Anticonvulsant drugs for management of pain: a systematic review

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Authors' objectives
To determine the effectiveness of anticonvulsant drugs in the management of pain.

Searching
MEDLINE was searched from 1966 to February 1994, and major medical and specialist journals were handsearched from 1950 to 1990; reference list of retrieved papers were examined. Authors of published reports were contacted for additional material.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Anticonvulsant drugs (carbamazepine, phenytoin, clonazepam, sodium valproate) in the treatment of pain conditions (chronic non-malignant, cancer, post-operative and acute herpes zoster). Studies of anticonvulsants used to treat drug-induced pain were excluded.

Participants included in the review
No patient characteristics, except for the condition causing pain, are reported.

Outcomes assessed in the review
The number of patients free of pain at the end of the study; complete, excellent, or very good response; and the number of patients who improved (improvement was defined a priori to be greater than 50% pain relief). Minor and major adverse effects were also assessed.

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 authors performed the selection.

Assessment of study quality
A three-item quality scale was used, based on randomisation, blinding and withdrawals (number of and reasons for). The included studies could score a minimum of 1 and a maximum of 5. Study quality was assessed independently, and then a consensus score was reached.

Data extraction
The authors do not state how the data were extracted for review, or how many of the authors performed the data extraction. However, the following information was taken from each report: number of patients, anticonvulsant drug, treatment regimen, study design, duration, follow-up, outcome measures and results, and minor and major adverse events.

Methods of synthesis
How were the studies combined?
Active treatment-controlled trials were combined using narrative synthesis, whilst placebo-controlled trials were combined using meta-analysis. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with a fixed-effect model. Numbers-needed-to-treat (NNT; with 95% CIs) were estimated for effectiveness, adverse effects and
drug-related withdrawal.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated.

Results of the review
Twenty studies in total were included, 13 with placebo control and 7 with active treatment control. There were 10 studies of carbamazepine, 1 of carbamazepine in combination with clomipramine, 5 of phenytoin, 2 of sodium valproate and 2 of clonazepam. Of the 13 placebo-controlled studies used in the meta-analysis, 3 evaluated the treatment of each of trigeminal neuralgia, diabetic neuropathy, migraine prophylaxis and other pain syndromes (not combined), and 1 study evaluated the treatment of acute post-operative pain. It is unclear from the tables whether the number of patients refers to each arm or the study total. Thus, the total number of patients cannot be reported.

Anticonvulsants appear to provide effective pain relief for the majority of patients with trigeminal neuralgia, diabetic neuropathy, and migraine prophylaxis, although adverse effects were common. NNT are as follows:

Trigeminal neuralgia (3 studies, maximum 539 patients): all studies compared carbamazepine with placebo; the NNT were 2.6 (95% CI: 2.2, 3.3) for effectiveness, 3.4 (95% CI: 2.5, 5.2) for adverse effects and 24 (95% CI: 13.5, 110.8) for drug-related withdrawal.

Diabetic neuropathy (3 studies, maximum 160 patients): the NNT were 2.5 (95% CI: 1.8, 4) for effectiveness, 3.1 (95% CI: 2.3, 4.8) for adverse effects and 20 (95% CI: 10.2, 446) for drug-related withdrawal.

Migraine prophylaxis (3 studies, maximum 236 patients): the NNT was 1.6 (95% CI: 1.3, 2) for effectiveness, 2.4 (95% CI: 1.9, 3.3) for adverse effects and 39.3 (95% CI: 14.6, infinity) for drug-related withdrawal. There was no evidence of effectiveness for irritable bowel syndrome or acute post-operative pain. Evidence of benefits for central pain after stroke, rheumatoid arthritis and cancer pain is unclear.

Authors’ conclusions
Anticonvulsants are effective for trigeminal neuralgia, diabetic neuropathy and migraine prophylaxis. Minor adverse effects occurred as frequently as beneficial effects. There is a need for high quality studies of the relative effectiveness of different anticonvulsants in treating chronic pain syndrome and for comparison of antidepressants with anticonvulsants.

CRD commentary
The lack of patient details is of concern; differences in patient characteristics could affect the effectiveness of the intervention and the generalisability of the study. The potential for publication bias exists since the search did not identify any unpublished studies. Although each study was given a quality score, the score was not used in the subsequent analysis. The studies are combined by condition for the meta-analysis, so different studies evaluating different drugs are combined. However, there is no attempt to test for heterogeneity between these studies, and this may restrict the reliability of the results. In general there was no discussion of differences between studies. The results for drug-related withdrawal should be treated with caution as the CIs are very wide.

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