Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy


CRD summary
The authors concluded that there was some evidence to support the short-term efficacy of amitriptyline 25mg/day for fibromyalgia, but no evidence to support the efficacy of amitriptyline at higher doses or for periods longer than eight weeks. Much of the review was well conducted, but the analyses may be misleading and the overall results should not be considered as reliable.

Authors' objectives
To review the effectiveness of amitriptyline in the treatment of fibromyalgia.

Searching
EMBASE, MEDLINE and The Cochrane Library were searched. Search terms and dates were reported. An RCT filter was used and no language restrictions were applied. Databases of ongoing trials were searched (no further details reported) and reference lists were checked.

Study selection
Double-blinded randomised controlled trials (RCT) that compared any dose of amitriptyline with placebo in patients with a clinical diagnosis of fibromyalgia or fibrositis according to any recognised criteria were considered for inclusion.

The studies included cross-over and parallel design RCTs. The dose of amitriptyline was either 25mg/day or 50mg/day. Duration of the intervention varied between eight and 24 weeks; most studies were eight weeks long. Diagnostic criteria used to select patients was most commonly American College of Rheumatology (ACR), but some older studies used Smythe or Yunus. The most commonly reported outcome measures were visual analogue scales (VAS) for patient global assessment, pain and physical global assessment. Tender point counts were reported in most studies. Most studies reported using acetaminophen or paracetamol for concurrent pain relief. Most patients were female (82% to 100%). Mean age ranged from 36.7 to 53.4 years across trials. Duration of fibromyalgia at baseline varied from 2.5 to 15.6 years.

Two independent reviewers selected studies for inclusion.

Assessment of study quality
Two independent reviewers assessed validity using two published scales (Schulz, Jadad), which included items on random sequence generation, concealment of treatment allocation, baseline homogeneity and intention-to-treat analysis. Each study was classed as high (3 to 5 points) or low (1-2 points) quality based on the Jadad score (maximum of 5 points). Any disagreements were resolved through discussion with a third reviewer.

Data extraction
Two independent reviewers extracted data. Any disagreements were resolved through discussion with a third reviewer. Authors were contacted for missing data (without success).

Methods of synthesis
Although meta-analysis was initially planned, assessment of heterogeneity using the $I^2$ statistic indicated high levels of statistical heterogeneity between studies. Results were grouped by outcome and dosage (25mg or 50mg) and presented as a narrative synthesis and in tables.

Results of the review
All 10 RCTs (n=615) included in this review were scored as high methodological quality. Sample size ranged from 22 to 126; five studies had fewer than 50 participants. Three trials used cross-over designs and seven were parallel. Six studies reported details of randomisation and five reported on allocation concealment. Three studies used an intention to
treat analysis. Most data was not suitable for meta-analysis as a result of clinical and statistical heterogeneity as well as missing data.

Overall the following outcomes improved significantly more in patients who received amitriptyline than those who received placebo: pain (three out of eight trials); fatigue (three out of six trials); sleep disturbance (five out of seven trials); patient global assessment (five out of nine trials); physician global assessment (four out of seven trials); and tender point counts (one out of eight trials).

**Amitriptyline 25mg versus placebo (six studies):** Significant differences in favour of the active intervention were found for the following outcomes: pain (three out of five trials); fatigue (three out of five trials); sleep disturbance (four out of five trials); patient global assessment (five out of six trials); and physician global assessment (four out of five trials).

**Amitriptyline 50mg versus placebo (four studies):** Significant benefits for sleep disturbance were found in one of two trials that measured this outcome. There were no significant differences for any of the other outcomes measured: pain (three trials); fatigue (one trial); patient global assessment (three trials); and physician global assessment (two trials).

Adverse events were reported rigorously by six studies. The mean adverse event rate for any dose of amitriptyline was 51.84% (2.8% to 95%) and for placebo was 36.63% (2.8% to 80%). All adverse events were reported to be mild or moderate. There were no differences in reported withdrawal due to side-effects between active and placebo groups.

**Authors' conclusions**
No definitive clinical recommendation on amitriptyline for fibromyalgia symptoms could be made. There was some evidence to support the short-term efficacy of amitriptyline 25mg/day, but no evidence to support the efficacy of amitriptyline at higher doses or for periods longer than eight weeks. Further research was recommended to determine long-term efficacy and safety.

**CRD commentary**
This review addressed a clear question with broad inclusion criteria. The searches covered the major databases and some sources of grey literature without language restrictions, which reduced the likelihood of publication and language biases; use of an RCT filter may have restricted the results. Study selection, validity assessment and data extraction were all performed by more than one reviewer with discussion of disagreements, which reduced the chance of reviewer error/bias. The validity assessment presented both summary scores and details of the individual items; these were both useful and informative. The authors noted that studies had important methodological flaws despite scoring highly on the Jadad criteria. Although the decision not to proceed with meta-analysis appeared appropriate given statistical and clinical heterogeneity, presentation of the results in terms of vote counting potentially ignored important clinical differences between the primary studies. The decision to narratively pool parallel and cross-over comparisons was not clearly justified. Although the authors drew the conclusion that studies using 50mg of amitriptyline did not demonstrate a therapeutic effect, these trials were all small in size and appeared not to have reported on many of the key outcome measures. The adverse event rates appeared to be calculated as an average of the rates reported by each of the primary studies; such an approach was likely to produce erroneous results and ignore the impact of amitriptyline dosage. In conclusion, this review used appropriate methods to reduce bias within the review processes, but the analyses may be misleading and the overall results should not be considered reliable.

**Implications of the review for practice and research**
**Practice:** The authors concluded that no definitive clinical recommendation on amitriptyline for fibromyalgia symptoms could be made.

**Research:** The authors concluded that more stringent RCTs with longer follow-up periods were required to assess long-term efficacy and safety of amitriptyline in the treatment of fibromyalgia symptoms. Further research would be particularly useful in exploring the place of amitriptyline within multi-disciplinary treatment plans.

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