Opioids in chronic non-cancer pain: systematic review of efficacy and safety
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CRD summary
This review assessed the efficacy and safety of opioids for chronic non-cancer pain. The authors concluded that opioids were effective for neuropathic and musculoskeletal pain in the short term, but no conclusions could be drawn for tolerance or addiction. Although only high-quality randomised controlled trials were included, the review methods were not described in full and this weakens the strength of the evidence.

Authors’ objectives
To assess the efficacy and safety of opioids in patients with chronic non-cancer pain.

Searching
The Oxford Pain Relief Database (1950 to 1994), MEDLINE (1966 to September 2003), EMBASE (1980 to September 2003) and the Cochrane Library (online, September 2003) were searched for reports in any language. Brief details of the search strategy were reported. The reference lists in reports and reviews were also checked. Abstracts and unpublished studies were excluded.

Study selection
Study designs of evaluations included in the review
Double-blind randomised controlled trials (RCTs) with at least 10 adult patients completing each treatment arm were eligible for inclusion.

Specific interventions included in the review
Studies that compared oral, transdermal or intravenous World Health Organization step 3 opioids (fentanyl, hydromorphone, methadone, morphine, oxycodone and oxymorphone) with placebo were eligible for inclusion. The studies used different dosing regimens (details were reported).

Participants included in the review
Studies of patients with chronic non-cancer pain were eligible for inclusion. The patients in the included studies had pain from osteoarthritis, diabetic and peripheral neuropathy, phantom limb pain, musculoskeletal pain, postherpetic neuralgia and mixed types of pain. The participants had suffered pain from over 3 months to over 1 year in the studies reporting this. Some patients had previously used opioids.

Outcomes assessed in the review
Studies that assessed pain intensity using validated pain scales (visual analogue scales, a 0 to 10 numerical rating scale, or a 4-point pain intensity categorical scale) were eligible for inclusion. The primary review outcome was pain intensity difference or pain relief. The secondary review outcomes were mood, functional status, quality of life and dose response. The review also assessed adverse effects. The review assessed outcomes over three time periods: during intravenous infusions lasting up to 5 hours; over 1 to 8 weeks for oral or transdermal treatment; and over 3 to 18 months of open-label follow-up. In addition, the review assessed the predictive value of intravenous opioids for later oral or transdermal opioids.

How were decisions on the relevance of primary studies made?
All four reviewers reached consensus on the included studies.

Assessment of study quality
The quality of the studies was assessed using the 5-point Jadad scale, which considers the reporting and handling of randomisation, blinding and handling of withdrawals. Study validity was assessed using the 5-item scale devised by...
Smith et al., which considers blinding, size of the treatment groups, outcomes, baseline pain, internal sensitivity and data analysis. The authors did not state who performed the validity assessment.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The studies were grouped by duration and type of treatment (intravenous opioid, oral opioid and open-label follow-up) and a narrative synthesis was undertaken. For the randomised phase of each study, the percentage change in pain was plotted, by study, for each treatment group using a bar chart. The relative risk (RR) with 95% confidence interval (CI) for adverse effects was calculated using a fixed-effect model. The number-needed-to-harm (NNH) and 95% CI were calculated where the RR showed a statistically significant difference between opioid and placebo.

How were differences between studies investigated?
Statistical heterogeneity among the studies was not tested, whereas homogeneity among the studies was examined visually using L’Abbe plots.

Results of the review
Fifteen double-blind RCTs (n=1,145) were included. Eleven RCTs (6 crossover and 5 parallel group) used oral opioids and four used intravenous opioids.

The studies scored high for quality (mean 4 out of 5, range: 3 to 5) and validity (mean 14 out of 16, range: 10 to 18). Only 6 studies reported a power calculation.

Intravenous opioids (4 crossover RCTs, 120 patients randomised, 115 completed).
All 4 studies found average pain relief of 30 to 60% with opioids, compared with a 5% increase to a 25% decrease with placebo. The results were similar for different types of neuropathic pain (results presented graphically).

Most of the patients reported adverse effects. Problems included a 90% rate of infusion termination before 5 hours with fentanyl (1 RCT) and the exclusion of 14% of patients who were unable to tolerate a morphine infusion (1 RCT); in the latter study, 60% of those included reported adverse events. One RCT did not report any adverse effects with a morphine infusion. Adverse effects included vomiting in 37% of patients receiving fentanyl (1 RCT).

Oral opioids (11 RCTs conducted over 4 days to 8 weeks, 1,025 patients randomised, 698 evaluable).
Mean pain relief with opioids was about 30% for neuropathic and nociceptive pain. Two RCTs found that oxycodone significantly reduced steady pain, brief pain and dynamic allodynia compared with placebo in patients with allodynia.

All 7 studies assessing the quality of sleep found a significant improvement with opioids.

Five RCTs found no significant difference with either an opioid or placebo for various measures of physical activity. Two studies reported lower disability scores with oxycodone compared with placebo.

One of 3 RCTs assessing quality of life using a validated tool found that oxycodone improved most quality of life domains.

There was no statistically significant difference in the rates of discontinuation for opioids and placebo (30% versus 26%; RR 1.0, 95% CI: 0.1, 1.2). The most common reasons for discontinuation were adverse effects with opioids and lack of efficacy with placebo. Patients taking opioids were more likely to report at least one adverse effect than patients taking placebo (80% versus 56%; NNH 4.2, 95% CI: 3.1, 6.4). The most common adverse effects with opioids were...
constipation (41% versus 11% with placebo; NNH for 3.4, 95% CI: 2.9, 4.0), somnolence (29% versus 10% with placebo) and nausea (32% versus 12% with placebo). Opioids also significantly increased vomiting (15% versus 3%), dizziness (20% versus 7%) and itching (15% versus 7%) compared with placebo.

Two of the 5 studies reporting withdrawal symptoms found none. The others reported withdrawal symptoms in 1 or 2 patients each. In one RCT, drug craving was reported in 8.7% (4 patients) with morphine compared with 4.3% (2 patients) with placebo. Two other studies reported no drug abuse or aberrant drug-related behaviour.

Two of the 3 studies assessing tolerance found pain intensity rose after the 4-week titration period, while the other found no evidence of tolerance.

Follow-up studies (8 RCTs with open-label follow-up).

The studies found that about 44% of patients remained on opioids after 7 months to 2 years. The most common reasons for discontinuation were adverse effects or lack of efficacy. All 3 studies assessing tolerance found no development of tolerance in the majority of patients: tolerance was 6% in one study, 1 of 9 remaining patients followed up over 2 years in a second study, and not reported in the third study. Two studies reported no signs of addiction (in 3 patients in 1 study). Severe withdrawal was reported in a total of 3 patients in 2 studies. One study reported that 3 out of 106 patients took more drug than prescribed.

Authors' conclusions
Opioids were effective for neuropathic and musculoskeletal pain in the short term in selected patients, but few patients continued with them in the longer term. There was insufficient information to draw conclusions about tolerance and addiction.

CRD commentary
The review addressed a clear question, defined in terms of participants, intervention, outcomes and study design. Several relevant sources were searched and the lack of language restrictions reduced the possibility of language bias. The exclusion of unpublished studies raised the possibility of publication bias, which was not examined. Methods were used to minimise bias in the study selection process. However, the methods used to assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce errors and bias. Only double-blind RCTs using validated outcome measures were included, and study validity was assessed using specified established criteria. There were inconsistencies in the number of studies reported in the abstract and the text for certain outcomes.

The studies were appropriately grouped and were generally combined in a narrative. Homogeneity was examined graphically. The review included only high-quality RCTs but the studies were generally small. This, in combination with the limitations outlined already and by the authors, means that the conclusions of the review should be interpreted cautiously. The authors appropriately highlighted the lack of data on tolerance and addiction.

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

Research: The authors stated there is a need for further research into the role of opioids in the treatment of chronic non-cancer pain. They stated that future studies assessing tolerance should also consider changes in opioid dosing, pain intensity and activity. In addition, there is a need for definitions for meaningful pain relief, tolerance, and addictive or problematic behaviour, and that genetic and endocrinological studies are required. The authors suggested that studies of designs other than RCTs may be of greater relevance to clinical practice, but that such studies should use standardised outcome measures. They further suggested that it is important to evaluate the impact of guidelines on the outcome of opioid treatment in chronic pain. (see Other Publications of Related Interest, nos.1-2).

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DOI
10.1016/j.pain.2004.09.019

Other publications of related interest

This additional published commentary may also be of interest. LeFort SM. Review: intravenous and oral opioids reduce chronic non-cancer pain but are associated with high rates of constipation, nausea, and sleepiness. Evid Based Nurs 2005;8:88.

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