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# Opioids for Chronic Noncancer Pain
## A Systematic Review and Meta-analysis

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**IMPORTANCE** Harms and benefits of opioids for chronic noncancer pain remain unclear.

**OBJECTIVE** To systematically review randomized clinical trials (RCTs) of opioids for chronic noncancer pain.

**DATA SOURCES AND STUDY SELECTION** The databases of CENTRAL, CINAHL, EMBASE, MEDLINE, AMED, and PsycINFO were searched from inception to April 2018 for RCTs of opioids for chronic noncancer pain vs any nonopioid control.

**DATA EXTRACTION AND SYNTHESIS** Paired reviewers independently extracted data. The analyses used random-effects models and the Grading of Recommendations Assessment, Development and Evaluation to rate the quality of the evidence.

**MAIN OUTCOMES AND MEASURES** The primary outcomes were pain intensity (score range, 0-10 cm on a visual analog scale for pain; lower is better and the minimally important difference [MID] is 1 cm), physical functioning (score range, 0-100 points on the 36-item Short Form physical component score [SF-36 PCS]; higher is better and the MID is 5 points), and incidence of vomiting.

**RESULTS** Ninety-six RCTs including 26 169 participants (61% female; median age, 58 years [interquartile range, 51-61 years]) were included. Of the included studies, there were 25 trials of neuropathic pain, 32 trials of nociceptive pain, 33 trials of central sensitization (pain present in the absence of tissue damage), and 6 trials of mixed types of pain. Compared with placebo, opioid use was associated with reduced pain (weighted mean difference [WMD], −0.69 cm [95% CI, −0.82 to −0.56 cm] on a 10-cm visual analog scale for pain; modeled risk difference for achieving the MID, 11.9% [95% CI, 9.7% to 14.1%]), improved physical functioning (WMD, 2.04 points [95% CI, 1.41 to 2.68 points] on the 100-point SF-36 PCS; modeled risk difference for achieving the MID, 8.5% [95% CI, 5.9% to 11.2%]), and increased vomiting (5.9% with opioids vs 2.3% with placebo for trials that excluded patients with adverse events during a run-in period). Low- to moderate-quality evidence suggested similar associations of opioids with improvements in pain and physical functioning compared with nonsteroidal anti-inflammatory drugs (pain: WMD, −0.60 cm [95% CI, −1.54 to 0.34 cm]; physical functioning: WMD, −0.90 points [95% CI, −2.69 to 0.89 points]), tricyclic antidepressants (pain: WMD, −0.13 cm [95% CI, −0.99 to 0.74 cm]; physical functioning: WMD, −5.31 points [95% CI, −13.77 to 3.14 points]), and anticonvulsants (pain: WMD, −0.90 cm [95% CI, −1.65 to −0.14 cm]; physical functioning: WMD, 0.45 points [95% CI, −5.77 to 6.66 points]).

**CONCLUSIONS AND RELEVANCE** In this meta-analysis of RCTs of patients with chronic noncancer pain, evidence from high-quality studies showed that opioid use was associated with statistically significant but small improvements in pain and physical functioning, and increased risk of vomiting compared with placebo. Comparisons of opioids with nonopioid alternatives suggested that the benefit for pain and functioning may be similar, although the evidence was from studies of only low to moderate quality.

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In 2016, an estimated 50 million adults in the United States were living with chronic noncancer pain,[1] many of whom were prescribed opioid medications.[2-4] From 2013 to 2016, the United States was the largest per-capita consumer of opioids in the world.[5,6] The effects of opioids on chronic pain are uncertain,[7] whereas the harms found to be associated with prescription opioids include diversion,[8] addiction,[9] overdose, and death.[10]

The most recent systematic review[11] of opioids for chronic noncancer pain included only effectiveness trials with 1 year of follow-up or longer and found no eligible randomized clinical trials (RCTs). The most recent review with studies that had less than 1 year of follow-up[12] included only studies published up to July 2009 and reported meta-analyses results as the standardized mean difference, which has limitations.[13] The review concluded that compared with placebo, opioids provided better pain relief for neuropathic and nociceptive pain than for fibromyalgia; however, no test for interaction was reported.[14]

This systematic review and meta-analysis of RCTs of opioids for chronic noncancer pain includes more recent data and addresses the limitations of the previous reviews.

### Key Points

**Question** Is the use of opioids to treat chronic noncancer pain associated with greater benefits or harms compared with placebo and alternative analgesics?

**Findings** In this meta-analysis that included 96 randomized clinical trials and 26 169 patients with chronic noncancer pain, the use of opioids compared with placebo was associated with significantly less pain (−0.69 cm on a 10-cm scale) and significantly improved physical functioning (2.04 of 100 points), but the magnitude of the association was small. Opioid use was significantly associated with increased risk of vomiting.

**Meaning** Opioids may provide benefit for chronic noncancer pain, but the magnitude is likely to be small.

## Methods

We followed the statement on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for RCTs,[15] registered our review (PROSPERO Identifier: CRD42012003023), and published our protocol[16] (the protocol also appears in Supplement 1). Prior to the analyses, we made the following changes to the protocol: we excluded RCTs reporting less than 4 weeks follow-up; and we included subgroup analyses of (1) enrichment trials (studies that excluded patients who reported no improvement, had problematic adverse events, or both during an open-label run-in period) vs trials that did not use the enrichment method, (2) parallel study design vs crossover trials, and (3) trials that reported change scores for treatment effects vs trials that only reported end-of-study treatment effects. In addition to these protocol changes made before conducting the analyses, we conducted a post hoc subgroup analysis of trials that administered combination products (opioid and acetaminophen) compared with opioids alone.

### Data Sources and Searches

An academic librarian developed the search strategies (eAppendix 1 in Supplement 2) without language restrictions and searched the databases of CENTRAL, CINAHL, EMBASE, MEDLINE, AMED, and PsycINFO from inception to April 1, 2018. We reviewed reference lists of eligible reports and contacted authors to obtain unpublished data.

### Eligibility Criteria

The included trials (1) enrolled patients with chronic noncancer pain, (2) randomized them to an oral or transdermal opioid (pure opioid or a combination product) vs any nonopioid control, and (3) conducted follow-up for at least 4 weeks. Conference abstracts and rarely used interventions (such as oral ketamine, mexiletine, propoxyphene, dextropropoxyphene, fedotozine, and asimadoline) for chronic noncancer pain in North America were excluded.

### Study Selection

Using a standardized form, 27 reviewers working in 13 teams screened titles, abstracts, and full-text articles reporting potentially eligible studies. Disagreements were resolved by discussion or by consultation with an adjudicator when necessary. We used online systematic review software (DistillerSR, Evidence Partners) to facilitate literature screening.

### Data Extraction

A pair of reviewers independently abstracted each article. The included data were study and patient characteristics, dose and duration of treatment, and patient-important outcomes as guided by the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials.[17,18]

The primary outcomes were pain, physical functioning, and vomiting incidence (a systematic review of patient values and preferences[19] identified nausea and vomiting as the opioid-induced adverse events that were most important to patients). We calculated the morphine-equivalent dose for each opioid by multiplying the quantity × the milligrams per unit dispensed × drug-specific conversion factors (eTable 1 in Supplement 2).[20] There are no established conversion factors for buprenorphine or cebranopadol. We used the longest follow-up reported.[21]

### Risk of Bias Assessment

Using a modified Cochrane risk of bias instrument, pairs of reviewers independently assessed the articles for risk of bias.[22,23] Response options for each item were "definitely or probably yes" (assigned a low risk of bias) and "definitely or probably no" (assigned a high risk of bias).

### Data Synthesis and Analysis

The adjusted κ statistic addressed interrater agreement regarding eligibility.[24] Continuous measures were converted to common scales on a domain-by-domain basis as follows: (1) pain intensity was converted to the 10-cm visual analog scale (VAS) for pain; (2) physical functioning to the 100-point 36-item Short Form Survey (SF-36) physical component

score; (3) emotional functioning to the 100-point SF-36 mental component score; (4) role functioning to the 100-point SF-36 subscale for role limitations due to physical problems; (5) social functioning to the 100-point SF-36 subscale for social functioning; and (6) sleep to the SF-36 sleep quality 100-mm VAS.[25]

All continuous outcome measures reported by more than 1 study were pooled and the weighted mean difference and the risk difference of achieving the minimally important difference were calculated. To estimate the probability of achieving greater than or equal to the minimally important difference in the control group, we used (1) the median or mean and standard deviation of the control group and (2) the established minimally important difference for each outcome in the treatment group. We used the pooled mean difference to estimate the mean in the treatment group and calculated the probability of achieving greater than or equal to the minimally important difference in the treatment group. We used probabilities in both groups to acquire the risk difference for achieving greater than or equal to the minimally important difference.[13]

The minimally important difference is the smallest amount of improvement in a treatment outcome that patients would recognize as important.[26] For example, the minimally important difference is about 1.0 cm for the 10-cm VAS for pain.[27] For the SF-36 items, the minimally important difference of 10 points was used for the individual domains (ie, role functioning and social functioning), 5 points for the summary scores (ie, physical functioning and emotional functioning), and 10 mm for sleep quality (measured using the 100-mm VAS).[28]

Adverse events are reported as binary outcomes. Due to the large number of adverse event types reported (n = 114), we explored the frequency distribution of adverse events and decided prior to analysis to pool the adverse events reported by 20 or more RCTs. Associations between treatment and adverse events are reported as relative risks (RRs) and risk differences and were determined using random-effects modeling and the DerSimonian-Laird method.[29] We conducted a post hoc sensitivity analysis using the Hartung-Knapp-Sidik-Jonkman method.[30] Change scores from baseline to the end of follow-up were used to account for interpatient variability. If the change scores were not reported, we calculated them using the baseline and end-of-study scores and the associated SDs using a correlation coefficient derived from the largest trial at the lowest risk of bias that reported a change score. We conducted subgroup analyses for reported vs converted change scores and only used the reported change score if a significant subgroup effect was found.

We contacted authors to obtain unpublished data for nonsignificant findings. If these data were unavailable, we addressed the risk of overestimating the magnitude of the association by imputing a weighted mean difference of 0 or an RR of 1 for the effect estimates and an associated variance using the hot-deck approach.[31] The sensitivity analyses excluded imputation for nonsignificant effects. Stata statistical software version 13.1 (StataCorp) was used. Comparisons were 2-tailed using a $P \leq .05$ threshold.

### Subgroup Analyses and Meta-Regression

The Cochran Q test and the $I^2$ statistic were used to examine statistical heterogeneity and explore treatment associations according to the following subgroups: (1) crossover vs parallel trials; (2) trials at risk of bias (on an item-by-item basis); (3) reported vs converted change scores for effect estimates; (4) studies of participants receiving disability benefits or involved in litigation vs those who were not receiving disability benefits or involved in litigation; (5) enriched enrollment trials vs not enriched; (6) trials with longer vs shorter (<3 months vs ≥3 months) follow-up; (7) higher vs lower doses of opioid, and (8) trials of combination products (opioid and acetaminophen) vs trials of opioids alone.

A clinical expert committee[32] blinded to the study results provided clinical categories for subgroup analysis and adjudicated trial populations as follows: (1) conditions associated with objective findings or not; (2) neuropathic vs nociceptive vs central sensitization; and (3) neuropathic vs nonneuropathic. Neuropathic pain results from injury to the nervous system (eg, diabetic neuropathy). Injury to other tissues producing noxious stimulus is defined as nociceptive pain (eg, osteoarthritis). Pain present without tissue damage is considered central sensitization (eg, fibromyalgia).

We conducted subgroup analyses if there were 2 or more studies in a given subgroup and conducted tests of interaction to establish whether the subgroups differed significantly from one another. We assessed the credibility of significant subgroup effects ($P < .05$) using previously suggested criteria (eTable 2 in Supplement 2).[14] Meta-regression was performed for length of follow-up, opioid dose, and loss to follow-up.

### Quality of Evidence

The Grading of Recommendations Assessment, Development and Evaluation was used to summarize the quality of evidence on an outcome-by-outcome basis as high, moderate, low, or very low.[33] We did not rate down the quality of evidence for risk of bias if the subgroup analysis showed no association of treatment effects with risk of bias. When there were at least 10 studies for meta-analysis,[34] we assessed publication bias by visual assessment of funnel plot asymmetry and by using the results from the Begg test.[35]

## Results

Of 44 345 citations, 88 English and 5 non-English reports met eligibility criteria. Three articles reported 2 RCTs each, resulting in 96 trials with 26 169 patients (**Figure 1** and eAppendix 2 in Supplement 2). There was agreement between reviewers at the full-text review stage (κ = 0.78). Of the 3 authors contacted for clarification of eligibility criteria, only 1 responded. Of the 11 authors contacted for additional data, only 2 responded.

### Study Characteristics

Among patients in the eligible trials, the median of the mean age was 58 years (interquartile range [IQR], 51-61 years). Among the 91 trials reporting sex distribution, 61% (15 397 of 25 462) of enrolled patients were female (median of individual trials,

58%; IQR, 47%-64%). Six trials included patients with different types of chronic pain, 25 included patients with neuropathic pain, 32 included patients with nociceptive pain, and 33 included patients with central sensitization (pain present in the absence of tissue damage; eTable 3 in Supplement 2).

Among 51 nonenrichment trials, the mean pain score at baseline was 6.54 cm on a 10-cm VAS (median of individual trials, 6.38 cm [IQR, 5.72-6.96 cm]; eTable 4 in Supplement 2). Of 83 trials comparing opioids with placebo, 14 added opioids or placebo to the pretrial analgesic therapy, 44 allowed additional analgesics on a limited basis, 5 were unclear regarding additional analgesic therapy, and 20 did not permit participants to receive additional analgesic therapy.

Among patients in the opioid groups in 87 trials, the median of the average morphine-equivalent dose per day was 45.0 mg (IQR, 28.2-78.3 mg; range, 7.5-242.7 mg). The median follow-up was 60 days (IQR, 30-84 days). There were 9 RCTs (9%) that reported no industry funding, 76 (79%) that reported receiving industry funding, and 11 (12%) that did not specify funding type.

Six trials (6%) reported whether patients were involved in litigation or receiving disability benefits[36-41]; one of these trials[39] enrolled 20 patients receiving compensation benefits and 1 patient with ongoing litigation. Sixty-nine trials (72%) excluded patients with current or prior substance use disorder and 45 trials (47%) excluded patients who had a diagnosed mental illness or were taking a psychotropic medication. No trials reported rates of addiction or enrollment of patients with a substance use disorder or other mental illness. Two trials reported rates of accidental opioid overdose. One trial of buprenorphine reported no accidental overdoses among 254 patients.[42] Another trial reported 1 accidental overdose with respiratory arrest among 191 patients in a trial of extended-release hydrocodone.[38]

## Risk of Bias

All trials were at risk of bias for at least 1 of the following domains; however, 51 (53%) adequately generated their randomization sequence, 48 (50%) adequately concealed allocation, 84 (88%) blinded patients, 84 (88%) blinded caregivers, 83 (87%) blinded data collectors, 82 (85%) blinded outcome assessors, and 6 (6%) included a blinded data analyst. There were 73 trials (76%) with frequent (≥20%) missing outcome data (eTable 5 in Supplement 2).

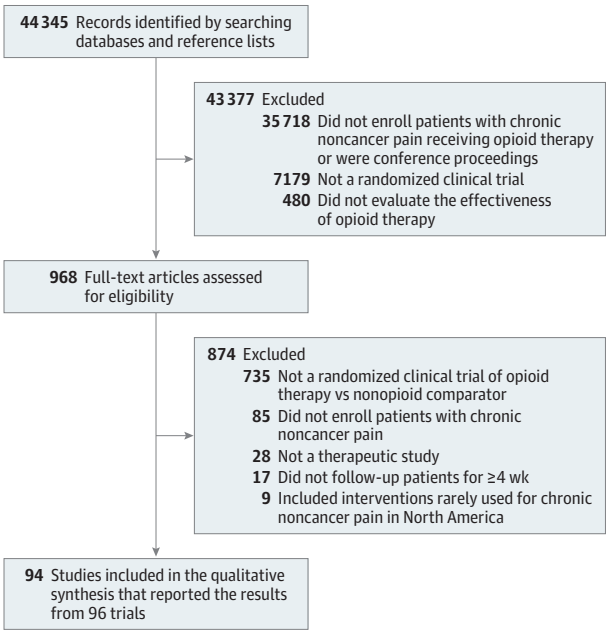
## Outcomes for Opioids vs Placebo

### Pain Relief

Although the difference did not reach the minimally important difference of 1 cm, opioids were associated with pain relief compared with placebo (weighted mean difference, −0.79 cm [95% CI, −0.90 to −0.68 cm] on a 10-cm VAS for pain, $P < .001$; modeled risk difference for achieving the minimally important difference, 13.6% [95% CI, 11.8% to 15.4%]). Studies with longer follow-up reported less pain relief (eFigures 1 and 2 in Supplement 2; $P = .04$ for interaction).

High-quality evidence from 42 RCTs that followed up patients for 3 months or longer (16 617 patients)[38,41-80] found that opioids were associated with reduced pain vs placebo (weighted mean difference, −0.69 cm [95% CI, −0.82 to −0.56 cm] on a 10-cm VAS for pain, $P < .001$; modeled risk difference for achieving the minimally important difference, 11.9% [95% CI, 9.7% to 14.1%]; **Figure 2**, the **Table**, and eFigure 3 in Supplement 2). The original data for pain relief appear in eTable 6 in Supplement 2. There were no differences in the magnitude of association based on category of chronic noncancer pain (eFigures 4-6 and eTable 7 in Supplement 2; range, $P = .13$ to $P = .45$ for interaction).

Figure 1. Diagram of the Study Selection Process for the Systematic Review and Meta-analysis




### Physical Functioning

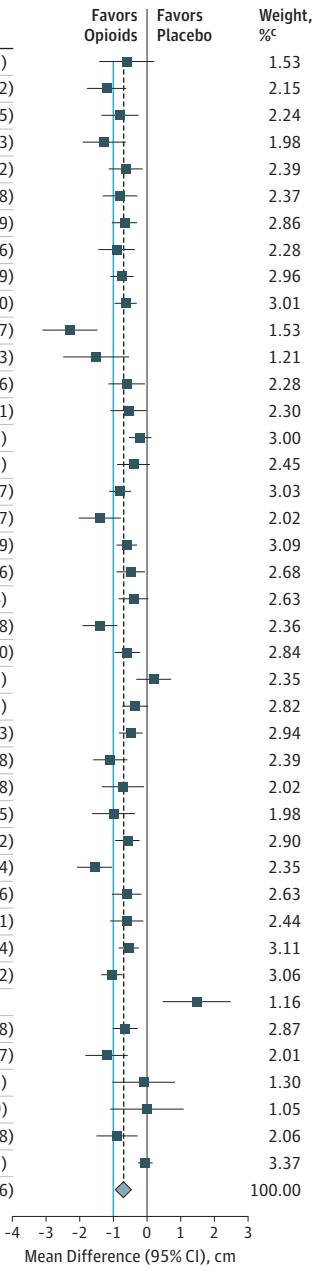
High-quality evidence from 51 RCTs (15 754 patients)[37,38,40,42,43,45-47,49-52,54,56,57,60,61,63-66,68,69,71-73,75-98] showed opioids were associated with a small improvement in physical functioning compared with placebo, but did not meet the criterion for the minimally important difference (weighted mean difference, 2.04 points [95% CI, 1.41-2.68 points] on the 100-point SF-36 physical component score, $P < .001$; minimally important difference, 5 points; modeled risk difference for achieving the minimally important difference, 8.5% [95% CI, 5.9%-11.2%]; the Table, **Figure 3**, and eFigure 7 in Supplement 2). Two trials reporting only $P$ values with significant improvement in physical functioning were excluded from the pooled analysis.[41,55]

### Emotional Functioning

Opioids were not significantly associated with emotional functioning compared with placebo (weighted mean difference, 0.14 points [95% CI, −0.58 to 0.86 points] on the 100-point SF-36 mental component score, $P = .70$). We found a subgroup effect among studies with reported vs converted change

Figure 2. Pain Relief on a 10-cm Visual Analog Scale Among Patients With Chronic Noncancer Pain Who Received Opioids vs Placebo in 42 High-Quality Randomized Clinical Trials

| Source | Opioids Group No. of Patients | Opioids Group Mean (95% CI), cm[a] | Placebo Group No. of Patients | Placebo Group Mean (95% CI), cm[a] | Between-Group Mean Difference (95% CI)[b] | Weight, %[c] |
|---|---|---|---|---|---|---|
| Fleischmann et al,[54] 2001 | 63 | -1.53 (-2.10 to -0.95) | 66 | -0.93 (-1.53 to -0.32) | -0.60 (-1.42 to 0.22) | 1.53 |
| Bennett et al,[46] 2003 | 156 | -1.90 (-2.34 to -1.46) | 157 | -0.70 (-1.09 to -0.31) | -1.20 (-1.78 to -0.62) | 2.15 |
| Ruoff et al,[69] 2003 | 151 | -1.87 (-2.29 to -1.45) | 142 | -1.07 (-1.43 to -0.70) | -0.80 (-1.35 to -0.25) | 2.24 |
| Babul et al,[45] 2004 | 124 | -3.04 (-3.50 to -2.58) | 122 | -1.77 (-2.23 to -1.31) | -1.27 (-1.91 to -0.63) | 1.98 |
| Emkey et al,[52] 2004 | 153 | -2.75 (-3.11 to -2.39) | 153 | -2.12 (-2.49 to -1.75) | -0.63 (-1.14 to -0.12) | 2.39 |
| Peloso et al,[64] 2004 | 164 | -1.36 (-1.77 to -0.94) | 161 | -0.56 (-0.87 to -0.24) | -0.80 (-1.32 to -0.28) | 2.37 |
| Gana et al,[56] 2006 | 806 | -2.15 (-2.32 to -1.98) | 205 | -1.48 (-1.82 to -1.15) | -0.67 (-1.04 to -0.29) | 2.86 |
| Webster et al,[41] 2006 | 608 | -3.40 (-3.58 to -3.23) | 101 | -2.50 (-3.02 to -1.98) | -0.90 (-1.44 to -0.36) | 2.28 |
| Burch et al,[48] 2007 | 393 | -3.03 (-3.24 to -2.82) | 196 | -2.29 (-2.57 to -2.01) | -0.74 (-1.09 to -0.39) | 2.96 |
| Fishman et al,[53] 2007 | 311 | -2.57 (-2.87 to -2.28) | 224 | -1.94 (-2.09 to -1.80) | -0.63 (-0.96 to -0.30) | 3.01 |
| Hale et al,[58] 2007 | 49 | 0.87 (0.27 to 1.47) | 18 | 3.16 (2.55 to 3.77) | -2.29 (-3.11 to -1.47) | 1.53 |
| Katz et al,[62] 2007 | 71 | 1.09 (0.51 to 1.67) | 47 | 2.60 (1.78 to 3.42) | -1.51 (-2.49 to -0.53) | 1.21 |
| Hanna et al,[59] 2008 | 163 | -2.10 (-2.50 to -1.70) | 165 | -1.50 (-1.87 to -1.13) | -0.60 (-1.14 to -0.06) | 2.28 |
| Vorsanger et al,[78] 2008 | 256 | 0.42 (0.11 to 0.72) | 126 | 0.96 (0.51 to 1.41) | -0.54 (-1.08 to -0.01) | 2.30 |
| Afilalo et al,[43] 2010 | 686 | -1.51 (-1.70 to -1.32) | 337 | -1.31 (-1.58 to -1.04) | -0.20 (-0.53 to 0.13) | 3.00 |
| Breivik et al,[47] 2010 | 86 | -0.90 (-1.29 to -0.51) | 91 | -0.50 (-0.81 to -0.19) | -0.40 (-0.89 to 0.09) | 2.45 |
| Buynak et al,[49] 2010 | 635 | -2.90 (-3.10 to -2.70) | 316 | -2.10 (-2.36 to -1.84) | -0.80 (-1.13 to -0.47) | 3.03 |
| Hale et al,[57] 2010 | 133 | 0.20 (-0.25 to 0.65) | 133 | 1.60 (1.15 to 2.05) | -1.40 (-2.03 to -0.77) | 2.02 |
| Katz et al,[60] 2010 | 171 | 0.10 (-0.11 to 0.31) | 173 | 0.70 (0.47 to 0.93) | -0.60 (-0.91 to -0.29) | 3.09 |
| DeLemos et al,[51] 2011 | 599 | -2.13 (-2.34 to -1.93) | 200 | -1.65 (-2.02 to -1.28) | -0.48 (-0.91 to -0.06) | 2.68 |
| Friedmann et al,[55] 2011 | 203 | -0.70 (-0.98 to -0.42) | 207 | -0.30 (-0.64 to 0.04) | -0.40 (-0.84 to 0.04) | 2.63 |
| Schwartz et al,[70] 2011 | 196 | 0 (-0.37 to 0.37) | 193 | 1.40 (1.03 to 1.77) | -1.40 (-1.92 to -0.88) | 2.36 |
| Steiner et al,[73] 2011 | 257 | 1.21 (0.93 to 1.49) | 283 | 1.79 (1.53 to 2.05) | -0.58 (-0.96 to -0.20) | 2.84 |
| Vojtaššák et al,[77] 2011 | 132 | -2.40 (-2.76 to -2.04) | 143 | -2.60 (-2.98 to -2.22) | 0.20 (-0.32 to 0.72) | 2.35 |
| Rauck et al,[65] 2013 | 649 | -2.25 (-2.47 to -2.03) | 331 | -1.90 (-2.21 to -1.59) | -0.35 (-0.73 to 0.03) | 2.82 |
| Rauck et al,[67] 2014 | 151 | 0.48 (0.23 to 0.73) | 151 | 0.96 (0.71 to 1.21) | -0.48 (-0.83 to -0.13) | 2.94 |
| Vinik et al,[76] 2014 | 146 | -0.04 (-0.36 to 0.28) | 131 | 1.05 (0.65 to 1.45) | -1.09 (-1.60 to -0.58) | 2.39 |
| Arai et al,[44] 2015[d] | 73 | -0.02 (-0.44 to 0.40) | 77 | 0.69 (0.22 to 1.16) | -0.71 (-1.34 to -0.08) | 2.02 |
| Arai et al,[44] 2015[d] | 84 | -0.03 (-0.49 to 0.43) | 79 | 0.96 (0.50 to 1.42) | -0.99 (-1.63 to -0.35) | 1.98 |
| Hale et al,[38] 2015 | 191 | -0.03 (-0.27 to 0.21) | 179 | 0.55 (0.27 to 0.83) | -0.58 (-0.94 to -0.22) | 2.90 |
| Katz et al,[61] 2015 | 122 | 0.29 (-0.01 to 0.59) | 100 | 1.85 (1.41 to 2.29) | -1.56 (-2.08 to -1.04) | 2.35 |
| Rauck et al,[66] 2015 and Weil et al,[79] 2017 | 146 | 0.60 (0.30 to 0.90) | 134 | 1.20 (0.87 to 1.53) | -0.60 (-1.04 to -0.16) | 2.63 |
| Trenkwalder et al,[75] 2015 | 61 | -2.30 (-2.67 to -1.93) | 73 | -1.70 (-2.04 to -1.36) | -0.60 (-1.09 to -0.11) | 2.44 |
| Wen et al,[80] 2015 | 296 | -3.69 (-3.90 to -3.48) | 292 | -3.15 (-3.37 to -2.93) | -0.54 (-0.84 to -0.24) | 3.11 |
| Gimbel et al,[42] 2016 | 254 | 0.88 (0.66 to 1.10) | 256 | 1.92 (1.69 to 2.15) | -1.04 (-1.36 to -0.72) | 3.06 |
| Mayorga et al,[63] 2016 | 50 | -1.45 (-2.17 to -0.73) | 48 | -2.93 (-3.67 to -2.19) | 1.48 (0.47 to 2.49) | 1.16 |
| Rauck et al,[68] 2016 | 209 | 0.94 (0.69 to 1.19) | 211 | 1.59 (1.31 to 1.87) | -0.65 (-1.02 to -0.28) | 2.87 |
| Simpson and Wlodarczyk,[72] 2016 | 89 | -3.30 (-3.76 to -2.84) | 92 | -2.10 (-2.55 to -1.65) | -1.20 (-1.83 to -0.57) | 2.01 |
| Tominaga et al,[74] 2016[d] | 60 | -3.00 (-3.51 to -2.49) | 31 | -2.90 (-3.71 to -2.09) | -0.10 (-1.03 to 0.83) | 1.30 |
| Tominaga et al,[74] 2016[d] | 60 | -2.60 (-3.18 to -2.02) | 31 | -2.60 (-3.57 to -1.63) | 0 (-1.09 to 1.09) | 1.05 |
| Christoph et al,[50] 2017 | 123 | -3.03 (-3.27 to -2.79) | 125 | -2.16 (-2.58 to -1.74) | -0.89 (-1.50 to -0.28) | 2.06 |
| Serrie et al,[71] 2017 | 650 | Not reported[e] | 337 | Not reported[e] | -0.05 (-0.27 to 0.17) | 3.37 |
| Overall | | | | | -0.69 (-0.82 to -0.56) | 100.00 |
| Test for heterogeneity: $I^2$ = 70.4%, $P$ < .001 | | | | | | |




The blue line represents the minimally important difference of 1 cm on the 10-cm visual analog scale for pain. The dashed vertical line represents the overall pooled measure of association.

[a] Within-group change from baseline data.

[b] Between-group differences in change from baseline data.

[c] Weights are from random-effects analyses.

[d] Article reported results from 2 randomized clinical trials.

[e] Article only reported between-group mean difference and 95% CI.

scores (eFigure 8 in Supplement 2; $P$ = .01 for interaction). High-quality evidence from 23 RCTs (8962 patients) reporting actual change scores indicated that opioids were not associated with emotional functioning (weighted mean difference, −0.44 points [95% CI, −1.09 to 0.20 points] on the 100-point SF-36 mental component score, $P$ = .53; Table).

### Role Functioning

Opioids were associated with improved role functioning compared with placebo (weighted mean difference, 2.80 points [95% CI, 0.99 to 4.61 points] on the 100-point SF-36 subscale for role limitations due to physical problems, $P$ < .001); however, the association was smaller in studies with reported

Table. GRADE Evidence Profile of Opioids vs Placebo for Patients With Chronic Noncancer Pain Included in Randomized Clinical Trials

| Outcome Measure | No. of Trials (N = 96) | No. of Patients (N = 26 169) | Follow-up, mo | Serious Risk of Bias?[a] | $I^2$ (95% CI), %[b] | Serious Indirectness or Imprecision?[c] | *P* Value for Publication Bias[d] | No. (%) of Patients Who Achieved the MID | | Risk Difference for Achieving the MID (95% CI), % | WMD (95% CI) | Quality of Evidence |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Placebo | Opioids | | | |
| Pain[e] | 42 | 16 617 | 3-6[f] | No | 70.4 (59.5 to 78.4) | No | .07 | 3232 (48.7) | 6048 (60.6) | 11.9 (9.7 to 14.1) | −0.69 cm (−0.82 to −0.56) | High |
| Physical functioning[g] | 51 | 15 754 | 1-6 | No | 65.7 (53.9 to 74.4) | No | .06 | 2992 (46.1) | 5058 (54.6) | 8.5 (5.9 to 11.2) | 2.04 points (1.41 to 2.68) | High |
| Emotional functioning[h] | 23[i] | 8962 | 1-4 | No | 47.2 (14.0 to 67.6) | No[j] | .86 | 1141 (35.0) | 1899 (33.3) | −1.7 (−4.2 to 0.8) | −0.44 points (−1.09 to 0.20) | High |
| Role functioning[k] | 16[i] | 5329 | 1-4 | No | 18.3 (0 to 54.6) | No[j] | .89 | 1113 (48.0) | 1475 (49.0) | 1.0 (−0.7 to 2.6) | 0.87 points (−0.54 to 2.28) | High |
| Social functioning[l] | 29 | 7623 | 1-4 | No | 19.7 (0 to 49.4) | No | .84 | 1527 (43.8) | 1920 (46.4) | 2.6 (0.7 to 4.5) | 1.58 points (0.45 to 2.70) | High |
| Sleep quality[m] | 15 | 6585 | 3-6[f] | No | 60.3 (30.0 to 77.5) | No | .06 | 1232 (47.2) | 2111 (53.1) | 5.9 (2.8 to 9.1) | 3.42 mm (1.58 to 5.26) | High |
| Vomiting[n] | | | | | | | | | | | | |
| Enrichment trials | 18 | 5961 | 1.5-4 | No | 0 (0 to 41.3) | No | .65 | 68 (2.3)[o] | 179 (5.9)[o] | 3.6 (2.1 to 5.4) | RR, 2.50 (1.89 to 3.30) | High |
| Nonenrichment trials | 33 | 11 268 | 1-6 | No | 0 (0 to 36.4) | No | .23 | 96 (2.3)[o] | 667 (9.4)[o] | 7.1 (5.4 to 9.3) | RR, 4.12 (3.34 to 5.07) | High |

Abbreviations: GRADE, Grading of Recommendations Assessment, Development and Evaluation; MID, minimally important difference; RR, relative risk; SF-36, 36-item Short Form; WMD, weighted mean difference.

[a] Assessed using a modified Cochrane risk of bias instrument.[22,23]

[b] An $I^2$ value between 75% and 100% indicates that heterogeneity may be considerable.

[c] Indirectness results if the intervention, patients, or outcomes are different from the research question under investigation. Imprecision refers to situations in which the 95% CI includes both benefit and harm.

[d] Tested using a symmetric funnel plot and the Begg test. Publication bias was not detected in any of the studies.

[e] Measured using a visual analog scale (VAS). Score range, 0 to 10 cm; lower is better (the MID is 1 cm).[27]

[f] Compared with placebo, opioids were associated with less pain relief (*P* = .04 for interaction) and less improvement in sleep quality (*P* = .03 for interaction) in studies with longer follow-up.

[g] Measured using the SF-36 physical component score. Score range, 0 to 100 points; higher is better (the MID is 5 points).[28]

[h] Measured using the SF-36 mental component score. Score range, 0 to 100 points; higher is better (the MID is 5 points).[28]

[i] Compared with placebo, opioids were associated with less improvement in emotional functioning (*P* = .01 for interaction) and role functioning (*P* = .007 for interaction) in studies that reported change scores directly vs studies for which change scores were converted from baseline and end-of-study scores.

[j] Rating down for imprecision was not performed because the 95% CI did not include patient-important effects for either benefit or harm.

[k] Measured using the SF-36 subscale for role limitations due to physical problems. Score range, 0 to 100 points; higher is better (the MID is 10 points).[28]

[l] Measured using the SF-36 subscale for social functioning. Score range, 0 to 100 points; higher is better (the MID is 10 points).[28]

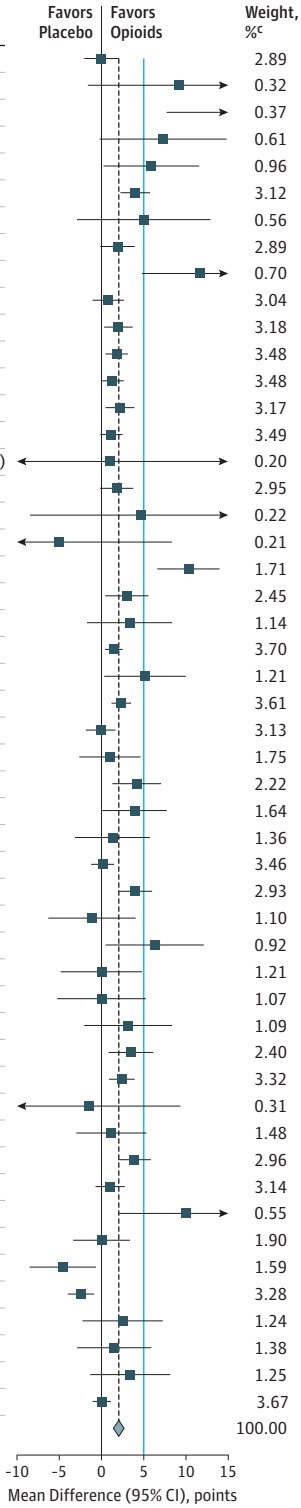
[m] Measured using the SF-36 sleep quality 100-mm VAS. Score range, 0 to 100 mm; higher is better (the MID is 10 mm).[28]

[n] Enrichment trials precede randomization with an open-label treatment phase during which patients with problematic adverse events, poor response to treatment, or both are excluded. Compared with placebo, opioids were associated with vomiting, but less so for enrichment vs nonenrichment trials (*P* = .007 for interaction).

[o] These patients experienced vomiting.

Figure 3. Physical Functioning Assessed by the 100-Point 36-Item Short Form Physical Component Score Among Patients With Chronic Noncancer Pain Who Received Opioids vs Placebo in 51 High-Quality Randomized Clinical Trials

| Source | Opioids Group No. of Patients | Opioids Group Mean (95% CI), points[a] | Placebo Group No. of Patients | Placebo Group Mean (95% CI), points[a] | Between-Group Mean Difference (95% CI)[b] | Weight, %[c] |
|---|---|---|---|---|---|---|
| Moran,[94] 1991 | 7 | Not reported | 8 | Not reported | 0 (-2.03 to 2.03) | 2.89 |
| Harati et al,[89] 1998 | 63 | Not reported | 64 | Not reported | 9.20 (-1.61 to 20.01) | 0.32 |
| Peloso et al,[95] 2000 | 31 | 26.13 (17.48 to 34.78) | 35 | 8.44 (2.69 to 14.19) | 17.69 (7.71 to 27.67) | 0.37 |
| Fleischmann et al,[54] 2001 | 63 | Not reported | 66 | Not reported | 7.30 (-0.21 to 14.81) | 0.61 |
| Caldwell et al,[81] 2002 | 222 | 11.59 (8.84 to 14.35) | 73 | 5.69 (0.65 to 10.73) | 5.91 (0.24 to 11.57) | 0.96 |
| Bennett et al,[46] 2003 | 156 | 5.00 (3.70 to 6.30) | 157 | 1.00 (-0.21 to 2.21) | 4.00 (2.24 to 5.76) | 3.12 |
| Gimbel et al,[86] 2003 | 82 | 24.00 (18.43 to 29.57) | 77 | 19.00 (13.22 to 24.78) | 5.00 (-2.90 to 12.90) | 0.56 |
| Ruoff et al,[69] 2003 | 145 | 6.10 (4.62 to 7.58) | 143 | 4.20 (2.78 to 5.62) | 1.90 (-0.13 to 3.93) | 2.89 |
| Babul et al,[45] 2004 | 124 | 23.94 (19.05 to 28.83) | 122 | 12.26 (7.34 to 17.19) | 11.68 (4.80 to 18.55) | 0.70 |
| Emkey et al,[52] 2004 | 153 | 5.60 (4.19 to 7.01) | 153 | 4.80 (3.58 to 6.02) | 0.80 (-1.05 to 2.65) | 3.04 |
| Peloso et al,[64] 2004 | 163 | 3.50 (2.20 to 4.80) | 163 | 1.50 (0.40 to 2.60) | 2.00 (0.31 to 3.69) | 3.18 |
| Gilron et al,[84] 2005 | 57 | 6.10 (5.14 to 7.06) | 57 | 4.30 (3.34 to 5.26) | 1.80 (0.47 to 3.13) | 3.48 |
| Gilron et al,[84] 2005[d] | 57 | 10.70 (9.74 to 11.66) | 57 | 9.40 (8.44 to 10.36) | 1.30 (-0.03 to 2.63) | 3.48 |
| Matsumoto et al,[93] 2005 | 348 | 3.97 (2.95 to 4.98) | 119 | 1.80 (0.41 to 3.19) | 2.17 (0.46 to 3.87) | 3.17 |
| Gana et al,[56] 2006 | 806 | 3.57 (2.99 to 4.16) | 205 | 2.40 (1.22 to 3.58) | 1.17 (-0.14 to 2.49) | 3.49 |
| Langford et al,[90] 2006 | 202 | 3.40 (-10.61 to 17.41) | 197 | 2.40 (1.41 to 3.39) | 1.00 (-12.96 to 14.96) | 0.20 |
| Freeman et al,[83] 2007 | 139 | 6.10 (4.70 to 7.50) | 129 | 4.30 (2.91 to 5.69) | 1.80 (-0.16 to 3.76) | 2.95 |
| Khoromi et al,[40] 2007 | 28 | 8.00 (-1.86 to 17.86) | 28 | 3.30 (-6.33 to 12.93) | 4.70 (-8.47 to 17.87) | 0.22 |
| Khoromi et al,[40] 2007[e] | 28 | 11.00 (1.14 to 20.86) | 28 | 16.00 (6.14 to 25.86) | -5.00 (-18.32 to 8.32) | 0.21 |
| Ma et al,[92] 2008 | 58 | 14.43 (11.46 to 17.40) | 58 | 4.14 (1.82 to 6.46) | 10.29 (6.60 to 13.98) | 1.71 |
| Thorne et al,[96] 2008 | 78 | Not reported | 79 | Not reported | 3.00 (0.43 to 5.57) | 2.45 |
| Vorsanger et al,[78] 2008 | 256 | -0.84 (-3.71 to 2.02) | 126 | -4.17 (-8.36 to 0.03) | 3.32 (-1.72 to 8.36) | 1.14 |
| Afilalo et al,[43] 2010 | 686 | 4.95 (4.36 to 5.55) | 337 | 3.50 (2.65 to 4.35) | 1.45 (0.42 to 2.49) | 3.70 |
| Breivik et al,[47] 2010 | 94 | 14.71 (11.18 to 18.23) | 96 | 9.56 (6.16 to 12.96) | 5.15 (0.32 to 9.98) | 1.21 |
| Buynak et al,[49] 2010 | 641 | 5.55 (4.85 to 6.25) | 316 | 3.20 (2.26 to 4.14) | 2.35 (1.18 to 3.52) | 3.61 |
| Gordon et al,[88] 2010 | 53 | 3.90 (2.34 to 5.46) | 53 | 4.00 (2.01 to 5.99) | -0.10 (-1.85 to 1.65) | 3.13 |
| Gordon et al,[87] 2010 | 52 | 4.60 (1.93 to 7.27) | 52 | 3.60 (1.01 to 6.19) | 1.00 (-2.63 to 4.63) | 1.75 |
| Hale et al,[57] 2010 | 133 | 0 (-2.06 to 2.06) | 133 | -4.17 (-6.22 to -2.11) | 4.17 (1.28 to 7.05) | 2.22 |
| Katz et al,[60] 2010 | 171 | -2.30 (-5.08 to 0.48) | 173 | -6.20 (-8.87 to -3.53) | 3.90 (0.07 to 7.73) | 1.64 |
| Zin et al,[98] 2010 | 23 | 4.39 (0.59 to 8.19) | 28 | 3.10 (0.37 to 5.83) | 1.29 (-3.15 to 5.73) | 1.36 |
| DeLemos et al,[51] 2011 | 599 | 3.13 (2.45 to 3.81) | 200 | 3.00 (1.82 to 4.18) | 0.13 (-1.23 to 1.49) | 3.46 |
| Steiner et al,[73] 2011 | 166 | 10.10 (8.63 to 11.57) | 195 | 6.10 (4.74 to 7.46) | 4.00 (2.01 to 5.99) | 2.93 |
| Vojtaššák et al,[77] 2011 | 132 | 13.59 (10.20 to 16.98) | 144 | 14.72 (10.75 to 18.69) | -1.13 (-6.30 to 4.04) | 1.10 |
| Chu et al,[82] 2012 | 48 | 8.42 (4.71 to 12.12) | 55 | 2.13 (-2.54 to 6.79) | 6.29 (0.48 to 12.10) | 0.92 |
| Uberall et al,[97] 2012 | 85 | Not reported | 96 | Not reported | 0 (-4.83 to 4.83) | 1.21 |
| Cloutier et al,[37] 2013 | 54 | Not reported | 54 | Not reported | 0 (-5.25 to 5.25) | 1.07 |
| Lee et al,[91] 2013 | 83 | 9.82 (5.81 to 13.83) | 87 | 6.67 (3.26 to 10.08) | 3.15 (-2.03 to 8.33) | 1.09 |
| Rauck et al,[65] 2013 | 649 | 16.48 (14.96 to 18.01) | 331 | 13.00 (10.84 to 15.16) | 3.48 (0.84 to 6.12) | 2.40 |
| Vinik et al,[76] 2014 | 146 | 0.10 (-0.97 to 1.17) | 131 | -2.30 (-3.41 to -1.19) | 2.40 (0.88 to 3.92) | 3.32 |
| Gilron et al,[85] 2015[e] | 51 | 3.90 (-4.00 to 11.80) | 51 | 5.40 (-2.40 to 13.20) | -1.50 (-12.34 to 9.34) | 0.31 |
| Hale et al,[38] 2015 | 191 | -5.37 (-8.33 to -2.42) | 179 | -6.54 (-9.50 to -3.58) | 1.17 (-2.99 to 5.32) | 1.48 |
| Katz et al,[61] 2015 | 193 | 7.52 (6.08 to 8.96) | 196 | 3.62 (2.29 to 4.95) | 3.90 (1.95 to 5.85) | 2.96 |
| Rauck et al,[66] 2015 and Weil et al,[79] 2017 | 146 | -1.68 (-2.89 to -0.47) | 134 | -2.70 (-3.96 to -1.44) | 1.02 (-0.71 to 2.75) | 3.14 |
| Trenkwalder et al,[75] 2015 | 76 | 20.00 (12.81 to 27.19) | 92 | 10.00 (6.42 to 13.58) | 10.00 (2.09 to 17.91) | 0.55 |
| Wen et al,[80] 2015 | 229 | Not reported | 210 | Not reported | 0 (-3.36 to 3.36) | 1.90 |
| Gimbel et al,[42] 2016 | 243 | 2.08 (-0.57 to 4.73) | 248 | 6.67 (3.73 to 9.60) | -4.58 (-8.52 to -0.65) | 1.59 |
| Mayorga et al,[63] 2016 | 50 | 1.97 (0.85 to 3.09) | 48 | 4.40 (3.24 to 5.55) | -2.43 (-4.00 to -0.86) | 3.28 |
| Rauck et al,[68] 2016 | 187 | -2.50 (-5.73 to 0.73) | 179 | -5.00 (-8.53 to -1.47) | 2.50 (-2.25 to 7.25) | 1.24 |
| Simpson and Wlodarczyk,[72] 2016 | 89 | 2.72 (-0.23 to 5.67) | 92 | 1.22 (-2.11 to 4.55) | 1.50 (-2.89 to 5.89) | 1.38 |
| Christoph et al,[50] 2017 | 77 | 16.20 (12.66 to 19.74) | 98 | 12.80 (9.55 to 16.05) | 3.40 (-1.34 to 8.14) | 1.25 |
| Serrie et al,[71] 2017 | 650 | 4.74 (4.10 to 5.37) | 337 | 4.70 (3.82 to 5.58) | 0.04 (-1.04 to 1.12) | 3.67 |
| Overall | | | | | 2.04 (1.41 to 2.68) | 100.00 |
| Test for heterogeneity: $I^2 = 65.7\%$, $P < .001$ | | | | | | |




The blue line represents the minimally important difference of 5 points on the 100-point 36-item Short Form physical component score. The dashed vertical line represents the overall pooled measure of association.

[a] Within-group change from baseline data.

[b] Between-group differences in change from baseline data.

[c] Weights are from random-effects analyses.

[d] Comparison was morphine plus gabapentin vs gabapentin alone.

[e] Comparison was morphine plus nortriptyline vs nortriptyline alone.

vs converted change scores (eFigure 9 in Supplement 2; $P = .007$ for interaction). When restricted to trials reporting actual change, high-quality evidence from 16 RCTs (5329 patients) demonstrated no association of opioids on role functioning compared with placebo (weighted mean difference, 0.87 points [95% CI, −0.54 to 2.28 points] on the 100-point SF-36 subscale for role limitations due to physical problems, $P = .23$; Table).

#### Social Functioning

High-quality evidence from 29 RCTs (7623 patients) showed an association of opioids with improved social functioning compared with placebo but did not meet the minimally important difference criterion (weighted mean difference, 1.58 points [95% CI, 0.45-2.70 points] on the 100-point SF-36 subscale for social functioning, $P = .006$; minimally important difference, 10 points; modeled risk difference for achieving the minimally important difference, 2.6% [95% CI, 0.7%-4.5%]; Table and eFigure 10 in Supplement 2).

#### Sleep Quality

Opioids were associated with improved sleep quality compared with placebo (weighted mean difference, 4.56 mm [95% CI, 2.88-6.24 mm] on the SF-36 sleep quality 100-mm VAS, $P < .001$; minimally important difference, 10 mm; modeled risk difference for achieving the minimally important difference, 5.9% [95% CI, 3.7%-8.1%]; eFigure 11 in Supplement 2); however, the association was smaller in studies with longer follow-up (eFigures 11 and 12 in Supplement 2; $P = .03$ for interaction). High-quality evidence from 15 RCTs (6585 patients) with follow-up lasting 3 months or longer found that opioids were associated with a small improvement in sleep quality compared with placebo but did not meet the criterion for the minimally important difference (weighted mean difference, 3.42 mm [95% CI, 1.58-5.26 mm] on the SF-36 sleep quality 100-mm VAS, $P < .001$; modeled risk difference for the minimally important difference, 5.9% [95% CI, 2.8%-9.1%]; Table).

#### Vomiting

Opioids were associated with an increased incidence of vomiting; however, this association was less in the 18 enrichment RCTs (5961 patients) compared with placebo (RR, 2.50 [95% CI, 1.89-3.30], $P < .001$; risk difference, 3.6% [95% CI, 2.1%-5.4%]) than in 33 nonenrichment RCTs (11 268 patients) compared with placebo (RR, 4.12 [95% CI, 3.34-5.07], $P < .001$; risk difference, 7.1% [95% CI, 5.4%-9.3%]; Table and eFigure 13 in Supplement 2; $P = .007$ for interaction). At least 20 RCTs reported each of the following adverse events: nausea, constipation, dizziness, drowsiness, headache, pruritus, and dry mouth. Except for headache, opioid use was associated with a higher incidence of these adverse events compared with placebo (eTable 8 in Supplement 2).

### Outcomes for Opioids vs Active Comparators

#### Opioids vs Nonsteroidal Anti-Inflammatory Drugs

Moderate-quality evidence from 9 RCTs (1431 patients) showed no difference in the association of opioids vs nonsteroidal anti-inflammatory drugs for pain relief (weighted mean difference, −0.60 cm [95% CI, −1.54 to 0.34 cm] on the 10-cm VAS for pain, $P = .21$). Moderate-quality evidence from 7 RCTs (1311 patients) suggested no difference in physical functioning between opioids and nonsteroidal anti-inflammatory drugs (weighted mean difference, −0.90 points [95% CI, −2.69 to 0.89 points] on the 100-point SF-36 physical component score, $P = .33$). High-quality evidence from 5 RCTs (2632 patients) showed an association of opioids with vomiting compared with nonsteroidal anti-inflammatory drugs (RR, 4.71 [95% CI, 2.92 to 7.60], $P < .001$; risk difference, 6.3% [95% CI, 3.2% to 11.1%]; eTable 9 in Supplement 2).

#### Opioids vs Tricyclic Antidepressants

Low-quality evidence from 3 RCTs (246 patients) suggested no difference in pain relief between opioids and nortriptyline (weighted mean difference, −0.13 cm [95% CI, −0.99 to 0.74 cm] on the 10-cm VAS for pain, $P = .78$). Low-quality evidence from 2 trials (158 patients) suggested no difference in physical functioning (weighted mean difference, −5.31 points [95% CI, −13.77 to 3.14 points] on the 100-point SF-36 physical component score, $P = .22$; eTable 10 in Supplement 2).

#### Opioids vs Anticonvulsants

Moderate-quality evidence from 3 RCTs (303 patients) suggested opioids were associated with greater pain relief than anticonvulsants (weighted mean difference, −0.90 cm [95% CI, −1.65 to −0.14 cm] on the 10-cm VAS for pain, $P = .02$; minimally important difference, 1 cm; modeled risk difference for achieving the minimally important difference, 16.2% [95% CI, 2.8% to 26.1%]). Low-quality evidence suggested no difference in physical functioning (weighted mean difference, 0.45 points [95% CI, −5.77 to 6.66 points] on the 100-point SF-36 physical component score, $P = .89$; eTable 11 in Supplement 2).

#### Opioids vs Synthetic Cannabinoids

Low-quality evidence from 1 crossover trial suggested no difference between opioids and nabilone for pain relief (73 patients; mean difference, −0.13 cm [95% CI, −1.04 to 0.77 cm] on the 10-cm VAS for pain, $P = .77$) or physical functioning (71 patients; mean difference, −1.2 points [95% CI, −4.50 to 2.10 points] on the 100-point SF-36 physical component score, $P = .48$; eTable 12 in Supplement 2).

#### Opioids vs Usual Care

Compared with usual care, low-quality evidence from 1 trial (111 patients) showed an association of opioids with greater pain relief (mean difference, −2.06 cm [95% CI, −2.65 to −1.48 cm] on the 10-cm VAS for pain, $P < .001$; minimally important difference, 1 cm; modeled risk difference for achieving the minimally important difference, 21.1% [95% CI, 18.7% to 22.1%]; eTable 13 in Supplement 2). The associations with additional outcomes for opioids vs active comparators appear in eTables 9 through 13 in Supplement 2.

### Additional Analyses

Most eligible trials allowed for postrandomization titration of opioid dose, which precluded between-trial subgroup

analyses of higher vs lower doses of opioids. In 6 RCTs that compared different doses of opioids, meta-regression of moderate-quality evidence showed no dose response for pain relief ($P$ = .39), functional recovery ($P$ = .22), or gastrointestinal adverse events ($P$ = .12) (eTable 14 and eFigures 14-16 in Supplement 2).

No additional subgroup analyses or meta-regressions proved credible (eTables 15-17 in Supplement 2). Associations were independent of whether trials administered pure opioids or opioids combined with acetaminophen; subgroup analysis found 1 significant test of interaction ($P$ = .002 for interaction), suggesting an association with improved role functioning with combination products, but with low credibility (eTable 15b in Supplement 2).

Sensitivity analyses excluding data imputation for nonsignificant effects showed larger but unimportant differences in measures of association (eTable 18 in Supplement 2). Sensitivity analyses using the Hartung-Knapp-Sidik-Jonkman method for pooling showed consistent results with the DerSimonian-Laird method (eTable 19 in Supplement 2).

## Discussion

Compared with placebo, opioids were associated with (1) small improvements in pain, physical functioning, and sleep quality; (2) unimportant improvements in social functioning; and (3) no improvements in emotional functioning or role functioning. Compared with placebo, opioids were associated with increased vomiting, drowsiness, constipation, dizziness, nausea, dry mouth, and pruritus.

Moderate- to low-quality evidence suggested that opioids were associated with similar improvements in pain and physical functioning compared with nonsteroidal anti-inflammatory drugs, tricyclic antidepressants, and synthetic cannabinoids and were associated with small improvements in pain but not physical functioning compared with anticonvulsants. These results were restricted to treatment lasting 1 to 6 months and may not apply to individuals with substance use disorder or other mental illness, to those involved in litigation, or to those receiving disability benefits.

Opioids were associated with less pain relief during longer trials perhaps as a result of opioid tolerance or opioid-induced hyperalgesia (a condition in which opioid use results in hypersensitivity to painful stimuli).[99] A reduced association with benefit over time might lead to prescription of higher opioid doses and consequent harms.[32] Moreover, long-term opioid therapy causes physical dependence,[100,101] and symptoms of opioid withdrawal (including pain) resolve when opioids are resumed. Therefore, patients may continue to use opioids after analgesic benefits have waned to avoid withdrawal.[102]

Although clinical practice guidelines discourage long-term opioid therapy for headache, fibromyalgia, or axial low back pain,[103,104] we found no evidence for differential condition-specific associations with neuropathic, nociceptive, or central sensitization conditions. Prior inferences may have been driven by systematic reviews focusing on average effects alone.[105,106] The limitations of calculating the average benefit associated with opioids are (1) the assumption that all patients experience comparable analgesia and (2) lack of consideration for the distribution around the mean and the proportion of patients who achieve the minimally important difference.[107] Therefore, we converted the average effects to the proportion of responders. Based on a prior study,[19] some patients may find the modeled proportion of 12% for achieving the minimally important difference for pain relief warrants a trial of treatment with opioids.

There were no differences in the associations of opioid dose with outcomes. This result was consistent with a prior RCT.[108] Although prescription of high-dose opioids (≥200 mg of a morphine-equivalent dose per day) is common,[109,110] only 21 of 96 trials addressed mean or median morphine-equivalent doses per day of 90 mg or greater.

Strengths of this review included (1) a comprehensive search for eligible RCTs in any language; (2) data imputation for missing nonsignificant outcomes; (3) use of minimally important differences; and (4) sensitivity analyses that addressed methodological differences, length of follow-up, and reported vs converted change scores.

### Limitations

This review has several limitations. First, it was not possible to assess the long-term associations of opioids with chronic noncancer pain because no trial followed up patients for longer than 6 months. Second, none of the included studies provided rates of developing opioid use disorder and only 2 reported rates of overdose. Third, numerous outcomes and comparisons were evaluated, including subgroup analyses. Some findings might be statistically significant by chance. Fourth, subgroup effects could not be evaluated for opioids vs active comparators when there were less than 2 trials in each subgroup. Fifth, the modeling of risk difference for achieving the minimally important difference was based on assumptions that could not be directly assessed and might not have been met.

Sixth, heterogeneity associated with pooled estimates for pain relief and functional improvement among trials of opioids vs placebo may have reduced evidence quality. Evidence quality was not downgraded because the magnitude and direction of the effects was largely consistent. Seventh, the quality of the evidence ratings are largely subjective and some might disagree with our assessments. Eighth, although litigation and wage replacement benefits likely influence treatment effects, there were insufficient data in the included trials to make conclusions regarding these issues. Ninth, trials of opioid therapy for chronic noncancer pain excluded patients with current or prior substance use disorders or other active mental illness; however, more than half of opioids prescribed in the United States are for patients diagnosed with a mental health disorder.[111,112]

## Conclusions

In this meta-analysis of RCTs of patients with chronic noncancer pain, evidence from high-quality studies showed that

opioid use was associated with statistically significant but small improvements in pain and physical functioning, and increased risk of vomiting compared with placebo. Comparisons of opioids with nonopioid alternatives suggested that the benefit for pain and functioning may be similar, although the evidence was from studies of only low to moderate quality.

## ARTICLE INFORMATION

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