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[Intervention Review]

Tramadol for neuropathic pain in adults

Rudolf Martin Duehmke[1], Sheena Derry[2], Philip J Wiffen[2], Rae F Bell[3], Dominic Aldington[4], R Andrew Moore[2]

[1]Cardiac Unit, Papworth Hospital, Cambridge, UK. [2]Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Oxford, UK. [3]Regional Centre of Excellence in Palliative Care, Haukeland University Hospital, Bergen, Norway. [4]Royal Hampshire County Hospital, Winchester, UK

Contact: Sheena Derry, Pain Research and Nuffield Department of Clinical Neurosciences (Nuffield Division of Anaesthetics), University of Oxford, Pain Research Unit, Churchill Hospital, Oxford, Oxfordshire, OX3 7LE, UK. sheena.derry@ndcn.ox.ac.uk.

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ABSTRACT

Background

This review is an update of a review of tramadol for neuropathic pain, published in 2006; updating was to bring the review in line with current standards. Neuropathic pain, which is caused by a lesion or disease affecting the somatosensory system, may be central or peripheral in origin. Peripheral neuropathic pain often includes symptoms such as burning or shooting sensations, abnormal sensitivity to normally painless stimuli, or an increased sensitivity to normally painful stimuli. Neuropathic pain is a common symptom in many diseases of the peripheral nervous system.

Objectives

To assess the analgesic efficacy of tramadol compared with placebo or other active interventions for chronic neuropathic pain in adults, and the adverse events associated with its use in clinical trials.

Search methods

We searched CENTRAL, MEDLINE, and Embase for randomised controlled trials from inception to January 2017. We also searched the reference lists of retrieved studies and reviews, and online clinical trial registries.

Selection criteria

We included randomised, double-blind trials of two weeks' duration or longer, comparing tramadol (any route of administration) with placebo or another active treatment for neuropathic pain, with subjective pain assessment by the participant.

Data collection and analysis

Two review authors independently extracted data and assessed trial quality and potential bias. Primary outcomes were participants with substantial pain relief (at least 50% pain relief over baseline or very much improved on Patient Global Impression of Change scale (PGIC)), or moderate pain relief (at least 30% pain relief over baseline or much or very much improved on PGIC). Where pooled analysis was possible, we used dichotomous data to calculate risk ratio (RR) and number needed to treat for an additional beneficial outcome (NNT) or harmful outcome (NNH), using standard methods. We assessed the quality of the evidence using GRADE and created 'Summary of findings' tables.

Main results

We identified six randomised, double-blind studies involving 438 participants with suitably characterised neuropathic pain. In each, tramadol was started at a dose of about 100 mg daily and increased over one to two weeks to a maximum of 400 mg daily or the maximum tolerated dose, and then maintained for the remainder of the study. Participants had experienced moderate or severe neuropathic pain for at least three months due to cancer, cancer treatment, postherpetic neuralgia, peripheral diabetic neuropathy, spinal cord injury, or

polyneuropathy. The mean age was 50 to 67 years with approximately equal numbers of men and women. Exclusions were typically people with other significant comorbidity or pain from other causes. Study duration for treatments was four to six weeks, and two studies had a cross-over design.

Not all studies reported all the outcomes of interest, and there were limited data for pain outcomes. At least 50% pain intensity reduction was reported in three studies (265 participants, 110 events). Using a random-effects analysis, 70/132 (53%) had at least 50% pain relief with tramadol, and 40/133 (30%) with placebo; the risk ratio (RR) was 2.2 (95% confidence interval (CI) 1.02 to 4.6). The NNT calculated from these data was 4.4 (95% CI 2.9 to 8.8). We downgraded the evidence for this outcome by two levels to low quality because of the small size of studies and of the pooled data set, because there were only 110 actual events, the analysis included different types of neuropathic pain, the studies all had at least one high risk of potential bias, and because of the limited duration of the studies.

Participants experienced more adverse events with tramadol than placebo. Report of any adverse event was higher with tramadol (58%) than placebo (34%) (4 studies, 266 participants, 123 events; RR 1.6 (95% CI 1.2 to 2.1); NNH 4.2 (95% CI 2.8 to 8.3)). Adverse event withdrawal was higher with tramadol (16%) than placebo (3%) (6 studies, 485 participants, 45 events; RR 4.1 (95% CI 2.0 to 8.4); NNH 8.2 (95% CI 5.8 to 14)). Only four serious adverse events were reported, without obvious attribution to treatment, and no deaths were reported. We downgraded the evidence for this outcome by two or three levels to low or very low quality because of small study size, because there were few actual events, and because of the limited duration of the studies.

Authors' conclusions

There is only modest information about the use of tramadol in neuropathic pain, coming from small, largely inadequate studies with potential risk of bias. That bias would normally increase the apparent benefits of tramadol. The evidence of benefit from tramadol was of low or very low quality, meaning that it does not provide a reliable indication of the likely effect, and the likelihood is very high that the effect will be substantially different from the estimate in this systematic review.

PLAIN LANGUAGE SUMMARY

Tramadol for treating neuropathic pain

Bottom line

We found low-quality evidence that oral tramadol has any important beneficial effect on pain in people with moderate or severe neuropathic pain. There is very little evidence from which to take these conclusions.

Background

Neuropathic pain is pain coming spontaneously or abnormally from damaged nerves. It is different from pain messages that are carried along healthy nerves from damaged tissue (a fall or cut, or burns). Neuropathic pain is often treated by different medicines (drugs) to those used for pain from damaged tissue, which we call painkillers.

Opioid painkillers (drugs like morphine) are sometimes used to treat neuropathic pain. Morphine is derived from plants, but many opioids are made in a laboratory rather than being extracted from plants. Tramadol is a laboratory-synthesised opioid drug.

Study characteristics

In January 2017, we searched for clinical trials in which tramadol was used to treat neuropathic pain in adults. Six studies met the inclusion criteria, randomising 438 participants to treatment with tramadol or placebo. Study duration was between four and six weeks. Not all reported the outcomes of interest.

Our definition of a good result was someone who had a high level of pain relief and was able to keep taking the medicine without side effects that made them stop treatment.

Key results

Three small studies reported that pain was reduced by half or better in some people. Pain reduction by half or better was experienced by 5 in 10 with tramadol and 3 in 10 with placebo. Side effects were experienced by 6 in 10 with tramadol and 3 in 10 with placebo, and 2 in 10 with tramadol and almost no-one with placebo stopped taking the medicine because of side effects.

Quality of the evidence

The evidence was mostly of low or very low quality. This means that the research does not provide a reliable indication of the likely effect and that the likelihood is very high that the effect will be different from what is shown in the analysis of these trials. Small studies like those in this review tend to overestimate results of treatment compared to the effects found in larger, better studies. There were also other problems that might lead to over-optimistic results. The low-quality evidence and the lack of any important benefit mean that we need new, large trials before we will know if tramadol is useful for the management of neuropathic pain.