A meta-analysis of pain response in the treatment of fibromyalgia

Roskell NS, Beard SM, Zhao Y, Le TK

CRD summary
This review concluded that eight active treatments showed evidence of an improvement in pain over placebo in patients with fibromyalgia. Indirect comparison of active treatments found no strong differences. These conclusions should be interpreted with caution in view of the risk of publication bias and the small number of included studies for each comparison.

Authors' objectives
To compare the efficacy and safety of drugs that were licensed or commonly used for the treatment of fibromyalgia.

Searching
PubMed, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for published studies up to February 2009. The following websites were also searched: American College of Rheumatology, European League Against Rheumatism and National Fibromyalgia Research Association. Key Journals (not reported) and reference lists were screened for additional studies.

Study selection
Randomised controlled studies (RCTs) were eligible if they evaluated duloxetine, fluoxetine, gabapentin, milnacipran, pramipexole, pregabalin, amitriptyline, cyclobenzaprine or tramadol with paracetamol, for at least four weeks treatment duration. Patients were at least 18 years old with clinical diagnosis of fibromyalgia. The following additional drugs were also eligible for inclusion: citalopram, ibuprofen, moclobemide, paroxetine, pirlindole, sodium oxybate, tenoxicam, tropisetron, venlafaxine, zolpidem and zopiclone. The eligible outcomes were: improvement in pain response of at least 30% from baseline; improvement in pain response of at least 50% from baseline; discontinuation due to adverse event.

All included studies compared active treatment with placebo. The treatment drug varied between studies. Two treatment doses were assessed for pregabalin and milnacipran. The tool used to assess pain response varied between included studies. Most included patients were female. The duration of follow-up ranged from one to six months. Included studies were conducted or published between 1988 and 2009.

Two reviewers independently assessed studies for inclusion, with any disagreements resolved by a third reviewer.

Assessment of study quality
The quality of studies was assessed using the Jadad scale, a five-point scale evaluating randomisation, blinding and withdrawal/drop-outs.

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

Data extraction
Data were extracted on event rates to enable the calculation of relative risks (RRs) with 95% confidence intervals (CIs).

The authors did not state how many reviewers performed data extraction.

Methods of synthesis
The studies were combined in a meta-analysis. The pooled relative risks with 95% confidence intervals were calculated using a random-effect model. Statistical heterogeneity was assessed using $\chi^2$. A network meta-analysis was conducted to estimate the relative efficacy of different treatment drugs; mixed treatment comparison models were performed by adjusting for covariates of months of follow-up and percentage of females.

Results of the review
Twenty-one RCTs were included in the review. All trials were double-blinded. Four trials had a cross-over design. All
trials had a quality score of at least three.

Compared with placebo, a significant benefit of 50% improvement in pain response was observed in patients treated with duloxetine (RR 1.60, 95% CI 1.22 to 2.10; two RCTs), milnacipran 200mg/day (RR 1.39, 95% CI 1.05 to 1.84; two RCTs), pregabalin 300mg/day (RR 1.53, 95% CI 1.09 to 2.15; two RCTs), pregabalin 450mg/day (RR 1.94, 95% CI 1.41 to 2.68; two RCTs), and tramadol plus paracetamol (RR 1.87, 95% CI 1.26 to 2.78; one RCT).

Compared with placebo, a significant benefit of 30% improvement in pain response was observed in patients treated with fluoxetine (RR 4.01, 95% CI 1.68 to 9.56; two RCTs), gabapentin (RR 1.65, 95% CI 1.10 to 2.48; one RCT), milnacipran 100mg/day (RR 1.31, 95% CI 1.12 to 1.52; two RCTs), duloxetine (RR 1.52, 95% CI 1.24 to 1.86; two RCTs), milnacipran 200mg/day (RR 1.40, 95% CI 1.22 to 1.62; three RCTs), pregabalin 300mg/day (RR 1.31, 95% CI 1.11 to 1.55; three RCTs), pregabalin 450mg/day (RR 1.50, 95% CI 1.20 to 1.88; three RCTs) and tramadol plus paracetamol (RR 1.77, 95% CI 1.26 to 2.48; one RCT).

A significantly increased risk of discontinuation due to adverse events was observed for milnacipran 100mg/day (RR 2.00, 95% CI 1.50 to 2.67; two RCTs), milnacipran 200mg/day (RR 2.58, 95% CI 1.98 to 3.37; three RCTs), pregabalin 300mg/day (RR 1.57, 95% CI 1.12, 95% CI 2.20; three RCTs) and pregabalin 450mg/day (RR 2.06, 95% CI 1.50 to 2.83; three RCTs).

No significant heterogeneity was observed in any pooled outcome. The mixed treatment comparison analyses showed no significant differences between any pairwise combinations of active treatments for either pain response endpoint.

Authors' conclusions
Eight active treatments showed evidence of an improvement in pain over placebo in patients with fibromyalgia. Indirect comparison of active treatments found no strong differences.

CRD commentary
This review's inclusion criteria were clear. Relevant databases were searched. Efforts were made to find published studies, but not unpublished studies which increased potential for publication bias. It was unclear whether any language restriction was applied in the search, which made it difficult to assess the risk of language bias. Steps were undertaken to minimise biases and errors in the study selection process, but it was unclear whether quality assessment and data extraction were also performed in duplicate. Appropriate criteria were used to assess study quality. Statistical heterogeneity was assessed and appropriate methods were used to pool the results. However, in view of the risk of publication bias and the small number of included studies for each comparison, the authors' conclusions should be interpreted with caution.

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

Research: The authors stated that further research was required to investigate the safety of those drugs that were licensed or commonly used for the treatment of fibromyalgia.

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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.