Antidepressants and anticonvulsants for diabetic neuropathy and postherpetic neuralgia: a quantitative systematic review

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Authors' objectives
To determine the relative efficacy and adverse effects of antidepressants and anticonvulsants in the treatment of diabetic neuropathy and postherpetic neuralgia.

Searching
The following sources were searched: MEDLINE from 1993 to June 1999, EMBASE from 1994 to February 1999, CINAHL from 1982 to March 1999, SIGLE from 1980 to December 1998, PubMed from 1998 (March 30) to 1999 (March 30), the Cochrane Library (Issue 1, 1999), and the Oxford Pain Relief Database from 1950 to 1994. The search terms were: 'anti*depressant*', 'tricyclic*', 'SSRI*', 'selective serotonin re*uptake inhibitor*' (SSRI), 'MAOI*', 'mono*amine*oxidase inhibitor', 'anti*convulsant*', 'anti*epileptic*', 'random*', 'trial', 'study', 'studies', 'analgesi*', 'pain*', 'neuropath*', 'neuralgia*', and fifty-five generic names of antidepressants and thirty-three generic names of anticonvulsants. There were no restrictions on publication language. Additional studies were identified from reference lists of retrieved articles and from two published reviews. Additional unpublished data were not sought.

Study selection
Study designs of evaluations included in the review
Double-blind, randomised controlled trials (RCTs) with treatment and placebo groups were included. Seventeen studies used a crossover design, of which two were of a multiple crossover design. One study was a parallel design. Trials using 'active' placebos were excluded from the safety analysis.

Specific interventions included in the review
Antidepressants or anticonvulsants versus placebo or benzotropine (an 'active' placebo). The antidepressants studied were imipramine, desipramine, amitriptyline, clomipramine, maprotiline, citalopram, fluoxetine, paroxetine, mianserin, an amitriptyline-fluphenazine combination, and a nortriptyline-fluphenazine combination. The anticonvulsants studied were phenytoin, carbamazepine and gabapentin. The dosages varied depending on the drug, and ranged from 12.5 to 3600 mg/day.

Participants included in the review
Adults with chronic pain due to diabetic neuropathy or postherpetic neuralgia. An adequate description of the diagnostic criteria for these conditions was required. For postherpetic neuralgia, the pain had to have been present for at least 3 months after zoster eruption.

Outcomes assessed in the review
The primary outcome was pain relief. Adverse effects were also assessed. The authors defined a clinically relevant outcome as an improvement on a measure of effectiveness equivalent to at least 50% pain relief. The effectiveness measures after the longest reported duration of treatment were used. These values depended on the type of measurement scale used and the number of points on the scale. The outcomes were assessed using the self-reported global scale, visual analogue scale, categorical pain relief scale, and neuropathy scale. Adverse effects were classified as minor if they were reported by a patient who continued with the medication and completed the trial. A major adverse effect was one that caused the patient to withdraw from the study.

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
Validity was assessed using the 3-item, 5-point scale of Jadad et al. (see Other Publications of Related Interest no.1). The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

**Data extraction**
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. For each study, the authors extracted details of the following: the condition studied; the number of patients enrolled and analysed; the design and duration of the study; the dosing regimen; the outcome measures used for pain; the analgesia outcomes reported; minor and/or major adverse effects; and other withdrawals not related to adverse effects. Data from the original studies, including a quality score and comments, are available on the Bandolier website. See Web Address at end of abstract.

**Methods of synthesis**

*How were the studies combined?*
For efficacy, the relative benefit and the number-needed-to-treat (NNT) were calculated, along with the 95% confidence intervals (CIs). For adverse events, the relative risk and the number-needed-to-harm (NNH) were calculated, along with the 95% CIs. The data were pooled using a fixed-effect model.

The results were presented as patient episodes, rather than the actual number of patients, as most of the included studies employed a crossover design.

*How were differences between studies investigated?*
The authors presented separate L’Abbe plots for antidepressants in diabetic neuropathy, antidepressants in postherpetic neuralgia, anticonvulsants in diabetic neuropathy, and anticonvulsants in postherpetic neuralgia. The pooled relative benefit and NNT were also given separately for these groups of trials.

Sensitivity analyses were conducted on studies of the use of antidepressants for diabetic neuropathy, as this was the largest data set. The observed difference in efficacy between tricyclic antidepressants and SSRIs led to further sensitivity analyses being conducted on the tricyclic antidepressant data. These investigated the type of scale used, the size of the treatment arms, and the duration of the study.

**Results of the review**
Twenty RCTs with 835 participants were included in the review: 16 studying diabetic neuropathy and 4 studying postherpetic neuralgia. For diabetic neuropathy, there were 12 RCTs (n=251) that investigated the use of antidepressants or antidepressant-fluphenazine combinations, and 4 (n=247) that investigated anticonvulsants. For postherpetic neuralgia, there were 3 RCTs (n=108) that investigated the use of antidepressants, and 1 (n=229) that investigated an anticonvulsant.

The mean and median quality score was 4, out of a possible 5.

In diabetic neuropathy, the pooled NNT for at least 50% pain relief was 3.4 (95% CI: 2.6, 4.7) with antidepressants, and 2.7 (95% CI: 2.2, 3.8) with anticonvulsants. Sensitivity analyses showed that tricyclic antidepressants (amitriptyline, clomipramine, desipramine, imipramine and maprotiline) had a relative benefit of 1.9 (95% CI: 1.5, 2.3), with an NNT for at least 50% pain relief of 3.5 (95% CI: 2.5, 5.6). SSRIs (citalopram, fluoxetine, and paroxetine), however, showed no difference in efficacy compared with the placebo.

In postherpetic neuralgia, both the antidepressants and anticonvulsants were significantly superior to placebo. The NNT for pain relief was 2.1 (95% CI: 1.7, 3) with antidepressants, and 3.2 (95% CI: 2.4, 5) with anticonvulsants.

When studies of diabetic neuropathy and postherpetic neuralgia were pooled, both antidepressants and anticonvulsants were significantly superior to placebo. The relative benefit was 1.9 (95% CI: 1.6, 2.3) for antidepressants, and 2.7 (95% CI: 2.1, 3.5) for anticonvulsants. The NNTs for pain relief were identical for both drug classes, i.e. 2.9 (95% CI: 2.4, 3.7) When examining anticonvulsants only, there was no difference in efficacy between gabapentin and the older
anticonvulsants (phenytoin and carbamazepine).

The majority of adverse effects observed with antidepressants were dry mouth, constipation, and blurred vision. With anticonvulsants, the most common effects were dizziness, somnolence, or disturbance in gait. For major adverse effects (leading to withdrawal from the study), antidepressants had a relative risk of 2.6 (95% CI: 1.5, 5) and an NNH of 17 (95% CI: 11, 43), compared with placebo; with anticonvulsants there was no significant difference from placebo. There was no difference in the incidence of adverse effects between SSRIs and placebo, whereas there was an increased risk with tricyclic antidepressants relative to placebo. Neither gabapentin or the phenytoin-carbamazepine combination showed a significant difference over placebo in the incidence of major adverse effects.

There was little difference in the incidence of minor adverse effects with either antidepressants or anticonvulsants, compared with placebo; the NNH (minor) values were approximately 3.

**Authors’ conclusions**
The present review showed that both drug classes were effective, with (combining the two syndromes) at least 50% pain relief achieved in two-thirds of the patient episodes treated with anticonvulsants and in half of those treated with antidepressants. The efficacy had a similar adverse effect burden.

**CRD commentary**
The review question, and the inclusion or exclusion criteria, were presented clearly. There was also evidence of a substantial effort to search the relevant literature. While the authors included a search of the grey literature, a paper had to have been published in full, in a journal, in order to meet the inclusion criteria. It is possible, therefore, that some studies may have been missed. The paper would have benefited from the inclusion of a forest plot. The validity of the included studies was adequately assessed and, despite being reported on the Bandolier website, was not used further in the review. Detailed information on the individual studies are also available on this website. However, there are no information on the patients’ characteristics, e.g. age and gender. The authors do not state how many reviewers performed the selection, validity assessment or data extraction, therefore, the reader is unable to judge possible bias in the review process. While the L’Abbe plots presented some information on heterogeneity, the authors did not explicitly address this issue in the text. The authors conducted some sensitivity analyses on a subgroup of included studies. However, some caution should be exercised when interpreting the conclusion, because these subgroup and sensitivity analyses appear to have been driven by the available data, rather than by a predefined rationale.

This review is largely an update of a previous review (see Other Publications of Related Interest no.2).

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

Research: The authors state that, based on their sensitivity analyses, they identified three methodological considerations for future trials. These were: (1) neuropathy scales may underestimate the pain relief achieved if the scale is presented as a single overall result; (2) the smaller the trial, the greater the tendency to overestimate efficacy; and (3) trials less than three weeks in duration underestimated the treatment effect.

**Funding**
European Union, Biomed 2 (grant number BMH4 CT950172) and Pain Research Funds.

**Bibliographic details**
PubMedID
11131263

Additional Data URL
http://www.jr2.ox.ac.uk/bandolier/painres/adacrev/rctdetai.html

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Anticonvulsants /therapeutic use; Antidepressive Agents /therapeutic use; Diabetic Neuropathies /drug therapy; Herpes Zoster /complications; Humans; Neuralgia /drug therapy /etiology

AccessionNumber
12001000024

Date bibliographic record published
30/04/2002

Date abstract record published
30/04/2002

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.