Systematic review of the comparative effectiveness of antiepileptic drugs for fibromyalgia

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CRD summary
This review concluded that the anti-epileptics pregabalin and gabapentin were moderately effective for treatment of fibromyalgia but that their long-term safety and efficacy were unknown. Despite some concerns about the synthesis, the authors’ conclusions are probably reliable.

Authors' objectives
To assess the comparative benefits and harms of different anti-epileptic drugs for the treatment of fibromyalgia.

Searching
MEDLINE, DARE and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 1996 to 2009. Documents from the Food and Drug Administration website and references from identified studies and reviews were also checked for additional studies. Search terms were reported. Only studies reported in English were included.

Study selection
Randomised controlled trials (RCTs) and observational studies that compared any anti-epileptic drug with placebo or another anti-epileptic were eligible for inclusion. Participants were adults aged at least 18 years with a diagnosis of fibromyalgia. Relevant outcomes were impact on pain (including functional status and sleep quality) and adverse events.

All except one of the included studies evaluated the use of pregabalin; one study assessed gabapentin. All control groups received placebo; one study used a single arm design. Most patients in the included studies were women with mean ages between 47 to 50 years. Trial duration ranged from eight to 26 weeks. Where reported baseline pain scores ranged from 5.7 to 7.8 on a 10-point severity scale.

Two reviewers independently selected the studies for the review; disagreements were resolved through consensus.

Assessment of study quality
Study validity was assessed as being good, fair or poor based on criteria from the U.S. Preventive Services Task Force which included methods of randomisation and allocation concealment, baseline comparability of treatment groups, use of intention-to-treat analysis, consideration of confounding factors in the analysis and overall and differential rates of loss to follow-up. Funding sources of trials were also noted.

Two reviewers independently performed the assessment; disagreements were resolved through consensus.

Data extraction
Data on population characteristics such as concurrent medications, aspects of study design and outcomes were extracted. The primary outcome was defined as a reduction in pain of at least 30% from baseline, assessed using an 11 point scale; duration of response, discontinuation rates and specific adverse event rates were also extracted. Intention-to-treat data were used where available. Data were extracted by one reviewer and checked by a second.

Methods of synthesis
Where two or more trials reported data on the same outcome they were statistically combined using a Mantel-Haenszel random-effects meta-analysis to calculate pooled relative risks (RR) with 95% confidence intervals (CI). It appeared that data on different doses from a single trial were used in the analyses. When a statistically significant effect was reported numbers-need-to-treat or numbers-needed-to-harm were calculated. Statistical heterogeneity was assessed using Cochran's Q test and I². There were insufficient studies for the formal assessment of publication bias.

Results of the review
Eight studies (3,114 patients) were included in the review. Six were RCTs, one was an open-label extension study and one a non-randomised single-arm study. Sample sizes ranged from 150 to 529; the RCT of gabapentin was
significantly smaller than the other trials.

All the RCTs were considered to have been fair quality; methods of blinding, allocation concealment and randomisation were unclear and losses to follow-up were high.

**Efficacy**: Short-term response (reduction of pain by at least 30%) was higher in patients treated with gabapentin (51%) than in those given placebo (RR 1.7, 95% CI 1.1 to 2.5; numbers-need-to-treat of five; one RCT; 150 patients). Response rates to pregabalin ranged from 26% to 50% with a pooled risk ratio of 1.4 (95% CI 1.3 to 1.6; numbers-need-to-treat of eight; four RCTs; 2,757 patients). There was no evidence of a dose-response effect. Data on time to loss of response were also reported.

**Safety**: The most common adverse events for both pregabalin and gabapentin were dizziness, headache, somnolence and oedema. Dizziness was the most common event with pregabalin (38% of patients) and headache was the most common with gabapentin (27% of patients); it appeared that this was statistically significantly higher than with pregabalin. Other frequent adverse events were weight gain, dry mouth, amblyopia and euphoria with pregabalin (numbers-needed-to-harm ranged from 11 to 21) and sedation and light-headedness with gabapentin (numbers-needed-to-harm were five for sedation and eight for light-headedness).

Discontinuation for adverse events was more common in pregabalin- and gabapentin-treated patients than in placebo groups; this difference was statistically significant in pregabalin trials.

**Authors’ conclusions**
Pregabalin and gabapentin were modestly effective for the treatment of fibromyalgia but their long-term safety and efficacy were unknown.

**CRD commentary**
The review question and the inclusion criteria were clear but it was not clear whether all included studies met the criterion for study design. The search was adequate. The authors reported using methods designed to reduce reviewer error and bias at all stages of the review process. Criteria used to assess the validity of the RCTs were reasonable. The synthesis appeared to include the use of multiple data sets from individual trials; it was not clear if there were controls for the fact that these data were not independent. While this may not have been appropriate it did not appear to have significantly altered the pooled estimate obtained. The authors’ conclusions are therefore probably still reliable in spite of this uncertainty.

**Implications of the review for practice and research**
**Practice**: The authors stated that the results of this review, which indicated short-term benefits of gabapentin and pregabalin in fibromyalgia treatment, should not be generalised to other unstudied anti-epileptic drugs. Clinicians should also be aware of the limitations of the evidence presented in this review.

**Research**: The authors stated that trials which directly compared different anti-epileptic drugs with each other and with other drug classes used in fibromyalgia treatment were required to determine the relative benefits and risks of each treatment. These studies need to have a longer duration and assess functional, quality of life and health outcomes. They should also include patients with a wide range of baseline symptoms and comorbidity, and be adequately powered and adjusted to include the impact of co-interventions.

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**Bibliographic details**

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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.