Efficacy of minor analgesics in primary dysmenorrhoea: a systematic review

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Authors' objectives
To quantify the efficacy and safety of naproxen, ibuprofen, mefenamic acid, aspirin and acetaminophen (paracetamol) in the treatment of primary dysmenorrhoea through a systemic overview of randomised controlled trials.

Searching
Electronic searches of MEDLINE, EMBASE and the Science Citation Index were carried out for the period of 1966 to end of March 1997 (details of the search strategies provided). Additional studies were identified through searching the bibliographies of retrieved articles and contacting drug manufacturers. Only English language articles were included in the review.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs).

Specific interventions included in the review
Orally administered naproxen (550mg, 275mg four times daily), ibuprofen (400mg, four times daily), mefenamic acid (250-500mg four times daily), aspirin (650mg four times daily), paracetamol (500mg four times daily) or paracetamol/dxtropropoxyphene (650/65mg four times daily). Interventions were compared directly or with placebo.

Participants included in the review
Women (13 to 45 years) with a diagnosis of primary dysmenorrhoea defined by a history of painful menstrual cycles and the exclusion of organic causes of dysmenorrhoea by physical examination. Trials involving women with secondary dysmenorrhoea due to organic disease or the use of the intrauterine device, and trials where the cause of dysmenorrhoea was not defined, were reviewed systemically but were not subject to statistical pooling.

Outcomes assessed in the review
The percentage of women with at least moderate relief of pain. Pain relief was described as at 'least moderate' if described as such by the authors in a scale of ordered categories or if there was at least 50% pain relief measured by the area under the curve. Secondary outcomes included the requirement for rescue analgesics, absence from work/school and the occurrence of restrictions to daily life.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
Validity was assessed on the basis of drop-outs and study design (parallel versus crossover).

Data extraction
Data extraction was undertaken by one of the authors and a 10% random sample was cross-validated by the second authors. An 'a priori' decision was made that if any obvious error was identified, then cross-validation of the complete data set would be undertaken. Any disagreements were resolved by discussion. The following items were recorded: year of publication, study design, type of dysmenorrhoea, dosage regimen, characteristics of the women (e.g. age, intensity of pain at baseline, sample size, number of drop-outs), efficacy outcomes (pain relief, requirement for rescue analgesics, restriction of daily life and absence from work or school) and side-effects.
Methods of synthesis
How were the studies combined?
The response rate ratio and rate difference with their associated 95% confidence intervals (95% CI) were calculated for the active treatment as compared to placebo for each comparison, using Rothman's method (see Other Publications Of Related Interest). If the studies were homogeneous the results were pooled using the fixed-effect model if not then a random-effects model was used. The treatments were compared indirectly by estimating the pooled results of each active treatment against placebo and then comparing the results of 95% CI, and directly by direct comparisons of analgesics without reference to the placebo groups even if provided.

How were differences between studies investigated?
The Q statistic for heterogeneity was used. Sensitivity analyses were performed where appropriate and the number needed to treat was also calculated.

Results of the review
Fifty-six studies (n=3449 participants) including 55 comparisons of analgesics with placebo and 12 direct comparisons of analgesics.

Pain relief: The pooled response rate ratios were in favour of treatment as versus placebo for naproxen (3.17, 95% CI: 2.72, 3.65, n=13); ibuprofen (2.41, 95% CI: 1.58, 3.68, n=9); mefenamic acid (2.03, 95% CI: 1.65, 2.48, n=3) and aspirin (1.60, 95% CI: 1.12, 2.29, n=5). The corresponding pooled rate differences were 0.39 (95% CI: 0.29, 0.49) for naproxen; 0.42 (95% CI: 0.26, 0.58) for ibuprofen; 0.42 (95% CI: 0.22, 0.61) for mefenamic acid and 0.10 (95% CI: 0.02, 0.18) for aspirin. The number needed to treat was 2.6 (95% CI: 2, 3.4) for naproxen, 2.4 (95% CI: 1.7, 3.8) for ibuprofen, 2.4 (95% CI: 1.6, 4.5) for mefenamic acid and 10 (95% CI: 5.5, 50) for aspirin.

Requirement for rescue analgesics: The pooled rate ratios were in favour of treatment versus placebo for ibuprofen (0.23, 95% CI: 0.13, 0.41, n=2); naproxen (0.38 95% CI: 0.32, 0.44, n=10); mefenamic acid (0.65, 95% CI: 0.52 to 0.80, n=1). Women taking aspirin required rescue analgesics as often as those receiving placebo (rate ratio=0.70, 95% CI: 0.58, 1.08, n=3). Both ibuprofen and naproxen seemed to be superior to mefenamic and aspirin.

Restriction of daily life: The pooled rate ratios were in favour of treatment versus placebo for ibuprofen (0.26, 95% CI: 0.16, 0.42, n=3) and naproxen (0.71, 95% CI: 0.60, 0.85, n=7). The corresponding rate differences were 42% for ibuprofen (95% CI: 20%, 64%) and 25% for naproxen (95% CI: 21%, 30%). Aspirin was not significantly superior to placebo (rate ratio=0.82, 95% CI: 0.64, 1.04. n=3).

Absence from work or school: The pooled rate ratio was in favour of naproxen versus placebo (0.29, 95% CI: 0.13, 0.66, n=7). There was no significant difference between placebo and ibuprofen (n=1) or aspirin (n=1).

Direct comparisons: No significant difference was found in pain relief between naproxen and ibuprofen (n=3). Comparisons between the other drugs only involved single trials. In terms of rate ratios naproxen was better than mefenamic acid (2.40, 95% CI: 1.39, 4.12) and aspirin (2.29, 95% CI: 1.16, 2.29); and ibuprofen was better than aspirin (1.90, 95% CI: 1.31, 2.78).

Adverse effects: In terms of rate ratios naproxen caused more side effects (1.45, 95% CI: 1.03, 2.04) and nausea (2.71, 95% CI: 1.00, 7.36) than placebo. Ibuprofen and mefenamic acid caused no more side effects than placebo, although the power of the trials was low. The combination of acetaminophen and dextropropoxyphene caused more adverse effects when compared directly with naproxen (19.4, 95% CI: 1.11, 3.41).

Sensitivity analyses: Sensitivity analyses were performed to investigate the possible influence of the design of the RCT on the measures of outcome and showed no statistically significant difference for any of the measures.

Authors' conclusions
Naproxen, ibuprofen, mefenamic acid and aspirin are all effective in primary dysmenorrhoea. Ibuprofen appears to have the most favourable risk-benefit ratio. Acetaminophen appears to be less effective than nonsteroidal anti-inflammatory drugs, but there was only one trial meeting our inclusion criteria and further studies are required.
CRD commentary
This is a clearly presented review featuring clear inclusion criteria and methods. Adequate attempts were made to locate relevant literature both published and unpublished, and the authors provided details of their search strategies in order to enable their work to be reproduced. However, evidence may have been excluded through restricting the review to only English language articles.

Although overall throughout the review clear methodological and analytical details are reported, the authors failed to record how the relevance of studies was assessed. The validity assessment was restricted to drop-outs and study design (parallel vs crossover). The results of the validity assessment were used to conduct sensitivity analyses.

The methods of analysis would appear to be appropriate and are clearly explained, with the authors first assessing the extent of study heterogeneity before pooling the data. It would therefore appear that the evidence presented supports the authors’ conclusions.

Implications of the review for practice and research
The authors did not state any implications for further research and practice.

Bibliographic details

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Other publications of related interest

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Subject indexing assigned by NLM

MeSH
Acetaminophen /therapeutic use; Adolescent; Adult; Analgesics /therapeutic use; Analgesics, Non-Narcotic /therapeutic use; Anti-Inflammatory Agents, Non-Steroidal /therapeutic use; Aspirin /therapeutic use; Dysmenorrhea /drug therapy; Female; Humans; Ibuprofen /therapeutic use; Mefenamic Acid /therapeutic use; Middle Aged; Naproxen /therapeutic use; Randomized Controlled Trials as Topic

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