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

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BACKGROUND: An enriched enrollment randomized withdrawal (EERW) design excludes potential participants who are nonresponders or who cannot tolerate the experimental drug before random assignment. It is unclear whether EERW design has an influence on the efficacy and safety of opioids for chronic noncancer pain (CNCP).

OBJECTIVES: The primary objective was to compare the results from EERW and non-EERW trials of opioids for CNCP. Secondary objectives were to compare weak versus strong opioids, subgroups of patients with different types of pain, and the efficacy of opiods compared with placebo versus other drugs.

METHODS: MEDLINE, EMBASE and CENTRAL were searched up to July 2009, for randomized controlled trials of any opioid for CNCP. Meta-analyses and meta-regressions were conducted to compare the results. Treatment efficacy was assessed by effect sizes (small, medium and large) and the incidence of adverse effects was assessed by a clinically relevant mean difference of 10% or greater.

RESULTS: Sixty-two randomized trials were included. In 61 trials, the duration was less than 16 weeks. There was no difference in efficacy between EERW and non-EERW trials for both pain (P=0.6) and function (P=0.3). However, EERW trials failed to detect a clinically relevant difference for nausea, vomiting, somnolence, dizziness and dry skin/itching compared with non-EERW. Opioids were more effective than placebo in patients with nociceptive pain (effect size=0.60, 95% CI 0.49 to 0.72) and neuropathic pain (effect size=0.56, 95% CI 0.38 to 0.73).

CONCLUSION: EERW trial designs appear not to bias the results of efficacy, but they underestimate the adverse effects. The present updated meta-analysis shows that weak and strong opioids are effective for CNCP of both nociceptive and neuropathic origin.

Key Words: *Chronic pain; Enriched design; Meta-analysis; Opioids; Systematic review*

Une comparaison entre des essais de retrait aléatoire à recrutement enrichi et non enrichi des opioïdes pour traiter les douleurs chroniques non cancéreuses

HISTORIQUE : Une méthodologie de retrait aléatoire à recrutement enrichi (RARE) exclut les participants potentiels qui ne répondent pas au traitement ou ne peuvent tolérer un médicament expérimental avant son attribution aléatoire. On ne sait pas si une méthodologie de RARE aura une influence sur l'efficacité et l'innocuité des opioïdes dans le traitement des douleurs chroniques non cancéreuses (DCNC).

OBJECTIFS : L'objectif primaire consistait à comparer les résultats des essais de RARE et des essais de retrait aléatoire à recrutement non enrichi (RARNE) des opioïdes pour traiter les DCNC. Les objectifs secondaires consistaient à comparer des opioïdes légers à des opioïdes puissants, des sous-groupes de patients présentant divers types de douleur et l'efficacité des opioïdes par rapport à un placebo et à d'autres médicaments.

MÉTHODOLOGIE : Les auteurs ont effectué des recherches dans MEDLINE, EMBASE et CENTRAL jusqu'en juillet 2009 afin de trouver des essais aléatoires et contrôlés sur tous les types d'opioïdes utilisés pour traiter les DCNC. Ils ont effectué des méta-analyses et des méta-régressions pour comparer les résultats. Ils ont évalué l'efficacité thérapeutique par l'ampleur de l'effet (petite, moyenne ou grande) et l'incidence des effets indésirables au moyen d'une différence moyenne pertinente sur le plan clinique de 10 % ou plus.

RÉSULTATS : Soixante-deux essais aléatoires étaient inclus, dont 61 s'étaient étalés sur moins de 16 semaines. On ne constatait pas de différence d'efficacité entre les essais de RARE et les essais de RARNE, tant pour les la douleur (P=0,6) que pour la fonction (P=0,3). Cependant, les essais de RARE ne permettaient pas de déceler de différence pertinente sur le plan clinique en matière de nausées, de vomissements, de somnolence, d'étourdissements et de sécheresse de la peau ou de démangeaisons par rapport aux essais de RARNE. Les opioïdes étaient plus efficaces qu'un placebo chez les patients ayant des douleurs nociceptives (ampleur de l'effet=0,60, 95 % IC 0,49 à 0,72) et des douleurs névropathiques (ampleur de l'effet=0,56, 95 % IC 0,38 à 0,73).

CONCLUSION : La méthodologie des essais de RARE ne semble pas biaiser les résultats d'efficacité, mais elle sous-estime les effets indésirables. La présente méta-analyse mise à jour démontre que des opioïdes légers et puissants sont efficaces pour traiter les DCNC d'origine nociceptive et névropathique.

An enriched enrollment randomized withdrawal (EERW) study is a type of randomized, controlled trial in which potential participants are assigned to receive the study drug for a period of time in an open-label prerandomization phase. If they benefit from the drug and can tolerate the side effects, they are randomly assigned to continue in the opioid group, or to receive the alternative drug (typically a placebo) (1,2).

This study design has been advocated as useful for studying drugs that provide benefit to only a minority of the people who take it (2). In the case of opioids, it is postulated that only a minority of people can tolerate the adverse effects, and some will not experience analgesic effects because they lack the relevant metabolizing enzymes. However, this type of design may be biased by unblinding of the participants or by provoking withdrawal symptoms that may confound the pain assessments. Moreover, the results of EERW-designed trials do not extrapolate well to more general populations (3).

In 2006, we published a systematic review of opioids for chronic noncancer pain (CNCP) (4). At that time, there were not many EERW trials to make a comparison possible. The primary objective of the present updated review is to compare the results between EERW and non-EERW trials of opioids for CNCP among the randomized trials included in the Canadian guideline for the safe and effective use of opioids for CNCP (5). Another objective is to assess the efficacy of weak versus strong opioids, in subgroups of various types of pain and type of comparison group used in the trials (placebo or other drugs).

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METHODS

Our group published a systematic review with a meta-analysis of randomized trials of opioids for CNCP in 2006 (4). We updated the searches in MEDLINE (1960 to July 2009), EMBASE (1988 to July 2009) and CENTRAL using the OVID interface. We also reviewed the reference lists in the retrieved articles, reviews and textbooks. Search strategies used for MEDLINE and EMBASE were the same as those used in the original meta-analysis (Appendix 1 and 2, respectively) One reviewer (EI) conducted the electronic searches and entered the data into Reference Manager 11 (Thomson Reuters, USA), removing all duplicates.

Two independent reviewers (AF and LC) screened all titles and abstracts for potential studies meeting the following inclusion criteria:

- Study characteristics: Randomized controlled trials in humans published in languages that could be read by members of our team, ie, English, French, Portuguese or Spanish. Studies published only as abstracts were excluded.
- Population: CNCP defined as pain lasting more than six months including neuropathic pain conditions, nociceptive pain (osteoarthritis, rheumatoid arthritis, back and musculoskeletal pain) and fibromyalgia (considered to be a functional pain syndrome). We excluded migraines, dental pain, ischemic pain due to vascular disease and abdominal pain (ie, chronic pancreatitis, kidney stones, etc) because these entities are usually not classified as CNCP.
- Interventions: Any trial in which the opioid was given via the oral, transdermal, transmucosal or rectal route for at least seven days. We excluded head-to-head comparisons between opioids. In the present review, we classified the potency of opioids as weak (propoxyphene, codeine, tramadol and hydrocodone) or strong (oxycodone, morphine, oxymorphone, fentanyl and buprenorphine) (6).
- Outcomes: Only pain (intensity or pain relief), function and side effects were obtained. Examples of functional outcomes that could be extracted are the following: Brief Pain Inventory; Fibromyalgia Impact Questionnaire; Multidimensional Pain Inventory (physical function); Neck Disability Index; Oswestry Disability Index; Nottingham Health Profile; Pain Disability Index, Physical Disability; Roland Disability Questionnaire, Short Form (SF)-36 or SF-12 (physical functional scale); and Western Ontario and McMaster Universities Arthritis Index (WOMAC).

Hard copies of potential studies were retrieved and assessed for inclusion and risk of bias. Two independent reviewers (AF and LC) met to reach consensus on the included studies and risk of bias. When in doubt, a third reviewer was consulted (AMG). When we needed more information that was not reported in a particular trial, we contacted the corresponding author of that study.

The risk of bias in each trial was assessed using the six domains recommended by the Cochrane Collaboration (Appendix 3): sequence generation, allocation concealment, blinding, incomplete outcome data, selective outcome reporting and other sources of biases (7). Under 'other sources of bias', we included information about whether there was a relationship with the pharmaceutical industry. We extracted the following information about the relationship with the pharmaceutical industry: author affiliation with industry, funding of study by industry, industry providing the study drug or statistical analysis performed by an industry-affiliated statistician. In case of affirmative response to any of these questions, we concluded that there was a relationship with the pharmaceutical industry and a potential to introduce bias.

Meta-analyses and meta-regressions were conducted using Comprehensive Meta Analysis (Biostat, USA) software, with the standardized mean difference being the 'effect size' (ES) for pain and functional outcomes. The ES were classified into small (≤0.5), medium (0.5 to <0.8) and large (≥0.8) as suggested by Cohen (8). For side effects, all meta-analyses were conducted using Revman 5 (Cochrane IMS, USA) using risk differences. Statistical heterogeneity was tested by Q test (χ^2) reported as I^2 (higher values indicate higher heterogeneity). A clinically relevant difference of side effects was defined when the incidence was at least 10% higher in the opioid group compared with the control group (4). All meta-analyses were conducted using a random-effects model, and meta-regression was conducted using a fixed-effects model.

Subgroups were decided a priori to assess the variations in ES: weak versus strong opioids group; etiology of pain group: nociceptive, neuropathic, fibromyalgia and mixed; and comparison group: placebo and other drugs. In the present review, weak opioids were propoxyphene, codeine, tramadol and hydrocodone, and strong opioids were oxycodone, morphine, oxymorphone, fentanyl and buprenorphine (6).

RESULTS

There were 41 randomized trials included in the 2006 meta-analysis (4). The updated literature searches added 21 new trials. We found one case of triplicate publication about the same trial (9-11). A total of 62 randomized trials were included in this update (9,12-72). Table 1 shows the characteristics of all included trials. Some trials are shown twice because they have multiple arms and comparisons. There were nine different opioids prescribed in these 62 trials: tramadol, codeine, propoxyphene, morphine, oxycodone, oxymorphone, methadone, transdermal buprenorphine and transdermal fentanyl.

All included trials were described as randomized; however, only 32 (51.6%) were judged to be adequate. All but two trials (28,33) were described as double-blinded, but only 40 trials were judged as having adequate methods of double-blinding; for example, double-dummy technique, capsule-in-capsule technique, or identical appearance of active and control medications. Two trials (32,34) stated that the outcomes assessors were supposed to be blinded, but they were able to recognize the allocation of the treatments.

A total of 11,927 patients were randomized, but only 7807 participants finished the trials (4120 dropouts). In the opioid group, the average dropout rate was 35%; 15% of the participants dropped out due to inadequate pain relief and 21% due to side effects (some patients dropped out for both reasons). In the control groups, the average dropout rate was 38% (with 30% of the dropouts due to inadequate pain relief and 10% due to side effects).

Forty-one trials had at least one author who was affiliated with the pharmaceutical industry. Ten trials were clearly not funded by pharmaceutical companies, five did not report any information about funding, and the remaining 47 were funded by the industry. In 47 trials, the drug was provided by the industry, in nine trials it was not, and this information was not reported in the remaining five trials. The statistical analysis was performed by an industry-affiliated statistician in nine trials, by someone not affiliated with the industry in 10 trials, and this was not reported in the remaining 43 trials. When the above information was combined, 54 of the 62 trials (87%) had some type of relationship with the pharmaceutical industry.

The study duration was shorter than six weeks in 46 trials (74%), between 11 and 16 weeks in 15 trials (24%) and 24 weeks in one trial (2%).

Regarding the CNCP diagnoses, 87.1% were classified as nociceptive pain (osteoarthritis, rheumatoid arthritis and back pain without radiculopathy), 9.2% as neuropathic pain (diabetic neuropathy, postherpetic neuralgia, phantom limb pain, 'neuropathic pain' and regional cervicobrachial pain syndrome), 3.2% as fibromyalgia and 0.41% as mixed nociceptive and neuropathic pain. The average age of the included population was 58.1 years (range 40 to 71 years); 63% were female and 85% were white.

Efficacy of opioids compared with placebo (Table 2)

Opioids were compared with placebo in 47 trials. Pain was assessed in all trials, and function in 31 trials. The results showed a medium ES in favour of opioids for pain (ES=0.58, 95% CI 0.48 to 0.67) and a small ES for function (ES=0.34, 95% CI 0.25 to 0.43).

TABLE 1
Characteristics of the 62 randomized trials included in the present updated systematic review (grouped by type of opioid)

Reference, year Country, design	Population type; Randomized, n (dropouts, n)	Interventions and comparison groups	Outcomes: Primary and secondary	Results (as reported in the studies)
Placebo-controlled (neuropathic pain)				
Harati et al (30), 1998 USA, parallel (non-EERW)	Diabetic neuropathy; 131 (49)	Tramadol 50–400 mg/d for 6 wks	**Primary:** Pain intensity* (5-point Likert scale) **Secondary:** Pain relief, quality of life (Medical Outcomes Study): physical functioning*, social functioning, current health perception, psychological distress, overall role functioning, and the two overall sleep problem indexes and sleep subscales	Tramadol, at an average dose of 210 mg/d, was significantly more effective than placebo. Patients on tramadol scored significantly better in physical and social functioning
Sindrup et al (64), 1999 Germany, crossover (non-EERW)	Polyneuropathy; 45 (11)	Tramadol 200–400 mg/d for 4 wks	**Primary:** Pain ratings* (0–10 NRS), paraesthesia and touch-evoked pain **Secondary:** Dynamic allodynia, rescue medication, patient's preference	Pain, paraesthesia, touch-evoked pain and allodynia were lower on tramadol than on placebo. NNT to obtain one patient with ≥50% pain relief was 4.3 (95% CI 2.4 to 20)
Boureau et al (17), 2003 France, parallel (non-EERW)	Postherpetic neuralgia; 127 (19)	Tramadol 100–400 mg/d for 6 wks	**Primary:** Pain intensity (100 mm VAS* and 5-point NRS) **Secondary:** Global improvement, quality of life (Nottingham scale) and rescue medication (paracetamol)	Mean pain intensity was significantly lower with tramadol in both per protocol and intention-to-treat populations. No significant difference was found between groups in pain intensity on a 5-point verbal scale or in quality-of-life measurement
Norrbrink and Lundeberg (46), 2009 Sweden, parallel (non-EERW)	Spinal cord injury with neuropathic pain at or below level >6 months; 35 (13)	Tramadol 50 mg tid – 400 mg/day for 4 wks	**Primary:** Present, general and worst pain. MPI subscale pain severity. Patient global impression of change **Secondary:** Anxiety, global life satisfaction and sleep quality	Significant differences in present pain, general pain and worst pain, as well as MPI favouring tramadol. Seven patients on active drug (30%) rated an improvement, but only 4 (17%) rated their pain to be much improved. One patient in the placebo group reported minimal improvement (8%). No patients in either group reported their pain to be very much improved
Watson and Babul (69), 1998 Canada, crossover (non-EERW)	Postherpetic neuralgia; 50 (12)	CR oxycodone 20–60 mg/d (mean 45 mg/d) for 4 wks	**Primary:** Pain intensity (100 mm VAS* and 5-point categorical scale) **Secondary:** Pain relief, steady pain, brief pain, skin pain, disability* (using a categorical scale: 0 = no disability, 3 = severe disability), BDI, POMS	Oxycodone was significantly better for pain relief, reductions in steady pain, allodynia, paroxysmal spontaneous pain, global effectiveness, disability and masked preference
Watson et al (68), 2003 Canada, crossover (non-EERW)	Diabetic neuropathy; 45 (3)	CR oxycodone 20–80 mg/d (mean 40 mg/d) for 4 wks	**Primary:** Pain intensity (100 mm VAS* and 5-point categorical scale) **Secondary:** Pain relief, steady pain, brief pain, skin pain, PDI*, SF-36, pain and sleep questionnaires	Oxycodone was significantly better for daily pain, steady pain, brief pain, skin pain, total pain and disability. NNT to obtain 1 patient with at least 50% pain relief was 2.6
Gimbel et al (26), 2003 USA, parallel (non-EERW)	Diabetic neuropathy; 159 (44)	CR oxycodone 20–120 mg/d (mean 37 mg/d) for 6 wks	**Primary:** Pain intensity* (0–10 NRS) **Secondary:** Current and worse pain, satisfaction, BPI* (physical function score), SF-36	Oxycodone provided more analgesia than placebo in the intention-to-treat cohort
Huse et al (32), 2001 Germany, crossover (non-EERW)	Phantom limb pain; 12 (3)	SR morphine 70–300 mg/d (mean 120 mg/d) for 4 wks	**Primary:** Pain intensity* (2 cm VAS) **Secondary:** PES, SDS, PRSS, WHYMPI, BSS	Based on pain diary data, 42% of patients on morphine showed a pain reduction of more than 50% compared with only 1 patient in the placebo group
Harke et al (31), 2001 Germany, parallel (non-EERW)	Peripheral neuropathy; 38 (3)	SR morphine 90 mg/d for 1 wk	Pain intensity* (0–10 numeric analogue scale), and reactivation of their spinal cord stimulator	The differences between morphine and placebo were not significant
Wu et al (71), 2008 USA, crossover (non-EERW)	Postamputation pain 60 (25)	SR morphine 15–180 mg/d for 6 wks	**Primary:** Average change in overall pain intensity from baseline to the final week of maintenance therapy using 0–10 NRS **Secondary:** Pain relief (0–100%) and the interference and general activity subscales from the MPI. Side effects	Morphine provided lower pain scores compared with placebo. The mean per cent pain relief during treatment with placebo and morphine was 19% and 53%, respectively. NNT to obtain 50% and 33% decreases in pain intensity with morphine were 5.6 and 4.5, respectively

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TABLE 1 – CONTINUED
Characteristics of the 62 randomized trials included in the present updated systematic review (grouped by type of opioid)

Reference, year Country, design	Population type; Randomized, n (dropouts, n)	Interventions and comparison groups	Outcomes: Primary and secondary	Results (as reported in the studies)
Placebo-controlled (neuropathic pain)				
Raja et al (52), 2002 USA, crossover (non-EERW)	Postherpetic neuralgia; 76 (32)	CR morphine 15–240 mg/d (mean 91 mg/d) for 6 wks or methadone 15 mg/d	**Primary:** Pain intensity* (0–10 NRS) **Secondary:** Pain relief, cognitive function, MPI* (physical functioning subscale), sleep, mood, global preference	Morphine reduced pain (1.9) more than placebo (0.2). Pain relief was greater with morphine (38%) compared with placebo (11%)
Gilron et al (25), 2005 Canada, crossover (non-EERW)	35 diabetic neuropathy and 22 postherpetic neuralgia; 57 (16)	A. SR morphine maximum tolerated for 5 wks B. SR morphine maximum tolerated combined with gabapentin for 5 wks C. Gabapentin maximum tolerated for 5 wks	**Primary:** Pain intensity* (0–10 NRS) **Secondary:** SF-MPQ, maximal tolerated doses, mood (BDI), SF-36 (physical function*), mental status (Mini-Mental) and global pain relief	Mean pain intensity at the maximal tolerated dose was 4.49 with placebo, 4.15 with gabapentin, 3.7 with morphine and 3.06 with gabapentin-morphine combination. Total scores in SF-36 were lower with gabapentin-morphine combination than with placebo or each drug alone
Khoromi et al (34), 2007 USA, crossover (non-EERW)	Chronic lumbar radiculopathy (sciatica); 55 (27)	A. SR morphine 15–90 mg/d B. Nortriptyline 25–100 mg/d C. Combination of each phase: 5+2+2 wks	**Primary:** Average leg pain during the 2 wks* **Secondary:** Global pain relief, ODI*, BDI and SF-36	None of the treatments produced significant reductions in average leg pain, or other leg or back pain scores
Simpson et al (63), 2007 USA, crossover (EERW)	Acute-on-chronic pain; 79 (4)	Fentanyl buccal tablet 100–800 µg Duration: 9 episodes or 21 days	**Primary:** Sum of pain intensity differences (0–10 NRS) in the first 60 min (SPID-60) **Secondary:** Proportion of breakthrough episodes with 33% and 50% improvement; time to significant pain relief, pain intensity differences, proportion of episodes with meaningful pain relief and proportion of episodes that required supplemental medication	SPID-60 was significantly greater for breakthrough pain episodes treated with fentanyl buccal tablets compared with those in which placebo was administered
Placebo-controlled (nociceptive pain)				
Roth (54), 1998 USA, parallel (EERW)	Osteoarthritis (not specified); 42 (8)	Tramadol 200–400 mg/d for 2 wks	**Primary:** Time to exit from the study due to therapeutic failure **Secondary:** Severity of pain* (0–3 numeric scale), ability to perform activities	Time to exit from the study because of insufficient pain relief was longer in the tramadol group. Pain at rest and severity of pain on motion were lower in the tramadol group. No differences were noted in general severity of current pain and on disability to perform ADLs
Silverfield et al (62), 2002 USA, parallel (non-EERW)	Osteoarthritis (not specified); 308 (68)	Tramadol 37.5–70 mg/d + acetaminophen 325–650 mg/d for 1.5 wks	**Primary:** Pain intensity* (0–3 numeric scale), pain relief **Secondary:** SPID, WOMAC* (physical function subscale)	The addition of tramadol/acetaminophen to NSAID or COX-2 selective inhibitor therapy was effective in the treatment of osteoarthritis flare pain
Emkey et al (22), 2004 USA, parallel (non-EERW)	Osteoarthritis (not specified); 307 (80)	Tramadol 37.5–300 mg/d + acetaminophen 325–2600 mg/d for 13 wks	**Primary:** Pain intensity* (100 mm VAS) **Secondary:** Pain relief, WOMAC* (physical function subscale), SF-36 survey	Mean final VAS scores, mean final pain relief rating scores, WOMAC physical function and SF-36 role-physical measures were all significantly better with tramadol/acetaminophen than with placebo
Fleischmann et al (23), 2001 USA, parallel (non-EERW)	Osteoarthritis knee; 129 (93)	Tramadol 50–400 mg/d for 12 wks	**Primary:** Pain intensity* (0–4 Likert scale) **Secondary:** Pain relief, WOMAC* (overall), global assessment, time to failure	Mean final pain intensity score, and all secondary outcomes were significantly better in the tramadol group than in the placebo group
Babul et al (13), 2004 USA, parallel (non-EERW)	Osteoarthritis knee; 246 (122)	CR tramadol 100–400 mg/d for 11 wks	**Primary:** Pain intensity* (100 mm VAS) **Secondary:** WOMAC* (physical function subscale), CSPI	Tramadol resulted in significant improvements in pain, stiffness, physical function, global status and sleep
Ruoff (55), 1999 USA, parallel (non-EERW)	Chronic joint pain; 465 (113)	A. Tramadol starting at 200 mg/d B. Tramadol starting at 50 mg/d and reaching 200 mg/d on day 4 C. Tramadol starting at 50 mg/d and reaching 200 mg/d on day 10 Duration of treatment: 2 wks	**Primary:** Discontinuation due to adverse effect or ineffectiveness	40 patients (30.8% of group taking 200 mg/d from day 1) reached the primary end point; 31 patients (24.0% from day 4); 20 patients (15.2% from day 10); and 3 patients (4.4% of placebo group)

TABLE 1 – CONTINUED
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Placebo-controlled (nociceptive pain)				
Schnitzer et al (60), 1999 USA, parallel (EERW)	Osteoarthritis knee; 240 (4)	Tramadol 200 mg/d + naproxen 750 mg/d reduced by 250 mg/d every 2 wks Duration total: 8 wks	**Primary:** Minimum effective naproxen dose	The addition of tramadol enabled a significant reduction in the dosage of naproxen without compromising pain relief
Schnitzer et al (59), 2000 USA, parallel (EERW)	Low-back pain; 254 (22)	Tramadol 200–400 mg/d (mean 242 mg/d) for 4 wks	**Primary:** Time to exit the double-blind trial **Secondary:** Pain intensity* (10 cm VAS), pain relief, SF-MPQ, RDQ*	Discontinuation rate due to therapeutic failure was 20.7% in the tramadol group and 51.3% in the placebo group. Pain scores, SF-MPQ and RDQ were significantly better in the tramadol group
Ruoff et al (56), 2003 USA, parallel (non-EERW)	Low-back pain; 322 (157)	Tramadol 37.5–300 mg/d (mean 157.5 mg/d) + acetaminophen 325–2600 mg/d for 13 wks	**Primary:** Pain intensity* (100 mm VAS) **Secondary:** PRRS, SF-MPQ, RDQ*, SF-36	Pain intensity, final PRRS scores, RDQ scores and many subscales of SF-MPQ and SF-36 were significantly better with tramadol than with placebo
Peloso et al (49), 2004 Canada, parallel (non-EERW)	Low-back pain; 338 (191)	Tramadol 37.5–300 mg/d (mean 158 mg/d) + acetaminophen 325–2600 mg/d for 91 days	**Primary:** Pain intensity* (100 mm VAS) **Secondary:** PRRS, SF-MPQ, SF-36, RDQ*, overall medication assessment	VAS, pain relief scores, RDQ, physical-related subcategories of MPQ and SF-36 were significantly better for tramadol/ acetaminophen than for placebo. More patients rated tramadol/acetaminophen as 'very good' or 'good' compared with placebo
Vorsanger et al (67), 2008 USA and Canada, parallel (EERW)	Chronic low-back pain; 386 (145)	A. CR tramadol 300 mg/d* for 12 wks B. CR tramadol 200 mg/d for 12 wks	**Primary:** Pain intensity VAS since the previous visit **Secondary:** Current pain intensity VAS*, global assessment of study medication, Roland Disability Index*, and overall sleep quality	The placebo group had greater mean deterioration for pain intensity since the previous visit (+12.2 mm) compared with patients who continued to receive tramadol 300 mg (+5.2 mm) and patients whose tramadol dose was reduced to 200 mg (+7.8 mm). There were better responses in the tramadol groups versus placebo for the secondary variables
Burch et al (18), 2007 Canada, parallel (EERW)	Osteoarthritis knee; 646 (155)	Tramadol (200–300 mg/d) for 12 wks	**Primary**: Pain intensity (11-point NRS)* **Secondary:** Patient and physician global impression of change	The absolute mean (± SD) reduction in pain intensity in the tramadol group was 3.0±2.1. There was a statistically significant difference from placebo
Kosinski et al (9), 2007; Gana et al (10), 2006; Schein et al (11), 2008 USA, parallel (non-EERW)	Osteoarthritis (knee or hip), ACR functional class I-III; 1020 (462)	A. ER tramadol 100 mg/d for 12 wks B. ER tramadol 200 mg/d for 12 wks C. ER tramadol 300 mg/d for 12 wks D. ER tramadol 400 mg/d for 12 wks	**Primary:** Pain intensity (100 mm VAS)* **Secondary:** Chronic pain sleep inventory	Mean pain reduction at 12 wks was –0.4 mm and –21.5 mm for tramadol ER and placebo, respectively (P<0.001)
Lee et al (39), 2006 Korea, parallel (non-EERW)	Rheumatoid arthritis pain inadequately controlled by NSAIDs and DMARD; 277 (10)	Tramadol 37.5 mg/d plus acetaminophen 325 mg/d for 1 wk	**Primary:** Mean daily pain relief score on a 6-point scale **Secondary:** Mean daily pain intensity (100 mm VAS)*, pain intensity at day 7, subjects' and investigators' mean overall assessment, physical function* (Health Assessment Questionnaire)	Pain relief scores and pain intensity scores were significantly better in the tramadol/ acetaminophen group than in the placebo group. Physical function did not differ significantly between tramadol/ acetaminophen and placebo
Thorne et al (65), 2008 Canada, crossover (non-EERW)	Osteoarthritis knee or hip; 100 (25)	CR tramadol: 150–300 mg for 8 wks	**Primary:** Daily diary pain intensity score* **Secondary:** WOMAC pain and physical function*	Tramadol resulted in significantly lower pain intensity (37.4±23.9) compared with placebo (45.1±24.3). WOMAC index subscale score for pain and physical function were significantly better with tramadol than with placebo
Boureau and Boccard (16), 1991 France, parallel (non-EERW)	Rheumatoid arthritis; 40 (2)	Codeine 90 mg/d + acetaminophen 1500 mg/d for 1 wk	**Primary:** Pain intensity (100 mm VAS* and 5-point Likert scale) **Secondary:** Pain relief, activity, sleep, overall efficacy	Analgesic efficacy was significantly better with codeine/acetaminophen than with placebo for all criteria except the number of awakenings

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Reference, year Country, design	Population type; Randomized, n (dropouts, n)	Interventions and comparison groups	Outcomes: Primary and secondary	Results (as reported in the studies)
Placebo-controlled (nociceptive pain)				
Arkinstall et al (12), 1995 Canada, crossover (non-EERW)	Mixed nociceptive; 46 (16)	CR codeine 200–400 mg/d for 1 wk	**Primary:** Pain intensity (100 mm VAS* and 5-point categorical scale) **Secondary:** Rescue acetaminophen + codeine consumption, PDI* and patients' and investigators' treatment preferences	The codeine group was significantly better on overall pain intensity (35±18) than placebo (49±16), and on categorical pain intensity and pain scores according to day and time of day. Daily rescue analgesic consumption was lower in the codeine group. Disability was lower in the codeine group compared with placebo
Peloso et al (50), 2000 Canada, parallel (non-EERW)	Osteoarthritis hip or knee; 103 (37)	CR codeine 100–400 mg/d for 4 wks	**Primary:** WOMAC – pain intensity* (0–500 VAS) **Secondary:** WOMAC* (stiffness and physical function), sleep, global assessment	All variables in the efficacy analysis indicated superiority of codeine over placebo. The WOMAC improved 44.8% over baseline in the codeine group compared with 12.3% in the placebo group
Roth et al (53), 2000 USA, parallel (non-EERW)	Osteoarthritis; 133 (70)	A. CR oxycodone 20 mg/d for 2 wks* B. CR oxycodone 40 mg/d for 2 wks	**Primary:** Pain intensity* (4-point NRS) **Secondary:** Quality of sleep, BPI, interference of pain on key functional activities	Oxycodone was superior to placebo in reducing pain intensity and the interference of pain with mood, sleep and enjoyment of life
Caldwell et al (20), 1999 USA, parallel (EERW)	Osteoarthritis; 107 (36)	A. IR oxycodone 20 mg/d + acetaminophen 1300 mg/d for 4 wks* B. CR oxycodone 20 mg/d for 4 wks	**Primary:** Pain intensity* (4-point NRS) **Secondary:** Global measure of sleep	Pain intensity and quality of sleep were significantly improved in both active groups compared with the placebo group
Webster et al (70), 2006 USA, parallel (non-EERW)	Low-back pain; 719 (391)	A. Oxycodone 10–80 mg/d once daily* B. Oxycodone 10–80 mg/d + ultra-low dose naltrexone once daily C. Oxycodone 10–80 mg/d + ultra-low dose naltrexone twice daily Duration: 12 wks	**Primary:** 11-point numerical diary pain intensity scale* **Secondary:** SF-12, ODI*, quality of analgesia, global assessment of study drug	All active treatment groups were significantly better than placebo on measures of pain reduction, physical component score of the SF-12 and ODI
Markenson et al (42), 2005 USA, parallel (non-EERW)	Osteoarthritis; 109 (73)	CR oxycodone 10–120 mg/d (mean 57 mg/d) for 12 wks	**Primary:** BPI average pain intensity*, WOMAC scores at days 30 and 60, the number of patients who discontinued the study due to inadequate pain control **Secondary:** BPI (pain interference and function), WOMAC, PGI, time to stable dosing, percentage of patients achieving stable dosing within 30 days, average daily dose at completion of initial titration, patient satisfaction, average and current pain intensity from pain diaries	Oxycodone was significantly superior to placebo in decreasing average pain intensity and in reducing pain-induced interference with general activity, walking ability (except at day 30) and normal work, as well as mood, sleep, relations with people (at days 60 and 90) and enjoyment in life. Daily functioning, as measured by WOMAC, was also significantly improved in the oxycodone group. In the placebo group, a significantly greater percentage of patients discontinued due to inadequate pain control
Chindalore et al (21), 2005 USA, parallel (non-EERW)	Osteoarthritis hip and knee; 362 (121)	A. Oxycodone 10 mg qid* B. Oxycodone 10 mg plus ultra-low dose naltrexone 0.001 mg qid C. Oxycodone 20 mg plus ultra-low dose naltrexone 0.001 mg bid Duration: 3 wks	**Primary:** Pain intensity measured by 11-point NRS* **Secondary:** Quality of analgesia, pain control, global assessment of study drug, SF-12, WOMAC	Although oxycodone was significantly better than placebo at wk 1, this treatment was not different from placebo at later time points. Oxycodone was significantly better than placebo on the pain subscale, the physical function scale and the WOMAC total score, but at wk 1 only
Ma et al (40), 2008 China, parallel (non-EERW)	Chronic neck pain with acute flare-ups; 116 (0 on day 7)	CR oxycodone 5–10 mg bid for 4 wks	**Primary and secondary:** Frequency of pain episodes, pain intensity* (VAS), quality of life (QOL)*, quality of sleep (QOS), side effects, withdrawal symptoms, SF-36, performance status, patient satisfaction	Results were extracted for the 7-day measurement. The frequency of pain episodes and VAS were decreased significantly with oxycodone. Improvements in QOL and QOS were significant on day 3 after treatment with oxycodone. Most domains of SF-36 were improved in the treated patients at end of study

TABLE 1 – CONTINUED
Characteristics of the 62 randomized trials included in the present updated systematic review (grouped by type of opioid)

Reference, year Country, design	Population type; Randomized, n (dropouts, n)	Interventions and comparison groups	Outcomes: Primary and secondary	Results (as reported in the studies)
Placebo-controlled (nociceptive pain)				
Caldwell et al (19), 2002 USA, parallel (non-EERW)	Osteoarthritis hip and/or knee; 295 (111)	A. ER morphine 30 mg/d (morning) for 4 wks* B. ER morphine 30 mg/d (evening) for 4 wks C. CR morphine 15 mg twice/d for 4 wks	**Primary:** WOMAC osteoarthritis index pain (0–500) and overall arthritis pain intensity* (0–100) **Secondary:** WOMAC stiffness and physical function* (0–1700)	Morphine once daily and morphine twice daily both reduced pain and improved several sleep measures compared with placebo. Analgesic efficacy was comparable between once daily and twice daily formulations
Moran (44), 1991 United Kingdom, crossover (non-EERW)	Rheumatoid arthritis; 20 (16)	CR morphine 20–120 mg/d for 2 wks	**Primary:** Pain intensity* (100 mm VAS) **Secondary:** Fries Index Health Assessment Questionnaire*, RS, GSS	Although only 4 patients completed the study, results showed a significant improvement in pain in those taking morphine
Moulin et al (45), 1996 Canada, crossover (non-EERW)	Musculoskeletal pain; 61 (18)	SR morphine 30–120 mg/d (mean 83.5 mg/d) for 6 wks	**Primary:** Pain intensity* (10 cm VAS) **Secondary:** Pain relief, MPQ, drug liking, rescue medication, SCL-90, POMS, SIP, PDI*, HSCS, patient's preferences	On VAS of pain, the morphine group showed a reduction in pain intensity relative to placebo in period I, and this group also fared better in a crossover analysis of the sum of pain intensity differences from baseline. No other significant differences were detected
Hale et al (29), 2007 USA, parallel (EERW)	Low-back pain; 143 (76)	ER oxymorphone 20–260 mg/d (mean 87.2 mg/d, median 60 mg/d) for 12 wks	**Primary:** Change in average pain intensity (VAS) from baseline to final study visit* **Secondary:** 24 h pain intensity, use of medication, patients' and physicians' overall satisfaction	Pain intensity increased significantly more for patients randomly assigned to placebo than for patients who continued their stabilized dose of oxymorphone. The increase from baseline to final visit was 31.6 mm with placebo and 8.7 mm with oxymorphone
Matsumoto et al (43), 2005 USA, parallel (non-EERW)	Osteoarthritis; 491 (222)	A. ER oxymorphone 40 mg bid* B. ER oxymorphone 20 mg bid C. CR oxycodone 20 mg bid Duration: 4 wks	**Primary:** Pain intensity (VAS) at wk 3 **Secondary:** Pain intensity from pain diary at wk 4*, WOMAC, patient and physician global assessments, dropouts due to lack of analgesia, sleep assessment, quality of life physical* and mental components (SF-36)	The primary end point showed a significant difference in favour of oxymorphone over placebo. Compared with placebo, both oxymorphone 20 mg and 40 mg produced greater reductions in the WOMAC subscales at wks 3 and 4
Kivitz et al (35), 2006 USA, parallel (non-EERW)	Osteoarthritis hip or knee; 370 (172)	A. ER oxymorphone 10 mg bid for 2 wks B. ER oxymorphone 20 mg bid for 1 wk, then 40 mg bid for 1 wk C. ER oxymorphone 20 mg bid for 1 wk, then 50 mg bid for 1 wk*	**Primary:** Arthritis pain intensity from VAS at wks 1 and 2* **Secondary:** WOMAC*, SF-36, Chronic Pain Sleep Inventory (CPSI), vital signs, clinical laboratory parameters and adverse events	Oxymorphone ER administered twice daily for 2 wks produced dose-related reductions in arthritis pain intensity and improvements in physical function
Zautra et al (72), 2005 USA, parallel (non-EERW)	Moderate to severe pain due to osteoarthritis; 107 (71)	A. CR oxycodone 10 mg bid for 2 wks They reported the results at 2 wks, but the study lasted for 3 months	**Primary:** Average 24 h pain rating* (average of 12 daily reports was used for the 2 wks post-test score on pain) **Secondary:** Positive and negative Watson's scale for affect. Vanderbilt multidimensional pain coping inventory. Coping efficacy and arthritis helplessness	Oxycodone administered twice daily for 2 wks demonstrated a significant reduction not only in 24 h pain intensity, but also in the other variables (coping and affect) favouring the active group A significant dropout rate was observed (75% and 59% in the placebo and active groups, respectively)
Portenoy et al (51), 2007 USA, parallel (EERW)	Acute on chronic low-back pain; 77 (3)	Fentanyl buccal tablets, maximum dose 800 µg per episode Duration: 3 wks	**Primary:** Electronic pain diary, 0–120 min after pain crisis. SPID-60 was the sum of pain intensity differences for the first 60 min **Secondary:** Proportion of breakthrough pain episodes with improvement >33% and 50%, pain relief at each post-treatment time point, proportion of episodes in which meaningful pain relief was obtained, time to meaningful pain relief, and proportion of episodes that required the use of supplemental medication	SPID-60 was significantly better in the fentanyl group. All secondary measures also favoured fentanyl

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TABLE 1 – CONTINUED
Characteristics of the 62 randomized trials included in the present updated systematic review (grouped by type of opioid)

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Placebo-controlled (nociceptive pain)				
Langford et al (38), 2006 Multicentre in Europe, parallel (non-EERW)	Osteoarthritis hip and knee. Moderate to severe pain; 416 (217)	Transdermal fentanyl (TDF) (25–100 µg) for 6 wks	**Primary:** Pain relief* (average AUC of the VAS scores over time) **Secondary:** WOMAC* score and its components	Transdermal fentanyl provided significantly better pain relief than placebo, as demonstrated by the primary AUC for VAS scores: –20 in the TDF group versus –14.6 in the placebo group. TDF was also associated with significantly better overall WOMAC scores and pain scores
Landau et al (37), 2007 UK and USA, parallel (EERW)	Noncancer pain (49% low back); 267 (12)	Buprenorphine transdermal (5–20 mg) for 2 wks	**Primary:** Proportion of subjects with ineffective treatment* **Secondary:** Time to ineffective treatment, proportion of subjects who reached ineffective treatment or discontinued for any reason, amount of escape medication used	The proportion with ineffective treatment was lower in the buprenorphine group than in the placebo group (51.2% versus 65%). The odds of ineffective treatment were 1.79 times greater for placebo than for buprenorphine
Placebo-controlled (fibromyalgia pain)				
Russell et al (57), 2000 USA, parallel (EERW)	Fibromyalgia; 69 (1)	Tramadol 50–400 mg/d for 6 wks	**Primary:** Number of patients exiting due to inadequate pain relief **Secondary:** Pain intensity* (10 cm VAS), pain relief, tender-point count, myalgic score, FMIQ* (0–100)	20 (57.1%) patients in the tramadol group successfully completed the double-blind phase compared with 9 (27%) in the placebo group
Bennett et al (15), 2003 USA, parallel (non-EERW)	Fibromyalgia; 315 (177)	Tramadol 37.5–300 mg/d + acetaminophen 325–2600 mg/d for 11.5 wks	**Primary:** Cumulative time of discontinuation due to lack of efficacy **Secondary:** Pain intensity* (100 mm VAS), pain relief, tender-point count, myalgic score, FMIQ*, SF-36,12-SQ	Discontinuation was less common in the tramadol group (48%) compared with the placebo group (62%). Tramadol-treated patients also had significantly less pain at the end of the study, better pain relief and better FMIQ scores
Placebo-controlled (mixed pain)				
Maier et al (41), 2002 Germany, crossover (non-EERW)	Neuropathic (67%) and nociceptive (32%); 49 (13)	SR morphine 10–180 mg/d for 1 wk (mean 114 mg/d)	**Primary:** Pain intensity* (0–10 NRS) **Secondary:** Tolerability of pain, sleep quality, physical fitness, mental state and mood, PDI*, symptom complaints	At 1 wk, 44% under morphine and 0% under placebo had full responsiveness. After 2 wks, 40% under morphine and 2% under placebo demonstrated full responsivenss
Opioids versus other analgesics				
Gobel and Stadler (28), 1995 Germany, parallel (non-EERW)	Postherpetic neuralgia; 35 (14)	Tramadol 200–600 mg/d for 6 wks Control: Clomipramine 50–100 mg/d with or without levomepromazine 25–50 mg/d	**Primary:** Pain intensity* (5-point verbal rating scale) **Secondary:** Psychological and physical condition	In both groups, the pain intensity decreased over the 6 wk treatment period. (Reviewers' comments: no significant difference between groups.) There were no essential differences in the current psychiatric/physical conditions during tramadol treatment
Pavelka et al (48), 1998 Czech Republic, crossover (non-EERW)	Osteoarthritis hip and knee; 60 (6)	Tramadol 150–300 mg/d for 4 wks Control: Diclofenac 75–150 mg/d	**Primary:** WOMAC osteoarthritis index (pain*, stiffness and physical disability*) **Secondary:** Drug preference	Both treatments modestly improved median pain intensity, parallelled by an improvement in functional parameters, and there were no statistically significant differences between the groups
Beaulieu et al (14), 2008 Canada, parallel (non-EERW)	Osteoarthritis knee or hip; 129 (32)	CR tramadol 200–400/d for 6 wks Control: SR diclofenac 75 mg/d for 6 wks	**Primary:** Daily pain intensity by VAS* and WOMAC* pain subscale	Mean change for WOMAC pain subscale was 73.2±99.9 for tramadol and 80.2±108 for diclofenac. Mean change for overall VAS pain score was 17.3±22.6 for tramadol and 16.4±24.4 for diclofenac
Parr et al (47), 1989 USA, parallel (non-EERW)	Pain in ≤2 joints; 846 (213)	D&A: Dextropropoxyphene 1080 mg/d + acetaminophen 1950 mg/d for 4 wks Control: SR diclofenac 100 mg/d	**Primary:** Pain intensity* (100 mm VAS) **Secondary:** Nottingham Health Profile (NHP)*, energy, sleep, social isolation and emotional reactions	Pain as measured by VAS showed 8% greater pain reduction with diclofenac compared with D&A. Physical mobility as measured by the NHP improved by 13% more with diclofenac compared with D&A
Salzman and Brobyn (58), 1983 USA, parallel (non-EERW)	Osteoarthritis; 57 (11 at 1 wk) in Salzman's group and 57 (7 at 1 wk) in Brobyn's	Propoxyphene 250 mg/d for 24 wks Control: Suprofen 800 mg/d	**Primary:** Pain intensity* (5-point NRS) **Secondary:** Pain relief, global improvement	Both suprofen and propoxyphene produced a considerable reduction in pain intensity from baseline after only 1 wk of treatment. This beneficial effect did not diminish with continued therapy. Further improvement occurred in both groups by 24 wks

TABLE 1 – CONTINUED
Characteristics of the 62 randomized trials included in the present updated systematic review (grouped by type of opioid)

Reference, year Country, design	Population type; Randomized, n (dropouts, n)	Interventions and comparison groups	Outcomes: Primary and secondary	Results (as reported in the studies)
Placebo-controlled (mixed pain)				
Glowinski and Boccard (27), 1999 France, parallel (non-EERW)	Rheumatoid arthritis; 60 (2)	Codeine 90 mg/d + acetaminophen 1500 mg/d for 1 wk Control: Diclofenac 100 mg/d + placebo	**Primary:** Global efficacy (5-point verbal scale) **Secondary:** Pain intensity* (100 mm VAS), impairment of activity (4-point scale), duration of morning stiffness, number of awakenings	Analgesic efficacy was not significantly different between the 2 groups on all criteria
Kjaersgaard-Andersen et al (36), 1990 Denmark, parallel (non-EERW)	Osteoarthritis hip; 161 (64)	Codeine 180 mg/d + acetaminophen 3 g/d for 4 wks Control: Acetaminophen 3 g/d. Rescue medication: Ibuprofen tablets 400 mg	**Primary:** Daily intake of rescue medication **Secondary:** Daily and weekly hip pain	At 7 days, the addition of codeine was better than acetaminophen alone. After this, there was no difference
Jamison et al (33), 1998 USA, parallel (non-EERW)	Back pain; 36 (3)	A. Oxycodone + SR morphine 90 mg/d for 16 wks***** B. SR oxycodone 40 mg/d for 16 wks. Control: Naproxen 1000 mg/d	**Primary:** Pain intensity* (0–100 scale) **Secondary:** Mood. Level of activity, number of hours and amount of study medication	Both opioid groups had significantly less pain and emotional distress than the naproxen-only group. No differences in activity level or hours of sleep were found
Vlok and Van Vuren (66), 1987 South Africa, crossover (non-EERW)	Osteoarthritis; 31 (3)	Codeine 20 mg/d + ibuprofen 400 mg/d + acetaminophen 500 mg/d for 4 wks Control: Ibuprofen 1200 mg/d	**Primary:** Pain intensity (VAS) **Secondary:** Pain analogue difference, drug choice	Combination of codeine + ibuprofen + acetaminophen was better than ibuprofen alone
Raja et al (52), 2002 USA, crossover (non-EERW)	Postherpetic neuralgia; 76 (32)	CR morphine up to 240 mg/d for 6 wks. Methadone was an alternative opioid Control: Nortriptyline up to 160 mg/d. Desipramine was an alternative antidepressant	**Primary:** Pain intensity* (0–10 NRS) **Secondary:** Pain relief, cognitive function, MPI* (physical functioning subscale), sleep, mood, global preference	The trend favouring opioids over tricyclic antidepressants fell short of significance, and reduction in pain with opioids did not correlate with that following tricyclics
Gilron et al (25), 2005 Canada, crossover (non-EERW)	35 diabetic neuropathy and 22 postherpetic neuralgia; 57 (16)	A. SR morphine maximum tolerated for 5 wks B. SR morphine maximum tolerated combined with gabapentin for 5 wks C. Gabapentin maximum tolerated for 5 wks	**Primary:** Pain intensity (0–10 NRS) **Secondary:** SF-MPQ, maximal tolerated doses, mood (BDI), SF-36, mental status (Mini-Mental) and global pain relief	Mean pain intensity at the maximal tolerated dose was 4.49 with placebo, 4.15 with gabapentin, 3.7 with morphine and 3.06 with gabapentin-morphine combination. Total scores in SF-36 were lower with gabapentin-morphine combination than with placebo or each drug alone
Wu et al (71), 2008 USA, crossover (non-EERW)	Postamputation pain; 60 (25)	A. SR morphine 15–180 mg/d for 6 wks B. Mexiletine: 75–1200 mg/d for 6 wks	**Primary:** Average change in overall pain intensity from the baseline to the last week of maintenance therapy using 0–10 NRS **Secondary:** Pain relief (0–100%) and the interference and general activity subscales from the MPI	Morphine treatment provided lower pain scores compared with placebo and mexiletine. The mean per cent pain relief during treatment with mexiletine, and morphine was 30% and 53%, respectively
Khoromi et al (34), 2007 USA, crossover (non-EERW)	Chronic lumbar radiculopathy (sciatica); 55 (27)	A. SR morphine 15–90 mg/d B. Nortriptyline 25–100 mg/d C. Combination duration: 9 wks	**Primary:** Average leg pain during the 2 wks **Secondary:** Global pain relief, ODI, BDI and SF-36	In the 28 of 61 patients who completed the study, none of the treatments produced significant reductions in average leg pain or other leg or back pain scores. Within the limitations of the modest sample size and high dropout rate, these results suggest that nortriptyline, morphine and their combination may have limited effectiveness in the treatment of chronic sciatica
Frank et al (24), 2008 UK, crossover (non-EERW)	Neuropathic pain; 96 (32)	A. Dihydrocodeine maximum 240 mg/d for 14 wks B. Nabilone maximum 2 mg/d for 14 wks	**Primary:** Difference in pain (VAS) computed over the last 2 wks of each treatment period **Secondary:** Change in mood, quality of life (SF-36 role physical)*, sleep and psychometric function	The mean score was 6.0 mm longer for nabilone than for dihydrocodeine in the available case analysis and 5.6 mm in the per protocol analysis. Dihydrocodeine provided better pain relief than the synthetic cannabinoid nabilone. Nabilone was significantly superior to dihydrocodeine on the SF-36 (role-physical)

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TABLE 1 – CONTINUED
Characteristics of the 62 randomized trials included in the present updated systematic review (grouped by type of opioid)

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N of 1 randomized trial				
Sheather-Reid and Cohen (61), 1998 Australia, non-EERW	Regional cervicobrachial pain; 8 (3)	A. Codeine 120 mg/d for 4 wks B. Ibuprofen 800 mg/d for 4 wks C. Placebo for 4 wks	**Primary:** Pain intensity (VAS) **Secondary:** Change in pain, uptime and hours of sleep	In none of the 5 subjects who completed the 12-week trial was analgesic efficacy of either drug shown

**Data used for meta-analysis. 12-SQ 12-Symptom Questionnaire; ACR American College of Rheumatology; ADL Activity of daily living; AUC Area under the curve; BDI Beck Depression Inventory; bid Twice daily; BPI Brief Pain Inventory; BSS Brief Stress Scale; COX-2 Cyclooxygenase-2; CR Controlled release; CSPI Chronic Pain Sleep Inventory; d Day; DMARD Disease-modifying antirheumatic drug; EERW Enriched enrollment randomized withdrawal; ER Extended release; FMIQ Fibromyalgia Impact Questionnaire; GSS Grip Strength Score; HSCS High Sensitivity Cognitive Screen; IR Immediate release; MPI Multidimensional Pain Inventory; NNT Number needed to treat; NRS Numeric rating scale; NSAID Nonsteroidal anti-inflammatory drug; ODI Oswestry Disability Index; PES Pain Experience Scale; POMS Profile of Mood State; PDI Pain Disability Index; PGI Patient Generated Index; PRRS Pain Relief Rating Scale; PRSS Pain-Related Self-Statement Scale; qid Four times daily; RDQ Roland Disability Questionnaire; RS Ritchie score; SCL-90 Symptom Check List-90; SDS Self-Rating Depression Scale; SF-36 Short Form 36 Health Survey; SF-MPQ Short-Form McGill Pain Questionnaire; SPID-60 Sum of pain intensity differences in the first 60 minutes; SIP Sickness Impact Profile; SR Sustained release; tid Three times daily; VAS Visual analogue scale; WHYMPI West Haven-Yale Multidimensional Pain Inventory. wk Week; WOMAC Western Ontario and McMaster Universities Osteoarthritis Composite Index*

TABLE 2
Efficacy and effectiveness of opioids for chronic noncancer pain

	Pain		Function	
Efficacy of opioids	**Studies, n**	**ES (95% CI)**	**Studies, n**	**ES (95% CI)**
Opioid versus placebo (all types of pain, all designs, all opioids)	47	0.58 (0.48 to 0.67)	31	0.34 (0.25 to 0.43)
Subgroup analysis: EERW design compared with non-EERW design				
Opioid versus placebo				
EERW design (all pains, all opioids)	8	0.62 (0.33 to 0.92)	3	0.24 (0.08 to 0.41)
Non-EERW design (all pains, all opioids)	39	0.57 (0.47 to 0.67)	28	0.36 (0.26 to 0.45)
Fixed effects meta-regression (between EERW and non-EERW)		P=0.65		P=0.33
Subgroup analysis: Weak compared with strong opioid				
Opioid versus placebo				
Weak opioids (all pains, all designs)	22	0.55 (0.45 to 0.66)	15	0.31 (0.21 to 0.41)
Strong opioids (all pains, all designs)	25	0.60 (0.43 to 0.77)	16	0.37 (0.22 to 0.52)
Fixed effects meta-regression (between weak and strong opioids)		P=0.91		P=0.41
Subgroup analyses: Various type of pain (nociceptive, neuropathic, fibromyalgia, mixed) Efficacy (opioid compared with placebo) and effectiveness (opioid compared with other drugs)				
Nociceptive pain				
Opioid versus placebo	31	0.60 (0.49 to 0.72)	21	0.38 (0.26 to 0.49)
Opioid versus nonsteroidal anti-inflammatory drugs	8	0.03 (–0.22 to 0.27)	3	–0.18 (–0.31 to –0.04)
Opioid versus acetaminophen	1	0.55 (0.11 to 0.99)	0	
Neuropathic pain				
Opioid versus placebo	13	0.56 (0.38 to 0.73)	7	0.24 (0.09 to 0.39)
Opioid versus tricyclic antidepressant	3	0.15 (–0.13 to 0.43)	2	0.03 (–0.26 to 0.33)
Opioid versus anticonvulsant	1	0.19 (–0.21 to 0.59)	1	–0.13 (–0.53 to 0.27)
Opioid versus cannabinoid	1	0.62 (0.15 to 1.09)	1	–0.65 (–1.16 to –0.14)
Fibromyalgia				
Opioid versus placebo	2	0.41 (0.21 to 0.61)	2	0.33 (0.13 to 0.54)
Mixed pain				
Opioid versus placebo	1	0.34 (–0.25 to 0.93)	1	0.35 (–0.23 to 0.94)

Effect size (ES): Small (ES≤0.5); medium (ES 0.5 to <0.8); large (ES≥0.8). EERW Enriched enrollment randomized withdrawal

Two trials were excluded because they examined the efficacy of opioids for acute-on-chronic pain (51,63). There were 14 trials with an enrichment design: two were excluded from the present review because the patients in both the opioid and the placebo groups received a short-acting opioid for breakthrough pain (73,74) and 12 were included (18,20,29,37,51,54,56,57,59,60,63,67).

From the randomized trials that reported data suitable for meta-analysis, the treatment effect among EERW trials was 0.62 (95% CI 0.33 to 0.92) and was 0.57 (95% CI 0.47 to 0.67) among the 39 non-EERW trials for pain outcomes. The difference between the treatment effects was not statistically significant (P=0.6). For functional outcomes, there were three EERW (ES=0.24, 95% CI 0.08 to 0.41) and 28 non-EERW trials (ES=0.36, 95% CI 0.26 to 0.45). The difference between the treatment effects was not statistically significant (P=0.3).

Regarding the subgroups of types of pain, the meta-analyses showed a medium ES for pain relief and small ES for functional outcomes for

TABLE 3
Adverse effects of opioids

	Randomized trial design									
	Non-EERW					EERW				
Adverse effects of opioids	Studies, n	Opioid, %	Placebo, %	Difference, % (95% CI)	P	Studies, n	Opioid, %	Placebo, %	Difference, % (95% CI)	P
1. Nausea	38	**28**	**9**	17 (13 to 21)	<0.00001	5	16	8	7 (0 to 14)	0.05
2. Constipation	37	**26**	**7**	20 (15 to 25)	<0.00001	4	**15**	**3**	11 (6 to 16)	<0.001
3. Somnolence/drowsiness	30	**24**	**7**	14 (10 to 18)	<0.00001	4	10	5	3 (1 to 7)	0.08
4. Dizziness/vertigo	33	**18**	**5**	12 (9 to 16)	<0.00001	3	10	5	5 (2 to 8)	0.001
5. Dry skin/itching/pruritus	25	**15**	**2**	10 (5 to 15)	<0.0001	3	5	2	3 (0 to 5)	0.05
6. Vomiting	23	**15**	**3**	11 (7 to 16)	<0.00001	3	2	1	1 (–2 to 3)	0.61
7. Dry mouth	21	12	6	6 (3 to 9)	<0.0001					
8. Headache	28	11	9	1 (–1 to 4)	0.23	4	7	5	1 (–2 to 4)	0.57
9. Sexual dysfunction	1	11	0	11 (–2 to 23)	0.1					
10. Hot flashes	2	10	3	6 (–3 to 15)	0.18					
11. Loss of appetite	5	10	1	7 (2 to 13)	0.004					
12. Abdominal pain	5	9	4	4 (–1 to 10)	0.11					
13. Fatigue	18	9	4	3 (0 to 7)	0.04					
14. Sleeplessness/insomnia	10	9	5	4 (1 to 6)	0.01					
15. Sweating	10	8	3	4 (0 to 7)	0.03					
16. Blurred vision	5	6	7	1 (–2 to 5)	0.47					
17. Confusion	5	6	8	–1 (–6 to 4)	0.76					
18. Muscle contractions	1	6	3	3 (–1 to 6)	0.19					
19. Diarrhea	14	5	6	–1 (–3 to 1)	0.3	1	4	5	–2 (–7 to 4)	0.56
20. Ataxia	1	5	0	5 (–3 to 12)	0.23					
21. Edema	1	5	2	2 (–5 to 10)	0.56					
22. Difficulty urinating	1	4	0	4 (–6 to 13)	0.45					
23. Application site reaction	1	4	11	–6 (–11 to –1)	0.01					
24. Heartburn	1	4	4	0 (–10 to 10)	1					
25. Anxiety	1	2	0	2 (–4 to 8)	0.46					
26. Weakness	2	1	3	–2 (–11 to 7)	0.7					

Bolded data: The difference between opioid and placebo is statistically significant (P<0.05) and clinically relevant (difference ≥10%). EERW Enriched enrollment randomized withdrawal

both nociceptive and neuropathic pain (Table 2). For fibromyalgia and mixed pain, the meta-analyses showed a small ES for both pain and functional outcomes (Table 2).

Effectiveness of opioids compared with other drugs (Table 2)

In patients with nociceptive pain, opioids were compared with non-steroidal anti-inflammatory drugs (NSAIDs) in eight trials reported in seven publications (14,27,33,47,48,58,66) and compared with acetaminophen in one trial (36). A meta-analysis of eight trials of opioids compared with NSAIDS showed no difference for pain outcome. When we assessed the type of opioid used in these trials, seven used a weak opioid (codeine, propoxyphene or tramadol) and one trial used a strong opioid (titrated dose of oxycodone and morphine) (33). When analyzed separately, the meta-analysis of the seven trials of weak opioids did not show that opioids are more effective than NSAIDs, but the strong opioid was shown to be more effective than 1000 mg of naproxen daily. NSAIDs were significantly better than opioids for function, but with a very small ES of 0.18.

There was only one trial for nociceptive pain comparing codeine plus acetaminophen with acetaminophen alone (36). It was found that at seven days, the addition of codeine was better than providing acetaminophen alone. After this period of time, there was no difference.

In patients with neuropathic pain, opioids were compared with tricyclic antidepressants in three trials (28,34,52), anticonvulsants in one (25) and cannabinoids in one (24). Opioids (either weak or strong) were not more effective than tricyclic antidepressants or anticonvulsants for either pain or function. We found one trial comparing dihydrocodeine with nabilone showing that dihydrocodeine provides better pain relief than nabilone, but the latter was significantly superior to dihydrocodeine on the SF-36 (role-physical) (24).

Adverse effects

The incidence of adverse effects was noticeably different in the trials that used a classical non-EERW design from those that used the EERW design (Table 3). Among the trials with a non-EERW design, the number of reported adverse effects was 26, while among the trials with an EERW design, only eight adverse effects were reported. Of the 26 adverse effects reported in the non-EERW design, six achieved a statistically significant and clinically relevant difference: nausea (17%, 95% CI 13% to 21%), constipation (20%, 95% CI 15% to 25%), somnolence/drowsiness (14%, 95% CI 10% to 18%), dizziness/vertigo (12%, 95% CI 9% to 16%), dry-skin/itching/pruritus (10%, 95% CI 5% to 15%) and vomiting (11%, 95% CI 7% to 16%). In the trials with an EERW design, only constipation (11%, 95% CI 6% to 16%) was found to be statistically significant and clinically relevant.

DISCUSSION

We identified 62 randomized trials of opioids for a variety of CNCP conditions. Opioids were shown to be effective when compared with placebo in improving pain and function, but the ES were only medium and small, respectively. These conclusions did not change when we analyzed subgroups of EERW/non-EERW design, weak/strong opioids, or when the diagnosis was nociceptive/neuropathic pain.

There is an important difference in side effects reported between EERW and non-EERW designs. Six adverse effects were observed more often in the opioid group than in the placebo group in the non-EERW

designs. Consumers of opioids should be aware of these effects to make better informed decisions before they are prescribed long-term opioids for CNCP.

All included studies were randomized trials, and the majority were judged to be of high methodological quality. However, most of these trials (74%) were of short duration (ie, shorter than six weeks), with ties to the pharmaceutical industry and a sizeable number of dropouts. Our analyses could only be performed on what was reported in the trials. On some occasions, we contacted the authors of the trials and were able to clarify some details and obtain more information.

The comparisons of opioids with other drugs were based on studies that were not designed as equivalence or noninferiority trials. Therefore, the conclusions derived from these studies should be accepted with some reservation.

Our conclusions are similar to other recently published systematic reviews on this topic. A recently published Cochrane review of oral or transdermal opioids for osteoarthritis of the knee or hip included 10 trials and concluded that, overall, opioids were more effective than control interventions in terms of pain relief and improvement of function. There were no substantial differences in effects according to type of opioid, analgesic potency (strong or weak), daily dose, duration of treatment or follow-up, methodological quality of trials or type of funding. Adverse events were more frequent in opioid groups compared with controls. They found, however, only small to moderate beneficial effect (75).

Another recent Cochrane review examined the long-term safety, efficacy and effectiveness of opioids for CNCP (76). They included 26 studies with 27 treatment groups, of which 12 were administered orally, five transdermally and 10 intrathecally. Twenty-five of the studies were case series, and there was one randomized trial comparing two opioids. They found that opioids were associated with a clinically significant reduction in pain; however, quality of life and functional status were inconclusive due to insufficient evidence and statistical findings.

More research is needed to determine the usefulness of EERW designs in the administration of opioids for CNCP. In principle, enrichment is a process of increasing the proportion of likely responders to a treatment, and is an efficient strategy for maximizing differences between drug and placebo effects in a clinical trial. Some investigators defend the use of enrichment design in opioids for CNCP because opioids may underperform in clinically heterogeneous contexts, which means that substantial efficacy in a particular subgroup of patient may be diluted or masked by poor efficacy in other subgroups. In the case of opioids, a low proportion of responders would produce an average response that would be moderate at best, concealing the good reponse in the minority of responders; therefore, a drug of potential clinical usefulness to some patients might be discarded because, on average, it did not appear to be very effective in a trial (2). On the other hand, disadvantages of EERW designs include an influence on the apparent efficacy, the limited external validity (generalizability) because of the sample selection procedure, and the invalidation of drug-placebo comparisons because of carryover effects or withdrawal symptoms (77).

There is also a need to assess whether chronic use of opioids provides more benefits than harms in the long-term. None of these randomized trials followed patients for more than one year to determine whether they continued to benefit from opioids.

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CONTRIBUTORS: All authors participated in the conception and writing of this review. Andrea Furlan was responsible for writing the protocol, and performed the data extraction, quality assessment, statistical analyses and report writing. Luis Chaparro was responsible for the data extraction and quality assessment. Emma Irvin was responsible for the literature searches and writing the methods. Angela Mailis-Gagnon was responsible for overseeing the project and editing the final manuscript.

APPENDIX 1
Search strategy for MEDLINE

Search terms for randomized trials	Search terms for chronic noncancer pain	Search terms for opioids
1. randomized controlled trial.pt.	32. PAIN/pc, dt, rh, th	38. exp Analgesics, opioid/
2. controlled clinical trial.pt.	33. Chronic Disease/dt, pc, rh, th	39. Codeine.mp.
3. Randomized Controlled Trials/	34. (chronic adj3 pain).mp	40. Fentanyl.mp.
4. Random Allocation/	35. Low Back Pain/	41. Hydrocodone.mp.
5. Double-Blind Method/	36. (low adj back adj pain).mp	42. Hydromorphone.mp.
6. Single-Blind Method/	37. or/ 32-36	43. Levorphanol.mp.
7. or/1-6		44. Meperidine.mp.
8. Animal/ not Human/		45. Morphine.mp.
9. 7 not 8		46. Oxycodone.mp.
10. clinical trial.pt.		47. Oxymorphone.mp.
11. explode Clinical Trials/		48. Pentazocine.mp.
12. (clinic$ adj25 trial$).tw.		49. Propoxyphene.mp.
13. ((singl$ or doubl$ or trebl$ or tripl$) adj(mask$ or blind$)).tw.		50. Sufentanil.mp.
14. Placebos/		51. Tramadol.mp
15. placebo$.tw.		52. or/ 38-51
16. random$.tw.		
17. Research Design/		
18. (latin adj square).tw.		
19. or/10-18		
20. 19 not 8		
21. 20 not 9		
22. Comparative Study/		
23. explode Evaluation Studies/		
24. Follow-Up Studies/		
25. Prospective Studies/		
26. (control$ or prospectiv$ or volunteer$).tw.		
27. Cross-Over Studies/		
28. or/22-27		
29. 28 not 8		
30. 29 not (9 or 21)		
31. 9 or 21 or 30		

Combining all searches

53. 31 and 37 and 52

dt Drug therapy; Exp Explode; mp Multipurpose; pc Prevention and control; Pt Publication type; rh Rehabilitation; th Therapy; tw Text word

APPENDIX 2
Search strategy for EMBASE

Search terms for randomized controlled trials	Search terms for chronic noncancer pain	Search terms for opioids
1. Randomized Controlled Trial/	43. Pain/pc, rh, dt, th	49. exp Narcotic Analgesic Agent/
2. (random: adj2 control: trial:).mp.	44. Chronic Disease/pc, rh, dt, th	50. Codeine.mp.
3. 1 or 2	45. (chronic adj3 pain).mp.	51. Fentanyl.mp.
4. control: clinical trial:.mp.	46. Low Back Pain/	52. Hydromorphone.mp.
5. (control: adj2 trial:).mp.	47. (low adj back adj pain).mp.	53. Levorphanol.mp.
6. 4 or 5	48. or/43-47	54. Meperidine.mp.
7. randomization/		55. Morphine.mp.
8. random: allocation:.mp.		56. Oxycodone.mp.
9. (random: adj2 allocation:).mp.		57. Oxymorphone.mp.
10. 8 or 9		58. Pentazocine.mp.
11. Double Blind Procedure/		59. Propoxyphene.mp.
12. double-blind method:.mp.		60. Tramadol.mp.sufentanil.mp
13. Single Blind Procedure/		61. Tramadol.mp
14. single-blind method:.mp.		62. or/49-61
15. or/1-14		
16. limit 15 to (amphibia or ape or bird or cat or cattle or chicken or dog or “ducks and geese” or fish or “frogs and toads” or goat or guinea pig or “hamsters and gerbils” or horse or monkey or mouse or “pigeons and doves” or “rabbits and hares” or rat or reptile or sheep or swine)		
17. exp animal/		
18. 15 and 17		
19. 16 or 18		
20. limit 15 to human		
21. 20 not 19		
22. Clinical Trial/		
23. exp clinical trial/		
24. (clinic: adj25 trial:).tw.		
25. ((singl: or doubl: or trebl: or tripl:) adj (mask: or blind:)).tw.		
26. PLACEBO/		
27. placebo:.mp.		
28. random:.tw.		
29. methodology/		
30. latin square design/		
31. (latin adj square). tw.		
32. or/22-31		
33. 32 not 19		
34. Comparative Study/		
35. evaluation/		
36. follow up/		
37. prospective study/		
38. (control: or prospectiv: or volunteer:).tw.		
39. Crossover Procedure/		
40. or/34-39		
41. 40 not 19		
42. 21 or 33 or 41		
Combining all searches		
63. 42 and 48 and 62		

dt Drug therapy; Exp Explode; mp Multipurpose; pc Prevention and control; Pt Publication type; rh Rehabilitation; th Therapy; tw Text word

APPENDIX 3
The Cochrane Collaboration’s tool for assessing risk of bias (7)

Domain	Description	Review authors’ judgement
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment	Was allocation adequately concealed?
Blinding of participants, personnel and outcome assessors: *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Was knowledge of the allocated intervention adequately prevented during the study?
Incomplete outcome data: *Assessments should be made for each main outcome (or class of outcomes)*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors	Were incomplete outcome data adequately addressed?
Selective outcome reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Are reports of the study free of suggestion of selective outcome reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were prespecified in the review’s protocol, responses should be provided for each question/entry	Was the study apparently free of other problems that could put it at a high risk of bias?

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