Gabapentin for neuropathic pain: systematic review of controlled and uncontrolled literature

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Authors' objectives
To assess the efficacy, effectiveness and side-effects of gabapentin for the treatment of neuropathic pain.

Searching
MEDLINE (from 1966 to March 2001), EMBASE (from 1980 to March 2001), the Science Citation Index (from 1993 to September 1999), and the Cochrane Controlled Trials Register (Issue 1, 2001) were searched. The authors also searched the reference lists in retrieved articles, reviews and book chapters, and contacted content experts for other relevant studies. The terms used in the search were 'pain', 'nociceptors', 'analgesia', 'neuropathy', 'neuropathic', 'allodynia', 'hyperalgesia', 'gabapentin', 'Neurontin' and registry number '60142-96-3'. The searches were not restricted by language.

Study selection
Study designs of evaluations included in the review
Controlled (randomised or non-randomised) and uncontrolled trials (case series or case reports) were eligible for inclusion. Abstracts and preliminary results were excluded.

Specific interventions included in the review
The specified intervention was gabapentin administered for pain relief, either alone or in conjunction with other drugs. The included interventions were gabapentin for the case series (dose not stated) and gabapentin for the controlled trials (900 to 3,600 mg/day). Placebo or amitriptyline (25 to 90 mg/day) were used in the control groups.

Participants included in the review
The participants specified were patients with any kind of neuropathic pain, as listed in detail in the appendix to the review.

Outcomes assessed in the review
The specified primary outcome was pain relief. Side-effects were also evaluated in the review. The authors classified pain relief as 'meaningful' (good result) or 'nonmeaningful' (bad result). Meaningful relief included statistically-significant changes in multiple quantitatively measured outcomes, 'good' to 'excellent' pain relief in well-defined categorical outcomes, and 'worthwhile' relief obtained through narratives. 'Nonmeaningful' relief included relief less than 30%, and 'mild' or 'no' relief of the original pain.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
Controlled trials were assessed for quality using the scoring system developed by Jadad. This method assessed randomisation, double-blinding, and withdrawals and drop-outs on a scale from 0 (low) to 5 (high). Uncontrolled studies were assessed for quality using a novel questionnaire devised by the authors. The questionnaire consisted of two primary questions: (1) did the patients have clear signs and symptoms of neuropathic pain; and (2) were the outcome measures well defined. The questionnaire was described in further detail in a table in the review. Two reviewers independently assessed the controlled trials and met to reach consensus on any disagreements. A third reviewer was consulted if necessary. The uncontrolled trials were assessed independently by all three reviewers. Consensus was used to reach a final decision.
Data extraction
The data were extracted by one reviewer and checked by another. The authors do not state how they resolved any disagreements. The authors of the included studies were contacted for missing data. The reviewers extracted information using a pre-determined checklist covering information on the study design, methodological quality, participants, intervention, control group and outcomes.

Methods of synthesis
How were the studies combined?
For uncontrolled studies, effectiveness was calculated as the number of patients who experienced 'meaningful' pain relief divided by the total number of patients who received gabapentin.

In controlled studies where the continuous and dichotomous outcomes were clinically and statistically homogeneous, the data were pooled. A fixed-effect model was used to calculate the relative benefit and 95% confidence intervals (CIs) for dichotomous outcomes, and the weighted mean difference and 95% CIs for continuous outcomes. When the data were clinically homogeneous, but statistically heterogeneous, the data were pooled using a random-effects model. When the data were clinically heterogeneous, the data were not pooled and were analysed in the same way as the uncontrolled trials.

How were differences between studies investigated?
Statistical homogeneity was assessed using the Cochran Q test. A subgroup analysis was conducted in which the data regarding the 'yes' answer for outcomes and diagnosis of neuropathic pain were separately analysed for 'low' and 'high' certainty, as well as being pooled together. A sensitivity analysis was also conducted to assess the influence of study quality on the pooled result.

Results of the review
The review included 35 reports of 31 studies (n=727). These included 6 controlled trials (4 placebo-controlled and 2 active-controlled), 15 case series, 7 case reports, 2 open-label trials and 1 retrospective review of charts.

Non-controlled studies (26 patient populations): 314 (79.5%) of the 395 patients experienced meaningful relief with gabapentin.

Controlled studies: the quality assessment on the 6 controlled trials found 2 high-quality and 2 low-quality placebo-controlled randomised controlled trials. Of the 2 active-controlled trials, one was high quality and one was low quality. In the placebo-controlled trials (n=4), the number of patients reporting moderate or excellent pain relief showed statistical homogeneity (chi-squared 7.06, d.f.=3) and resulted in a relative benefit of 2.5 (95% CI: 1.9, 3.4).

The visual analog scale (VAS) results (n=2) gave a weighted VAS mean difference of -11.1 mm (95% CI: -13.2, -11.1; chi-squared 3.56, d.f.=1). The short form of the McGill Pain Questionnaire (SF-MPQ) (n=2) reported a weighted final SF-MPQ mean difference of -5.89 (95% CI: -6.20, -5.59; chi-squared 0.13, d.f.=1). The patients' global impression of change results (n=2) gave a relative benefit of 2.44 (95% CI: 1.8, 3.31; chi-squared 4.76, d.f.=1). The clinicians' global impression of change (n=2) gave a relative benefit of 2.65 (95% CI: 1.86, 3.78; chi-squared 0.78, d.f.=1). The SF-36 Quality of Life questionnaire was measured (n=2), but the results were not pooled. Both studies reported an improvement in the SF-36 for the gabapentin group in comparison with placebo.

There were no differences between data analysed separately for 'high- certainty' versus 'low-certainty' answers for the questions pertaining to (1) the diagnosis of neuropathic pain, and (2) measurable outcomes. The sensitivity analysis showed that the results obtained for the number of patients reporting moderate or excellent pain relief were consistent and independent of the methodological quality of the included studies.

Side-effects (n=29): fewer and less severe side-effects were reported in the uncontrolled studies.

Authors' conclusions
Gabapentin seems to be effective in multiple painful neuropathic conditions. The variable prescribing patterns of the
uncontrolled studies raise the suspicion that effectiveness may be reduced if one limits the administration of the drug to very low doses, whereas rapid dose escalation may be associated with increased central nervous system side-effects. Well-designed controlled trials may provide insight into different symptom sensitivity to the drug.

CRD commentary
In this review, both the research question and the inclusion criteria were clearly stated and the process of the review was also well-reported. The review included a good literature search, did not impose language restrictions, and searched for unpublished literature through contacts with content experts. A limitation of the literature review was that there was no analysis of publication bias. The authors were cautious in only including study populations once, even though multiple reports of individual studies were found. The review does not report who, or how many of the authors, selected the studies. The included studies were assessed for quality, and the results of the assessment were used to group the studies in the narrative discussion and for further subgroup analyses. A combination of narrative and statistical pooling was performed, which was appropriate given the varying study designs and measurement of outcomes in the included studies. The conclusions of this review appear to follow from the results.

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

Research: The authors state that further well-designed controlled trials may provide insight into differential symptom sensitivity to the drug.

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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.