Gabapentin and pregabalin in the treatment of fibromyalgia: a systematic review and a meta-analysis

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CRD summary
The authors concluded that pregabalin, at a dose of 450mg daily, was most likely to be effective in treating patients with fibromyalgia, but adverse events were not negligible. Further evidence was necessary to clarify these conclusions. Given the unclear quality of included trials, the authors’ cautious conclusion and recommendations for further research seem reasonable.

Authors' objectives
To evaluate the efficacy and safety/tolerability of gabapentin and pregabalin for treating patients with fibromyalgia.

Searching
PubMed, EMBASE, PsycINFO, Web of Science, CINAHL, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to October 2008 for articles in English. Search terms were reported. Key journals and references of relevant studies and reviews were scanned. Experts were contacted. Abstracts from annual meetings in Clinical Pharmacology were searched to identify further studies including unpublished material.

Study selection
Double-blind randomised controlled trials (RCTs) that compared the efficacy of gabapentin or pregabalin with placebo in patients with fibromyalgia (aged 18 years or above) were eligible for inclusion.

The primary outcomes of interest appeared to be the proportion of patients who responded to treatment (patients with over 30% reduction in mean pain score from baseline to endpoint) and patients who dropped out due to lack of drug efficacy. Secondary outcomes appeared to be safety and tolerability assessment based on adverse events and drop-outs due to adverse events.

All included trials were conducted in the USA. Most trials (except one) assessed pregabalin. The drug regimes varied between and within trials. In all trials, participants were mainly women. The adopted inclusion criteria varied between trials. Adverse events reported included risk of dizziness, somnolence, dry mouth, weight gain, and peripheral oedema.

Two reviewers independently selected studies for inclusion. Disagreements were resolved by the involvement of an independent third reviewer.

Assessment of study quality
Trial quality was assessed using the Jadad scale for randomisation, allocation concealment, blinding, and withdrawals/drop-outs.

Two reviewers independently carried out the quality assessment. Disagreements were resolved by consensus.

Data extraction
Where possible, data were extracted to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Authors were contacted to retrieve missing relevant data.

Two reviewers independently extracted the data.

Methods of synthesis
Where possible, odd ratios and 95% confidence intervals were pooled in fixed-effect or random-effects meta-analyses. Numbers needed to treat (NNT) and numbers needed to harm (NNH) were also calculated.

Heterogeneity was assessed using X^2 and I^2 (I^2 over 50% represented significant heterogeneity; I^2 below 25% represented insignificant heterogeneity). Analyses were carried out separately for daily pregabalin doses of 600mg.
450mg, and 300mg.

Indirect comparisons were conducted on the efficacy of different doses. Sensitivity analysis excluded one trial that did not evaluate pregabalin at 600mg daily. There were no planned subgroup analyses.

Publication bias was assessed using the Egger test.

Results of the review
Four trials were included in the review. One trial evaluated gabapentin (n=150 patients). Three trials evaluated pregabalin (n=2,022 patients). Quality scores ranged from 6 to 8 (not fully explained with Jadad criteria); methodological limitations were noted.

600mg pregabalin daily: For patients who received 600mg of pregabalin per day, response to treatment was significantly higher compared with placebo (OR 1.70, 95% CI 1.27 to 2.29; I²=12.9%; two trials; NNT 8 patients, 95% CI 6 to 19). The active treatment group had significantly fewer drop-outs due to lack of efficacy (OR 0.19, 95% CI 0.09 to 0.4; I²=2.7%; two trials), but drop-outs due to adverse events were higher in the pregabalin group than placebo (OR 3.57, 95% CI 2.4 to 5.31; I² =1.6%; two trials; NNH 6, 95% CI 4 to 9).

450mg pregabalin daily: Treatment response was significantly higher for patient who received 450 mg of pregabalin compared with placebo (OR 1.92, 95% CI 1.49 to 2.12; I²=46.3%; three trials; NNT 7, 95% CI 5 to 11). Drop-outs due to lack of efficacy were lower in this group than placebo (OR 0.3, 95% CI 0.18 to 0.51; I²=0; three trials). Drop-outs due to adverse events were higher in the pregabalin group than placebo (OR 2.28, 95% CI 1.58 to 3.29; I²=0; three trials; NNH 11, 95% CI 7 to 23).

300mg pregabalin daily: Treatment response was higher for this group than placebo (OR 1.53, 95% CI 1.18 to 1.98; I²=0; three studies; NNT=11, 95% CI 7 to 28). Drop-outs due to lack of efficacy were lower in the pregabalin group than placebo (OR 0.36, 95% CI 0.22 to 0.59; I²=0; three trials). Drop-outs due to adverse events were higher in the pregabalin group than placebo (OR 1.65, 95% CI 1.12 to 2.42; I²=0%; three trials; NNH =10, 95% CI 10 to 99).

Pregabalin adverse events: Risks of dizziness, somnolence, dry mouth, weight gain, and peripheral oedema were significantly higher in the pregabalin group compared with placebo, for all three doses of pregabalin.

Gabapentin: Compared with placebo, one trial of gabapentin showed significantly higher response to treatment compared to placebo. Risk of dizziness, sedation, light-headedness, and weight gain were reported significantly more in patients who received gabapentin.

There were no significant differences between drug doses in the indirect comparison and sensitivity analyses, although 450mg pregabalin showed a higher treatment response than 300mg.

Publication bias was not reported.

Authors' conclusions
Pregabalin, at a dose of 450mg daily, was most likely to be effective in treating patients with fibromyalgia, although adverse events were not negligible. Further evidence was necessary for more conclusive inferences.

CRD commentary
This review addressed a clear question. Inclusion criteria were replicable for all aspects except outcomes. A number of relevant data sources were accessed. Attempts were made to minimise publication bias, but the extent of its impact was not reported. The restriction to English language articles meant that language bias could not be ruled out. The review process was conducted with efforts to minimise error and bias.

An appropriate quality assessment tool was applied to the included trials. The scoring system was not fully explained, and (despite high scores) some important methodological limitations were highlighted. The authors acknowledged potential drawbacks in the limited number of included studies, and limited generalisability of the findings to patients with secondary fibromyalgia. The chosen method of synthesis seemed appropriate in most cases, although substantial heterogeneity in the analysis of 450mg pregabalin suggested that a fixed-effect meta-analysis might have over-estimated
the treatment effect.

The authors' cautious conclusion and their recommendations for research seem reasonable.

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

**Practice:** The authors stated that patients with fibromyalgia should be routinely evaluated for anxiety and depression symptoms before treatment.

**Research:** The authors stated that further research should consider direct comparison of active treatments (pregabalin and gabapentin) for fibromyalgia with placebo internal-validation. Research on combinations of pharmacological and non-pharmacological treatments was also warranted. Attention should be given to baseline patient characteristics, sample size, dosage, titration period, durability of efficacy, and the mechanisms of drug action. Cost-effectiveness analysis was recommended.

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