Opioids for chronic noncancer pain:
a meta-analysis of effectiveness and side effects

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Abstract

Background: Chronic noncancer pain (CNCP) is a major health problem, for which opioids provide one treatment option. However, evidence is needed about side effects, efficacy, and risk of misuse or addiction.

Methods: This meta-analysis was carried out with these objectives: to compare the efficacy of opioids for CNCP with other drugs and placebo; to identify types of CNCP that respond better to opioids; and to determine the most common side effects of opioids. We searched MEDLINE, EMBASE, CENTRAL (up to May 2005) and reference lists for randomized controlled trials of any opioid administered by oral or transdermal routes or rectal suppositories for CNCP (defined as pain for longer than 6 mo). Extracted outcomes included pain, function or side effects. Methodological quality was assessed with the Jadad instrument; analyses were conducted with Revman 4.2.7.

Results: Included were 41 randomized trials involving 6019 patients: 80% of the patients had nociceptive pain (osteoarthritis, rheumatoid arthritis or back pain); 12%, neuropathic pain (postherpetic neuralgia, diabetic neuropathy or phantom limb pain); 7%, fibromyalgia; and 1%, mixed pain. The methodological quality of 87% of the studies was high. The opioids studied were classified as weak (tramadol, propoxyphene, codeine) or strong (morphine, oxycodone). Average duration of treatment was 5 (range 1–16) weeks. Dropout rates averaged 33% in the opioid groups and 38% in the placebo groups. Opioids were more effective than placebo for both pain and functional outcomes in patients with nociceptive or neuropathic pain or fibromyalgia. Strong, but not weak, opioids were significantly superior to naproxen and nortriptyline, and only for pain relief. Among the side effects of opioids, only constipation and nausea were clinically and statistically significant.

Interpretation: Weak and strong opioids outperformed placebo for pain and function in all types of CNCP. Other drugs produced better functional outcomes than opioids, whereas for pain relief they were outperformed only by strong opioids. Despite the relative shortness of the trials, more than one-third of the participants abandoned treatment.

Chronic non–cancer-related pain (CNCP) includes chronic pain of a nociceptive or neuropathic nature with variable influence by psychological and socio-environmental factors. Opioids are the most potent analgesics available and are well established for the treatment of severe acute,[1] surgical[2] and cancer pain.[3] However, their use to ameliorate CNCP is still controversial because of the side effects of opioids, the physical tolerance they build up (with the related withdrawal reactions and possibility of addiction) and anxiety over disapproval by regulatory bodies.[4]

The prevalence of CNCP varies according to the type of pain and the population studied. A study conducted in the United Kingdom in a community in the greater London area to quantify the prevalence of chronic pain found that 46.5% of the general population reported chronic pain; low-back problems and arthritis were the leading causes.[5] A recent epidemiological study in Denmark[6] found that nearly 130 000 adults, corresponding to 3% of the Danish population, regularly used opioids. CNCP had a prevalence of 19%, and 12% of those who had CNCP used opioid medications.

The objectives of this review were 4-fold: to determine the efficacy of opioids for CNCP compared with placebo; to compare the effectiveness of opioids for CNCP with that of other drugs; to identify categories of CNCP with better response to opioids; and to determine the most common side effects and complications of opioid therapy for CNCP, including incidences of opioid addiction and sexual dysfunction.

Methods

We followed the QUOROM guidelines for reporting meta-analyses of randomized controlled trials.[7] We searched the literature up to May 2005 through the OVID interface: MEDLINE (from 1966), EMBASE (from 1988), the Cochrane Database of Systematic Reviews, the Cochrane Controlled Trials Register (CENTRAL), the ACP Journal Club and DARE. We also reviewed the reference lists in the articles, reviews and textbooks retrieved. Our search strategies for MEDLINE and EMBASE are available online as Appendix 1 and Appendix 2, respectively (all appendices for this article are available at www.cmaj.ca/cgi/content/full/174/11/1589/DC1). A single reviewer (J.A.S.) ran the electronic searches and entered the data into Reference Manager 10, removing all duplicates.

Each of 2 independent reviewers (A.D.F., J.A.S.) screened

all titles and abstracts for studies that might meet the following inclusion criteria.

- Study characteristics: randomized controlled trials published in English, French or Spanish (the languages that could be read by the members of our team). Studies published only as abstracts were excluded.
- Study populations: people with CNCP, defined as pain for longer than 6 months, including neuropathic pain, osteoarthritis, rheumatoid arthritis, fibromyalgia, and back and musculoskeletal pain. Migraines, dental pain, abdominal pains (from chronic pancreatitis, kidney stones, etc.) and ischemic pain from vascular disease were excluded because they are usually not classified as CNCP.
- Interventions: any opioid administered via an oral, transdermal or rectal route for 7 days or more. We excluded comparisons of different opioids. We included tramadol, a centrally acting, synthetic opioid analgesic with 2 complementary mechanisms of action: binding of parent and M1 metabolite to μ-opioid receptors and weak inhibition of reuptake of norepinephrine and serotonin.[8,9] In our review we classified the opioids studied as weak (propoxyphene, codeine, tramadol) or strong (oxycodone, morphine).[10]
- Outcomes: the data extracted were those quantifying pain (intensity or relief), function and side effects.

Hard copies of potential studies were retrieved and the same 2 independent reviewers met to reach consensus on the studies to be included. When in doubt, the study authors were contacted; if this was not possible, a third reviewer (A.M.G.) was consulted.

Methodological quality was assessed by the same 2 independent reviewers (unmasked to authors, journals or results), who met to reach consensus. In cases of disagreement, a third reviewer was consulted. We scored the studies from 0 to 5 with the instrument developed by Jadad and colleagues,[11] which has 3 questions about a study's methods of random-

ization and double-blinding, and numbers of withdrawals. Studies scoring 3, 4 or 5 were considered to be of high quality; 0, 1 or 2, of low quality. The sensitivity analysis was repeated, but with the upper limit for low quality changed to 3, to see if this changed the main conclusion.

Meta-analyses were conducted with Revman 4.2.7 software, with standardized mean differences (SMDs) for pain relief and functional outcomes. For side effects, absolute risk differences (RDs) were calculated. Statistical heterogeneity was tested by Q test (χ^2) and reported with the I^2 statistic (in which higher values indicate higher heterogeneity). All meta-analyses were carried out with use of a random effects model. Sensitivity analyses were calculated within subgroups of studies (decided a priori) to assess the robustness of the main conclusions. Cumulative meta-analysis was conducted with STATA. The clinical significance of side effects was considered when the incidence was 10% or higher in the opioid or reference group.

Results

Data was abstracted from 41 randomized trials that met the inclusion criteria (Appendix 3). The characteristics of all the trials included for meta-analysis are summarized in Appendix 4 (www.cmaj.ca/cgi/content/full/174/11/1589/DC1). We found that 90% were either funded by or had 1 or more co-authors affiliated with the pharmaceuticals industry.

Although all trials included were described as randomized, patient assignment was judged adequate to be called random in only 17. The remainder did not report the randomization method, and its adequacy could could not be gauged. Thirty-nine trials were described as double-blinded (the exceptions were Jamison[12] and Gobel[13] and their respective co-investigators); the majority of these (30 trials) were judged as having adequate methods of double-blinding, for example

Table 1: Types and doses of opioid medications and their associated pain diagnoses.

Medication*	Mean dose (range), mg/d		Type of pain diagnosed; no. of trials (patients)				Total no. of trials (patients)
			Nociceptive	Neuropathic	Mixed	Fibromyalgic	
Codeine	120	(20-180)	4 (292)	1 (3)	—	—	5 (295)
Codeine CR	295.4	(100-400)	2 (149)	—	—	—	2 (149)
Dextropropoxyphene	180	—	1 (846)	—	—	—	1 (846)
Morphine	NR	(20-120)	1 (20)	1 (12)	1 (49)	—	3 (81)
Morphine CR	75.5	(15-240)	1 (295)	3 (114)	—	—	4 (409)
Morphine SR	83.5	(20-300)	1 (61)	—	—	—	1 (61)
Oxycodone IR	40.3	(20-60)	1 (107)	—	—	—	1 (107)
Oxycodone CR	38.5	(10-120)	1 (133)	3 (254)	—	—	4 (387)
Oxycodone + morphine SR†	41.1	(2.9-200)	—	—	1 (23)	—	1 (23)
Propoxyphene	260	—	2 (228)	—	—	—	2 (228)
Tramadol	218	(37.5-600)	11 (2711)	4 (338)	—	2 (384)	17 (3433)
Totals			25 (4842)	12 (721)	2 (72)	2 (384)	41 (6019)

Note: CR = controlled release, NR = not reported, SR = sustained release, IR = immediate release.
*Oxycodone and morphine were categorized as strong opioids; the others, as weak opioids.
†Morphine-equivalent doses.

the double-dummy technique, the capsule-in-capsule technique, or just identical appearance of active and control medications. The average dropout rate in the opioid groups was 33%: 15% left because pain relief was inadequate and 21% withdrew because of side effects (some patients dropped out for both reasons). In the control groups, the average dropout rate was 38%: 30% because pain relief was inadequate and 10% because of side effects.

A total of 6019 patients with CNCP were included in this systematic review: 80% classified as having nociceptive pain (osteoarthritis, rheumatoid arthritis and back pain without radiculopathy); 12%, neuropathic pain (including diabetic neuropathy, postherpetic neuralgia, phantom limb pain and regional cervicobrachial pain syndrome); 7%, fibromyalgia; and 1%, mixed nociceptive and neuropathic pain. The average age of the people involved was 58.1 (range 40–71) years; 63% of participants were female and 85%, white.

Table 1 shows the 5 different opioids prescribed in these 41 trials: codeine, morphine, oxycodone, tramadol and propoxyphene. All were administered orally; the range of doses used were reported in all 41 studies; the average dose, only in 28. Trials with parallel groups were longer than those of crossover design (5.6 v. 3.8 weeks, on average). Treatment duration also varied according to type of pain (Table 2): Durations of opioid therapy during the studies of fibromyalgia and mixed types of pain (mean lengths 8.8 and 8.5 weeks, respectively) were about twice as long as those involving patients with nociceptive and neuropathic pain (4.8 and 4.3 weeks, respectively).

Efficacy of opioids compared with placebo

Although we found 30 placebo-controlled trials of opioids for pain relief, only 28 reported data that could be meta-analyzed. Meta-analysis of these 28 studies showed results in favour of opioids (SMD –0.60, 95% confidence interval [CI] –0.69 to –0.50; Appendix 5); the 2 trials not included in the meta-analyses[14,15] also had findings in favour of opioids. The sensitivity analysis (Appendix 6) showed no change in the conclusions with the type of opioid, methodological quality of the study (with cut-off points of either 2 or 3 points) or study design. Only for the patient category of "mixed pain" was the difference between opioids and placebo statistically nonsignificant, and this was a single trial with a small patient sample. Cumulative meta-analysis of these 28 trials (Appendix 7) revealed that the efficacy of opioids compared with placebo reached a stable effect size in 2002; in other words, the additional 8 trials published in 2003 and 2004 did not change the conclusions.

Similarly, the meta-analysis of the 20 trials that had data on functional outcomes showed results in favour of opioids (SMD –0.31, 95% CI –0.41 to –0.22; Appendix 8). The sensitivity analysis (Appendix 6) showed that in all cases the benefit of opioids compared with placebo for functional outcomes was statistically significant except for long-acting morphine, patients with "mixed pain" and "low quality" studies (defined as having 2 or fewer points in the Jadad scale). In these 3 cases, the overall effect was in favour of opioids,

Table 2: Duration of opioid therapy				
	No. of studies	Duration of therapy (wk)		
Diagnosis		Average	Minimum	Maximum
Nociceptive pain	25	4.8	1	13
Neuropathic pain	12	4.4	1	6
Mixed pain	2	8.5	1	16
Fibromyalgia	2	8.8	6	11.5
Total	41	5.0	1	13

but the confidence interval included the null effect. Our cumulative meta-analysis of these 20 trials (Appendix 9, www.cmaj.ca/cgi/content/full/174/11/1589/DC1) corroborated the results of the cumulative meta-analysis of pain-relief outcomes.

Effectiveness of opioids compared with other drugs

Meta-analysis of the 8 trials with suitable data available that compared opioids and other analgesics for pain relief (which are summarized in Appendix 4D) showed that the difference between was statistically nonsignificant (SMD –0.05, 95% CI –0.32 to 0.21; Appendix 10). Sensitivity analysis (Appendix 11) showed that this conclusion did not change with the type of comparison group (nonsteroidal anti-inflammatory drugs [NSAIDs] or tricyclic antidepressants [TCAs]) or with the study's methodological quality (high or low). However, when sensitivity analysis was conducted based on the type of opioids, the strong opioids (oxycodone, morphine) were significantly more effective than other drugs for pain relief (SMD –0.34, 95% CI –0.67 to –0.01). One trial[16] not included in the meta-analysis showed that the addition of codeine to a regimen of acetaminophen was superior to acetaminophen alone at 7 days of follow-up, but not afterward.

For functional outcomes, the other analgesics were significantly more effective than were opioids (SMD 0.16, 95% CI 0.03 to 0.30; Appendix 12, www.cmaj.ca/cgi/content/full/174/11/1589/DC1). This is primarily explained by the findings of 1 study[17] that accounted for 74% of our meta-analysis, in which the authors compared dextropropoxyphene (a weak opioid) with diclofenac. In the other 2 comparisons of tramadol versus diclofenac[18] and controlled-release morphine versus nortriptyline[19], the differences were not statistically significant.

Side effects and other problematic outcomes

There were 6 side effects that occurred significantly more often among those taking opioids than those in the placebo groups: constipation (RD 16%, 95% CI 10%–22%); nausea (RD 15% (11%–19%); dizziness or vertigo (RD 8% (5%–12%); somnolence or drowsiness (RD 9% (5%–13%); vomiting (RD 5% (2%–7%); and dry skin, itching or pruritus (RD 4% (1%–6%). Risk differences for the other side effects noted (diarrhea, appetite loss, abdominal pain, dry mouth, headache,

fatigue, blurred vision or accommodation disturbance, sleeplessness or insomnia, confusion, and sweating) were all statistically nonsignificant.

Compared with other drugs, only 3 side effects occurred significantly more frequently with opioids: the RD for nausea was 14% (95% CI 4%–25%); constipation, 9% (1%–17%); and somnolence or drowsiness, 6% (0–11%). One side effect, diarrhea (RD –2%, 95% CI –3% to 0), occurred less often with opioids than with other drugs. Risk differences for the other 12 side effects (vomiting, dizziness, dry skin, loss of appetite, abdominal pain, dry mouth, headache, fatigue, vision disturbance, insomnia, confusion and sweating) were not statistically significant.

Patients with history of addiction (alcohol or drugs) were excluded from 25 trials.[12,14,18–40] In the others, this information was unreported. With regard to the incidence of opioid addiction developed during the trials, only 3[13,33,41] asked participants about symptoms and signs of addiction. Of these, 2 used indirect questioning; the other[33] inquired if the patients experienced "drug craving," and reported that 8.7% in the morphine and 4.3% in the placebo group developed drug craving.

Only 4 studies[29,32,33,42] inquired about sexual activity by using the Pain Disability Index (PDI). This index consists of 7 self-reported disability subscales, one of which refers to sexual activity; each scale is graded from 0 to 10, where 0 = no disability and 10 = total disability. Only 2 studies give a specific score on sexual activity. In the first,[32] with 46 patients randomly assigned to receive controlled-release codeine or placebo, the score was 4.1 and 6.3, respectively. In the other,[29] which involved 45 patients, the score was 3.4 for controlled-release oxycodone and 4.5 for placebo. Both studies, therefore, suggested that patients taking opioid medications self-reported better sexual function than those taking placebo.

Interpretation

This systematic review demonstrated that, based on the available trials analyzed:

- Opioids were effective in the treatment of CNCP overall; they reduced pain and improved functional outcomes better than placebo.
- Opioids were more effective than placebo for both nociceptive and neuropathic pain syndromes.
- Tramadol reduced pain and improved functional outcomes in patients with fibromyalgia.
- Strong opioids (oxycodone and morphine) were significantly superior, statistically, to naproxen and nortriptyline (respectively) for pain relief but not for functional outcomes.
- Weak opioids (propoxyphene, tramadol and codeine) did not significantly outperform NSAIDs or TCAs for either pain relief or functional outcomes.
- Clinically (> 10%) and statistically, only constipation and nausea were significantly more common with opioids.
- Although recent studies[43,44] have indicated that endocrinological abnormalities and erectile dysfunction can be ex-

perienced by patients taking opioid medication for chronic conditions, most researchers did not ask participants about sexual dysfunction. The few studies in our review that collected such data were relatively short for the observation of any endocrinological abnormalities. The only 2 studies[29,32] that reported data on sexual function showed that patients taking opioids actually perceived themselves as doing better in terms of sexual behaviour compared with those in the control groups. Improvement of well-being secondary to better pain control may account for this result: the PDI is a patient-rated global rating of function and does not measure variables such as libido, sexual dysfunction or gonadal function, and cannot be used to estimate the risk of hypogonadism.

- Addiction or opioid abuse in patients with chronic pain cannot be assumed not to exist (despite popular statements), because the existing randomized trials are not designed to evaluate it; the duration of the trials was too short to allow for the development or detection of aberrant drug use, even if appropriate screening tools for addiction had been used. An adequate measure of "diagnosis of addiction" is also lacking in every study. For example, it is hazardous to equate reported "drug craving" or "reported symptoms and signs of addiction" with addiction. At best, this analysis suggests that only in a minority of comparative trials have investigators even attempted to approach this question. Furthermore, none of the studies have been methodologically sound enough to allow for conclusions about opioid addiction or abuse.

In regard to the contentious issue of whether opioids for pain patients can improve function, this meta-analysis depends on standardized measures of function that were adopted in the respective studies. Such instruments are often self-reported measures, such as the Pain Disability Index. The specific functional change is measured narrowly in terms of the functional measure used. For example, one cannot assume that functional improvement should be interpreted to mean improvement in any and all functions.

Most trials that compare opioids with other drugs were not adequately designed as equivalence or noninferiority trials.[45,46] We therefore have some reservations about declaring any equivalence between opioids and these other drugs. There is a need for well-designed equivalence trials to compare opioids and other drugs.

Chronic pain is a long-term disorder. The studies included in this meta-analysis had various follow-up periods; most trials were not long enough to estimate the duration of efficacy of opioids in chronic pain, the potential for opioid tolerance, or long-range adverse effects such as hypogonadism or opioid abuse.

The majority of the studies included in this review were funded by the pharmaceutical industry. However, there is insufficient information to determine whether or not pharmaceutical-industry funding might introduce publication bias by not publishing small or unfavourable studies.

The results of our review were similar to those of others recently conducted. In 2004, Kalso and colleagues[47] systematically reviewed studies of World Health Organization step 3

opioids for CNCP and found the mean decrease with opioids in pain intensity in most studies to be at least 30%, with comparable effects on neuropathic and musculoskeletal pain. Their review did not include evidence from studies of weak opioids (tramadol or codeine), nor did it assess the effectiveness of opioids compared with other analgesics. A Cochrane systematic review by Duhmke and associates[48] published in 2004 showed that tramadol is an effective treatment for neuropathic pain. Eisenberg and coworkers' 2005 systematic review[49] of 8 randomized controlled trials of opioid agonists (excluding tramadol) for neuropathic pain demonstrated opioid efficacy for spontaneous neuropathic pain with intermediate-term follow-up. Moore and McQuay[50] recently published a systematic review of the side effects of opioids for chronic nonmalignant pain; they found the most common adverse effects to be dry mouth (25%), nausea (21%) and constipation (15%).

Our cumulative meta-analyses for placebo-controlled trials of orally administered opioids in regard to pain relief and functional outcomes showed that additional placebo-controlled trials of these outcomes are desirable only for other-than-oral routes of administration. For example, we found no reports of placebo-controlled trials of transdermal or rectal routes of administration of opioids, nor infusion programs for chronic pain. More refined experimental strategies will be required to assess other outcomes such as opioid abuse or addiction, sexual dysfunction and hypogonadism. Solid conclusions about the relative effectiveness and risk or benefit of opioids compared with other nonopioid drugs are still to be determined in adequately designed equivalence trials. Future trials of opioids for CNCP should consistently have well-defined methods and follow-up periods adequate in length to assess long-term complications such as sexual dysfunction or addiction. More attention should be paid to factors affecting methodological rigour, such as success of blinding, avoidance of dropouts, and adequate intention-to-treat analysis.

This article has been peer reviewed.

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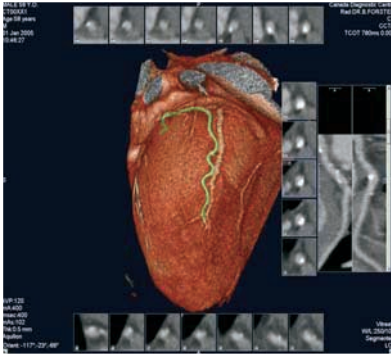
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