Do antidepressants have an analgesic effect in psychogenic pain and somatoform pain disorder: a meta-analysis

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Authors' objectives
To determine whether antidepressants have an analgesic effect in psychogenic pain and somatoform pain disorder.

Searching
The following electronic databases were searched: MEDLINE (1966-), PsycINFO (1966-), Science Citation Index (1974-) and the National Library of Medicine Database (1966-). The following MeSH terms were used as search terms: 'pain and antidepressants', 'psychogenic pain or somatoform pain disorder' and 'antidepressants'. Manual searches of pain treatment outcome literature, pain books and pain meetings abstracts were also carried out. English and non-English language literature was reviewed.

Study selection
Study designs of evaluations included in the review
Randomised, placebo-controlled trials.

Specific interventions included in the review
Antidepressants including dothiepin (150mg/day), amitriptyline (30-75mg/day), femoxetine (400mg/day), zimelidine (200mg/day), phenelzine (45mg/day), clomipramine/mianserin (150mg/60mg/day) and mianserin (up to 90mg/day).

Participants included in the review
Male and female patients diagnosed with psychogenic pain disorder or somatoform pain disorder, including pain in the face, back, neck, pain from tension headaches and pain of mixed etiology.

Outcomes assessed in the review
Pain intensity as measured using a pain rating scale. Pain rating scales used included the Visual Analog Scale, the McGill Visual Analog Scale and unspecified scales rating pain on 4 or 5 point scales. Other measures of pain intensity included the mean daily headache duration time, proportion of headache free time and a rating scale of minor, moderate or marked headaches. Studies which did not report sufficient information to enable a p value (based on change scores between pre-drug pain intensities and post-drug pain intensities) to be calculated for the drug/placebo comparison, were excluded from the review.

How were decisions on the relevance of primary studies made?
Studies were assessed for relevance independently by two of the authors and discrepancies were resolved in conference.

Assessment of study quality
Study validity was assessed according to the method used by Onghena and van Houdenhove (see Other Publications of Related Interest). The ten items used were:

1. Drug side effect invalidated double blindness or not reported.

2. Drop-outs either invalidated randomisation or not reported.

3. Depression was neither an exclusion or inclusion criteria

4. Assessments of psychometric properties not reported or doubtful.

5. Duration of drug treatment less than 4wks.
6. Problems with statistical analysis.
7. Sample size too small.
8. No dose specification reported.
9. Compliance not monitored or not reported.
10. Use of analgesics not reported.

Judgements of study validity were made independently by two of the authors and discrepancies were resolved in conference.

**Data extraction**
Data were extracted independently by two of the authors and discrepancies were resolved in conference. The following items of information were extracted: study design, type of pain, participant characteristics, treatment regimen, length of follow-up, depression control and method used to assess pain intensity.

**Methods of synthesis**
How were the studies combined?
For each study a single one-tailed p value for the drug/placebo comparison was calculated, based on change scores between pre-drug pain intensities and post-drug pain intensities, for both the antidepressant drug and the placebo. The p values were combined and z values calculated, with each study been given equal weight in the analysis. The z values were combined to give an overall z score and effect sizes were calculated from the overall z score and the z scores of each individual study. Finally, the number of hypothetical studies, with findings of no effect, necessary in order to render the overall p value non-significant was calculated (ie the 'file drawer number'). The maximum number of unpublished studies that might reasonably exist (the 'tolerance') was also estimated.

How were differences between studies investigated?
Chi-squared tests for heterogeneity were performed. The analyses were repeated separately on the five headache pain studies and the remaining studies, to determine whether the overall results were confounded by the results of the antidepressant effect on headache pain.

**Results of the review**
Eleven studies including seven placebo-controlled double-blind randomised controlled trials and four placebo-controlled double-blind crossover trials. A total of 832 participants were included in the studies, 413 participants were assigned to antidepressant treatment and 419 to placebo.

All of the studies suffered from at least one flaw in terms of the ten defined quality criteria, with 9/11 of the studies having at least four problems with quality issues. No significant heterogeneity was detected between the p values from the 11 studies (chi-squared=7.92, 10 df, NS). The combined difference showed that antidepressants decreased pain intensity significantly more than placebo (z=5.71, p<0.0001). The overall effect size was large (mean=0.48) and ranged from 0 to 0.91. The number of unpublished studies (file drawer number) showing no difference between drug and placebo that would be necessary to make the results non-significant was estimated to be 133. The number of non-significant studies that could be reasonable argued to exist (tolerance level) was calculated to be 65, suggesting that the significant difference between the drug and placebo was unlikely to be due to publication bias.

The combined effect size for headache pain was much greater than that for mixed pain, but both were at least moderate in size and significant (for headache z=4.75, p<0.01, effect size=0.59 and for mixed pain z=3.08, p<0.01, effect size=0.39).

**Authors' conclusions**
The results indicate that in patients diagnosed with psychogenic pain or somatoform pain disorder, antidepressant treatment resulted in a reduction in pain that was significantly greater than that of placebo.

**CRD commentary**
This is a clearly reported review based on a well-defined research question and inclusion criteria. The literature search incorporated both electronic and manual searches of relevant literature and considered all articles regardless of their language of publication. Additional statistical analyses to consider the possible effect of publication bias suggested that the overall review findings were robust. The authors clearly reported the methodological details of the review process and carried out both an assessment of study quality and an analysis of study heterogeneity. The method of analysis seemed appropriate and it would appear that the evidence reported supports the authors' conclusions, however issues raised by the authors regarding study quality and the difficulties in identifying patients suffering from psychogenic and somatoform pain, should be borne in mind when interpreting the findings.

**Implications of the review for practice and research**
Practice: The authors stated that the review revealed statistically significant effects of antidepressants in psychogenic pain and somatoform pain disorder. However, it was not clear whether the observed effect was important in terms of clinical outcomes such as patient management and quality of life.

Research: The authors stated ‘well designed and adequately powered randomised clinical trials now need to be conducted with the Diagnostic Statistical Manual of Mental Disorders 4th Edition (DSM-IV) diagnosis of pain disorder to determine whether chronic pain patients diagnosed with this disorder respond with an analgesic effect to antidepressants’.

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**Other publications of related interest**

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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.