Antiepileptic drugs in treatment of pain caused by diabetic neuropathy

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CRD summary
This review determined the antiepileptic drugs that had the best analgesic potential for managing pain in patients suffering from painful diabetic neuropathy. The authors concluded that there was analgesic benefit of antiepileptic drugs in these patients. Given the methodological and reporting limitations to this review, this conclusion may not be reliable.

Authors' objectives
To determine which antiepileptic drugs have the best analgesic potential for managing pain in patients with painful diabetic neuropathy.

Searching
MEDLINE, the Cochrane Library, EMBASE and LILACS databases were searched (January 1966 to September 2005) for studies in English or Spanish. Search terms were reported. Reference lists were also scanned and a manual search of nine specified journals was conducted.

Study selection
Randomised controlled trials (RCTs) that studied the analgesic effect of antiepileptic drugs, compared to placebo, in adults suffering painful diabetic neuropathy, were eligible for inclusion. Trials that contained no relevant categorical measurements, case reports, summarised publications and studies of treatments still in the research phase were excluded. The measurement of effect was some degree of improvement in pain as measured by an objective test and relative risk as measurement of effect.

The included trials investigated the analgesic effects of carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, topiramate and valproic acid.

The authors did not state how the papers were selected for review, or how many reviewers performed the selection.

Assessment of study quality
Methodological quality of primary trials was assessed based on the following criteria: method of assignment of participants to an intervention, blinding, follow-up, definitions regarding cases and clinical results. The Jadad scale (which assessed randomisation, blinding and withdrawals) was also used to obtain a quality score out of a maximum of 5 points.

It appeared that validity was independently assessed by three authors.

Data extraction
Data were extracted into contingency tables of exposure to antiepileptic drug versus improvement in pain. The response variable was binary.

It appeared that three authors performed data extraction and discrepancies resolved by consensus.

Methods of synthesis
Homogeneous studies were combined using meta-analysis. Relative risks of any improvement in pain were pooled in fixed-effect and random-effects meta-analyses. Necessary-number-to-treat and associated 95% confidence intervals were calculated for each anti-epileptic drug. Statistical heterogeneity was assessed using the Q test and Galbraith's plot and publication bias tested with Begg and Egger's tests and a funnel plot. Heterogeneous trials were combined by reporting the number of trials with statistically significant treatment differences.
**Results of the review**

The authors reported that fifteen RCTs were included (n=2,035 patients). The Jadad scores ranged from 2 to 5 (nine trials scored 5). However, there appeared to be thirteen unique references to trials in the tables.

There was evidence of statistical heterogeneity (p=0.0001, $\chi^2=41.73$) and the authors also reported clinical heterogeneity was present. The funnel plot and the Begg and Egger test did not indicate publication bias was present.

The relative risks and confidence intervals (CIs) of the 15 RCTs were reported individually due to heterogeneity. Twelve RCTs reported a statistically significant increase in analgesia with an anticonvulsant in diabetic neuropathy, including: one trial of phenytoin, two trials of gabapentin, one trial of lamotrigine, one trial of valproic acid, five trials of pregabalin, one trial of topiramate and one trial of oxcarbazepine.

Subgroup analysis was performed on six RCTs (n=1,129 patients) that reported 50% or greater improvement in pain as the criteria for clinical effectiveness of the drug, had similar methodology and had a minimum five weeks follow-up. These investigated pregabalin, topiramate and oxcarbazepine. There was a statistically significant improvement in analgesia with an anticonvulsant (relative risk 2.33, 95% CI: 1.88 to 2.89). Pregabalin had the lowest necessary-number-to-treat of 3.24 (95% CI: 2.12 to 6.81). There was no evidence of statistical heterogeneity or publication bias in this subgroup.

**Authors' conclusions**

The meta-analysis demonstrated the analgesic benefit of antiepileptic drugs in patients suffering with diabetic neuropathy.

**CRD commentary**

The review question was clear and the inclusion criteria for participants, study design, intervention and outcome were well defined. Relevant databases were searched. However unpublished literature was not sought and the authors commented that relevant studies may have been missed, leading to publication bias. Also, only studies in English and Spanish were included, which may have introduced language bias. Validity assessment was performed, but the processes of study selection, validity and data extraction were not well reported, so it was not clear whether there may have been potential for bias and error in the review process.

There was evidence of clinical and statistical heterogeneity, so only a subgroup of more homogeneous trials were pooled in meta-analysis, which was appropriate. However, this only evaluated three of the eight drugs that were in the original meta-analysis. Few details of the primary trials were provided. Also, the authors expressed that there may be issues regarding the measures of pain used and lack of consensus in the definition of diabetic neuropathy. Given the limitations to this review, the authors' conclusion may not be reliable.

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

**Practice:** The authors did not state implications for practice.

**Research:** The authors stated that future studies should administer the medication over more prolonged periods of time and objectively evaluate their effects on measures of quality of life.

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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.