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Effects of treatments for symptoms of painful diabetic neuropathy: systematic review

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ABSTRACT

Objective To evaluate the effects of treatments for the symptoms of painful diabetic neuropathy.

Design Systematic review.

Data sources Articles (English and full text) on double blind randomised trials found by searching with the key words anticonvulsant, antidepressant, non-steroidal anti-inflammatory drugs, tramadol, opioid, ion channel blocker, diabetic neuropathy, diabetic peripheral neuropathy, peripheral neuropathy, and neuropathy. The search included Medline, Embase, EMB reviews-AP Journal club, and the Cochrane central register of controlled trials.

Study selection Randomised controlled trials comparing topically applied and orally administered drugs with a placebo in adults with painful diabetic neuropathy.

Data extraction Data were extracted to examine quality of methods, characteristics of studies and patients, efficacy, and side effects. The primary outcome was dichotomous information for 50% or moderate reduction of pain. Secondary outcomes were 30% reduction of pain and withdrawals related to adverse events.

Results Odds ratios were calculated for achievement of 30%, 50%, or moderate pain relief and for withdrawals related to adverse effects. Twenty five reports were included and seven were excluded. The 25 included reports compared anticonvulsants (n=1270), antidepressants (94), opioids (329), ion channel blockers (173), N-methyl-D-aspartate antagonist (14), duloxetine (805), capsaicin (277), and isosorbide dinitrate spray (22) with placebo. The odds ratios in terms of 50% pain relief were 5.33 (95% confidence interval 1.77 to 16.02) for traditional anticonvulsants, 3.25 (2.27 to 4.66) for newer generation anticonvulsants, and 22.24 (5.83 to 84.75) for tricyclic antidepressants. The odds ratios in terms of withdrawals related to adverse events were 1.51 (0.33 to 6.96) for traditional anticonvulsants, 2.98 (1.75 to 5.07) for newer generation anticonvulsants, and 2.32 (0.59 to 9.69) for tricyclic antidepressants. Insufficient dichotomous data were available to calculate the odds ratios for ion channel blockers.

Conclusion Anticonvulsants and antidepressants are still the most commonly used options to manage diabetic neuropathy. Oral tricyclic antidepressants and traditional anticonvulsants are better for short term pain relief than newer generation anticonvulsants. Evidence of the long term effects of oral antidepressants and anticonvulsants is still lacking. Further studies are needed on opioids, N-methyl-D-aspartate antagonists, and ion channel blockers.

INTRODUCTION

Diabetic neuropathy is a common complication of diabetes. An Australian population based survey of 2436 patients with known or newly diagnosed diabetes showed that 13.1% of them had peripheral neuropathy.¹ Another multicentre study in the United Kingdom showed that 22-32% of 6363 diabetic patients had peripheral neuropathy.² Similar results have been reported by an Italian multicentre study, which showed that 32.3% of 8757 diabetic patients had neuropathy.³

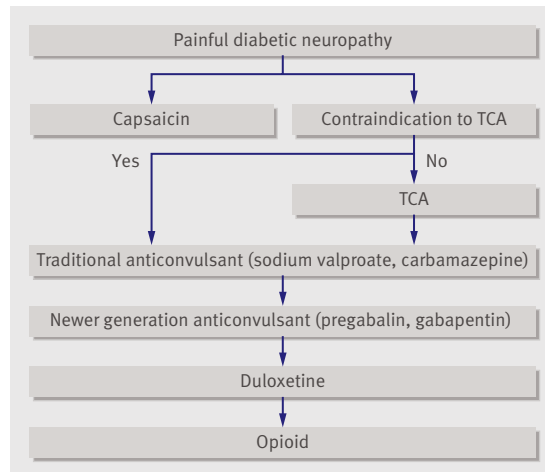
Symptoms of neuropathic pain are commonly reported in patients with diabetic neuropathy. Partanen and colleagues found that among 132 patients, 7-13% had pain and paraesthesias when they were diagnosed as having type 2 diabetes mellitus.⁴ The prevalences of pain and of paraesthesia were 20% and 33% 10 years after diagnosis.⁴

Tight glycaemic control has been shown to be effective in slowing the progression of diabetic neuropathy.⁵⁻⁸ Antidepressants and anticonvulsants are commonly used to reduce the intensity of pain in patients with painful diabetic neuropathy. In the clinical setting, despite the use of various analgesics to manage the neuropathic pain of diabetic neuropathy, the problem persists. We did a systematic review to explore the effectiveness of analgesics in managing diabetic neuropathy.

METHODS

Search strategy to identify studies—We identified randomised trials that studied analgesics used to treat

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Proposed treatment algorithm for painful diabetic neuropathy

diabetic neuropathy by using Medline(R) (1966 to 2006), Embase (1980 to 2006), EMB reviews-AP Journal club (1991 to 2006), and the Cochrane central register of controlled trials (2006). We identified additional reports from the reference lists of the retrieved papers. Key words used in the search included neuropathy and anticonvulsant, non-steroidal anti-inflammatory drugs, ion channel blocker, antiepileptic/anticonvulsant, antidepressant or antidepressants, tramadol, opioid, pregabalin, duloxetine, and capsaicin.

Selection criteria—Participants were adults aged 18 years and above with diabetic neuropathy. The interventions involved the administration of oral or topical analgesics. The classes of drugs included paracetamol, antidepressants, opioids, non-steroidal anti-inflammatory drugs, *N*-methyl-D-aspartate antagonists, tramadol, capsaicin, and anticonvulsants. The comparator was a placebo. The primary and secondary outcomes of the studies had to include subjective reports of pain relief or pain intensity. We included randomised controlled trials that investigated the analgesic effects of pain relieving drugs for patients with diabetic neuropathy.

Quality assessment—We used a three item quality scale to score each report.⁹ We excluded studies without randomisation and blinding and trials with a quality score of 2 or less. We assessed use of concealment and intention to treat analysis. We did not consider trials with a sample size under 10.

Data extraction—We reviewed the title and abstracts of studies against our inclusion criteria and retrieved studies identified from the reference list of the available articles. We compared full reports of the studies with the inclusion criteria. Two reviewers extracted data independently.

Outcome—We defined clinical success as a 50% reduction in pain. This was the number of patients with a “moderate,” “good,” or “notable” improvement in global assessment of treatment or at least moderate pain relief on a suitable categorical scale. Secondary

outcomes were 30% reduction in pain and the number of patients who withdrew as a result of adverse events.

Data analysis—We combined the results and expressed them as odds ratios. We assessed homogeneity. We followed QUOROM guidelines.¹⁰

RESULTS

Description of the studies

We screened 1231 citations for eligibility. We retrieved 32 full text articles published in English. We included 25 articles that met the inclusion criteria,^{w1-w25} and 17 of them were included in the meta-analysis of treatment efficacy.

Anticonvulsants

Ten trials, with a total of 1576 patients, investigated traditional and newer generation anticonvulsants, including sodium valproate,^{w13 w14} gabapentin,^{w6} lamotrigine,^{w7} carbamazepine,^{w5} pregabalin,^{w10-w12} and oxcarbazepine.^{w8 w9} The carbamazepine trial used a crossover design. Two of the pregabalin studies and one of the oxcarbazepine studies were dose response trials.^{w9 w11 w12} The treatment period varied from two weeks to three months.

The pooled odds ratio of treatment efficacy with traditional anticonvulsants was 5.33 (95% confidence interval 1.77 to 16.02). The pooled odds ratio for withdrawal related to adverse events with traditional anticonvulsants was 1.51 (0.33 to 6.96). The pooled odds ratio of treatment efficacy with newer generation anticonvulsants was 3.25 (2.27 to 4.66). The pooled odds ratio for withdrawal related to adverse events with traditional anticonvulsants was 2.98 (1.75 to 5.07). The common side effects from use of anticonvulsants were somnolence and dizziness, and the major adverse reaction was liver derangement (two participants).^{w13 w14}

Antidepressants

Four trials with a total of 94 patients investigated the tricyclic antidepressants desipramine,^{w16} imipramine,^{w17} and amitriptyline^{w15} and the selective serotonin reuptake inhibitor citalopram.^{w1} All of them were crossover studies with treatment periods between three and six weeks.

Although we could extract no data from the published report on citalopram, this study used published data from a previous study.¹¹ The odds ratio in terms of 50% pain relief with citalopram was 3.5 (0.3 to 38.2), and the odds ratio for withdrawal related to adverse events was 5.6 (0.3 to 125.5). The pooled odds ratio for treatment efficacy of tricyclic antidepressants was 22.24 (5.83 to 84.75). The pooled odds ratio for adverse effect related to withdrawal from tricyclic antidepressants was 2.32 (0.59 to 9.69). The most common adverse effect related to withdrawal was dry mouth and sedation.

Serotonin noradrenaline reuptake inhibitor

Two trials with a total of 805 patients investigated duloxetine.^{w18 w19} Both trials used a 12 week parallel

WHAT IS ALREADY KNOWN ON THIS TOPIC

Current guidelines recommend the use of antidepressants and anticonvulsants in the treatment of painful diabetic neuropathy

WHAT THIS STUDY ADDS

Oral tricyclic antidepressants and traditional anticonvulsants are better for short term pain relief than newer generation anticonvulsants

Evidence of the long term effects of oral antidepressants and anticonvulsants is still lacking

group design, and both of them were dose response trials. The pooled odds ratio in terms of 50% pain relief with duloxetine 60 mg was 2.55 (1.73 to 3.77), and the odds ratio for withdrawal related to adverse events was 2.36 (1.05 to 5.35). For duloxetine 120 mg, the odds ratios were 2.10 (1.03 to 4.27) for 50% pain relief and 4.65 (2.18 to 9.94) for withdrawal related to adverse events. The most frequently reported adverse events were nausea, somnolence, dizziness, and constipation.

Ion channel blockers

Three trials investigated mexiletine in a total of 173 patients. One trial used a crossover design,^{w20} and another was a dose response study.^{w21} The pooled weighted mean difference of the mean score on a visual analogue scale for pain intensity for mexiletine 600 mg and 720 mg versus placebo was -1.87 (-2.64 to -1.11). One study reported no statistical differences between mexiletine 600-675 mg and a placebo with a three week treatment period.^{w22} The pooled odds ratio for adverse effect related withdrawal from mexiletine was 1.08 (0.13 to 8.80). The adverse effects related to withdrawal were itching, pain, headache, nausea, and vomiting.^{w22}

N-methyl-D-aspartate antagonists

Only one trial, with a total of 14 patients, investigated dextromethorphan.^{w23} This trial used a crossover design, with a six week treatment period and a one week washout. The odds ratio in terms of 50% pain relief with a mean daily dose of 381 mg dextromethorphan was 31.2 (1.5 to 633.1). No extractable dichotomous data on adverse events related to withdrawal have been published.

Opioids

Three trials with a total of 329 patients investigated controlled release oxycodone and tramadol.^{w2 w24 w25} One of the controlled release oxycodone trials used a crossover design.^{w2} In another trial, a 37 mg average daily dose of controlled release oxycodone reportedly had a superior analgesic effect compared with placebo.^{w24}

Although we could extract no data from the published report on tramadol, this study used and published data from a previous study.¹¹ The odds ratio of 50% pain relief was 3.8 (1.8 to 8.0) for tramadol at an average daily dose of 210 mg. The pooled odds ratio for treatment efficacy of opioids was 4.25 (2.33 to 7.77). The pooled odds ratio for withdrawal from opioids

related to adverse events was 4.06 (1.16 to 14.21). The most common adverse events were constipation, somnolence, nausea, dyspepsia, and headache.

Topical agents

One trial with a total of 22 patients investigated isosorbide dinitrate spray.^{w4} This trial used a crossover design, with a four week treatment period and a two week washout. We could extract no dichotomous data from the published reports. The author reported that significant relief from burning sensation occurred in the treatment group.

One trial with a total of 277 patients investigated 0.075% capsaicin cream.^{w3} This trial used an eight week parallel group design. The odds ratio in terms of 50% pain relief was 2.37 (1.32 to 4.26), and the odds ratio of withdrawal related to adverse events was 4.02 (1.45 to 11.16). The most common adverse events were a burning sensation at the site of application, coughing or sneezing, accidental irritation to other body parts, and rashes.

DISCUSSION

Our systematic review shows that tricyclic antidepressants, traditional anticonvulsants, and opioids have better efficacy than newer generation anticonvulsants, a selective serotonin reuptake inhibitor, and a serotonin noradrenaline reuptake inhibitor for relieving the pain of diabetic neuropathy. Most trials were of good methodological quality, although sample size was small and some of the trials used a crossover design without a washout period.

Some of the trials included in this review used the crossover method; only four of them mentioned using a washout period. In a study with no washout period, the carryover effect may not be eliminated from the first period of the treatment effect; we therefore used only the data from the first period to calculate the efficacy of the drugs (if we could extract the data). However, this may lead to selection bias, resulting in an underestimation of the effect of the drug.^{12 w3}

A single study investigated N-methyl-D-aspartate antagonists, and estimating the effect of the drug on the basis of only one study is difficult. For ion channel blockers, three trials reported contradictory results, so we could not calculate the efficacy of this treatment. Although the odds ratio of 50% pain relief for tramadol was 3.8, that for withdrawal related to adverse events was greater for tramadol than for other treatments. For anticonvulsants, the odds ratio for 50% pain relief was greater with traditional anticonvulsants than with newer generation anticonvulsants. In contrast, the odds ratio for withdrawals related to adverse events was greater for newer generation anticonvulsants than for traditional anticonvulsants. Finally, the treatment period was less than six months in all of the studies, so the long term effect of these drugs cannot be judged.

In the clinical setting, management of neuropathic pain focuses on two aspects: disease modifying treatment such as glycaemic control and the use of

analgesics to reduce the intensity of the pain. Although pain intensity may not be sufficient to reflect the outcome of treatment, it is a common outcome measure in clinical research. Few studies reported treatment efficacy for different qualities of pain such as allodynia and burning pain.^{w4 w11 w18}

Conclusions

Although an increasing number of trials have investigated different kinds of drugs to manage neuropathic pain, anticonvulsants and antidepressants are still the options most commonly used for painful diabetic neuropathy. Long term studies of the efficacy and adverse effects of anticonvulsants and antidepressants are needed, as these drugs are commonly used in clinical setting. Further studies are needed on ion channel blockers, *N*-methyl-D-aspartate antagonists, and opioids, as well as non-pharmacological strategies. In addition, their treatment efficacy for common painful symptoms needs to be explored. We propose a treatment algorithm based on the available data (figure).

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CORRECTIONS AND CLARIFICATIONS

Intimate partner violence

In this editorial by Lorraine E Ferris, the 13 reference numbers within the text somehow “dropped off” the page proofs and so did not appear in the version published in the printed journal or in the pdf (which is the same as the print version) on bmj.com (*BMJ* 2007;334:706-7, 7 Apr, doi: 10.1136/bmj.39168.644757.BE). However, readers can see the complete article, with all the references and reference numbers intact, at www.bmj.com/cgi/content/full/334/7596/706.

Report recommends tighter legislation and better road design to reduce traffic injuries and deaths

In this News item by Susan Mayor, the correct URL for the World Health Organization’s policy briefing is www.euro.who.int/InformationSources/Publications/Catalogue/20070420_1 (*BMJ* 2007;334:867, 28 Apr, doi: 10.1136/bmj.39195.366169.DB).

Recurrent pharyngo-tonsillitis

Several errors crept unseen into this editorial by Paul Little (*BMJ* 2007;334:909, 5 May, doi: 10.1136/bmj.39184.617049.80) because of a loophole in a minor part of our submission and editorial process; we are improving this bit of the process to ensure such errors can’t infiltrate again. Firstly, in the opening paragraph, 8/34 is 24% [not 21%], and the 21% cited as an adjusted relative risk is in fact a value for absolute risk reduction. Secondly, in the version published in the printed journal (and in the pdf), the third sentence of the final paragraph

should read: “Until such evidence is available, I would advise patients who have had four episodes of sore throat in one year or three in six months that they are likely to have on average two episodes (12 days) of sore throat in the next six months and two or three days of fever if they decide not to have the operation; if they decide to have the operation they are likely to have about 13 days of severe pain immediately after surgery, and then on average half an episode (3 days) of sore throat in the next six months and half a day of fever.”

Is presumed consent the answer to organ shortages?

At a late stage in the editorial process, we shortened a sentence in this Head to Head article by Linda Wright (*BMJ* 2007;334:1089, 26 May, doi: 10.1136/bmj.39199.492894.AD) in such a way that it seemed to be the author who was claiming that more people might donate kidneys if there was a financial incentive. In fact, she was repeating other people’s claims.

Managing suspected research misconduct

In this editorial by Charles Young and Fiona Godlee (*BMJ* 2007;334:378-9, 24 Feb, doi: 10.1136/bmj.39129.611516.80), the third author of the article cited as reference 1 should be Evans, not Smith. The full reference is therefore: Roberts I, Smith R, Evans S. Doubts over head injury studies. *BMJ* 2007;334:392-4, 24 Feb doi: 10.1136/bmj.39118.480023.BE.