Published in final edited form as:
J Am Geriatr Soc. 2010 July ; 58(7): 1353–1369. doi:10.1111/j.1532-5415.2010.02920.x.

Outcomes Associated with Opioid Use in the Treatment of Chronic Non-Cancer Pain Among Older Adults: A Systematic Review and Meta-Analysis

Maria Papaleontiou, MD[1], **Charles R. Henderson Jr.**[2], **Barbara J. Turner, MD**[3], **Alison A. Moore, MD, MPH**[4], **Yelena Olkhovskaya, MD, PhD**[5], **Leslie Amanfo, BS**[5], and **M. Carrington Reid, MD, PhD**[5]

[1]Department of Medicine, Saint Peter's University Hospital, New Brunswick, NJ

[2]Department of Human Development, Cornell University, Ithaca, NY

[3]Department of Medicine, University of Pennsylvania, Philadelphia, PA

[4]Division of Geriatrics, David Geffen School of Medicine, University of California, Los Angeles, CA

[5]Division of Geriatrics and Gerontology, Weill Cornell Medical College, New York, NY

Abstract

This systematic review summarizes existing evidence regarding the efficacy, safety, and abuse/misuse potential of opioids as treatment for chronic non-cancer pain (CP) in older adults. Multiple databases were searched to identify relevant studies published in English (1/1/80-7/1/09) with a mean study population age of 60 years or above. Forty-three articles were identified and retained for review. The weighted mean subject age was 64.1 years (mean age range: 60-73). Studies enrolled patients with osteoarthritis (70%), neuropathic pain (13%), or other pain-producing disorders (17%). The mean duration of treatment studies (n=40) was 4 weeks (range = 1.5–156 weeks), and only 5 (12%) lasted longer than 12 weeks. In meta-analyses, effect sizes were −0.557 (p<0.001) for pain reduction, −0.432 (p<0.001) for physical disability reduction, and 0.859 (p=0.309) for improved sleep. The effect size for the SF-36 physical component score was 0.191 (p = 0.171) and −0.220 (p =0.036) for the mental component score. Adults ages 65 and above (vs. less than 65) were equally likely to benefit from treatment. Common adverse events included constipation (median frequency of occurrence = 30%), nausea (28%), dizziness (22%), and prompted opioid discontinuation in 25% of cases. Abuse/misuse behaviors were negatively associated with advancing age. Among older adults with CP and no significant comorbidity, short-term use of opioids is associated with reductions in pain intensity, improved physical functioning, but decreased mental health functioning. The long-term safety, efficacy, and abuse potential of this treatment practice in diverse populations of older persons remain to be determined.

Corresponding Author Dr. Cary Reid Division of Geriatrics and Gerontology, 525 E 68th Street, Box 39, Weill Cornell Medical College, New York, NY 10065. Phone: 212-746-1729, Fax: 212-746-4888, mcr2004@med.cornell.edu.

Authors Contributions:
Study Conception and Design: MC Reid, AA Moore, BJ Turner, M Papaleontiou, CR Henderson, Jr.
Acquistion of Data: MC Reid, M Papaleontiou, Y Olkhovskaya, L Amanfo Analysis and Interpretation of Data: MC Reid, AA Moore, BJ Turner, M Papaleontiou, CR Henderson, Jr.
Manuscript Preparation/Revision: MC Reid, AA Moore, BJ Turner, M Papaleontiou, CR Henderson, Jr., Y Olkhovskaya, L Amanfo
Final Approval of Manuscript: MC Reid, AA Moore, BJ Turner, M Papaleontiou, CR Henderson, Jr., Y Olkhovskaya, L Amanfo

Sponsor's Role: The John A. Hartford Foundation and NIH had no role in designing, conducting, or reporting the study.

Conflict of Interest: The editor in chief has reviewed the conflict of interest checklist provided by the authors and has determined that the authors have no financial or any other kind of personal conflicts with this paper.

Keywords

opioid; pain; older adults

INTRODUCTION

Prior systematic reviews have reported on short-term outcomes associated with opioid medications as a treatment for chronic non-cancer pain.[1-5] Opioids reduced pain scores significantly among patients with osteoarthritis,[1-3] as well as those with neuropathic pain,[1,4] but not chronic back pain.[5] Opioids were also associated with improved functional outcomes in two reviews.[2,3] These benefits may be limited, however, by the occurrence of adverse events, which prompted opioid discontinuation in up to 31% of cases.[1-3]

Of note, none of the reviews focused on older populations or reported age-stratified results. An examination of the evidence regarding opioid safety and efficacy in older populations is needed for several reasons. Chronic non-cancer pain is a highly prevalent, costly, and often disabling disorder in later life.[6-8] Prevalence studies indicate that 40% to 50% of older adults report the presence of a chronic pain disorder.[7-9] The deleterious consequences of inadequately treated pain are far-reaching and include impaired quality of life, sleep, immune function, as well as activities of daily living (ADL) impairment.[10-15] In addition, non-steroidal anti-inflammatory agents, the most commonly prescribed class of analgesic medications, have potentially serious gastrointestinal and cardiovascular side effects and can exacerbate comorbid conditions that are prevalent in later life.[16,17] Some authors have suggested that opioids are underutilized as a treatment for chronic pain in older populations,[18] possibly due to provider concerns about the uncertainty of the value and safety of opioids as a treatment for this disorder,[19] as well as their concerns about patient addiction and untoward side effects.[20] Accordingly, we conducted a comprehensive review of the literature to identify studies that examined opioid medications as a treatment for chronic non-cancer pain in older persons and reported efficacy, safety, or abuse/misuse outcome data.

METHODS

Data Sources and Searches

We searched the Ovid/Medline, PubMed, MD Consult, CINAHL, and Cochrane Controlled Trail databases (1/1/80-7/1/09) to identify pertinent articles for review. MeSH terms included opioid analgesics, pain, elderly, aged, treatment outcome, and *adverse effects.* Other keywords included *chronic pain, non-malignant pain, efficacy, abuse*, and *misuse.* Citation abstracts were independently reviewed by two investigators to determine their suitability for inclusion in the review. Clinical experts and clinicaltrials.gov were also queried.

Study Selection

Studies were eligible if they: 1) were published in English; 2) evaluated one or more opioid medications (administered orally or transdermally); and 3) reported results (i.e., efficacy, safety, or abuse/misuse data) on older adults as evidenced by a minimum mean study population age of ≥60 years or reported age-stratified results for older age subgroups. Because tramadol is used to treat chronic pain in older persons,[21,22] it was included along with the conventional opioids. Due to the small number of studies that examined opioid abuse/misuse outcomes, articles examining this outcome were also retained if the mean age of the sample was < 60 years but included some subjects ages ≥ 60 years and examined age as a predictor of opioid abuse/misuse.

A QUORUM (Quality of Reporting of Meta-analyses) flow diagram (see Figure) shows an overview of the study selection process. The reference lists from all 38 articles meeting the study criteria were reviewed. Five additional studies were included after reviewing the reference lists, yielding a final sample of 43 articles.

Data Abstraction

Two investigators independently abstracted study outcomes. Information regarding eligibility criteria used for subject selection, study design, study duration, participants' demographic and clinical characteristics, source of study funding, condition studied, as well as type and dosage of opioid studied was abstracted. We focused on three pre-specified outcomes: 1) efficacy; 2) safety/tolerability; and 3) occurrence of abuse/misuse behaviors. As most studies employed multiple pain measures, we selected average pain intensity and pain relief scores when present; otherwise pain severity was extracted if present. We extracted Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores that were the most commonly used physical function measures. Quality of life was most often measured by the SF-36 instrument.

Quality Assessment

Retained studies were evaluated for methodological quality.[23,24] Previously employed threshold scores[5] were used to assign a quality score of 'excellent'. For clinical trials (n=31), a quality score of ≥ 10 (score range, 0-13), was considered excellent,[5] whereas for observational studies (n=12), a score of ≥ 12 (score range, 0-15)[25] was considered excellent.[5]

Data Synthesis and Analysis

Data Synthesis for Univariate Analyses—For the primary efficacy outcomes (pain, physical function, physical quality of life, mental quality of life and sleep), we calculated an average change score by subtracting baseline from follow-up score and then dividing the result by the respective baseline score for the active treatment and placebo control groups. We abstracted data on the most commonly reported adverse events only, i.e., prevalence rate ≥15% in either the treatment or control arm. Dropout rates due to adverse events or lack of efficacy were recorded when present.

Data Synthesis for Meta Analyses—Pain intensity was most often measured on a 0-10 scale, but sometimes on a 0-100 visual analog scale. Physical function was measured by WOMAC in all nine studies reporting this outcome, and quality of life was measured by the SF-36 instrument in the four studies with this outcome available to be included in the meta-analyses. Sleep quality was measured in a variety of ways. We used the overall measure of sleep where it was reported alone or, if not, other measures of sleep functioning.

Most studies reported mean outcomes with standard deviations or standard errors for placebo and active treatment either at baseline and follow up or at one of the 2 time points plus differences scores over time with standard errors for the difference. From these data, we derived for each study a 2×2 set of variables (treatment by time); the 2 difference scores (follow up minus baseline) for placebo and active; and standard deviations for these 6 variables. For the dose-ranging studies (n=3), we examined the medication protocols and averaged the outcomes across the active treatment conditions (with pooled standard deviations) to provide a 2-level treatment variable comparable with the majority of studies that had only a single active treatment.

Statistical Models—We carried out meta-analyses for pain and physical function outcomes using 2 types of models. The first was a statistical mixed model with treatment group (placebo versus active) and time of assessment (a repeated measure, baseline versus follow up) as fixed classification factors; the interaction of these 2 factors; and studies included in the model as levels of a random classification factor. The dependent variables were the outcome means (e.g., pain reduction) for the treatment and time groups divided by their standard deviations. Treatment effects across studies are tested by the interaction of treatment and time in this model.

The second model eliminated the repeated-measures factor for time of assessment and used the standardized mean difference over time (the mean difference divided by the standard deviation of the difference) as the dependent variable. The effect of opioids on the outcome is examined by the treatment main effect in this model. This model allowed inclusion of 2 additional studies in the analysis.

An examination of the results for pain and physical function outcomes revealed consistency between the 2 models, and only results from the second model using standardized difference scores are reported below.

Too few studies reported analysis for physical and mental quality of life and quality of sleep to include studies in the model as levels of a random factor (or to regard studies as fixed and include them in that way). For these outcomes, we carried out an analysis of the standardized difference scores in a model that included the fixed factor for treatments.

We also examined models in which additional independent variables were included. Pain type (osteoarthritis versus neuropathic), opioid potency (low/medium versus high), duration of action (short- versus long-acting agents), and whether the study allowed for co-analgesic use (yes versus no) were each included as additional fixed classification factors in the above models for pain and physical function (separate models for each additional variable). We focused on the interaction of these variables with treatment and time (or simply with treatment in the second basic model), as well as on the treatment contrasts at each level of the added variable. Methodologic quality score (entered as a quantitative variable) was examined as a covariate in the 2 basic models. To assess for age effects on treatment outcomes, mean participant age (range = 60-73) was entered as a covariate in both models. The homogeneity of the regressions of outcomes such as pain on age and on methodologic quality score were tested for treatment and time—i.e., the interaction of age and study quality with treatment and time.[26]

Most of the studies in the meta-analyses were not restricted to patients ages 65 or older and did not report results stratified by age. To augment the analysis of mean age described above, we also carried out an analysis limited to the studies that reported data specific to older age groups (i.e., those 65 years of age and older), comparing outcomes for older and younger age groups.

Two types of diagnostic analyses pertaining to the meta-analysis itself were carried out. Heterogeneity of treatment differences across studies, which may result from differences in study protocols, variable definitions, implementation, or overall quality, was tested by a standard statistic, Cochran's Q.[27] The hypothesis of study homogeneity was rejected, indicating that mixed models (studies random) were more appropriate than fixed effect models. Mixed models are also preferable by general principles and for greater generalizability of results.

We also examined the question of publication bias—whether there was a tendency in the sample of studies for there to be a lack of publication of certain types of studies—by a funnel plot with 1/(standard error), a measure of sample size, plotted against effect size.[28]

RESULTS

Study Characteristics

Of the 43 studies, 40 (93%) provided efficacy data.[29-68] One of the 40 treatment studies[58] also provided information on rates of abuse/misuse, while three provided data only on rates of abuse/misuse.[69-71] The mean duration of the treatment studies was 4 weeks (range = 1.5–156 weeks), with only 5 (12%) lasting longer than 12 weeks. Thirty-one of the 40 treatment studies employed a randomized control design: 19 compared opioid treatment with placebo, 5 examined the effects of opioid treatment as ‘add on’ therapy, 4 compared different types of opioids with one another or with different opioid dosing schedules, and 3 compared opioid therapy to another active treatment. Of the remaining 9 studies, 8 were open-label observational studies with no control group and one was a retrospective cohort study. Of the 3 studies that provided data on abuse/misuse outcomes, one was a secondary analysis, another employed a retrospective cohort design, and the third was a prospective cohort investigation. Most efficacy studies (78%) were sponsored by pharmaceutical companies.

Study Quality

Of the 31 randomized trials, 24 (77%) were assigned an excellent methodologic quality score[5,23] with a median quality score of 10 (range, 9-13). Of the remaining 12 articles (all observational studies), 7 (58%) were deemed to have excellent methodologic quality with a median quality score[24,25] of 13 (range, 9-15).

Study Participant Characteristics

The 40 treatment studies provided information on 8,690 patients. The weighted mean age for this group of studies was 64.1 years (range, 60 to 73). In the 21 studies that reported race/ethnicity data, all but one[51] assessed outcomes in largely non-Hispanic white populations.

Table 1 shows that most treatment studies enrolled patients with osteoarthritis-related pain (n=28). Twenty-nine studies (72%) excluded subjects with a current or past history of substance abuse, while 25 (63%) excluded subjects with significant concomitant disease(s), but these were not described. The 4 studies that examined abuse/misuse outcomes included 16,098 patients. [One study analyzed administrative data on 15,160 patients.[69]] The weighted mean age for this subgroup of studies was 60.3 years (range 52 to 62.4).

Study Drug Characteristics

Twenty-six studies examined outcomes associated with low- to medium-potency opioids (e.g., tramadol, codeine), whereas 14 reported data on high-potency opioids (e.g., fentanyl, morphine), and most (72%) used extended-release formulations. Over half (59%) of the efficacy studies allowed for dose adjustments. The average oral morphine equivalent opioid dose was 63 mg/day (range = 24-165).

Efficacy Outcomes

Results of Studies Comparing Opioid Treatment with Placebo or with Other Treatments as an Add-On Therapy—Eighteen treatment studies provided sufficient data to permit meta-analysis; all 18 employed a randomized, placebo-controlled trial design. Most of the studies (78%) had an excellent methodologic quality score (14/18 = 78%). Meta-analyses (Table 2) revealed significant reductions in both pain intensity and physical disability, along with non-significant improvements in sleep and physical quality of life. A small, but significant reduction in mental health functioning was found among patients receiving opioids versus those who received a placebo.

Table 3 summarizes the association of other independent variables on pain and physical function outcomes. The effect size for pain intensity reduction among patients with neuropathic pain was more than double the one found for patients with osteoarthritis. Drug potency, duration of action, and allowing co-analgesic use during the trial had no effect on these outcomes. In other sensitivity analyses, there was no association between pain and physical function outcomes and study methodologic quality score or mean age of study participants.

Results of Studies Conducting Head-to-Head Comparisons—Only three studies compared opioid therapy to another active treatment (either a non-steroidal or a tricyclic antidepressant).[42,55,64] One found a nonsignificant difference in level of neuropathic pain reduction (effect size = 0.206) for long-acting morphine use versus tricyclic anti-depressant (nortriptylline or desipramine) therapy.[64] Among patients with osteoarthritis, no difference in level of pain reduction was found (effect size = −0.066) between long-acting tramadol use and non-steroidal (diclofenac) therapy.[42] Another study of osteoarthritis pain found that a weak opioid (propoxyphene) provided comparable analgesic efficacy to suprofen, but provided inadequate data to calculate an effect size.[55]

Results of Studies Examining the Effect of Age on Treatment Outcomes: Six studies[29,30,47,53,56,60] included 788 subjects ages 65 and older and assessed for age effects. A meta-analysis could not be conducted because of data limitations. All six studies reported that analgesic efficacy was independent of age and documented significant pain reductions in both older (65 years and above) and younger (less than 65 years) study patients. Significant treatment effects in favor of opioid therapy for patients 65 years and above were also reported for other outcomes including physical functioning,[47,53,56] sleep,[47,56] and quality of life.[47]

Abuse/Misuse Outcomes

Four studies[58,69-71] reported outcomes regarding opioid abuse/misuse. Three studies operationalized drug abuse/misuse as the presence of selected patient behaviors (e.g., seeking opioid prescriptions from multiple physicians, forging prescriptions, or reports of lost or stolen prescriptions, while the fourth required that an ICD code for opioid abuse or dependence be present in the patient's medical record. One 36-month retrospective cohort study of 644 patients with osteoarthritis (mean age 63) found that 3% of participants demonstrated opioid abuse behaviors.[58] In a study of 15,160 veterans receiving opioid medications, fewer than 1% of patients 60 years of age or older over versus 4% of those under 60 ($p < 0.001$) had a recorded diagnosis of opioid abuse or dependence.[69] A prospective cohort study[70] of 196 opioid-treated patients with chronic pain found that advancing age was associated with a lower likelihood of abuse/misuse (adjusted OR = 0.95; 95% CI = 0.90-0.99). Finally, a retrospective cohort study of 98 primary care patients with chronic pain,[71] found that advancing age was also associated with a decreased likelihood of abuse/misuse behaviors (adjusted OR = 0.94; 95% CI = 0.89-0.99).

Adverse Events

Among opioid-treated patients, the most commonly reported adverse advents were constipation with a median frequency of occurrence of 30% (range 12–52%); nausea 28% (12–61%); dizziness 22% (10–37%); and somnolence 21% (10–39%). Occurrence rates for these outcomes were lower in the placebo control groups (Table 1). Most adverse events were rated by investigators as either ‘mildly’ or ‘moderately’ severe and all resolved after stopping the medication. Numbers need to harm and corresponding 95% confidence intervals were calculated for the most prevalent adverse events and included: nausea (5.9; 95% CI 4.5-7.3), constipation (6.3; 95% CI, 4.3-8.4) somnolence (8.6; 95% CI, 5.9-11.4) and dizziness (9.1; 95% CI, 6.3-11.9).

Only three studies assessed for possible age effects regarding adverse events.[29,47,53] In one study,[47] older (≥ 65 years) participants receiving opioid therapy were more likely to report constipation (28% vs. 17%, $p < 0.001$), fatigue (9% vs. 4%, $p = 0.016$), and anorexia (6% vs. 3%, $p = 0.028$), as compared to opioid-treated patients less than 65 years of age. In a second study,[53] older patients receiving opioid therapy reported higher rates of somnolence (9% vs. 3%, no p value provided) and vomiting (13% vs. 7%, no p value provided) when compared to patients receiving treatment who were less than 65. In the third study,[29] complaints of somnolence among patients 65 years of age and above were greater than for those younger than 65 ($p = 0.02$), but the study did not provide occurrence rates for either age group.

Discontinuation Rates

One in four opioid treated patients discontinued treatment due to an adverse event, with a median rate of discontinuation of 25% (range = 3–52%). Only 8% (2–24%) of participants receiving a placebo or comparator drug discontinued treatment on account of an adverse event. The median rate of withdrawal due to a lack of drug efficacy was 8% (0–47%) among opioid treated patients and 16% (0–67%) in the control patients.

Examination of Publication Bias

A funnel plot with 1/(standard error), a measure of sample size, plotted against effect size showed no clustering of studies in the lower-right of the funnel that would indicate lack of publication of smaller or nonsignificant studies (data not shown).

DISCUSSION

Among young-old patients (mean age across studies ranged from 60 to 73 years) without significant comorbidities, short-term use of opioids is associated with modest, but favorable effects on both pain and physical functioning. The observed effect sizes are comparable to those reported in other reviews[1-4] of opioid analgesic effects in all age groups. Our results further suggest that the effects of treatment on pain may be enhanced among older individuals with neuropathic versus osteoarthritis-related pain. A recent systematic review[4] demonstrated significant efficacy associated with opioid use (relative to placebo) for the treatment of neuropathic pain. Opioids are generally considered second-line agents for the treatment of neuropathic pain because of side effects and a paucity of evidence demonstrating long-term efficacy.[72] Our result showing greater opioid-related pain reduction for neuropathic (vs. nociceptive) pain conditions should be regarded as preliminary, given the small number of studies (n=4) examining treatment outcomes among patients with neuropathic pain.

Opioid treatment was also associated with moderate (but non-significant) improvements in sleep, while physical quality of life (as measured by the SF-36) was not affected. A small, negative effect on mental health functioning was found. The clinical significance of this finding remains unclear and is in contrast to recent investigations of persons with chronic pain, which found either no effect[1,73] or improved mood with treatment among the subgroup of patients that achieved good pain relief.[54]

In sensitivity analyses, use of high potency opioids was not associated with greater reductions in pain or physical disability relative to use of low-to-medium potency opioids.

While long-acting (vs. short-acting) opioid formulations were found to have larger effect sizes for both pain and physical functioning, between group differences were not significant. Establishing the benefits of long versus short-acting opioid agents in older populations is needed, given that guidelines[10,74] continue to recommend use of long-acting formulations, whereas clinicians continue to prescribe mostly short-acting agents for chronic pain in their older patients.[21,75,76] Few studies reported on abuse/misuse outcomes, which is a particularly salient outcome as many clinicians cite concerns about potential patient addiction as a reason for not prescribing opioid therapy.[20,77] Of the four studies retained in our sample, one[58] reported a prevalence rate of 3%, while three[69-71] found that advancing age was negatively associated with abuse/misuse behaviors. These results contrast with the higher prevalence of aberrant opioid medication taking behaviors (range = 5-24%) reported in one review of nonelderly chronic back pain patients.[5] Before concluding that older adults are less likely to abuse/misuse opioids, additional research is needed given the short-term nature of most studies in our review and the fact that a sizeable majority excluded persons with a history of substance abuse, which is a recognized risk factor for opioid abuse.[71]

An important question in clinicians' minds is whether opioid therapy is comparable or superior in terms of safety and efficacy when compared with non-opioid analgesic agents. Only three studies[42,55,64] in our sample conducted such appraisals. These preliminary results suggest that short-term outcomes of opioid therapy are comparable to those obtained with either non-steroidal or tricyclic antidepressant therapy. What constitutes comparable analgesic therapy given increasing concerns[17] about the safety of non-steroidal anti-inflammatory agents is an important and unresolved question. Comparative effectiveness studies are needed and could include evaluations of opioid use versus nonpharmacologic treatments to include complementary therapies.

A recently published guideline calls for minimizing use of non-steroidal analgesic agents in the treatment of chronic non-cancer pain in older adults, because of the significant risk profile associated with the use of these agents.[17] The guideline recommends that clinicians consider opioid therapy for older patients who continue to report substantial pain or experience pain-related impairment in function.[17] Research published prior to the release of the guideline indicates that as many as one in four older adults with chronic non-cancer pain already receive opioid therapy.[21,78] Such a recommendation will likely translate into an increasing number of older adults who receive a course of opioid therapy for chronic non-cancer pain, providing strong support for a careful review of the evidence base regarding the efficacy and safety of this treatment approach among older adults.

Our study confirms an earlier report[10] highlighting the paucity of pain treatment research focusing exclusively on older populations. Of the 40 treatment studies retained in this review, only 6 (15%) reported results on participants (n=788) ages 65 and above. All 6 studies (which excluded individuals with significant comorbidity) reported that outcomes were comparable in younger (less than 65 years of age) and older (65+) age groups. With few exceptions, adverse event rates were comparable. In a secondary analysis that included data from 18 studies in our sample, the degree of pain reduction did not vary as a function of participant mean age (range = 60–73 years), suggesting further that older adults may also obtain benefit from opioid therapy. Thus, available evidence suggests that adults ages 65 and above without significant comorbidity are equally likely to benefit from opioid therapy as younger adults with respect to pain reduction. There are currently insufficient data to determine whether and to what extent the positive treatment effects observed in the current study extend to important subgroups of older adults, including those with multiple comorbidities, functional impairment, cognitive deficits, as well as those taking multiple medications.

Additional study limitations associated with the retained articles include the following: First, studies followed patients for brief periods of time. Thus, the long-term effects of opioid use on pain, physical and metabolic function, and other relevant outcomes (e.g., likelihood of developing tolerance) remain to be determined. Second, most studies examined fixed doses of long-acting opioids, while prior studies[21,76] suggest that physicians are more likely to prescribe short-acting agents on an as needed basis for patients with chronic non-cancer pain. The positive treatment effects observed in the current study may overestimate the 'true' benefits of opioid therapy given that the prescribing patterns of the studies correlate poorly with how these medications are actually prescribed in practice. Finally, 78% of the studies were sponsored by pharmaceutical companies, raising concerns about the possibility of reporting bias.

Limitations of this review include the possibility that our search strategy failed to identify all pertinent articles. However, a broad array of search terms and data bases was employed along with a careful review of the references from all retained articles in an attempt to eliminate this bias. In addition, most of the retained articles generated positive results, raising the question of possible publication bias, although there was no indication in a funnel plot of exclusion of smaller or nonsignificant studies.

In conclusion, the clinical management of older adults with chronic non-cancer pain disorders remains challenging, in part due to complex risk–benefit decisions that clinicians routinely face regarding pharmacologic interventions in this age group. Our findings support recommendations[17,79] that short-term opioid trials are reasonable for older adults without comorbidity and either nociceptive or neuropathic pain. Once a decision is made to proceed with an opioid trial, frequent surveillance for ongoing attainment of therapeutic goals and adverse events is mandatory. Given that previous pain treatment studies enrolled few older adults and excluded those with significant comorbidity, it remains unclear whether older adults with multiple comorbidities or functional or cognitive impairment also benefit from such interventions. Future research on the long-term safety and efficacy of this treatment practice—with a particular focus on enrolling diverse groups of older adults with chronic non-cancer pain and ascertaining geriatric relevant outcomes (e.g., fall risk, ADL functioning, cognition, quality of life)—is now needed to improve the management of later-life pain.

Acknowledgments

The Robert Wood Johnson Foundation's Program of Research Integrating Substance Use in Mainstream Healthcare (PRISM) funded this study. This work was also supported by the John A. Hartford Foundation (Hartford Center of Excellence in Geriatric Medicine Award to Weill Cornell Medical College) and the Cornell-Columbia Translational Research Institute on Pain in Later Life: An Edward R. Roybal Center for Translational Research on (P30 AG22845-02) Award. This research project was supported by grants from the Robert Wood Johnson Foundation, the John A. Hartford Foundation and the National Institute on Aging.

REFERENCES

1. Kalso E, Edwards JE, Moore A, et al. Opioids in chronic non-cancer pain: systematic review of efficacy and safety. Pain. 2004; 112:372–380. [PubMed: 15561393]
2. Avouac J, Gossec L, Dougados M. Efficacy and safety of opioids for osteoarthritis: A meta-analysis of randomized controlled trials. Osteoarthritis Cartilage. 2007; 15:957–965. [PubMed: 17398122]
3. Furlan AD, Sandoval JA, Mailis-Gagnon A, et al. Review: Opioids are more effective than placebo but not other analgesics for chronic noncancer pain. CMAJ. 2006; 174:1589–1594. [PubMed: 16717269]
4. Eisenberg E, McNichol ED, Carr DM. Efficacy and safety of opioid agonists in the treatment of neuropathic pain of nonmalignant origin. JAMA. 2005; 293:3043–3052. [PubMed: 15972567]

5. Martell BA, O'Connor PG, Kerns RD, et al. Systematic review: Opioid treatment for chronic back pain: Prevalence, efficacy, and association with addiction. Ann Intern Med. 2007; 146:116–127. [PubMed: 17227935]
6. Elliott AM, Smith BH, Penny KI, et al. The epidemiology of chronic pain in the community. Lancet. 1999; 354:1248–1252. [PubMed: 10520633]
7. Helme RD, Gibson SJ. The epidemiology of pain in elderly people. Clin Geriatr Med. 2001; 17:417–431. [PubMed: 11459713]
8. Blyth FM, March LM, Brnabic AJM, et al. Chronic pain in Australia: A prevalence study. Pain. 2001; 89:127–134. [PubMed: 11166468]
9. Soldato M, Liperoti R, Landi F, et al. Non-malignant daily pain and risk of disability among older adults in home care in Europe. Pain. 2007; 129:304–310. [PubMed: 17156918]
10. American Geriatrics Society Panel on Persistent Pain in Older Persons. The management of persistent pain in older persons. J Am Geriatr Soc. 2002; 50:S205–224. [PubMed: 12067390]
11. Bryant LL, Grigsby J, Swenson C, et al. Chronic pain increases the risk of decreasing physical performance in older adults: The San Luis Valley Health and Aging Study. J Gerontol Med Sci. 2007; 62:989–996.
12. Reid MC, Williams CS, Gill TM. Back pain and decline in lower extremity physical function among community-living older persons. J Gerontol Med Sci. 2005; 60:793–797.
13. Scudds RJ, Robertson JM. Empirical evidence of the association between the presence of musculoskeletal pain and physical disability in community-dwelling senior citizens. Pain. 1998; 75:229–235. [PubMed: 9583758]
14. Bryant LL, Grigsby J, Swenson C, et al. Chronic pain increases the risk of decreasing physical performance in older adults: The San Luis Valley Health and Aging Study. J Gerontol Med Sci. 2007; 62:989–996.
15. Leveille SG, Fried L, Guralnik JM. Disabling symptoms: What do older women report? J Gen Intern Med. 2002; 17:766–773. [PubMed: 12390552]
16. Bell GM, Schnitzer TJ. Cox-2 inhibitors and other nonsteroidal anti-inflammatory drugs in the treatment of pain in the elderly. Clin Geriatr Med. 2001; 17:489–502. [PubMed: 11459717]
17. American Geriatric Society Panel on the Pharmacological Management of Peristent Pain in Older Persons. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 2009; 57:1331–1346. [PubMed: 19573219]
18. Auret K, Schug SA. Underutilization of opioids in elderly patients with chronic pain: Approaches to correcting the problem. Drugs Aging. 2005; 22:641–654. [PubMed: 16060715]
19. Upshur CC, Luckmann RS, Savageau JA. Primary care provider concerns about management of chronic pain in community clinic populations. J Gen Intern Med. 2006; 21:652–655. [PubMed: 16808752]
20. Lin JJ, Alfandre D, Moore C. Physician attitudes toward opioid prescribing for patients with persistent noncancer pain. Clin J Pain. 2007; 23:799–803. [PubMed: 18075408]
21. Solomon DH, Avorn J, Wang PH, et al. Prescription opioid use among older adults with arthritis or low back pain. Arthr Rheum. 2006; 55:35–41. [PubMed: 16463409]
22. Deshpande A, Furlan A, Mailis-Gagnon A, et al. Opioids for chronic low-back pain. Cochrane Database of Systematic Reviews. 2007; (3):CD004959.
23. Jadad AR, Moore A, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: Is blinding necessary? Controlled Clin Trials. 1996; 17:1–12. [PubMed: 8721797]
24. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomized and non-randomized studies of health care interventions. J Epidemiol Community Health. 1998; 52:377–384. [PubMed: 9764259]
25. Ferro MA, Speechley KN. Depressive symptoms among mothers of children with epilepsy: A review of prevalence, associated factors, and impact on children. Epilepsia. 2009; 50:2344–2354. [PubMed: 19694788]
26. Henderson CR Jr. Analysis of covariance in the mixed model: higher level, nonhomogeneous, and random regressions. Biometrics. 1982; 38:623–640. [PubMed: 7171692]

27. DerSimonian R, Laird N. Meta-analysis in clinical trials. Controlled Clinical Trials. 1986; 7:177–188. [PubMed: 3802833]
28. Egger M, Smith G Davey, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315:629–634. [PubMed: 9310563]
29. Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock, controlled-release oxycodone therapy for osteoarthritis-related pain: Placebo-controlled trial and long-term evaluation. Arch Intern Med. 2000; 160:853–860. [PubMed: 10737286]
30. Malonne H, Coffiner M, Sonet B, et al. Efficacy and tolerability of sustained-release tramadol in the treatment of symptomatic osteoarthritis of the hip or knee: a multicenter, randomized, double-blind, placebo-controlled study. Clin Ther. 2004; 26:1774–1782. [PubMed: 15639689]
31. Peloso PM, Bellamy N, Bensen W, et al. Double blind randomized placebo control trial of controlled-release codeine in the treatment of osteoarthritis of the hip or knee. J Rheumatol. 2000; 27:764–771. [PubMed: 10743822]
32. Caldwell JR, Rapoport RJ, Davis JC, et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: Results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. J Pain Symptom Manage. 2002; 23:278–291. [PubMed: 11997197]
33. Markenson JA, Croft J, Zhang PG, et al. Treatment of persistent pain associated with osteoarthritis with controlled-release oxycodone tablets in a randomized controlled clinical trial. Clin J Pain. 2005; 21:524–535. [PubMed: 16215338]
34. Loet XL, Pavelka K, Richarz U. Transdermal fentanyl for the treatment of pain caused by osteoarthritis of the knee or hip: an open, multicentre study. BMC Musculoskelet Dis. 2005; 6:31.
35. Kjaersgaard-Andersen P, Nafei A, Skov O, et al. Codeine plus paracetamol versus paracetamol in longer-term treatment of chronic pain due to osteoarthritis of the hip.A randomized, double-blind, multi-centre study. Pain. 1990; 43:309–318. [PubMed: 2293142]
36. Zautra AJ, Smith BW. Impact of controlled-release oxycodone on efficacy beliefs and coping Efforts among osteoarthritis patients with moderate to severe pain. Clin J Pain. 2005; 21:471–477. [PubMed: 16215331]
37. Choquette D, McCarthy TG, Rodrigues JF, et al. Transdermal fentanyl improves pain control and functionality in patients with osteoarthritis: An open-label Canadian trial. Clin Rheumatol. 2008; 27:587–595. [PubMed: 18038178]
38. Langford R, McKenna F, Ratcliffe S, et al. Transdermal fentanyl for improvement of pain and functioning in osteoarthritis: A randomized, placebo-controlled trial. Arthritis Rheum. 2006; 54:1829–1837. [PubMed: 16729276]
39. Hale M, Tudor IC, Khanna S, et al. Efficacy and tolerability of once-daily OROS hydromorphone and twice-daily extended-release oxycodone in patients with chronic, moderate to severe osteoarthritis pain: Results of a 6-week, randomized, open-label, noninferiority analysis. Clin Ther. 2007; 29:874–888. [PubMed: 17697906]
40. Kivitz A, Ma C, Ahdieh H, Galer BS. A 2-week, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, phase III trial comparing the efficacy of oxymorphone extended release and placebo in adults with pain associated with osteoarthritis of the hip or knee. Clin Ther. 2006; 28:352–364. [PubMed: 16750450]
41. Matsumoto AK, Babul N, Ahdieh H. Oxymorphone extended-release tablets relieve moderate to severe pain and improve physical function in osteoarthritis: Results of a randomized, double-blind, placebo- and active-controlled phase III trial. Pain Med. 2005; 6:357–366. [PubMed: 16266356]
42. Beaulieu AD, Peloso PM, Haraoui B, et al. Once-daily, controlled-release tramadol and sustained-release diclofenac relieve chronic pain due to osteoarthritis: A randomized controlled trial. Pain Res Manag. 2008; 13:103–110. [PubMed: 18443672]
43. Fleischmann RM, Caldwell JR, Roth SH, et al. Tramadol for the treatment of joint pain associated with osteoarthritis: A randomized, double-blind, placebo-controlled trial. Curr Ther Res. 2001; 62:113–127.
44. Schnitzer TJ, Kamin M, Olson WH. Tramadol allows reduction of naproxen dose among patients with naproxen-responsive osteoarthritis pain: A randomized, double-blind, placebo-controlled study. Arthritis Rheum. 1999; 42:1370–1377. [PubMed: 10403264]

45. Babul N, Noveck R, Chipman H, et al. Efficacy and safety of extended-release, once-daily tramadol in chronic pain: A randomized 12-week clinical trial in osteoarthritis of the knee. J Pain Symptom Manage. 2004; 28:59–71. [PubMed: 15223085]
46. Karlsson M, Berggren AC. Efficacy and safety of low-dose transdermal buprenorphine patches (5,10, and 20 microg/h) versus prolonged-release tramadol tablets (75, 100, 150, and 200 mg) in patients with chronic osteoarthritis pain: A 12-week, randomized, open-label, controlled, parallel-group noninferiority study. Clin Ther. 2009; 31:503–513. [PubMed: 19393841]
47. Vorsanger G, Xiang J, Jordan D, et al. Post hoc analysis of a randomized, double-blind, placebo-controlled efficacy and tolerability study of tramadol extended release for the treatment of osteoarthritis pain in geriatric patients. Clin Ther. 2007; 29:2520–2535. [PubMed: 18164919]
48. Burch F, Fishman R, Messina N, et al. A comparison of the analgesic efficacy of Tramadol Contramid OAD versus placebo in patients with pain due to osteoarthritis. J Pain Symptom Manage. 2007; 34:328–338. [PubMed: 17583466]
49. Mongin G, Yakusevich V, Kope A, et al. Efficacy and safety of a novel once-daily tablet formulation of tramadol. Clin Drug Invest. 2004; 24:545–558.
50. Emkey R, Rosenthal N, Wu SC, et al. Efficacy and safety of tramadol/acetaminophen tablets (Ultracet) as add-on therapy for osteoarthritis pain in subjects receiving a COX-2 nonsteroidal antiinflammatory drug: a multicenter, randomized, double-blind, placebo-controlled trial. J Rheumatol. 2004; 31:150–156. [PubMed: 14705234]
51. Choi CB, Song JS, Kang YM, et al. A 2-week, multicenter, randomized, double-blind, double-dummy, add-on study of the effects of titration on tolerability of tramadol/acetaminophen combination tablet in Korean adults with knee osteoarthritis pain. Clin Ther. 2007; 29:1381–1389. [PubMed: 17825689]
52. Silverfield JC, Kamin M, Wu SC, et al. Tramadol/acetaminophen combination tablets for the treatment of osteoarthritis flare pain: A multicenter, outpatient, randomized, double-blind, placebo-controlled, parallel-group, add-on study. Clin Ther. 2002; 24:282–296. [PubMed: 11911558]
53. Rosenthal NR, Silverfield JC, Wu SC, et al. Tramadol/acetaminophen combination tablets for the treatment of pain associated with osteoarthritis flare in an elderly patient population. J Am Geriatr Soc. 2004; 52:374–380. [PubMed: 14962151]
54. Roth SH. Efficacy and safety of tramadol HCl in breakthrough musculoskeletal pain attributed to osteoarthritis. J Rheumatol. 1998; 25:1358–1363. [PubMed: 9676769]
55. Salzman RT, Brobyn RD. Long-term comparison of suprofen and propoxyphene in patients with osteoarthritis. Pharmacology. 1983; 27(Suppl 1):55–64. [PubMed: 6361792]
56. Sasaki J, Weil AJ, Ross EL, et al. Effectiveness of polymer-coated extended-release morphine sulfate capsules in older patients with persistent moderate-to-severe pain: A subgroup analysis of a large, open-label, community-based trial. Cur Ther Res. 2007; 68:137–150.
57. Berliner MN, Giesecke T, Bornhovd KD. Impact of transdermal fentanyl on quality of life in rheumatoid arthritis. Clin J Pain. 2007; 23:530–534. [PubMed: 17575494]
58. Ytterberg SR, Mahowald ML, Woods SR. Codeine and oxycodone use in patients with chronic rheumatic disease pain. Arthritis Rheum. 1998; 41:1603–1612. [PubMed: 9751092]
59. Ringe JD, Faber H, Bock O, et al. Transdermal fentanyl for the treatment of back pain caused by vertebral osteoporosis. Rheumatol Int. 2002; 22:199–203. [PubMed: 12215866]
60. Peniston JH, Gould E. Oxymorphone extended release for the treatment of chronic low back pain: A retrospective pooled analysis of enriched-enrollment clinical trial data stratified according to age, sex, and prior opioid use. Clin Ther. 2009; 31:347–358. [PubMed: 19302907]
61. Watson CP, Moulin D, Watt-Watson J, et al. Controlled-release oxycodone relieves neuropathic pain: a randomized controlled trial in painful diabetic neuropathy. Pain. 2003; 105:71–78. [PubMed: 14499422]
62. Hanna M, O'Brien C, Wilson MC. Prolonged-release oxycodone enhances the effects of existing gabapentin therapy in painful diabetic neuropathy patients. Eur J Pain. 2008; 12:804–813. [PubMed: 18262450]
63. Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain. A randomized trial in post-herpetic neuralgia. Neurology. 1998; 50:1837–1841. [PubMed: 9633737]

64. Raja SN, Haythornthwaite JA, Pappagallo M, et al. Opioids versus antidepressants in post-herpetic neuralgia: A randomized, placebo-controlled trial. Neurology. 2002; 59:1015–1021. [PubMed: 12370455]

65. Boureau F, Legallicier P, Kabir-Ahmadi M. Tramadol in post-herpetic neuralgia: A randomized, double-blind, placebo-controlled trial. Pain. 2003; 104:323–331. [PubMed: 12855342]

66. Franco ML, Seoane A. Usefulness of transdermal fentanyl in the management of nonmalignant chronic pain: A prospective, observational, multicenter study. Pain Clinic. 2002; 14:99–112.

67. Gatti A, Sabato AF, Carucci A, et al. Adequacy assessment of oxycodone/paracetamol (acetaminophen) in multimodal chronic pain: A prospective observational study. Clin Drug Investig. 2009; 29(Suppl 1):31–40.

68. Mariconti P, Collini R. Tramadol SR in arthrosic and neuropathic pain. Minerva Anesthesiol. 2008; 74:63–68.

69. Edlund MJ, Steffick D, Hudson T, et al. Risk factors for clinically recognized opioid abuse and dependence among veterans using opioids for chronic non-cancer pain. Pain. 2007; 129:355–362. [PubMed: 17449178]

70. Ives TJ, Chelminski PR, Hammett-Stabler CA, et al. Predictors of opioid misuse in patients with chronic pain: A prospective cohort study. BMC Health Serv Res. 2006; 6:46. [PubMed: 16595013]

71. Reid MC, Engles-Horton LL, Weber MB, et al. Use of opioid medications for chronic noncancer pain syndromes in primary care. J Gen Intern Med. 2002; 17:173–179. [PubMed: 11929502]

72. Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: Evidence-based recommendations. Pain. 2007; 132:237–251. [PubMed: 17920770]

73. Dillie KS, Fleming MF, Mundt MP, et al. Quality of life associated with daily opioid therapy in a primary care chronic pain sample. J Am Board Fam Med. 2008; 21:108–117. [PubMed: 18343858]

74. Kalso E, Allan L, Dellemijn PL, et al. Recommendations for using opioids in chronic non-cancer pain. Eur J Pain. 2003; 7:381–386. [PubMed: 12935789]

75. Won AB, Lapane KL, Vallow S, et al. Persistent nonmalignant pain and analgesic prescribing patterns in elderly nursing home residents. J Am Geriatr Soc. 2004; 52:867–874. [PubMed: 15161448]

76. Reid MC, Papaleontiou M, Olkhovskaya Y, et al. Should we be prescribing opioids for chronic pain in our older patients? J Am Geriatr Soc. 2008; (Suppl):S175.

77. Nwokeji ED, Rascati KL, Brown CM, et al. Influences of attitudes on family physicians' willingness to prescribe long-acting opioid analgesics for patients with nonmalignant pain. Clin Therap. 2007; 29(Suppl):589–602.

78. Barry LC, Gill T, Kerns RD, et al. Effective pain reduction strategies among community living older persons with chronic pain. J Gerontol Med Sci. 2005; 60:1569–1575.

79. Anonymous. The use of opioids for the treatment of chronic pain. A consensus statement from the American Academy of Pain Medicine and the American Pain Society. Clin J Pain. 1997; 13:6–8. [PubMed: 9084947]

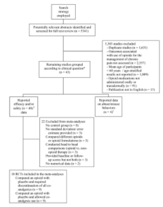

Figure.
Flow diagram of included and excluded studies

Table 1

Studies reporting on opioid efficacy and safety among older adults with chronic non-malignant pain

Ref. #	Condition Site	Study / Subject Characteristics			% of Treatment or Control Group Reporting/Experiencing		% Discontinuing Treatment Due To	
	Opioid / Reference Group	Size / Race Ethnicity*	Mean Age ± SD or (range)†	Length	Efficacy Outcome‡§	Adverse Event Outcomes§	Adverse Events§	Lack of Efficacy§
Osteoarthritis								
[29]	Spine, knee or other Controlled Release Oxycodone (10 mg bid, 20 mg bid) / Placebo	N = 133 NRM	62 (32-90)	2 weeks (placebo-controlled trial)	Pain intensity ↓ 28% / 31% / 13%1¶	Nausea 27% / 41% / 11% Dizziness 30% / 20% / 9% Somnolence 25% / 27% / 4% Constipation 23% / 32% / 7% Pruritus 18% / 16% / 2%	27% / 32% / 4%	27% / 11% / 49%
	Controlled Release Oxycodone (dose escalated to maximum of 40 mg qd)	N = 106	62 (32-90)	24 weeks (extension trial)	Pain intensity ↓ 27%	Constipation 52% Somnolence 30% Nausea 24% Pruritus 20% Nervousness 15%	37%	8%
[30]	Hip or knee Controlled Release Tramadol (200 mg qd) / Placebo	N = 230 100% W	67.1 ± 7.1 (Tramadol) 66.4 ± 9.2 (Placebo)	2 weeks	Pain intensity ↓ 41% / 27%**	Nausea 23% / 7% Vomiting 17% / 1%	22% / 2%	NR
[31]	Hip or knee Controlled Release Codeine (50 mg bid; dose escalated up to 200 mg bid) / Placebo	N = 103 NR	61.6 ± 11.2	4 weeks	Pain intensity ↓ 55% / 16%†† WOMAC scores‡‡ Stiffness ↓ 48% / 17%** Physical function ↑ 49% / 17%‡‡	Constipation 49% / 11% Somnolence 39% / 10% Dizziness 33% / 8%	29% / 8%	1% / 10%
[32]	Hip or knee Controlled Release Morphine preparations (Once daily MS04, 30 mg given in AM, once daily MS04 given in PM; controlled release MS04 15 mg given twice daily / Placebo	N = 295 84% W 14% AA 2% O	62.6 ± 9.5 (24-hr prep in AM) 63.1 ± 11.1 (24-hr prep in PM) 61.9 ± 10.4 (Twice daily prep) 61.9 ± 10.7 (Placebo)	4 weeks (placebo-controlled trial)	Pain intensity ↓ 26% / 22% / 22% / 14% WOMAC scores: Stiffness ↓ 17% / 17% / 14% / 11% Physical function ↑ 18% / 19% / 14% / 8%	Constipation 49% / 40% / 29% / 4% Nausea 21% / 32% / 26% / 10% Somnolence 16% / 12% / 12% / 0% Vomiting 6% / 16% / 8% / 1%	23% / 25% / 24% / 7%	12% / 16% / 11% / 19%

Ref. #	Condition Site / Opioid / Reference Group	Study / Subject Characteristics: Size / Race Ethnicity[*]	Mean Age ± SD or (range)[†]	Length	% of Treatment or Control Group Reporting/Experiencing: Efficacy Outcome[‡§]	Adverse Event Outcomes[§]	% Discontinuing Treatment Due To: Adverse Events[§]	Lack of Efficacy[§]
	24 hour prep in AM / 24 hour prep in PM (both doses escalated if needed)	N = 181		26 weeks (open-label extension trial)	Significant treatment effects observed for pain and physical function outcomes during weeks 4 to 26[§§]	Constipation 37% / 32% Nausea 12% / 20% Diarrhea 15% / 10% Somnolence 15% / 10%	36% / 30%	11% / 7%
[33]	Hip, knee, spine or other Controlled Release Oxycodone (10 mg bid, dose escalated up to a maximum of 60 mg bid / Placebo	N = 109 93% W 6% AA 1% H	63 (38-89)	13 weeks	Pain intensity ↓ 26% / 9%[¶] Pain relief ↑ 21 % / ↓ 8%[**] Overall WOMAC score ↓ 28% / 1%[††], [//]	Constipation 48% / 10% Nausea 41% / 14% Somnolence 32% / 10% Dizziness 32% / 6% Pruritus 21% / 0% Headache 20% / 20%	36% / 4%	16% / 67%
[34]	Hip or knee Fentanyl (25 µg/h, dose escalated if needed) / No reference group	N = 159 NR	67 (47-88)	4 weeks	Pain relief ↑ 64% WOMAC scores: Stiffness ↓ 23%[††] Physical function ↑ 23%[††] SF-36 quality of life (physical) ↑ 15%[††] SF-36 quality of life (mental) ↑ 6%[¶]	Nausea 32% Vomiting 26% Somnolence 16%	22%	1%
[35]	Hip Codeine (60 mg tid) with paracetamol (1 g tid) / Paracetamol (1 g tid)	N = 161 NR	66 (27-82) (Codeine + Paracetamol) 67 (42-82) (Paracetamol)	4 weeks	Decreased pain intensity reported by 45% / 40% of patients	Nausea 41% / 8% Dizziness 31% / 1% Vomiting 23% / 4% Constipation 21% / 9% Somnolence 17% / 7%	48% / 14%	NR
[36]	Site not specified Controlled Release (CR) Oxycodone (10 mg bid, dose escalated up to maximum daily dose of 120 mg) / Placebo	N = 107 93% W 7% O	62.6 ± 12.2 (CR Oxycodone) 64 ± 10.7 (Placebo)	2 weeks	Pain intensity ↓ 25% / 7%[††]	NR	36% / 4%	16% / 67%
[37]	Hip or knee Fentanyl (25 µg/h, dose escalated if needed) / No reference group	N = 81 93%W 7%O	60 ± 11	8 weeks	Pain intensity ↓ 28%[††] WOMAC scores: Stiffness ↓ 27%[††] Physical function ↑ 24%[††]	Nausea 43% Dizziness 26% Headache 23% Constipation 21%	42%	NR
[38]	Hip or knee	N = 399 NR	66 ± 0.7 (Fentanyl)	6 weeks	Pain intensity ↓ 32% / 24%[¶] Significant treatment effects reported for	Nausea 44% / 19% Vomiting 28% / 3% Somnolence 22% / 4%	27% / 10%	7% / 32%

NIH-PA Author Manuscript
NIH-PA Author Manuscript

Ref. #	Condition Site Opioid / Reference Group	Study / Subject Characteristics Size / Race Ethnicity*	Mean Age ± SD or (range)†	Length	% of Treatment or Control Group Reporting/Experiencing Efficacy Outcome‡§	Adverse Event Outcomes§	% Discontinuing Treatment Due To Adverse Events§	Lack of Efficacy§
	Fentanyl (25 μg/h, dose escalated if needed) / Placebo		66 ± 0.7 (Placebo)		overall WOMAC score + pain & physical function subscales§§			
[39]	Hip or knee Controlled Release Hydromorphone (8 mg qd, dose escalated as needed) /Controlled Release Oxycodone (10 mg bid, dose escalated if needed) / No reference group	N = 140 86% W 9% AA 5% O	63.6 (38-91)	6 weeks	Pain intensity ↓ 24% / 16% Pain relief ↑ 64% / 53% WOMAC scores: Stiffness ↓ 33% / 32% Physical function ↑ 31% / 28%	Nausea 35% / 30% Constipation 30% / 25% Somnolence 25% / 18% Vomiting 17% / 12% Dizziness 14% / 22%	35% / 33%	1% / 4%
[40]	Hip or knee Controlled Release Oxymorphone (10 mg bid, 40 mg bid, 50 mg bid) / Placebo	N = 370 90% W 8% AA 2% O	62¶¶	xs2 weeks	Pain intensity ↓ 21% / 28% / 29% / 17%**	Nausea 23% / 41% / 55% / 9% Constipation 18% / 27% / 22% / 4% Dizziness 16% / 22% / 31% / 6% Headache 11% / 15% / 19% / 10% Vomiting 10% / 27% / 35% / 2% Somnolence 10% / 23% / 21% / 3% Pruritus 5% / 20% / 24% / 1%	25% / 55% / 52% / 10%	7% / 5% / 4% / 16%
[41]	Hip or knee Controlled Release Oxymorphone (20 mg bid, 40 mg bid) / Controlled Release Oxycodone (20 mg bid) / Placebo	N = 491 86% W 11% AA 2% H 1% O	63.4 ± 1 (Oxymorphone 20 mg) 61.4 ± 1 (Oxymorphone 40 mg) 62.7 ± 1 (Oxycodone 20 mg) 61.7 ± 1 (Placebo)	4 weeks	Pain intensity ↓ 25%¶ / 27%¶ / 22% / 17%	Nausea 61% / 60% / 43% / 11% Constipation 40% / 32% / 36% / 11% Somnolence 30% / 31% / 27% / 5% Dizziness 29% / 31% / 26% / 4% Vomiting 23% / 34% / 10% / 2% Pruritus 19% / 20% / 8% / 2% Dry mouth 12% / 12% / 15% / 1% Headache 6% / 11% / 18% / 11%	38% / 47% / 25% / 5%	4% / 7% / 10% / 27%
[42]	Hip or knee Controlled Release Tramadol titrated up to 200, 300, or 400 mg Qd / Diclofenac SR 75 mg	N = 97 NR	62.2 ± 7.3	6 weeks	Pain intensity ↓ 28% / 31% WOMAC scores: Stiffness ↓ 27% / 32% Physical function ↑ 29% / 29%	Nausea 24% / 11% Dizziness 24% / 18% Constipation 21% / 15% Somnolence 18% / 8%	16% / 15%	NR
[43]	Knee Tramadol (50 mg every 2 days, dose escalated up	N = 129 91% W 7% AA	62.5 (35-75)	12 weeks	Pain intensity ↓ 23% / 13%¶ Pain relief ↑ 43% / ↓ 57%**	Nausea 18% / 3%	22% / 15%	41% / 65%

Ref. #	Condition Site Opioid / Reference Group	Study / Subject Characteristics Size / Race Ethnicity*	Mean Age ± SD or (range)†	Length	% of Treatment or Control Group Reporting/Experiencing Efficacy Outcome‡§	Adverse Event Outcomes§	% Discontinuing Treatment Due To Adverse Events§	Lack of Efficacy§
	to 200 mg qd) / Placebo	2% O			Overall WOMAC score ↓ 17%¶, ///, *** Significant treatment effects reported for WOMAC pain, stiffness and physical function subscales‡‡			
[44]	Knee Tramadol (200 mg qd) plus naproxen (1 g qd) / Placebo plus naproxen (1 g qd)	N = 240 82% W 15% AA 3% O	61¶¶	13 weeks	Total daily dose of naproxen needed for pain relief decreased by 78% in tramadol arm	Nausea 27 % / NR Dizziness 21% / NR Constipation 17% / NR Somnolence 15% / NR	22% / 13%	NR
[45]	Knee Controlled Release Tramadol (100 mg qd, dose escalated up to 400 mg qd / Placebo	N = 246 82% W 12% AA 3% H 3% O	61¶¶ (Tramadol)	12 weeks	Pain intensity ↓ 49% / 27%†† WOMAC scores: Stiffness ↓ 43% / 18%†† Physical function ↑ 44% / 21%††	Dizziness 33% / 12% Nausea 24% / 8% Constipation 26% / 6% Headache 15%	27% / 7%	15% / 37%
[46]	Hip or knee Transdermal Buprenorphine patches (5 ug/hr escalated to a maximum dose of 20 ug/hr /Controlled Release Tramadol 75, 100, 150 or 200 mg/day escalated to maximum daily dose of 400mg/day	N = 135 99% W 1% O	64.4 (Buprenorphine patch) 64.2 (Tramadol)	12 weeks	Pain intensity ↓ 49% / 27%	Nausea 30% / 25% Constipation 18% / 8% Dizziness 16% / 5% Fatigue 13% / 18%	15% / 29%	NR
[47]	Hip or knee Controlled Release Tramadol (100 mg qd, 200 mg qd, 300 mg qd, 400 mg qd) / Placebo	N = 318 85% W 11% AA 2% H 1% A 1% O	69¶¶	12 weeks (post-hoc analysis with subjects ≥ 65 years of age)	Pain intensity ↓ 23% / 26%¶ / 33%** / 20% / 16% WOMAC scores: Stiffness ↓ 30% / 38%¶ / 39%¶ / 29% / 21% Phys. function ↑ 28% / 34% / 38%¶ / 25% /21%	Constipation 13% / 20% / 38% / 42% / 10% Dizziness 17% / 17% / 27% / 30% / 4% Nausea 13% / 28% / 29% / 25% / 8% Somnolence 11% / 15% / 11% / 24% / 2% Headache 16% / 15% / 11% / 22% / 4% Pruritus 9% / 9% / 9%/ 15% / 2%	23% / 26% / 42% / 39% / 6%	16% / 14% / 9% / 13% / 29%
[48]	Knee Tramadol (200 mg or	N = 646 85% W 8% H 5% AA	63 (40-80)	12 weeks	Pain intensity ↓ 42% / 32%††	Nausea 15% / 6%	10% / 5%	8% / 10%

Ref. #	Condition Site / Opioid / Reference Group	Study / Subject Characteristics: Size / Race Ethnicity[*]	Mean Age ± SD or (range)[†]	Length	% of Treatment or Control Group Reporting/Experiencing: Efficacy Outcome[‡§]	Adverse Event Outcomes[§]	% Discontinuing Treatment Due To: Adverse Events[§]	Lack of Efficacy[§]
	300 mg qd) / Placebo	2% O						
[49]	Knee Controlled Release Tramadol (100–400 mg bid) / Controlled Release Tramadol (100-400 mg qd)	N = 431 NR	60.3 ± 9.3 (Tramadol bid) 60.8 ± 9 .3 (Tramadol qd)	12 weeks	Pain intensity ↓ 31% / 30% WOMAC scores: Stiffness ↓ 49% / 49% Physical function ↑ 52% / 50%	Dizziness 37% / 26% Nausea 34% / 33% Constipation 30% / 34% Somnolence 21% / 30% Headache 18% / 13%	10% / 9%	1% / 1%
[50]	Hip or knee Tramadol / Acetaminophen (37.5 mg / 325 mg) qid (dose escalated if needed) plus COX2 inhibitor / Placebo plus COX2 inhibitor	N = 307 86% W 13% AA 1% A	61 (40-75)	13 weeks	Pain intensity ↓ 40% / 31%[¶] WOMAC scores: Stiffness ↓ 27% / 22% Physical function ↑ 30% / 24%[¶] SF-36 quality of life (physical) ↑ 20% / 17% SF-36 quality of life (mental) ↑ 2% / 2%	All adverse effects <15%	13% / 4%	8% / 17%
[51]	Knee Tramadol / Acetaminophen titration group (37.5 mg / 325 mg qd to tid)/ Tramadol / Acetaminophen non-titration group (37.5 mg / 325 mg tid)	N = 250 100% A	60.2 ± 7.8	2 weeks	Pain intensity ↓ 26% / 27%[††] WOMAC scores: Stiffness ↓ 24% / 31% Physical function ↑ 29% / 25%	Nausea 12% / 25% Vomiting 4% / 17% Dizziness 10% / 22%	11% / 26%	0% / 0%
[52]	Flare of OA pain / Hip or knee Tramadol / Acetaminophen (37.5 mg / 325 mg qid) / Placebo	N = 308 88% W 12% AA	60.1 ± 9.9	1.5 weeks	Pain intensity ↓ 42% / 29%[††] WOMAC scores: Stiffness ↓ 36% / 30% Physical function ↑ 37% / 30%[¶]	Nausea 17% / 4%	Nausea 17% / 4%	1% / 0%
[53]	Flare of OA pain / Hip or knee Tramadol / Acetaminophen (37.5 mg / 325 mg) plus NSAID qid / Placebo plus NSAID qid	N = 113 89% W 11% AA	70.3 ± 3.4	1.5 weeks	Pain intensity ↓ 40% / 32%[¶] WOMAC scores: Stiffness ↓ 34% / 25% Physical function ↑ 37% / 26%[¶]	Nausea 19% / 5%	16% / 9%	0% / 0%
[54]	Breakthrough musculoskeletal pain / Hip, knee or spine	N = 42 NR	65.9[¶¶] (Tramadol)	2 weeks	% reporting moderate / severe pain at rest 15% / 43%[¶]	Constipation 45% / 0% Nausea 35% / 14% Drowsiness 25% / 14% Vertigo 20% / 5%	5% / 24%	14% / 38%

Ref. #	Condition Site Opioid / Reference Group	Study / Subject Characteristics Size / Race Ethnicity*	Mean Age ± SD or (range)†	Length	% of Treatment or Control Group Reporting/Experiencing Efficacy Outcome‡§	Adverse Event Outcomes§	% Discontinuing Treatment Due To Adverse Events§	Lack of Efficacy§
	Tramadol (250 mg qd) / Placebo		67¶¶ (Placebo)			Dizziness 15% / 0%		
[55]	Spine, hand or knee	N = 114 NR	64.7¶¶ (Propoxy-phene)	24 weeks	Pain intensity ↓ 56% / 59%	Nausea 25% / 24% Epigastric distress 20% / 7% Dizziness 15% / 13%	34% / 24%	2% / 4%
	Propoxyphene (65 mg qid) / Suprofen (200 mg qid)		59.2¶¶ (Suprofen)					
[56]	Back pain and chronic pain, site not specified Polymer coated controlled release morphine; initial dose varied with each patient / Dose escalated if needed / No reference group	N = 148 89%W 11%O	73.5 ± 5.5	4 weeks	Pain intensity ↓ 33%†† SF-36 quality of life (mental) ↑ 15%** SF-36 quality of life (physical) ↑ 19%‡‡	Constipation 20%	19%	2%
Rheumatoid Arthritis								
[57]	Site not specified Fentanyl (25 μg/h, dose escalated if needed) / No reference group	N = 226 NR	66 ± 12 (Fentanyl)	4 weeks	Pain intensity ↓ 50%‡‡ Functional ability (ADL) ↑ 37%¶ Functional ability (Social) ↑ 38%¶	All adverse effects <15%	10%	NR
[58]	Site not specified Codeine and / or Oxycodone (doses varied)	N = 342 NR	62.7 ± 12.8 (short-term use) 62.4 ± 11 (long-term use)	3 year (retro-spective cohort study)	Pain severity ↓ 56% / 57%†††	Constipation 12% / 16%	NR	NR
Back Pain								
[59]	Vertebral fracture related pain Fentanyl (25 μg/h, dose escalated if needed) / No reference group	N = 64 NR	71 ± 9	4 weeks	Pain intensity at rest ↓ 55%†† Pain intensity on movement ↓ 47%†† Quality of life ↑ 38%††	Nausea / Vomiting 28% Dizziness 19%	20%	NR
[60]	Chronic low back pain due to diverse causes Controlled Release	N = 348 NR	312 < 65 36 ≥65	12 weeks	Oxymorphone responders randomized to either continued oxymorphone or placebo in this randomized withdrawal trial	All adverse effects < 15%	9% / 9%	11% / 43%

Ref. #	Condition Site	Study / Subject Characteristics			% of Treatment or Control Group Reporting/Experiencing		% Discontinuing Treatment Due To	
	Opioid / Reference Group	Size / Race Ethnicity*	Mean Age ± SD or (range)†	Length	Efficacy Outcome‡§	Adverse Event Outcomes§	Adverse Events§	Lack of Efficacy§
	Oxymorphone (5mg q12 for opioid naïve patients, higher doses for opioid experienced patients, dose escalated if needed / Placebo				Pain intensity levels remained stable in treatment arm but increased 59% in subjects receiving placebo††			
Neuropathic Pain								
[61]	Diabetic Neuropathy Controlled Release Oxycodone (10 mg bid, escalated to maximum dose of 40 mg bid) / Active Placebo (benztropine 0.25 mg bid; escalated to maximum dose of 1 mg bid)	N = 45 NR	63 ± 9.4	4 weeks	Pain intensity ↓ 68% / 28%†† Total pain and disability ↓ 47 % / 19%**	Nausea 36% / 18% Constipation 29% / 9% Somnolence 20% / 24% Dizziness 16% / 7%	32% / 17%	5% / 30%
[62]	Diabetic Neuropathy Controlled Release Oxycodone (5mg bid, dose escalated if needed plus gabapentin) / gababentin + placeb	N=338 99%W	60.1	12 weeks	Pain intensity ↓ 33% / 18%**	Constipation 27% /6% Nausea 26% / 11% Somnolence 22% / 5% Fatigue 18% / 8% Dizziness 15% / 4%	16% / 5%	3% / 12%
[63]	Post-Herpetic Neuralgia Controlled Release Oxycodone (10 mg bid) / Placebo	N=50 NR	70 ± 11	4 weeks	% with at least moderate pain relief 58% / 18%††	All adverse effects <15%	10% / 6%	0% / 2%
[64]	Post-Herpetic Neuralgia Morphine (mean dose = 91 mg qd) or Methadone (15 mg qd) / Tricyclic anti-depressant (nortriptylline, mean dose = 89 mg qd or desipramine, mean dose = 63 mg qd) / Placebo	N = 76 88 % W 11 % AA 1% O	71 ± 12	8 weeks	Pain intensity ↓ 32% / 19% / 3%†† Pain relief ↑ 38% / 32% / 11%††	Nausea 39% / 6% / 7% Constipation 30% / 11% / 11% Drowsiness 30% / 11% / 14% Dizziness 18% / 17% / 7% Loss of appetite 17% / 2%/ 2%	9% / 3% / NR	0% / 0% / NR
[65]	Post-Herpetic Neuralgia Tramadol (100 mg, escalated to maximum	N = 127 NR	65.7 ± 11.9 (tramadol) 67.9 ± 11.7 (placebo)	4 weeks	Pain intensity ↓ 58% / 44%¶ Quality of life ↑ 46% / 46%	All adverse effects <15%	9% / NR	NR

Ref. #	Condition Site	Study / Subject Characteristics			% of Treatment or Control Group Reporting/Experiencing		% Discontinuing Treatment Due To	
	Opioid / Reference Group	Size / Race Ethnicity*	Mean Age ± SD or (range)†	Length	Efficacy Outcome‡§	Adverse Event Outcomes§	Adverse Events§	Lack of Efficacy§
	dose of 400 mg for age < 75 and 300 mg for age ≥ 75) / Placebo							
Neuropathic or Non-Neuropathic Pain								
[66]	Neuropathic or non-neuropathic pain Fentanyl (25 μg/h, dose escalated if needed) / No reference group	N = 236 NR	66.2 (30-91)	24 weeks	Pain intensity ↓ 47%¶ Quality of life ↑ 35%**	Dizziness 25% Somnolence 23% Nausea 22% Vomiting 15% Constipation 15%	29%	NR
[67]	Neuropathic or osteoarticular pain Oxycodone + Acetaminophen / No reference group	N = 150 NR	60 (26-85) Neuropathic group 68 (26-84) Osteoarticular group	6 weeks	Pain intensity ↓ 17% neuro Pain intensity ↓ 35% osteo	NR	53% neuro 26% osteo	NR
[68]	Arthritic (71%) or neuropathic (29%) pain Controlled Release Tramadol, initial dose 100-200 mg qd, dose escalated up to 400 mg qd if needed / No reference group	N = 100 NR	61 ± 12	4 weeks	Pain intensity ↓ 72%** for arthritis pain patients Pain intensity ↓ 66%** for neuropathic pain patients	NR	0%	NR

*Race/ethnicity codes: W = Non-Hispanic White, AA = African-American, H = Hispanic, A = Asian, O = Other.

†Mean age provided for entire sample or for treatment/comparison arm groups when no overall mean age provided.

‡Results are reported as proportionate change scores, (follow-up–baseline scores)/baseline score, unless otherwise specified.

§Results in this column correspond to the treatments or placebo listed (in the order in which they appear) in column 1.

//NR = Not reported.

¶$p \leq 0.05$.

**$p \leq 0.01$.

††$p \leq 0.001$.

NIH-PA Author Manuscript
NIH-PA Author Manuscript

‡‡ A lower total WOMAC score indicates a better outcome.

§§ Proportionate changes could not be calculated as the study did not report baseline scores for these outcomes.

//// Changes in the overall WOMAC score are reported as the study did not report baseline scores for the WOMAC subscales.

¶¶ Neither standard deviation nor range were reported for age.

*** Tested for differences in treatment vs. reference group scores at follow-up.

††† Subjects rated pain severity before and after a single dose of pain medication.

Table 2

Meta-Analysis of Primary Outcomes

Outcome	Number of studies*	No. subjects receiving opioid treatment	No. subjects receiving placebo or non-opioid therapy	Distributional assumption for studies	Placebo mean change†	Active mean change‡	Effect size (active – placebo) §	Probability for test of effect size//
Pain	18	3,005	1,865	random	−.6845	−1.2461	−.5571	<.0001
Physical Function	9	1,822	935	random	−.5660	−.9977	−.4317	.0015
Quality of Life (Physical)	4	972	512	fixed	.4099	.6010	.1911	.1713
Quality of Life (Mental)	4	972	512	fixed	.1844	−.0361	−.2205	.0305
Sleep	6	1,019	435	fixed	.7723	1.6309	.8586	.3092

Each outcome was analyzed in a separate model. The dependent variables were standardized difference scores (Time 2 – Time 1). The model for pain and physical function included a fixed classification factor for Treatment (placebo versus active) and studies as levels of a random factor. For the other outcomes, because of the limited number of studies reporting these outcomes, studies were regarded as fixed but not included in the model.

* Studies included only randomized, placebo controlled trials reporting sufficient data to allow for an estimation of effect size.

† Least squares means from the model for placebo.

‡ Least squares means from the model for active treatment.

§ Difference of the 2 least squares means (active – placebo).

// Test of the treatment effect.

Table 3

Meta-Analyses of Pain and Physical Function Outcomes by Pain Type, as well Potency, Formulation of Study Drug, and Co-analgesic Use

Variable	Out-come	Number of Studies*	No. Subjects Receiving Opioid Treatment	No. Subjects Receiving Placebo or Non-opioid Therapy	Distributional Assumption for Studies	Placebo Mean Change†	Active Mean Change‡	Effect Size (Active – Placebo)§	Probability For test of Effect Size//	Probability for Test of Interaction of Treatment and Second Variable¶
Pain Type										
Osteoarthritis	Pain	14	2,571	1,428	random	−.6830	−1.1403	−.4573	<.0001	.0259
Neuropathic		4	434	437		−.6895	−1.5961	−.9065	<.0001	
Drug Potency										
Low/Medium	Pain	13	1,910	1,346	random	−.6848	−1.2463	−.5615	<.0001	.9374
High		5	1,095	519		−.6837	−1.2293	−.5456	.0053	
Low/Medium	Phys Fxn	5	771	460	random	−.5831	−1.0570	−.4739	.0080	.6394
High		4	1,051	475		−.5446	−.9236	−.3791	.0342	
Drug Formulation										
Short-Acting	Pain	4	464	382	random	−.9495	−1.3649	−x.4154	.0393	.3981
Long-Acting		14	2,541	1,483		−.6088	−1.2064	−.5976	<.0001	
Short-Acting	Phys Fxn	3	517	211	random	−.9589	−1.2014	−.2425	.2144	.2989
Long-Acting		6	1,305	724		−.4537	−.9395	−.4858	.0021	
Co-analgesic Use Allowed										
Yes	Pain	9	1,181	1097	random	−.7277	−1.2220	−.4942	.0052	.9520
No		9	1,824	768		−.6975	−1.2050	−.5075	.0043	
Yes	Phys Fxn	4	608	513	random	−.6908	−1.0859	−.3951	.0301	.7462
No		5	1,214	422		−.4662	−.9271	−.4610	.0095	

Each outcome was analyzed in a separate model for each of the 4 additional independent variables. The dependent variables were standardized difference scores (Time 2 – Time 1). The models included fixed classification factors for Treatment (placebo versus active), one of the additional independent variables, the interaction of the 2 variables, and studies as levels of a random factor. The table presents results for 7 models, 4 for pain and 3 for physical function (there are no studies reporting the outcome for physical function that examine neuropathic pain).

* Studies included only randomized, placebo controlled trials reporting sufficient data to allow for an estimation of effect size.

† Least squares means from the model for placebo.

‡ Least squares means from the model for active treatment.

[§]Difference of the 2 least squares means (active – placebo). Larger negative differences are results in favor of the active treatment.

[//]Test of the treatment effect for a given level of pain type, potency, short/long acting, or co-analgesic use.

[¶]Test of the interaction of treatment and either pain type, potency, short/long acting, or co-analgesic use; that is, the test of whether the treatment effect differs by level of the additional variable.