Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis

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**CRD summary**
This review investigated antidepressant treatment for fibromyalgia syndrome (FMS), compared with pharmacological placebo. The authors concluded that treatment with antidepressants for FMS significantly reduced pain, fatigue, sleep disturbances and depression and improved the health-related quality of life (HRQOL). The review was generally well-conducted and the conclusion was likely to be reliable.

**Authors’ objectives**
To assess the efficacy of antidepressants in the treatment of fibromyalgia syndrome (FMS).

**Searching**
MEDLINE, PsycINFO, Scopus and The Cochrane Library were searched without language restriction from inception to August 2008. Search terms were reported. The reference lists of relevant publications were also screened.

**Study selection**
Randomised controlled trials (RCTs) that compared antidepressants – including tricyclic and tetracyclic antidepressants (TCAs), selective serotonin re-uptake inhibitors (SSRIs), serotonin and noradrenaline re-uptake inhibitors (SNRIs) or monoamine oxidase inhibitors (MAOIs) – with a pharmacological placebo in patients with FMS defined using recognised criteria were eligible for inclusion. Studies that reported only categorical data were excluded if missing data were unavailable, as were studies assessing combinations of antidepressants, cyclobenzaprine or S-adenosylmethionine. The primary review outcomes were pain, fatigue, sleep and depressed mood. The secondary outcome was health-related quality of life (HRQOL).

Included studies had a median duration of eight weeks (range 4-28 weeks). All studies permitted additional therapy with paracetamol or acetaminophen. A number also allowed use of other analgesics. All excluded patients with severe physical diseases and a majority excluded those with severe mental disorders. Almost all participants were female. Sixteen studies used a parallel design and two studies used a crossover design.

Two reviewers independently assessed studies for inclusion. Any disagreements were resolved by discussion.

**Assessment of study quality**
The quality of studies was assessed using the van Tulder test described by the Cochrane Collaboration Back Review Group. Studies scoring at least 8 out of 11 points were classified as high quality. It was also assessed using the Jadad test, a 5-point scale evaluating randomisation, blinding and allocation concealment. Studies scoring 5 were classified as high quality.

The authors did not state how the validity assessment was performed.

**Data extraction**
Data on the point estimates (mean values, mean changes and standard deviations) for selected variables were extracted in standard forms. Intention-to-treat data were extracted where possible. Standard errors were converted into standard deviations where required. Study authors were contacted for missing data.

Two reviewers independently extracted the data from studies. Two other reviewers checked the data. Any disagreements were resolved by discussion.

**Methods of synthesis**
The studies were combined in meta-analyses. Weighted mean differences (WMDs) for continuous outcomes, with 95%
confidence intervals (CIs), were calculated where a same outcome scale was employed and standardised mean difference (SMDs) calculated where different scales were used. The studies were weighted using the inverse variance method. The magnitude of effect sizes was assessed using the Cohen categories. Statistical heterogeneity was investigated using $I^2$ statistics. The authors used a random-effects model for the meta-analyses if $I^2$ was 50 per cent or more, otherwise a fixed-effects model was employed.

Sensitivity analyses were conducted on different classes of antidepressants used. Publication bias was visualised using funnel plots and assessed using fail-safe N analysis.

**Results of the review**

Eighteen RCTs (n=1,427) were included in the meta-analysis, five of which had multiple treatment groups. The sample size varied from 14 to 294. The median of follow-up rates of patients receiving antidepressants was 71 per cent and for patients receiving placebos was 78 per cent.

Five studies were judged as high quality using the Jadad score. Seven studies were judged as high quality using the van Tulder score. Four studies were judged as high quality using both measures.

When the studies were pooled, antidepressants were significantly associated with a reduction of pain compared with control group (SMD -0.43, 95% confidence interval, CI: -0.55, -0.30, p<0.001; 22 treatment arms), a reduction of fatigue (SMD -0.13, 95%CI: -0.26, -0.01, p=0.04; 14 treatment arms), a reduction of depressed mood (SMD -0.26, 95% CI: -0.39, -0.12, p<0.001; 10 treatment arms), and an improvement of sleep (SMD -0.32, 95%CI -0.46, -0.18, p=0.001; 13 treatment arms) and HRQOL (SMD -0.31, 95%CI -0.42, -0.20, p<0.001; 12 treatment arms). Based on the evaluation of the effect size, the effect was clinically negligible for fatigue and small for the other outcomes.

For each antidepressant class, when the studies were pooled a large effect in pain reduction was significantly associated with TCAs (SMD, -1.64, 95%CI: -2.57, -0.71, p<0.001; six trials), a medium effect for MAOIs (SMD -0.54, 95% CI: -1.02, -0.07, p=0.03; three trials), and a small effect for SSRIs (SMD -0.39, 95%CI: -0.77, -0.01, p=0.04; six trials) and SNRIs (SMD -0.36, 95%CI: -0.46, -0.25, p<0.001; three trials).

Statistically significant heterogeneity was only observed in the outcome of pain (P=0.01, $I^2$ =44.3%). Sensitivity analyses of drug classes did not materially affect the results.

No evidence of publication bias was found according to the visual scanning of forest plots and the fail-safe N analysis; the fail-safe N ranged from 168 to 924. The authors did not report the results of publication bias assessed by the funnel plots.

**Authors’ conclusions**

Antidepressant medications for FMS were associated with a reduction in pain, fatigue, sleep disturbances and depression, and an improvement of HRQOL.

**CRD commentary**

This review’s inclusion criteria were clear. Several relevant databases were searched. Efforts were made to find published studies but not unpublished studies, thereby introducing the potential for publication bias. Publication bias was further evaluated and little evidence of it was found, however, funnel plots were not presented in the report. No language restrictions were applied, which limited the possibility of language bias. Steps were taken to minimise bias by having more than one reviewer independently undertake the study selection and data extraction, but it was unclear whether the quality assessment processes were also performed in duplicate. Adequate details of the primary studies was provided. Relevant criteria were used to examine the study quality.

Appropriate statistical methods were used to pool the results. Statistical heterogeneity was explored as well as assessed and although significant heterogeneity was found in the outcome of pain, the studies generally showed the same direction of treatment effect. However, the use of $I^2$ heterogeneity thresholds to determine the use of a fixed or random effects model may not be appropriate. This review was generally well conducted. The authors’ conclusions reflected the evidence presented and are likely to be reliable.
Implications of the review for practice and research
Practice: the authors stated that short-term usage of amitriptyline and duloxetine should be considered for the treatment of pain and sleep disturbances in FMS.

Research: the authors stated that the long-term efficacy of antidepressants for FMS should be evaluated for future research. Further studies should assess the maintenance of treatment effect after therapy ceases and the impact on cost of FMS management. These studies should include patients with somatic and mental comorbidities.

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