Acute treatment and prevention of menstrually related migraine headache: evidence-based review
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CRD summary
This review found evidence to support the use of a number of medications in the acute treatment and short-term prevention of menstrually related migraine. Overall the review was well conducted, but the authors' specific recommendations for particular treatment regimes, especially where based on more limited evidence, should be treated with caution.

Authors' objectives
To review the evidence for acute and short-term preventative treatment of menstrually related migraine.

Searching
The authors searched MEDLINE (from 1966), EMBASE (from 1980) and The Cochrane Library; they updated their search prior to final revision of the report. Search terms were reported. References of review articles on menstrually related migraine were searched. Abstracts presented at 2007 meetings of four relevant associations were reviewed and authors of any relevant abstracts contacted to request the full data set.

Study selection
Eligible studies needed to be prospective double-blind randomised controlled trials (RCTs) of any pharmacological agent compared to placebo or another drug for symptomatic relief or prevention of menstrually related migraine. Studies of either parallel or crossover design were eligible provided they had at least 20 patients. Trials needed to include women aged 18 or older with menstrually related migraine or pure menstrual migraine. Participants were those who fulfilled International Headache Society criteria for diagnosis of migraine and had menstrually related migraine for at least two out of three cycles. Both trials of short-term prevention of menstrually related migraine and acute treatment were located. Age range criteria for all included trials was 18 to 65 years. Outcome endpoints varied for prevention studies; acute trials commonly reported two-hour pain response or two-hour pain-free rate and had as their most common endpoints two-hour pain response or two-hour pain-free rate.

Two reviewers independently screened titles and abstracts for relevance. Discrepancies were resolved by discussion.

Assessment of study quality
Trials were evaluated using quality criteria developed by USPSTF (US Preventive Services Task Force). Studies were rated good, fair and poor according to the criteria: assembly and maintenance of comparable groups; adequate randomisation and allocation concealment; confounders distributed equally; absence of overall high or important differential loss to follow-up; measurement instruments acceptable and applied equally; masking of outcome assessment; clear definition of interventions; all important outcomes considered; and intention-to-treat analysis performed.

It appeared that two reviewers were involved in the assessment of study quality.

Data extraction
Overall numbers and percentages of patients who reported adverse events were extracted. Outcomes related to efficacy were extracted. P values for comparisons in adverse events between intervention and placebo were reported.

Two reviewers independently extracted study data. Discrepancies were resolved by discussion.

Methods of synthesis
Trials were combined in meta-analysis by treatment type. Odds ratios and risk differences were calculated with their corresponding 95% confidence intervals. $X^2$ and I$^2$ statistics were used to assess heterogeneity. Where trial estimates were homogeneous, they were combined using a fixed-effect model. Where trials were statistically heterogeneous, but clinically similar, the random-effects model was used. Clinically heterogeneous trials were not combined. Results for trials not combined were summarised individually for trials of good or fair quality.

**Results of the review**

Nineteen trials were included in the review (n=4,296 participants). Three trials were rated good, six were fair and 10 were poor.

**Short-term prevention of menstrually related migraine:** (10 trials)

Four RCTs compared transdermal oestradiol to placebo. The trials were too clinically heterogeneous to combine in meta-analysis. The three trials rated fair found statistically significant results in favour of oestradiol when compared to placebo. One trial rated good found statistically significant differences between frovatriptan 2.5mg twice daily when compared to placebo. Adverse events did not vary significantly between groups. One fair trial assessed naratriptan and found statistically significant differences from placebo for the naratriptan 1mg twice daily group, but not for the group treated with 2.5mg. Other agents were assessed only in single poor-quality trials.

**Acute treatment of menstrually related migraine:** (nine trials)

Sumatriptan at 100mg was found to be superior to placebo (OR 4.33, 95% CI 2.96 to 6.32; two trials (one good, one poor) 509 patients). Sumatriptan at 50mg was found to be superior to placebo (OR 3.02, 95% CI 2.08 to 4.38; two trials (one good, one poor) 516 patients). Adverse events were not statistically significantly different between treatment groups.

Zolmitriptan was superior to placebo (OR 2.97, 95% CI 1.98 to 4.45; two trials (one fair, one poor) 1,519 menstrually related migraine). Adverse events were mild and there were no statistically significant differences between groups.

One RCT of poor quality was located for naratriptan. One fair quality trial was located for mefenamic acid and found a statistically significant difference between treatment groups in relation to two-hour pain free rates (66.6% versus 8.3%, p<0.05). Mild epigastric pain occurred in 8% of patients who took mefenamic acid, but did not cause treatment discontinuation.

Rizatriptan at 10mg was found to be superior to placebo (OR 2.34, 95% CI 1.68 to 3.25; two trials (both good) 707 patients). Adverse events were significantly less in the placebo group; no serious adverse events were reported.

**Authors’ conclusions**

There was evidence to support the use of a number of medications in acute treatment and short-term prevention of menstrually related migraine. Choosing among evidence-based regimens should be clinically based.

**CRD commentary**

This review was based on defined inclusion criteria for patients, intervention, outcome and study design. Searching encompassed a range of resources and included attempts to identify unpublished material. Quality was assessed and methods of synthesis conducted appropriately. Use of two reviewers throughout the review process helped to minimise risks of bias and error. Conclusions were appropriate, but specific recommendations for particular agents (especially where based on one trial) should be treated with some caution. The recommendation for further research into the relative efficacy of the various agents appeared appropriate; such trials would need to be sufficiently large to ensure the evaluation of both benefits and risks.

**Implications of the review for practice and research**

Practice: The authors stated that clinicians should routinely offer 50mg or 100mg sumatriptan, mefenamic acid or 10mg rizatriptan for symptomatic therapy of menstrually related migraine. Oestradiol gel 1.5mg should be routinely offered to women with pure menstrual migraine or menstrually related migraine for the prevention of migraine. 2.5mg frovatriptan twice daily should be offered premenstrually to women with menstrually related migraine for short-term
prevention. Naratriptan 1mg twice daily could also be offered. There was insufficient evidence for the remaining agents. Clinicians should use clinical considerations to choose between treatment strategies and take into account medical comorbidities, adverse events of individual agents, cost and individual preferences.

**Research:** The authors stated that a comparison of the relative efficacy of treatment strategies may help clinicians decide between treatments. Studies that compared acute treatment to preventative treatment strategies could be performed to test patient preference and compliance.

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