CRD summary
This review concluded that in older adults with chronic non-cancer pain, short-term opioid use was associated with significant pain reduction and better physical functioning but poorer mental health functioning. The long-term safety, efficacy and abuse potential of opioid use in diverse elderly patient groups remained undetermined. The authors' cautious conclusions were appropriate in view of limitations in the evidence.

Authors' objectives
To evaluate the efficacy, safety, abuse and misuse of opioids as treatment for chronic non-cancer pain in older adults.

Searching
MEDLINE, MD Consult, CINAHL, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov were searched from January 1980 to January 2009 for publications in English; search terms were reported. Clinical experts were contacted for relevant information. The bibliography of each retrieved article was handsearched.

Study selection
Studies that evaluated tramadol or one or more conventional opioids (oral or transdermal) for chronic non-cancer pain in older participants (mean age ≥60 years) or that reported age-stratified results for older subgroups were eligible for inclusion. Outcomes related to efficacy, safety and tolerability and abuse and misuse were eligible. The primary efficacy outcomes were pain, physical function, physical quality of life (QoL), mental QoL and sleep. Studies that assessed opium misuse and abuse outcomes where the mean age was under 60 years were included if some patients were at least 60 years old.

The intervention in most studies was of low to medium potency opioids such as tramadol and codeine and (in a third of studies) high-potency opioids such as fentanyl and morphine, mostly with extended release formulations. Average oral morphine equivalent opioid dose was 63mg/day (range 24 to 165). Mean treatment duration was four weeks (range 1.5 to 156 weeks). The most common cause of pain was osteoarthritis (70% of patients) and the next commonest was neuropathic pain (13% patients). Weighted mean patient age was 64.1 years (range 60 to 73 years). Where reported, most patients were white non-Hispanic. Multiple pain measures were used. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) was used for physical function and Medical Outcomes Study 36-item Short Form Survey SF-36 instrument for QoL in all relevant studies.

Two independent reviewers performed study selection.

Assessment of study quality
Study quality was assessed on the basis of the Jadad scale and Downs method. For clinical trials, criteria assessed included randomisation assignment, blinding, appropriate comparators, sample size, and identical outcome measurement (maximum score 13). For observational studies, criteria assessed included reporting, external and internal validity, confounding adjustment and study power (maximum score 15). An excellent quality score was 10 or more for clinical trials and 12 or more for observational studies.

The authors did not report how many reviewers assessed study quality.

Data extraction
Means with standard deviations (SDs) or standard errors were used to calculate mean differences between the active treatment and control groups. Data were extracted only for the most commonly observed adverse events (prevalence
rate of ≥15% in the treatment or control arm). Drop-out rates (%) due to adverse events or lack of efficacy were extracted. The preferred measures of pain extracted were average pain intensity (scale zero to 10) and pain relief scores or (third choice) pain severity.

Two reviewers independently performed data extraction.

**Methods of synthesis**
Mean differences were pooled to assess the effects of both treatment and time of assessment (a repeated measure at follow-up versus baseline) giving standardised mean differences (SMDs). A fixed-effect model was used where there was no significant heterogeneity and a random-effects model was moving where was significant heterogeneity. Presence of study heterogeneity was detected using the Cochrane Q statistic. Sensitivity analyses were performed to find the effect of certain factors on pain and physical function. Publication bias was assessed visually using funnel plots. Meta-analyses for efficacy included only data from randomised controlled trials (RCTs).

**Results of the review**
Forty-three studies were identified. There were 40 studies of efficacy (n=8,691, range 42 to 646): 31 RCTs (n=6,837) and 12 observational studies (n=1,854) that included eight open-label studies with no controls. One of the studies of efficacy provided data on abuse and misuse. Three studies provided data solely on abuse and misuse. The four studies that assessed misuse and abuse outcomes included 16,098 patients. Mean quality score for RCTs was 10 (range 9 to 13). Twenty-four RCTs and seven observational studies had an excellent quality score (median quality score 13, range 9 to 15).

**Efficacy (RCTs only)**
Opioid versus placebo only (18 RCTs) gave a significant reduction in pain (SMD -0.557, p<0.001; 18 studies) and physical function (SMD -0.432, p<0.001; nine studies). The effect was not significant for improved sleep (six studies). For quality of life, there was a significant decrease in the mental component score (SMD -0.220, p=0.04; four studies) and no significant effect on the physical component score (four studies). Sensitivity analyses found the effect size for pain reduction was greater for patients with neuropathic pain (SMD -0.907, p<0.001; four studies) than for those with osteoarthritis (SMD -0.457, p<0.001; 14 studies). There was no association between pain and physical function outcomes and study quality score or mean participant age.

**Opioid versus active treatment (three studies)**
Head-to-head comparison studies found no significant differences in effect for opioid compared to non-steroidal anti-inflammatory or long acting tramadol.

**Abuse and misuse (four studies)**
Two studies found older patients were significantly less likely to misuse or abuse opioids (adjusted odds ratio (AOR) 0.95, 95% confidence intervals (CI) 0.90 to 0.99) and (AOR 0.94, 95% CI 0.89 to 0.99). All four studies found low levels of abuse and misuse.

**Adverse events (41 studies)**
For opioid-treated patients, occurrence rates for the most common events were constipation 30% (range 12% to 52%), nausea 28% (range 12% to 61%), dizziness 22% (range 10% to 37%) and somnolence 21% (range 10% to 39%). Events were mostly rated as mildly or moderately severe and were lower than in placebo control groups. Numbers needed to harm and data for age effects were reported.

There was no evidence of publication bias.

**Authors’ conclusions**
In older adults with chronic pain and no significant comorbidity, short-term use of opioids was associated with reduction in pain intensity and better physical functioning but poorer mental health functioning. The long-term safety, efficacy and abuse potential of this treatment practice in diverse populations of older persons remained undetermined.

**CRD commentary**
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched. The restriction to studies published in English increased the risk of language bias. A limited search for unpublished studies was made, so it was not possible to rule out publication bias. Funnel plots indicated no evidence of publication bias. Study quality was assessed using suitable criteria. Full details of
study quality were not provided. Efforts were made to reduce error and bias in study selection and data extraction; it was not reported whether this also applied to validity assessment. Three observational studies appeared to be substudies, secondary analyses or extension trials and so the number breakdown by type of study was unclear. No details of the studies of misuse and abuse were provided in the tables.

Statistical heterogeneity was assessed, but no relevant data were provided. The statistical method used for meta-analysis was appropriate. Relevant sensitivity analyses were performed. Although there were many high-quality studies, follow-up was generally relatively short and there was limited evidence for neuropathic pain (recognised by the authors).

Pharmaceutical companies sponsored 78% of the studies in the review.

The authors’ cautious conclusions are appropriate in view of limitations in the evidence identified.

Implications of the review for practice and research

Practice: The authors recommended that short-term opioid treatment for chronic non-cancer pain was used for older patients without comorbidity and with nociceptive or neuropathic pain. They recommended frequent surveillance for efficacy and adverse events.

Research: The authors identified a need for studies that compared the benefits of long- versus short-acting opioids in older patients, compared opioids versus non-opioid analgesic agents (particularly nonsteroidal anti-inflammatory agents) and that compared opioids with nonpharmacological treatments (including complementary therapies). Studies should enrol diverse groups of older adults and assess relevant geriatric outcomes.

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