The relative efficacy of phenothiazines for the treatment of acute migraine: a meta-analysis

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CRD summary
The authors concluded that phenothiazines were more effective than placebo for the treatment of migraine headache and had higher rates of clinical success than other agents. These conclusions are supported by the results of the review and are likely to be reliable.

Authors' objectives
To determine the relative effectiveness of phenothiazines compared with placebo and other active agents for the treatment of acute migraine.

Searching
MEDLINE, EMBASE, CINAHL and the Cochrane Library databases, plus international clinical trial registers, were searched to December 2008. Search terms were reported. The related articles function in PubMed was used to identify additional studies. Authors of trials shown as completed in clinical trials registers that had not yet been published were contacted for further information. The review was restricted to full text articles published in peer reviewed journals.

Study selection
Randomised controlled trials (RCTs) that compared a parenterally administered phenothiazine (chlorpromazine, prochlorperazine and methotrimeprazine) with placebo or an active parenterally administered comparison, for the treatment of patients with acute migraine, were eligible for inclusion. Acute migraine had to be defined using the criteria established by the International Classification of Headache Disorders, or with a reasonable attempt made to specifically include migraine headaches rather than all benign headaches. Trials had to report data on headache intensity/clinical outcome within two hours of treatment.

The primary review outcome was relief of headache. Secondary outcomes were clinical success as defined by trial authors. If clinical success was not reported, use of rescue medication was used as a proxy.

Included trials compared chlorpromazine (0.04 to 0.1mg/kg or 12.5 to 25mg), prochlorperazine (10mg) or methotrimeprazine (37.5mg) with placebo, metoclopramide (0.1mg/kg or 10 to 20mg), sumatriptan (6mg), meperidine (0.4 mg/kg or 75mg), ketorolac (30 to 60 mg) or sodium valproate (500mg). The majority of included trials compared interventions to active comparators. Phenothiazines were administered intravenously or intramuscularly. None of the trials included co-administration of other agents. Headaches were either diagnosed according to International Headache Society criteria, defined criteria or were physician diagnosed. Some trials also administered diphenhydramine or metoclopramide in addition to the studied drugs.

Abstracts identified by the searches were screened by one reviewer; full papers were ordered for potentially relevant abstracts and screened by two reviewers for inclusion. Disagreements were resolved through consensus or referral to a third reviewer.

Assessment of study quality
Two reviewers independently assessed trial quality using the Jadad scale. Trials were assigned a summary quality score with a maximum of 5 points. Disagreements were resolved through consensus or referral to a third reviewer.

Data extraction
Two reviewers independently extracted data as odds ratios (OR) and 95% confidence intervals (CI). Disagreements were resolved through consensus or referral to a third reviewer.

Methods of synthesis
Random effects models were used to estimate summary odds ratios and 95% confidence intervals. The proportion of patients treated with phenothiazines that had complete headache relief and clinical success were calculated. The authors
did not state that they assessed heterogeneity, but results of $X^2$ and $I^2$ tests were reported on forest plots. Results were also reported separately for the subgroup of trials in which metoclopramide was the comparator.

**Results of the review**
Thirteen RCTs were included in the review (n=814 patients). Jadad quality scores ranged from 1 to 5 points (out of 5), with all but two RCTs scoring at least 4 points.

Phenothiazines lead to significantly greater headache relief (OR 15.0, 95% CI 7.6 to 29.8; five RCTs) and clinical success (OR 8.9, 95% CI 4.1 to 19.5; four RCTs) compared with placebo. Phenothiazines also resulted in significantly greater clinical success (OR 2.0, 95% CI 1.3 to 3.3; 10 RCTs) compared with active comparators, but there was no significant difference in headache relief (five RCTs). Results were similar when the analysis was restricted to trials that used metoclopramide as the active comparator.

There was no evidence of statistical heterogeneity for any of the outcomes evaluated.

Overall, 48% (95% CI 43 to 54) of patients treated with phenothiazines had complete relief of headache, and 78% (95% CI 74 to 82) reported clinical success.

**Authors' conclusions**
Phenothiazines were more effective than placebo for the treatment of migraine headache and had higher rates of clinical success than other agents against which they were compared.

**CRD commentary**
The review addressed a clearly stated objective supported by defined inclusion criteria. An extensive literature search was conducted that included attempts to locate unpublished studies, but the review was restricted to published studies; so there was a possibility of publication bias. Appropriate steps were taken to minimise bias and errors at all stages of the review process.

Trial quality was assessed using appropriate criteria, but results were only presented as summary scores, which made the results difficult to interpret, but most appeared to generally be of good quality. Appropriate methods were used to pool results, although clinical heterogeneity between trials mean that these should be interpreted with some caution. No details were reported on adverse events, or whether these differed for phenothiazines compared with other active agents.

The authors' conclusions are supported by the results of the review and are likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that their findings support the recommendation of phenothiazines for treatment of migraine in the emergency department.

**Research:** The authors did not state any implications for research.

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