Treatment of chronic headache with antidepressants: a meta-analysis
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Authors' objectives
To determine the overall efficacy of treatment of chronic headache with antidepressants. In addition, to determine whether efficacy varies among classes of antidepressant medications, by type of headache, or by potentially important patient characteristics, such as depression.

Searching
MEDLINE from 1966 to December 1998, PsycLIT from 1974 to December 1998, and EMBASE from 1974 to December 1998, were searched for papers in any language describing studies in humans. The following text and keywords were used: 'antidepressive agents', 'serotonin uptake inhibitors', 'monoamine oxidase inhibitors', 'tricyclic', 'amoxapine', 'clomipramine', 'trimipramine', 'desipramine', 'doxepin', 'imipramine', 'maprotiline', 'amitriptyline', 'nortriptyline', 'protriptyline', 'trazodone', 'nefazodone', 'fluoxetine', 'fluvoxamine', 'paroxetine', 'sertraline', 'femoxetine', 'venlafaxine', 'bupropion', 'citalopram', 'mianserin', 'pizotyline', 'pizotifen', 'headache', 'tension headache', 'chronic headache', and 'migraine'. The Cochrane Database of Systematic Reviews and the Cochrane Controlled Trials Register were also searched. Federal Research in Progress was searched for unpublished studies. The references of the reviewed articles were examined for additional studies.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials were included in the review. The included studies were of parallel and crossover designs.

Specific interventions included in the review
Antidepressants. The authors specified only that the included studies must have at least one group receiving an antidepressant. The treatments used in the included studies were: amitriptyline (10 to 150 mg/day), pizotifen (1.5 to 3 mg/day), opipramol (50 mg, three times daily), doxepin (10 to 100 mg), clomipramine (30 to 150 mg), femoxetine (300 to 600 mg/day), mianserin (30 to 60 mg), maprotiline (75 mg/day), pizotyline (0.5 mg, three times daily), fluvoxamine (50 to 100 mg), amitriptylinoxide (90 mg), and citalopram (20 mg/day). Of the included studies, 19 used tricyclic antidepressants, 18 used serotonin antagonists, and 7 used selective serotonin re-uptake inhibitors. The duration of treatment ranged from 4 to 27 weeks (mean: 10). The comparators were either placebo, other antidepressant analgesics or, in one case, metoprolol.

Participants included in the review
Chronic headache. The authors did not specify any inclusion or exclusion criteria with respect to the characteristics of the participants. Where stated, the mean age of the participants in the included studies varied from 33 to 61 years, and 28 to 100% were female. Twenty-three of the included studies focused on migraines, 11 on tension headaches, 3 on both migraine and tension headaches, and one study on neither (condition not specified in the review).

Outcomes assessed in the review
The authors specified only that the included studies must report measurable outcomes. No two included studies defined their outcomes in the same way. The outcomes used included headache index scores, headache frequency, the number of days with a headache, attack severity, and the number of hours with a headache.

How were decisions on the relevance of primary studies made?
The studies were screened for inclusion by reviewing the published article on the basis of the specified inclusion criteria.

The authors do not state how many of the reviewers performed the selection.
Assessment of study quality
Study quality was assessed using the 6-item instrument developed and validated by Jadad et al. (see Other Publications of Related Interest no.1). Study quality was assessed independently, in duplicate, and any disagreements were resolved by consensus.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

The data extracted from the primary studies included the following: study setting; country of origin; the inclusion and exclusion criteria; treatment characteristics (dose, duration, follow-up); demographic characteristics; the number of participants enrolled and analysed; assessment of co-morbid psychiatric disease; concurrent use of analgesic medications; any adverse effects and outcomes; and the study conclusions. The outcomes were extracted as either dichotomous or continuous variables, depending on how they were reported in the studies. Both types of outcome were extracted if available.

Methods of synthesis
How were the studies combined?
The primary studies were combined by a meta-analysis, using the random-effects model of DerSimonian and Laird (see Other Publications of Related Interest no.2) to calculate summary rate ratios, rate differences and standardised mean differences.

The sensitivity of the meta-analysis to changes in various assumptions was evaluated using several measures. The sensitivity to the existence of unpublished studies was assessed using a 'file drawer' test (see Other Publications of Related Interest no.3). The relative influence of each study on the results was determined by sequentially dropping studies and calculating the resulting summary measures. Meta-regression and subgroup analyses were conducted to investigate whether the results differed by type of headache, class of antidepressant, study design (parallel versus crossover), sample size, year of publication, gender, quality score, percentage losses to follow-up not included in the analysis, and duration of treatment. In addition, the summary measures were re-calculated with the 'worst case' assumption, i.e. that all placebo drop-outs responded whereas all treatment drop-outs failed to respond, in order to test the effect of failure to analyse on an intention to treat basis.

Publication bias was assessed using the methods of Egger et al. (see Other Publications of Related Interest no.4).

How were differences between studies investigated?
The heterogeneity of the dichotomous and continuous outcomes was assessed visually with Galbraith plots (see Other Publications of Related Interest no.5) and by using the chi-squared test.

Results of the review
A total of 38 randomised placebo-controlled trials (1,882 participants) were included in the review. Nineteen of these (1,342 participants) used parallel designs, whilst the remaining 19 (540 participants) used crossover designs.

Patients receiving antidepressants were twice as likely to report headache improvement; the rate ratio was 2.0 (95% confidence interval, CI: 1.6, 2.4). Since more of the treated patients (31%, 95% CI: 23, 40) improved than those receiving placebo, clinicians would need to treat 3.2 patients for one patient to improve (number-needed-to-treat 3.2). The average amount of improvement (standardised mean difference) was 0.94 (95% CI: 0.65, 1.2), an effect considered large. The treated patients also consumed less analgesic medication; the standardised mean difference was -0.7 (95% CI: -0.94, -0.5). There were no differences in outcomes amongst the following:

- the three classes of agent studied, i.e. tricyclic antidepressants, serotonin antagonists, selective serotonin re-uptake inhibitors;
- the type of headache, i.e. migraine versus tension;
the quality score;
the trial design, i.e. parallel versus crossover;
the sample size;
the year of publication;
the length of treatment;
the gender of the participants; and
the percentage of patients lost to follow-up.

The assessment of depression across the studies was insufficient to determine whether the effects of antidepressant medications on headache were independent of their effects on depression.

**Authors' conclusions**
Antidepressants were effective in preventing chronic headaches. Further study is needed to determine whether this is independent of depression, and whether the different classes of agent exhibit different efficacy.

**CRD commentary**
The research question addressed by the review was clear, though broad. There was a lack of predefined inclusion criteria, which reflected the wide scope of the review. The literature search was thorough and comprehensive, no language restrictions were placed on searches, and attempts were made to identify unpublished literature. The methodological quality of the included studies was appropriately assessed using a validated instrument, and sensitivity analyses were conducted to determine the impact of study quality on the review's findings. The methodological and participant characteristics of the primary studies were reported in detail, and further sensitivity analyses were conducted to assess their impact on the findings of the review. There appears to be a discrepancy in the numbers of primary studies focusing on different types of headache, as reported in the abstract of the review and the 'Results' section.

The authors' conclusions follow clearly from the results. The limitations of this meta-analysis, in terms of the lack of available study data on the incidence of concomitant depression and the rates of use of analgesic medication, were discussed in detail by the authors.

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

Research: The authors state that studies that determine whether particular subgroups of patients are more likely to respond to antidepressant therapy (such as depressed patients or those with high analgesic use) would be helpful. It would also be useful to define more effective treatment regimens in terms of the target dose, treatment duration, or interaction with analgesic medications. Further research on selective serotonin re-uptake inhibitors is warranted, because the number of studies using this commonly prescribed class of agents was small.

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**Bibliographic details**
PubMedID
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Other publications of related interest

This additional published commentary may also be of interest. Badgett R. Review: antidepressants improve headache in patients with chronic headache. Evid Based Med 2002;7:57.

Indexing Status
Subject indexing assigned by NLM

MeSH
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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.