Treatment of functional chest pain with antidepressants: a meta-analysis


CRD summary
This review concluded that antidepressant medications were associated with improvements in pain and psychological symptoms in patients with functional chest pain, but there may be an increase in side-effects. The review had some data limitations and there was evidence of statistical variation, which means that the evidence may not be reliable and the authors' conclusions should be interpreted cautiously.

Authors' objectives
To investigate the efficacy of antidepressant treatments for functional chest pain.

Searching
MEDLINE, PsycINFO, Scopus and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to July 2011, with no language restrictions. Search terms were reported. Reference lists of relevant articles and reviews were also searched.

Study selection
Randomised controlled trials (RCTs) of antidepressants versus pharmacological placebo for the treatment of functional chest pain in patients with normal coronary anatomy were eligible for inclusion. The definition of functional chest pain was based on the symptom and medical negative examination. The relevant outcomes were pain, psychological symptoms, and quality of life.

The included trials studied imipramine (25 to 50mg/day), paroxetine (10 to 50mg/day), sertraline (50 to 200mg/day), fluoxetine (20mg/day), and venlafaxine (75mg/day) over three to 16 weeks. Some patients received other medications; non-pharmacological interventions were not reported. The mean age of patients was 23.5 to 60 years (where reported). Outcomes were measured using various questionnaires and self-reported measures. Exclusion criteria varied between trials. Most trials were conducted in outpatients in China, South Korea, USA and Europe.

Two reviewers independently performed study selection.

Assessment of study quality
Trial quality was assessed using the Jadad scale, which appraised randomisation, allocation concealment, blinding and follow-up; the maximum score was out of 5. Trials that scored 5 were considered high quality, those that scored 4 were deemed moderate quality and those that scored 3 or less were deemed low quality.

The authors did not state how many reviewers undertook quality assessment.

Data extraction
Data were extracted on pain, psychological symptoms and quality of life. These were used to calculate mean differences, with 95% confidence intervals (CIs). Where possible, data were extracted on an intention-to-treat principle. Means and their standard deviations were used to calculate mean differences. Where data was not available as values, graphical data were used. Data on standard errors were converted into standard deviations. Data on adverse events were also extracted and used to calculate odds ratios (ORs) with 95% confidence intervals. Trial authors were contacted for missing data.

Two reviewers extracted data; discrepancies were resolved by discussion.

Methods of synthesis
A fixed-effect meta-analysis was undertaken to calculate standardised mean differences (SMDs), weighted mean differences (WMDs) and odds ratios, with 95% confidence intervals. Continuous variables were assessed using non-parametric tests. Effect sizes were calculated using Cohen's d (0.2 to 0.5 = small effect; 0.5 to 0.8 = medium effect; >0.8 = large effect). Statistical heterogeneity was assessed using I². Random-effects meta-analysis was used when
heterogeneity was detected.

Sensitivity analysis was undertaken according to antidepressant class. Results were assessed by pain measures (visual analogue scales or diary); trials from China and the UK were removed.

Publication bias was assessed using funnel plots and file-drawer test.

**Results of the review**

Seven trials (319 patients) were included in the review. Five trials scored 5 on the Jadad scale and were deemed high quality. Two trials scored 4 and were deemed moderate quality. The proportion of patients that completed treatment ranged from 69.6% to 100% in the intervention group and 73.3% to 100% in the control group.

Antidepressants showed a statistically significant reduction in pain (SMD -1.26, 95% CI -2.43 to -0.18; I²=94%; seven RCTs) and psychological symptoms (SMD -0.87, 95% CI -1.67 to -0.08; I²=89%; six RCTs), but there was no significant difference in quality of life (WMD 2.00, 95% CI -2.54 to 6.54; I²=0%; two RCTs) compared with placebo. Antidepressants were associated with statistically significant more adverse events (OR 0.34, 95%CI 0.15 to 0.78; I²=14%; four RCTs) compared with placebo.

Sensitivity analysis indicated differences in results across the different classes of antidepressants. Other sensitivity analyses were reported in the review.

There was some evidence of publication bias, but it was not thought to be significant enough to change the overall results of the meta-analysis.

**Authors' conclusions**

Antidepressant medications were associated with improvements in pain and psychological symptoms, but there may be an increase in side-effects.

**CRD commentary**

Inclusion criteria for the review were clearly defined. Several relevant databases were searched with no language restrictions. Publication bias was assessed and was detected, although the meaningfulness of an analysis with less than 10 trials was questionable. Attempts were made to reduce error and bias during study selection and data extraction, but it was unclear if the same methods were used for quality assessment.

Quality assessment showed that the quality of the evidence base was generally good. The authors noted that patient demographics and co-morbidities were not reported in the trials, which could be a source of unknown heterogeneity. Many outcomes were self-reported. Trials were combined using suitable effects meta-analysis. Statistical heterogeneity was assessed, although significant heterogeneity was present in some analyses, which indicated that the data may not have been suitable for pooling. There were also slight discrepancies between the results reported in text and figures. The authors noted limitations with small trial sample sizes, use of other medications, and short treatment duration.

Given these limitations, together with the high levels of statistical heterogeneity and the use of self-reported outcomes measures, the evidence may not be reliable and the authors' conclusions should be interpreted cautiously.

**Implications of the review for practice and research**

**Practice:** The authors stated that short-term usage of imipramine (for all the ages) and venlafaxine (for young adults 20 to 29 years old) could be considered for treating pain in functional chest pain. Before initiating treatment, concomitant diseases related to potential adverse effects of the drugs and patients' preferences should be considered.

**Research:** The authors stated that more high quality and strictly controlled trials of antidepressants for functional chest pain were needed, as were longer-term trials. The effects of factors including psychiatric co-morbidity, gender, age, ethnic group, and treating period on the outcomes should be studied.

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