Treatment of fibromyalgia syndrome with gabapentin and pregabalin: a meta-analysis of randomized controlled trials

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CRD summary
The authors concluded that there was strong evidence that gabapentin and pregabalin could reduce pain, improve sleep and improve health related quality of life for patients with fibromyalgia syndrome. This was a generally well-conducted review. However, limited studies (number and quality), restricted generalisability and prevalent side effects indicate the authors' conclusion should be treated with extreme caution.

Authors' objectives
To assess the efficacy of gabapentin and pregabalin in the treatment of fibromyalgia syndrome.

Searching
MEDLINE, PsycINFO, Scopus and The Cochrane Library were searched to October 2008 without language restrictions. Search terms were reported. Bibliographies of retrieved articles were handsearched for additional material. Pfizer was contacted and Food and Drug Administration databases were searched to find further published and unpublished studies. Corresponding authors or Pfizer were contacted if there were incomplete outcomes.

Study selection
Randomised controlled trials (RCTs) that involved treatment of fibromyalgia syndrome (diagnosed according to American College of Rheumatology criteria) with gabapentin or pregabalin compared to placebo were eligible for inclusion in the review. Studies had to report means or mean change scores and standard deviations for continuous data and absolute numbers or percentages for dichotomous outcomes.

The review assessed pain, sleep, depression, health-related quality of life, fatigue, anxiety and adverse effects. Measures used in individual studies were reported. Most studies were carried out in USA. Most patients were white and female. Average age was 48.3 to 50 years old. Studies lasted for eight to 26 weeks. Gabapentin dosages ranged from 1,200mg/day to 2,400mg/day. Pregabalin doses ranged from 150mg/day to 600mg/d. The percentage of potential patients who were randomised ranged from 31.9% to 75.7%. In some studies patients received co-medication with acetaminophen and aspirin. In all included studies, patients had an average pain score of 4 or more out of 10. Studies excluded: patients less than 18 years old; patients with unstable somatic disease or severe mental disorders; patients applying for disability or engaged in litigation related to fibromyalgia syndrome; and patients with creatine clearance of less than 60mL/min.

Two reviewers independently selected studies for inclusion in the review. Disagreements were resolved by discussion or use of a third reviewer.

Assessment of study quality
Methodological quality of studies was assessed by the van Tulder score with 11 items. Possible scores were 1 (low) to 11 (high). External quality of studies was assessed by five reported questions to determine details of patients, interventions, outcomes, clinical effect and potential side effects.

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

Data extraction
Where possible, intention-to-treat data were extracted. Standardised mean difference (SMD, Hedge's g) were calculated for continuous outcomes. Where possible, percentages of patients who reported 30% or greater and 50% or greater reductions in pain were extracted.
Data were extracted into standardised forms by two independent reviewers. Disagreements were resolved by discussion or consultation with a third reviewer.

**Methods of synthesis**

Descriptive data were compared using non-parametric tests (p value, <0.05 was significant). Heterogeneity was assessed using the $X^2$ test.

A random-effects meta-analysis was used to combine SMDs and 95% CIs for continuous data. Heterogeneity was assessed using the $I^2$ test. One study that was of a different study design was excluded from meta-analysis.

Number needed to treat (NNT) and number needed to harm (NNH), with 95% confidence intervals (CIs), were calculated for 30% or greater reduction in pain (NNT) and adverse events (NNH).

Cohen's categories were used to classify magnitude of effect size (g>0.2 to 0.5=small, g>0.5 to <0.8=medium, g>0.8=large).

**Results of the review**

Six RCTs were included in the review (total number of participants 8,733). Studies ranged between a Tuldor score of 6 and 9. Five RCTs were included in meta-analyses: four evaluated pregabalin and one evaluated gabapentin. The authors stated that none of the studies controlled for the amount of co-medications or changes in other therapies and that external validity was limited due to exclusion of several disease states that were relevant to fibromyalgia syndrome and a limited demographic of patients.

The percentage of completers ranged from 38.4% to 78.6% for treatment groups and from 19.2% to 82.7% for placebo groups. Numbers reported below were numbers of patients included in the analysis and included double counting of some control groups.

**Pain (five studies, n=4,250, 13 comparisons):** Compared with placebo, gabapentin and pregabalin were associated with a significant but small reduction in pain in fibromyalgia syndrome patients (SMD -0.28, 95% CI -0.36 to -0.20, $I^2$=41.7%). NNT for a 30% or greater reduction in pain was 8.5 (95% CI 6.4 to 12.6).

Compared with placebo, gabapentin and pregabalin significantly improved sleep function (SMD -0.39, 95% CI -0.48 to -0.29, $I^2$=42.7%; four studies, 10 comparisons), anxiety (SMD -0.18, 95% CI -0.27 to -0.10; two studies, n=2,237, six comparisons), health-related quality of life (SMD -0.30, 95% CI -0.46 to -0.15, $I^2$=43.4%; two studies, four comparisons) and fatigue (SMD -0.16, 95% CI -0.23 to -0.09; three studies, nine comparisons).

Gabapentin and pregabalin did not significantly affect levels of depression in fibromyalgia syndrome patients.

Based on Cohen's categories for size effect, gabapentin and pregabalin had a negligible effect on fatigue and anxiety and a small effect on pain, sleep and health-related quality of life; the reductions were statistically significant.

**Adverse events:** Adverse events were inconsistently reported. Compared to placebo, gabapentin and pregabalin were associated with a significant greater risk of withdrawal due to adverse events (NNH 9.5, 95% CI 7.6 to 12.8). Pregabalin was associated with significantly greater risks of dizziness, somnolence, weight gain, peripheral oedema and negative neurocognitive effects than placebo. Gabapentin was associated with significantly greater risks of dizziness and weight gain than placebo.

**Authors' conclusions**

There was strong evidence that gabapentin and pregabalin reduced pain, improved sleep and improved health-related quality of life for patients with fibromyalgia syndrome. External validity of studies was limited due to exclusion of patients with severe somatic and mental disorders.

**CRD commentary**
This review question was clear and inclusion criteria were defined for participants, interventions and study design; criteria did not appear to be specified for outcomes. Four databases plus other relevant sources were searched. Efforts were made to find both published and unpublished studies without language restriction, which minimised potential for language and publication biases. Sufficient attempts were made to minimise reviewer errors and biases in the review process. Study quality was assessed, but generally only aggregate scores were reported and this made it difficult to evaluate the quality of the evidence presented. The authors noted restricted generalisability of results due to the limited demographic of patients. Sufficient study details were provided. Data were pooled using meta-analysis and heterogeneity was assessed, but where multiple comparison groups shared a control, no adjustment was made for statistical dependency and this may have influenced results. Only one study examined the effect of gabapentin. Five studies examined pregabalin, all sponsored by Pfizer. The review was generally well conducted. In view of the small number of studies of limited quality, small effect size, double-counting of control groups and prevalent side effects, the authors’ conclusions should be treated with extreme caution.

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

**Practice**: The authors recommend that clinicians should take concomitant conditions and patient preference into account before starting treatment with gabapentin or pregabalin. Patients should be offered non-pharmacological therapies of proven efficacies as alternative or additional treatments. Gabapentin and pregabalin can be considered for treating sleep and pain problems in patients with fibromyalgia syndrome and their effects should be monitored long-term to ensure that benefits outweighed the risks of treatment.

**Research**: The authors stated that future studies should examine whether benefits of gabapentin and pregabalin for symptoms of fibromyalgia syndrome lasted after treatment stopped and whether the drugs reduced costs of treating patients with fibromyalgia syndrome. Studies should included patients with somatic and mental health problems and seek to identify patient characteristics associated with both positive and negative treatment outcomes.

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