrual migraine attacks	Phytoestrogen: 4.7; placebo: 10.3	<0.01	ITT analysis not used; allocation concealment unclear
24	579	Good	Frovatriptan 2.5 mg OD or BID for 6 days vs placebo, 3 cycles assessed	Incidence of menstrual migraine headache	Frovatriptan 2.5 mg OD: 52%; frovatriptan 2.5 mg BID: 41%; placebo: 67%	<0.0001	
25	37	Fair	Estradiol 1.5 mg gel for 8 days vs placebo, 6 cycles assessed	No. of days on which a menstrually related migraine attack occurred	Estradiol: 131 migraine days; placebo: 171 migraine days; RR 0.78, CI (0.62, 0.99)	0.03	Some, but not all confounders discussed

ITT = intent-to-treat.

DESCRIPTION OF STUDIES A total of 170 abstracts were found by the combined searches. A total of 147 abstracts did not meet inclusion criteria. A total of 23 full text articles were reviewed. On reading the full text articles, 5 did not meet inclusion criteria (table e-1 on the *Neurology*® Web site at www.neurology.org).[11-15] The remaining 18 studies were included in the analysis: 10 on short-term prevention of MRM[16-25] and 8 on acute treatment of MRM.[26-33] The repeat search done prior to submission of the final manuscript yielded one further study on acute treatment of MRM.[34] Review of the 2007 abstracts of the IHS, AHS, AAN, and ANA meetings yielded 3 trials.[35,36,37] We were unable to obtain further data on these trials.

Trials of acute therapies for MRM were fairly uniform in their inclusion criteria. Trials involved women with regular MC aged 18 to 65, with a history of MRM in at least two of the three previous MC. All trials using triptans excluded women with cardiac disease, uncontrolled hypertension, or concomitant use of ergotamine or a monoamine oxidase inhibitor (MAOI). Pregnancy or lactation was also an exclusion criterion for all trials. The most common endpoints used were the 2-hour pain

Table 3 Summary of recommendations for acute abortive treatments for menstrually related migraine headache

Maneuver	Effectiveness	Levels of evidence	Recommendation
Sumatriptan	Direct evidence that sumatriptan 50 and 100 mg are effective in decreasing pain in menstrually related migraine. Increased rate of nonserious adverse events: nausea, dizziness, pressure/tightness.	Four randomized, controlled clinical trials; 1 good, 3 poor quality. Overall rating: I-good	Grade "B": Good evidence to treat with sumatriptan in menstrually related migraine; benefits outweigh harms; improves important health outcomes.
Zolmitriptan	Evidence to support that zolmitriptan 2.5 mg is effective in decreasing pain in menstrually related migraine. Evidence to support much higher rate of nonserious adverse events in zolmitriptan treated patients compared to placebo.	Two randomized, controlled clinical trials; 1 fair, 1 poor quality. Overall rating: I-fair	Grade "C": Fair evidence that zolmitriptan can improve menstrually related migraine but the balance of benefits and harms is too close to justify a general recommendation.
Naratriptan	Insufficient evidence that naratriptan 2.5 mg is effective in decreasing pain in menstrually related migraine. Incidence of adverse effects similar to placebo.	1 randomized controlled clinical trial; poor quality. Overall rating: I-poor	Grade "I": Insufficient evidence to recommend for or against routinely providing naratriptan for menstrually related migraine. Evidence that naratriptan is effective is of poor quality and the balance of benefits and harms cannot be determined.
Mefenamic acid	Direct evidence that mefenamic acid 500 mg three times daily is effective in decreasing pain in menstrually related migraine. Infrequent mild adverse events.	1 randomized controlled clinical trial; fair quality. Overall rating: I-fair	Grade "B": Fair evidence to treat with mefenamic acid in menstrually related migraine; benefits outweigh harms; improves important health outcomes.
Rizatriptan	Direct evidence that rizatriptan 10 mg is effective in decreasing pain in menstrually related migraine. Increased rate of nonserious adverse events in rizatriptan group compared to placebo.	2 randomized controlled clinical trials; good quality. Overall rating: I-good	Grade "B": Good evidence to treat with rizatriptan in menstrually related migraine; benefits outweigh harms; improves important health outcomes.

response, or the 2-hour pain-free rate. The 2-hour pain response is a reduction of at least two points in the four-point pain severity scale, with 0 = no pain, 1 = mild pain, 2 = moderate pain, and 3 = severe pain. The 2-hour pain-free rate is the proportion of patients who are pain-free at 2 hours post medication dose. A summary of the trial characteristics, methodologic flaws, and results can be seen in table 1.

Clinical trials for short-term prevention of MRM included women 18 to 65 with regular MC. Trials varied in their requirements for MRM frequency. All trials excluded pregnant or lactating women. Trials using estrogens excluded women taking hormonal contraceptives. Trials using triptans excluded women with heart disease, uncontrolled hypertension, or concomitant use of ergotamine or MAOI. Outcome measures varied between trials. Some trials assessed the proportion of patients in the treatment vs control groups experiencing a MRM; other trials counted the number of migraine days occurring over several cycles. A summary of the trial characteristics, methodologic flaws, and results can be seen in table 2.

RESULTS Which acute treatments for MRM are effective in reducing pain? See table 3 for recommendation summary.

Sumatriptan. There are four RCTs comparing sumatriptan to placebo: one of good quality[28] and three of poor quality.[26,29,31] The studies by Nett et al. and Landy et al. were parallel group trials of sumatriptan 50 or 100 mg vs placebo for a single MRM; the study by Fachinetti et al. was a parallel group study of sumatriptan 6 mg subcutaneous injection vs placebo for two MRM; and the study by Dowson et al. was a two group cross-over study. Due to clinical heterogeneity, the Dowson et al. trial was not combined statistically with the other trials.

Sumatriptan 100 mg. Two-hour pain-free response: The two studies included 509 patients.[28,29] Both studies found sumatriptan 100 mg superior to placebo. The summary therapeutic gain was 34% (CI 26%, 42%). The summary OR was 4.33 (CI 2.96, 6.32) (figure e-A).

Adverse events: The summary risk difference for AEs was −0.07 (CI −0.18, 0.03) in favor of the placebo group (figure e-B).

Sumatriptan 50 mg. Two-hour pain-free response: The two studies included 516 patients.[28,29] Both

studies found sumatriptan 50 mg superior to placebo. The summary therapeutic gain was 25% (CI 17%, 33%). The summary OR was 3.02 (CI 2.08, 4.38) (figure e-C).

Adverse events: The summary risk difference for AEs was −0.06 (CI −0.16, 0.04) in favor of the placebo group (figure e-D).

Recommendation B. We recommend that clinicians routinely offer sumatriptan 50 or 100 mg for symptomatic therapy of MRM. We found good evidence that sumatriptan provides moderate benefit and that the benefits outweigh AEs. The 100 mg dose confers greater net benefit. Sumatriptan cannot be used in women with cardiac disease, uncontrolled hypertension, or concomitant ergotamine/MAOI use.

Zolmitriptan. *Evidence.* There are two RCTs of zolmitriptan compared to placebo, one of fair[33] and one of poor[30] quality. Both studies were parallel group studies of zolmitriptan (1, 2.5, or 5 mg) vs placebo for one[30] or two[33] MRM over 3 months.

Zolmitriptan any dose. Two-hour pain response: Both studies used the 2-hour pain response as their primary outcome measure, and included 1,519 MRM. Both studies found zolmitriptan superior to placebo. A random effects model was used for statistical heterogeneity. The summary therapeutic gain was 26% (CI 15%, 37%). The summary OR was 2.97 (CI 1.98, 4.45) (figure e-E).

Adverse events: AEs reported in the studies were mild and there were no life-threatening AEs. The most common AEs were dizziness, paraesthesias, and fatigue. A random effects model was used for statistical heterogeneity. The summary risk difference was 0.20 (−0.51, 0.10) in favor of the placebo group (figure e-F).

Recommendation C. We make no recommendation for or against routine provision of zolmitriptan for symptomatic therapy of MRM. We found fair evidence that zolmitriptan provides moderate benefit but the balance of benefits and AEs is too close to justify a general recommendation. Though the number of patients withdrawing from the study due to AEs was low, the number of AEs in the treatment group is very high, and it is unclear if patients felt that the therapeutic benefit of the treatment was enough to accept the AEs.

Naratriptan. *Evidence.* There is one RCT comparing naratriptan with placebo for acute treatment of MRM.[32] This study was rated as poor due to fatal flaws.

Recommendation I. The evidence is insufficient to recommend for or against routinely providing naratriptan for symptomatic treatment of MRM. Evidence that naratriptan is effective is of poor quality, and the balance of benefit and harms cannot be determined.

Mefenamic acid. *Evidence.* There is one fair quality RCT comparing the nonsteroidal anti-inflammatory drug mefenamic acid (500 mg taken three times daily beginning at onset of MRM, and continued for the duration of the MC) with placebo.[27] Al-Waili studied 24 patients in a crossover design. Two-hour pain-free rates were 66.6% in the mefenamic acid group compared to 8.3% in the placebo group ($p < 0.05$, therapeutic gain 58.3%). Mild epigastric pain occurred in 8% of patients during the mefenamic acid treatment phase but did not cause treatment discontinuation.

Recommendation B. We recommend that clinicians routinely offer mefenamic acid for MRM as symptomatic therapy. We found fair evidence that mefenamic acid provides substantial benefit and that the benefits outweigh AEs. Mefenamic acid should not be used in patients with peptic ulcer disease or previous gastrointestinal bleeding.

Rizatriptan. *Evidence.* There are two good quality RCTs comparing rizatriptan 10 mg to placebo in the acute treatment of MRM.[34] Both studies were identical in design and were published together in the same article, though the results for each study were presented individually. Patients treated a single MRM with rizatriptan or placebo.

Rizatriptan 10 mg. Two-hour pain response: The two studies included 707 patients. Both studies found rizatriptan superior to placebo. The summary therapeutic gain was 20% (CI 12%, 27%). The summary OR was 2.34 (CI 1.68, 3.25) (figure e-G).

Adverse events: There were no serious AEs reported in either study. The most common AEs reported were dry mouth, fatigue, dizziness, paraesthesia, and somnolence. The summary risk difference for AEs was −0.07 (CI −0.13, −0.02) in favor of the placebo group (figure e-H).

Recommendation B. We recommend that clinicians routinely offer rizatriptan 10 mg to women with MRM for symptomatic therapy. We found good evidence that rizatriptan provides moderate benefit and that the benefits outweigh AEs. Rizatriptan cannot be used in women with cardiac disease, uncontrolled hypertension, or concomitant ergotamine/MAOI use.

Which short-term preventive treatments for MRM are effective in preventing migraine? See table e-2 for recommendation summary.

Transdermal estradiol. *Evidence.* There are four RCTs comparing transdermal estradiol with placebo: three for the prevention of MRM[17,20,25] and one for the prevention of PMM.[16] Due to signifi-

cant clinical heterogeneity, meta-analysis of these trials was not possible.

In the study of DeLignieres et al.,[16] 20 women with PMM were treated with 1.5 mg of transdermal estradiol or placebo over three cycles beginning 2 days prior to the expected onset of headache and continued for 7 days. A total of 96.3% of patients experienced a migraine during the placebo phase, compared to 30.8% during the estradiol treatment phase ($p < 0.01$, ARR 65.5%). One patient experienced a migraine (5%) 3 days after stopping estradiol.

In the two fair studies, Dennerstein et al.[17] and MacGregor et al.[25] treated women with MRM with 1.5 mg of transdermal estradiol or placebo from day −2 to +5 for two cycles each in the study of Dennerstein et al., and from day −6 to +2 for three cycles each in the study of MacGregor et al. Both studies found a significant reduction in the number of migraine days reported in the estradiol treated cycles compared to placebo (44% and 23% reduction).

Dennerstein et al. found 2 of 22 women experienced amenorrhea during the estradiol treated cycles. No other AEs were reported. MacGregor et al. found that of the 22 women who benefited from using the estradiol gel, 15 experienced post gel migraine (they had more migraine days during the 5 days after the estradiol gel compared to the 5 days after placebo).

Recommendation B. We recommend that clinicians routinely offer estradiol gel 1.5 mg perimenstrually to women with PMM or MRM for the prevention of migraine. We found fair evidence that transdermal estradiol applied perimenstrually provides substantial reduction in the occurrence of PMM and moderate reduction in the occurrence of MRM. The benefits outweigh AEs. Women should be evaluated individually for the occurrence of post-gel migraine; if this occurs, clinicians should evaluate if there is a net benefit to treatment. Estradiol gel should not be used in women on hormonal contraception or women with breast cancer.

Frovatriptan. *Evidence.* There has been one good quality RCT of the use of frovatriptan in the short-term prevention of MRM.[24] In a three-way crossover study, 546 patients over three MC were treated with placebo, frovatriptan 2.5 mg once daily, or frovatriptan 2.5 mg twice daily for 6 days perimenstrually in a randomized sequence. The incidence of MRM was 41% in the frovatriptan 2.5 mg BID treated cycles, 52% in the frovatriptan 2.5 mg OD treated cycles, and 67% in the placebo treated cycles ($p < 0.0001$, ARR 26%, frovatriptan 2.5 mg BID vs placebo).

AEs were reported in 40.2% of placebo treated cycles, 42.9% of frovatriptan 2.5 mg OD treated cycles, and 44.3% of frovatriptan 2.5 mg BID treated cycles (nonsignificant). The most commonly reported AEs were headache, nausea, dizziness, nasopharyngitis, and dysmenorrhea, and were not significantly different between groups.

Recommendation B. We recommend that clinicians routinely offer frovatriptan 2.5 mg BID perimenstrually to women with MRM for short-term prevention. We found good evidence that frovatriptan taken perimenstrually provides moderate benefit and that the benefits outweigh AEs. The once daily dose of frovatriptan has minimal net benefit compared to placebo. Frovatriptan should not be used in women with cardiac disease, uncontrolled hypertension, or concomitant use of ergotamine/MAOI.

Naratriptan. *Evidence.* The use of naratriptan in the short-term prevention of MRM has been assessed in one fair quality study.[22] Newman et al. treated women with naratriptan 1 or 2.5 mg or placebo twice daily for 5 days starting 2 days perimenstrually for four cycles. The median number of MRM over the four cycles was two for the naratriptan 1 mg BID group, compared to four in the placebo treated group ($p < 0.05$). There was no significant difference from placebo for the naratriptan 2.5 mg BID group.

AEs occurred in 13% of placebo patients, 13% of naratriptan 1 mg BID patients, and 17% of naratriptan 2.5 mg BID patients. The most common AEs reported were dizziness, dry mouth, chest symptoms, malaise, and paraesthesia. No serious AEs occurred.

Recommendation B. We recommend that clinicians routinely offer naratriptan 1 mg BID perimenstrually for short-term prevention of MRM. We found fair quality evidence that naratriptan taken perimenstrually provides moderate benefit and that the benefits outweigh AEs. There is no benefit from the 2.5 mg dose of naratriptan. Naratriptan should not be used in women with cardiac disease, uncontrolled hypertension, or concomitant use of ergotamine/MAOI.

Nimesulide, magnesium, phytoestrogens, and naproxen. *Evidence.* Single studies have assessed the use of nimesulide,[21] magnesium,[19] phytoestrogens,[23] and naproxen[18] for the short-term prevention of MRM. All of these studies were rated poor due to fatal flaws.

Recommendation I. The evidence is insufficient to recommend for or against routinely offering nimesulide, magnesium, phytoestrogens, and naproxen to patients with MRM as short-term

preventive therapy. Evidence that these treatments are effective is of poor quality, and the balance of benefits and harms cannot be determined.

How should clinicians choose between management strategies for MRM headache? There have been no trials comparing the efficacy of different treatments in the management of MRM. Therefore, there is no evidence with which to answer this question. Clinicians must use clinical considerations to help them decide among treatment strategies.

Clinical considerations. Important clinical considerations in choosing among treatments include medical comorbidities, AEs of individual agents, cost, and individual preferences. For example, patients with coronary disease should not take triptans and patients with a history of gastrointestinal bleeding should not take nonsteroidal anti-inflammatory drugs. For patients who do not have health insurance, analysis of cost of medications is appropriate. For patients who are adverse to taking medication for several days continuously, a symptomatic treatment is probably favorable. The different treatment options should be discussed to take into account patient values and preferences to aid the decision-making process.

FUTURE DIRECTIONS

While there are many evidence-based treatments for MRM, there are potential areas for future research. A comparison of the relative efficacy of treatment strategies may be useful to help clinicians decide among treatments. In addition to prevention of migraine as an outcome, patient preferences regarding the treatment should be sought. Studies comparing acute treatment to preventive treatment strategies could be performed, to see which strategies patients prefer and find easier to comply with.

Three studies presented at the AAN and AHS meetings in 2007 will likely extend the existing evidence on the treatment and short-term prevention of MRM. A study of frovatriptan for the short-term prevention of MRM presented by Brandes et al.[36] found a significant reduction in the incidence of MRM compared to placebo, supporting the results of the previously published trial.[24] A combination tablet of sumatriptan 85 mg and naproxen sodium 500 mg for the acute treatment of MRM in women with dysmenorrhea was assessed in two identical RCTs presented together at the AHS.[37] This combination treatment led to significantly higher 2-hour pain-free rates compared to placebo. A trial of zolmitriptan for short-term prevention of MRM[35] found that a significantly greater number of patients taking zolmitriptan 2.5 mg TID or BID achieved a greater than 50% reduction in the frequency of MRM over three cycles compared to placebo. It is expected that when the results of these trials are published in full and can undergo quality assessment, evidence-based recommendations can be made for their use in the treatment of MRM.

CONCLUSION

There is evidence to support the use of a number of medications in the acute treatment and short-term prevention of MRM. Trials in this area are ongoing, and new therapies for this disabling condition are on the horizon. Choosing among evidence-based regimens should be clinically based.

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APPENDIX

US Preventive Services Task Force (USPSTF) grades of recommendations.

- A: The USPSTF strongly recommends that clinicians routinely provide the service to eligible patients. The task force found good evidence that the service improves important health outcomes and concludes that benefits substantially outweigh harms.
- B: The USPSTF strongly recommends that clinicians routinely provide the service to eligible patients. The task force found at least fair evidence that the service improves important health outcomes and concludes that benefits outweigh harms.
- C: The USPSTF makes no recommendation for or against routine provision of the service. The task force found at least fair evidence that the service can improve health outcomes but concludes that the balance of benefits and harms is too close to justify a general recommendation.
- D: The USPSTF recommends against routinely providing the service to (asymptomatic) patients. The task force found at least fair evidence that the service is ineffective or that harms outweigh benefits.
- I: The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing the service. Evidence that the service is effective is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

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