A comparison between enriched and nonenriched enrollment randomized withdrawal trials of opioids for chronic noncancer pain

Furlan AD, Chaparro LE, Irvin E, Mailis-Gagnon A

CRD summary
This review concluded that enriched enrolment randomised withdrawal trials did not affect efficacy, but did underestimate adverse effects. Given the small proportion of enriched enrolment randomised withdrawal trials and that the comparisons of opioids with other drugs were based on trials that were not designed to be equivalence trials, the authors' conclusions should be interpreted with caution.

Authors' objectives
The primary aim was to compare the effect of enriched enrolment randomised withdrawal trials with non-enriched randomised withdrawal trials of opioids for chronic non-cancer pain. Secondary aims were to compare weak versus strong opioids, subgroups of patients with different types of pain, and the safety of opioids versus placebo or other drugs. This updated a review by the same group (see Other Publications of Related Interest).

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to July 2009; the search strategies for MEDLINE and EMBASE were reported. Reference lists of relevant articles, reviews and textbooks were checked. Only full-text articles published in English, French, Portuguese or Spanish were included.

Study selection
Randomised controlled trials (RCTs) were eligible for inclusion if patients received opioids (by oral, transdermal, transmucosal, or rectal administration) for at least seven days for the treatment of chronic non-cancer pain. Trials had to report the outcomes of pain, function and adverse events. Chronic non-cancer pain was defined as pain lasting more than six months, including neuropathic pain conditions, nociceptive pain, and fibromyalgia. Head-to-head comparisons of opioids, and trials of migraine, dental pain, ischaemic pain due to vascular disease or abdominal pain were excluded.

The included trials were conducted across the world, between 1991 and 2008. Nine different opioids were studied: tramadol, codeine, propoxyphene, morphine, oxycodone, oxymorphone, methadone, transdermal buprenorphine, and transdermal fentanyl. The comparator groups received either placebo or another drug, such as non-steroidal anti-inflammatory drugs, paracetamol, tricyclic antidepressants, anticonvulsants, or cannabinoids. Most participants (87.1%) had a diagnosis of nociceptive pain; 9.2% had neuropathic pain, 3.2% had fibromyalgia, and 0.41% had mixed nociceptive and neuropathic pain. The mean patient age was 58.1 years (range 40 to 71 years) and 63% of patients were female. A wide range of measures was used across the trials to assess pain and function; most were questionnaire based.

Two reviewers independently selected articles for inclusion in the review. Disagreements were resolved by consensus or consultation with a third reviewer.

Assessment of study quality
Methodological quality was assessed using the Cochrane Risk of Bias tool, which considered: sequence generation, allocation concealment, blinding (participants, personnel and outcome assessors), incomplete outcome data, selective outcome reporting, and other sources of bias (including any relationship with the pharmaceutical industry).

Two reviewers independently assessed trial validity; disagreements were resolved by consensus or consultation with a third reviewer.

Data extraction
Standardised mean differences (effect sizes) were extracted from each trial for pain and function outcomes, and side-
Effect data were extracted to calculate risk differences. Where additional information was required, the authors of the trials were contacted. Opioids were classified as weak (propoxyphene, codeine, tramadol and hydrocodone) or strong (oxycodone, morphine, oxymorphone, fentanyl and buprenorphine).

Two authors extracted the data.

**Methods of synthesis**

Pooled effect sizes and risk differences were calculated, along with 95% confidence intervals, using a random-effects model. Statistical heterogeneity was investigated using $\chi^2$ and $I^2$. A clinically relevant difference in adverse effects was defined as a mean difference of 10% or more between opioids and control.

Subgroup analyses were planned for opioid strength (weak or strong), etiology of pain groups (nociceptive, neuropathic, fibromyalgia or mixed), and comparator (placebo or other drug). Meta-regression was performed, using a fixed-effect model.

**Results of the review**

Sixty-two RCTs (crossover or parallel design) were included in the review; 11,927 participants were randomised. Sixty-one trials lasted less than sixteen weeks. The mean dropout rate was 35% in the opioid group and 38% in the control group. Thirty-two trials were considered to be of adequate quality.

A medium effect size was found for pain (ES 0.58, 95% CI 0.48 to 0.67; 47 RCTs) and a small effect size was found for function (ES 0.34, 95% CI 0.25 to 0.43; 31 RCTs) in favour of opioids, compared with placebo.

In enriched trials, the treatment effect for pain outcomes was 0.62 (95% CI 0.33 to 0.92; eight RCTs) and in non-enriched trials it was 0.57 (95% CI 0.47 to 0.67; 39 RCTs). The difference between these treatment effects was not statistically significant (p=0.6). In enriched trials, the treatment effect for functional outcomes was 0.24 (95% CI 0.08 to 0.41; three RCTs) and in non-enriched trials it was 0.36 (95% CI 0.26 to 0.45; 28 RCTs). The difference between these treatment effects was not significant (p=0.3). The results of subgroup analyses for type of pain and opioid strength were reported.

Non-enriched trials reported 26 types of adverse event and enriched trials reported eight types. Compared with placebo, a significant and clinical difference was found for nausea, constipation, somnolence/drowsiness, dizziness/vertigo, dry skin/itching/pruritus, and vomiting in non-enriched trials, but only constipation in the enriched trials.

Opioids were compared with other drugs in 14 trials; the results generally suggested that differences were not statistically significant.

**Authors’ conclusions**

Enriched enrolment randomised withdrawal trials did not appear to affect efficacy, but they did underestimate the adverse effects. Weak and strong opioids were effective for chronic non-cancer pain of neuropathic or nociceptive origin.

**CRD commentary**

The review question was supported by clear inclusion and exclusion criteria. Several databases were searched, but the search was restricted by language and publication status and the possibility of bias cannot be ruled out. Appropriate methods appear to have been used to minimise reviewer error and bias in the selection of trials, data extraction and validity assessment.

Appropriate criteria were considered in the validity assessment, but few results were reported. As acknowledged by the authors, the generalisability of the results for enriched populations was limited, due to the sample selection procedure and the invalidation of drug-placebo comparisons, due to carryover effects or withdrawal symptoms. Most of the trials were non-enriched enrolment randomised withdrawal, of short duration, and had high drop-out rates. The outcomes were largely self-reported and subject to inherent biases.

The authors’ conclusion was supported by the results, but the proportion of enriched enrolment randomised withdrawal...
trials was small and the comparisons of opioids with other drugs were based on trials that were not designed to be equivalence trials; caution is advised.

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

**Practice:** The authors stated that patients should be aware of the effects of opioids so that they can make an informed decision about their long-term use.

**Research:** The authors state that more research was needed to determine the usefulness of enriched enrolment randomised withdrawal designs in the administration of opioids for chronic non-cancer pain. There was a need to determine the benefits and harms of long-term opioid use.

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