Meta-analysis of the efficacy and safety of naproxen sodium in the acute treatment of migraine

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CRD summary
This review concluded that naproxen sodium was more effective than placebo, but might produce more adverse events, in the acute treatment of moderate or severe migraine attacks in adults. Trials were needed to compare it with other active treatments. These conclusions reflect the results, but the small number of trials and omission of the trial selection process should be considered.

Authors' objectives
To determine the efficacy and safety of naproxen sodium in the treatment of acute migraine.

Searching
MEDLINE, EMBASE, EBM reviews, and the Cochrane Library were searched, without language restriction, for articles from their inception to June 2009; the search terms were reported. The reference lists of relevant articles were searched.

Study selection
Double-blind randomised controlled trials (RCTs) were eligible for inclusion if they compared naproxen sodium (tablets) with placebo, in adult patients, for the treatment of moderate or severe migraine attacks. The outcomes of interest were headache relief at two hours, headache relief at four hours, pain free at two hours, relief of migraine symptoms, sustained headache relief, sustained pain relief, headache recurrence, and safety. The definitions of these outcomes were reported.

Most of the included trials used naproxen sodium 500mg; one trial used 825mg. All trials included placebo as a comparator; other comparators included naratriptan, ergotamine, celecoxib, and lysine clonixinate. Where reported, the participants included men and women (not pregnant and not lactating), between the ages of 18 and 65 years. The number of episodes in a given period prior to screening varied across trials. Headache relief at two hours was the primary outcome.

The authors did not state how many reviewers selected trials.

Assessment of study quality
The methodological quality of the trials was assessed using the five-point Jadad scale. A trial with a score of three points was considered to be of high quality. Two reviewers independently assessed trial quality and any disagreements were resolved by a third reviewer.

Data extraction
The data were extracted to permit the calculation of risk ratios and their associated confidence intervals. Intention-to-treat data were extracted by two reviewers independently and any disagreements were resolved by a third reviewer.

Methods of synthesis
Trials were combined by outcome and pooled risk ratios with 95% confidence intervals were calculated using a fixed-effect analysis. Statistical heterogeneity was assessed using the \( \chi^2 \) and \( I^2 \) tests. A random-effects model was used when significant heterogeneity was found (p<0.1). A sensitivity analysis, excluding one trial with a high dose of naproxen sodium (825mg), was performed. The number needed to treat was calculated. Publication bias was assessed by the visual inspection of a funnel plot and the Egger test.

Results of the review
Four RCTs (n=2,168) were included in the meta-analysis. All four trials were deemed to be of high quality, with Jadad
scores ranging from three to five, and they were all conducted in the USA.

**Headache relief:** Naproxen sodium was more effective than placebo in achieving headache relief at two hours (RR 1.58, 95% CI 1.41 to 1.77) and at four hours (RR 1.51, 95% CI 1.37 to 1.66). The numbers needed to treat were seven at two hours and six at four hours. The effect remained unchanged when the trial that used 825mg of naproxen sodium was excluded. No evidence of significant statistical heterogeneity, nor publication bias was found.

**Other outcomes:** Naproxen sodium was more effective than placebo in being pain free at two hours (RR 2.22, 95% CI 1.46 to 3.37, I²=63%). The effect was unchanged with the exclusion of the high dose trial and heterogeneity was reduced (I²=51%). It was more effective than placebo for the relief of migraine symptoms: nausea (RR 1.78, 95% CI 1.17 to 2.69, I²=79%), photophobia (RR 1.73, 95% CI 1.43 to 2.10, I²=0%), and phonophobia (RR 1.68, 95% CI 1.40 to 2.02, I²=0%). For nausea, no significant difference was found after the exclusion of the high dose trial. Naproxen sodium was more effective than placebo in sustained headache relief (RD 0.12, 95% CI 0.08 to 0.15, I²=0%), and sustained pain-free response (RR 1.95, 95% CI 1.21 to 3.13, I²=68%). No significant heterogeneity was found for sustained pain-free response after the exclusion of the high dose trial. No statistically significant differences were found in headache recurrence.

**Adverse events:** Compared with placebo, the risk of an adverse event was greater with naproxen sodium (RR 1.29, 95% CI 1.04 to 1.60). The most commonly reported adverse events were nausea, dizziness, dyspepsia, and abdominal pain.

**Authors' conclusions**
The evidence suggested that naproxen sodium was more effective than placebo, but might produce more adverse events, in the acute treatment of moderate or severe migraine in adults. Head-to-head trials were needed to establish its effectiveness relative to other active treatments.

**CRD commentary**
The review question was defined and supported by clear inclusion criteria. Several relevant databases were searched, without language restriction, but no further attempts were made to locate unpublished trials. No evidence of publication bias was found, but it is difficult to assess this accurately with a small numbers of trials. The authors reported methods designed to reduce error and bias for data extraction and validity assessment, but did not report them for study selection. The validity assessment used appropriate criteria, but only the summary scores were reported. The decision to use meta-analysis appears to have been appropriate and reasonable steps were taken to assess heterogeneity.

The authors' conclusion reflects the results presented and is likely to be reliable, but the small number of trials and the omission of the process for study selection should be considered.

**Implications of the review for practice and research**
**Practice:** The authors stated that naproxen sodium should be prescribed, instead of naproxen, in acute migraine attack due to its faster onset of action.

**Research:** The authors' suggested that high quality trials, with head-to-head comparisons of naproxen sodium with other active treatments, were required.

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**Bibliographic details**

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.