Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin: systematic review and meta-analysis of randomized controlled trials

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CRD summary
This review assessed the efficacy and safety of opioid agonists for the treatment of neuropathic pain. The authors concluded that there was equivocal evidence for opioids compared with placebo in the short term, but that opioids reduced pain in the intermediate term (8 days to 8 weeks). The authors' conclusions are likely to be reliable.

Authors' objectives
To assess the efficacy and safety of opioid agonists for the treatment of neuropathic pain.

Searching
MEDLINE (1966 to December 2004) and the Cochrane CENTRAL Register (Issue 4, 2004) were searched for studies in any language. The reference lists of reviews and retrieved articles were also checked.

Study selection
Study designs of evaluations included in the review
Randomised, blinded controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared one or more opioid agonists or different doses of the same agonist with placebo, each other, or another class of drug used for neuropathic pain were eligible for inclusion. Partial agonists, agonist-antagonists, drugs other than opioid agonists used in combination with opioids, and epidural and intrathecal opioids were excluded. Drugs administered orally, rectally, transdermally, intravenously, intramuscularly, or subcutaneously were eligible for inclusion. In the included studies, drugs were administered in the short term (single injection to 8 hours with outcomes assessed at less than 24 hours) or intermediate term (treatment duration from 8 days to 8 weeks).

Participants included in the review
Studies of men and women of all ages and races or ethnicities, and who were experiencing central or peripheral neuropathic pain of any aetiology, were eligible for inclusion. Studies of patients with neuropathic and other types of pain were excluded if they did not report the results separately for neuropathic pain.

Outcomes assessed in the review
Studies measuring neuropathic pain with validated measurement tools were eligible for inclusion. Studies reporting adverse events were also included.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The studies were assessed using the Jadad scale, which is based on the description of randomisation, blinding and withdrawals. The scores ranged from 0 to 5 (5 indicating a better methodological score). Validity was assessed, but the authors did not state who performed the assessment.

Data extraction
Two reviewers independently extracted the data into a standardised table. Any discrepancies in the extracted data were
resolved by discussion. When possible, all data were normalised to a 0- to 100-mm visual analogue scale (VAS). The number of patients experiencing adverse events was also extracted. Where data allowed, the number-needed-to-harm (NNH) and 95% confidence intervals (CIs) were calculated for the most common adverse effects.

Methods of synthesis
How were the studies combined?
Studies presenting sufficient data were combined in a fixed-effect model to calculate differences in post-intervention pain intensity or pain relief using weighted mean differences (WMDs). Short-term and intermediate-term trials were pooled separately. Relative risks with 95% CIs were calculated for adverse events.

A funnel plot was used to assess publication bias in the intermediate-term trials.

How were differences between studies investigated?
The chi-squared test was used to evaluate heterogeneity between and within the studies.

Results of the review
Twenty-two RCTs (670 opioid-treated patients) were included in the review. Of these, 14 were short-term crossover RCTs (n=267) and 8 were intermediate-terms RCTs (5 crossover and 3 parallel group; n=799).

The median Jadad score for all studies was 4 (range: 2 to 5).

Intermediate-term trials (8 RCTs).

Six studies scored 5 points on the Jadad score for validity.

A meta-analysis of 6 RCTs (n=521) found that the mean post-treatment VAS score for pain intensity after opioid use was 14 units lower on a 0- to 100-mm scale than after placebo (95% CI: -18, -10, P<0.001). No statistically significant heterogeneity was detected (P=0.27).

Short-term trials (14 RCTs).

The short-term individual trials had mixed results. Only 4 RCTs presented sufficient data for a meta-analysis. The meta-analysis showed that opioids reduced peripheral pain (WMD -15, 95% CI: -23, -7), based on 138 patients, and central pain (WMD -18, 95% CI: -30, -5), based on 42 patients. No statistically significant heterogeneity was detected (P=0.94 and P=0.78, respectively).

Adverse events.

The most common adverse event was nausea (NNH 3.6, 95% CI: 2.9, 4.8), followed by constipation (NNH 4.6, 95% CI: 3.4, 7.1), drowsiness (NNH 5.3, 95% CI: 3.7, 8.3), vomiting (NNH 6.2, 95% CI: 4.6, 11.1) and dizziness (NNH 6.7, 95% CI: 4.8, 10.0).

The funnel plot showed no evidence of publication bias among intermediate-term trials.

Authors' conclusions
Short-term studies provided only equivocal evidence regarding the efficacy of opioids in reducing the intensity of neuropathic pain. Intermediate-term studies demonstrated significant efficacy of opioids over placebo for neuropathic pain, which was likely to be clinically important. The reported adverse events of opioids were common but not life-threatening.

CRD commentary
The authors addressed a clear question with explicit inclusion criteria. Two relevant databases were searched but the
search terms were not given. Unpublished studies were excluded, thus raising the possibility of publication bias; however, there was no evidence of publication bias among intermediate-term studies. Methods to reduce reviewer error and bias were in place in the data extraction process but it was unclear how many reviews were involved in selecting the studies and assessing the quality of the included studies. Although the studies were assessed using a validated tool, this was not an exhaustive assessment of quality and many important aspects of trial design were not considered.

Statistical heterogeneity was assessed and studies presenting sufficient data were combined in meta-analysis. The authors discussed the clinical relevance of the review's findings. The authors' conclusions were appropriately based on the combination of studies with similar characteristics and are likely to be reliable.

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

Practice: The authors stated that further longer-term studies would be required before the use of opioids for neuropathic pain could be considered established.

Research: The authors stated that future studies should evaluate wider dose ranges of opioids, assess the risk of abuse and addiction, and investigate longer-term efficacy and safety of opioids and their effect on quality of life.

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