Comparative Effectiveness Review
Number 229

Opioid Treatments for Chronic Pain

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Key Messages

Purpose of Review
To assess the effectiveness and harms of opioid therapy for chronic noncancer pain, alternative opioid dosing strategies, and risk mitigation strategies

Key Messages

- Opioids are associated with small improvements versus placebo in pain and function, and increased risk of harms at short-term (1 to <6 months) followup; evidence on long-term effectiveness is very limited, and there is evidence of increased risk of serious harms that appear to be dose dependent.
- At short-term followup, evidence showed no differences between opioids versus nonopioid medications in improvement in pain, function, mental health status, sleep, or depression.
- Evidence on the effectiveness and harms of alternative opioid dosing strategies and the effects of risk mitigation strategies is lacking, although provision of naloxone to patients might reduce the likelihood of opioid-related emergency department visits, a taper support intervention might improve functional outcomes compared to no taper support, and co-prescription of benzodiazepines and gabapentinoids might increase risk of overdose.
- No instrument has been shown to be associated with high accuracy for predicting opioid overdose, addiction, abuse, or misuse.

This report is based on research conducted by the Pacific Northwest Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-2015-00009-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

This report may periodically be assessed for the currency of conclusions. If an assessment is done, the resulting surveillance report describing the methodology and findings will be found on the Effective Health Care Program website at www.effectivehealthcare.ahrq.gov. Search on the title of the report.

People using assistive technology may not be able to fully access information in this report. For assistance contact EPC@ahrq.hhs.gov.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States.

The Centers for Disease Control and Prevention requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the following EPC: Pacific Northwest Evidence-based Practice Center (Contract No. 290-2015-00009-I).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new healthcare technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

To bring the broadest range of experts into the development of evidence reports and health technology assessments, AHRQ encourages the EPCs to form partnerships and enter into collaborations with other medical and research organizations. The EPCs work with these partner organizations to ensure that the evidence reports and technology assessments they produce will become building blocks for healthcare quality improvement projects throughout the Nation. The reports undergo peer review and public comment prior to their release as a final report.

AHRQ expects that the EPC evidence reports and technology assessments, when appropriate, will inform individual health plans, providers, and purchasers as well as the healthcare system as a whole by providing important information to help improve healthcare quality.

If you have comments on this evidence report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

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Opioid Treatments for Chronic Pain

Structured Abstract

Objectives. Chronic pain is common, and opioid therapy is frequently prescribed for this condition. This report updates and expands on a prior Comparative Effectiveness Review on long-term (≥1 year) effectiveness and harms of opioid therapy for chronic pain, including evidence on shorter term (1 to 12 months) outcomes.

Data sources. A prior systematic review (searches through January 2014), electronic databases (Ovid MEDLINE®, Embase®, PsycINFO®, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews through August 2019), reference lists, and clinical trials registries.

Review methods. Predefined criteria were used to select studies of patients with chronic pain prescribed opioids that addressed effectiveness or harms versus placebo, no opioid use, or nonopioid pharmacological therapies; different opioid dosing methods; or risk mitigation strategies. Effects were analyzed at short-term (1 to <6 months), intermediate-term (≥6 to <12 months), and long-term (≥12 months) followup. Studies on the accuracy of risk prediction instruments for predicting opioid use disorder or misuse were also included. Random effects meta-analysis was conducted on short-term trials of opioids versus placebo, opioids versus nonopioids, and opioids plus nonopioids versus an opioid or nonopioid alone. Magnitude of effects was classified as small, moderate, or large using predefined criteria, and strength of evidence was assessed.

Results. We included 115 randomized controlled trials (RCTs), 40 observational studies, and 7 studies of predictive accuracy; 134 were new to this update. Opioids were associated with small benefits versus placebo in short-term pain, function, and sleep quality. There was a small dose-dependent effect on pain, and effects were attenuated at longer (3 to 6 month) versus shorter (1 to 3 month) followup. Opioids were associated with increased risk of discontinuation due to adverse events, gastrointestinal adverse events, somnolence, dizziness, and pruritus versus placebo. In observational studies, opioids were associated with increased risk of an opioid abuse or dependence diagnosis, overdose, all-cause mortality, fractures, falls, and myocardial infarction versus no opioid use; there was evidence of a dose-dependent risk for all outcomes except fracture and falls.

There were no differences between opioids and nonopioid medications in pain, function, or other short-term outcomes. Opioid plus nonopioid combination therapy was associated with little improvement in pain at short-term followup versus an opioid alone. Co-prescription of benzodiazepines or gabapentinoids was associated with increased risk of overdose versus an opioid alone. No RCT evaluated intermediate- or long-term benefits of opioids versus placebo. One trial found stepped therapy starting with opioids to be associated with higher pain intensity and no difference in function or other outcomes versus stepped therapy starting with nonopioid therapy.

Limited evidence indicated no differences between long- and short-acting opioids in effectiveness, but long-acting opioids were associated with increased risk of overdose. One RCT

found a taper support intervention associated with greater improvement in function but no difference in pain versus usual care.

Estimates of diagnostic accuracy for various risk prediction instruments were highly inconsistent, and there was no evidence on the effectiveness of risk mitigation strategies for improving clinical outcomes, with the exception of one study that found provision of naloxone associated with decreased emergency department visits.

Trials of patients with prescription opioid dependence found buprenorphine maintenance associated with better outcomes than buprenorphine taper and similar effects of methadone versus buprenorphine. Evidence was insufficient to evaluate benefits and harms of opioid therapy in patients at higher risk for opioid use disorder.

Conclusions. At short-term followup, for patients with chronic pain, opioids are associated with small beneficial effects versus placebo but are associated with increased risk of short-term harms and do not appear to be superior to nonopioid therapy. Evidence on intermediate-term and long-term benefits remains very limited, and additional evidence confirms an association between opioids and increased risk of serious harms that appears to be dose-dependent. Research is needed to develop accurate risk prediction instruments, determine effective risk mitigation strategies, clarify risks associated with co-prescribed medications, and identify optimal opioid tapering strategies.

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Summary of Changes Since the Previous Report

This systematic review is an update to an earlier 2014 Agency for Healthcare Research and Quality (AHRQ) report[1] and is one of three concurrent systematic reviews on treatment of chronic pain. The other concurrent reviews address nonopioid pharmacological treatments and noninvasive nonpharmacological treatments. The scope and Key Questions for this update were the same as for the original review and expanded to also include studies on: (1) shorter term (1 to 12 month) outcomes of therapy involving opioids, (2) effects of opioid plus nonopioid combination therapy, (3) effects of tramadol, (4) effects of naloxone co-prescription, (5) risks of co-prescribed benzodiazepines, (6) risks of co-prescribed gabapentinoids, and (7) effects of co-prescribed cannabis.

An additional 134 studies were added from this update to the 27 included in the 2014 AHRQ report, for a total of 162 studies. Summary strength of evidence tables were updated based on evidence from the 2014 AHRQ report and new evidence identified for this update.

The 2014 AHRQ report did not include meta-analyses. For the update report, meta-analyses were conducted to summarize newly included data on short-term (1 to <6 month) outcomes for opioids versus placebo, opioids versus non-opioids, and opioids plus non-opioids versus opioids or non-opioids alone. Opioids were associated with small effects on pain and function at short-term follow-up, and increased risk of short-term harms (Tables i and ii). There were no differences between opioids versus nonopioids or opioids plus a nonopioid versus either an opioid or nonopioid alone for short-term function. Although there were no long-term randomized trials of opioids versus placebo, one new trial of patients with chronic low back pain or pain associated with osteoarthritis evaluated outcomes at 1 year.[2]

Table i. Efficacy of opioid treatments for chronic pain: function and pain outcomes

	Function Short Term	**Function Intermediate Term**	**Function Long Term**	**Pain Short Term**	**Pain Intermediate Term**	**Pain Long Term**
Intervention A Versus B	Effect Size SOE	Effect Size SOE	Effect Size SOE	Effect Size SOE	Effect Size SOE	Effect Size SOE
Opioids vs. placebo	Small +++	No evidence	No evidence	Small +++	No evidence	No evidence
Opioids vs. nonopioids	None ++	No evidence	None ++	None ++	No evidence	None ++
Opioid + nonopioid vs. nonopioid	None +	No evidence	No evidence	None ++	No evidence	No evidence
Opioid + nonopioid vs. opioid alone	None +	No evidence	No evidence	None[a] ++	No evidence	No evidence

Effect size: None or small, moderate, or large favoring intervention A
SOE: + = low, ++ = moderate, +++ = high
[a] The effect was statistically significant but below the threshold for small
Abbreviations: SOE=strength of evidence

Table ii. Adverse effects of opioid treatments for chronic pain

Intervention A vs. B	Discontinuation Due to AEs Effect Size SOE	Serious AEs Effect Size SOE	Nausea Effect Size SOE	Vomiting Effect Size SOE	Constipation Effect Size SOE	Dizziness Effect Size SOE	Headache Effect Size SOE	Somnolence Effect Size SOE	Pruritus Effect Size SOE
Opioids vs. placebo	Large +++	Small ++	Large +++	Large +++	Large +++	Large +++	None +++	High +++	High +++
Opioids vs. nonopioids	Moderate ++	Small ++	Moderate +++	Large +++	Large +++	NSAID: Moderate ++ Gabapentinoid: Low None Nortriptyline: Moderate +	Small +++	Moderate +++	High +++
Opioid + nonopioid vs. nonopioid	Moderate +	Insufficient evidence	Small +	Insufficient evidence	Large +[a]	Small +	None +	Moderate +[a]	Insufficient evidence
Opioid + nonopioid vs. opioid alone	None +	Insufficient evidence	None +	Small +	None +	Small +	None +	None +	None +

Effect size: None or small, moderate, or large increase in risk for intervention A

SOE: + = low, ++ = moderate, +++ = high

Abbreviations: AE=adverse effects; SOE=strength of evidence

[a] There was a statistically significant interaction with trial quality and effects were statistically significant when a poor-quality trial was excluded

Table iii summarizes other evidence reviewed for this update, showing the number of studies included for each topic in the 2014 AHRQ report, the number of studies included in this update, main findings, and the strength of evidence ratings (ratings that are new or changed from the prior report are shaded in gray). Although there were no long-term randomized trials of opioids versus placebo, one new trial of patients with chronic low back pain or pain associated with osteoarthritis evaluated outcomes at 1 year.[2] It found no differences between stepped therapy with opioids versus stepped therapy starting with nonopioids in function, sleep, or mental health outcomes; opioids were associated with slightly worse effects (by ~0.5 point on a 0 to 10 scale) on pain. For areas newly addressed by this update, limited evidence indicates that co-use of cannabis with opioids was not associated with improved pain or function and does not reduce opioid use compared with use of opioids alone; that co-use of benzodiazepines and gabapentinoids with opioids was associated with increased risk of overdose compared with use of opioids alone; and that provision of naloxone in patients prescribed opioids was associated with reduced risk of emergency department visits. New observational studies were consistent with the 2014 AHRQ report in finding an association between use of prescription opioids and risk of addiction, overdose, fractures, falls, and cardiovascular events; a new study also found an association between opioid use and risk of all-cause mortality. New observational studies were also consistent with the 2014 AHRQ report in finding associations between higher doses of opioids and risks of overdose, addiction, and endocrinological adverse events; new studies also found an association between higher dose and increased risk of incident or refractory depression. Evidence on the effectiveness of tapering strategies was largely limited to one trial that found a taper support intervention associated with better functional outcomes versus usual opioid care.[3] New evidence on the accuracy of risk prediction instruments was consistent with the 2014 AHRQ report, which found highly inconsistent estimates of diagnostic accuracy and methodological limitations in the studies. New evidence on the effectiveness of opioid dosing strategies and risk mitigation strategies addressed in the 2014 AHRQ report was limited and did not result in any changes to the conclusions or strength of evidence ratings.

Table iii. Summary of additional outcomes

Intervention	Outcome	2014 AHRQ Report	2019 Update	Main Findings	Strength of Evidence
Opioid vs. no opioid therapy	Opioid abuse, dependence, or addiction	1 cohort study (N=568,640)	2 cohort studies (N=666,780)	Opioids associated with increased risk	Low
	Overdose	1 cohort study (N=9940)	2 cohort studies (N=108,080)	Opioids associated with increased risk	Low
	All-cause mortality	No studies	1 cohort study (N=22,912)	Opioids associated with increased risk	Low
	Fracture	2 observational studies (N=24,080	6 observational studies (N=48,250)	Opioids associated with increased risk	Low
	Cardiovascular events	2 observational studies (N=437,817)	3 cohort studies (N=505,626)	Opioids associated with increased risk	Low
	Endocrinological harms	1 cross-sectional study (N=11,327)	1 cross-sectional study (N=11,327)	Unable to determine	Insufficient

Intervention	Outcome	2014 AHRQ Report	2019 Update	Main Findings	Strength of Evidence
Opioid + cannabis vs. opioid	Pain, function, opioid discontinuation, opioid dose	Not addressed	1 observational study (N=1514)	No association	Low[a]
Opioid + benzodiazepine vs. opioid	Overdose	Not addressed	3 observational studies (N=140,002)	Opioid + benzodiazepine associated with increased risk	Low[a]
Opioid + gabapentinoid vs. opioid	Overdose	Not addressed	3 observational studies (N=799,013)	Opioid + gabapentinoid associated with increased risk	Low[a]
Methods for initiating and titrating opioids	Pain	2 RCTs (N=81)	2 RCTs (N=81)	Unable to assess	Insufficient
	Opioid use disorder or related outcomes	No studies	No studies	No studies	No studies
Short-acting vs. long-acting opioids	Pain, function	No studies	2 RCTs (N=184)	No differences	Low
	Overdose	No studies	1 cohort (N=840,606)	Long-acting associated with increased risk	Low
Long-acting opioid vs. a different long-acting opioid	Pain, function, and other effectiveness outcomes	3 RCTs (N=1850)	16 RCTs (N=7356)	No patterns showing differential effectiveness, with some differences in opioid dosing between arms	Moderate[b]
Long-acting opioid vs. a different long-acting opioid	Overdose	1 cohort study (N=108,492)	4 cohort studies (N=193,166)	Methadone associated with increased risk vs. morphine in 2 studies of Medicaid patients and decreased risk in 1 study of VA patients	Low
Short + long-acting opioid vs. long-acting opioid alone	All	No studies	No studies	No studies	No studies
Scheduled, continuous vs. as-needed dosing	All	No studies	No studies	No studies	No studies
Opioid dose escalation vs. dose maintenance	Pain, function	1 RCT (N=140)	1 RCT (N=140)	No differences; doses were similar in the two arms	Low
	Opioid withdrawal due to misuse	1 RCT (N=140)	1 RCT (N=140)	No difference	Low

Intervention	Outcome	2014 AHRQ Report	2019 Update	Main Findings	Strength of Evidence
Opioid rotation vs. maintenance of current opioid therapy	All	No studies	No studies	No studies	No studies
Strategies for treating acute exacerbations of chronic pain	Pain (immediate)	4 RCTs (N=476)	4 RCTs (N=476)	Buccal fentanyl more effective than placebo or oral opioid for immediate pain relief	Moderate
	Longer-term outcomes, addiction, abuse	No studies	No studies	No studies	No studies
Tapering off opioids vs. continuation of opioids	Pain, function	1 RCT (N=10)	1 RCT (N=34)	No difference	Low[c]
	Opioid dose	No studies	1RCT (N=34)	Taper associated with lower dose	Low[c]
Tapering protocols and strategies	Pain, tapering completion, opioid withdrawal	2 nonrandomized trials (N=150)	1 RCT (N=21)	Varenicline associated with no differences versus placebo as an adjunct to tapering	Low[c]
Tapering protocols and strategies	Opioid-related emergency department visit	No studies	1 cohort study (N=494)	Each additional week to discontinuation associated with 7% reduction in risk	Low
Opioid Risk Tool	Diagnostic accuracy	3 studies (N=496)	6 studies (N=1025)	Sensitivity: 0.20 to 0.99 Specificity: 0.16 to 0.88	Low[c]
SOAPP Version 1	Diagnostic accuracy	2 studies (N=203)	2 studies (N=203)	Sensitivity: 0.68 and 0.73 Specificity: 0.38	Low
SOAPP-R	Diagnostic accuracy	No studies	4 studies (N=840)	Sensitivity: 0.25 to 0.53 Specificity: 0.62 to 0.77	Low[b]
Brief Risk Interview	Diagnostic accuracy	No studies	3 studies (N=577)	Sensitivity 0.73 to 0.83 Specificity: 0.43 to 0.88	Low[a]
Naloxone co-prescription	Emergency department visits	Not addressed	1 nonrandomized study (N=1985)	Naloxone associated with decreased risk of emergency department visits versus no naloxone	Low[a]
	All-cause mortality, opioid poisoning deaths	No studies	1 nonrandomized study (N=1985)	No difference	Low[a]

Intervention	Outcome	2014 AHRQ Report	2019 Update	Main Findings	Strength of Evidence
Prescription opioid use disorder: Taper vs. maintenance	Drug use	No studies	1 RCT (N=113)	Buprenorphine taper inferior to maintenance	Low[a]
Prescription opioid use disorder: Buprenorphine vs. methadone	Drug use, pain function	No studies	1 RCT (N=54)	No differences	Low[a]

Ratings that are new or changed from the prior report are shaded in gray.
Abbreviations: AHRQ=Agency for Healthcare Research and Quality; RCT=randomized controlled trial; SOAPP= Screening and Opioid Assessment for Patients with Pain; SOAPP-R= Screening and Opioid Assessment for Patients with Pain-Revised Version; VA=Veterans Affairs Department; vs.=versus.
[a] Not addressed in the 2014 AHRQ report
[b] The SOE was low in the 2014 AHRQ report
[c] The SOE was insufficient in the 2014 AHRQ report

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Evidence Summary

Introduction

Chronic pain is common and is associated with an annual cost conservatively estimated at $560 to $635 billion, can result in impaired physical and mental functioning and reduced quality of life, and is the leading cause of disability in the United States.[1] Chronic pain is caused by a variety of conditions and is influenced by multiple biological, psychological, and social factors.

Opioids are often prescribed for chronic pain. In the United States, prescription of opioid medications for chronic pain more than tripled from 1999 to 2015.[2] This increase was accompanied by marked increases in rates of opioid use disorder and drug overdose mortality[2-4] involving prescription opioids. From 1999 to 2014, over 165,000 people died from overdose related to prescription opioids in the United States,[5] with an estimated 17,087 prescription opioid overdose deaths in 2016.[2] In October 2017, the U.S. Department of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis.[6]

In 2013, the Agency for Healthcare Research and Quality (AHRQ) commissioned a comparative effectiveness review on the effectiveness and risks of opioid therapy for chronic pain, focusing on studies with long-term (≥12 months) followup.[7] The review addressed the risks and benefits of opioids for chronic pain, dosing strategies, and risk assessment and risk mitigation strategies. The 2014 AHRQ report found insufficient evidence to show benefits of long-term opioid therapy for chronic pain, due to the absence of trials with followup of at least 1 year. The review found that long-term opioid therapy was associated with increased risk of overdose, opioid abuse, and other harms; some harms (including overdose risk) were dose-dependent. Information on the effectiveness of opioid dosing strategies and risk mitigation strategies was limited.

The 2014 AHRQ report and a subsequent update[5] commissioned by the Centers for Disease Control and Prevention (CDC) were used as the basis for developing the 2016 CDC guideline on opioids for chronic pain.[5,8] The CDC guideline includes the following recommendations: use nonopioid therapy as the preferred therapy for chronic pain; perform risk assessment and initiate long-term opioid therapy only when benefits are likely to exceed risks; use risk mitigation strategies; and apply dose thresholds ("caution" with increasing doses >50 morphine equivalent dose [MED] per day, "avoid" increasing doses >90 MED/day).[5] Of the 12 recommendations in the CDC guideline, all except for one (treatment for opioid use disorder) were assessed as being supported by low quality evidence. Although a number of opioid prescribing practices were declining at the time that the CDC guideline was published, the rate of decline increased following its release.[9]

Rationale for This Review

The purpose of this review is to update the 2014 AHRQ report [7] on opioids for chronic pain. This update includes new evidence for questions covered in the 2014 AHRQ report, including efficacy and harms, comparisons with nonopioid therapies, dosing strategies, dose-response relationships, risk mitigation strategies, discontinuation and tapering of opioid therapy, and population differences. This review is one of three concurrent AHRQ systematic reviews on treating chronic pain; the other reviews address nonpharmacologic treatments[10] and nonopioid pharmacological treatments.[11]

Scope and Key Questions

This Comparative Effectiveness Review focused on opioid treatments with short-term (1 to <6 months), intermediate-term (6 to <12 months), and long-term followup (≥12 months); with Key Questions on effectiveness and comparative effectiveness, harms and adverse events, dosing strategies, and risk assessment and risk mitigation strategies.

Key Question 1. Effectiveness and Comparative Effectiveness

a. In patients with chronic pain, what is the effectiveness of opioids versus placebo or no opioid for outcomes related to pain, function, and quality of life after short-term followup (1 to <6 months), intermediate-term followup (6 to <12 months), and long-term followup (≥12 months)?

b. How does effectiveness vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], visceral pain, fibromyalgia, sickle cell disease, inflammatory pain, headache disorders, and degree of nociplasticity); (2) patient demographics (e.g., age, race, ethnicity, gender, socioeconomic status); (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities, and high risk for opioid use disorder); (4) the mechanism of action of opioids used (e.g., pure opioid agonists, partial opioid agonists such as buprenorphine, or drugs with mixed opioid and nonopioid mechanisms of action such as tramadol or tapentadol)?

c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacologic or nonpharmacologic, including cannabis) on outcomes related to pain, function, and quality of life after short-term followup (1 to <6 months), intermediate-term followup (6 to <12 months), and long-term followup (≥12 months)?

d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacologic or nonpharmacologic, including cannabis) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used after short-term followup (1 to <6 months), intermediate-term followup (6 to <12 months), and long-term followup (≥12 months)?

Key Question 2. Harms and Adverse Events

a. In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on: (1) opioid use disorder, abuse, or misuse; (2) overdose (intentional and unintentional); and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?

b. How do harms vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], visceral pain, fibromyalgia, sickle cell disease, inflammatory pain, headache disorders, and degree of nociplasticity); (2) patient demographics; (3) patient comorbidities (including past or current opioid use disorder or at high risk for opioid use disorder); (4) the dose of opioids used and duration of therapy; (5) the mechanism of action of opioids used (e.g., pure opioid agonists, partial opioid agonists such as buprenorphine, or drugs with opioid and nonopioid mechanisms of action such as tramadol and tapentadol); (6) use of sedative hypnotics; (7) use of gabapentinoids; (8) use of cannabis?

c. In patients with chronic pain, what are the comparative risks of opioids versus nonopioid therapies on: (1) opioid use disorder, abuse, or misuse; (2) overdose (intentional and unintentional); and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and mental health harms (e.g., depression)?

d. In patients with chronic pain, what are the comparative risks of opioids plus nonopioid interventions (pharmacologic or nonpharmacologic, including cannabis) versus opioids or nonopioid interventions alone on: (1) opioid use disorder, abuse, or misuse; (2) overdose (intentional and unintentional); and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and mental health harms (e.g., depression)?

Key Question 3. Dosing Strategies

a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?

b. In patients with chronic pain, what is the comparative effectiveness of short-acting versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?

c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; and overdose?

d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids versus long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?

e. In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous versus as-needed dosing of opioids on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?

f. In patients with chronic pain, what is the comparative effectiveness of opioid dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?

g. In patients with chronic pain, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life, and doses of opioids used?

h. In patients with chronic pain, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?

i. In patients with chronic pain, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and opiate withdrawal symptoms?

j. In patients with chronic pain, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, opiate withdrawal symptoms, and likelihood of opioid cessation?

k. In patients with chronic pain, what is the comparative effectiveness of different opioid dosages and durations of therapy for outcomes related to pain, function, and quality of life?

Key Question 4. Risk Assessment and Risk Mitigation Strategies

a. In patients with chronic pain being considered for opioid therapy, what is the accuracy of instruments and tests (including metabolic and/or genetic testing) for predicting risk of opioid use disorder, abuse, or misuse, and overdose?

b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments and tests (including metabolic and/or genetic testing) on outcomes related to opioid use disorder, abuse, or misuse, and overdose?

c. In patients with chronic pain who are prescribed opioid therapy, what is the effectiveness of risk mitigation strategies, including (1) opioid management plans, (2) patient education, (3) urine drug screening, (4) use of prescription drug monitoring program data, (5) use of monitoring instruments, (6) more frequent monitoring intervals, (7) pill counts, (8) use of abuse-deterrent formulations, (9) consultation with mental health providers when mental health conditions are present, (10) avoidance of co-prescribing of sedative hypnotics, and (11) co-prescribing of naloxone on outcomes related to opioid use disorder, abuse, or misuse, and overdose?

d. In patients with chronic pain, what is the comparative effectiveness of treatment strategies for managing patients with opioid use disorder related to prescription opioids on outcomes related to pain, function, quality of life, opioid use disorder, abuse, misuse, and overdose?

Contextual Questions

1. What are clinician and patient values and preferences related to opioids and medication risks, benefits, and use?

2. What are the costs and cost-effectiveness of opioid therapy and risk mitigation strategies?

Contextual questions are not addressed using systematic methods, but provide a summary of the most relevant and high quality evidence.

Methods

The methods for this systematic review follow the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews.*[12] See the review protocol (https://effectivehealthcare.ahrq.gov/topics/opioids-chronic-pain/protocol) and the full report for additional details.

Review Protocol

A multidisciplinary Technical Expert Panel was convened for this update review and provided input into the draft protocol as did the AHRQ Task Order Officer and representatives from the CDC. The final version of the protocol for this review was posted on the AHRQ Effective Health Care Program website (https://effectivehealthcare.ahrq.gov/topics/opioids-chronic-pain/protocol) and registered in the PROSPERO international database of prospectively registered systematic reviews (CRD42019127423).

Literature Search Strategy

We conducted electronic searches in Ovid® MEDLINE®, Embase®, PsycINFO®, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews in August 2019. Searches were conducted from January 2014 for Key Questions addressed in the 2014 AHRQ report (searches conducted through August 2014). For questions or areas not covered by the 2014 AHRQ publication, searches were conducted from database inception. Reference lists of included systematic reviews were screened for additional studies and relevant references from the 2014 AHRQ report were carried forward. A Federal Register notification for a Supplemental Evidence And Data for Systematic review (SEADS) portal was posted for submission of unpublished studies.

Inclusion and Exclusion Criteria, Study Selection, and Data Abstraction

Inclusion and exclusion criteria were developed *a priori* based on the Key Questions and PICOTS (Population, Interventions, Comparators, Outcomes, Timing, and Setting) and are detailed in Table 1 of the report and the published protocol. Randomized controlled trials (RCTs) reporting outcomes at least 1 month following completion of treatment. Trials comparing opioids with placebo or no intervention, nonopioids, or different opioids were included, as well as trials comparing opioids plus nonopioids with opioids and nonopioids. Outcomes of interest were pain, function, health status/quality of life, mental health outcomes, sleep, doses of opioid used (for comparisons involving opioids and nonopioid therapy) and harms.

For Key Question 4a, studies on the predictive utility of risk prediction instruments and other risk assessment methods compared against a reference standard were included. Details regarding process and inclusion/exclusion of studies are provided in the full report and Appendixr B. We

abstracted data on study characteristics, funding source, populations, interventions, comparators, and results.

Quality Assessment of Individual Studies

Study quality was independently assess by two investigators using predefined criteria, randomized trials were evaluated using criteria and methods developed by the Cochrane Back and Neck Group,[13] cohort and other observational studies of interventions were evaluated using criteria developed by the U.S. Preventive Services Task Force,[6] and studies of diagnostic accuracy were assessed using Quality Assessment of Diagnostic Accuracy Studies – Version 2 (QUADAS-2).[14] These criteria were used in conjunction with the approach recommended in the AHRQ Methods Guide. [15] Studies were rated as "good," "fair," or "poor". The quality ratings of studies included in the 2014 AHRQ report were reviewed to insure consistency in quality assessment.

Data Analysis and Synthesis

A random effects meta-analysis using the profile likelihood method was performed on short-term randomized trials of opioids versus placebo, opioids versus nonopioids, opioids plus nonopioids versus nonopioids alone, and opioids plus nonopioids versus opioids alone at short-term followup.[16] Pooled relative risks were calculated for pain, function, and harms (discontinuation due to adverse events, serious adverse events, somnolence, nausea, vomiting, constipation, dizziness, headache, and pruritus).

Different opioid arms within the same study were combined so each study was represented once in a meta-analysis, in order to avoid overweighting and the issue of correlation within the same study. For pooling mean difference or standard mean difference (SMD), adjusted mean difference from the analysis of covariance model or other appropriate regression model was used if reported by the study, followed by difference in change score and followup score. Missing standard deviations for followup and change scores were imputed.

For meta-analyses of opioids versus placebo, the main analysis was stratified by opioid type. For meta-analyses involving nonopioids (opioids versus nonopioids, opioids plus nonopioids vs. opioids, and opioids plus nonopioids versus nonopioids), the main analysis was stratified by the nonopioid. Additional stratified analyses were performed on pain type (neuropathic, fibromyalgia, or musculoskeletal/mixed), duration of followup (1 to <3 months or 3 to 6 months), trial quality (good, fair, or poor), use of a crossover design, opioid status (opioid-naïve, opioid-experienced, mixed, or not reported), publication date (prior to 2007 or in or after 2007), geographic region (United States or Canada, Europe or Australia, Asia, or multiple/mixed), and receipt of industry funding. Opioid dose was analyzed in categories based on the thresholds in the 2016 CDC guideline: less than 50, 50 to less than 90, or 90 or more mg MED/day.[5] For opioids versus placebo, opioid dose was also analyzed as a continuous variable in a meta-regression for the outcomes mean improvement in pain and function. For opioids versus placebo, analyses were also stratified according to whether the trial used an enriched enrollment randomized withdrawal (EERW) design. In the EERW design, patients are randomized to continuation of the opioids or discontinuation (placebo) following a run-in period to determine responsiveness to opioids and tolerability. Because the EERW design was seldom used before 2007, another stratified analysis on this factor was restricted to trials published in or after 2007.

For trials that reported likelihood of a pain or function response, the main analysis was based (in descending order of priority) on the proportion of patients experiencing 30 percent or more

improvement in pain or function, improvement in pain or function at an alternative threshold closest to 30 percent or more, or "moderate" or "good" improvement in pain or function or pain relief using a categorical scale. The analysis was also performed on the likelihood of experiencing 50 percent or more improvement in pain. Trials that reported likelihood of a pain response varied with regard to whether patients lost to followup were excluded or considered nonresponders. In the primary analysis we used the data as reported in the trials; as a sensitivity analysis, all patients lost to followup were considered nonresponders.

Statistical heterogeneity was assessed using the I^2 statistic[17] and the Cochran χ^2 test. . All meta-analyses were conducted using Stata/SE 14.0 (StataCorp, College Station, TX).

For long-term data and other comparisons and outcomes, there were insufficient data to perform meta-analysis. Evidence was synthesized qualitatively using the methods described in the AHRQ Methods Guide (see Grading the Strength of Evidence, below).[15] For analyses with more than 10 trials that were sufficiently homogeneous with regard to populations, interventions, and outcomes, funnel plots and the Egger test were conducted for small sample effects.

The magnitude of effects for pain and function were classified using the same system as in the 2018 AHRQ noninvasive treatment for chronic pain review[18] and an earlier AHRQ comparative effectiveness review on treatments for low back pain.[19] A small effect was defined for pain as a mean between-group difference following treatment of 0.5 to 1.0 points on a 0- to 10-point numeric rating scale or visual analog scale and for function as a SMD of 0.2 to 0.5 or a mean difference of 5 to 10 points on the 0 to 100-point Oswestry Disability Index (ODI), 1 to 2 points on the 0 to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent. A moderate effect was defined for pain as a mean difference of 10 to 20 points on a 0- to 100-point visual analog scale (VAS) and for function as an SMD of 0.5 to 0.8, or a mean difference of 10 to 20 points on the ODI, 2 to 5 points on the RDQ, or equivalent. Large/substantial effects were defined as greater than moderate. We applied similar thresholds to other outcomes measures.[20] \

Grading the Strength of Evidence

The overall strength of evidence for each KQ and primary outcome (pain, function) was graded high, moderate, low, or insufficient based on study limitations; consistency of results across studies; the directness of the evidence linking the interventions with health outcomes; effect estimate precision; and reporting bias.[15] Summary strength of evidence tables were updated based on all the evidence, from the 2014 AHRQ report and this updated review.

Peer Review and Public Commentary

Experts were invited to provide external peer review of this systematic review; AHRQ and an associate editor also provided comments. In addition, the draft report was posted on the AHRQ website for 4 weeks to for public comment. Comments were reviewed and used to inform revisions to the final report.

Results

We included 115 randomized controlled trials, 40 observational studies, and seven studies of diagnostic accuracy of opioid risk prediction instruments to address four Key Questions and two Contextual Questions (Table A). The population of interest is adults with various types of chronic pain. The full report outlines the populations, interventions, comparators, and outcomes

considered in our review, along with more detailed analysis of the findings (and reporting of insufficient evidence).

Table A. Summary of findings

Key Question[a]	Summary of Findings
1a. Opioids vs. placebo or no opioid	• Opioids were associated with a small mean improvement vs. placebo in pain intensity at short-term followup (71 trials, N=19,616, SOE: high). • Opioids were associated with increased likelihood vs. placebo of experiencing a pain response at short-term followup (44 trials, N=12,481, SOE: high). • Opioids were associated with a small mean improvement vs. placebo in function at short-term followup (44 trials, N=12,427, SOE: high). • Opioids were associated with a mean improvement below the threshold for small vs. placebo in SF-36 measures of physical health status at short-term followup (23 trials, N=8005, SOE: high). • No difference between opioids vs. placebo in mean improvement on SF-36 measures of mental health status at short-term followup (21 trials, N=7586, SOE: high) • Opioids were associated with a small mean improvement vs. placebo in sleep quality at short-term followup (25 trials, N=6720, SOE: moderate).
1b. How does effectiveness vary depending on: the specific type or cause of pain; patient demographics; patient comorbidities; or opioid type?	• Effects of opioids vs. placebo on mean improvement in pain were greater at short-term followup in trials of patients with neuropathic pain (20 trials, N=2568) than musculoskeletal pain (50 trials, N=16,979) (SOE: low). • Limited evidence found similar effects of opioids vs. placebo when analyses were stratified by age (4 trials), sex (2 trials), and race (1 trial) (SOE: low). • Analyses of 70 placebo-controlled trials found no interactions between type of opioid on short-term pain, function, SF-36 health status, sleep, depression, or adverse effects; 5 trials directly comparing different types of opioids found a mixed mechanism agent associated with greater pain relief vs. a pure opioid agonist with fewer side effects and 3 trials that directly compared a partial vs. pure opioid agonist found no differences between a partial vs. pure opioid agonist (SOE: moderate).
1c. Opioids vs. nonopioid therapies	• No differences between opioids vs. nonopioids in mean improvement in pain (14 trials, N=2195) or likelihood of a pain response at short-term followup (12 trials, N=2886) at short-term followup (SOE: moderate). • There were no differences between opioids vs. nonopioids in mean improvement in function at short-term followup (11 trials, N=2010, SOE: high). • Opioids were associated with a greater improvement than nonopioids in SF-36 measures of physical health status at short-term followup that was below the threshold for small (6 trials, N=1423, SOE: moderate). • There were no differences between opioids vs. nonopioids in SF-36 mental health status (6 trials, N=1427), sleep (7 trials, N=1694), anxiety (3 trials, N=414) or depression (7 trials, N=748) at short-term followup (SOE: low for anxiety, moderate for other outcomes). • There were no interactions between nonopioid type and effects on any short-term outcome.

Key Question[a]	Summary of Findings
1d. Opioids plus nonopioid interventions vs. opioids or nonopioid interventions alone	Opioid plus nonopioid vs. nonopioid • No differences between an opioid plus nonopioid vs. a nonopioid alone in mean improvement in pain at short-term followup (6 trials, N=628), likelihood of a pain response (6 trials, N=765), function (4 trials, N=549), or other outcomes (SOE: low for all outcomes). Opioid plus nonopioid vs. opioid • An opioid plus nonopioid was associated with greater improvement in pain at short-term followup vs. an opioid alone that was below the threshold for small (5 trials, N=623, SOE: low). • No statistically significant differences between an opioid plus nonopioid vs. an opioid alone in likelihood of a pain response (5 trials, N=831) or mean improvement in function (4 trials, N=521) though estimates favored combination therapy (SOE: low). • No differences between an opioid plus nonopioid vs. an opioid alone in mean improvement in SF-36 measures of physical or mental health status, sleep, anxiety, or depression, though analyses were limited by small numbers of trials (SOE: low). • Four trials of patients with neuropathic pain found an opioid plus nonopioid associated with lower doses of opioid used vs. an opioid alone, with pain relief better with combination therapy (SOE: low). • One cohort study of patients with chronic pain prescribed opioids found no association between degree of self-reported cannabis use and pain, function, likelihood of opioid discontinuation, or opioid dose through up to 4 years of followup; cannabis use was associated with increased anxiety (SOE: low).
2a. Harms of opioids vs. placebo or no opioid	• Opioids were associated with increased risk of discontinuation due to adverse events vs. placebo at short-term followup (61 trials, N=19,994, SOE: high). • There was no difference between opioids vs. placebo in risk of serious adverse events at short-term followup (38 trials, N=13,160, SOE: moderate). • Opioids were associated with increased risk of nausea (60 trials, N=19,718), vomiting (49 trials, N=17,388), and constipation (58 trials, N=19,351) vs. placebo at short-term followup (SOE: high). • Opioids were associated with increased risk of somnolence vs. placebo at short-term followup (52 trials, N=17,458, SOE: high). • Opioids were associated with increased risk of dizziness vs. placebo at short-term followup (53 trials, N=18,396, SOE: high). • Opioids were associated with increased risk of pruritus vs. placebo at short-term followup (30 trials, N=11,454, SOE: high). • Opioids were not associated with increased risk of headaches versus placebo at short-term followup (48 trials, N=17,405, SOE: high). • Two cohort studies found an association between opioid use and increased risk of abuse, dependence, or addiction (SOE: low). • Two cohort studies found an association between opioid use and increased risk of overdose events (SOE: low). • One cohort study found prescription of long-acting opioids associated with increased risk of all-cause mortality vs. nonopioid medications (SOE: low). • Six observational studies found an association between opioid use and risk of fracture and three observational studies found an association between opioid use and risk of falls, though differences were not statistically significant in all studies and estimates decreased with longer duration of opioid use in some studies (SOE: low). • Two observational studies found an association between opioid use and increased risk of myocardial infarction (SOE: low). • One cross-sectional study of men with back pain found long-term opioid use associated with increased risk for use of medications for erectile dysfunction or testosterone replacement vs. nonuse (SOE: low). • One cohort study found no association between any long-term opioid use and increased risk of attempted suicide/self-harm (SOE: low).

Key Question[a]	Summary of Findings
2b. How do harms vary depending on: (1) the specific type or cause of pain; (2) patient demographics; (3) patient comorbidities; (4) the dose of opioids used and duration of therapy; (5) opioid type; (6) use of sedative hypnotics; (7) use of gabapentinoids; (8) use of marijuana?	• Analyses of placebo-controlled trials found no interactions between the pain type and risk of harms (SOE: low). • Three cohort studies found an association between concurrent use of benzodiazepines and opioids vs. opioids alone; in one study the risk of overdose decreased with longer duration of concurrent use (SOE: low). • Three observational studies found an association between concurrent use of gabapentinoids and opioids vs. opioids alone and increased risk of overdose; risks were higher at increased gabapentinoid doses (SOE: low). *Dose/duration* • Analyses of placebo-controlled trials indicated no interaction between higher opioid dose category and increased risk of short-term harms; trials directly comparing higher vs. lower dose were limited but reported similar findings (SOE: low). • Two cohort studies found higher doses of long-term opioid therapy associated with increased risk of opioid abuse, dependence, or addiction compared with lower doses (SOE: low). • Four observational studies consistently found an association between higher doses of long-term opioids and risk of overdose or overdose mortality (SOE: low). • One cohort study found higher dose of opioids associated with increased risk of all-cause mortality; longer duration was associated with decreased risk of all-cause mortality (SOE: low). • One cohort study found modest associations between higher dose of long-term opioid and increased risk of falls and major trauma (SOE: low). • One case-control study found opioid dose higher than20 mg MED/day associated with increased odds of road trauma injury when the analysis was restricted to drivers, with no dose-dependent association at doses higher than 20 mg MED/day (SOE: low). • Three cohort studies found association between higher opioid dose and risk of various endocrinological adverse events (SOE: low). • One cohort study found an association between longer duration of therapy and increased risk of new-onset depression; there was no association between higher dose and increased risk. A smaller study by the same authors reported similar findings for treatment-resistant depression (SOE: low). *Co-prescription of benzodiazepines or gabapentinoids* • Three cohort studies found an association between concurrent use of benzodiazepines and opioids versus opioids alone and increased risk of overdose; in one study, the risk decreased with longer duration of concurrent use (SOE: low). • Three observational studies found an association between concurrent use of gabapentinoids and opioids versus opioids alone and increased risk of overdose; risks were higher at increased gabapentinoid doses (SOE: low).
2c. Harms of opioids vs. nonopioid therapies	• Opioids were associated with increased risk of discontinuation due to adverse events (12 trials, N=3637), somnolence (12 trials, N=3377), nausea (11 trials, N=3137), constipation (12 trials, N=3377), vomiting (6 trials, N=2644), pruritus (5 trials, N=2577, and headache (8 trials, N=2759) vs. a nonopioid at short-term followup (SOE: moderate [discontinuation due to adverse events, constipation, somnolence] to high [nausea, vomiting, headache, pruritus]).
2d. Harms of opioids plus nonopioid interventions vs. opioids or nonopioid interventions alone	Opioid plus nonopioid vs. nonopioid • An opioid plus nonopioid was associated with increased risk of nausea (5 trials, N=330) and constipation (6 trials, N=633) vs. a nonopioid alone at short-term followup. Effects on risk of discontinuation due to adverse events were not statistically significant (6 trials, N=707). Effects on risk of somnolence (6 trials, N=663) and constipation (6 trials, N=663) were also no statistically significant, but there was an interaction with trial quality and effects were statistically significant when a poor-quality trial was excluded (SOE: low for discontinuation due to adverse events, moderate for nausea, constipation, and somnolence). Opioid plus nonopioid vs. opioid • No differences between an opioid plus nonopioid vs. an opioid alone in risk of discontinuation due to adverse events (5 trials, N=782), nausea (5 trials, N=585), constipation (6 trials, N=860), or somnolence (6 trials, N=860) vs. an opioid alone at short-term followup.

Key Question[a]	Summary of Findings
3b. Short-acting vs. long-acting opioids	• Two trials found no differences in effectiveness or harms between long- vs. short-acting formulations of the same opioid administered at similar doses (SOE: low). • A cohort study found long-acting opioid associated with increased risk of overdose vs. short-acting opioids; risk decreased with longer duration of exposure (SOE: low).
3c. Different long-acting opioids	• Four trials (N=2721) of long-acting oxycodone vs. tapentadol reported mean differences in pain, but the dose was lower in the oxycodone arms. Oxycodone was associated with increased risk of discontinuation due to adverse events and gastrointestinal adverse events, with no difference in risk of serious adverse events (SOE: low). • Three trials (N=1405) compared similar doses of long-acting oxycodone vs. morphine; effects on pain, SF-36 physical and mental health; adverse events were inconsistent, with some trials reporting no differences (SOE: low). • Three trials (N=957) compared transdermal fentanyl vs. long-acting morphine. Two trials reported no differences in pain or other outcomes. The third trial found a small difference in pain intensity favoring transdermal fentanyl. Two trials found a lower likelihood of constipation with transdermal fentanyl than long-acting morphine but discontinuations due to adverse events was higher with transdermal fentanyl (SOE: low). • Other long-acting opioid comparisons were evaluated in one or two trials, with no differences in effects (SOE: low) • Two cohort studies of Medicaid patients found methadone associated with increased risk of overdose or all-cause mortality vs. morphine and one cohort study of Veterans Affairs patients found methadone associated with decreased risk (SOE: low).
3f. Opioid dose escalation vs. dose maintenance or use of dose thresholds	• One trial of more liberal dose escalation vs. maintenance of current doses found no difference in outcomes related to pain, function, or risk of discontinuation due to opioid misuse, but opioid doses were similar (52 vs. 40 mg MED /day at the end of the trial) (SOE: low).
3h. Different strategies for treating acute exacerbations of chronic pain	• Two randomized trials found buccal fentanyl more effective than placebo for treating acute exacerbations of pain in patients prescribed long-term opioid therapy for chronic pain, based on pain relief measured up to 2 hours after dosing (SOE: moderate). • Two randomized trials found buccal fentanyl more effective than oral opioids for treating acute exacerbations of pain in patients prescribed long-term opioid therapy for chronic pain, based on pain relief measured up to 2 hours after dosing. (SOE: moderate).
3i. Decreasing opioid doses or tapering off opioids vs. continuation of opioids	• One trial found a taper support intervention associated with no difference vs. usual care at 22 weeks in BPI pain severity, but greater improvement in BPI pain interference; effects persisted at 34-week followup. Effects on opioid dose were not statistically significant (SOE: low).
3j. Different tapering protocols and strategies	• One trial of patients undergoing tapering in a 15-day intensive outpatient interdisciplinary pain program found no differences between varenicline vs. placebo as an adjunct to tapering in median time to tapering completion, opioid withdrawal symptoms, pain, or depression (SOE: low). • One cohort study of patients prescribed 120 mg MED/day or more of long-term opioid therapy found each additional week to discontinuation associated with a 7% reduction in risk of an opioid-related emergency department visit or hospitalization (SOE: low).
3k. Different opioid dosages and durations of therapy	• In head-to-head trials, opioid doses of 50 to 90 mg MED/day were associated with a minimally greater (below the threshold for small) improvement mean pain intensity versus doses less than 50 mg MED/day; there was no difference in mean improvement in function. Analyses of placebo-controlled trials also found an interaction (p=0.005) between higher opioid dose and greater improvement in mean pain intensity, with some evidence of a plateauing effect at 50 mg or greater MED/day (SOE: moderate). • In analyses of placebo-controlled trials, effects on mean improvement in pain were larger at 1 to 3 months than at 3 to 6 months; similar patterns were observed for likelihood of pain response and mean improvement in function (SOE: low).

Key Question[a]	Summary of Findings
4a. Accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse	• Two studies (N=203) evaluated the Screening and Opioid Assessment for Patients with Pain (SOAPP) Version 1 instrument. In one study, sensitivity was 0.68 and specificity was 0.38 at a cutoff score of at least 8, for a PLR of 1.11 and NLR of 0.83 for predicting positive urine drug tests. One study reported a sensitivity for predicting opioid discontinuation due to aberrant drug-related behavior of 0.73 at a cutoff score of greater than 6 (SOE: low). • Four studies (N=840) evaluated the Screening and Opioid Assessment for Patients with Pain-Revised (SOAPP-R). At a cutoff score of at least 18, sensitivity ranged from 0.25 to 0.53 and specificity ranged from 0.62 to 0.77 for predicting aberrant drug-related behaviors (4 studies). The AUROC ranged from 0.52 to 0.55 (3 studies) (SOE: low). • One study (n=263) found the Pain Medication Questionnaire associated with a sensitivity of 0.34, specificity of 0.77, and AUROC of 0.57 for predicting opioid discontinuation due to abuse (SOE: low). • Three new studies (N=577) evaluated the Brief Risk Interview (BRI). A BRI high-risk assessment was associated with sensitivities that ranged from 0.73 to 0.83 and specificities that ranged from 0.43 to 0.88 for predicting opioid misuse or abuse, with AUROCs of 0.65 and 0.93 in two studies (SOE: low). • One study (N=257) evaluated the Brief Risk Questionnaire. At a cutoff score of at least 3, sensitivity was 0.80, specificity 0.41, and the AUROC was 0.61 (SOE: low).
4c. Risk mitigation strategies	• One cohort study found co-prescription of naloxone in patients prescribed opioids for chronic pain associated with no difference between no naloxone in all-cause mortality or opioid poisoning deaths, though naloxone co-prescription was associated with decreased risk of ED visits at 1 year followup (SOE: low). • No study evaluated the effectiveness of other risk mitigation strategies vs. non-use of the risk mitigation strategy for improving outcomes related to misuse, opioid use disorder, and overdose.
4d. Treatment strategies for managing patients with opioid use disorder related to prescription opioids	• A trial of patients with prescription opioid dependence not requiring opioids for a pain diagnosis found buprenorphine taper associated with a lower percentage of negative urine samples, more days per week of illicit opioid use, and higher risk of relapse vs. buprenorphine maintenance (SOE: low). • A trial of patients with opioid dependence due to prescription opioids for chronic pain found no difference between methadone vs. buprenorphine/naloxone in likelihood of study retention, pain, or function; there were also no differences in likelihood of a positive urine for opioids, cocaine, or other drugs, though patients randomized to methadone were less likely to self-report opioid use (SOE: low).

[a]No studies addressed Key Questions 3d, 3e,3g, 4b. For Key Question 3a, evidence was insufficient.
AUROC = area under the receiver operating curve; BPI = Brief Pain Inventory; BRI = Brief Risk Interview; DIRE = Diagnosis, Intractability, Risk and Efficacy Inventory; ED = emergency department; MED = morphine equivalent dose; NLR=negative likelihood raio; ORT = Opioid Risk Tool; PLR=positive likelihood ratio; SOAPP = Screening and Opioid Assessment for Patients with Pain; SOAPP-R = Screening and Opioid Assessment for Patients with Pain (Revised); SOE = strength of evidence

The full report of our review presents additional detail on the findings for the Key Questions and in addition addresses the two Contextual Questions on (1) clinician and patient values and preferences, and (2) costs and cost-effectiveness or opioid therapy and risk mitigation strategies.

Discussion

Key Findings and Strength of Evidence

This report updates the 2014 AHRQ report. The key findings, including SOE ratings, are summarized in Table A and reflect the combined evidence from the 2014 AHRQ report and this update. For short-term outcomes, data were available from over 71 placebo-controlled trials of opioids. All trials were 6 months in duration or less, with most (87.5%) trials 3 months or less. Opioids were associated with beneficial effects versus placebo, but MDs were small: for pain, less than 1 point on a 0 to 10 scale and for function, an SMD of 0.22 (or <1 point on the 0 to 10 BPI interference scale and <1 point on the 0 to 24 RDQ. Some differences were statistically

significant but below the pre-defined threshold for small (<0.5 on a 0 to 10 scale or an SMD <0.2); average effects in this range are unlikely to be clinically significant in most patients.

Effects of opioids versus placebo on short-term health status/quality of life, sleep quality, and mental health outcomes were reported less frequently than pain and function. Opioids were associated with a small mean improvement in short-term sleep quality versus placebo and might be associated with a small mean short-term improvement in SF-36 mental health status. Effects on SF-36 physical health status were below the threshold for small and there was no effect on mental health outcomes.

Effects of opioids on short-term outcomes were generally consistent across opioid types. For pain, effects were somewhat greater in trials of neuropathic than musculoskeletal pain, with an average difference of about 0.5 point on a 0 to 10 scale. Study methods also had some effect on findings, with use of a crossover design associated with larger effects for some outcomes.

Opioids were associated with increased risk of short-term, bothersome harms versus placebo, including discontinuation due to adverse events (number needed to harm [NNH 10], gastrointestinal events [NNH 7.1 for nausea, 14.3 for vomiting, and 7.1 for constipation], somnolence [NNH 11.1], dizziness [NNH 12.5], and pruritus [NNH 14.3]). There were few serious adverse events and no difference between opioids versus placebo in risk in the short-term trials, though serious adverse events were not well-defined by the trials

Evidence on short-term outcomes does not address the practice of long-term use of opioids and associated benefits and harms. As in the 2014 AHRQ report, we identified no long-term (>1 year) RCTs of opioid therapy versus placebo. One new cohort study found no association between long-term opioid therapy versus no opioids and pain, function or other outcomes.[21] New observational studies were consistent with the 2014 AHRQ report in finding an association between use of prescription opioids and risk of addiction,[22] overdose,[22] fractures,[23-25] falls[24,26] and cardiovascular events;[27] a new study also found an association between opioid use and risk of all-cause mortality.[27] New observational studies were also consistent with the 2014 AHRQ report in finding associations between higher doses of opioids and risks of overdose, addiction, and endocrinological adverse events;[22,23,26-29] new studies also found an association between higher dose and increased risk of incident or refractory depression.[30,31] Effects of longer duration of opioid exposure varied across outcomes, from increasing risk (all-cause mortality, depression) to decreasing risk. Limited evidence indicated an association between co-prescription of gabapentinoids[32-34] or benzodiazepines[35-37] and increased risk of overdose, with most pronounced risk occurring soon after initiation of these medications.

This update also expanded upon the 2014 AHRQ report by including short-term randomized trials that directly compared opioids versus nonopioids and combination therapy with an opioid plus nonopioid versus an opioid or nonopioid alone. There were no differences between opioids versus nonopioids in short-term pain, function, health status/quality of life, sleep quality, or mental health outcomes, though opioids were associated with increased risk of short-term adverse effects. The most commonly evaluated nonopioids were NSAIDS, gabapentinoids, and nortriptyline. All trials of combination therapy evaluated patients with neuropathic pain and primarily evaluated gabapentinoids or nortriptyline, potentially limiting applicability of findings to other pain types and other nonopioids. Evidence on long-term effects of combination therapy versus an opioid or nonopioid alone, including effects on overdose risk and risks related to opioid use disorder, was lacking.

Evidence on the effectiveness of different opioid dosing strategies remains very limited. One trial included in the 2014 AHRQ report found no differences between a more liberal dose

escalation strategy versus maintenance of current doses in pain, function, or discontinuation due to opioid misuse, but the liberal escalation strategy was associated with only a small difference in opioid doses (52 vs. 40 mg MED/day). [38] There were no clear differences between short- and long-acting opioids or between different long-acting opioids in effects on pain or function, but in most trials doses were titrated to achieve adequate pain control. None of the head-to-head trials were designed to evaluate overdose, abuse, addiction, or related outcomes. Evidence on comparative risks of methadone versus other opioids remains limited and inconsistent in showing increased risk of outcomes related to overdose.[27,39,40] Evidence on benefits and harms of different methods for initiating and titrating opioids, scheduled and continuous versus as-needed dosing of opioids, use of opioid rotation, and methods for titrating or discontinuing patients off opioids remains unavailable or too limited to reach reliable conclusions.

New evidence on the accuracy of risk prediction instruments was consistent with the 2014 AHRQ report, which found highly inconsistent estimates of diagnostic accuracy, methodological limitations and few studies of risk assessment instruments other than the Opioid Risk Tool (ORT) and Screening and Opioid Assessment for Patients with Pain-Revised (SOAPP-R). Studies on the accuracy of risk instruments for identifying aberrant behavior in patients already prescribed opioids were not addressed in this review.

Evidence on the effectiveness of risk mitigation strategies also remains very limited. One new observational study found provision of naloxone to patients prescribed opioids in primary care clinics associated with decreased likelihood of emergency department visits, but no difference in risk of overdose.[41] Evidence of opioid tapering versus usual care was largely limited to a trial that found a taper support intervention associated with better functional outcomes and a trend towards lower opioid doses versus usual opioid care.[42] Regarding alternative tapering methods, one small new trial found no difference between tapering with varenicline versus tapering with placebo in likelihood of opioid abstinence, pain, or depression.[43] A cohort study found discontinuation of opioid therapy associated with increased risk of overdose mortality versus continuation, but there was no statistically significant difference in risk of all-cause mortality. [44] It was not possible to determine a causal association between opioid discontinuation and overdose mortality because most patients had a safety reason for discontinuation, the study did not attempt to control for potential confounders other than age and race, most patients received opioids from another provider after discontinuation, and there was no information about time to discontinuation. Rather, the findings may indicate that patients with indications for opioid discontinuation are at high risk for opioid-related adverse events.

No trial compared different rates of opioid tapering, though one observational study found an association between longer time to opioid discontinuation in patients on long-term, high-dose opioid therapy and decreased risk of opioid-related emergency department visit or hospitalization.[45] The Food and Drug Administration recently issued a warning on not discontinuing long-term opioid therapy abruptly.[46] No study evaluated the effectiveness of risk mitigation strategies, such as use of risk assessment instruments, opioid management plans, patient education, urine drug screening, prescription drug monitoring program data review, monitoring instruments, more frequent monitoring intervals, pill counts, abuse-deterrent formulations, or avoidance of co-prescribing of benzodiazepines on risk of overdose, addiction, abuse or misuse.

Evidence on the effectiveness of interventions for opioid use disorder in patients with prescription opioid dependence or opioid use disorder was also limited and might have limited applicability to patients currently prescribed opioids for chronic pain

Limitations

Meta-analyses could not be conducted for most questions due to small numbers of studies, methodological limitations, and heterogeneity across studies in interventions evaluated, study designs, and outcomes assessed. Although we restricted inclusion of observational studies to those that controlled for potential confounders, even well-conducted observational studies are susceptible to residual confounding and bias. Evidence from randomized trials was almost exclusively restricted to trials ≤6 months in duration, and most trials had methodological shortcomings. Few studies evaluated how benefits and harms vary in subgroups defined by demographic characteristics, characteristics of the pain condition, medical or psychological comorbidities, and substance use history.

Implications and Conclusions

Our review has implications for clinical and policy decision making. Findings support the recommendation in the 2016 CDC guideline[5] that opioids are not first-line therapy and to preferentially use nonopioid alternatives, based on small short-term benefits, increased risk of harms (including serious harms such as opioid use disorder and overdose) and similar benefits compared with nonopioid therapies. Evidence on long-term benefits remains very limited, and additional evidence confirms an association between opioids and increased risk of serious harms that appears to be dose-dependent. Most clinical and policy decisions regarding risk mitigation strategies and opioid dosing strategies for chronic noncancer pain must still be made on the basis of weak or insufficient evidence, and research on the effectiveness of different opioid prescribing methods and risk mitigation strategies remains a priority.

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Introduction

Background

Nature and Burden of Chronic Pain

Chronic pain, often defined as pain lasting longer than 3 to 6 months, or past the time of normal tissue healing, is common.[1] The Centers for Disease Control and Prevention (CDC) estimates that 20.4 percent of U.S. adults in 2016 had chronic pain and 8.0 percent had high impact (resulting in limitations in major life domains) chronic pain.[2] Chronic pain is associated with an annual cost conservatively estimated at $560 to $635 billion, can result in impaired physical and mental functioning and reduced quality of life, and is the leading cause of disability in the United States.[1] Chronic pain is caused by a variety of conditions and is influenced by multiple biological, psychological, and social factors. Therefore, optimal approaches to the management of chronic pain should consider psychological and social factors as well as underlying biological mechanisms and physical manifestations of chronic pain (the "biopsychosocial" framework or perspective).[3]

Opioids and Chronic Pain

Opioids are often prescribed for chronic pain. In the United States, prescription of opioid medications for chronic pain more than tripled from 1999 to 2015.[4] This increase was accompanied by marked increases in rates of opioid use disorder and drug overdose mortality[4-6] involving prescription opioids. From 1999 to 2014, over 165,000 people died from overdose related to prescription opioids in the United States,[7] with an estimated 17,087 prescription opioid overdose deaths in 2016.[4] In October 2017, the U.S. Department of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis.[8]

Nationally, opioid prescribing trends began to plateau in 2010, likely due to implementation of opioid-related practice guidelines and other state-based initiatives. However, overdoses involving heroin, and more recently, illicitly manufactured fentanyl,[4,9] have markedly increased since 2010; therefore, the total number of drug overdose deaths was still rising as of 2017.[10] The majority of heroin users report their first opioid of abuse was a prescribed opioid, and concerns have been raised that efforts to reduce prescribing may result in the unintended consequence of increased illicit opioid use.[11]

In 2013, the Agency for Healthcare Research and Quality (AHRQ) commissioned a Comparative Effectiveness Review on the effectiveness and risks of opioid therapy for chronic pain, focusing on studies with long-term (≥1 year) followup.[12] The review, published in 2014, addressed the risks and benefits of opioids for chronic pain, dosing strategies, and risk assessment and risk mitigation strategies. The review found insufficient evidence to show benefits of long-term opioid therapy for chronic pain, due to the absence of trials with followup of at least 1 year. The review found that long-term opioid therapy was associated with increased risk of overdose, opioid abuse, and other harms; some harms (including overdose risk) were dose-dependent. Information on the effectiveness of opioid dosing strategies and risk mitigation strategies was limited.

The 2014 AHRQ report[12] and a subsequent update[7] commissioned by the CDC were used as the basis for developing the 2016 CDC guideline on opioids for chronic pain.[7,13] The CDC guideline includes the following recommendations: use nonopioid therapy as the preferred

therapy for chronic pain; perform risk assessment and initiate long-term opioid therapy only when benefits are likely to exceed risks; use risk mitigation strategies; and apply dose thresholds ("caution" with increasing doses >50 morphine equivalent dose [MED] per day, "avoid" increasing doses >90 MED/day).[7] Of the 12 recommendations in the CDC guideline, all except for one (treatment for opioid use disorder) were assessed as being supported by low quality evidence. Although a number of opioid prescribing practices were declining at the time that the CDC guideline was published, the rate of decline increased following its release.[14]

Rationale for This Review

The purpose of this review is to update the 2014 AHRQ report [12] on opioids for chronic pain, given the ongoing magnitude of the opioid crisis, the low quality of evidence in the 2014 AHRQ report to support most of the recommendations in the 2016 CDC guideline, the availability of new evidence, and concerns for potential unintended consequences of implementing the guideline (e.g., increased use of illicit opioids, increased suicidality, worsening quality of life or function, reduced access to primary care,[15] or implementation of guidelines in ways in which it was not intended[13,16]).

This update includes new evidence for questions covered in the 2014 AHRQ report, including efficacy and harms, comparisons with nonopioid therapies, dosing strategies, dose-response relationships, risk mitigation strategies, discontinuation and tapering of opioid therapy, and population differences. This update expands upon the 2014 AHRQ report by addressing shorter-term (1 to 12 months) as well as long-term (≥12 months) outcomes, effects of opioid plus nonopioid combination therapy, effects of tramadol, effects of naloxone co-prescription, risks of co-prescribed benzodiazepines, risks of co-prescribed gabapentinoids, and effects of co-prescribed cannabis. This update also includes contextual questions on clinician and patient values and preferences; the 2014 AHRQ report[12] did not include these contextual questions, though the CDC update[7] addressed similar contextual questions. This review is one of three concurrent AHRQ systematic reviews on treating chronic pain; the other reviews address nonpharmacological treatments[17] and nonopioid pharmacological treatments.[18]

Scope and Key Questions

Key Questions

Key Question 1. Effectiveness and Comparative Effectiveness

a. In patients with chronic pain, what is the effectiveness of opioids versus placebo or no opioid for outcomes related to pain, function, and quality of life after short-term followup (1 to <6 months), intermediate-term followup (6 to <12 months), and long-term followup (≥12 months)?

b. How does effectiveness vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], visceral pain, fibromyalgia, sickle cell disease, inflammatory pain, headache disorders, and degree of nociplasticity); (2) patient demographics (e.g., age, race, ethnicity, gender, socioeconomic status); (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities, and high risk for opioid use disorder); (4) the mechanism of action of opioids used (e.g., pure opioid agonists, partial opioid agonists such as buprenorphine, or drugs with mixed opioid and nonopioid mechanisms of action such as tramadol or tapentadol)?

c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacologic or nonpharmacologic, including cannabis) on outcomes related to pain, function, and quality of life after short-term followup (1 to <6 months), intermediate-term followup (6 to <12 months), and long-term followup (≥12 months)?

d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacologic or nonpharmacologic, including cannabis) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used after short-term followup (1 to <6 months), intermediate-term followup (6 to <12 months), and long-term followup (≥12 months)?

Key Question 2. Harms and Adverse Events

a. In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on: (1) opioid use disorder, abuse, or misuse; (2) overdose (intentional and unintentional); and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?

b. How do harms vary depending on: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], visceral pain, fibromyalgia, sickle cell disease, inflammatory pain, headache disorders, and degree of nociplasticity); (2) patient demographics; (3) patient comorbidities (including past or current opioid use disorder or at high risk for opioid use disorder); (4) the dose of opioids used and duration of therapy; (5) the mechanism of action of opioids used (e.g., pure opioid agonists, partial opioid agonists such as buprenorphine, or drugs with opioid and nonopioid mechanisms of action such as tramadol and tapentadol); (6) use of sedative hypnotics; (7) use of gabapentinoids; (8) use of cannabis?

c. In patients with chronic pain, what are the comparative risks of opioids versus nonopioid therapies on: (1) opioid use disorder, abuse, or misuse; (2) overdose (intentional and unintentional); and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and mental health harms (e.g., depression)?

d. In patients with chronic pain, what are the comparative risks of opioids plus nonopioid interventions (pharmacologic or nonpharmacologic, including cannabis) versus opioids or nonopioid interventions alone on: (1) opioid use disorder, abuse, or misuse; (2) overdose (intentional and unintentional); and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and mental health harms (e.g., depression)?

Key Question 3. Dosing Strategies

a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?

b. In patients with chronic pain, what is the comparative effectiveness of short-acting versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?

c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; and overdose?

d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids versus long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?

e. In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous versus as-needed dosing of opioids on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?

f. In patients with chronic pain, what is the comparative effectiveness of opioid dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?

g. In patients with chronic pain, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life, and doses of opioids used?

h. In patients with chronic pain, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?

i. In patients with chronic pain, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and opiate withdrawal symptoms?

j. In patients with chronic pain, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, opiate withdrawal symptoms, and likelihood of opioid cessation?

k. In patients with chronic pain, what is the comparative effectiveness of different opioid dosages and durations of therapy for outcomes related to pain, function, and quality of life?

Key Question 4. Risk Assessment and Risk Mitigation Strategies

a. In patients with chronic pain being considered for opioid therapy, what is the accuracy of instruments and tests (including metabolic and/or genetic testing) for predicting risk of opioid use disorder, abuse, or misuse, and overdose?

b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments and tests (including metabolic and/or genetic testing) on outcomes related to opioid use disorder, abuse, or misuse, and overdose?

c. In patients with chronic pain who are prescribed opioid therapy, what is the effectiveness of risk mitigation strategies, including (1) opioid management plans, (2) patient education, (3) urine drug screening, (4) use of prescription drug monitoring program data, (5) use of monitoring instruments, (6) more frequent monitoring intervals, (7) pill counts, (8) use of abuse-deterrent formulations, (9) consultation with mental health providers when mental health conditions are present, (10) avoidance of co-prescribing of sedative hypnotics, and (11) co-prescribing of naloxone on outcomes related to opioid use disorder, abuse, or misuse, and overdose?

d. In patients with chronic pain, what is the comparative effectiveness of treatment strategies for managing patients with opioid use disorder related to prescription opioids on outcomes related to pain, function, quality of life, opioid use disorder, abuse, misuse, and overdose?

Contextual Questions

1. What are clinician and patient values and preferences related to opioids and medication risks, benefits, and use?

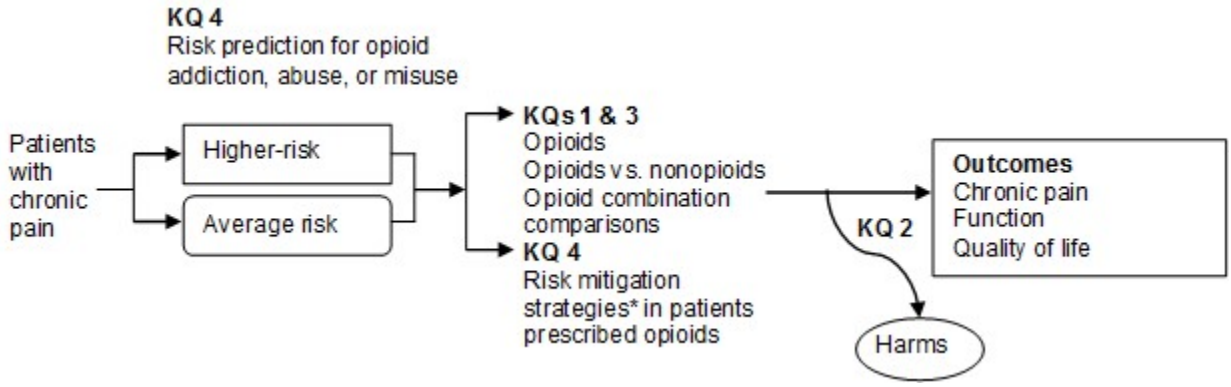
2. What are the costs and cost-effectiveness of opioid therapy and risk mitigation strategies?

Contextual questions are not addressed using systematic methods, but provide a summary of the most relevant and high-quality evidence.

Analytic Framework

The analytic framework outlines the Key Questions and patient populations, interventions, and outcomes (Figure 1).

Figure 1. Analytic framework



Abbreviations: KQ=Key Question.

*Including opioid management plans, patient education, urine drug screen, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, use of abuse-deterrent formulations, consultation with mental health providers when mental health conditions are present, avoidance of benzodiazepine co-prescribing, and co-prescribing of naloxone.

Methods

This Comparative Effectiveness Review (CER) follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter the "AHRQ Methods Guide").[19] All methods were determined a priori and a protocol was developed through a process that included public input and was published on the AHRQ website (https://effectivehealthcare.ahrq.gov/topics/opioids-chronic-pain/protocol) and on the PROSPERO systematic reviews registry (CRD42019127423).

Literature Search Strategy

We conducted electronic searches in Ovid® MEDLINE®, Elsevier Embase®, PsycINFO®, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews in August 2019 (see Appendix A for full strategies). Searches were conducted from January 2014 for Key Questions addressed in the 2014 AHRQ report (which had searches conducted through August 2014). For questions or areas not covered by the 2014 AHRQ report, searches were conducted from database inception. Reference lists of included systematic reviews were screened for additional studies and relevant references from the 2014 AHRQ report were carried forward. A Federal Register notification for a Supplemental Evidence And Data for Systematic review (SEADS) portal was posted for submission of unpublished studies.

Using the pre-established criteria above to screen citations identified through our searches, we determined eligibility for full-text review, with any citation deemed not relevant by one reviewer screened by a second reviewer.[19] Citations deemed potentially eligible were retrieved for full-text screening, with each article independently reviewed for eligibility by two reviewers. Any disagreements were resolved by consensus.

Inclusion and Exclusion Criteria and Study Selection

The criteria for inclusion and exclusion of studies for this CER are based on the Key Questions. The population of interest is adults (≥18 years of age) with various types (regardless of underlying pain mechanism)[20] of chronic pain (defined as pain lasting >3 months), including persons with acute exacerbations of chronic pain (for specific questions or subquestions), pregnant or breastfeeding women, and persons with opioid use disorder related to use of prescription opioids. Details regarding the populations, interventions, comparators, and outcomes are summarized in Table 1 and described in detail by Key Question in Appendix B. For this review, opioids includes pure opioid agonists, partial agonists (e.g., buprenorphine), and dual mechanism agents. The dual mechanism agents were tramadol and tapentadol; the dual mechanism medication cebranopadol was excluded because it has a novel mechanism of action and is not approved in the United States.[21] Opioids were sustained-release/long-acting (collectively referred to as "long-acting") or short-acting; inclusion was restricted to non-parenteral (oral, transdermal, buccal, sublingual) administration. Outcomes of interest were pain, function, health status/quality of life, mental health outcomes (depression and anxiety), sleep, doses of opioid used (for comparisons involving opioids and nonopioid therapy) and harms (including overdose, opioid use disorder, abuse, misuse, all-cause mortality, gastrointestinal harms, somnolence, dizziness, headache, fractures, motor vehicle accidents, endocrinological harms, cardiovascular events, and suicidality). Opioid use disorder and related outcomes includes outcomes referred to in studies as abuse, dependence, misuse, and aberrant drug-related behaviors. The terminology related to these outcomes has evolved over time and some experts

have recommended avoiding some terms due to potential stigma;[22] we used the terms "abuse" and "misuse" in this report if reported in the studies and a preferred term (e.g., opioid use disorder, opioid dependence) was not clearly interchangeable. In the Diagnostic and Statistical Manual of Mental Disorders-Fourth edition (DSM-IV), opioid use disorder was broken into two separate diagnoses of opioid abuse and opioid dependence; in DSM-V these diagnoses were combined into a single diagnosis of opioid use disorder. In this report, the outcome opioid dependence refers to an opioid use disorder as defined by DSM-IV (or similarly), not physical dependence without an opioid use disorder. Intermediate outcomes such as pharmacokinetic and pharmacodynamic measures were excluded.

For all Key Questions, studies with at least 1 month of followup were included. Results were stratified according to short-term (1 to <6 months), intermediate term (6 to <12 months), and long-term (≥12 months) followup. For opioid initiation strategies, treatment of acute exacerbations of chronic pain, and tapering strategies we included studies with less than 1 month followup. Observational studies on the association between risk of overdose, substance use disorder and misuse, all-cause mortality, gastrointestinal harms, somnolence, dizziness, headache, fractures, motor vehicle accidents, endocrinological harms, cardiovascular events, and suicidality, cohort and case-control studies were included if they enrolled patients with chronic pain, reported risks associated with use of long-acting opioids, and/or reported risks associated with use of more than 1 month or effects of duration of use on risk; studies which could have evaluated risks of short-term opioid therapy for acute pain were excluded.

For Key Question 4a, studies on the predictive utility of risk prediction instruments and other risk assessment methods compared against a reference standard were included. For all Key Questions, we included randomized controlled trials (RCTs). We also included cohort studies and case-control studies for studies on risk of overdose, mortality, substance use disorder, falls, endocrinological adverse effects, motor vehicle accidents, cardiovascular events, and long-term (≥12 months) effectiveness. For all Key Questions, we excluded uncontrolled observational studies, case series, and case reports.

We excluded studies published only as conference abstracts, restricted inclusion to English-language articles, and excluded studies of nonhuman subjects. Studies had to report original data to be included.

Table 1. Inclusion and exclusion criteria

PICOTS	Include	Exclude
Populations and Conditions	All KQs: Adults (age ≥18 years) with chronic pain (pain lasting >3 months). KQs 1b, 2b: Subgroups based on specific type or cause of pain, patient demographics, patient comorbidities	• Pain at the end of life • Acute pain • Pain due to active malignancy • Pain due to sickle cell crisis • Episodic migraine

PICOTS	Include	Exclude
Interventions	KQs 1a-c, 2a-c: Long- or short-acting opioids (including partial agonists and dual mechanism agents) KQs 1d and 2d: Opioid + nonopioid (pharmacologic or nonpharmacologic) KQ 3: Opioid dosing strategy (initiation and titration strategy [3a], short-acting opioid [3b], long-acting opioid [3c], short plus long-acting opioid [3d], scheduled, continuous dosing [3e], opioid dose escalation [3f], opioid rotation [3g], treatments for acute exacerbations of chronic pain [3h], decreasing opioid doses or tapering off opioids [3i], tapering protocols and strategies [3j]) KQs 4a-b: Instruments, genetic metabolic tests for predicting risk of opioid use disorder, abuse, misuse, and overdose KQ 4c: Risk mitigation strategies (opioid management plans, patient education, urine drug screening, use of prescription drug monitoring program data, use of monitoring instruments, more frequent monitoring intervals, pill counts, use of abuse-deterrent formulations, consultation with mental health providers when mental health conditions are present, avoidance of benzodiazepine co-prescribing, co-prescribing of naloxone)	• Intravenous or intramuscular administration of opioids • Surgical or interventional procedures
Comparators	KQs 1a, 1b and 2a, 2b: Placebo or no opioid therapy KQs 1c and 2c: Nonopioid therapies (pharmacologic or nonpharmarmacologic [noninvasive]) KQs 1d and 2d: Nonopioid therapy or opioid alone KQ 3: Alternative opioid dosing strategy (alternative initiation and titration strategy [3a], long-acting opioid [3b], alternative long-acting opioid [3c], long-acting opioid alone [3d], as-needed dosing [3e], dose maintenance or use of dose thresholds [3f], maintenance of current opioid therapy [3g], other treatment for acute exacerbation of chronic pain [3h], continuation of opioids [3i], other tapering protocols or strategies [3j], other dose of same opioid [3k]) KQ 4a: Reference standard for opioid use disorder, abuse, misuse, or overdose KQ 4b: Usual care KQ 4c: Other treatment strategies	• Nonpharmacologic treatment (comparison with nonopioids included in review of nonpharmacologic treatments) • Opioid treatment
Outcomes	Pain, function, and quality of life Mood, sleep Doses of opioids used (KQs 1c and 1d) Harms: Discontinuation due to adverse events, serious adverse events, overdose, substance misuse, substance use disorder related outcomes, other harms (gastrointestinal, somnolence, pruritus, dizziness, headache, fracture, motor vehicle accidents, cardiovascular events, endocrinological effects) KQ 4a: Measures of diagnostic accuracy	• Intermediate outcomes (e.g., pharmacokinetics/pharmacodynamics, drug-drug interactions, dose conversions)
Timing	Short- (1 to <6 months), intermediate- (6 to <12 months), and long-term (≥12 months) treatment duration	• Studies or outcomes reported with <1 month duration of treatment
Setting	Outpatient settings (e.g., primary care, pain clinics, emergency rooms, urgent care clinics)	• Inpatient settings (for tapering treatment initiation in inpatient settings and continued as outpatient permitted)

PICOTS	Include	Exclude
Study Design	All KQs: Randomized controlled trials KQs 1 and 2: Cohort and case-control studies for long-term (≥12 months) outcomes KQs 3 and 4: Cohort studies KQ 4a: Studies reporting diagnostic accuracy English language publications	• Uncontrolled observational studies, case series, and case reports • Non-English language publications

Abbreviations: KQ=Key Question; PICOTS=Population, Interventions, Comparators, Outcomes, Timing, Setting

Data Abstraction and Data Management

For studies meeting inclusion criteria, evidence tables were constructed with the following data: author, year of publication, country, study design (including use of crossover or enriched enrollment randomized withdrawal [EERW] design for randomized trials), duration of treatment sample size, eligibility criteria, population and clinical characteristics (including age, sex, race/ethnicity, pain condition, duration of chronic pain, severity of pain at baseline, presence of psychological or medical comorbidities, prior opioid use, substance use history, and risk for opioid use disorder), intervention characteristics (including the specific opioid used and dose), receipt of industry funding, and results for outcomes of interest. Studies were classified as enrolling opioid-naïve patients (patients not exposed to opioids on a daily or near daily basis), opioid-experienced patients, or mixed populations. Evidence tables included relevant studies from the 2014 AHRQ report[12] as well as new studies identified in current searches.

Effects on pain were abstracted as mean difference in pain intensity (continuous) and likelihood of experiencing improvement in pain (dichotomous) based on meeting a certain threshold ("pain response"). For pain as a continuous variable, we abstracted (in descending order of prioritization) adjusted mean differences in effects on pain intensity from baseline to followup, unadjusted differences in change from baseline, and differences in followup scores. For the primary dichotomous pain outcome, we abstracted (in descending order of prioritization) the proportion of patients experiencing improvement in pain intensity of 30 percent or greater, improvement in pain at an alternative threshold (e.g., ≥25%, ≥50%, or >2 point improvement on a 0 to 10 scale), or pain relief rated as moderate, good, or similar using a categorical scale. For an alternative pain response outcome, we also abstracted the proportion of patients experiencing improvement in pain intensity of 50 percent or more, or 5 points or more on a 0 to 10 scale. Effects on function were based on the mean improvement in a functional scale (dichotomous) or the proportion of patients meeting a defined threshold of functional improvement (dichotomous). Effects on health status/quality of life, sleep, depression, and anxiety were based on mean improvements in scales designed to assess these domains. For pain, function, sleep, depression, and anxiety, negative values for mean improvement indicate a better outcome; for health status/quality of life, positive values indicate a better outcome. If necessary, the scale was reversed for consistency in the direction of effect for each outcome. Effects on harms were based on the proportion of patients experiencing harms. Pain conditions were categorized as neuropathic (e.g., diabetic neuropathy, postherpetic neuralgia, radiculopathy, polyneuropathy, postampuation, or spinal cord injury related), fibromyalgia, musculoskeletal (e.g., low back pain without radiculopathy or osteoarthritis), mixed (e.g., neuropathic and musculoskeletal), or other (e.g., abdominal pain, sickle cell, headache). The classification of pain conditions roughly correlates to primarily neuropathic, nociplastic (a newer term referring to pain arising from altered nociception without underlying tissue damage, resulting in hypersensitivity),[20] and nociceptive pain mechanisms; however, multiple pain mechanisms can be present in a given pain

condition or patient and the studies were not designed to measure underlying pain mechanisms. Opioid types were classified as pure agonist, partial agonist (buprenorphine), or mixed (dual mechanism; tramadol or tapentadol) and opioid doses were converted to mg morphine equivalent dose (MED)/day based on published drug-specific conversion factors.[23] For trials that reported an opioid dose range but did not report the mean dose, the midpoint of the range was used. Buprenorphine was not converted to MED/day, due to uncertainty regarding the conversion factor and because it is unlikely that buprenorphine as a partial agonist is associated with overdose in the same dose-dependent manner as pure opioid agonists.[24] The duration of followup was categorized as short-term (1 to <6 months), intermediate term (6 to <12 months), and long-term (≥12 months) followup.

Study data was abstracted by one team member and all data were verified for accuracy and completeness by a second team member. A record of studies excluded at the full-text level with reasons for exclusion was maintained (Appendix C).

Quality (Risk of Bias) Assessment of Individual Studies

Predefined criteria were used to assess the quality of individual controlled trials and observational studies (Appendix D). RCTs were evaluated using criteria and methods developed by the Cochrane Back and Neck Group,[25] cohort and other observational studies of interventions were evaluated using criteria developed by the U.S. Preventive Services Task Force,[8] and studies of diagnostic accuracy were assessed using Quality Assessment of Diagnostic Accuracy Studies – Version 2 (QUADAS-2).[26] These criteria were used in conjunction with the approach recommended in the AHRQ Methods Guide.[19] Studies were rated as "good," "fair," or "poor". The quality ratings of studies included in the 2014 AHRQ report were reviewed to ensure consistency in quality assessment.

Studies rated "good" are considered to have the least risk of bias, and their results are generally considered valid. Good-quality intervention studies include clear descriptions of the population, setting, interventions, and comparison groups; utilize valid methods for allocating patients to treatments; clearly report attrition and have low attrition; utilize appropriate methods for preventing bias; and utilize appropriate measurement of outcomes. Good-quality diagnostic accuracy studies use unbiased methods to select patients; report interpretation of the index test without knowledge of the reference standard; report a pre-defined threshold for a positive index test; report use of an appropriate reference standard; apply the reference standard to all patients; report interpretation of the reference standard blinded to the results of the index test; and report low attrition.[26]

Studies rated "fair" are susceptible to some bias, though not enough to invalidate the results. These studies may not meet all the criteria for a rating of good-quality, but no flaw or combination of flaws is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems. The fair-quality category is broad, and studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are likely to be valid, while others may be only possibly valid.

Studies rated "poor" have significant flaws that imply biases of various types that may invalidate the results. They have a serious or "fatal" flaw (or combination of flaws) in design, analysis, or reporting; large amounts of missing information; discrepancies in reporting; or serious problems in the delivery of the intervention. The results of these studies are at least as likely to reflect flaws in the study design as to show true difference between the compared interventions. Poor-quality studies were not excluded *a priori*, but effects of study quality were

evaluated when synthesizing evidence (e.g., in stratified analyses for meta-analysis or qualitatively when meta-analysis was not performed).

Quality was independently assessed by two team members. Disagreements were resolved by consensus.

Data Analysis and Synthesis

A random effects meta-analysis using the profile likelihood method was performed on short-term randomized trials of opioids versus placebo, opioids versus nonopioids, opioids plus nonopioids versus nonopioids alone, and opioids plus nonopioids versus opioids alone at short-term followup.[27] Pooled relative risks (RR) were calculated for pain, function, and harms (discontinuation due to adverse events, serious adverse events, somnolence, nausea, vomiting, constipation, dizziness, headache, and pruritus). Pooled mean differences were calculated for pain, function, health status/quality of life, sleep quality, and mental health outcomes (depression and anxiety). For the meta-analysis, pain scales were converted to a common 0 to 10 scale. For health status, the meta-analysis pooled Short-Form 36- item (SF-36) measures and measures derived from the SF-36 (e.g., Short-Form 12-item [SF-12]). SF-36 measures of physical and mental health status were pooled separately. For physical health status, the Physical Component Summary (PCS) score was pooled; if this was not reported, the Physical Function Subscale was used instead. For mental health status, the Mental Component Summary (MCS) score was pooled; if this was not reported, the Mental Health or Emotional Role Functioning Subscales were used (in descending order of priority). For other continuous outcomes, the meta-analysis was based on the pooled standardized mean differences (SMDs), due to differences in the scales used.

For the primary analysis on likelihood of pain response, data were pooled (in order of descending priority) for 30 percent or more improvement, an alternative numerical threshold closest to 30 percent or more improvement, or "moderate" or "good" pain relief on a categorical scale. The analysis was repeated for 50 percent or more improvement. Trials varied with regard to whether patients lost to followup were considered non-responders or excluded from the analysis. For the main analysis, the likelihood of pain response was analyzed using data as reported in the trials and a sensitivity analysis in which missing patients were considered nonresponders was also conducted.

Different opioid arms within the same study were combined so each study was represented once in a meta-analysis, in order to avoid overweighting and the issue of correlation within the same study. For pooling mean difference or SMD, adjusted mean difference from the analysis of covariance model or other appropriate regression model was used if reported by the study, followed by difference in change score and followup score. Missing standard deviations for followup and change scores were imputed and details were provided in Appendix E.

For meta-analyses of opioids versus placebo, the main analysis was stratified by opioid type. For meta-analyses involving nonopioids (opioids vs. nonopioids, opioids plus nonopioids vs. opioids, and opioids plus nonopioids vs. nonopioids), the main analysis was stratified by the nonopioid. Additional stratified analyses were performed on pain type (neuropathic, fibromyalgia, or musculoskeletal/mixed), duration of followup (1 to <3 months or 3 to 6 months), trial quality (good, fair, or poor), use of a crossover design, opioid status (opioid-naïve, opioid-experienced, mixed, or not reported), publication date (prior to 2007 or in or after 2007), geographic region (United States or Canada, Europe or Australia, Asia, or multiple/mixed), and receipt of industry funding. Opioid dose was analyzed in categories based on the thresholds in

the 2016 Centers for Disease Control and Prevention guideline: less than 50, 50 to less than 90, or 90 or more mg MED/day.[7] For opioids versus placebo, opioid dose was also analyzed as a continuous variable in a meta-regression for the outcomes mean improvement in pain and function. For opioids versus placebo, analyses were also stratified according to whether the trial used an EERW design. In the EERW design, patients are randomized to continuation of the opioids or discontinuation (placebo) following a run-in period to determine responsiveness to opioids and tolerability. Because the EERW design was seldom used before 2007, another stratified analysis on this factor was restricted to trials published in or after 2007. Data from 3 to 6 months were limited and very few studies reported data from both 1 to less than 3 months and 3 to 6 months data. Effects of duration of followup were evaluated by pooling data from 1 to less than 3 months data and 3 to 6 months data separately. For trials that reported function, sleep, health status, and mental health outcomes as continuous outcomes, mean differences based on the original scale were also pooled separately for the most commonly utilized measures.

For trials that reported likelihood of a function response, the main analysis was based (in descending order of priority) on the proportion of patients experiencing 30 percent or more improvement in function, improvement in function at an alternative threshold closest to 30 percent or more, or "moderate" or "good" improvement in function or relief using a categorical scale. The analysis was also performed on the likelihood of experiencing 50 percent or more improvement in function. Trials that reported likelihood of a function response varied with regard to whether patients lost to followup were excluded or considered nonresponders. In the primary analysis we used the data as reported in the trials; as a sensitivity analysis, all patients lost to followup were considered nonresponders.

Statistical heterogeneity was assessed using the I^2 statistic[28] and the Cochran χ^2 test. . All meta-analyses were conducted using Stata/SE 14.0 (StataCorp, College Station, TX).

For long-term data and other comparisons and outcomes, there were insufficient data to perform meta-analysis. Evidence was synthesized qualitatively using the methods described in the AHRQ Methods Guide (see Grading the Strength of Evidence, below).[19] For analyses with more than 10 trials that were sufficiently homogeneous with regard to populations, interventions, and outcomes, funnel plots and the Egger test were conducted for small sample effects.

The magnitude of effects for pain and function were classified using the same system as in the 2018 AHRQ noninvasive treatment for chronic pain review[29] and an earlier AHRQ comparative effectiveness review on treatments for low back pain.[30] A small effect was defined for pain as a mean between-group difference following treatment of 0.5 to 1.0 points on a 0- to 10-point numeric rating scale (NRS) or visual analog scale (VAS) and for function as a SMD of 0.2 to 0.5 or a mean difference of 5 to 10 points on the 0 to 100-point Oswestry Disability Index (ODI), 1 to 2 points on the 0 to 24-point Roland-Morris Disability Questionnaire (RDQ), or equivalent. A moderate effect was defined for pain as a mean difference of 10 to 20 points on a 0- to 100-point VAS and for function as an SMD of 0.5 to 0.8, or a mean difference of 10 to 20 points on the ODI, 2 to 5 points on the RDQ, or equivalent. Large/substantial effects were defined as greater than moderate. We applied similar thresholds to other outcomes measures.[31] Small effects using this system may not meet proposed thresholds for clinically meaningful effects.[32] However, there is variability in estimated minimum clinically important differences across studies, and the clinical relevance of effects classified as small might vary for individual patients depending on preferences, baseline symptom severity, harms, cost, and other factors.[33,34]

Grading the Strength of Evidence

Regardless of whether evidence was synthesized quantitatively or qualitatively, the strength of evidence (SOE) was assessed, using the approach described in the AHRQ Methods Guide.[19] The SOE was reviewed by the entire team of investigators prior to assigning a final grade, based on the following factors:

- Study limitations (low, medium, or high level of study limitations)
- Consistency (consistent, inconsistent, or unknown/not applicable)
- Directness (direct or indirect)
- Precision (precise or imprecise)
- Reporting bias (suspected or undetected)

When pooled estimates were available, evidence was rated inconsistent if the I^2 was greater than 40 percent, unless findings were consistent in subgroup analyses and there were sufficient trials (>20) for subgroup analyses to be informative. Evidence was rated down for study limitations if there were few good-quality trials and estimates differed in analyses stratified by study quality. Evidence was rated imprecise if the pooled estimate confidence interval crossed the null and the threshold for small magnitude of effects.

The SOE was assigned an overall grade of high, moderate, low, or insufficient according to a four-level scale by evaluating and weighing the combined results of the above domains, defined as:

- High—We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
- Moderate—We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
- Low—We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient—We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Assessing Applicability

Applicability was assessed in accordance with the AHRQ's Methods Guide,[35] which is based on the PICOTS (Population, Interventions, Comparators, Outcomes, Timing, Setting) framework. Applicability addresses the extent to which outcomes associated with an intervention are likely to be similar across different patients and settings in clinical practice based on the populations, interventions, comparisons, and outcomes evaluated in the studies. Factors potentially affecting applicability identified a priori include eligibility criteria and patient factors (e.g., demographic characteristics, duration or severity of pain, underlying pain condition, presence of medical and mental health comorbidities, event rates and symptom severity in treatment and control groups), intervention factors (e.g., dose and duration of therapy, intensity and frequency of monitoring, level of adherence support, use of co-interventions), comparisons (e.g., type of comparator, effectiveness and feasibility of active comparators), outcomes (e.g., use

of unvalidated or nonstandardized outcomes, measurement of short-term or surrogate outcomes), settings (e.g., primary care vs. specialty setting, geographic region), and study design features (e.g., use of run-in periods or EERW design). To the extent possible, these factors were assessed to qualitatively determine the situations for which the evidence is most relevant and its applicability to clinical practice in typical U.S. settings.

Peer Review and Public Commentary

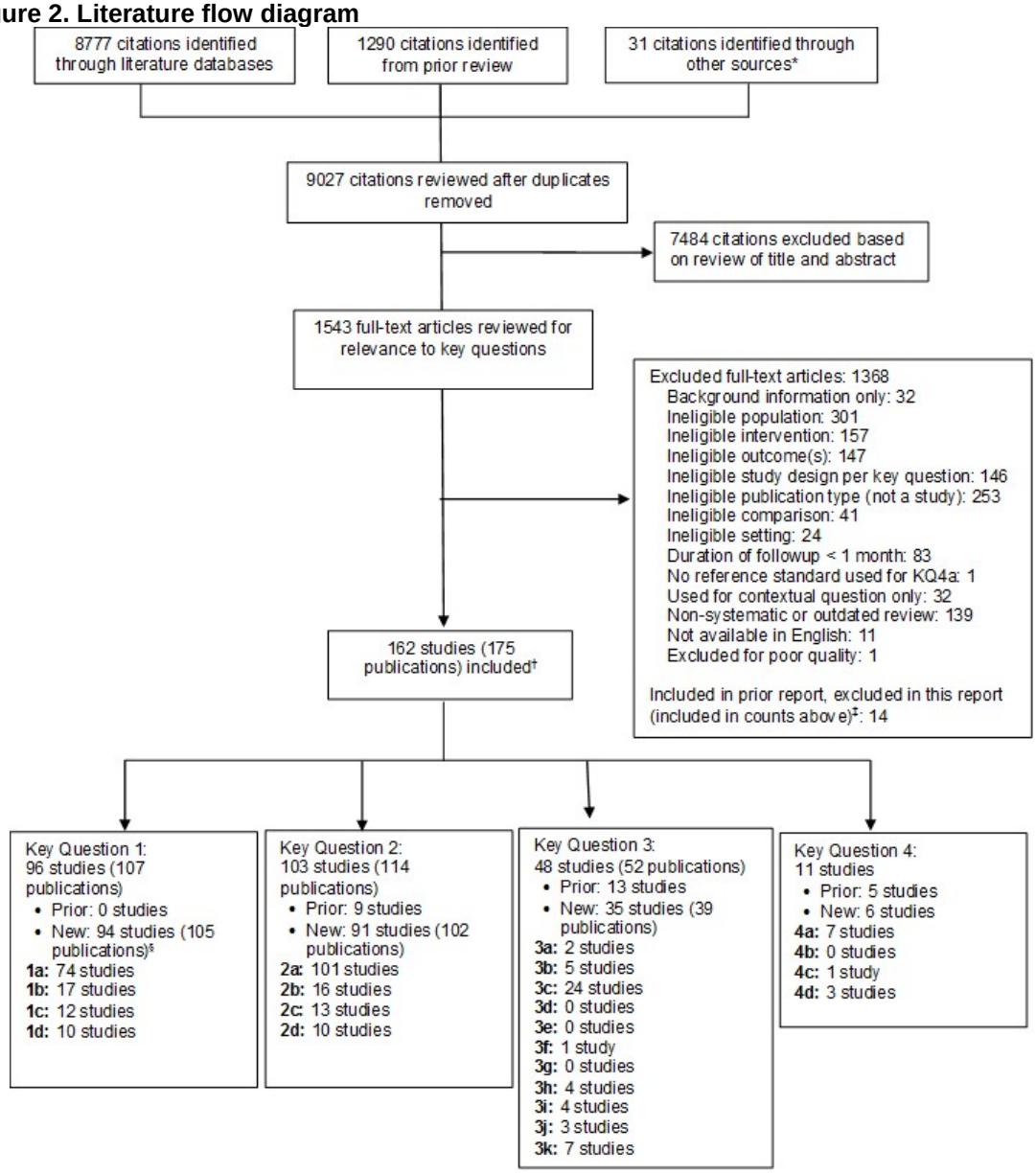
Experts were invited to provide external peer review of this systematic review; AHRQ and an associate editor also provided comments. In addition, the draft report was posted on the AHRQ website for 4 weeks for public comment. Comments were reviewed and used to inform revisions to the final report.

Results

Results of Literature Search

A total of 9027 references from electronic database searches and reference lists were reviewed; from these, 1543 full-text papers were evaluated for inclusion, including 41 included in the 2014 Agency for Healthcare Research and Quality (AHRQ) report. After review of full-text papers 1368 articles were excluded, including 14 from the 2014 AHRQ report; 11 uncontrolled observational studies of abuse or misuse outcomes,[36-46] one study conducted in inpatients, [47] one study of cancer patients with acute pain,[48] and one study of abrupt cessation, which was not evaluating a tapering protocol.[49] Across all Key Questions 115 randomized controlled trials (RCTs), 40 observational studies, and 7 studies of diagnostic accuracy of opioid risk prediction instruments were included (Figure 2 and Appendix F). Of these, 27 studies were included in the 2014 AHRQ report and 134 studies were added for this update. Most (118) of the new studies were added as a result of expanding the scope to include shorter-term randomized trials of opioids.

Figure 2. Literature flow diagram



*Other sources include reference lists of relevant articles, studies, and systematic reviews, suggestions from reviewers, etc.

†162 studies in 175 publications provided data; some addressed more than one Key Question.

‡11 uncontrolled observational studies of abuse or misuse outcomes (Banta-Green, 2009; Boscarino, 2010; Reid, 2002; Compton, 2008; Cowan, 2003; Fleming, 2007; Hojsted, 2010; Portenoy, 2007; Saffier, 2007; Schneider, 2010; Wasan, 2009), one study conducted in inpatients (Ralphs, 1994), one study of cancer patients with acute pain (Davies, 2011), and one study of abrupt cessation, which was not evaluating a tapering protocol (Cowan, 2005).

§The majority of these studies were included from Busse J, Wang L, Kamal El Din M, et al. Opioids for chronic non-cancer pain: A systematic review of randomized controlled trials. *Pain pract*. 2018;18:54-55.

Key Question 1a. In patients with chronic pain, what is the effectiveness of opioids versus placebo or no opioid for outcomes related to pain, function, and quality of life after short-term followup (1 to <6 months), intermediate-term followup (6 to <12 months), and long-term followup (≥12 months)?

Key Points

Short-Term Followup

- Opioids were associated with a small mean improvement versus placebo in pain intensity at short-term followup (71 trials, N=19,616, mean difference -0.79 point on a 0 to 10 scale, 95% confidence interval [CI], -0.93 to -0.67, I2=71%) (strength of evidence [SOE]: high).
- Opioids were associated with increased likelihood versus placebo of experiencing a pain response at short-term followup (44 trials, N=12,481, relative risk [RR] 1.35, 95% CI, 1.24 to 1.48, I2=81%; absolute risk difference [ARD] 15%, 95% CI, 11% to 19%) (SOE: high).
- Opioids were associated with a small mean improvement versus placebo in function at short-term followup (44 trials, N=12,427, standardized mean difference [SMD] -0.22, 95% CI, -0.28 to -0.16, I2=53%) (SOE: high).
- Opioids were associated with a mean improvement below the threshold for small versus placebo in Short-Form 36-item (SF-36) measures of physical health status at short-term followup (23 trials, N=8005, mean difference 1.64 points on a 0 to 100 scale, 95% CI, 1.10 to 2.17, I2=0%) (SOE: high)
- There was no difference between opioids versus placebo in mean improvement on SF-36 measures of mental health status at short-term followup (21 trials, N=7586, -0.48 point on a 0 to 100 scale, 95% CI, -1.39 to 0.44, I2=65%) (SOE: high)
- Opioids were associated with a small mean improvement versus placebo in sleep quality at short-term followup (25 trials, N=6720, SMD -0.25, 95% CI, -0.32 to -0.19, I2=11%) (SOE: moderate).
- There was no difference between opioids versus placebo in depression severity at short-term followup (8 trials, N=1079, SMD 0.00, 95% CI, -0.22 to 0.18, I2=40%) (SOE: moderate).

Intermediate- and Long-Term Followup

- No placebo-controlled trial evaluated outcomes at intermediate- or long-term followup. One cohort study found opioids associated with decreased likelihood of improvement in Brief Pain Inventory (BPI) pain severity versus nonusers at 1 year (61.5% vs. 76.1%, ARD -14.6%, p=0.001), but there was no difference in likelihood of improvement in BPI pain interference (62.3% vs. 67.5%, ARD -5.2%, p=0.16); there were no differences on either BPI subscale at 2 years (SOE: low).

Description of Included Studies

Seventy-three randomized trials compared opioids versus placebo for chronic pain (Table 2).[50-126] Sample sizes ranged from 7 to 806 (total N=20,502). None of the trials were included in

the 2014 AHRQ report, which was restricted to trials with duration of followup of 1 year or more. The duration of followup was less than 6 months in all trials; 33 trials followed patients for less than 3 months and 40 trials followed patients for 3 to 6 months. The pain condition was neuropathic in 20 trials, fibromyalgia in one trial, and musculoskeletal (one trial enrolled a mixed population that primarily had musculoskeletal pain) in 51 trials. The duration of pain ranged from 3 months to 16.5 years and the proportion of female participants ranged from 5 percent to 94 percent. Baseline pain ranged from 2.5 to 8.2 on a 0 to 10 scale. All trials excluded patients with a history of substance use disorder or active substance use and mental health comorbidities or severe mental health comorbidities; or did not describe eligibility status based on these factors. Fifteen trials restricted enrollment to opioid-naïve patients,[51,54,76,77,81,84,88,99,100,104,107,108,110,111,123-125,127] seven trials to opioid-experienced patients,[68,70,72,73,83,91,98,115] and 37 trials to mixed populations of opioid-naïve and experienced patients;[50,52,55,56,58-62,65-67,69,74,75,79,80,82,85-87,89,90,92,94-96,102,103,109,112-114,116,117,120,121,126] while 14 trials did not describe prior opioid experience.[53,57,63,64,71,78,93,97,101,105,106,118,119,122] Sixty-eight trials were conducted in the United States, Canada, Europe, or Australia; and five trials in Asia. The opioid type was a pure opioid agonist in 40 trials, partial agonist (buprenorphine) in eight trials, and mixed agent (tramadol or tapentadol) in 25 trials. The mean opioid dose ranged from 12 to 186 mg morphine equivalent dose (MED)/day; in 15 trials the mean dose was less than 50 mg MED/day, in 27 trials 50 to 90 mg, and in 21 trials greater than 90 mg. In 10 trials, the opioid was buprenorphine and the MED/day was not calculated.

Table 2. Study characteristics of trials of opioids versus placebo

Study, Year Country Quality	Total Patients Randomized	1: EERW Design 2: Crossover Design 3: Industry Funded	1: Pain Condition 2: Duration of Pain (Months)* 3: Opioid-Naïve 4: Baseline Pain	Age (Years)* Female (%) Race/Ethnicity	Opioid Dose; MED Duration of Treatment
Afilalo, 2010[50] International Fair	1030	1. No 2. No 3. Yes	1: Osteoarthritis of knee 2: NR 3: NR 4: NR	Age: 58 Female: 60% White: 75%	Tapentadol SR/Oxycodone SR 200 to 500 mg (mean 350 mg)/40 to 100 mg (mean 70 mg); 140 mg/105 mg MED 15 weeks
Arai, 2015a[51] Japan Poor	150	1. Yes 2. No 3. Yes	1: Osteoarthritis or low back pain 2: 74 3: No 4: 29.3 (VAS 0 to 100)	Age: 66 Female: 67% White: NR	Fentanyl patch 25 to 50 mcg/hour (mean 15.1 mcg/hour); 36 mg MED 12 weeks
Arai, 2015[51] Japan Poor	163	1. Yes 2. No 3. Yes	1: Post-herpetic neuralgia, complex regional pain syndrome, or chronic postoperative pain 2: 46.5 3: No 4: 28.9 (VAS 0 to 100)	Age: 67 Female: 49% White: NR	Fentanyl patch 25 to 50 mcg/hour (mean 18.6 mcg/hour); 45 mg MED 12 weeks
Babul, 2004[52] USA Fair	246	1: No 2: No 3: Yes	1: Osteoarthritis 2: 154.9 3: Mixed 4: 76.9 (VAS 0 to 100)	Age: 61.4 Female: 62% White: 82%	Tramadol SR 200 to 400 mg (mean 276 mg); 55 mg MED 12 weeks

Study, Year Country Quality	Total Patients Randomized	1: EERW Design 2: Crossover Design 3: Industry Funded	1: Pain Condition 2: Duration of Pain (Months)* 3: Opioid-Naïve 4: Baseline Pain	Age (Years)* Female (%) Race/Ethnicity	Opioid Dose; MED Duration of Treatment
Boureau, 2003[53] France Good	127	1: No 2: No 3: Yes	1: Postherpetic neuralgia 2: 6.8 3: Mixed 4: 60.5 (VAS 0 to 100)	Age: 67 Female: 71% White: NR	Tramadol 100 to 400 mg (mean 276 mg); 55 mg MED 6 weeks
Breivik, 2010[54] International Fair	199	1: No 2: No 3: Yes	1: Osteoarthritis 2: NR 3: No 4: 10.7 (WOMAC pain 0 to 20)	Age: 62.9 Female: 68% White: 100%	Buprenorphine patch 5 to 20 mcg/hour (mean 11.0 mcg/hour); NA 24 weeks
Burch, 2007[55] International Good	646	1: Yes 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: 7.2 (VAS 0 to 10)	Age: 62 Female: 63% White: 85%	Tramadol SR 200 to300 mg (mean 275 mg); 55 mg MED 12 weeks
Buynak, 2010[56] USA Fair	981	1: No 2: No 3: Yes	1: Low back pain 2: NR 3: Mixed 4: 7.5 (NRS 0 to 10)	Age: 49.9 Female: 57% White: 72%	Tapentadol SR/Oxycodone SR 200 to 500 mg (mean 313 mg)/40 to 100 mg (mean 53 mg); 125 mg/80 mg MED 15 weeks
Caldwell, 1999[57] USA Fair	70	1: Yes 2: No 3: Yes	1: Osteoarthritis 2: NR 3: NR 4: NR	Age: 57.5 Female: 61% White: NR	Oxycodone SR 20 to 60 mg (mean 40 mg); 60 mg MED 4 weeks
Caldwell, 2002[58] USA Fair	295	1: No 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: 319.6 (WOMAC pain 0 to 500)	Age: 62 Female: 62% White: 84%	Morphine SR (qd or bd) 30 mg; 30 mg MED 4 weeks
Christoph, 2017[59] Germany Fair	252	1: No 2: No 3: Yes	1: Low back pain 2: 124.8 3: Mixed 4: 7.2 (NRS 0 to 10)	Age: 58 Female: 61% White: 99.6%	Tapentadol SR 400 mg; 160 mg MED 14 weeks
Chu, 2012[60] USA Fair	139	1: No 2: No 3: No	1: Low back pain 2: NR 3: Mixed 4: 49.8 (VAS o to 100)	Age: 45 Female: 44% White: 65%	Morphine SR 30 to 120 mg (mean 78 mg); 78 mg MED 4.5 weeks
Cloutier, 2013[61] Canada Fair	83	1: No 2: Yes 3: Yes	1: Low back pain 2: 165.6 3: Mixed 4: 61.4 (VAS 0 to 100)	Age: 51 Female: 50% White: NR	Oxycodone SR + Naloxone 20 to 80 mg (mean 36 mg); 54 mg MED 4 weeks
DeLemos, 2011[62] USA Fair	808	1: No 2: No 3: Yes	1: Osteoarthritis 2: 97.2 3: Mixed 4: 302.1 (WOMAC pain 0 to 500)	Age: 60 Female: 63% White: 81%	Tramadol SR 100, 200, or 300 mg (mean 200 mg); 40 mg MED 12 weeks
Fishman, 2007[63] USA Canada Fair	552	1: No 2: No 3: Yes	1: Osteoarthritis 2: NR 3: NR 4: 297.5 (WOMAC pain 0 to 500)	Age: 61 Female: 62% White: NR	Tramadol SR 100, 200, or 300 mg (mean 201 mg); 40 mg MED 12 weeks
Fleischmann, 2001[64] USA Poor	129	1: No 2: No 3: Yes	1: Osteoarthritis 2: 7.9 3: NR 4: 2.8 (NRS 0 to 4)	Age: 63 Female: 62% White: 91%	Tramadol 200 to 400 mg (mean NR); 60 mg MED 12 weeks

Study, Year Country Quality	Total Patients Randomized	1: EERW Design 2: Crossover Design 3: Industry Funded	1: Pain Condition 2: Duration of Pain (Months)* 3: Opioid-Naïve 4: Baseline Pain	Age (Years)* Female (%) Race/Ethnicity	Opioid Dose; MED Duration of Treatment
Friedmann, 2011[65] USA Fair	412	1: Yes 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: 5.3 (NRS 0 to 10)	Age: 58 Female: 70% White: 82%	Oxycodone SR 40 mg (mean 27.5 mg); 41 mg MED 12 weeks
Gilron, 2005[67] Canada Fair	1020	1: No 2: No 3: Yes	1: Osteoarthritis 2: 93.6 3: Mixed 4: 69.1 (VAS 0 to 100)	Age: 58 Female: 62% White: 78%	Tramadol SR 100 to 400 mg; 50 mg MED 12 weeks
Gilron, 2005[67] Canada Fair	57	1: No 2: Yes 3: No	1: Diabetic neuropathy 2: 54.7 3: Mixed 4: 5.0 (VAS 0 to 10)	Age: 56 (median) Female: 44% White: 98%	Morphine Up to 120 mg (mean 45 mg); 45 mg MED 5 weeks
Gimbel, 2003[69] USA Fair	159	1: No 2: No 3: Yes	1: Diabetic neuropathy 2: NR 3: Mixed 4: 6.8 (VAS 0 to 10)	Age: 59 Female: 48% White: 84%	Oxycodone SR 10 to 120 mg (mean 37 mg); 56 mg MED 6 weeks
Gimbel, 2016[68] USA Fair	511	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Yes 4: 2.9 (NRS 0 to 10)	Age: 54 Female: 55% White: 77%	Buprenorphine buccal 300 to 1800 mcg (mean 1320 mcg); NA 12 weeks
Gordon, 2010[70] Canada Fair	78	1: No 2: Yes 3: Yes	1: Low back pain 2: 154.8 3: Yes 4: 60.9 (VAS 0 to 100)	Age: 51 Female: 60% White: NR	Buprenorphine patch 10 to 30 mcg/hour (mean 30 mcg/hour); NA 4 weeks
Gordon, 2010[71] Canada Fair	79	1: No 2: Yes 3: Yes	1: Low back pain 2: 169.2 3: NR 4: 61.4 (VAS 0 to 100)	Age: 55 Female: 47% White: NR	Buprenorphine 5 to 20 mcg/hour (mean 15.5 mcg/hour); NA 4 weeks
Hale, 2007[73] USA Fair	143	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Yes 4: 23.0 (VAS 0 to 100)	Age: 47 Female: 45% White: 87%	Oxymorphone SR Mean 80 mg; 120 mg MED 12 weeks
Hale, 2010[72] (also Nalamachu 2014)[91] USA Fair	268	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Yes 4: 3.2 (NRS 0 to 10)	Age: 49 Female: 50% White: 85%	Hydromorphone SR 12 to 64 mg (mean 37.3 mg); 186 mg MED 12 weeks
Hale, 2015[75] USA Good	371	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Mixed 4: 3.4 (NRS 0 to 10)	Age: 52 Female: 51% White: 71%	Hydrocodone SR 60 to 180 mg (mean 100 mg); 120 mg MED 12 weeks
Hale, 2015[74] USA Fair	391	1: Yes 2: No 3: Yes	1: Low back pain or osteoarthritis 2: 147.6 3: Mixed 4: 6.6 (NRS 0 to 10)	Age: 53 Female: NR White: 75%	Hydrocodone SR 30 to 180 mg (mean NR); NR 12 weeks
Hanna, 2008[76] UK Good	338	1: No 2: No 3: Yes	1: Diabetic neuropathy 2: NR 3: No 4: 6.4 (NRS 0 to 10)	Age: 60 Female: 36% White: 99%	Oxycodone SR NR; NR 12 weeks

Study, Year Country Quality	Total Patients Randomized	1: EERW Design 2: Crossover Design 3: Industry Funded	1: Pain Condition 2: Duration of Pain (Months)* 3: Opioid-Naïve 4: Baseline Pain	Age (Years)* Female (%) Race/Ethnicity	Opioid Dose; MED Duration of Treatment
Harati, 1998[77] USA Fair	131	1: No 2: No 3: Yes	1: Diabetic neuropathy 2: NR 3: Yes 4: 2.6 (NRS 0 to 10)	Age: 59 Female: 40% White: NR	Tramadol Up to 400 mg (mean 210 mg); 42 mg MED 6 weeks
Huse, 2001[78] Germany Poor	12	1: No 2: Yes 3: Yes	1: Phantom limb pain 2: 197.9 3: NR 4: 4.65 (VAS 0 to 10)	Age: 51 Female: 17% White: NR	Morphine SR 70 to 300 mg (mean NR); 185 mg MED 4 weeks
Katz, 2007[81] USA Fair	205	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: No 4: 19.1 (VAS 0 to 100)	Age: 50 Female: 53% White: 90%	Oxymorphone SR Mean 39.2 mg; 118 mg MED 12 weeks
Katz, 2010[79] USA Fair	344	1: Yes 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: 3.2 (NRS 0 to 10)	Age: 54 Female: 58% White: 72%	Morphine SR 20 to 160 mg (mean 43.5); 44 mg MED 12 weeks
Katz, 2015[80] USA Fair	389	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Mixed 4: 3.0 (NRS 0 to 10)	Age: 50 Female: 53% White: 71%	Oxycodone SR 40 to 160 mg (mean 78 mg); 117 mg MED 12 weeks
Kawamata, 2019[126] Japan Fair	130	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Mixed 4: NR	Age: 64 Female: 50% White: 0%	Oxycodone SR 10 to 80 mg (mean NR); 68 mg MED 5 weeks
Khoromi, 2007[82] USA Fair	55	1: No 2: Yes 3: No	1: Low back pain with radiculopathy 2: 60 (median) 3: Mixed 4: 4.9 (NRS 0 to 10)	Age: 53 (median) Female: 45% White: NR	Morphine SR Up to 90 mg (mean 62 mg); 62 mg MED 7 weeks
Langford, 2006[83] Europe Fair	416	1: No 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Yes 4: 73.2 (VAS 0 to 100)	Age: 66 Female: 64% White: NR	Fentanyl 25 to 100 mg (mean 43.9 mcg/hour); 105 mg MED 6 weeks
Lin, 2016[84] USA Poor	21	1: No 2: No 3: No	1: Low back pain 2: 99.6 3: No 4: NR	Age: 42 Female: NR White: 77%	Morphine SR 30 to 120 mg (mean 72 mg); 72 mg MED 4.5 weeks
Markenson, 2005[85] USA Fair	109	1: No 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: 6.6 (BPI 0 to10)	Age: 63 Female: 72% White: 93%	Oxycodone SR 20 to 120 mg (mean 44 mg); 66 mg MED 13 weeks
Matsumoto, 2005[86] USA Fair	491	1: No 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: NR	Age: 62 Female: 61% White: 86%	Oxymorphone SR 40 to 80 mg; 180 mg MED 4 weeks
Mayorga, 2016[87] USA Fair	98	1: No 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: NR	Age: 60 Female: 51% White: 80%	Oxycodone SR 40 to 100 mg (mean NR); 105 mg MED 16 weeks
Moran, 1991[88] UK Poor	20	1: No 2: No 3: Yes	1: Rheumatoid arthritis 2: NR 3: Yes 4: NR	Age: NR Female: 5% White: NR	CR Morphine 20 to 120 mg; 70 mg MED 5 weeks

Study, Year Country Quality	Total Patients Randomized	1: EERW Design 2: Crossover Design 3: Industry Funded	1: Pain Condition 2: Duration of Pain (Months)* 3: Opioid-Naïve 4: Baseline Pain	Age (Years)* Female (%) Race/Ethnicity	Opioid Dose; MED Duration of Treatment
Moulin, 1996[89] Canada Poor	61	1: No 2: Yes 3: Yes	1: Mixed (primarily musculoskeletal) 2: 49.2 3: Mixed 4: NR	Age: 40 Female: 59% White: NR	Morphine Up to 120 mg (mean 83.5 mg); 84 mg MED 6 weeks
Munera, 2010[90] USA Fair	315	1: No 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: 8.2 (NRS 0 to 10)	Age: 61 Female: 67% White: 85%	Buprenorphine patch 5 to 20 mcg/hour (mean NR); NA 4 weeks
Niesters, 2014[92] The Netherlands Good	25	1: No 2: No 3: Yes	1: Diabetic neuropathy 2: 72 (median) 3: Mixed 4: 7.8 (NRS 0 to 10)	Age: 78 (median) Female: 42% White: NR	Tapentadol SR 200 titrated to 500 mg (mean 433 mg); 173 mg MED 4 weeks
Norrbrink, 2009[93] Sweden Fair	36	1: No 2: No 3: No	1: Neuropathic pain after spinal cord injury 2: 175.2 3: NR 4: Median 3 vs. 5 (NRS 0 to 10)	Age: 51 Female: 20% White: NR	Tramadol 150 to 400 mg (median 250 mg); 50 mg MED 4 weeks
Peloso, 2000[94] Canada Fair	103	1: No 2: No 3: Yes	1: Osteoarthritis 2: 10.3 3: Mixed 4: 258 (WOMAC pain 0 to 500)	Age: 62 Female: 62% White: NR	Codeine SR 100 to 400 mg (mean 312 mg); 31 mg MED 4 weeks
Raja, 2002[95] USA Fair	76	1: No 2: Yes 3: No	1: Postherpetic neuralgia 2: 32.3 3: Mixed 4: NR	Age: 71 Female: 55% White: 88%	Morphine SR Up to 240 mg (mean 91 mg); 91 mg MED 8 weeks
Rauck, 2013[96] USA Poor	990	1: No 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: 7.4 (NRS 0 to 10)	Age: 60 Female: 64% White: 88%	Hydromorphone SR 8 to 16 mg (mean 12 mg); 60 mg MED 14 weeks
Rauck, 2014[98] USA Poor	302	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Yes 4: 3.1 (NRS 0 to 10)	Age: 51 Female: 55% White: 80%	Hydrocodone SR 40 to 200 mg (mean 119 mg); 143 mg MED 12 weeks
Rauck, 2015[97] USA Fair	281	1: Yes 2: No 3: Yes	1: Low back pain 2: 149 3: NR 4: 3.0 (NRS 0 to 10)	Age: 50 Female: 56% White: 73%	Oxycodone SR + Naltrexone 20 to 160 mg (mean 64 mg); 96 mg MED 12 weeks
Rauck, 2016[99] USA Fair	461	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: No 4: 7.2 (NRS 0 to 10)	Age: 50 Female: 62% White: 70%	Buprenorphine buccal 300 to 900 mcg (mean 660 mcg); NR 12 weeks
Russell, 2000[100] USA Fair	69	1: Yes 2: No 3: Yes	1: Fibromyalgia 2: 56.4 3: No 4: NR	Age: 49 Female: 94% White: 81%	Tramadol 50 to 400 mg (mean NR); 45 mg MED 6 weeks
Schnitzer, 2000[101] USA Poor	254	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: NR 4: NR	Age: 41 Female: 50% White: 93%	Tramadol 200 to 400 mg (mean NR); 60 mg MED 4 weeks

Study, Year Country Quality	Total Patients Randomized	1: EERW Design 2: Crossover Design 3: Industry Funded	1: Pain Condition 2: Duration of Pain (Months)* 3: Opioid-Naïve 4: Baseline Pain	Age (Years)* Female (%) Race/Ethnicity	Opioid Dose; MED Duration of Treatment
Schwartz, 2011[102] USA Fair	395	1: Yes 2: No 3: Yes	1: Diabetic neuropathy 2: 70.1 3: Mixed 4: 3.5 (NRS 0 to 10)	Age: 60 Female: 40% White: 70%	Tapentadol SR 100 to 250 mg (mean NR); 70 mg MED 12 weeks
Serrie, 2017[103] Europe Fair	990	1: No 2: No 3: Yes	1: Knee pain 2: NR 3: Mixed 4: 7.3 (NRS 0 to 10)	Age: 62 Female: 72% White: NR	Tapentadol SR/Oxycodone SR 200 to 500 mg (mean 315 mg)/ 40 to 100 mg (mean 54 mg); 126 mg/81 mg MED 15 weeks
Simpson, 2016[104] Australia Fair	186	1: No 2: No 3: Yes	1: Diabetic neuropathy 2: NR 3: No 4: 5.8 (NRS 0 to 10)	Age: 63 Female: 33% White: 94%	Buprenorphine patch 5 to 40 mcg/hour (mean 20 mcg/hour); NR 12 weeks
Sindrup, 1999[106] Denmark Poor	45	1: No 2: Yes 3: Yes	1: Polyneuropathy 2: 36 (median) 3: NR 4: NR	Age: 57 (median) Female: 39% White: NR	Tramadol Up to 400 mg (mean 364 mg); 73 mg MED 4 weeks
Sindrup, 2012[105] Denmark, Germany Fair	64	1: No 2: Yes 3: Yes	1: Polyneuropathy 2: NR 3: NR 4: 6.0 (NRS 0 to 10)	Age: 58 Female: 31% White: NR	Tramadol SR 100 to 400 mg (mean NR); 50 mg MED 4 weeks
Steiner, 2011[107] (also Yarlas 2013)[123] USA Fair	541	1: Yes 2: No 3: Yes	1: Low back pain 2: 109.2 3: No 4: 2.6 (NRS 0 to 10)	Age: 49 Female: 55% White: 70%	Buprenorphine patch 10 or 20 mcg/hour (mean NR); NR 12 weeks
Thorne, 2008[109] Canada Fair	116	1: No 2: Yes 3: Yes	1: Osteoarthritis 2: 99.6 3: Mixed 4: 50.8 (VAS 0 to 100)	Age: 61 Female: 55% White: NR	Tramadol SR 150 to 400 mg (mean 340 mg); 68 mg MED 4 weeks
Tominaga, 2016a[110] Japan Poor	91	1: No 2: No 3: Yes	1: Osteoarthritis or low back pain 2: NR 3: No 4: 6.9 (NRS 0 to 10)	Age: NR Female: NR White: NR	Tapentadol SR 50 to500 mg (mean 237 mg); 95 mg MED 12 weeks
Tominaga, 2016b[110] Japan Poor	91	1: No 2: No 3: Yes	1: Diabetic neuropathy or post-herpetic neuralgia 2: NR 3: No 4: 6.8 (NRS 0 to 10)	Age: NR Female: NR White: NR	Tapentadol SR 50 to 500 mg (mean 274 mg); 110 mg MED 12 weeks
Trenkwalder, 2015[111] Poland Fair	202	1: No 2: No 3: Yes	1: Parkinson's disease 2: 40.8 3: No 4: 7.3 (NRS 0 to 10)	Age: 67 Female: 48% White: NR	Oxycodone SR + Naloxone Oxycodone 10 to 40 mg (mean 19 mg) + Naloxone 5 to 20 mg; 28 mg MED 16 weeks
Uberall, 2012[112] Germany Fair	240	1: No 2: No 3: Yes	1: Low back pain 2: 74.1 3: Mixed 4: 6.0 (NRS 0 to 10)	Age: 58 Female: 58% White: 98%	Tramadol SR 200 mg; 40 mg MED 4 weeks

Study, Year Country Quality	Total Patients Randomized	1: EERW Design 2: Crossover Design 3: Industry Funded	1: Pain Condition 2: Duration of Pain (Months)* 3: Opioid-Naïve 4: Baseline Pain	Age (Years)* Female (%) Race/Ethnicity	Opioid Dose; MED Duration of Treatment
Vinik, 2014[113] USA Fair	318	1: Yes 2: No 3: Yes	1: Diabetic neuropathy 2: NR 3: Mixed 4: 3.6 (NRS 0 to 10)	Age: 59 Female: 41% White: 81%	Tapentadol SR 200 to 500 mg (mean NR); 140 mg MED 12 weeks
Vojtassak, 2011[114] Slovakia, UK Fair	288	1: No 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: 7.8 (BPI 0 to 10)	Age: 66 (median) Female: 72% White: 100%	Oxymorphone SR 4 mg; 12 mg MED 16 weeks
Vondrackova, 2008[115] Czech Republic Germany Fair	464	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Yes 4: NR	Age: 56 Female: 62% White: NR	Oxycodone SR/Oxycodone SR + Naloxone 20 or 40 mg/20 or 40 mg + 10 or 20 mg (mean NR); 45 mg MED 12 weeks
Vorsanger, 2008[117] USA Fair	386	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Mixed 4: 29.0 (VAS 0 to 100)	Age: 48 Female: 50% White: 84%	Tramadol SR 200 to 300 mg (mean NR); 50 mg MED 12 weeks
Watson, 1998[118] Canada Fair	50	1: No 2: Yes 3: Yes	1: Postherpetic neuralgia 2: 31 3: NR 4: NR	Age: 70 Female: 58% White: NR	Oxycodone 20 to 60 mg (mean 45 mg); 68 mg MED 4 weeks
Watson, 2003[119] Canada Fair	45	1: No 2: Yes 3: Yes	1: Diabetic neuropathy 2: NR 3: NR 4: 67 (VAS 0 to 100)	Age: 63 Female: 47% White: NR	Oxycodone SR 20 to 80 mg (mean 40 mg); 60 mg MED 4 weeks
Webster, 2006[120] USA Fair	307	1: No 2: No 3: NR	1: Low back pain 2: NR 3: Mixed 4: 7.6 (VAS 0 to 10)	Age: 48 Female: 61% White: NR	Oxycodone 10 to 80 mg (mean 39 mg); 58 mg MED 6 weeks
Wen, 2015[121] USA Fair	588	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Mixed 4: 7.4 (NRS 0 to 10)	Age: 49 Female: 57% White: 68%	Hydrocodone SR 20 to 120 mg (mean NR); 84 mg MED 12 weeks
Wu, 2008[122] USA Fair	60	1: No 2: Yes 3: No	1: Postamputation pain 2: 51.3 3: NR 4: 6.8 (NRS 0 to 10)	Age: 63 Female: 22% White: 85%	Morphine SR 30 to 180 mg (mean 112 mg); 112 mg MED 6 weeks

Abbreviations: bd=twice a day; BPI=Brief Pain Inventory; EERW=enriched enrollment randomized withdrawal; MED=morphine equivalent dose; NA=not applicable; NR=not reported; NRS=numeric rating scale; qd=once a day; SR=sustained release; VAS=Visual Analog Scale; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

*Mean, unless otherwise reported

Five trials were rated good-quality,[53,55,75,76,92] 55 trials fair-quality,[50,52,54,56-63,65-74,77,79-83,85-87,90,91,93-95,97,99,100,102-105,107-109,111-129] and 13 trials poor-quality[51,64,78,84,88,89,96,98,101,106,110] (Appendix Table G-1). Methodological shortcomings frequently present in the fair- and poor-quality trials included unclear randomization, unclear allocation concealment, unclear whether outcome assessors were blinded, high attrition, and differences between groups in attrition. Fourteen trials used a crossover design[61,67,70,71,78,82,89,95,105,106,109,118,119,122] and 25 trials used an enriched enrollment randomized withdrawal (EERW) design;[51,55,57,65,68,72-75,79-81,91,97-

[102,107,108,113,115,116,121,123-129] the remainder used a parallel group non-EERW randomized trial design. All trials except eight[60,67,82,84,93,95,120,122] reported industry funding.

One new, good-quality prospective propensity-matched cohort study (n=674) of patients in multidisciplinary pain centers in Portugal compared effects of opioid use versus non-use on pain and function at 1 and 2 years (Appendix Tables G-2, H-1, and H-2).

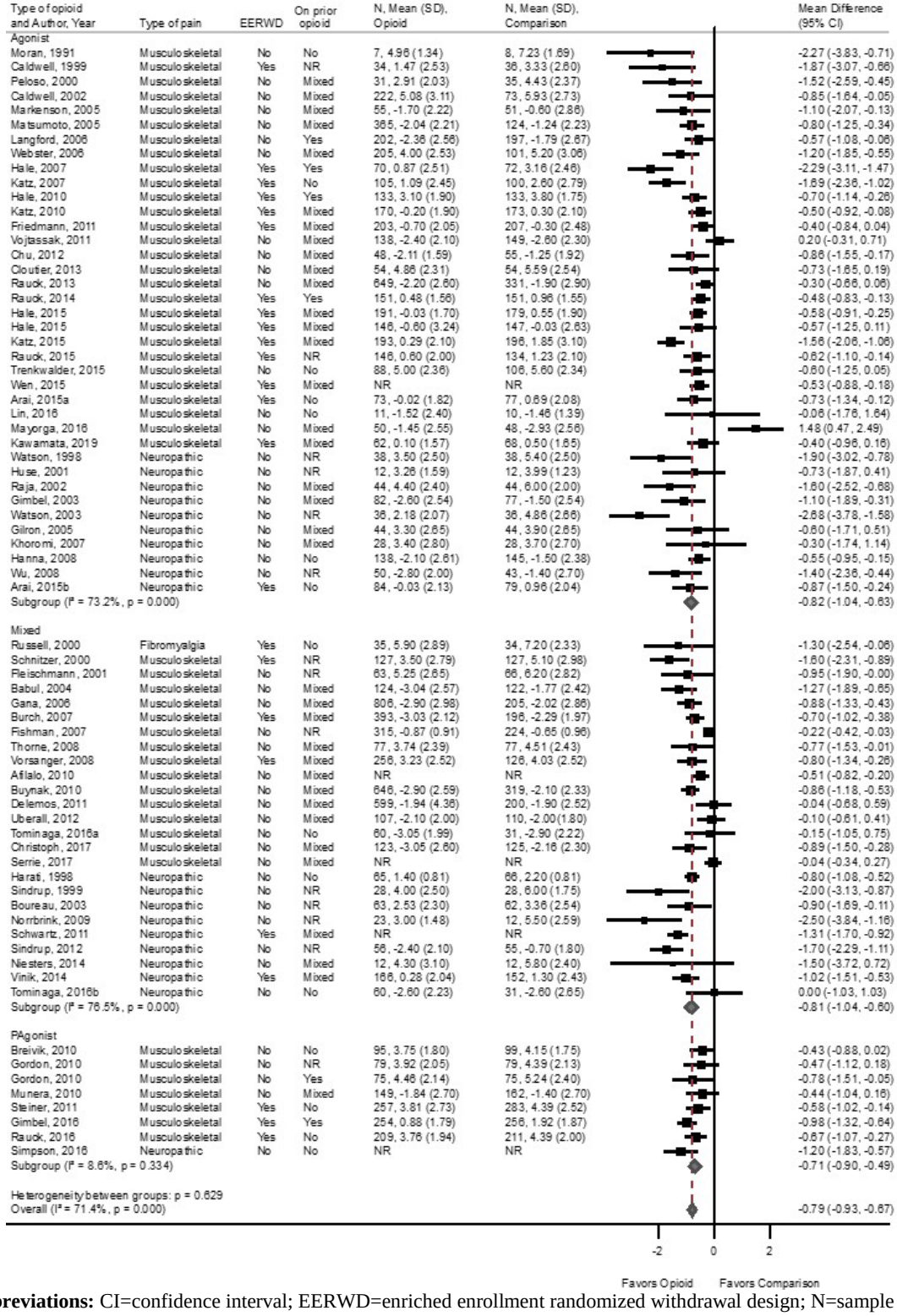
Detailed Synthesis

Short-Term Followup (1 to <6 Months)

Pain

Opioids were associated with a small mean improvement versus placebo in pain measured at short-term (1 to <6 months) followup (71 trials, N=19,616, mean difference -0.79 point on a 0 to 10 scale, 95% CI, -0.93 to -0.67, I^2=71%; Figure 3, Table 3).[50-88,90,92-114,117-122,126] Trials published prior to 2007 reported a larger effect on pain (22 trials, N=4274, mean difference -1.12, 95% CI, -1.37 to -0.92, I^2=29%) than trials published in or after 2007 (49 trials, N=15,342, mean difference -0.66, 95% CI, -0.81 to -0.52, I^2=73%), with a difference of 0.46 point (p for interaction=0.001). There were no interactions between trial quality (p for interaction=0.90), industry funding (p for interaction=0.41), geographic region (p for interaction=0.57), or use of EERW design (p for interaction=0.34) and effects on pain (Table 4). However, when the analysis was restricted to trials published in or after 2007 (only one EERW trial was published prior to 2007) effects on pain were larger in trials that used an EERW design (21 trials, N=7178, mean difference -0.81, 95% CI, -0.99 to -0.64, I^2=62%)[51,55,65,68,72-75,79-81,91,97-99,102,107,108,113,117,121,123-129] than trials without an EERW design (28 trials, N=8164, mean difference -0.52, 95% CI, -0.74 to -0.31, I^2=73%);[50,54,56,59-63,70,71,76,82,84,87,90,92,93,96,103-105,109-112,114,122] the difference in pooled estimates was 0.29 point (p for interaction=0.047). Trials that used a crossover design reported larger effects (13 trials, N=1234, mean difference -1.19, 95% CI, -1.58 to -0.81, I^2=48%)[61,67,70,71,78,82,95,105,106,109,118,119,122] than parallel group trials (58 trials, N=18,655, mean difference -0.73, 95% CI, -0.86 to -0.60, I^2=70%);[50-60,62-66,69,72,73,76,77,79,81,83-88,90-94,96-98,100-104,107,108,110-114,116,117,120,121,123-127] the difference in pooled estimates was 0.46 point (p for interaction=0.03).

Figure 3. Meta-analysis of improvement in mean pain measures for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; N=sample size; NR=not reported; ; PAgonist=partial agonist; SD=standard deviation.

Table 3. Pain and function results for opioids versus placebo

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Pain (Continuous)*	Pain (Dichotomous)*	Function (Continuous)*	Function (Dichotomous)*
Afilalo, 2010[50] International Fair	1: 15 weeks 2: 1030 3: Osteoarthritis of knee	1a: Tapentadol SR 200 to 500 mg (mean 350 mg) 1b: Oxycodone SR 40 to 100 mg (mean 70 mg) 2: Placebo	NRS 0 to 10 1a: Difference -0.70 (95% CI, -1.04 to -0.33) (ANCOVA) 1b: Difference -0.3 (95% CI, -0.68 to 0.02) (ANCOVA)	≥30% pain relief 1a: 43.0% (148/344) 1b: 24.8% (85/342) 2: 35.9% (121/337)	WOMAC Physical function subscale standardized to 0 to 10 (95% CI) 1a: Difference -0.27 (-0.42 to -0.13) (ANCOVA) 1b: Difference -0.17 (-0.34 to 0.00) (ANCOVA)	NR
Arai, 2015a[51] Japan Poor	1: 12 weeks 2: 150 3: Osteoarthritis or low back pain	1: Fentanyl patch 25 to 50 mcg/hour (mean 15.1 mcg/hour) 2: Placebo	VAS 0 to 100 Difference -7.3 (95% CI, -13.5 to -1.1) (ANCOVA)	NR	NR	NR
Arai, 2015[51] Japan Poor	1: 12 weeks 2: 163 3: Postherpetic neuralgia, complex regional pain syndrome, or chronic postoperative pain	1: Fentanyl patch 25 to 50 mcg/hour (mean 18.6 mcg/hour) 2: Placebo	VAS 0 to 100 Difference -8.7 (95% CI, -15.0 to -2.4) (ANCOVA)	NR	NR	NR
Babul, 2004[52] USA Fair	1: 12 weeks 2: 246 3: Osteoarthritis	1: Tramadol SR 200 to 400 mg (mean 276 mg) 2: Placebo	VAS 0 to 100 Difference -12.7 (CI, NR) (ANCOVA)	NR	WOMAC physical function 0 to 1700 Difference -198.5 (95% CI, NR) (ANCOVA)	NR
Boureau, 2003[53] France Good	1: 6 weeks 2: 127 3: Postherpetic neuralgia	1: Tramadol 10 to 400 mg (mean 276 mg) 2: Placebo	VAS 0 to 100 Difference -9.0 (95% CI, -16.9 to -0.9) (ANCOVA)	Pain relief ≥50% 1: 64.1% (41/64) 2: 49.2% (31/63)	NR	NR
Breivik, 2010[54] International Fair	1: 24 weeks 2: 199 3: Osteoarthritis	1: Buprenorphine patch 5 to 20 mcg/hour (mean 11.0 mcg/hour) 2: Placebo	WOMAC Pain 0 to 20 Difference -0.86 (95% CI, -1.76 to 0.05) (General linear model)	NR	WOMAC Physical function 0 to 68 Difference -2.90 (95% CI, -5.86 to 0.06) (General linear model)	EQ-5D, no difference, data not provided
Burch, 2007[55] International Good	1: 12 weeks 2: 646 3: Osteoarthritis	1: Tramadol SR 200 to 300 mg (mean 275 mg) 2: Placebo	NRS 0 to 10 Difference -0.7 (95% CI, -1.02 to -0.38) (ANCOVA)	Improve ≥2 points on 0 to 10 NRS 1: 86.1% (372/432) 2: 79.4% (170/214)	NR	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Pain (Continuous)*	Pain (Dichotomous)*	Function (Continuous)*	Function (Dichotomous)*
Buynak, 2010[56] USA Fair	1: 15 weeks 2: 981 3: Low back pain	1a: Tapentadol SR 200 to 500 mg (mean 313 mg) 1b: Oxycodone SR 40 to 100 mg (mean 53 mg) 2: Placebo	NRS 0 to 10 1a: Difference -0.8 (95% CI, -1.22 to -0.47) (ANCOVA) 1b: Difference -0.9 (95% CI, -1.24 to -0.49) (ANCOVA)	≥30% improvement in pain 1a: 39.3% (125/318) 1b: 30.2% (99/328) 2: 27.0% (86/319)	BPI Interference 0 to 10 1a: Difference -0.7 (SE 0.19) (ANCOVA) 1b: Difference -0.4 (SE 0.19) (ANCOVA)	NR
Caldwell, 1999[57] USA Fair	1: 4 weeks 2: 70 3: Osteoarthritis	1: Oxycodone SR 20 to 60 mg (mean 40 mg) 2: Placebo	Categorical scale 0 to 3, mean change (SD) 1: 0.44 (0.13) 2: 1.00 (0.13) (ANCOVA)	NR	NR	NR
Caldwell, 2002[58] USA Fair	1: 4 weeks 2: 295 3: Osteoarthritis	1: Morphine SR 30 mg, qd or bd (mean NR) 2: Placebo	WOMAC 0 to 500 VAS pain, % change from baseline (SD) 1: -20.7 (SD 4.3) 2: -6.5 (SD 4.4)	NR	WOMAC Physical Function 0 to 1700, mean change (SD) 1: -197.11 (41.13) 2: -96.7 (43.00)	NR
Christoph, 2017[59] Germany Fair	1: 14 weeks 2: 252 3: Low back pain	1: Tapentadol SR 400 mg (mean NR) 2: Placebo	NRS 0 to 10, mean change (SD) 1: -3.05 (2.60) 2: -2.16 (2.30)	≥30% improvement in pain 1: 45.2% (57/126) 2: 37.3% (47/126)	Oswestry Disability Index 0 to 100, mean change (SD) 1: -16.20 (15.60) 2: -12.80 (16.20) (mixed effects model)	NR
Chu, 2012[60] USA Fair	1: 4.5 weeks 2: 139 3: Low back pain	1: Morphine SR 30 to 120 mg (mean 78 mg) 2: Placebo	VAS 0 to 100, mean change (SD) 1: -21.1 (15.9) 2: -12.5 (19.2)	NR	Roland Morris Disability Questionnaire 0 to 24, mean change (SD) 1: -2.02 (3.06) 2: -0.51 (4.14)	NR
Cloutier, 2013[61] Canada Fair	1: 4 weeks 2: 83 3: Low back pain	1: Oxycodone SR 20 to 80 mg (mean 36 mg) + Naloxone 2: Placebo	VAS 0 to 100 1: 48.6 (23.1) 2: 55.9 (25.4)	NR	Pain Disability Index 0 to 70, 70=worse function 1: 34.3 (15.6) 2: 37.5 (15.2)	NR
DeLemos, 2011[62] USA Fair	1: 12 weeks 2: 808 3: Osteoarthritis	1: Tramadol SR 100, 200, or 300 mg (mean 200 mg) 2: Placebo	WOMAC Pain 0 to 500, mean change (SD) 1: -97 (8.9) 2: -94.9 (8.9)	NR	WOMAC Physical Function 0 to 1700, mean change (SD) 1: -300.7 (29.0) 2: -290.1 (29.1) (ANCOVA)	NR
Fishman, 2007[63] USA Canada Fair	1: 12 weeks 2: 552 3: Osteoarthritis	1: Tramadol SR 100, 200, or 300 mg (mean 201 mg) 2: Placebo	WOMAC Pain 0 to 500 Difference -11.24 (SD 57.2) (ANCOVA)	WOMAC improved >30% 1: 60.5% (198/327) 2: 49.3% (112/227)	WOMAC Physical Function 0 to 1700, median change (SD) 1: -46% (NR) 2: -27% (NR)	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Pain (Continuous)*	Pain (Dichotomous)*	Function (Continuous)*	Function (Dichotomous)*
Fleischmann, 2001[64] USA Poor	1: 12 weeks 2: 129 3: Osteoarthritis	1: Tramadol 200 to 400 mg (mean NR) 2: Placebo	NRS 0 to 4 1: 2.10 (1.06) 2: 2.48 (1.13)	Moderate or complete pain relief 1: 34.9% (22/63) 2: 16.7% (11/66)	WOMAC Physical Function 0 to 10 1: 4.19 (2.06) 2: 4.92 (2.29)	NR
Friedmann, 2011[65] USA Fair	1: 12 weeks 2: 412 3: Osteoarthritis	1: Oxycodone SR up to 40 mg (mean 27.5 mg) 2: Placebo	NRS 0 to 10, mean change (SD) 1: -0.70 (2.05) 2: -0.30 (2.48) (ANCOVA)	Global assessment good, very good, or excellent 1: 48.8% (99/203) 2: 35.7% (74/207)	WOMAC Physical Function 0 to 10 No difference, data NR	NR
Gana, 2006[66] (also Vorsanger 2007)[116] USA Fair	1: 12 weeks 2: 1020 3: Osteoarthritis	1: Tramadol SR 100 to 400 mg (mean NR) 2: Placebo	VAS 0 to 100, mean change (SD) 1: -29.0 (29.8) 2: -20.2 (28.6) (ANCOVA)	NR	WOMAC Physical Function 0 to 1700, mean change (SD) 1: -336.9 (408.4) 2: -234.3 (402.3) (ANCOVA)	NR
Gilron, 2005[67] Canada Fair	1: 5 weeks 2: 57 3: Diabetic neuropathy	1: Morphine up to 120 mg (mean 45 mg) 2: Lorazepam	VAS 0 to 10 (McGill Pain Questionnaire) 1: 3.3 (0.4) 2: 3.9 (0.4)	Pain relief at least moderate 1: 61.4% (35/57) 2: 22.8% (13/57)	BPI general activity 0 to 10 1: 3.1 (0.4) 2: 4.5 (0.4)	NR
Gimbel, 2003[69] USA Fair	1: 6 weeks 2: 159 3: Diabetic neuropathy	1: Oxycodone SR 10 to 120 mg (mean 37 mg) 2: Placebo	NRS 0 to 10, mean change (SD) 1: -2.6 (0.28) 2: -1.5 (0.29) (ANCOVA)	NR	BPI Physical function score 0 to 10, mean change (SD) 1: -2.4 (0.28) 2: -1.9 (0.29) (ANCOVA)	NR
Gimbel, 2016[68] USA Fair	1: 12 weeks 2: 511 3: Low back pain	1: Buprenorphine buccal 300 to 1800 mcg (mean 1320 mcg) 2: Placebo	NRS 0 to 10 Difference -0.98 (-1.32 to -0.64) (ANCOVA)	≥30% improvement in pain intensity from screening 1: 64.2% (163/254) 2: 30.5% (78/256)	Roland Morris Disability Questionnaire 0 to 24 Difference -1.20 (95% CI, -2.08 to -0.31) (ANCOVA)	NR
Gordon, 2010[70] Canada Fair	1: 4 weeks 2: 78 3: Low back pain	1: Buprenorphine patch 10 to 30 mcg/hour (mean 30 mcg/hour) 2: Placebo	VAS 0 to 100 1: 44.6 (21.4) 2: 52.4 (24.0)	Moderately or highly effective 1: 39.7% (31/78) 2: 23.1% (18/78)	Quebec Back Disability Scale 0 to 100, higher score=greater disability, mean change (SD) 1: -19.3% (NR) 2: -11.9% (NR)	NR
Gordon, 2010[71] Canada Fair	1: 4 weeks 2: 79 3: Low back pain	1: Buprenorphine patch 5 to 20 mcg/hour (mean 15.5 mcg/hour) 2: Placebo	VAS 0 to 100 1: 39.2 (20.5) 2: 43.9 (21.3)	Moderately or highly effective 1: 30.4% (24/79) 2: 20.2% (16/79)	Quebec Back Disability Scale 0 to 5, higher score=greater disability 1: 2.3 (0.9) 2: 2.4 (1.0)	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Pain (Continuous)*	Pain (Dichotomous)*	Function (Continuous)*	Function (Dichotomous)*
Hale, 2007[73] USA Fair	1: 12 weeks 2: 143 3: Low back pain	1: Oxymorphone SR (mean 80 mg) 2: Placebo	VAS 0 to 100 Difference -23.0 (SD NR) (ANCOVA)	NR	NR	NR
Hale, 2010[72] (also Nalamachu 2014)[91] USA Fair	1: 12 weeks 2: 268 3: Low back pain	1: Hydromorphone SR 12-64 mg (mean 37.3 mg) 2: Placebo	NRS 0 to 10 1: 3.1 (NR) 2: 3.8 (NR)	≥30% improvement in pain intensity 1: 60.6% (80/132) 2: 42.1% (56/133)	Roland Morris Disability Questionnaire 0 to 24 1: 8.2 (NR) 2: 11 (NR)	NR
Hale, 2015[75] USA Good	1: 12 weeks 2: 371 3: Low back pain	1: Hydrocodone SR 60 to 180 mg (mean 100 mg) 2: Placebo	NRS 0 to 10 Difference -0.58 (95% CI, -0.91 to -0.25) (ANCOVA)	Increase in average pain intensity <30% and score <5 1: 9.9% (19/191) 2: 13.1% (25/191)	Roland Morris Disability Questionnaire 0 to 24 Difference 0.28 (95% CI, -0.65 to 1.20) (ANCOVA)	NR
Hale, 2015[74] USA Fair	1: 12 weeks 2: 391 3: Low back pain or osteoarthritis	1: Hydrocodone SR 30-180 mg (mean NR) 2: Placebo	NRS 0 to 10, mean change (SD) 1: -0.6 (NR) 2: -0.03 (NR)	Increase in average pain intensity ≤33% 1: 89.0% (130/146) 2: 76.2% (112/147)	Patient Assessment of Function No differences (data NR)	NR
Hanna, 2008[76] UK Good	1: 12 weeks 2: 338 3: Diabetic neuropathy	1: Oxycodone SR (doses and mean NR) 2: Placebo	NRS 0 to 10 Difference -0.55 (95% CI, -0.95 to -0.15) (ANCOVA)	Pain relief good or very good 1: 40.2% (68/169) 2: 30.8% (52/169)	NR	NR
Harati, 1998[77] USA Fair	1: 6 weeks 2: 131 3: Diabetic neuropathy	1: Tramadol up to 400 mg (mean 210 mg)	NRS 0 to 4 1: 1.4 (0.1) 2: 2.2 (0.1)	NR	NR	NR
Huse, 2001[78] Germany Poor	1: 4 weeks 2: 12 3: Phantom limb pain	1: Morphine SR 70 to 300 mg (mean NR) 2: Placebo	VAS 0 to 10 1: 3.26 (1.59) 2: 3.99 (1.23)	Improvement in pain >25% 1: 50% (6/12) 2: 16.7% (2/12)	NR	NR
Katz, 2007[81] USA Fair	1: 12 weeks 2: 205 3: Low back pain	1: Oxymorphone SR (mean 39.2 mg) 2: Placebo	VAS 0 to 100 Difference -16.9 (95% CI, -23.6 to -10.1) (ANCOVA)	≥30% reduction in pain intensity (from screening to final visit) 1: 62.8% (66/105) 2: 34% (34/100)	NR	NR
Katz, 2010[79] USA Fair	1: 12 weeks 2: 344 3: Osteoarthritis	1: Morphine SR 20 to 160 mg (mean 43.5 mg) 2: Placebo	NRS 0 to 10, mean change (SD) 1: -0.2 (1.9) 2: 0.3 (2.1)	≥30% improvement in pain intensity 1: 72.5% (124/171) 2: 57.8% (100/173)	WOMAC Physical Function 0 to 100 (normalized), mean change (SD) 1: 2.3 (18.4) 2: 6.2 (17.8)	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Pain (Continuous)*	Pain (Dichotomous)*	Function (Continuous)*	Function (Dichotomous)*
Katz, 2015[80] USA Fair	1: 12 weeks 2: 389 3: Low back pain	1: Oxycodone SR 40 to 160 mg (mean 78 mg) 2: Placebo	NRS 0 to 10 Difference -1.56 (95% CI, -2.1 to -1.1) (ANCOVA)	≥30% improvement in pain intensity 1: 49.2% (95/193) 2: 33.2% (65/196)	Roland Morris Disability Questionnaire 0 to 24, mean change (SD) 1: 0.4 (4.83) 2: 0.7 (5.32) (ANCOVA)	NR
Kawamata, 2019[126] Japan Fair	1: 5 weeks 2: 130 3: Low back pain	1: Oxycodone SR 10 to 80 mg (mean NR) 2: Placebo	BPI average pain intensity 0 to 10, mean change (SD) 1: 0.1 (1.57) 2: 0.5 (1.65)	Adequate pain relief† 1: 64.5% (40/62) 2: 58.8% (40/68)	Roland Morris Disability Questionnaire 0 to 24, mean change (SD) 1: 0.1 (3.94) 2: 1.2 (3.30)	NR
Khoromi, 2007[82] USA Fair	1: 7 weeks 2: 55 3: Low back pain with radiculopathy	1: Morphine SR up to 90 mg (mean 62 mg) 2: Placebo	NRS 0 to 10 Difference -0.3 (CI, NR) (Linear mixed model)	Pain relief moderate or greater 1: 23.6% (13/55) 2: 20.0% (11/55)	Oswestry Disability Index 0 to 100 1: 25.7 (16.5) 2: 30.5 (15.9)	NR
Langford, 2006[83] Europe Fair	1: 6 weeks 2: 416 3: Osteoarthritis	1: Fentanyl 25 to 100 mg (mean 43.9 mcg/hour) 2: Placebo	VAS 0 to 100 1: -23.6 (25.6) 2: -17.9 (26.7)	NR	WOMAC Physical Function 0 to 10, mean change (SD) 1: -1.1 (1.4) 2: -0.7 (1.4)	NR
Lin, 2016[84] USA Poor	1: 4.5 weeks 2: 21 3: Low back pain	1: Morphine SR 30 to 120 mg (mean 72 mg) 2: Placebo	NRS 0 to 10, mean change (SD) 1: -1.52 (2.40) 2: 1.46 (1.39)	NR	NR	NR
Markenson, 2005[85] USA Fair	1: 13 weeks 2: 109 3: Osteoarthritis	1: Oxycodone SR 20 to 120 mg (mean 44 mg) 2: Placebo	BPI average pain intensity 0 to 10, mean change (SD) 1: -1.70 (0.30) 2: -0.60 (0.40)	Improvement in pain ≥30% 1: 37.5% (21/56) 2: 17.6% (9/51)	BPI, interference composite 0 to 10, mean change (SD) 1: -1.90 (0.30) 2: -0.60 (0.30) (ANCOVA)	NR
Matsumoto, 2005[86] USA Fair	1: 4 weeks 2: 491 3: Osteoarthritis	1a: Oxymorphone SR 40 to 80 mg (mean NR) 1b: Oxycodone SR 40mg (mean NR) 2: Placebo	WOMAC pain 0 to 500, mean change (SD) 1a: -109 (110.0) 1b: -88 (111.8) 2: -62 (111.4)	NR	WOMAC Physical Function (0 to 1700), mean change (SD) 1a: -305 (548) 1b: -225 (559) 2: -175 (557) (ANCOVA)	NR
Mayorga, 2016[87] USA Fair	1: 16 weeks 2: 98 3: Osteoarthritis	1: Oxycodone SR 40 to 100 mg (mean NR) 2: Placebo	NRS 0 to 10, mean change (SD) 1: -1.45 (2.55) 2: -2.93 (2.56)	≥30% improvement in pain intensity 1: 24.0% (12/50) 2: 47.9% (23/48)	WOMAC Physical Function Subscale 0 to 100 1: -1.34 (2.69) 2: -2.99 (2.70)	NR
Moran, 1991[88] UK Poor	1: 5 weeks 2: 20 3: Rheumatoid arthritis	1: CR Morphine 20 to 120 mg (mean NR) 2: Placebo	VAS 0 to 100 (followup only) 1: 49.6 (13.4) 2: 72.3 (16.9)	Mild or no pain 1: 30% (3/10) 2: 10% (1/10)	Health Activities Questionnaire 0 to 3, 3=full incapacity 1: 2.3 (0.6) 2: 2.3 (0.6)	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Pain (Continuous)*	Pain (Dichotomous)*	Function (Continuous)*	Function (Dichotomous)*
Moulin, 1996[89] Canada Poor	1: 6 weeks 2: 61 3: Mixed (primarily musculoskeletal)	1: Morphine up to 120 mg (mean 83.5 mg) 2: Benztropine	NR	NR	Pain Disability Index 0 to 70 Difference -0.4 (95% CI, -2.8 to 2.0)	NR
Munera, 2010[90] USA Fair	1: 4 weeks 2: 315 3: Osteoarthritis	1: Buprenorphine patch 5 to 20 mcg/hour (mean NR) 2: Placebo	NRS 0 to 10, mean change (SD) 1: -1.84 (2.7) 2: -1.40 (2.7) (ANCOVA)	Treatment success (good, very good, or excellent patient satisfaction) 1: 42.8% (65/152) 2: 31.9% (52/163)	NR	NR
Niesters, 2014[92] The Netherlands Good	1: 4 weeks 2: 25 3: Diabetic neuropathy	1: Tapentadol SR 200 mg, titrated to 500 mg (mean 433 mg) 2. Placebo	NRS 0 to 10 1: 4.3 (3.1) 2: 5.8 (2.4)	NR	NR	NR
Norrbrink, 2009[93] Sweden Fair	1: 4 weeks 2: 36 3: Neuropathic pain after spinal cord injury	1: Tramadol 150 to 400 mg (median 250 mg) 2: Placebo	NRS 0 to 10, median (IQR) 1: 3 (2 to 4) 2: 5.5 (3.5 to 7)	Much or very much improved on Patient Global Impression of Change 1: 17.4% (4/23) 2: 0% (0/12)	Multidimensional Pain Inventory 0 to 6, higher score=worse function, median (IQR) 1: 2.45 (1.55 to 3.55) 2: 3.64 (1.65 to 5.34)	NR
Peloso, 2000[94] Canada Fair	1: 4 weeks 2: 103 3: Osteoarthritis	1: Codeine SR 100 to 400 mg (mean 312 mg) 2: Placebo	WOMAC pain 0 to 500 1: 145.4 (101.3) 2: 221.3 (118.7)	NR	WOMAC physical function 0 to 1700 1: 456.2 (316.2) 2: 687.5 (415.5)	NR
Raja, 2002[95] USA Fair	1: 8 weeks 2: 76 3: Postherpetic neuralgia	1: Morphine SR up to 240 mg (mean 91 mg) 2: Placebo	NRS 0 to 10 1: 4.4 (2.4) 2: 6.0 (2.0)	Improvement in pain >33% 1: 52.6% (40/76) 2: 17.1% (13/76)	Multidimensional Pain Inventory, interference 0 to 6 1: 2.3 (1.5) 2: 2.5 (1.5)	NR
Rauck, 2013[96] USA Poor	1: 14 weeks 2: 990 3: Osteoarthritis	1: Hydromorphone SR 8 or 16 mg (mean 12 mg) 2: Placebo	NRS 0 to 10, mean change (SD) 1: -2.2 (2.6) 2: -1.9 (2.9)	NR	WOMAC Physical Function 0 to 68, mean change (SD) 1: -1.6 (2) 2: -1.3 (2) (ANCOVA)	NR
Rauck, 2014[98] USA Poor	1: 12 weeks 2: 302 3: Low back pain	1: Hydrocodone SR 40 to 200 mg (mean 119 mg) 2: Placebo	NRS 0 to 10 1: 0.48 (1.56) 2: 0.96 (1.55) (ANCOVA)	≥30% improvement in pain intensity 1: 67.5% (102/151) 2: 31.1% (47/151)	NR	NR
Rauck, 2015[97] USA Fair	1: 12 weeks 2: 281 3: Low back pain	1: Oxycodone SR 20 to 160 mg (mean 64 mg) + Naltrexone 2: Placebo	NRS 0 to 10 Difference -0.62 (95% CI, -1.11 to -0.14) (ANCOVA)	≥30% improvement in pain intensity 1: 57.5% (84/146) 2: 44.0% (59/134)	Roland Morris Disability Questionnaire 0 to 24 Difference 0.18 (p=0.75, CI, and SD NR)	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Pain (Continuous)*	Pain (Dichotomous)*	Function (Continuous)*	Function (Dichotomous)*
Rauck, 2016[99] USA Fair	1: 12 weeks 2: 461 3: Low back pain	1: Buprenorphine buccal 300 to 900 mcg (mean 660 mcg) 2: Placebo	NRS 0 to 10 Difference -0.67 (95% CI, -1.07 to -0.26) (ANCOVA)	≥30% improvement in pain intensity from screening 1: 63.1% (132/209) 2: 46.9% (99/211)	Roland Morris Disability Questionnaire 0 to 24 Difference -0.75 (95% CI, -1.77 to 0.27) (No adjustment)	NR
Russell, 2000[100] USA Fair	1: 6 weeks 2: 69 3: Fibromyalgia	1: Tramadol 50 to 400 mg (mean NR) 2: Placebo	VAS 0 to 10, 1: 5.9 (2.89) 2: 7.2 (2.33)	Pain relief moderate, a lot, or complete 1: 57.1% (20/35) 2: 26.5% (9/34)	Fibromyalgia Impact Questionnaire 0 to 100, 100=more disability 1: 44.6 (17.96) 2: 47.2 (15.72)	NR
Schnitzer, 2000[101] USA Poor	1: 4 weeks 2: 254 3: Low back pain	1: Tramadol 200 to 400 mg (mean NR) 2: Placebo	VAS 0 to 10 1: 3.5 (2.79) 2: 5.1 (2.98)	NR	Roland Disability Questionnaire 0 to 24 1: 8.8 (6.2) 2: 10.2 (6.2)	RDQ ≥14 1: 24.4% (31/127) 2: 33.1% (42/127)
Schwartz, 2011[102] USA Fair	1: 12 weeks 2: 395 3: Diabetic neuropathy	1: Tapentadol 100 to 250 mg (mean NR) 2: Placebo	NRS 0 to 10 Difference -1.31 (95% CI, -1.70 to -0.92) (ANCOVA)	≥30% improvement in pain intensity 1: 53.1% (104/196) 2: 42.0% (81/193)	NR	NR
Serrie, 2017[103] Europe Fair	1: 15 weeks 2: 990 3: Knee pain	1a: Tapentadol SR 200 to 500 mg (mean 315 mg) 1b: Oxycodone SR 40 to 100 mg (mean 54 mg) 2: Placebo	NRS 0 to 10 1a: Difference -0.3 (95% CI, -0.61 to 0.09) 1b: Difference 0.2 (95% CI, -0.16 to 0.54) (ANCOVA)	≥30% improvement in pain intensity 1a: 41.1% (131/319) 1b: 26.0% (86/331) 2: 40.8% (138/338)	WOMAC, Physical Function scale unclear, appears to be 0 to 4 1a: Difference -0.1 (95% CI, -0.23 to 0.07) 1b: Difference -0.1 (95% CI, -0.25 to 0.08) (ANCOVA)	NR
Simpson, 2016[104] Australia Fair	1: 12 weeks 2: 186 3: Diabetic neuropathy	1: Buprenorphine patch 5 to 40 mcg/hour (mean 20 mcg/hour) 2: Placebo	NRS 0 to 10 Difference -1.20 (95% CI, -1.83 to -0.57) (Generalized linear mixed model)	≥30% improvement in pain intensity 1: 49.5% (46/93) 2: 40.9% (38/93)	BPI General Activity 0 to 10, mean change (SD) 1: -1.85 (2.96) 2: -1.89 (2.79) (generalized linear mixed model)	NR
Sindrup, 1999[106] Denmark Poor	1: 4 weeks 2: 45 3: Polyneuropathy	1: Tramadol up to 400 mg (mean 364 mg) 2: Placebo	NRS 0 to 10, median (range) 1: 4 (0 to 10) 2: 6 (2 to 9)	NR	NR	NR
Sindrup, 2012[105] Denmark, Germany Fair	1: 4 weeks 2: 64 3: Polyneuropathy	1: Tramadol SR 200 mg 2: Placebo	NRS 0 to 10 Difference -1.7 (SE 0.3) (No adjustment)	≥30% improvement in pain intensity 1: 50% (32/64) 2: 17.2% (11/64)	NR	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Pain (Continuous)*	Pain (Dichotomous)*	Function (Continuous)*	Function (Dichotomous)*
Steiner, 2011[107] (also Yarlas 2013)[123] USA Fair	1: 12 weeks 2: 541 3: Low back pain	1: Buprenorphine patch 10 or 20 mcg/hour (mean NR) 2: Placebo	NRS 0 to 10 Difference -0.58 (95% CI, -1.02 to -0.14) (ANCOVA)	≥30% improvement in pain intensity 1: 52.9% (136/257) 2: 46.1% (131/284)	BPI Interference 0 to 10 1: 2.4 (NR) 2: 3.5 (NR)	NR
Thorne, 2008[109] Canada Fair	1: 4 weeks 2: 116 3: Osteoarthritis	1: Tramadol SR 150 to 400 mg (mean 340 mg) 2: Placebo	VAS 0 to 100 1: 37.4 (23.9) 2: 45.1 (24.3)	Moderately or highly effective 1: 55.8% (43/77) 2: 24.7% (19/77)	Pain Disability Index, total pain and disability 0 to 70, 70=greater disability 1: 22.8 (14.5) 2: 27.2 (14.8)	NR
Tominaga, 2016[110] Japan Poor	1: 12 weeks 2: 91 3: Osteoarthritis or low back pain	1: Tapentadol SR 50 to 500 mg (mean 237 mg) 2: Placebo	NRS 0 to 10, mean change (SD) 1: -3.05 (1.99) 2: -2.90 (2.22) (ANCOVA)	≥30% improvement in pain intensity 1: 55% (33/60) 2: 61.3% (19/31)	NR	NR
Tominaga, 2016[110] Japan Poor	1: 12 weeks 2: 91 3: Diabetic neuropathy or postherpetic neuralgia	1: Tapentadol SR 50 to 500 mg (mean 274 mg) 2: Placebo	NRS 0 to 10, mean change (SD) 1: -2.6 (2.23) 2: -2.6 (2.65) (ANCOVA)	≥30% improvement in pain intensity 1: 48.3% (29/60) 2: 41.9% (13/31)	NR	NR
Trenkwalder, 2015[111] Poland Fair	1: 16 weeks 2: 202 3: Parkinson's disease	1: Oxycodone SR 10 to 40 mg (mean 19 mg) + Naloxone 5-20 mg 2: Placebo	NRS 0 to 10 Difference -0.7 (95% CI, -1.3 to -0.1) (Mixed model repeated measures)	NR	NR	NR
Uberall, 2012[112] Germany Fair	1: 4 weeks 2: 240 3: Low back pain	1: Tramadol SR 200 mg 2: Placebo	NRS 0 to 10, mean change (SD) 1: -2.1 (2.0) 2: -2.0 (1.8) (ANCOVA)	≥30% improvement in pain intensity 1: 44.8% (52/116) 2: 47.5% (57/120)	Modified Pain Disability Index No difference, data NR	NR
Vinik, 2014[113] USA Fair	1: 12 weeks 2: 318 3: Diabetic neuropathy	1: Tapentadol SR 200 to 500 mg (mean NR) 2: Placebo	NRS 0 to 10, mean change (SD) 1: 0.28 (2.04) 2: 1.30 (2.43)	≥30% improvement in pain intensity 1: 55.4% (92/166) 2: 45.4% (69/152)	BPI interference 0 to 10, mean change (SD) 1: -3.0 (2.07) 2: -2.6 (2.38)	NR
Vojtassak, 2011[114] Slovakia UK Fair	1: 16 weeks 2: 288 3: Osteoarthritis	1: Oxymorphone SR 4 mg (mean NR) 2: Placebo	BPI pain intensity 0 to 10, mean change (SD) 1: -2.4 (2.1) 2: -2.6 (2.3)	NR	WOMAC Physical Function 0 to 100, mean change (SD) 1: -11.93 (13.17) 2: -11.90 (14.35) (mixed model for repeated measures)	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Pain (Continuous)*	Pain (Dichotomous)*	Function (Continuous)*	Function (Dichotomous)*
Vondrackova, 2008[115] Czech Republic Germany Fair	1: 12 weeks 2: 464 3: Low back pain	1: Oxycodone SR 20 or 40 mg (mean NR) 1b: Oxycodone SR + Naloxone 20 or 40 mg + 10 or 20 mg (mean NR) 2: Placebo	NRS 0 to 10, improved vs. placebo (p=0.008), data NR	NR	NR	NR
Vorsanger, 2008[117] USA Fair	1: 12 weeks 2: 386 3: Low back pain	1: Tramadol SR 200 or 300 mg (mean NR) 2: Placebo	VAS 0 to 100 1: 32.3 (25.2) 2: 40.3 (25.2)	NR	Roland Morris Disability Index 0 to 24, 1: 8.4 (5.7) 2: 9.8 (5.9)	NR
Watson, 1998[118] Canada Fair	1: 4 weeks 2: 50 3: Postherpetic neuralgia	1: Oxycodone 20 to 60 mg (mean 45 mg) 2: Placebo	VAS 0 to 100 1: 35 (25) 2: 54 (25)	NR	Categorical scale 0 to 3, 3=more disability 1: 0.3 (0.8) 2: 0.7 (1.0)	NR
Watson, 2003[119] Canada Fair	1: 4 weeks 2: 45 3: Diabetic neuropathy	1: Oxycodone SR 20 to 80 mg (mean 40 mg) 2: Placebo	VAS 0 to 100 1: 21.8 (20.7) 2: 48.6 (26.6)	NR	Pain Disability Index 0 to 70, 70=total disability 1: 16.8 (15.6) 2: 25.2 (16.7)	NR
Webster, 2006[120] USA Fair	1: 6 weeks 2: 307 3: Low back pain	1: Oxycodone 10 to 80 mg (mean 39 mg) 2: Placebo	NRS 0 to 10 1: 4.0 (2.53) 2: 5.2 (3.06)	NR	NR	NR
Wen, 2015[121] USA Fair	1: 12 weeks 2: 588 3: Low back pain	1: Hydrocodone SR 20 to 120 mg (mean NR) 2: Placebo	NRS 0 to 10 Difference -0.53 (95% CI, -0.88 to -0.18) (Mixed model repeated measures)	≥30% improvement in pain intensity from screening 1: 64.9% (192/296) 2: 53.1% (155/292)	Oswestry Disability Index, BPI Short Form No differences, data NR	NR
Wu, 2008[122] USA Fair	1: 6 weeks 2: 60 3: Postamputation pain	1: Morphine SR 30 to 180 mg (mean 112 mg) 2: Placebo	NRS 0 to 10, mean change (SD) 1: -2.8 (2.0) 2: -1.4 (2.7) (general estimating equations)	≥33% improvement in pain 1: 55% (33/60) 2: 31.7% (19/60)	Multidimensional Pain Inventory No differences, data NR	NR

Abbreviations: ANCOVA=analysis of covariance; bd=twice a day; BPI=Brief Pain Inventory; CI=confidence interval; CR=controlled release; IQR=interquartile range; IR=immediate release; NR=not reported; NRS=numeric rating scale; qd=once a day; RDQ=Roland-Morris Disability Questionnaire; SD=standard deviation; SR=sustained release; VAS=visual analog scale; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

*Mean (SD), unless otherwise reported

†≥30% improvement in pain intensity and pain intensity ≤3 and no aggravation resulting in dose escalation, addition, or change

Table 4. Pooled analyses of improvement in mean pain and function measures for opioids versus placebo

Analysis	Pain (Continuous), MD (95% CI) on 0 to 10 Scale*	I^2	Number of Trials (N)	p†	Function (Continuous), SMD (95% CI)*	I^2	Number of Trials (N)	p†
All trials	-0.79 (-0.93 to -0.67)	71%	71 (19,616)	--	-0.22 (-0.28 to -0.16)	53%	44 (12,481)	--
Opioid type: Opioid agonist	-0.82 (-1.04 to -0.63)	73%	38 (8505)	0.85	-0.20 (-0.30 to -0.10)	57%	243 (5369)	0.72
• **Partial agonist**	-0.71 (-0.90 to -0.49)	8.6%	8 (2470)	--	-0.25 (-0.46 to -0.03)	69%	6 (1731)	--
• **Mixed mechanism**	-0.81 (-1.04 to -0.60)	76%	25 (8641)	--	-0.22 (-0.30 to -0.15)	19%	14 (5327)	--
Pain type: Musculoskeletal	-0.67 (-0.81 to -0.54)	68%	50 (16,979)	**0.009**	-0.21 (-0.28 to -0.15)	60%	34 (11,319)	0.86
• **Neuropathic**	-1.15 (-1.43 to -0.91)	52%	20 (2568)	--	-0.23 (-0.40 to -0.11)	0%	9 (1039)	--
• **Fibromyalgia**	-1.30 (-2.54 to -0.06)	--	1 (69)	--	-0.15 (-0.62 to 0.32)	--	1 (69)	--
Followup: 1 to 3 months	-0.83 (-0.96 to -0.70)	69%	65 (17,665)	--‡	-0.38 (-0.44 to -0.32)	67%	35 (9652)	--‡
• **3 to 6 months**	-0.30 (-0.83 to 0.23)	78%	8 (2243)	--	-0.13 (-0.35 to 0.09)	74%	6 (1502)	--
Trial quality: Good	-0.64 (-0.84 to -0.45)	0%	5 (1391)	0.90	0.06 (-0.14 to 0.27)	--	1 (382)	0.24
• **Fair**	-0.82 (-0.98 to -0.67)	76%	54 (15,949)	--	-0.23 (-0.30 to -0.17)	54%	38 (10,575)	--
• **Poor**	-0.75 (-1.14 to -0.43)	52%	12 (2276)	--	-0.17 (-0.30 to -0.06)	0%	5 (1470)	--
Opioid dose (mg MED/day): <50	-0.48 (-0.72 to -0.28)	51%	14 (3748)	**0.009**	-0.15 (-0.35 to -0.03)	25%	7 (1948)	0.26
• **50-90**	-1.07 (-1.32 to -0.85)	61%	26 (6271)	--	-0.26 (-0.34 to -0.19)	0%	18 (4109)	--
• **>90**	-0.73 (-0.91 to -0.55)	71%	31 (9597)	--	-0.18 (-0.28 to -0.07)	73%	19 (6370)	--
EERW design	-0.86 (-1.05 to -0.69)	64%	24 (7571)	0.34	-0.22 (-0.34 to -0.10)	67%	13 (4034)	0.99
• **Non-EERW design**	-0.75 (-0.94 to -0.58)	73%	47 (12,045)	--	-0.21 (-0.28 to -0.15)	33%	31 (8393)	--
EERW design, 2007 or after	-0.81 (-0.99 to -0.64)	62%	21 (7178)	**0.047**	-0.22 (-0.36 to -0.09)	72	11 (3711)	0.43
• **Non-EERW design**	-0.52 (-0.74 to -0.31)	73%	28 (8164)	--	-0.15 (-0.25 to -0.06)	42%	16 (5061)	--
Crossover design	-1.19 (-1.58 to -0.81)	48%	13 (1234)	**0.03**	-0.27 (-0.41 to -0.14)	0%	9 (840)	0.48
• **Parallel group**	-0.73 (-0.86 to -0.60)	70%	58 (18,655)	--	-0.21 (-0.28 to -0.14)	60%	35 (11,587)	--
Opioid status: Naïve	-0.73 (-0.92 to -0.57)	0%	15 (2754)	0.05	-0.26 (-0.50 to 0.01)	65%	6 (1199)	0.53
• **Experienced**	-0.88 (-1.41 to -0.44)	72%	6 (1769)	--	-0.32 (-0.54 to -0.15)	14%	3 (1175)	--
• **Mixed**	-0.68 (-0.85 to -0.51)	68%	36 (13,072)	--	-0.19 (-0.25 to -0.12)	38%	28 (9101)	--
• **Not reported**	-1.27 (-1.73 to -0.88)	76%	14 (2022)	--	-0.22 (-0.44 to -0.07)	24%	7 (952)	--
Publication date: Prior to 2007	-1.12 (-1.37 to -0.92)	29%	22 (4274)	**0.001**	-0.28 (-0.35 to -0.21)	0%	17 (3655)	0.09
• **In or after 2007**	-0.66 (-0.81 to -0.52)	73%	49 (15,342)	--	-0.18 (-0.27 to -0.10)	65%	27 (8772)	--
Region: USA or Canada	-0.84 (-0.99 to -0.70)	69%	50 (14,643)	0.57	-0.22 (-0.30 to -0.15)	58%	34 (10,191)	0.57
• **Europe or Australia**	-0.82 (-1.27 to -0.44)	80%	14 (3078)	--	-0.15 (-0.27 to -0.05)	0%	8 (1798)	--
• **Asia**	-0.53 (-0.84 to -0.17)	0%	5 (625)	--	-0.30 (-0.65 to 0.04)	--	1 (130)	--
• **Multiple§**	-0.60 (-0.89 to -0.31)	0%	2 (1270)	--	-0.44 (-0.70 to -0.18)	--	1 (308)	--
Industry funding: Yes	-0.77 (-0.91 to -0.64)	73%	63 (18,826)	0.41	-0.21 (-0.27 to -0.15)	56%	39 (12,057)	0.23
• **No industry funding**	-1.11 (-1.62 to -0.57)	3.8%	7 (484)	--	-0.36 (-0.58 to -0.15)	0%	5 (370)	--

Note: Statistically significant p values are bolded

Abbreviations: CI=confidence interval; MD=mean difference; MED=morphine equivalent dose; SMD= standardized mean difference; EERW=enriched enrollment randomized withdrawal; N=total sample size.

*Negative values indicate improvement in pain or function

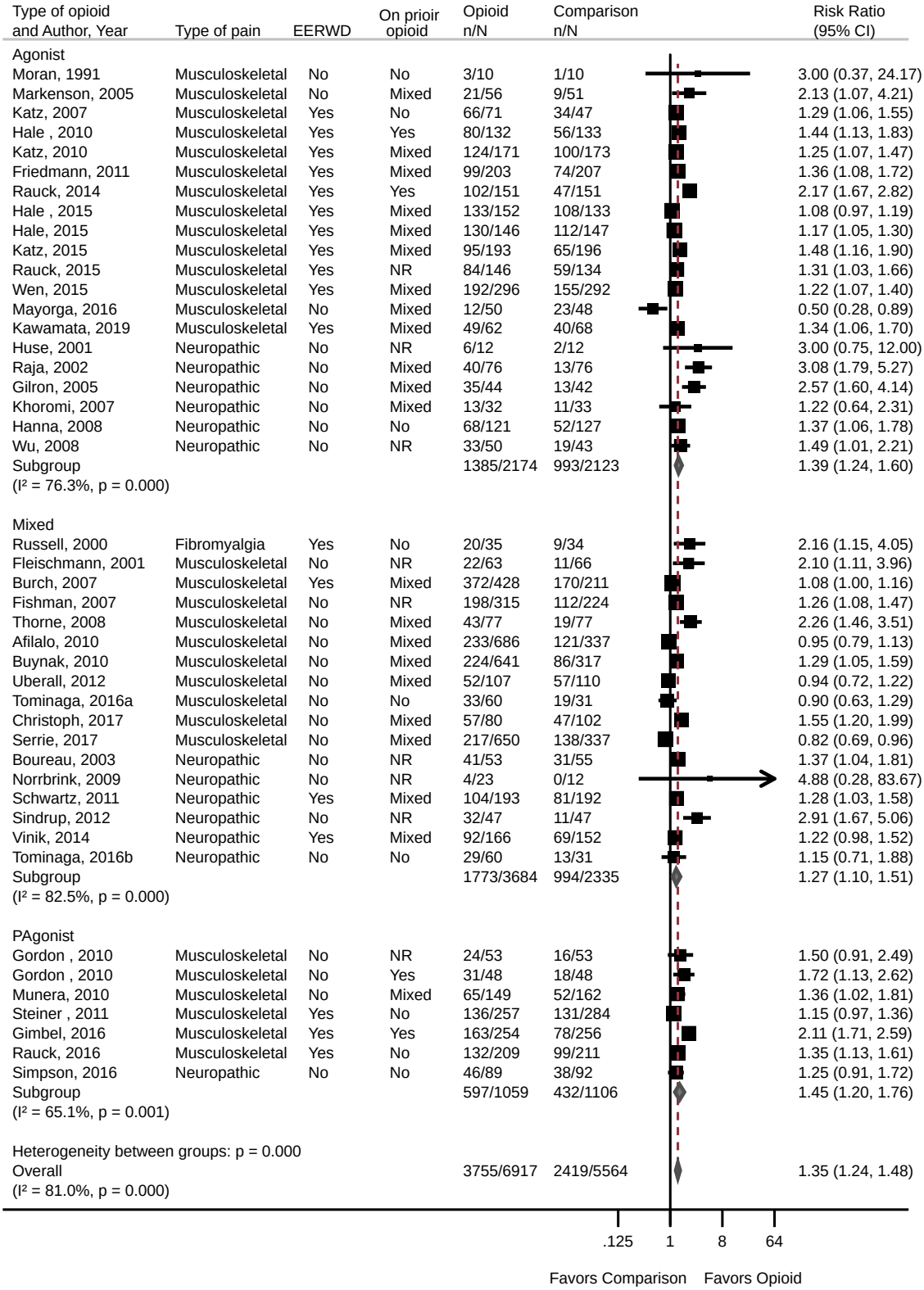
†p value is for interaction

‡The p for interaction was not calculated because some trials reported both 1 to 3 month and 3 to 6 month outcomes

§USA/Canada and Europe/Australia

Opioids were also associated with an increased likelihood of a pain response at short-term (1 to <6 months) followup (44 trials, N=12,481, RR 1.35, 95% CI, 1.24 to 1.48, I^2=81%; ARD 15%, 95% CI, 11% to 19%; Figure 4, Table 3). Pain response was defined in 28 trials as 30 percent or greater or 33 percent or greater improvement in pain intensity from baseline, four trials used other numerical thresholds (>25%,[78] ≥30%,[126] ≥50%,[53] or ≥2 point improvement on a 0 to 10 scale[55]), and 12 trials[64,65,67,70,71,76,82,88,90,93,100,109] used a categorical scale (at least moderate pain relief, good response, or similar). The estimate was similar when the analysis was restricted to trials that based pain response on changes on a numerical scale (32 trials, N=10,792, RR 1.29, 95% CI, 1.17 to 1.42, I^2=85%; Table 5). Estimates were also similar when trials were stratified according to followup at 1 to 3 months or at 3 to 6 months. Trials that used a crossover design reported a larger effect on the likelihood of experiencing an improvement in pain (9 trials, N=870, RR 1.99, 95% CI, 1.60 to 2.52, I^2=25%) than parallel group trials (35 trials, N=11,611, RR 1.27, 95% CI, 1.17 to 1.38, I^2=77%; p for interaction=0.001), trials published prior to 2007 (8 trials, N=695, RR 2.09, 95% CI, 1.60 to 2.91, I^2=35%) reported a larger effect than trials published in or after 2007 (36 trials, N=11,786, RR 1.29, 95% CI, 1.19 to 1.40, I^2=80%; p for interaction=0.002), and trials that reported industry funding (39 trials, N=12,050, RR 1.31, 95% CI, 1.21 to 1.43, I^2=79%) reported a smaller effect than trials without industry funding (5 trials, N=431, RR 1.99, 95% CI, 1.29 to 3.16, I^2=41%; p for interaction=0.03; Table 5). There were no interactions between trial quality (p for interaction=0.51), use of an EERW design (p for interaction=0.89), or geographic region (p for interaction=0.22) and effects on likelihood of a pain response. The primary analysis used data for pain response as reported in the trials; results were similar when patients missing from the analysis were considered nonresponders (44 trials, N=13,152, RR 1.35, 95% CI, 1.24 to 1.49, I^2=80%). Findings were also similar when pain response was defined as 50 percent or more improvement or greater than a 5-point improvement on a 0 to 10 scale (26 trials, N=9,485, RR 1.31, 95% CI, 1.18 to 1.47, I^2=70%).

Figure 4. Meta-analysis of likelihood of experiencing a pain response for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; n=number with a pain response; N=overall sample; NR=not reported; PAgonist=partial agonist.

Table 5. Pooled analyses of likelihood of experiencing a pain response for opioids versus placebo

Analysis	Pain, RR (95% CI)	I^2	Number of Trials (N)	p*
All trials[†]	1.35 (1.24 to 1.48)	81%	44 (12,481)	--
Opioid type: Opioid agonist	1.39 (1.24 to 1.60)	76%	20 (4297)	0.47
• **Partial agonist**	1.45 (1.20 to 1.76)	65%	7 (2165)	--
• **Mixed mechanism**	1.27 (1.10 to 1.51)	82%	17 (6019)	--
Pain type: Musculoskeletal	1.29 (1.17 to 1.43)	84%	30 (10,532)	0.16
• **Neuropathic**	1.53 (1.29 to 1.92)	56%	13 (1880)	--
• **Fibromyalgia**	2.16 (1.15 to 4.05)	--	1 (69)	--
Followup: 1 to 3 months	1.35 (1.24 to 1.48)	78%	40 (11,076)	--[‡]
• **3 to 6 months**	1.19 (0.68 to 2.17)	87%	5 (1503)	--
Trial quality: Good	1.10 (1.04 to 1.30)	0%	4 (1280)	0.51
• **Fair**	1.36 (1.24 to 1.51)	79%	34 (10,544)	--
• **Poor**	1.56 (1.03 to 2.56)	63%	6 (657)	--
Opioid dose (mg MED/day): <50	1.36 (1.08 to 1.88)	75%	6 (1665)	0.57
• **50-90**	1.46 (1.23 to 1.86)	73%	12 (2454)	--
• **>90**	1.31 (1.17 to 1.47)	82%	26 (8362)	--
EERW design	1.33 (1.22 to 1.47)	78%	18 (6286)	0.89
• **Non-EERW design**	1.39 (1.19 to 1.65)	79%	26 (8075)	--
EERW design, 2007 or after	1.32 (1.21 to 1.45)	78%	17 (6217)	0.44
• **Non-EERW design**	1.25 (1.07 to 1.47)	76%	19 (5569)	--
Crossover design	1.99 (1.60 to 2.52)	25%	9 (870)	**0.001**
• **Parallel group**	1.27 (1.17 to 1.38)	77%	35 (11,611)	--
Opioid status: Naïve	1.25 (1.14 to 1.38)	0%	9 (1779)	**0.04**
• **Experienced**	1.86 (1.46 to 2.32)	45%	4 (1173)	--
• **Mixed**	1.26 (1.12 to 1.44)	86%	22 (8121)	--
• **Not reported**	1.38 (1.24 to 1.86)	0%	9 (1408)	--
Publication: Prior to 2007	2.09 (1.60 to 2.91)	35%	8 (695)	**0.002**
• **In or after 2007**	1.29 (1.19 to 1.40)	80%	36 (11,786)	--
Region: USA or Canada	1.41 (1.29 to 1.56)	74%	30 (8659)	0.22
• **Europe or Australia**	1.35 (1.01 to 2.02)	79%	9 (1848)	--
• **Asia**	1.17 (0.83 to 1.53)	17%	3 (312)	--
• **Multiple**[§]	1.06 (0.90 to 1.16)	0%	2 (1662)	--
Industry funding: Yes	1.31 (1.21 to 1.43)	79%	39 (12,050)	**0.03**
• **No industry funding**	1.99 (1.29 to 3.16)	41%	5 (431)	--
Numerical scale	1.29 (1.17 to 1.42)	84%	32 (10,792)	**0.03**
• **Categorical scale**	1.60 (1.39 to 1.95)	18%	12 (311)	--
• **All trials, missing=non-responder**	1.35 (1.24 to 1.49)	81%	44 (13,152)	--
• **>50% improvement or >5 point improvement on 0 to 10 scale**	1.31 (1.18 to 1.47)	70%	26 (9485)	--

Note: Statistically significant p values are bolded

Abbreviations: CI=confidence interval; EERW=enriched enrollment randomized withdrawal; MED=morphine equivalent dose; N= total sample size; RR=risk ratio; USA=United States of America.

*p value for interaction

[†]Based on >30% (or closest) improvement; for trials reporting improvement using a categorical scale, at least moderate improvement

[‡]The p for interaction was not calculated because some trials reported both 1 to 3 month and 3 to 6 month outcomes

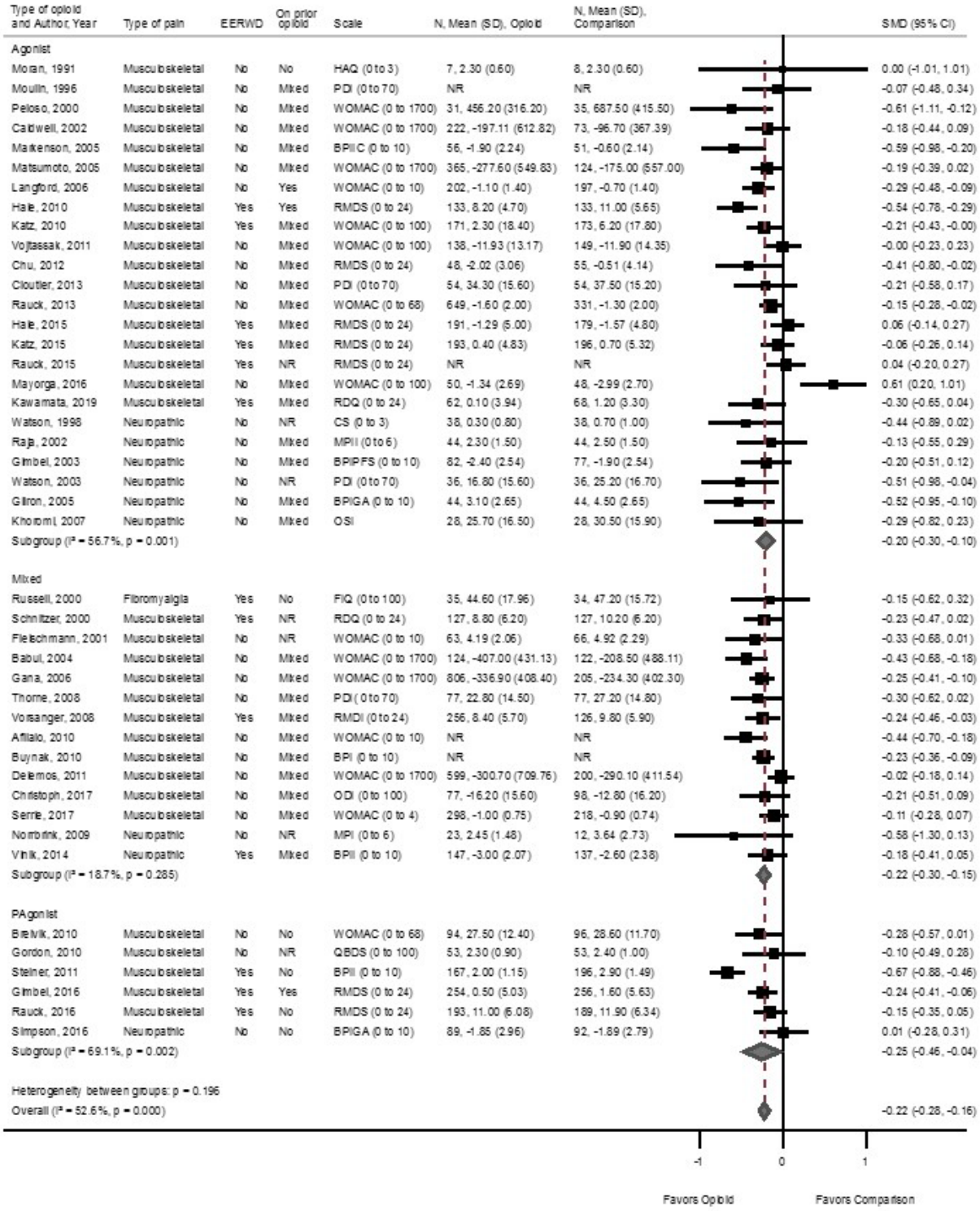
[§]USA/Canada and Europe/Australia

Function

Opioids were associated with a small mean improvement versus placebo in function measured at short-term (1 to <6 months) followup (44 trials, N=12,427, SMD -0.22, 95% CI, -0.28 to -0.16, I^2=53%; Figure 5, Table 3). Measures of function varied; the most commonly utilized measures were the BPI (7 trials, N=2146, mean difference -0.68 point on a 0 to 10 scale, 95% CI, -0.97 to -0.39, I^2=22%),[56,67,69,85,104,107,108,113] the Pain Disability Index (4 trials, N=426, mean difference -2.66 points on a 0 to 70 scale, 95% CI, -7.15 to 0.11, I^2=48%),[61,89,109,119] the Western Ontario and McMaster Universities Arthritis Index for osteoarthritis (15 trials, N=6157, mean difference -3.06 points standardized to a 0 to 100 scale, 95% CI, -5.20 to -1.40, I^2=79%),[50,52,54,58,62,64,66,79,83,86,87,94,96,103,114] and the Roland-Morris Disability Questionnaire (RDQ) for low back pain (10 trials, N=3078, mean difference -0.93 point on a 0 to 24 scale, 95% CI, -1.55 to -0.35, I^2=56%).[60,68,72,75,80,97,99,101,117,126] There were no interactions between trial quality (p for interaction=0.24), use of an EERW design (p for interaction=0.99 overall and 0.43 when restricted to trials published in or after 2007), geographic region (p for interaction=0.57), publication before or after 2007 (p for interaction=0.10), use of crossover design (p for interaction=0.49), or reported industry funding (p=0.23; Table 4). Five trials reported no difference between opioids versus placebo in function but could not be pooled because data were not provided.[65,74,112,121,122]

Only two trials reported effects of opioids versus placebo on the likelihood of experiencing functional improvement; both trials evaluated patients with low back pain. One trial[107,108] (n=539) found the buprenorphine patch associated with slightly increased likelihood of experiencing 30 percent or more improvement in the BPI interference subscale (RR 1.14, 95% CI, 1.04 to 1.25) and one trial[101] (n=254) found no effect of tramadol on the likelihood of attaining a RDQ score of 14 or more (RR 0.72, 95% CI, 0.50 to 1.09).

Figure 5. Meta-analysis of improvement in mean function measures for opioids versus placebo



Abbreviations: BPI=Brief Pain Inventory; BPIGA= Brief Pain Inventory General Activity; BPII=Brief Pain Inventory Inference; BPIIC=Brief Pain Inventory Inference Composite; BPIPFS= Brief Pain Inventory Physical Function Scale; CI=confidence interval; CS= Categorical scale; EERWD=enriched enrollment randomized withdrawal design; FIQ= Fibromyalgia Impact Questionnaire; HAQ= Health Activities Questionnaire; MPI= Multidimensional Pain Inventory; MPII= Multidimensional Pain Inventor Interference; N=overall sample; NR=not reported; ODI= Oswestry Disability Index; OSI=Oswestry Index; PAgonist=partial agonist; PDI= Pain Disability Index; QBDS= Quebec Back Disability Scale; RDQ=Roland-Morris Disability

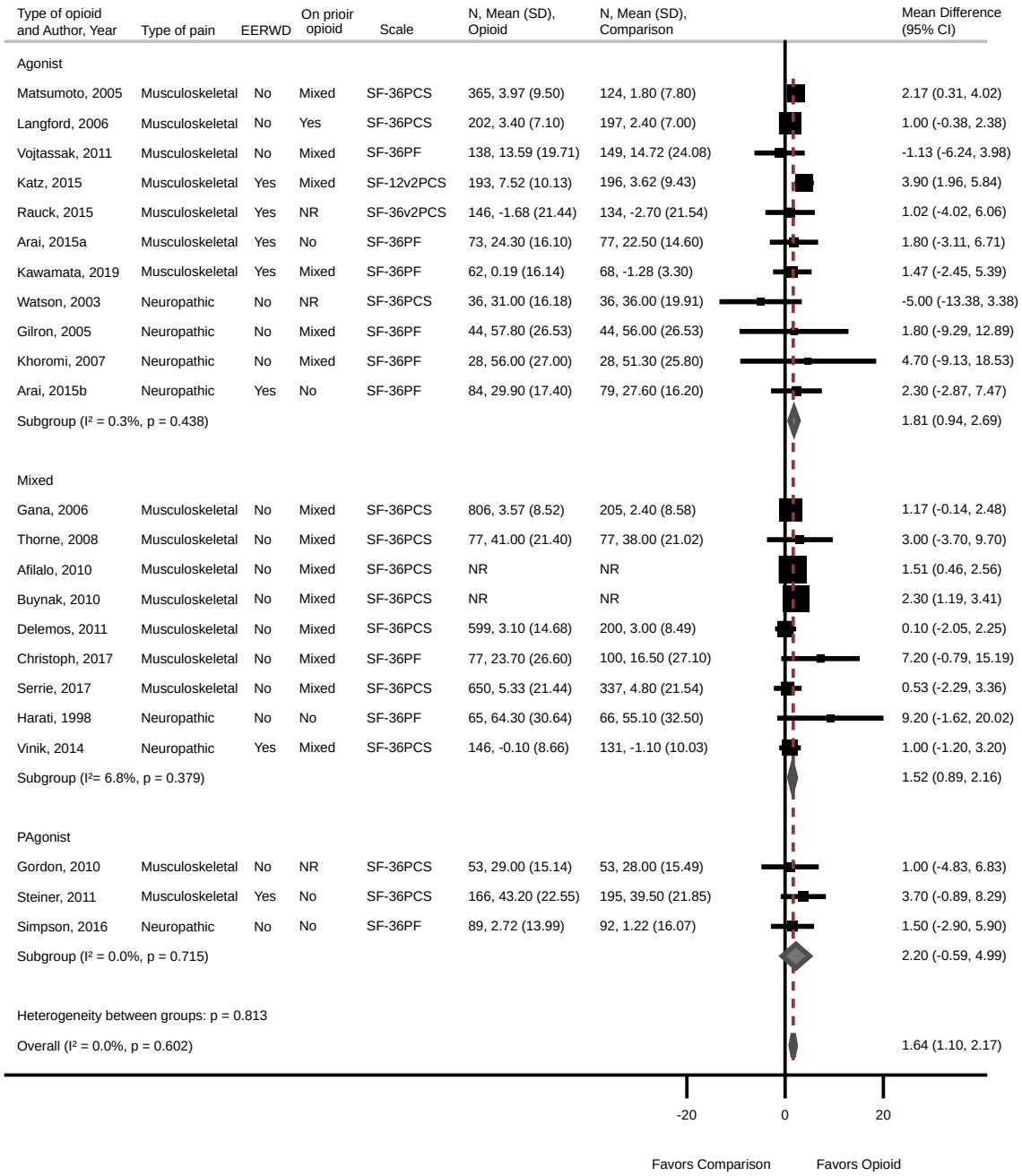
Questionnaire; RMDI= Roland Morris Disability Index; RMDS= Roland Morris Disability Scale; SD=standard deviation; SMD=standardized mean difference; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

Health Status/Quality of Life

Opioids were associated with a beneficial effect of less than 2 points on a 0 to 100 scale (below the 5 point threshold for "small") versus placebo on SF-36 measures of physical health status (PCS or Physical Function Subscale) at short-term (1 to <6 months) followup (23 trials, N=8005, mean difference 1.64 points, 95% CI, 1.10 to 2.17, I^2=0%; Figure 6, Table 6).[50,51,56,59,62,66,67,71,77,80,82,83,86,97,103,104,107-109,113,114,119,126] There was no difference between opioids versus placebo on SF-36 measures of mental health status (MCS, Mental Health Subscale, or Role Emotional Subscale) (21 trials, N=7586, mean difference -0.48 point on a 0 to 100 scale, 95% CI, -1.39 to 0.44, I^2=65%). [50,51,56,59,62,66,67,71,80,82,83,86,97,103,104,107-109,113,119,126] There were no interactions between trial quality, use of an EERW design, publication prior to or after 2007, geographic region, use of a crossover design, or reporting industry funding and effects on SF-36 physical or mental measures (Table 7). Six trials[61,69,70,74,112,121] reported no difference between opioids versus placebo on SF-36 or related measures but could not be pooled because data were not provided; one other trial[65] reported that opioids were superior to placebo on the SF-12 PCS with no difference on the SF-12 MCS, but also did not provide data.

Three trials that used other measures to evaluate quality of life/health status reported results consistent with the SF-36 analysis. One trial found no difference between opioids versus placebo on the Nottingham Health Profile,[53] one trial found opioids associated with greater improvement in the EuroQoL Quality of Life Scale-5 Dimension (EQ-5D) but the data and statistical significance were not reported,[76] and one trial found no difference between opioids versus placebo on the EQ-5D 3-Level version (EQ-5D-3L).[111]

Figure 6. Meta-analysis of improvement in mean SF-36 physical function measures for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD= enriched enrollment randomized withdrawal design; N=sample size; NR=not reported; PAgonist=partial agonist; SD=standard deviation; SF-12v2PCS=Short Form-12 Version 2 Physical Component Scale; SF-36 PCS= Short Form-36 Physical Component Scale; SF-36 PFF=Short Form-36 Physical Function Form.

Table 6. Quality of life, sleep, and mental health outcomes for opioids versus placebo

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Quality of Life*	Sleep*	Mental Health Outcomes*
Afilalo, 2010[50] International Fair	1: 15 weeks 2: 1030 3: Osteoarthritis of knee	1a: Tapentadol SR 200 to 500 mg (mean 350 mg) 1b: Oxycodone SR 40 to 100 mg (mean 70 mg) 2: Placebo	SF-36 PCS 1a: Difference 2.8 (95% CI, 1.56 to 3.95) (ANCOVA) 1b: Difference 0.3 (95% CI, -0.94 to 1.45) (ANCOVA) SF-36 MCS 1a: Difference -1.1 (95% CI, -2.44 to 0.17) 1b: Difference -3.0 (95% CI, -4.34 to -1.72)	NR	NR
Arai, 2015[51] Japan Poor	1: 12 weeks 2: 150 3: Osteoarthritis or low back pain	1: Fentanyl patch 25 to 50 mcg/hour (mean 15.1 mcg/hour) 2: Placebo	SF-36 Physical functioning 1: 24.3 (16.1) 2: 22.5 (14.6) SF-36 Role emotional 1: 49.9 (9.8) 2: 51 (10.4)	NR	NR
Arai, 2015[51] Japan Poor	1: 12 weeks 2: 163 3: Postherpetic neuralgia, complex regional pain syndrome, or chronic postoperative pain	1: Fentanyl patch 25 to 50 mcg/hour (mean 18.6 mcg/hour) 2: Placebo	SF-36 Physical functioning 1: 29.9 (17.4) 2: 27.6 (16.2) SF-36 Role emotional 1: 47.1 (11.1) 2: 47.2 (9.6)	NR	NR
Babul, 2004[52] USA Fair	1: 12 weeks 2: 246 3: Osteoarthritis	1: Tramadol SR 200 to 400 mg (mean 276 mg) 2: Placebo	NR	Chronic Pain Sleep Inventory, overall sleep quality 0 to 100, 100=excellent Difference -6.4 (CI, NR) (scale reversed) (ANCOVA)	NR
Boureau, 2003[53] France Good	1: 6 weeks 2: 127 3: Postherpetic neuralgia	1: Tramadol 10 to 400 mg (mean 276 mg) 2: Placebo	Nottingham Health Profile (0 to 100, 100=maximum perceived distress) 1: 5.7 (6) 2: 6.7 (7)	NR	NR
Breivik, 2010[54] International Fair	1: 24 weeks 2: 199 3: Osteoarthritis	1: Buprenorphine patch 5 to 20 mcg/hour (mean 11.0 mcg/hour) 2: Placebo	NR	Sleep quality, scale not provided No difference (data not provided)	NR
Burch, 2007[55] International Good	1: 12 weeks 2: 646 3: Osteoarthritis	1: Tramadol SR 200 to 300 mg (mean 275 mg) 2: Placebo	NR	NR	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Quality of Life*	Sleep*	Mental Health Outcomes*
Buynak, 2010[56] USA Fair	1: 15 weeks 2: 981 3: Low back pain	1a: Tapentadol SR 200 to 500 mg (mean 313 mg) 1b: Oxycodone SR 40 to 100 mg (mean 53 mg) 2: Placebo	SF-36 PCS 1a: Difference 2.3 (SE 0.65) (ANCOVA) 1b: Difference 2.3 (SE 0.65) (ANCOVA) SF-36 MCS 1a: Difference 0.1 (SE 0.70) (ANCOVA) 1b: Difference -0.7 (SE 0.69) (ANCOVA)	Sleep questionnaire, categorical scale (4 categories); distribution of ratings improved with tapentadol (p=0.003) but not oxycodone (p=0.091) vs. placebo, data otherwise not provided	NR
Caldwell, 1999[57] USA Fair	1: 4 weeks 2: 70 3: Osteoarthritis	1: Oxycodone SR 20 to 60 mg (mean 40 mg) 2: Placebo	NR	1 to 5 scale (5=excellent) 1: 2.3 (NR) 2: 3.4 (NR) (scale reversed)	NR
Caldwell, 2002[58] USA Fair	1: 4 weeks 2: 295 3: Osteoarthritis	1: Morphine SR 30 mg, qd or bd (mean NR) 2: Placebo	NR	Overall quality of sleep 0 to 100 VAS, higher=better sleep 1: Change -10.9 (NR) 2: Change -2 (NR) (scale reversed)	NR
Christoph, 2017[59] Germany Fair	1: 14 weeks 2: 252 3: Low back pain	1: Tapentadol SR 400 mg (mean NR) 2: Placebo	SF-36 Physical functioning 1: Change 23.7 (26.6) 2: Change 16.5 (27.1) SF-36 Mental health 1: Change 11.8 (22.7) 2: Change 9.5 (23.3)	Chronic Pain Sleep Inventory overall, 0 to 100, 100=excellent 1: 29.1 (25.6) 2: 43 (28.7)	NR
Chu, 2012[60] USA Fair	1: 4.5 weeks 2: 139 3: Low back pain	1: Morphine SR 30 to 120 mg (mean 78 mg) 2: Placebo	NR	NR	BDI 0 to 63, % change (SD) 1: 13 (87.6) 2: -5.8 (101.4)
Cloutier, 2013[61] Canada Fair	1: 4 weeks 2: 83 3: Low back pain	1: Oxycodone SR 20 to 80 mg (mean 36 mg) 2: Placebo	SF-36 no differences, data NR	Pain and Sleep Questionnaire 0 to 500, 500=worse sleep 1: 200.2 (128.2) 2: 257.4 (127.8)	NR
DeLemos, 2011[62] USA Fair	1: 12 weeks 2: 808 3: Osteoarthritis	1: Tramadol SR 100, 200, or 300 mg (mean 200 mg) 2: Placebo	SF-36 PCS 1: Change 3.1 (0.6) 2: Change 3.0 (0.6) (ANCOVA) SF-36 MCS 1: Change -0.5 (0.6) 2: Change -0.3 (0.6) (ANCOVA)	Chronic Pain Sleep Inventory 0 to 100, 100=excellent 1: -12.7 (2) 2: -8.6 (2.1) (ANCOVA)	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Quality of Life*	Sleep*	Mental Health Outcomes*
Fishman, 2007[63] USA Canada Fair	1: 12 weeks 2: 552 3: Osteoarthritis	1: Tramadol SR 100, 200, or 300 mg (mean 201 mg) 2: Placebo	NR	NR	NR
Fleischmann, 2001[64] USA Poor	1: 12 weeks 2: 129 3: Osteoarthritis	1: Tramadol 200 to 400 mg (mean NR) 2: Placebo	NR	NR	NR
Friedmann, 2011[65] USA Fair	1: 12 weeks 2: 412 3: Osteoarthritis	1: Oxycodone SR up to 40 mg (mean 27.5 mg) 2: Placebo	SF-12 PCS opioid superior (p=0.003), data otherwise NR SF-12 MCS no difference (p=0.06), data otherwise NR	NR	NR
Gana, 2006[66] (also Vorsanger 2007) USA Fair	1: 12 weeks 2: 1020 3: Osteoarthritis	1: Tramadol SR 100 to 400 mg (mean NR) 2: Placebo	SF-36 PCS 1: Change 3.57 (8.52) 2: Change 2.4 (8.58) (ANCOVA) SF-36 MCS 1: Change 0.13 (8.52) 2: Change -0.3 (8.58) (ANCOVA)	Overall sleep quality 0 to 100, 100=excellent 1: -15 (NR) 2: -9 (NR) (scale reversed)	NR
Gilron, 2005[67] Canada Fair	1: 5 weeks 2: 57 3: Diabetic neuropathy	1: Morphine up to 120 mg (mean 45 mg) 2: Lorazepam	SF-36 PCS 1: 57.8 (4) 2: 56 (4) SF-36 MCS 1: 78 (2.6) 2: 73.4 (2.6)	BPI, sleep 0 to 10, 10=pain completely interferes 1: 1.6 (0.4) 2: 3.4 (0.4)	BDI 0 to 63 1: 6.7 (1) 2: 8.5 (1)
Gimbel, 2003[69] USA Fair	1: 6 weeks 2: 159 3: Diabetic neuropathy	1: Oxycodone SR 10 to 120 mg (mean 37 mg) 2: Placebo	SF-36 (no difference reported, no data)	Sleep quality 0 to 10, 10=excellent 1: -1.2 (0.24) 2: -0.5 (0.24) (scale reversed) (ANCOVA)	NR
Gimbel, 2016[68] USA Fair	1: 12 weeks 2: 511 3: Low back pain	1: Buprenorphine buccal 300 to 1800 mcg (mean 1320 mcg) 2: Placebo	NR	NR	NR
Gordon, 2010[70] Canada Fair	1: 4 weeks 2: 78 3: Low back pain	1: Buprenorphine patch 10 to 30 mcg/hour (mean 30 mcg/hour) 2: Placebo	SF-36 PCS, % change (SD) 1: 18.2 (NR) 2: 14.3% (NR) SF-36 MCS no difference (data not provided)	Pain and Sleep Questionnaire, total 0 to 500, 500=worse sleep 1: 177.6 (125.5) 2: 232.9 (131.9)	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Quality of Life*	Sleep*	Mental Health Outcomes*
Gordon, 2010[71] Canada Fair	1: 4 weeks 2: 79 3: Low back pain	1: Buprenorphine patch 5 to 20 mcg/hour (mean 15.5 mcg/hour) 2: Placebo	SF-36 PCS 1: 29 (NR) 2: 28 (NR) SF-36 MCS 1: 45 (NR) 2: 46 (NR)	Pain and Sleep Questionnaire 0 to 500, 500=worse sleep, total 1: 172.4 (122.8) 2: 178.2 (112.6)	NR
Hale, 2007[73] USA Fair	1: 12 weeks 2: 143 3: Low back pain	1: Oxymorphone SR (mean 80 mg) 2: Placebo	NR	NR	NR
Hale, 2010[72] (also Nalamachu 2014)[91] USA Fair	1: 12 weeks 2: 268 3: Low back pain	1: Hydromorphone SR 12 to 64 mg (mean 37.3 mg) 2: Placebo	NR	NR	NR
Hale, 2015[75] USA Good	1: 12 weeks 2: 371 3: Low back pain	1: Hydrocodone SR 60 to 180 mg (mean 100 mg) 2: Placebo	NR	MOS Sleep Scale No differences (data NR)	NR
Hale, 2015[74] USA Fair	1: 12 weeks 2: 391 3: Low back pain or osteoarthritis	1: Hydrocodone SR 30 to 180 mg (mean NR) 2: Placebo	SF-36 "no differences on most subscales" (data NR)	NR	NR
Hanna, 2008[76] UK Good	1: 12 weeks 2: 338 3: Diabetic neuropathy	1: Oxycodone SR (doses and mean NR) 2: Placebo	EQ-5D greater improvement in oxycodone group, data and statistical significance NR	Not specified (fewer nights disturbed sleep with oxycodone than placebo, p<0.05, data otherwise NR)	NR
Harati, 1998[77] USA Fair	1: 6 weeks 2: 131 3: Diabetic neuropathy	1: Tramadol up to 400 mg (mean 210 mg) 2: Placebo	SF-36 Physical Functioning 1: 64.3 (SE 3.8) 2: 55.1 (SE 4)	Not specified No difference reported in text (no data)	Not specified No difference reported in text (no data)
Huse, 2001[78] Germany Poor	1: 4 weeks 2: 12 3: Phantom limb pain	1: Morphine SR 70 to 300 mg (mean NR) 2: Placebo	NR	NR	NR
Katz, 2007[81] USA Fair	1: 12 weeks 2: 205 3: Low back pain	1: Oxymorphone SR (mean 39.2 mg) 2: Placebo	NR	NR	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Quality of Life*	Sleep*	Mental Health Outcomes*
Katz, 2010[79] USA Fair	1: 12 weeks 2: 344 3: Osteoarthritis	1: Morphine SR 20 to 160 mg (mean 43.5 mg) 2: Placebo	NR	MOS Sleep Scale, sleep adequacy 0 to 100, 100=better sleep 1: 2.2 (21.4) 2: 5.4 (24.5) (scale reversed)	BDI 0 to 63 1: -1.4 (4.5) 2: -0.9 (3.9)
Katz, 2015[80] USA Fair	1: 12 weeks 2: 389 3: Low back pain	1: Oxycodone SR 40 to 160 mg (mean 78 mg) 2: Placebo	SF-12v2 PCS 1: 7.52 (10.13) 2: 3.62 (9.43) (ANCOVA) SF-12v2 MCS 1: 2.55 (10.42) 2: 0.67 (11.17) (ANCOVA)	NR	NR
Kawamata, 2019[126] Japan Fair	1: 5 weeks 2: 130 3: Low back pain	1: Oxycodone SR 10 to 80 mg (mean NR) 2: Placebo	SF-36 Physical functioning 1: 0.19 (16.14) 2: -1.28 (3.30) SF-36 Mental health 1: 2.85 (14.09) 2: 2.00 (13.94)	BPI, sleep 0 to 10, 10=pain completely interferes 1: -0.10 (1.57) 2: 0.30 (1.65)	NR
Khoromi, 2007[82] USA Fair	1: 7 weeks 2: 55 3: Low back pain with radiculopathy	1: Morphine SR up to 90 mg (mean 62 mg) 2: Placebo	SF-36 Physical functioning 1: 56 (27) 2: 51.3 (25.8) SF-36 Mental health 1: 68 (21) 2: 69 (24)	NR	BDI 0 to 63 1: 9.6 (8.5) 2: 9 (8.5)
Langford, 2006[83] Europe Fair	1: 6 weeks 2: 416 3: Osteoarthritis	1: Fentanyl 25 to 100 mg (mean 43.9 mcg/hour) 2: Placebo	SF-36 PCS 1: 3.4 (7.1) 2: 2.4 (7) SF-36 MCS 1: -0.9 (12.8) 2: 1.1 (9.8)	NR	NR
Lin, 2016[84] USA Poor	1: 4.5 weeks 2: 21 3: Low back pain	1: Morphine SR 30 to 120 mg (mean 72 mg) 2: Placebo	NR	NR	NR
Markenson, 2005[85] USA Fair	1: 13 weeks 2: 109 3: Osteoarthritis	1: Oxycodone SR 20 to 120 mg (mean 44 mg) 2: Placebo	NR	BPI, sleep 0 to 10, 10=pain completely interferes 1: -2.8 (0.4) 2: -0.9 (0.4) (ANCOVA)	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Quality of Life*	Sleep*	Mental Health Outcomes*
Matsumoto, 2005[86] USA Fair	1: 4 weeks 2: 491 3: Osteoarthritis	1a: Oxymorphone SR 40 to 80 mg (mean NR) 1b: Oxycodone SR 40mg (mean NR) 2: Placebo	SF-36 PCS 1a: 3.95 (9.8) 1b: 40 (8.9) 2: 1.8 (7.8) (ANCOVA) SF-36 MCS, 1a: 0.54 (12) 1b: 0.8 (10.1) 2: 2.2 (10) (ANCOVA)	Overall sleep quality 0 to 100 VAS 1a: -16 (34) 1b: -15.3 (29.1) 2: -7.7 (27.8) (ANCOVA) (scale reversed)	NR
Mayorga, 2016[87] USA Fair	1: 16 weeks 2: 98 3: Osteoarthritis	1: Oxycodone SR 40 to 100 mg (mean NR) 2: Placebo	NR	NR	NR
Moran, 1991[88] UK Poor	1: 5 weeks 2: 20 3: Rheumatoid arthritis	1: CR Morphine 20 to 120 mg (mean NR) 2: Placebo	NR	NR	NR
Moulin, 1996[89] Canada Poor	1: 6 weeks 2: 61 3: Mixed (primarily musculoskeletal)	1: Morphine up to 120 mg (mean 83.5 mg) 2: Benztropine	NR	NR	Symptom Check List-90 30 to 81 Difference 0.0 (95% CI, -1.9 to 1.9)
Munera, 2010[90] USA Fair	1: 4 weeks 2: 315 3: Osteoarthritis	1: Buprenorphine patch 5-20 mcg/hour (mean NR) 2: Placebo	NR	NR	NR
Niesters, 2014[92] The Netherlands Good	1: 4 weeks 2: 25 3: Diabetic neuropathy	1: Tapentadol SR 200 mg, titrated to 500 mg (mean 433 mg) 2: Placebo	NR	NR	NR
Norrbrink, 2009[93] Sweden Fair	1: 4 weeks 2: 36 3: Neuropathic pain after spinal cord injury	1: Tramadol 150 to 400 mg (median 250 mg) 2: Placebo	NR	Sleep quality 1 to 5, 5=worse sleep quality, median (IQR) 1: 2.7 (2.3 to 3.2) 2: 2.9 (2.4 to 3.4)	HAD Anxiety 0 to 21, median (IQR) 1: 6 (1 to 8) 2: 9 (5.5 to 12) HAD Depression 0 to 21, median (IQR) 1: 3 (2 to 6) 2: 5 (2 to 4.5)
Peloso, 2000[94] Canada Fair	1: 4 weeks 2: 103 3: Osteoarthritis	1: Codeine SR 100 to 400 mg (mean 312 mg) 2: Placebo	NR	Need medication to sleep 0 to 100, higher=worse sleep 1: 9.3 (21.9) 2: 22.3 (30.3)	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Quality of Life*	Sleep*	Mental Health Outcomes*
Raja, 2002[95] USA Fair	1: 8 weeks 2: 76 3: Postherpetic neuralgia	1: Morphine SR up to 240 mg (mean 91 mg) 2: Placebo	NR	Multidimensional Pain Inventory, sleep 0 to 6 1: 2.5 (1.7) 2: 2.9 (1.9)	BDI 0 to 63 1: 12.1 (8.9) 2: 9.9 (7.9)
Rauck, 2013[96] USA Poor	1: 14 weeks 2: 990 3: Osteoarthritis	1: Hydromorphone SR 8 or 16 mg (mean 12 mg) 2: Placebo	NR	MOS Sleep Scale, Sleep Problem Index II 0 to 100, 100=worse sleep, mean change (SD) 1: -13.5 (32.2) 2: -9.1 (26.2) (ANCOVA)	NR
Rauck, 2014[98] USA Poor	1: 12 weeks 2: 302 3: Low back pain	1: Hydrocodone SR 40 to 200 mg (mean 119 mg) 2: Placebo	NR	NR	NR
Rauck, 2015[97] USA Fair	1: 12 weeks 2: 281 3: Low back pain	1: Oxycodone SR 20 to 160 mg (mean 64 mg) + Naltrexone 2: Placebo	SF-36v2 PCS Difference: 1.02 (CI, NR) (ANCOVA) SF-36v2 MCS Difference: -0.69 (CI, NR) (ANCOVA)	NR	NR
Rauck, 2016[99] USA Fair	1: 12 weeks 2: 461 3: Low back pain	1: Buprenorphine buccal 300 to 900 mcg (mean 660 mcg) 2: Placebo	NR	MOS Sleep Scale No difference (data NR)	NR
Russell, 2000[100] USA Fair	1: 6 weeks 2: 69 3: Fibromyalgia	1: Tramadol 50 to 400 mg (mean NR) 2: Placebo	NR	NR	NR
Schnitzer, 2000[101] USA Poor	1: 4 weeks 2: 254 3: Low back pain	1: Tramadol 200 to 400 mg (mean NR) 2: Placebo	NR	NR	NR
Schwartz, 2011[102] USA Fair	1: 12 weeks 2: 395 3: Diabetic neuropathy	1: Tapentadol 100 to 250 mg (mean NR) 2: Placebo	NR	NR	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Quality of Life*	Sleep*	Mental Health Outcomes*
Serrie, 2017[103] Europe Fair	1: 15 weeks 2: 990 3: Knee pain	1a: Tapentadol SR 200 to 500 mg (mean 315 mg) 1b: Oxycodone SR 40 to 100 mg (mean 54 mg) 2: Placebo	SF-36 PCS, mean change (SD) 1a: 6.4 (NR) 1b: 4.3 (NR) 2: 4.8 (NR) (ANCOVA) SF-36 MCS, mean change (SD) 1a: 1.1 (NR) 1b: -0.3 (NR) 2: 1.7 (NR) (ANCOVA)	No difference in proportion with sleep good or excellent (60.2% vs. 54% vs. 54.6%)	NR
Simpson, 2016[104] Australia Fair	1: 12 weeks 2: 186 3: Diabetic neuropathy	1: Buprenorphine patch 5 to 40 mcg/hour (mean 20 mcg/hour) 2: Placebo	SF-36 Physical functioning 1: Change 2.72 (13.99) 2: Change 1.22 (16.07) (linear mixed model) SF-36 Mental health 1: Change 2.23 (16.69) 2: Change 5.52 (14.74) (linear mixed model)	Daily Sleep Interference Scale 0 to 10, 10=worst sleep 1: -3.53 (2.51) 2: -2.38 (2.59) (generalized linear mixed model)	BDI-II total score 0 to 63 1: -1.79 (7.64) 2: -3.93 (6.01) (generalized linear mixed)
Sindrup, 1999[106] Denmark Poor	1: 4 weeks 2: 45 3: Polyneuropathy	1: Tramadol up to 400 mg (mean 364 mg) 2: Placebo	NR	NR	NR
Sindrup, 2012[105] Denmark; Germany Fair	1: 4 weeks 2: 64 3: Polyneuropathy	1: Tramadol SR 200 mg 2: Placebo	NR	Sleep Problem Scale 0 to 20, 20=greater sleep disturbance Difference -0.6 (SE 0.43)	Major Depression Inventory 0 to 50, 50=worse depression Difference -1.2 (SE 1.13)
Steiner, 2011[107] (also Yarlas, 2013)[123] USA Fair	1: 12 weeks 2: 541 3: Low back pain	1: Buprenorphine patch 10 or 20 mcg/hour (mean NR) 2: Placebo	SF-36 PCS 1: 43.2 (NR) 2: 39.5 (NR) SF-36 MCS 1: 51.8 (NR) 2: 48.4 (NR)	MOS Sleep Scale, sleep disturbance subscale 0 to 100, 100=greater sleep disturbance Difference -4.4 (95% CI, -7.5 to -1.3)	NR
Thorne, 2008[109] Canada Fair	1: 4 weeks 2: 116 3: Osteoarthritis	1: Tramadol SR 150 to 400 mg (mean 340 mg) 2: Placebo	SF-36 PCS (0 to 100) 1: 41 (NR) 2: 38 (NR) SF-36 MCS (0 to 100) 1: 43 (NR) 2: 41 (NR)	Pain and Sleep Questionnaire, total pain and sleep 0 to 500, higher=worse sleep 1: 104.7 (98) 2: 141 (108.2)	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Quality of Life*	Sleep*	Mental Health Outcomes*
Tominaga, 2016[110] Japan Poor	1: 12 weeks 2: 91 3: Osteoarthritis or low back pain	1: Tapentadol SR 50 to 500 mg (mean 237 mg) 2: Placebo	NR	NR	NR
Tominaga, 2016[110] Japan Poor	1: 12 weeks 2: 91 3: Diabetic neuropathy or postherpetic neuralgia	1: Tapentadol SR 50 to 500 mg (mean 274 mg) 2: Placebo	NR	NR	NR
Trenkwalder, 2015[111] Poland Fair	1: 16 weeks 2: 202 3: Parkinson's disease	1: Oxycodone SR 10 to 40 mg (mean 19 mg) + Naloxone 5 to 20 mg 2: Placebo	EQ-5D-3L Difference 0.1 (95% CI, 0.0 to 0.15) (mixed model)	NR	HAD Anxiety 0 to 21 Difference 0.7 (95% CI, 0.1 to 1.3) (mixed model) HAD Depression 0 to 21 Difference 0.3 (95% CI, -0.3 to 0.9) (mixed model)
Uberall, 2012[112] Germany Fair	1: 4 weeks 2: 240 3: Low back pain	1: Tramadol SR 200 mg 2: Placebo	SF-12 no differences, data NR	NR	NR
Vinik, 2014[113] USA Fair	1: 12 weeks 2: 318 3: Diabetic neuropathy	1: Tapentadol SR 200 to 500 mg (mean NR) 2: Placebo	SF-36 PCS 1: -0.1 (8.66) 2: -1.1 (10.03) (ANCOVA) SF-36 MCS 1: 0.1 (6.52) 2: -2.3 (6.4) (ANCOVA)	NR	NR
Vojtassak, 2011[114] Slovakia; UK Fair	1: 16 weeks 2: 288 3: Osteoarthritis	1: Oxymorphone SR 4 mg (mean NR) 2: Placebo	SF-36 physical functioning subscale 1: 13.59 (19.72) 2: 14.72 (24.08) (mixed model)	MOS Sleep subscale, Index I score 0 to 100, 100=greater sleep disturbance 1: Change -5.77 (17.45) 2: Change -5.65 (14.3) (mixed model)	NR
Vondrackova, 2008[115] Czech; Republic; Germany Fair	1: 12 weeks 2: 464 3: Low back pain	1: Oxycodone SR 20 or 40 mg 1b: Oxycodone SR + Naloxone 20 or 40 mg + 10 or 20 mg (mean NR) 2: Placebo	NR	BPI-SF, improved vs. placebo (p=0.003), data not provided BPI-SF, improved vs. placebo (p=0.006), data not provided	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Quality of Life*	Sleep*	Mental Health Outcomes*
Vorsanger, 2008[117] USA Fair	1: 12 weeks 2: 386 3: Low back pain	1: Tramadol SR 200 or 300 mg (mean NR) 2: Placebo	NR	Overall sleep quality 0 to 100 VAS, higher=better sleep 1: 48 (25.7) 2: 55.3 (25.8) (scale reversed)	NR
Watson, 1998[118] Canada Fair	1: 4 weeks 2: 50 3: Postherpetic neuralgia	1: Oxycodone 20 to 60 mg (mean 45 mg) 2: Placebo	NR	NR	POMS and BDI No difference reported in test (no data)
Watson, 2003[119] Canada Fair	1: 4 weeks 2: 45 3: Diabetic neuropathy	1: Oxycodone SR 20 to 80 mg (mean 40 mg) 2: Placebo	SF-36 PCS 1: 31 (NR) 2: 36 (NR) SF-36 MCS 1: 38 (NR) 2: 43 (NR)	NR	NR
Webster, 2006[120] USA Fair	1: 6 weeks 2: 307 3: Low back pain	1: Oxycodone 10 to 80 mg (mean 39 mg) 2: Placebo	NR	NR	NR
Wen, 2015[121] USA Fair	1: 12 weeks 2: 588 3: Low back pain	1: Hydrocodone SR 20 to 120 mg (mean NR) 2: Placebo	SF-36 No differences (data NR)	MOS Sleep Scale No difference (data NR)	NR
Wu, 2008[122] USA Fair	1: 6 weeks 2: 60 3: Postamputation pain	1: Morphine SR 30 to 180 mg (mean 112 mg) 2: Placebo	NR	NR	NR

Abbreviations: ANCOVA=analysis of covariance; bd= twice a day; BDI=Beck Depression Scale; BPI=Brief Pain Inventory; BPI-SF=Brief Pain Inventory short form; CI=confidence interval; HAD=Hospital Anxiety and Depression Scale; IQR=interquartile range; MOS=Medical Outcomes Study; NR=not reported; POMS=Profile of Mood States; qd=once a day; SD=standard deviation; SE=standard error; SF 12v2 PCS=Short Form – 12 items Physical Component Summary; SF-36 MCS= Short Form-36 Mental Component Summary; SF-36 PCS=Short Form-36 Physical Component Summary; SR=sustained release; VAS=Visual Analog Scale.

*Mean (SD), unless otherwise specified

Table 7. Pooled analyses of improvement in SF-36 measures of physical and mental health status for opioids versus placebo

Analysis	SF-36 PCS or Physical Functioning Subscale, MD (95% CI) on 0 to 100 Scale*	I^2	Number of Trials (N)	p†	SF-36 MCS or Mental Health Subscale, MD (95% CI) on 0 to 100 Scale*	I^2	Number of Trials (N)	p†
All trials	1.64 (1.10 to 2.17)	0%	23 (8005)	--	-0.48 (-1.39 to 0.44)	65%	21 (7586)	--
Opioid type: Opioid agonist	1.82 (0.48 to 2.96)	0.3%	11 (2503)	0.80	-1.78 (-2.76 to -0.58)	8%	10 (2216)	0.16
• **Partial agonist**	2.20 (-0.82 to 5.13)	0%	3 (648)	--	0.26 (-4.82 to 4.54)	75%	3 (648)	--
• **Mixed mechanism**	1.54 (0.82 to 2.15)	6.8%	9 (4854)	--	-0.01 (-1.11 to 1.27)	74%	8 (4722)	--
Pain type: Musculoskeletal	1.68 (1.09 to 2.27)	0%	16 (7037)	0.67	-0.61 (-1.48 to 0.32)	62%	15 (6749)	0.65
• **Neuropathic**	1.26 (-0.53 to 3.29)	0%	7 (968)	--	-0.31 (-3.62 to 2.75)	67%	6 (837)	--
• **Fibromyalgia**	No studies	--	--	--	No studies	--	--	--
Followup: 1 to 3 months	1.66 (1.10 to 2.20)	0%	21 (6841)	--	-0.46 (-1.46 to 0.52)	67%	19 (6423)	--
• **3 to 6 months**	1.27 (-2.74 to 9.49)	58%	2 (1164)	--	-1.11 (-3.25 to 2.76)	0.2%	2 (1163)	--
Trial quality: Good	No studies	--	--	0.83	No studies	--	--	--
• **Fair**	1.64 (1.07 to 2.17)	0%	21 (7692)	--	-0.47 (-1.48 to 0.54)	68%	19 (7273)	0.94
• **Poor**	2.04 (-2.04 to 6.13)	0%	2 (313)	--	-0.59 (-3.27 to 2.08)	0%	2 (313)	--
Opioid dose (mg MED/day): <50	0.66 (-1.03 to 2.98)	0%	6 (1618)	0.23	-0.20 (-0.40 to 0.00)	0%	4 (1200)	0.79
• **50-90**	1.06 (-0.26 to 2.25)	0%	6 (2410)	--	0.29 (-2.53 to 2.01)	42%	5 (1423)	--
• **>90**	1.90 (1.28 to 2.66)	0%	11 (3977)	--	-0.73 (-2.04 to 0.57)	75%	12 (4963)	--
EERW design	2.38 (0.79 to 3.79)	0%	7 (1750)	0.17	0.28 (-1.76 to 2.25)	76%	7 (1750)	0.22
• **Non-EERW design**	1.49 (0.89 to 2.02)	0%	16 (6255)	--	-0.80 (-1.66 to -0.05)	55%	14 (5836)	--
EERW design, 2007 or after	2.38 (0.79 to 3.79)	0%	7 (1750)	0.28	0.28 (-1.76 to 2.25)	76%	7 (1750)	0.36
• **Non-EERW design**	1.61 (0.60 to 2.32)	0%	10 (4065)	--	-0.70 (-1.64 to 0.21)	51%	9 (3777)	--
Crossover design	0.81 (-3.00 to 4.55)	0%	5 (476)	0.65	-0.28 (-3.91 to 3.51)	52%	5 (476)	0.86
• **Parallel group**	1.66 (1.12 to 2.20)	0%	18 (7529)	--	-0.51 (-1.47 to 0.45)	69%	16 (7110)	--
Opioid status: Naïve	2.64 (0.32 to 5.02)	0%	5 (986)	0.51	0.20 (-3.19 to 3.04)	67%	4 (855)	0.55
• **Experienced**	1.00 (-0.38 to 2.38)	--	1 (399)	--	-2.00 (-4.24 to 0.24)	--	1 (399)	--
• **Mixed**	1.72 (1.05 to 2.35)	4%	14 (6162)	--	-0.33 (-1.39 to 0.85)	69%	13 (5874)	--
• **Not reported**	-0.02 (-4.52 to 3.61)	0%	3 (458)	--	-1.77 (-4.98 to 0.80)	26%	3 (458)	--
Publication: Prior to 2007	1.30 (0.43 to 2.25)	5.4%	6 (2190)	0.34	-1.16 (-3.40 to 0.92)	65%	5 (2059)	0.38
• **In or after 2007**	1.81 (1.03 to 2.50)	0%	17 (5815)	--	-0.26 (-1.31 to 0.82)	66%	16 (5527)	--
Region: USA or Canada	1.87 (0.99 to 2.72)	11%	14 (4850)	0.69	-0.05 (-1.39 to 1.24)	70%	13 (4719)	0.48
• **Europe or Australia**	0.98 (-0.29 to 2.30)	0%	5 (2031)	--	-1.56 (-2.98 to -0.17)	0%	4 (1743)	--
• **Asia**	1.78 (-0.90 to 4.51)	0%	3 (443)	--	-0.33 (-2.45 to 1.91)	0%	3 (443)	--
• **Multiple‡**	1.51 (-0.70 to 3.72)	--	1 (681)	--	-2.08 (-3.22 to 0.93)	--	1 (681)	--
Industry funding: Yes	1.64 (1.09 to 2.17)	0%	21 (7861)	0.77	-0.54 (-1.48 to 0.37)	67%	19 (7442)	0.31
• **No industry funding**	2.93 (-7.02 to 13.28)	0%	2 (144)	--	3.08 (-6.03 to 10.45)	0%	2 (144)	--

Abbreviations: CI=confidence interval; EERW=enriched enrollment randomized withdrawal; MCS=Mental Health Component Score; MD = mean difference; MED=morphine equivalent dose; N=total sample size; PCS=Physical Health Component Score; SF-36=Short-Form 36-item.

*Positive results indicate improved health status

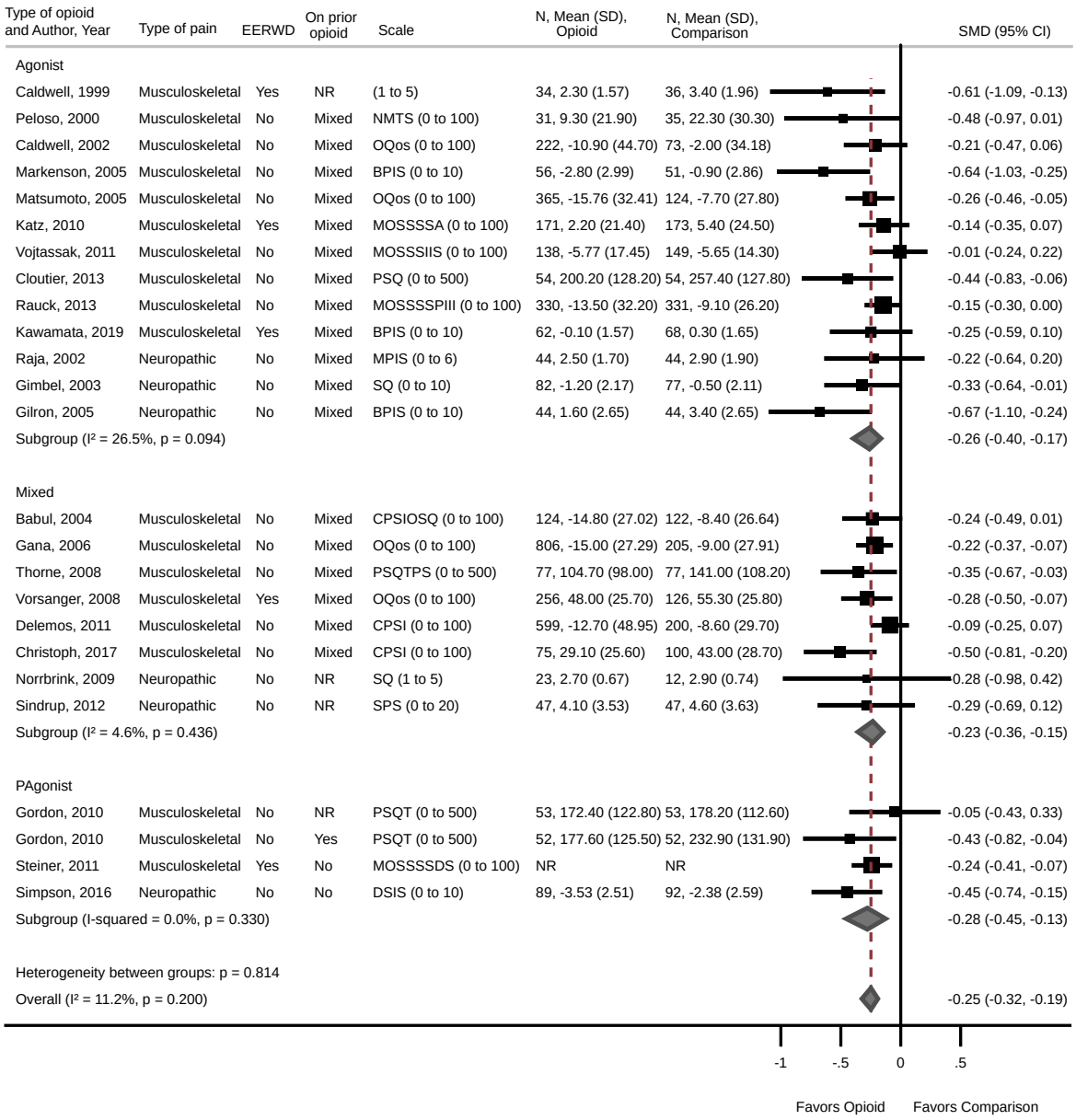
†p value is for interaction

‡USA/Canada and Europe/Australia

Sleep

Opioids were associated with a small mean improvement in sleep quality versus placebo at short-term (1 to <6 months) followup (25 trials, N=6720, SMD -0.25, 95% CI, -0.32 to -0.19, I^2=11%; Figure 7, Table 6).[52,57-59,61,62,66,67,69-71,79,85,86,93-96,104,105,107-109,114,117,126] Measures of sleep varied; the most commonly utilized measures were the Medical Outcomes Study Sleep Scale (4 trials, N=1833, mean difference -3.04 points on a 0 to 100 scale, 95% CI, -5.49 to -0.53, I^2=15%),[79,96,107,108,114] the Pain and Sleep Questionnaire (4 trials, N=364, mean difference -37.01 points on a 0 to 500 scale, 95% CI, -58.22 to -15.80, I^2=1.9%),[61,70,71,109] the Chronic Pain Sleep Inventory (3 trials, N=1220, mean difference -7.58 points on a 0 to 100 scale, 95% CI, -14.20 to -1.76, I^2=39%),[52,59,62] and the BPI sleep item (3 trials, N=325, mean difference -1.22 on a 0 to 10 scale, 95% CI -2.52 to -0.13).[67,85,126] There were no interactions between trial quality (p for interaction=0.29), use of an EERW design (p for interaction=0.92), publication prior to or after 2007 (p for interaction=0.17), geographic region (p for interaction=0.96), use of a crossover design (p for interaction=0.20), or reporting industry funding (p for interaction=0.27) and effects on sleep (Table 8). Five trials[54,75,77,99,121] that reported no difference between opioids versus placebo in sleep quality and three trials[56,76,115] that reported improved sleep quality with opioids could not be pooled because data were not provided.

Figure 7. Meta-analysis of improvement in mean sleep measures for opioid versus placebo



Abbreviations: BPIS=Brief Pain Inventory Sleep; CI=confidence interval; CPSI= Chronic Pain Sleep Inventory; CPSIOSQ= Chronic Pain Sleep Inventory Overall Sleep Quality; DSIS= Daily Sleep Interference Scale; EERWD= enriched enrollment randomized withdrawal design; MOSSSIIS= Medical Outcomes Study Sleep Scale Index I Score; MOSSSSA=Medical Outcomes Study Sleep Scale Sleep Adequacy; MOSSSSDS= Medical Outcomes Study Sleep Scale Sleep Disturbance Subscale; MOSSSSPIII= Medical Outcomes Study Sleep Scale Sleep Problem Index II; MPIS= Multidimensional Pain Inventory Sleep; N=samle size; NMTS=need medication to sleep; NR=not reported; OQos=Overall Quality of sleep; PAgonist=partial agonist; PSQ= Pain and Sleep Questionnaire; PSQT= Pain and Sleep Questionnaire Total; PSQTPS= Pain and Sleep Questionnaire Total Pain and Sleep; SD=standard deviation; SMD=standardized mean difference; SPS= Sleep Problem Scale; SQ=Sleep quality.

Table 8. Pooled analyses of mean improvement in sleep and depression measures for opioids versus placebo

Analysis	Sleep, SMD (95% CI)*	I^2	Number of Trials (N)	p†	Depression, SMD (95% CI)*	I^2	Number of Trials (N)	p†
All trials	-0.25 (-0.32 to -0.19)	11%	25 (6720)	--	0.00 (-0.22 to 0.18)	40%	8 (1079)	--
Opioid type: Opioid agonist	-0.26 (-0.40 to -0.17)	26%	13 (2892)	0.92	-0.01 (-0.19 to 0.20)	5.1%	5 (77)	0.14
• **Partial agonist**	-0.28 (-0.45 to -0.13)	0%	4 (932)	--	0.31 (0.02 to 0.60)	--	1 (181)	--
• **Mixed mechanism**	-0.23 (-0.36 to -0.15)	4.6%	8 (2896)	--	-0.35 (-1.03 to 0.13)	0%	2 (128)	--
Pain type: Musculoskeletal	-0.22 (-0.30 to -0.17)	0%	19 (6075)	0.09	-0.03 (-0.30 to 0.31)	0%	2 (538)	0.90
• **Neuropathic**	-0.38 (-0.54 to -0.22)	0%	6 (645)	--	-0.02 (-0.36 to 0.25)	49%	6 (541)	
• **Fibromyalgia**	No studies	--	--	--	No studies	--	--	--
Followup: 1 to 3 months	-0.25 (-0.32 to -0.19)	11%	25 (6720)	--	-0.04 (-0.29 to 0.18)	45%	7 (885)	--
• **3 to 6 months**	No studies	--	--	--	0.14 (-0.14 to 0.43)	--	1 (194)	--
Trial quality: Good	No studies	--	--	--	No studies	--	--	--
• **Fair**	-0.26 (-0.34 to -0.20)	13%	24 (6059)	0.29	0.00 (-0.22 to 0.18)	40%	8 (1079)	--
• **Poor**	-0.15 (-0.30 to 0.00)	--	1 (661)	--	No studies	--	--	--
Opioid dose (mg MED/day): <50	-0.15 (-0.36 to -0.05)	0%	6 (1879)	0.14	-0.03 (-0.30 to 0.31)	0%	2 (538)	0.13
• **50-90**	-0.26 (-0.37 to -0.19)	0%	12 (3157)	--	-0.22 (-0.69 to 0.16)	0%	3 (184)	--
• **>90**	-0.29 (-0.41 to -0.19)	0%	7 (1684)	--	0.31 (0.02 to 0.60)	--	1 (181)	--
EERW design	-0.24 (-0.36 to -0.14)	0%	5 (1467)	0.92	-0.12 (-0.33 to 0.09)	--	1 (344)	0.67
• **Non-EERW design**	-0.26 (-0.36 to -0.19)	26%	20 (5253)	--	0.02 (-0.26 to 0.23)	41%	7 (735)	--
EERW design, 2007 or after	-0.23 (-0.34 to -0.11)	0%	4 (1397)	0.97	-0.12 (-0.33 to 0.09)	--	1 (181)	0.73
• **Non-EERW design**	-0.24 (-0.38 to -0.13)	37%	11 (2704)	--	0.03 (-0.35 to 0.29)	42%	5 (559)	--
Crossover design	-0.34 (-0.50 to -0.19)	0%	7 (742)	0.20	-0.05 (-0.33 to 0.24)	5.8%	4 (325)	0.80
• **Parallel group**	-0.23 (-0.31 to -0.17)	3.1%	18 (5978)	--	0.02 (-0.42 to 0.33)	55%	4 (754)	--
Opioid status: Naïve	-0.29 (-0.57 to -0.10)	0%	2 (722)	0.78	0.22 (-0.04 to 0.49)	0%	2 (375)	0.10
• **Experienced**	-0.43 (-0.82 to -0.04)	--	1 (104)	--	No studies	--	--	--
• **Mixed**	-0.23 (-0.32 to -0.17)	12%	18 (5589)	--	-0.07 (-0.25 to 0.19)	0%	4 (576)	--
• **Not reported**	-0.27 (-0.58 to -0.01)	0%	4 (305)	--	-0.35 (-1.03 to 0.13)	0%	2 (128)	--
Publication: Prior to 2007	-0.30 (-0.42 to -0.21)	0%	10 (2619)	0.17	0.00 (-0.64 to 0.63)	34%	2 (176)	0.96
• **In or after 2007**	-0.22 (-0.31 to -0.15)	14%	15 (4101)	--	0.00 (-0.28 to 0.21)	42%	6 (903)	--
Region: USA or Canada	-0.24 (-0.31 to -0.18)	0%	19 (5818)	0.96	-0.07 (-0.25 to 0.19)	0%	4 (576)	0.87
• **Europe or Australia**	-0.29 (-0.55 to -0.06)	44%	5 (772)	--	0.00 (-0.51 to 0.35)	58%	4 (503)	--
• **Asia**	-0.25 (-0.59 to 0.10)	--	1 (130)	--	No studies	--	--	--
• **Multiple‡**	No studies	--	--	--	No studies	--	--	--
Industry funding: Yes	-0.24 (-0.31 to -0.18)	5.9%	22 (6509)	0.27	0.04 (-0.22 to 0.29)	45%	4 (812)	0.56
• **No industry funding**	-0.42 (-0.78 to -0.02)	0%	3 (211)	--	-0.10 (-0.57 to 0.29)	36%	4 (267)	--

Abbreviations: CI=confidence interval; EERW=enriched enrollment randomized withdrawal; N= total sample size; SMD= standardized mean difference.

*Negative results indicate improved sleep or depression

†p value for interaction

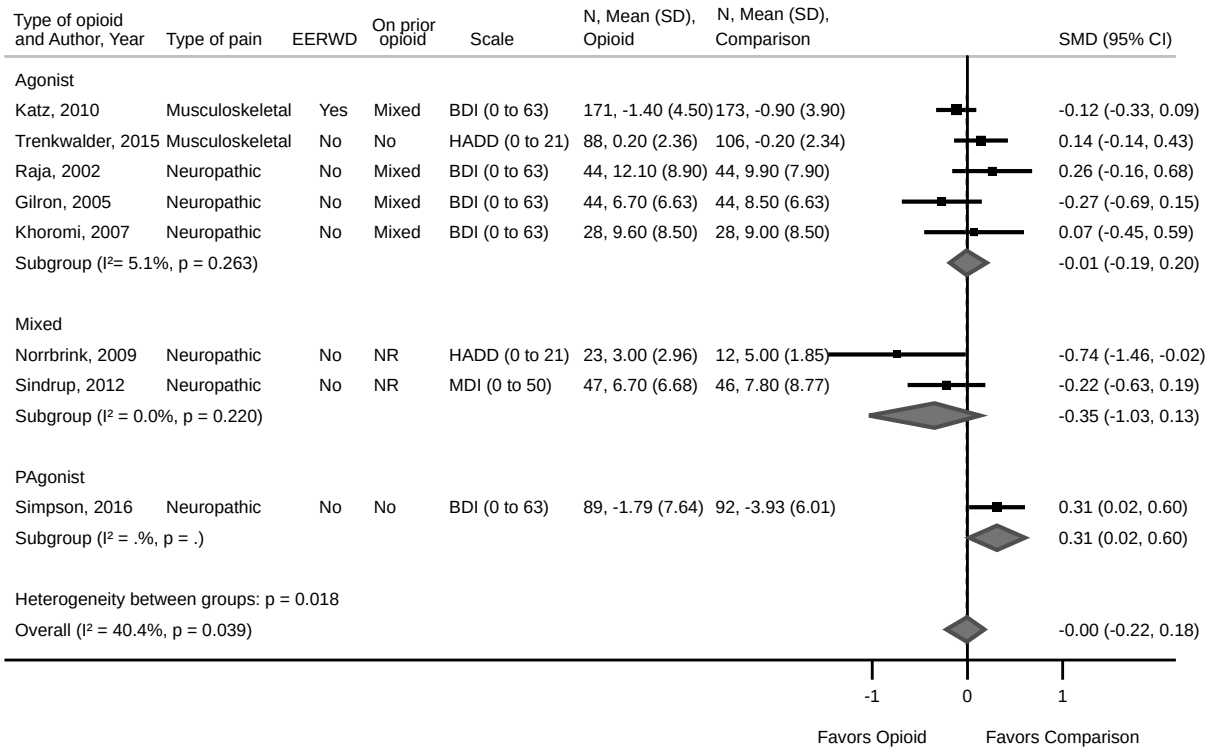
‡USA/Canada and Europe/Australia

Mental Health Outcomes

Few trials reported effects of opioids on mental health outcomes. There was no difference between opioids versus placebo in severity of depression at short-term (1 to <6 months) followup (8 trials, N=1079, SMD 0.00, 95% CI, -0.22 to 0.18, I^2=40%; Figure 8, Table 6).[67,79,82,93,95,104,105,111] Depression severity was measured using the Beck Depression Inventory (5 trials, N=757, mean difference 0.30 point on a 0 to 63 scale, 95% CI, -1.29 to 2.17, I^2=54%)[67,79,82,95,104] or the Hospital Anxiety and Depression Scale-Depression (2 trials, N=229, mean difference -0.46 point on a 0 to 21 scale, 95% CI, -3.48 to 1.89, I^2=0%).[93,111] There were no interactions between use of an EERW design (p for interaction=0.67), publication before or after 2007 (p for interaction=0.96), geographic region (p for interaction=0.87), use of a crossover design (p for interaction=0.80), or reporting industry funding (p for interaction=0.56) and effects on depression (Table 8). All trials were rated fair-quality.

Two trials found no difference between opioids versus placebo in anxiety, based on the Hospital Anxiety and Depression Scale-Anxiety (N=229, mean difference 0.60 on a 0 to 21 scale, 95% CI, -3.58 to 1.82, I^2=0%)[93,111] One trial (n=61) found no difference between opioids versus placebo in general mental health status, based on the Symptom Check List-90 (difference 0.0, 95% CI, -1.9 to 1.9).[89] Two trials reported no difference between opioids versus placebo in mental health outcomes but could not be pooled because data were not provided.[77,118]

Figure 8. Meta-analysis of improvement in mean depression measures for opioids versus placebo



Abbreviations: BDI=Beck Depression Inventory; CI=confidence interval; EERWD= enriched enrollment randomized withdrawal design; HADD=Hospital Anxiety and Depression Scale-Depression; MDI=Multidimenstional Inventory; N=sample size; NR=not reported; PAgonist=partial agonist; SD=standard deviation; SMD=standardized mean difference.

Intermediate (6 to <12 Months) and Long-Term (≥12 Months) Followup

No placebo-controlled trial evaluated opioids versus placebo at intermediate or long-term followup. One new prospective cohort study (n=529) compared patients with chronic noncancer pain prescribed opioids for 6 months or more versus propensity score-matched patients not prescribed opioids (Appendix Tables H-1 and H-2).[130] The median dose of prescribed opioids ranged from 60 mg MED/day at baseline and at 6 months and 90 mg MED/day at 12 and 24 months and pain types were musculoskeletal (62%), neuropathic (25%), and chronic postsurgical and posttraumatic (14%). Variables included in the propensity score model were age, pain duration, educational status, professional activity, type of pain (musculoskeletal, neuropathic, postsurgical), mental health comorbidities (anxiety, depression), medical comorbidities, alcohol and drug consumption, results on the Short version of Treatment Outcomes in Pain Survey (S-TOPS) questionnaire, and baseline BPI activity interference and pain severity scores. At baseline, 60 percent of patients were prescribed opioids with 16 percent of prescriptions for "strong" opioids (buprenorphine, fentanyl, methadone, morphine, oxycodone, tapentadol, or hydromorphone); mean doses of prescribed opioids were not reported. Opioid users had decreased likelihood of improvement in BPI pain severity versus nonusers at 1 year (61.5% vs. 76.1%, ARD -14.6%, p=0.001), with no difference in likelihood of improvement in BPI activity interference (62.3% vs. 67.5%, ARD -5.2%, p=0.16). There were no differences on either BPI subscale at 2 years. Opioid users had decreased likelihood of improvement on the S-TOPS pain symptom dimension compared with nonusers at 2 years (57.1% vs. 71.7%, p=0.004), but no differences on the physical function, family/social disability, or role emotional disability dimensions. Findings were not stratified according to the type of pain.

Key Question 1b. How does effectiveness vary depending on: (1) the specific type or cause of pain, (2) patient demographics, (3) patient comorbidities, or (4) the mechanism of action of opioids used?

Key Points

- Effects of opioids versus placebo on mean improvement in pain were greater at short-term followup in trials of patients with neuropathic pain than musculoskeletal pain, with a difference of about 0.5 points on a 0 to 10 scale (p for interaction=0.009) (SOE: low).
- Limited evidence found similar effects of opioids versus placebo when analyses were stratified by age (4 trials), sex (2 trials), and race (1 trial) (SOE: low).
- One post-hoc analysis of a trial found no interaction between presence of depression and effects of buprenorphine in patients with low back pain; otherwise, no trial stratified analyses based on substance use or mental health comorbidities (SOE: insufficient).
- Analyses of placebo-controlled trials found no interactions between type of opioid (pure agonist, partial agonist, or mixed mechanism) on short-term pain, function, SF-36 health status, sleep, depression, or adverse effects; five trials directly comparing different types of opioids found a mixed mechanism agent associated with greater pain relief and fewer side effects versus a pure opioid agonist and three trials found no differences between a partial versus pure opioid agonist (SOE: moderate).

Detailed Synthesis

Specific Type or Cause of Pain

Fifty-one placebo-controlled trials of opioids evaluated musculoskeletal pain, 20 trials neuropathic pain, and one trial of fibromyalgia. The most frequently evaluated musculoskeletal conditions were low back pain (25 trials), osteoarthritis (22 trials), or both (2 trials). The most frequently evaluated neuropathic pain conditions were diabetic neuropathy (8 trials), postherpetic neuralgia (3 trials), or both (3 trials). No placebo-controlled trial enrolled patients with sickle cell disease, visceral pain, or headache

Effects of opioids versus placebo on mean improvement in pain were greater at short-term followup in trials of patients with neuropathic pain (20 trials, N=2568, mean difference -1.15 points on a 0 to 10 scale, 95% CI, -1.43 to -0.91, I^2=52%)[51,53,67,69,76,77,82,92,93,95,102,104-106,110,113,118,119,122] than musculoskeletal pain (50 trials, N=16,979, mean difference -0.67 point, 95% CI, -0.81 to -0.54, I^2=68%),[50-52,54-66,68,70-75,79-81,83-88,90,91,94,96-99,101,103,107-112,114,116,117,120,121,123-129] with a difference of about 0.5 point (p for interaction=0.009). One trial (n=69) of patients with fibromyalgia reported a mean difference of -1.30 points (95% CI, -2.54 to -0.06).[100] Among pain type categories, estimates were similar for the main musculoskeletal pain conditions (osteoarthritis and low back pain) and for the main neuropathic pain conditions (diabetic neuropathy and postherpetic neuralgia). In two trials of patients with chronic low back pain, effects of opioids did not vary according to the presence or degree of a neuropathic component as measured using a scale.[59,72,91] There were no interactions between pain type and likelihood of a pain response. There were also no interactions between pain type and function, SF-36 health status, sleep, or depression (Tables 4, 5, 7, and 8).

Patient Demographics and Clinical Characteristics

Evidence to assess the interaction between patient demographics and effects of opioids was very limited. Four trials found that effects of opioids versus placebo were similar when analyses were stratified by age (older or younger than 65 years).[66,80,102,116,121,128] Two trials[102,121] found similar effects of opioids when analyses were stratified by sex; one of these trials[121] also found no interaction by race. Details regarding the socioeconomic status of patients enrolled in trials were very limited and no trials analyzed the effects of socioeconomic status on estimates.

Effects of opioids versus placebo on short-term pain and function were similar when trials were stratified according to whether they enrolled opioid-naïve or opioid-experienced patients (Tables 4, 5, 7, and 8). However, most trials enrolled mixed populations or did not report prior opioid experience. Two trials that enrolled mixed populations found similar effects of opioids in opioid-naïve and experienced patients.[95,102] One placebo-controlled trial found similar effects of opioids in subgroups stratified by baseline pain severity.[56]

Patient Comorbidities

Evidence to assess the interaction between patient comorbidities and effects of opioids was very limited. Trials either excluded patients with current or past substance use history or history of mental health disorders or did not describe eligibility based on these characteristics. One post-hoc analysis of a trial found no interaction between presence of depression and effects of buprenorphine in patients with low back pain;[107,108,124] otherwise, no trial stratified analyses based on substance use or mental health comorbidities. In addition, no trial assessed the

interaction between risk for opioid use disorder or medical comorbidities and effects of opioids, other than one trial that found no interaction with body mass index.[121]

Opioid Type

Thirty-eight placebo-controlled trials evaluated a pure opioid agonist, eight trials a partial opioid agonist, and 25 trials a mixed mechanism medication. The partial agonist was buprenorphine (five trials evaluated the patch and two trials evaluated a buccal formulation) and the mixed mechanism medication was tramadol in 16 trials and tapentadol in nine trials. There were no interactions between type of opioid (pure agonist, partial agonist, or mixed mechanism) and effects on pain, function, SF-36 health status, sleep, or depression (Tables 4, 5, 7, and 8).

Six trials (N=5209) directly compared tapentadol (a mixed mechanism medication) versus oxycodone (an opioid agonist).[50,56,103,131-135] Effects on pain intensity ranged from no difference to favoring tapentadol by up to -1.0 point on a 0 to 10 scale; however, mean mg MED/day was higher in the tapentadol than oxycodone arms (differences 35 to 45 mg). Despite a lower opioid dose, long-acting oxycodone was associated with increased risk of adverse events. The difference between long-acting oxycodone versus tapentadol in the proportion of patients who discontinued from the study due to adverse events ranged from 14 to 23 percent, for constipation from 10 to 18 percent, for nausea from -4 to 17 percent, and for vomiting from 6 to 16 percent; however, effects on the proportion of patients with serious adverse events were inconsistent and most trials found no differences (ranged -1.4% to 3.3%).

Three trials compared transdermal buprenorphine (a partial agonist) versus a pure opioid agonist.[136-138] Two trials (N=415) found no differences between transdermal buprenorphine versus sustained-release tramadol in mean improvement in pain or sleep.[136,137] Rates of discontinuation due to adverse events and specific adverse events were similar or showed no consistent differences. One small trial (n=46) of transdermal buprenorphine versus transdermal fentanyl found no differences in pain, function, mood, or adverse events.[138]

Key Question 1c. In patients with chronic pain, what is the comparative effectiveness of opioids versus nonopioid therapies (pharmacologic or nonpharmacologic, including cannabis) on outcomes related to pain, function, and quality of life after short-term followup (1 to <6 months), intermediate-term followup (6 to <12 months), and long-term followup (≥12 months)?

Key Points

- There were no differences between opioids versus nonopioids in mean improvement in pain (14 trials, N=2195 mean difference -0.29 on a 0 to 10 scale, 95% CI, -0.61 to 0.03, I^2=62%) or likelihood of a pain response (12 trials, N=2886, RR 1.28, 95% CI, 0.90 to 1.85, I^2=94%) at short-term followup (SOE: moderate).
- There were no differences between opioids versus nonopioids in mean improvement in function at short-term followup (11 trials, N=2010, SMD 0.00, 95% CI, -0.14 to 0.12, I^2=26%) (SOE: high).
- Opioids were associated with less improvement than nonopioids in SF-36 measures of physical health status at short-term followup that was below the threshold for small (6

trials, N=1423, mean difference -1.80 points on a 0 to 100 scale, 95% CI, -5.45 to -0.12, I^2=11%) (SOE: moderate).

- There were no differences between opioids versus nonopioids in SF-36 mental health status (6 trials, N=1427, mean difference -0.63 point on a 0 to 100 scale, 95% CI, -4.27 to 0.91, I^2=38%), sleep (7 trials, N=1694, SMD 0.02, 95% CI, -0.10 to 0.12, I^2=0%), anxiety (3 trials, N=414, SMD 0.00, 95% CI, -0.62 to 0.36, I^2=8.9%), or depression (7 trials, N=748, SMD 0.05, 95% CI, -0.09 to 0.22, I^2=0%) at short-term followup (SOE: low for anxiety, moderate for other outcomes).
- There were no interactions between nonopioid type and effects on any short-term outcome.
- One trial found stepped therapy with opioids associated with no differences versus stepped therapy initiated with nonopioid therapy in BPI interference at 12 months (3.4 vs. 3.3, mean difference 0.1, 95% CI, -0.5 to 0.7), but opioid therapy stepped care was associated with higher BPI pain intensity (4.0 vs. 3.5, mean difference 0.5, 95% CI, 0.0 to 1.0). There were no differences in measures of depression, anxiety, sleep quality, or physical or mental health status (SOE: moderate).

Description of Included Studies

Sixten trials (in 15 publications) compared opioids versus nonopioids for chronic pain (Table 9).[62,67,82,95,122,139-147] Sample sizes ranged from 28 to 809 (total N=3456). None of the trials were included in the 2014 AHRQ report, which was restricted to trials with 1 year or more followup. The duration of followup was 6 months or less in all trials except for one 12-month trial[143] (published subsequent to the 2014 AHRQ report). In the trials that were less than 6 months in duration, 11 trials followed patients for less than 3 months and four trials followed patients for 3 to 6 months. The nonopioid was an nonsteroidal antiinflammatory drug (NSAID) in six trials, an antiemetic in one trial,[122] an antiarrhythmic drug in one trial,[140] an anticonvulsant in three trials,[67,147,148] and an antidepressant in four trials.[82,95,141,146] In the last trial, stepped care with opioids was compared wth a stepped care nonopioid prescribing strategy starting with acetaminophen and NSAIDs; antidepressants, anticonvulsants, and topical medications were added at subsequent steps (tramadol could be added in the final step).[143] The opioid type was a pure opioid agonist in 10 trials and mixed agent (tramadol or tapentadol) in six trials. The mean opioid dose ranged from 14 to 112 mg MED/day. The pain type was neuropathic in seven trials and musculoskeletal in nine trials. The duration of pain ranged from 32.3 to 129.6 months and the proportion of female participants ranged from 13 to 87 percent. Baseline pain ranged from 4.9 to 7.8 on a 0 to 10 scale. Nine trials did not report whether they enrolled patients with a history of mental health comorbidities and the other seven excluded patients with mental health comorbidities or those with serious mental health comorbidities;[62,67,82,95,122,140,142] all trials excluded patients with a history of opioid or substance use disorder or active substance use disorder. One trial[143] excluded patients receiving daily or near-daily opioids, nine trials enrolled mixed populations of opioid-naïve and experienced patients, six trials did not describe prior opioid experience, and no trial restricted the sample to opioid-experienced patients. Fourteen trials were conducted in the United States, Canada, or Europe; one in Brazil;[146] and one in Asia.[147]

One trial[143] was rated good-quality, 13 trials fair-quality, and two trials[142,147] poor-quality (Appendix Table G-1). Methodological shortcomings frequently present in the fair- and poor-quality trials included unclear methods of randomization and allocation concealment, high overall attrition, and large between-group differences in attrition. Seven trials used a crossover

design and none used an EERW design; the remainder used a parallel group non-EERW randomized trial design. All trials except for five[82,95,122,143,147] reported industry funding.

Table 9. Study characteristics of trials of opioids versus nonopioids

Study, Year Country Quality	Total Patients Randomized	1: EERW Design 2: Crossover Design 3: Industry Funded	1: Pain Condition 2: Duration of Pain (Months)* 3: Opioid-Naïve 4: Baseline Pain	Age (Years)* Female (%) Race/Ethnicity	Opioid Dose; MED Duration of Treatment	Control
Beaulieu, 2008[139] Canada Fair	129	1: No 2: No 3: Yes	1: Osteoarthritis 2: 129.6 3: Mixed 4: 257.1 (WOMAC 0 to 500)	Age: 62.2 Female: 67% White: NR	Tramadol SR 200 to 400 mg (mean 370 mg); 74 mg MED 8 weeks	Diclofenac SR 150 to 300 mg (mean 284 mg)
DeLemos, 2011[62] USA Fair	809	1: No 2: No 3: Yes	1: Osteoarthritis 2: 97.6 3: Mixed 4: 302.5 (WOMAC 0 to 500)	Age: 60.3 Female: 62% White: 82%	Tramadol SR 100, 200, or 300 mg (mean 200 mg); 40 mg MED 12 weeks	Celecoxib Dose NR
Frank, 2008[140] UK Fair	96	1: No 2: Yes 3: Yes	1: Neuropathic pain 2: 76.4 3: Mixed 4: 69.6 (VAS 0 to 100)	Age: 50.2 Female: 48% White: NR	Dihydrocodeine 30 to 240 mg (mean NR); 14 mg MED 6 weeks	Nabilone up to 2 mg (mean NR)
Gatti, 2009[148] Italy Poor	240	1: No 2: No 3: NR	1: Mixed neuropathic pain 2: NR 3: Mixed 4: 7.5 vs. 5.6 (NRS 0 to 10)	Age: 63.2 Female: 58% White: NR	Oxycodone SR Range NR (mean 36 mg); 54 mg MED 13 weeks	Pregabalin range NR (mean 289.5 mg)
Gilron, 2015[141] Canada Fair	52	1: No 2: Yes 3: Yes	1: Peripheral neuropathic pain 2: 73.2 3: Mixed 4: 5.3 (NRS 0 to 10)	Age: 66 (median) Female: 27% White: 100%	Morphine SR Up to 100 mg (mean 65 mg); 65 mg MED 6 weeks	Nortriptyline up to 100 mg (mean 84 mg)
Gilron, 2005[67] Canada Fair	57	1: No 2: Yes 3: No	1: Diabetic neuropathy and postherpetic neuralgia 2: 54.7 vs. 56.3 3: Mixed 4: 44 (VAS 0 to 100)	Age: 60 to 68 (median) Female: 44% White: 98%	Morphine SR Up to 120 mg (mean 45 mg); 45 mg MED 5 weeks	Gabapentin up to 3200 mg (mean 2207 mg)
Hwang, 2019[147] South Korea Poor	76	1: No 2: No 3: No	1: Neuropathic pain 2: NR 3: NR 4: 6.6 (NRS 0 to 10)	Age: 58.6 Female: 56% White: 0%	Transdermal Fentanyl Starting dose of 12 mcg/hour, maximum dose NR (mean 25.0 mcg/hour); 60 mg MED 8 weeks	Gabapentin up to 2400 mg (mean 1580 mg)

Study, Year Country Quality	Total Patients Randomized	1: EERW Design 2: Crossover Design 3: Industry Funded	1: Pain Condition 2: Duration of Pain (Months)* 3: Opioid-Naïve 4: Baseline Pain	Age (Years)* Female (%) Race/Ethnicity	Opioid Dose; MED Duration of Treatment	Control
Jamison, 1998[142] USA Poor	36	1: No 2: No 3: Yes	1: Back pain 2: 79.1 3: NR 4: 68.8 (VAS 0 to 100)	Age: 42.6 Female: 58% White: NR	Oxycodone IR 5 to 20 mg (mean NR); 19 mg MED 16 weeks	Naproxen up to 1000 mg (mean NR)
Khoromi, 2007[82] USA Fair	55	1: No 2: Yes 3: No	1: Low back pain with radiculopathy 2: 60 (median) 3: Mixed 4: 4.9 (NRS 0 to 10)	Age: 53 (median) Female: 45% White: NR	Morphine SR Up to 90 mg (mean 62 mg); 62 mg MED 7 weeks	Nortriptyline up to 100 mg (mean 84 mg)
Krebs, 2018[143] USA Good	240	1: No 2: No 3: No	1: Low back pain and osteoarthritis 2: NR 3: Excluded 4: 5.4 (BPI, pain severity 0 to 10)	Age: 58.2 Female: 13% White: 86%	Mixed opioids, stepped therapy (mean 21 mg MED at 3 months and 26 mg MED at 12 months) 52 weeks	Nonopioids, stepped therapy, tramadol at 3rd step (mean 1 mg)
O'Donnell, 2009a[144] USA Fair	796	1: No 2: No 3: Yes	1: Low back pain 2: 90.6 3: NR 4: NR	Age: 48.5 Female: 58% White: 64%	Tramadol IR 200 mg (mean NR); 40 mg MED 6 weeks	Celecoxib 400 mg (mean NR)
O'Donnell, 2009b[144] USA Fair	802	1: No 2: No 3: Yes	1: Low back pain 2: 91.5 3: NR 4: NR	Age: 46.9 Female: 57% White: 68%	Tramadol IR 200 mg (mean NR); 40 mg MED 6 weeks	Celecoxib 400 mg (mean NR)
Pavelka, 1998[145] Czech Republic and Germany Fair	60	1: No 2: Yes 3: Yes	1: Osteoarthritis 2: NR 3: NR 4: NR	Age: range 44 to 85 Female: 87% White: NR	Tramadol IR Up to 300 mg (mean 165 mg); 33 mg MED 4 weeks	Diclofenac up to 150 mg (mean 87 mg)
Raja, 2002 [95] USA Fair	76	1: No 2: Yes 3: No	1: Postherpetic neuralgia 2: 32.3 3: Mixed 4: 6.5 (NRS 0 to 10)	Age: 71 Female: 55% White: 88%	Morphine SR Up to 240 mg (mean 91 mg); 91 mg MED 8 weeks	Nortriptyline up to 160 mg (mean 89 mg)
Rigo, 2017[146] Brazil Fair	28	1: No 2: No 3: No	1: Neuropathic pain 2: 12 (median); range 6 to 36 3: Mixed 4: 7.8 vs. 7.1 (NRS 0 to 10)	Age: 49.1 Female: 54% White: NR	Methadone 9 mg (mean NR); 42 mg MED 13 weeks	Ketamine 90 mg (mean NR)

Study, Year Country Quality	Total Patients Randomized	1: EERW Design 2: Crossover Design 3: Industry Funded	1: Pain Condition 2: Duration of Pain (Months)* 3: Opioid-Naïve 4: Baseline Pain	Age (Years)* Female (%) Race/Ethnicity	Opioid Dose; MED Duration of Treatment	Control
Wu, 2008[122] USA Fair	60	1: No 2: Yes 3: No	1: Postamputation pain 2: 51.3 3: NR 4: 6.7 (NRS 0 to 10)	Age: 63.4 Female: 22% White: 85%	Morphine SR 30 to 180 mg (mean 112 mg); 112 mg MED 6 weeks	Mexiletine 150 to 1200 mg (mean 933 mg)

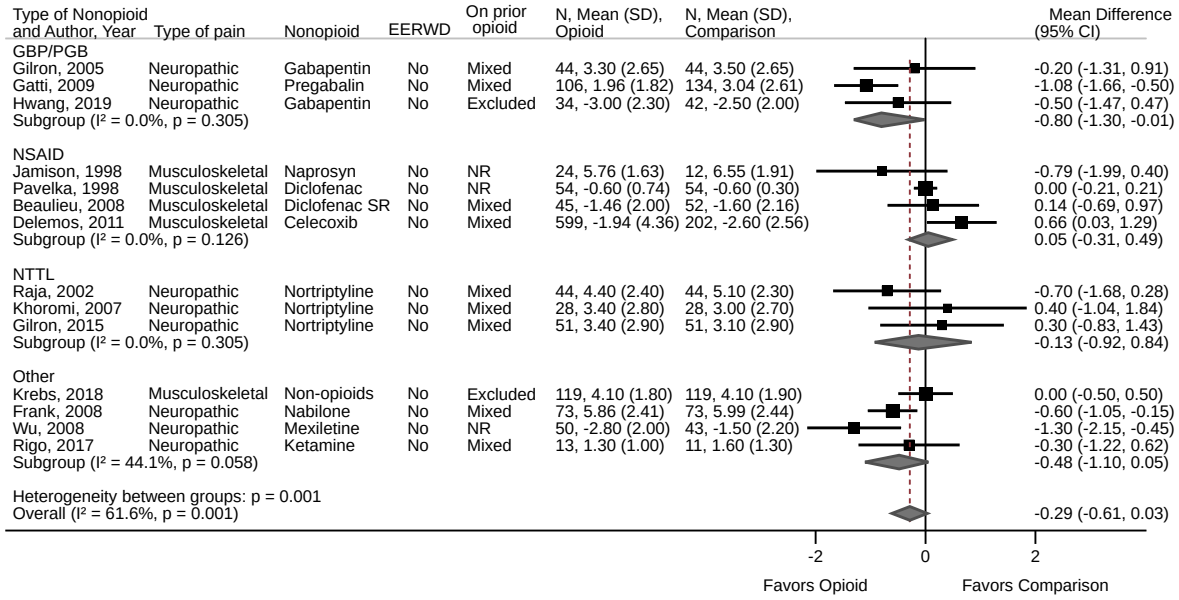
Abbreviations: BPI=Brief Pain Inventory; EERW=enriched enrollment randomized withdrawal; IR=immediate release; MED=morphine equivalent dose; NR=not reported; NRS=Numeric Rating Scale; SD=sustained release; SR=sustained release; VAS=Visual Analog Scale; WOMAC=The Western Ontario and McMaster Universities Osteoarthritis Index.

Detailed Synthesis

Short-Term (1 to <6 Months) Outcomes

There was no difference between opioids versus nonopioids in mean improvement in pain at short-term followup (14 trials, N=2195, mean difference -0.29 on a 0 to 10 scale, 95% CI, -0.61 to 0.03, I^2=62%; Figure 9, Table 10).[62,67,82,95,122,139-143,145-148] There was no interaction between the type of nonopioid and effects on mean pain intensity (p for interaction=0.20). For NSAIDs (4 trials, N=1042), the mean difference was 0.05 (95% CI, -0.31 to 0.49, I^2=0%); for nortriptyline (3 trials, N=246), the mean difference was -0.13 (95% CI, -0.92 to 0.84, I^2=0%); and for gabapentin or pregabalin (3 trials, N=404) the mean difference was -0.80 (95% CI -1.30 to -0.01; I^2=0%). Other nonopioids were evaluated in one trial each **(**Figure 9, Table 11). In a stratified analysis, trials of neuropathic pain reported greater mean improvement in pain (9 trials, N=913, mean difference -0.63, 95% CI, -0.91 to -0.23, I^2=0%) than trials of musculoskeletal pain (5 trials, N=1280, mean difference 0.04, 95% CI, -0.18 to 0.34, I^2=0%), with a difference of 0.67 point (p for interaction=0.01). There were no interactions between trial quality, opioid dose, use of crossover design, opioid experience, publication date, or industry funding and effects on pain (Table 11).

Figure 9. Meta-analysis of improvement in mean pain measures for opioids versus nonopioids



Abbreviations: CI=confidence interval; EERWD= enriched enrollment randomized withdrawal design; GBP=gabapentin; N=sample size; NR=not reported; NSAID=nonsteroidal antiinflammatory drugs; NTTL=nortryptiline; PGB=pregabalin; SD=standard deviation.

Table 10. Pain and function results for opioids versus nonopioids

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Pain (Continuous)*	Pain (Dichotomous)	Function (Continuous)*	Function (Dichotomous)
Beaulieu, 2008[139] Canada Fair	1: 8 weeks 2: 129 3: Osteoarthritis	1: Tramadol SR 200 to 400 mg (mean 370 mg) 2: Diclofenac SR 150 to 300 mg (mean 284 mg)	WOMAC 0 to 500 1: Change -73.2 (99.9) 2: Change -80.2 (108.1) (ANCOVA)	Global effectiveness moderate or marked 1: 48% (30/62) 2: 42% (28/66)	WOMAC physical function 0 to 1700 1: 633.9 (406.7) 2: 607.1 (456.2)	NR
DeLemos, 2011[62] USA Fair	1: 12 weeks 2: 809 3: Osteoarthritis	1: Tramadol SR 100, 200, or 300 mg (mean 200 mg) 2: Celecoxib, dose NR (mean NR)	WOMAC Pain 0 to 500 1: Change -97 (8.9) 2: Change -130 (9.0) (ANCOVA)	NR	WOMAC Physical Function 0 to 1700 1: Change -300.7 (29.0) 2: Change -429.2 (29.3) (ANCOVA)	NR
Frank, 2008[140] UK Fair	1: 6 weeks 2: 96 3: Neuropathic pain	1: Dihydrocodeine 30 to 240 mg (mean NR) 2: Nabilone up to 2 mg (mean NR)	VAS 0 to 100 Difference -6.0 (95% CI, -10.5 to -1.4)	≥10 mm improvement in pain intensity 1: 13% (12/96) 2: 3% (3/96)	NR	NR
Gatti, 2009[148] Italy Poor	1: 13 weeks 2: 240 3: Mixed neuropathic pain	1: Oxycodone SR range NR (mean 36 mg) 2: Pregabalin range NR (mean 289.5 mg)	NRS 0 to 10 1: 1.96 (NR) 2: 3.04 (NR	Treatment "effective" or "very effective" 1: 95% (101/106) 2: 20% (23/134)	Brief Pain Inventory, general activity 0 to 10 1: 2.97 (NR) 2: 3.67 (NR)	NR
Gilron, 2015[141] Canada Fair	1: 6 weeks 2: 52 3: Peripheral neuropathic pain	1: Morphine SR up to 100 mg (mean 65 mg) 2: Nortriptyline up to 100 mg (mean 84 mg)	NRS 0 to 10 1: 3.4 (2.9) 2: 3.1 (2.9)	Improvement in pain ≥30% 1: 25% (13/51) 2: 37% (19/51)	Brief Pain Inventory, general activity 0 to 10 1: 2.1 (0.3) 2: 1.8 (0.3)	NR
Gilron, 2005[67] Canada Fair	1: 5 weeks 2: 57 3: Diabetic neuropathic postherpetic neuralgia	1: Morphine up to 120 mg (mean 45 mg) 2: Gabapentin up to 3200 mg (mean 2207 mg)	VAS 0 to 10 (McGill Pain Questionnaire) 1: 3.3 (0.4) 2: 3.5 (0.4)	Pain relief at least moderate 1: 79.5% (35/44) 2: 61.4% (27/44)	Brief Pain Inventory, general activity 0 to 10 1: 3.1 (0.4) 2: 3.0 (0.4)	
Hwang, 2019[147] South Korea Poor	1: 8 weeks 2: 76 3: Neuropathic pain	1: Transdermal fentanyl titrated from 12 mcg/hour (mean 25.0 mcg/hour) 2: Gabapentin up to 2400 mg (mean 1580 mg)	NRS 0 to 10 1: Change -3.0 (2.3) 2: Change -2.5 (2.0)	NR	Oswestry Disability Index 0 to 100 1: Change -9.1 (18.2) 2: Change -9.7 (12.3)	NR
Jamison, 1998[142] USA Poor	1: 16 weeks 2: 36 3: Back pain	1: Oxycodone IR 5 to 20 mg (mean NR) 2: Naproxen up to 100 mg (mean NR)	VAS 0 to 100 1: 59.8 (16.65) 2: 65.5 (19.05)	NR	Level of activity 0 to 100, 100=vigorous exercise 1: 49.3 (49.33) 2: 51.5 (21.01)	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Pain (Continuous)*	Pain (Dichotomous)	Function (Continuous)*	Function (Dichotomous)
Khoromi, 2007[82] USA Fair	1: 7 weeks 2: 55 3: Low back pain with radiculopathy	1: Morphine SR up to 90 mg (mean 62 mg) 2: Nortriptyline up to 100 mg (mean 84 mg)	NRS 0 to 10 Difference -0.3 (95% CI, NR) for morphine vs. placebo and Difference -0.5 (95% CI, NR) for nortriptyline vs. placebo (Linear mixed models)	Pain relief moderate or greater 1: 24% (13/55) 2: 22% (12/55)	Oswestry Disability Index 0 to 100 1: 25.7 (16.5) 2: 27.5 (16.7)	NR
Krebs, 2018[143] USA Good	1: 52 weeks (26 week data used in meta-analyses are reported here) 2: 240 3: Low back pain and osteoarthritis	1: Mixed opioids (stepped therapy, mean dose 21 mg) 2: Nonopioids (stepped therapy, Tramadol in 3rd step, mean dose 1 mg)	Brief Pain Inventory, pain severity Difference 0.0 (95% CI, -0.5 to 0.5) (mixed models)	≥30% improvement in pain intensity 1: 39% (47/119) 2: 47% (56/119)	Brief Pain Inventory, pain interference 0 to 10 Difference -0.2 (95% CI, -0.8 to 0.4) (mixed models)	≥30% improvement in BPI interference 1: 60% (70/116) 2: 54% (63/116)
O'Donnell, 2009a[144] USA Fair	1: 6 weeks 2: 796 3: Low back pain	1: Tramadol IR 200 mg (mean NR) 2: Celecoxib 400 mg (mean NR)	NR	≥30% improvement in pain intensity 1: 50% (194/389) 2: 63% (254/402)	NR	NR
O'Donnell, 2009b[144] USA Fair	1: 6 weeks 2: 802 3: Low back pain	1: Tramadol IR 200 mg (mean NR) 2: Celecoxib 400 mg (mean NR)	NR	≥30% improvement in pain intensity 1: 55% (218/396) 2: 64% (254/396)	NR	NR
Pavelka, 1998[145] Czech; Republic; and Germany Fair	1: 4 weeks 2: 60 3: Osteoarthritis	1: Tramadol IR up to 300 mg (mean 165 mg) 2: Diclofenac up to 150 mg (mean 87 mg)	WOMAC intensity 0 to 100 1: Change -6 (IQR -10 to 0) 2: Change -6 (IQR -6 to -2)	Global assessment, good or very good 1: 52% (31/60) 2: 57% (34/60)	WOMAC physical function 0 to 100 1: Change -4 (IQR -8 to 1) 2: Change -3 (IQR -11 to 2)	NR
Raja, 2002[95] USA Fair	1: 8 weeks 2: 76 3: Postherpetic neuralgia	1: Morphine SR up to 240 mg (mean 91 mg) 2: Nortriptyline up to 160 mg (mean 89 mg)	NRS 0 to 10 1: 4.4 (2.4) 2: 5.1 (2.3)	Improvement in pain >33% 1: 53% (40/76) 2: 34% (26/76)	Multidimensional Pain Inventory, interference 0 to 6 1: 2.3 (1.5) 2: 2.5 (1.6)	NR
Rigo, 2017[146] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic	1: Methadone 9 mg (mean NR) 2: Ketamine 90 mg (mean NR)	VAS 0 to 10 1: 13 (1.3) 2: 1.6 (1.3)	NR	NR	NR

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Pain (Continuous)*	Pain (Dichotomous)	Function (Continuous)*	Function (Dichotomous)
Wu, 2008[122] USA Fair	1: 6 weeks 2: 60 3: Postamputation pain	1: Morphine SR 30 to 180 mg (mean 112 mg) 2: Mexiletine 150 to 1200 mg (mean 933 mg)	NRS 0 to 10 1: Change -2.8 (2.0) 2: Change -1.5 (2.2) (General estimating equations)	≥33% improvement in pain 1: 55% (33/60) 2: 27% (16/60) ≥50% improvement in pain 1: 38% (23/60) 2: 18% (11/60)	Multidimensional Pain Inventory no differences, data NR	NR

Abbreviations: ANCOVA=analysis of covariance; CI=confidence interval; CR=controlled release; IR=immediate release; NR=not reported; NRS=numeric rating scale; SR=sustained release; VAS=visual analog scale; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

*Mean (SD), unless otherwise reported.

Table 11. Pooled analyses of improvement in mean pain and function measures for opioids versus nonopioids

Analysis	Pain (Continuous), MD (95% CI) on 0 to 10 Scale*	I^2	Number of Trials (N)	p†	Function (Continuous), SMD (95% CI)*	I^2	Number of Trials (N)	p†
All trials	-0.29 (-0.61 to 0.03)	62%	14 (2193)	--	0.00 (-0.14 to 0.12)	26%	11 (1930)	--
Nonopioid: Gabapentinoid	-0.80 (-1.30 to -0.01)	0%	3 (404)	0.20	-0.13 (-0.34 to 0.18)	0%	3 (404)	0.37
Nortriptyline	-0.13 (-0.92 to 0.84)	0%	3 (246)		-0.01 (-0.30 to 0.26)	0%	3 (246)	--
NSAIDs	0.05 (-0.31 to 0.49)	0%	4 (1042)		0.14 (-0.12 to 0.27)	0%	4 (1042)	--
Other	-0.48 (-1.10 to 0.05)	44%	4 (501)		-0.09 (-0.34 to 0.17)	--	1 (238)	--
Pain type: Musculoskeletal	0.04 (-0.18 to 0.34)	0%	5 (1280)	0.01	0.06 (-0.15 to 0.22)	20%	5 (1280)	0.31
Neuropathic	-0.63 (-0.91 to 0.23)	0%	9 (913)	--	-0.09 (-0.24 to 0.11)	0%	6 (650)	--
Trial quality: Good	0.00 (-0.50 to 0.50)	--	1 (238)	0.22	-0.09 (-0.34 to 0.17)	--	1 (238)	0.27
Fair	-0.17 (-0.56 to 0.21)	58%	10 (1603)	--	0.10 (-0.10 to 0.21)	1.8%	7 (1340)	--
Poor	-0.91 (-1.39 to -0.29)	0%	3 (352)	--	-0.16 (-0.38 to 0.18)	0%	3 (352)	--
Opioid dose (mg MED/day): <50	-0.11 (-0.49 to 0.24)	47%	7 (1441)	0.19	0.06 (-0.16 to 0.22)	21%	5 (1271)	0.65
50-90	-0.30 (-0.91 to 0.46)	46%	5 (571)	--	-0.07 (-0.25 to 0.16)	3.5%	5 (571)	--
>90	-1.04 (-1.87 to -0.15)	0%	2 (181)	--	-0.13 (-0.55 to 0.29)	--	1 (88)	--
Crossover design	-0.34 (-0.79 to 0.10)	49%	7 (681)	0.72	-0.03 (-0.22 to 0.16)	0%	5 (442)	0.80
Parallel group	-0.23 (-0.75 to 0.27)	60%	7 (1512)	--	0.00 (-0.19 to 0.18)	41%	6 (1488)	
Opioid status: Naïve	-0.10 (-0.84 to 0.43)	0%	2 (314)	0.72	-0.06 (-0.32 to 0.24)	0%	2 (314)	0.87
Experienced	No studies	--	--	--	No studies	--	--	--
Mixed	-0.22 (-0.65 to 0.25)	56%	9 (1642)	--	0.02 (-0.17 to 0.18)	35%	7 (1472)	--
Not reported	-0.55 (-1.64 to 0.32)	64%	3 (237)	--	-0.08 (-0.48 to 0.36)	0%	2 (144)	--
Publication date: Prior to 2007	-0.06 (-0.71 to 0.15)	0%	4 (320)	0.91	-0.06 (-0.28 to 0.16)	0%	4 (334)	0.64
In or after 2007	-0.28 (-0.70 to 0.17)	64%	10 (1873)	--	0.01 (-0.16 to 0.17)	37%	7 (1608)	--
Industry funding: Yes	-0.20 (-0.71 to 0.31)	74%	7 (1530)	0.56	0.02 (-0.18 to 0.21)	40%	6 (710)	0.57
No industry funding	-0.38 (-0.84 to 0.04)	22%	7 (663)	--	-0.06 (-0.23 to 0.11)	0%	5 (1220)	--

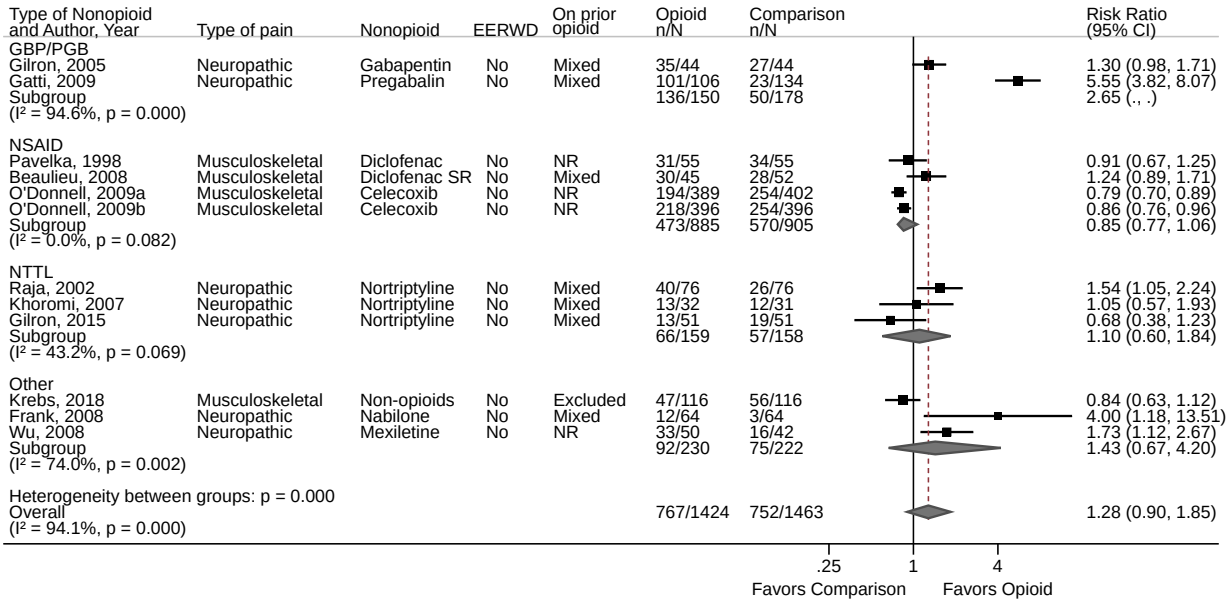
Abbreviations: CI=confidence interval; MD=mean difference; MED=morphine equivalent dose; N=total sample size; NSAIDs=nonsteroidal antiinflammatory drugs; SMD=standard mean difference.

*Negative values indicate improvement in pain or function

†p value for interaction

There was also no difference between opioids versus nonopioids in likelihood of a pain response at short-term followup (12 trials, N=2887, RR 1.28, 95% CI, 0.90 to 1.85, I^2=94%; Figure 10, Table 10).[67,82,95,122,139-141,143-145,148] One poor-quality trial reported a substantially higher estimate (RR 5.55, 95% CI 3.82 to 8.07) than a good-quality trial (RR 0.84, 95% CI 0.63 to 1.12) or the fair-quality trials (10 trials, N=2415, RR 1.09, 95% CI 0.89 to 1.39, I^2=77%; p for interaction=0.01). Stratified according to opioid dose, effects on likelihood of a pain response were not observed in trials in which the dose was less than 50 mg MED/day (6 trials, N=2141, RR 0.91, 95% CI 0.79 to 1.18, I^2=57%);[67,140,143-145] although effects were stronger in trials in which the dose was 50 to 90 mg MED/day (4 trials, N=502, RR 1.53, 95% CI 0.55 to 4.14, I^2=92%)[82,139,141,148] or greater than 90 mg MED/day (2 trials, N=244, RR 1.62, 95% CI 1.16 to 2.28, I^2=0%)[95,122] there was no statistically significant interaction (p for interaction=0.56). There were no interactions between nonopioid type or other factors and likelihood of a pain response (Table 12).

Figure 10. Meta-analysis of likelihood of experiencing a pain response for opioids versus nonopioids



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; n=sample with a pain response; N=overall sample; NR=not reported; NSAID=nonsteroidal antiinflammatory drugs; NTTL=nortryptiline; PGB=pregabalin; SD=standard deviation.

Table 12. Pooled analyses of likelihood of experiencing a pain response for opioids versus nonopioids

Analysis	Pain, RR (95% CI)	I^2	Number of Trials (N)	p*
All trials†	1.28 (0.90 to 1.85)	94%	12 (2887)	--
Nonopioid type: NSAID	0.85 (0.77 to 1.06)	0%	4 (1790)	0.21
Gabapentinoid	2.65 (0.46 to 15.49)	95%	2 (328)	--
Nortriptyline	1.10 (0.60 to 1.84)	43%	3 (317)	--
Other	1.43 (0.67 to 4.20)	74%	3 (452)	--
Opioid type: Opioid agonist	1.55 (0.93 to 2.65)	89%	8 (1097)	0.18
Mixed mechanism	0.85 (0.77 to 1.06)	0%	4 (1790)	--
Trial quality: Good	0.84 (0.63 to 1.12)	--	1 (232)	0.01
Fair	1.09 (0.89 to 1.39)	77%	10 (2415)	--
Poor	5.55 (3.82 to 8.07)	--	1 (240)	--
Opioid dose (mg MED/day): <50	0.91 (0.79 to 1.18)	57%	6 (2141)	0.56
50-90	1.53 (0.55 to 4.14))	92%	4 (2141)	--
>90	1.62 (1.16 to 2.28)	0%	2 (244)	--
Crossover design	1.23 (0.94 to 1.68)	47%	7 (735)	0.995
Parallel group	1.29 (0.60 to 2. 85)	98%	5 (2152)	--
All trials, missing=nonresponder	1.29 (0.90 to 1.88)	94%	12 (3093)	--

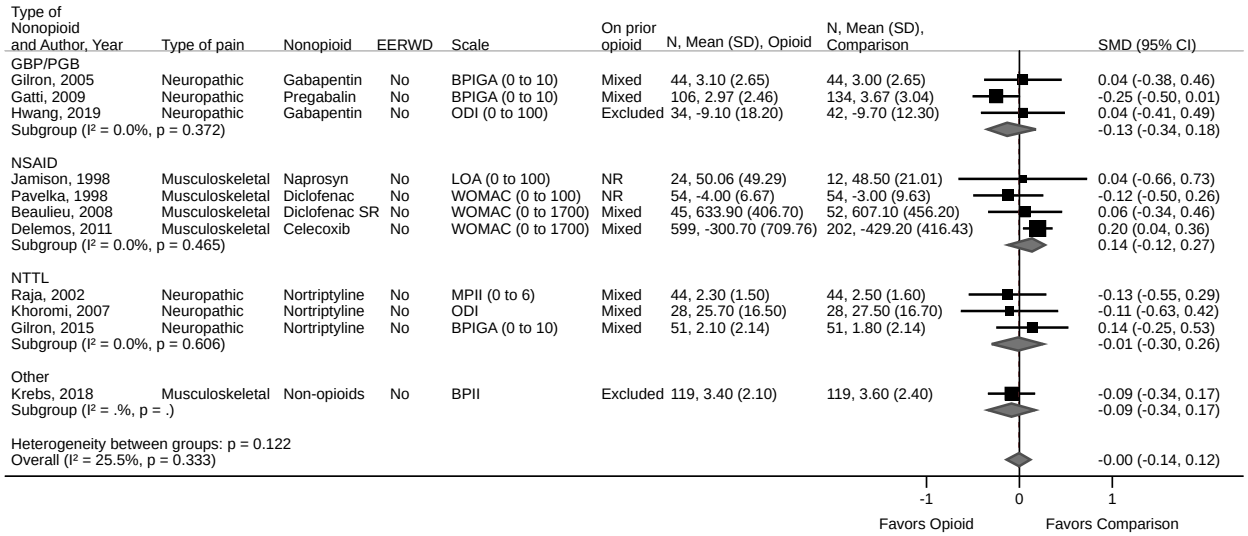
Abbreviations: CI=confidence interval; RR=risk ratio; N=number of trials; NSAID=nonsteroidal anti-inflammatory drug; MED=morphine equivalent dose.

*p value for interaction

†Based on >30% (or closest) improvement; for trials reporting improvement using a categorical scale, at least moderate improvement

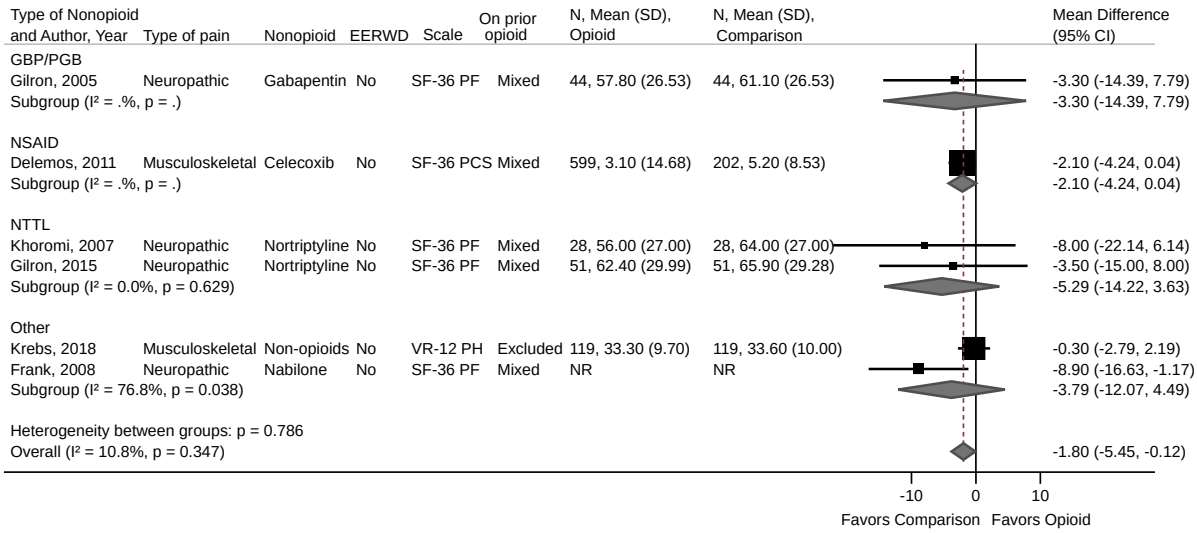
There were no differences between opioids versus nonopioids in mean improvement in function at short-term followup (11 trials, N=2010, SMD 0.00, 95% CI, -0.14 to 0.12, I^2=26%; Figure 11, Table 10).[62,67,82,95,139,141-143,145,147,148] Opioids were associated with greater improvement than nonopioids in SF-36 physical health status that was below the threshold for small magnitude of effect (6 trials, N=1423, mean difference -1.80 points on a 0 to 100 scale, 95% CI, -5.45 to -0.12, I^2=11%; Figure 12, Table 13).[62,67,82,140,141,143] There were no differences between opioids versus nonopioids in SF-36 mental health status (6 trials, N=1427, mean difference -0.63 point on a 0 to 100 scale, 95% CI, -4.27 to 0.91, I^2=38%; Figure 13, Table 13),[62,67,82,140,141,143] sleep (7 trials, N=1694, SMD 0.02, 95% CI, -0.10 to 0.12, I^2=0%; Figure 14, Table 13),[62,67,95,139,140,143,148] anxiety (3 trials, N=414, SMD 0.00, 95% CI, -0.62 to 0.36, I^2=9%; Figure 15, Table 13),[140,142,143] or depression (7 trials, N=748, SMD 0.05, 95%% CI, -0.09 to 0.22, I^2=0%; Figure 16, Table 13).[67,82,95,140-143] There were no interactions between the type of nonopioid or other factors and effects on any outcome.

Figure 11. Meta-analysis of improvement in mean function measures for opioids versus nonopioids



Abbreviations: BPIGA= Brief Pain Inventory General Activity; BPII=Brief Pain Inventory Inference; CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; n=sample with events; LOA=level of activity; MPII= Multidimensional Pain Inventory Interference; N=sample size; NR=not reported; NSAID=nonsteroidal antiinflammatory drugs; NTTL=nortryptiline; PGB=pregabalin; ODI= Oswestry Disability Index; SD=standard deviation; SMD=standardized mean difference; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

Figure 12. Meta-analysis of improvement in mean SF-36 physical function measures for opioids versus nonopioids



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; N=sample size; NR=not reported; NSAID=nonsteroidal antiinflammatory drugs; NTTL=nortryptiline; PGB=pregabalin; SD=standard deviation; SF-36 PCS= Short Form-36 Physical Component Scale; SF-36 PF=Short Form-36 Physical Function VR-12 PH=Veterans RAND 12 Item Health Survey Physical Health.

Table 13. Quality of life, sleep, and mental health outcomes for opioids versus nonopioids

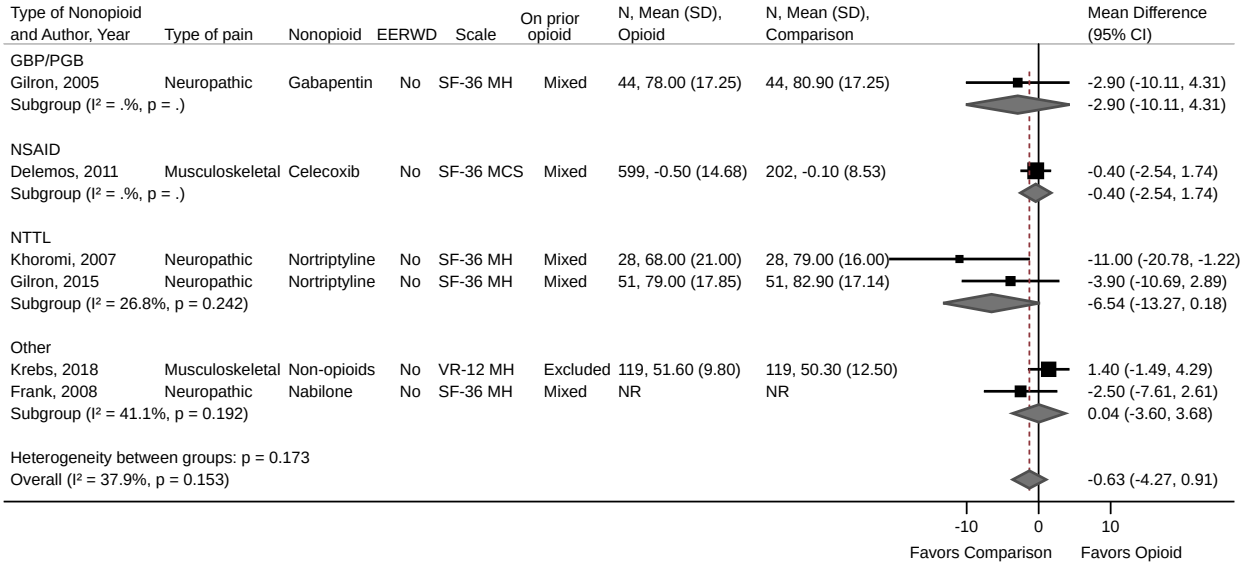
Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Quality of Life*	Sleep*	Mental Health Outcomes*
Beaulieu, 2008 [139] Canada Fair	1: 8 weeks 2: 129 3: Osteoarthritis	1: Tramadol SR 200 to 400 mg (mean 370 mg) 2: Diclofenac SR 150 to 300 mg (mean 284 mg)	NR	Pain and Sleep Index, overall 0 to 500, 500=greater impact of pain on sleep 1: 117.3 (120.7) 2: 140.1 (143.6)	NR
DeLemos, 2011[62] USA Fair	1: 12 weeks 2: 809 3: Osteoarthritis	1: Tramadol SR 100, 200, or 300 mg (mean 200 mg) 2: Celecoxib, dose NR (mean NR)	SF-36 PCS 1: Change 3.1 (0.6) 2: Change 5.2 (0.6) SF-36 MCS 1: Change -0.5(0.6) 2: Change -0.1(0.6) (ANCOVA)	Chronic Pain Sleep Inventory 0 to 100, 100=excellent 1: Change -12.7 (2.0) 2: Change -16.4 (2.1) (ANCOVA)	NR
Frank, 2008 [140] UK Fair	1: 6 weeks 2: 96 3: Neuropathic pain	1: Dihydrocodeine 30 to 240 mg (mean NR) 2: Nabilone up to 2 mg (mean NR)	SF-36 PCS Difference -8.9 (95% CI, -16.7 to -1.1) SF-36 MCS Difference -2.5 (95% CI, -7.6 to 2.7)	Scale unclear Difference -0.2 (95% CI, -0.5 to 0.1)	HAD Depression Difference 0.2 (95% CI, -0.9 to 1.2) HAD Anxiety Difference 0.6 (95% CI, -0.3 to 1.4)
Gatti, 2009[148] Italy Poor	1: 13 weeks 2: 240 3: Mixed neuropathic pain	1: Oxycodone SR range NR (mean 36 mg) 2: Pregabalin range NR (mean 289.5 mg)	NR	BPI, sleep 0 to 10, 10=pain completely interferes 1: 2.65 (NR) 2: 2.29 (NR)	NR
Gilron, 2015 [141] Canada Fair	1: 6 weeks 2: 52 3: Peripheral neuropathic pain	1: Morphine SR up to 100 mg (mean 65 mg) 2: Nortriptyline up to 100 mg (mean 84 mg)	SF-36 PCS 1: 62.4 (4.2) 2: 65.9 (4.1) SF-36 MCS 1: 79.0 (2.5) 2: 82.9 (2.4)	NR	BDI II 0 to 63 1: 6.7 (0.9) 2: 5.2 (0.8)
Gilron, 2005[67] Canada Fair	1: 5 weeks 2: 57 3: Diabetic neuropathy and postherpetic neuralgia	1: Morphine SR up to 120 mg (mean 45 mg) 2: Gabapentin up to 3200 mg (mean 2207 mg)	SF-36 PCS 1: 62.4 (4) 2: 61.1 (4) SF-36 MCS 1: 81 (2.6) 2: 80.9 (2.6)	BPI, sleep 0 to 10, 10=pain completely interferes 1: 1.6 (0.4) 2: 1.5 (0.4)	NR
Jamison, 1998[142] USA Poor	1: 16 weeks 2: 36 3: Back pain	1: Oxycodone IR 5 to 20 mg (mean NR) 2: Naproxen up to 100 mg (mean NR)	NR	Hours of sleep 1: 5.9 (2.05) 2: 6.1 (2.69)	Depression 0 to 100, 100=extreme 1: 16.4 (24.5) 2: 26.9 (32.11) Anxiety (0 to 100, 100=extreme) 1: 15.0 (21.89) 2: 31.6 (33.58)
Khoromi, 2007 [82] USA Fair	1: 7 weeks 2: 55 3: Low back pain	1: Morphine SR up to 90 mg (mean 62 mg) 2: Nortriptyline up to 100 mg (mean 84 mg)	SF-36 PCS 1: 56 (27) 2: 64 (27) SF-36 MCS 1: 68 (21) 2: 79 (16)	NR	BDI 0 to 63 1: 9.6 (8.5) 2: 7.3 (7.1)

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Quality of Life*	Sleep*	Mental Health Outcomes*
Krebs, 2018 [149] USA Good	1: 52 weeks 2: 240 3: Low back pain and osteoarthritis	1: Mixed opioids (stepped therapy, mean dose 21 mg) 2: Nonopioids (stepped therapy, Tramadol in 3rd step, mean dose 1 mg)	VR-12 Physical health Difference -0.3 (95% CI, -2.8 to 2.2) VR-12 Mental health Difference 1.4 (95% CI, -1.5 to 4.3) (Mixed models)	PROMIS sleep disturbance 8 to 32, higher score=worse 1: 22.2 (8.8) 2: 22.0 (9.0)	PHQ-8 Depression 0 to 24, 24=worse Difference -0.4 (95% CI, -1.6 to 0.8) GAD-7 Anxiety 0 to 21, 21=worse Difference -0.2 (95% CI, -1.3 to 0.8) (Mixed models)
O'Donnell, 2009a[144] USA Fair	1: 6 weeks 2: 796 3: Low back pain	1: Tramadol IR 200 mg (mean NR) 2: Celecoxib 400 mg (mean NR)	NR	NR	NR
O'Donnell, 2009b[144] USA Fair	1: 6 weeks 2: 802 3: Low back pain	1: Tramadol IR 200 mg (mean NR) 2: Celecoxib 400 mg (mean NR)	NR	NR	NR
Pavelka, 1998[145] Czech Republic and Germany Fair	1: 4 weeks 2: 60 3: Osteoarthritis	1: Tramadol IR up to 300 mg (mean 165 mg) 2: Diclofenac up to 150 mg (mean 87 mg)	NR	NR	NR
Raja, 2002[95] USA Fair	1: 8 weeks 2: 76 3: Postherpetic neuralgia	1: Morphine SR up to 240 mg (mean 91 mg) 2: Nortriptyline up to 160 mg (mean 89 mg)	NR	Multidimensional Pain Inventory, sleep 0 to 6 1: 2.5 (1.7) 2: 2.5 (1.9)	BDI 0 to 63 1: 12.1 (8.9) 2: 10.0 (7.6)
Rigo, 2017 [146] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic pain	1: Methadone 9 mg (mean NR) 2: Ketamine 90 mg (mean NR)	NR	NR	NR
Wu, 2008[122] USA Fair	1: 6 weeks 2: 60 3: Postamputation pain	1: Morphine SR 30 to 180 mg (mean 112 mg) 2: Mexiletine 150 to 1200 mg (mean 933 mg)	NR	NR	NR

Abbreviations: ANCOVA=analysis of covariance; BDI=Beck Depression Inventory; BPI=Brief Pain Inventory; CR=controlled release; CI=confidence interval; HAD=Hospital Anxiety and Depression Scale; NR=not reported; PHQ-8=Personal Health Questionnaire-8; PROMIS=Patient-Reported Outcomes Measurement Information System; SD=standard deviation; SF-36 MCS= Short Form-36 Mental Component Summary; SF-36 PCS=Short Form-36 Physical Component Summary; SR=sustained release;VR-12=Veterans RAND 12 Item Health Survey.

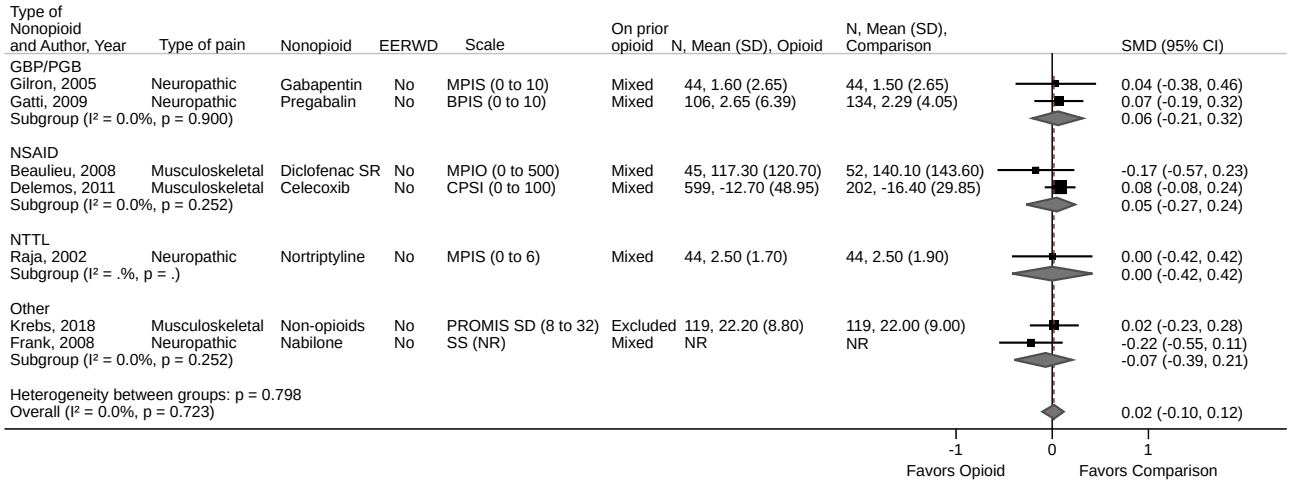
*Mean (SD), unless otherwise stated

Figure 13. Meta-analysis of improvement in mean SF-36 mental health measures for opioids versus nonopioids



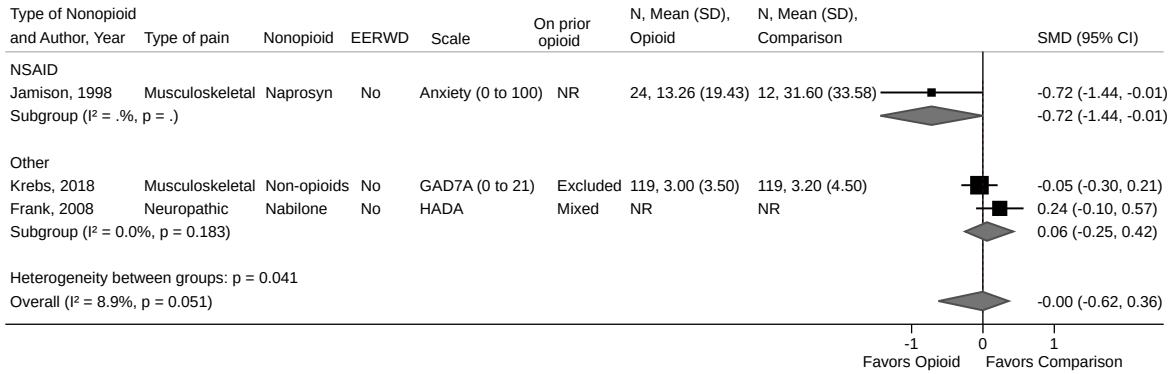
Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; N=sample size; NR=not reported; NSAID=nonsteroidal antiinflammatory drugs; NTTL=nortryptiline; PGB=pregabalin; SD=standard deviation; SF-36 MCS= Short Form-36 Mental Component Scale; SF-36 MH=Short Form-36 Mental Health; VR-12 MH=Veterans RAND 12 Item Health Survey Mental Health.

Figure 14. Meta-analysis of improvement in mean sleep measures for opioids versus nonopioids



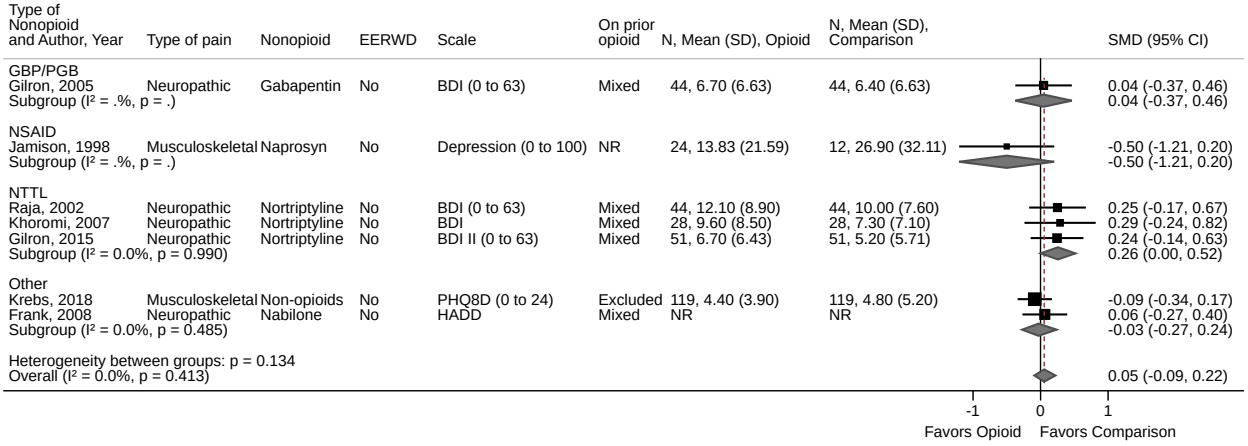
Abbreviations: BPIS=Brief Pain Inventory Sleep; CI=confidence interval; CPSI= Chronic Pain Sleep Inventory; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; MPIS= Multidimensional Pain Inventory Sleep; N=samlpe size; NR=not reported; NSAID=nonsteroidal antiinflammatory drugs; NTTL=nortryptiline; PGB=pregabalin; PROMS SD=Patient Reported Outcomes Measurement Scale Sleep Disturbance; SD=standard deviation; SMD=standardized mean difference; SS= Sleep Scale.

Figure 15. Meta-analysis of improvement in mean anxiety measures for opioids versus nonopioids



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GAD7A=Generalized Anxiety Disorder 7-item scale; HADA=Hospital Anxiety and Depression Scale-Anxiety; N=sample size; NR=not reported; NSAID=nonsteroidal antiinflammatory drugs; SD=standard deviation; SMD=standardized mean difference.

Figure 16. Meta-analysis of improvement in mean depression measures for opioids versus nonopioids



Abbreviations: BDI=Beck Depression Inventory; CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; HADD=Hospital Anxiety and Depression Scale-Depression; GBP=gabapentin; N=sample size; NR=not reported; NSAID=nonsteroidal antiinflammatory drugs; NTTL=nortryptiline; PGB=pregabalin; PHQ8D=Personal Health Questionnaire-8-Depression; SD=standard deviation; SMD=standardized mean difference.

Long-Term (≥1 Year) Outcomes

One RCT of opioids versus nonopioids evaluated outcomes at 1 year.[143] The Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) Trial randomized Veterans Affairs patients (n=240) with low back or osteoarthritis pain to stepped care starting with an opioid (first step immediate-release morphine, oxycodone, or hydrocodone/acetaminophen; second step sustained-release morphine or oxycodone; third step transdermal fentanyl) versus stepped care starting with nonopioid medications (first step acetaminophen or an NSAID; second step nortriptyline, amitriptyline, gabapentin, or a topical analgesic; third step pregabalin, duloxetine, or tramadol); patients received care within a collaborative care model that included case management and the ability to report progress electronically. Mean age was 58 years and the proportion female 13 percent; mean pain score at baseline was 5.4 on a 0 to 10 scale. Eleven percent of the patients in the nonopioid arm received tramadol, a step three option. At 1 year, the mean opioid dose was 26 mg MED/day in the opioid arm versus 1 mg MED/day in the

nonopioid arm. Most (67%) of patients in the opioid stepped care arm were prescribed 1 to less than 50 mg MED/day at 1 year.

At 1 year, opioid therapy stepped care was associated with no difference versus nonopioid therapy stepped care in BPI interference (3.4 vs. 3.3, mean difference 0.1, 95% CI, -0.5 to 0.7). However, opioid therapy stepped care was associated with higher BPI pain intensity (4.0 vs. 3.5, mean difference 0.5, 95% CI, 0.0 to 1.0). There were no differences in measures of depression, anxiety, sleep quality, or physical or mental health status (Appendix Tables H-1 and H-2).[143]

Doses of Opioids Used

Evidence on how effects of opioids versus nonopioids varied according to the dose of opioids used was very limited. In almost all trials, opioid use in the nonopioid arm was not permitted or measured. In the SPACE trial (n=240) tramadol was permitted as part of the third step in the nonopioid therapy arm.[143] At 12 months, the mean opioid dose was higher in the opioid than nonopioid arm (21 vs. 1 mg MED/day, $p<0.001$), though pain was higher in the opioid therapy arm (difference 0.5 point on a 0 to 10 scale).

Key Question 1d. In patients with chronic pain, what is the comparative effectiveness of opioids plus nonopioid interventions (pharmacologic or nonpharmacologic, including cannabis) versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used after short-term followup (1 to <6 months), intermediate-term followup (6 to <12 months), and long-term followup (≥12 months)?

Opioids Plus Nonopioids Versus Nonopioids for Chronic Pain

Key Points

- There were no differences between an opioid plus nonopioid versus a nonopioid alone in mean improvement in pain at short-term followup (6 trials, N=628, mean difference -0.36 on a 0 to 10 scale, 95% CI, -1.14 to 0.53, I^2=70%), likelihood of a pain response (6 trials, N=765, RR 1.46, 95% CI, 0.76 to 2.74, I^2=91%; excluding two poor-quality trials, N=308, RR 1.21, 95% CI 0.95 to 1.66, I^2=23%), function (4 trials, N=549, SMD -0.26, 95% CI, -0.63 to 0.17, I^2=66%), or other outcomes (SOE: low).

Description of Included Studies

Seven trials compared an opioid plus nonopioid versus nonopioid for chronic pain.[67,82,141,146,148,150,151] Sample sizes ranged from 28 to 303 (total N=715). None of the trials were included in the 2014 AHRQ report, which was restricted to trials with 1 year or more followup. The duration of followup was less than 6 months in all trials; five trials followed patients for less than 3 months and two trials followed patients for 3 to 6 months. The nonopioid was nortriptyline in two trials, gabapentin in one trial, pregabalin in two trials, ketamine in one trial, and acetaminophen in one trial. The opioid type was a pure opioid agonist in all trials. The mean opioid dose ranged from 34 to 120 mg MED/day. The pain type was neuropathic in six trials and musculoskeletal in one trial. The duration of pain ranged from 12 to 108.5 months and the proportion of female participants ranged from 27 to 58 percent. Baseline pain ranged from 5

to 7.5 on a 0 to 10 scale. No trials explicitly enrolled patients with a history of substance use disorder or mental health comorbidities; trials either excluded patients with a history of opioid or substance use disorder or mental health comorbidities or did not describe eligibility status based on these factors. No trial restricted enrollment to opioid-naïve patients or opioid-experienced patients, and all trials enrolled mixed populations of opioid-naïve and experienced patients. Six trials were conducted in the United States, Canada, Europe, or Australia; the remaining trial was conducted in Brazil[146] (Table 14).

Five trials were rated fair-quality[67,82,141,146,151] and two were rated poor-quality (Appendix Table G-1).[148,150] Methodological shortcomings in the fair- and poor-quality trials included unclear methods of randomization and allocation concealment and high attrition. Three trials used a crossover design and the others used a parallel group non-EERW randomized trial design. Two trials reported industry funding and the other five trials did not.

Table 14. Study characteristics of trials of opioids plus nonopioids versus nonopioids

Study, Year Country Quality	Total Patients Randomized	1: EERW Design 2: Crossover Design 3: Industry Funded	1: Pain Condition 2: Duration of Pain* (Months) 3: Opioid-Naïve 4: Baseline Pain*	Age (Years)* Female (%) Race/Ethnicity	Opioid Dose; MED Duration of Treatment	Control
Gatti, 2009[148] Italy Poor	303	1: No 2: No 3: NR	1: Mixed neuropathic pain 2: NR 3: Mixed 4: 7.4 vs. 7.5	Age: 63.2 Female: 58% White: NR	Oxycodone SR + pregabalin Mean 36 mg + 142 mg (mean NR); 54 mg MED 13 weeks	Pregabalin range NR (mean 289.5 mg)
Gilron, 2005[67] Canada Fair	57	1: No 2: Yes 3: No	1: Diabetic neuropathy and postherpetic neuralgia 2: 54.7 vs. 56.3 3: Mixed 4: 44 (SD 5)	Age: 60 to 68 (median) Female: 44% White: 98%	Morphine + gabapentin Up to 60 mg (mean 34 mg) + 2400 mg (mean 1705 mg); 60 mg MED 5 weeks	Gabapentin up to 3200 mg (mean 2207 mg)
Gilron, 2015[141] Canada Fair	52	1: No 2: Yes 3: Yes	1: Peripheral neuropathic pain 2: 73.2 vs. 76.8 3: Mixed 4: 52 (SD 5.3)	Age: 66 (median) Female: 27% White: 100%	Morphine SR + nortriptyline Up to 100 mg (mean 6 mg) + up to 100 m (mean 60 mg); 60 mg MED 6 weeks	Nortriptyline up to 100 mg (mean 65 mg)
Khoromi, 2007[82] USA Fair	55	1: No 2: Yes 3: No	1: Low back pain with radiculopathy 2: 60 (median); range 4 to 444 3: Mixed 4: 28 (SD 4.9)	Age: 53 (median) Female: 45% White: NR	Morphine SR + nortriptyline Up to 90 mg (mean 49 mg) + up to 100 mg (mean 55 mg); 49 mg MED 7 weeks	Nortriptyline up to 100 mg (mean 84 mg)
Kjaersgaard-Andersen, 1990[150] Denmark Poor	158	1: No 2: No 3: NR	1: Osteoarthritis 2: NR 3: NR 4: NR	Age: 66.5 Female: 46% White: NR	Codeine acetaminophen 180 mg + 3000 mg (mean NR); 1 mg MED 4 weeks	Acetaminophen 3000 mg (mean NR)
Rigo, 2017[146] Brazil Fair	28	1: No 2: No 3: No	1: Neuropathic pain 2: 12 (median); range 6 to 36 3: Mixed 4: 13 (SD 7.8)	Age: 49.1 Female: 54% White: NR	Methadone + ketamine 9 mg + 90 mg (mean NR); 42 mg MED 13 weeks	Ketamine 90 mg (mean NR)
Zin, 2010[151] Australia Fair	62	1: No 2: No 3: No	1: Diabetic neuropathy and postherpetic neuralgia 2: 34.9 vs. 27.2 3: NR 4: NR	Age: 68.4 Female: 44% White: 97%	Oxycodone 10 mg + pregabalin 75 to 600 mg (mean 231 mg); 15 mg MED 5 weeks	Pregabalin 75 to 600 mg (mean 228 mg)

Abbreviations: EERW=enriched enrollment randomized withdrawal; MED=morphine equivalent dose; NR=Not reported; SD=standard deviation; SR=sustained release.

*Mean, unless otherwise noted

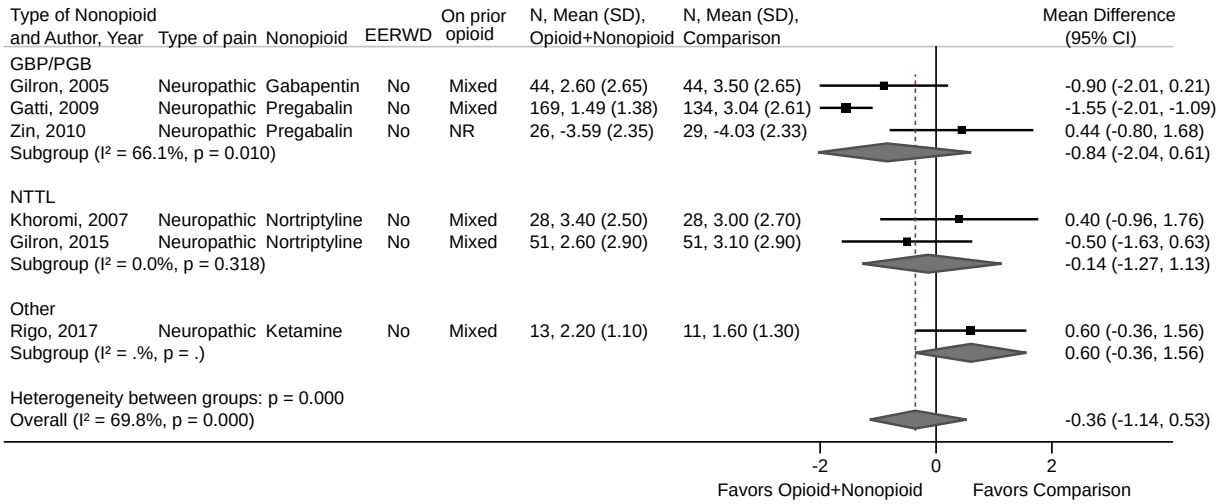
Detailed Synthesis

Short-Term (1 to <6 Months) Outcomes

There was no difference between an opioid plus nonopioid versus a nonopioid alone in mean improvement in pain at short-term followup (6 trials, N=628, mean difference -0.36 on a 0 to 10 scale, 95% CI, -1.14 to 0.53, I^2=70%; Figure 17, Table 15),[67,82,141,146,148,151] or function (4 trials, N=549, SMD -0.26, 95% CI, -0.63 to 0.17, I^2=66%; Figure 18, Table 15).[67,82,141,148] For likelihood of a pain response, the pooled estimate favored an opioid plus nonopioid versus a nonopioid alone, but the estimate was imprecise and statistical heterogeneity was very high (6 trials, N=765, RR 1.46, 95% CI 0.76 to 2.74, I^2=91%, Figure 19, Table 16).[67,82,141,148,150,151] When two poor-quality trials[148,150] were excluded, the estimate was attenuated and remained statistically non-significant (4 trials, N=308, RR 1.21, 95% CI 0.95 to 1.66, I^2=23%).[67,82,141,151] There were also no differences between an opioid plus nonopioid versus a nonopioid alone in mean improvement in SF-36 measures of physical (Figure 20, Table 17)[67,82,141,151] or mental health status (Figure 21, Table 17),[67,82,141,151] sleep (Figure 22, Table 17),[67,148,151] or depression (Figure 23, Table 17),[67,82,141] though analyses were limited by small numbers of trials. There were no interactions between nonopioid type and effects on any outcome (Tables 16 and 18); all trials evaluated pure opioid agonists, enrolled patients with neuropathic pain, and were rated fair-quality.

Trials of opioids plus nonopioid therapy versus nonopioid therapy alone were not designed to evaluate effects on doses of opioids used. Opioids were administered as part of one of the interventions and opioid use in the nonopioid therapy alone arm was not permitted or measured.

Figure 17. Meta-analysis of improvement in mean pain measures for opioids plus nonopioids versus nonopioids



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; N=sample size; NR=not reported; NTTL=nortryptiline; PGB=pregabalin; SD=standard deviation.

Table 15. Pain and function results for opioids plus nonopioids versus nonopioids

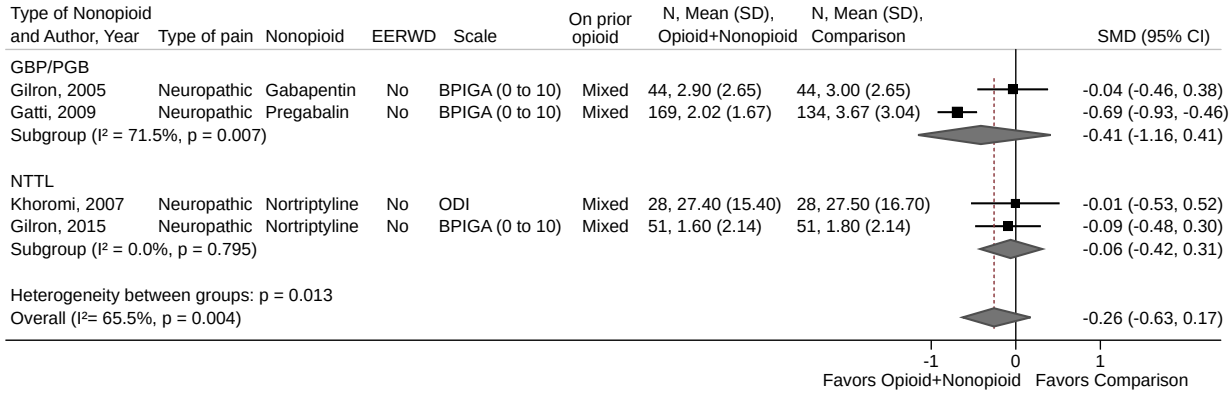
Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid + Nonopioid 2: Nonopioid	Pain* (Continuous)	Pain (Dichotomous)	Function* (Continuous)
Gatti, 2009[148] Italy Poor	1: 13 weeks 2: 303 3: Mixed neuropathic pain	1: Oxycodone SR (mean 36 mg) + pregabalin (mean142 mg) 2: Pregabalin (mean 289 mg)	NRS 0 to 10 1: 1.49 (NR) 2: 3.04 (NR)	Treatment "effective" or "very effective" 1: 91.1% (154/169) 2: <20% (NR)	BPI, general activity 0 to 10 1: 2.02 (NR) 2: 3.67 (NR)
Gilron, 2005[67] Canada Fair	1: 5 weeks 2: 57 3: Diabetic neuropathy and postherpetic neuralgia	1: Morphine up to 60 mg (mean 34 mg) + gabapentin 2400 mg (mean 1705 mg) 2: Gabapentin up to 3200 mg (mean 2207 mg)	VAS 0 to 10 1: 2.6 (0.4) 2: 3.5 (0.4)	Pain relief at least moderate 1: 56.1% (32/57) 2: 47.4% (27/57)	BPI, interference 0 to 10 1: 2.9 (0.4) 2: 3.0 (0.4)
Gilron, 2015[141] Canada Fair	1: 6 weeks 2: 52 3: Peripheral neuropathic pain	1: Morphine SR up to 100 mg (mean 60 mg) + nortriptyline up to 100 mg (mean 60 mg) 2: Nortriptyline up to 100 mg (mean 65 mg)	NRS 0 to 10 1: 2.6 (2.9) 2: 3.1 (2.9)	Improvement in pain ≥30% 1: 52.9% (27/51) 2: 37/2% (19/51)	BPI, interference 0 to 10 1: 1.6 (0.3) 2: 1.8 (0.3)
Khoromi, 2007[82] USA Fair	1: 7 weeks 2: 55 3: Low back pain with radiculopathy	1: Morphine SR up to 90 mg (mean 49 mg) + nortriptyline up to 100 mg (mean 55 mg) 2: Nortriptyline up to 100 mg (mean 84 mg)	NRS 0 to 10 1: 3.4 (2.5) 2: 3.0 (2.7)	Pain relief moderate or greater 1: 32.7% (18/55) 2: 21.8% (12/55)	Oswestry Disability Index 0 to 100 1: 27.4 (15) 2: 27.5 (17)
Kjaersgaard-Andersen, 1990[150] Denmark Poor	1: 4 weeks 2: 158 3: Osteoarthritis	1: Codeine 180 mg + acetaminophen 3000 mg (mean NR) 2: Acetaminophen 3000 mg (mean NR)	NR	Slight or no pain 1: 12.5% (10/80) 2: 21.6% (16/74)	NR
Rigo, 2017 [146] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic pain	1: Methadone 9 mg + ketamine 90 mg (mean NR) 2: Ketamine 90 mg (mean NR)	NRS 0 to 10 1: 2.20 (1.10) 2: 1.60 (1.30)	NR	NR
Zin, 2010 [151] Australia Fair	1: 5 weeks 2: 62 3: Diabetic neuropathy and postherpetic neuralgia	1: Oxycodone 10 mg + pregabalin 75 to 600 mg (mean 231 mg); 2: Pregabalin 75 to 600 mg (mean 228 mg)	VAS 0 to 10 Difference 0.44 (CI, NR)	≥2 cm improvement in pain intensity and pain intensity <4 cm 1: 69.0% (20/29) 2: 75.7% (25/33)	NR

Abbreviations: BPI=Brief Pain Inventory; CI=confidence interval; NR=not reported; NRS=numeric rating scale; SD=standard deviation; SF-36 MCS=Short Form-36 Mental Component Summary; SF-36 PCS=Short Form-36 Physical Component Summary; SR=sustained release; VAS=Visual Analog Scale.

*Means (SD), unless otherwise reported

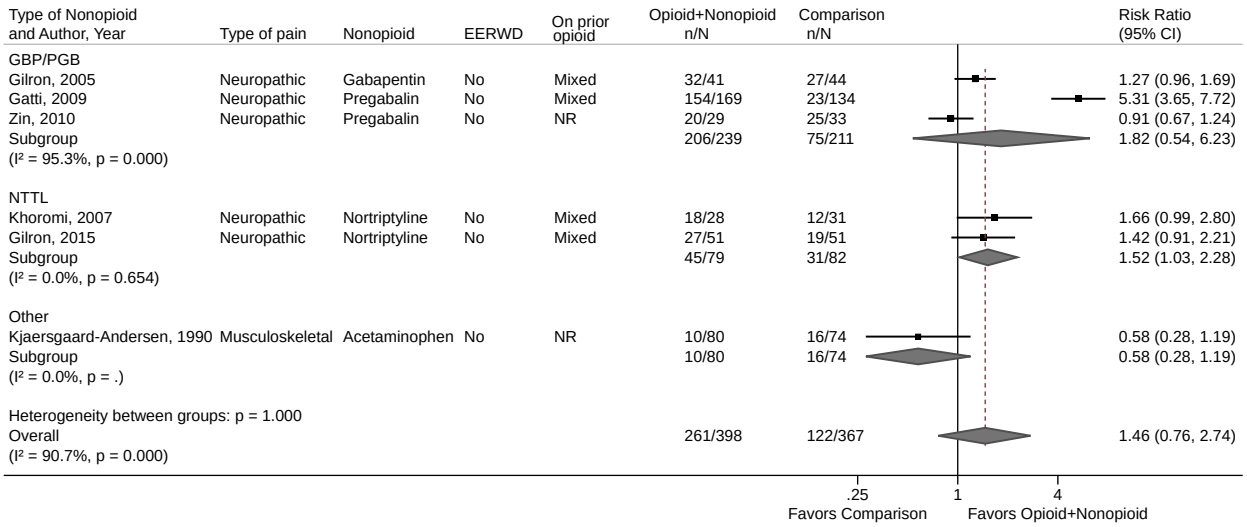
Note: No studies reported function (dichotomous)

Figure 18. Meta-analysis of improvement in mean function measures for opioids plus nonopioids versus nonopioids



Abbreviations: BPIGA= Brief Pain Inventory General Activity; CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; ODI= Oswestry Disability Index; N=sample size; NR=not reported; NTTL=nortryptiline; PGB=pregabalin; SD=standard deviation; SMD=standardized mean difference.

Figure 19. Meta-analysis of likelihood of experiencing a pain response for opioids plus nonopioids versus nonopioids



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; n=sample with a pain response; N=overall sample; NR=not reported; NTTL=nortryptiline; PGB=pregabalin.

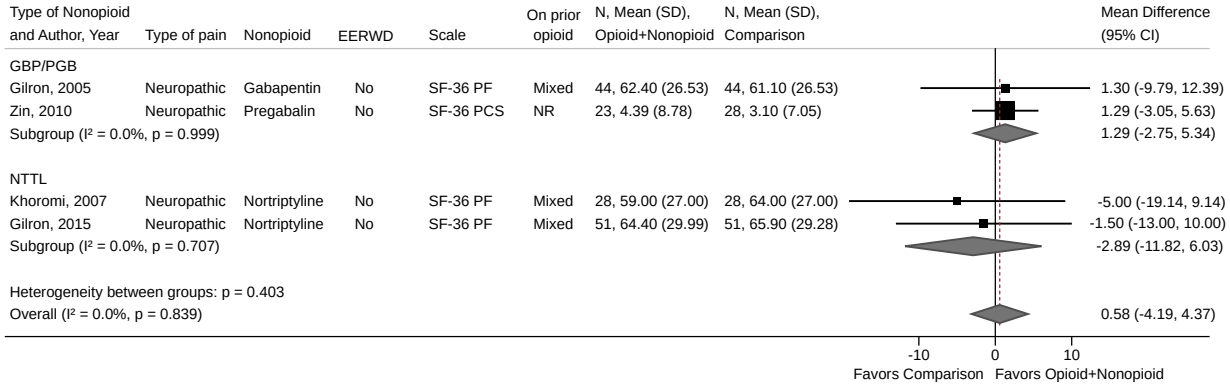
Table 16. Pooled analyses of likelihood of experiencing a pain response for opioids plus nonopioids versus nonopioids

Analysis	Pain, RR (95% CI)	I^2	Number of Trials (N)	p*
All trials	1.46 (0.76 to 2.74)	91%	6 (765)	--
Nonopioid type: Gabapentinoid	1.82 (0.54 to 6.23)	95%	3 (450)	0.55
Nortriptyline	1.52 (1.03 to 2.28)	0%	2 (161)	--
Acetaminophen	0.58 (0.28 to 1.19)	--	1 (154)	--
Trial quality: Fair	1.21 (0.95 to 1.66)	23%	4 (308)	0.60
Poor	1.83 (0.12 to 25.56)	93%	2 (457)	--
Opioid dose (mg MED/day): <50	1.09 (0.71 to 1.57)	38%	4 (360)	0.13
50-90	2.78 (0.56 to 13.50)	90%	2 (405)	--

Abbreviations: CI=confidence interval; RR=risk ratio; N=number of trials; MED=morphine equivalent dose.

*p value for interaction

Figure 20. Meta-analysis of improvement in mean SF-36 physical function measures for opioids plus nonopioids versus nonopioids



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; N=sample size; NR=not reported; NTTL=nortryptiline; PGB=pregabalin; SD=standard deviation; SF-36 PCS= Short Form-36 Physical Component Scale; SF-36 PF=Short Form-36 Physical Function.

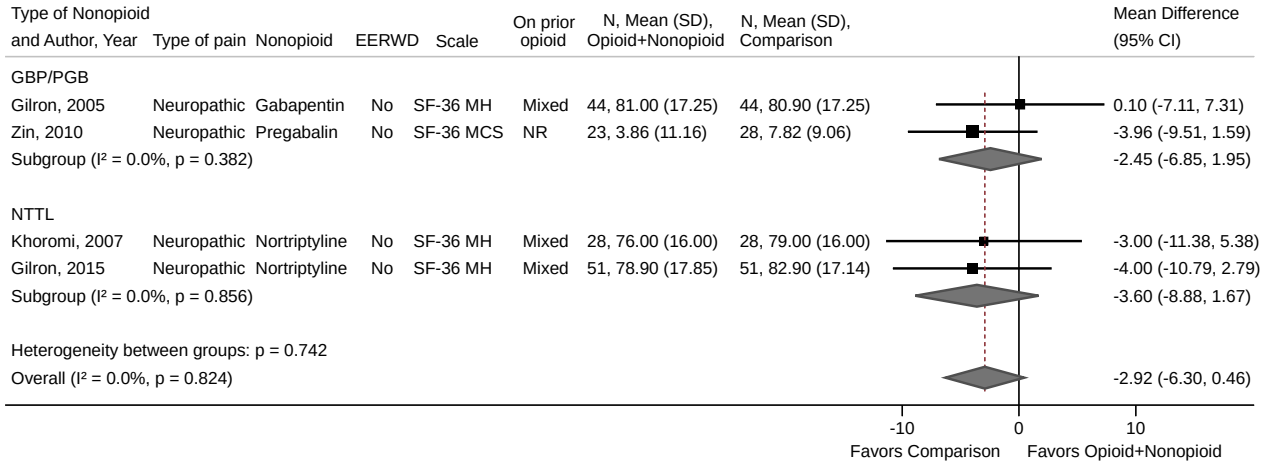
Table 17. Quality of life, sleep, and mental health outcomes for opioids plus nonopioids versus nonopioids

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid + Nonopioid 2: Nonopioid	Quality of Life*	Sleep*	Mental Health Outcomes*
Gatti, 2009[148] Italy Poor	1: 13 weeks 2: 303 3: Mixed neuropathic pain	1: Oxycodone SR (mean 36 mg) + pregabalin (mean142 mg) 2: Pregabalin (mean 289 mg)	NR	BPI, sleep 0 to 10 1: 2.22 (NR) 2: 2.29 (NR)	NR
Gilron, 2005[67] Canada Fair	1: 5 weeks 2: 57 3: Diabetic neuropathy and postherpetic neuralgia	1: Morphine up to 60 mg (mean 34 mg) + gabapentin 2400 mg (mean 1705 mg) 2: Gabapentin up to 320 mg (mean 2207 mg)	SF-36 PCS 1: 62.4 (4) 2: 61.1 (4) SF-36 MCS 1: 81 (2.6) 2: 80.9 (2.6)	BPI sleep 0 to 10 1: 1.1 (0.4) 2: 1.5 (0.4)	BDI 0 to 63 1: 6 (1) 2: 6.4 (1)
Gilron, 2015[141] Canada Fair	1: 6 weeks 2: 52 3: Peripheral neuropathic pain	1: Morphine SR up to 100 mg (mean 60 mg) + nortriptyline up to 100 mg (mean 60 mg) 2: Nortriptyline up to 100 mg (mean 65 mg)	SF-36 PCS 1: 64.4 (4.2) 2: 65.9 (4.1) SF-36 MCS 1: 78.9 (2.5) 2: 82.9 (2.4)	NR	BDI II 0 to 63 1: 6.1 (0.9) 2: 5.2 (0.8)
Khoromi, 2007[82] USA Fair	1: 7 weeks 2: 55 3: Low back pain with radiculopathy	1: Morphine SR up to 90 mg (mean 49 mg) + nortriptyline up to 100 mg (mean 55 mg) 2: Nortriptyline up to 100 mg (mean 84 mg)	SF-36 PCS 1: 59 (27) 2: 64 (27) SF-36 MCS 1: 76 (16) 2: 79 (16)	NR	BDI 0 to 63 1: 6 (5) 2: 7.3 (7.1)
Kjaersgaard-Andersen, 1990[150] Denmark Poor	1: 4 weeks 2: 158 3: Osteoarthritis	1: Codeine 180 mg + acetaminophen 3000 mg (mean NR) 2: Acetaminophen 3000 mg (mean NR)	NR	NR	NR
Rigo, 2017 [146] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic pain	1: Methadone 9 mg + ketamine 90 mg (mean NR) 2: Ketamine 90 mg (mean NR)	NR	NR	NR
Zin, 2010 [151] Australia Fair	1: 5 weeks 2: 62 3: Diabetic neuropathy and postherpetic neuralgia	1: Oxycodone 10 mg + pregabalin 75 to 600 mg (mean 231 mg); 2: Pregabalin 75-600 mg (mean 228 mg)	SF-36 PCS Difference 1.29 (CI, NR) SF-36 MCS Difference -3.96 (CI, NR)	Sleep interference on VAS 0 10 Difference -1.11 (CI, NR)	NR

Abbreviations: BDI=Beck Depression Inventory; BPI=Brief Pain Inventory; CI=confidence interval; NR=not reported; SF-36 MCS= Short Form-36 Mental Component Summary; SF-36 PCS=Short Form-36 Physical Component Summary; SR=sustained release; VAS=Visual Analog Scale.

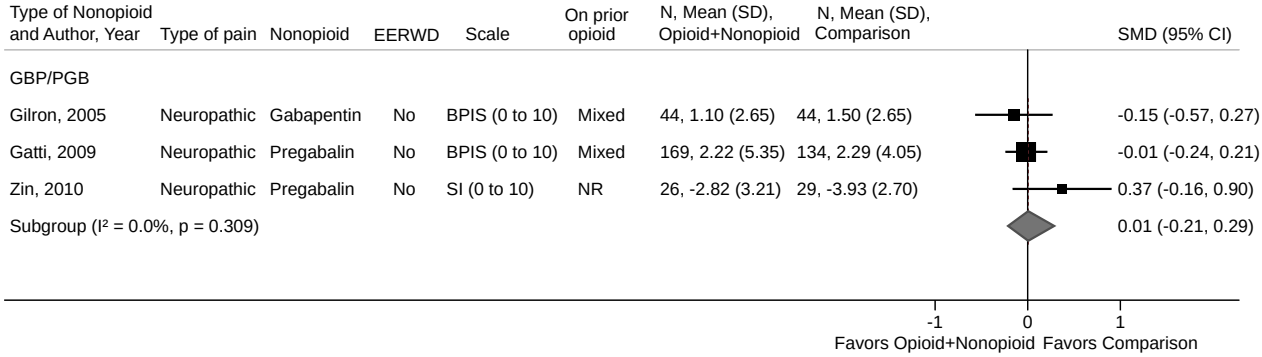
*Means (standard deviation), unless otherwise reported

Figure 21. Meta-analysis of improvement in mean SF-36 mental health measures for opioids plus nonopioids versus nonopioids



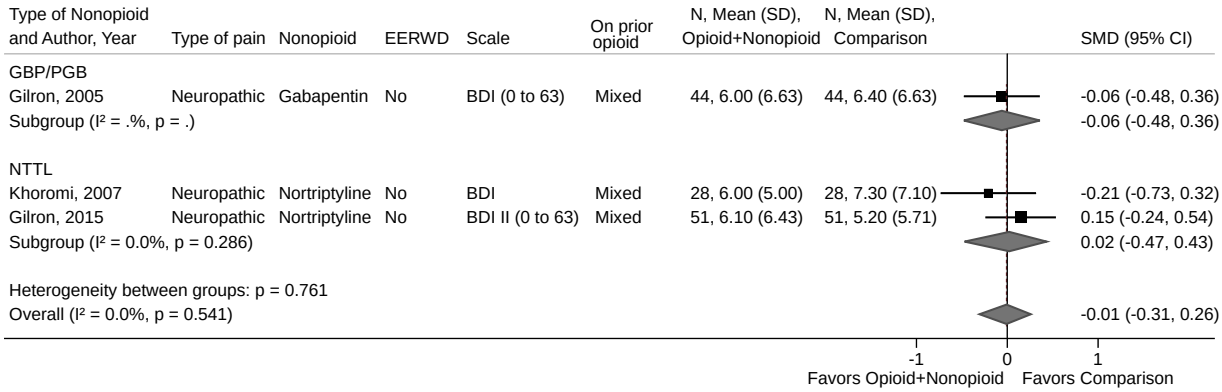
Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; N=sample size; NR=not reported; NTTL=nortryptiline; PGB=pregabalin; SD=standard deviation; SF-36 MCS= Short Form-36 Meantal Component Scale; SF-36 MH=Short Form-36 Mental Health.

Figure 22. Meta-analysis of improvement in mean sleep measures for opioids plus nonopioids versus nonopioids



Abbreviations: BPIS=Brief Pain Inventory Sleep; CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; N=sample size; NR=not reported; PGB=pregabalin; SD=standard deviation; SI=Sleep Interference; SMD=standardized mean difference.

Figure 23. Meta-analysis of improvement in mean depression measures for opioids plus nonopioids versus nonopioids



Abbreviations: BDI=Beck Depression Inventory; BDI II=Beck Depression Inventory II; CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; N=sample size; NTTL=nortryptiline; PGB=pregabalin; SD=standard deviation; SMD=standardized mean difference.

Table 18. Pooled analyses of improvement in mean pain and function measures for opioids plus nonopioids versus nonopioids

Analysis	Pain (Continuous), MD (95% CI) on 0 to 10 Scale*	I^2	Number of Trials (N)	p†	Function (Continuous), SMD (95% CI)*	I^2	Number of Trials (N)	p†
All trials	-0.36 (-1.14 to 0.53)	70%	6 (628)	--	-0.26 (-0.63 to 0.17)	66%	4 (549)	--
Nonopioid: Gabapentinoid	-0.84 (-2.04 to 0.61)	66%	3 (451)	0.46	-0.41 (-1.16 to 0.41)	72%	2 (391)	0.43
Nortriptyline	-0.14 (-1.27 to 1.13)	0%	2 (158)	--	-0.06 (-0.42 to 0.31)	0%	2 (158)	--
Ketamine	0.60 (-0.36 to 1.56)	--	1 (24)	--	No studies	--	--	--
Opioid type: Opioid agonist	-0.36 (-1.14 to 0.53)	70%	6 (633)	--	-0.26 (-0.63 to 0.17)	66%	4 (549)	--
Pain type: Neuropathic	-0.36 (-1.14 to 0.53)	70%	6 (633)	**--**	-0.26 (-0.63 to 0.17)	66%	4 (549)	--
Trial quality: Good	No studies	--	--	--	No studies	--	--	--
Fair	0.00 (-0.67 to 0.68)	16%	5 (330)	0.05	-0.05 (-0.31 to 0.21)	0%	3 (246)	0.07
Poor	-1.55 (-2.01 to -1.09)	--	1 (303)	--	-0.69 (-0.93 to -0.46)	--	1 (303)	--
Opioid dose (mg MED/day): <50	0.13 (-0.68 to 0.94)	18%	4 (228)	0.09	-0.03 (-0.40 to 0.35)	0%	2 (144)	0.36
50-90	-1.40 (-2.14 to -0.01)	0%	2 (405)	--	-0.44 (-1.12 to 0.32)	70%	2 (405)	--
>90	No studies	--	--	**--**	No studies	--	--	--
Crossover design	-0.43 (-1.22 to 0.47)	0%	3 (249)	0.93	-0.05 (-0.31 to 0.21)	0%	3 (246)	0.07
Parallel group	-0.28 (-1.86 to 1.46)	83%	3 (384)	--	-0.69 (-0.93 to -0.46)	--	1 (303)	--

Abbreviations: CI=confidence interval; MD = mean difference; MED= morphine equivalent dose; mg=milligram; N= total sample size; SMD=standard mean difference.

*Negative values indicate improvement in pain or function

†p value for interaction

Opioids Plus Nonopioids Versus Opioids for Chronic Pain

Key Points

- An opioid plus nonopioid was associated with greater improvement in pain at short-term followup versus an opioid alone that was below the threshold for a small magnitude of effect (5 trials, N=623, mean difference -0.40, 95% CI, -0.72 to -0.07, I^2=0%) (SOE: low)
- There were no statistically significant differences between an opioid plus nonopioid versus an opioid alone in likelihood of a pain response (5 trials, N=831, RR 1.19, 95% CI, 0.97 to 1.68, I^2=76%) or mean improvement in function (4 trials, N=521, SMD -0.25, 95% CI, -0.49 to 0.09, I^2=28%), though estimates favored combination therapy (SOE: low).
- There were no differences between an opioid plus nonopioid versus an opioid alone in mean improvement in SF-36 measures of physical or mental health status, sleep, anxiety, or depression, though analyses were limited by small numbers of trials (SOE: low).
- Four trials of patients with neuropathic pain found an opioid plus nonopioid associated with lower doses of opioid used (difference 5 to 13 mg MED/day) versus an opioid alone, with pain relief better by 0.3 to 0.9 points with combination therapy (SOE: low).
- One cohort study of patients with chronic pain prescribed opioids found no association between degree of self-reported cannabis use and pain, function, likelihood of opioid discontinuation, or opioid dose through up to 4 years of followup; cannabis use was associated with increased anxiety (SOE: low).

Description of Included Studies

Six trials compared an opioid plus nonopioid versus opioid for chronic pain (Table 19).[67,82,141,146,148,152] None of the trials were included in the 2014 AHRQ report, which was restricted to trials with 1 year or more followup. The duration of followup was 6 months or less in all trials; four trials followed patients for less than 3 months and two trials followed patients for 3 to 6 months. Sample sizes ranged from 28 to 313 (total N=780). Two trials evaluated long-acting morphine plus nortriptyline,[82,141] and one trial each evaluated methadone plus ketamine,[146] morphine plus gabapentin,[67] long-acting oxycodone plus pregabalin,[148] and long-acting tapentadol plus pregabalin.[152] The opioid type was a pure opioid agonist in five trials, and mixed agent (tapentadol) in one trial. The mean opioid dose ranged from 34 mg to 120 mg MED/day. The pain type was neuropathic in all trials. The duration of pain ranged from 1 to 9 years and the proportion of female participants ranged from 27 to 58 percent. Baseline pain ranged from 4.9 to 8.4 on a 0 to 10 scale. All trials excluded patients with a history of opioid or substance use disorder or mental health comorbidities or did not describe eligibility status based on these factors. All trials enrolled mixed populations of opioid-naïve and experienced patients. Five trials were conducted in the United States, Canada, Europe, or Australia; and one trial in Brazil.

Five trials were rated fair-quality[67,82,141,146,152] and one poor-quality[148] (Appendix Table G-1). Methodological shortcomings frequently present in the fair- and poor-quality trials included unclear randomization, unclear allocation concealment, and high attrition. Three trials used a crossover design;[67,82,141] the remainder used a parallel group non-EERW randomized trial design. Two trials reported industry funding.[67,152]

Table 19. Study characteristics of trials of opioids plus nonopioids versus opioids

Study, Year Country Quality	Total Patients Randomized	1: EERW Design 2: Crossover Design 3: Industry Funded	1: Pain Condition 2: Duration of Pain (Months)* 3: Opioid-Naïve 4: Baseline Pain*	Age (Years)* Female (%) Race/Ethnicity	Opioid Dose; MED Duration of Treatment	Control
Baron, 2015[152] Germany, Poland, Spain, Belgium, Austria, Denmark, the Netherland Fair	313	1: No (open-label run-in with tapentadol) 2: No 3: Yes	1: Low back pain with neuropathic component 2: 108.5 (118.9) 3: Mixed 4: 8.4 (1.07) vs. 8.4 (1.11)	Age: 57.4 (11.4) Female: 58% White: 99.7%	Tapentadol SR + pregabalin 300 mg + 150-300 mg (mean NR); 120 mg MED 8 weeks	Tapentadol SR 300-500 mg (mean NR)
Gatti, 2009[148] Italy Poor	275	1: No 2: No 3: NR	1: Mixed neuropathic pain 2: NR 3: Mixed 4: 7.4 vs. 7.5	Age: 63.2 Female: 58% White: NR	Oxycodone SR pregabalin Mean 36 mg + 142 mg; 54 mg MED 13 weeks	Oxycodone SR (mean 46 mg)
Gilron, 2005[67] Canada Fair	57	1: No 2: Yes 3: No	1: Diabetic neuropathy or postherpetic neuralgia 2: 54.7 (56.3) 3: Mixed 4: 5 (0.4)	Age: 60-68 (median) Female: 44% White: 98%	Morphine + gabapentin up to 60 mg (mean 34 mg) + 2400 mg (mean 1705 mg); 34 mg MED 5 weeks	Morphine up to 120 mg (mean 45 mg)
Gilron, 2015[141] Canada Fair	52	1: No 2: Yes 3: Yes	1: Peripheral neuropathic pain 2: 73.2 (76.8) 3: Mixed 4: 5.3 (1.4)	Age:66 (median) Female: 27% White: 100%	Morphine SR + nortriptyline Up to 100 mg (mean 49 mg) + up to 100 mg (mean 55 mg); 60 mg MED 6 weeks	Morphine SR up to 100 mg (mean 84 mg)
Khoromi, 2007[82] USA Fair	55	1: No 2: Yes 3: No	1: Low back pain with radiculopathy 2: 60 (median); range 4 to 444 3: Mixed 4: 4.9 (2.43)	Age: 53 (median) Female: 45% White: NR	Morphine SR + nortriptyline Up to 90 mg (mean 49 mg) + up to 100 mg (mean 55 mg); 49 mg MED 7 weeks	Morphine SR up to 90 mg (mean 62 mg)
Rigo, 2017[146] Brazil Fair	28	1: No 2: No 3: No	1: Neuropathic 2: 12 (median); range 6 to 36 3: Mixed 4: 13 (7.8)	Age: 48.5 Female: 58% White: NR	Methadone + ketamine 9 mg + 90 mg; 42 mg MED (mean NR) 13 weeks	Methadone 9 mg

Abbreviations: EERW=enriched enrollment randomized withdrawal; MED=morphine equivalent dose; NR=Not reported; SR=sustained release.

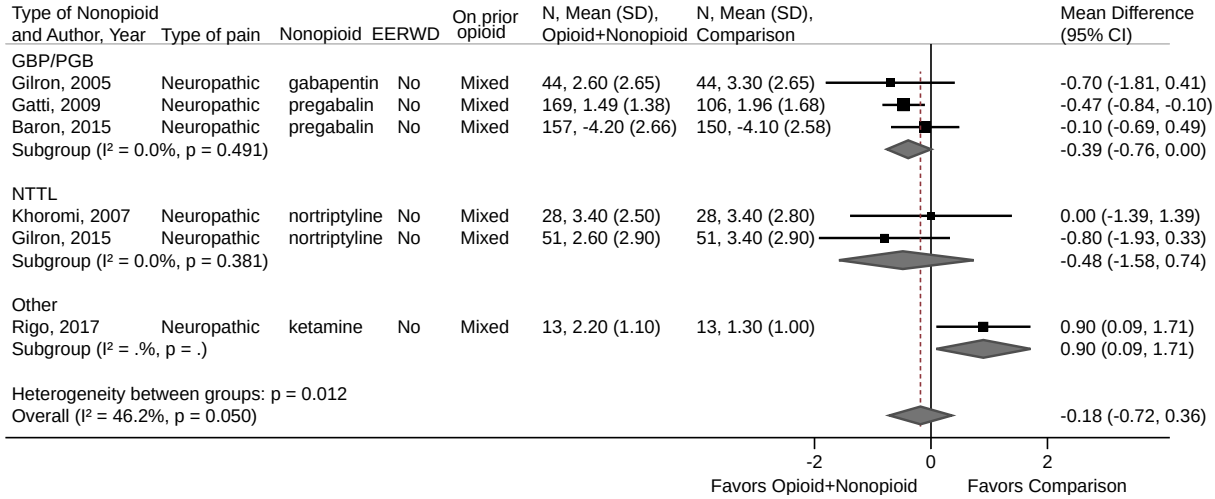
*Mean (SD), unless otherwise noted

Detailed Synthesis

Short-Term (1 to <6 Months) Outcomes

An opioid plus nonopioid was associated with greater mean improvement in pain at short-term followup that was below the threshold for a small magnitude of effect (6 trials, N=854, mean difference -0.18, 95% CI, -0.72 to 0.36, I^2=46%; Figure 24, Table 20) versus an opioid alone.[67,82,141,146,148,152] In a stratified analysis, estimates were very similar when the nonopioid was a gabapentinoid (3 trials, N=670, mean difference -0.39, 95% CI, -0.76 to 0.00, I^2=0%) or nortriptyline (2 trials, N=158, mean difference -0.48, 95% CI, -1.58 to 0.74, I^2=0%; p for interaction=0.86) (Table 21). Results were similar for likelihood of a pain response (5 trials, N=831, RR 1.19, 95% CI, 0.97 to 1.68, I^2=76%; Figure 25, Table 21).[67,82,141,148,152] Effects on mean improvement in function were small and not statistically significant (4 trials, N=521, SMD -0.25, 95% CI, -0.49 to 0.09, I^2=28%; Figure 26, Table 20),[67,82,141,148] with no interaction with nonopioid type (Table 22). There were no differences between an opioid plus nonopioid versus an opioid alone in mean improvement in SF-36 measures of physical (Figure 27, Table 23)[67,82,141,152] or mental (Figure 28, Table 23)[67,82,141,152] health status, sleep (Figure 29, Table 23),[67,148] anxiety (Figure 30, Table 23),[152] or depression (Figure 31, Table 23),[67,82,141,152] though analyses were limited by small numbers of trials. The combination of an opioid plus nortriptyline was associated with greater improvement in SF-36 measures of mental health status versus an opioid alone, based on two trials (N=158, mean difference 12.34, 95% CI, 1.77 to 22.77, I^2=32%), though there was no interaction with nonopioid type (p=0.11). There were no interactions between trial quality, opioid dose, or use of crossover design and effects on these outcomes (Table 21 and 2**2**). All trials evaluated an opioid agonist and enrolled patients with neuropathic pain.

Figure 24. Meta-analysis of improvement in mean pain measures for opioids plus nonopioids versus opioids



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; N=sample size; NTTL=nortryptiline; PGB=pregabalin; SD=standard deviation.

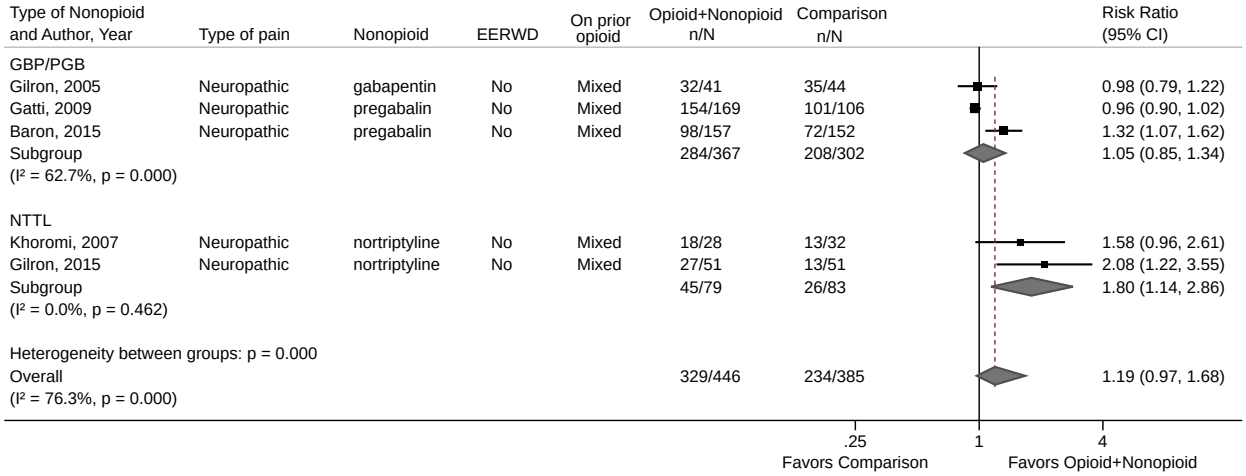
Table 20. Pain and function results for opioids plus nonopioids versus opioids

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid + Nonopioid 2: Opioid	Pain* (Continuous)	Pain (Dichotomous)	Function* (Continuous)
Baron, 2015[152] Germany, Poland, Spain, Belgium, Austria, Denmark, the Netherland Fair	1: 8 weeks 2: 313 3: Low back pain with neuropathic component	1: Tapentadol SR 300 mg + pregabalin 150 to 300 mg (mean NR) 2: Tapentadol SR 300 to 500 mg (mean NR)	NRS 0 to 10 1: Change -4.2 (2.66) 2: Change -4.1 (2.58)	Much or very much improved 1: 62.4% (98/157) 2: 47.4% (72/152)	NR
Gatti, 2009[148] Italy Poor	1: 13 weeks 2: 275 3: Mixed neuropathic pain	1: Oxycodone SR (mean 36 mg) + pregabalin (mean142 mg) 2: Oxycodone SR (mean 46 mg)	NRS 0 to 10 1: 1.49 (NR) 2: 1.96 (NR)	Treatment "effective" or "very effective" 1: 91.1% (154/169) 2: 95.3% (101/106)	BPI, general activity 0 to 10 1: 2.02 (NR) 2: 2.97 (NR)
Gilron, 2005[67] Canada Fair	1: 5 weeks 2: 57 3: Diabetic neuropathic postherpetic neuralgia	1: Morphine up to 60 mg (mean 34 mg) + gabapentin 2400 mg (mean 1705 mg) 2: Morphine up to 120 mg (mean 45 mg)	McGill Pain Questionnaire, VAS 0 to 10 1: 2.6 (0.4) 2: 3.3 (0.4)	Pain relief at least moderate 1: 78.0% (32/41) 2: 79.5% (35/44)	BPI, general activity 0 to 10 1: 2.9 (0.4) 2: 3.1 (0.4)
Gilron, 2015[141] Canada Fair	1: 6 weeks 2: 52 3: Peripheral neuropathic pain	1: Morphine SR up to 100 mg (mean 49 mg) + nortriptyline up to 100 mg (mean 55 mg) 2: Morphine SR up to 100 mg (mean 84 mg)	NRS 0 to 10 1: 2.6 (2.9) 2: 3.4 (2.9)	Improvement in pain ≥30% 1: 52.9% (27/51) 2: 25.5% (13/51)	BPI, general activity 0 to 10 1: 1.6 (0.3) 2: 2.1 (0.3
Khoromi, 2007[82] USA Fair	1: 7 weeks 2: 55 3: Low back pain with radiculopathy	1: Morphine up to 90 mg (mean 49 mg) + nortriptyline up to 100 mg (mean 55 mg) 2: Morphine SR up to 90 mg (mean 62 mg)	NRS 0 to 10 1: 3.4 (2.5) 2: 3.4 (2.8)	Pain relief moderate or greater 1: 64.3% (18/28) 2: 40.6% (13/32)	Oswestry Disability Index 0 to 100 1: 27.4 (15.4) 2: 25.7 (16.5)
Rigo, 2017[146] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic	1: Methadone 9 mg + ketamine 90 mg 2: Methadone 9 mg	VAS 0 to 10 1: 13 (2.2) 2: 13 (1.3)	NR	NR

Abbreviations: BPI=Brief Pain Inventory; NR=not reported; NRS=numeric rating scale; SD=standard deviation; SR=sustained release; VAS=Visual Analog Scale.

*Means (SD), unless otherwise reported

Figure 25. Meta-analysis of likelihood of experiencing a pain response for opioids plus nonopioids versus opioids



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; n=sample with a pain response; N=overall sample; NR=not reported; NTTL=nortryptiline; PGB=pregabalin

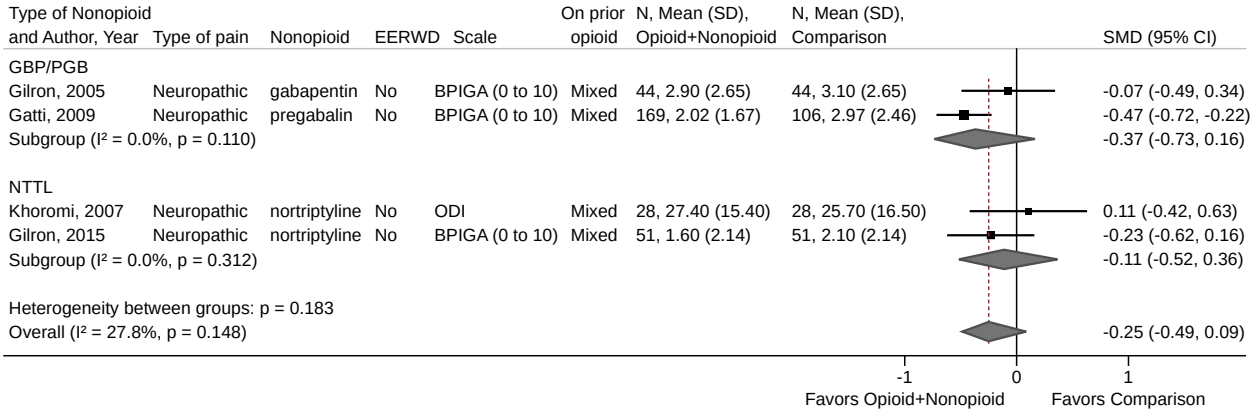
Table 21. Pooled analyses of likelihood of experiencing a pain response for opioids plus nonopioids versus opioids

Analysis	Pain, RR (95% CI)	I^2	Number of Trials (N)	p*
All trials	1.19 (0.97 to 1.68)	76%	5 (831)	--
Nonopioid type: Gabapentinoid	1.05 (0.85 to 1.34)	63%	3 (669)	0.11
Nortriptyline	1.80 (1.14 to 2.86)	0%	2 (162)	--
Trial quality: Fair	1.31 (0.99 to 1.93)	56%	4 (556)	0.44
Poor	0.96 (0.90 to 1.02)	--	1 (275)	--
Opioid dose (mg MED/day): <50	1.06 (0.74 to 2.02)	0%	2 (145)	0.98
50-90	0.97 (0.52 to 1.81)	0%	2 (377)	--
>90	1.32 (1.07 to 1.62)	--	1 (309)	--

Abbreviations: CI=confidence interval; RR=risk ratio; N=number of trials; MED=morphine equivalent dose.

*p value for interaction

Figure 26. Meta-analysis of improvement in mean function measures for opioids plus nonopioids versus opioids



Abbreviations: BPIGA= Brief Pain Inventory General Activity; CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; N=sample size; NTTL=nortryptiline; PGB=pregabalin; ODI= Oswestry Disability Index; SD=standard deviation; SMD=standardized mean difference.

Table 22. Pooled analysis of improvement in mean pain and function measures for opioids plus nonopioids versus opioids

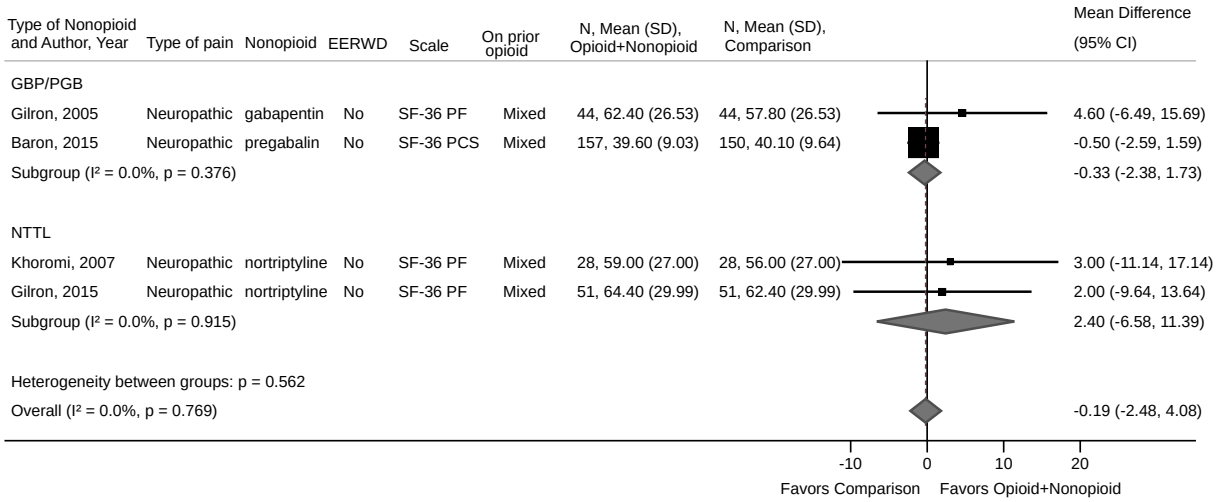
Analysis	Pain (Continuous), MD (95% CI) on 0 to 10 Scale*	I^2	Number of Trials (N)	p†	Function (Continuous), SMD (95% CI)*	I^2	Number of Trials (N)	p†
All trials	-0.18 (-0.72 to -0.36)	46%	6 (854)	--	-0.25 (-0.49 to 0.09)	28%	4 (521)	--
Nonopioid: Gabapentinoid	-0.39 (-0.76 to 0.00)	0%	3 (670)	0.13	-0.37 (-0.73 to 0.16)	0%	2 (363)	0.49
Nortriptyline	-0.48 (-1.58 to 0.74)	0%	2 (158)	--	-0.11 (-0.52 to 0.36)	0%	2 (158)	--
Opioid type: Opioid agonist	-0.18 (-0.72 to -0.36)	46%	6 (854)	--	-0.25 (-0.49 to 0.09)	28%	4 (521)	--
Pain type: Neuropathic	-0.18 (-0.72 to -0.36)	46%	6 (854)	--	-0.25 (-0.49 to 0.09)	28%	4 (521)	--
Trial quality: Fair	-0.06 (-0.79 to 0.58)	41%	5 (579)	0.57	-0.10 (-0.36 to 0.19)	0%	3 (246)	0.17
Poor	-0.47 (-0.84 to -0.10)	--	1 (275)	--	-0.47 (-0.72 to -0.22)	--	1 (275)	
Opioid dose (mg MED/day): <50	0.17 (-1.07 to 1.25)	45%	3 (170)	0.60	0.00 (-0.39 to 0.40)	0%	2 (144)	0.18
50-90	-0.50 (-1.09 to -0.05)	0%	2 (377)	--	-0.40 (-0.67 to -0.06)	0%	2 (377)	--
>90	-0.10 (-0.69 to 0.49)	--	1 (307)	--	No studies	--	--	--
Crossover design	-0.57 (-1.28 to 0.20)	0%	3 (249)	0.37	-0.10 (-0.36 to 0.19)	0%	3 (246)	0.17
Parallel group	0.00 (-0.80 to 0.97)	70%	3 (608)	--	-0.47 (-0.72 to -0.22)	--	1 (275)	--

Abbreviations: CI=confidence interval; MD = mean difference; MED=morphine equivalent dose; N= total sample size; SMD=standard mean difference.

*Negative values indicate improvement in pain or function

†p value for interaction

Figure 27. Meta-analysis of improvement in mean SF-36 physical function measures for opioids plus nonopioids versus opioids



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; N=sample size; NTTL=nortryptiline; PGB=pregabalin; SD=standard deviation; SF-36 PCS= Short Form-36 Physical Component Scale; SF-36 PF=Short Form-36 Physical Function.

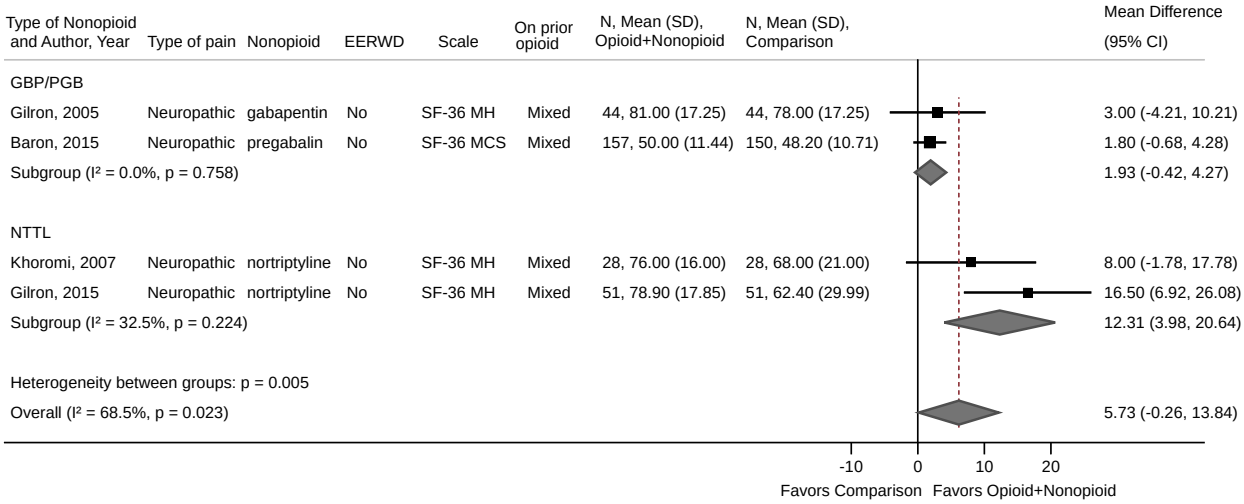
Table 23. Quality of life, sleep, and mental health outcomes for opioids plus nonopioids versus opioids

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid + Nonopioid 2: Opioid	Quality of Life*	Sleep*	Mental Health Outcomes*
Baron, 2015[152] Germany, Poland, Spain, Belgium, Austria, Denmark, the Netherland Fair	1: 8 weeks 2: 313 3: Low back pain with neuropathic component	1: Tapentadol SR 300 mg + pregabalin 150 to 300 mg (mean NR) 2: Tapentadol SR 300 to 500 mg (mean NR)	SF-36 PCS 1: 39.6 (9.03) 2: 40.1 (9.64) SF-36 MCS 1: 50 (11.44) 2: 48.2 (10.71)	NR	HAD depression 1: 5.4 (4.08) 2: 6.2 (4.94) HAD anxiety 1: 5.8 (4.44) 2: 6.0 (4.77)
Gatti, 2009[148] Italy Poor	1: 13 weeks 2: 275 3: Mixed neuropathic pain	1: Oxycodone SR (mean 36 mg) + pregabalin (mean142 mg) 2: Oxycodone SR (mean 46 mg)	NR	NR	BPI, sleep 0 to 10 1: 2.22 (NR) 2: 3.00 (NR)
Gilron, 2005[67] Canada Fair	1: 5 weeks 2: 57 3: Diabetic neuropathic postherpetic neuralgia	1: Morphine up to 60 mg (mean 34 mg) + gabapentin 2400 mg (mean 1705 mg) 2: Morphine up to 120 mg (mean 45 mg)	SF-36 PCS 1: 62.4 (4) 2: 57.8 (4) SF-36 MCS 1: 64.4 (4.2) 2: 62.4 (4.2)	BPI, sleep 0 to 10 1: 1.1 (0.4) 2: 1.6 (0.4)	BDI 0 to 63 1: 6 (1) 2: 6.7 (1)
Gilron, 2015[141] Canada Fair	1: 6 weeks 2: 52 3: Peripheral neuropathic pain	1: Morphine SR up to 100 mg (mean 49 mg) + nortriptyline up to 100 mg (mean 55 mg) 2: Morphine SR up to 100 mg (mean 84 mg)	SF-36 PCS 1: 81 (2.6) 2: 78.9 (2.5) SF-36 MCS 1: 78.9 (2.5) 2: 62.4 (4.2)	NR	BDI II 0 to 63 1: 6.1 (0.9) 2: 6.7 (0.9)
Khoromi, 2007[82] USA Fair	1: 7 weeks 2: 55 3: Low back pain with radiculopathy	1: Morphine up to 90 mg (mean 49 mg) + nortriptyline up to 100 mg (mean 55 mg) 2: Morphine SR up to 90 mg (mean 62 mg)	SF-36 PCS 1: 59 (27) 2: 56 (27) SF-36 MCS 1: 76 (16) 2: 68 (21)	NR	BDI 0 to 63 1: 6 (5) 2: 9.6 (8.5)
Rigo, 2017[146] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic	1: Methadone 9 mg + ketamine 90 mg (mean NR) 2: Methadone 9 mg (mean NR)	NR	NR	NR

Abbreviations: BDI=Becky Depression Inventory; BPI=Brief Pain Inventory; HAD=Hospital Anxiety and Depression Scale; NR=not reported; SF-36 MCS= Short Form-36 Mental Component Summary; SF-36 PCS=Short Form-36 Physical Component Summary; SR=sustained release.

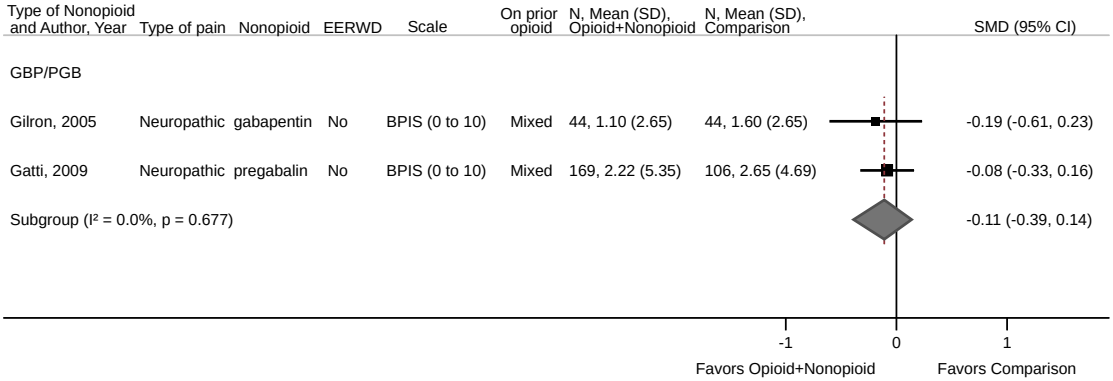
*Means (standard deviation), unless otherwise reported

Figure 28. Meta-analysis of improvement in mean SF-36 mental health measures for opioids plus nonopioids versus opioids



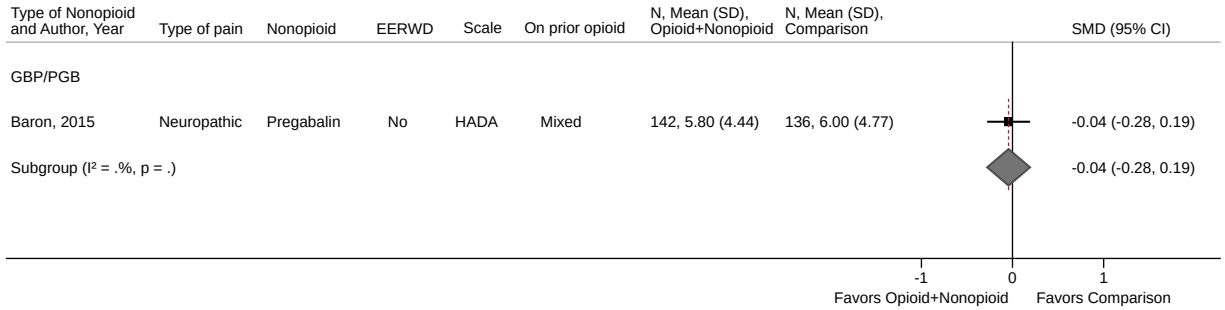
Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; N=sample size; NTTL=nortryptiline; PGB=pregabalin; SD=standard deviation; SF-36 MCS= Short Form-36 Mental Component Scale; SF-36 MH=Short Form-36 Mental Health.

Figure 29. Meta-analysis of improvement in mean sleep measures for opioids plus nonopioids versus opioids



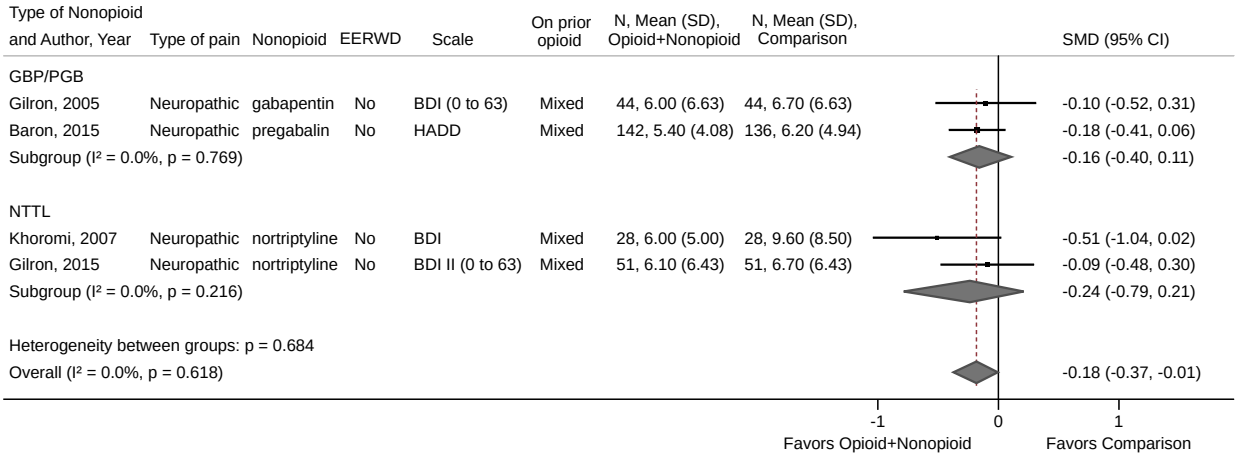
Abbreviations: BPIS=Brief Pain Inventory Sleep; CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; N=samlpe size; PGB=pregabalin; SD=standard deviation; SMD=standardized mean difference.

Figure 30. Meta-analysis of improvement in mean anxiety measures for opioids plus nonopioids versus opioids



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; GBP=gabapentin; HADA=Hospital Anxiety and Depression Scale-Anxiety; N=sample size; PGB=pregabalin; SD=standard deviation; SMD=standardized mean difference.

Figure 31. Meta-analysis of improvement in mean depression measures for opioids plus nonopioids versus opioids



Abbreviations: BDI=Beck Depression Inventory; BDI II=Beck Depression Inventory II; CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; HADD=Hospital Anxiety and Depression Scale-Depression; GBP=gabapentin; N=sample size; NTTL=nortryptiline; PGB=pregabalin; SD=standard deviation; SMD=standardized mean difference.

Doses of Opioids Used

Three randomized trials of opioids plus nonopioids versus opioids alone titrated opioid doses and reported the doses of opioids used at short-term followup.[67,82,141,148] Combination therapy was consistently associated with decreased mean opioid doses versus opioid therapy alone at similar or better levels of pain relief, though differences were modest and differences were statistically significant in only one trial. In three trials (n=370) of patients with neuropathic pain, mean daily morphine dose was 5 to 10 mg lower with morphine plus gabapentin than morphine alone (mean 34.4 vs. 45.3 mg, p=0.02, 60.2 vs. 65.4 mg, p=0.41 and 35.8 vs. 46.1 mg, p not reported); pain relief was 0.35 to 0.9 point better with combination therapy on a 0 to 10 scale.[67,141,148] A trial of patients (n=28) with lumbar radiculopathy found mean daily morphine dose lower with morphine plus nortriptyline than morphine alone (mean 49 vs. 62 mg/day, p=0.09); pain relief was 0.3 point better with combination therapy.[82]

Cannabis Use

Two cohort studies evaluated effects of cannabis use in patients prescribed opioids for chronic pain (Appendix Tables G-2, H3, and H4).[153,154] One fair-quality Australian cohort study (n=1514) of patients prescribed opioids that evaluated outcomes for 4 years found no association between self-reported level of cannabis use (categorized as near-daily/daily use [≥20 days/month]; less frequent use [< 20 days/month]; or no use) and the opioid dose at the following assessment, after adjustment for the opioid dose at the prior assessment, age, sex, pain duration, pain intensity, anxiety, substance use disorder, and time (mg MED/day 97.1 vs 95.1 vs 85.5, respectively; p=0.27 for near-daily/daily vs. no use and p=0.69 for less frequent vs. no use).[153] At baseline, 43 percent reported cannabis use, 13 percent use in the past 12 months, and 8 percent in the past month. There were also no differences in adjusted BPI pain severity (5.2 vs. 5.1 vs. 4.9, respectively) or pain interference (5.2 vs. 5.7 vs. 5.4, respectively) (BPI score range 0

to 10). In unadjusted analyses, cannabis use was not associated with increased likelihood of opioid discontinuation at 4 years or earlier time points (at 4 years, 21.5% vs. 9.0% vs. 20.9%, respectively; RR 1.05, 95% CI, 0.60 to 1.84 for near-daily/daily use vs. no use and RR 0.38, 95% CI, 0.17 to 0.83) or lower opioid dose (at 4 years, 49 vs. 63 vs. 55 mg MED/day, respectively), and cannabis use was associated with increased anxiety based on the Generalized Anxiety Disorder scale (at 4 years, 7.3 vs. 6.4 vs. 4.3, respectively on a 0 to 21 scale [scores <5 considered mild anxiety]; p<0.0001 for near-daily/daily use vs. no use and p=0.0005 for less frequent vs. no use). Findings were similar in the subgroup of patients with neuropathic pain. Cannabis use was illegal in Australia during most of the study, which could have impacted the reliability of cannabis use self-report. Because study participants could have already been using cannabis at baseline, the study was limited in its ability to evaluate effects of cannabis initiation.

A small (n=66), poor-quality retrospective cohort study found that patients prescribed opioids for chronic pain who enrolled in the New Mexico Medical Cannabis Program (MCP) were more likely to reduce their daily opioid dose between the first 3 months of study enrollment and the last 3 months of study enrollment (reduction 83.8% vs 44.8% OR 5.12, 95% CI, 1.56 to 16.88).[154] The mean dose was 24.4 vs 16.2 mg intravenous MED/day [converted from oral doses] in the first 3 months of observation (p=0.10). There was a slight monthly trend towards lower prescribed opioid dose in patients enrolled in the MCP (difference -0.64 mg intravenous morphine, 95% CI, -1.10 to -0.18, p=0.008). A limitation of the study is the unavailability of information regarding actual use of cannabis. In addition, the extent to which physicians were aware of enrollment in the MCP and the degree to which this influenced recommendations regarding opioid tapering was not evaluated.

Key Question 2a. In patients with chronic pain, what are the risks of opioids versus placebo or no opioid on: (1) opioid use disorder, abuse, or misuse; (2) overdose (intentional and unintentional); and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and psychological harms (e.g., depression)?

Key Points

- Opioids were associated with increased risk of discontinuation due to adverse events versus placebo at short-term followup (61 trials, N=19,994, RR 2.25, 95% CI, 1.86 to 2.73, I^2=72%; ARD 10%, 95% CI, 7% to 12%) (SOE: high).
- There was no difference between opioids versus placebo in risk of serious adverse events at short-term followup (38 trials, N=13,160, RR 1.23, 95% CI, 0.88 to 1.74, I^2=36%) (SOE: moderate).
- Opioids were associated with increased risk of nausea (60 trials, N=19,718, RR 2.46, 95% CI, 2.17 to 2.80, I^2=50%; ARD 14%, 95% CI, 11% to 17%), vomiting (49 trials, N=17,388, RR 3.57, 95% CI, 2.98 to 4.34, I^2=15%; ARD 7%, 95% CI, 6% to 9%), and constipation (58 trials, N=19,351, RR 3.38, 95% CI, 2.96 to 3.92, I^2=21%; ARD 14%, 95% CI, 11% to 17%) versus placebo at short-term followup (SOE: high).
- Opioids were associated with increased risk of somnolence versus placebo at short-term followup (52 trials, N=17,458, RR 2.97, 95% CI, 2.44 to 3.66, I^2=48%; ARD 9%, 95% CI, 7% to 12%) (SOE: high).

- Opioids were associated with increased risk of dizziness versus placebo at short-term followup (53 trials, N=18,396, RR 2.66, 95% CI, 2.37 to 2.99, I^2=0%; ARD 8%, 95% CI, 6% to 10%) (SOE: high).
- Opioids were associated with increased risk of pruritus versus placebo at short-term followup (30 trials, N=11,454, RR 3.51, 95% CI, 2.47 to 5.16, I^2=50%; ARD 7%, 95% 4% to 10%) (SOE: high).
- Opioids were not associated with increased risk of headaches versus placebo at short-term followup (48 trials, N=17,405, RR 1.06, 95% CI, 0.95 to 1.17, I^2=0%) (SOE: high).
- Two cohort studies found an association between opioid use and increased risk of opioid abuse, dependence, or addiction (SOE: low).
- Two cohort studies found an association between opioid use and increased risk of overdose events (SOE: low).
- One cohort study found prescription of long-acting opioids associated with increased risk of all-cause mortality versus nonopioid medications (SOE: low).
- Six observational studies found an association between opioid use and risk of fracture and three observational studies found an association between opioid use and risk of falls, though differences were not statistically significant in all studies; estimates decreased with longer duration of opioid use in some studies (SOE: low).
- Two observational studies found an association between opioid use and increased risk of myocardial infarction (SOE: low).
- One cross-sectional study of men with back pain found long-term opioid use associated with increased risk for use of medications for erectile dysfunction or testosterone replacement versus nonuse (SOE: low).
- One cohort study found no association between any long-term opioid use and increased risk of attempted suicide/self-harm (SOE: low).

Description of Included Studies

The randomized trials described in Key Question 1a were utilized to assess the association between opioids versus placebo or no opioid and risk of discontinuation due to adverse events, serious adverse events, gastrointestinal adverse events, somnolence, dizziness, somnolence, headaches, and pruritus of opioids short-term followup. The trials were not designed to assess risk of overdose, opioid use disorder, abuse, misuse, all-cause mortality, fractures, falls, cardiovascular events, endocrinological adverse effects, and suicidality/suicide risk; for these outcomes, thirteen observational studies were utilized (see specific outcomes for descriptions of studies).[155-167]

Detailed Synthesis

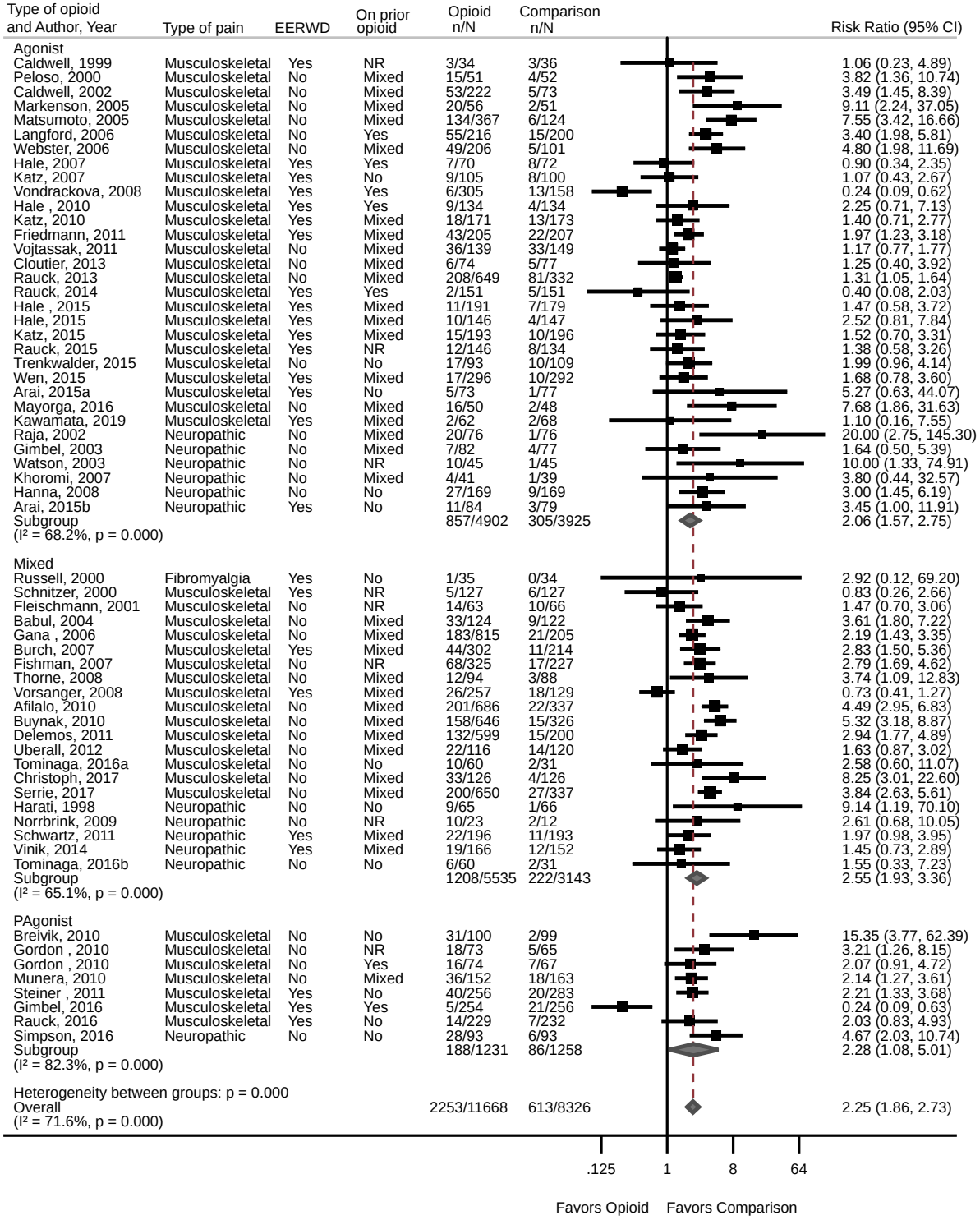
Discontinuation Due to Adverse Events and Serious Adverse Events

Opioids were associated with increased risk of study discontinuation due to adverse events versus placebo at short-term followup (61 trials, N=19,994, RR 2.25, 95% CI, 1.86 to 2.73, I^2=72%; ARD 10%, 95% CI, 7% to 12%; Figure 32, Table 24).[50-52,54-59,61-66,68-77,79-83,85-87,90,93-104,107-115,117,119-121,126] Trials that utilized an EERW design reported a lower risk of withdrawal due to adverse events (25 trials, N=8011, RR 1.35, 95% CI, 1.02 to 1.78, I^2=54%) than trials that did not utilize this design (36 trials, N=11,983, RR 3.06, 95% CI, 2.50 to 3.81, I^2=62%) and trials

published prior to 2007 reported a higher risk of discontinuation due to adverse events (16 trials, N=4039, RR 3.21, 95% CI, 2.29 to 4.73, I^2=42%) than trials published in or after 2007 (45 trials, N=15,955, RR 2.02, 95% CI, 1.62 to 2.51, I^2=74%). There were no interactions between trial quality, crossover design, geographic region, and presence of industry funding and effects on risk of discontinuation due to adverse events (Table 25).

There was no difference between opioids versus placebo in risk of serious adverse events (38 trials, N=13,160, RR 1.23, 95% CI, 0.88 to 1.74, I^2=36%).[50,51,54,56,59,61,63-65,68,71-75,79-81,85,87,89,90,96,97,99,102-105,107-109,111,114,115,119,121,126] Serious adverse events were generally not well defined by the trials. No interactions were observed in stratified analyses (Table 25).

Figure 32. Meta-analysis of risk of discontinuation due to adverse events for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; n=number who discontinued due to adverse events; N=overall sample; NR=not reported; PAgonist=partial agonist.

Table 24. Summary table of adverse events for opioids versus placebo

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Afilalo, 2010[50] Inter-national Fair	1: 15 weeks 2: 1030 3: Osteoarthritis of knee	1a: Tapentadol SR 200-500 mg (mean 350 mg) 1b: Oxycodone SR 40 to 100 mg (mean 70 mg) 2: Placebo	1a: 17.7% (61/344) 1b: 40.9% (140/342) 2: 6.5% (22/337)	1a: 1.2% (4/344) 1b: 2.9% (10/342) 2: 1.8% (6/337)	1a: 21.5% (74/344) 1b: 36.5% (125/342) 2: 6.8% (23/337)	1a: 5.2% (18/344) 1b: 17.8% (61/342) 2: 3.3% (11/337)	1a: 18.9% (65/344) 1b: 36.8% (126/342) 2: 6.5% (22/337)	1a: 17.7% (61/344) 1b: 19.0% (65/342) 2: 4.7% (16/337)	1a: 14.8% (51/344) 1b: 14.6% (50/342) 2: 16.6% (56/337)	1a: 10.7% (37/344) 1b: 19.6% (67/342) 2: 4.1% (14/337)	1a: 7.0% (24/344) 1b: 12.6% (43/342) 2: 1.2% (4/337)
Arai, 2015[51] Japan Poor	1: 12 weeks 2: 150 3: Osteoarthritis or low back pain	1: Fentanyl patch 25 to 50 mcg/hour (mean 15.1 mcg/hour) 2: Placebo	1: 6.8% (5/73) 2: 1.3% (1/77)	1: 2.7% (2/73) 2: 0% (0/77)	1: 6.8% (5/73) 2: 7.8% (6/77)	1: 4.1% (3/73) 2: 1.3% (1/77)	1: 8.2% (6/73) 2: 3.9% (3/77)	1: 1.4% (1/73) 2: 2.6% (2/77)	1: 0% (0/73) 2: 1.3% (1/77)	1: 4.1% (3/73) 2: 0% (0/77)	NR
Arai, 2015[51] Japan Poor	1: 12 weeks 2: 163 3: Postherpetic neuralgia, complex regional pain syndrome, or chronic post-op pain	1: Fentanyl patch 25 to 50 mcg/hour (mean 18.6 mcg/hour) 2: Placebo	1: 13.1% (11/84) 2: 3.8% (3/79)	1: 9.5% (8/84) 2: 5.1% (4/79)	1: 15.5% (13/84) 2: 12.6% (10/79)	1: 5.9% (5/84) 2: 1.3% (1/79)	1: 14.3% (12/84) 2: 12.6% (10/79)	1: 7.1% (6/84) 2: 3.8% (3/79)	NR	1: 14/3% (12/84) 2: 6.3% (5/79)	1: 5.9% (5/84) 2: 0% (0/79)
Babul, 2004[52] USA Fair	1: 12 weeks 2: 246 3: Osteoarthritis	1: Tramadol SR 200 to 400 mg (mean 276 mg) 2: Placebo	1: 26.6% (33/124) 2: 7.4% (9/122)	NR	1: 24.2% (30/124) 2: 8.2% (10/122)	1: 7.3% (9/124) 2: 0% (0/122)	1: 25.8% (32/124) 2: 5.7% (7/122)	1: 33.1% (41/124) 2: 12.3% (15/122)	1: 15.3% (19/124) 2: 16.4% (20/122)	1: 8.1% (10/124) 2: 1.6% (2/122)	1: 7.3% (9/124) 2: 1.6% (2/122)
Boureau, 2003[53] France Good	1: 6 weeks 2: 127 3: Postherpetic neuralgia	1: Tramadol 10 to 400 mg (mean 276 mg) 2: Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
Breivik, 2010[54] Inter-national Fair	1: 24 weeks 2: 199 3: Osteoarthritis	1: Buprenorphine patch 5 to 20 mcg/hour (mean 11.0 mcg/hour) 2: Placebo	1: 31% (31/100) 2: 2.0% (2/99)	1: 5% (5/100) 2: 4.0% (4/99)	1: 24% (24/100) 2: 5.0% (5/99)	1: 16% (16/100) 2: 2.0% (2/99)	1: 24% (24/100) 2: 5.0% (5/99)	1: 25% (25/100) 2: 9.1% (9/99)	1: 7% (7/100) 2: 6.1% (6/99)	1: 4% (4/100) 2: 0% (0/99)	NR

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Burch, 2007[55] International Good	1: 12 weeks 2: 646 3: Osteoarthritis	1: Tramadol SR 200 to 300 mg (mean 275 mg) 2: Placebo	1: 14.6% (44/302) 2: 5.1% (11/214)	NR	1: 15.3% (66/432) 2: 5.6% (12/214)	NR	1: 14.1% (61/432) 2: 4.2% (9/214)	1: 9.7% (42/432) 2: 3.7% (8/214)	NR	1: 6.7% (29/432) 2: 3.7% (8/214)	NR
Buynak, 2010[56] USA Fair	1: 15 weeks 2: 981 3: Low back pain	1a: Tapentadol SR 200 to 500 mg (mean 313 mg) 1b: Oxycodone SR 40 to 100 mg (mean 53 mg) 2: Placebo	1a: 16.0% (51/318) 1b: 32.6% (107/328) 2: 4.6% (15/326)	1a: 2.2% (7/318) 1b: 3.4% (11/328) 2: 0.9% (3/319)	1a: 20.1% (64/318) 1b: 34.5% (113/328) 2: 9.1% (29/319)	1a: 9.1% (29/318) 1b: 19.2% (63/328) 2: 1.6% (5/319)	1a: 13.8% (44/318) 1b: 26.8% (88/328) 2: 5.0% (16/319)	1a: 11.9% (38/318) 1b: 17.1% (56/328) 2: 5.6% (18/319)	1a: 19.8% (63/318) 1b: 16.8% (55/328) 2: 13.8% (44/319)	1a: 13.2% (42/318) 1b: 16.2% (53/328) 1c: 2.5% (8/319)	1a: 7.2% (23/318) 1b: 16.8% (55/328) 2: 1.9% (6/319)
Caldwell, 1999[57] USA Fair	1: 4 weeks 2: 70 3: Osteoarthritis	1: Oxycodone SR 20 to 60 mg (mean 40 mg) 2: Placebo	1: 8.8% (3/34) 2: 8.3% (3/36)	NR	NR	NR	NR	NR	NR	NR	NR
Caldwell, 2002[58] USA Fair	1: 4 weeks 2: 295 3: Osteoarthritis	1: Morphine SR 30 mg, qd or bd (mean NR) 2: Placebo	1: 23.9% (53/222) 2: 6.8% (5/73)	NR	1: 26.1% (58/222) 2: 9.6% (7/73)	1: 9.9% (22/222) 2: 1.4% (1/73)	1: 39.2% (87/222) 2: 4.1% (3/73)	1: 10.4% (23/222) 2: 1.4% (1/73)	1: 5.4% (12/222) 2: 5.5% (4/73)	1: 13.5% (30/222) 2: 0% (0/73)	1: 5.8% (13/222) 2: 0% (0/73)
Christoph 2017[59] Germany Fair	1: 14 weeks 2: 252 3: Low back pain	1: Tapentadol SR 400 mg (mean NR) 2: Placebo	1: 26.2% (33/126) 2: 3.2% (4/126)	1: 2.4% (3/126) 2: 1.6% (2/126)	1: 26.2% (33/126) 2: 6.3% (8/126)	1: 11.9% (15/126) 2: 4.0% (5/126)	1: 39.2% (22/126) 2: 4.0% (5/126)	1: 28.6% (36/126) 2: 8.7% (11/126)	1: 7.9% (10/126) 2: 8.7% (11/126)	1: 14.3% (18/126) 2: 4.8% (6/126)	NR
Chu, 2012[60] USA Fair	1: 4.5 weeks 2: 139 3: Low back pain	1: Morphine SR 30 to 120 mg (mean 78 mg) 2: Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Cloutier, 2013[61] Canada Fair	1: 4 weeks 2: 83 3: Low back pain	1: Oxycodone SR 20 to 80 mg (mean 36 mg) + Naloxone 2: Placebo	1: 8.1% (6/74) 2: 6.5% (5/77)	1: 2.7% (2/74) 2: 2.6% (2/77)	1: 12.2% (9/74) 2: 11.7% (9/77)	1: 5.4% (4/74) 2: 3.9% (3/77)	1: 8.1% (6/74) 2: 2.6% (2/77)	1: 4.0% (374) 2: 2.6% (2/77)	NR	1: 5.4% (4/74) 2: 0% (0/77)	NR
DeLemos, 2011[62] USA Fair	1: 12 weeks 2: 808 3: Osteoarthritis	1: Tramadol SR 100, 200, or 300 mg (mean 200 mg) 2: Placebo	1: 22.0% (132/599) 2: 7.5% (15/200)	1: 0% (0/599) 2: 0% (0/200)	1: 20.7% (124/599) 2: 8.5% (17/200)	1: 7.2% (43/599) 2: 2.5% (5/200)	1: 16.4% (98/599) 2: 2.5% (5/200)	1: 20.5% (123/599) 2: 7.5% (15/200)	1: 12.8% (77/599) 2: 13% (26/200)	1: 8.5% (51/599) 2: 1% (2/200)	1: 7.8% (47/599) 2: 0.5% (1/200)
Fishman, 2007[63] USA, Canada Fair	1: 12 weeks 2: 552 3: Osteoarthritis	1: Tramadol SR 100, 200, or 300 mg (mean 201 mg) 2: Placebo	1: 20.9% (68/325) 2: 7.5% (17/227)	1: 0.6% (2/325) 2: 0.9% (2/227)	1: 19.1% (62/325) 2: 5/7% (13/227)	1: 8.0% (26/325) 2: 0.4% (1/227)	1: 12.4% (39/315) 2: 1.3% (3/227)	1: 14.1% (46/325) 2: 4.8% (11/227)	1: 6.8% (22/325) 2: 7.9% (18/227)	1: 12.0% (39/325) 2: 0.9% (2/227)	1: 8.3% (27/325) 2: 0% (0/227)
Fleisch-mann, 2001[64] USA Poor	1: 12 weeks 2: 129 3: Osteoarthritis	1: Tramadol 200 to 400 mg (mean NR) 2: Placebo	1: 22.2% (14/63) 2: 15.1% (10/66)	1: 0% (0/63) 2: 3.0% (2/66)	1: 17.5% (11/63) 2: 3.0% (2/66)	NR	1: 12.7% (8/63) 2: 0% (0/66)	1: 9.5% (6/63) 2: 3.0% (2/66)	1: 7.9% (5/63) 2: 0% (0/66)	NR	1: 9.5% (6/63) 2: 0% (0/66)
Fried-mann, 2011[65] USA Fair	1: 12 weeks 2: 412 3: Osteoarthritis	1: Oxycodone SR up to 40 mg (mean 27.5 mg) 2: Placebo	1: 21.0% (43/205) 2: 10.6% (22/207)	1: 2.4% (5/205) 2: 1.0% (2/207)	1: 20.0% (41/205) 2: 9.7% (20/207)	1: 14.1% (29/205) 2: 2.9% (6/207)	1: 17.1% (35/205) 2: 4/3% (9/207)	1: 8.3% (17/205) 2: 4.3% (9/207)	1: 4.9% (10/205) 2: 5.3% (11/207)	1: 11.2% (23/205) 2: 1.9% (4/207)	1: 3.4% (7/205) 2: 2.9% (6/207)

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Gana, 2006[66] (also Vor-sanger 2007)[116] USA Fair	1: 12 weeks 2: 1020 3: Osteoarthritis	1: Tramadol SR 100 to 400 mg (mean NR) 2: Placebo	1: 22.4% (183/815) 2: 10.2% (21/205)	NR	1: 22.1% (178/806) 2: 7.3% (15/205)	1: 7.3% (59/806) 2: 2.9% (6/205)	1: 20.3% (164/806) 2: 6.3% (13/205)	1: 20.9% (169/806) 2: 6.3% (13/205)	1: 13.9% (112/806) 2: 8.3% (17/205)	1: 12.0% (97/806) 2: 2.4% (5/205)	1: 8.1% (65/806) 2: 1.5% (3/205)
Gilron, 2005[67] Canada Fair	1: 5 weeks 2: 57 3: Diabetic neuropathy	1: Morphine up to 120 mg (mean 45 mg) 2: Lorazepam	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gimbel, 2003[69] USA Fair	1: 6 weeks 2: 159 3: Diabetic neuropathy	1: Oxycodone SR 10 to 120 mg (mean 37 mg) 2: Placebo	1: 8.5% (7/82) 2: 5.2% (4/77)	NR	1: 36.6% (30/82) 2: 7.8% (6/77)	1: 20.7% (17/82) 2: 2.6% (2/77)	1: 42.7% (35/82) 2: 14.3% (11/77)	1: 31.7% (26/82) 2: 10.4% (8/77)	1: 11.0% (9/82) 2: 23.4% (18/77)	1: 40.2% (33/82) 2: 1.3% (1/77)	1: 24.4% (20/82) 2: 7.8% (6/77)
Gimbel, 2016[68] USA Fair	1: 12 weeks 2: 511 3: Low back pain	1: Buprenorphine buccal 300 to 1800 mcg (mean 1320 mcg) 2: Placebo	1: 2.0% (5/254) 2: 8.2% (21/256)	1: 1.6% (4/254) 2: 1.6% (4/256)	1: 7.5% (19/254) 2: 7.4% (19/256)	1: 5.5% (14/254) 2: 2.3% (6/256)	1: 2.7% (7/254) 2: 0.8% (2/256)	1: 0.8% (2/254) 2: 0.8% (2/256)	1: 2.4% (6/254) 2: 3.1% (8/256)	1: 0% (0/254) 2: 0% (0/256)	NR
Gordon, 2010[70] Canada Fair	1: 4 weeks 2: 78 3: Low back pain	1: Buprenorphine patch 10 to 30 mcg/hour (mean 30 mcg/hour) 2: Placebo	1: 21.6% (16/74) 2: 10.4% (7/67)	1: 0% (0/73) 2: 0% (0/68)	1: 53.4% (39/73) 2: 17.6% (12/68)	1: 21.9% (16/73) 2: 4.4% (3/68)	1: 16.4% (12/73) 2: 5.9% (4/68)	1: 32.9% (24/73) 2: 4.4% (3/68)	1: 12.3% (9/73) 2: 4.4% (3/68)	1: 21.9% (16/73) 2: 7.3% (5/68)	1: 23.3% (17/73) 2: 20.6% (14/68)
Gordon, 2010[71] Canada Fair	1: 4 weeks 2: 79 3: Low back pain	1: Buprenorphine patch 5 to 20 mcg/hour (mean 15.5 mcg/hour) 2: Placebo	1: 24.6% (18/73) 2: 7.7% (5/65)	1: 0% (0/73) 2: 1.5% (1/65)	1: 38.3% (28/73) 2: 16.9% (11/65)	1: 15.1% (11/73) 2: 4.6% (3/65)	1: 27.4% (23/73) 2: 21.5% (14/65)	1: 21.9% (16/73) 2: 7.7% (5/65)	1: 10.9% (8/73) 2: 9.2% (6/65)	1: 30.1% (22/73) 2: 6/1% (4/65)	1: 30.1% (22/73) 2: 27.7% (18/65)

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Hale, 2007[73] USA Fair	1: 12 weeks 2: 143 3: Low back pain	1: Oxymorphone SR (mean 80 mg) 2: Placebo	1: 10.0% (7/70) 2: 11.1% (8/72)	1: 2.8% (2/70) 2: 0% (0/72)	1: 2.8% (2/70) 2: 1.4% (1/72)	1: 0% (0/70) 2: 1.4% (1/72)	1: 5.7% (4/70) 2: 1.4% (1/72)	1: 0% (0/70) 2: 0% (0/72)	1: 2.8% (2/70) 2: 0% (0/72)	1: 2.8% (2/70) 2: 0% (0/72)	1: 1.4% (1/70) 2: 0% (0/72)
Hale, 2010[72] (also Nala-machu 2014)[91] USA Fair	1: 12 weeks 2: 268 3: Low back pain	1: Hydromorphone SR 12 to 64 mg (mean 37.3 mg) 2: Placebo	1: 6.7% (9/134) 2: 3.0% (4/134)	1: 4.5% (6/134) 2: 3.0% (4/134)	1: 8.9% (12/134) 2: 7.5% (10/134)	1: 6.0% (8/134) 2: 4.5% (6/134)	1: 7.5% (10/134) 2: 3.7% (5/134)	NR	1: 5.2% (7/134) 2: 7.5% (10/134)	1: 0.7% (1/134) 2: 0% (0/134)	NR
Hale, 2015[75] USA Good	1: 12 weeks 2: 371 3: Low back pain	1: Hydrocodone SR 60 to 180 mg (mean 100 mg) 2: Placebo	1: 5.7% (11/191) 2: 3.9% (7/179)	1: 1.6% (3/191) 2: 1.7% (3/179)	1: 10.5% (20/191) 2: 7.8% (14/179)	1: 4.2% (8/191) 2: 3.3% (6/179)	1: 14.1% (19/146) 2: 4.8% (7/147)	1: 1.0% (2/191) 2: 2.2% (4/179)	1: 5.7% (11/191) 2: 4.5% (8/179)	1: 3.1% (6/191) 2: 1.1% (2/179)	1: 1.0% (2/191) 2: 1.1% (2/179)
Hale, 2015[74] USA Fair	1: 12 weeks 2: 391 3: Low back pain or osteoarthritis	1: Hydrocodone SR 30 to 180 mg (mean NR) 2: Placebo	1: 6.8% (10/146) 2: 2.7% (4/147)	1: 2.0% (3/146) 2: 2.0% (3/147)	1: 13.0% (19/146) 2: 6.1% (9/147)	1: 6.2% (9/146) 2: 3.4% (5/147)	1: 13.0% (19/146) 2: 4.8% (7/147)	1: 2.0% (3/146) 2: 0.7% (1/147)	1: 6.8% (10/146) 2: 5.4% (8/147)	1: 1.0% (3/146) 2: 0.7% (1/147)	1: 2.0% (3/146) 2: 0.7% (1/147)
Hanna, 2008[76] UK Good	1: 12 weeks 2: 338 3: Diabetic neuropathy	1: Oxycodone SR (doses and mean NR) 2: Placebo	1: 16.0% (27/169) 2: 5.3% (9/169)	NR	1: 25.6% (43/168) 2: 10.8% (18/167)	1: 9.5% (16/168) 2: 4.2% (7/167)	1: 26.8% (45/168) 2: 6.0% (10/167)	1: 14.9% (25/168) 2: 3.6% (6/167)	1: 10.1% (17/168) 2: 9.6% (16/167)	1: 22.0% (37/168) 2: 5.4% (9/167)	NR
Harati, 1998[77] USA Fair	1: 6 weeks 2: 131 3: Diabetic neuropathy	1: Tramadol up to 400 mg (mean 210 mg)	1: 13.8% (9/65) 2: 1.5% (1/66)	NR	1: 23.1% (15/65) 2: 1.5% (1/66)	1: 4.6% (3/65) 2: 0% (0/66)	1: 21.5% (14/65) 2: 3.0% (2/66)	1: 4.6% (3/65) 2: 0% (0/66)	1: 16.9% (11/65) 2: 4.5% (3/66)	1: 12.3% (8/65) 2: 6.1% (4/66)	1: 6.1% (4/65) 2: 0% (0/66)

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Huse, 2001[78] Germany Poor	1: 4 weeks 2: 12 3: Phantom limb pain	1: Morphine SR 70 to 300 mg (mean NR) 2: Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
Katz, 2007[81] USA Fair	1: 12 weeks 2: 205 3: Low back pain	1: Oxymorphone SR (mean 39.2 mg) 2: Placebo	1: 8.6% (9/105) 2: 8% (8/100)	1: 1.9% (2/105) 2: 3% (3/100)	1: 11.4% (12/105) 2: 9% (9/100)	1: 7.6% (8/105) 2: 1% (1/100)	1: 6.7% (7/105) 2: 1% (1/100)	1: 4.8% (5/105) 2: 3% (3/100)	1: 3.8% (4/105) 2: 2% (2/100)	1: 1.9% (2/105) 2: 0% (0/100)	1: 2.8% (3/105) 2: 1.0% (1/100)
Katz, 2010[79] USA Fair	1: 12 weeks 2: 344 3: Osteoarthritis	1: Morphine SR 20 to 160 mg (mean 43.5 mg) 2: Placebo	1: 10.5% (18/171) 2: 7.5% (13/173)	1: 3.5% (6/171) 2: 1.7% (3/173)	1: 11.7% (20/171) 2: 7.5% (13/173)	1: 7.0% (12/171) 2: 2.3% (4/173)	1: 7.0% (12/171) 2: 4.0% (7/173)	1: 1.7% (3/171) 2: 1.7% (3/173)	1: 7.0% (12/171) 2: 3.5% (6/173)	1: 1.2% (1/171) 2: 2.9% (5/173)	1: 0.6% (1/171) 2: 0.6% (1/173)
Katz, 2015[80] USA Fair	1: 12 weeks 2: 389 3: Low back pain	1: Oxycodone SR 40 to 160 mg (mean 78 mg) 2: Placebo	1: 7.8% (15/193) 2: 5.1% (10/196)	1: 1.0% (2/193) 2: 1.0% (2/196)	1: 10.9% (21/193) 2: 4.6% (9/196)	NR	1: 5.2% (10/193) 2: 0.5% (1/196)	NR	NR	NR	NR
Kawa-mata, 2019[126] Japan Fair	1: 5 weeks 2: 130 3: Low back pain	1: Oxycodone SR 10 to 80 mg (mean NR) 2: Placebo	1: 3.2% (2/62) 2: 2.9% (2/68)	1: 3.2% (2/62) 2: 0% (0/68)	NR	NR	NR	NR	NR	NR	NR
Khoromi, 2007[82] USA Fair	1: 7 weeks 2: 55 3: Low back pain with radiculopathy	1: Morphine SR up to 90 mg (mean 62 mg) 2: Placebo	1: 9.7% (4/41) 2: 2.6% (1/39)	NR	1: 7.1% (2/28) 2: 0% (0/28)	NR	1: 64.3% (18/28) 2: 7.1% (2/28)	1: 14.3% (4/28) 2: 3.6% (1/28)	1: 14.3% (4/28) 2: 14.3% (4/28)	1: 25.0% (7/28) 2: 3.6% (1/28)	NR
Langford, 2006[83] Europe Fair	1: 6 weeks 2: 416 3: Osteoarthritis	1: Fentanyl 25 to 100 mg (mean 43.9 mcg/hour) 2: Placebo	1: 25.5% (55/216) 2: 7.5% (15/200)	NR	1: 43.5% (94/216) 2: 18.5% (37/200)	1: 28.2% (61/216) 2: 2.5% (5/200)	1: 10.2% (22/216) 2: 1.5% (3/200)	1: 12.0% (26/216) 2: 5.0% (10/200)	1: 10.6% (23/216) 2: 11.5% (23/200)	1: 22.2% (48/216) 2: 3.5% (7/200)	NR

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Lin, 2016[84] USA Poor	1: 4.5 weeks 2: 21 3: Low back pain	1: Morphine SR 30 to 120 mg (mean 72 mg) 2: Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
Marken-son, 2005[85] USA Fair	1: 13 weeks 2: 109 3: Osteoarthritis	1: Oxycodone SR 20 to 120 mg (mean 44 mg) 2: Placebo	1: 35.7% (20/56) 2: 3.9% (2/51)	1: 5.3% (3/56) 22: 0% (0/51)	1: 41.1% (23/56) 2: 13.7% (7/51)	1: 12.5% (7/56) 2: 2.0% (1/51)	1: 48.2% (27/56) 2: 9.8% (5/51)	1: 32.1% (18/56) 2: 5.9% (3/51)	1: 19.6% (11/56) 2: 19.6% (10/51)	1: 32.1% (18/56) 2: 9.8 (5/51)	1: 21.4% (12/56) 2: 0% (0/51)
Matsu-moto, 2005[86] USA Fair	1: 4 weeks 2: 491 3: Osteoarthritis	1a: Oxymorphone SR 40 to 80 mg (mean NR) 1b: Oxycodone SR 40mg (mean NR) 2: Placebo	1a: 42.6% (103/242) 1b:24.8% (31/125) 2: 4.8% (6/124)	NR	1a: 60.4% (145/240) 1b: 43.2% (54/125) 2: 10.5% (13/124)	1a: 28.3% (68/240) 1b: 10.4% (13/125) 2: 1.6% (2/124)	1a: 36.2% (87/240) 1b: 36.0% (45/125) 2: 11.3% (14/124)	1a: 30.0% (72/240) 1b: 25.6% (32/125) 2: 4.0% (5/124)	1a: 8.3% (20/240) 1b: 18.4% (23/125) 2: 11.3% (14/124)	1a: 30.8% (74/240) 1b: 27.2% (34/125) 2: 4.8% (6/124)	1a: 22.1% (53/240) 1b: 8.0% (10/125) 2: 2.4% (3/124)
Mayorga, 2016[87] USA Fair	1: 16 weeks 2: 98 3: Osteoarthritis	1: Oxycodone SR 40 to 100 mg (mean NR) 2: Placebo	1: 32.0% (16/50) 2: 4.2% (2/48)	1: 2.0% (1/50) 2: 2.1% (1/48)	1: 28.0% (14/50) 2: 8.3% (4/48)	1: 16.0% (8/50) 2: 6.2% (3/48)	1: 32.0% (16/50) 2: 0% (0/48)	1: 14.0% (7/50) 2: 2.1% (1/48)	1: 18.4% (23/125) 2: NR	1: 22.0% (11/50) 2: 4.2% (2/48)	NR
Moran, 1991[88] UK Poo r	1: 5 weeks 2: 20 3: Rheumatoid arthritis	1: CR Morphine 20 to 120 mg (mean NR) 2: Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
Moulin, 1996[89] Canada Poor	1: 6 weeks 2: 61 3: Mixed (primarily musculoskeletal)	1: Morphine up to 120 mg (mean 83.5 mg) 2: Benztropine	NR	1: 28% (13/46) 2: 2% (1/46)	1: 39% (18/46) 2: 7% (3/46)	1: 39% (18/46) 2: 2% (1/46)	1: 41% (19/46) 2: 4% (2/46)	1: 37% (17/46) 2: 2% (1/46)	NR	NR	NR

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Munera, 2010[90] USA Fair	1: 4 weeks 2: 315 3: Osteoarthritis	1: Buprenorphine patch 5 to 20 mcg/hour (mean NR) 2: Placebo	1: 23.7% (36/152) 2: 11.0% (18/163)	1: 0% (0/152) 2: 1.2% (2/163)	1: 27.0% (41/152) 2: 8.0% (13/163)	1: 10.5% (16/152) 2: 2.4% (4/163)	1: 9.9% (15/152) 2: 1.8% (3/163)	1: 19.7% (30/152) 2: 8.6% (14/163)	1: 22.4% (34/152) 2: 15.3% (25/163)	1: 15.1% (23/152) 2: 4.9% (8/163)	1: 5.3% (8/152) 2: 2.4% (4/163)
Niesters, 2014[92] The Nether-lands Good	1: 4 weeks 2: 25 3: Diabetic neuropathy	1: Tapentadol SR 200 mg, titrated to 500 mg (mean 433 mg)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Norrbrink 2009[93] Sweden Fair	1: 4 weeks 2: 36 3: Neuropathic pain after spinal cord injury	1: Tramadol 150 to 400 mg (median 250 mg) 2: Placebo	1: 43.5% (10/23) 2: 16.7% (2/12)	NR	1: 39.1% (9/23) 2: 25.0% 3/12)	NR	1: 34.8% (8/23) 2: 33.3% (4/12)	1: 52.2% (12/23) 2: 25.0% (3/12)	NR	1: 73.9% (17/23) 2: 16.7% (2/12)	NR
Peloso, 2000[94] Canada Fair	1: 4 weeks 2: 103 3: Osteoarthritis	1: Codeine SR 100 to 400 mg (mean 312 mg) 2: Placebo	1: 29.4% (15/51) 2: 8.3% (4/52)	NR	1: 49.0% (25/51) 2: 11.5% (6/52)	NR	NR	1: 33.3% (17/51) 2: 7.7% (4/52)	NR	1: 39.2% (20/51) 2: 9.6% (5/52)	NR
Raja, 2002[95] USA Fair	1: 8 weeks 2: 76 3: Postherpetic neuralgia	1: Morphine SR up to 240 mg (mean 91 mg) 2: Placebo	1: 26.3% (20/76) 2: 1.3% (1/76)	NR	1: 39.5% (30/76) 2: 6.6% (5/76)	NR	1: 30.3% (23/76) 2: 10.5% (8/76)	1: 13.1% (10/76) 2: 6.6% (5/76)	NR	1: 30.3% (23/76) 2: 14.5% (11/76)	NR
Rauck, 2013[96] USA Poor	1: 14 weeks 2: 990 3: Osteoarthritis	1: Hydromorphone SR 8 or 16 mg (mean 12 mg) 2: Placebo	1: 32.0% (208/649) 2: 24.4% (81/332)	1: 3.2% (21/649) 2: 1.5% (5/332)	1: 33.3% (216/649) 2: 9.6% (32/332)	1: 10.3% (67/649) 2: 2.1% (7/332)	1: 44.1% (286/649) 2: 11.7% (39/332)	1: 12.6% (82/649) 2: 6.0% (20/332)	1: 12.9% (84/649) 2: 11.4% (38/332)	1: 15.7% (102/649) 2: 4.8% (16/332)	1: 10.2% (66/649) 2: 2.4% (8/332)

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Rauck, 2014[98] USA Poor	1: 12 weeks 2: 302 3: Low back pain	1: Hydrocodone SR 40 to 200 mg (mean 119 mg) 2: Placebo	1: 1.3% (2/151) 2: 3.3% (5/151)	NR	1: 7.3% (11/151) 2: 3.3% (4/151)	1: 4.6% (7/151) 2: 0.7% (1/151)	1: 7.9% (12/151) 2: 0% (0/151)	1: 2.0% (3/151) 2: 0.7% (1/151)	1: 0% (0/151) 2: 1.3% (2/151)	1: 0.7% (1/151) 2: 0% (0/151)	1: 0% (0/151) 2: 0% (0/151)
Rauck, 2015[97] USA Fair	1: 12 weeks 2: 281 3: Low back pain	1: Oxycodone SR 20 to 160 mg (mean 64 mg) + Naltrexone 2: Placebo	1: 8.2% (12/146) 2: 6.0% (8/134)	1: 3.4% (5/146) 2: 1.5% (2/134)	1: 14.4% (21/146) 2: 3.7% (5/134)	1: 6.2% (9/146) 2: 3.0% (4/134)	1: 3.4% (5/146) 2: 2.2% (3/134)	1: 4.1% (6/146) 2: 0.7% (1/134)	1: 1.4% (2/146) 2: 5.2% (7/134)	1: 0.7% (1/146) 2: 0.7% (1/134)	1: 1.4% (2/146) 2: 0% (0/134)
Rauck, 2016[99] USA Fair	1: 12 weeks 2: 461 3: Low back pain	1: Buprenorphine buccal 300 to 900 mcg (mean 660 mcg) 2: Placebo	1: 6.1% (14/229) 2: 3.0% (7/232)	1: 1.3% (3/229) 2: 0.4% (1/232)	1: 10.0% (23/229) 2: 7.3% (17/232)	1: 3.9% (9/229) 2: 0.4% (1/232)	NR	1: 1.7% (4/229) 2: 0.4% (1/232)	1: 2.2% (5/229) 2: 3.4% (8/232)	1: 0.9% (2/229) 2: 0.4% (1/232)	NR
Russell, 2000[100] USA Fair	1: 6 weeks 2: 69 3: Fibromyalgia	1: Tramadol 50 to 400 mg (mean NR) 2: Placebo	1: 2.8% (1/35) 2: 0% (0/34)	NR	NR	NR	NR	NR	NR	NR	NR
Schnitzer 2000[101] USA Poor	1: 4 weeks 2: 254 3: Low back pain	1: Tramadol 200 to 400 mg (mean NR) 2: Placebo	1: 3.9% (5/127) 2: 4.7% (6/127)	NR	1: 8.7% (11/127) 2: 2.4% (3/127)	NR	NR	NR	1: 4.7% (6/127) 2: 3.1% (4/127)	NR	NR
Schwartz 2011[102] USA Fair	1: 12 weeks 2: 395 3: Diabetic neuropathy	1: Tapentadol 100 to 250 mg (mean NR) 2: Placebo	1: 11.2% (22/196) 2: 5.7% (11/193)	1: 5.1% (10/196) 2: 1.5% (3/193)	1: 13.8% (27/196) 2: 6.2% (12/193)	1: 6.6% (13/196) 2: 1.0% (2/193)	1: 6.1% (12/196) 2: 1.0% (2/193)	1: 7.6% (15/196) 2: 1.5% (3/193)	1: 5.1% (10/196) 2: 5.2% (10/193)	NR	NR

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Serrie, 2017[103] Europe Fair	1: 15 weeks 2: 990 3: Knee pain	1a: Tapentadol SR 200 to 500 mg (mean 315 mg) 1b: Oxycodone SR 40 to 100 mg (mean 54 mg) 2: Placebo	1a: 18.8% (60/319) 1b: 42.3% (140/331) 2: 8.0% (27/337)	1a: 0.6% (2/319) 1b: 3.9% (13/331) 2: 12.2% (41/337)	1a: 20.4% (65/319) 1b: 37.5% (124/331) 2: 6.2% (21/337)	1a: 10.3% (33/319) 1b: 26.0% (86/331) 2: 3.8% (13/337)	1a: 17.9% (57/319) 1b: 35.0% (116/331) 2: 9.2% (31/337)	1a: 21.9% (70/319) 1b: 26.9% (89/331) 2: 8.6% (29/337)	1a: 10.3% (33/319) 1b: 8.1% (27/331) 2: 9.2% (31/337)	1a: 10.6% (34/319) 1b: 14.5% (48/331) 2: 3.8% (13/337)	1a: 1.2% (4/319) 1b: 10.9% (36/331) 2: 1.8% (6/337)
Simpson, 2016[104] Australia Fair	1: 12 weeks 2: 186 3: Diabetic neuropathy	1: Buprenorphine patch 5 to 40 mcg/hour (mean 20 mcg/hour) 2: Placebo	1: 30.1% (28/93) 2: 6.4% (6/93)	1: 7.5% (7/93) 2: 4.3% (4/93)	NR	NR	NR	NR	NR	NR	NR
Sindrup, 1999[106] Denmark Poor	1: 4 weeks 2: 45 3: Polyneuropathy	1: Tramadol up to 400 mg (mean 364 mg) 2: Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
Sindrup, 2012[105] Den-mark, Germany Fair	1: 4 weeks 2: 64 3: Polyneuropathy	1: Tramadol SR 200 mg 2: Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
Steiner, 2011[107] (also Yarlas 2013)[123] USA Fair	1: 12 weeks 2: 541 3: Low back pain	1: Buprenorphine patch 10 or 20 mcg/hour (mean NR) 2: Placebo	1: 15.6% (40/256) 2: 7.1% (20/283)	1: 1.2% (3/256) 2: 0.7% (2/283)	1: 12.5% (32/256) 2: 10.9% (31/283)	1: 4.3% (11/256) 2: 1.8% (5/283)	1: 3.5% (9/256) 2: 1.1% (3/283)	1: 3.9% (10/256) 2: 1.1% (3/283)	1: 5.5% (14/256) 2: 4.9% (14/283)	1: 1.6% (4/256) 2: 2.1% (6/283)	NR

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Thorne, 2008[109] Canada Fair	1: 4 weeks 2: 116 3: Osteoarthritis	1: Tramadol SR 150 to 400 mg (mean 340 mg) 2: Placebo	1: 12.8% (12/94) 2: 3.4% (3/88)	1: 0% (0/94) 2: 1.1% (1/88)	1: 42.5% (40/94) 2: 25.0% (22/88)	1: 6.4% (6/94) 2: 2.3% (2/88)	1: 23.4% (22/94) 2: 5.7% (5/88)	1: 5.3% (5/94) 2: 3.4% (3/88)	1: 2.1% (2/94) 2: 6.8% (6/88)	1: 37.2% (35/94) 2: 21.6% (19/88)	1: 3.2% (3/94) 2: 3.4% (3/88)
Tomin-aga, 2016[110] Japan Poor	1: 12 weeks 2: 91 3: Osteoarthritis or low back pain	1: Tapentadol SR 50 to 500 mg (mean 237 mg) 2: Placebo	1: 16.7% (10/60) 2: 6.4% (2/31)	NR	1: 33.3% (20/60) 2: 16/1% (5/31)	1: 20.0% (12/60) 2: 3.2% (1/31)	1: 21.7% (13/60) 2: 6.4% (2/31)	NR	NR	1: 36.7% (22/60) 2: 9.7% (3/31)	NR
Tomin-aga, 2016[110] Japan Poor	1: 12 weeks 2: 91 3: Diabetic neuropathy or postherpetic neuralgia	1: Tapentadol SR 50 to 500 mg (mean 274 mg) 2: Placebo	1: 10.0% (6/60) 2: 6.4% (2/31)	NR	1: 31.7% (19/60) 2: 0% (0/31)	1: 18.3% (11/60) 2: 3.2% (1/31)	1: 26.7% (16/60) 2: 0% (0/31)	NR	NR	1: 28.3% (17/60) 2: 9.7% (3/31)	NR
Trenk-walder, 2015[111] Poland Fair	1: 16 weeks 2: 202 3: Parkinson's disease	1: Oxycodone SR 10 to 40 mg (mean 19 mg) + Naloxone 5 to 20 mg (mean NR) 2: Placebo	1: 18.3% (17/93) 2: 9.2% (10/109)	1: 5.4% (5/92) 2: 6.4% (7/109)	1: 19.6% (18/92) 2: 11.9% (13/109)	1: 7.6% (7/92) 2: 2.7% (3/109)	1: 17.4% (16/92) 2: 5.5% (6/109)	1: 13.0% (12/92) 2: 11.0% (12/109)	1: 6.5% (6/92) 2: 8.2% (9/109)	1: 13.0% (12/92) 2: 13.8% (15/109)	NR
Uberall, 2012[112] Germany Fair	1: 4 weeks 2: 240 3: Low back pain	1: Tramadol SR 200 mg (mean NR) 2: Placebo	1: 19.0% (22/116) 2: 11.7% (14/120)	1: 0% (0/116) 2: 0% (0/120)	1: 19.0% (22/116) 2: 2.5% (3/120)	1: 11.2% (13/116) 2: 0.8% (1/120)	1: 4.3% (5/116) 2: 2.5% (3/120)	1: 12.9% (15/116) 2: 3.3% (4/120)	1: 3.4% (4/116) 2: 1.7% (2/120)	1: 6.0% (7/116) 2: 2.5% (3/120)	NR
Vinik, 2014[113] USA Fair	1: 12 weeks 2: 318 3: Diabetic neuropathy	1: Tapentadol SR 200 to 500 mg (mean NR) 2: Placebo	1: 11.4% (19/166) 2: 7.9% (12/152)	NR	1: 21.1% (35/166) 2: 9.9% (15/152)	1: 12.6% (21/166) 2: 4.6% (7/152)	1: 5.4% (9/166) 2: 0% (0.152)	1: 7.2% (12/166) 2: 2.0% (3/152)	1: 2.4% (4/166) 2: 5.3% (8/152)	1: 7.2% (12/166) 2: 0.6% (1/152)	NR

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Vojtassak 2011[114] Slovakia UK Fair	1: 16 weeks 2: 288 3: Osteoarthritis	1: Oxymorphone SR 4 mg (mean NR) 2: Placebo	1: 25.9% (36/139) 2: 22.1% (33/149)	1: 2.9% (4/139) 2: 4.7% (7/149)	NR	NR	NR	NR	NR	NR	NR
Vond-rackova, 2008[115] Czech Republic, Germany Fair	1: 12 weeks 2: 464 3: Low back pain	1: Oxycodone SR 20 or 40 mg 1b: Oxycodone SR + Naloxone 20 or 40 mg + 10 or 20 mg (mean NR) 2: Placebo	1a: 4.0% (6/151) 1b: 0% (0/154) 2: 8.2% (13/158)	1a: 0% (0/151) 1b: 2.6% (4/154) 2: 0.6% (1/158)	1a: 7.9% (12/151) 1b: 6.5% (10/154) 2: 7.0% (11/158)	1a: 4.6% (7/151) 1b: 5.2% (8/154) 2: 3.2% (5/158)	1a: 11.9% (18/151) 1b: 8.4% (13/154) 2: 5.1% (8/158)	1a: 6.0% (9/151) 1b: 1.3% (2/154) 2: 3.8% (6/158)	1a: 4.0% (6/151) 1b: 1.3% (2/154) 2: 7.0% (11/158)	1a: 5.3% (8/151) 1b: 2.6% (4/154) 2: 2.5% (4/158)	NR
Vor-sanger, 2008[117] USA Fair	1: 12 weeks 2: 386 3: Low back pain	1: Tramadol SR 200 or 300 mg (mean NR) 2: Placebo	1: 10.1% (26/257) 2: 13.9% (18/129)	NR	1: 13.6% (35/257) 2: 7.0% (9/129)	NR	1: 10.1% (26/257) 2: 0.8% (1/129)	1: 12.1% (31/257) 2: 9.3% (12/129)	1: 13.2% (34/257) 2: 10.8% (14/129)	NR	NR
Watson, 1998[118] Canada Fair	1: 4 weeks 2: 50 3: Postherpetic neuralgia	1: Oxycodone 20 to 60 mg (mean 45 mg) 2: Placebo	1: NR 2: 0% (0/NR)	1: 0% (0/NR) 2: NR	NR	NR	NR	NR	NR	NR	NR
Watson, 2003[119] Canada Fair	1: 4 weeks 2: 45 3: Diabetic neuropathy	1: Oxycodone SR 20 to 80 mg (mean 40 mg) 2: Placebo	1: 22.2% (10/45) 2: 2.2% (1/45)	1: 0% (0/45) 2: 6.7% (3/45)	1: 35.5% (16/45) 2: 17.8% (8/45)	1: 11.1% (5/45) 2: 4.4% (2/45)	1: 28.9% (13/45) 2: 8.9% (4/45)	1: 15.5% (7/45) 2: 6.7% (3/45)	1: 11.1% (5/45) 2: 6.7% (3/45)	1: 20.0% (9/45) 2: 24.4% (11/45)	1: 8.9% (4/45) 2: 2.2% (1/45)

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Webster, 2006[120] USA Fair	1: 6 weeks 2: 307 3: Low back pain	1: Oxycodone 10 to 80 mg (mean 39 mg) 2: Placebo	1: 23.8% (49/206) 2: 4.9% (5/101)	NR	1: 60.2% (124/206) 2: 20.8% (21/101)	1: 22.8% (47/206) 2: 8.9% (9/101)	1: 70.9% (146/206) 2: 27.7% (28/101)	1: 36.9% (76/206) 2: 12.9% (13/101)	NR	1: 83.0% (171/206) 2: 49.5% (50/101)	1: 51.0% (105/206) 2: 4.9% (5/101)
Wen, 2015[121] USA Fair	1: 12 weeks 2: 588 3: Low back pain	1: Hydrocodone SR 20 to 120 mg (mean NR) 2: Placebo	1: 5.7% (17/296) 2: 3.4% (10/292)	1: 0.7% (2/296) 2: 1.7% (5/292)	1: 8.1% (24/296) 2: 5.5% (16/292)	1: 6.1% (18/296) 2: 3.1% (9/292)	1: 3.4% (10/296) 2: 2.4% (7/292)	1: 3.0% (9/296) 2: 1.7% (5/292)	1: 2.0% (6/296) 2: 1.7% (5/292)	1: 1.0% (3/296) 2: 0.7% (2/292)	NR
Wu, 2008[122] USA Fair	1: 6 weeks 2: 60 3: Postamputation pain	1: Morphine SR 30 to 180 mg (mean 112 mg) 2: Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR

Abbreviations: bd=twice a day; NR=not reported; qd=once a day; SR=sustained release

Table 25. Pooled analyses of risk of discontinuation due to adverse events, serious adverse events, and somnolence for opioids versus placebo

Analysis	Discontinuation Due to Adverse Events (95% CI)	I^2	# of Trials (N)	p*	Serious Adverse Events (95% CI)	I^2	# of Trials (N)	p*	Somnolence (95% CI)	I^2	# of Trials (N)	p*
All trials	2.25 (1.86 to 2.73)	72%	61 (19,994)	--	1.23 (0.88 to 1.74)	36%	38 (13,160)	--	2.97 (2.44 to 3.66)	48%	52 (17,458)	--
Opioid type: Opioid agonist	2.06 (1.57 to 2.75)	68%	32 (8827)	0.64	1.42 (1.01 to 2.01)	0%	22 (6205)	0.48	2.72 (2.01 to 3.78)	57%	30 (8100)	0.43
• **Partial agonist**	2.28 (1.08 to 5.01)	82%	8 (2489)	--	1.27 (0.68 to 2.38)	0%	7 (2348)	--	2.80 (1.47 to 4.95)	0%	6 (1793)	--
• **Mixed mechanism**	2.55 (1.93 to 3.36)	65%	21 (8678)	--	0.95 (0.39 to 2.34)	63%	9 (4607)	--	3.40 (2.60 to 4.69)	28%	16 (7565)	--
Pain type: Musculoskeletal	2.14 (1.72 to 2.66)	77%	48 (17,793)	0.47	1.16 (0.81 to 1.70)	37%	33 (12,204)	0.37	3.09 (2.48 to 3.91)	47%	40 (15,748)	0.45
• **Neuropathic**	3.02 (2.25 to 4.05)	25%	12 (2132)	--	1.91 (0.89 to 3.73)	0%	5 (956)	--	3.00 (2.27 to 3.98)	56%	12 (1710)	--
• **Fibromyalgia**	2.92 (0.12 to 69.20)	--	1 (69)	--	No studies	--	--	--	No studies	--	--	--
Trial quality: Good	2.52 (1.48 to 3.97)	0%	3 (1224)	0.38	0.94 (0.19 to 4.58)	--	1 (370)	0.29	2.81 (1.33 to 5.69)	5.0%	3 (1351)	0.97
• **Fair**	2.37 (1.91 to 2.97)	73%	50 (16,609)	--	1.11 (0.78 to 1.63)	36%	32 (11,275)	--	3.00 (2.37 to 3.87)	56%	43 (14,329)	--
• **Poor**	1.35 (1.09 to 1.87)	0%	8 (2161)	--	2.34 (1.07 to 5.69)	0%	5 (1515)	--	3.14 (2.09 to 4.68)	0%	6 (1778)	--
Opioid dose (mg MED/day): <50	1.99 (1.35 to 3.06)	68%	14 (4207)	0.51	1.30 (0.77 to 2.27)	0%	8 (2573)	0.54	2.62 (1.55 to 4.74)	55%	13 (3936)	0.18
• **50-90**	1.97 (1.48 to 2.71)	55%	19 (5820)	**--**	1.66 (0.67 to 3.57)	25%	11 (2967)	--	2.55 (1.77 to 4.23)	60%	13 (4559)	--
• **>90**	2.55 (1.86 to 3.47)	74%	28 (9967)	**--**	1.06 (0.67 to 1.73)	42%	19 (7620)	--	3.59 (2.93 to 4.38)	0%	26 (8963)	--
EERW design	1.35 (1.02 to 1.77)	54%	25 (8011)	**<0.005**	1.59 (1.08 to 2.34)	0%	18 (6096)	0.15	2.10 (1.38 to 3.30)	5.5%	17 (5944)	0.12
• **Non-EERW design**	3.06 (2.50 to 3.81)	62%	36 (11,983)	--	1.00 (0.59 to 1.70)	50%	20 (7064)	--	3.21 (2.58 to 4.11)	56%	35 (11,514)	--
EERW design, 2007 or after	1.37 (1.01 to 1.84)	59%	22 (7618)	**0.001**	1.59 (1.08 to 2.34)	0%	18 (6096)	0.10	2.10 (1.38 to 3.30)	5.5%	17 (5944)	0.08
• **Non-EERW design**	2.81 (2.19 to 3.68)	67%	23 (8337)	--	0.92 (0.55 to 1.57)	49%	16 (6646)	--	3.31 (2.60 to 4.36)	34%	22 (7921)	--
Crossover design	2.90 (1.83 to 5.97)	0%	7 (934)	0.26	1.16 (0.21 to 5.06)	37%	6 (781)	0.95	1.98 (1.36 to 3.32)	24%	9 (1090)	0.07
• **Parallel group**	2.18 (1.78 to 2.67)	74%	54 (19,060)	--	1.22 (0.87 to 1.75)	38%	32 (12,379)	--	3.23 (2.61 to 4.05)	43%	43 (16,368)	--

Analysis	Discontinuation Due to Adverse Events (95% CI)	I^2	# of Trials (N)	p*	Serious Adverse Events (95% CI)	I^2	# of Trials (N)	p*	Somnolence (95% CI)	I^2	# of Trials (N)	p*
Opioids status: Naïve	2.59 (1.96 to 3.90)	0%	13 (2825)	**0.02**	1.40 (0.84 to 2.34)	0%	8 (2104)	0.77	2.23 (1.39 to 3.77)	31%	11 (2566)	0.61
• **Opioid experienced**	0.90 (0.36 to 2.20)	81%	7 (2242)	--	1.49 (0.66 to 3.71)	0%	4 (1383)	--	3.53 (1.61 to 6.89)	13%	6 (1732)	--
• **Mixed**	2.50 (2.01 to 3.16)	71%	33 (13,379)	--	1.23 (0.75 to 2.11)	53%	20 (8356)	--	3.12 (2.49 to 4.04)	46%	29 (11,972)	--
• **Not reported**	2.05 (1.32 to 2.96)	7.5%	8 (1548)	--	0.84 (0.23 to 2.22)	0%	6 (1317)	--	2.98 (1.18 to 7.79)	60%	6 (1188)	--
Publlication: Prior to 2007	3.21 (2.29 to 4.73)	42%	16 (4039)	**0.04**	1.54 (0.10 to 18.16)	56%	4 (418)	0.52	3.07 (1.98 to 5.15)	72%	13 (3593)	0.93
• **In or after 2007**	2.02 (1.62 to 2.51)	73%	45 (15,955)	--	1.19 (0.86 to 1.69)	36%	34 (12,742)	--	2.96 (2.39 to 3.71)	27%	39 (13,865)	--
Region: USA or Canada	2.12 (1.72 to 2.62)	65%	44 (14,566)	0.71	1.51 (1.06 to 2.12)	0%	26 (8990)	0.21	3.08 (2.40 to 4.06)	53%	38 (12,505)	0.97
• **Europe or Australia**	2.54 (1.29 to 5.14)	88%	10 (3264)	--	0.81 (0.40 to 1.92)	56%	8 (2704)	--	2.74 (1.61 to 4.82)	50%	8 (2789)	--
• **Asia**	2.46 (1.20 to 4.96)	0%	5 (625)	--	2.39 (0.82 to 10.87)	0%	3 (438)	--	2.98 (1.61 to 5.74)	0%	4 (495)	--
• **Multiple†**	3.90 (2.11 to 6.28)	0%	2 (1539)	--	1.15 (0.44 to 2.96)	--	1 (1023)	--	2.88 (1.14 to 5.96)	0%	2 (1669)	--
Industry funding: Yes	2.18 (1.79 to 2.65)	72%	57 (19,420)	0.26	1.23 (0.88 to 1.74)	36%	38 (13,160)	--	3.15 (2.54 to 3.95)	42%	46 (16,728)	0.30
• **No industry funding**	4.69 (1.34 to 23.08)	0%	3 (267)	--	No studies	--	--	--	2.22 (1.39 to 4.10)	0%	5 (423)	--

Note: Statistically significant p values are bolded

Abbreviations: CI=confidence interval; EERW=enriched enrollment randomized withdrawal; MED=morphine equivalent dose; N= total sample size.

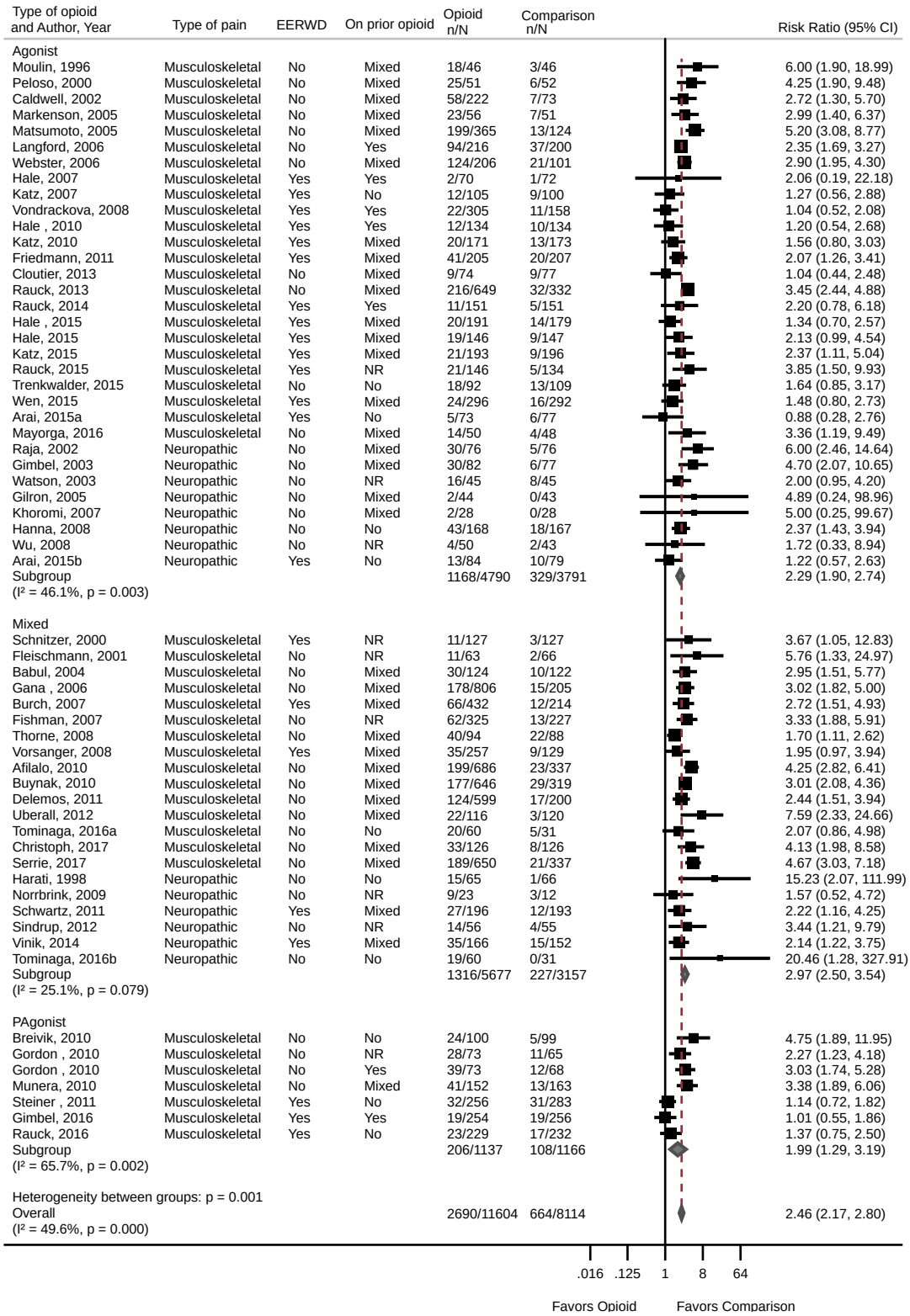
*p for interaction

†USA/Canada and Europe/Australia

Gastrointestinal Adverse Events

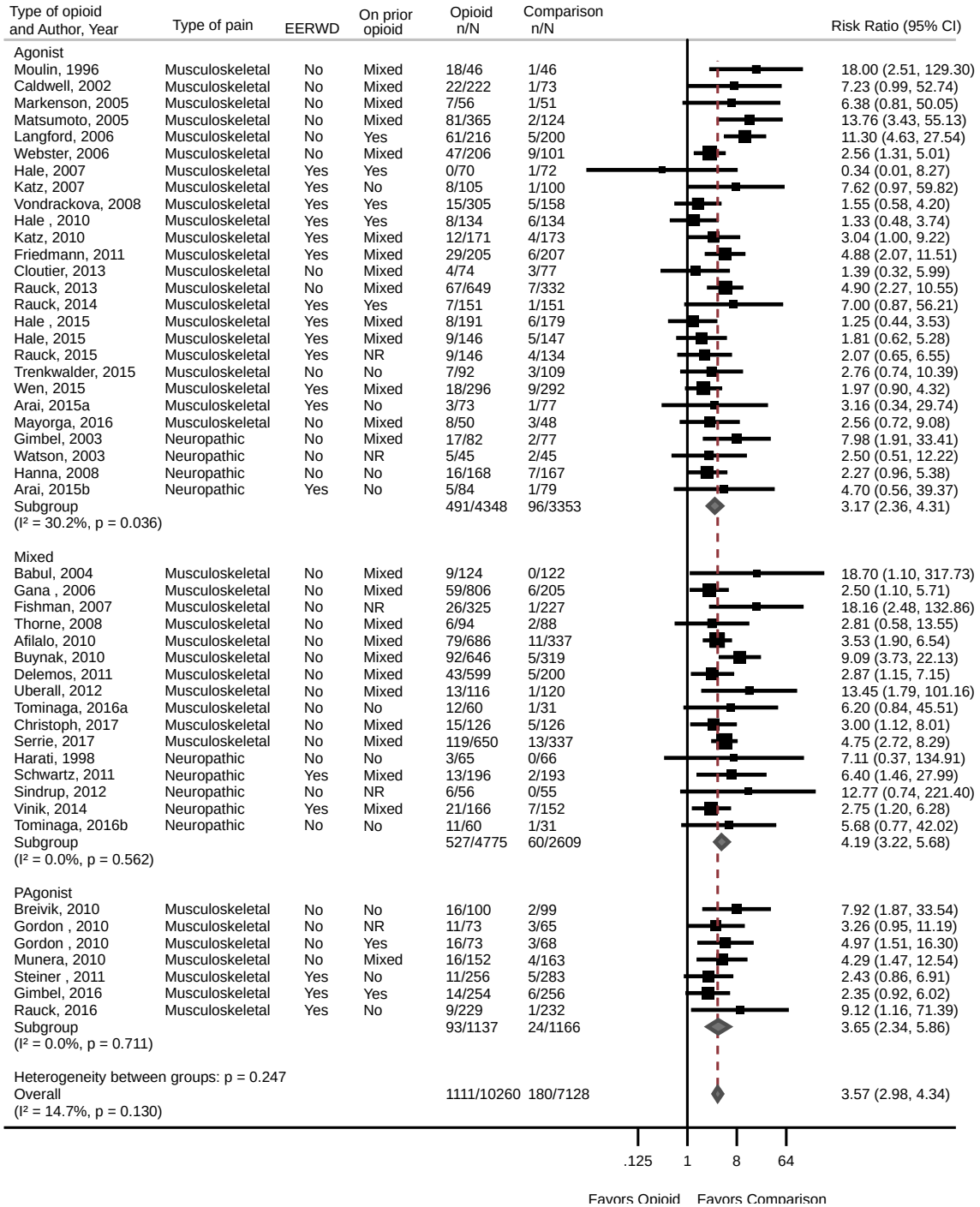
Opioids were associated with increased risk of nausea (60 trials, N=19,718, RR 2.46, 95% CI, 2.17 to 2.80, I^2=50%; ARD 14%, 95% CI, 11% to 17%, Figure 33, Table 24),[50-52,54-56,58,59,61-77,79-83,85-90,93-99,101-103,105,107-113,117,119-122] vomiting (49 trials, N=17,388, RR 3.57, 95% CI, 2.98 to 4.34, I^2=15%; ARD 7%, 95% CI, 6% to 9%, Figure 34, Table 24),[50-52,54,56,58,59,61-63,65,66,68-77,79,81,83,85-87,89,90,96-99,102,103,105,107-113,115,119-121] and constipation (58 trials, N=19,351, RR 3.38, 95% CI, 2.96 to 3.92, I^2=21%; ARD 14%, 95% CI, 11% to 17%, Figure 35, Table 24)[50-52,54-56,58,59,61-77,79-83,85-87,89,90,93,95-99,102,103,105,107-113,115,117,119-122] versus placebo at short-term followup. Trials that utilized an enriched EERW design reported lower risk of gastrointestinal adverse events than trials that did not use this study design (pooled RR estimates were 1.64 vs. 3.06, respectively, for nausea [p for interaction<0.005], 2.46 vs. 4.33 for vomiting [p for interaction=0.003], and 2.58 vs. 3.69 for constipation [p for interaction=0.03]). There were no interactions between trial quality, use of crossover design, publication date, geographic region, or industry funding and risk of gastrointestinal events (Table 26).

Figure 33. Meta-analysis of risk of nausea for opioids versus placebo



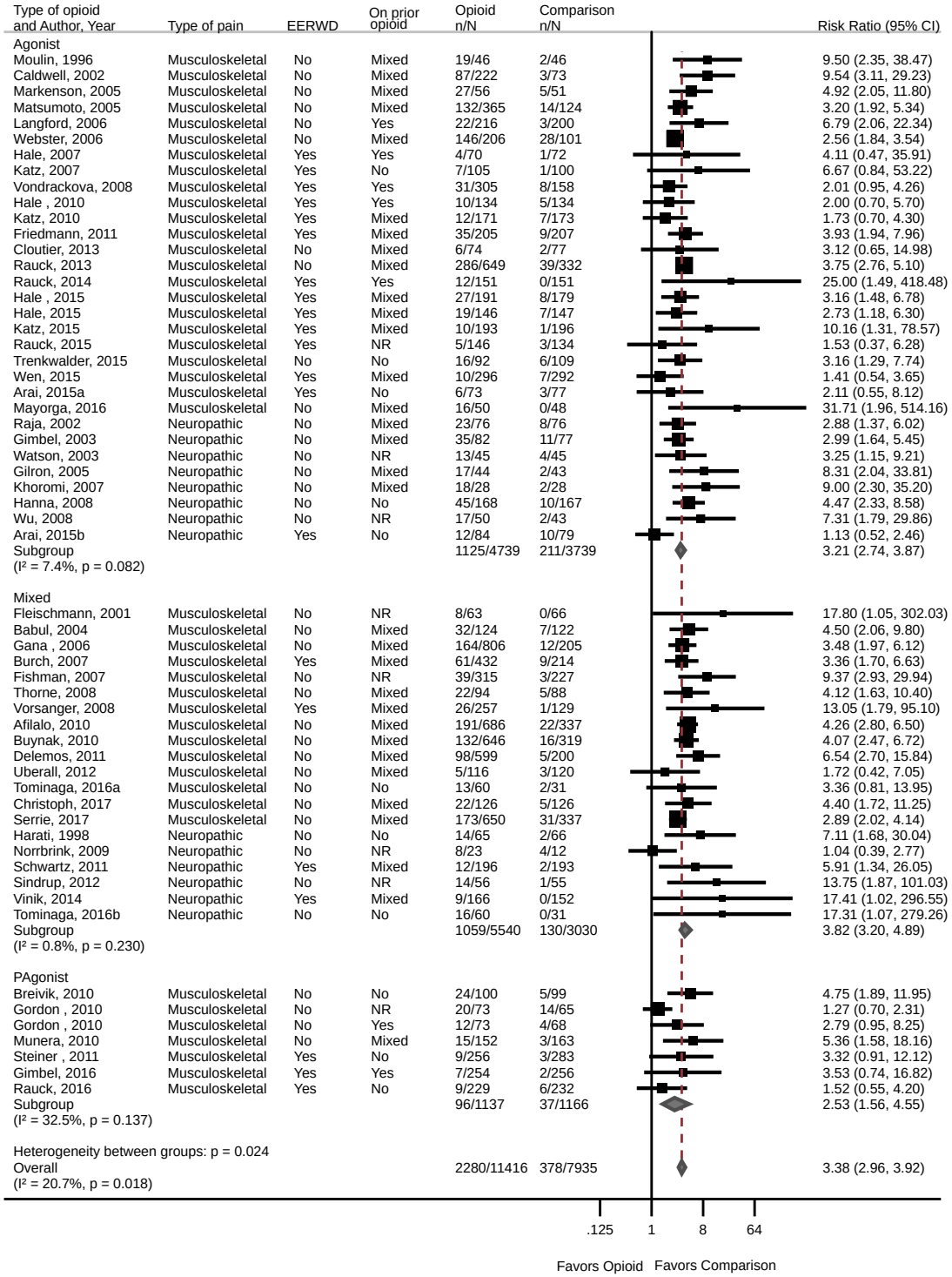
Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; n=number who experienced nausea; N=overall sample; NR=not reported; PAgonist=partial agonist.

Figure 34. Meta-analysis of risk of vomiting for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; n=number who experienced vomiting; N=overall sample; NR=not reported; PAgonist=partial agonist.

Figure 35. Meta-analysis of risk of constipation for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; n=number who experienced constipation; N=overall sample; NR=not reported; PAgonist=partial agonist.

Table 26. Pooled analyses of risk of nausea, vomiting, and constipation for opioids versus placebo

Analysis	Nausea (95% CI)	I^2	# of Trials (N)	p*	Vomiting (95% CI)	I^2	# of Trials (N)	p*	Constipation (95% CI)	I^2	# of Trials (N)	p*
All trials	2.46 (2.17 to 2.80)	50%	60 (19,718)	--	3.57 (2.98 to 4.34)	15	49 (17,388)	--	3.38 (2.96 to 3.92)	21%	58 (19,351)	--
Opioid type: Opioid agonist	2.29 (1.90 to 2.74)	46%	32 (8581)	0.06	3.17 (2.36 to 4.31)	30	26 (7701)	0.32	3.21 (2.74 to 3.87)	7.4%	31 (8478)	0.10
• **Partial agonist**	1.99 (1.29 to 3.19)	66%	7 (2303)	--	3.65 (2.34 to 5.86)	0	7 (2303)	--	2.53 (1.56 to 4.55)	32%	7 (2303)	--
• **Mixed mechanism**	2.97 (2.50 to 3.54)	25%	21 (8834)	--	4.19 (3.22 to 5.68)	0	16 (7384)	--	3.82 (3.20 to 4.89)	0.8%	20 (8570)	--
Pain type: Musculoskeletal	2.43 (2.10 to 2.81)	55%	46 (17,508)	0.64	3.57 (2.91 to 4.43)	21	40 (15,601)	0.89	3.34 (2.93 to 3.88)	13%	44 (17,141)	0.93
• **Neuropathic**	2.51 (1.97 to 3.58)	0%	14 (2210)	--	3.90 (2.50 to 6.10)	0	9 (1787)	--	3.78 (2.50 to 6.44)	47%	14 (2210)	--
• **Fibromyalgia**	No studies	--	--	--	No studies	--	--	--	No studies	--	--	--
Trial quality: Good	2.14 (1.32 to 3.27)	0%	3 (1351)	0.79	1.78 (0.71 to 4.10)	0	2 (705)	0.06	3.68 (2.40 to 5.58)	0%	3 (1351)	0.96
• **Fair**	2.48 (2.15 to 2.86)	52%	48 (16,114)	--	3.58 (2.94 to 4.41)	14	40 (14,813)	--	3.36 (2.90 to 3.98)	21%	47 (16,001)	--
• **Poor**	2.62 (1.68 to 4.28)	34%	9 (2253)	--	5.60 (3.18 to 10.36)	0	7 (1870)	--	3.64 (1.97 to 9.28)	48%	8 (1999)	--
Opioid dose (mg MED/day): <50	2.19 (1.63 to 3.08)	39%	13 (3936)	0.68	3.61 (2.42 to 5.87)	0	11 (3746)	0.97	3.43 (2.23 to 5.50)	50%	12 (3823)	0.97
• **50-90**	2.57 (2.13 to 3.08)	19%	19 (5920)	--	3.30 (2.40 to 5.10)	0	13 (4414)	--	3.35 (2.79 to 4.27)	5.7%	18 (5666)	**--**
• **>90**	2.51 (2.05 to 3.08)	60%	28 (9862)	--	3.61 (2.75 to 4.75)	28	21 (9228)	--	3.36 (2.80 to 4.13)	13%	28 (9862)	**--**
EERW design	1.64 (1.40 to 1.94)	5.8%	22 (7872)	**<0.005**	2.46 (1.88 to 3.25)	0	18 (6197)	0.003	2.58 (2.03 to 3.38)	1.0%	21 (7618)	**0.03**
• **Non-EERW design**	3.06 (2.70 to 3.48)	24%	38 (11,846)	--	4.33 (3.50 to 5.54)	7.3	31 (11,191)	--	3.69 (3.17 to 4.47)	24%	37 (11,733)	--
EERW design, 2007 or after	1.62 (1.38 to 1.91)	5.2%	21 (7618)	**<0.005**	2.46 (1.88 to 3.25)	0	18 (6197)	0.009	2.58 (2.03 to 3.38)	1.0%	21 (7618)	0.06
• **Non-EERW design**	2.91 (2.44 to 3.45)	32%	23 (8032)	--	4.10 (3.24 to 5.18)	0	20 (7848)	--	3.70 (2.97 to 4.80)	35%	23 (8022)	--
Crossover design	2.45 (1.78 to 3.65)	27%	11 (1293)	0.93	3.65 (2.04 to 6.81)	0	7 (905)	0.93	3.85 (2.47 to 6.66)	43%	11 (1293)	0.95
• **Parallel group**	2.46 (2.14 to 2.83)	52%	49 (18,425)	--	3.57 (2.94 to 4.40)	18	42 (16,483)	--	3.35 (2.96 to 3.83)	6.2%	47 (18,058)	--
Opioids status: Naïve	1.72 (1.30 to 2.51)	26%	11 (2566)	**0.007**	3.60 (2.29 to 6.13)	0	11 (2566)	0.94	3.06 (2.03 to 4.84)	27%	11 (2566)	0.35

Analysis	Nausea (95% CI)	I^2	# of Trials (N)	p*	Vomiting (95% CI)	I^2	# of Trials (N)	p*	Constipation (95% CI)	I^2	# of Trials (N)	p*
• **Opioid experienced**	1.72 (1.10 to 2.57)	48%	7 (2242)	--	3.03 (1.34 to 6.48)	53	7 (2242)	--	2.90 (1.86 to 5.32)	0%	7 (2242)	--
• **Mixed**	2.83 (2.44 to 3.28)	40%	33 (13,228)	--	3.62 (2.94 to 4.53)	5.0	26 (11,409)	--	3.51 (3.12 to 4.07)	0.4%	32 (13,125)	--
• **Not reported**	2.74 (2.05 to 3.67)	0%	9 (1682)	--	3.50 (1.78 to 9.12)	0	5 (1171)	--	3.19 (1.57 to 7.76)	61%	8 (1418)	--
Publication: Prior to 2007	3.28 (2.72 to 4.18)	14%	16 (4068)	**0.003**	5.65 (3.33 to 10.66)	37	11 (3343)	0.07	3.61 (2.86 to 5.04)	12%	14 (3711)	0.29
• **In or after 2007**	2.20 (1.90 to 2.56)	51%	44 (15,650)	--	3.30 (2.72 to 3.97)	3.2	38 (14,045)	--	3.24 (2.73 to 3.90)	30%	44 (15,640)	--
Region: USA or Canada	2.41 (2.10 to 2.77)	43%	45 (14,654)	0.25	3.27 (2.68 to 4.10)	6.6	36 (13,005)	0.52	3.54 (3.04 to 4.26)	19%	43 (14,287)	0.24
• **Europe or Australia**	2.80 (1.84 to 4.33)	63%	9 (2900)	--	4.66 (2.68 to 8.63)	36	8 (2865)	--	2.93 (2.18 to 4.21)	0%	9 (2900)	--
• **Asia**	1.50 (0.86 to 3.24)	0%	4 (495)	--	4.90 (1.73 to 13.89)	0	4 (495)	--	1.75 (0.96 to 6.36)	0%	4 (495)	--
• **Multiple†**	3.68 (2.04 to 5.88)	0%	2 (1669)	--	3.53 (1.90 to 6.54)	--	1 (1023)	--	3.99 (2.45 to 6.08)	0%	2 (1669)	--
Industry funding: Yes	2.43 (2.13 to 2.78)	51%	54 (18,988)	0.73	3.64 (3.01 to 4.44)	16	48 (17,081)	--	3.43 (3.00 to 3.99)	15%	52 (18,621)	0.64
• **No industry funding**	3.16 (1.26 to 7.37)	15%	5 (423)	--	No studies	--	--	--	3.80 (1.64 to 10.30)	54%	5 (423)	--

Note: Statistically significant p values are bolded

Abbreviations: EERW=enriched enrollment randomized withdrawal; CI=confidence interval; MED=morphine equivalent dose; N= total sample size.

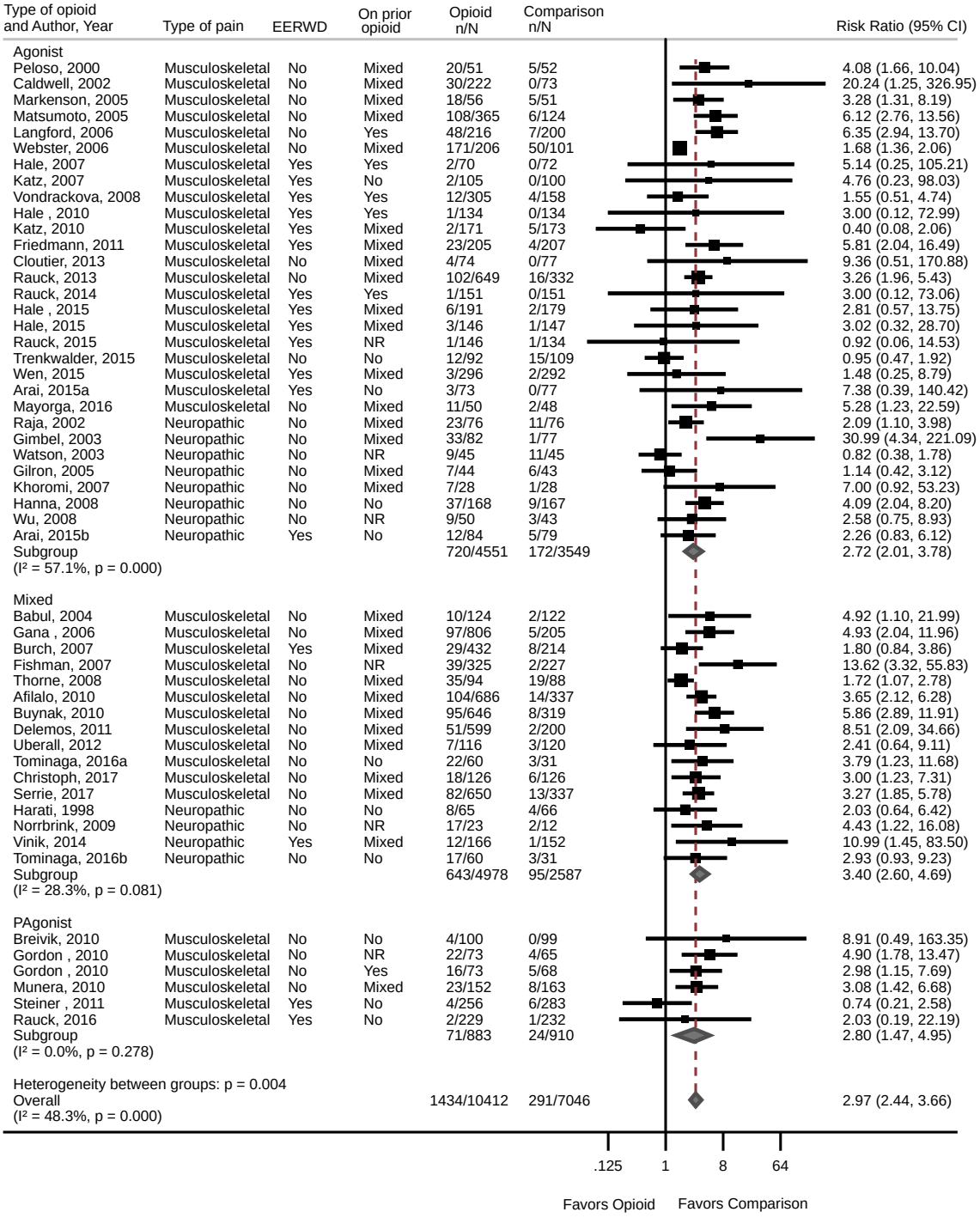
*p for interaction

†USA/Canada and Europe/Australia

Other Short-Term Adverse Events

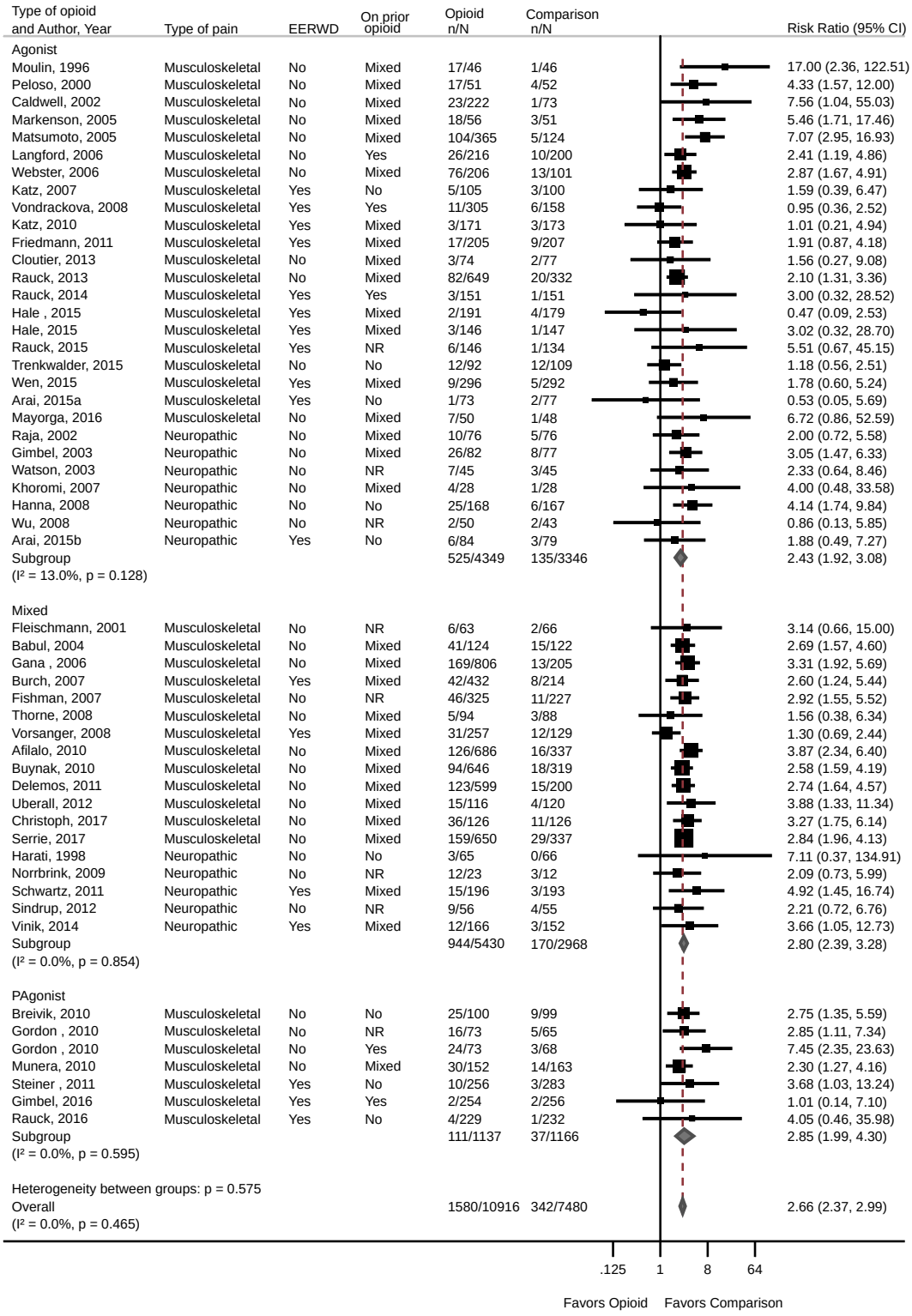
Opioids were associated with increased risk of somnolence (52 trials, N=17,458, RR 2.97, 95% CI, 2.44 to 3.66, I^2=48%; ARD 9%, 95% CI, 7% to 12%; Figure 36, Table 24),[50-52,54-56,58,59,61-63,65-67,69-77,79,81-83,85-87,90,93-99,103,107-113,115,119-122] dizziness (53 trials, N=18,396, RR 2.66, 95% CI, 2.37 to 2.99, I^2=0%; ARD 8%, 95% CI, 6% to 10%; Figure 37, Table 24),[50-52,54-56,58,59,61-66,68-71,74-77,79,81-83,85-87,89,90,93-99,102,103,105,107-109,111-113,115,117,119-122] and pruritus (30 trials, N=11,454, RR 3.51, 95% CI, 2.47 to 5.16, I^2=50%; ARD 7%, 95% 4% to 10%; Figure 38, Table 24)[50-52,56,58,62-67,69-71,73-75,77,79,81,85,86,90,96,97,103,105,109,119,120] versus placebo at short-term followup. Findings on these harms were consistent in analyses stratified according to trial quality, use of an EERW design, crossover design, publication date, region, and receipt of industry funding; though statistically significant interactions were observed between use of a crossover design and lower risk of pruritus and publication prior to 2007 and higher risk of pruritus (Table 27). There was no association between opioids versus placebo and risk of headache at short-term followup (48 trials, N=17,405, RR 1.06, 95% CI, 0.95 to 1.17, I^2=0%, Figure 39, Table 24).[50-52,54,56,58,59,62-77,79,81-83,85-87,90,96-99,101-103,105,107-109,111-113,115,117,119,121]

Figure 36. Meta-analysis of risk of somnolence for opioids versus placebo



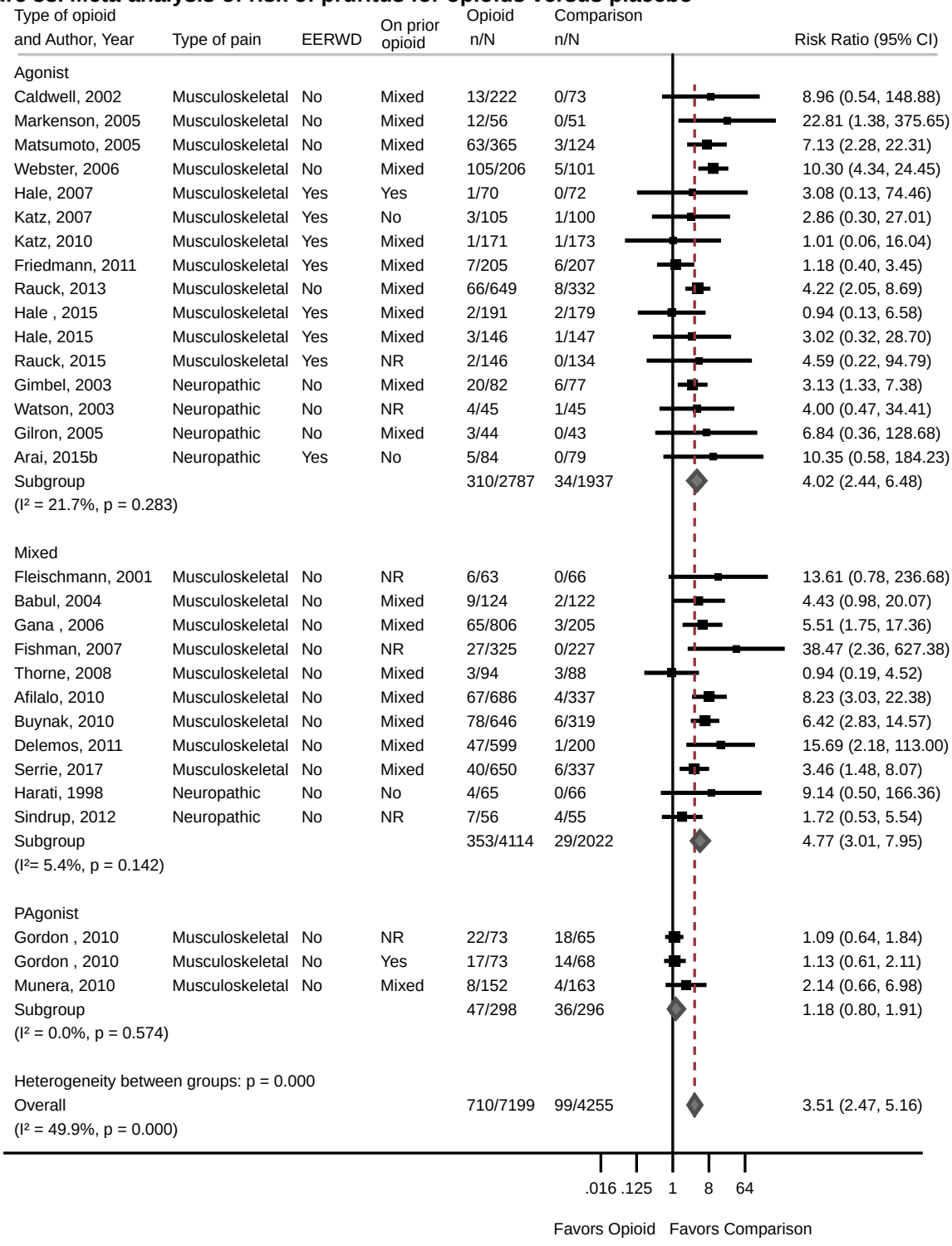
Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; n=number who experienced somnolence; N=overall sample; NR=not reported; PAgonist=partial agonist.

Figure 37. Meta-analysis of risk of dizziness for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; n=number who experienced dizziness; N=overall sample; NR=not reported; PAgonist=partial agonist.

Figure 38. Meta-analysis of risk of pruritus for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; n=number who experienced pruritus; N=overall sample; NR=not reported; PAgonist=partial agonist.

Table 27. Pooled analyses of risk of dizziness, headache, and pruritus for opioids versus placebo

Analysis	Dizziness (95% CI)	I^2	# of Trials (N)	p*	Headache (95% CI)	I^2	# of Trials (N)	p*	Pruritus (95% CI)	I^2	# of Trials (N)	p*
All trials	2.66 (2.37 to 2.99)	0%	53 (18,396)	--	1.06 (0.95 to 1.17)	0%	48 (17,405)	--	3.51 (2.47 to 5.16)	50%	30 (11,454)	--
Opioid type: Opioid agonist	2.43 (1.92 to 3.08)	13%	28 (7695)	0.48	0.96 (0.79 to 1.14)	0%	24 (7131)	0.31	4.02 (2.44 to 6.48)	22%	16 (4724)	0.02
• **Partial agonist**	2.85 (1.99 to 4.30)	0%	7 (2303)	--	1.23 (0.87 to 1.67)	0%	7 (2303)	--	1.18 (0.80 to 1.91)	0%	3 (594)	--
• **Mixed mechanism**	2.80 (2.39 to 3.28)	0%	18 (8398)	--	1.09 (0.94 to 1.29)	4.7%	17 (7971)	--	4.77 (3.01 to 7.95)	5.4%	11 (6136)	--
Pain type: Musculoskeletal	2.64 (2.33 to 2.99)	0%	41 (16,364)	0.76	1.06 (0.95 to 1.19)	0%	39 (15,729)	0.64	3.56 (2.37 to 5.52)	57%	24 (10,713)	0.99
• **Neuropathic**	2.80 (2.00 to 3.91)	0%	12 (2032)	--	1.02 (0.66 to 1.75)	28%	9 (1676)	--	3.10 (1.67 to 6.69)	0%	6 (741)	--
• **Fibromyalgia**	No studies	--	--	--	No studies	--	--	--	No studies	--	--	--
Trial quality: Good	2.61 (0.65 to 5.70)	0%	3 (1351)	0.72	1.13 (0.62 to 2.15)	0%	2 (705)	0.84	0.94 (0.13 to 6.58)	--	1 (370)	0.40
• **Fair**	2.70 (2.39 to 3.06)	0%	44 (15,228)	--	1.04 (0.92 to 1.17)	3.3%	41 (14,884)	--	3.49 (2.38 to 5.31)	53%	26 (9811)	--
• **Poor**	2.26 (1.47 to 4.26)	0%	6 (1817)	--	1.15 (0.73 to 1.94)	0%	5 (1816)	--	4.74 (2.20 to 17.31)	0%	3 (1273)	--
Opioid dose (mg MED/day): <50	2.22 (1.55 to 3.07)	9.5%	12 (3849)	0.19	0.98 (0.74 to 1.40)	0%	11 (3670)	0.72	5.20 (1.87 to 17.92)	34%	8 (2783)	0.49
• **50-90**	2.54 (2.10 to 3.10)	0%	18 (9515)	--	1.12 (0.88 to 1.39)	0%	14 (4689)	--	4.22 (2.53 to 6.89)	19%	10 (3323)	--
• **>90**	2.97 (2.50 to 3.53)	0%	23 (8881)	--	1.05 (0.90 to 1.20)	0%	23 (9046)	--	2.81 (1.62 to 5.01)	60%	12 (5348)	--
EERW design	1.85 (1.40 to 2.50)	0%	18 (6819)	0.007	0.95 (0.74 to 1.20)	0%	19 (6674)	0.35	1.75 (0.86 to 4.00)	0%	8 (2209)	0.18
• **Non-EERW design**	2.87 (2.53 to 3.26)	0%	35 (11,577)	--	1.08 (0.96 to 1.22)	0.1%	29 (10,731)	--	3.95 (2.66 to 6.17)	58%	22 (9245)	--
EERW design, 2007 or after	1.85 (1.40 to 2.50)	0%	18 (6819)	0.02	0.94 (0.72 to 1.19)	0%	18 (6420)	0.33	1.75 (0.86 to 4.00)	0%	8 (2209)	0.47
• **Non-EERW design**	2.71 (2.32 to 3.16)	0%	21 (7850)	--	1.08 (0.94 to 1.24)	0%	18 (7571)	--	2.95 (1.71 to 5.54)	68%	11 (6194)	--
Crossover design	2.74 (1.78 to 4.22)	0%	10 (1206)	0.89	1.33 (0.76 to 2.25)	0%	7 (805)	0.38	1.22 (0.85 to 1.91)	0%	6 (749)	<0.005
• **Parallel group**	2.66 (2.35 to 3.00)	0%	43 (17,190)	--	1.05 (0.93 to 1.16)	0%	41 (16,600)	--	4.66 (3.38 to 6.47)	13%	24 (10,705)	--
Opioid status: Naïve	2.29 (1.45 to 3.66)	9.7%	9 (2384)	0.70	1.11 (0.78 to 1.60)	0%	8 (2221)	0.58	5.58 (1.18 to 30.02)	0%	3 (499)	0.11
• **Experienced**	2.25 (0.93 to 5.40)	39%	5 (1832)	--	0.82 (0.50 to 1.42)	0%	7 (2242)	--	1.17 (0.49 to 4.08)	0%	2 (283)	--
• **Mixed**	2.76 (2.42 to 3.15)	0%	31 (12,752)	--	1.08 (0.95 to 1.21)	0%	26 (11,388)	--	4.22 (2.91 to 5.97)	25%	19 (9372)	--
• **Not reported**	2.58 (1.75 to 3.78)	0%	8 (1428)	--	1.08 (0.72 to 1.94)	0%	7 (1554)	--	2.54 (0.99 to 11.87)	40%	6 (1300)	--
Publication: Prior to 2007	3.25 (2.59 to 4.11)	0%	14 (3727)	0.05	1.12 (0.84 to 1.54)	18%	12 (3414)	0.61	6.91 (4.49 to 10.62)	0%	11 (3051)	0.02

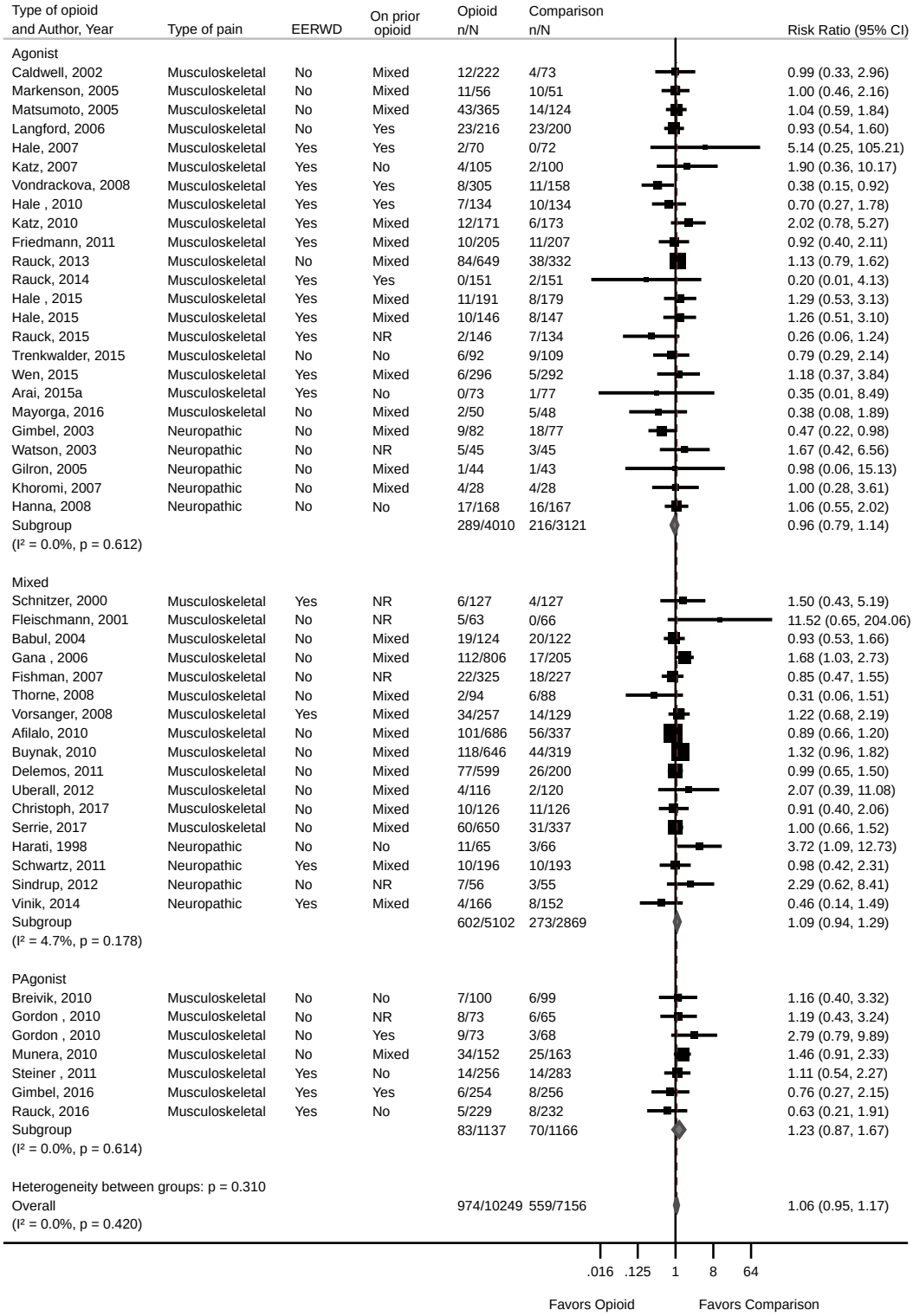
Analysis	Dizziness (95% CI)	I^2	# of Trials (N)	p*	Headache (95% CI)	I^2	# of Trials (N)	p*	Pruritus (95% CI)	I^2	# of Trials (N)	p*
• **In or after 2007**	2.48 (2.13 to 2.84)	0%	39 (14,669)	--	1.04 (0.92 to 1.17)	0%	36 (13,991)	--	2.65 (1.72 to 4.25)	53%	19 (8403)	--
Region: USA or Canada	2.70 (2.34 to 3.13)	0%	40 (13,514)	0.37	1.12 (0.98 to 1.26)	0%	38 (13,367)	0.35	3.44 (2.31 to 5.32)	52%	26 (9170)	0.62
• **Europe or Australia**	2.44 (1.74 to 3.07)	0%	9 (2900)	--	0.94 (0.71 to 1.23)	0%	8 (2865)	--	2.72 (0.98 to 6.46)	0%	2 (1098)	--
• **Asia**	1.38 (0.21 to 5.79)	0%	2 (313)	--	0.35 (0.02 to 8.49)	--	1 (150)	--	10.35 (0.58 to 184.2)	--	1 (163)	--
• **Multiple†**	3.41 (1.85 to 5.68)	0%	2 (1669)	--	0.89 (0.66 to 1.20)	--	1 (1023)	--	8.23 (3.03 to 22.38)	--	1 (1023)	--
Industry funding: Yes	2.68 (2.37 to 3.02)	0%	48 (17,753)	0.64	1.06 (0.95 to 1.17)	0%	46 (17,262)	0.92	3.23 (2.27 to 4.78)	46%	28 (11,060)	0.31
• **No industry funding**	1.97 (0.99 to 3.84)	0%	4 (336)	--	1.00 (0.23 to 4.35)	0%	2 (143)	--	6.84 (0.36 to 128.7)	--	1 (87)	--

Abbreviations: CI=confidence interval; EERW= enriched enrollment randomized withdrawal; MED=morphine equivalanet dose; N= total sample size

*p for interaction

†USA/Canada and Europe/Australia

Figure 39. Meta-analysis of risk of headache for opioids versus placebo



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; n=number who experienced a headache; N=overall sample; NR=not reported; PAgonist=partial agonist.

Opioid Use Disorder, Dependence, and Related Outcomes

The 2014 AHRQ report included one fair-quality retrospective study that evaluated risk of opioid use disorder (defined as opioid abuse or dependence based on the International Classification of Disease 9th Revision [ICD-9] codes) in patients newly diagnosed with chronic noncancer pain in a large administrative database; patients were followed for 18 months. It found prescribed long-term opioids (receipt of ≥91 days' supply of opioids within a 12-month period) associated with increased risk of opioid use disorder versus no use (Appendix Table G-2 and H-5).[160] Rates of opioid abuse or dependence were 0.72, 1.28 and 6.1 percent in those prescribed low (1 to 36 mg MED/day), medium (36 to 120 mg MED/day) and high (≥120 mg MED/day) opioid doses, respectively, during the 12 months after the new chronic pain diagnosis, versus 0.004 percent in those with no opioid prescription. Compared with no opioid prescription and after adjustment for age, sex, history of substance abuse/dependence diagnosis and other comorbidities, chronic opioid use was associated with significantly increased risk of abuse or dependence for all doses of opioids (low dose: OR 15, 95% CI, 10 to 21; medium dose: odds ratio [OR] 29, 95% CI, 20 to 41; high dose: OR 122, 95% CI, 73 to 206).

A new, fair-quality cohort study followed 98,140 patients in the UK Clinical Practice Research Datalink primary care database with a musculoskeletal condition who started long-term opioid therapy (≥3 opioid prescriptions in 90 days) for a median of 3.4 years (Appendix Table H-5).[155] The incidence of opioid addiction was 10.9 per 10,000 person-years in patients with long-term opioids and 3.7 per 10,000 in patients without long-term opioids. Long-term opioid use was associated with increased risk of addiction versus no long-term opioid use, after adjustment for age, sex, smoking and alcohol status, body mass index, depression, co-morbidity, NSAID use, prior adverse events, and other factors (hazard ratio [HR] 2.83, 95% CI, 2.13 to 3.76). In this study, there was no association between long-term opioid use and risk of "control" conditions not associated with opioids (eczema, psoriasis).

Overdose

The 2014 AHRQ report included one fair-quality retrospective cohort study (n=9940) on risk of overdose with opioid use versus nonuse in patients in a U.S. integrated healthcare system.[159] The study evaluated patients with a new episode of opioid use (defined as no opioid prescription in the past 6 months), a chronic noncancer pain diagnosis within 2 weeks before the initial opioid prescription, and at least three opioid prescriptions in the first 90 days of the episode (Appendix Table G-2, H-6, and H-7). The mean duration of followup was 42 months, and short-acting opioids were the most frequently prescribed type; 10 percent of patients predominantly received long-acting opioids. The annual overdose rate was 256 per 100,000 person-years in patients who recently received prescribed opioids versus 36 per 100,000 person-years in people who did not. After adjustment for smoking, depression, substance abuse, comorbid conditions, pain site, age, sex, recent sedative-hypnotic prescription, and recent initiation of opioid use, prescribed opioids was associated with increased risk of any overdose event (HR 5.2, 95% CI, 2.1 to 12.5) and serious overdose event (HR 8.4, 95% CI, 2.5 to 28) compared with no prescribed opioid.

A previously described (see Opioid Use Disorder, Dependence, and Related Outcomes) new cohort study of 98,140 patients in the UK Clinical Practice Research Datalink primary care reported an incidence of opioid overdose of 11.6 per 10,000 person-years in patients with long-term opioids and 4.8 per 10,000 in patients without long-term opioids (adjusted HR 2.24, 95% CI, 1.73 to 2.89).[155]

All-Cause Mortality

One new fair-quality retrospective cohort study (n=22,912) evaluated all-cause mortality risk in Medicaid patients prescribed long-acting opioids or a control medication (anticonvulsants or cyclic antidepressants; Appendix Table G-2, H-6, and H-7).[166] Analyses were adjusted for baseline propensity score decile (based on 122 demographic and clinical covariates) age, and calendar year. Prescription of long-acting opioids was associated with increased risk of all-cause mortality versus control treatments (adjusted HR 1.64, 95% CI, 1.26 to 2.12; risk difference 68.5 excess deaths per 10,000 person-years). The risk was similar when outcomes were restricted to out-of-hospital deaths other than unintentional overdose (adjusted HR 1.72, 95% CI, 1.24 to 2.39, risk differences 47.4 excess deaths per 10,000 person-years).

Fractures and Falls

The 2014 AHRQ report included two observational studies on the association between opioid use and fracture in patients with chronic pain or on long-term opioid therapy (Appendix Table G-2, H-8, and H-9);[163,167] analyses adjusted for demographic factors, clinical factors, and concomitant medication use. A fair-quality cohort study (n=2431) of patients 60 years and older with noncancer pain found current opioid use associated with increased risk of fracture versus no current use, though the difference was not statistically significant (confirmed nonvertebral fracture rate 6% vs. 4%; HR 1.28, 95% CI, 0.99 to 1.64).[167] A good-quality case-control study (21,739 persons with hip, humerus or wrist fractures and 85,326 age and sex-matched nonfracture controls) found current opioid use associated with increased risk of fracture versus nonuse (adjusted OR 1.27, 95% CI, 1.21 to 1.33).[163] The risk was highest with one prescription (OR 2.70, 95% CI, 2.34 to 3.13) and decreased with higher numbers of prescriptions, with no increased risk for patients with more than 20 cumulative prescriptions.

Four new cohort studies[156,161,164,168] (sample sizes ranged from 2902 to 7447, total N=19,330) evaluated the association between opioid use versus nonuse and fractures and three new cohort studies[155,161,165] evaluated the association between opioid use versus nonuse and risk of falls (one study[161] evaluated both outcomes). Sample sizes ranged from 2902 to 17310 (total N=24,443).[155] The average age of patients in the studies ranged from 60 to 83 years. Two studies[156,161] only evaluated men and in the other four studies patients were predominantly female. All of the new studies were rated fair-quality; methodological shortcomings included unclear enrollment of an inception cohort, not blinding the outcome assessor, and not reporting attrition. All of the studies controlled for demographic and clinical confounders.

The new cohort studies consistently found an association between opioid use versus nonuse and increased risk of fractures, though effects were not always statistically significant. A propensity-score controlled study (n=2902) of community-dwelling men with persistent musculoskeletal pain found opioid use was not associated with an increased risk of any clinical fracture (nonvertebral fracture or clinically recognized vertebral fracture, adjusted HR 1.13, 95% CI 0.94 to 1.36) or hip fracture (adjusted HR 1.64, 95% CI 0.97 to 2.79), although there was a trend towards increased risk with opioid use for both outcomes.[161] A study (n=17,310) of Medicare beneficiaries (mean age 80 years) with osteoarthritis or rheumatoid arthritis found short-acting and long-acting opioid use each associated with increased risk of hip, humerus/ulna, or wrist fracture versus NSAID use (adjusted HR 2.6, 95% CI, 1.5 to 4.4 and HR 5.1, 95% CI, 3.7 to 7.1, respectively).[165] A study (n=7,447) of veterans with spinal cord injury found opioid use associated with increased risk of lower extremity fracture versus nonuse (adjusted HR 1.82, 95% CI, 1.59 to 2.09).[156] However, fracture risk decreased with longer duration of use compared

with less than 6 month of use, adjusted HR was 0.36 (95% CI, 0.26 to 0.50) for 6 to 12 months, 0.5 (95% CI, 0.43 to 0.75) for 1 to 2 years, 0.50 (95% CI, 0.36 to 0.70) for 2 to 3 years, and 0.37 (95% CI, 0.27 to 0.51) for 3 or more years. of the fourth study (n=9,500) found opioid use associated with increased risk of hip fracture versus nonuse (age adjusted incidence 3.47 vs. 1.94 per 100 person-years, HR 1.96, 95% CI, 1.27 to 3.02).[168] The risk of hip fracture was increased relative to nonuse with weak opioids (HR 1.70, 95% CI, 0.89 to 3.26), buprenorphine (HR 1.98, 95% CI, 1.33 to 2.95), and strong opioids (HR 2.72, 95% CI, 1.25 to 5.93). The risk was lower at 61 to 365 days than at 1 to 60 days, but was highest at >365 days (HR 2.60, 95% CI, 0.93 to 7.29).

The above study of community-dwelling men that reported fracture risk also found a small, non-statistically significant association between opioid use versus nonuse and risk of falls (adjusted RR 1.10, 95% CI, 0.99 to 1.24).[161] Another study (n=4231) of persons 45 to 79 years of age with or at risk for osteoarthritis (mean age 60 years) found opioid use associated with increased risk of recurrent falls, defined as two or more falls over 12 months (adjusted HR 1.22, 95% CI, 1.04 to 1.45).[164] The risk associated with opioids was similar to the risk associated with antidepressants (adjusted HR 1.25, 95% CI, 1.10 to 1.40) and slightly higher than the risk for nonopioid prescription pain medications (NSAIDs, salicylates, or triptans) (adjusted HR 1.08, 95% 0.95 to 1.23) or other-the-counter pain medications (adjusted HR 1.13, 95% CI, 1.00 to 1.28). A previously described (see Opioid Use Disorder, Dependence, and Related Outcomes) new cohort study of 98,140 patients in the UK Clinical Practice Research Datalink primary care reported an incidence of falls of 548.9 per 10,000 person-years in patients with long-term opioid use and 369.5 per 10,000 in patients without long-term opioid use (adjusted HR 1.23, 95% CI, 1.19 to 1.28).[155] This study also reported an incidence of major trauma of 375.7 per 10,000 person-years in patients with long-term opioid use and 285.4 per 10,000 in patients without long-term opioid use (adjusted HR 1.14, 95% CI, 1.10 to 1.19).[155]

Cardiovascular Events

The 2014 AHRQ report included two observational studies on the association between long-term opioid use for chronic pain and risk of myocardial infarction (Appendix Tables G-2, H-10, and H-11).[157,162] A fair-quality cohort study (n=426,124) found receipt of chronic opioid therapy associated with increased risk of myocardial infarction (adjusted incident rate ratio [IRR] 2.66, 95% CI, 2.30 to 3.08) and myocardial infarction or revascularization (adjusted IRR 2.38, 95% CI, 2.15 to 2.63) compared to a matched general population control group not prescribed opioids or cyclo-oxygenase-2 selective NSAIDs.[157] The study controlled for age, sex, cardiovascular and other comorbidities, and concomitant medication use; it did not control for pain condition or pain severity. A good-quality case-control study (11,693 myocardial infarction cases and 44,897 age and sex-matched controls) found current opioid therapy associated with increased risk of myocardial infarction versus nonuse, after adjustment for a number of factors, including smoking status, comorbidities, concomitant medications, type of pain, and recent or past opioid use (adjusted OR 1.28, 95% CI, 1.19 to 1.37).[162] Recent (within 31 to 365 days) use was also associated with increased risk (OR 1.17, 95% CI, 1.10 to 1.24). The risk was highest with 11 to 50 cumulative prescriptions (OR 1.38, 95% CI, 1.28 to 1.49) but was statistically significant with one to two, three to ten, or greater than 50 cumulative prescriptions (OR range 1.09 to 1.25).

A new, propensity-matched cohort study (n=22,912) of Medicaid patients with chronic noncancer pain described above (see all-cause mortality) found prescription of long-acting opioids associated with increased risk of cardiovascular mortality versus prescription of control

medications (anticonvulsants or cyclic antidepressants) (adjusted HR 1.65, 95% CI, 1.10 to 2.46; risk difference of 28.9 excess deaths, 95% CI, 4.6 to 65.3 per 10,000 person-years).[166] No study evaluated the association between long-term opioid therapy for chronic pain versus no opioid therapy and risk of arrhythmia or sudden death.

Endocrinological Harms

The 2014 AHRQ report included one study on the association between opioid use versus nonuse and endocrinological harms (Appendix Table G-4, H-12, and H-13).[158] In a cross-sectional analysis of men with back pain (n=11,327) in an integrated healthcare system, long-term opioid use (defined as ≥120 days or >90 days with 10 or more fills) was associated with increased likelihood of use of medications for erectile dysfunction or testosterone replacement versus no opioid use (adjusted OR 1.5, 95% CI, 1.1 to 1.9), after adjustment for age, co-morbidities, hospitalizations, use of sedative-hypnotics, dose of opioids, type of opioid, depression, and smoking status. Median opioid dose in men on chronic opioid therapy was 30 mg MED/day (19% received ≥120 mg) and 42 percent received long-acting opioids. A limitation of this study is that the patient sample was a mix of acute, subacute, and chronic back pain, and the study did not control for duration of pain. In addition, due to the cross-sectional design, it is not possible to determine whether endocrinological problems preceded or resulted from opioid use.

Suicidality and Suicide Events

A previously described (see Opioid Use Disorder, Dependence, and Related Outcomes) new cohort study of 98,140 patients in the UK Clinical Practice Research Datalink primary care found no association between long-term opioid use versus no long-term use and risk of attempted suicide/self-harm (incidence 0.7 vs. 0.6 per 10,000 person-years, adjusted HR 1.01, 95% CI, 0.42 to 2.45).[155]

Key Question 2b. How do harms vary depending on: (1) the specific type or cause of pain, (2) patient demographics, (3) patient comorbidities, (4) the dose of opioids used and duration of therapy, (5) the mechanism of action of opioids used, (6) use of sedative hypnotics, (7) use of gabapentinoids, (8) use of cannabis?

Key Points

- Analyses of placebo-controlled trials found no interactions between the pain type and risk of harms (SOE: low).
- Evidence was too limited to determine effects of patient demographics and comorbidities on risk of harms (SOE: insufficient).
- Three cohort studies found an association between concurrent use of benzodiazepines and opioids versus opioids alone and increased risk of overdose; in one study, the risk decreased with longer duration of concurrent use (SOE: low).
- Three observational studies found an association between concurrent use of gabapentinoids and opioids versus opioids alone and increased risk of overdose; risks were higher at increased gabapentinoid doses (SOE: low).

- There was insufficient evidence to determine effects of concurrent use of cannabis plus opioids versus opioids alone on risk of harms (SOE: insufficient).
- Dose/Duration
- Analyses of placebo-controlled trials indicated no interaction between higher opioid dose category and increased risk of short-term harms; trials directly comparing higher versus lower dose were limited but reported similar findings (SOE: low).
- Two cohort studies found higher doses of long-term opioid therapy associated with increased risk of opioid abuse, dependence, or addiction compared with lower doses (SOE: low).
- Four observational studies consistently found an association between higher doses of long-term opioid therapy and risk of overdose or overdose mortality (SOE: low).
- One cohort study found higher dose of opioids associated with increased risk of all-cause mortality; longer duration was associated with decreased risk of all-cause mortality (SOE: low).
- Three observational studies reported inconsistent findings regarding a dose-response association between opioids and risk of fractures (SOE: insufficient).
- One cohort study found modest associations between higher dose of long-term opioid therapy and increased risk of falls and major trauma (SOE: low).
- Two cohort studies reported inconsistent findings regarding a dose-response association between opioids and risk of cardiovascular events (SOE: insufficient).
- One case-control study found opioid dose higher than 20 mg MED/day associated with increased odds of road trauma injury when the analysis was restricted to drivers, with no dose-dependent association at doses higher than 20 mg MED/day (SOE: low).
- Three cohort studies found associations between higher opioid dose and risk of various endocrinological adverse events (use of erectile dysfunction medications or testosterone replacement, androgen deficiency, or female reproductive dysfunction) (SOE: low).
- One cohort study found an association between longer duration of opioid therapy and increased risk of new-onset depression; there was no association between higher dose and increased risk. A smaller study by the same authors reported similar findings for treatment-resistant depression (SOE: low).
- Evidence from one cohort study was insufficient to determine the association between higher opioid doses and risk of attempted suicide/self-harm, due to the small number of events and imprecise estimates (SOE: insufficient).

Detailed Synthesis

Type or Cause of Pain

Analyses of short-term placebo-controlled trials found no interactions between pain type and risk of short-term adverse events (discontinuation due to adverse events, serious adverse events, gastrointestinal adverse events, somnolence, dizziness, headache, or pruritus) (Tables 25-27). One trial of stepped therapy with opioids versus stepped therapy initiated with nonopioids found similar adverse symptom scores at 12 months in patients with back pain and those with osteoarthritis.[143]

Patient Demographics and Comorbidities

Evidence on the interaction between patient demographic or comorbidities and risk of harms was very limited. One trial found somewhat greater differences between stepped therapy with opioids versus stepped therapy starting with nonopioid therapy in adverse event symptom scores (0 to 19 scale) in men compared with women (0.7 point vs. 2.0 point) and in persons less than 65 years versus those 65 years or older (1.4 vs. 0.2 point).[143]

Dose of Opioid Used and Duration of Therapy

In analyses of placebo-controlled trials, there were no interactions between higher dose of opioid (<50, 50 to <90, or ≥90 mg MED/day) and increased risk of short-term harms, including discontinuation due to adverse events, serious adverse events, somnolence, gastrointestinal adverse events, dizziness, or pruritus (**Tables 25-27**). Only six trials directly compared harms associated with higher versus lower opioid dose categories, with no indications of dose effects for these harms.[62,63,66,86,96,117] Trials did not report how risk of harms varied according to duration of therapy.

Opioid Abuse, Addiction, and Related Outcomes

A study included in the 2014 AHRQ report and described in Key Question 2a evaluated the association between dose of long-term opioid therapy and risk of abuse or dependence (Appendix Table G-2 and H-5).[160] Based on ICD-9 diagnosis codes, of the proportion of patients with abuse or dependence was 0.7 percent with low dose opioids (1 to 36 mg MED/day), 1.3 percent with medium dose (36 to 120 mg MED/day), and 6.1 percent with high dose opioids (≥120 mg MED/day). Compared with no opioid prescription, the odds ratio for abuse or dependence after adjustment for age, sex, history of substance abuse and other comorbidities was 15 (95% CI, 10 to 21) for low dose, 29 (95% CI, 20 to 41) for medium dose, and 122 (95% CI, 73 to 205) for high dose opioids.

A new, previously described (see Key Question 2a) fair-quality cohort study of 98,140 patients with long-term opioid use (≥3 opioid prescriptions over 90 days) also found an association between higher opioid dose and increased risk of opioid addiction. Adjusted HR was 1.06 (95% CI, 0.71 to 1.60) for long-term opioid use at less than 20 mg MED/day, 3.59 (95% CI, 2.55 to 5.06) at 20 to less than 50 mg MED/day, and 9.33 (95% CI, 6.55 to 13.29) at 50 mg or more MED/day (reference no long-term opioid use).[155]

Overdose

Three observational studies evaluated the association between higher opioid dose and risk of overdose (Appendix Tables G-2, G-3, H-6, and H-7).[159,169,170] Two studies[159,169] were included in the 2014 AHRQ report and one new study[170] was added for this update. Sample size was 9940 in the cohort study and the number of cases was 399 and 498 (total cases was 897) in two case-control studies. All studies adjusted for demographic factors, clinical factors, and use of medications. Two studies were rated good-quality[169,170] and one study was rated fair-quality; methodological limitations in the fair-quality study included unclear reporting of key factors at baseline, unclear whether the outcome assessor was blinded, and high attrition.

Both studies included in the 2014 AHRQ report found an association between higher opioid dose and increased risk of overdose. A good-quality population-based, nested case-control study (498 cases) reported an adjusted odds ratio (OR) for opioid-associated mortality of 1.32 (95% CI, 0.94 to 1.84) for 20 to 49 mg/day, 1.92 (95% CI, 1.30 to 2.85) for 50 to 99 mg/day, 2.04 (95 %

CI, 1.28 to 3.24) for 100 to 199 mg/day, and 2.88 (95% CI, 1.79 to 4.63) for 200or more mg/day (reference was 1 to 19 mg MED/day).[169] A fair-quality retrospective cohort study (n=9,940) of patients with recently diagnosed noncancer pain found higher opioid dose associated with greater overdose risks: 20 to 49 mg/day was associated with a HR of 1.44 (95% CI, 0.57 to 3.62), 50 to 99 mg/day with a HR of 3.73 (95% CI, 1.47 to 9.5), and 100 mg/day or more with an HR of 8.87 (3.99 to 19.72) (reference was 1 to 19 mg MED/day).[159] The risk for serious (e.g. death or life threatening overdose) overdose showed a similar pattern, with HRs of 1.19 (95% CI, 0.4 to 3.6) for 20 to 49 mg MED/day, 3.11 (95% CI, 1.01 to 9.51) for 50 to 99 mg/day, and 11.18 (95% CI, 4.80 to 26.03) for 100 mg/day or more.

The two new studies also found an association between higher opioid dose and risk of overdose. A good-quality nested case-control study of patients with chronic pain in the Veterans Healthcare Administration (VHA) database matched 221 cases of opioid-related deaths to 483,278 controls on sex, age, race and ethnicity, mental health comorbidities, medical comorbidities, and medication use.[170] Prior to the index date, 66.5 percent of cases and controls had used an opioid for more than 90 days. After adjusting for potential confounders, mean prescribed opioid dose (in MED/day) was higher in cases versus controls (98.1 vs. 47.7 mg, $p<0.001$). Findings were similar when persons prescribed 300 mg MED/day or more were excluded (74.7 vs 40.2, $p<0.001$). Opioid dose was associated with an area under the receiver operating characteristic curve (AUROC) of 0.71 (95% CI, 0.66 to 0.76; $p<0.001$) for predicting opioid-related death. A previously described (see Key Question 2a) cohort study of 98,140 patients with long-term opioid use (≥3 opioid prescriptions over 90 days) reported an adjusted HR for overdose of 1.59 (95% CI, 1.16 to 2.19) for long-term opioid use at greater than 20 mg MED/day, HR of 2.83 (95% CI, 2.04 to 3.92) at 20 to less than 50 mg MED/day, and HR of 3.81 (95% CI, 2.50 to 5.80) at 50 mg MED/day or more (reference no long-term opioid use).[155]

All-Cause Mortality

One new, fair-quality cohort study (n=22,912) described in Key Question 2a of Medicaid patients evaluated the association between dose and duration of long-acting opioids and risk of all-cause mortality (Appendix Table G-2, H-6, and H-7).[166] The risk of all-cause mortality associated with long-acting opioids increased with higher dose: the adjusted HR was 1.54 (95% CI, 1.01 to 2.34) in patients prescribed an opioid dose of 60 mg MED/day or less and 1.94 (95% CI, 1.40 to 2.70) in patients prescribed an opioid dose more than 60 mg MED/day (HRs relative to prescription of anticonvulsants or cyclic antidepressants). The excess risk was highest in the first 30 days and limited to the first 180 days: the adjusted HR was 4.16 (95% CI, 2.2 to 7.63) for duration of 30 days or more, the adjusted HR was 1.56 (95% CI, 1.05 to 2.30) for 31 to 180 days, and the adjusted HR was 1.03 (95% CI, 0.67 to 1.57) for more than 180 days.

Fractures and Falls

A fair-quality cohort study included in the 2014 AHRQ report and described in Key Question 2a of people aged 60 years or older (mean age 73 years) found that risk of fracture increased from an adjusted HR of 1.20 (95% CI, 0.92 to 1.56) at an opioid dose of 1 to less than 20 mg MED/day to 2.00 (95 percent CI, 1.24 to 3.24) at 50 mg MED/day or more. CIs overlapped and the overall test for dose response did not reach statistical significance ($p = 0.06$; Appendix Table G-2, H-8, and H-9).[167]

Two new retrospective cohort studies (n=7447 and 17,310, total N=24,757) described in KQ 2a also evaluated the association between higher opioid dose and risk of fracture.[156,165] Both

studies adjusted for demographic and clinical factors, including comorbidities and other medications. A good-quality study (n=7447) of veterans with spinal cord injuries (mean age 58 years) found less than 225 mg codeine-equivalent dose/day (1 mg codeine=0.15 mg morphine) associated with greater risk of lower extremity fracture than more than 225 mg ($p<0.0001$).[156] A fair-quality study (n=17,310) of patients with osteoarthritis or rheumatoid arthritis found that risk of hip, humerus/ulnar, and wrist fractures increased with higher doses of opioids.[165] Relative to NSAID use, opioid use at 75 mg codeine-equivalents per day or less was associated with an adjusted HR of 2.2 (95% CI, 0.9 to 5.2), for 75 to 225 mg/day the adjusted HR was 4.6 (95% CI, 3.2 to 6.6), and for greater than 225 mg the adjusted HR was 5.1 (95% CI, 3.7 to 7.2).

Two observational studies found an association between longer duration of opioid use and decreased risk of fracture. One case-control study (21,739 cases) included in the 2014 AHRQ report found the risk of fracture was highest with one prescription (OR 2.70, 95% CI, 2.34 to 3.13) and decreased with higher numbers of prescriptions, with no increased risk for patients with more than 20 cumulative prescriptions.[163] A new cohort study (n=7447) of veterans with spinal cord injury reported an adjusted HR of 0.36 (95% CI, 0.26 to 0.50) for 6 to 12 months use of opioids, 0.5 (95% CI, 0.43 to 0.75) for 1 to 2 years, 0.50 (95% CI, 0.36 to 0.70) for 2 to 3 years, and 0.37 (95% CI, 0.27 to 0.51) for 3 years or more (HRs relative to <6 months use).[156]

A previously described (see Key Question 2a) cohort study of 98,140 patients with long-term opioid use (≥3 opioid prescriptions over 90 days) found modest associations between higher opioid dose and increased risk of major trauma and falls.[155] For major trauma, the HR was 1.09 (95% CI, 1.04 to 1.14) for long-term opioid use at less than 20 mg MED/day, 1.24 (95% CI, 1.16 to 1.32) at 20 to less than 50 mg MED/day, and 1.34 (95% CI, 1.20 to 1.50) at 50 mg MED/day or more (reference no long-term opioid use). For falls, the HR increased from 1.17 (95% CI, 1.12 to 1.21) at less than 20 mg MED/day to 1.64 (95% CI, 1.50 to 1.80) at 50 mg MED/day or more.

Cardiovascular Events

A fair-quality cohort study included in the 2014 AHRQ report and described in Key Question 2a found a trend towards increased risk of myocardial infarction with higher cumulative opioid exposure in patients using long-term opioid therapy (Appendix Table G-2, H-10, and H-11).[157] Compared with a cumulative dose of 0 to less than 1350 mg MED over 90 days, the adjusted IRR for myocardial infarction for 1350 to less than 2700 mg was 1.21 (95% CI, 1.02 to 1.45), for 2700 to less than 8100 mg was 1.42 (95% CI, 1.21 to 1.67), for 8100 to less than 18,000 mg was 1.89 (95% CI, 1.54 to 2.33), and for 18,000 mg or greater was 1.73 (95% CI, 1.32 to 2.26).

Motor Vehicle Accidents

A good-quality nested case-control study included in the 2014 AHRQ report evaluated the association between opioid dose and risk of motor vehicle accidents in Ontario, Canada (Appendix Tables G-3, H-14, and H-15).[171] Cases (n=5300) who visited an emergency department with an injury related to road trauma were matched on sex, age, index year, and disease risk index to controls (n=5300). All patients had received at least one opioid prescription; the average duration of opioid use was 7.1 years in cases and 6.8 years in controls. Although there was no association between opioid dose and risk of road trauma in the combined group of drivers and passengers at the time of the accident, doses of opioids greater than 20 mg MED/day were associated with increased odds of road trauma when the analysis was restricted to drivers. There was no dose-dependent association at doses higher than 20 mg MED/day. Relative to 1 to less than 20 mg MED/day, the odds of road trauma among drivers after adjustment for age,

alcoholism history, concomitant medication use, total number of drugs, and number of physician and emergency department visits was 1.21 (95% CI, 1.02 to 1.42) for 20 to 49 mg, 1.29 (95% CI, 1.06 to 1.57) for 50 to 99 mg, 1.42 (95% CI, 1.15 to 1.76) for 100 to 199 mg, and 1.23 (95% CI, 1.02 to 1.49) for 200 mg or more (SOE: low).

Endocrinological Harms

One study included in the 2014 AHRQ report and described in Key Question 2a evaluated the association between opioid dose and risk of endocrinological harms. It was a fair-quality cross-sectional study (n=11,327) of men with back pain that found a daily opioid dose of 120 mg MED/day or more to be associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus 0 to less than 20 mg MED/day (OR 1.6, 95% CI, 1.03 to 2.4), after adjustment for duration of opioid use, age, co-morbidities, hospitalizations, use of sedative-/hypnotics, type of opioid, depression, and smoking status (Appendix Table G-2, H-12, and H-13).[158] There was no increased risk at doses of 20 to less than 120 mg MED/day.

Two new studies evaluated the association between opioid dose or duration and risk of endocrinological harms. A fair-quality retrospective cohort study (n=1,159) of men with chronic pain on stable doses of opioids (≥90-day supply) found increased dose of hydrocodone associated with increased risk of testosterone deficiency (per 10 mg dose increase, adjusted OR 1.18, 95% CI, 1.09 to 1.28).[172] For other opioids (fentanyl, hydromorphone, methadone, morphine, and oxycodone), estimates indicated no dose-related risk or were imprecise. Testosterone levels were evaluated within 100 days of receiving opioids, with no assessment of baseline (prior to opioid initiation) testosterone level. A fair-quality, matched cohort study (n=44,260) of women aged 18 to 55 years of age in the UK Clinical Practice Research Datalink primary care database found long-term (≥90 days) opioid use versus short-term use to be associated with increased risk of abnormal menstruation (adjusted HR 1.13, 95% CI, 1.05 to 1.21), menopause (adjusted HR 1.16, 95% CI, 1.10 to 1.23), and low libido (adjusted HR 1.19, 95% CI, 0.96 to 1.48), with no effect on risk of infertility (adjusted HR 0.82, 95% CI, 0.64 to 1.06).[173] Analyses adjusted for existing reproductive dysfunction, thyroid conditions, gynecological conditions, body mass index, smoking status, alcohol use, age, illegal opioid use, and NSAID use.

Suicidality/Suicide Events

A previously described (see Key Question 2a) cohort study of 98,140 patients with long-term opioid use (≥3 opioid prescriptions over 90 days) evaluated the association between higher dose and risk of attempted suicide/self-harm, but estimates were too imprecise for reliable conclusions, due to the small number of events (nine total).[155]

Depression

No study in the 2014 AHRQ report evaluated the association between opioid use and risk of depression. A new, fair-quality retrospective cohort study (n=107,755) of patients in three administrative databases found an association between longer duration of opioid use and risk of new-onset depression.[174] Relative to 1 to 30 days of opioid use, 31 to 90 days of opioid use was associated with adjusted HRs for new-onset depression in the three databases that ranged from 1.18 to 1.33 and more than 90 days was associated with adjusted HRs that ranged from 1.31 to 2.26 (Appendix Table G-2, H-16, and H-17). There was no association between dose and risk of new-onset depression. A study (n=6,223) by the same authors that focused on veterans with

chronic pain found no association between higher (>50 mg MED/day) versus lower dose and risk of treatment-resistant depression (HR 1.07, 95% CI, 0.88 to 1.30).[175] However, longer duration of use was associated with increased risk (relative to 1 to 30 days, adjusted HR 1.29, 95% CI, 1.09 to 1.45 for 31 to 90 days and adjusted HR 1.52, 95% CI, 1.32 to 1.74 for >90 days). Treatment-resistant depression was defined as use of electroconvulsive therapy, monoamine oxidase inhibitor prescription, use of two or more concurrent antidepressants, or use of augmentation therapy (e.g., prescription of a mood stabilizing agent or atypical antipsychotic after antidepressant treatment).

Opioid Type

An analysis of short-term placebo-controlled trials found an interaction between opioid type and risk of pruritus (p for interaction=0.02), with a higher RR for opioid agonists (16 trials, N=4724, RR 4.02, 95% CI, 2.44 to 6.48) and mixed mechanism medications (11 trials, N=6136, RR 4.77, 95% CI, 3.01 to 7.95) than for partial agonists (3 trials, N=594, RR 1.18 95% CI, 0.80 to 1.91); however, only three trials evaluated partial agonists. There were no interactions between opioid type and risk of discontinuation due to adverse events, serious adverse events, gastrointestinal adverse events, somnolence, dizziness, headache, or pruritus (Tables 25-27).

Evidence on the interaction between opioid type and risk of opioid use disorder, overdose, mortality, fractures, falls, or cardiovascular events was very limited. One clinical trial (n=11,352) with partial randomization found tramadol associated with decreased risk of substance abuse over 12 months compared with hydrocodone or NSAIDs (2.7%, 4.9%, and 2.5%, respectively)[176] (Appendix Table G-2 and H-5). Abuse was defined by an index based on presence of inappropriate use, use for purposes other than intended, inability to stop use, or evidence of opioid withdrawal symptoms.

Use of Sedative Hypnotics

Three retrospective cohort studies (n=9940, 71,428, and 315,428) evaluated the association between co-prescribed benzodiazepines plus opioids versus opioids alone and risk of opioid-related overdose (Table 28, Appendix Tables H-18 and H-19).[159,177,178] The studies were based on data collected from different settings (Medicare, commercially insured, or managed care organization). All studies adjusted for demographic factors, clinical factors, and other medication use. One study was rated good-quality[159] and two studies fair-quality, primarily due to risk of residual confounding (Appendix Table G-2).

A previously described retrospective cohort study (n=9940) of individuals with chronic pain and three or more opioid prescriptions over a 90-day period also examined risks of co-prescribed sedative hypnotics, which included benzodiazepines, skeletal muscle relaxants, and barbiturates. Co-prescribing of a sedative hypnotic was associated with increased risk of opioid overdose versus no sedative hypnotic (for a 1 to 22 day supply, HR 3.4, 95% CI, 1.6 to 7.2). Overdose risk did not increase with increasing duration (days' supply) of sedative hypnotic use. Although risks associated with co-prescription of benzodiazepines were not reported separately, the majority of individuals prescribed sedative hypnotics were prescribed benzodiazepines.

A second retrospective cohort study (n=71,428)[177] of Medicare beneficiaries found concurrent benzodiazepine and opioid prescribing associated with a 5-fold increased risk of overdose versus opioid prescribing alone (HR 5.05, 95% CI, 3.68 to 6.93). Risk of overdose decreased as the duration of concurrent use increased (HR 1.87, 95% CI, 1.25 to 2.80 from 91 to

180 days of concurrent use, HR 0.63, 95% CI, 0.37 to 1.05 from 181 to 270 days, and HR 0.19, 95% CI, 0.11 to 0.33 at >270 days).

The third study (n=58,814) evaluated commercially insured individuals with at least one opioid prescription; analyses were also performed on the subgroup of persons with chronic opioid use (≥10 prescriptions or >120 days' supply in a given year). Concurrent opioid and benzodiazepine use was associated with increased risk of overdose (annualized incidence 2.42% vs. 1.16%, adjusted odds ratio 2.14; 95% CI, 2.05 to 2.24). There was also an association between concurrent use and increased risk of overdose among persons with chronic opioid use, though the estimate was slightly attenuated (5.36% vs. 3.13%, adjusted odds ratio 1.81; 95% CI, 1.67 to 1.96).

Table 28. Observational studies of opioid and benzodiazepine co-prescribing

Author, Year Study Design Duration	Sample	Interventions, N	Results	Quality
Dunn, 2010[159] Retrospective cohort 90 days	Adults ≥18 years of age with >1 opioid prescription (none in 6 months prior) and ≥3 prescriptions filled in first 90 days and diagnosis of chronic non-cancer pain in 2 weeks prior to first opioid prescription Mean age, years: 54 Female: 60% Tobacco use: 29% Depression: 27% SUDs: 6% Mean Charlson score: 0.71 Pain diagnosis: back 38%, extremity pain 30%, osteoarthritis 13%, injury 12%, neck 9%	A. No sedative-hypnotic exposure in 90 days before overdose B. Sedative-hypnotic exposure of 1- to 22-day supply during prior 90 days C. Sedative-hypnotic exposure of 23 to 44 day supply during prior 90 days D. Sedative-hypnotic exposure of 45- to 71-day supply during prior 90 days E. Sedative-hypnotic exposure of ≥72-day supply during prior 90 days n=9940	Total opioid exposed: 148 per 100,000 person-years No opioid exposure: 36 per 100,000 person-years (reference) Any opioid use: 256 per 100,000 person-years; A vs. B vs. C vs. D vs. E HR (95% CI) for overdose with sedative-hypnotic use A. Reference B. 3.4 (1.6 to 7.2) C. 0.9 (0.2 to 4) D. 3.7 (1.6 to 8.9) E. 2.7 (1.2 to 6)	Good

Author, Year Study Design Duration	Sample	Interventions, N	Results	Quality
Hernandez, 2018[177] Retrospective cohort, 365 days	≥1 opioid prescription in 2014 and continuously enrolled from first opioid claim end of study or death A vs. B vs. C vs. D vs. E Mean age, years: 68 vs. 71 vs. 66 vs. 64 vs. 60 Female: 63% vs. 72% vs. 70% vs. 72% vs. 64% White: 82% vs. 88% vs. 88% vs. 88% vs. 89% Disability: 38% vs. 32% vs. 43% vs. 51% vs. 63% Pain diagnosis: 76% vs. 65% vs. 65% vs. 65% vs. 64% Depression: 54% vs. 69% vs. 74% vs. 76% vs. 76% Anxiety: 2% vs. 6% vs. 8% vs. 8% vs.11%	A. Opioid use only (n=50,583) B. Opioid/benzo used 1 to 90 days (n=3603) C. Opioid/benzo used 91 to 180 days (n=2930) D. Opioid/benzo used 181 to 270 days (n=4082) E. Opioid/benzo used >271 days (n=10,050)	A vs. B vs. C vs. D vs. E Frequency of opioid overdose by days of overlap (unadjusted): 0.33% (166/50,583) vs. 1.64% (59/3603) vs. 1.09% (32/2930) vs. 0.47% (19/4082) vs. 0.14% (14/10,050) Covariate adjusted Cox proportional hazard model (HR, 95% CI): reference vs. 5.1 (3.7 to 7.0) vs. 1.9 (1.3 to 2.8) vs. 0.6 (0.4 to 1.1) vs. 0.2 (0.1 to 0.3)	Fair
Sun, 2017[178] Retrospective cohort	Continuous enrollment in a plan with medical and pharmacy benefits from 2001 to 2013, aged 18 to 64 years and ≥1 opioid prescription A vs. B Mean age, years: 44.5 vs. 42.4; p<0.001 Depression: 17% vs. 4.4%; p<0.001 Psychosis: 0.55% vs. 0.13%; p<0.001 Drug abuse: 1.2% vs. 0.22%; p<0.001 Alcohol abuse: 1.1% vs. 0.3%; p<0.001 MI: 0.41% vs. 0.13%; p<0.001 Dementia: 0.28% vs. 0.12%; p<0.001 CVD: 0.65% vs. 0.19%; p<0.001 COPD: 4.7% vs. 2.0%; p<0.001	A. Benzodiazepine (n=5425) B. No benzodiazepine (n=53,389)	A vs. B Annual adjusted incidence of opioid overdose: 2.42% vs. 1.16%; adjusted OR 2.14 (95% CI, 2.05 to 2.24); p<0.001 Intermittent opioid users: 1.45% vs. 1.02%; adjusted OR 1.42 (95% CI, 1.33 to 1.51); p<0.001 Chronic opioid users: 5.36% vs. 3.13%; adjusted OR 1.81 (95% CI,1.67 to 1.96); p<0.001	Fair

Abbreviations: CI=confidence interval; COPD=chronic obstructive pulmonary; CVD=cardiovascular disease; HR=hazard ratio; disease; MI=myocardial infarction; OR=odds ratio; SUDs=substance use disorders.

Use of Gabapentinoids

Three fair-quality observational studies evaluated risks of exposure to gabapentin or pregabalin plus opioids versus opioids alone in patients with chronic pain (Appendix Table H-20 and H-21).[179-181] All studies conducted analyses adjusted for demographic factors, clinical factors, and concomitant medication use. The studies were rated fair-quality; methodological shortcomings included baseline differences between exposure groups with potential for residual confounding (Appendix Table G-3).

Two case-control studies (2683 total cases) found exposure to gabapentin (adjusted OR 1.49, 95% CI, 1.18 to 1.88)[179] and pregabalin (OR 1.68, 95% CI, 1.19 to 2.36)[180] each associated with increased risk of overdose death compared to opioids alone. Risk increased at higher doses. Low-dose (≤899 mg/day) gabapentin was associated with an adjusted OR of 1.32 (95% CI, 0.89 to 1.96) compared with adjusted ORs of 1.58 (95% CI, 1.09 to 2.27) for moderate-dose (900 to 1799 mg/day) and 1.56 (95% CI, 1.06 to 2.28) for higher-dose (≥1800 mg/day).[179] Low-dose (≤300 mg/day) pregabalin was associated with an adjusted OR of 1.52 (95% CI, 1.04 to 2.22) and higher dose (>300 mg/day) associated with an adjusted OR of 2.51 (95% CI, 1.24 to 5.06) for drug-related mortality.[180]

A cohort study (n=796,330) evaluated risks associated with use of gabapentin plus opioids and opioids alone, including dose-dependent risks based on degree of "overuse" (defined as gabapentin dose >2700 mg/day and opioid dose >50 mg MED/day).[181] No overuse was defined as 0 to 1 claim over 12 months from first study medication claim (or from a random proxy date in the case of zero claims) above the thresholds; mild overuse as two or more claims or one to two calendar quarters above the thresholds; and sustained overuse as three or more rolling calendar quarters above the thresholds. Use of gabapentin plus opioids was associated with increased risk of drug-related inpatient hospitalization and drug-related emergency department use compared with opioids alone at all levels of overuse, with evidence of a dose dependent effect. For patients without overuse as defined in the trial, the adjusted OR of drug-related inpatient hospitalization was 1.64 (95% CI, 1.46 to 1.85) in patients prescribed gabapentin plus opioids compared to 0.69 (95% CI, 0.64 to 0.74) for opioids alone (the reference was prescribed gabapentin without overuse). The adjusted OR for drug-related inpatient hospitalization was 4.72 (95% CI, 2.66 to 8.37) for sustained overuse of both drugs and 2.95 (95% CI, 2.46 to 3.54) for sustained overuse of one drug (in patients prescribed both), compared to 1.61 (95% CI, 1.44 to 1.80) for sustained overuse of opioids alone (without gabapentin prescription). Similar patterns were observed for risk of drug-related emergency department visits, all-cause inpatient hospitalizations, all-cause emergency department visits, and specific drug-related symptoms (adverse drug reaction/detoxification or addiction, altered mental state, or respiratory depression) (Appendix Tables H-20 and H-21).

Use of Cannabis

One cohort study described earlier (see Key Question 1d) of patients prescribed opioids for chronic noncancer pain found an association between self-reported cannabis use versus non-use and increased anxiety, but the analysis was unadjusted.[153] No other evidence on effects of concurrent cannabis on risks associated with use of opioids was available.

Key Question 2c. In patients with chronic pain, what are the comparative risks of opioids versus nonopioid therapies on: (1) opioid use disorder, abuse, or misuse; (2) overdose (intentional and unintentional); and (3) other harms including gastrointestinal-related harms, falls, fractures, motor

vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and mental health harms (e.g., depression)?

Key Points

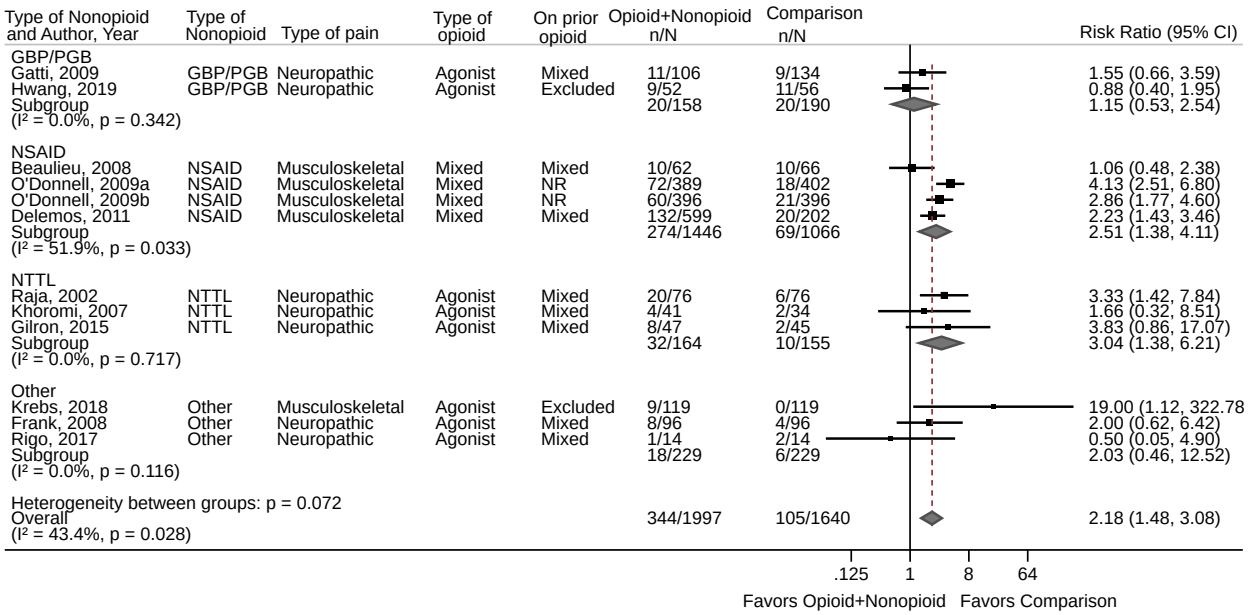
- Opioids were associated with increased risk of discontinuation due to adverse events (12 trials, N=3637, RR 2.18, 95% CI, 1.48 to 3.08, I^2=43%; ARD 9%, 95% CI, 5% to 11%) somnolence (12 trials, N=3377, RR 2.11, 95% CI, 1.39 to 3.47, I^2=61%; ARD 7%, 95% CI, 0% to 23%), nausea (11 trials, N=3137, RR 2.77, 95% CI, 2.09 to 4.18, I^2=13%; ARD 12%, 95% CI, 7% to 18%), constipation (12 trials, N=3377, RR 2.92, 95% CI, 1.80 to 5.21, I^2=70%; ARD 16%, 95% CI, 7% to 26%), vomiting (6 trials, N=2644, RR 4.62, 95% CI, 2.94 to 7.24, I^2=0%; ARD 6%, 95% CI, 3% to 10%), pruritus (5 trials, N=2577, RR 4.22, 95% CI, 2.45 to 8.20, I^2=0%; ARD 5%, 95% CI, 4% to 7%), and headache (8 trials, N=2791, RR 1.35, 95% CI, 1.08 to 1.70, I^2=0%, ARD 3%, 95% CI, 1% to 5%) versus a nonopioid at short-term followup (SOE: moderate [discontinuation due to adverse events, constipation, somnolence] to high [nausea, vomiting, headache, pruritus]).

Detailed Synthesis

Opioids were associated with increased risk of discontinuation due to adverse events (12 trials, N=3637, RR 2.18, 95% CI, 1.48 to 3.08, I^2=43%; ARD 9%, 95% CI, 5% to 11%; Figure 40),[62,82,95,139-141,143,144,146-148] nausea (11 trials, N=3137, RR 2.77, 95% CI, 2.09 to 4.18, I^2=13%; ARD 12%, 95% CI, 7% to 18%; Figure 41),[62,67,82,95,122,139,141,144,146,147] vomiting (6 trials, N=2644, RR 4.62, 95% CI, 2.94 to 7.24, I^2=0%; ARD 6%, 95% CI, 3% to 10%; Figure 42),[62,139,144,146,147] constipation (12 trials, N=3377, RR 2.92, 95% CI, 1.80 to 5.21, I^2=70%; ARD 16%, 95% CI, 7% to 26%; Figure 43),[62,67,82,95,122,139,141,144,146-148] somnolence (12 trials, N=3377, RR 2.11, 95% CI, 1.39 to 3.47, I^2=61%; ARD 7%, 95% CI, 0% to 23%; Figure 44),[62,67,82,95,122,139,141,144,146-148] pruritus (5 trials, N=2577, RR 4.22, 95% CI, 2.45 to 8.20, I^2=0%; ARD 5%, 95% CI, 4% to 7%; Figure 45),[62,67,141,144] and headache (8 trials, N=2791, RR 1.35, 95% CI, 1.08 to 1.70, I^2=0%, ARD 3%, 95% CI, 1% to 5%; Figure 46)[62,67,82,139,144,146,147] versus a nonopioid at short-term followup (Table 29). The estimate for serious adverse events (4 trials, N=1949, RR 0.63, 95% CI, 0.08 to 4.87, I^2=57%; Figure 47)[139,143,144] was imprecise. There was no statistically significant difference between opioids versus nonopioids in risk of dizziness overall (12 trials, N=3377, RR 1.33, 95% CI, 0.78 to 2.05, I^2=65%; Figure 48).[62,67,82,95,122,139,141,144,146-148] However, stratified by opioid type (p for interaction=0.03), opioids were associated with increased risk of dizziness versus NSAIDS (4 trials, N=2512, RR 2.12, 95% CI, 1.45 to 3.00, I^2=16%), but not gabapentinoids (3 trials, N=439, RR 0.60, 95% CI, 0.15 to 1.09, I^2=0%) or nortriptyline (3 trials, N=310, RR 1.31, 95% CI, 0.64 to 4.27, I^2=0%). In other stratified analyses, opioids were associated with increased risk of constipation, dizziness, and somnolence versus nonopioids in fair-quality trials, but not in poor-quality trials (p for interaction <0.05 in each case) (Tables 30 and 31). Trials of opioid agonists were associated with increased risk of nausea but decreased risk of dizziness compared with trials of mixed mechanism agents; in both cases all trials of opioid agonists also evaluated patients with musculoskeletal pain. Otherwise, there were no interactions between nonopioid type, opioid type, opioid dose, or use of crossover design and effects on these harms; all trials except one[143] were rated fair-quality (Tables 30 and 31).

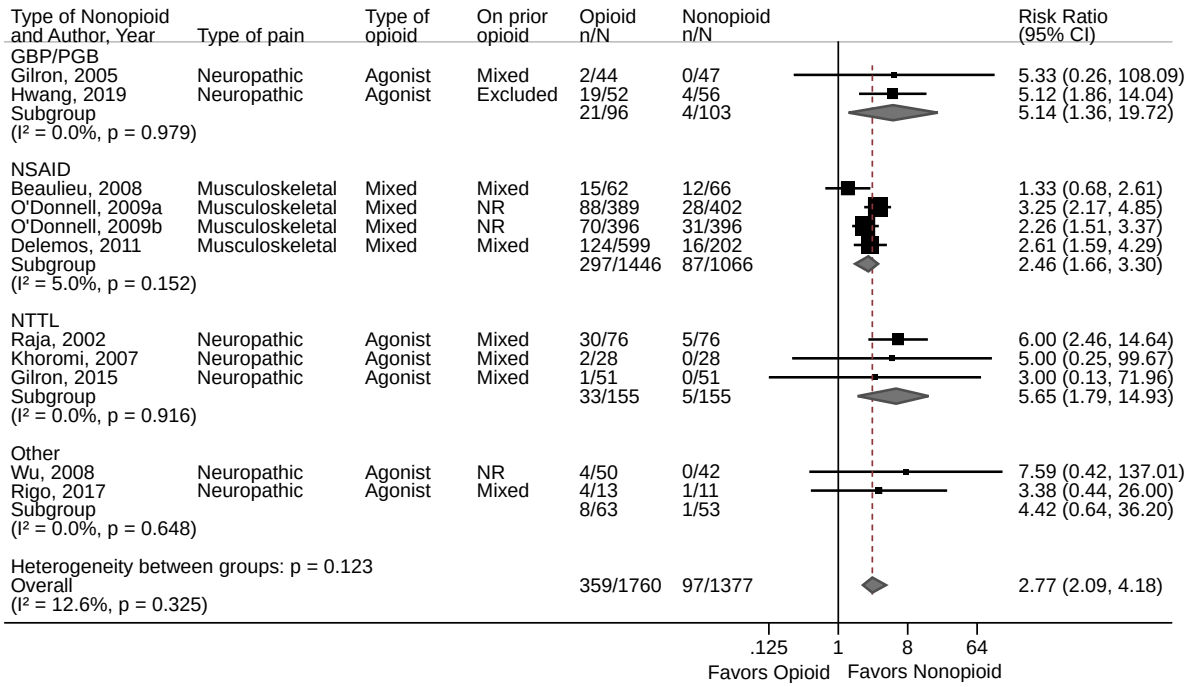
No study evaluated the association between an opioid plus nonopioid versus a nonopioid alone and risk of overdose or opioid use disorder and related outcomes.

Figure 40. Meta-analysis of risk of discontinuation due to adverse events for opioids versus nonopioids



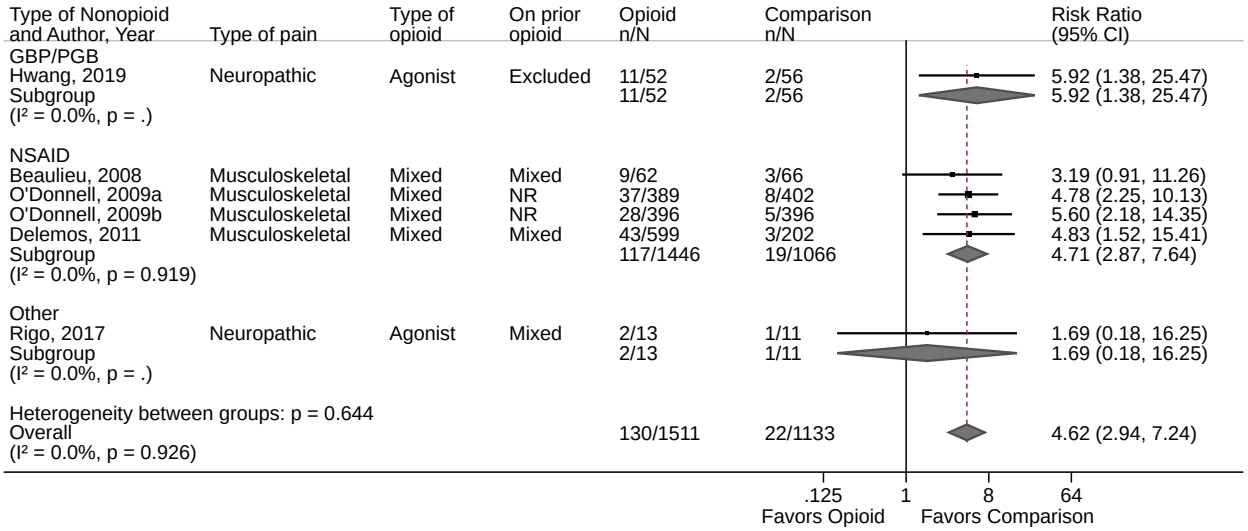
Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who discontinued due to adverse events; N=overall sample; NR=not reported; NSAID=nonsteroidal inflammatory drugs; NTTL=nortryptiline; PGB=pregabalin.

Figure 41. Meta-analysis of risk of nausea for opioids versus nonopioids



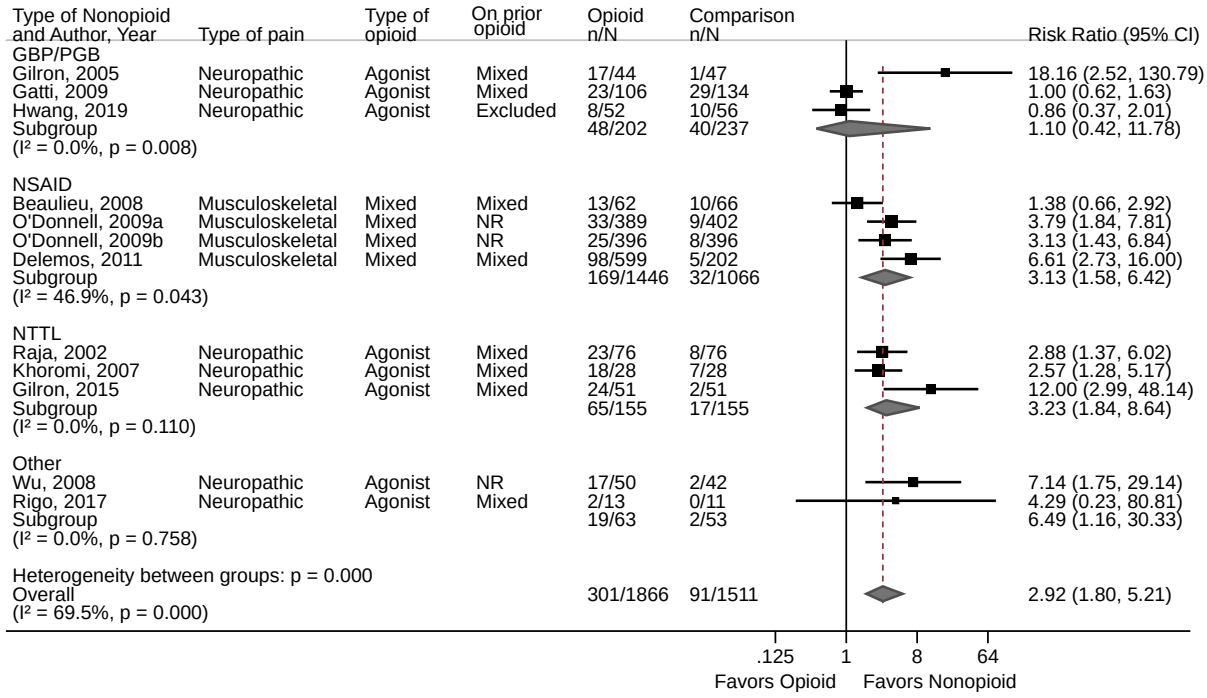
Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced nausea; N=overall sample; NR=not reported; NSAID=nonsteroidal inflammatory drugs; NTTL=nortryptiline; PGB=pregabalin.

Figure 42. Meta-analysis of risk of vomiting for opioids versus nonopioids



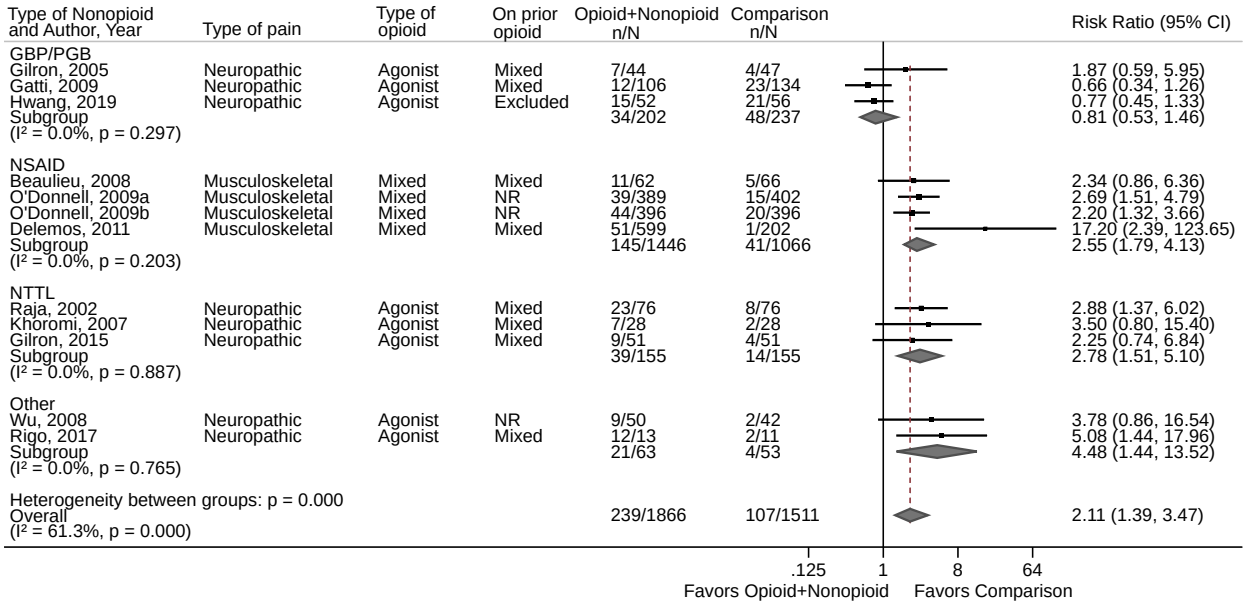
Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced vomiting; N=overall sample; NR=not reported; NSAID=nonsteroidal inflammatory drugs; PGB=pregabalin.

Figure 43. Meta-analysis of risk of constipation for opioids versus nonopioids



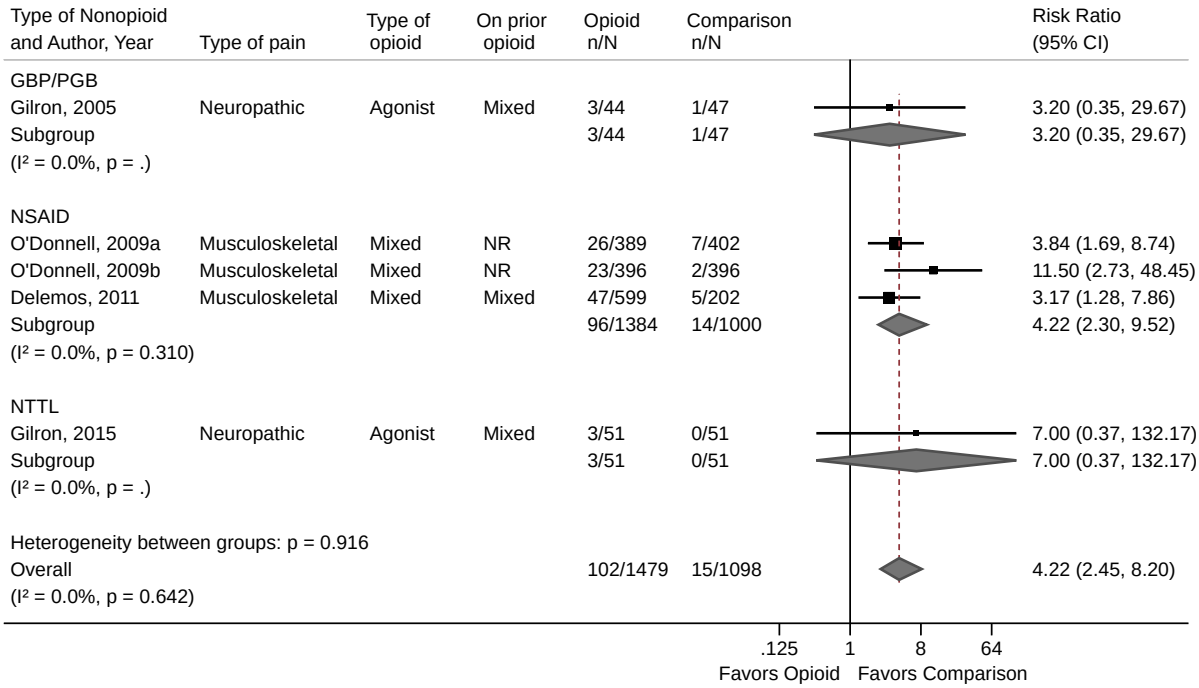
Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced constipation; N=overall sample; NR=not reported; NSAID=nonsteroidal inflammatory drugs; NTTL=nortryptiline; PGB=pregabalin.

Figure 44. Meta-analysis of risk of somnolence for opioids versus nonopioids



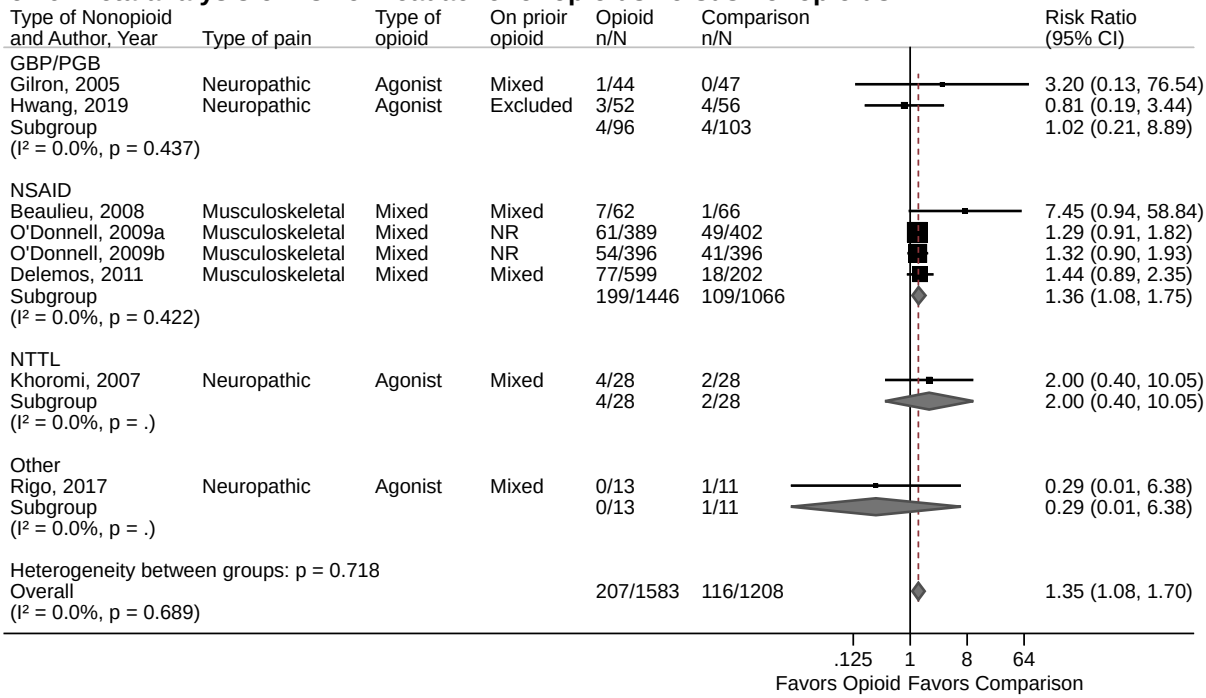
Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced somnolence; N=overall sample; NR=not reported; NSAID=nonsteroidal inflammatory drugs; NTTL=nortryptiline; PGB=pregabalin.

Figure 45. Meta-analysis of risk of pruritus for opioids versus nonopioids



Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced pruritus; N=overall sample; NSAID=nonsteroidal inflammatory drugs; NTTL=nortryptiline; PGB=pregabalin.

Figure 46. Meta-analysis of risk of headache for opioids versus nonopioids



Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced a headache; N=overall sample; NR=not reported; NSAID=nonsteroidal inflammatory drugs; NTTL=nortryptiline; PGB=pregabalin.

Table 29. Summary table of adverse events for opioids versus nonopioids

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Beaulieu, 2008[139] Canada Fair	1: 8 weeks 2: 129 3: Osteoarthritis	1: Tramadol SR 200 to 400 mg (mean 370 mg) 2: Diclofenac SR 150 to 300 mg (mean 284 mg)	1: 16% (10/62) 2: 15% (10/66)	1: 0% (0/62) 2: 15% (10/66)	1: 24% (15/62) 2: 18% (12/66)	1: 15% (9/62) 2: 5% (3/66)	1: 21% (13/62) 2: 15% (10/66)	1: 24% (15/62) 2: 18% (12/66)	1: 11% (7/62) 2: 2% (1/66)	1: 18% (11/62) 2: 8% (5/66)	NR
DeLemos 2011[62] USA Fair	1: 12 weeks 2: 809 3: Osteoarthritis	1: Tramadol SR 100, 200, or 300 mg (mean 200 mg) 2: Celecoxib, dose NR	1: 22% (132/599) 2: 10% (20/202)	1: 0% (0/599) 2: 0% (0/202)	1: 21% (124/599) 2: 8% (16/202)	1: 7% (43/599) 2: 1% (3/202)	1: 16% (98/599) 2: 2% (5/202)	1: 21% (123/599) 2: 12% (24/202)	1: 13% (77/599) 2: 9% (18/202)	1: 9% (51/599) 2: 0.5% (1/202)	1: 8% (47/599) 2: 2% (5/202)
Frank, 2008[140] UK Fair	1: 6 weeks 2: 96 3: Neuropathic pain	1: Dihydrocodeine 30 to 240 mg (mean NR) 2: Nabilone up to 2 mg (mean NR)	1: 8% (8/96) 2: 4% (4/96)	NR	NR	NR	NR	NR	1: 19 events in 73 patients 2: 20 events in 73 patients	1: 102 events in 73 patients 2: 79 events in 73 patients	NR
Gilron, 2015[141] Canada Fair	1: 6 weeks 2: 52 3: Peripheral neuropathic pain	1: Morphine SR up to 100 mg (mean 65 mg) 2: Nortriptyline up to 100 mg (mean 84 mg)	1: 17% (8/47) 2: 4% (2/45)	NR	1: 2% (1/51) 2: 0% (0/51)	1: 0% (0/51) 2: 0% (0/51)	1: 47% (24/51) 2: 4% (2/51)	1: 8% (4/51) 2: 2% (1/51)	1: 0% (0/51) 2: 0% (0/51)	1: 18% (9/51) 2: 8% (4/51)	1: 6% (3/51) 2: 0% (0/51)
Gilron, 2005[67] Canada Fair	1: 5 weeks 2: 57 3: Diabetic neuropathic postherpetic neuralgia	1: Morphine up to 120 mg (mean 45 mg) 2: Gabapentin up to 3200 mg (mean 2207 mg)	NR	NR	NR	NR	NR	NR	NR	NR	NR

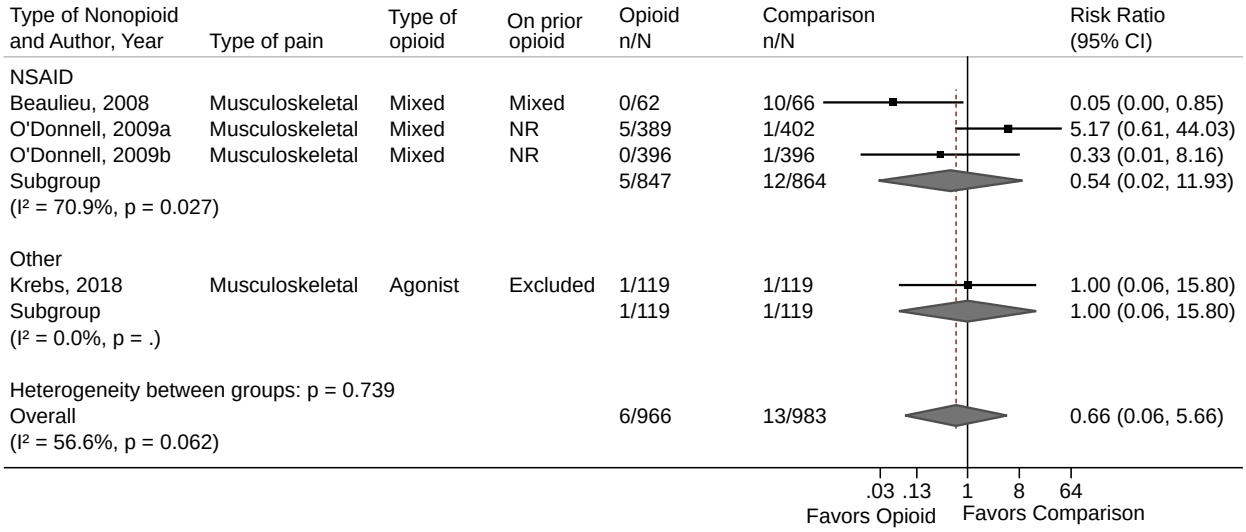
Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Hwang, 2019[147] South Korea Poor	1: 8 weeks 2: 76 3: Neuropathic pain	1: Transdermal fentanyl titrated from 12 mcg/hour (mean 25.0 mcg/hour) 2: Gabapentin up to 2400 mg (mean 1580 mg)	1: 4.7% (9/52) 2: 19.6% (11/56)	NR	1: 36.5% (19/52) 2: 7.1% (4/56)	1: 21.1% (11/52) 2: 3.6% (2/56)	1: 15.4% (8/52) 2: 17.8% (10/56)	1: 30.8% (16/52) 2: 44.6% (25/56)	1: 5.8% (3/52) 2: 7.1% (4/56)	1: 28.8% (15/52) 2: 37.5% (21/56)	NR
Jamison, 1998[142] USA Poor	1: 16 weeks 2: 36 3: Back pain	1a: Oxycodone IR 5 to 20 mg 1b: Oxycodone IR 5 to 20 mg + Morphine SR up to 200 mg 2: Naproxen up to 1000 mg	NR	NR	1: 13.9% 2: 4.7%	NR	1: 17.8% 2: 10.4%	1: 18.8% 2: 9.4%	1: 20.2% 2: 15.1%	1: 22.1% 2: 14.6%	1: 14.9% 2: 8.9%
Khoromi, 2007[82] USA Fair	1: 7 weeks 2: 55 3: Low back pain with radiculopathy	1: Morphine SR up to 90 mg (mean 62 mg) 2: Nortriptyline up to 100 mg (mean 84 mg)	1: 10% (4/41) 2: 6% (2/34)	NR	1: 7% (2/28) 2: 0% (0/28)	NR	1: 64% (18/28) 2: 25% (7/28)	1: 14% (4/28) 2: 7% (2/28)	1: 14% (4/28) 2: 7% (2/28)	1: 25% (7/28) 2: 7% (2/28)	NR
Krebs, 2018 [143] USA Good	1: 52 weeks 2: 240 3: Low back pain and osteoarthritis	1: Mixed opioids (stepped therapy, mean dose 21 mg) 2: Nonopioids (stepped therapy, Tramadol in 3rd step, mean dose 1 mg)	1: 8% (9/119) 2: 0% (0/119)	1: 1% (1/119) 2: 1% (1/119)	NR	NR	NR	NR	NR	NR	NR

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Moran, 1991[88] UK Poor	1: 5 weeks 2: 20 3: Rheumatoid arthritis	1: CR Morphine 20-120 mg (mean NR) 2: Placebo	NR	NR	NR	NR	NR	NR	NR	NR	NR
O'Donnell, 2009a[144] USA Fair	1: 6 weeks 2: 796 3: Low back pain	1: Tramadol IR 200 mg (mean NR) 2: Celecoxib 400 mg (mean NR)	1: 19% (72/389) 2: 4% (18/402)	1: 1% (5/389) 2: 0.2% (1/402)	1: 23% (88/389) 2: 7% (28/402)	1: 10% (37/389) 2: 2% (8/402)	1: 8% (33/389) 2: 2% (9/402)	1: 16% (61/389) 2: 6% (23/402)	1: 16% (61/389) 2: 12% (49/402)	1: 10% (39/389) 2: 4% (15/402)	1: 7% (26/389) 2: 2% (7/402)
O'Donnell,2009b[144] USA Fair	1: 6 weeks 2: 802 3: Low back pain	1: Tramadol IR 200 mg (mean NR) 2: Celecoxib 400 mg(mean NR)	1: 15% (60/396) 2: 5% (21/396)	1: 0% (0/396) 2: 0.2% (1/396)	1: 18% (70/396) 2: 8% (31/396)	1: 7% (28/396) 2: 1% (5/396)	1: 6% (25/396) 2: 2% (8/396)	1: 13% (53/396) 2: 5% (19/396)	1: 14% (54/396) 2: 19% (41/396)	1: 11% (44/396) 2: 5% (20/396)	1: 6% (23/396) 2: 0.5% (2/396)
Pavelka, 1998[145] Czech Republic and Germany Fair	1: 4 weeks 2: 60 3: Osteoarthritis	1: Tramadol IR up to 300 mg (mean 165 mg) 2: Diclofenac up to 150 mg (mean 87 mg)	1: 8% (5/60) 2: 2% (1/60)	NR	NR	NR	NR	NR	NR	NR	NR
Raja, 2002[95] USA Fair	1: 8 weeks 2: 76 3: Postherpetic neuralgia	1: Morphine SR up to 240 mg (mean 91 mg) 2: Nortriptyline up to 160 mg (mean 89 mg)	1: 26% (20/76) 2: 8% (6/76)	NR	1: 39% (30/76) 2: 7% (5/76)	NR	1: 30% (23/76) 2: 11% (8/76)	1: 13% (10/76) 2: 13% (10/76)	NR	1: 30% (23/76) 2: 11% (8/76)	NR
Rigo, 2017 [146] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic	1: Methadone 9 mg (mean NR) 2: Ketamine 90 mg (mean NR)	NR	NR	NR	NR	NR	NR	NR	NR	NR

Study Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid 2: Control	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Wu, 2008[122] USA Fair	1: 6 weeks 2: 60 3:Postamputation pain	1: Morphine SR 30 to 180 mg (mean 112 mg) 2: Mexiletine 150 to 1200 mg (mean 933 mg)	NR	NR	1: 8% (4/50) 2: 0% (0/42)	NR	1: 34% (17/50) 2: 5% (2/50)	1: 4% (2/50) 2: 5% (2/42)	NR	1: 18% (9/50) 2: 5% (2/42)	NR

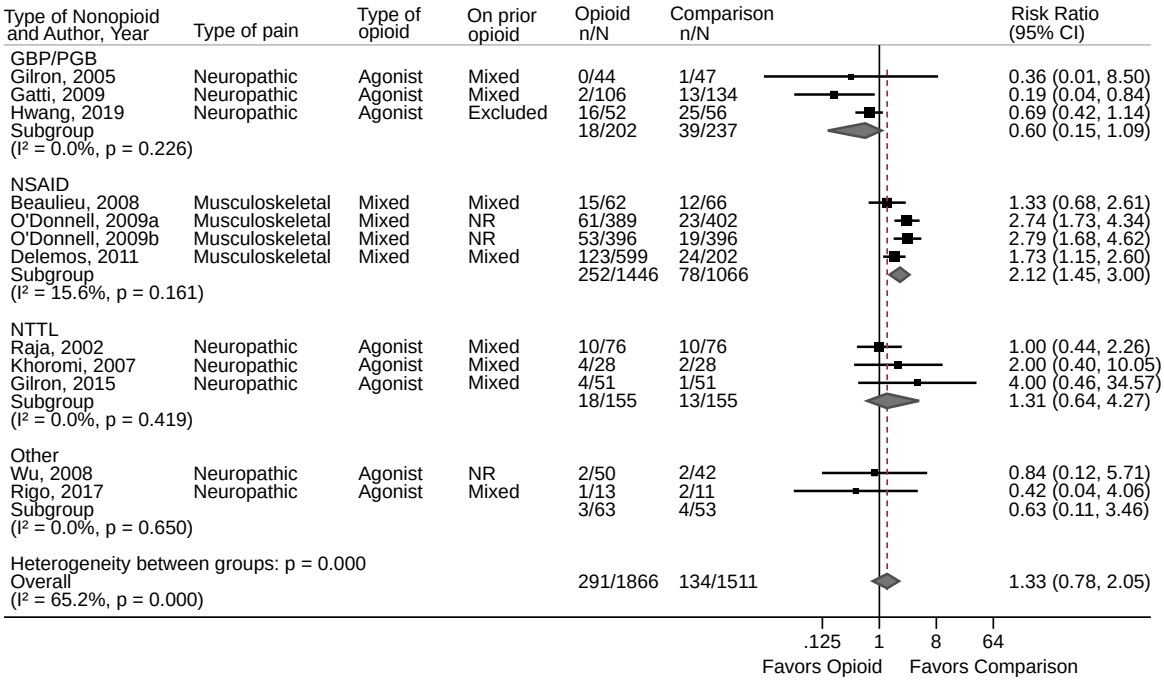
Abbreviations: CR=controlled release; IR=immediate release; NR=not reported; SR=sustained release; UK=United Kingdom; USA=United States of America.

Figure 47. Meta-analysis of risk of serious adverse events for opioids versus nonopioids



Abbreviations: CI=confidence interval; n=number who experienced a serious adverse event; N=overall sample; NR=not reported; NSAID=nonsteroidal inflammatory drugs.

Figure 48. Meta-analysis of risk of dizziness for opioids versus nonopioids



Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced dizziness; N=overall sample; NR=not reported; NSAID=nonsteroidal inflammatory drugs; NTTL=nortryptiline; PGB=pregabalin.

Table 30. Pooled analyses of risk of discontinuation due to adverse events and somnolence for opioids versus nonopioids

Analysis	Discontinuation Due to Adverse Events (95% CI)	I^2	Number of Trials (N)	p*	Somnolence (95% CI)	I^2	Number of Trials (N)	p*
All trials	2.18 (1.48 to 3.08)	43%	12 (3637)	--	2.11 (1.39 to 3.47)	61%	12 (3377)	--
Nonopioid type: NSAID	2.51 (1.38 to 4.11)	52%	4 (2512)	0.39	2.55 (1.79 to 4.13)	0%	4 (2512)	0.01
• **Gabapentinoid**	1.15 (0.53 to 2.54)	0%	3 (348)	--	0.81 (0.53 to 1.46)	0%	3 (439)	--
• **Nortriptyline**	3.04 (1.38 to 6.21)	0%	3 (319)	--	2.78 (1.51 to 5.10)	0%	3 (310)	--
• **Other**	2.03 (0.46 to 12.52)	0%	3 (458)	--	4.48 (1.44 to 13.52)	0%	2 (116)	--
Opioid type: Opioid agonist	1.82 (1.11 to 3.25)	17%	8 (1125)	0.46	1.80 (1.03 to 3.53)	62%	8 (865)	0.30
• **Mixed**	2.51 (1.38 to 4.11)	52%	4 (2512)	--	2.55 (1.79 to 4.13)	0%	4 (2512)	--
Pain type: Musculoskeletal	2.60 (1.53 to 4.54)	45%	5 (2750)	0.28	2.55 (1.79 to 4.13)	0%	4 (2512)	0.30
• **Neuropathic**	1.71 (1.02 to 2.92)	16%	7 (887)	--	1.80 (1.03 to 3.53)	62%	8 (865)	--
Trial quality: Good	19.00 (1.12 to 322.78)	--	1 (238)	0.10	No studies	--	--	--
• **Fair**	2.52 (1.68 to 3.44)	23%	9 (3051)	--	2.68 (2.03 to 3.58)	0%	10 (3029)	<0.005
• **Poor**	1.15 (0.53 to 2.54)	0%	2 (348)	--	0.72 (0.44 to 1.17)	0%	2 (348)	--
Opioid dose (mg MED/day): <50	2.83 (1.92 to 4.00)	3.6%	6 (2842)	0.06	2.64 (1.87 to 4.45)	0%	5 (2499)	0.10
• **50-90**	1.27 (0.83 to 2.17)	0%	5 (643)	--	1.25 (0.69 to 2.88)	52%	5 (634)	--
• **>90**	3.33 (1.42 to 7.84)	--	1 (152)	--	3.04 (1.37 to 7.39)	0%	2 (244)	--
Crossover design	2.74 (1.45 to 4.94)	0%	4 (511)	0.54	2.68 (1.65 to 4.35)	0%	5 (493)	0.99
• **Parallel group**	2.01 (1.18 to 3.20)	60%	8 (3126)	--	1.95 (1.02 to 4.44)	77%	7 (2884)	--

Abbreviations: CI=confidence interval; MED=morphine equivalent dose; N= total sample size; NSAID=non-steroidal antiimflammatory drug.

*p for interaction

Table 31. Pooled analyses of risk of nausea, constipation, and dizziness for opioids versus nonopioids

Analysis	Nausea (95% CI)	I^2	Number of Trials (N)	p*	Constipation (95% CI)	I^2	Number of Trials (N)	p*	Dizziness (95% CI)	I^2	Number of Trials (N)	p*
All trials	2.77 (2.09 to 4.18)	13%	11 (3137)	--	2.92 (1.80 to 5.21)	70%	12 (3377)	--	1.33 (0.78 to 2.05)	65%	12 (3377)	--
Nonopioid type: NSAID	2.46 (1.66 to 3.30)	5.0%	4 (2512)	0.25	3.13 (1.58 to 6.42)	47%	4 (2512)	0.43	2.12 (1.45 to 3.00)	16%	4 (2512)	0.03
• **Gabapentinoid**	5.14 (1.36 to 19.72)	0%	2 (199)	--	1.10 (0.42 to 11.78)	0%	3 (439)	--	0.60 (0.15 to 1.09)	0%	3 (439)	--
• **Nortriptyline**	5.65 (1.79 to 14.93)	0%	3 (310)	--	3.23 (1.84 to 8.64)	0%	3 (310)	--	1.31 (0.64 to 4.27)	0%	3 (310)	--
• **Other**	4.42 (0.64 to 36.20)	0%	2 (116)	--	6.49 (1.16 to 30.33)	0%	2 (116)	--	0.63 (0.11 to 3.46)	0%	2 (116)	--
Opioid type: Opioid agonist	5.29 (2.89 to 9.50)	0%	7 (625)	0.05	2.94 (1.42 to 7.35)	75%	8 (865)	0.87	0.76 (0.49 to 1.24)	0%	8 (865)	0.005
• **Mixed**	2.46 (1.66 to 3.30)	5.0%	4 (2512)	--	3.13 (1.58 to 6.42)	47%	4 (2512)	--	2.12 (1.45 to 3.00)	16%	4 (2512)	--
Pain type: Musculoskeletal	2.46 (1.66 to 3.30)	5.0%	4 (2512)	0.05	3.13 (1.58 to 6.42)	47%	4 (2512)	0.87	2.12 (1.45 to 3.00)	16%	4 (2512)	0.005
• **Neuropathic**	5.29 (2.89 to 9.50)	0%	7 (625)	--	2.94 (1.42 to 7.35)	75%	8 (865)	--	0.76 (0.49 to 1.24)	0%	8 (865)	--
Trial quality: Fair	2.67 (1.97 to 3.94)	7.8%	10 (3029)	0.31	3.63 (2.47 to 6.15)	34%	10 (3029)	0.01	1.87 (1.22 to 2.51)	21%	10 (3029)	0.01
• **Poor**	5.12 (1.86 to 14.04)	--	1 (108)	--	0.97 (0.56 to 1.59)	0%	2 (348)	--	0.60 (0.13 to 1.27)	0%	2 (348)	--
Opioid dose (mg MED/day): <50	2.70 (2.06 to 3.60)	0%	5 (2499)	0.22	4.43 (2.83 to 8.09)	0%	5 (2499)	0.13	2.20 (1.39 to 3.08)	3.7%	5 (2499)	0.08
• **50-90**	2.47 (0.94 to 8.61)	32%	4 (394)	--	1.73 (0.81 to 4.48)	70%	5 (634)	--	0.90 (0.43 to 2.19)	24%	5 (634)	--
• **>90**	6.12 (1.88 to 21.80)	0%	2 (244)	--	3.50 (1.51 to 11.92)	0%	2 (244)	--	0.97 (0.35 to 2.53)	0%	2 (244)	--
Crossover design	5.74 (2.39 to 13.07)	0%	5 (493)	0.09	4.31 (2.43 to 11.96)	28%	5 (493)	0.11	1.18 (0.62 to 2.55)	0%	5 (493)	0.96
• **Parallel group**	2.57 (1.87 to 3.54)	2%	6 (2644)	--	2.11 (1.12 to 4.21)	70%	7 (2884)	--	1.30 (0.60 to 2.35)	81%	7 (2884)	--

Abbreviations: CI=confidence interval; MED=morphine equivalent dose; N=total sample size.

*p for interaction

Key Question 2d. In patients with chronic pain, what are the comparative risks of opioids plus nonopioid interventions (pharmacologic or nonpharmacologic, including cannabis) versus opioids or nonopioid interventions alone on: (1) opioid use disorder, abuse, or misuse; (2) overdose (intentional and unintentional); and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and mental health harms (e.g., depression)?

Opioids Plus Nonopioids Versus Nonopioids

Key Points

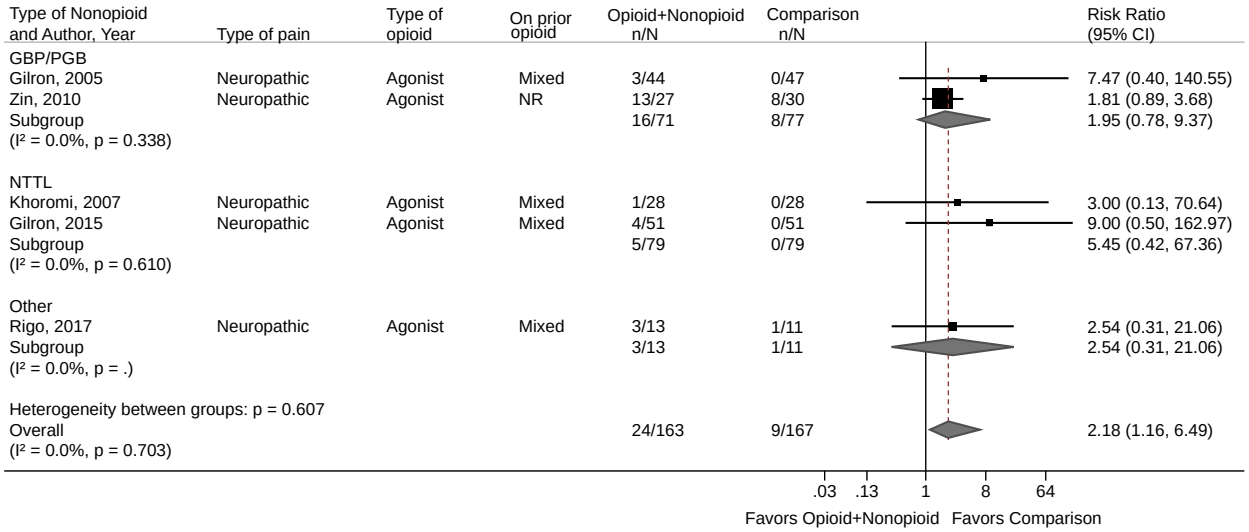
- An opioid plus nonopioid was associated with increased risk of nausea (5 trials, N=330, RR 2.18, 95% CI, 1.16 to 6.49, I^2=0%; ARD 7%, 95% CI, 2% to 12%), constipation (6 trials, N=633, RR 2.74, 95% CI, 1.28 to 7.44, I^2=70%; ARD 23%, 95% CI, 7% to 41%), and somnolence (5 trials [excluding a poor-quality trial], N=330, RR 2.44, 95% CI, 1.32 to 4.52, I^2=0%; ARD 11%, 95% CI, 4% to 17%) versus a nonopioid alone at short-term followup. Effects on risk of discontinuation due to adverse events were not statistically significant (6 trials, N=707, RR 1.99, 95% CI, 0.89 to 4.26, I^2=34%) (SOE: low for discontinuation due to adverse events, moderate for nausea, constipation, and somnolence).

Detailed Synthesis

An opioids plus nonopioid was associated with increased risk of nausea (5 trials, N=330, RR 2.18, 95% CI, 1.16 to 6.49, I^2=0%; ARD 7%, 95% CI, 2% to 12%; Figure 49),[67,82,141,146,151] and constipation (6 trials, N=633, RR 2.74, 95% CI, 1.28 to 7.44, I^2=70%; ARD 23%, 95% CI, 7% to 41%; Figure 50)[67,82,141,146,148,151] versus a nonopioid alone at short-term followup (Table 32). Combination therapy was associated with a non-statistically significant increased risk of discontinuation due to adverse events (6 trials, N=707, RR 1.99, 95% CI, 0.89 to 4.26, I^2=34%; Figure 51),[82,141,146,148,150,151] dizziness (6 trials, N=633, RR 1.30, 95% CI, 0.12 to 2.09, I^2=0%; Figure 52), [67,82,141,146,148,151] and somnolence (6 trials, N=663, RR 1.39, 95% CI, 0.41 to 5.25, I^2=72%; Figure 53),[67,82,141,146,148,151] with some imprecision in estimates. Estimates were based on few trials and imprecise for serious adverse events (1 trial, n=62, RR 0.38, 95% CI, 0.02 to 8.93),[151] headache (3 trials, N=137, RR 1.18, 95% CI, 0.42 to 3.00, I^2=0%),[82,146,151] vomiting (2 trials, N=81, RR 1.68, 95% CI, 0.43 to 6.56, I^2=0%),[146,151] or pruritus (2 trials, N=148, RR 3.49, 95% CI, 0.32 to 37.88, I^2=31%).[67,151] There was an interaction between trial quality and effects on somnolence (p for interaction=0.01) and constipation (p for interaction=0.04). Excluding a poor-quality trial[148] resulted in a statistically significant association between combination therapy and increased risk of somnolence, with no statistical heterogeneity (5 trials, N=330, RR 2.44, 95% CI 1.32 to 4.52, I^2=0%); the effects on constipation remained statistically significant (5 trials, N=330, RR 3.23, 95% CI 2.10 to 7.57, I^2=0%).[67,82,141,146,148,151] There were no interactions between nonopioid type, opioid dose, or use of crossover design and effects on these harms, but analyses were limited by the small number of trials (Tables 33 and 34). All trials evaluated an opioid agonist in patients with neuropathic pain.

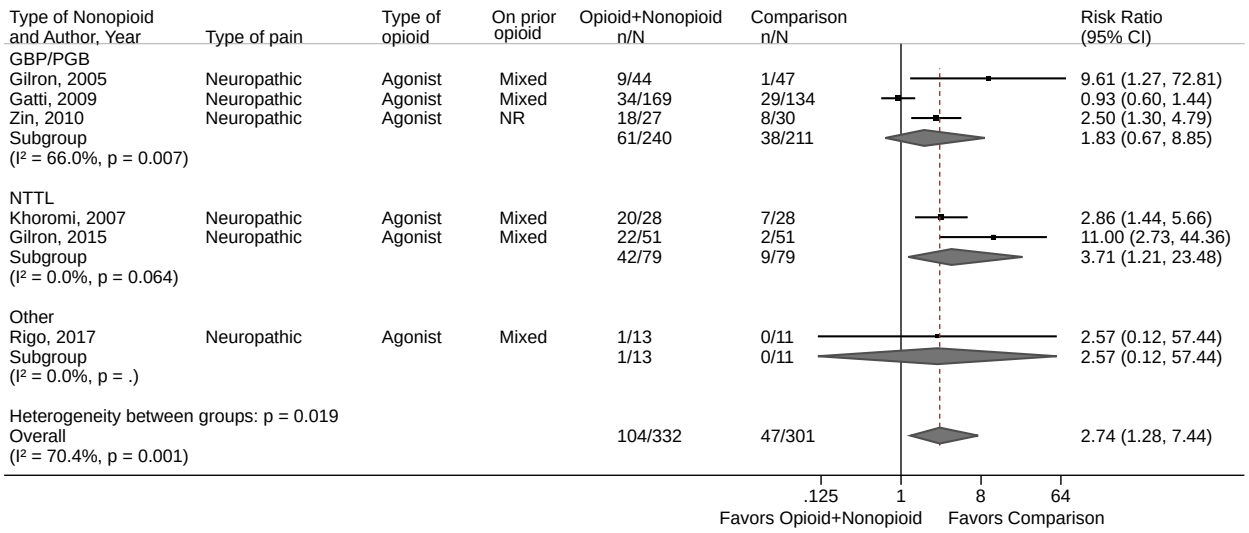
No study evaluated the association between an opioid plus nonopioid versus a nonopioid alone and risk of overdose or opioid use disorder and related outcomes.

Figure 49. Meta-analysis of risk of nausea for opioids plus nonopioids versus nonopioids



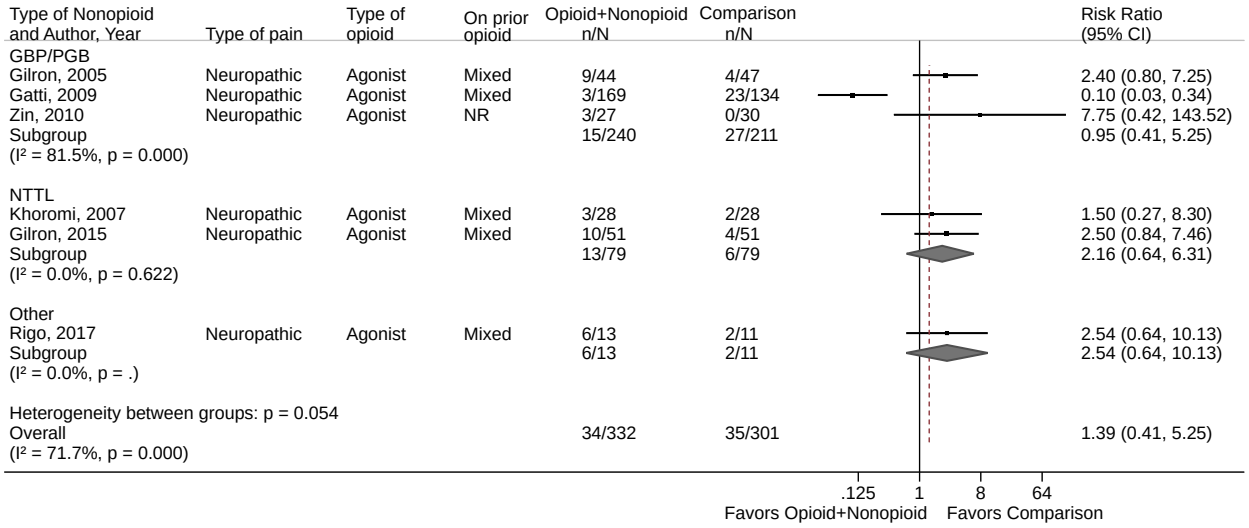
Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced nausea; N=overall sample; NR=not reported; NTTL=nortryptiline; PGB=pregabalin.

Figure 50. Meta-analysis of risk of constipation for opioids plus nonopioids versus nonopioids



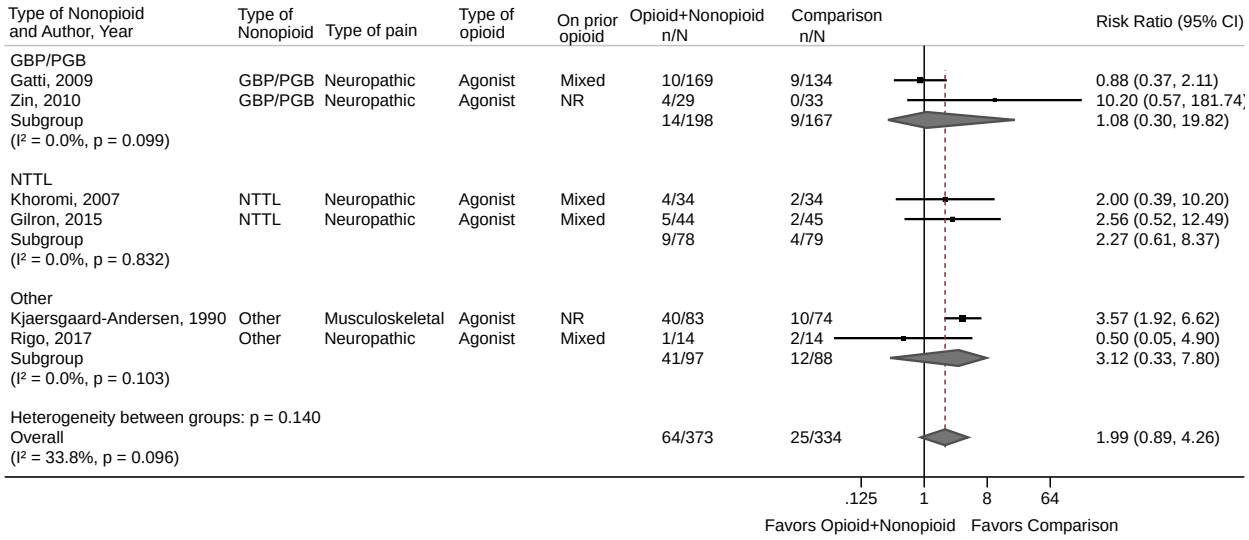
Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced constipation; N=overall sample; NTTL=nortryptiline; PGB=pregabalin.

Figure 51. Meta-analysis of risk of somnolence for opioids plus nonopioids versus nonopioids



Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced somnolence; N=overall sample; NTTL=nortryptiline; PGB=pregabalin.

Figure 52. Meta-analysis of risk of discontinuation due to adverse events for opioids plus nonopioids versus nonopioids



Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who discontinued due to adverse events; N=overall sample; NR=not reported; NTTL=nortryptiline; PGB=pregabalin.

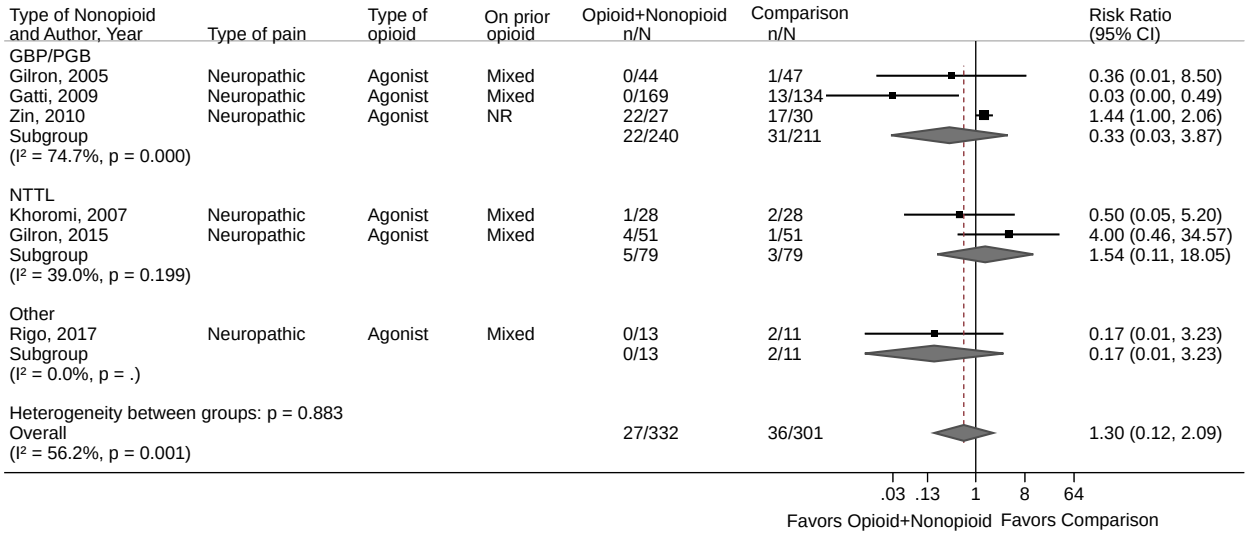
Table 32. Summary table of adverse events for opioids plus nonopioids versus nonopioids

Study, Year Country Quality	1: Duration of Followup 2: TotalPpatients Randomized 3: Pain Condition	1: Opioid + Nonopioid 2: Nonopioid	Discontinuation Due to Adverse Events	Serious Adverse eEents	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Gatti, 2009[148] Italy Poor	1: 13 weeks 2: 303 3: Mixed neuropathic pain	1: Oxycodone SR (mean 36 mg) + pregabalin (mean142 mg) 2: Pregabalin (mean 289 mg)	1: 5.9% (10/169) 2: 6.7% (9/134)	NR	NR	NR	1: 20.1% (34/169) 2: 21.6% (29/134)	1: 0% (0/169) 2: 9.7% (13/134)	NR	1: 1.8% (3/169) 2: 17.2% (23/134)	NR
Gilron, 2005[67] Canada Fair	1: 5 weeks 2: 57 3: Diabetic neuropathy and postherpetic neuralgia	1: Morphine up to 60 mg (mean 34 mg) + gabapentin 2400 mg (mean 1705 mg) 2: Gabapentin up to 3200 mg (mean 2207 mg)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gilron, 2015[141] Canada Fair	1: 6 weeks 2: 52 3: Peripheral neuropathic pain	1: Morphine SR up to 100 mg (mean 60 mg) + nortriptyline up to 100 mg (mean 60 mg) 2: Nortriptyline up to 100 mg (mean 65 mg)	1: 11.4% (5/44) 2: 4.4% (2/45)	NR	1: 7.8% (4/51) 2: 0% (0/51)	1: 0% (0/51) 2: 0% (0/51)	1: 43.1% (22/51) 2: 3.9% (2/51)	1: 7.8% (4/51) 2: 2.0% (1/51)	1: 0% (0/51) 2: 0% (0/51)	1: 19.6% (10/51) 2: 7.8% (4/51)	1: 0% (0/51) 2: 0% (0/51)
Khoromi, 2007[82] USA Fair	1: 7 weeks 2: 55 3: Low back pain with radiculopathy	1: Morphine SR up to 90 mg (mean 49 mg) + nortriptyline up to 100 mg (mean 55 mg) 2: Nortriptyline up to 100 mg (mean 84 mg)	1: 11.8% (4/34) 2: 5.9% (2/34)	NR	1: 3.6% (1/28) 2: 0% (0/28)	NR	1: 71.4% (20/28) 2: 25.0% (1/28)	1: 3.6% (1/28) 2: 7.1% (2/28)	1: 14.3% (4/28) 2: 7.1% (2/28)	1: 10.7% (3/28) 2: 7.1% (2/28)	NR
Kjaersgaard-Andersen, 1990[150] Denmark Poor	1: 4 weeks 2: 158 3: Osteoarthritis	1: Codeine 180 mg + acetaminophen 3000 mg (mean NR) 2: Acetaminophen 3000 mg (mean NR)	1: 48.2% (40/83) 2: 13.5% (10/74)	NR	NR	NR	NR	NR	NR	NR	NR

Study, Year Country Quality	1: Duration of Followup 2: TotalPpatients Randomized 3: Pain Condition	1: Opioid + Nonopioid 2: Nonopioid	Discontinuation Due to Adverse Events	Serious Adverse eEents	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Rigo, 2017 [146] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic pain	1: Methadone 9 mg + ketamine 90 mg (mean NR) 2: Ketamine 90 mg(mean NR)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Zin, 2010[151] Australia Fair	1: 5 weeks 2: 62 3: Diabetic neuropathy and postherpetic neuralgia	1: Oxycodone 10 mg + pregabalin 75 to 600 mg (mean 231 mg); 2: Pregabalin 75-600 mg (mean 228 mg)	1: 13.8% (4/29) 2: 0% (0/33)	1: 0% (0/29) 2: 3.0% (1/33)	1: 48.1% (13/27) 2: 26.7% (8/30)	1: 11.1% (3/27) 2: 6.7% (2/30)	1: 66.7% (18/27) 2: 26.7% (8/30)	1: 81.5% (22/27) 2: 56.7% (17/30)	1: 22.2% (6/27) 2: 20.0% (6/30)	1: 11.1% (3/27) 2: 0% (0/30)	1: 18% (5/27) 2: 0% (0/30)

Abbreviations: NR=not reported; SR=sustained release.

Figure 53. Meta-analysis of risk of dizziness for opioids plus nonopioids versus nonopioids



Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced dizziness; N=overall sample; NR=not reported; NTTL=nortryptiline; PGB=pregabalin.

Table 33. Pooled analyses of risk of discontinuation due to adverse events and somnolence for opioids plus nonopioids versus nonopioids

Analysis	Discontinuation Due to Adverse Events (95% CI)	I^2	Number of Trials (N)	P*	Somnolence (95% CI)	I^2	Number of Trials (N)	P*
All trials	1.99 (0.89 to 4.26)	34%	6 (707)	--	1.39 (0.41 to 5.25)	72%	6 (663)	--
Nonopioid type: Gabapentinoid	1.08 (0.30 to 19.82)	0%	2 (365)	0.93	0.95 (0.06 to 21.37)	82%	3 (451)	0.85
• **Nortriptyline**	2.27 (0.61 to 8.37)	0%	2 (157)	--	2.16 (0.64 to 6.31)	0%	2 (158)	--
• **Other**	3.12 (0.33 to 7.80)	0%	2 (185)	--	2.54 (0.64 to 10.13)	--	1 (24)	--
Opioid type: Opioid agonist	1.99 (0.89 to 4.26)	34%	6 (707)	--	1.38 (0.41 to 5.25)	72%	6 (663)	--
Pain type: Musculoskeletal	3.57 (1.92 to 6.62)	--	1 (157)	0.14	No trials	--	--	--
• **Neuropathic**	1.29 (0.67 to 3.45)	0%	5 (550)	--	1.38 (0.41 to 5.25)	72%	6 (663)	--
Trial quality: Fair	2.05 (0.72 to 5.95)	0%	4 (247)	0.91	2.44 (1.32 to 4.52)	0%	5 (330)	0.01
• **Poor**	1.90 (0.33 to 9.63)	--	2 (460)	--	0.10 (0.03 to 0.34)	--	1 (303)	--
Opioid dose (mg MED/day): <50	3.10 (1.12 to 5.68)	0%	4 (315)	0.18	2.41 (1.13 to 5.24)	0%	4 (228)	0.24
• **50-90**	1.13 (0.42 to 4.72)	0%	2 (392)	--	0.52 (0.01 to 23.76)	--	2 (517)	--
Crossover design	2.27 (0.61 to 8.37)	0%	2 (157)	0.83	2.25 (1.05 to 4.64)	0%	3 (249)	0.51
• **Parallel group**	1.86 (0.54 to 6.25)	50%	4 (550)	--	0.95 (0.06 to 22.76)	79%	2 (384)	--

Abbreviations: CI=confidence interval; MED=morphine equivalent dose; N= total sample size.

*p for interaction

Table 34. Pooled analyses of risk of nausea, constipation, and dizziness for opioids plus nonopioids versus nonopioids

Analysis	Nausea (95% CI)	I^2	Number of Trials (N)	P*	Constipation (95% CI)	I^2	Number of Trials (N)	P*	Dizziness (95% CI)	I^2	Number of Trials (N)	P*
All trials	2.18 (1.16 to 6.49)	0%	5 (330)	--	2.74 (1.28 to 7.44)	70%	6 (633)	--	1.30 (0.12 to 2.09)	0%	6 (633)	--
Nonopioid type: Gabapentinoid	1.95 (0.78 to 9.37)	0%	2 (148)	0.71	1.83 (0.67 to 8.85)	66%	3 (451)	0.68	1.33 (0.04 to 4.50)	0%	3 (451)	0.66
• **Nortriptyline**	5.45 (0.42 to 67.36)	0%	2 (158)	--	3.71 (1.21 to 23.48)	0%	2 (158)	--	1.54 (0.11 to 18.05)	0%	2 (158)	--
• **Ketamine**	2.54 (0.31 to 21.06)	--	1 (24)	--	2.57 (0.12 to 57.44)	--	1 (24)	--	0.17 (0.01 to 3.23)	--	1 (24)	--
Opioid type: Opioid agonist	2.18 (1.16 to 6.49)	0%	5 (330)	--	2.74 (1.28 to 7.44)	70%	6 (663)	--	1.30 (0.12 to 2.09)	0%	6 (663)	--
Pain type: Neuropathic	2.18 (1.16 to 6.49)	0%	5 (330)	--	2.74 (1.28 to 7.44)	70%	6 (663)	--	1.30 (0.12 to 2.09)	0%	6 (663)	--
Trial quality: Fair	2.18 (1.16 to 6.49)	0%	5 (330)	--	3.23 (2.10 to 7.57)	0%	5 (330)	0.04	1.38 (0.56 to 2.11)	0%	5 (330)	0.06
• **Poor**	No trials	--	--	--	0.93 (0.60 to 1.44)	--	1(303)	--	0.03 (0.00 to 0.49)	--	1 (303)	--
Opioid dose (mg MED/day): <50	2.04 (1.03 to 5.56)	0%	4 (228)	0.40	2.84 (1.78 to 5.09)	0%	4 (228)	0.76	1.34 (0.30 to 1.99)	0%	4 (228)	0.89
• **50-90**	9.00 (0.50 to 162.97)	--	1 (102)	--	2.65 (0.16 to 60.10)	81%	2 (405)	--	0.41 (0.001 to 130.71)	--	2 (405)	--
Crossover design	6.07 (1.01 to 35.62)	0%	3 (249)	0.30	4.52 (1.89 to 19.36)	18%	3 (249)	0.14	1.15 (0.15 to 6.38)	0%	3 (249)	0.49
• **Parallel group**	1.87 (0.77 to 5.19)	0%	2 (81)	--	1.47 (0.59 to 4.47)	50%	3 (384)	--	1.31 (0.04 to 6.97)	0%	3 (384)	--

Abbreviations: CI=confidence interval; MED=morphine equivalent dose; N= total sample size

*p for interaction

Opioids Plus Nonopioids Versus Opioids

Key Points

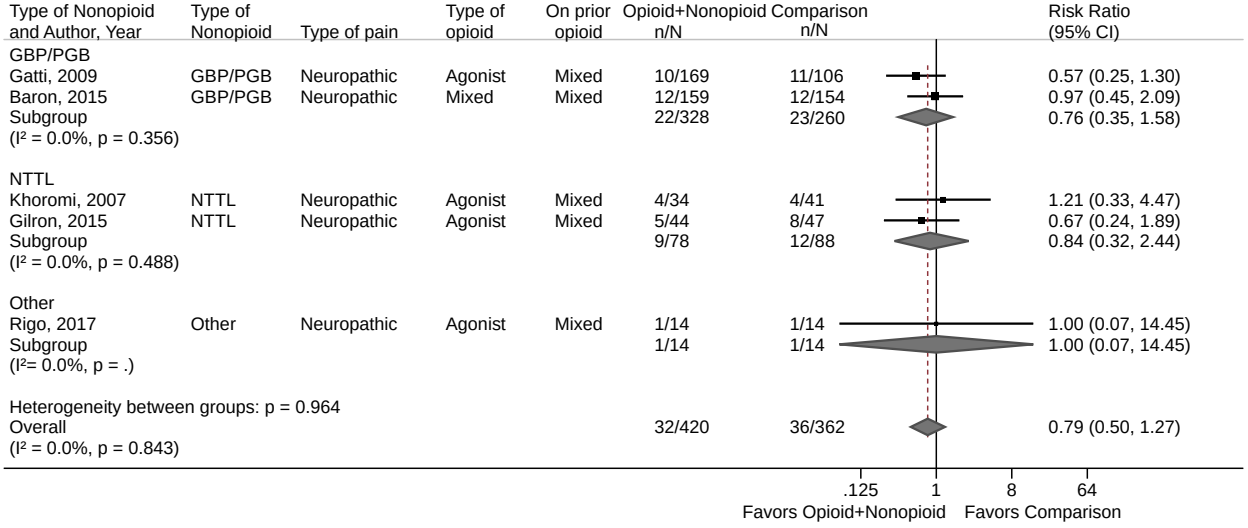
- There were no differences between an opioid plus nonopioid versus an opioid alone in risk of discontinuation due to adverse events (5 trials, N=782, RR 0.79, 95% CI, 0.50 to 1.27, I^2=0%), nausea (5 trials, N=585, RR 0.98, 95% CI, 0.57 to 1.84, I^2=0%), constipation (6 trials, N=860, RR 0.91, 95% CI, 0.67 to 1.13, I^2=0%), or somnolence (6 trials, N=860, RR 0.72, 95% CI, 0.35 to 1.33, I^2=58%) versus an opioid alone at short-term followup.

Detailed Synthesis

There were no differences between an opioid plus nonopioid versus an opioid alone in risk of discontinuation due to adverse events (5 trials, N=782, RR 0.79, 95% CI, 0.50 to 1.27, I^2=0%; Figure 54),[82,141,146,148,152] nausea (5 trials, N=585, RR 0.98, 95% CI, 0.57 to 1.84, I^2=0%; Figure 55),[67,82,141,146,152] constipation (6 trials, N=860, RR 0.91, 95% CI, 0.67 to 1.13, I^2=0%; Figure 56),[67,82,141,146,148,152] or somnolence (6 trials, N=860, RR 0.72, 95% CI, 0.35 to 1.33, I^2=58%; Figure 57),[67,82,141,146,148,152] versus an opioid alone at short-term followup (Table 35). Some estimates favored the opioid plus nonopioid combination, possibly due to lower average opioid doses used (see Key Question 1d). Estimates for serious adverse events (1 trial, n=313, RR 0.58, 95% CI, 0.14 to 2.39),[152] dizziness (5 trials, N=772, RR 1.22, 95% CI, 0.23 to 1.99, I^2=0%; Figure 58),[82,141,146,148,152] headache (3 trials, N=457, RR 1.12, 95% CI, 0.46 to 2.25, I^2=0%; Figure 59),[67,82,152] vomiting (2 trials, N=339, RR 1.68, 95% CI, 0.34 to 8.19, I^2=0%; Figure 60),[146,152] and pruritus (2 trials, N=190, RR 0.25, 95% CI, 0.03 to 1.91, I^2=0%; Figure 61)[67,141] were less precise. There were no interactions between nonopioid type, opioid type, opioid dose, trial quality, or use of crossover design and effects on these harms, but analyses were limited by the small number of trials (Table 36 and 37).

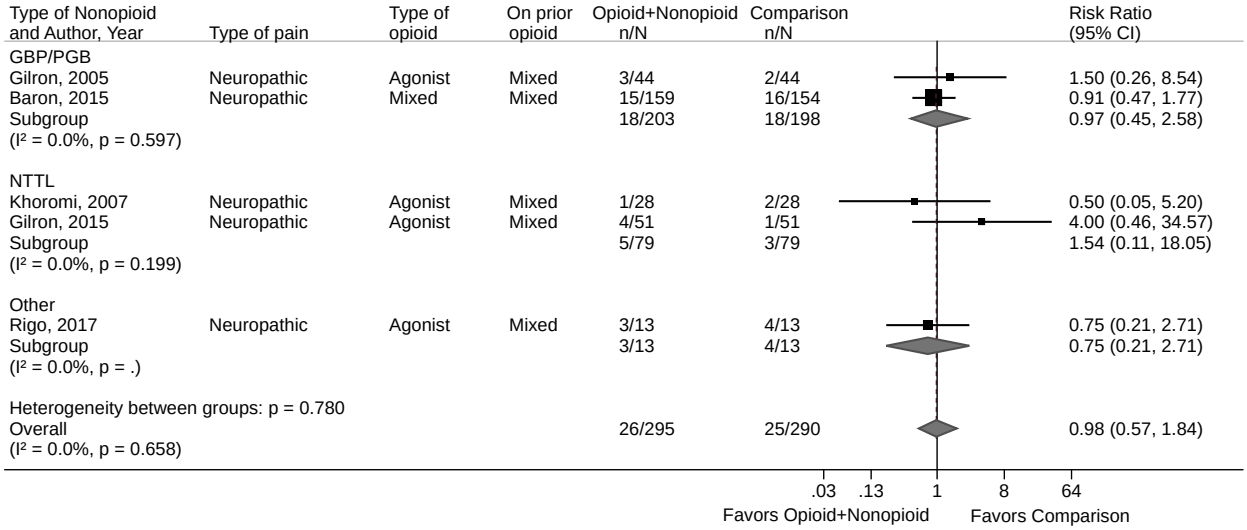
No study evaluated the association between an opioid plus nonopioid versus a nonopioid alone and risk of overdose or opioid use disorder and related outcomes.

Figure 54. Meta-analysis of risk of discontinuation due to adverse events for opioids plus nonopioids versus opioids



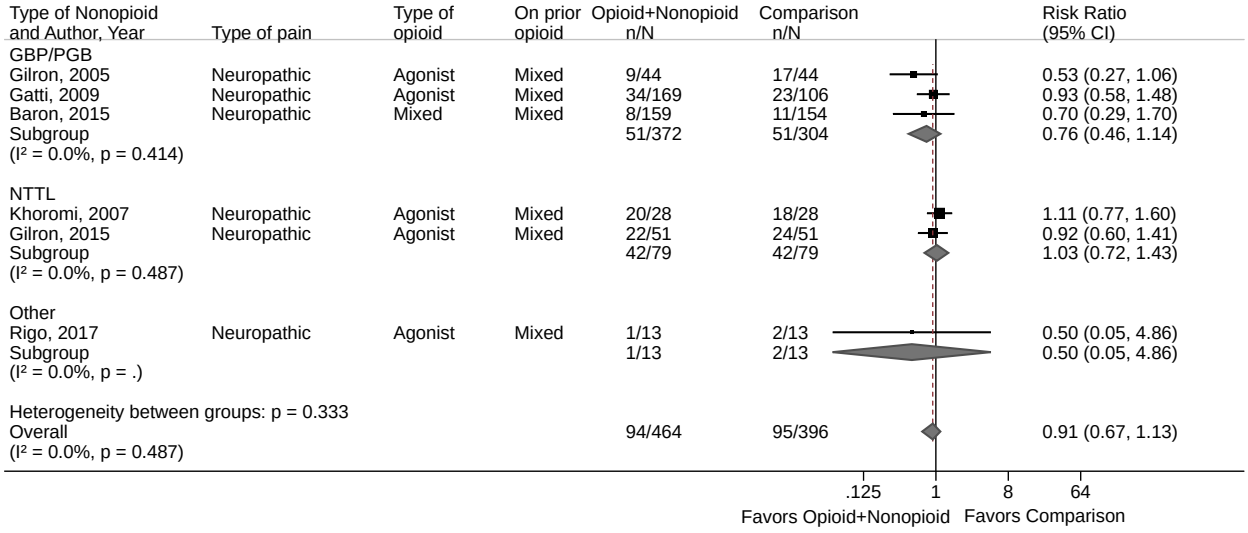
Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who discontinued due to adverse events; N=overall sample; NTTL=nortryptiline; PGB=pregabalin.

Figure 55. Meta-analysis of risk of nausea for opioids plus nonopioids versus opioids



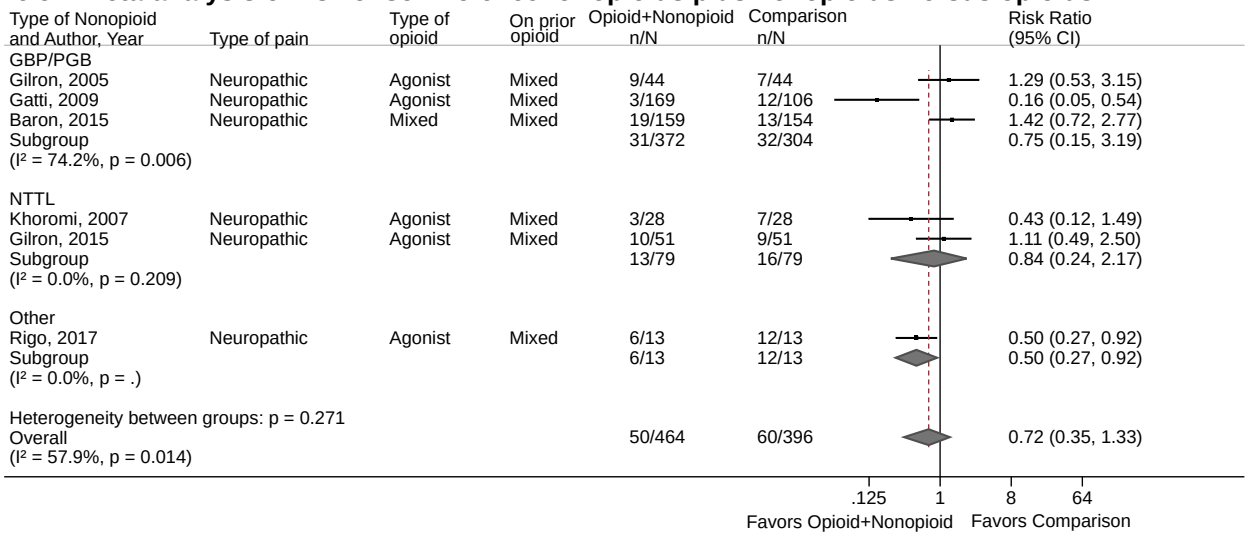
Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced nausea; N=overall sample; NTTL=nortryptiline; PGB=pregabalin.

Figure 56. Meta-analysis of risk of constipation for opioids plus nonopioids versus opioids



Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced constipation; N=overall sample; NTTL=nortryptiline; PGB=pregabalin.

Figure 57. Meta-analysis of risk of somnolence for opioids plus nonopioids versus opioids



Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced somnolence; N=overall sample; NTTL=nortryptiline; PGB=pregabalin.

Table 35. Summary table of adverse events for opioids plus nonopioids versus opioids

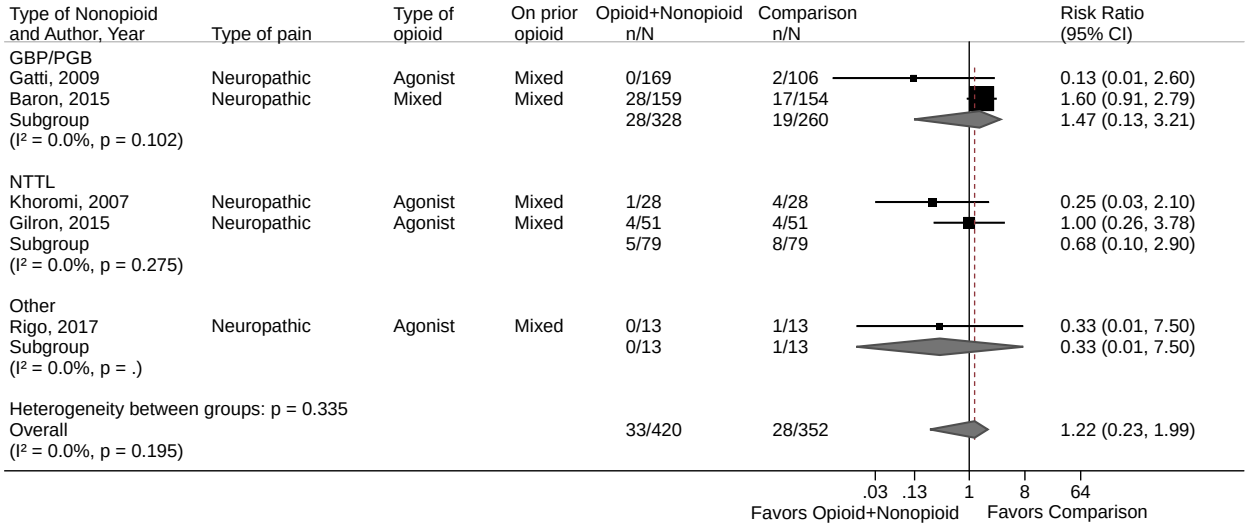
Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid + Nonopioid 2: Opioid	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Baron, 2015[152] Germany, Poland, Spain, Belgium, Austria, Denmark, the Netherland Fair	1: 8 weeks 2: 313 3: Low back pain with neuropathic component	1: Tapentadol SR 300 mg + pregabalin 150 to 300 mg 2: Tapentadol SR 300 to 500 mg (mean NR)	1: 7.5% (12/159) 2: 7.8% (12/154)	1: 1.9% (3/159) 2: 3.2% (5/154)	1: 9.4% (15/159) 2: 10.4% (16/154)	1: 3.1% (5/159) 2: 5.8% (9.154)	1: 5.0% (8/159) 2: 7.1% (11/154)	1: 17.6% (28/159) 2: 8.2% (13/154)	1: 8.2% (13/159) 2: 6.5% (10/154)	1: 11.9% (19/159) 2: 8.4% (13/154)	NR
Gatti, 2009[148] Italy Poor	1: 13 weeks 2: 275 3: Mixed neuropathic pain	1: Oxycodone SR (mean 36 mg) + pregabalin (mean142 mg) 2: Oxycodone SR (mean 46 mg)	1: 5.9% (10/169) 2: 10.4% (11/106)	NR	NR	NR	1: 20.1% (34/169) 2: 21.7% (23/106)	1: 0% (0/169) 2: 1.9% (2/106)	NR	1: 1.8% (3/169) 2: 11.3% (12/106)	NR
Gilron, 2005[67] Canada Fair	1: 5 weeks 2: 57 3: Diabetic neuropathic postherpetic neuralgia	1: Morphine up to 60 mg (mean 34 mg) + gabapentin 2400 mg (mean 1705 mg) 2: Morphine up to 120 mg (mean 45 mg)	NR	NR	NR	NR	NR	NR	NR	NR	NR
Gilron, 2015[141] Canada Fair	1: 6 weeks 2: 52 3: Peripheral neuropathic pain	1: Morphine SR up to 100 mg (mean 49 mg) + nortriptyline up to 100 mg (mean 55 mg) 2: Morphine SR up to 100 mg (mean 84 mg)	1: 11.4% (5/44) 2: 17.0% (8/47)		1: 7.8% (4/51) 2: 2.0% (1/51)	1: 0% (0/51) 2: 0% (0/51)	1: 43.1% (22/51) 2: 47.0% (24/51)	1: 7.8% (4/51) 2: 7.8% (4/51)	1: 0% (0/51) 2: 0% (0/51)	1: 19.6% (10/51) 2: 17.6% (9/51)	1: 0% (0/51) 2: 5.9% (3/51)

Study, Year Country Quality	1: Duration of Followup 2: Total Patients Randomized 3: Pain Condition	1: Opioid + Nonopioid 2: Opioid	Discontinuation Due to Adverse Events	Serious Adverse Events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Khoromi, 2007[82] USA Fair	1: 7 weeks 2: 55 3: Low back pain with radiculopathy	1: Morphine up to 90 mg (mean 49 mg) + nortriptyline up to 100 mg (mean 55 mg) 2: Morphine SR up to 90 mg (mean 62 mg)	1: 11.8% (4/34) 2: 9.7% (4/41)		1: 3.6% (1/28) 2: 7.1% (2/28)	NR	1: 71.4% (20/28) 2: 64.3% (18/28)	1: 3.6% (1/28) 2: 14.3% (4/28)	1: 14.3% (4/28) 2: 14.3% (4/28)	1: 10.7% (3/28) 2: 25.0% (7/28)	NR
Rigo, 2017[146] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic	1: Methadone 9 mg + ketamine 90 mg (mean NR) 2: Methadone 9 mg (mean NR)	1: 7.1% (1/14) 2: 7.1% (1/14)	NR	1: 23.1% (3/13) 2: 30.8% (4/13)	1: 15.4% (2/13) 2: 15.4% (2/13)	1: 7.7% (1/13) 2: 15.4% (2/13)	1: 0% (0/13) 2: 0% (0/13)	1: 0% (0/13) 2: 0% (0/13)	1: 46.1% (6/13) 2: 92.3% (12/13)	NR

Abbreviations: NR=not reported; SR=sustained release.

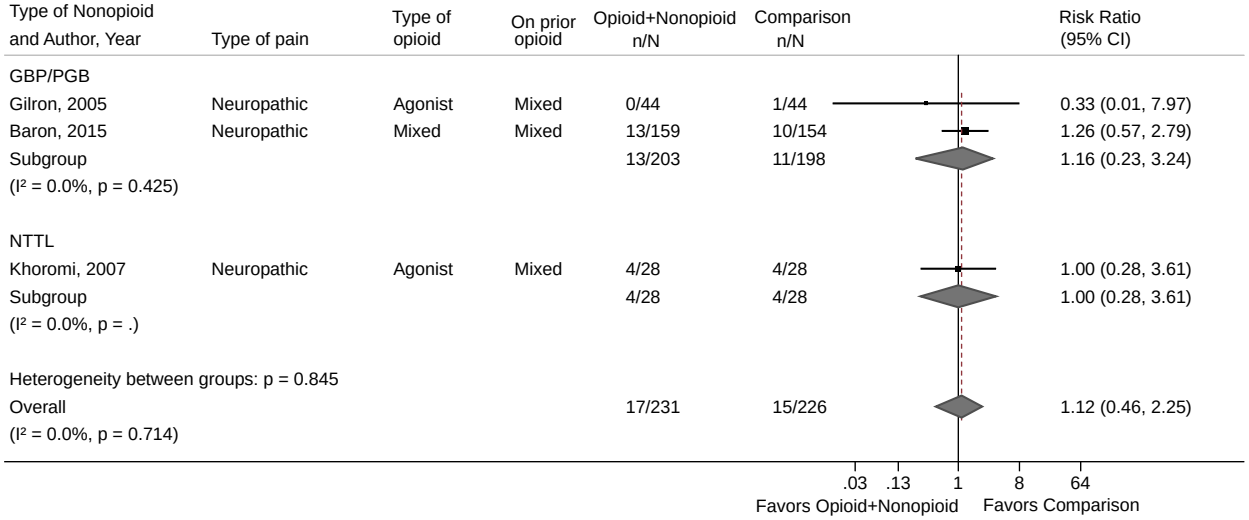
*Means (standard deviation), unless otherwise reported

Figure 58. Meta-analysis of risk of dizziness for opioids plus nonopioids versus opioids



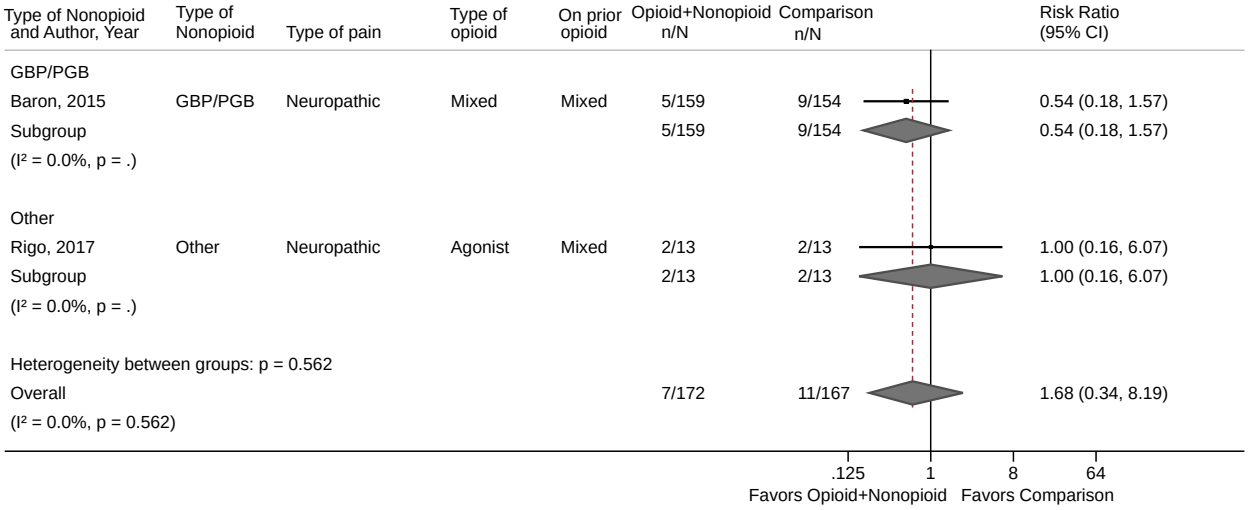
Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced dizziness; N=overall sample; NTTL=nortryptiline; PGB=pregabalin.

Figure 59. Meta-analysis of risk of headache for opioids plus nonopioids versus opioids



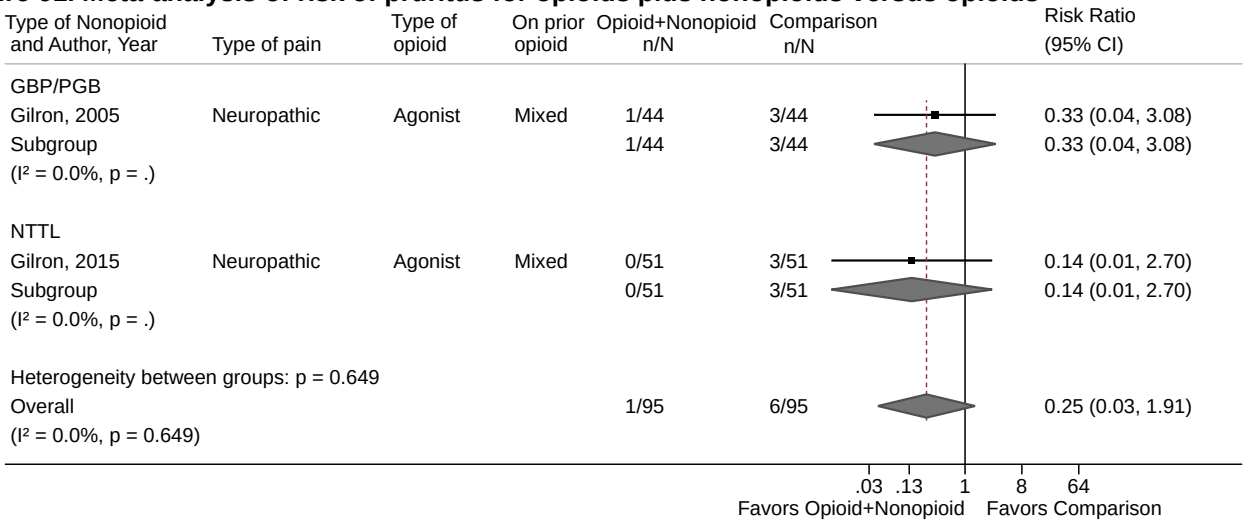
Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced a headache; N=overall sample; NTTL=nortryptiline; PGB=pregabalin.

Figure 60. Meta-analysis of risk of vomiting for opioids plus nonopioids versus opioids



Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced vomiting; N=overall sample; PGB=pregabalin.

Figure 61. Meta-analysis of risk of pruritus for opioids plus nonopioids versus opioids



Abbreviations: CI=confidence interval; GBP=gabapentin; n=number who experienced pruritus; N=overall sample; NTTL=nortryptiline; PGB=pregabalin.

Table 36. Pooled analyses of risk of discontinuation due to adverse events and somnolence for opioids plus nonopioids versus opioids

Analysis	Discontinuation Due to Adverse Events (95% CI)	I^2	Number of Trials (N)	p*	Somnolence (95% CI)	I^2	Number of Trials (N)	p*
All trials	0.79 (0.50 to 1.27)	0%	5 (782)	--	0.72 (0.35 to 1.33)	58%	6 (860)	--
Nonopioid type: Gabapentinoid	0.76 (0.35 to 1.58)	0%	2 (588)	0.96	0.75 (0.14 to 3.19)	74%	3 (676)	0.94
• **Nortriptyline**	0.84 (0.32 to 2.44)	0%	2 (166)	--	0.84 (0.24 to 2.17)	0%	2 (158)	--
• **Ketamine**	1.00 (0.07 to 14.45)	--	1 (28)	--	0.50 (0.27 to 0.92)	--	1 (26)	--
Opioid type: Opioid agonist	0.70 (0.40 to 1.35)	0%	4 (469)	0.56	0.61 (0.27 to 1.21)	49%	5 (547)	0.34
• **Mixed**	0.97 (0.45 to 2.09)	--	1 (313)	--	1.42 (0.72 to 2.77)	--	1 (313)	--
Pain type: Neuropathic	0.79 (0.50 to 1.27)	0%	5 (782)	--	0.75 (0.14 to 3.19)	58%	6 (860)	--
Trial quality: Fair	0.91 (0.51 to 1.61)	0%	4 (507)	0.42	0.88 (0.51 to 1.49)	34%	5 (585)	0.09
• **Poor**	0.57 (0.25 to 1.30)	--	1 (275)	--	0.16 (0.05 to 0.54)	--	1 (275)	--
Opioid dose (mg MED/day): <50	1.16 (0.26 to 4.97)	0%	2 (103)	0.60	0.64 (0.31 to 1.41)	5%	3 (170)	0.64
• **50-90**	0.61 (0.29 to 1.30)	0%	2 (366)	--	0.47 (0.04 to 4.46)	70%	2 (377)	--
• **>90**	0.97 (0.45 to 2.09)	--	1 (313)	--	1.42 (0.72 to 2.77)	--	1 (313)	--
Crossover design	0.84 (0.32 to 2.44)	0%	2 (166)	0.87	0.98 (0.47 to 1.77)	0%	3 (246)	0.52
• **Parallel group**	0.77 (0.39 to 1.51)	0%	3 (616)	--	0.55 (0.13 to 1.97)	75%	3 (614)	--

Abbreviations: CI=confidence interval; MED=morphine equivalent dose; N= total sample size

*p for interaction

Table 37. Pooled analyses of risk of nausea, constipation, and dizziness for opioids plus nonopioids versus opioids

Analysis	Nausea (95% CI)	I^2	Number of Trials (N)	p*	Constipation (95% CI)	I^2	Number of Trials (N)	p*	Dizziness (95% CI)	I^2	Number of Trials (N)	p*
All trials	0.98 (0.57 to 1.84)	0%	5 (585)	--	0.91 (0.67 to 1.13)	0%	6 (860)	--	1.22 (0.23 to 1.99)	0%	5 (772)	--
Nonopioid type: Gabapentinoid	0.97 (0.45 to 2.58)	0%	2 (401)	0.81	0.76 (0.46 to 1.14)	0%	3 (676)	0.48	1.47 (0.13 to 3.212)	0%	2 (588)	0.88
• **Nortriptyline**	1.54 (0.11 to 18.05)	0%	2 (158)	--	1.03 (0.72 to 1.43)	0%	2 (158)	--	0.68 (0.10 to 2.90)	0%	2 (158)	--
• **Ketamine**	0.75 (0.21 to 2.71)	--	1 (26)	--	0.50 (0.05 to 4.86)	--	1 (26)	--	0.33 (0.01 to 7.50)	--	1 (26)	--
Opioid type: Opioid agonist	1.10 (0.45 to 3.05)	0%	4 (272)	0.75	0.93 (0.67 to 1.16)	0%	5 (547)	0.58	0.52 (0.11 to 1.43)	0%	4 (459)	0.20
• **Mixed**	0.91 (0.47 to 1.77)	--	1 (313)	--	0.70 (0.29 to 1.70)	--	1 (313)	--	1.60 (0.91 to 2.79)	--	1 (313)	--
Pain type: Neuropathic	0.98 (0.57 to 1.84)	0%	5 (585)	--	0.91 (0.67 to 1.13)	0%	6 (860)	--	1.22 (0.23 to 1.99)	0%	5 (772)	--
Trial quality: Fair	0.98 (0.57 to 1.84)	0%	5 (585)	--	0.91 (0.59 to 1.17)	0%	5 (585)	0.87	1.30 (0.36 to 2.14)	0%	4 (497)	0.29
• **Poor**					0.93 (0.58 to 1.48)	--	1 (275)	--	0.13 (0.01 to 2.60)	--	1 (275)	--
Opioid dose (mg MED/day): <50	0.86 (0.31 to 2.41)	0%	3 (170)	0.53	0.86 (0.35 to 1.56)	22%	3 (170)	0.89	0.27 (0.04 to 2.25)	0%	2 (82)	0.47
• **50-90**	4.00 (0.46 to 34.57)	--	1 (102)	--	0.92 (0.64 to 1.33)	0%	2 (377)	--	0.72 (0.05 to 3.54)	--	2 (377)	--
• **>90**	0.91 (0.47 to 1.77)	--	1 (313)	--	0.70 (0.29 to 1.70)	--	1 (313)	--	1.60 (0.91 to 2.79)	--	1 (313)	--
Crossover design	1.52 (0.38 to 5.79)	0%	3 (246)	0.47	0.94 (0.57 to 1.27)	0%	3 (246)	0.78	0.68 (0.10 to 2.90)	0%	2 (158)	0.76
• **Parallel group**	0.87 (0.40 to 1.78)	0%	2 (339)	--	0.86 (0.48 to 1.34)	0%	3 (614)	--	1.40 (0.14 to 2.60)	0%	3 (614)	--

Abbreviations: CI=confidence interval; MED=morphine equivalent dose; N= total sample size

*p for interaction

Key Question 3a. In patients with chronic pain, what is the comparative effectiveness of different methods for initiating and titrating opioids for outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?

Key Points

- Two trials included in the 2014 AHRQ report on effects of titration with immediate-release versus sustained-release opioids reported inconsistent results on outcomes related to pain and had methodological limitations (SOE: insufficient).
- No trial was designed to assess risk of opioid use disorder or related outcomes (SOE: insufficient).

Detailed Synthesis

No new studies on the comparative effectiveness of different methods for initiating and titrating opioids were identified. The 2014 AHRQ report included one fair-quality and one poor-quality,[142] open-label trials of sustained-release versus immediate release opioids for titrating patients with chronic noncancer pain to "stable pain control" (Appendix Table G-1 and H-22).[142,182] One trial (n=57) found no difference between long-acting versus short-acting oxycodone and likelihood of achieving stable pain control, the time to achieve stable pain control, and the degree of pain control achieved after up to 10 days.[182] The other trial (n=24) found titrated doses of sustained-release morphine plus immediate-release oxycodone slightly superior to fixed-dose, immediate-release oxycodone for pain intensity, but no differences on measures of function, sleep, and psychological distress.[142] Results of this trial are difficult to interpret because of differences between study arms other than use of sustained-release versus immediate-release opioids, including use of different dosing protocols (titrated versus fixed differences) and because the maximum dose of opioids varied (up to 200 mg MED/day in the titrated dose arm versus up to 20 mg/day in the fixed-dose oxycodone arm); the average dose of opioids was not reported. Neither trial was designed to assess outcomes related to risk of opioid use disorder or related outcomes.

Key Question 3b. In patients with chronic pain, what is the comparative effectiveness of short-acting versus long-acting opioids on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?

Key Points

- Two trials found no differences in effectiveness or harms between long- versus short-acting formulations of the same opioid administered at similar doses (SOE: low).
- A cohort study found long-acting opioids associated with increased risk of overdose versus short-acting opioids (adjusted HR 2.33, 95% CI, 1.26 to 4.32); risk decreased with longer duration of exposure (SOE: low).

Description of Included Studies

The 2014 AHRQ report did not include any trials of short-acting versus long-acting opioids, but was restricted to trials with at least 1 year followup. For this update, we identified four trials that compared a sustained-release or long-acting opioid versus an immediate-release or short-acting opioid for chronic pain at short-term (1 to <6 month) followup[108,142,183-185] (Table 38; Appendix Tables H-23 and H-24). Sample sizes ranged from 36 to 662 (total N=946). One trial compared sustained-release versus immediate-release tramadol (dose 150 to 400 mg taken once daily),[183] one trial compared sustained-release versus immediate-release dihydrocodeine (doses 120 to 240 mg/day),[184] one trial compared transdermal buprenorphine (7-day patch at 5 or 20 mcg/hour) versus oral immediate-release oxycodone (40 mg/day),[108,185] and the final trial compared fixed-dose long-acting morphine plus titrated short-acting oxycodone (mean 41 mg MED/day) versus fixed-dose short-acting oxycodone (maximum 30 mg MED/day, mean not reported).[142] The pain type was mixed in all trials. The duration of pain ranged from 6.6 to 20.0 years in two trials that reported this information. All of the trials were conducted in the United States or Europe.

Three of the trials were rated fair-quality and one was rated poor-quality[142] (Appendix Table G-1). Methodological shortcomings included unclear randomization methods, unclear or no blinding of outcome assessor, high attrition, and selective reporting of outcomes. One trial used an EERW design;[108,185] the remainder were parallel group randomized trials without enriched enrollment. All trials except one[184] reported industry funding.

One new fair-quality cohort study (n=840,606) also evaluated the association between long- versus short-acting opioids and risk of unintentional overdose[186] (Appendix Table G-2, H-25, and H-26).

Table 38. Head-to-head trials of short-acting versus long-acting opioids

Author Year Study Design Duration	Setting/ Data Source Country	Interventions, N	Results	Quality
Adler, 2002[183] RCT 4 weeks	Unclear setting U.K.	A. Tramadol 150 to 400 mg taken once daily (n=137) B. Tramadol 50 to 100 mg taken TID or QID (n=65)	A vs. B Pain (0 to 100), mean: 21 vs. 22 Use of escape medication 2 hours after taking study drug: 8% vs. 15%, estimated from graph Use of escape medication 3 hours after taking study drug: 16% vs. 4%, estimated from graph	Fair

Author Year Study Design Duration	Setting/ Data Source Country	Interventions, N	Results	Quality
Jamison, 1998[142] RCT 16 weeks	Single center pain clinic USA	A. Long acting morphine + short-acting oxycodone (titrated doses) + Naproxen B. Short-acting oxycodone (set dose) + Naproxen C. Naproxen A vs. B vs. C Mean dose 41.1 mg vs. NR (max 20 mg oxycodone/day) vs. NR In all groups, max 1000 mg/day of naproxen 16 weeks (n=36)	A vs. B vs. C Average pain (0 to 100), mean (SD): 54.9 (15.87) vs. 59.8 (16.65) vs. 65.5 (19.05) Current pain (0 to 100), mean (SD): 51.3 (18.98) vs. 55.3 (20.87) vs. 62.7 (22.81) Highest pain (0 to 100), mean (SD): 71.4 (20.93) vs. 75.5 (13.26) vs. 78.9 (19.43) Anxiety (0 to 100), mean (SD): 11.2 (16.05) vs. 15.0 (21.89) vs. 31.6 (33.58) Depression (0 to 100), mean (SD): 10.8 (17.55) vs. 16.4 (24.50) vs. 26.9 (32.11) Irritability (0 to 100), mean (SD): 17.7 (17.27) vs. 20.5 (23.12) vs. 33.7 (34.21) Level of activity (0 to 100), mean (SD): 49.3 (49.25) vs. 49.3 (49.33) vs. 51.5 (21.01) Hours of sleep per night, mean (SD): 5.9 (2.32) vs. 5.9 (2.05) vs. 6.1 (2.69)	Poor
Pedersen, 2014[184] RCT 8 weeks	Single pain center Norway	A. Dihydrocodeine SR 120 to 240 mg/day (dosed 2 to 3 times/day) + paracetamol 2 to 4 g/day (mean NR) (n=28) B. Dihydrocodeine IR 120 to 240 mg/day (dosed 4 to 6 times/day) + paracetamol 2 to 4 g/day (mean NR) (n=30)	A vs. B, at last week of trial participation Average pain intensity (0 to 10), median (IQR): 4.93 (3.11 to 6.21) vs. 5.00 (3.29 to 6.14) SF-8 PCS (0 to 100), mean (SD): 33.77 (7.36) vs. 37.28 (7.96), p=0.18 SF-8 MCS (0 to 100), mean (SD): 46.43 (9.87) vs. 43.78 (13.60), p=0.51 Pittsburgh Sleep Quality Index (0 to 21, higher scores indicate poorer sleep quality), median (IQR): 11.0 (8.0 to 15.0) vs. 8.0 (5.0 to 13.0) Beck Depression Inventory (0 to 63), median (IQR): 26.0 (24.5 to 37.5) vs. 30.5 (24.5 to 34.75)	Fair
Steiner, 2011[185] RCT 12 weeks	75 centers USA	A. Buprenorphine 7-day patch 20 mcg/hour (n=219) B. Buprenorphine 7-day patch 5 mcg/hour (n=222) C. Oxycodone IR capsules 40 mg/day (n=221)	A vs. C Pain (0 to 10), difference (SE) versus B: -0.67 (0.16) vs. -0.75 (0.16) MOS sleep disturbance subscale, difference (95% CI) versus B: -6.23 (-9.64 to -2.82) vs. -2.65 (-6.01 to 0.70) Oswestry Disability Index (0 to 100), difference (95% CI) versus B: -1.72 (-3.55 to 0.11) vs. -1.99 (-3.79 to -0.18)	Fair

Abbreviations: CI=confidence interval; IQR=interquartile range; IR=immediate-release; MCS=mental component summary; MOS=Medical Outcomes Study; NR=not reported; PCS=physical component summary; QD=once a day; QID=four times a day; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation; SE=standard error; SF-8=Short Form-8; SR=sustained release; TID=three times a day; U.K.=United Kingdom; USA=United States of America.

Detailed Synthesis

The two trials that compared the long- versus short-acting versions of the same opioid (tramadol [n=146] or dihydrocodeine [n=38]) reported no differences in mean improvement in pain, function, sleep, or mood.[183,184] There were also no differences in discontinuation due to adverse events or specific adverse events.

The other two trials compared a long-acting opioid versus a short-acting, different opioid. Results are difficult to interpret due to the evaluation of different types of opioids (partial agonist versus agonist) and use of different opioid doses. One trial (n=660) found similar effects of 7-day buprenorphine patches at 20 mcg/hour versus immediate-release oxycodone 40 mg/day in pain and function. Transdermal buprenorphine 20 mcg/hour was associated with increased risk of discontinuation due to adverse events (13% vs. 7%, RR 1.82, 955 CI, 1.02 to 3.26), though rates of specific adverse events were similar between groups. The other trial (n=24) found long-acting morphine plus short-acting oxycodone associated with less pain versus short-acting oxycodone after 16 weeks, but is difficult to interpret due to differences in mean opioid doses and because patients in the long-acting morphine arm could also use short-acting oxycodone.

A propensity score-adjusted cohort study of patients with chronic noncancer pain in a Veterans Health Administration database (n=840,606) found long-acting opioids associated with increased risk of overdose versus short-acting opioids (adjusted HR 2.33, 95% CI, 1.26 to 4.32).[186] The risk decreased with longer duration of exposure (adjusted HR 5.2, 95% CI, 1.89 to 14.72 at ≤14 days; adjusted HR 2.30, 95% CI, 0.67 to 7.90 at 15 to 60 days; and adjusted HR 1.50, 95% CI, 0.68 to 3.33 at >60 days).

Key Question 3c. In patients with chronic pain, what is the comparative effectiveness of different long-acting opioids on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; and overdose?

Key Points

- Four trials (N=2721) of long-acting oxycodone versus tapentadol reported mean differences in pain that ranged from -0.1 to -1.0 on a 0 to 10 scale, but the dose was lower in the oxycodone arms (range in differences 35 to 45 mg MED/day); oxycodone was associated with increased risk of discontinuation due to adverse events and gastrointestinal adverse events, with no difference in risk of serious adverse events (SOE: low).
- Three trials (N=1405) compared similar doses of long-acting oxycodone versus morphine; effects on pain, SF-36 physical and mental health, and adverse events were inconsistent, with some trials reporting no differences (SOE: low).
- Three trials (N=957) compared transdermal fentanyl versus long-acting morphine. Two trials reported no differences in pain or other outcomes. The third trial found a small difference in pain intensity favoring transdermal fentanyl (difference ~5 points on a 0 to 100 scale). Two trials found a lower likelihood of constipation with transdermal fentanyl than long-acting morphine but discontinuation due to adverse events was higher with transdermal fentanyl (SOE: low).
- Other long-acting opioid comparisons were evaluated in one or two trials, with no differences in effects (SOE: low).

- Two cohort studies of Medicaid patients found methadone associated with increased risk of overdose or all-cause mortality versus morphine and one cohort study of Veterans Affairs patients found methadone associated with decreased risk (SOE: low).

Description of Included Studies

Sixteen trials (in 20 publications) compared one sustained-release or long-acting opioid versus another sustained-release or long-acting opioid for chronic pain (Table 39; Appendix Tables H-27 and H-28).[50,56,86,131,132,135-138,187-197] Sample sizes ranged from 18 to 1121 (total N=7356). Three trials were included in the 2014 AHRQ report, which was restricted to trials with 1 year or more followup.[135,138,188] One of the trials in the 2014 AHRQ report compared transdermal fentanyl versus sustained-release morphine,[188] one trial compared sustained-release tapentadol versus sustained-release oxycodone,[135] and one compared transdermal buprenorphine versus transdermal fentanyl.[138] The duration of followup in all of the new trials was 6 months or less;[50,56,86,131,132,136,137,187,189-191,193-198] six trials followed patients for less than 3 months and seven trials followed patients for 3 to 6 months. The sustained-release or long-acting opioids evaluated oxycodone (10 trials), tapentadol (4 trials), morphine (6 trials), hydromorphone (2 trials), oxymorphone (1 trial), tramadol (2 trials), transdermal fentanyl (4 trials), and transdermal buprenorphine (3 trials). The mean opioid dose ranged from 35 to 240 mg MED/day. The pain type was musculoskeletal in ten trials,[50,56,86,135-137,190,191,194-198] neuropathic in one trial,[131,132] and mixed in five trials.[138,187-189,193] The duration of pain ranged from 6 months to 50 years. Mean baseline pain ranged from 2.5 to 7.6 on a 0 to 10 scale. All trials excluded patients with a history of opioid or substance use disorder or mental health comorbidities or did not describe eligibility status based on these factors. Two trials restricted enrollment to opioid-naïve patients,[138,194,195] two trials to opioid-experienced patients,[196-198] and seven trials enrolled mixed populations of opioid-naïve and experienced patients;[56,131,132,135,136,187,189-191,193] five trials did not describe prior opioid experience.[50,86,137,188] Fifteen trials were conducted in the United States, Canada, Europe, or Australia; and one trial in China.

One trial was rated good-quality,[137] 14 trials fair-quality,[50,56,86,131,132,135,136,187-191,193-198] and one trial poor-quality[138] (Appendix Table G-1). Methodological shortcomings frequently present in the fair- and poor-quality trials included unclear randomization, unclear allocation concealment, and high attrition. Two trials used a crossover design[187,198] and two trials used an EERW design;[190,191,194,195] the remainder used a parallel group non-EERW randomized trial design. All trials except one[138] reported industry funding.

The 2014 AHRQ report also included two fair-quality cohort studies (n=5684 and 98,068) that compared overdose and related outcomes associated with different sustained-release or long-acting opioids.[199,200] Two additional fair-quality cohort studies (n=50,658 and 38,756) on risk of overdose and related outcomes with different opioids were identified for this update.[201,202]

Table 39. Head-to-head trials and observational studies of different long-acting opioids

Author Year Study Design Duration	Setting/ Data Source Country	Interventions, N	Results	Quality
Afilalo, 2010[50] RCT 15 weeks	87 sites in the USA, 15 in Canada, 6 in New Zealand, and 4 in Australia	A. Tapentadol SR 200 to 500 mg/day (mean 350 mg) (n=346) B. Oxycodone SR 40 to 100 mg/day (mean 70 mg) (n=345) C. Placebo (n=339)	A vs. B vs. C, at 12 weeks Average pain intensity, ≥30% reduction: 43.0% (148/344) vs. 24.9% (85/342) vs. 35.9% (121/337), RR 1.73 (95% CI, 1.39 to 2.16) for A vs. B Average pain intensity, ≥50% reduction: 32.0% (110/344) vs. 17.3% (59/342) vs. 24.3% (82/337), RR 1.85 (95% CI, 1.40 to 2.45) for A vs. B PGIC of very much improved, much improved, or minimally improved: 79.5% (205/258) vs. 73.5% (147/200) vs. 59.0% (161/273), RR 1.08 (95% CI, 0.97 to 1.20)	Fair
Allan, 2001[187] RCT, crossover 4 weeks	35 centers in Belgium, Canada, Denmark, Finland, U.K., the Netherlands, South Africa	A. Fentanyl transdermal titrated from 25 mcg/hour (mean 57.3 mcg/hour) (n=126) B. Long acting morphine titrated from 60 mg/day (mean 133.1 mg/day) (n=130)	A vs. B Pain intensity (0 to 100), mean: 57.8 vs. 62.9, p<0.001 Pain control "good" or "very good": 35% (87/247) vs. 23% (54/234), p=0.002, RR 1.53 (95% CI, 1.14 to 2.04) SF-36 PCS (0 to 100), mean (95% CI): 28.6 (27.5 to 29.7) vs. 27.4 (26.3 to 28.5), p=0.004 SF-36 MCS (0 to 100), mean (95% CI): 44.4 (42.8 to 46.0) vs. 43.1 (41.5 to 44.8), p=0.030 Patient global efficacy "good" or "very good": 60% vs. 36%, p<0.001	Fair
Allan, 2005[188] Randomized trial 13 months	Multicenter (number of sites not clear) Europe	A: Transdermal fentanyl (titrated from 25 mcg/hour) (Mean dose 57 mcg/hour) (n=338) B: Sustained-release morphine (titrated from 30 mg q 12 hours) (Mean dose: 140 mg) (n=342)	A vs. B Pain score (mean, 0 to 100 VAS) at 56 weeks (N=608): 56.0 vs. 55.8 Severe pain at rest: No differences in ITT analysis (data not provided) Quality of life (SF-36): No differences between interventions Loss of working days: No differences between interventions Discontinuation due to lack of efficacy: 5% (18/335) vs. 4% (15/342), RR 1.22 (0.63 to 2.39)	Fair
Baron, 2016 (2 publications)[131,132] RCT 12 weeks	Unclear Germany	A. Tapentadol SR 50 to 250 mg BID (mean 379 mg) (n=130) B. Oxycodone SR/naloxone 10 to 40/5 to 20 mg BID + up to oxycodone SR 10 mg BID (mean 75 mg) (n=128)	A vs. B Pain (0 to 10 NRS), LS mean change (SEM), week 12: -3.7 (0.25) vs. -2.7 (0.26), p<0.001 for test for non-inferiority and p=0.003 for test for superiority PGIC rating very much or much improved: 54.3% (70/129) vs. 29.6% (37/125), RR 1.83 (95% CI, 1.34 to 2.51) painDETECT (0 to 38), LS mean change (SEM): -10.8 (0.67) vs. -7.9 (0.69), p=0.002 SF-12 PCS (0 to 100) at 12 weeks, mean (SD): 40.5 (9.34) vs. 37.8 (8.84) SF-12 MCS (0 to 100) at 12 weeks, mean (SD): 51.1 (11.04) vs. 48.7 (11.57)	Fair

Author Year Study Design Duration	Setting/ Data Source Country	Interventions, N	Results	Quality
Binsfeld, 2010[189] RCT 24 weeks	64 sites Europe	A. Hydromorphone SR 8 to 32 mg QD (mean 18.4 mg) B. Oxycodone SR 20 to 80 mg BID (mean 43.8 mg) (n=512)	A vs. B BPI Pain Right Now (0 to 10), MD: -0.12 (95% CI, -0.53 to 0.29) MOS sleep subscale, sleep interference, MD: -2.87 (95% CI, -5.94 to 0.19)	Fair
Buynak, 2010[56] RCT 15 weeks	85 sites in the USA, 15 in Canada, 3 in Australia	A. Tapentadol SR 100 to 250 mg BID (mean 313 mg) (n=321) B. Oxycodone SR 20 to 50 mg BID (mean 53 mg) (n=334) C. Placebo (n=326)	A vs. B vs. C, at 12 weeks Pain (0 to 10 NRS), mean (SD) change: -2.9 (2.66) vs. -2.9 (2.52) vs. -2.1 (2.33) Average pain intensity, ≥30% reduction: 39.7% (125/315) vs. 30.4% (99/326) vs. 27.1% (86/317), RR 1.31 (95% CI, 1.06 to 1.62) for A vs. B Average pain intensity, ≥50% reduction: 27.0% (85/315) vs. 23.3% (76/326) vs. 18.9% (60/317), RR 1.16 (95% CI, 0.89 to 1.51) for A vs. B PGIC rating much improved or very much improved: 55.5% (131/236) vs. 60.0% (126/210) vs. 32.7% (80/245), RR 0.93 (95% CI, 0.79 to 1.08)	Fair
Chung, 2018[201] Retrospective cohort Duration not applicable	Tennessee Medicaid recipients USA	A. Transdermal fentanyl (median 100 mg/day MED) (n=8717) B. Oxycodone CR (median 120 mg/day MED) (n=14,118) C. Morphine SR (median 90 mg/day MED) (n=27,823)	A vs. B vs. C Unintentional opioid overdose: 0.25% (15/5957) person-years vs. 0.21% (30/14,423) person-years vs. 0.34% (77/22,686) person-years All deaths: 1.7% (101/5957) person-years vs.1.3% (196/14,423) person-years vs. 1.6% (364/22,686) person-years Adjusted HR (95% CI), A vs. C Unintentional opioid overdose: 0.77 (0.44 to 1.34) All deaths: 0.96 (0.77 to 1.21) Adjusted HR (95% CI), C vs. B Unintentional opioid overdose: 1.67 (1.06 to 2.63) All deaths: 1.27 (1.05 to 1.52	Fair
Hale, 2007[191] RCT 6 weeks	Unclear USA	A. Hydromorphone SR 8 to 64 mg QD (mean 15.8 mg) (n=71) B. Oxycodone SR 10 to 80 mg BID (mean 24.0 mg) (n=69)	A vs. B Pain relief (0 to 10), mean (SD): 2.3 (0.95) vs. 2.3 (1.00) Pain intensity (0 to 10), mean change (SD) from baseline: -0.6 (0.80) vs. -0.4 (1.15), p=NS Patients rated treatment effectiveness good, very good, or excellent: 67.2% (43/64) vs. 66.7% (40/60), RR 1.01 (95% CI, 0.79 to 1.30) WOMAC total score, mean (SD) change from baseline: -2.0 (1.90) vs. -1.8 (2.14) WOMAC pain subscale, mean (SD) change from baseline: -2.1 (1.96) vs. -2.0 (2.03) WOMAC stiffness subscale, mean (SD) change from baseline: -2.2 (2.37) vs. -2.2 (2.72) WOMAC physical function subscale, mean (SD) change from baseline: -1.9 (1.99) vs. -1.7 (2.1) Sleep disruption and daytime somnolence: 25.7 (17.82) vs. 35.3 (22.56), p<0.012 MOS sleep problems index, mean (SD) change from baseline: -13.3 (21.10) vs. -5.2 (22.09), p<0.045	Fair

Author Year Study Design Duration	Setting/ Data Source Country	Interventions, N	Results	Quality
Hale, 2009[133] and Vorsanger, 2010[134] RCT 90 days	Multiple primary and specialty care treatment centers Canada and USA	A. Tapentadol IR 50 to 600 mg/day (mean 284 mg) (n=703) B. Oxycodone IR 10 to 90 mg/day (mean 42 mg) (n=175)	A vs. B, at end of treatment Pain (0 to 10 NRS), mean (SD): 4.9 (2.42) vs. 5.2 (2.40) PGIC "very much improved," "much improved," and "minimally improved"): 66% vs. 62%	Fair
Hartung, 2007[199] Retrospective cohort study Duration not applicable	Medicaid claims USA	A. Transdermal fentanyl (n=1,546) B. Methadone (n=974) C. ER oxycodone (n=1,866) D. ER morphine (n=1,298)	A vs. B vs. C (reference: D) Mortality: adjusted HR 0.71 (95% CI, 0.46 to 1.08) vs. HR 0.71 (95% CI, 0.54 to 0.94) vs. 0.80 (95% CI, 0.63 to 1.02) ED encounter or hospitalization involving an opioid-related adverse event (HR 0.45, 95% CI, 0.26 to 0.77) Among patients with noncancer pain: Fentanyl associated with higher risk of ED encounters than sustained-release morphine (HR 1.27, 95% CI, 1.02 to 1.59) Methadone associated with greater risk of overdose symptoms than sustained-release morphine (HR 1.57, 95% CI, 1.03 to 2.40) No significant differences between methadone and long-acting morphine in risk of death (adjusted HR 0.71, 95% CI, 0.46 to 1.08)	Fair
Karlsson, 2009[136] RCT 12 weeks	14 sites Sweden	A. Buprenorphine 7-day patches 5 to 20 mcg/hour (mean NR) (n=69) B. Tramadol SR tables 150 to 400 mg/day (mean NR) (n=66)	A vs. B, at study completion Pain (0 to 10), LSM change from baseline (95% CI): -2.26 (-2.76 to -1.76) vs. -2.09 (-2.61 to -1.58) Patient rating "very good" or "good": 64.7% (44/68) vs. 53.2% (33/62), RR 1.22 (0.91 to 1.63), p=0.039 Decrease in number of nights waking because of pain: 2 vs. 2 Improvement in sleep quality by 1 category: 59% vs. 48% Patient preference for patch over tablet: 70.3% (90/128) WOMAC, EQ-5D: No differences between groups	Fair

Author Year Study Design Duration	Setting/ Data Source Country	Interventions, N	Results	Quality
Krebs, 2011[200] Retrospective cohort study Duration not applicable	VA United States	A. Methadone (n=28,554) B. Long-acting morphine sulfate (n=79,938)	All-cause mortality: Unadjusted: 3.4% (3,347/98,068) patients died Highest mortality within 1st 30 days methadone: 1.2% (334/27,885) MS: 3.7% (2,597/70,183); raw death rates form MS higher than methadone for all 30-day intervals; Death rate: Quintile #1: 0.042 vs. 0.133 Quintile #2: 0.034 vs. 0.078 Quintile #3: 0.025 vs. 0.053 Quintile #4: 0.022 vs. 0.034 Quintile #5: 0.017 vs. 0.020 Propensity adjusted mortality (HR): Overall risk of mortality lower with methadone than morphine, adjusted HR: 0.56 (95% CI, 0.51 to 0.62) Quintile #1: 0.36 (95% CI, 0.26 to 0.49) Quintile #2: 0.46 (95% CI, 0.37 to 0.56) Quintile #3: 0.50 (95% CI, 0.41 to 0.61) Quintile #4: 0.66 (95% CI, 0.54 to 0.81) Quintile #5: 0.92 (95% CI, 0.74 to 1.16) Results robust in validation dataset	Fair
Leng, 2015[137] RCT 8 weeks	6 sites China	A. Buprenorphine 7-day patches 5 to 20 mcg/hour (mean 7.5 mcg/hour) (n=141) B. Tramadol SR tablets 100 to 400 mg/day (mean 236 mg/hour) (n=139)	A vs. B, at study completion Pain (0 to 10 VAS) mean (SD) change from baseline: -3.30 (2.29) vs. -3.75 (2.15) Number of nights waking from pain, mean (SD) improvement from baseline: -0.79 (1.47) vs. -1.06 (1.98) "Good" or "very good" sleep: 68.63% (70/102) vs. 68.57% (72/105), RR 1.00 (0.83 to 1.20)	Good
Matsumoto, 2005[86] RCT 4 weeks	Multicenter USA	A. Oxymorphone SR 20 mg BID x 2 weeks, then 40 mg BID (n=121) B. Oxymorphone SR 20 mg BID (n=121) C. Oxycodone SR 10 mg BID x 2 weeks, then 20 mg BID (n=125) D. Placebo (n=124)	A vs. B vs. C vs. D, at week 4 Pain (0 to 100 VAS), mean change (SD) from baseline: -26 (NR) vs. -24 (NR) vs. -22 (NR) vs. -17 (NR) WOMAC Pain (0 to 500), mean change (SD) from baseline: -118 (110) vs. -102 (109) vs. -88 (125) vs. -62 (111) WOMAC Function (0 to 1700), mean change (SD) from baseline:-320 (550) vs. -290 (545) vs. -225 (559) vs. -175 (557) Patient's global assessment (0 to 100 VAS), mean change (SE) from baseline: -28.6 (3.3) vs. -23.2 (3.2) vs. -25.4 (2.8) vs. -19.5 (2.7) SF-36 PCS (0 to 100), mean change (SE) from baseline: 4.5 (0.9) vs. 3.4 (0.9) vs. 4.0 (0.8) vs. 1.8 (0.7) SF-36 MCS (0 to 100), mean change (SE) from baseline: -0.4 (1.1) vs. 1.5 (1.1) vs. -0.8 (0.9) vs. 2.22 (0.9) Sleep, overall quality (0 to 100, 100=excellent), mean change (SE) from baseline: 18.2 (3.2) vs. 13.8 (3.0) vs. 15.3 (2.5) vs. 7.7 (2.5)	Fair

Author Year Study Design Duration	Setting/ Data Source Country	Interventions, N	Results	Quality
Mitra, 2013[138] Randomized trial 12 months	1 site Australia	A: Transdermal buprenorphine initial dose=-5 mcg/hour (n=22) B: Transdermal fentanyl initial dose=12.5 mcg/hour (n=24) Both titrated to optimal doses over 4 weeks; increased doses beyond that given as clinically indicated	A vs. B Pain reduction ≥3 points (0 to 10): 50% (8/16) vs. 43% (6/14) at 3 months, RR 1.17 (95% CI, 0.53 to 2.54), 8% vs. 8% at 6 months (n/N NR), 11% vs. 11% at 12 months (n/N NR) Depression, Anxiety, and Stress Scale 21 (0 to 126), mean: 50 vs. 58 at 3 months (p=NS), 30 vs. 62 at 6 months (p<0.05), 38 vs. 58 at 12 months (p=NS) Physical Disability Index-7 (0 to 70), mean: 39 vs. 38 at 3 months, 30 vs. 40 at 6 months, 35 vs. 41 at 12 months Score of pain, physical activity, additional rescue medication, additional general practitioner/emergency department visit, sleep quality, mood, and side effects of pain medication (SPAASMS) score (0 to 28), mean: 12 vs. 13 at 3 months, 11 vs. 14 at 6 months, 14 vs. 14 at 12 months	Poor
Nicholson, 2006[193] RCT 24 weeks	5 outpatient pain centers USA	A. Morphine SR titrated from previous dose (mean 79 mg/day) (n=53) B. Oxycodone SR titrated from previous dose (mean 85 mg/day) (n=59)	A vs. B, mean improvement from baseline SF-36 PCS: +2.5 vs. +2.1, p=NS SF-36 MCS: +0.8 vs. +4.2, p for differences between groups NR, but p<0.05 vs. baseline only for sustained-release oxycodone BPI pain intensity: -1.9 vs. -1.4, p=NS BPI sleep Interference scale: -2.6 vs. -1.6, p<0.05 Patient global assessment: +2.6 vs. +1.7, p=NS Use of concomitant medications: 80% vs. 88%, p=NS	Fair
Niemann, 2000[198] RCT, crossover 4 weeks	Multicenter Denmark	A. Fentanyl transdermal 25 to 100 mcg/hour (mean 55.6 mcg/hour) B. Morphine SR dose range NR (mean 128.3 mg/day) (n=18)	A vs. B Patient preference of "preference" or "strong preference": 47% (8/17) vs. 41.2% (7/17), RR 1.14 (0.54 to 2.44), p=NS Pain control "good" or "very good" (n=18): 44% (8/18) vs. 33.3% (6/18), RR 1.33 (0.58 to 3.07), p=NS Quality of Life: No differences in physical functioning, general health, role physical, pain intensity, social functioning, mental health, and side effects summary median scores	Fair
Rauck, 2006 and 2007[194,195] RCT 8 weeks	Multicenter USA	A. Morphine SR once daily (mean 64 mg/day) (n=203) B. Oxycodone SR twice daily (mean 53 mg/day) (n=189)	A vs. B, mean change from baseline BPI (0 to 10): -3.1 vs. -2.8, p=NR >2 point improvement in BPI: 55% (73/132) vs. 44% (59/134), p=0.03 PSQI: 33% vs. 17%, p=0.006 SF-12 PCS: 23% vs. 19%, p=NS SF-12 MCS: 23% vs. 16%, p=NS Mean demands score on WLQ: 22.1 vs. 20.9	Fair

Author Year Study Design Duration	Setting/ Data Source Country	Interventions, N	Results	Quality
Ray, 2015[202] Retrospective cohort NA	Medicaid enrollees USA	A. Morphine SR B. Methadone	HR (95% CI) A vs. B All deaths: 1.46 (1.17 to 1.83), p<0.001 Sudden unexpected death: 1.47 (1.13 to 1.90), p=0.04 -Opioid overdose only: 2.54 (1.33 to 4.84), p=0.005 -Sudden cardiac death only: 1.12 (0.80 to 1.59), p=0.51 -Both opioid overdose and sudden cardiac death: 2.02 (1.21 to 3.37), p=0.07 Other respiratory/cardiovascular deaths: 1.78 (0.91 to 3.46), p=0.09 Other deaths: 1.26 (0.70 to 2.26), p=0.45	Fair
Ueberall, 2015 and 2016[196,197] RCT 12 weeks	88 medical centers Germany	A. Oxycodone/ naloxone SR (mean 113 mg MED/day) (n=301) B. Oxycodone SR (mean 107 MED/day) (n=300) C. Morphine SR (mean 108 MED/day) (n=300)	A vs. B vs. C, at end of study Pain intensity (0 to 100), mean (SD): 27.1 (21.3) vs. 28.6 (21.7) vs. 20.0 (20.4) Pain improved ≥50% from baseline: 65.5% (197/301) vs. 50.7% (n/N NR) vs. 43.3% (n/N NR) EQ-5D, mean (SD): 0.79 (0.23) vs. 0.69 (0.28) vs. 0.68 (0.30) EQ-5D index improvement beyond MCID: 70.3% vs. 58.7% vs. 57.7%, p=0.003 A vs. B and p=0.002 A vs. C Quality of Life Impairment by Pain (QLIP) inventory (0 to 40, 40=least affected), mean (SD): 30.6 (4.9) vs. 27.5 (5.8) vs. 26.4 (5.9) Adequate sleep duration: 95% vs. 83.3% vs. 83% QLIP improved ≥30% from baseline: 90.7% (273/301) vs. 73.3% (220/300) vs. 67.3% (202/300), RR 1.09 (95% CI, 0.98 to 1.21) B vs. C SF-12 PCS, mean (SD) change from baseline: 10.4 (13.6) vs. 7.9 (15.1) vs. 7.7 (12.1) SF-12 MCS, mean (SD) change from baseline: 5.0 (12.4) vs. 2.5 (10.0) vs. 2.3 (10.8)	Fair
Wild, 2010[135] Randomized trial 12 months	53 sites in North America; 36 sites in Europe	A. Tapentadol ER 100-250 mg BID (adjustable) (n=894) B. Oxycodone CR 20-50 mg BID (adjustable) (n=223)	Mean (SE) pain intensity score: decreased from 7.6 (0.05) and 7.6 (0.11) at baseline to 4.4 (0.09) and 4.5 (0.17) Global assessment, very much improved or much improved: 48.1% (394/819) vs 41.2% (73/177) Concomitant nonopioid analgesics (NSAIDS, ASA, acetaminophen): 19.9% (178/894) vs. 17% (38/223)	Fair

Abbreviations: ASA=acetylsalicylic acid; BID=twice daily; BPI =Brief Pain Inventory; CI=confidence interval; CR=controlled release; ED=emergency department; EQ-5D= EuroQoL Quality of Life Scale-5 Dimension; ER=extended release; HR=hazard ratio; IQR=interquartile range; IR=immediate-release; ITT=intent to treat; LBP=low back pain; LS=least square; LSM=least squares mean; LSMD=least squares mean difference; mcg=microgram; MCID=minimal clinically important difference; MCS=mental component summary; MD = mean difference; MED=morphine equivalent dose; mg=milligram; MOS=Medical Outcomes Study; MS=morphine sulfate; NR=not reported; NRS=Numeric Rating Scale; NS=not significant; NSAIDS=non-steroidal anti-inflammatory drug; PCS=physical component summary; PGIC=Patient Global Impression of Change; PSQI=Pittsburgh Sleep Quality Index; QD=once a day; QID=four times a day; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation; SE=standard error; SEM=standard error of the mean; SF-12=Short Form-12; SF-36=Short Form-36; SPAASMS= score, physical, activity level, additional pain medication, additional physician/ER visits, sleep quality, mood, medication side-effects; SR=sustained release; TID=three times a day; U.K.=United Kingdom; USA=United States of America; VA=Veterans Affairs; VAS=visual analog scale; WLQ=Work Limitations Questionnaire; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

Detailed Synthesis

Overall, direct comparisons of long-acting opioids did not indicate patterns showing differential effectiveness or harms, with inconsistency among trials that compared the same long-acting opioids. When differences were observed, the magnitude was small or below the threshold for small. In addition, doses of compared long-acting opioids in mg MED/day were not equivalent in some trials based on published conversion ratios,[23] complicating interpretation. In some trials, opioid doses were titrated to pain relief, which could limit their usefulness for evaluating comparative effectiveness.

Oxycodone was the most frequently evaluated long-acting opioid in head-to-head comparisons. Ten trials compared long-acting oxycodone versus tapentadol (4 trials, N=3390),[50,56,131,132,135] morphine (3 trials, N=1405),[193-197] hydromorphone (2 trials, N=652),[189-191] or oxymorphone (1 trial, n=491).[86] Four trials of long-acting oxycodone versus tapentadol reported MDs in pain that ranged from -0.1 to -1.0 on a 0 to 10 scale, but the dose was lower in the oxycodone arms (range in differences 35 to 45 mg MED/day).[50,56,131,132,135] Differences between long-acting oxycodone versus tapentadol in function or SF-36 physical or mental health did not meet the threshold for small. Despite a lower opioid dose, long-acting oxycodone was associated with increased risk of adverse events. The difference between long-acting oxycodone versus tapentadol in discontinuation due to adverse events ranged from 14 percent to 22 percent, for constipation from 10 percent to 18 percent, for nausea from -4 percent to 15 percent, for vomiting from 6 percent to 13 percent; however, there was no difference in risk of serious adverse events (differences ranged from -1.4% to 1.6%). Three trials compared similar doses of long-acting oxycodone versus morphine; effects on pain, SF-36 physical and mental health, and adverse events were inconsistent, with some trials reporting no differences.[193-197] Two trials[189-191] reported no differences between long-acting oxycodone versus hydromorphone in pain or other outcomes and one trial[86] reported no differences between long-acting oxycodone versus oxymorphone.

Three trials (N=957) compared transdermal fentanyl versus long-acting morphine.[187,188,198] Two trials reported no differences in pain or other outcomes.[188,198] The third trial found a small difference in pain intensity favoring transdermal fentanyl (difference ~5 points on a 0 to 100 scale), with trivial effects (difference <1.5 points on a 0 to 100 scale) on SF-36 physical and mental health; in this trial, the dose of fentanyl was higher than that of morphine by ~20 mg MED/day.[187] Two trials found that the proportion of patients with constipation was lower with transdermal fentanyl than with long-acting morphine (difference 6% and 13%) but discontinuation due to adverse events was higher with transdermal fentanyl (difference 7% and 6%).[187,188]

Three trials compared transdermal buprenorphine versus another long-acting opioid.[136-138] Two trials (N=415) found no differences between transdermal buprenorphine versus sustained-release tramadol in mean improvement in pain or sleep.[136,137] Rates of discontinuation due to adverse events and specific adverse events were similar or showed no consistent differences. One small trial (n=46) of transdermal buprenorphine versus transdermal fentanyl found no differences in pain, function, mood, or adverse events.[138]

The 2014 AHRQ report included two cohort studies that reported somewhat inconsistent results regarding risks of different long-acting opioids. In one study of Medicaid patients (n=5684), long-acting oxycodone was associated with lower risk versus long-acting morphine of an emergency department encounter or hospitalization involving an opioid-related adverse event (HR 0.45, 95% CI, 0.26 to 0.77) or death (HR 0.71, 95% CI, 0.54 to 0.94), after adjusting for

opioid dose, comorbidities, concomitant medications, and other potential confounders.[199] Among patients with noncancer pain, compared with long-acting morphine, fentanyl was associated with higher risk of emergency department encounters (HR 1.27, 95% CI, 1.02 to 1.59) and methadone was associated with greater risk of overdose symptoms (HR 1.57, 95% CI, 1.03 to 2.40). There were no significant differences between methadone versus long-acting morphine in risk of death (adjusted HR 0.71, 95% CI, 0.46 to 1.08) or overdose symptoms. Another study (n=98,068) of patients within the Veterans Affairs health system found methadone associated with lower mortality risk versus morphine in a propensity-stratified analysis (adjusted HR 0.56, 95% CI, 0.51 to 0.62).[200]

Two new cohort studies compared risks of different opioids in Medicaid patients in the same state. One study[201] (n=50,658) found long-acting morphine associated with higher risk of unintentional opioid overdose (RR 1.67, 95% CI, 1.06 to 2.63) and all-cause death (RR 1.27, 95% CI, 1.05 to 1.52) than long-acting oxycodone and one study[202] (n=38,756) found methadone associated with increased risk of out-of-hospital death (an indicator of overdose deaths or sudden unexpected death, potentially due to arrhythmia) versus morphine (HR 1.46, 95% CI, 1.17 to 1.83), resulting in 72 excess deaths per 10,000 person-years of followup. Results were similar when the analysis was restricted to patients on methadone doses of less than 20 mg/day and morphine doses of less than 60 mg/day (HR 1.59, 95% CI, 1.01 to 2.51).

Key Question 3d. In patients with chronic pain, what is the comparative effectiveness of short- plus long-acting opioids versus long-acting opioids alone on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?

No study compared short- plus long-acting opioids versus long-acting opioids alone (SOE: insufficient).

Key Question 3e. In patients with chronic pain, what is the comparative effectiveness of scheduled, continuous versus as-needed dosing of opioids on outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; overdose; and doses of opioids used?

No study compared long-term opioid therapy using scheduled, continuous dosing versus as-needed dosing (SOE: insufficient).

Key Question 3f. In patients with chronic pain, what is the comparative effectiveness of opioid dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life?

Key Points

- One trial of more liberal dose escalation versus maintenance of current doses found no difference in outcomes related to pain, function, or risk of discontinuation due to opioid misuse, but opioid doses were similar (52 vs. 40 mg MED/day at the end of the trial) (SOE: low).

Detailed Synthesis

No new studies were identified for this update. The 2014 AHRQ report included one fair-quality randomized trial (n=140) of more liberal dose escalation (doses increased for inadequate pain relief using preset dosing guidelines) versus maintenance of current doses (doses only increased if medically necessary due to clear dosage tolerance or acute injury) (Table 40; Appendix Table G-1, H-31, and H-32).[203] The trial enrolled Veterans Affairs patients with primarily musculoskeletal chronic (>6 months) pain.[203] Over 90 percent of enrollees were male and initial opioid doses were about 30 mg MED/day. Both short- and long-acting opioids were prescribed, with long-acting opioids used more in patients prescribed higher doses. Average pain at baseline was about 7 on a 0 to 10 scale, and mean Oswestry Disability Index (ODI) score was about 48 (0 to 100 scale, indicating moderate functional disability). The trial was fair-quality, primarily due to high attrition. Although doses at the end of the 12-month trial were higher in the dose escalation group, the difference in opioid doses prescribed at the end of the trial was relatively small (mean 52 vs. 40 mg MED/day).

The trial found no difference between dosing strategies at 12 months in mean pain (5.6 for escalating dose vs. 6.2 for stable dose on a 0 to 10 scale, p=0.11), proportion with 1.5 point or greater improvement in VAS pain rating (28% vs. 20%, RR 1.4, 95% CI, 0.76 to 2.5), mean ODI scores (46 vs. 45, p=0.85), proportion with 10-point or greater improvement in ODI score (29% vs. 23%, RR 1.0, 95% CI, 0.61 to 1.8), or use of nonopioid medications or physical therapy. There was also no significant difference in all-cause study discontinuations (49% vs. 56%, RR 0.88, 95% CI, 0.64 to 1.2). Discontinuation due to opioid misuse was frequent, with no difference between groups (24% vs. 30%, RR 0.79, 95% CI, 0.46 to 1.4).

Table 40. Trial of opioid dose escalation versus dose maintenance

Author, Year Study Design Duration	Sample	Interventions, N	Results	Quality
Naliboff, 2011[203] RCT 12 months	n=140 Patients referred to chronic pain clinic; nonmalignant chronic pain for ≥6 months; clinician determination that patient was eligible for long-term opioids. Mean age: 53 vs. 52 years Female: 11% vs. 1% Race: NR Mean worst VAS 8.4 (SD 1.2) vs. 8.0 (SD 1.7) Pain: -78% vs. 77% musculoskeletal -19% vs. 19% neuropathic -3% vs. 4% complex Initial MED/day: 29.2 (SD 19.6) vs. 32.3 (SD 23.1) mg	A. Escalating opioid dose; mean MED/day 52 mg (n=67) B. Stable opioid dose; mean MED/day 40 mg (n=73)	A vs. B Mean (SD) VAS usual pain at 12 months: 5.6 (1.5) vs. 6.2 (1.5); p=0.11* Usual pain VAS decrease ≥1.5 points: 28% (19/67) vs. 20% (15/73); RR 1.38 (95% CI, 0.76 to 2.49) Mean (SD) VAS pain relief at 12 months: 6.0 (1.7) vs. 5.3 (1.8); p=0.11* Increase in pain relief ≥1.5 points: 29% (19/67) vs. 15% (11/73); RR 1.88 (95% CI, 0.97 to 3.66) Worst pain VAS decrease ≥1.5 points: 14% (9/67) vs. 6% (4/73); RR 2.45 (95% CI, 0.79 to 7.59) Mean (SD) ODI at 12 months: 45.8 (14.8) vs. 45.0 (19.4); p=0.85* ODI decrease ≥10 points: 29% (19/67) vs. 23% (20/73); RR 1.04 (95% CI, 0.61 to 1.76) Overall discontinuation: 49% (33/67) vs. 56% (41/73); RR 0.88 (95% CI, 0.64 to 1.20) Discontinuation due to opioid misuse: 24% (16/67) vs. 30% (22/73); RR 0.79 (95% CI, 0.46 to 1.38)	Fair

Abbreviations: CI=confidence interval, mcg=micrograms, MED=morphine equivalent dose, mg=milligram, NR=not reported, NS=not significant, OR=odds ratio, RR=relative risk, SD=standard deviation, VAS=visual analog scale.

Key Question 3g. In patients with chronic pain, what is the comparative effectiveness of opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life, and doses of opioids used?

No study compared opioid rotation versus maintenance of current opioid therapy (SOE: insufficient).

Key Question 3h. In patients with chronic pain, what is the comparative effectiveness of different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life?

Key Points

- Two randomized trials found buccal fentanyl more effective than placebo for treating acute exacerbations of pain in patients prescribed long-term opioid therapy for chronic pain, based on pain relief measured up to 2 hours after dosing (SOE: moderate).
- Two randomized trials found buccal fentanyl more effective than oral opioids for treating acute exacerbations of pain in patients prescribed long-term opioid therapy for chronic pain, based on pain relief measured up to 2 hours after dosing. (SOE: moderate).
- No study evaluated long-term benefits or harms (SOE: insufficient).

Detailed Synthesis

No new studies were identified for this update. The 2014 AHRQ report included two good-quality placebo-controlled, randomized trials (n=77 and 79) of buccal fentanyl[204,205] and two good-quality head-to-head trials (n=183 and 137) of buccal fentanyl versus oral opioids[206,207] for exacerbations of chronic noncancer pain of various etiologies (Table 41, Appendix Table G-1, H-33, and H-34). The trials enrolled opioid-tolerant patients and focused on pain relief immediately (15 minutes to 2 hours) after dosing. The trials did not evaluate longer-term outcomes, risk of overdose, or opioid use disorder and related outcomes. All of the trials were funded by the manufacturer of buccal fentanyl and used an open-label run-in period, excluding 25 percent to 40 percent of patients prior to randomization due to lack of efficacy or adverse events.

Buccal fentanyl was more effective than placebo over a 3-week period at relieving pain exacerbations based on outcomes measured up to 2 hours after dosing. One trial found buccal fentanyl associated with a higher proportion of patients with at least 50 percent reduction in pain intensity 15 minutes after dosing (12% vs. 5%, $p \leq 0.0001$); differences were maintained through 2 hours.[204] The other trial reported similar results; the proportion of pain exacerbation episodes with at least 33 percent improvement in pain was 42 percent versus 18 percent at 30 minutes ($p<0.0001$) and 48 percent versus 16 percent at 2 hours ($p<0.0001$).[205]

The head-to-head trials found fentanyl buccal tablets associated with significantly greater immediate pain relief than oral oxycodone, but differences were very small (pain reduction 0.82 vs. 0.60, $p<0.0001$ and 0.88 vs. 0.76, $p<0.001$ on a 0 to 10 scale at 15 minutes). There were also significant differences in "meaningful pain relief" (undefined) (45% vs. 36%, $p<0.05$ and 46% vs. 38%, $p<0.01$ at 30 minutes).[206,207] The pain condition in most patients in both trials was back or neck pain, osteoarthritis, fibromyalgia, traumatic injury, or complex regional pain syndrome.

Table 41. Trials of different strategies for treating exacerbations of chronic pain in patients on long-term opioid therapy

Author, Year Study Design Duration	Sample	Interventions, N	Results	Quality
Ashburn, 2011[206] Randomized trial (crossover) Duration: up to 42 days total	n=183 Patients aged 18 to 80 years with >3 months of chronic pain receiving >60 mg/day MED, with 1 to 4 episodes of breakthrough pain per day Mean age: 48.8 years Female sex: 62% Race: 92% White, 5% Black, 3% other Pain intensity in 24 hours prior to enrollment: 5.1 Indication (most common): 57% back pain, 11% osteoarthritis, 8% neck pain, 9% fibromyalgia, 4% traumatic injury, 4% complex regional pain syndrome	A. Fentanyl buccal tablet (n=183) B. Oxycodone (n=183)	A vs. B Pain intensity difference (from before drug administration; 0 to 10 scale) at 30 minutes: 1.95 vs. 1.60 (p<0.05) Pain relief (0 to 5 scale) at 30 minutes: 1.50 vs. 1.23 (p<0.05) Meaningful pain relief within 30 minutes: 45% vs. 36% of episodes (p<0.05)	Good
Portenoy, 2007[205] Randomized trial 3 weeks	n=77 Patients aged 18 to 80 years with chronic low back pain Mean age: 47 years Female gender: 55% Nonwhite race: 12% Baseline pain intensity: 5.1 (10 point scale) Primary etiology of low back pain degenerative disc disease: 68%	A. Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B. Placebo (n=77) Dose of buccal fentanyl: 800 mcg 56%; 600 mcg 24%; 400 mcg 15%; 200 mcg 5%	A vs. B Sum of the pain intensity differences from 5 through 60 minutes: 8.3 vs. 3.6 Proportion of breakthrough pain episodes with “meaningful” pain reduction: 70% (289/413) vs. 30% (63/207) (p<0.0001) Proportion of breakthrough pain episodes with ≥33% reduction in pain intensity after 30 minutes: 42% (172/413) vs. 18% (18/207) (p<0.0001) Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 30 minutes: 30% (122/413) vs. 13% (27/207) (p<0.0001) Proportion of breakthrough pain episodes with ≥33% reduction in pain intensity after 120 minutes: 65% (269/413) vs. 28% (57/207) (p<0.0001) Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 120 minutes: 48% (198/413) vs. 16% (33/207) (p<0.0001)	Good

Author, Year Study Design Duration	Sample	Interventions, N	Results	Quality
Simpson, 2007[204] Randomized trial (crossover) 3 weeks	n=79 18 to 80 years old, >3 months history of chronic neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, traumatic injury, or complex regional pain syndrome, on chronic opioids (at least 60 mg/day or morphine or equivalent), pain intensity <7 on a 0 to 10 scale, 1 to 4 daily episodes of breakthrough pain	A. Buccal fentanyl 100 to 800 mcg for an episode of breakthrough pain B. Placebo (n=79) Dose of buccal fentanyl: 800 mcg 54%; 600 mcg 19%; 400 mcg 18%; 200 mcg 5%, 100 mcg 5%	A vs. B Sum of the pain intensity differences from 5 through 60 minutes: 9.63 vs. 5.73 (p<0.001) Proportion of breakthrough pain episodes with 'meaningful' pain reduction: 69% vs. 36% (p<0.0001) Proportion of breakthrough pain episodes with ≥50% reduction in pain intensity after 15 minutes: 12% vs. 5% (p≤0.0001), p<0.0001 for each subsequent time point from 30 to 120 minutes Use of supplemental medication: 14% (59/432) vs. 36% (77/213) (OR 0.28, 95% CI, 0.18 to 0.42)	Good
Webster, 2013[207] Randomized trial (crossover) Up to 42 days	N=274 Mean age: 50.8 years Female sex: 58% Race: 91% White, 7% Black, 2% other Pain intensity in 24 hours prior to enrollment: 5.1	A. Fentanyl buccal tablet (n=137) B. Oxycodone (n=137)	A vs. B Pain intensity difference (from before drug) at 15 minutes: 0.88 vs. 0.76 (0 to 10 scale) (p<0.001) Pain relief at 15 minutes: 38% vs. 34% (p<0.05) Meaningful pain relief within 15 minutes: 17% vs. 16% (p=NS) Meaningful pain relief within 30 minutes: 46% vs. 38% (p<0.01)	Good

Abbreviations: CI=confidence interval, mcg=micrograms, MED=morphine equivalent dose, mg=milligram, NR=not reported, NS=not significant, OR=odds ratio.

Key Question 3i. In patients with chronic pain, what are the effects of decreasing opioid doses or of tapering off opioids versus continuation of opioids on outcomes related to pain, function, quality of life, and opiate withdrawal symptoms?

Key Points

- One small trial found a taper support intervention associated with no difference versus usual care at 22 weeks in BPI pain severity (4.72 vs. 5.77, adjusted mean difference -0.68 on a 0 to 10 scale, 95% CI, -2.01 to 0.64), but greater improvement in BPI pain interference (adjusted mean difference -1.39 on a 0 to 10 scale, 95% CI, -2.78 to -0.01); effects persisted at 34-week followup. Effects on opioid dose were not statistically significant (99.51 vs. 138.2 mg MED/day, adjusted difference -26.7, 95% CI, -83.0 to 29.6) (SOE: low).

Detailed Synthesis

One small, poor-quality trial (n=10) in the 2014 AHRQ report found abrupt cessation of morphine associated with increased risk of discontinuation versus continuation of morphine but was excluded from this update because it did not evaluate a tapering protocol and only evaluated immediate (60 hours) outcomes.[49] Three other small trials not included in the 2014 AHRQ report

compared tapering versus continuation of opioid therapy in patients with chronic pain (Table 42; Appendix Tables H-35 and H-36).[149,208,209] Sample sizes ranged from 12 to 35 (total N=81) and the mean duration of pain ranged from 12 to 14 years. In two trials, the mean opioid dose prior to tapering was 253 mg MED/day (range 225.6 to 284); one trial did not report baseline duration of pain or opioid dose.[208] The tapering interventions evaluated in the trials varied. One trial evaluated a taper support program including mental health consultation, motivational interviewing, and pain self-management training;[209] one trial evaluated a buprenorphine taper following inpatient induction;[208] and one trial performed a scheduled taper of 10 percent per week (10 weeks to discontinuation) with clonidine for management of withdrawal symptoms.[149] The duration of followup ranged from 22 weeks to 6 months. Two trials[208,209] were conducted in the U.S. and one trial[149] in Europe.

One trial was rated fair-quality[209] and two trials were rated poor-quality (Appendix Table G-1).[149,208] All trials were open-label; the poor-quality trial also had high attrition and crossover, with early termination or failure to report planned outcomes due to attrition.

The fair-quality trial (n=34) compared a 22-week taper support intervention consisting of a mental health assessment and 18 weekly 30-minute motivational interviewing and pain self-management training sessions versus continued opioid treatment as usual.[209] Mean age was 54.4 years, 72 percent were female, and mean baseline opioid dose 225.7 mg MED/day. The duration of chronic pain was 13.8 years. At 22 weeks, there was no difference between the taper support intervention versus usual care in BPI pain severity (4.72 vs. 5.77, adjusted mean difference -0.68 on a 0 to 10 scale, 95% CI, -2.01 to 0.64), but taper support was associated with greater improvement in BPI pain interference (adjusted mean difference -1.39 on a 0 to 10 scale, 95% CI, -2.78 to -0.01) and prescription opioid problems based on the Prescription Opioid Difficulty Scale (adjusted mean difference -4.90 on a 0 to 32 scale, 95% CI, -8.40 to -0.80). Effects on BPI pain interference and prescription opioid problems persisted at 34-week followup (adjusted mean difference -1.21, 95% CI, -2.43 to 0.02 and -4.74, 95% CI, -1.13 to 0.64, respectively). Taper support was associated with lower opioid dose compared to usual care, but the difference was not statistically significant (99.51 vs. 138.2 mg MED/day, adjusted difference -26.7, 95% CI, -83.0 to 29.6).

The two poor-quality trials reported high attrition rates that prevented full reporting of intended outcomes. One trial (n=35) of patients stabilized on high doses of opioids compared tapering by 10 percent of the opioid dose weekly to cessation with clonidine for withdrawal symptoms versus maintenance of opioid doses.[149] Mean opioid doses at baseline were 367 versus 221 mg MED/day (p=0.09) in the tapering and maintenance groups, respectively. Although the trial planned to report 6-month outcomes, outcomes were only reported at 4 to 6 weeks due to high attrition, with 1/15 completing the final follow up in the intervention group and 12/20 completing followup in the control group. At 4 to 6 weeks (n=30), there were no differences between tapering versus maintenance in opioid dose (226.6 vs 300.8 mg MED/day, p=0.45), pain (6.5 vs 5.1 on a 0 to 10 scale, p=.09), and anxiety (6.7 vs. 6.3, p=0.96) or depression (6.4 vs. 6.0, p=0.86) measured on the Hospital Anxiety Depression Scale, though some estimates were imprecise. A small trial (n=12) of patients with prescription opioid dependence and chronic pain who were transitioned to sublingual buprenorphine/naloxone compared a four month taper to cessation versus buprenorphine maintenance, but was terminated early without reporting of planned outcomes because five of six patients in the taper arm crossed over to maintenance and the sixth patient had a relapse requiring hospitalization.[208]

Other data from randomized trials on harms associated with tapering versus usual care were limited. The taper support trial reported one patient discontinued taper support due to adverse events (increased pain and depression));[209] the trial of buprenorphine taper[208] reported one discontinuation due to relapse, with no other adverse events reported. Suicidality or suicide events were not described in any of the trials.

One cohort study (n=572) of patients with chronic pain on long-term opioid therapy enrolled in an opioid registry found discontinuation from the registry associated with increased risk of overdose death after adjusting for age and race (4.9% vs. 1.8%, adjusted HR 2.94, 95% CI 1.01 to 8.61), but the difference in risk of overall mortality was not statistically significant (adjusted HR 1.35, 95% CI 0.92 to 1.98, Appendix Tables H-37 and H-38).[210]About three-quarters of patients had a provider-initiated reason for discontinuing opioids (e.g., abnormal urine toxicology screen, behavioral issues, or other safety concerns), suggesting a higher risk of opioid-related adverse events. The study was rated poor-quality because it did not attempt to adjust for factors other than age and race; in addition, there was no information regarding the rate of opioid discontinuation and 74 percent of discontinued patients subsequently filled at least one opioid prescription (Appendix Table G-2).

Table 42. Trials of effects of decreasing opioid doses or of tapering off opioids

Author, Year Study Design Duration	Sample	Interventions, N	Results	Quality
Blondell, 2010[208] Open-label RCT 6 months	Men and women aged ≥18 years, documented CNCP and self-identified addiction to prescription opioids Mean (SD) age, years: 44 (6.4) vs. 46 (14.6) Female: 50% White: 92% History of alcohol use only: 33% History of alcohol and drug abuse: 33% Prior SUD treatment: 42%	A. Steady dose (n=6) B. Tapering doses (n=6)	Mean stable dose of buprenorphine: 7.5 mg/day at hospital discharge; 9.8 mg/day at 4 weeks Study terminated early because none of the 6 participants in tapering dose arm could complete the 6-month protocol -5 switched to stable dose arm (2 in month 1; 1 in month 2; 1 in month 3; 1 in month 4) -1 was admitted to inpatient unit after relapse after 2nd month (terminated due to ethical reasons) In the stable dose arm, 5 completed 6-month protocol and 1 withdrew due to cost of medication. (0/6 vs. 5/6 completed, p=0.015) At 6-month followup: 10 participants completed 5 and 5; 8 receiving opioid replacement therapy, 6 reported improved pain control and physical functioning.	Poor

Author, Year Study Design Duration	Sample	Interventions, N	Results	Quality
Kurita, 2018[149] Open-label RCT 6 months	Patients on waiting list to pain center aged ≥18 years, ≥7 years schooling, pain duration ≥6 months, treatment with oral opioids >3 months, and daily opioid dose ≥60 mg oral MED Mean (SD) age, years: 56.3 (9.2) vs. 50.6 (14.4) Female: 40% vs. 75%, p=0.04 Race: NR Mean (SD) opioid use duration, years: 9.9 (7.1) vs. 6.6 (4.7) Mean opioid dose, MED/day: 367.4 vs. 220.8 Mean pain duration, years: 15.1 vs. 11.4 Mean years of education: 10.9 vs. 12.0 PHQ-9 score ≥10: 61% vs. 53%	A. Tapered off treatment (n=15) B. Maintained on same treatment (n=20)	A vs. B Mean (SD) opioid dose, MED/day: 230.6 (142.6) vs. 345.8 (273.3), p=0.23 at 2 to 3 weeks; 226.6 (144.4) vs. 300.8 (238.5), p=0.446 at 4 to 6 weeks Mean (SD) sleep, minutes: 380 (146) vs. 212 (96), p=0.09 at 2 to 3 weeks; 360 (121) vs. 353 (169), p=0.718 at 4 to 6 weeks Mean (SD) average pain: 6.3 (1.6) vs. 5.4 (2.3), p=0.245 at 2 to 3 weeks; 6.5 (1.4) vs. 6.3 (2.0), p=1.0 Mean (SD) pain now: 6.3 (2.2) vs. 5.4 (2.3), p=0.245 at 2 to 3 weeks; 6.5 (1.4) vs. 5.1 (2.0), p=0.09 at 4 to 6 weeks Mean (SD) anxiety: 6.9 (3.7) vs. 6.6 (4.3), p=0.65 at 2 to 3 weeks; 6.7 (4.0) vs. 6.3 (3.6), p=0.96 at 4 to 6 weeks Mean (SD) depression: 5.0 (4.7) vs. 5.0 (3.3), p=0.65 at 2 to 3 weeks; 6.4 (4.7) vs. 6.0 (3.7), p=0.856 at 4 to 6 weeks	Poor
Sullivan, 2017[209] RCT 22 weeks	Patients with CNCP on opioids who were willing to taper opioid dose by ≥50% A vs. B Mean age, years: 54.4 (overall) Female: 67% vs. 77% White: 72% vs. 94% Black: 5.6% vs. 0% Asian: 11% vs. 5.6% Other race/ethnicity: 11% vs. 0% Mean opioid use duration: 10.2 years (overall) Mean opioid dose, MED/day: 207.2 vs. 245.2 Mean pain duration: 13.8 years (overall) College graduate, graduate, or professional school: 44% vs. 29% PHQ-9 score ≥10: 61% vs. 53% Mean (SD) BPI pain severity (0 to 10): 5.68 (1.36) vs. 6.26 (1.49) Mean (SD) BPI interference (0 to 10): 6.03 (1.88) vs. 6.60 (2.36) Mean (SD) Prescribed Opioids Difficulties Scale, opioid problems (0 to 32): 12.72 (10.97) vs. 12.00 (10.47)	A. Tapering (n=18) B. Usual care (n=17)	A vs. B, adjusted difference (95% CI) Mean opioid dose, MED/day: -42.95 (-92.4 to 6.6) at 22 weeks; -26.7 (-83 to 29.6) at 34 weeks Mean opioid dose, change from baseline: -25% (-52% to 2%) at 22 weeks; -22% (-52% to 8%) at 34 weeks Mean BPI pain severity (0 to 10): -0.68 (-2.01 to 0.64) at 22 weeks; -0.91 (-2.30 to 0.48) at 34 weeks Mean BPI interference (0 to 10): -1.39 (-2.01 to 0.64) at 22 weeks; -1.21 (-2.43 to 0.02) at 34 weeks Mean PODS Opioid Problems (0 to 32): -4.90 (-8.40 to -0.80) at 22 weeks; -4.74 (-1.13 to 0.64) at 34 weeks Mean PODS Opioid Concerns (0 to 32): 0.16 (-3.74 to 4.06) at 22 weeks; 1.62 (-3.27 to 6.51) at 34 weeks Mean Insomnia Severity Index (0 to 28): -3.13 (-7.22 to 0.96) at 22 weeks; -1.19 (-5.49 to 3.11) at 34 weeks Mean PHQ-9: -2.21 (-6.62 to 2.21) at 22 weeks; -1.89 (-6.23 to 2.44) at 34 weeks Mean GAD-7: -2.73 (-5.99 to 0.53) at 22 weeks; -2.39 (-5.79 to 1.01) at 34 weeks	Fair

Abbreviations: BPI=The Brief Pain Inventory; CNCP=chronic non-cancer pain; GAD-7=General Anxiety Disorder 7-item; MED=morphine equivalent dose; PHQ-9=Patient Health Questionnaire-9; PODS=The Prescribed Opioids Difficulties Scale; RCT=randomized controlled trial; SD=standard deviation; SUD=substance use disorder.

Key Question 3j. In patients with chronic pain, what is the comparative effectiveness of different tapering protocols and strategies on measures related to pain, function, quality of life, opiate withdrawal symptoms, and likelihood of opioid cessation?

Key Points

- One trial of patients undergoing tapering in a 15-day intensive outpatient interdisciplinary pain program found no differences between varenicline versus placebo as an adjunct to tapering in median time to tapering completion, opioid withdrawal symptoms, pain, or depression (SOE: low).
- One cohort study of patients prescribed 120 mg MED/day or more of long-term opioid therapy found each additional week to discontinuation associated with a 7 percent reduction in risk of an opioid-related emergency department visit or hospitalization (SOE: low).

Detailed Synthesis

The 2014 AHRQ report included two poor-quality, nonrandomized prospective trials that reported similar rates of opioid abstinence after 3 to 6 months in patients allocated to different methods for opioid discontinuation or tapering.[47,211] One trial did not meet inclusion criteria for the update because the intervention was conducted completely as an inpatient.[47] In the second study, patients (n=42) underwent detoxification over 3 weeks plus counseling or detoxification with maintenance therapy if detoxification was unsuccessful.[211] Mean duration of opioid use was 7.2 years in the detoxification plus counseling group and 9.2 years in the detoxification plus maintenance group; opioid doses ranged widely (e.g., codeine daily doses ranged from 240 to 2400 mg/day). Detoxification plus counseling was associated with decreased likelihood of completing three weeks of therapy versus detoxification plus maintenance (23.8% [5/21] vs. 95.2% [20/21], RR 0.25, 95% CI, 0.12 to 0.54). However, there was no difference between groups in likelihood of opioid abstinence at 6 months (9.5% [2/21] vs. 19.0% [4/21], RR 0.50, 95% CI, 0.10 to 2.44). Effects on pain, function, quality of life, or withdrawal symptoms were not reported (Table 43; Appendix Tables H-39 and H-40).

One new randomized trial (n=21) evaluated effects of varenicline versus placebo as an adjunct for tapering in patients enrolled in a 15-day, intensive (8 hours/day) outpatient interdisciplinary pain program (Table 43; Appendix Tables H-39 and H-40).[212] Mean baseline opioid dose was 135 versus 75 mg MED/day in the varenicline and placebo groups, respectively. There were no differences between groups in median time to tapering completion (18 vs. 15 days), opioid withdrawal symptoms based on the clinical opioid withdrawal scale (COWS, p=0.26), pain (p not reported), or depression based on the Center for Epidemiologic Studies Depression Scale (CES-D) (p not reported). No adverse effects were observed or reported in either group. The trial was rated fair-quality due to differences in baseline opioid doses and non-blinding of treating clinicians (Appendix Table G-1).

One fair-quality cohort study (n=494) evaluated Medicaid beneficiaries who had been prescribed opioids at 120 mg MED/day or more for 90 days and then discontinued opioids.[213]

Sixty percent of patients had a diagnosed substance use disorder, though less than 1 percent received medication for opioid use disorder. The median time to opioid discontinuation was 1 day (half did not fill any prescription for reduced opioid dosage prior to discontinuation), with 86 percent discontinuing within 21 days. After controlling for sociodemographic and clinical factors, each additional day to discontinuation was associated with a 1 percent lower risk of an emergency department visit or hospitalization with a diagnosis of opioid poisoning or a substance use disorder (equivalent to a 7% lower risk for each additional week to discontinuation).

Table 43. Trials of effects of different tapering protocols and strategies

Author, Year Study Design Duration	Sample	Interventions, N	Results	Quality
Hooten, 2015[212] Single blinded placebo-controlled trial 15 days	Patients recruited at time of admission to interdisciplinary treatment program from June 2011 to May 2012 who were ≥21 years, on ≥60 mg/day MED, non-cancer chronic pain of >6 months duration A vs. B Median (IQR) age, years: 49.0 (36.0 to 60) vs. 46.0 (29.0 to 53) Female: 14% vs. 36% Mean BMI: 24.7 vs 33.1 White: 100% vs. 100% Mean years of education: 14 vs. 16 Mean pain duration, years: 7 vs. 5 Median (IQR) opioid dose, MED: 135 (90 to 180) vs. 75 (60 to 142.5); p>0.1 Median (IQR) MPI pain severity: 50.6 (45.3 to 55.9) vs. 53.3 (47.9 to 61.2) Mean CES-D: 31 (24 to 37) vs. 30 (17 to 25)	A. Varenicline (n=10) B. Placebo (n=11)	A vs. B Median (IQR) duration of opioid taper, days: 18 (14 to 19) vs. 15 (14 to 17) Median (IQR) MPI dismissal: 34.6 (24 to 53.3) vs. 41.3 (34.0 to 43.9) Median (IQR) change from baseline MPI: 16.0 (2.7 to 21.3) vs. 12.0 (6.6 to 23.3), between group p=NS Median (IQR) CES dismissal: 10.0 (6.0 to 14.0) vs. 12.0 (9.0 to 16.0) change: 21(10 to 32) vs. 18(0 to 28), p=NS Median (IQR) value of regression coefficient withdrawal symptoms: -0.116 (-0.248 to 0.025) vs. 0.086 (-0.264 to 0.332), p=0.258	Fair
Tennant, 1982[211] Non-randomized clinical trial 3 to 18 months	Patients on opioids who volunteered for outpatient treatment for withdrawing opioids A vs. B Mean age, years: 33 vs. 44 Female: 48% vs. 52% Nonwhite race: 19% vs. 14% Duration of opioid use, years: 7.2 vs. 9.2 Proportion with chronic pain: 62% vs. 71% Back/spine disorder: 24% vs. 19% Use of codeine: 67% vs. 48%	A. Detoxification/ counseling (n=21) B. Detoxification/ maintenance (n=21)	A vs. B Proportion remaining in treatment past 3 weeks: 24% (5/21) vs. 95% (20/21) Abstinent after 90 days: 10% (2/21) vs. 19% (4/21)	Poor

Abbreviations: BMI=body mass index; CES=Centers for Epidemiologic Studies; CES-D=Centers for Epidemiologic Studies-Depression scale; IQR=interquartile range; MED=morphine equivalent dose; MPI=Multidimensional Pain Inventory; NS=not significant.

Key Question 3k. In patients with chronic pain, what is the comparative effectiveness of different opioid dosages and durations of therapy for outcomes related to pain, function, and quality of life?

Key Points

- In head-to-head trials, opioid doses of 50 to 90 mg MED/day were associated with a minimally greater (below the threshold for small) improvement in mean pain intensity versus doses less than 50 mg MED/day (5 trials, N=2625, mean difference -0.26, 95% CI -0.57 to -0.02, I^2=38%); there was no difference in mean improvement in function. Analyses of placebo-controlled trials also found an interaction (p=0.009) between higher opioid dose and greater improvement in mean pain intensity, with some evidence of a plateauing effect at 50 mg or greater MED/day (SOE: moderate).
- In analyses of placebo-controlled trials, effects on mean improvement in pain were larger at 1 to 3 months (65 trials, N=17,373, mean difference -0.83 on a 0 to 10 scale, 95% CI -0.96 to -0.70, I^2=69%) than at 3 to 6 months (8 trials, N=2243, mean difference -0.30, 95% CI -0.83 to 0.23, I^2=78%); similar patterns were observed for likelihood of pain response and mean improvement in function (SOE: low).

Description of Included Studies

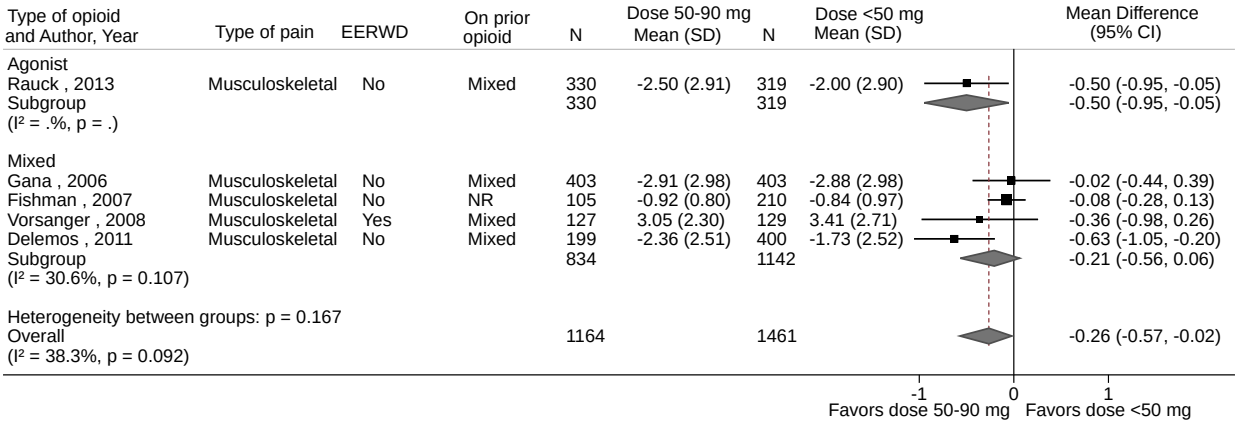
Seven trials directly compared effects of different opioid doses.[62,63,66,86,96,117,214] Sample sizes ranged from 81 to 815 (total N=3091). None of the trials were included in the 2014 AHRQ report, which was restricted to trials with 1 year or more followup. The duration of followup was 6 months or less in all trials; two trials followed patients for less than 3 months and five trials followed patients for 3 to 6 months. The opioid was tramadol sustained release (SR) in four trials,[62,63,66,117] oxymorphone SR in one trial,[86] hydromorphone SR in one trial,[96] and levorphanol in one trial.[214] The opioid type was a pure opioid agonist in three trials and mixed agent (tramadol) in four trials. The lowest opioid dose in the opioid dose comparisons ranged from 20 mg to 122.8 mg MED/day and the highest opioid dose ranged from 60 to 240 MED/day. All trials were conducted in the United States or Canada. The pain type was musculoskeletal in all trials. The duration of pain ranged from greater than 5 to 8 years and the proportion of female participants ranged from 50 to 64 percent. Baseline pain ranged from 2.0 to 7.5 on a 0 to 10 scale. All trials excluded patients with a history of opioid or substance use disorder or mental health comorbidities or did not describe eligibility status based on these factors. Six trials enrolled mixed populations of opioid-naïve and experienced patients; one trial did not describe prior opioid experience.

Six trials were rated fair-quality and one trial poor-quality (Appendix Table G-1). Methodological shortcomings frequently present in the fair and poor-quality trials included unclear randomization, unclear allocation concealment, unclear reporting of blinding of outcome assessor, and high attrition, with high between-group differences in attrition. None of the trials used a crossover design and only one trial used an EERW design; the remainder used a parallel group non-EERW randomized trial design. All trials except one[214] reported industry funding.

Detailed Synthesis

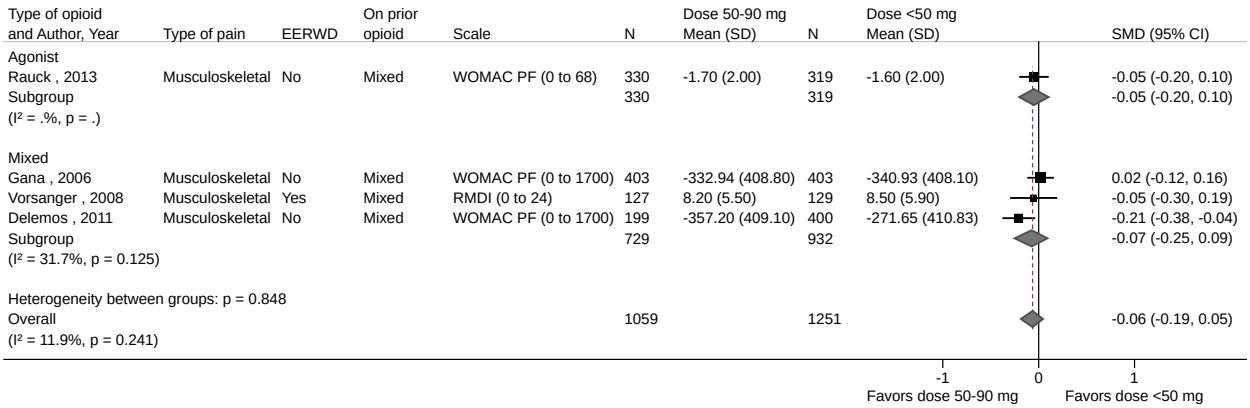
In trials that directly compared different opioid doses, 50 to 90 mg MED/day was associated with a mean improvement in pain versus less than 50 mg MED/day; however, the difference was below the threshold for a small effect (5 trials, N=2625, mean difference -0.26, 95% CI, -0.57 to -0.02, I^2=38%; Figure 62).[62,63,66,96,117] Four trials evaluated a mixed mechanism agent (N=1976, mean difference -0.21, 95% CI, -0.56 to 0.06, I^2=31%) and one trial evaluated an opioid agonist (N=649, mean difference -0.50, 95% CI, -0.95 to -0.05), with no statistically significant interaction with opioid type (p=0.17); all trials evaluated patients with musculoskeletal or mixed pain. In one trial[214] of greater than 90 mg versus less than 50 mg MED/day (n=81, mean difference -1.13, 95% CI, -2.25 to -0.01) and one trial[86] of greater than 90 mg versus 50 to 90 mg MED/day (n=365, mean difference -0.44, 95% CI, -0.96 to 0.08), effects on pain favored the higher dose, though the difference was only statistically significant in the first study. There was no difference between 50 to 90 mg versus less than 50 mg MED/day on mean improvement in function (4 trials, N=2310, SMD -0.06, 95% CI, -0.19 to 0.05, I^2=12%; Figure 63).[62,66,96,117] One trial found no difference between greater than 90 mg versus 50 to 90 mg MED/day in function (N=365, SMD -0.14, 95% CI, -0.36 to 0.07).[86]

Figure 62. Meta-analysis of improvement in mean pain measures for different opioid doses



Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; N=overall sample; NR=not reported; SD=standard deviation.

Figure 63. Meta-analysis of improvement in mean function measures for different opioid doses

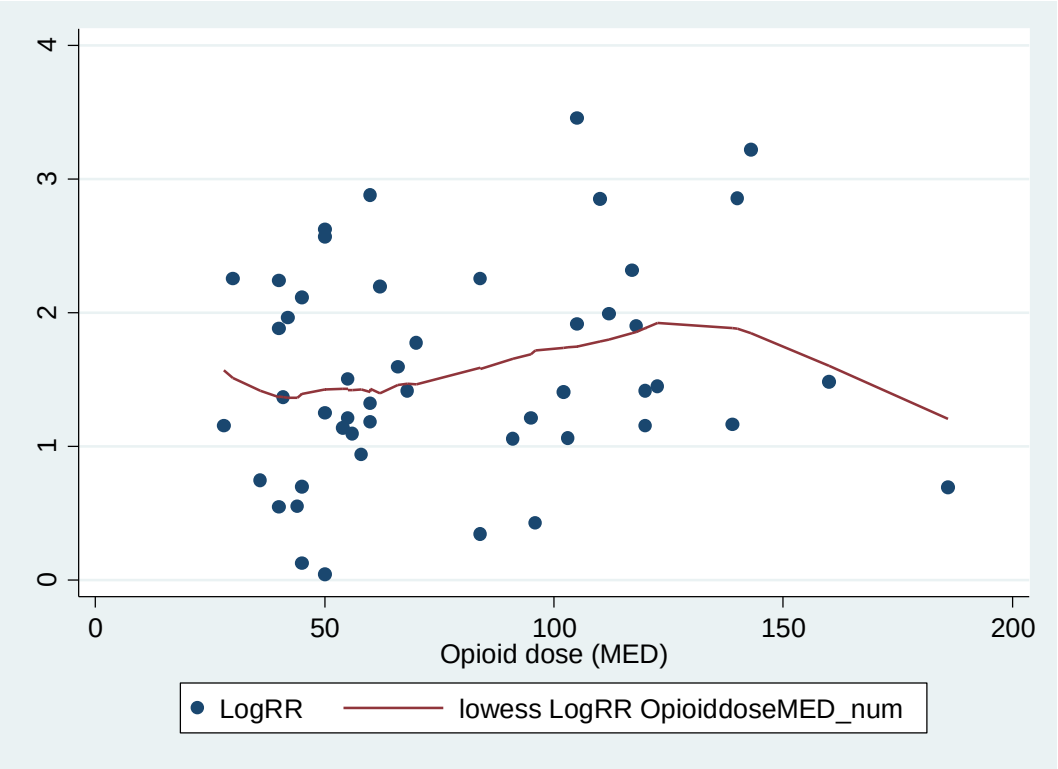


Abbreviations: CI=confidence interval; EERWD=enriched enrollment randomized withdrawal design; N=overall sample; NR=not reported; RMDI= Roland Morris Disability Index; SD=standard deviation; SMD=standardized mean difference; WOMAC PF=Western Ontario and McMaster Universities Osteoarthritis Index Physical Function.

A meta-regression of placebo-controlled trials (k=61) found no association between opioid dose (mean mg MED/day) and pain intensity (p=0.77; Figure 64). However, the effect size appeared to increase until approximately 60 mg MED/day before leveling off. There were no associations between increasing opioid dose and function or other effectiveness outcomes (Tables 3 and 7). When opioid dose was categorized as less than 50 mg, 50 to less than 90 mg, or 90 mg or more MED/day, there was an interaction (p=0.009) between higher dose category and mean improvement in pain, with some indication of a plateauing effect (Table 4). Versus placebo, the mean improvement was -0.48 on a 0 to 10 scale (14 trials, N=3748, 95% CI, -0.72 to -0.28, I^2=51%) at less than 50 mg MED/day, -1.07 (26 trials, N=6271, 95% CI, -1.32 to -0.85, I^2=61%) at 50 to less than 90 mg, and -0.73 (31 trials, N=9597, 95% CI, -0.91 to -0.55, I^2=71%) at more than 90 mg MED/day. However, for likelihood of achieving a pain response, risk estimates were similar across opioid dose categories with no interaction (RR estimates ranged from 1.31 to 1.46, p for interaction=0.57; Table 5).

In analyses of placebo-controlled trials, effects on mean improvement in pain were larger at 1 to 3 months (65 trials, N=17,373, mean difference -0.83 on a 0 to 10 scale, 95% CI, -0.96 to -0.70, I^2=69%) than at 3 to 6 months (8 trials, N=2243, mean difference -0.30, 95% CI, -0.83 to 0.23, I^2=78%), with a difference in pooled estimates of -0.53 point (Table 4). A similar pattern was observed for likelihood of a pain response (40 trials, N=11,076, RR 1.35, 95% CI, 1.24 to 1.48, I^2=78% at 1 to 3 months and 5 trials, N=1503, RR 1.19, 95% CI, 0.68 to 2.17, I^2=87% at 3 to 6 months; Table 5) and mean improvement in function (65 trials, N=17,373, SMD -0.38, 95% CI, -0.44 to -0.32, I^2=67% at 1 to 3 months and 8 trials, N=2243, SMD -0.13, 95% -0.35 to 0.09, I^2=74% at 3 to 6 months; Table 5).

Figure 64. Meta-regression of pain intensity by opioid dose



Abbreviations: logRR=log ratio of spatial densities; lowess = locally weighted scatterplot smoothing; MED=morphine equivalent dose

Key Question 4a. In patients with chronic pain being considered for opioid therapy, what is the accuracy of instruments and tests (including metabolic and/or genetic testing) for predicting risk of opioid use disorder, abuse, or misuse; and overdose?

Key Points

- Six studies (N=1,025; three fair-quality, three poor-quality) evaluated the Opioid Risk Tool (ORT); three studies were new. Estimates of diagnostic accuracy were very inconsistent. At a cutoff score of at least 4, sensitivity ranged from 0.20 to 0.99 (6 studies) and specificity ranged from 0.16 to 0.88 (4 studies) for predicting opioid misuse or abuse; the AUROC ranged from 0.53 to 0.74 in three studies (SOE: insufficient).
- Two studies (N=203) included in the 2014 AHRQ report evaluated the Screening and Opioid Assessment for Patients with Pain (SOAPP) Version 1 instrument. In one fair-quality study, sensitivity was 0.68 and specificity was 0.38 at a cutoff score of at least 8, for a positive likelihood ratio (PLR) of 1.11 and negative likelihood ratio (NLR) of 0.83 for predicting aberrant urine drug tests. One poor-quality study reported a sensitivity for predicting opioid discontinuation due to aberrant drug-related behavior of 0.73 at a cutoff score of greater than 6. (SOE: low)
- Four studies (N=840; two fair-quality, two poor-quality) evaluated the Screening and Opioid Assessment for Patients with Pain-Revised (SOAPP-R); three studies were new.

At a cutoff score of at least 18, sensitivity ranged from 0.25 to 0.53 and specificity ranged from 0.62 to 0.77 for predicting aberrant drug-related behaviors (4 studies). The AUROC ranged from 0.52 to 0.55 (3 studies). (SOE: low)

- Evidence was insufficient from one poor-quality study (n=48) included in the 2014 AHRQ report to evaluate the diagnostic accuracy of the Diagnosis, Intractability, Risk and Efficacy Inventory (DIRE) instrument. (SOE: insufficient)
- One fair-quality study (n=263) included in the 2014 AHRQ report found the Pain Medication Questionnaire associated with a sensitivity of 0.34, specificity of 0.77, and AUROC of 0.57 for predicting opioid discontinuation due to abuse. (SOE: low)
- Three new studies (N=577; two poor-quality, one fair-quality) evaluated the Brief Risk Interview (BRI). A BRI high-risk assessment was associated with sensitivities that ranged from 0.73 to 0.83 and specificities that ranged from 0.43 to 0.88 for predicting opioid misuse or abuse, with AUROCs of 0.65 and 0.93 in two studies. (SOE: low)
- One new fair-quality study (N=257) evaluated the Brief Risk Questionnaire (BRQ). At a cutoff score of at least 3, sensitivity was 0.80, specificity 0.41, and the AUROC was 0.61. (SOE: low).

Description of Included Studies

Seven studies evaluated the accuracy of instruments administered prior to initiation of opioid therapy, for predicting risk of misuse or abuse of prescribed opioids (Tables 44 and 45; Appendix Tables G-5, H-41, and H-42).[215-221] Sample sizes ranged from 48 to 257 (total N=1228). Four studies[215,216,220,221] were included in the 2014 AHRQ report and three studies[217-219] were added for this update. Six studies (three new) evaluated the ORT,[216-221] one study the SOAPP Version 1,[215,220] four studies (three new) the SOAPP-R,[216-219] one study the DIRE Score,[220] three studies (all new) the BRI,[217-219] and one new study the BRQ.[219] The mean age of participants ranged from 43 to 55 years and the proportion female ranged from 33 to 67 percent. Back pain was the most common pain condition and neck pain the next most common condition, in studies that reported this information. All studies were conducted in U.S. pain clinics. The duration of followup was 6 months in four studies,[216-219] 12 months in one study,[221] a mean of 3.8 months in one study,[220] and was not reported in one study.[215] Opioid misuse or abuse was based on discontinuation of opioids due to abuse, an aberrant (indicating drug misuse or abuse) urine drug test, or documentation of various aberrant behaviors during followup (including a positive urine drug test). Four studies were prospective,[215,218,219,221] two studies were retrospective,[216,220] and in one study[217] it was unclear if the design was prospective or retrospective.

Four studies[215,216,219,221] were rated fair-quality and three studies[217,218,220] were rated poor-quality (Appendix Table G-5). Common shortcomings were use of methods for assessing opioid misuse or abuse that were not well-standardized or defined and not reporting assessment of drug behaviors blinded to results of the risk prediction instrument. The poor-quality studies did not evaluate a validation sample (i.e., only evaluated the same population used to develop the instrument),[217] only evaluated cases (persons with opioid misuse or abuse)[220], or did not clearly enroll a consecutive sample.[217,220] In one poor-quality study approximately 40 percent of the population evaluated for predictive accuracy were evaluated for but did not receive opioids, and there were data discrepancies in diagnostic accuracy estimates.[217]

Table 44. Studies of risk assessment instruments

Author Year, Quality	Population, N	Risk Assessment Instrument	Method of Administration	Reference Standard
Akbik, 2006[215] Fair	n=155 Mean age (SD): 43 years (9.6) Female sex: 33% Race: 86% White, other races not reported Pain: 39% back pain	SOAPP 0 to 56 scale; high risk ≥8	Self-report	Positive urine drug test
Jones, 2012[216] (Study 2) Fair	n=263 Mean age (SD): 48 years (13) Female sex: 56% Race: 96% White, other races not reported Pain: 45% low back pain, 21% arthritis or fibromyalgia, 14% joint pain, 10% pelvic or abdominal pain, 7% neck or upper back pain	ORT 0 to 25 scale; high risk ≥8 PMQ 0 to 104 scale; high risk ≥30 SOAPP-R 0 to 24 scale; high risk ≥18 Clinician assessment	Self-report (SOAPP-R, ORT, PMQ); clinician interview	Opioid discontinuation due to abuse
Moore, 2009[220] Poor	n=48 Mean age (SD): 44 years (11) Female sex: 60% Race not reported Pain not reported	SOAPP 0 to 56 scale; high risk ≥8 DIRE 7 to 21 scale; high-risk ≤13 ORT 0 to 26 scale; high risk ≥8 Clinician assessment	Self-report (SOAPP, DIRE, ORT); clinician interview	Opioid discontinuation due to abuse*
Webster, 2005[221] Fair	n=185 Mean age (SD): 44 years (13) Female sex: 58% Race not reported Pain: 45% back; 18% head; 16% neuropathic; 16% musculoskeletal; 5% visceral	ORT 0 to 25 scale; high risk ≥8	Self-report	Documentation in medical record of aberrant behavior during followup
Jones, 2013[217] Poor	n=196 Mean age (range): 50 years (22 to 91) Female sex: 58% Race not reported Pain: 60% back, 18% neck	BRI (interview given ratings from low risk to high risk) ORT 0 to 26 scale; high risk ≥8 SOAPP-R 0 to 24 scale; high risk ≥18	Self-report (ORT, SOAPP-R); clinician interview (BRI)	Documentation of aberrant behavior during followup
Jones, 2014[218] Poor	n=124 Mean age (range): not reported (19 to 85 years); 32% 40 to 49 years of age Female sex: 67% White: 80% Pain: 44% back, 26% neck, 13% headache	BRI (interview given 1 of 6 rating levels from low risk to high risk) ORT 0 to 26 scale; high risk ≥4 SOAPP-R 0 to 24 scale; high risk ≥18	Self-report (ORT, SOAPP-R); clinician interview (BRI)	Documentation of aberrant behavior during followup

Author Year, Quality	Population, N	Risk Assessment Instrument	Method of Administration	Reference Standard
Jones, 2015[219] Fair	n=257 Mean age (range): 55 years (21 to 82) Female sex: 49% White: 96% Pain: 43% back; 19% neck, 12% joint , 7% arm or leg, 4% abdominal	BRQ 0 to 24 scale; high risk ≥3 ORT 0 to 26 scale; high risk ≥4 SOAPP-R 0 to 24 scale; high risk ≥18 BRI (interview given 1 of 6 rating levels from low risk to high risk)	Self-report (BRQ, ORT, SOAPP-R); clinician interview (BRI)	Documentation of aberrant behavior during followup

*Retrospective study; only patients who had discontinued opioids due to aberrant drug-related behavior were included.

Abbreviations: BRI=Brief Risk Interview; BRQ= Brief Risk Questionnaire; DIRE=Diagnosis Intractability Risk and Efficacy Inventory; ORT=Opioid Risk Tool; PMQ=Pain Medication Questionnaire; SD=standard deviation; SOAPP=Screening and Opioid Assessment for Patients with Pain; SOAPP-R=Screening and Opioid Assessment for Patients with Pain-Revised.

Table 45. Predictive value of risk assessment instruments

Scale	Studies	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)	AUROC
DIRE	Moore, 2009[220]	Score <14: 0.17	Not calculable*	Not calculable*	Not calculable*	Not calculable*
ORT	Jones, 2012[216]	Score >4: 0.20 (0.15 to 0.27)	Score >4: 0.88 (0.82 to 0.93)	Score >4: 1.65 (0.78 to 3.51)	Score >4: 0.91 (0.78 to 1.06)	0.54
	Moore, 2009[220]	Score ≥4: 0.45	Not calculable*	Not calculable*	Not calculable*	Not calculable*
	Webster, 2005[221]	Score ≥4: 0.99 (0.92 to 0.99)	Score ≥4: 0.16 (95% CI, 0.10 to 0.24)	Score ≥4: 0.99 (0.92 to 0.999) Score 1 to 3: 0.08 (0.01 to 0.62) Score 4 to 7: 0.57 (0.44 to 0.74) Score ≥8: 14.34 (5.35 to 38)	Score ≥4: 0.16 (0.10 to 0.24)	NR
	Jones, 2013[217]	Score ≥4: 0.58† (NR)	Score ≥4: 0.54† (NR)	Score ≥4: 1.26	Score ≥4: 0.78	NR
	Jones, 2014[218]	Score ≥4: 0.75 (0.43 to 0.95)	Score ≥4: 0.86 (0.78 to 0.92)	Score ≥4: 5.25 (3.00 to 9.18)	Score ≥4: 0.29 (0.11 to 0.78)	0.74
	Jones, 2015[219]	Score ≥4: 0.32 (0.22 to 0.44)	Score ≥4: 0.82 (0.75 to 0.87)	Score ≥4: 1.76 (1.12 to 2.77)	Score ≥4: 0.83 (0.70 to 0.98)	0.57
PMQ	Jones, 2012[216]	Score ≥30: 0.34 (0.20 to 0.51)	Score ≥30: 0.77 (0.69 to 0.80)	Score ≥30: 1.46 (CI, 0.87 to 2.45)	Score ≥30: 0.86 (0.68 to 1.08)	0.57

Scale	Studies	Sensitivity (95% CI)	Specificity (95% CI)	Positive Likelihood Ratio (95% CI)	Negative Likelihood Ratio (95% CI)	AUROC
SOAPP-R	Jones, 2012[216]	Score ≥18: 0.39 (0.26 to 0.54)	Score ≥18: 0.69 (0.63 to 0.75)	Score ≥18: 1.27 (0.86 to 1.90)	Score ≥18: 0.88 (0.70 to 1.10)	0.54
	Jones, 2013[217]	Score >17: 0.53 (NR)	Score >17: 0.62 (NR)	High risk 1.39	High risk: 0.76	NR
	Jones, 2014[218]	Score >17: 0.25 (0.055 to 0.57)	Score >17: 0.73 (0.64 to 0.81)	Score >17: 0.93 (0.33 to 2.61)	Score >17: 1.02 (0.73 to 1.45)	0.52
	Jones, 2015[219]	Score >17: 0.33 (0.23 to 0.45)	Score >17: 0.77 (0.70 to 0.83)	Score >17: 1.44 (0.95 to 2.19)	Score >17: 0.87 (0.72 to 1.04)	0.55
SOAPP	Moore, 2009[220]	Score >6: 0.73 (NR)	Not calculable*	Not calculable*	Not calculable*	Not calculable
	Akbik, 2006[215]	Score ≥8: 0.68 (0.52 to 0.81)	Score ≥8: 0.38 (0.29 to 0.49)	Score ≥8: 1.11 (0.86 to 1.43)	Score ≥8: 0.83 (0.50 to 1.36)	NR
BRI	Jones, 2013[217]	High risk rating:‡ 0.73 (NR)	High risk rating:‡ 0.43 (NR)	High risk rating:‡ 1.28	High risk rating:‡ 0.63	NR
	Jones, 2014[218]	High risk rating: 0.83 (0.52 to 0.98)	High risk rating: 0.88 (0.81 to 0.94)	High risk rating: 7.18 (4.06 to 12.70)	High risk rating: 0.19 (0.05 to 0.67)	0.93
	Jones, 2015[219]	High risk rating: 0.79 (0.68 to 0.87)	High risk rating: 0.51 (0.44 to 0.59)	High risk rating: 1.61 (1.33 to 1.94)	High risk rating: 0.42 (0.26 to 0.66)	0.65
BRQ	Jones, 2015[219]	Score ≥3: 0.80 (0.69 to 0.88)	Score ≥3: 0.41 (0.34 to 0.49)	Score ≥3: 1.36 (1.15 to 1.61)	Score ≥3: 0.49 (0.30 to 0.79)	0.61

*Retrospective study; only patients who had discontinued opioids due to aberrant drug-related behavior were included.

†Sensitivity also reported as 0.48, specificity also reported as 0.57.

‡Medium to very high rating.

Abbreviations: AUROC=area under receiver operating characteristic curve; BRI=Brief Risk Interview; BRQ=Brief Risk Questionnaire; CI=confidence interval; DIRE=Diagnosis Intractability Risk and Efficacy Inventory; NR=not reported; ORT=Opioid Risk Tool; PMQ=Pain Medication Questionnaire; SOAPP=Screening and Opioid Assessment for Patients with Pain; SOAPP-R=Screening and Opioid Assessment for Patients with Pain-Revised.

Detailed Synthesis

Opioid Risk Tool (ORT)

The ORT is a 10-item, patient self-report instrument.[221] Scores range from 0 to 24, with higher scores indicating increased risk of opioid misuse or abuse. In the initial study reporting development and assessment of the ORT, low-risk was defined as a score of 3 or less (6% of low-risk patients had aberrant behaviors over 12 months followup), moderate risk as a score of 4 to 7 (28%), and high risk as 8 or higher (91%); positive likelihood ratios were 0.08 (95% CI, 0.01 to 0.62), 0.57 (95% CI, 0.44 to 0.74), and 14.34 (95% CI, 5.35 to 38), respectively (Table 45).[221]

Six studies (N=1,025; three fair-quality, three poor-quality), including the initial study described above, evaluated the accuracy of the ORT administered prior to initiation of opioid

therapy for predicting misuse or abuse.[216-221] Three studies[216,220,221] were included in the 2014 AHRQ report and three studies[217-219] were new. Estimates of diagnostic accuracy were very inconsistent. At a cutoff score of at least 4 (combining the moderate and high-risk categories), sensitivity ranged from 0.20 to 0.99 (6 studies)[216-221] and specificity ranged from 0.16 to 0.88 (5 studies).[216-219,221] Positive likelihood ratios ranged from 1.17 to 5.25 and negative likelihood ratios from 0.078 to 0.91. The AUROC ranged from 0.53 to 0.74 in three studies.[216,218,219] The highest sensitivity (0.99) and lowest specificity (0.19) were reported in the initial study reporting the ORT.[221] Inconsistency remained present when the initial study was excluded (sensitivity 0.20 to 0.75 and specificity 0.54 to 0.88),[216-220] when findings were restricted to the three fair-quality studies (sensitivity 0.20 to 0.99 and specificity 0.16 to 0.88),[216,219,221] or when findings were restricted to the three new studies (sensitivity 0.32 to 0.75 and specificity 0.54 to 0.86).[217-219]

Screening and Opioid Assessment for Patients with Pain (SOAPP) Version 1

The SOAPP Version 1 instrument is a 14-item, patient self-report instrument.[222] Scores range from 0 to 56, with higher scores indicating increased risk of opioid misuse or abuse. The initial study reporting the development and testing of the SOAPP Version 1 instrument evaluated patients already receiving long-term opioid therapy and did not meet inclusion criteria for this review; at a cutoff score of at least 8, it reported a sensitivity of 0.86 and specificity of 0.72 (Table 45).[222]

Two studies (N=203) included in the 2014 AHRQ report evaluated the accuracy of the SOAPP Version 1 instrument administered prior to initiation of opioid therapy for predicting misuse or abuse.[215,220] In one fair-quality study (n=155), sensitivity was 0.68 and specificity was 0.38 at a cutoff score of at least 8 for predicting a positive urine drug test, for a positive likelihood ratio of 1.11 and negative likelihood ratio of 0.83.[215] In a poor-quality study (n=48), sensitivity for predicting opioid discontinuation due to aberrant drug-related behavior was 0.73 based on a cutoff score of more than 6.[220] Other measures of diagnostic accuracy were not reported in this study and could not be calculated.

Screening and Opioid Assessment for Patients with Pain-Revised (SOAPP-R)

The SOAPP-R is a 24-item instrument, patient self-report instrument derived from the SOAPP Version 1 instrument.[222] It was designed to include more subtle and socially acceptable items for assessing risk of opioid misuse or abuse than the SOAPP Version 1. Scores on the SOAPP-R range from 0 to 96, with high-risk defined as a score of 18 or more. The initial study reporting the development and testing of the SOAPP-R evaluated patients already receiving opioid therapy and did not meet inclusion criteria for this review; it reported a sensitivity of 0.81 and specificity of 0.68 (Table 45).[222]

Four studies (N=840; two fair-quality, two poor-quality) evaluated the SOAPP-R instrument administered prior to initiation of opioid therapy for predicting opioid misuse or abuse.[216-219] One study[216] was included in the 2014 AHRQ report and three studies[217-219] are new. Sensitivity of the SOAPP-R ranged from 0.25 to 0.53 and specificity ranged from 0.62 to 0.77, for positive likelihood ratios that ranged from 0.93 to 1.39 and negative likelihood ratios that ranged from 0.76 to 1.02. The AUROC was reported in three studies[216,218,219] and ranged from 0.52 to 0.55. When findings were restricted to the three new studies, results were similar (sensitivity 0.25 to

0.53 and specificity 0.62 to 0.77).[217-219] In the two fair-quality studies, sensitivities were 0.33 and 0.39, specificities were 0.69 and 0.77, and the AUROCs were 0.54 and 0.55.[216,219]

Four studies directly compared the predictive accuracy of the SOAPP-R and the ORT.[216-219] There was no consistent pattern indicating higher accuracy with one instrument compared with the other. AUROC estimates were very similar in two studies[216,219] and the ORT was associated with a higher AUROC than the SOAPP-R in a third study[218] (0.74 vs. 0.52). One study which did not report the AUROC found a slightly higher sensitivity with the ORT than the SOAPP-R (0.58 vs. 0.54) but a slightly lower specificity (0.54 vs. 0.62).[217]

Diagnosis, Intractability, Risk and Efficacy Inventory (DIRE) Score

The DIRE Score is a 7-item clinician-rated instrument.[223] It was originally designed to predict effective pain relief and compliance with long-term opioid therapy and not as a measure specifically to predict misuse or abuse. DIRE scores range from 7 to 21, with lower scores indicating unsuitable candidates for opioid therapy (cutoff score ≤13). The DIRE Score was evaluated in one poor-quality study (n=48) included the 2014 AHRQ report.[220] It found a sensitivity of 0.17 for predicting opioid discontinuation due to abuse; other measures of diagnostic accuracy were not reported and could not be calculated (Table 45). In this study, the accuracy of the DIRE score was lower than the ORT (0.45) or the SOAPP Version 1 instrument (0.73).

Pain Medication Questionnaire (PMQ)

The PMQ is a 26-item patient self-report instrument.[224] Scores range from 0 to 104, with higher scores indicating higher risk of opioid misuse or abuse. The PMQ was evaluated in one fair-quality study (n=263) included in the 2014 AHRQ report.[216] At a cutoff score of greater than 30, sensitivity was 0.34 and specificity 0.77 for predicting opioid discontinuation due to abuse, for a positive likelihood ratio of 1.46 and negative likelihood ratio of 0.86 (Table 45). In this study, the AUROC estimates were similar for the PMQ (0.57) the ORT (0.53) and the SOAPP-R (0.57).

Brief Risk Interview (BRI)

The BRI is a standardized, brief (6 to 12 minute) interview that involves ratings in 12 domains.[217] Patients are assigned one of six risk categories, ranging from low to very high. Three studies (N=577, two poor-quality and one fair-quality) evaluated the accuracy of the BRI for predicting opioid misuse or abuse.[217-219] None of the studies were included in the 2014 AHRQ report. Being classified as high-risk (defined as a medium, medium high, high, or very high BRI assessment) was associated with a sensitivity of 0.73 to 0.79 and specificity of 0.43 to 0.88, for positive likelihood ratio that ranged from 1.28 to 7.18 and negative likelihood ratios that ranged from 0.19 to 0.63. The AUROC was 0.65 and 0.93 in two studies (Table 45).[218,219] In one fair-quality study, the sensitivity was 0.79, the specificity was 0.51, and the AUROC was 0.65.[219]

All three studies directly compared the BRI with the ORT and SOAPP-R. Findings were somewhat inconsistent. In one study, the BRI (0.93) was associated with a substantially higher AUROC than with the ORT (0.74) or SOAPP-R (0.52).[218] In another study, the BRI was associated with a higher AUROC than the ORT or SOAPP-R, but the difference was smaller (0.65 vs. 0.57 vs. 0.55, respectively).[219] In the third study, the BRI was associated with higher sensitivity but lower specificity than the ORT or SOAPP-R; the AUROC was not reported.[217]

Brief Risk Questionnaire (BRQ)

The BRQ is a 12-item patient self-report instrument derived from the BRI.[219] Scores on the BRQ range from 0 to 24, with high-risk defined as a score of 3 or more. One new, fair-quality study (n=257) evaluated the accuracy of the BRQ for predicting opioid misuse or abuse.[219] Sensitivity was 0.80, specificity was 0.41, for a positive likelihood ratio or 1.35 and negative likelihood ratio of 0.49. In this study, the AUROC for the BRQ was slightly higher (0.61) than for the ORT (0.57) or SOAPP-R (0.55), but the statistical significance of this finding was not reported (Table 45).

Key Question 4b. In patients with chronic pain, what is the effectiveness of use of risk prediction instruments and tests (including metabolic and/or genetic testing) on outcomes related to opioid use disorder, abuse, or misuse, and overdose?

No study evaluated the effectiveness of risk prediction instruments compared to not using a risk prediction instrument for reducing outcomes related to overdose, addiction, abuse, or misuse (SOE: insufficient).

Key Question 4c. In patients with chronic pain who are prescribed opioid therapy, what is the effectiveness of risk mitigation strategies, including (1) opioid management plans, (2) patient education, (3) urine drug screening, (4) use of prescription drug monitoring program data, (5) use of monitoring instruments, (6) more frequent monitoring intervals, (7) pill counts, (8) use of abuse-deterrent formulations, (9) consultation with mental health providers when mental health conditions are present, (10) avoidance of co-prescribing of sedative hypnotics, and (11) co-prescribing of naloxone on outcomes related to opioid use disorder, abuse, or misuse, and overdose?

Key Points

- One cohort study found co-prescription of naloxone in patients prescribed opioids for chronic pain associated with no difference between no naloxone in all-cause mortality (2.5% vs. 3.3%, RR 0.77, 95% CI, 0.45 to 1.31) or opioid poisoning deaths (0.3% vs. 0.2%, RR 1.08, 95% CI, 0.18 to 6.4), though naloxone co-prescription was associated with decreased risk of ED visits (at 1 year, IRR 0.37, 95% CI, 0.22 to 0.64) followup (SOE: low).
- No study evaluated the effectiveness of other risk mitigation strategies versus non-use of the risk mitigation strategy for improving outcomes related to misuse, opioid use disorder, and overdose.

Detailed Synthesis

One new fair-quality cohort study (n=1,985) compared co-prescription of naloxone in persons prescribed opioids for chronic pain in primary care clinics versus no naloxone[225] co-prescription (Appendix Table G-2 and H-43). The median dose of opioids prescribed was 53 mg MED/day (range 2 to 4200). Naloxone co-prescription was associated with a decreased risk of

emergency department visits per additional month (IRR 0.94, 95% CI, 0.89 to 0.998); these effects corresponded to a 47 percent reduction at 6 months (IRR 0.53, 95% CI, 0.34 to 0.83) and a 63 percent reduction at 1 year (IRR 0.37, 95% CI, 0.22 to 0.64). Analyses adjusted for age, race/ethnicity, sex, opioid dose at baseline, and history of opioid-related emergency department visits. There was no difference between naloxone co-prescription versus no co-prescription in all-cause mortality (2.5% vs. 3.3%, RR 0.77, 95% CI, 0.45 to 1.31) or opioid poisoning deaths (0.3% vs. 0.2%, RR 1.08, 95% CI, 0.18 to 6.4).

No study evaluated the effectiveness of other risk mitigation strategies versus non-use of the risk mitigation strategy for improving outcomes related to misuse, opioid use disorder, and overdose.

Key Question 4d. In patients with chronic pain, what is the comparative effectiveness of treatment strategies for managing patients with opioid use disorder related to prescription opioids on outcomes related to pain, function, quality of life, opioid use disorder, abuse, misuse, and overdose?

Key Points

- A trial of patients with prescription opioid dependence not receiving opioids for a pain diagnosis found buprenorphine taper associated with a lower percentage of negative urine samples (35.2% vs. 53.2%), more days per week of illicit opioid use (1.27 vs. 0.47), and higher risk of relapse (28% vs. 5%) versus buprenorphine maintenance (SOE: low).
- A trial of patients with opioid dependence due to prescription opioids for chronic pain found no difference between methadone versus buprenorphine/naloxone in likelihood of study retention, pain, or function; there were also no differences in likelihood of a positive urine drug test for unprescribed opioids, cocaine, or other illicit drugs, though patients randomized to methadone were less likely to self-report opioid use (SOE: low).

Detailed Synthesis

The 2014 AHRQ report included no trials on the effectiveness of treatment strategies for managing patients with opioid use disorder or dependence related to prescription opioids. Three trials (N=179) not included in the 2014 AHRQ report evaluated effects of different treatment strategies in patients with opioid use disorder related to prescription opioids[192,208,226] (Appendix Table G-1, H-44, and H-45). Two trials compared buprenorphine maintenance versus taper, but one trial[226] excluded patients receiving opioids for pain and the other was a small trial[208] that was terminated early due to high crossover, without reporting of planned outcomes. The third trial compared methadone versus buprenorphine/naloxone in patients prescribed opioids for chronic noncancer pain; less than half of patients reported use of opioids at baseline.[192]

A fair-quality RCT (n=113) compared buprenorphine taper versus buprenorphine maintenance therapy among patients with prescription opioid dependence (based on criteria in Diagnostic and Statistical Manual of Mental Disorders – Fourth Version – Text Revision [DSM-IV-TR]).[226] Patients who "required" opioids for a pain diagnosis were excluded and the proportion of patients with chronic pain or prescribed opioids for chronic pain in the past was not reported. The buprenorphine taper was initiated after 6 weeks of stabilization (target dose 16 mg/day), lasted for 3 weeks, and included medications for opioid withdrawal; after completion of the taper patients were offered naltrexone treatment. The mean buprenorphine dose during the

induction and stabilization phase was 15 mg/day and did not differ between groups. Patients were excluded if they had a history of heroin dependence or injection drug use, used heroin as the primary opioid in the last 3 months, or had undergone methadone maintenance treatment. Buprenorphine taper was associated with a lower percentage of urine samples negative for opioids versus maintenance (35.2%, 95% CI, 26.2% to 44.2% vs. 53.2%, 95% CI, 44.3% to 62.05%), more days per week of illicit opioid use once they were no longer receiving buprenorphine (mean 1.27, 95% CI, 0.60 to 1.94 vs. 0.47, 95% CI, 0.19 to 0.74 during last 7 weeks of trial), and fewer maximum consecutive weeks of opioid abstinence (mean 2.70, 95% CI, 1.72 to 3.75 vs. 5.20, 95% CI, 4.16 to 6.20). Patients in the taper group were also more likely to have relapse with protective transfer (28% vs. 5%, p=0.001) and were less likely to complete the trial (11% vs. 66%, p<0.001).

One small (n=12) poor-quality trial performed buprenorphine induction in patients prescribed opioids for chronic noncancer pain with opioid use disorder (based on self-report and confirmed with a checklist based on DSM-IV), followed by randomization to buprenorphine taper versus maintenance.[208] The trial was terminated early without reporting of planned outcomes because all patients randomized to the taper arm switched to maintenance or experienced a relapse; five of six patients in the maintenance arm completed the trial.

One fair-quality RCT (n=54) compared methadone versus buprenorphine/naloxone in patients with opioid dependence due to prescription opioids[192] for chronic noncancer pain. Opioid dependence was defined as a Drug Abuse Screening Test Score greater than 4 and meeting DSM-IV-TR criteria for opioid dependence. Although all patients met criteria for opioid dependence, only 21 out of 54 reported use of opioids at the baseline visit (mean opioid dose not reported). Baseline pain was 6.4 and baseline function 5.0 (both measured on a 0 to 10 scale). Methadone was titrated to 20 to 60 mg/day and buprenorphine/naloxone to up to 16/4 mg/day. There was no difference between methadone versus buprenorphine/naloxone versus methadone in likelihood of retention in study (OR 0.93, 95% CI, 0.32 to 2.69), pain (percent change from baseline 88.6% vs. 87.45%, p=0.92), or function. Patients randomized to methadone were less likely to self-report other opioid use; however, there were no differences in likelihood of a urine drug test positive for unprescribed opioids, cocaine, or other drugs; or in self-reported use of alcohol or other drugs. There was no difference in risk of self-reported side effects (69.2% vs. 61.5%, OR 1.12, 95% CI, 0.21 to 6.05); the trial did not report overdose episodes.

Contextual Question 1. What are clinician and patient values and preferences related to opioids and medication risks, benefits, and use?

A contextual review conducted for the 2016 CDC guideline found data indicating that that physicians frequently lack confidence in their ability to prescribe opioids safely,[227] to predict[228] or identify [229]prescription medication misuse or opioid use disorder, and to discuss these issues with their patients.[229,230] Clinicians reported favorable beliefs and attitudes about effects of opioids on pain and quality of life; however,[231] most considered prescription opioid use disorder to be a significant problem, with many concerned about risks of opioid use disorder and overdose mortality. The contextual review also found evidence that clinicians do not consistently utilize risk mitigation strategies such as review of prescription drug monitoring program (PDMPs) data,[232,233] urine drug testing,[234] and opioid treatment agreements;[235] administrative and logistical barriers were noted.[236]

The contextual review found limited evidence on patient values and preferences regarding opioids for chronic pain. One study found that patients are unfamiliar with the term “opioids” but

more familiar with "narcotics." Patients associated the term "narcotics" with "addiction" or "abuse," and about half feared "addiction" from long-term "narcotic" use.[237] There was evidence that most patients experienced side effects with opioids, with side effects rather than pain relief accounting for most of the variation in patient preferences regarding use of opioids.[238] One study found that patients with chronic pain emphasized effectiveness of goal setting for increasing motivation and functioning.[237] Patients on higher doses reported reliance on opioids despite ambivalence about their benefits;[239] reliance was not dependent on the degree of pain reduction, reported problems, concerns, side effects, or perceived helpfulness.[240]

Some new information on physician and patient preferences and values regarding opioid prescribing is available. A survey of 961 clinicians found that 82 percent were reluctant to prescribe opioids and 47 percent expressed confidence in their care of chronic noncancer pain patients.[241] Sixty-seven percent were aware of the Centers for Disease Control and Prevention (CDC) guideline and 55 percent were enrolled in the state Prescription Drug Monitoring Program; only 2 percent always or frequently prescribed naloxone to patients on opioids. Guideline awareness was associated with increased confidence in caring for chronic noncancer pain patients and knowledge of a patient overdose event was associated with increased likelihood of expressing concern about patient opioid dependence and addiction. A national, web-based survey of primary care clinicians (n=1010) regarding prescription opioid use disorder found beliefs that individuals with this condition and physicians were primarily responsible for addressing this issue.[242] Although the survey indicated negative attitudes towards people with prescription opioid use disorder, most clinicians believed treatment could be effective. Support of policies was highest for policies to monitor prescribing among patients potentially at risk for an opioid use disorder and to improve physician education and training. A survey of providers in a multispecialty medical practice found that clinicians highly concerned about opioid misuse, addiction, and physiological dependence were more confident prescribing opioids but more reluctant to prescribe.[243] Such providers were more likely to report screening for substance use disorders and discontinuation of opioid prescribing due to aberrant opioid use disorders, and less likely to prescribe opioids and benzodiazepines concurrently. Highly concerned clinicians were more likely to work in clinics that engaged in "best practices" regarding urine drug screening, prescription drug monitoring program review, and opioid medication agreements. A survey of physicians in Maryland regarding PDMPs found that most participants felt that PDMPs improved opioid prescribing by decreasing opioid prescription amounts and increasing comfort with prescribing opioids.[244] Barriers towards PDMP review were noted, including not knowing about the program, registration difficulties, and difficulty accessing data.

There were also some new data on patient values and preferences. A systematic review published subsequent to the 2016 CDC review summarized evidence on patient values and preferences regarding outcomes associated with opioids for chronic noncancer pain.[245] It found that patients rank pain relief, nausea, and vomiting as highly significant outcomes. Personality changes were also ranked highly when considered as an outcome, and constipation ranked just below pain, nausea, and vomiting. Addiction was only evaluated in two studies and rated as less important than pain relief. No study in the systematic review evaluated preferences regarding opioid overdose, death, or diversion. An online survey of over 3000 patients 1 year after the release of the CDC guideline found that 84 percent reported more pain and worse quality of life and 42 percent said they had considered suicide; however, the study did not attempt to sample chronic pain patients scientifically.[246] No peer-reviewed study on patient preferences regarding the 2016 CDC guideline was identified.

Contextual Question 2. What are the costs and cost-effectiveness of opioid therapy and risk mitigation strategies?

A contextual review conducted for the 2016 CDC guideline estimated (based on studies published after 2010) yearly direct and indirect costs related to prescription opioidsat $53.4 billion for nonmedical use of prescription opioids;[247] $55.7 billion for abuse, dependence (i.e., opioid use disorder), and misuse of prescription opioids;[248] and $20.4 billion for opioid-related overdoses.[249] In 2012, total expenses for outpatient prescription opioids were estimated at $9.0 billion, an increase of 120 percent from 2002.[250] The contextual review also included an analysis of 2008 claims data from a national sample representing over 16 million lives on annual costs of pharmacological and nonpharmacological treatments for osteoarthritis and low back pain, two of the most common chronic pain conditions.[251] In patients with osteoarthritis, direct annual mean costs of opioids ($287.4 [SD $1,652.1]) were higher than costs for acetaminophen ($84.4 [standard deviation {SD} 207.8]), non-cyclooxygenase-2 selective non-steroidal anti-inflammatory drugs ($119.3 [SD 212.3]), and topical capsaicin ($3.8 [SD 4.7]) but lower than serotonin norepinephrine reuptake inhibitors ($1,157.7 [SD 924.1]) or transdermal lidocaine ($563.2 [SD 720.6]). Costs of opioids were lower than massage therapy ($183.2 [SD 900.3]) and heat/cold application ($121.7 [SDS 382.3]) but higher than other nonpharmacological therapies such as cognitive behavioral therapy, chiropractic care, biofeedback, acupuncture, and physical therapy (range $318.7 to $1037.4). However, this analysis was not designed to assess the costs of alternative treatments relative to effectiveness. The contextual review found limited information on costs of strategies to reduce risks associated with prescription opioids. One study included in the CDC contextual review estimated costs of urine drug testing (including screening and confirmatory tests) at $211 to $363 per test.[252]

An analysis not included in the CDC contextual review estimated the total economic burden of fatal overdose, abuse, and dependence of prescription opioids in 2013 at $78.5 billion, with $28.9 billion related to increased healthcare and substance abuse treatment costs.[253] More recent data indicate that spending on opioid prescriptions peaked at $1,567 million in 2009, with a decrease to $1,222 million in 2016.[254] However, costs of treatment for opioid addiction and overdose increased ($646 million in 2009 and $2,628 million in 2016). Data also indicate that Medicaid spending on opioids has declined since 2014, though spending on buprenorphine has increased.[255]

No study formally evaluated the cost-effectiveness of opioid therapy versus no opioid therapy or nonopioid pharmacological therapy for noncancer pain. A modeling study that estimated 80 percent of opioid overdose deaths attributable to illicit opioids projected that interventions targeting prescription opioid misuse such as prescription monitoring programs would decrease the number of opioid overdose deaths by 3.0 percent to 5.3 percent, indicating the importance of efforts to address illicit opioid use.[256] However, it did not perform a cost-effectiveness analysis of different intervention strategies. There were also no cost-effectiveness analyses of risk mitigation strategies in persons prescribed opioids for chronic pain; a challenge to conducting such analyses is the lack of evidence evaluating effectiveness of such strategies. A systematic review that included 43 economic evaluation studies of treatments for opioid use disorder found evidence supporting the cost-effectiveness of methadone maintenance therapy, with less evidence for other opioid use disorder therapies.[257] A recent U.K. analysis found buprenorphine and methadone maintenance therapy both to be highly cost-effective[258] and another analysis found immediate access to opioid agonist maintenance treatment in California publicly funded drug treatment facilities to be cost saving compared with other strategies.[259]

Discussion

Key Findings and Strength of Evidence

The key findings of this review are summarized in Tables 46 and 47 and the summary of evidence table (Appendix I). This review updates findings from the 2014 Agency for Healthcare Researchand Quality (AHRQ) report on long-term benefits and harms of opioids for chronic noncancer pain, alternative opioid dosing strategies, risk mitigation strategies, and management of prescription opioid use disorder. It also expands upon the 2014 AHRQ report by adding evidence from randomized trials reporting short-term outcomes, including tramadol as an opioid intervention, addressing risks of co-prescribing benzodiazepines and gabapentin, and addressing effects of co-use of cannabis.

Table 46. Efficacy of opioid treatments for chronic pain: function and pain outcomes

	Function Short Term	**Function Intermediate Term**	**Function Long Term**	**Pain Short Term**	**Pain Intermediate Term**	**Pain Long Term**
Intervention A Versus B	Effect Size SOE	Effect Size SOE	Effect Size SOE	Effect size SOE	Effect Size SOE	Effect Size SOE
Opioids vs. placebo	Small +++	No evidence	No evidence	Small +++	No evidence	No evidence
Opioids vs. nonopioids	None ++	No evidence	None ++	None ++	No evidence	None ++
Opioid + nonopioid vs. nonopioid	None +	No evidence	No evidence	None ++	No evidence	No evidence
Opioid + nonopioid vs. opioid alone	None +	No evidence	No evidence	None* ++	No evidence	No evidence

Effect size: None or small, moderate, or large favoring intervention A

SOE: + = low, ++ = moderate, +++ = high

* The effect was statistically significant but below the threshold for small

Abbreviations: SOE=strength of evidence.

Table 47. Adverse effects of opioid treatments for chronic pain

Intervention A Versus B	Discontinuation Due to AEs Effect Size SOE	Serious AEs Effect Size SOE	Nausea Effect Size SOE	Vomiting Effect Size SOE	Constipation Effect Size SOE	Dizziness Effect Size SOE	Headache Effect Size SOE	Somnolence Effect Size SOE	Pruritus Effect Size SOE
Opioids vs. placebo	Large +++	Small ++	Large +++	Large +++	Large +++	Large +++	None +++	High +++	High +++
Opioids vs. nonopioids	Moderate ++	Small ++	Moderate +++	Large +++	Large +++	NSAID: Moderate ++ Gabapentinoid: Low None Nortriptyline: Moderate +	Small +++	Moderate +++	High +++
Opioid + nonopioid vs. nonopioid	Moderate +	Insufficient evidence	Small +	Insufficient evidence	Large +*	Small +	None +	Moderate +*	Insufficient evidence
Opioid + nonopioid vs. opioid alone	None +	Insufficient evidence	None +	Small +	None +	Small +	None +	None +	None +

Effect size: None or small, moderate, or large increase in risk for intervention A

SOE: + = low, ++ = moderate, +++ = high

Abbreviations: AE=adverse effects; NSAID=non-steroidal antiinflammatory drug; SOE=strength of evidence.

*There was a statistically significant interaction with trial quality and effects were statistically significant when a poor-quality trial was excluded

For short-term outcomes, data were available from over 70 placebo-controlled trials of opioids. All trials were 6 months in duration or less, with most (87.5%) trials 3 months or less. Opioids were associated with beneficial effects versus placebo, but mean differences were small: for pain, less than 1 point on a 0 to 10 scale and for function, an standardized mean difference (SMD) of 0.22 (or <1 point on the 0 to 10 Brief Pain Inventory [BPI] interference scale and <1 point on the 0 to 24 Roland-Morris Disability Questionnaire [RDQ]). Although these are less than proposed minimum clinically important differences,[32] assessing mean differences (MDs) may obscure larger benefits experienced by some patients, since effects are averaged with patients who experience no benefit.[260,261] Some differences were statistically significant but below the pre-defined threshold for small (<0.5 on a 0 to 10 scale or an SMD <0.2); average effects in this range are unlikely to be clinically significant in most patients. Evaluating pain as a dichotomous outcome, opioids were associated with a number needed to treat of ~6.7 to achieve one additional case of short-term pain relief (e.g., ≥30% improvement in pain or at least moderate improvement). Very few trials evaluated dichotomous outcomes other than pain. Analyses indicate an association between higher opioid dose and greater short-term effects on pain, though effects appear to plateau at around 50 mg morphine equivalent dose (MED)/day and incremental benefits of doses greater than 50 mg MED/day were relatively small, ranging from 0.25 to 0.60 points on a 0 to 10 scale. There was also some evidence that effects of opioids dissipate with longer duration of therapy; for mean improvement in pain the effect was about 0.5 point less on a 0 to 10 scale at 3 to 6 months compared with at 1 to 3 months.

Effects of opioids versus placebo on short-term health status/quality of life, sleep quality, and mental health outcomes were reported less frequently than pain and function. Opioids were associated with a small mean improvement in short-term sleep quality versus placebo and might be associated with a small mean short-term improvement in Short-Form 36-item (SF-36) mental health status. Effects on SF-36 physical health status were below the threshold for small and there was no effect on mental health outcomes.

Effects of opioids on short-term outcomes were generally consistent across opioid types (opioid agonist, partial agonist, or mixed medication agent). For pain, effects were somewhat greater in trials of neuropathic than musculoskeletal pain, with an average difference of about 0.5 point on a 0 to 10 scale. Study methods also had some effect on findings, with use of a crossover design associated with larger effects for some outcomes. In addition, nearly half (42% [20/48]) of placebo-controlled trials published since 2007 used an enriched enrollment randomized withdrawal (EERW) design.[262] In an EERW designed study, patients are randomized to continuation of the opioids or discontinuation (placebo) following a run-in period to determine responsiveness to opioids and tolerability. Patients who do not respond to the study drug or who cannot tolerate it are excluded from randomization. Thus the EERW design enrolls patients who intentionally differ from unselected patients in chronic pain who are being considered for opioids. In addition, blinding may be ineffective in EERW designed trials because opioid discontinuation may result in withdrawal or cessation of opioid-related side effects. A previous review concluded that the EERW design does not appear to bias the results of efficacy for opioids but it underestimates the adverse effects.[263] In our analyses, the EERW design was associated with larger effects on pain than not using this design (difference ~0.30 point in trials published since 2007) and lower risk of discontinuation due to adverse events and gastrointestinal adverse events.

Opioids were associated with increased risk of short-term, bothersome harms versus placebo, including discontinuation due to adverse events (number needed to harm [NNH 10],

gastrointestinal events [NNH 7.1 for nausea, 14.3 for vomiting, and 7.1 for constipation], somnolence [NNH 11.1], dizziness [NNH 12.5], and pruritus [NNH 14.3]). There were few serious adverse events and no difference between opioids versus placebo in risk in the short-term trials, though serious adverse events were not well-defined by the trials. Randomized trials generally excluded patients with a history of substance use disorder and were not designed to assess effects of opioids on serious but less common harms such as overdose, addiction, mortality, cardiovascular events, and fractures. Although the 2014 AHRQ report included uncontrolled studies reporting rates of addiction, abuse or dependence in patients prescribed opioids, results were difficult to interpret due to the lack of a control group and wide variation in estimates, likely due to differences in patient populations and methods for defining and identifying these outcomes. Uncontrolled studies were not included in this update, though a recent systematic review that included such studies found that rates of misuse ranged from 21 to 29 percent (range, 95% confidence interval [CI], 13 to 38%) and rates of addiction ranged from 8 to 12 percent (range, 95% CI, 3 to 17%).[264]

Evidence on short-term outcomes does not address the practice of long-term use of opioids and associated benefits and harms. As in the 2014 AHRQ report, we identified no long-term (>1 year) randomized controlled trials (RCTs) of opioid therapy versus placebo. One new cohort study found no association between long-term opioid therapy versus no opioids and pain, function or other outcomes.[130] New observational studies were consistent with the 2014 AHRQ report in finding an association between use of prescription opioids and risk of addiction,[155] overdose,[155] fractures,[156,161,164] falls[161,165] and cardiovascular events;[166] a new study also found an association between opioid use and risk of all-cause mortality.[166] New observational studies were also consistent with the 2014 AHRQ report in finding associations between higher doses of opioids and risks of overdose, addiction, and endocrinological adverse events;[155,156,165,166,170,173] new studies also found an association between higher dose and increased risk of incident or refractory depression.[174,175] Effects of longer duration of opioid exposure varied across outcomes, from increasing risk (all-cause mortality, depression) to decreasing risk. Although three studies found an association between use of opioids and endocrinological adverse effects, interpreting results was a challenge because of use of a cross-sectional design, measurement of outcomes indirectly associated with endocrinological effects (e.g., use of medications for erectile dysfunction or testosterone replacement, or female reproductive dysfunction), or failure to measure baseline endocrinological status. Limited evidence indicated an association between co-prescription of gabapentinoids[179-181] or benzodiazepines[159,177,178] and increased risk of overdose, with most pronounced risk occurring soon after initiation of these medications. Although findings from observational studies are based on studies that controlled for potential confounders, all findings are susceptible to residual confounding. In addition, because most observational studies did not clearly restrict inclusion to patients with chronic pain who were prescribed long-term opioid therapy, we included studies that met at least one of these criteria; therefore, some studies could have included some patients with acute pain or exposed to a shorter duration of opioid therapy.

This update also expanded upon the 2014 AHRQ report by including short-term randomized trials that directly compared opioids versus nonopioids and combination therapy with an opioid plus nonopioid versus an opioid or nonopioid alone. There were no differences between opioids versus nonopioids in short-term pain, function, health status/quality of life, sleep quality, or mental health outcomes, though opioids were associated with increased risk of short-term adverse effects. The most commonly evaluated nonopioids were non-steroidal antiinflamattory

drugs (NSAIDS), gabapentinoids, and nortriptyline. Although there were no statistically significant interactions between nonopioid type and effects on pain or function, subgroup analyses by nonopioid type and opioid dose level were limited by small numbers of trials and analyses could have been underpowered to detect subgroup differences. One trial of patients with chronic low back pain or pain associated with osteoarthritis (mean pain intensity 5.4 on a 0 to 10 scale at baseline) evaluated outcomes at 1 year.[143] It found no differences between stepped therapy with opioids versus stepped therapy starting with nonopioids in function, sleep, or mental health outcomes; opioids were associated with slightly worse effects (by ~0.5 point on a 0 to 10 scale) on pain. Although tramadol was an option in step 3 of the nonopioid stepped therapy arm, only 11 percent received tramadol; mean opioid doses were 26 vs. 1 mg MED/day at 12 months.

There were also no differences between combination therapy versus a nonopioid alone in short-term effectiveness but increased risk of short-term adverse effects, though findings were based on only six trials. Combination therapy was associated with greater improvement in pain versus an opioid alone, but the difference was below the threshold for small (~0.4 point on a 0 to 10 scale); however, combination therapy was also associated with a small (5 to 13 mg MED/day) opioid-sparing effect. Estimates of effects on pain response and function were imprecise but favored combination therapy over opioid therapy alone. All trials of combination therapy evaluated patients with neuropathic pain and primarily evaluated gabapentinoids or nortriptyline, potentially limiting applicability of findings to other pain types and other nonopioids. Evidence on long-term effects of combination therapy versus an opioid or nonopioid alone, including effects on overdose risk and risks related to opioid use disorder, was lacking.

Evidence on the effectiveness of different opioid dosing strategies remains very limited. One trial included in the 2014 AHRQ report found no differences between a more liberal dose escalation strategy versus maintenance of current doses in pain, function, or discontinuation due to opioid misuse, but the liberal escalation strategy was associated with only a small difference in opioid doses (52 vs. 40 mg MED/day).[203] There were no clear differences between short- versus long-acting opioids or between different long-acting opioids in effects on pain or function, but in most trials doses were titrated to achieve adequate pain control. None of the head-to-head trials were designed to evaluate overdose, abuse, addiction, or related outcomes. Evidence on comparative risks of methadone versus other opioids remains limited and inconsistent in showing increased risk of outcomes related to overdose.[166,199,200] Factors that might explain the inconsistency in comparative risks of methadone include differences across the studies in the healthcare settings and populations evaluated. Evidence on benefits and harms of different methods for initiating and titrating opioids, scheduled and continuous versus as-needed dosing of opioids, use of opioid rotation, and methods for titrating or discontinuing patients off opioids remains unavailable or too limited to reach reliable conclusions. The 2014 AHRQ report found buccal or intranasal fentanyl more effective than placebo or oral opioids for treatment of exacerbations of chronic pain, based on immediate effects (up to 2 hours after administration). None of the trials of buccal or intranasal fentanyl were designed to assess long-term benefits or harms, including overdose, abuse, or addiction, and no new trials were identified for this update. In 2007, the U.S. Food and Drug Administration (FDA) released a public health advisory due to case reports of deaths and other life-threatening adverse effects in patients prescribed buccal fentanyl.[265]

New evidence on the accuracy of risk prediction instruments was consistent with the 2014 AHRQ report, which found highly inconsistent estimates of diagnostic accuracy, methodological

limitations and few studies of risk assessment instruments other than the Opioid Risk Tool and Screening and Opioid Assessment for Patients with Pain - Revised. Studies on the accuracy of risk instruments for identifying aberrant behavior in patients already prescribed opioids were not addressed in this review.

Evidence on the effectiveness of risk mitigation strategies also remains very limited. One new observational study found provision of naloxone to patients prescribed opioids in primary care clinics associated with decreased likelihood of emergency department visits, but no difference in risk of overdose.[225] Evidence of opioid tapering versus usual care was largely limited to a trial that found a taper support intervention associated with better functional outcomes and a trend towards lower opioid doses versus usual opioid care.[209] Two other trials of tapering versus usual care had small samples and reported high attrition and crossover from the tapering arm, resulting in early termination and inability to report planned outcomes.[149,208] Regarding alternative tapering methods, one small new trial found no difference between tapering with varenicline versus tapering with placebo in likelihood of opioid abstinence, pain, or depression.[212] A cohort study found discontinuation of opioid therapy associated with increased risk of overdose mortality versus continuation, but there was no statistically significant difference in risk of all-cause mortality.[210] It was not possible to determine a causal association between opioid discontinuation and overdose mortality because most patients had a safety reason for discontinuation, the study did not attempt to control for potential confounders other than age and race, most patients received opioids from another provider after discontinuation, and there was no information about time to discontinuation. Rather, the findings may indicate that patients with indications for opioid discontinuation are at high risk for opioid-related adverse events.

No trial compared different rates of opioid tapering, though one observational study found an association between longer time to opioid discontinuation in patients on long-term, high-dose opioid therapy and decreased risk of opioid-related emergency department visit or hospitalization. In this study, the median time to discontinuation was 1 day, indicating abrupt discontinuation without a taper in half of the patients; 86 percent of patients were discontinued within 21 days and 60 percent had a diagnosis of substance use disorder but were not referred for treatment.[213] The FDA recently issued a warning on not discontinuing long-term opioid therapy abruptly.[266] No study evaluated the effectiveness of risk mitigation strategies, such as use of risk assessment instruments, opioid management plans, patient education, urine drug screening, prescription drug monitoring program data review, monitoring instruments, more frequent monitoring intervals, pill counts, abuse-deterrent formulations, or avoidance of co-prescribing of benzodiazepines on risk of overdose, addiction, abuse or misuse.

Evidence on the effectiveness of interventions for opioid use disorder in patients with prescription opioid dependence or opioid use disorder was also limited and might have limited applicability to patients currently prescribed opioids for chronic pain. One trial found buprenorphine taper associated with lower likelihood of drug use compared with buprenorphine maintenance, but excluded patients receiving opioids for pain.[226] Another trial found no difference between methadone versus buprenorphine/naloxone in likelihood of study retention or likelihood of a positive urine drug test for non-prescribed opioids, but fewer than half of patients reported opioid use at baseline,[192] and another small trial was terminated early because all patients randomized to a buprenorphine taper switched to maintenance or had a relapse.[208]

Findings in Relation to What Is Already Known

Our findings regarding short-term effects of opioids are consistent with a recent systematic review by Busse et al that also found small effects on short-term pain and function, and increased risk of bothersome harms.[267] Our review differed from Busse et al by excluding trials of opioids plus nonopioids that did not include a comparison to opioids or nonopioids alone, inclusion of additional trials,[74,85,119,122,139,143-146,148] and evaluating likelihood of pain response based on data reported by the trials (rather than modeling response rates based on average effects). Unlike the review by Busse et al, our review found some evidence of an association between higher opioid dose and greater effects on pain in head-to-head trials; however, the observed difference was below the threshold for a small effect. Our findings regarding similar effects of opioid versus nonopioid therapy are consistent with a concurrent review that found nonopioid pharmacological therapies for chronic pain associated with similar small effects.[18] A systematic review of randomized trials that used an EERW design reported estimates that were consistent with the results reported in our subgroup analyses of such trials.[268]

Like our review, other systematic reviews of opioid therapy for chronic pain also found no long-term, placebo-controlled randomized trials.[267,269,270] Our findings are also consistent with an earlier systematic review on comparative benefits and harms of different long-acting opioids and short- versus long-acting opioids, which found no clear differences in outcomes, primarily based on short-term randomized trials.[271] Our findings are also consistent with a recent systematic review that found limited evidence and inconsistent estimates on the accuracy of instruments for predicting prescription opioid misuse or abuse.[272]

Several recent systematic reviews evaluated effects of risk mitigation strategies. Unlike our review, which found no evidence on effects of risk mitigation strategies on risk of abuse, addiction, or related outcomes, a review by Starrels et al found use of opioid management plans and urine drug screens to be associated with decreased risk of misuse behaviors.[273] However, this conclusion was based on studies that did not meet inclusion criteria for our review because effects of opioid management plans and urine drug screens could not be separated from other concurrent opioid prescribing interventions, use of a historical control group, or use of a before-after study design. Another systematic review found no clear effects of prescription drug monitoring programs on rates of overdose or substance use disorder, based primarily on studies evaluating policy-level interventions that were outside the scope of our review.[274] A systematic review of tapering found limited evidence that tapering or dose reductions may be associated with improved outcomes in patients prescribed opioids.[275] It included additional studies that did not meet criteria for our review, including case series and other uncontrolled studies and studies that did not evaluate a tapering intervention, but which reported opioid doses and discontinuations as an outcome.

Applicability

A number of issues could impact the applicability of our findings. Most randomized trials were conducted in pain clinics or unspecified settings, which might reduce applicability to primary care settings, where most opioids are prescribed. Patients typically had moderate pain, which might reduce applicability to patients with mild or severe pain; there was insufficient evidence to determine effects of baseline pain severity on outcomes. As noted previously, for some observational studies it was not always clear if all patients had chronic pain or were prescribed long-term opioid therapy. Although we inferred the presence of chronic pain based on

the duration of opioid therapy or use of long-acting opioids, inclusion of patients with acute pain cannot be excluded. Some potentially relevant studies were excluded because it was not possible to determine whether the sample evaluated had chronic pain or received long-term therapy. Analyses of placebo-controlled trials indicated no interaction between geographic setting and effects of opioids on various outcomes, suggesting applicability of trials conducted in different countries to U.S. practice.

Selection of patients could also impact applicability. Randomized trials typically excluded patients at high risk of opioid use disorder or with significant psychological and medical comorbidities; those such patients are commonly prescribed opioids in clinical practice.[274] In addition, over 40 percent of placebo-controlled trials published since 2007 utilized an EERW design. This method preselects patients who respond to and tolerate initial exposure to opioids, and patients who are randomized to opioid withdrawal may experience symptoms associated with withdrawal or recognize symptoms of opioid discontinuation, resulting in loss of blinding. Such patients intentionally differ from unselected patients presenting with pain, and the benefits observed in EERW designed trials might be greater and harms lower than seen in actual clinical practice.[270,276] Our analyses found interactions between use of an EERW design and greater effects on mean improvement in pain and lower risk of gastrointestinal harms.

Another factor impacting applicability is that randomized trials were designed to address short-term (<6 months) outcomes, as opioids are often prescribed for years or decades and given the physiological effects of tolerance likely to be impacted by characteristics of opioids such asphysiological tolerance. Further, shrot-term trials were not designed to evaluate important harms such as overdose, addiction, fracture, and others. Trials of buccal fentanyl for exacerbations of chronic pain focused exclusively on immediate (episode-based) outcomes and were not designed to assess long-term outcomes, including outcomes related to the potential for abuse.[48,204-207]

Implications for Clinical and Policy Decision Making

Our review has implications for clinical and policy decision making. Findings of this review, with expansion of scope to include short-term trials, support the recommendation in the 2016 Centers for Disease Control and Prevention (CDC) guideline[7] that opioids are not first-line therapy for chronic pain and to preferentially use nonopioid alternatives. This is based on only small short-term benefits of opioids versus placebo, increased risk of harms (including serious harms such as opioid use disorder and overdose) and similar benefits compared with nonopioid therapies. Two concurrent, complementary reviews on nonpharmacological therapies for chronic pain and nonopioid pharmacological therapies also support the CDC recommendation: one review found that several nonopioid pharmacological therapies are associated with benefits of similar magnitude to opioids,[18] and the other review found several nonpharmacological therapies associated with benefits of similar magnitude to opioids that persisted longer than 1 month after completion of therapy.[17] Collectively, these findings provide support for efforts to improve access and reimbursement to nonopioid pharmacological therapies and nonpharmacological therapies.[277]

Our findings are also consistent with a review conducted prior to publication of the 2016 CDC guideline that found broad agreement among opioid guidelines regarding recommended use of a number of risk mitigation strategies despite weak evidence, such as risk-assessment guided patient assessment for opioid therapy, urine drug testing, use of prescription monitoring program data, abuse-deterrent formulations, and opioid management plans.[278] The 2016 CDC

guideline classified 11 of 12 recommendations as supported by lower quality (type 3 or 4) evidence. Our updated findings indicate that most clinical and policy decisions regarding risk mitigation strategies and opioid dosing strategies for chronic noncancer pain must still be made on the basis of weak or insufficient evidence. Although guidelines recommend use of risk assessment instruments prior to initiating opioids in order to inform decisions related to opioid prescribing, no instrument has been shown to accurately predict opioid overdose, addiction, abuse, or misuse.

An area of controversy is whether there are dose thresholds that warrant more intense monitoring or consideration for tapering, and if so, the appropriate threshold.[16,279] New evidence is consistent with prior studies showing dose-dependent harms associated with opioids; however risk estimates across studies at specific thresholds vary, complicating decisionmaking in this area. Evidence on the effectiveness of tapering opioid doses versus usual care and the effectiveness of different tapering strategies remains very limited, with no trials comparing difference tapering regimens. Co-use of cannabis and gabapentinoids were not addressed in the 2016 CDC guideline; although these topics were included in this update, evidence to inform decisionmaking was limited.

Limitations of the Systematic Review Process

We excluded non-English language articles and did not search for studies published only as abstracts. We did not conduct statistical and graphical methods for assessing for small sample effects (a potential marker for publication bias) due to heterogeneity in study design methods, patient populations, and interventions evaluated in the trials. Searches on clinical trial registries and public solicitation did not identify unpublished studies suggesting publication bias, though some trials that evaluated outcomes of interest did not report data for pooling. This could have resulted in reporting bias, as trials tended not to report poolable data for nonstatistically significant results, usually for secondary outcomes (e.g., sleep quality, SF-36 physical or mental health status, or mental health measures). We addressed a potential limitation of the 2014 AHRQ report by expanding inclusion to trials with as little as 1 month of followup; however, shorter (<1 month) duration trials were still excluded for most Key Questions. We did not have access to individual patient data, which limited our ability to evaluate subgroup effects. Observational studies were included for some questions. Although we restricted inclusion of observational studies to those that controlled for potential confounders, even well-conducted observational studies are susceptible to residual confounding and bias. Meta-analyses could not be conducted for most questions due to small numbers of studies, methodological limitations, and heterogeneity across studies in interventions evaluated, study designs, and outcomes assessed. Statistical heterogeneity was present in a number of analyses. We used a random effects model appropriate for analyses with statistical heterogeneity (the profile likelihood method) and performed stratified analyses on factors related to study design, interventions, and patient populations, with generally robust findings.

Limitations of Evidence Base

The evidence base had limitations. Evidence on outcomes associated with different risk mitigation strategies remains very limited or unavailable. Aside from trials comparing short-term effects of different opioids, evidence on comparative benefits and harms of different opioid dosing strategies was also very limited. Evidence from randomized trials was almost exclusively restricted to trials of 6 months in duration or less. Most trials had significant methodological

shortcomings and observational studies were typically based on administrative databases with limited information on key clinical characteristics (e.g., chronicity of pain, severity of baseline pain and function). Close to half of the placebo-controlled trials published since 2007 utilized an EERW design, with some evidence of exaggerated estimates of treatment benefit and attenuated estimates of harms. Studies varied in measures used to assess outcomes such as function, quality of life, sleep, or psychological outcomes and some studies evaluated but did not provide data for these outcomes, potentially biasing pooled estimates. Few studies evaluated how benefits and harms vary in subgroups defined by demographic characteristics, characteristics of the pain condition, medical or psychological comorbidities, and substance use history. Studies of musculoskeletal pain primarily focused on low back pain and osteoarthritis and the most commonly evaluated neuropathic pain conditions were diabetic neuropathy and postherpetic neuralgia; evidence was lacking for certain pain conditions, including fibromyalgia, chronic headache, chronic abdominal pain, and chronic pain related to sickle cell disease. Some observational studies on the association between use of opioids and risk of harms were excluded because patients receiving short-term opioid therapy for acute pain could not clearly be excluded. For example, three studies found concurrent benzodiazepine and opioid prescribing associated with increased risk of overdose compared with an opioid alone, but two of these studies did not restrict enrollment to patients with chronic pain or evaluate risks associated with more prolonged opioid use (i.e., patients could have received short-term opioids for acute pain).[280-282]

Research Recommendations

Many research gaps limit the full understanding of the effectiveness, comparative effectiveness, and harms of opioid therapy for chronic pain, as well as of the effectiveness of different dosing methods and risk mitigation strategies, and effectiveness in special populations, including older adults and persons whto have survived cancer. Patients at higher risk for or with a history of or current opioid use disorder or misuse or with mental health and medical comorbidities are commonly treated with opioids in clinical practice, but evidence in these populations is very limited. Studies that enroll such patients and evaluate how benefits and harms vary compared with patients without such factors would be very helpful for understanding differential effects in such populations. Studies are also needed to better understand how underlying pain mechanisms (e.g., nociceptive, neuropathic, and nociplastic),[20] presence of specific pain conditions (e.g., autoimmune, congenital, sickle cell, hypermobility, or other) and presence of genetic polymorphisms affecting opioid metabolism impact effectiveness of therapies, potentially informing selection of treatments. Nociplastic pain refers to pain arising from altered nociception without underlying tissue damage, resulting in hypersensitivity. Few trials enrolled patients with conditions strongly characterized by nociplastic pain (e.g., fibromyalgia), though a nociplastic component may be present in many pain conditions. Studies should measure multiple important outcomes, including pain, function, quality of life, sleep, mental health outcomes, misuse and opioid use disorder using standardized methods. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) group has issued recommendations on measurement of outcomes in studies of chronic pain, including measurement of misuse and abuse outcomes in analgesic clinical trials.[283] Research is also needed to better understand how patients value different outcomes (beneficial and harmful) associated with opioid prescribing, and effects of strategies that consider such preferences into decisionmaking.

Research is also needed to develop and validate instruments for accurately predicting risk of opioid use disorder or misuse, and to determine how using risk prediction instruments impacts treatment decisions and, ultimately, patient outcomes. More research is needed on the comparative benefits and harms of different opioids or formulations and different prescribing methods and formulations (e.g., round-the-clock versus as-needed, short-acting versus long-acting), ideally evaluating longer-term outcomes.

Research is needed to understand the effects of risk mitigation strategies such as provision of naloxone, urine drug screening, use of prescription drug monitoring program data, and abuse-deterrent formulations on clinical outcomes such as rates of overdose, abuse, addiction, and misuse. One before-after study found the introduction of an abuse-deterrent opioid was followed by patients switching to other prescription opioids or illicit opioids,[284] highlighting the need for research to understand both the positive and negative clinical effects of risk mitigation strategies. More research is also needed on the comparative effectiveness of alternative tapering strategies and outcomes associated with concomitant use of cannabis or gabapentinoids with opioids.

It is important for future studies on opioids to evaluate long-term outcomes, including newer or emerging harms potentially associated with long-term use (e.g., refractory opioid dependence, impaired social and emotional cognition, workforce nonparticipation, and effects on functions of the endogenous opioid system [endocrine, immune, cognitive, and emotional]).[285] Long-term randomized trials of opioid therapy are difficult to implement due to challenges in recruitment and strong patient preferences about treatment, difficulty in blinding, participant attrition and crossover, and ethical factors (e.g., long-term allocation of patients with pain to placebo or allocation to non-use of risk mitigation strategies recommended in clinical practice guidelines). Nonetheless, pragmatic and other non-traditional randomized trial approaches could be used to address these challenges.[286] Observational studies could also help address a number of these research questions, but should be specifically designed to evaluate patients with chronic pain prescribed long-term opioid therapy and appropriately measure and address potential confounders. Well-designed clinical registries that enroll patients with chronic pain prescribed and not prescribed chronic opioids could help address the limitations of studies based solely or primarily on administrative databases, which are often unable to fully characterize the pain condition (e.g., duration, type, and severity) or other clinical characteristics and frequently do not have information regarding outcomes related to pain, function, and quality of life. Such registry studies could be designed to extend the observations from randomized trials of opioids versus placebo or other treatments, but would differ from currently available studies by following patients who discontinue or do not start opioids, in addition to those who continue on or start opioid therapy.

Conclusions

At short-term followup, for patients with chronic pain, opioids are associated with small beneficial effects versus placebo but are associated with increased risk of short-term harms and do not appear to be superior to nonopioid therapy. Evidence on intermediate-term and long-term benefits remains very limited and additional evidence confirms an association between opioids and increased risk of serious harms that appears to be dose-dependent. Research is needed to develop accurate risk prediction instruments, determine effective risk mitigation strategies, clarify risks associated with co-prescribed medications, and identify optimal opioid tapering strategies.

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Abbreviations and Acronyms

Abbreviation/ Acronym	Definition
AHRQ	Agency for Healthcare Research and Quality
ARD	Absolute risk difference
AUROC	Area under the receiver operator curve
BPR	Brief Pain Inventory
BRI	Brief Risk Interview
BRQ	Brief Risk Questionnaire
CDC	Centers for Disease Control and Prevention
CER	Comparative effectiveness review
CES-D	Centers for Epidemiology
CI	Confidence interval
CR	Controlled release
DIRE	Diagnosis, Intractability, Risk and Efficacy Inventory
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition – Text Revision
EERW	Enriched enrollment randomized withdrawal
FDA	U.S. Food and Drug Administration
HR	Hazard ratio
ICD-9	International Classification of Diseases – 9th Revision
IMMPACT	Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
IRR	incident rate ratio
MCP	New Mexico Medical Cannabis Program
MCS	Mental Component Summary
MD	Mean difference
MED	Morphine equivalent doses
NLR	Negative likelihood ratio
NSAID	Non-steroidal anti-inflammatory drug
ODI	Oswestry Disability Index
OR	Odds ratio
ORT	Opioid Risk Tool
PCS	Physical Component Summary
PDMP	Prescription drug monitoring programs
PLR	Positive likelihood ratio
PMQ	Pain Medication Questionnaire
QUADAS-2	using Quality Assessment of Diagnostic Accuracy Studies – Version 2
RCT	Randomized controlled trial
RDQ	Roland-Morris Disability Questionnaire
RR	Relative risk
SD	Standard deviation
SEADS	Supplemental Evidence And Data for Systematic review
SF-12	Short-Form 12-item
SF-36	Short-Form 36-item
SMD	Standardized mean difference
SOAPP	Screening and Opioid Assessment for Patients with Pain
SOAPP-R	Screening and Opioid Assessment for Patients with Pain - Revised
SOE	Summary of evidence
SPACE	Strategies for Prescribing Analgesics Comparative Effectiveness
S-TOPS	Short version of Treatment Outcomes in Pain Survey
VAS	Visual Analog Scale
VHA	Veterans Health Administration

Appendix A. Search Strategies

Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R)

Key Questions 1-3

1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. 9 or 10 or 11
13. 8 and 12
14. limit 13 to english language
15. 14 not (intravenous or intramuscular or injection* or intrathecal or epidural or block or preoperative or perioperative or acute).ti.
16. limit 15 to yr="2014 -Current"
17. limit 16 to (comparative study or controlled clinical trial or randomized controlled trial)
18. exp cohort studies/
19. cohort$.tw.
20. controlled clinical trial.pt.
21. epidemiologic methods/
22. limit 21 to yr=1966-1989
23. exp case-control studies/
24. (case$ and control$).tw.
25. or/18-20,22-24
26. randomized controlled trial.pt.
27. (random* or placebo* or control* or trial or blind*).ti,ab.
28. (animals not humans).sh.
29. (comment or editorial or meta-analysis or practice-guideline or review or letter).pt.
30. (26 or 27) not (28 or 29)
31. 16 and (25 or 30)
32. 17 or 31
33. limit 16 to (meta analysis or systematic reviews)
34. review.pt.
35. (medline or medlars or embase or pubmed or cochrane).tw,sh.
36. (scisearch or psychinfo or psycinfo).tw,sh.

37. (psychlit or psyclit).tw,sh.
38. cinahl.tw,sh.
39. ((hand adj2 search$) or (manual$ adj2 search$)).tw,sh.
40. (electronic database$ or bibliographic database$ or computeri?ed database$ or online database$).tw,sh.
41. (pooling or pooled or mantel haenszel).tw,sh.
42. (peto or dersimonian or der simonian or fixed effect).tw,sh.
43. or/35-42
44. 34 and 43
45. meta-analysis.pt.
46. meta-analysis.sh.
47. (meta-analys$ or meta analys$ or metaanalys$).tw,sh.
48. (systematic$ adj5 review$).tw,sh.
49. (systematic$ adj5 overview$).tw,sh.
50. (quantitativ$ adj5 review$).tw,sh.
51. (quantitativ$ adj5 overview$).tw,sh.
52. (quantitativ$ adj5 synthesis$).tw,sh.
53. (methodologic$ adj5 review$).tw,sh.
54. (methodologic$ adj5 overview$).tw,sh.
55. (integrative research review$ or research integration).tw.
56. or/45-55
57. 44 or 56
58. 16 and 57
59. 33 or 58
60. 32 or 59

Key Questions 4a and 4b
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13

16. 14 or 15
17. Decision Support Techniques/
18. "Predictive Value of Tests"/
19. Prognosis/
20. Risk Assessment/
21. Risk Factors/
22. Proportional Hazards Models/
23. "Reproducibility of Results"/
24. "Sensitivity and Specificity"/
25. (sensitivity or specificity or accuracy).ti,ab,kf.
26. (risk and (predict$ or assess$)).ti,ab,kf.
27. or/17-26
28. 16 and 27
29. limit 28 to yr="2014 -Current"
30. limit 29 to english language

Key Question 4c

1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Patient Compliance/
18. Health Services Misuse/
19. Substance Abuse Detection/
20. Drug Monitoring/
21. (urine adj7 (screen$ or test$ or detect$)).ti,ab,kf.
22. Contracts/
23. Patient Education as Topic/
24. Drug Overdose/
25. or/17-24

26. risk$.ti,ab,kf.
27. ("risk evaluation and mitigation" or "rems").ti,ab,kf.
28. Risk Reduction Behavior/ or Risk/
29. or/26-28
30. 16 and 25 and 29
31. limit 30 to yr="2014 -Current"
32. Naloxone/
33. naloxone.ti,ab,kf.
34. 16 and 29 and (32 or 33)
35. 31 or 34

Key Question 4d
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Patient Compliance/
18. Health Services Misuse/
19. Substance Abuse Detection/
20. Drug Monitoring/
21. (urine adj7 (screen$ or test$ or detect$)).ti,ab,kf.
22. (abus$ or misus$ or diversion$ or divert$).ti,ab,kf.
23. (opioid$ adj7 (contract$ or agree$)).ti,ab,kf.
24. Contracts/
25. Patient Education as Topic/
26. Drug Overdose/
27. or/17-26
28. Substance Abuse Detection/
29. Opiate Substitution Treatment/
30. Risk Management/

31. or/28-30
32. 16 and 27 and 31
33. Treatment Outcome/
34. (treatment and (outcome or strateg$ or plan$)).ti,ab,kf.
35. 32 and (33 or 34)
36. limit 35 to yr="2014 -Current"

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

Key Questions 1-3

1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. 9 or 10 or 11
13. 8 and 12
14. limit 13 to english language
15. 14 not (intravenous or intramuscular or injection* or intrathecal or epidural or block or preoperative or perioperative or acute).ti.
16. limit 15 to yr="2014 -Current"

Key Questions 4a and 4b

1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.

11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Decision Support Techniques/
18. "Predictive Value of Tests"/
19. Prognosis/
20. Risk Assessment/
21. Risk Factors/
22. Proportional Hazards Models/
23. "Reproducibility of Results"/
24. "Sensitivity and Specificity"/
25. (sensitivity or specificity or accuracy).ti,ab,kf.
26. (risk and (predict$ or assess$)).ti,ab,kf.
27. or/17-26
28. 16 and 27
29. limit 28 to yr="2014 -Current"
30. limit 29 to english language

Key Question 4c
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Patient Compliance/
18. Health Services Misuse/
19. Substance Abuse Detection/

20. Drug Monitoring/
21. (urine adj7 (screen$ or test$ or detect$)).ti,ab,kf.
22. Contracts/
23. Patient Education as Topic/
24. Drug Overdose/
25. or/17-24
26. risk$.ti,ab,kf.
27. ("risk evaluation and mitigation" or "rems").ti,ab,kf.
28. Risk Reduction Behavior/ or Risk/
29. or/26-28
30. 16 and 25 and 29
31. limit 30 to yr="2014 -Current"
32. Naloxone/
33. naloxone.ti,ab,kf.
34. 16 and 29 and (32 or 33)
35. 31 or 34

Key Question 4d
1. Chronic Pain/
2. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
3. Pain/
4. chronic.ti,ab,kw.
5. 3 and 4
6. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
7. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
8. 1 or 2 or 5 or 6 or 7
9. exp Analgesics, Opioid/
10. opioid*.ti,ab,kw.
11. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw,sh,hw.
12. exp Opioid-Related Disorders/
13. (opioid adj2 (abuse or addict* or misuse or diversion)).ti,ab,kf.
14. 8 and (or/9-11)
15. 12 or 13
16. 14 or 15
17. Patient Compliance/
18. Health Services Misuse/
19. Substance Abuse Detection/
20. Drug Monitoring/
21. (urine adj7 (screen$ or test$ or detect$)).ti,ab,kf.
22. (abus$ or misus$ or diversion$ or divert$).ti,ab,kf.
23. (opioid$ adj7 (contract$ or agree$)).ti,ab,kf.
24. Contracts/

25. Patient Education as Topic/
26. Drug Overdose/
27. or/17-26
28. Substance Abuse Detection/
29. Opiate Substitution Treatment/
30. Risk Management/
31. or/28-30
32. 16 and 27 and 31
33. Treatment Outcome/
34. (treatment and (outcome or strateg$ or plan$)).ti,ab,kf.
35. 32 and (33 or 34)
36. limit 35 to yr="2014 -Current"

Database: EBM Reviews - Cochrane Database of Systematic Reviews
All Key Questions
1.chronic.ti,ab,kw.
2. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab,kw.
3. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab,kw.
4. opioid*.ti,ab,kw.
5. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,kw.
6. (or/1-3) and (4 or 5)
7. 5 not postoperative.ti.
8. limit 7 to full systematic reviews

Database: PsycINFO
All Key Questions
1. exp arthralgia/ or exp back pain/ or cancer pain/ or exp headache/ or exp musculoskeletal pain/ or neck pain/ or exp neuralgia/ or exp nociceptive pain/ or pain, intractable/ or fibromyalgia/ or myalgia/
2. exp pain/
3. chronic.ti,ab,id.
4. 2 and 3
5. ((chronic or persistent or intractable or refractory) adj1 pain).ti,ab.
6. (((back or spine or spinal or leg or musculoskeletal or neuropathic or nociceptive or radicular) adj1 pain) or headache or arthritis or fibromyalgia or osteoarthritis).ti,ab.
7. 1 or 4 or 5 or 6
8. exp Opiates/
9. (buprenorphine or codeine or fentanyl or hydrocodone or hydromorphone or methadone or morphine or oxycodone or oxymorphone or tapentadol).ti,ab,id,hw.
10. opioid*.ti,ab,id.
11. or/8-10
12. 7 and 11
13. 12 not (intravenous or intramuscular or injection* or intrathecal or epidural or block or preoperative or perioperative or acute).ti.

14. limit 13 to english language
15. limit 14 to yr="2014 -Current"
16. exp animals/
17. 15 not 16

Database: Elsevier Embase® Online

All Key Questions

('chronic pain'/exp OR 'chronic pain' OR 'arthralgia'/exp OR arthralgia OR 'back pain'/exp OR 'back pain' OR 'backache'/exp OR backache OR 'cancer pain'/exp OR 'cancer pain' OR 'headache'/exp OR headache OR 'musculoskeletal pain'/exp OR 'musculoskeletal pain' OR 'neck pain'/exp OR 'neck pain' OR 'neuralgia'/exp OR neuralgia OR 'fibromyalgia'/exp OR fibromyalgia OR 'myalgia'/exp OR myalgia) AND ('opiate'/exp OR 'opiate' OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR methadone OR morphine OR naloxone OR oxycodone OR oxymorphone OR tapentadol) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim) AND [2014-2019]/py AND 'human'/de AND ('clinical article'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative effectiveness'/de OR 'controlled clinical trial'/de OR 'controlled study'/de OR 'cross-sectional study'/de OR 'double blind procedure'/de OR 'major clinical study'/de OR 'meta analysis'/de OR 'multicenter study'/de OR 'observational study'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'systematic review'/de) NOT (postoperative OR intravenous OR intramuscular OR injection* OR intrathecal OR epidural OR block OR preoperative OR perioperative OR acute) AND [english]/lim

Appendix B. Inclusion and Exclusion Criteria

Table B-1. PICOTS

Key Question	Population	Intervention	Comparator	Outcome
1a, 1b	Adults (age ≥18 years) with various types of chronic pain including pregnant/breast-feeding women and patients treated with opioids for opioid use disorder 1b subgroups: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including low back pain], fibromyalgia, sickle cell disease, inflammatory pain, and headache disorders); (2) patient demographics (e.g., age, race, ethnicity, gender); (3) patient comorbidities (including past or current alcohol or substance use disorders, mental health disorders, medical comorbidities and high risk for opioid use disorder)	Long- or short-acting opioids (including partial agonists and dual mechanism agents) Exclude: Intravenous or intramuscular administration of opioids	Placebo or no opioid therapy	Pain, function, and quality of life
1c	Adults (age ≥18 years) with various types of chronic pain	Long- or short-acting opioids (including partial agonists and dual action medications) Exclude: Intravenous or intramuscular administration of opioids	Nonopioid therapies (pharmacologic [antiepileptic drugs, benzodiazepines, nonsteroidal antiinflammatory drugs, skeletal muscle relaxants, serotonin norepinephrine reuptake inhibitors, topical lidocaine, topical capsaicin, topical diclofenac, tricyclica antidepressants, acetaminophen, memantine, and cannabis] or nonpharmacologic [noninvasive])	Pain, function, and quality of life; doses of opioids used
1d	Adults (age ≥18 years) with various types of chronic pain	Opioids plus nonopioid interventions (pharmacologic or nonpharmacologic) Exclude: Intravenous or intramuscular administration of opioids	Opioids or nonopioid interventions alone, including cannabis	Pain, function, and quality of life, doses of opioids used

Key Question	Population	Intervention	Comparator	Outcome
2a, 2b	Adults (age ≥18 years) with various types of chronic pain 2b subgroups: (1) the specific type or cause of pain (e.g., neuropathic, musculoskeletal [including back pain], fibromyalgia, sickle cell disease, inflammatory pain, headache disorders); (2) patient demographics; (3) patient comorbidities (including past or current substance use disorder or at high risk for opioid use disorder); (4) the dose of opioids used; (5) the mechanisms of actions of the opioids; and (6) use of sedative hypnotics	Long- or short-acting opioids (including tapentadol, buprenorphine, and tramadol) opioids Exclude: Intravenous or intramuscular administration of opioids	Placebo or no opioid	Substance misuse, substance use disorder and related outcomes, overdose, and other harms
2c	Adults (age ≥18 years) with various types of chronic pain	Long- or short-acting opioids (including partial agonists and dual action medications) Exclude: Intravenous or intramuscular administration of opioids	Nonopioid therapies (pharmacologic [antiepileptic drugs, benzodiazepines, nonsteroidal antiinflammatory drugs, skeletal muscle relaxants, serotonin norepinephrine reuptake inhibitors, topical lidocaine, topical capsaicin, topical diclofenac, tricyclica antidepressants, acetaminophen, memantine, and cannabis] or nonpharmacologic [noninvasive])	Substance misuse, substance use disorder and related outcomes, overdose, and other harms
2d	Adults (age ≥18 years) with various types of chronic pain	Opioids plus nonopioid interventions (pharmacologic or nonpharmacologic) Exclude: Intravenous or intramuscular administration of opioids	Opioids or nonopioid interventions alone, including cannabis	Substance misuse, substance use disorder and related outcomes, overdose, and other harms
3a	Adults (age ≥18 years) with various types of chronic pain	Long- or short-acting opioids (including tapentadol, buprenorphine, and tramadol)	Other opioids with different dose initiation and titration strategies	Pain, function, and quality of life; doses of opioids used

Key Question	Population	Intervention	Comparator	Outcome
3b	Adults (age ≥18 years) with various types of chronic pain	Short-acting opioid	Long-acting opioid	Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose and other harms; doses of opioids used
3c	Adults (age ≥18 years) with various types of chronic pain	Long-acting opioid	Other long-acting opioid	Pain, function, and quality of life; risk of misuse, opioid use disorder, and overdose and other harms; doses of opioids used
3d	Adults (age ≥18 years) with various types of chronic pain	Short- and long-acting opioid	Long-acting opioid	Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose and other harms; doses of opioids used
3e	Adults (age ≥18 years) with various types of chronic pain	Scheduled, continuous dosing	As-needed dosing	Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose, and other harms; doses of opioids used
3f	Adults (age ≥18 years) with various types of chronic pain	Opioid dose escalation	Dose maintenance or use of dose thresholds	Pain, function, and quality of life
3g	Adults (age ≥18 years) with various types of chronic pain	Opioid rotation	Maintenance of current opioid therapy	Pain, function, and quality of life; doses of opioids used
3h	Adults (age ≥18 years) with various types of chronic pain and an acute exacerbation	Treatments for acute exacerbations of chronic pain	Other treatments for acute exacerbations of chronic pain	Pain, function, and quality of life
3i	Adults (age ≥18 years) with various types of chronic pain	Decreasing opioid doses or of tapering off opioids	Continuation of opioids	Pain, function, and quality of life; opiate withdrawal and other harms (including overdose, use of illicit opioids, suicidality, and anger/violence)
3j	Adults (age ≥18 years) with various types of chronic pain	Tapering protocols and strategies	Other tapering protocols or strategies	Pain, function, quality of life, likelihood of opioid cessation, opiate withdrawal symptoms and other harms (including overdose, use of illicit opioids, suicidality, and anger/violence)
3k	Adults (age ≥18 years) with various types of chronic pain	Dosage of opioid	Other dose of same opioid	Pain, function, and quality of life; risk of misuse, opioid use disorder, overdose and other harms

Key Question	Population	Intervention	Comparator	Outcome
4a	Adults (age ≥18 years) with various types of chronic pain	Instruments, genetic/metabolic tests for predicting risk of misuse, opioid use disorder, and overdose	Reference standard for misuse, opioid use disorder, or overdose; or other benchmarks	Measures of diagnostic accuracy
4b	Adults (age ≥18 years) with various types of chronic pain	Use of risk prediction instruments, genetic/metabolic tests	Usual care or other control	Misuse, opioid use disorder, overdose and other harms
4c	Adults (age ≥18 years) with various types of chronic pain	Risk mitigation strategies, including (1) opioid management plans, (2) patient education, (3) urine drug screening, (4) use of prescription drug monitoring program data, (5) use of monitoring instruments, (6) more frequent monitoring intervals, (7) pill counts, (8) use of abuse-deterrent formulations, (9) consultation with mental health providers when mental health conditions are present, (10) avoidance of benzodiazepine co-prescribing and (11) co-prescribing of naloxone	Usual care	Pain, function, quality of life, misuse, opioid use disorder, overdose and other harms (including use of illicit opioids, suicidality, and anger/violence)
4d	Adults (age ≥18 years) with various types of chronic pain and opioid use disorder	Treatment strategies	Other treatment strategies	Pain, function, quality of life, misuse, opioid use disorder, overdose, other harms, pain, function, and quality of life

Appendix C. List of Excluded Studies

Exclusion Codes:
2 = Background paper
3 = Paper used for contextual question
4 = Ineligible population
5 = Ineligible intervention or no intervention
6 = Ineligible comparison
7 = Ineligible outcome
8 = Ineligible setting
9 = Ineligible publication type
10 = Ineligible study design
11 = Not available in English language
12 = Outdated review article or non systematic review
13 = Inadequate duration
14 = No reference standard used for KQ 4a
15= Poor-quality

1. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. Rockville, MD: Agency for Healthcare Research and Quality. https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview. Accessed June 19 2019. Exclusion: 2
2. 2017 CDC Survey Results. Pain News Network. https://www.painnewsnetwork.org/2017-cdc-survey/. Accessed Jul 17 2019. Exclusion: 3
3. Oxycodone for neuropathic pain and fibromyalgia-little evidence. Drug and Therapeutics Bulletin. 2014;52(9):100. doi: 10.1136/dtb.2014.9.0275. Exclusion: E9
4. Abdel Shaheed C, Maher CG, Williams KA, et al. Efficacy, tolerability, and dose-dependent effects of opioid analgesics for low back pain: a systematic review and meta-analysis. JAMA Internal Medicine. 2016 Jul 01;176(7):958-68. doi: https://dx.doi.org/10.1001/jamainternmed.2016.1251. PMID: 27213267. Exclusion: E12
5. Aboussouan A, Huffman K, Jimenez X. Sustained benefits of an interdisciplinary chronic pain rehabilitation program in women with chronic pelvic pain. Pain Medicine (United States). 2018;19(4):894-5. doi: 10.1093/pm/pny044. Exclusion: E5
6. Adams EH, Chwiecko P, Ace-Wagoner Y, et al. A Study of AVINZA® (Morphine Sulfate Extended-Release Capsules) for Chronic Moderate-to-Severe Noncancer Pain Conducted Under Real-World Treatment Conditions—The ACCPT Study. Pain Pract. 2006 2006/12/01;6(4):254-64. doi: 10.1111/j.1533-2500.2006.00094.x. Exclusion: E10
7. Adams LL, Gatchel RJ, Robinson RC, et al. Development of a self-report screening instrument for assessing potential opioid medication misuse in chronic pain patients. Journal of Pain & Symptom Management. 2004 May;27(5):440-59. doi: 10.1016/j.jpainsymman.2003.10.009. PMID: 15120773. Exclusion: E7
8. Adler JA, Mallick-Searle T. An overview of abuse-deterrent opioids and recommendations for practical patient care. Journal of multidisciplinary healthcare. 2018;11:323-32. doi: https://dx.doi.org/10.2147/JMDH.S166915. PMID: 30026658. Exclusion: E12
9. Adu J, Chung CP, Munters LA, et al. Fibromyalgia patients taking opioids have low self-efficacy and high pain catastrophizing but no reduction in pain or improvement in activity. Arthritis and Rheumatology. 2014;66:S491. doi: 10.1002/art.38914. Exclusion: E9
10. Afilalo M, Morlion B. Efficacy of tapentadol ER for managing moderate to severe chronic pain. Pain Physician. 2013;16(1):27-40. Exclusion: E12
11. Agarwal S, Polydefkis M, Block B, et al. Transdermal fentanyl reduces pain and improves functional activity in neuropathic pain states. Pain Medicine. 2007 Oct-Nov;8(7):554-62. PMID: 17883740. Exclusion: E10
12. Agboola FO, Kumar VM, Synnott PG, et al. Abuse-deterrent formulations of opioids: effectiveness and economic impact. Value in Health. 2018;21:S191. doi: 10.1016/j.jval.2018.12.005. PMID: 30975392. Exclusion: E9

13. Ahmedzai S. New approaches to pain control in patients with cancer. European Journal of Cancer. 1997 Jul;33 Suppl 6:S8-14. PMID: 9404234. Exclusion: E12

14. Ahmedzai S, Brooks D. Transdermal fentanyl versus sustained-release oral morphine in cancer pain: preference, efficacy, and quality of life. The TTS-Fentanyl Comparative Trial Group. J Pain Symptom Manage. 1997 May;13(5):254-61. PMID: 9185430. Exclusion: E4

15. Ahmedzai SH, Leppert W, Janecki M, et al. Long-term safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate-to-severe chronic cancer pain. Supportive Care in Cancer. 2015 Mar;23(3):823-30. doi: https://dx.doi.org/10.1007/s00520-014-2435-5. PMID: 25218610. Exclusion: E10

16. Ahmedzai SH, Nauck F, Bar-Sela G, et al. A randomized, double-blind, active-controlled, double-dummy, parallel-group study to determine the safety and efficacy of oxycodone/naloxone prolonged-release tablets in patients with moderate/severe, chronic cancer pain. Palliative Medicine. 2012 Jan;26(1):50-60. doi: 10.1177/0269216311418869. PMID: 21937568. Exclusion: E4

17. Ahn JS, Lin J, Ogawa S, et al. Transdermal buprenorphine and fentanyl patches in cancer pain: a network systematic review. Journal of Pain Research. 2017;10:1963-72. doi: 10.2147/JPR.S140320. PMID: 28860851. Exclusion: E4

18. Aiyer R, Gulati A, Gungor S, et al. Treatment of chronic pain with various buprenorphine formulations: a systematic review of clinical studies. Anesth Analg. 2018 Aug;127(2):529-38. doi: 10.1213/ANE.0000000000002718. PMID: 29239947. Exclusion: E12

19. Aiyer R, Mehta N, Gungor S, et al. A systematic review of NMDA receptor antagonists for treatment of neuropathic pain in clinical practice. Clinical Journal of Pain. 2018 May;34(5):450-67. doi: https://dx.doi.org/10.1097/AJP.0000000000000547. PMID: 28877137. Exclusion: E5

20. Ajo R, Segura A, Inda MM, et al. Opioids increase sexual dysfunction in patients with non-cancer pain. Journal of Sexual Medicine. 2016 09;13(9):1377-86. doi: https://dx.doi.org/10.1016/j.jsxm.2016.07.003. PMID: 27555508. Exclusion: E10

21. Alam A, Juurlink DN. The prescription opioid epidemic: an overview for anesthesiologists. Canadian Journal of Anaesthesia. 2016 Jan;63(1):61-8. doi: https://dx.doi.org/10.1007/s12630-015-0520-y. PMID: 26507535. Exclusion: E12

22. Alberts D, Von Hoff D, Forman N, et al. Relationship between effective doses of fentan yl sublingual spray and around-the-clock tran sdermal fentanyl in patients with breakthrough cancer pain. Supportive Care in Cancer. 2014;22(1):S123-S4. doi: 10.1007/s00520-014-2222-3. PMID: 27020837. Exclusion: E9

23. Alberts DS, Rauck RL, Parikh N, et al. Fentanyl sublingual spray for breakthrough cancer pain in patients receiving transdermal fentanyl. Journal of Clinical Oncology. 2014;32(31)doi: 10.2217/pmt-2015-0009. PMID: 27020837 Exclusion: E9

24. Alberts DS, Smith CC, Parikh N, et al. Fentanyl sublingual spray for breakthrough cancer pain in patients receiving transdermal fentanyl. Pain Management. 2016 Oct;6(5):427-34. doi: https://dx.doi.org/10.2217/pmt-2015-0009. PMID: 27020837. Exclusion: E13

25. Alburaih A, Witting MD. Effectiveness of a rural emergency department (ED)-based pain contract on ED visits among ED frequent users. Journal of Emergency Medicine. 2018 09;55(3):327-32.e1. doi: https://dx.doi.org/10.1016/j.jemermed.2018.04.056. PMID: 29858142. Exclusion: E4

26. Aldington D, Cole P, Knaggs R, et al. Hydromorphone for neuropathic pain in adults. Cochrane Database of Systematic Reviews. 2015;2015(3)doi: 10.1002/14651858.CD011604. PMID: 27216018. Exclusion: E9

27. Alharbi GS, Chen LC, Knaggs R. Efficacy of anticonvulsant, antidepressant and opioid in treating neuropathic pain: a systematic review and meta-analysis. Pharmacoepidemiology and Drug Safety. 2016;25:582. doi: 10.1002/pds.4070. Exclusion: E9

28. Alinejad S, Ghaemi K, Abdollahi M, et al. Nephrotoxicity of methadone: a systematic review. Springerplus. 2016;5(1):2087. doi: https://dx.doi.org/10.1186/s40064-016-3757-1. PMID: 28018795. Exclusion: E4

29. Allegri N, Mennuni S, Rulli E, et al. Systematic review and meta-analysis on neuropsychological effects of long-term use of opioids in patients with chronic noncancer pain. Pain Pract. 2018 Oct 24;24:24. doi: https://dx.doi.org/10.1111/papr.12741. PMID: 30354006. Exclusion: 2

30. Allen C, Meeraus W, Donegan K. The comparative risk of all-cause mortality in older patients prescribed opioids for non-malignant pain: a retrospective observational cohort study. Drug Safety. 2015;Conference: 15th ISoP Annual Meeting "Cubism in Pharmacovigilance" Prague Czech Republic. Conference Start:. 20151027 Conference End: 20151030. Conference Publication:(var.pagings) 38 (10):962-3. Exclusion: E9

31. Allen C, Meeraus W, Donegan K. Comparative risk of cause-specific mortality in older patients prescribed codeine or tramadol for non-malignant pain: retrospective cohort study. Drug Safety. 2017;40(10):993-4. doi: 10.1007/s40264-017-0580-8. Exclusion: E9

32. Allen MA. Opioid analgesics: is it time for risk stratification prior to use? CJEM Canadian Journal of Emergency Medical Care. 2017 09;19(5):414. doi: https://dx.doi.org/10.1017/cem.2017.359. PMID: 28750692. Exclusion: E9

33. Almenara S, Planelles B, López-Gil S, et al. Pharmacogenetics of pain and analgesia of tapentadol in chronic pain. Basic and Clinical Pharmacology and Toxicology. 2016;119:33. Exclusion: E9

34. Almenara S, Planelles B, Muriel J, et al. Iatrogenically induced opioid dependence, pharmacogenetics and pain. Basic and Clinical Pharmacology and Toxicology. 2016;119:15. Exclusion: E9

35. Amato F, Ceniti S, Mameli S, et al. High dosage of a fixed combination oxycodone/naloxone prolonged release: efficacy and tolerability in patients with chronic cancer pain. Supportive care in cancer. 2017. Exclusion: E10

36. Amato F, Ceniti S, Palmieri V, et al. Cancer pain therapy with a fixed combination of prolonged-release oxycodone/naloxone: a real-life scenario. Regional Anesthesia and Pain Medicine. 2014;39(5):e301-e2. doi: 10.1097/AAP.0000000000000142. Exclusion: E9

37. American Academy of Family Physicians. CDC Clarifies Opioid Guideline Dosage Thresholds. 2018. https://www.aafp.org/news/health-of-the-public/20180112cdcopioidclarify.html. Accessed September 20 2019. Exclusion: 2

38. American College of Medical T. Safety issues regarding prescription opioids. Journal of Medical Toxicology: Official Journal of the American College of Medical Toxicology. 2016 Mar;12(1):142-4. doi: https://dx.doi.org/10.1007/s13181-015-0529-1. PMID: 26732680. Exclusion: E9

39. Anastassopoulos KP, Chow W, Tapia CI, et al. Economic study on the impact of side effects in patients taking oxycodone controlled-release for noncancer pain. J Manag Care Spec Pharm. 2012 Oct;18(8):615-26. PMID: 23127149. Exclusion: E10

40. Anastassopoulos KP, Chow W, Tapia CI, et al. Reported side effects, bother, satisfaction, and adherence in patients taking hydrocodone for non-cancer pain. J Opioid Manag. 2013 Mar-Apr;9(2):97-109. doi: 10.5055/jom.2012.0151. PMID: 23709319. Exclusion: 3

41. Anderson JT, Haas AR, Percy R, et al. Chronic opioid therapy after lumbar fusion surgery for degenerative disc disease in a workers' compensation setting. Spine. 2015 Nov;40(22):1775-84. doi: https://dx.doi.org/10.1097/BRS.0000000000001054. PMID: 26192725. Exclusion: E7

42. Andresen V, Lass A, Banerji V, et al. Users of weak opioids have a smaller spectrum of constipation symptoms, but a similar degree of bother from constipation, as users of potent opioids. United European Gastroenterology Journal. 2017;5(5):A71. doi: 10.1177/2050640617725668. Exclusion: E9

43. Anonymous. Long-acting opioids for chronic non-cancer pain: a review of the clinical efficacy and safety. Canadian Agency for Drugs and Technologies in Health. CADTH Rapid Response Reports. 2015 08 27;08:27. PMID: 26985539. Exclusion: E12

44. Anonymous. Education and assessment for overdose prevention: a review of the clinical evidence and guidelines. Canadian Agency for Drugs and Technologies in Health. CADTH Rapid Response Reports. 2015 09 24;09:24. PMID: 26468567. Exclusion: E12

45. Anonymous. Erratum: efficacy and tolerability of buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain: results of a phase 3, enriched enrollment, randomized withdrawal study (Pain (2016) 157 (2517-2526)). Pain. 2017;158(2):366. Exclusion: E9

46. Antony A, Fishman MA, Hunter CW, et al. Absence due to disability increases after starting opioid use in chronic pain. Neuromodulation. 2019;22(3):E170-E1. doi: 10.1111/ner.12950. Exclusion: E9

47. Apelt SM, Scherbaum N, Golz J, et al. Safety, effectiveness and tolerance of buprenorphine-naloxone in the treatment of opioid dependence: results from a nationwide non-interventional study in routine care. Pharmacopsychiatry; 2013. p. 94-107. Exclusion: E4

48. Argoff C, Arnstein P, Stanos S, et al. Relationship between change in pain intensity and functional outcomes in patients with chronic pain receiving twice daily extended-release hydrocodone bitartrate. Journal of Opioid Management. 2015 Sep-Oct;11(5):417-24. doi: https://dx.doi.org/10.5055/jom.2015.0291. PMID: 26535969. Exclusion: E6

49. Argoff CE, Kahan M, Sellers EM. Preventing and managing aberrant drug-related behavior in primary care: systematic review of outcomes evidence. Journal of Opioid Management. 2014 Mar-Apr;10(2):119-34. doi: https://dx.doi.org/10.5055/jom.2014.0201. PMID: 24715667. Exclusion: E12

50. Argoff CE, Silvershein DI. A comparison of long and short-acting opioids for the treatment of chronic noncancer pain: tailoring therapy to meet patient needs. Mayo Clinic Proceedings. 2009 Jul;84(7):602-12. doi: http://dx.doi.org/10.1016/S0025-6196(11)60749-0. PMID: 19567714. Exclusion: E12

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Appendix D. Quality Rating Criteria

Randomized Controlled Trials

The criteria for rating the quality of randomized controlled trials were based on those developed by the Cochrane Back and Neck Group:[1,2]

- Selection bias
- Performance bias
- Detection bias
- Attrition bias
- Reporting bias
- Other sources of bias

Selections for each criteria were: Yes, No, and Unclear.

Observational Studies

The criteria for rating the quality of observational studies were based on the U.S. Preventive Services Task Force quality assessment criteria:[3]

- Initial assembly of comparable groups:
- Consideration of potential confounders, with either restriction or measurement for adjustment in the analysis; consideration of inception cohorts
- Maintenance of comparable groups (includes attrition, cross-overs, adherence, contamination)
- Important differential loss to followup or overall high loss to followup
- Measurements: equal, reliable, and valid (includes masking of outcome assessment)
- Clear definition of interventions
- All important outcomes considered
- Adjustment for potential confounders

The quality ratings applied were Good, Fair, or Poor.

Diagnostic Accuracy Studies

The criteria for rating the quality of diagnostic accuracy studies were based on QUADAS-2:[4]

- Patient selection
- Index test(s)
- Reference standard
- Flow and timing

Response options for all questions were: Yes, No, Unclear, or Not applicable.

Overall rating options were: Good, Fair, or Poor.

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Appendix E. Detailed Statistical Methods

- For followup score, missing standard deviation (SD) was imputed by assuming constant coefficient of variation (CV) across included studies.
- For change score, it is not appropriate to assume constant CV to impute missing SD given variability in treatment effects among studies. Instead:
  - If baseline mean and SD were available, we imputed followup SD assuming constant CV and calculated SD for change score assuming rho = 0.5
  - If baseline mean was available and SD was not, we imputed followup SD assuming constant CV and used it as change score SD (This is equivalent to assuming the same baseline and followup SD, and calculating SD for change score assuming rho = 0.5.)
  - If both baseline mean and SD were not available, we imputed change score SD as the average of follow up SD of other studies for the same outcome.
- The imputed values were based on all available data from the same outcome, which did not appear to vary much by type of pain or opioid.

Appendix F. List of Included Studies

1. Adams EH, Breiner S, Cicero TJ, et al. A comparison of the abuse liability of tramadol, NSAIDs, and hydrocodone in patients with chronic pain. J Pain Symptom Manage. 2006 May;31(5):465-76. doi: 10.1016/j.jpainsymman.2005.10.006. PMID: 16716877.
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Appendix G. Quality Tables

Table G-1. Quality assessments of randomized controlled trials

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	ITT analysis?	Acceptable levels of overall attrition and between-group differences in attrition?	Avoidance of selective outcomes reporting?	Crossover design: assessment of carryover?	Quality rating
Adler, 2002	Yes	Yes	Yes	Yes	Yes	Yes	Unclear	No/Yes (29.9% vs. 32.3%)	Unclear	NA	Fair
Afilalo, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	NA	Fair
Allan, 2001	Yes	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes/Yes	Yes	Yes	Fair
Allan, 2005	Yes	Yes	Yes	No	No	No	Yes	No (49%)/Yes (52% vs. 47%)	Yes	NA	Fair
Arai, 2015a	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/Yes	Yes	NA	Poor
Arai, 2015b	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Poor
Ashburn, 2011	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes/Yes	Yes	NA	Good
Babul, 2004	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Baron, 2015	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes/Yes	Yes	NA	Fair
Baron, 2016	Unclear	Unclear	Yes	No	No	No	Yes	No/No (34% vs. 63%)	Yes	NA	Fair
Beaulieu, 2008	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Binsfield, 2010	Unclear	Yes	Yes	No	No	No	Yes	No/Yes (54.7% vs. 56.8%)	Unclear	NA	Fair
Blondell, 2010	Yes	Yes	Yes	Unclear	No	No	No	No	No	NA	Poor
Boureau, 2003	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes/Yes	Yes	NA	Good
Breivik, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	NA	Fair
Burch, 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	NA	Good
Buynak, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Caldwell, 1999	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Unclear	NA	Fair
Caldwell, 2002	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/Yes	Unclear	NA	Fair
Christoph, 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	NA	Fair
Chu, 2012	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Cloutier, 2013	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No/Yes	Yes	Yes	Fair
DeLemos, 2011	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Fair
Fiellin, 2014	Yes	Unclear	Yes	Unclear	No	No	Yes	No/No (89% vs. 34%)	Yes	NA	Fair
Fishman, 2007	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Fleischmann, 2001	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	No/Yes	Yes		Poor

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	ITT analysis?	Acceptable levels of overall attrition and between-group differences in attrition?	Avoidance of selective outcomes reporting?	Crossover design: assessment of carryover?	Quality rating
Frank, 2008	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	Yes	Fair
Friedmann, 2011	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Gana, 2006	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No/Yes	Unclear	NA	Fair
Gatti, 2009	Unclear	Unclear	Yes	No	No	No	Yes	No/No	Yes		Poor
Gilron, 2005	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes	No/Yes	Yes	Yes	Fair
Gilron, 2015		Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	Yes	Fair
Gimbel, 2003	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Gimbel, 2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	NA	Fair
Gordon, 2010 (Clin Ther)	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	No/No	Yes	Yes	Fair
Gordon, 2010 (Pain Res Manage)	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	No/No	Yes	Yes	Fair
Hale, 2007 (J Pain)	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Fair
Hale, 2007 (Clin Ther)	Unclear	Yes	Yes	No	No	No	Yes	No/Yes	Yes	NA	Fair
Hale, 2009 and Vorsanger, 2010	Yes	Yes	Yes	Unclear	Yes	Yes	Unclear	No/Yes (42% vs. 49%)	Yes	NA	Fair
Hale, 2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	NA	Fair
Hale, 2015 (Journal of Opioid Management)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes/Yes	Yes	NA	Good
Hale, 2015 (Journal of Pain Research)	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Hanna, 2008	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	NA	Good
Harati, 1998	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Hooten, 2015	Yes	Yes	Unclear	Yes	No	Yes	Unclear	Yes/No	Yes	NA	Fair
Hwang, 2019	Unclear	Unclear	Yes	Yes	Yes	Yes	No	No/Yes	Yes	NA	Poor
Huse, 2001	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes	Yes/Yes	Yes	No	Poor
Jamison, 1998	Unclear	Unclear	Unclear	No	No	No	Yes	Yes/Yes	Unclear	NA	Poor

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	ITT analysis?	Acceptable levels of overall attrition and between-group differences in attrition?	Avoidance of selective outcomes reporting?	Crossover design: assessment of carryover?	Quality rating
Karlsson, 2009	Yes	Yes	Yes	No	No	No	Yes	No/No (20% vs. 32%)	Yes	NA	Fair
Katz, 2007	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	NA	Fair
Katz, 2010	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Katz, 2015	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Fair
Kawamata, 2019	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Fair
Khoromi, 2007	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No/No	Yes	Yes	Fair
Kjaersgaard-Andersen, 1990	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/No	Unclear	NA	Poor
Krebs, 2018	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes/Yes	Yes	NA	Good
Kurtia, 2018	Unclear	Yes	No	Unclear	No	No	No	Unclear	Yes	NA	Poor
Langford, 2006	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Leng, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No (26%)/Yes (28% vs. 24%)	Yes	NA	Good
Lin, 2016	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Unclear	Yes	NA	Poor
Markenson, 2005	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Fair
Matsumoto, 2005	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	No/No	Yes	NA	Fair
Mayorga, 2016	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Fair
Mitra, 2013	Yes	No	Unclear	Yes	No	Unclear	Unclear	No (35%)/Yes (41% vs. 38%)	Unclear	NA	Poor
Moran, 1991	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Poor
Moulin, 1996	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	No/Unclear	Yes	Yes	Poor
Munera, 2010	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Naliboff, 2011	Yes	Yes	Yes	Unclear	No	Yes	Yes	No/No	Yes	NA	Fair
Neumann, 2013	Yes	Yes	Yes	No	No	No	No	No (48%)/Yes	Yes	NA	Fair
Nicholson, 2006	Yes	Unclear	Yes	Yes	No	No	Yes	No/Yes (57% vs. 51%)	Yes	NA	Fair
Niemann, 2000	Unclear	Unclear	Yes	Unclear	Unclear	Unclear	Yes	Yes/Yes	Yes	Yes	Fair
Niesters, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes/Yes	Yes	NA	Good

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	ITT analysis?	Acceptable levels of overall attrition and between-group differences in attrition?	Avoidance of selective outcomes reporting?	Crossover design: assessment of carryover?	Quality rating
Norrbrink, 2009	Unclear	Yes	No	Yes	Yes	Yes	Yes	No/No	Unclear	NA	Fair
O'Donnell, 2009a	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes/No	Yes	NA	Fair
O'Donnell, 2009b	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes/No	Yes	NA	Fair
Pavelka, 1998	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes/Yes	Unclear	Yes	Fair
Pedersen, 2014	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No/Yes (36% vs. 33%)	Unclear	NA	Fair
Peloso, 2000	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Portenoy, 2007	Yes	Yes	NA	Yes	Yes	Yes	Yes	Yes/Yes	Yes	NA	Good
Raja, 2002	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No/No	Yes	Yes	Fair
Rauck, 2006 and 2007	Yes	Yes	No	No	No	No	Yes	No/Yes (46% vs. 42%)	Yes	NA	Fair
Rauck, 2013	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/No	Yes		Poor
Rauck, 2014	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Poor
Rauck, 2015	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Poor
Rauck, 2016	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Rigo, 2017	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Yes/No (7.1% vs. 21.4% vs. 7.1%)	Yes	NA	Fair
Rowbotham, 2003	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Fair
Russell, 2000	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	Yes/Yes	Yes	NA	Fair
Salzman, 1999	Unclear	Unclear	Yes	No	No	No	Yes	Yes	Unclear	NA	Fair
Schnitzer, 2000	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Poor
Schwartz, 2011	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Serrie, 2017	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/No	Yes	NA	Fair
Simpson, 2007	Yes	Unclear	NA	Yes	Yes	Yes	Yes	Yes/Yes	Yes	NA	Good
Simpson, 2016	Unclear	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Fair
Sindrup, 1999	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	No/No	Yes	Yes	Poor
Sindrup, 2012	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No/Unclear	Yes	Yes	Fair

Author, year	Randomization adequate?	Allocation concealment adequate?	Groups similar at baseline?	Outcome assessors masked?	Care provider masked?	Patient masked?	ITT analysis?	Acceptable levels of overall attrition and between-group differences in attrition?	Avoidance of selective outcomes reporting?	Crossover design: assessment of carryover?	Quality rating
Steiner, 2011	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Steiner, 2011	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/No (33% vs. 42% vs. 28%)	Yes	NA	Fair
Sullivan, 2017	Unclear	Unclear	Yes	Unclear	No	No	Yes	Yes	Yes	NA	Fair
Tennant, 1982	No	No	No	No	No	No	Yes	Unclear	Unclear	NA	Poor
Thorne, 2008	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	No/Yes	Yes	Yes	Fair
Tominaga, 2016a	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	NA	Poor
Tominaga, 2016b	Unclear	Unclear	Unclear	Unclear	Yes	Yes	Yes	Unclear	Yes	NA	Poor
Trenkwalder, 2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Uberall, 2012	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes/Yes	Yes	NA	Fair
Ueberall, 2016	Yes	Yes	Yes	Yes	No	No	Yes	No/No (25.2% vs. 38.3% vs. 35.5%)	Yes	NA	Fair
Vinik, 2014	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Vojtassak, 2011	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Fair
Vondrackova, 2008	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	Yes/Yes	Yes	NA	Fair
Vorsanger, 2008	Yes	Unclear	Yes	Unclear	Yes	Yes	Yes	No/No	Yes	NA	Fair
Watson, 1998	Unclear	Yes	Unclear	Unclear	Yes	Yes	Yes	No/Yes	Yes	Yes	Fair
Watson, 2003	Yes	Unclear	Unclear	Unclear	Yes	Yes	Yes	No/Yes	Unclear	Yes	Fair
Webster, 2006	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	No/Yes	Yes	NA	Fair
Webster, 2013	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes/Yes	Yes	NA	Good
Wen, 2015	Unclear	Unclear	Yes	Unclear	Yes	Yes	Yes	No (25%)Yes	Yes	NA	Fair
Wild, 2010	Yes	Yes	Yes	No	No	No	Yes	No/No	Yes	NA	Fair
Wu, 2008	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	No/Yes	Yes	Yes	Fair
Zin, 2010	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes/Yes	Yes	NA	Fair

Abbreviations: ITT=intention-to-treat; NA=not applicable.

See Appendix F. Included Studies for full citations

Table G-2. Quality assessments of cohort studies

Author, year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures and potential confounders (i.e., age, sex, other medications)?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition or missing data?	Is there important differential loss to followup or overall high loss to followup or missing data?	Did the study perform appropriate statistical analyses on potential confounders (i.e., age, sex, other medications)?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality rating
Adams, 2006	Unclear	Yes	Unclear	No	Yes	Yes	Unclear	Yes	Fair
Bedson, 2019	Unclear	Unclear	Yes	No	No	Unclear	Yes	Yes	Fair
Bohnert, 2016	Yes	Yes	Yes	Unclear	Yes	No	Yes	Yes	Good
Campbell, 2018	Yes	No	Yes	Unclear	Yes	No	Yes	Yes	Fair
Carbone, 2013	Yes	Yes	Yes	Unclear	Yes	No	Yes	Yes	Good
Carman, 2011	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Chung, 2018	Yes	Yes	Yes	No	No	Unclear	Yes	Yes	Fair
Coffin, 2016	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Dunn, 2010	Yes	Unclear	Yes	Yes	Yes	NA	Yes	Yes	Good
Edlund, 2014	Yes	Unclear	Yes	Unclear	No	No	Yes	Yes	Fair
Hartung, 2007	Yes	No	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Hernandez, 2018	Yes	No	Yes	No	Yes	No	Yes	Yes	Fair
James, 2019	Unclear	No	Yes	No	Yes	Yes	No	Yes	Poor
Krebs, 2011	Yes	No	Yes	No	Yes	No	Yes	Yes	Fair
Krebs, 2016	Unclear	No	Yes	No	Yes	Yes	Yes	Yes	Fair
Lo-Ciganic, 2017	Unclear	No	Yes	No	Yes	No	Yes	Yes	Fair
Mark, 2019	Yes	Unclear	Yes	No	No	Unclear	Yes	Yes	Fair
Miller, 2011	Unclear	Mostly, some differences in prior medication usage	Yes	No	No	Unclear	Yes	Yes	Fair
Miller, 2015	Yes	Yes	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Peckham, 2018	Yes	No	Unclear	Unclear	NA	NA	Yes	Yes	Fair
Ray, 2015	Unclear	Yes	Yes	No	No	Unclear	Yes	Yes	Fair
Ray, 2016	Unclear	Yes	Yes	No	No	Unclear	Yes	Yes	Fair
Richardson, 2018	Unclear	Yes	Yes	No	No	Unclear	Yes	Yes	Fair
Rubinstein, 2017	Unclear	No	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Saunders, 2010	Yes	Unclear	Yes	Unclear	No	Unclear	Yes	Yes	Fair

Author, year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria (inception cohort)?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures and potential confounders (i.e., age, sex, other medications)?	Were outcome assessors and/or data analysts blinded to the exposure being studied?	Did the article report attrition or missing data?	Is there important differential loss to followup or overall high loss to followup or missing data?	Did the study perform appropriate statistical analyses on potential confounders (i.e., age, sex, other medications)?	Were outcomes prespecified and defined, and ascertained using accurate methods?	Quality rating
Scherrer, 2016 (J Pain)	Unclear	Unclear	Yes	No	Yes	No	Yes	Yes	Fair
Scherrer, 2016 (Prev Med)	Yes	No	Yes	Unclear	No	Unclear	Yes	Yes	Fair
Sun, 2017	Yes	No	Yes	No	Yes	No	Yes	Yes	Fair
Taipale, 2019	Yes	No	Yes	Yes	NA	NA	Unclear	Yes	Fair
Veiga, 2018	Yes	Yes	Yes	No	Yes	No	Yes	Yes	Good
Vigil, 2017	Yes	No	Yes	Unclear	Yes	No	No	Yes	Fair

Abbreviations: NA=not applicable.

Based on United States Preventive Services Task Force Quality Assessment Criteria (see Methods section for details).

See Appendix F. Included Studies for full citations

Table G-3. Quality assessments of case-control studies

Author, Year	Did the study attempt to enroll all or random sample of cases using predefined criteria?	Were the controls derived from the same population as the cases?	Were the groups comparable at baseline on key prognostic factors?	Were enrollment rates similar in cases and controls invited to participate?	Did the study use accurate methods for identifying outcomes?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Did the study perform appropriate statistical analyses on potential confounders?	Quality rating
Gomes, 2011	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good
Gomes, 2013	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good
Gomes, 2017	Yes	Yes	No	NA	Yes	Yes	Yes	Fair
Gomes, 2018	Yes	Yes	No	NA	Yes	Yes	Yes	Fair
Li, 2013a	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good
Li, 2013b	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Good

Based on United States Preventive Services Task Force Quality Assessment Criteria (see Methods section for details).

See Appendix F. Included Studies for full citations

Table G-4. Quality assessments of cross-sectional studies

Author, Year	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Were outcome assessors blinded to patient characteristics?	Did the article report attrition?	Is there overall high loss to followup?	Were prespecified outcomes assessed in all patients?	Quality
Deyo, 2013	Yes	Unclear	NA	NA	Yes	Fair

Abbreviations: NA=not applicable.

Based on United States Preventive Services Task Force Quality Assessment Criteria (see Methods section for details).

See Appendix F. Included Studies for full citations

Table G-5. Quality assessments of diagnostic accuracy studies

Author, year	Evaluates population other than the one used to derive the instrument	Avoided case-control design	Consecutive series of patients or a random subset	Describes patient demographics, opioid prescribing characteristics, and underlying conditions	Adequate description of screening instrument	Appropriate criteria included in screening instrument	Adequate description of methods for identifying aberrant drug-related behaviors	Appropriate criteria used to identify aberrant drug related behaviors	Aberrant drug-related behaviors assessed in all enrollees	Blinded assess-ment of aberrant drug-related behaviors	Quality rating
Akbik, 2006	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Unclear	Fair
Jones, 2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Unclear	Fair
Jones, 2013	No	Yes	Unclear	Yes	Yes	Yes	Yes	No	Unclear	Unclear	Poor*
Jones, 2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	Unclear	Poor
Jones, 2015	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Unclear	Unclear	Fair
Moore, 2009	Yes	No	No	Yes	Yes	Yes	Yes	No	No	Unclear	Poor
Webster, 2005	No	Yes	Yes	Yes	Yes	Yes	No	Unclear	Unclear	Unclear	Fair

*Jones, 2013 also downgraded because ~40% of population evaluated for predictive accuracy did not receive opioids and discrepancies in study in reported sensitivity and specificity
Based on various methods sources (see Methods section for details).
See Appendix F. Included Studies for full citations

Appendix H. Data Abstraction

Table H-1. Key Question 1: Long-term cohort study of opioids versus placebo for chronic pain – study characteristics

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders	Enrolled Analyzed Loss to Followup
Veiga, 2018	Prospective cohort study conducted at 4 multidisciplinary chronic pain centers in Portugal	Pain condition: Mixed Age: ≥18 years Pain severity: Not specified Psychiatric disease: Excluded Substance use: Excluded from those analyzed Prior opioid use: Not specified	A. Opioid users B. Non-users	A vs. B Aged 18 to 45 years: 18.9% vs. 14.1% Aged 45 to 60 years: 31.3% vs. 31.7% Aged 60 to 75 years: 35.4% vs. 34.6% Aged >75 years: 14.5% vs. 19.6% Female: 74.2% vs. 71.1% Pain duration, median (IQR): 4.0 (2.0 to 10) vs. 5.0 (2.0 to 14.0) years Musculoskeletal pain: 62% Neuropathic pain: 25% Chronic postsurgical and posttraumatic pain: 14% Median prescribed opioid dose: 60 mg MED/day	Used propensity score matching to match cases (opioid users) with controls (non-users). Before and after sample matching, nonparametric and parametric tests performed; chi-square tests used for categorical variables.	A vs. B Enrolled: 674 Analyzed: 488 (371 vs. 117)

Abbreviations: IQR=interquartile range.

See Appendix F. Included Studies for full citation

Table H-2. Key Question 1: Long-term cohort study of opioids versus placebo for chronic pain – study results

Author, Year	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Veiga, 2018	Variables for the propensity score model included: sex, age, pain duration (in years), educational status/ professional activity, pain type, anxiety, depression, diabetes mellitus, dyslipidemia, cardiac disease, chronic respiratory disease, hypertension, obesity, alcohol and drug consumption, S-TOPS questionnaire dimensions at baseline, BPI interference and severity scores at baseline	A vs. B, proportion with clinical improvement from baseline BPI interference scale: 62.3% (231/371) vs. 67.5% (79/117) at 12 months, RR 0.92 (95% CI, 0.79 to 1.07); 57.4% (222/371) vs. 62.3% (73/117) at 24 months, RR 0.96 (95% CI, 0.81 to 1.13) BPI severity scale: 61.5% (228/371) vs. 76.1% (89/117) at 12 months, RR 0.81 (95% CI, 0.71 to 0.92); 53.4% (198/371) vs. 59.0% (69/117) at 24 months, RR 0.90 (95% CI, 0.76 to 1.08) S-TOPS Pain symptoms: 66.8% (248/371) vs. 76.9% (90/117) at 12 months, RR 0.87 (95% CI, 0.77 to 0.98); 57.1% (221/371) vs. 71.7% (85/117) at 24 months, RR 0.82 (95% CI, 0.71 to 0.94) S-TOPS Physical function of lower body: 38.8% (144/371) vs. 50.4% (59/117) at 12 months, RR 0.77 (95% CI, 0.62 to 0.96); 45.5% (169/371) vs. 36.7% (43/117) at 24 months, RR 1.24 (95% CI, 0.95 to 1.61) S-TOPS Physical function of upper body: 47.9% (70/371) vs. 60.9% (23/117) at 12 months, RR 0.96 (95% CI, 0.63 to 1.46); 20.2% (75/371) vs. 14.5% (17/117) at 24 months, RR 1.39 (95% CI, 0.86 to 2.26) S-TOPS Satisfaction with outcome: 67.6% (251/371) vs. 53.8% (63/117) at 12 months, RR 0.12 (95% CI, 0.08 to 0.19); 64.4% (239/371) vs. 47.0% (55/117) at 24 months, RR 1.37 (95% CI, 1.11 to 1.68) S-TOPS Satisfaction with care: 60.9% (226/371) vs. 47.9% (56/117) at 12 months, RR 1.27 (95% CI, 1.03 to 1.56); 56.3% (209/371) vs. 46.1% (54/117) at 24 months, RR 1.22 (95% CI, 0.98 to 1.51) S-TOPS Family/social disability: 45.5% (176/371) vs. 53.2% (63/117) at 12 months, RR 0.88 (95% CI, 0.72 to 1.07); 46.0% (169/371) vs. 47.0% (55/117) at 24 months, RR 0.97 (95% CI, 0.77 to 1.21) S-TOPS Role emotional disability: 42.3% (157/371) vs. 41.0% (48/117) at 12 months, RR 1.03 (95% CI, 0.80 to 1.32); 33.7% (125/371) vs. 41.9% (49/117) at 24 months, RR 0.80 (95% CI, 0.62 to 1.04)	North Portugal Regional Operational Programme and the European Regional Development Fund	Good

Abbreviations: BPI=Brief Pain Inventory; CI=confidence interval; IQR=interquartile range; RR=relative risk; S-TOPS=Shortened Treatment Outcomes in Pain Survey.

See Appendix F. Included Studies for full citations

Table H-3. Key Question 1: Studies of cannabis use in patients prescribed opioids for chronic pain – study characteristics

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders	Screened Eligible Enrolled Analyzed Loss to Followup
Campbell, 2018	Prospective cohort, recruited through community pharmacies, Australia	Adults, chronic (>3 months) non-cancer pain, prescribed opioids (fentanyl, morphine, oxycodone, buprenorphine, methadone, hydromorphone) for >6 weeks. Excluded: prescribed opioids for opioid substitution therapy for heroin dependence or those with cancer	A. Near daily or daily use (>20 days/month): 3% at baseline B. Less frequent use (1 to 19 days/month): 5% at baseline C. No cannabis use: 91% at baseline	Age, median (IQR), years: 58 (48 to 67) Female: 56% Back or neck pain: 77% Arthritis: 62% Neuropathic pain: 62% Duration of chronic pain, median (IQR): 10 (4.5 to 20.0) years Baseline BPI Pain Severity Score, mean (SD): 5.1 (1.8) Baseline BPI Pain Interference Score, mean (SD): 5.7 (2.3) Duration prescribed strong opioid, median (IQR): 4 (1.5 to 10.0) years Baseline oral morphine equivalents, median mg/day (IQR): 75 (36 to 150) Baseline cannabis lifetime use: 43% # of pain conditions, median (IQR): 2 (2 to 3) Unemployed: 49% Retired: 31%	Phone interviews and self-completed surveys	Screened: 2091 Eligible: 1873 Enrolled: 1514 Analyzed: 1235 at 1 year, 1277 at 2 years, 1211 at 3 years, 1217 at 4 years
Vigil, 2017	Historical cohort, Single physician single rehabilitation clinic, New Mexico Medical Cannabis Program (MCP)	Adults, enrolled at rehabilitation clinic; at least 2 opioid prescriptions in 3 months prior to start of observation period; prescribed < 200 mg/day IV morphine equivalents Excluded: Inflammatory conditions (such as rheumatoid arthritis)	A. Self-referral to MCP with diagnosis of "severe chronic pain" from musculoskeletal condition annually validated by 2 independent physicians (n=37) B. Non-MCP patients with diagnosis of common chronic back pain condition with no current usage of cannabis (n=29)	A. Age, mean (SD), years: 53.6 (9.5) Male 45.9% Back pain 86% Knee pain 5% Hip pain 3% Wrist pain 3% Shoulder pain 3% Daily opioid dosage 1st 3 months, mean (SD): 24.4 mg (23.3) B. Age, mean (SD), years: 59.7 (13.8) Female 31% Back pain 100% Daily opioid dosage 1st 3 months, mean (SD): 16.2 mg (14.8)	New Mexico Prescription Monitoring Program and self-completed surveys (only completed by MCP patients)	Screened: 146 Screened: 53 Eligible/Enrolled: 37 Eligible/Enrolled: 29 Analyzed: 37 Analyzed: 29 Completed survey: 33

Abbreviations: BPI=Brief Pain Inventory; IQR=interquartile range; IV=intravenous; mg=milligram; MCP=medical cannabis program; SD=standard deviation.

See Appendix F. Included Studies for full citations

Table H-4. Key Question 1: Studies of cannabis use in patients prescribed opioids for chronic pain – study results

Author, Year	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Campbell, 2018	Outcome at previous year, age sex, duration of pain, generalized anxiety disorder severity, history of substance use, and pain self-efficacy; pain severity adjusted for oral morphine equivalent, pain interference adjusted for pain severity and oral morphine equivalent, and oral morphine equivalent adjusted for pain severity	A vs. B vs. C BPI pain severity score, mean (SE): 5.2 (0.14) vs. 5.1 (0.13) vs. 4.9 (0.03) compared to previous wave, p=0.20 for A vs. C and p=0.06 for B vs. C BPI pain interference, mean (SE): 5.2 (0.19) vs. 5.7 (0.16) vs. 5.4 (0.04) compared to previous wave, p=0.13 for A vs. C and p=0.23 for B vs. C Oral morphine equivalents, mean mg/day (SE): 97.1 (12.7) vs. 95.1 (8.8) vs. 85.5 (1.7), compared to previous wave p=0.27 for A vs. C and p=0.69 for B vs. C Discontinued opioids (unadjusted): 18.9% vs. 7.1% vs. 13.8% at 2 years, RR 1.44 (95% CI, 0.71 to 2.94) for A vs. C and RR 0.48 (95% CI, 0.19 to 1.21) for B vs. C; 21.5% vs. 9.0% vs. 20.9% at 4 years, RR 1.05 (95% CI, 0.60 to 1.84) for A vs. C and RR 0.38 (95% CI, 0.17 to 0.83) for B vs. C GAD 7-item severity score mean (SE) (unadjusted, 0 to 21, higher score=greater anxiety): 6.9 vs. 7.5 vs. 4.5 at 2 years, p=0.0004 for A vs. C and p<0.0001 for B vs. C; 7.3 vs. 6.4 vs. 4.3 at 4 years, p<0.0001 for A vs. C and p=0.0005 for B vs. C	National Health and Medical Research Council & Australian Government	Fair
Vigil, 2017	Control for age and gender	A vs. B Ceased opioid prescriptions: 40.5% (15/37) vs. 3.4% (1/29), p<0.001; OR (95% CI): 17.27 (1.89 to 157.36) Reduced prescribed daily opioid: 83.8% (31/37) vs. 44.8% (13/29), p=0.001; OR (95% CI): 5.12 (1.56 to 16.88) Change in prescribed daily opioid dosage (mg), mean (SD): -12.0 (23.4) vs. -3.9 (13.2) (p=0.101) Percent point change in prescribed daily opioid dosage, mean (SD): -47.0% (63.1) vs. 10.4% (114.9) (p=0.013)	University of New Mexico Cannabis Research Fund	Fair

Abbreviations: BPI=Brief Pain Inventory; CI=confidence interval; mg=milligrams; GAD=Generalized Anxiety Disorder; OR=odds ratio; RR=risk ratio; SD=standard deviation; SE=standard error.

See Appendix F. Included Studies for full citations

Table H-5. Key Question 2a: Studies of long-term opioid use and abuse, misuse, and related outcomes – study characteristics and results

Author, Year	Type of Study Setting	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
Adams, 2006	Prospective cohort Setting not described	Patients aged 18 to 74 years, initiating a new therapy of NSAIDs, hydrocodone, or tramadol, with pain lasting ≥4 months	n=11,352 Age 18 to 35 years: 13.2% Age 36 to 50 years: 36.1% Age 51 to 65 years: 33.9% Age ≥66 years: 16.8% Female: 68.2% White: 84.0% Black: 12.7% Asian: 0.4% Native American: 1.1% Other race: 1.7%	Dose: NR Duration: NR overall Indication: 19.9% osteoarthritis, 16.6% other disorders of the back, 10.0% other disorders of the soft tissue, 8.0% other/unspecified joint disorders, 6.3% rheumatoid arthritis, 15.6% disc, knee, and cervical disorders	Abuse index (inappropriate use, use for purposes other than intended, inability to stop use, and evidence of opioid withdrawal)	Hydrocodone (n=4278) vs. tramadol (n=4965) vs. NSAID (n=8589) Cases of abuse: 4.9% (208/4278) vs. 2.7% (133/4965) vs. 2.5% (218/8589), p<0.01	Fair
Bedson, 2019	Prospective cohort UK Clinical Practice Research Datalink primary care database	Patients aged ≥18 years starting a new long-term opioid episode at the time of a recorded noninflammatory, potentially painful musculoskeletal condition	N=98,140 Median (IQR) age, years: 61 (47 to 73) Female: 59%	Dose: median average daily dose of 12.3 mg MED Duration: median 3.4 years (IQR 1.5 to 5.8) Indication: musculoskeletal pain	Unclear	Long-term opioid use vs. not on long term opioid Cases of abuse: 142 vs. 90 Adjusted HR (95% CI), not on long-term opioid as reference Overall for all long-term opioid users: 2.83 (2.13 to 3.76) <20 mg MED/day: 1.06 (0.71 to 1.60) 20 to <50 mg MED/day: 3.59 (2.55 to 5.06) ≥50 mg MED/day: 9.33 (6.55 to 13.29)	Fair

Author, Year	Type of Study Setting	Eligibility Criteria	Population Characteristics	Opioid Dose, Duration, and Indication	Method of Ascertaining and Defining Abuse/Misuse	Main Results	Quality
Edlund, 2014	Retrospective HMO, PPO and point-of-service 2000-2005 database review, United States	Patients aged ≥18 years with a new chronic non-cancer pain diagnosis, no cancer diagnosis, and no opioid use or opioid use disorder diagnosis in prior 6 months	n=568,640 (197,269 prescribed opioids in first year; of these, 5.5% had chronic use, >90-day supply) Mean age not reported; 11% age 18 to 30, 20% age 31 to 40, 27% age 41 to 50, 30% age 51 to 64, 12% ≥ age 65 Female: 58% Race: NR Mean duration of pain: all patients newly diagnosed	Dose: Among those with any opioid use, median = 36 mg/day MED. Daily MED categorized as none, low (1 to 36 mg), medium (36 to 120 mg), or high (≥120 mg). Duration: Mean NR; users identified as "chronic" had ≥91 days Indication: NR; inclusion criteria required newly diagnosed chronic non-cancer pain	Diagnosis of opioid abuse or dependence (ICD-9-CM code 304.00 or 305.50) within 18 months of first chronic non-cancer pain diagnosis	<u>Opioid abuse or dependence</u> No opioid prescription: 0.004% (150/371,371) Low dose, chronic: 0.72% (50/6902) Medium dose, chronic: 1.28% (47/3654) High dose, chronic: 6.1% (23/378) <u>Abuse or dependence, opioid use vs. no use</u> Low dose, chronic: aOR* 15 (95% CI, 10 to 21) Medium dose, chronic: aOR 29 (95% CI, 20 to 41) High dose, chronic: aOR 122 (95% CI, 73 to 206)	Fair

Abbreviations: aOR=adjusted odds ratio; CI=confidence interval; CM=clinical modification; HMO=health management organization; HR=hazard ratio; ICD=international classification of disease; IQR=interquartile range; MED=morphine equivalent dose; mg=milligrams; NR=not reported; OR=odds ratio; NSAID=nonsteroidal antiinflammatory drug; PPO=preferred provider organization; UK=United Kingdom; vs.=versus.

*Adjusted for age, sex, number of tracer pain sites, number of nonsubstance mental health disorders, previous substance abuse or dependence diagnosis, Charlson score.

See Appendix F. Included Studies for full citations

Table H-6. Key Question 2a: Studies of long-term opioid use and overdose – study characteristics

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method for Assessing Outcomes and Confounders	Enrolled Analyzed Loss to Followup
Bedson, 2019	Prospective cohort U.K. Clinical Practice Research Datalink primary care database	Patients aged ≥18 years starting a new long-term opioid episode at the time of a recorded noninflammatory, potentially painful musculoskeletal condition	A. Long-term opioid use 1. <20 mg MED/day 2. 20 to <50 mg MED/day 3. ≥50 mg MED/day B. No long-term opioid used	Median (IQR) age, years: 61 (47 to 73) Female: 59%	Unclear	Enrolled: 98,140 Analyzed: 98,140
Bohnert, 2016	Nested case-control	VHA patients with a chronic pain diagnosis (by ICD-9 codes) who were prescribed an opioid on the index date (a new prescription with at least a 2-year gap since last prescription episode) and who filled the prescription at a VHA facility.	Cases: died of an opioid-related overdose (unintentional or unknown) (n=399 matched a control) Controls: random sample from a serious mental illness registry who received opioids (n=483,278)	Mean age, years: 48.4 Female: 2.3% White: 86.9% Charlson comorbidity index Score of 0: 70.1% Score of 1: 17.7% Score of 2: 12.2%	Controls matched on sex, age, race and ethnicity, substance use disorder diagnosis, depression, other psychiatric diagnosis, acute pain, comorbid chronic diseases, Charlson score, use of benzodiazepines, antidepressants, and anticonvulsants, and ≥90 days of continuous opioid use at index date.	Cases Enrolled: 399, 221 matched to controls Controls Analyzed: 483,278 Loss to followup: None

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method for Assessing Outcomes and Confounders	Enrolled Analyzed Loss to Followup
Dunn, 2010	Retrospective cohort Group Health United States	Age >18 years starting new episode of opioid use (no opioids in past 6 months) from 1997 to 2005; having ≥3 opioid scripts filled in first 90 days of episode; diagnosis of chronic noncancer pain in 2 weeks before first opioid script.	Morphine equivalent doses: A. 1 to <20 mg/day B. 20 to <49 mg/day C. 50 to <99 mg/day D. ≥100 mg/day	Mean (SD; range) age, years: 54 (16.8; 18 to 99) Female: 59.6% Race: NR Pain diagnosis: 37.9% back; 30.3% extremity; 12.7% osteoarthritis; 12.3% injury, contusion, or fracture; 8.9% neck Opioid dose, mean (median): 13.3 mg (6.0 mg) Sedative-hypnotic use, any: 74.7% Muscle relaxant: 52.3% Benzodiazepine: 42.7% Charlson Score, mean (SD; range): 0.71 (1.48;0 to 14) Smoking: 29.5% Depression: 26.9% Substance abuse: 6.2% <u>Opioid</u> Hydrocodone: 46.3% Oxycodone: 24.5% Codeine combination: 11.6% Long-acting morphine: 6.2% Any short acting opioid: 90.4% Any long-acting opioid: 9.6%	All patients in HMO meeting inclusion criteria	Enrolled: 9940 Analyzed: 9940 Loss to followup: 32% left cohort during study; 7% died Mean duration of followup (range): 42 months (<1 to 119)
Gomes, 2011	Case-control Canada	Residents aged 15 to 64 years with public drug coverage and an opioid for nonmalignant pain (1997 to 2006)	Cases: Died of an opioid-related cause (n=498 matched a control) Controls: received opioids (n=1714) A. 1 to <20 mg/day B. 20 to <50 mg/day C. 50 to <100 mg/day D. 100 to <200 mg/day E. ≥200 mg/day	Total cohort n= 607,156 Mean (SD) age, years: 44.49 (8.25) cases, 44.72 (8.20) controls Sex (NR male or female): 58.8% cases, 58.0% controls	Controls matched on disease risk index (0.2 SD caliper), age, gender, index year, and Charlson	Primary-analysis: 593 with 498 matched Secondary-analysis: 873 with 781 matching

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method for Assessing Outcomes and Confounders	Enrolled Analyzed Loss to Followup
Ray, 2016	Retrospective cohort Tennessee Medicaid enrollees	Patients initiating therapy with the study drugs who had a diagnosis of chronic pain in the past 90 days	A. Long-acting opioid (morphine SR, oxycodone CR, transdermal fentanyl, methadone) B. Anticonvulsant or cyclic antidepressant	A vs. B Mean (SD) age, years: 47.9 (10.5) vs. 47.9 (107) Female: 60% vs. 60% Back pain: 75% vs. 76% Other musculoskeletal pain: 63% vs. 64% Abdominal pain: 18% vs. 18% Headache: 12% vs. 12% Other neurologic pain: 17% vs. 16%	Hospital death was defined as occurring if patients were admitted to the hospital on a day during which they had used one of the study drugs and died either while in the hospital or within 30 days of admission. All other deaths were considered out-of-hospital deaths (including patients who died in the emergency department) and were further classified as unintentional medication overdose or other deaths. The latter included cardiovascular, respiratory, other injury, or other deaths	Enrolled: 45,824 (22,912 vs. 22,912) Analyzed: 45,824 (22,912 vs. 22,912)

Abbreviations: HMO=health management organization; MED=morphine equivalent dose; NR=not reported; SD=standard deviation; SR=sustained release; U.K.=United Kingdom; VHA=Veterans Health Administration; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-7. Key Question 2a: Studies of long-term opioid use and overdose – study results

Author, Year	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Bedson, 2019	Age, sex, year of start of followup, ever smoking, ever alcohol drinking, overweight (BMI ≥25 kg/m^2), geographical region, deprivation level, prior recorded depression, co-prescribing of NSAID, and total number of co-morbid conditions.	Incidence of opioid overdose (A vs. B): 11.6 vs. 4.8 per 10,000 person-years Incidence of attempted suicide/self-harm (A vs. B): 0.7 vs. 0.6 per 10,000 person-years Attempted suicide/self-harm for A with B as reference: 1.01 (0.42 to 2.45) Adjusted HR (95% CI) of opioid overdose (B as reference) A: 2.24 (1.73 to 2.89) 1: 1.59 (1.16 to 2.19) 2: 2.83 (2.04 to 3.92) 3: 3.81 (2.50 to 5.80)	Unclear	Fair
Bohnert, 2016	Sex, age, race and ethnicity, substance use disorder diagnosis, depression, other psychiatric diagnosis, acute pain, comorbid chronic diseases, Charlson score, use of benzodiazepines, antidepressants, and anticonvulsants, and ≥90 days of continuous opioid use at index date.	Cases vs. controls Mean (SD) prescribed dose: 98.1 MEM (112.7) vs. 47.7 MEM (65.2), p<0.001 Median (IQR) prescribed dose: 60 MEM (30 to 120) vs. 25 MEM (15 to 45) Opioid dose was a good predictor of cases versus controls: ROC curve analysis: AUC 0.71 (95% CI, 0.66 to 0.76), p<0.001 Hosmer to Lemeshow goodness of fit, week 2 :13.37, p≤0.01	CDC and VHA	Good
Dunn, 2010	Sedative-hypnotic use as time-varying covariate Age, sex, smoking, depression diagnosis, substance abuse diagnosis, index pain diagnosis, chronic disease comorbidity adjustors (RxRisk & Charlson)	51 patients with overdose events (148 per 100,000 person to years) 40 serious overdose events (116 per 100,000 person to years) 6 fatal overdose events (17 per 100,000 person to years) Rate of any overdose per 100,000 person to years (95% CI); HR (95% CI) No opioid: 36 (13 to 70); 0.31 (0.12 to 0.80); 6 overdose events A. (reference): 160 (100 to 233); 1.0 B. 260 (95 to 505); 1.44 (0.57 to 3.62) C. 677 (249 to 1317); 3.73 (1.47 to 9.5) D. 1791 (894 to 2995); 8.87 (3.99 to 19.72) Opioid dose, any: 256 (187 to 336); 5.16 (2.14 to 12.48); 45 overdose events HR, serious events (95% CI) No opioid: 0.19 (0.05 to 0.68) A. (reference): 1.0 B. 1.19 (0.4 to 3.6); C. 3.11 (1.01 to 9.51); D. 11.18 (4.8 to 26.03); Opioid dose, any: 8.39 (2.52 to 27.98)	National Institute of Drug Abuse and Wellcome Trust	Good

Author, Year	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Gomes, 2011	Opioid exposure categorized by Average Daily Dose: <20mg, 20 to 49mg, 50 to 99mg, 100 to 199mg, ≥200mg Logistic models adjusted for: duration, income, history of EtOH abuse, interacting prescription drugs, total number of different opioids dispensed, long-acting opioid used, number of physicians prescribing opioids, number of pharmacies dispensing opioids	Risk estimates reported as adjusted OR (95% CI) Risk of opioid overdose death A. 1 (reference) B. 1.32 (0.94 to 1.84) C. 1.92 (1.30 to 2.85) D. 2.04 (1.28 to 3.24) E. 2.88 (1.79 to 4.63) Secondary using 120 to day exposure window risk of opioid overdose death A. 1 (reference) B. 0.93 (0.60 to 1.42) C. 1.31 (0.86 to 1.99) D. 1.47 (0.98 to 2.19) E. 2.24 (1.62 to 3.10)	MOHLTC Drug Innovation Fund and ICES, a nonprofit research institute sponsored by the Ontario MOHLTC	Good
Ray, 2016	The primary models included age, calendar year, and study medication as time-dependent covariates, estimated via a counting process formulation that accommodates nonproportional hazards	Adjusted HR (95% CI) A vs. B All deaths: 1.64 (1.26 to 2.12) Out-of-hospital deaths: 1.90 (1.40 to 2.58) Unintentional overdose: 3.37 (1.47 to 7.70) Out-of-hospital, not overdose death: 1.72 (1.24 to 2.39) Cardiovascular cause: 1.65 (1.10 to 2.46) Respiratory cause: 3.00 (0.81 to 11.09) Other injury cause: 1.15 (0.54 to 2.47) Other causes: 3.72 (1.04 to 13.30) In hospital deaths: 1.00 (0.59 to 1.69) All deaths in those taking high doses: 1.94 (1.40 to 2.70) All deaths in those taking low doses: 1.54 (1.01 to 2.34)	Government	Fair

Abbreviations: BMI=body mass index; CDC=Centers for Disease Control and Prevention; CI=confidence interval; EtOH=alcohol; HR=hazard ratio; ICES=Institute for Clinical Evaluative Sciences; IQR=interquartile range; MOHLTC=Ministry of Health and Long-Term Care; NSAID=nonsteroidal antiinflammatory drug; OR=odds ratio; SD=standard deviation; VHA=Veterans Health Administration; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-8. Key Question 2a: Studies of long-term opioid use and fractures – study characteristics

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method for Assessing Outcomes and Confounders
Bedson, 2019	Prospective cohort U.K. Clinical Practice Research Datalink primary care database	Patients aged ≥18 years starting a new long-term opioid episode at the time of a recorded noninflammatory, potentially painful musculoskeletal condition	A. Long-term opioid use 1. <20 mg MED/day 2. 20 to <50 mg MED/day 3. ≥50 mg MED/day B. No long-term opioid used	Median (IQR) age, years: 61 (47 to 73) Female: 59%	Unclear
Carbone, 2013	Cohort VA Spinal Cord Dysfunction Registry, United States	All male Veterans with a traumatic spinal cord injury with at least 2 years duration. Fracture incidence and opioid use was also obtained.	Duration of use of opioids prior to the incident fracture, was stratified by: 0 days (reference), <6 months, 6 months to ≤1 year, 1 to ≤2 years, 2 to ≤3 years, and ≥3 years, and dose stratified by < 224 mg and >225 mg	Mean age, years: 58 Female: 0% Duration of spinal cord injury >10 years: 80% Charlson Comorbidity index: 3.84 Treatment for osteoporosis: 55%	ICD-9 codes for fractures of the lower extremity, including: femoral neck (820.x), intertrochanteric (820.21, 820.31), subtrochanteric (820.22, 820.32), pelvis (808.x), femur (820.x, 821.x), patella (822.x), and tibia/fibula (823.x). Only incident fractures were included. A fracture was considered incident (i.e. a new episode of fracture and not coding of follow-up care for a prior fracture), if there were no encounters with the same three-digit ICD-9 codes within a 120-day period prior to the fracture. They excluded 140 fractures that had received codes indicating an external cause of injury (E codes).
Krebs, 2016	Prospective cohort 6 sites, United States	Men ≥65 years with back, hip, or knee pain most or all of the time	A. Opioid use B. Opioid non-use	A vs. B Mean (SD) age, years: 74.7 (6.4) vs. 73.7 (5.9) Female: 0% White: 89.2% vs. 91.9% Mean (SD) BMI: 28.8 (4.5) vs. 28.0 (4.0) Back pain: 61.2% vs. 27.6% Hip pain: 59.7% vs. 49.0% Knee pain: 65.1% vs. 67.0%	Falls and fractures were self-reported on questionnaires every 4 months. Fractures were confirmed by x-ray or review of imaging reports. Physical performance was assessed using tests of grip strength, chair stands, gait speed, and dynamic balance. Each individual test was scored from 0=unable to complete to 5=best and converted to quintiles based on score distributions. The individual test scores were summed to create an overall physical performance score with a possible range of 0 to 20, where lower scores indicated worse performance.

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method for Assessing Outcomes and Confounders
Li, 2013	Nested case control United Kingdom	Cohort: Patients with noncancer pain with at least 1 opioid prescription between 1/1/90 and 12/31/08 in the General Practice Research Database Cases (n=21,739): First-time diagnosed fracture of the hip, humerus, or wrist during 1990 to 2008, age 18 to 80 years, >2 years of medical history before index date; excluding patients with cancer, dementia, metabolic bone disease, Cushing syndrome, hyperparathyroidism, long-term immobilization, or alcohol or drug abuse, fracture within 2 years, MVA within 90 days, osteoporosis diagnosis prior to index date Controls (n=85,326): Up to 4 controls without fracture selected for each case, matched on age, sex, index date, and general practice	A. Opioid nonuse B. Current cumulative opioid use 1 prescription C. 2 to 3 opioid prescriptions D. 4 to 5 opioid prescriptions E. 6 to 20 opioid prescriptions F. 21 to 50 opioid prescriptions G. 51 to 100 opioid prescriptions H. >100 opioid prescriptions 1. Opioid nonuse 2. Current use 3. Recent use 4. Past use	Mean age, years: 62 Female: 77% Race: NR Pain condition: NR Pain duration: NR Pain severity: NR Mean dose: NR Most commonly prescribed opioids: dihydrocodeine, codeine, propoxyphene, tramadol	Used General Practice Research Database, in which drug exposures and diagnoses (including fracture) have been validated

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method for Assessing Outcomes and Confounders
Lo-Ciganic, 2017	Prospective cohort 4 sites, United States	Aged 45 to 79 years with or at high-risk for knee osteoarthritis	A. Opioid users B. Antidepressant users C. Prescription pain medication users D. Over the counter pain medication users E. Nutraceutical users F. No pain medication use	A vs. B vs. C vs. D vs. E vs. F Mean (SD) age, years: 60.1 (9.2) vs. 59.3 (8.7) vs. 62.8 (9.1) vs. 61.8 (9.1) vs. 61.3 (9.0) vs. 61.2 (9.3) Female: 71.9% vs. 74.4% vs. 59.5% vs. 57.3% vs. 52.9% vs. 53.8% White: 72.8% vs. 87.8% vs. 78.8% vs. 75.3% vs. 88.3% vs. 79.0% Mean (SD) BMI: 30.8 (5.2) vs. 29.1 (5.3) vs. 29.3 (4.8) vs. 28.9 (4.9) vs. 27.5 (4.4) vs. 28.0 (4.6) History of falls in previous year: 26.3% vs. 25.4% vs. 14.7% vs. 15.2% vs. 14.8% vs. 11.5% Mean (SD) PCS SF-12 score: 39.6 (9.9) vs. 48.4 (9.6) vs. 46.5 (9.2) vs. 47.0 (9.1) vs. 51.4 (7.6) vs. 51.7 (7.5) Mean (SD) MCS SF-12 score: 50.6 (10.4) vs. 49.2 (9.8) vs. 55.2 (7.4) vs. 54.0 (8.1) vs. 54.8 (7.0) vs. 54.5 (6.7) Mean (SD) PASE score: 146.2 (78.9) vs. 156.7 (82.8) vs. 152.5 (84.4) vs. 165.8 (84.3) vs. 169.2 (79.6) vs. 163.0 (79.4) Mean (SD) pain NRS: 5.0 (2.9) vs. 3.6 (2.7) vs. 3.8 (2.7) vs. 4.2 (2.7) vs. 2.8 (2.3) vs. 2.6 (2.5)	Falls were self-reported
Miller, 2011	Prospective cohort New Jersey Medicare recipients, United States	Medicare beneficiaries with osteoarthritis or rheumatoid arthritis who initiated monotherapy with a NSAID or an opioid between January 1, 1999 and December 31, 2006	A. Short-acting opioids B. Long-acting opioids C. NSAIDs Additional subgroups: D. Low-dose opioid (≤75 mg equivalents of codeine/day) E. Medium-dose opioid (76 to 225 mg equivalents of codeine/day) F. High-dose opioid (>225 mg equivalents of codeine/day)	A vs. B vs. C Mean (SD) age, years: 81.1 (7.1) vs. 81.5 (7.7) vs. 79.7 (7.0) Female: 84.0% vs. 84.3% vs. 84.0% White: 92.6% vs. 90.1% vs. 84.6% History of previous fractures: 13.9% vs. 10.7% vs. 6.5% Osteoporosis: 31.1% vs. 35.1% vs. 29.3% Chronic back pain: 33.1% vs. 29.2% vs. 28.6% Use of benzodiazepines: 24.3% vs. 25.4% vs. 20.6%	Fractures of the hip, humerus/ulna, or wrist, identified by a combination of diagnosis (ICD-9CM codes) and procedure (CPT codes)

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method for Assessing Outcomes and Confounders
Saunders, 2010	Cohort Group Health Cooperative, United States	Age ≥60 years, initiating opioids (no opioid prescriptions in prior 6 months) with ≥3 prescriptions in 90 days and a diagnosis of non-cancer pain 2 to 3 weeks prior to the index prescription.	Opioid dose: A. Not currently using B. 1 to <20 mg/day C. 20 to <50 mg/day D. >50 mg/day E. Any use	Mean age, years: 73 Female: 66% Race: NR Depression diagnosis: 22% Substance abuse diagnosis: 3.8% Dementia diagnosis: 4.8% Prior fracture: 2.6% HRT/bisphosphonate use: 34% Rx Risk Score, mean (SD): 4272 (2455) Charlson Index , mean (SD): 1.32 (2.0) Pain diagnosis at index visit 42% back pain, 4.8% neck pain, 25% osteoarthritis, 2.4% headache, 34% extremity pain, 5.3% abdominal pain/hernia, 0.6% menstrual/menopausal pain, 0.2% temporomandibular disorder pain Mean (SD) MED, mg: 12.8 mg (17.0) Sedative hypnotic use: 60% Antidepressant use: 57% Opioid prescribed: Hydrocodone: 42% Oxycodone: 24% Codeine combination: 14% Long-acting morphine: 8.3%	Fractures initially identified by ICD-9 codes (800xx-804xx; 807xx-809xx; 810xx-829xx; 2000-2006, excluded vertebral fractures) and verified by medical record review; medication data from Group Health Cooperative automated pharmacy files (over 90% of prescriptions); covariates from automated health care data
Taipale, 2019	Cohort Special Reimbursement Register, Finland	Persons diagnosed with Alzheimer's Disease between 2010 and 2011	A: Opioid user B: Nonuser of opioids	A vs. B Mean (SD) age, years: 83.0 (6.9) vs. 83.0 (6.8) Female: 66.7% vs. 66.7% Race: NR Previous opioid use: 9.7% vs. 3.3%	Fractures identified from records in the Hospital Discharge register; corresponding ICD-10 codes of S72.0-S72.2 Propensity score representing the probability of opioid use given the measured confounders was derived with logistic regression model to balance potential confounding factors between opioid users and nonusers

Abbreviations: BMI=body mass index; CM=clinical modification; CPT=current procedural terminology; ICD=international classification of disease; IQR=interquartile range; MED=morphine equivalent dose; MCS=mental component subscale; NR=not reported; NRS=numerical rating scale; NSAID=nonsteroidal antiinflammatory drug; PCS=physical component subscale; SD=standard deviation; SF-12=short form 12-item; U.K.=United Kingdom; VA=Veterans Affairs; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-9. Key Question 2a: Studies of long-term opioid use and fractures – study results

Author, Year	Enrolled Analyzed Loss to Followup	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Bedson, 2019	Enrolled: 98,140 Analyzed: 98.140	Age, sex, year of start of followup, ever smoking, ever alcohol drinking, overweight (BMI ≥25 kg/m^2), geographical region, deprivation level, prior recorded depression, co-prescribing of NSAID, and total number of co-morbid conditions.	Incidence of falls (A vs. B): 548.9 vs. 369.5 per 10,000 person-years Incidence of major trauma (A vs. B): 375.7 vs. 285.4 per 10,000 person-years Adjusted HR (95% CI), B as reference Falls for A : 1.23 (1.19 to 1.28) Falls for 1: 1.17 (1.12 to 1.21) Falls for 2: 1.34 (1.27 to 1.42) Falls for 3: 1.64 (1.50 to 1.80) Major trauma for A: 1.14 (1.10 to 1.19) Major trauma for 1: 1.09 (1.04 to 1.14) Major trauma for 2: 1.24 (1.16 to 1.32) Major trauma for 3: 1.34 (1.20 to 1.50)	Unclear	Fair
Carbone, 2013	Enrolled: 7447 Analyzed: Unclear Loss to followup: 0 (4.5% of our cohort was missing data on race, 22.7% was missing data on completeness of injury, and 13% was missing data on duration of injury)	Age, race, duration of spinal cord injury, level of spinal cord injury, and completeness of spinal cord injury (complete/incomplete/ unknown), Charlson comorbidity indices, Medication use that may be associated with fracture risk (including heparin, corticosteroids, loop diuretics, thiazide diuretics, proton pump inhibitors serotonin receptor agonists, thiazolidinediones), and pharmacological treatments for osteoporosis (teriparatide, bisphosphonates, calcitonin), calcium, and vitamin D.	Higher doses (>225 mg/day of codeine equivalents) were significantly positively associated with fracture risk in adjusted models (p<0.0001).	VA	Good
Krebs, 2016	Enrolled: 2902 (390 vs. 2512) Analyzed: 2732 (129 vs. 2603) Loss to followup: 89 (3.1%) dropped out; overall 30.5% attrition	Propensity score matching was done based on age, BMI, total hip BMD, race/ethnicity, smoking status, current alcohol use, and health status.	A vs. B Unadjusted RR (95% CI) of falling: 1.37 (1.23 to 1.54) Unadjusted HR (95% CI) of any clinical fracture: 1.09 (0.92 to 1.28) Unadjusted HR (95% CI) of hip fracture: 2.14 (1.36 to 3.38) Unadjusted difference (95% CI) between groups in change in physical performance score from baseline: 0.048 (-0.062 to 0.158) Adjusted PS-restricted cohort HR (95% CI) of mortality: 1.22 (0.94 to 1.58) Adjusted PS-restricted cohort HR (95% CI) of clinical fracture/death composite outcome: 1.14 (0.88 to 1.48) Adjusted PS-restricted cohort HR (95% CI) of hip fracture/death composite outcome: 1.22 (0.94 to 1.58)	NIH	Fair

Author, Year	Enrolled Analyzed Loss to Followup	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Li, 2013	Enrolled: NR Analyzed: 21,739 fracture cases and 85,326 controls Number not analyzable: NR	Smoking, BMI, number of general practice visits, recorded years before index date, opioid use (new vs. prevalent), comorbidities, comedications, types of pain, recent/past opioid use (matched on age, sex, index date, and general practice)	Adjusted OR (95% CI) for risk of hip, humerus, or wrist fracture A. 1 (reference) B. 2.70 (2.34 to 3.13) C. 1.90 (1.67 to 2.17) D. 1.44 (1.22 to 1.69) E. 1.17 (1.08 to 1.27) F. 1.06 (0.98 to 1.15) G. 1.06 (0.96 to 1.16) H. 1.12 (0.99 to 1.25) 1. 1 (reference) 2. 1.27 (1.21 to 1.33) 3. 1.05 (0.99 to 1.13) 4. 0.96 (0.92 to 1.01)	None	Good

Author, Year	Enrolled Analyzed Loss to Followup	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Lo-Ciganic, 2017	Enrolled: 4231 Analyzed: 4231 at 12 months, 3891 at 24 months, 3764 at 36 months, 3762 at 48 months Loss to followup: NR	A vs. B vs. C vs. D vs. E vs. F Falls at 12 months: 28.1% (32/114) vs. 22.0% (123/559) vs. 14.2% (100/706) vs. 13.3% (95/712) vs. 13.8% (92/667) vs. 10.3% (152/1473) Falls at 24 months: 24.5% (26/106) vs. 21.0% (104/496) vs. 13.1% (69/526) vs. 15.8% (98/620) vs. 11.5% (78/676) vs. 10.4% (152/1467 Falls at 36 months: 22.9% (25/109) vs. 22.9% (114/497) vs. 16.2% (76/468) vs. 13.5% (75/557) vs. 14.9% (93/624) vs. 10.8% (163/1509) Falls at 48 months: 19.7% (27/137) vs. 21.9% (106/484) vs. 15.6% (70/449) vs. 17.1% (100/584) vs. 12.0% (69/576) vs. 12.3% (189/1532) Recurrent falls at 12 months: 28.1% (32/114) vs. 22.0% (123/559) vs. 14.2% (100/706) vs. 13.3% (95/712) vs. 13.8% (92/667) vs. 10.3% (152/1473) Full adjusted analysis, RR (95% CI) of recurrent falls at 12 months A. 1.22 (1.04 to 1.45), p=0.02 B. 1.25 (1.10 to 1.41), p<0.0001 C. 1.08 (0.95 to 1.23), p=0.25 D. 1.13 (1.00 to 1.28), p=0.05 E. 1.13 (0.99 to 1.28), p=0.05 F. Reference	A vs. B vs. C vs. D vs. E vs. F Falls at 12 months: 28.1% (32/114) vs. 22.0% (123/559) vs. 14.2% (100/706) vs. 13.3% (95/712) vs. 13.8% (92/667) vs. 10.3% (152/1473) Falls at 24 months: 24.5% (26/106) vs. 21.0% (104/496) vs. 13.1% (69/526) vs. 15.8% (98/620) vs. 11.5% (78/676) vs. 10.4% (152/1467 Falls at 36 months: 22.9% (25/109) vs. 22.9% (114/497) vs. 16.2% (76/468) vs. 13.5% (75/557) vs. 14.9% (93/624) vs. 10.8% (163/1509) Falls at 48 months: 19.7% (27/137) vs. 21.9% (106/484) vs. 15.6% (70/449) vs. 17.1% (100/584) vs. 12.0% (69/576) vs. 12.3% (189/1532) Recurrent falls at 12 months: 28.1% (32/114) vs. 22.0% (123/559) vs. 14.2% (100/706) vs. 13.3% (95/712) vs. 13.8% (92/667) vs. 10.3% (152/1473) Full adjusted analysis, RR (95% CI) of recurrent falls at 12 months A. 1.22 (1.04 to 1.45), p=0.02 B. 1.25 (1.10 to 1.41), p<0.0001 C. 1.08 (0.95 to 1.23), p=0.25 D. 1.13 (1.00 to 1.28), p=0.05 E. 1.13 (0.99 to 1.28), p=0.05 F. Reference	NIH	Fair

Author, Year	Enrolled Analyzed Loss to Followup	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Miller, 2011	Enrolled: 17,310 (11,549 vs. 887 vs. 4874) Analyzed: 17,310 (11,549 vs. 887 vs. 4874) Loss to followup: NR	Models adjusted for 39 baseline covariates, including age, sex, race, diagnoses, comorbidities, and use of medications.	A vs. B vs. C vs. D vs. E vs. F Incidence of fracture events (95% CI) over entire study period: 53 (34 to 79) vs. 128 (118 to 138) vs. 25 (17 to 34) vs. 120 (111 to 130) vs. 53 (20 to 111) vs. 115 (98 to 134) vs. 126 (115 to 138) Incidence of fracture events (95% CI) in the first 15 days of taking medication: 121 (33 to 310) vs. 902 (813 to 998) vs. 90 (55 to 151) vs. 847 (764 to 936) vs. 781 (627 to 961) vs. 890 (790 to 998) Incidence of fracture events (95% CI) after the first 15 days of taking medication: 47 (28 to 53) vs. 46 (39 to 53) vs. 16 (10 to 24) vs. 29 (6 to 86) vs. 49 (37 to 64) vs. 46 (39 to 54) HR (95% CI) of fracture event Overall: 2.6 (1.5 to 4.4) vs. 5.1 (3.7 to 7.1) vs. reference vs. 2.2 (0.9 to 5.2) vs. 4.6 (3.2 to 6.6) vs. 5.1 (3.7 to 7.2) First 2 weeks after starting medication: 1.3 (0.4 to 3.8) vs. 8.0 (4.9 to 13.0) vs. NR vs. NR vs. NR vs. NR Doses of <75 mg equivalents of codeine/day vs. doses of 76 to 225 mg equivalents of codeine/day: 4.6 (3.2 to 6.6) Doses of <75 mg equivalents of codeine/day vs. doses greater than 225 mg equivalents of codeine/day: 5.1 (3.7 to 7.2) Among high dose opioid users (NSAIDs group as reference): 2.8 (1.6 to 4.7) vs. 6.4 (4.6 to 8.9) Among high dose opioid users A vs. B: 2.1 (1.3 to 3.5)	Government	Fair
Saunders, 2010	Enrolled, 2341 Analyzed: 2341 Loss to followup: NR Duration of followup (mean, person-months) (SD): 32.7 (21.3)	Age, sex, tobacco use, depression diagnosis, substance abuse diagnosis, dementia diagnosis, index pain diagnosis, chronic disease comorbidity adjustors, sedative-hypnotic use, antidepressant use, HRT/ bisphosphonate use, and prior fractures.	Fracture rate: 5.0%/year <u>Adjusted HRs (95% CI) for risk of fracture</u> A. 1 (reference) B. 1.20 (0.92 to 1.56) C. 1.34 (0.89 to 2.01) D. 2.00 (1.24 to 3.24) E. 1.28 (0.99 to 1.64)	National Institute of Drug Abuse	Fair

Author, Year	Enrolled Analyzed Loss to Followup	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Taipale, 2019	Enrolled: 4752 opioid users and 4752 matched controls Analyzed: 9500 Loss to followup: NR Median duration of followup: 141 to 681 days	Age, sex, time since Alzheimer's diagnosis, University hospital catchment area, occupational socioeconomic position, drug use at the start of followup, comorbidities, number of days hospitalized in the prior year.	A vs. B Age-adjusted incidence rate of hip fractures (95% CI): 3.47 (2.62 to 4.33) vs. 1.94 (1.65 to 2.22) Attributable risk of hip fractures in opioid use: 1.53 per 100 person-years HR (95% CI) of risk of hip fracture: 1.96 (1.27 to 3.02) The risk of hip fracture increased by the increasing opioid strength, with buprenorphine and strong opioid use being associated with hip fractures while weak opioids were not. However, the confidence intervals were wide and partially overlapping between the categories.	None	Fair

Abbreviations: BMD=bone mineral density; BMI=body mass index; CI=confidence interval; HR=hazard ratio; HRT=hormone replacement therapy; NIH=National Institutes of Health; NSAID=nonsteroidal antiinflammatory drug; NR=not reported; RR=risk ratio; PS=propensity score; VA=Veterans Administration; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-10. Key Question 2a: Studies of long-term opioid use and cardiovascular outcomes – study characteristics

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders	Screened Eligible Enrolled Analyzed Loss to Followup
Carman, 2011	Retrospective cohort United States	Claim submitted for dispensing of opioids or COX-2 inhibitors for ≥180 days from July 2002 to December 2005, patients aged ≥18 years; controls from general populations matched on age, sex, and cohort entry date Exclude: History of MI or revascularization, cancer	A. Opioids (n=148,657) B. Rofecoxib (n=44,236) C. Celecoxib (n=64,072) D. Valdecoxib (n=20,502) E. General population not using opioids or COX-2 inhibitors (n=148,657) 1. 0 to <1350 mg MED per 90 days 2. 1350 to <2700 mg MED per 90 days 3. 2700 to <8100 mg MED per 90 days 4. 8100 to <18,000 mg MED per 90 days 5. ≥18,000 mg MED per 90 days	A vs. B vs. C vs. D vs. E Age 18 to 29 years: 4.7% vs. 1.2% vs. 0.8% vs. 1.2% vs. 4.7% Age 30 to 39 years: 16.3% vs. 5.4% vs. 4.1% vs. 5.3% vs. 16.3% Age 40 to 49 years: 33.9% vs. 20.7% vs. 17.6% vs. 20.1% vs. 33.9% Age 50 to 64 years: 36.7% vs. 56.0% vs. 56.3% vs. 56.5% vs. 36.7% Age ≥ 65 years: 8.4% vs. 16.6% vs. 21.2% vs. 16.9% vs. 8.4% Female sex: 40.3% vs. 39.5% vs. 39.6% vs. 34.9% vs. 40.3% Diabetics: 11.7% vs. 10.2% vs. 12.4% vs. 11.1% vs. 4.1% Pain condition: NR Duration of pain: NR severity of pain: NR Opioids prescribed: NR	All relevant claims in database during study period	Screened: NR Eligible, enrolled, analyzed: 426,124
Li, 2013	Case-control U.K. General Practice Research Database	Cases (n=11,693): Age 18 to 80 years, 2 years of medical history data before index (onset of MI symptoms) Controls: (n=44,897): up to 4 controls matched on age, gender, index date, and practice site using risk-set sampling Excluded: history of cancer, ischemic heart disease, heart failure, stroke, congenital heart disorders, heart transplant, arrhythmias, treated hypertension, diabetes, ETOH/drug abuse, hepatic or renal disease before index, cardiac surgery in the 90 days prior to index.	A. Non-use B. Current (0 to 30 days from index) C. Recent (31 to 365 days out) D. Past Use (366 to 730 days out) Cumulative use (number of prescriptions): 1. 1 to 2 2. 3 to 10 3. 11 to 50 4. >50	Mean age (years): 61.8 vs. 61.6 Female sex: 31.1% vs. 31.3% Low BMI (<18.5): 1.2% vs. 1.2% Normal BMI: 25.8% vs. 28.9% Overweight: 31.7% vs. 30.2% Obese: 13.8% vs. 11.3% Arthritis: 25% vs. 24.2% Rheumatoid arthritis: 3.2% vs. 1.8% Fibromyalgia: 1.1% Duration or severity of pain: NR Codeine: 16% vs. 15% Dihydrocodeine: 9.6% vs. 8.1% Propoxyphene: 13% vs. 11% Current smoker: 38.6% vs. 23.3%	Used General Practice Research Database, which has been validated on drug exposure and diagnoses (including MI)	Screened: 1,700,000 Eligible: Not reported Enrolled: 11,693 cases and 44,897 controls Analyzed: 11,693 cases and 44,897 controls

Abbreviations: U.K.=United Kingdom; MED=morphine equivalent dose; MI=myocardial infarction; vs.=versus.

See Appendix C. Included Studies for full citations

Table H-11. Key Question 2a: Studies of long-term opioid use and cardiovascular outcomes – study results

Author, Year	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Carman, 2011	Incidence rates adjusted for age and sex; incidence rate ratio adjusted for age sex, cardiovascular and other comorbidities, and use of concomitant medications	Adjusted incidence rate of MI, incidence rate ratio A. 5.93 (95% CI, 5.58 to 6.30); IRR 2.66 (95% CI, 2.30 to 3.08) B. 3.54 (95% CI, 3.11 to 4.01); IRR 1.94 (95% CI, 1.65 to 2.29) C. 3.53 (95% CI, 3.15 to 3.94); IRR 1.79 (95% CI, 1.53 to 2.10) D. 3.40 (95% CI, 2.76 to 4.14); IRR 1.74 (95% CI, 1.41 to 2.16) E. 1.58 (95% CI, 1.40 to 1.78); IRR 1 (reference) Adjusted incidence rates of MI or revascularization, incidence rate ratio A. 11.91 (95% CI, 11.40 to 12.43); IRR 2.38 (95% CI, 2.15 to 2.63) B. 7.98 (95% CI, 7.33 to 8.67); IRR 1.93 (95% CI, 1.72 to 2.15) C. 7.94 (95% CI, 7.36 to 8.54); IRR 1.81 (95% CI, 1.62 to 2.01) D. 7.53 (95% CI, 6.56 to 8.60); IRR 1.75 (95% CI, 1.50 to 2.01) E. 3.38 (95% CI, 3.12 to 3.67); IRR 1 (reference) Dosing Compared to a cumulative dose of 0 to 1350 mg MED over 90 days, the IRR for 1350 to <2700 was 1.21 (95% CI, 1.02 to 1.45), for 2700 to <8100 mg was 1.42 (95% CI, 1.21 to 1.67), for 8100 to <18,000 mg was 1.89 (95% CI, 1.54 to 2.33), and for >18,000 mg was 1.73 (95% CI, 1.32 to 2.26)	Industry	Fair
Li, 2013	Age, gender, smoking, body mass index, number of general practice visits, years of medical history, opioid new versus prevalent use, co-morbidities, concomitant medications, abdominal and pelvic pain and other pain	Risk of MI (adjusted OR) A. 1 (reference) B. 1.28 (95% CI, 1.19 to 1.37) C. 1.17 (95% CI, 1.10 to 1.24) D. 1.06 (95% CI, 0.98 to 1.14) 1. 1.10 (95% CI, 1.03 to1.18) 2. 1.09 (95% CI, 1.02 to 1.17) 3. 1.38 (95% CI, 1.28 to 1.49) 4. 1.25 (95% CI, 1.11 to 1.40)	None disclosed	Good

Abbreviations: CI=confidence interval; IRR=incidence rate ratio; MED=morphine equivalent dose; mg=milligram; MI=myocardial infarction; OR=odds ratio.

See Appendix F. Included Studies for full citations

Table H-12. Key Question 2a: Studies of long-term opioid use and endocrine outcomes – study characteristics

Author, year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders	Enrolled Analyzed
Deyo, 2013	Cross-sectional Integrated healthcare, United States	Ambulatory males aged ≥18 years with diagnoses associated with low back pain Exclude: patients with evidence of systemic disease or trauma	A. Patients prescribed medication for erectile dysfunction or testosterone replacement (n=909) B. Patients not prescribed medication for erectile dysfunction or testosterone replacement (n=10,418)	A vs. B Mean age (years): 55.7 vs. 48.0 Female sex: 0% Race: 89% White, 3% Black, 3% Asian/Pacific Islander, 1% American Indian, 3.9% other (among records with race/ethnicity data available, 59% of total sample) Sedative-hypnotic use: 24.4% vs. 15.6% Diagnosis of depression: 17.3% vs. 11.3%	Review of medical and pharmacy records	Enrolled: 11,327 Analyzed: 11,327
Richardson, 2018	Matched cohort UK Clinical Practice Research Datalink primary care database	Women aged 18 to 55 years, starting a long-term opioid, with a coded noninflammatory potentially painful musculoskeletal condition	A. Long-term opioid use, defined as ≥90 days B. Short-term opioid use	A vs. B Median (IQR) age, years: 43 (35 to 49) vs. 43 (36 to 49) Female: 100% vs. 100% White: 70.4% vs. 60.8%	Searched databases for relevant codes	Enrolled: 44,260 Analyzed: 44, 260
Rubinstein, 2017	Retrospective cohort, Kaiser Permanente Northern California	Men using opioids daily for non-cancer pain in the 100 days before a testosterone test. Men with cancer, a history of cancer, or endocrine disorders other than stable treated hypothyroidism within the year before the test date were excluded.	A. Androgen deficient (defined as morning serum total testosterone <250 ng/dL) B. Not androgen deficient	A vs B Demographics not reported by condition, reported according to specific opioid used. Secondary variables: Obese: 49.1% vs 50.9% Diabetes: 50% vs 50% Hypertension: 45.3% vs 54.7% Hyperlipidemia: 44.1% vs 55.9% Statins: 49% vs 51%	Electronic medical record and administrative databases	Eligible: 1,585 Analyzed: 1159

Abbreviations: IQR=interquartile range; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-13. Key Question 2a: Studies of long-term opioid use and endocrine outcomes – study results

Author, Year	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Deyo, 2013	Age, comorbidity score, number of hospitalizations, sedative-hypnotic use, duration of opioid use, morphine dose at last dispensing, type of opioid (short- vs. long-acting), depression, and smoking status	No opioid use vs. short-term use vs. episodic use vs. long-term use Prescription for sildenafil, tadalafil, or vadenafil 6 months before or after index visit: 6.3% (294/4,655) vs. 6.9% (324/4,696) vs. 7.3% (12/164) vs. 11.3% (204/1,812), p<0.001 Testosterone replacement 6 months before or after index visit: 0.5% (25/2,655) vs. 0.6% (30/4,696) vs. 1.2% (2/164) vs. 2.4% (44/1,812), p<0.001 Testosterone replacement or erectile dysfunction treatment: 6.7% (312/4,655) vs. 7.4% (346/4,696) vs. 7.9% (13/164) vs. 13.1% (238/1,812), p<0.001; OR 1.5, 95% CI, 1.1 to 1.9 Dosing Daily opioid dose of >120 mg MED/day associated with increased risk of use of medications for erectile dysfunction or testosterone replacement versus 0 to <20 mg MED/day (OR 1.6, 95% CI, 1.0 to 2.4)	National Institutes of Health/National Center for Research Resources	Fair
Richardson, 2018	Thyroid conditions, low BMI <18 (as a coded condition), adrenal conditions and obesity (as a coded condition), and BMI (categorized as <25 kg/m2, ≥25 kg/m2 (overweight) or missing) was recorded at the date closest to the start of follow-up, structural gynecology condition and illegal opioid misuse.	Adjusted HR (95% CI), A vs. B Abnormal menstruation: 1.13 (1.05 to 1.21) Menopause: 1.16 (1.10 to 1.23) Low libido: 1.19 (0.96 to 1.48) Infertility: 0.82 (0.64 to 1.06)	North Staffordshire Primary Care Research Consortium	Fair
Rubinstein, 2017	Specific opioid, dose, age, obesity, diabetes, hypertension, hyperlipidemia, statin use	Effect of dose (per 10mg MED), OR (95% CI) Fentanyl: 0.96 (0.88 to 1.03) Hydrocodone: 1.18 (1.09 to 1.28) Hydromorphone: 1.34 (0.61 to 2.94) Methadone: 0.99 (0.97 to 1.02) Morphine: 1.05 (0.99 to 1.11) Oxycodone: 1.01 (1.00 to 1.02)	Kaiser Permanente Northern California Community Benefit program	Fair

Abbreviations: CI=confidence interval; HR=hazard ratio; MED=morphine equivalent dose; OR=odds ratio; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-14. Key Question 2a: Study of long-term opioid use and motor vehicle accidents – study characteristics

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Sampling Strategy	Screened Eligible Enrolled Analyzed Loss to Followup
Gomes, 2013	Case-control Canada	Residents aged 15 to 64 with public drug coverage and an opioid prescription (excluding methadone (2003 to 2011) ≥6 months of continuous eligibility for public drug coverage before their index date and ≥1 opioid prescription with a duration that overlapped their index date. Cases and controls were excluded if they had invalid patient identifiers, had missing information about age or sex, received palliative care services in the 6 months before their index date, lived in a long-term care home at the index date, or had a prescription for a nonstudy opioid with a duration that overlapped the index date.	Cases: ED with an external cause of injury related to road trauma (codes V00 to V89 from ICD-10) (n=5,300 matched a control) Controls: (n=5300) A. 1<20 mg/day B. 20<50 mg/day C. 50<100 mg/day D. 100<200 mg/day E.≥200 mg/day	Cases vs. Controls Mean age (years): 45.76 vs. 45.75 Female sex: 48.6% Urban resident: 83.75% vs. 83.98 Social Assistance:22% vs. 21% Disability support: 67.9% vs. 66.6% Duration of use (years): 7.09 vs. 6.84 <u>Charlson score</u> No hospitalization: 61.7% vs. 62.3% 0: 23.4% vs. 22.4% 1: 6.85% vs. 6.32% 2: 7.96% vs. 8.49%	Incidence density sampling Cases were matched to controls by sex, age (within 3 years), index year (within 1 year), ED visit for road trauma in the past year, and disease risk index (within 0.2 SD). Cases with no matched controls were excluded from analyses.	Screened population: 549,878 Eligible Cases: 5,300 Eligible Controls: 43,736 Controls matched 1:1

Abbreviations: ED=emergency room; ICD=international classification of disease; SD=standard deviation; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-15. Key Question 2a: Study of long-term opioid use and motor vehicle accidents – study results

Author, Year	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Gomes, 2013	Logistic models adjusted for: age, past (3 years) hospitalization for alcoholism, past (1 year) ED visit for alcoholism, duration of opioid treatment, medication use in past 180 days (i.e., selective serotonin reuptake inhibitors, other antidepressants, antipsychotics, benzodiazepines and other depressants of the central nervous system, separately), number of drugs dispensed in the past 180 days, and numbers of physician and ED visits in the past 1 year.	Risk estimates reported as adjusted OR Risk of motor vehicle crash A. 1 (reference) B. 1.09 (95% CI, 0.97 to 1.21) C. 1.07 (95% CI, 0.94 to 1.22) D. 1.08 (95% CI, 0.93 to 1.24) E. 1.00 (95% CI, 0.88 to 1.15) Dosing Relative to 1 to <20 mg MED/day, the odds of road trauma among drivers after adjustment for age, alcoholism history, concomitant medication use, total number of drugs, and number of physician and emergency department visits was 1.21 (1.02 to 1.42) for 20 to 49 mg, 1.29 (1.06 to 1.57) for 50 to 99 mg, 1.42 (1.15 to 1.76) for 100 to 199 mg, and 1.23 (1.02 to 1.49) for >200 mg	MOHLTC Drug Innovation Fund and ICES, a nonprofit research institute sponsored by the Ontario MOHLTC.	Good

Abbreviations: CI=confidence interval; ED=emergency department; ICES=Institute for Clinical Evaluative Sciences; MED=morphine equivalent dose; MOHLTC=Ministry of Health and Long-Term Care; OR=odds ratio.

See Appendix F. Included Studies for full citations

Table H-16. Key Question 2a: Studies of long-term opioid use and risk of depression – study characteristics

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method for Assessing Outcomes and Confounders	Screened Eligible Enrolled Analyzed
Scherrer, 2016 (Prev Med)	Retrospective cohort VHA	18 to 80 years of age, with a diagnosis of depression and free of cancer and HIV, diagnosed with depression. Patients were opioid-free for the 24-month interval prior to the observation period. Incident opioid use could occur at any time prior to onset of treatment-resistant depression. Patients were defined as having TRD if any of the following were recorded in the medical record: a) electroconvulsive therapy, b) MAOI prescription, c) two or more antidepressants (any SSRI, SNRI, TCA or "other" non-MAOI antidepressant) at the same time overlapping by at least 31 days, or d) augmentation therapy (i.e. prescription of a mood stabilizing or atypical antipsychotic after antidepressant treatment).	A. TRD B. No TRD	A vs. B Mean age (years): 48.2 vs. 49.6 Female: 16.4% vs. 12.5% White: 80.1% vs. 76.7% Maximum pain score (0 to 10): 9.3 vs. 8.9	VHA electronic medical record and administrative databases	Screened: NR Eligible: 7,919 Enrolled: 7,919 Analyzed: 6,223
Scherrer, 2016 (J Pain)	Retrospective cohort 3 administrative databases	Opioid naïve prior to study entry, 18 to 80 years of age without depression at start of study and ≥1 visit after followup periods started Excluded patients with cancer	A. 1 to 30 days of opioid use (n=88,610) B. 31 to 90 days of opioid use (n=17,090) C. >90 days of opioid use (n=8055) 1. Opioid dose of 1 to 50 mg/day MED 2. Opioid dose of 51 to 100 mg/day MED 3. Opioid dose of >100 mg/day MED	Characteristics were provided by database Mean age, years: 44.6 to 55.4 Female: 25% White: 68.7% Arthritis: 79.3% Back pain: 64.9% Headache: 24.5% Musculoskeletal pain: 68.0% Neuropathic pain: 28.4% Mean (SD) maximum pain score: 8.4 (2.2) – only provided from VHA database	VHA electronic medical record and administrative databases	Screened: NR Eligible: NR Enrolled: 107,775 Analyzed: 107,775

Abbreviations: MAOI=monoamine oxidase inhibitor; MED=morphine equivalent dose; SD=standard deviation; SNRI=serotonin-norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant; TRD=treatment resistant depression; VHA=Veterans Health Administration; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-17. Key Question 2a: Studies of long-term opioid use and risk of depression – study results

Author, Year	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Scherrer, 2016 (Prev Med)	Pain, psychiatric and physical comorbidities, other prescription medication, health care utilization and demographics	Risk of TRD, A vs. B Opioid dose > 50 mg HR 1.07, 95% CI, 0.88 to 1.30	National Institutes of Health	Fair
Scherrer, 2016 (J Pain)	Hazard ratios for time to new-onset depression were estimated using Cox proportional hazards models in which opioid use duration and MED were time-dependent variables. Fully adjusted Cox models included additional, time-dependent control variables for painful conditions and, in the VHA cohort, pain scores to account for change in pain after opioid initiation.	Adjusted HR (95% CI) for new onset depression in VHA and BSWH databases, with multiple models run A. Reference B. 1.18 (1.10 to 1.25) to 1.31 (1.05 to 1.65) C. 1.31 (1.22 to 1.40) to 2.26 (1.63 to 3.14) 1. Reference 2. 0.78 (0.60 to 1.03) to 1.20 (1.10 to 1.31) 3. 0.71 (0.40 to 1.28) to 1.74 (1.49 to 2.04)	National Institutes of Mental Health	Fair

Abbreviations: BSWH=Baylor Scott and White Health; CI=confidence interval; HR=hazard ratio; MED=morphine equivalent dose; TRD=treatment resistant depression; VHA=Veterans Health Administration; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-18. Key Question 2: Studies of co-prescribing benzodiazepines and long-term opioids and overdose – study characteristics

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Exposures assessed	Method of Ascertaining and Defining Outcome	Methods to Control Confounding
Dunn, 2010	Retrospective cohort Integrated managed care system (Group Health Cooperative; Washington) 1997 to 2005	Adults ≥18 years of age with >1 opioid prescription (none in 6 months prior) and ≥ 3 prescriptions filled in first 90 days and diagnosis of chronic non-cancer pain in 2 weeks prior to first opioid prescription Exclusion: cancer, not enrolled for at least 270 days preceding study entry Followup started on 90th day of episode Individuals censored from followup for disenrollment or end of study	Opioid exposure (MED per day) calculated for continuously updated 90 day exposure window from day 91 of chronic use period Days' supply of sedative hypnotics dispensed (benzodiazepine, barbiturate, muscle relaxants) for 90 day exposure windows as percent of days with coverage	Opioid overdose or adverse event identified from electronic medical records using ICD9 codes Fatal overdoses from Washington vital statistics	Cox proportional hazards model used to estimate risk for overdose conditional on average daily opioid dose (time varying 90-day exposure windows) Baseline covariates: age, sex, tobacco use, diagnosis of depression, SUDs, pain diagnosis, Charlson Index Sedative-hypnotic use assessed as a time-varying covariate
Hernandez, 2018	Retrospective cohort Medicare Part D 2014	≥1 opioid prescription in 2014 and continuously enrolled from first opioid claim end of study or death Exclusions: cancer diagnosis in 2013 or 2014	Time dependent variables: A. Opioid supply only on day before overdose or censoring (reference) B. Opioid and benzodiazepine supply on day before overdose or censoring and history of 1 to 90 days C. Opioid and benzodiazepine supply on day before overdose or censoring and history of 91 to 180 days D. Opioid and benzodiazepine supply on day before overdose or censoring and history of 181 to 270 days E. Opioid and benzodiazepine supply on day before overdose or censoring and history of ≥271 days	Inpatient or outpatient claim with an opioid overdose diagnosis code	Cox proportional hazard models comparing opioid/benzodiazepine exposure variables to opioid only exposure Baseline covariates: age, sex, race, disability, CMS priority chronic conditions including alcohol use disorder, anxiety, depression, drug use disorder, fibromyalgia, pain, PTSD, psychosis, schizophrenia

Author, Year	Type of Study Setting Duration	Eligibility Criteria	Exposures assessed	Method of Ascertaining and Defining Outcome	Methods to Control Confounding
Sun, 2017	Retrospective cohort Marketscan data (private insurance plans) 2001 to 2013	Continuous enrollment in a plan with medical and pharmacy benefits from 2001 to 2013, aged 18 to 64 years and ≥1 opioid prescription Excluded patients with cancer	≥1 days of concurrent benzodiazepine use in any given calendar year (fill dates and day supply)	Primary outcome: ED or inpatient admission for opioid overdose (ICD9 for opioid poisoning or adverse event - respirator depression) only if occurring within 7 days of an opioid prescription episode (fill date and day supply).	Multivariate logistic regression comparing the association between concurrent benzodiazepine/opioid use and opioid overdose Baseline covariables: age, sex, year, and ICD9 codes for a variety of chronic conditions (e.g. depression, psychosis, drug abuse, alcohol abuse, etc.). Sensitivity analyses: alternative definitions of overlap (25% of opioid days' supply), opioid overdose within 30 days of opioid episode, less restrictive 2 year enrollment criteria

Abbreviations: ED=emergency department; ICD=international classification of disease; MED=morphine equivalent dose; PTSD=post-traumatic stress disorder.

See Appendix F. Included Studies for full citations

Table H-19. Key Question 2: Studies of co-prescribing benzodiazepines and long-term opioids and overdose – study results

Author, Year	Interventions	Population Characteristics	Main Results	Quality
Dunn, 2010	A. No sedative-hypnotic exposure in 90 days before overdose B. Sedative-hypnotic exposure of 1 to 22 days supply during prior 90 days C. Sedative-hypnotic exposure of 23 to 44 day supply during prior 90 days D. Sedative-hypnotic exposure of 45 to 71 day supply during prior 90 days E. Sedative-hypnotic exposure of ≥72 day supply during prior 90 days	n=9940 Mean age: 54 years Female: 60% Tobacco use: 29% Depression: 27% SUDs: 6% Mean Charlson score: 0.71 Pain diagnosis: back 38%, extremity pain 30%, osteoarthritis 13%, injury 12%, neck 9% Any sedative-hypnotic: 75% Any muscle relaxant: 52% Any benzodiazepine: 43% Sedative-hypnotic ≥45 of 90 day episode: 32%	Total opioid exposed: 148 per 100,000 person-years No opioid exposure: 36 per 100,000 person- years (reference) Any opioid use: 256 per 100,000 person-years A vs. B vs. C vs. D vs. E HR (95% CI) for overdose with sedative-hypnotic use A. Reference (no sedative hypnotic) B. 3.4 (1.6 to 7.2) C. 0.9 (0.2 to 4) D. 3.7 (1.6 to 8.9) E. 2.7 (1.2 to 6)	Good
Hernandez, 2018	A. Opioid use only (n=50,583) B. Opioid/benzo used 1 to 90 days (n=3603) C. Opioid/benzo used 91 to 180 days (n=2930) D. Opioid/benzo used 181 to 270 days (n=4082) E. Opioid/benzo used >271 days (n=10,050)	A vs. B vs. C vs. D vs. E Mean age, years: 68 vs. 71 vs. 66 vs. 64 vs. 60 Female: 63% vs. 72% vs. 70% vs.72% vs. 64% White: 82% vs. 88% vs. 88% vs.88% vs. 89% Disability: 38% vs. 32% vs. 43% vs.51% vs. 63% Pain diagnosis: 76% vs. 65% vs.65% vs. 65% vs. 64% Depression: 54% vs. 69% vs. 74% vs. 76% vs. 76% Anxiety: 2% vs. 6% vs. 8% vs. 8% vs. 11%	A vs. B vs. C vs. D vs. E Frequency of opioid overdose by days of overlap (unadjusted): 0.33% (166/50,583) vs. 1.64% (59/3,603) vs. 1.09% (32/2,930) vs. 0.47% (19/4,082) vs. 0.14% (14/10,050) Covariate adjusted Cox proportional hazard model (HR, 95% CI): reference vs. 5.1 (3.7 to 7.0) vs. 1.9 (1.3 to 2.8) vs. 0.6 (0.4 to 1.1) vs. 0.2 (0.1 to 0.3)	Fair
Sun, 2017	A. Benzodiazepine (n=5425) B. No benzodiazepine (n=53,389)	Only reports demographics for year 1 (2001) cohort (n=58,814) Mean age, years: 44.5 vs. 42.4; p<0.001 Depression: 17% vs. 4.4%; p<0.001 Psychosis: 0.55% vs. 0.13%; p<0.001 Drug abuse: 1.2% vs. 0.22%; p<0.001 Alcohol abuse: 1.1% vs. 0.3%; p<0.001 MI: 0.41% vs. 0.13%; p<0.001 Dementia: 0.28% vs. 0.12%; p<0.001 CVD: 0.65% vs. 0.19%; p<0.001 COPD: 4.7% vs. 2.0%; p<0.001	A vs. B Annual adjusted incidence of opioid overdose: 2.42% vs. 1.16%; adjusted OR 2.14 (95% CI, 2.05 to 2.24); p<0.001 Intermittent opioid users: 1.45% vs. 1.02%; adjusted OR 1.42 (95% CI, 1.33 to 1.51); p<0.001 Chronic opioid users: 5.36% vs. 3.13%; adjusted OR 1.81 (95% CI,1.67 to 1.96); p<0.001	Fair

Abbreviations: CI=confidence interval; COPD=chronic obstructive pulmonary disease; CVD=cardiovascular disease; HR=hazard ratio; OR=odds ratio; SUDs=substance use disorders; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-20 Key Question 2: Studies of exposure to gabapentin or pregabalin in long-term prescription opioid users with chronic pain – study characteristics

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders	N Analyzed
Gomes, 2017	Case control population-based, publically-funded Ontario	Cases: Patients prescribed at least 1 opioid prescription over the study period: morphine, codeine, oxycodone, meperidine, hydromorphone, fentanyl who died from opioid-related death not homicide or suicide; Up to 4 controls per case matched on age, gender, year of index date, history of CKD, disease risk index; opioids not for cancer pain; residents of Ontario between 1 August 1997 and December 31, 2013	A. Cases (n=1256) B. Controls (n=4619)	A vs. B Mean age, years: 48 vs. 48 Female: 43% vs.43% Daily opioid dose: <20 MED: 11% vs. 25% 20 to 49 MED: 18% vs. 29% 50 to 99 MED: 16% vs. 15% 100 to 199 MED: 15% vs. 11% ≥200 MED: 40% vs. 21%	Review of claims and other databases	5,875
Gomes, 2018	Case control population-based, publically-funded Ontario	Cases: Patients prescribed ≥1 opioid prescription over the study period: morphine, codeine, oxycodone, meperidine, hydromorphone, fentanyl who died from opioid-related death not homicide or suicide; Up to 4 controls per case matched on age, gender, year of index date, history of CKD, Charlson Comorbidity Index; opioids not for cancer pain; residents of Ontario and received prescription opioids between 1 August 1997 and 31 December 2016	A. Cases (n=1417) B. Controls (n=5097)	A vs. B Mean age: 48 vs. 49 Female sex: 44% vs.45% Daily opioid dose: <20 MED: 13% vs. 25% 20-49 MED: 23% vs. 30% 50-99 MED: 20% vs. 18% 100-199 MED: 17% vs. 11% ≥200 MED: 27% vs. 16%	Review of claims and other databases	5,097
Peckham, 2018	Retrospective cohort study; commercial claims database	Filled prescription for ≥120 days of treatment for gabapentin and/or 1 opioid; no chronic kidney disease or cancer; 12-month followup	A. Gabapentin only (n=44,152) B. Opioids only (n=736,835) C. Both gabapentin and C. Opioids (n=15,343)	A vs. B vs. C Mean age, years: 50 vs. 44 vs. 50 Female: 63% vs. 60% vs. 61%	Review of claims database	796,330

Abbreviations: CKD=chronic kidney disease; MED=morphine equivalent dose; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-21. Key Question 2: Studies of exposure to gabapentin or pregabalin in long-term prescription opioid users with chronic pain – study results

Author, Year	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Gomes, 2017	Opioid dose, age, medication use in prior 120 days (pregabalin, SSRIs, other antidepressants, benzodiazepines, other psychotropic drugs/CNS depressants, methadone, bupronorphine), number of drugs dispensed in past 6 months, receipt of long-acting opioid, alcohol use disorder, Charlson Comorbidity Index, chronic lung disease, diabetes, number of opioid prescribed and number of pharmacies that dispensed opioids for patient in past 6 months.	Coprescription for opioids and gabapentin was associated with increased risk of opioid-related mortality: OR 1.99 (95% CI, 1.61 to 2.47); AOR 1.49 (95% CI, 1.18 to 1.88) vs. opioid prescription alone With high dose gabapentin: OR 2.20 (95% CI, 1.58 to 3.08); AOR 1.58 (95% CI, 1.09 to 2.27) With moderate dose gabapentin: OR 2.05 (95% CI, 1.46 to 2.87); AOR 1.56 (95% CI, 1.06 to 2.28) With low dose gabapentin: OR 1.70 (95% CI, 1.17 to 2.48); AOR 1.32 (95% CI, 0.89 to 1.97)	Government	Fair
Gomes, 2018	Recent exposure to gabapentin, SSRIs, other antidepressants, benzodiazepines or other CNS depressants, number of medications dispensed in past 6 months, Charlson comorbidity index, number of physicians and pharmacies prescribing and dispensing in past 6 months, receipt of long-acting opioid, opioid dose	Coprescription for opioids and pregabalin was associated with increased risk of opioid-related mortality: OR 1.85 (95% CI, 1.36 to 2.53); AOR 1.68 (95% CI, 1.19 to 2.36) With high dose pregabalin: OR 3.02 (95% CI, 1.58 to 5.77); AOR 2.51 (95% CI, 1.24 to 5.06) With low or moderate dose pregabalin: OR 1.74 (95% CI, 1.22 to 2.49); AOR 1.52 (95% CI, 1.04 to 2.22)	Government	Fair
Peckham, 2018	Demographic and clinical factors, other benzodiazepines and hypnotics	Reference is to no overuse of gabapentin **Drug-related hospitalizations with opioids and gabapentin AOR (95% CI)** No overuse: 1.65 (1.46 to 1.85) Mild overuse: 2.66 (2.31 to 3.06) Sustained overuse 1 med: 2.95 (2.46 to 3.54) Sustained overuse both meds: 4.72 (2.67 to 8.37) **Drug-related hospitalizations with opioids alone AOR (95% CI)** No overuse: 0.69 (0.64 to 0.74) Mild overuse: 1.29 (1.20 to 1.39) Sustained overuse: 1.611 (1.44 to 1.80) **Drug-related ED visits with opioids and gabapentin AOR (95% CI)** No overuse: 1.50 (1.32 to 1.70) Mild overuse: 1.41 (1.18 to 1.68) Sustained overuse 1 med: 1.26 (0.98 to 1.62) Sustained overuse both meds: 2.73 (1.34 to 5.56) **Drug-related hospitalizations with opioids alone AOR (95% CI)** No overuse: 1.01 (0.95 to 1.08) Mild overuse: 1.12 (0.1.03 to 1.20) Sustained overuse: 1.10 (0.97 to 1.24)	No funding was used	Fair

Abbreviations: AOR=adjusted odds ratio; CI=confidence interval; OR=odds ratio; SSRI=selective serotonin reuptake inhibitor; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-22. Key Question 3a: Trials of different methods for initiating and titrating opioids – study characteristics and results

Author, Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Jamison, 1998	RCT 16 weeks	Single center Pain clinic United States	Chronic back pain >6 months duration, age 25 to 65 years, average pain intensify >40 on scale of 0 to 100, unsuccessful response to traditional pain treatment Exclude: Cancer, acute osteomyelitis or acute bone disease, spinal stenosis and neurogenic claudication, non-ambulatory, significant psychiatric history, pregnancy, treatment for drug or alcohol abuse, clinically unstable systemic illness, acute herniated disc within 3 months	A. Long acting morphine + short-acting oxycodone (titrated doses) + Naproxen B. Short-acting oxycodone (set dose) + Naproxen C. Naproxen A vs. B vs. C Mean dose 41.1 mg vs. NR (max 20 mg oxycodone/day) vs. NR In all groups, max 1000 mg/day of naproxen 16 weeks	Mean age (years): 43 Female sex: 57% Race: NR Indication: 39% failed back syndrome, 25% myofascial pain syndrome, 19% degenerative spine disease, 14% radiculopathy, 3% discogenic back pain Prior opioid use: NR Mean pain duration: 79 months	Screened: 48 Eligible: NR Enrolled: 36 Analyzed: 36	A vs. B vs. C Average pain (mean, 0 to 100 VAS): 54.9 vs. 59.8 vs. 65.5 Current pain (mean, 0 to 100 VAS): 51.3 vs. 55.3 vs. 62.7 Highest pain (mean, 0 to 100 VAS): 71.4 vs. 75.5 vs. 78.9 Anxiety (mean): 11.2 vs. 15.0 vs. 31.6 Depression (mean): 10.8 vs. 16.4 vs. 26.9 Irritability (mean): 17.7 vs. 20.5 vs. 33.7 Level of activity (mean, 0 to 100 scale): 49.3 vs. 49.3 vs. 51.5 Hours of sleep (mean): 5.9 vs. 5.9 vs. 6.1	A vs. B vs. C Any adverse event: 76% vs. 70% vs. 61% Constipation: 7% vs. 3% vs. 11% Nausea: 54% vs. 42% vs. 33% Vomiting: 18% vs. 12% vs. 7% Pruritus: 4% vs. 2% vs. 7% Dizziness: 7% vs. 7% vs. 7% Somnolence: 9% vs. 7% vs. 0% Headache: 18% vs. 15% vs. 13% Dry mouth: 0% vs. 2% vs. 6% Diarrhea: 7% vs. 5% vs. 2% Discontinuation due to adverse events: 54% (29/54) vs. 34% (20/59) vs. 130% (6/54) (p=0.008 for A or C vs. B) Discontinuation due to nausea and/or vomiting: 46% (25/54) vs. 22% (13/59) vs. 22% (12/54)	Industry	Poor

Author, Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Salzman, 1999	RCT 10 days	Multicenter Rheumatology clinics and others United States	18 years or older, chronic stable moderate to severe back pain despite analgesic therapy with or without opioids Exclude: Contraindication to opioid history of substance abuse, unable to discontinue nonstudy narcotic, or current oxycodone dose >80 mg/day Titration to 80 mg without achieving pain control	A. Sustained-release Oxycodone (titrated) B. Immediate-release Oxycodone (titrated) Titration comparison Mean dose A. 104 mg/day Mean dose B. 113 mg/day 10 days	Mean age: 56 years Female: 54% White: 87% Hispanic: 13% Indication: Intervertebral disc disease, nerve root entrapment, spondylolisthesis, osteoarthritis, and other non-malignant conditions Pain duration: NR	Screened: NR Eligible: NR Enrolled: 57 Analyzed: 57	A vs. B Mean decrease in pain intensity (0 to 3 scale): 1.1 vs. 1.3 (NS) Proportion achieving stable analgesia: 87% (26/30) vs. 96% (26/27) (p=0.36) Time to stable pain control: 2.7 vs. 3.0 days (p=0.90). Mean number of dose adjustments: 1.1 vs. 1.7 adjustments (p=0.58)	A vs. B Constipation: 30% (9/30) vs. 37% (10/27) Nausea: 50% (15/30) vs. 33% (9/27) Vomiting: 20% (6/30) vs. 4% (1/27) Pruritus: 30% (9/30) vs. 26% (7/27) Dizziness: 30% (9/30) vs. 22% (6/27) Somnolence: 27% (8/30) vs. 37% (10/27) Postural hypotension: 0% vs. 0% Confusion: 3% (1/30) vs. 0% Dry mouth: 0% vs. 11% (3/27) Nervousness: 0% vs. 7% (2/27) Asthenia: 7% (2/30) vs. 11% (3/27) Headache: 13% (4/30) vs. 26% (7/27) Discontinuation due to adverse events: 20% (6/30) vs. 7% (2/27)	Industry	Fair

Abbreviations: NR=not reported; NS=not significant; RCT=randomized controlled trial; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-23. Key Question 3b: Head-to-head trials of short-acting versus long-acting opioids for chronic pain – study characteristics

Author, year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample characteristics	Screened Eligible Randomized Analyzed
Adler, 2002	RCT 4 weeks	Unclear setting in U.K.	Pain condition: Osteoarthritis Age: ≥18 years Pain severity: Moderate to severe, not otherwise specified Psychiatric disease: Not specified Substance use: Not specified Prior opioid use: Not specified	A. Tramadol 150 to 400 mg taken once daily (SR) B. Tramadol 50 to 100 mg taken TID or QID (IR)	A vs. B Mean age, years: 62.5 vs. 62.6 Female: 54% vs. 63% Race: NR Pain duration: NR, but stated most >5 years	A vs. B Screened: NR Eligible: 279 Randomized: 202 (137 vs. 65) Analyzed: 146 (101 vs. 45)
Jamison, 1998	RCT 16 weeks	Single center pain clinic in the USA	Pain condition: Chronic back pain Age: 25 to 65 years Pain severity: >40 on 0 to 100 VAS Psychiatric disease: Excluded Substance use: Excluded Prior opioid use: Not specified	A. Long acting morphine + short-acting oxycodone (titrated doses) + Naproxen B. Short-acting oxycodone (set dose) + Naproxen C. Naproxen A vs. B vs. C Mean dose 41.1 mg vs. NR (max 20 mg oxycodone/day) vs. NR In all groups, max 1000 mg/day of naproxen 16 weeks	Mean age, years: 43 Female: 57% Race: NR Indication: -Failed back syndrome: 39% -Myofascial syndrome: 25% -Degenerative spine disease: 19% -Radiculopathy: 14% -Discogenic back pain: 3% Mean pain duration: 79 months	Screened: 48 Eligible: NR Enrolled: 36 Analyzed: 36
Pedersen, 2014	RCT 8 weeks	Single pain center in Norway	Pain condition: Mixed Age: 18 to 75 years Pain severity: Not specified Psychiatric disease: Excluded patients with severe mental disorders Substance use: Excluded Prior opioid use: Required to have prior daily codeine intake between 150 to 300 mg	A. Dihydrocodeine SR 120 to 240 mg/day (dosed 2 to 3 times/day) + paracetamol 2 to 4 g/day (mean NR) B. Dihydrocodeine IR 120 to 240 mg/day (dosed 4 to 6 times/day) + paracetamol 2 to 4 g/day (mean NR)	A vs. B Median (IQR) age, years: 49.0 (42.3 to 56.5) vs. 44.5 (39.0 to 60.0) Female: 61% vs. 47% Median (IQR) BMI: 24.1 (22.2 to 27.7) vs. 29.4 (25.7 to 31.9) Median (IQR) duration of pain, years: 11.5 (8.0 to 18.5) vs. 17.0 (8.8 to 20.0) Median (IQR) duration of opioid use, years: 5.0 (3.0 to 8.0) vs. 10.0 (4.5 to 15.5)	A vs. B Screened: 128 Eligible: NR Randomized: 58 (28 vs. 30) Analyzed: 38 (18 vs. 20)

Author, year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample characteristics	Screened Eligible Randomized Analyzed
Steiner, 2011	RCT 12 weeks	75 centers in the USA	Pain condition: Low back pain Age: ≥18 years Pain severity: Not specified Psychiatric disease: Not specified Substance use: Not specified Prior opioid use: Excluded	A. Buprenorphine 7-day patch 20 mcg/hour B. Buprenorphine 7-day patch 5 mcg/hour C. Oxycodone IR capsules 40 mg/day	A vs. B vs. C Mean (SD) age, years: 50.4 (11.93) vs. 50.2 (12.88) vs. 49.5 (12.37) Female: 46% vs. 52% White: 88% vs. 93% vs. 91% Black: 10% vs. 6% vs. 6% Asian: 0 vs. 1% vs. 0.5% Other race: 2% vs. 0 vs. 2% Mean (SD) weight, kg: 90.24 (21.35) vs. 88.44 (22.61) vs. 90.80 (20.50) Musculoskeletal pain: 93% vs. 93% vs. 88% Neuropathic pain: 7% vs. 7% vs. 11%	A vs. B vs. C Screened: 2066 Eligible: NR Randomized: 662 (219 vs. 222 vs. 221) Analyzed: 660 (219 vs. 221 vs. 220)

Abbreviations: BMI=body mass index; IQR=interquartile range; IR=immediate release; NR=not reported; QID=four times daily; RCT=randomized controlled trial; SR=sustained release; TID=three times daily; U.K.=United Kingdom; USA=United States of America; VAS=visual analogue scale; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-24. Key Question 3b: Head-to-head trials of short-acting versus long-acting opioids for chronic pain – study results

Author, Year	Results	Adverse Events and Discontinuation Due To Adverse Events	Funding Source	Quality
Adler, 2002	A vs. B, after treatment Pain (0 to 100), mean: 21 vs. 22 Difference from baseline: -26 vs. -29 Use of escape medication 2 hours after taking study drug: 8% vs. 15%, estimated from graph Use of escape medication 3 hours after taking study drug: 16% vs. 4%, estimated from graph	A vs. B Constipation: 23% vs. 31% Nausea: 36% vs. 36% Vomiting: 19% vs. 18% Dizziness: 20% vs. 17% Headache: 18% vs. 15% Drowsiness: 15% vs. 25% GI related AEs: 62% vs. 65% CNS related AEs: 48% vs. 52% Overall discontinuation: 29.9% (41/137) vs. 32.3% (21/65), RR 0.93 (95% CI, 0.60 to 1.43) Discontinuation due to AEs: 21.9% (30/137) vs. 15.4% (10/65), RR 1.42 (95% CI, 0.74 to 2.73) Discontinuation due to lack of efficacy: 5.8% (8/137) vs. 4.6% (3/62), RR 1.26 (95% CI, 0.35 to 4.61) Discontinuation due to AEs and lack of efficacy: 1.4% (2/137) vs. 4.6% (3/65), RR 0.32 (95% CI, 0.05 to 1.85)	Industry	Fair
Jamison, 1998	A vs. B vs. C Average pain (0 to 100), mean (SD): 54.9 (15.87) vs. 59.8 (16.65) vs. 65.5 (19.05) Current pain (0 to 100), mean (SD): 51.3 (18.98) vs. 55.3 (20.87) vs. 62.7 (22.81) Highest pain (0 to 100), mean (SD): 71.4 (20.93) vs. 75.5 (13.26) vs. 78.9 (19.43) Anxiety (0 to 100), mean (SD): 11.2 (16.05) vs. 15.0 (21.89) vs. 31.6 (33.58) Depression (0 to 100), mean (SD): 10.8 (17.55) vs. 16.4 (24.50) vs. 26.9 (32.11) Irritability (0 to 100), mean (SD): 17.7 (17.27) vs. 20.5 (23.12) vs. 33.7 (34.21) Level of activity (0 to 100), mean (SD): 49.3 (49.25) vs. 49.3 (49.33) vs. 51.5 (21.01) Hours of sleep per night, mean (SD): 5.9 (2.32) vs. 5.9 (2.05) vs. 6.1 (2.69)	A vs. B, RR (95% CI) Constipation: 30% (9/30) vs. 37% (10/27), RR 0.81 (0.39 to 1.69) Nausea: 50% (15/30) vs. 33% (9/27), RR 1.50 (0.79 to 2.85) Vomiting: 20% (6/30) vs. 4% (1/27), RR 5.40 (0.69 to 42.04) Pruritus: 30% (9/30) vs. 26% (7/27), RR 1.16 (0.50 to 2.68) Dizziness: 30% (9/30) vs. 22% (6/27), RR 1.35 (0.55 to 3.30) Somnolence: 27% (8/30) vs. 37% (10/27), RR 0.62 (0.28 to 1.35) Postural hypotension: 0% vs. 0% Confusion: 3% (1/30) vs. 0%, RR 2.71 (0.11 to 63.84) Dry mouth: 0% vs. 11% (3/27), RR 0.13 (0.01 to 2.39) Nervousness: 0% vs. 7% (2/27), RR 0.18 (0.01 to 3.60) Asthenia: 7% (2/30) vs. 11% (3/27), RR 0.60 (0.11 to 3.32) Headache: 13% (4/30) vs. 26% (7/27), RR 0.51 (0.17 to 1.56) Discontinuation due to AEs: 20% (6/30) vs. 7% (2/27), RR 2.70 (0.59 to 12.26)	Industry	Poor

Author, Year	Results	Adverse Events and Discontinuation Due To Adverse Events	Funding Source	Quality
Pedersen, 2014	A vs. B, at last week of trial participation Average pain intensity (0 to 10), median (IQR): 4.93 (3.11 to 6.21) vs. 5.00 (3.29 to 6.14) SF-8 PCS (0 to 100), mean (SD): 33.77 (7.36) vs. 37.28 (7.96), p=0.18 SF-8 MCS (0 to 100), mean (SD): 46.43 (9.87) vs. 43.78 (13.60), p=0.51 PSQI (0 to 21, higher scores indicate poorer sleep quality), median (IQR): 11.0 (8.0 to 15.0) vs. 8.0 (5.0 to 13.0) BDI (0 to 63), median (IQR): 26.0 (24.5 to 37.5) vs. 30.5 (24.5 to 34.75)	A vs. B, RR (95% CI) Total AEs: 36 vs. 22 Constipation: 39.3% (11/28) vs. 26.7% (8/30), RR 1.47 (0.70 to 3.12) Nausea: NR vs. 13.3% (4/30) Fatigue: 10.7% (3/28) vs. NR Headache: 25% (7/28) vs. 10% (3/30), RR 2.50 (0.71 to 8.73) Dry mouth: 14.3% (4/28) vs. NR Overall discontinuation: 35.7% (10/28) vs. 33.3% (10/30), RR 1.11 (0.55 to 2.25) Discontinuation due to lack of efficacy: 14.3% (4/28) vs. 13.3% (4/30), RR 1.07 (0.30 to 3.88) Discontinuation due to lack of efficacy and AEs: 10.7% (3/28) vs. 3.3% (1/30), RR 3.21 (0.35 to 29.12) Discontinuation due to AEs: 14.3% (4/28) vs. 10% (3/30), RR 1.43 (0.35 to 5.82)	Unclear	Fair
Steiner, 2011	A vs. C Pain (0 to 10), difference (SE) vs. B: -0.67 (0.16), p<0.001 vs. -0.75 (0.16), p<0.001 MOS sleep disturbance subscale, difference (95% CI) vs. B: -6.23 (-9.64 to -2.82) vs. -2.65 (-6.01 to 0.70) Oswestry Disability Index, difference (95% CI) vs. B: -1.72 (-3.55 to 0.11) vs. -1.99 (-3.79 to -0.18)	A vs. B vs. C, RR (95% CI) A vs. C Any AE: 77% (169/219) vs. 59% (131/221) vs. 73% (160/220), RR 1.06 (0.95 to 1.18) SAE: 2% (5/219) vs. 3% (6/221) vs.4% (9/220), RR 0.56 (0.19 to 1.64) Constipation: 6% (14/219) vs. 3% (7/221) vs. 6% (14/220), RR 1.00 (0.49 to 2.06) Nausea: 12% (27/219) vs. 8% (18/221) vs. 8% (18/220), RR 1.51 (0.85 to 2.65) Vomiting NOS: 5% (11/219) vs. 2% (5/221) vs. 4% (9/220), RR 1.23 (0.52 to 2.90) Somnolence: 5% (10/219) vs. 2% (4/221) vs. 5% (11/220), RR 0.91 (0.40 to 2.11) Death (double-blind phase): 0 Overall discontinuation: 33% (73/219) vs. 42% (93/221) vs. 28% (61/220), RR 1.20 (0.90 to 1.60) Discontinuation due to AE: 13% (29/219) vs. 6% (14/221) vs. 7% (16/220), RR 1.82 (1.02 to 3.25) Discontinuation due to AE during run-in period: 13%	Industry	Fair

Abbreviations: AE=adverse event; BDI=Beck Depression Inventory; CI=confidence interval; CNS=central nervous system; GI=gastrointestinal; MCS=mental component subscale; MOS=Medical Outcomes Study; NOS=not otherwise specified; NR=not reported; PCS=physical component subscale; PSQI= Pittsburgh Sleep Quality Index; RR=risk ratio; SD=standard deviation; SE=standard error; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-25. Key Question 3b: Observational studies of short-acting versus long-acting opioids for chronic pain – study characteristics

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method for Assessing Outcomes and Confounders	Enrolled Analyzed Loss to Followup
Miller, 2015	Cohort study VHA health system databases	Patients with chronic noncancer pain who filled a new opioid analgesic prescription between January 1, 2000, and December 31, 2009.	Mean MED were categorized as 1 mg to <20 mg, 20 mg to <50 mg, 50 mg to <100 mg, and ≥100 mg	Median age: 60 years Female: 6.5% White: 71% Initial mean daily dose: 15 mg	Unintentional overdoses coded as drug or medication poisonings of accidental intent using ICD-9-CM codes (E850.x-860.x) or undetermined intent (E980.x or drug poisoning [960.x-980.x] without an accompanying external cause of injury code). If an e-code indicated that the poisoning was self-inflicted (E950.x) or assault-related (E962.x), it was not counted as an event.	Enrolled: 840,606 Analyzed: 840,606 Loss to followup: none

Abbreviations: ICD-9-CM= International Classification of Diseases, Ninth Revision, Clinical Modification; MED=morphine equivalent dose; VHA=Veterans Health Administration.

See Appendix F. Included Studies for full citations

Table H-26. Key Question 3b: Observational studies of short-acting versus long-acting opioids for chronic pain – study results

Author, Year	Adjusted Variables for Statistical Analysis	Main Results	Funding Source	Quality
Miller, 2015	Age, sex, race, and % service-connected disability (a measure of disability, ranging from 0% to 100%), clinical characteristics(prior falls and fractures, other medical diagnoses, and psychiatric diagnoses), VHA health care utilization (general mental health clinic services, services provided in the PTSD clinic, and use of specific therapies, including intensive therapy, rehabilitation, and substance abuse disorder treatment; emergency department and urgent care visits; and inpatient hospitalizations), and comedication with nonopioid agents (selective cyclooxygenase 2 inhibitors and other NSAIDs).	Overdose risk was greater for patients initiating higher dose therapy, with the risk among those receiving therapy with more than 50 mg equivalents of morphine being at more than twice the risk of overdose events compared with those receiving opioids at 1 to 20 to mg equivalents	CDC	Fair

Abbreviations: CDC=Centers for Disease Control and Prevention; NSAIDs: nonsteroidal antiinflammatory drugs; PTSD=post-traumatic stress disorder; VHA=Veterans Health Administration.

See Appendix F. Included Studies for full citations

Table H-27. Key Question 3c: Head-to-head trials of different long-acting opioids – study characteristics

Author, Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Randomized Analyzed
Afilalo, 2010	RCT 15 weeks	87 sites in the USA, 15 in Canada, 6 in New Zealand, and 4 in Australia	Pain condition: Osteoarthritis of the knee Age: ≥40 years Pain severity: Not specified Psychiatric disease: Excluded patients with unstable psychiatric disease Substance use: Excluded Prior opioid use: Not specified	A. Tapentadol SR 200 to 500 mg/day (mean 350 mg) B. Oxycodone SR 40 to 100 mg/day (mean 70 mg) C. Placebo	A vs. B vs. C Mean (SD) age, years: 58.4 (10.09) vs. 58.2 (10.29) vs. 58.2 (9.15) Female: 62.8% vs. 59.1% vs. 59.3% White: 75.6% vs. 71.6% vs. 79.2% Black: 14.2% vs. 13.2% vs. 11.3% Hispanic: 6.1% vs. 10.8% vs. 5.9% Other race: 4.1% vs. 4.4% vs. 3.6% Mean (SD) BMI: 33.61 (7.967) vs. 34.16 (8.185) vs. 35.08 (9.329) Mean (SD) weight, kg: 94.80 (23.664) vs. 97.43 (24.445) vs. 100.28 (26.720) Severe baseline pain: 85.2% vs. 83.0% vs. 81.8%	A vs. B vs. C Screened: 1578 Eligible: 1030 Randomized: 1030 (346 vs. 345 vs. 339) Analyzed: 1023 (344 vs. 342 vs. 337)
Allan, 2001	RCT, crossover 4 weeks	35 centers in Belgium, Canada, Denmark, Finland, U.K., the Netherlands, South Africa	Pain condition: Mixed Age: ≥18 years Pain severity: Not specified Psychiatric disease: Excluded patients with psychiatric illnesses Substance use: Not specified Prior opioid use: Mixed	A. Fentanyl transdermal titrated from 25 mcg/hour (mean 57.3 mcg/hour) B. Long acting morphine titrated from 60 mg/day (mean 133.1 mg/day)	A vs. B Mean (range) age, years: 50.9 (28 to 82) vs. 51.9 (26 to 82) Female: 47.6% vs. 46.2% White: 99% vs. 97% Neuropathic pain: 25% vs. 27% Other/mixed pain: 51% vs. 49% Both neuropathic and nociceptive pain: 25% vs. 24% Mean (SE) duration of chronic pain, years: 9.5 (0.74) vs. 9.1 (0.73) Morphine or morphine sulfate use before study: 72% vs. 79%	A vs. B Screened: NR Eligible: 256 Randomized: 256 (126 vs. 130) Analyzed: 212

Author, Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Randomized Analyzed
Allan, 2005	RCT 13 months	Multicenter in Europe	Pain condition: Low back pain Age: ≥18 years Pain severity: Not specified Psychiatric disease: Not specified Substance use: Excluded Prior opioid use: Not specified	A. Fentanyl transdermal titrated from 25 mcg/hour (mean 57 mcg/hour) B. Morphine SR titrated from 60 mg/day SR morphine (mean 140 mg)	Mean age: 54.0 years Female: 61% Race: NR Nociceptive: 35% Neuropathic: 4% Other/mixed and neuropathic: 46% Other/mixed with psychologic factors: 3% Neuropathic with psychologic factors: 4% Mechanical low back pain: 83% Inflammatory: 8% Trauma/surgery: 39% Metabolic: 1% Other: 3% Mean pain duration: 124.7 months	A vs. B Screened: NR Eligible: NR Randomized: 683 (338 vs. 342; 3 group assignment NR)
Baron, 2016 (2 publications)	RCT 12 weeks	Unclear, Germany	Pain condition: Low back pain with neuropathic component Age: ≥18 years Pain severity: ≥6 on 0 to 10 NRS Psychiatric disease: Not specified Substance use: Excluded Prior opioid use: Mixed	A. Tapentadol SR 50 to 250 mg BID (mean 379 mg) B. Oxycodone SR/naloxone 10 to 40/5 to 20 mg BID + up to oxycodone SR 10 mg BID (mean 75 mg)	A vs. B Mean (SD) age, years: 58.1 (11.48) vs. 58.4 (12.23) Female: 59.2% vs. 65.6% White: 100% vs. 100% Mean (SD) BMI: 29.8 (5.55) vs. 29.0 (5.69) Positive painDETECT score: 73.8% vs. 75.8%	A vs. B Screened: NR Eligible: NR Randomized: 258 (130 vs. 128) Analyzed: 258 (130 vs. 128)
Binsfeld, 2010	RCT 24 weeks	64 sites in Europe	Pain condition: Mixed Age: ≥18 years Pain severity: Moderate to severe, not otherwise specified Psychiatric disease: Not specified Substance use: Not specified Prior opioid use: Mixed	A. Hydromorphone SR 8 to 32 mg QD (mean 18.4 mg) B. Oxycodone SR 20 to 80 mg BID (mean 43.8 mg)	A vs. B Mean (SD) age, years: 57.1 (13.1) vs. 58.0 (12.8) Female: 55.9% vs. 60.8% Chronic LBP: 57.9% vs. 56.4% Musculoskeletal pain such as osteoarthritis, RA: 22.4% vs. 26.4% Neuropathic pain (postherpetic neuralgia, diabetic polyneuropathies): 10.2% vs. 9.2% Other chronic pain conditions responsive to opioids: 9.4% vs. 8.0% Prior opioid use: 69.7% vs. 71.2%	A vs. B Screened: NR Eligible: NR Randomized: 512 Analyzed: 504 (254 vs. 250)

Author, Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Randomized Analyzed
Buynak, 2010	RCT 15 weeks	85 sites in the USA, 15 in Canada, 3 in Australia	Pain condition: Low back pain Age: ≥18 years Pain severity: ≥5 on 0 to 10 NRS Psychiatric disease: Excluded patients with presence of a clinically significant psychiatric disease Substance use: Excluded Prior opioid use: Mixed	A. Tapentadol SR 100 to 250 mg BID (mean 313 mg) B. Oxycodone SR 20 to 50 mg BID (mean 53 mg) C. Placebo	A vs. B vs. C Mean (SD) age, years: 49.4 (13.21) vs. 50.0 (14.21) vs. 50.4 (14.05) Age ≥65 years: 12.3% vs. 16.8% vs. 17.2% Female: 61.0% vs. 55.2% vs. 57.7% White: 72.0% vs. 73.5% vs. 74.3% Black: 19.5% vs. 16.8% vs. 15.7% Hispanic: 5.7% vs. 6.4% vs. 6.6% Other race: 2.8% vs. 3.4% vs. 3.4% Mean BMI (SD): 32.09 (9.121) vs. 31.36 (7.449) vs. 31.33 (8.143) Mean NRS score (SD): 7.5 (1.33) vs. 7.5 (1.21) vs. 7.6 (1.33) Moderate pain intensity: 11.1% vs. 10.2% vs. 13.2% Severe pain intensity: 88.9% vs. 89.8% vs. 86.8% Prior opioid use: 56.0% vs. 50.3% vs. 53.9%	A vs. B vs. C Screened: 1589 Eligible: 979 Randomized: 981 (321 vs. 334 vs. 326) Analyzed: 965 (318 vs. 328 vs. 319)
Hale, 2007 and Gajria, 2008	RCT 6 weeks	Unclear, USA	Pain condition: Osteoarthritis of the knee or hip Age: ≥18 years Pain severity: ≥2 on 0 to 3 scale Psychiatric disease: Not specified Substance use: Not specified Prior opioid use: Unclear	A. Hydromorphone SR 8 to 64 mg QD (mean 15.8 mg) B. Oxycodone SR 10 to 80 mg BID (mean 24.0 mg)	A vs. B Mean (SD) age, years: 62.9 (10.32) vs. 64.2 (13.12) Female: 76.6% vs. 61.7% White: 82.8% vs. 88.3% Black: 9.4% vs. 8.3% Other race: 7.8% vs. 3.3% Mean BMI (SD): 34.2 (8.01) vs. 31.4 (6.34) Mean pain intensity (SD): 2.5 (0.50) vs. 2.5 (0.50)	A vs. B Screened: NR Eligible: NR Randomized: 140 (71 vs. 69) Analyzed: 124 (64 vs. 60)*
Karlsson, 2009	RCT 12 weeks	14 sites in Sweden	Pain condition: Osteoarthritis of knee or hip Age: >18 years Pain severity: ≥4 on 0 to 10 BS-11 Psychiatric disease: Not specified Substance use: Excluded Prior opioid use: Mixed	A. Buprenorphine 7-day patches 5 to 20 mcg/hour (mean NR) B. Tramadol SR tables 150 to 400 mg/day (mean NR)	A vs. B Mean (SD) age, years: 64.4 (11.1) vs. 64.2 (9.3) Female: 59.4% vs. 53.8% White: 98.6% vs. 100% Asian: 1.4% vs. 0 Mean (SD) BS-11 score: 6.16 (1.35) vs. 6.21 (1.55)	A vs. B Screened: 172 Eligible: NR Randomized: 135 (69 vs. 66) Analyzed: 134 (69 vs. 65)

Author, Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Randomized Analyzed
Leng, 2015	RCT 8 weeks	6 sites in China	Pain condition: Musculoskeletal pain Age: 18 to 80 years Pain severity: Moderate to severe pain, not otherwise specified Psychiatric disease: Excluded patients with mental disorders Substance use: Excluded Prior opioid use: Unclear	A. Buprenorphine 7-day patches 5 to 20 mcg/hour (mean 7.5 mcg/hour) B. Tramadol SR tablets 100 to 400 mg/day (mean 236 mg/hour)	A vs. B Mean (SD) age, years: 57.23 (10.30) vs. 56.77 (11.60) Female: 68.4% vs. 69.9% Mean (SD) weight, kg: 66.70 (10.92) vs. 66.60 (10.89) Intervertebral disk disease: 18.4% vs. 26.3% Spondylolisthesis: 1.5% vs. 0.8% Osteoarthritis: 61.8% vs. 56.4% LBP: 7.4% vs. 9.8% Other reasons for pain: 14.7% vs. 16.5% Mean (SD) duration of pain, weeks: 221.10 (309.77) vs. 194.35 (278.28)	A vs. B Screened: NR Eligible: NR Randomized: 280 (141 vs. 139) Analyzed: 269 (136 vs. 133)
Matsumoto, 2005	RCT 4 weeks	Multicenter in the USA	Pain condition: Osteoarthritis of the knee or hip Age: >40 years Pain severity: Not specified Psychiatric disease: Not specified Substance use: Excluded Prior opioid use: Not specified	A. Oxymorphone SR 20 mg BID x 2 weeks, then 40 mg BID B. Oxymorphone SR 20 mg BID C. Oxycodone SR 10 mg BID x 2 weeks, then 20 mg BID D. Placebo	A vs. B vs. C vs. D Median age, years: 61 vs. 63 vs. 63 vs. 62 Female: 64% vs. 56% vs. 58% vs. 65% Nonwhite race: 12% vs. 18% vs. 10% vs. 14% Knee osteoarthritis: 78% vs. 77% vs. 75% vs. 75% Duration of osteoarthritis >5 years: 64% vs. 71% vs. 67% vs. 77%	A vs. B vs. C vs. D Screened: NR Eligible: NR Randomized: 491 (121 vs. 121 vs. 125 vs. 124) Analyzed: 489 (121 vs. 119 vs. 125 vs. 124)
Mitra, 2013	RCT 12 months	1 site in Townsville, Australia	Pain condition: Mixed Age: >18 years Pain severity: Not specified Psychiatric disease: Excluded patients with comorbid psychiatric history Substance use: Not specified Prior opioid use: Excluded	A. Buprenorphine patch titrated from 5 mcg/hour (mean NR) B. Fentanyl patch titrated from 12.5 mcg/hour (mean NR)	Mean (range) age, years: 49 (22 to 80) Female: 52% Back pain: 61% Other types of pain: 39% Mean duration of pain (range): 11.7 years (6 months to 50 years) Duration of followup: 3 months (35%), 6 months (13%), 12 months (52%)	A vs. B Screened 82 Eligible: NR Randomized: 46 (22 vs. 24) Analyzed: 30 (14 vs. 16)

Author, Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Randomized Analyzed
Nicholson, 2006	RCT 24 weeks	5 outpatient pain centers in the USA	Pain condition: Mixed, predominantly non-neuropathic Age: 18 to 85 years Pain severity: ≥4 on 0 to 10 BPI Psychiatric disease: Not specified Substance use: Not specified Prior opioid use: Mixed	A. Morphine SR titrated from previous dose (mean 79 mg/day) B. Oxycodone SR titrated from previous dose (mean 85 mg/day)	A vs. B Overall mean (range) age, years: 51.3 (20 to 83) Female: 62.8% vs. 40.7%, p<0.05 Overall white: 93.8% Back pain: 62.8% vs. 51.9% Neck pain: 20.9% vs. 16.7% Arthralgia: 7.0% vs. 14.8% Osteoarthritis NOS: 7.0% vs. 13.0% Pain in limb: 2.3% vs. 18.5%, p=0.021	A vs. B Screened: NR Eligible: NR Randomized: 112 (53 vs. 59) Analyzed: 97 (43 vs. 54)
Niemann, 2000	RCT, crossover 4 weeks	Multicenter in Denmark	Pain condition: Pancreatitis Age: ≥18 years Pain severity: Not specified Psychiatric disease: Not specified Substance use: Not specified Prior opioid use: Required to be currently treated by opioids	A. Fentanyl transdermal 25 to 100 mcg/hour (mean 55.6 mcg/hour) B. Morphine SR dose range NR (mean 128.3 mg/day)	Median age, years: 47 Female: 33.3% Race: NR Etiology of chronic pancreatitis: -Alcohol abuse: 94.4% -Sjögren's syndrome: 5.6% Median duration of chronic abdominal pain: 9 years	Screened: NR Eligible: NR Randomized: 18 Analyzed: 18
Rauck, 2006 and 2007	RCT 8 weeks	Multicenter in the USA	Pain condition: Low back pain Age: 30 to 70 years Pain severity: >4 on 0 10 BPI Psychiatric disease: Not specified Substance use: Not specified Prior opioid use: Excluded those treated with SR opioid, used SR opioid in last 6 months	A. Morphine SR once daily (mean 64 mg/day) B. Oxycodone SR twice daily (mean 53 mg/day)	A vs. B Median (range) age, years: 50 (28 to 70) vs. 50 (29 to 73) Female: 63.5% vs. 58.2% White: 75.9% vs. 82.5% Black: 23.2% vs. 16.9% Other race: 1% vs. 0.5% Median weight, kg: 87 vs. 91 Mechanical cause of back pain: 76.4% vs. 84.7%, p<0.04 Nonmechanical cause of back pain: 23.6% vs. 15.3% Nerve involvement: 36.9% vs. 27%, p<0.04 Median length of back pain, years: 7 vs. 6	A vs. B Screened: NR Eligible: NR Randomized: 392 (203 vs. 189) Analyzed: 266 (132 vs. 134)

Author, Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Randomized Analyzed
Ueberall, 2015 and 2016	RCT 12 weeks	88 medical centers in Germany	Pain condition: Low back pain Age: ≥18 years Pain severity: Moderate to severe, not otherwise specified Psychiatric disease: Not specified Substance use: Not specified Prior opioid use: Required an around-the clock therapy with any of the 3 mentioned WHO step III opioids	A. Oxycodone/ naloxone SR (mean 113 mg morphine equivalents) B. Oxycodone SR (mean 107 morphine equivalents) C. Morphine SR (mean 108 morphine equivalents)	A vs. B vs. C Mean (SD) age, years: 46.1 (9.9) vs. 46.7 (9.9) vs. 46.5 (9.3) Female: 55.8% vs. 55.3% vs. 56% Mean (SD) BMI: 27.4 (5.0) vs. 27.0 (4.5) vs. 27.3 (5.9) Pain duration >3 to 12 months: 49.8% vs. 50% vs. 52.3% Pain duration >1 year: 30.9% vs. 30% vs. 30.3% Mean (SD) pain intensity: 47.2 (18.9) vs. 46.8 (21.2) vs. 47.7 (21.4)	A vs. B vs. C Screened: 901 Eligible: 901 Randomized: 901 (301 vs. 300 vs. 300) Analyzed: 901 (301 vs. 300 vs. 300)
Wild, 2010	RCT 12 months	53 sites in North America; 36 sites in Europe	Pain condition: Low back pain or osteoarthritis of the knee or hip Age: ≥18 years Pain severity: ≥4 on 0 to 10 NRS Psychiatric disease: Not specified Substance use: Excluded Prior opioid use: Mixed	A. Tapentadol SR 100 to 250 mg BID (mean 390 mg) B. Oxycodone SR 20 to 50 mg BID (mean 74 mg)	A vs. B Mean (SD) age, years: 56.8 (12.5) vs. 58.1 (11.8) Age <65 years: 72.6% vs. 70% Female: 57.6% vs. 56.1% White:88.6% vs. 91.0% Black: 6.7% vs. 5.8% Hispanic: 2.9% vs. 1.8% Other: 1.8% vs. 1.3% BMI: 31.7 vs. 31.8 Mean pain intensity (SD): 7.6 (1.5) vs 7.6 (1.62) Moderate pain: 10% vs 13% Severe pain: 90% vs 87% No prior opioid use: 47.1% vs 49.8%	A vs. B Screened: 1123 Eligible: NR Randomized: 1121 Received drug: 1117 (894 vs. 223)

Abbreviations: BID=twice daily; BMI=body mass index; BPI=Brief Pain Inventory; BS-11=numerical 11 point box; LBP=low back pain; NR=not reported; NRS=numerical rating scale; QD=four times daily; RCT=randomized controlled trial; SD=standard deviation; SE=standard error; SR=sustained release; U.K.=United Kingdom; USA=United States of America; vs.=versus; WHO=World Health Organization.

*1 of the investigators, who had enrolled 14 patients at a single site (7 in each treatment group), was issued a Notice of Initiation of Disqualification Proceedings and Opportunity to Explain by the FDA's Division of Scientific Investigation, these patients are excluded from the analysis in this paper.

See Appendix F. Included Studies for full citations

Table H-28. Key Question 3c: Head-to-head trials of different long-acting opioids – study results

Author, Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Afilalo, 2010	A vs. B vs. C, at 12 weeks Average pain intensity, ≥30% reduction: 43.0% (148/344) vs. 24.9% (85/342) vs. 35.9% (121/337), RR 1.73 (95% CI, 1.39 to 2.16) for A vs. B Average pain intensity, ≥50% reduction: 32.0% (110/344) vs. 17.3% (59/342) vs. 24.3% (82/337), RR 1.85 (95% CI, 1.40 to 2.45) for A vs. B PGIC of very much improved, much improved, or minimally improved: 79.5% (205/258) vs. 73.5% (147/200) vs. 59.0% (161/273), RR 1.08 (95% CI, 0.97 to 1.20) A vs. C, LSMD (95% CI) at week 12 Pain (0 to 10 NRS): -0.7 (-1.04 to -0.33) WOMAC, pain subscale: -0.27 (-0.422 to -0.126), p<0.001 WOMAC, function subscale: -0.21 (-0.357 to -0.060), p=0.006 EQ-5D: 0.05 (0.02 to 0.09), p=0.004 SF-36, PCS: 2.8 (1.56 to 3.95), p<0.001 SF-36, MCS: -1.1 (-2.44 to 0.17) B vs. C, LSMD (95% CI) at week 12 Pain (0 to 10 NRS): -0.3 (-0.68 to 0.02) WOMAC, pain subscale: -0.17 (-0.338 to 0.000) WOMAC, function subscale: -0.20 (-0.373 to -0.034), p=0.019 EQ-5D: -0.01 (-0.05 to 0.02) SF-36, PCS: 0.3 (-0.94 to 1.45) SF-36 MCS: -3.0 (-4.34 to -1.72), p<0.001	A vs. B vs. C, RR (95% CI) for A vs. B Serious AEs: 1.2% (4/344) vs. 2.9% (10/342) vs. 1.8% (6/337), RR 0.40 (0.13 to 1.26) Constipation: 18.9% (148/344) vs. 36.8% (126/342) vs. 6.5% (22/337), RR 1.17 (0.97 to 1.40) Nausea: 21.5% (74/344) vs. 36.5% (125/342) vs. 6.8% (23/337), RR 0.59 (0.46 to 0.75) Vomiting: 5.2% (18/344) vs. 17.8% (61/342) vs. 3.3 (11/337), RR 0.29 (0.18 to 0.49) Pruritus: 7.0% (24/344) vs. 12.6% (43/342) vs. 1.2% (4/337), RR 0.55 (0.34 to 0.89) Dizziness: 17.7% (61/344) vs. 19.0% (65/342) vs. 4.7% (16/337), RR 0.93 (0.68 to 1.28) Death: 0 vs. 0.3% (1/344) vs. 0, RR 0.33 (0.01 to 8.15) Mild opioid withdrawal (COWS), 2 to 4 days after end of treatment: 17.1% (6/35) vs. 13.5% (5/37) vs. 0% (0/23), RR 1.27 (0.42 to 3.78) Mild opioid withdrawal (COWS) ≥5 days after end of treatment: 1.4% (1/70) vs. 11.9% (10/84) vs. 8.5% (5/59), RR 0.12 (0.02 to 0.91) Moderate opioid withdrawal (COWS) ≥5 days after end of treatment: 0% (0/70) vs. 2.4% (2/84) vs. 0% (0/59), RR 0.24 (0.01 to 4.91) SOWS: no statistically significant differences in LSM SOWSs total scores for A vs. C Discontinued due to AEs: 42.7% (147/344) vs. 64.6% (221/342) vs. 38.6% (130/337), RR 0.66 (0.57 to 0.76)	Industry	Fair

Author, Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Allan, 2001	A vs. B Pain intensity (0 to 100), mean: 57.8 vs. 62.9, p<0.001 Pain control "good" or "very good": 35% (87/247) vs. 23% (54/234), p=0.002, RR 1.53 (95% CI, 1.14 to 2.04) SF-36 PCS (0 to 100), mean (95% CI): 28.6 (27.5 to 29.7) vs. 27.4 (26.3 to 28.5), p=0.004 SF-36 MCS (0 to 100), mean (95% CI): 44.4 (42.8 to 46.0) vs. 43.1 (41.5 to 44.8), p=0.030 Patient global efficacy "good" or "very good": 60% vs. 36%, p<0.001	A vs. B Overall AEs: 74% vs. 70% "Serious" (not defined): 2.8% vs. 3.8% Constipation: 16% (41/250) vs. 22% (52/238), RR 0.75 (95% CI, 0.52 to 1.08) Constipation by bowel function questionnaire: 29% (71/250) vs. 48% (112/238), p<0.001, RR 0.60 (95% CI, 0.47 to 0.77) Nausea: 26% (64/250) vs. 18% (44/238), RR 1.38 (95% CI, 0.98 to 1.95) Vomiting: 10% (25/250) vs. 10% (24/238), RR 0.99 (95% CI, 0.58 to 1.69) Dizziness: 11% (28/250) vs. 4% (9/238), RR 2.96 (95% CI, 1.43 to 6.14) Somnolence: 18% (45/250) vs. 14% (34/238), RR 1.26 (95% CI, 0.84 to 1.89) Deaths: None Discontinuation due to AE (all patients): 11% (27/250) vs. 4% (10/238), RR 2.57 (95% CI, 1.27 to 5.19) Discontinuation due to AE (patients not previously on fentanyl or morphine): 11% (7/66) vs. 9.8% (6/66), RR 1.17 (95% CI, 0.41 to 3.29)	Industry	Fair

Author, Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Allan, 2005	A vs. B Pain intensity (0 to 100 VAS), mean at 56 weeks: 56.0 vs. 55.8 Severe pain at rest: no differences in ITT analysis (data not provided) Quality of life (SF-36): no differences between interventions Loss of working days: no differences between interventions	A vs. B, RR (95% CI) Any AE: 87% vs. 91% Constipation (ITT): 52% (176/338) vs. 65% (220/338), RR 0.80 (0.70 to 0.91), p<0.05 Nausea: 54% vs. 50% Vomiting: 29% vs. 26% Pruritus: 15% vs. 20% Dizziness: 25% vs. 24% Somnolence: 17% vs. 30% Fatigue: 17% vs. 14% Application site reactions: 9% in transdermal fentanyl group. Deaths: None Addiction: None reported Use of laxatives: 53% (177/336) vs. 66% (221/336), RR 0.80 (0.70 to 0.91), p<0.001 Use of antiemetics/anticholinergics: 38% vs. 36% Use of antihistamines: 21% vs. 12%, p=0.002 Overall discontinuation: 52% (177/338) vs. 47% (162/342), RR 1.10 (0.95 to 1.29) Discontinuation due to AEs: 37% (125/335) vs. 31% (104/337), p=0.098, RR 1.21 (0.98 to 1.49) Discontinuation due to lack of efficacy: 5% (18/335) vs. 4% (15/342), RR 1.22 (0.63 to 2.39)	Industry	Fair

Author, Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Baron, 2016 (2 publications)	A vs. B Pain (0 to 10 NRS), LS mean change (SEM), week 12: -3.7 (0.25) vs. -2.7 (0.26), p<0.001 for test for non-inferiority and p=0.003 for test for superiority PGIC rating very much or much improved: 54.3% (70/129) vs. 29.6% (37/125), RR 1.83 (95% CI, 1.34 to 2.51) painDETECT (0 to 38), LS mean change (SEM): -10.8 (0.67) vs. -7.9 (0.69), p=0.002 SF-12 PCS (0 to 100) at 12 weeks, mean (SD): 40.5 (9.34) vs. 37.8 (8.84) SF-12 MCS (0 to 100) at 12 weeks, mean (SD): 51.1 (11.04) vs. 48.7 (11.57)	A vs. B, RR (95% CI) ≥1 TEAE: 76.9% (100/130) vs. 83.6% (107/128), RR 0.92 (0.81 to 1.04) Serious TEAE: 2.3% (3/130) vs. 1.6% (2/128), RR 1.48 (0.15 to 8.69) Constipation: 15.4% (20/130) vs. 25.8% (33/128), RR 0.60 (0.36 to 0.98), p≤0.045 Nausea: 22.3% (29/130) vs. 18.0% (23/128), RR 1.24 (0.76 to 2.03) Vomiting: 7.7% (10/130) vs. 16.4% (21/128), p≤0.045, RR 0.47 (0.23 to 0.96) Pruritus: 6.2% (8/130) vs. 8.6% (11/128), RR 0.72 (0.30 to 1.72) Dizziness: 18.5% (24/130) vs. 17.2% (22/128), RR 1.07 (0.64 to 1.81) Fatigue: 30.0% (39/130) vs. 24.2% (31/128), RR 1.24 (0.83 to 1.85) Mean (SD) testosterone concentration in men ≤64 years at final evaluation, nmol/L (n=19 vs. 11): 11.21 (3.678) vs. 8.99 (4.320) Men ≤64 years with testosterone levels below normal range at final evaluation: 10.5% (2/19) vs. 45.5% (5/11), RR 0.23 (0.05 to 1.00) No TEAE-related patterns of opioid-induced androgen deficiency in men ≤64 years Overall discontinuation: 33.8% (44/130) vs. 62.5% (80/128), RR 0.54 (0.41 to 0.71) Discontinuation due to AEs: 21.5% (28/130) vs. 42.2% (54/128), p<0.001, RR 0.51 (0.35 to 0.75) -Discontinuation due to GI AEs: 14.6% (19/130) vs. 21.1% (27/128), RR 0.69 (0.41 to 1.18) -Discontinuation due to nervous system AEs: 4.6% (6/130) vs. 17.2% (22/128), p=0.001, RR 0.27 (0.11 to 0.64) -Discontinuation due to dizziness: 3.1% vs. 12.5%, p=0.005 -Discontinuation due to skin and subcutaneous tissue AEs: 2.3% vs. 8.6%, p≤0.03	Industry	Fair

Author, Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Binsfeld, 2010	A vs. B BPI pain right now (0 to 10), mean difference: -0.12 (95% CI, -0.53 to 0.29) MOS sleep subscale, sleep interference, mean difference: -2.87 (95% CI, -5.94 to 0.19)	A vs. B, RR (95% CI) Total AEs: 81.1% (206/254) vs. 84.8% (212/250), RR 0.96 (0.88 to 1.03) SAE: 9.8% (25/254) vs. 8.4% (21/250), RR 1.17 (0.67 to 2.04) Constipation: 28.7% (73/254) vs. 26.0% (65/250), RR 1.10 (0.83 to 1.47) Nausea: 26.8% (68/254) vs. 31.6% (79/250), RR 0.85 (0.64 to 1.11) Vomiting: 12.6% (32/254) vs. 14.4% (36/250), RR 0.87 (0.56 to 1.36) Deaths: NR Addiction: NR Abuse: NR Cognitive changes: NR Overall discontinuation: 54.7% (139/254) vs. 56.8% (142/250), RR 0.96 (0.82 to 1.13) Discontinuation due to AE: 26.4% (67/254) vs. 25.2% (63/250), RR 1.05 (0.78 to 1.41) Discontinuation due to lack of efficacy: 8.7% (22/254) vs. 7.2% (18/250), RR 1.20 (0.66 to 2.19)	Industry	Fair

Author, Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Buynak, 2010	A vs. B vs. C, at 12 weeks Pain (0 to 10 NRS), mean (SD) change: -2.9 (2.66) vs. -2.9 (2.52) vs. -2.1 (2.33) Average pain intensity, ≥30% reduction: 39.7% (125/315) vs. 30.4% (99/326) vs. 27.1% (86/317), RR 1.31 (95% CI, 1.06 to 1.62) for A vs. B Average pain intensity, ≥50% reduction: 27.0% (85/315) vs. 23.3% (76/326) vs. 18.9% (60/317), RR 1.16 (95% CI, 0.89 to 1.51) for A vs. B PGIC rating much improved or very much improved: 55.5% (131/236) vs. 60.0% (126/210) vs. 32.7% (80/245), RR 0.93 (95% CI, 0.79 to 1.08) A vs. C, LSMD (95% CI, or SE) at week 12 Pain (0 to 10 NRS): -0.8 (-1.22 to -0.47), p<0.001 -Moderate baseline pain intensity: -1.8 (-3.15 to -0.48), p=0.009 -Severe baseline pain intensity: -0.8 (-1.23 to -0.41), p<0.001 BPI: -0.7 (0.18), p<0.001 SF-36 PCS: 2.3 (0.65), p<0.001 SF-36 MCS: 0.1 (0.70) EQ-5D: 0.0 (0.002), p=0.02 B vs. C, LSMD (95% CI, or SE) at week 12 Pain (0 to 10 NRS): -0.9 (-1.24 to -0.49), p<0.001 -Moderate baseline pain intensity: -1.5 (-2.63 to -0.29), p=0.015 -Severe baseline pain intensity: -0.8 (-1.21 to -0.40), p<0.001 BPI: -0.5 (0.17), p=0.002 SF-36 PCS: 2.3 (0.65), p<0.001 SF-36 MCS: -0.7 (0.69) EQ-5D: 0.1 (0.02), p=0.019	A vs. B vs. C, RR (95% CI) for A vs. B Reported ≥1 TEAE: 75.5% (240/318) vs. 84.8% (278/328) vs. 59.6% (190/319), RR 0.89 (0.82 to 0.96) Serious TEAEs: 2.2% (7/318) vs. 3.4% (11/328) vs. 0.9% (3/319), RR 0.66 (0.26 to 1.67) Constipation: 13.8% (44/318) vs. 26.8% (88/328) vs. 5.0% (16/319), RR 0.52 (0.37 to 0.71) Nausea: 20.1% (64/318) vs. 34.5% (113/328) vs. 9.1% (29/319), RR 0.58 (0.45 to 0.76) Vomiting: 9.1% (29/318) vs. 19.2% (63/328) vs. 1.6% (5/319), RR 0.47 (0.31 to 0.72) Pruritus: 7.2% (23/318) vs. 16.8% (55/328) vs. 1.9% (6/319), RR 0.43 (0.27 to 0.68) Dizziness: 11.9% (38/318) vs. 17.1% (56/328) vs. 5.6% (18/319), RR 0.70 (0.48 to 1.02) Insomnia: 4.1% (13/318) vs. 7.6 (25/328) vs. 2.8 (9/319), RR 0.54 (0.28 to 1.03) Deaths: 0 vs. 0 vs. 0	Industry	Fair

Author, Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Hale, 2007 and Gajria, 2008	A vs. B Pain relief (0 to 10), mean (SD): 2.3 (0.95) vs. 2.3 (1.00) Pain intensity (0 to 10), mean change (SD) from baseline: -0.6 (0.80) vs. -0.4 (1.15), p=NS Patients rated treatment effectiveness good, very good, or excellent: 67.2% (43/64) vs. 66.7% (40/60), RR 1.01 (95% CI, 0.79 to 1.30) WOMAC total score, mean (SD) change from baseline: -2.0 (1.90) vs. -1.8 (2.14) WOMAC pain subscale, mean (SD) change from baseline: -2.1 (1.96) vs. -2.0 (2.03) WOMAC stiffness subscale, mean (SD) change from baseline: -2.2 (2.37) vs. -2.2 (2.72) WOMAC physical function subscale, mean (SD) change from baseline: -1.9 (1.99) vs. -1.7 (2.1) Sleep disruption and daytime somnolence: 25.7 (17.82) vs. 35.3 (22.56), p<0.012 MOS sleep problems index, mean (SD) change from baseline: -13.3 (21.10) vs. -5.2 (22.09), p<0.045	A vs. B, RR (95% CI) Any AE: 78.9% (56/71) vs. 79.1% (53/67), RR 1.00 (0.84 to 1.18) SAE: 4.2% (3/71) vs. 1.5% (1/67), RR 2.83 (0.30 to 26.55) Constipation: 29.6% (21/71) vs. 25.4% (17/67), RR 1.17 (0.68 to 2.01) Nausea: 35.2% (25/71) vs. 29.9% (20/67), RR 1.18 (0.73 to 1.91) Vomiting: 16.9% (12/71) vs. 11.9% (8/67), RR 1.41 (0.62 to 3.25) Dizziness (excluding vertigo): 14.1% (10/71) vs. 22.4% (15/67), RR 0.63 (0.30 to 1.30) Somnolence: 25.4% (18/71) vs. 17.9% (12/67), RR 1.41 (0.74 to 2.71) Headache: 5.6% (4/71) vs. 10.4% (7/67), RR 0.54 (0.16 to 1.76) Total discontinuation: 39.4% (28/71) vs. 39.1% (27/69), RR 1.01 (0.67 to 1.52) Discontinuation due to AE: 35.2% (25/71) vs. 32.8% (22/67), RR 1.07 (0.67 to 1.71)	Industry	Fair
Karlsson, 2009	A vs. B, at study completion Pain (0 to 10), LSM change from baseline (95% CI): -2.26 (-2.76 to -1.76) vs. -2.09 (-2.61 to -1.58) Patient rating "very good" or "good": 64.7% (44/68) vs. 53.2% (33/62), RR 1.22 (0.91 to 1.63), p=0.039 Decrease in number of nights waking because of pain: 2 vs. 2 Improvement in sleep quality by 1 category: 59% vs. 48% Patient preference for patch over tablet: 70.3% (90/128) WOMAC, EQ-5D: No differences between groups	A vs. B, RR (95% CI) Any AEs: 88.4% vs. 78.5% Constipation: 18.8% (21/69) vs. 7.7% (5/65), RR 3.96 (1.58 to 9.87) Nausea: 30.4% (21/69) vs. 24.6% (16/65), RR 1.24 (0.71 to 2.15) Pruritus: 2.9% (2/69) vs. 9.2% (6/65), RR 0.31 (0.06 to 1.50) Dizziness: 15.9% (11/69) vs. 4.6 (3/65), RR 3.45 (1.01 to 11.83) Fatigue: 13.0% (9/69) vs. 18.5% (12/65), RR 0.71 (0.32 to 1.56) Hyperhidrosis: 14.5% (10/69) vs. 6.2% (4/65), RR 2.35 (0.78 to 7.14) Vertigo: 13.0% (9/69) vs. 1.5% (1/65), RR 8.48 (1.10 to 65.08) Headache: 11.6% (8/69) vs. 10.8% (7/65), RR 1.08 (0.41 to 2.80) Arthralgia: 5.8% (4/69) vs. 3.1% (2/65), RR 1.88 (0.36 to 9.94) Application site pruritus: 5.8% (4/69) vs. 0, RR 8.49 (0.46 to 154.59) Edema, peripheral: 5.8% (4/69) vs. 0, RR 8.49 (0.46 to 154.59) Nasopharyngitis: 5.8% (4/69) vs. 0, RR 8.49 (0.46 to 154.59) Overall discontinuation: 20.3% (14/69) vs. 32.3% (21/65), RR 0.63 (0.35 to 1.13) Discontinuation due to AEs: 14.5% (10/69) vs. 28.8% (19/66), RR 0.50 (0.25 to 1.00)	Industry	Fair

Author, Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Leng, 2015	A vs. B, at study completion Pain (0 to 10 VAS) mean (SD) change from baseline: -3.30 (2.29) vs. -3.75 (2.15) Number of nights waking from pain, mean (SD) improvement from baseline: -0.79 (1.47) vs. -1.06 (1.98) "Good" or "very good" sleep: 68.63% (70/102) vs. 68.57% (72/105), RR 1.00 (0.83 to 1.20)	A vs. B, RR (95% CI) Any AE: 56.74% (80/141) vs. 61.59% (85/139), RR 0.93 (0.76 to 1.13) SAEs: 0 vs. 2.2% (3/139), RR 0.14 (0.01 to 2.70) Constipation: 6.0% (9/141) vs. 7.5% (10/139), RR 0.89 (0.37 to 2.12) Nausea: 21.0% (30/141) vs. 21.7% (30/139), RR 0.98 (0.63 to 1.54) Vomiting: 9.6% (14/141) vs. 10.6% (15/139), RR 0.92 (0.46 to 1.83) Dizziness: 24.0% (34/141) vs. 17.4% (24/139), RR 1.40 (0.87 to 2.23) Somnolence: 6.0% (9/141) vs. 7.5% (10/139), RR 0.89 (0.37 to 2.12) Cutaneous reaction: 5.4% (8/141) vs. 6.2% (9/139), RR 0.88 (0.35 to 2.20) Mild to moderate erythema at patch site: 14.9% (21/141) vs. 13.0% (18/139), RR 1.15 (0.64 to 2.06) Use of antiemetics: 2.8% (4/141) vs. 4.4% (6/139), RR 0.66 (0.19 to 2.28) Use of cathartics: 0.7% (1/141) vs. 2.9% (4/139), RR 0.25 (0.03 to 2.18) Mean (SD) SOWS score: 0.53 (1.18) vs. 0.55 (1.64) Overall discontinuation: 28.4% (40/141) vs. 23.7% (33/139), RR 1.19 (0.80 to 1.78) Discontinuation due to AEs: 20.6% (29/141) vs. 18.0% (25/139), RR 1.14 (0.71 to 1.85) Discontinuation due to lack of efficacy: 0.74% (1/136) vs. 0, RR 3.06 (0.13 to 74.61)	Industry	Good

Author, Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Matsumoto, 2005	A vs. B vs. C vs. D, at week 4 Pain (0 to 100 VAS), mean change (SD) from baseline: -26 (NR) vs. -24 (NR) vs. -22 (NR) vs. -17 (NR) WOMAC Pain (0 to 500), mean change (SD) from baseline: -118 (110) vs. -102 (109) vs. -88 (125) vs. -62 (111) WOMAC Function (0 to 1700), mean change (SD) from baseline:-320 (550) vs. -290 (545) vs. -225 (559) vs. -175 (557) Patient's global assessment (0 to 100 VAS), mean change (SE) from baseline: -28.6 (3.3) vs. -23.2 (3.2) vs. -25.4 (2.8) vs. -19.5 (2.7) SF-36 PCS (0 to 100), mean change (SE) from baseline: 4.5 (0.9) vs. 3.4 (0.9) vs. 4.0 (0.8) vs. 1.8 (0.7) SF-36 MCS (0 to 100), mean change (SE) from baseline: -0.4 (1.1) vs. 1.5 (1.1) vs. -0.8 (0.9) vs. 2.22 (0.9) Sleep, overall quality (0 to 100, 100=excellent), mean change (SE) from baseline: 18.2 (3.2) vs. 13.8 (3.0) vs. 15.3 (2.5) vs. 7.7 (2.5)	A vs. B vs. C vs. D, RR (95% CI) A vs. C Any AE: 91% vs. 95% vs. 88% vs. 57% Constipation: 32% (39/121) vs. 40% (48/119) vs. 36% (45/125) vs. 11% (14/124), RR 0.89 (0.63 to 1.27) Nausea: 60% (72/121) vs. 61% (73/119) vs. 43% (54/125) vs. 10% (13/124), RR 1.38 (1.07 to 1.77) Vomiting: 34% (4/121) vs. 23% (27/119) vs. 10% (13/125) vs. 2% (2/124), RR 0.32 (0.11 to 0.95) Pruritus: 20% (30/121) vs. 19% (23/119) vs. 8% (10/125) vs. 2% (3/124), RR 3.10 (1.58 to 6.06) Dizziness: 31% (38/121) vs. 29% (34/119) vs. 26% (32/125) vs. 4% (5/124), RR 1.23 (0.82 to 1.83) Somnolence: 31% (38/121) vs. 30% (36/119) vs. 27% (34/125) vs. 5% (6/124), RR 1.15 (0.78 to 1.70) Dry mouth: 12% (14/121) vs. 12% (14/119) vs. 15% (19/125) vs. 0.8% (1/124), RR 0.76 (0.40 to 1.45) Headache: 11% (13/121) vs. 29% (7/119) vs. 26% (23/125) vs. 4% (14/124), RR 0.58 (0.31 to 1.10) Overall discontinuation: 56% (68/121) vs. 48% (58/121) vs. 40% (50/125) vs. 37% (46/124), RR 1.40 (1.08 to 1.83) Discontinuation due to AEs: 47% (57/121) vs. 38% (46/121) vs. 25% (31/125) vs. 5% (34/124), RR 1.90 (1.33 to 2.72)	Industry	Fair
Mitra, 2013	A vs. B Pain reduction ≥3 points (0 to 10): 50% (8/16) vs. 43% (6/14) at 3 months, RR 1.17 (95% CI, 0.53 to 2.54), 8% vs. 8% at 6 months (n/N NR), 11% vs. 11% at 12 months (n/N NR) Depression, Anxiety, and Stress Scale 21 (0 to 126), mean: 50 vs. 58 at 3 months (p=NS), 30 vs. 62 at 6 months (p<0.05), 38 vs. 58 at 12 months (p=NS) Physical Disability Index-7 (0 to 70), mean: 39 vs. 38 at 3 months, 30 vs. 40 at 6 months, 35 vs. 41 at 12 months Score of pain, physical activity, additional rescue medication, additional general practitioner/emergency department visit, sleep quality, mood, and side effects of pain medication (SPAASMS) score (0 to 28), mean: 12 vs. 13 at 3 months, 11 vs. 14 at 6 months, 14 vs. 14 at 12 months	A vs. B Number patients with local skin reaction at 9 months: 0 vs. 1 (estimated from graph) Side effects scale score at 12 months: ≤1 vs. ≤1 (estimated from graph) Discontinued due to AEs or unsatisfactory relief (not separated by AEs only): 41% (8/22) vs. 37.5% (8/24), RR 1.09 (95% CI, 0.49 to 2.41)	Private Practice Research Fund of Townsville	Poor

Author, Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Nicholson, 2006	A vs. B, mean improvement from baseline SF-36 PCS: +2.5 vs. +2.1, p=NS SF-36 MCS: +0.8 vs. +4.2, p for differences between groups NR, but p<0.05 vs. baseline only for sustained-release oxycodone BPI pain intensity: -1.9 vs. -1.4, p=NS BPI sleep Interference scale: -2.6 vs. -1.6, p<0.05 Patient global assessment: +2.6 vs. +1.7, p=NS Use of concomitant medications: 80% vs. 88%, p=NS	A vs. B, RR (95% CI) Any AE: NR Serious AEs: 12 overall Constipation: 26% (13/50) vs. 10% (6/58), RR 2.51 (1.03 to 6.12), p=0.04 Nausea: 14% (7/50) vs. 14% (8/58), RR 1.01 (0.40 to 2.60) Dizziness: 2% (1/50) vs. 5% (3/58), RR 0.77 (0.13 to 4.44) Somnolence: 10% (5/50) vs. 7% (4/58), RR 1.45 (0.41 to 5.11) Fatigue: 4% (2/50) vs. 2% (1/58), RR 2.32 (0.22 to 24.83) Cognitive disorder: 4% (2/50) vs. 2% (1/58), RR 2.32 (0.22 to 24.83) Headache: 4% (2/50) vs. 0%, RR 5.78 (0.28 to 117.72) Edema: 0% vs. 3% (2/58), RR 0.23 (0.01 to 4.71) Sedation: 0% vs. 5% (3/58), RR 0.16 (0.01 to 3.12) Overall discontinuation: 57% (30/53) vs. 51% (30/59), RR 1.11 (0.79 to 1.57) Discontinuation due to AEs: 28% (15/53) vs. 22% (13/59), RR 1.28 (0.67 to 2.44) Discontinuation due to lack of efficacy: 2% (1/53) vs. 7% (4/59), RR 0.28 (0.03 to 2.41)	Industry	Fair
Niemann, 2000	A vs. B Patient preference of "preference" or "strong preference": 47% (8/17) vs. 41.2% (7/17), RR 1.14 (0.54 to 2.44), p=NS Pain control "good" or "very good" (n=18): 44% (8/18) vs. 33.3% (6/18), RR 1.33 (0.58 to 3.07), p=NS Quality of life: no differences in physical functioning, general health, role physical, pain intensity, social functioning, mental health, and side effects summary median scores	NR	Industry	Fair

Author, Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Rauck, 2006 and 2007	A vs. B, mean change from baseline BPI (0 to 10): -3.1 vs. -2.8, p=NR >2 point improvement in BPI: 55% (73/132) vs. 44% (59/134), p=0.03 PSQI: 33% vs. 17%, p=0.006 SF-12 PCS: 23% vs. 19%, p=NS SF-12 MCS: 23% vs. 16%, p=NS Mean demands score on WLQ: 22.1 vs. 20.9	A vs. B, RR (95% CI) SAE: 3% (7/203) vs. 5% (9/189), RR 0.72 (0.27 to 1.90) Constipation: 87% vs. 89% Nausea: 50% vs. 47% Vomiting: 24% vs. 19% Dizziness: 58% vs. 64% Drowsiness: 85% vs. 84% Dry mouth: 82% vs. 76% Itchiness: 65% vs. 57% Drug abuse or diversion: 0% (0/203) vs. 2% (4/189), RR 0.10 (0.00 to 1.91) Overall discontinuation: 46% (93/203) vs. 42% (79/189), RR 1.10 (0.87 to 1.37) Discontinuation due to AEs: 19% (38/203) vs. 14% (27/189), RR 1.31 (0.83 to 2.06) Discontinuation due to lack of efficacy: 5% (10/203) vs. 3% (6/189), RR 1.55 (0.57 to 4.19)	Industry	Fair

Author, Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Ueberall, 2015 and 2016	A vs. B vs. C, at end of study Pain intensity (0 to 100), mean (SD): 27.1 (21.3) vs. 28.6 (21.7) vs. 20.0 (20.4) Pain improved ≥50% from baseline: 65.5% (197/301) vs. 50.7% (n/N NR) vs. 43.3% (n/N NR) EQ-5D, mean (SD): 0.79 (0.23) vs. 0.69 (0.28) vs. 0.68 (0.30) EQ-5D index improvement beyond MCID: 70.3% vs. 58.7% vs. 57.7%, p=0.003 A vs. B and p=0.002 A vs. C QLIP inventory (0 to 40, 40=least affected), mean (SD): 30.6 (4.9) vs. 27.5 (5.8) vs. 26.4 (5.9) Adequate sleep duration: 95% vs. 83.3% vs. 83% QLIP improved ≥30% from baseline: 90.7% (273/301) vs. 73.3% (220/300) vs. 67.3% (202/300), RR 1.09 (95% CI, 0.98 to 1.21) B vs. C SF-12 PCS, mean (SD) change from baseline: 10.4 (13.6) vs. 7.9 (15.1) vs. 7.7 (12.1) SF-12 MCS, mean (SD) change from baseline: 5.0 (12.4) vs. 2.5 (10.0) vs. 2.3 (10.8)	A vs. B vs. C, RR (95% CI) of B vs. C Constipation: 29.6% (89/301) vs. 55.3% (166/300) vs. 56.7% (170/300), RR 0.98 (0.85 to 1.12) Nausea: 0.7% (2/301) vs. 3% (9/300) vs. 4.7% (14/300), RR 0.64 (0.28 to 1.46) Dizziness: 1.7% (5/301) vs. 8% (24/300) vs. 9.3% (28/300), RR 0.86 (0.51 to 1.44) Fatigue: 19.6% (59/301) vs. 30% (90/300) vs. 30% (90/300), RR 1.00 (0.78 to 1.28) Lack of appetite: 5.6% (17/301) vs. 11.3% (34/300) vs. 17.3% (52/300), RR 0.48 (0.30 to 0.75) Daytime tiredness: 11.3% (34/301) vs. 18.7% (56/300) vs. 21% (63/300), RR 0.89 (0.64 to 1.23) Lack of drive: 10.3% (31/301) vs. 16.7% (50/300) vs. 19.3% (58/300), RR 0.86 (0.61 to 1.21) Impaired concentration: 12.3% (37/301) vs. 23.7% (71/300) vs. 23.3% (70/300), RR 1.01 (0.76 to 1.35) Gastric complaints: 15.3% (46/301) vs. 23.3% (70/300) vs. 23.7% (71/300), RR 0.98 (0.74 to 1.32) Sleep disturbance: 9.6% (29/301) vs. 22.3% (67/300) vs. 23% (69/300), RR -0.97 (0.72 to 1.30) Feeling down: 10.3% (31/301) vs. 20.7% (62/300) vs. 24.7% (74/300), RR 0.84 (0.62 to 1.13) BFI (0 to 100), mean: 30.0 (26.2) vs. 48.2 (32.3) vs. 53.6 (33.1), p<0.001 for A vs. B and C Overall discontinuation: 25.2% vs. 38.3% vs. 35.5%	Industry	Fair

Author, Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Wild, 2010	A vs. B Pain (0 to 10 NRS), decrease in mean (SE) at 12 months: 4.4 (0.09) vs. 4.5 (0.17) Global assessment score very much or much improved at 12 months: 48.1% (394/819) vs. 41.2% (73/177), RR 1.17 (95% CI, 0.96 to 1.41) Concomitant nonopioid analgesic use (NSAIDS, ASA, acetaminophen): 19.9% (178/894) vs. 17% (38/223), RR 1.17 (95% CI, 0.85 to 1.60)	A vs. B, RR (95% CI) ≥1 TEAE: 85.7% (766/894) vs. 90.6% (202/223), RR 0.94 (0.90 to 0.99) Serious TEAEs: 5.5% (49/894) vs. 4.0% (9/223), RR 1.36 (0.68 to 2.72) Constipation: 22.6% (202/894) vs. 38.6% (86/223), RR 0.58 (0.48 to 0.72) Nausea: 18.1% (162/894) vs. 33.2% (74/223), RR 0.55 (0.43 to 0.69) Vomiting: 7.0% (63/894) vs. 13.5% (30/223), RR 0.52 (0.35 to 0.79) Pruritus: 5.4% (48/894) vs. 10.3% (23/223), RR 0.52 (0.32 to 0.84) Dizziness: 14.8% (132/894) vs. 19.3% (43/223), RR 0.76 (0.56 to 1.04) Deaths: 0 vs. 0 Relevant AEs on labs, vitals, ECGs: 0 vs. 0 Mean change (SE) PAC-SYM: 0.3 (0.05) vs. 0.5 (O.14) COWS,5 days post treatment, score <5 (no withdrawal): 88% (145/166) vs. 84% (42/50), RR 1.04 (0.91 to 1.19) Mean SOWS at 2-5 days post treatment: 6.9-9.5 vs. 7.5-12.3 Overall discontinuation: 53.8% vs. 36% Discontinuation due to AEs: 22.7% (203/894) vs. 36.8% (82/223), RR 0.62 (0.50 to 0.76)	Industry	Fair

Abbreviations: AE=adverse events; ASA=aspirin; BFI=Bowel Function Index; BPI=Brief Pain Inventory; CI=confidence interval; COWS=Clinical Opiate Withdrawal Scale; EQ-5D=European Quality of Life 5-Dimensions Scale; ITT=intention-to-treat; LS=least squares; LSM=lease square means; LSMD=least standard mean difference; MCS=mental component subscale; MOS=Medical Outcomes Study; NR=not reported; NS=not significant; NRS=numerical rating scale; NSAID=nonsteroidal antiinflammatory drug; PCS=physical component subscale; PGIC=Patient Global Impression of Change; QLIP=Quality of Life Impairment by Pain; RR=risk ratio; SAE=serious adverse events; SD=standard deviation; SE=standard error; SEM=standard error mean; TEAE=treatment emergent adverse events; SF-12=short form 12-items; SF-36=short-form 36-items; SPAASMS= S-Score for pain, P-Physical activity levels, A-Additional pain medication, A-Additional Physician/ER Visits, S-Sleep, M-Mood, S-Side effects; SOWS=Subjective Opiate Withdrawal Scale; vs.=versus; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index.

See Appendix F. Included Studies for full citations

Table H-29. Key Question 3c: Observational studies of different long-acting opioids – study characteristics

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders	Enrolled Analyzed Loss to Followup
Chung, 2018	Retrospective cohort Tennessee Medicaid recipients, United States	Age 30 to 74 years who filled prescriptions for transdermal fentanyl, oxycodone CR, or morphine SR between January 1, 1999 and December 31, 2011	A. Transdermal fentanyl (median 100 mg/day MED) (n=8717) B. Oxycodone CR (median 120 mg/day MED) (n=14,118) C. Morphine SR (median 90 mg/day MED) (n=27,823)	A vs. B vs. C Median (IQR) age, years: 50 (42 to 58) vs. 48 (42 to 56) vs. 48 (42 to 55) Female: 67.7% vs. 53.9% vs. 59.6% White: 85.3% vs. 85.7% vs. 84.6% Back pain: 76.5% vs. 78.2% vs. 80.7% Other musculoskeletal pain: 12.9% vs. 11.8% vs. 10.7% Other pain: 1.8% vs. 1.4% vs. 1.3%	Proportional hazard regression models used to estimate the HRs	Screened: NR Eligible: NR Enrolled: 50, 658 (8717 vs. 14,118 vs. 27,823) Analyzed: 50,658 (8717 vs. 14,118 vs. 27,823) Loss to followup: NR
Hartung, 2007	Retrospective cohort Medicaid claims United States	Patients prescribed at least one ≥ 28-day supply of methadone, ER oxycodone, ER morphine, or transdermal fentanyl	A. Methadone (n=974) B. ER oxycodone (n=1,866) C. Transdermal fentanyl (n=1,546) D. ER morphine (n=1,298)	A vs. B vs. C vs. D Mean age, years: 70.6 vs. 51.1 vs. 57.4 vs. 58.5 Female: 74% vs. 63% vs. 65% vs. 65% Non-White: 6.1% vs. 10.5% vs. 7.7% vs. 9.6% Mean MED dose: 96 vs. 247 vs. 67 vs. 74 mg Cancer: 19.9% vs. 18.3% vs. 25.2% vs. 26.1% Osteoarthritis: 13.7% vs. 22.6% vs. 19.3% vs. 18.0% Back pain: 17.5% vs. 41.8% vs. 35.0% vs. 27.3%	Review of claims using ICD-9 codes	Enrolled: 5,684 Analyzed: 5,684

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders	Enrolled Analyzed Loss to Followup
Krebs, 2011	Retrospective cohort VA United States	New prescription for ≥ 28 days' supply of PO methadone or LA morphine tabs/caps from a VA outpatient pharmacy between 1/1/2000 and 12/31/2007. Preceded by 30 day window free of LA opioid prescriptions. Excluded: Liquid/IV forms of methadone/morphine; metastatic cancer, palliative care, receiving methadone for addiction; methadone 40 mg diskettes; < 17 or > 100 years of age; missing gender data.	A. Methadone (n=28,554) B. Long-acting morphine sulfate (n=79,938)	A vs. B Mean (SD) age, years : 56 (12) vs. 59 (13) Female: 7% vs. 5% Non-White: 52% vs. 49% MI: 9% vs. 11% CHF: 15% vs. 19% PVD: 17% vs. 20% CVD: 15% vs. 17% COPD: 35% vs. 38% Diabetes: 31% vs. 33% Malignancy: 15% vs. 26% Depression: 62% vs. 54% Bipolar: 10% vs. 8% Anxiety: 32% vs. 27% EtOH: 25% vs. 22% Drug disorders: 25% vs. 18% Tobacco: 47% vs. 42% Back pain: 85% vs. 76% Joint/limb pain: 86% vs. 82% Headache: 25% vs. 21% Neuropathic pain: 35% vs. 29% Overall Mean (SD) daily LA MS dose: 67.5 mg (77.4); median (IQR) 46.7 (45) Mean (SD) daily methadone dose: 25.4 mg (25.8); median (IQR): 20 (20) 99th percentile MS: 360 to 7200 mg 99th percentile methadone: 124 to 560 mg	All patients meeting eligibility criteria	Enrolled: 108,492 Analyzed: 98,068 Loss to followup: 3,347 (died); 94,721 (censored)

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders	Enrolled Analyzed Loss to Followup
Ray, 2015	Retrospective cohort Tennessee Medicaid enrollees	Aged 30 to 70 years, with a filled prescription for methadone or morphine SR (January 1997 to December 2009)	A: Morphine SR B: Methadone	A vs. B Median (IQR) age, years: 48 (42 to 55) vs. 47 (41 to 54) Female: 57.9% vs. 57.8% White: 84.4% vs. 84.5% Back pain: 78.2% vs. 77.2% Other musculoskeletal pain: 11.8% vs. 10.7% Other chronic pain: 2.8% vs. 1.4% Median (IQR) opioid dose, mg/day: 90 (60 to 100) vs. 40 (20 to 60)	Deaths were classified into 3 subgroups: (1) sudden unexpected deaths consistent with either opioid overdose or life-threatening arrhythmias, (2) other respiratory or cardiovascular deaths for which opioid involvement was possible but less certain, and (3) other deaths, which were less likely to be related to opioid toxic effects. Classification was based on the death certificate–documented underlying cause of death, adjudication of terminal medical records and computerized files with both the terminal medical encounters and death certificate information-	Screened: NR Eligible: NR Enrolled: 38,756 (32,742 vs. 6014)

Abbreviations: CHF=congestive heart failure; CI=confidence interval; COPD=chronic obstructive pulmonary disease; CR=controlled release; CVD=cardiovascular disease; ED=emergency department; ER=extended release; EtOH=Ethyl alcohol; HR=hazard ratio; ICD-9=International Classification of Diseases; IQR=interquartile range; IV=intravenous; LA=long acting; MED=morphine equivalent dose; mg=milligram; MI=myocardial infarction; MS=morphine sulfate; PO=oral route; PVD=peripheral vascular disease; SD=standard deviation; SR= sustained release; VA=Veterans Affairs; VISN=Veterans integrated service networks; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-30. Key Question 3c: Observational studies of different long-acting opioids – study results

Author, Year	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Chung, 2018	Adjusted for potential differences among groups using propensity scores that included 145 covariates such as demographic variables, calendar time, opioid indication, use of other opioids, cardiovascular medications and diagnoses, respiratory conditions, musculoskeletal diseases, indicators of frailty, other comorbidities, and medical care utilization	A vs. B vs. C Unintentional opioid overdose: 0.25% (15/5957) person-years vs. 0.21% (30/14,423) person-years vs. 0.34% (77/22,686) person-years All deaths: 1.7% (101/5957) person-years vs.1.3% (196/14,423) person-years vs. 1.6% (364/22,686) person-years Adjusted HR (95% CI), A vs. C Unintentional opioid overdose: 0.77 (0.44 to 1.34) All deaths: 0.96 (0.77 to 1.21) Adjusted HR (95% CI), C vs. B Unintentional opioid overdose: 1.67 (1.06 to 2.63) All deaths: 1.27 (1.05 to 1.52)	NIH	Fair
Hartung, 2007	Age, sex, race, long-term care residence, number of unique prescribers, disease severity, concomitant prescriptions known to interact with opioids, type of presumed pain diagnosis, history of abuse or dependence, enrollment in a substance abuse treatment program	A vs. B vs. C (reference: D) Mortality: adjusted HR: 0.71 (95% CI, 0.46 to 1.08) vs. HR 0.71 (95% CI, 0.54 to 0.94) vs. 0.80 (95% CI, 0.63 to 1.02) ED encounter or hospitalization involving an opioid-related adverse event: HR 0.45 (95% CI, 0.26 to 0.77) Among patients with noncancer pain Fentanyl associated with higher risk of ED encounters than sustained-release morphine (HR 1.27, 95% CI, 1.02 to 1.59) Methadone associated with greater risk of overdose symptoms than sustained-release morphine (HR 1.57, 95% CI, 1.03 to 2.40) No significant differences between methadone and long-acting morphine in risk of death (adjusted HR 0.71, 95% CI, 0.46 to 1.08) or overdose symptoms	NR	Fair

Author, Year	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Krebs, 2011	Propensity score for receiving methadone was estimated with logistic regression model that included age, gender, race, geographic area (VISN), depression, anxiety, bipolar dx, schizophrenia, ETOH, drug, tobacco disorders, back pain, joint/limb pain, headache, neuropathic pain Medical comorbidities included via Romano adaptation of Charlson Comorbidity Score Quintiles calculated and then used in Cox model Interaction term consisting of propensity quintile and opioid group	All-cause mortality: Unadjusted: 3.4% (3,347/98,068) patients died Highest mortality within 1st 30 days methadone: 1.2% (334/27,885) MS: 3.7% (2,597/70,183); raw death rates form MS higher than methadone for all 30-day intervals; Death rate: Quintile #1: 0.042 vs. 0.133 Quintile #2: 0.034 vs. 0.078 Quintile #3: 0.025 vs. 0.053 Quintile #4: 0.022 vs. 0.034 Quintile #5: 0.017 vs. 0.020 Propensity adjusted mortality (HR): Overall risk of mortality lower with methadone than morphine, adjusted HR: 0.56 (95% CI, 0.51 to 0.62) Quintile #1: 0.36 (95% CI, 0.26 to 0.49) Quintile #2: 0.46 (95% CI, 0.37 to 0.56) Quintile #3: 0.50 (95% CI, 0.41 to 0.61) Quintile #4: 0.66 (95% CI, 0.54 to 0.81) Quintile #5: 0.92 (95% CI, 0.74 to 1.16) Results robust in validation dataset	VA	Fair
Ray, 2015	The relative risk of death between groups defined by study opioid use status, adjusted for patient characteristics, was estimated with the hazard ratio (HR) from a proportional hazards regression model, with study opioid use as a time-dependent covariate. The HRs were adjusted for potential differences between patients currently receiving methadone and morphine SR. Patient characteristics were described by 196 covariates, which included calendar time, demographic factors, opioid indication, use and dose of non study opioids, cardiovascular medications and diagnoses, psychiatric medications and diagnoses, medications for musculoskeletal disorders, respiratory conditions, indicators of frailty, other proarrhythmic medications, other comorbidity, and recent medical care utilization.	HR (95% CI) A vs. B All deaths: 1.46 (1.17 to 1.83), p<0.001 Sudden unexpected death: 1.47 (1.13 to 1.90), p=0.04 -Opioid overdose only: 2.54 (1.33 to 4.84), p=0.005 -Sudden cardiac death only: 1.12 (0.80 to 1.59), p=0.51 -Both opioid overdose and sudden cardiac death: 2.02 (1.21 to 3.37), p=0.07 Other respiratory/cardiovascular deaths: 1.78 (0.91 to 3.46), p=0.09 Other deaths: 1.26 (0.70 to 2.26), p=0.45	Government	Fair

Abbreviations: CHF=congestive heart failure; CI=confidence interval; COPD=chronic obstructive pulmonary disease; CR=controlled release; CVD=cardiovascular disease; ED=emergency department; ER=extended release; EtOH=Ethyl alcohol; HR=hazard ratio; ICD-9=International Classification of Diseases; IQR=interquartile range; IV=intravenous; LA=long acting; MED=morphine equivalent dose; MI=myocardial infarction; MS=morphine sulfate; PO=oral route; PVD=peripheral vascular disease; SD=standard deviation; SR= sustained release; VA=Veterans Affairs; VISN=Veterans integrated service networks.

See Appendix F. Included Studies for full citations

Table H-31. Key Question 3f: Trial of opioid dose escalation versus dose maintenance or use of maximum dose ceilings – study characteristics

Author, Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup
Naliboff, 2011	RCT 12 months	VA pain clinic USA	Patients referred to chronic pain clinic; nonmalignant chronic pain for at least 6 months; clinician determination that patient was eligible for long-term opioids. Excluded: anticipated surgery, post-op pain, pulmonary disease or CHF, current or history of substance abuse disorder, hospitalization for psychiatric disorder in past 2 years	A. Escalating opioid dose; mean MED 52 mg (n=67) B. Stable opioid dose; mean MED 40 mg (n=73)	A vs. B Mean age, years: 53 vs. 52 Female: 11% vs. 1% Race not reported Pain: -78% vs. 77% musculoskeletal -19% vs. 19% neuropathic -3% vs. 4% complex Initial morphine equivalent 29.2 (SD 19.6) vs. 32.3 (SD 23.1) mg Mean usual VAS 7.0 (SD 1.9) vs. 6.7 (SD 1.8) Mean worst VAS 8.4 (SD 1.2) vs. 8.0 (SD 1.7) Mean ABC score 1.5 (SD 2.0) vs. 1.6 (SD 2.1) Mean ODI 48.6 (SD 12.6) vs. 47.8 (SD 14.0)	Screened: not reported Eligible: 140 Enrolled: 140 Analyzed: 134 Loss to followup: 7% (10/140)

Abbreviations: ABC=Assessment of Blood Consumption; CHF=chronic heart failure; MED=morphine equivalent dose; ODI=Oswestry Disability Index; SD=standard deviation; USA=United States of America; VAS=visual analogue scale; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-32. Key Question 3f: Trial of opioid dose escalation versus dose maintenance or use of maximum dose ceilings – study results

Author, year	Results	Adverse events and discontinuation due to adverse events	Funding source	Quality
Naliboff, 2011	A vs. B Mean (SD) VAS usual pain at 12 months: 5.6 (1.5) vs. 6.2 (1.5); p=0.11* Usual pain VAS decrease ≥1.5 points: 28% (19/67) vs. 20% (15/73); RR 1.38 (95% CI, 0.76 to 2.49) Mean (SD) VAS pain relief at 12 months: 6.0 (1.7) vs. 5.3 (1.8); p=0.11* Increase in pain relief ≥1.5 points: 29% (19/67) vs. 15% (11/73); RR 1.88 (95% CI, 0.97 to 3.66) Worst pain VAS decrease ≥1.5 points: 14% (9/67) vs. 6% (4/73); RR 2.45 (95% CI, 0.79 to 7.59) Mean (SD) ODI at 12 months: 45.8 (14.8) vs. 45.0 (19.4); p=0.85* ODI decrease ≥10 points: 29% (19/67) vs. 23% (20/73); RR 1.04 (95% CI, 0.61 to 1.76) Use of nonopioid treatments (A. n=64; B. n=70): -NSAID: 55% (35/64) vs. 60% (42/70); RR 0.92 (95% CI, 0.68 to 1.22) -Muscle relaxant: 15% (10/64) vs. 20% (14/70); RR 0.78 (95% CI, 0.37 to 1.63) -Antiseizure: 63% (40/64) vs. 66% (46/70); RR 0.95 (95% CI, 0.74 to 1.23) -Antianxiety: 29% (19/64) vs. 34% (24/70); RR 0.87 (95% CI, 0.53 to 1.42) -Antidepressants: 71% (45/64) vs. 69% (48/70); 1.03; (95% CI, 0.82 to 1.28) -Topical: 17% (11/64) vs. 16% (11/70); RR 1.06 (95% CI, 0.49 to 2.28) -Injectable: 26% (17/64) vs. 36% (25/70); RR 0.74 (95% CI, 0.44 to 1.24) -Physical therapy: 48% (31/64) vs. 63% (44/70); RR 0.77 (95% CI, 0.57 to 1.05)	A vs. B Discontinuation overall: 49% (33/67) vs. 56% (41/73); RR 0.88 (95% CI, 0.64 to 1.20) Discontinuation due to opioid misuse: 24% (16/67) vs. 30% (22/73); RR 0.79 (95% CI, 0.46 to 1.38)	Department of Veterans Affairs	Fair

Abbreviations: CI=confidence interval; NSAID=nonsteroidal antiinflammatory drug; ODI=Oswestry Disability Index; RR=risk ratio; SD=standard deviation; VAS=visual analogue scale; vs.=versus.

*p-value calculated based on completers (A: n=34; B: n=32)

See Appendix F. Included Studies for full citations

Table H-33. Key Question 3h: Trials of different strategies for treating acute exacerbations of chronic pain in patients on long-term opioid therapy – study characteristics

Author, Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed
Ashburn, 2011	RCT, crossover Up to 42 days total (2 treatment periods of 10 BTP episodes each within 21 days)	46 centers in the USA	Pain condition: Mixed Age: 18 to 80 years Pain severity: ≤6 on 0 to 10 NRS, with 1 to 4 episodes per day of BTP, each lasting <4 hours Psychiatric disease: Excluded Substance use: Excluded Prior opioid use: ≥60 mg/day MED	A. Fentanyl buccal tablet B. Oxycodone	Mean (SD) age, years: 48.8 (9.3) Female: 62% White: 92% Black: 5% Other race: 3% Back pain: 57% Osteoarthritis: 11% Neck pain: 8% Fibromyalgia: 9% Traumatic injury: 4% Complex regional pain syndrome: 4% Mean (SD) pain intensity in 24 hours prior to enrollment: 5.1 (1.1)	Screened: 486 Eligible: 360 Enrolled: 323 (titration phase) Analyzed: 320 (safety), 183 (efficacy)
Portenoy, 2007	RCT 3 weeks	16 centers in the USA	Pain condition: Low back pain Age: 18 to 80 years Pain severity: ≤6 on a 0 to 10 NRS, with BTP <4 hours Psychiatric disease: Excluded Substance use: Excluded Prior opioid use: ≥60 mg/day MED	A: Buccal fentanyl 100 to 800 mcg for an episode of BTP B: Placebo Dose of buccal fentanyl: 56% at 800 mcg; 24% at 600 mcg; 15% at 400 mcg; 5% at 200 mcg	NR for randomization groups Mean (SD) age, years: 46.6 (10.21) Female: 55% White: 88% Black: 8% Other race: 4% Primary etiology of low back pain degenerative disc disease: 68% Mean (SD) pain intensity: 5.1 (1.21)	Screened: 124 Eligible: NR Enrolled: 105 (in open-label dose titration), 77 (in randomized phase; randomized to one of 3 treatment sequences consisting of 6 fentanyl buccal tablets and 3 placebo tablets in different orders)

Author, Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed
Simpson, 2007	RCT, crossover 3 weeks	Multicenter clinic setting not described, in the USA	Pain condition: Neuropathic pain Age: 18 to 80 years Pain severity: <7 on 0 to 10 NRS, 1 to 4 episodes of BTP per day Psychiatric disease: Excluded Substance use: Excluded Prior opioid use: ≥60 mg/day MED	A. Buccal fentanyl 100 to 800 mcg for an episode of BTP B. Placebo Dose of buccal fentanyl: 800 mcg 54%; 600 mcg 19%; 400 mcg 18%; 200 mcg 5%, 100 mcg 5%	NR for randomization groups Mean (SD) age, years: 48.3 (10.42) Female: 63% White: 92% Black: 8% Other race: 0% Mean (SD) BMI: 32.7 (10.15) Diabetic peripheral neuropathy: 32% Complex regional pain syndrome: 23% Traumatic injury: 19% Idiopathic peripheral neuropathy: 13% Radiculopathy: 6% Postherpetic neuralgia: 4% Other reason for pain: 4% Mean (SD) pain intensity: 5.1 (1.03)	Screened: 129 Eligible: NR Enrolled: 103 (in open-label dose titration), 79 (in randomized phase; randomized to one of 3 crossover treatment sequences consisting of 6 fentanyl buccal tablets and 3 placebo tablets)
Webster, 2013	RCT, crossover Up to 42 days total (2 treatment periods of 10 BTP episodes each within 21 days)	42 sites in the USA	Pain condition: Mixed Age: 18 to 80 years Pain severity: ≤6 on 0 to 10 NRS, 1 to 4 episodes of BTP per day Psychiatric disease: Excluded Substance use: Excluded Prior opioid use: ≥60 mg/day MED	A. Fentanyl buccal tablet B. Oxycodone	Mean (SD) age, years: 50.8 (9.9) Female: 58% White: 91% Black: 7% Other race: 2% Mean (SD) pain intensity in 24 hours prior to enrollment: 5.1 (1.0)	Screened: 307 Eligible: NR Enrolled: 213 (titration phase) Analyzed: 211 (safety), 137 (efficacy)

Abbreviations: BTP=breakthrough pain; MED=morphine equivalent dose; NR=not reported; RCT=randomized controlled trial; SD=standard deviation; USA=United States of America; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-34. Key Question 3h: Trials of different strategies for treating acute exacerbations of chronic pain in patients on long-term opioid therapy – study results

Author, Year	Results	Adverse Events and Discontinuation Due To Adverse Events	Funding Source	Quality
Ashburn, 2011	A vs. B Pain intensity (0 to 10) at 15 minutes, mean difference (SD): 0.82 (1.12) vs. 0.60 (0.88), p<0.001 Pain intensity (0 to 10) at 30 minutes, mean difference (SD): 1.95 (1.47) vs. 1.60 (1.27), p<0.05 Pain relief (0 to 5) at 15 minutes, mean (SD): 0.69 (0.74) vs. 0.53 (0.67), p<0.05 Pain relief (0 to 5) at 30 minutes, mean (SD): 1.50 (0.83) vs. 1.23 (0.76), p<0.05 Meaningful pain relief within 15 minutes: 16% vs. 12% of episodes, p<0.05 Meaningful pain relief within 30 minutes: 45% vs. 36% of episodes, p<0.05 Any pain relief within 15 minutes: 39% vs. 31% of episodes, p<0.05 Any pain relief within 30 minutes: 71% vs. 66% of episodes, p<0.05	A vs. B, RR (95% CI) Any AE: 38% (106/281) vs. 31% (88/284); RR 1.22 (0.97 to 1.53) SAE: 2 (in 1 patient) vs. 0 Nausea: 9% (26/281) vs. 4% (11/284), RR 2.39 (1.20 to 4.74) Pruritus: 0.7% (2/281) vs. 2% (7/284), RR 0.29 (0.06 to 1.38) Dizziness: 3% (9/281) vs. 0.7% (2/284), RR 4.55 (0.99 to 20.86) Somnolence: 2% (6/281) vs. 2% (5/284), RR 1.21 (0.37 to 3.93) Diarrhea: 2% (6/281) vs. 1% (3/284), RR 2.02 (0.51 to 8.00) Headache: 4% (12/281) vs. 3% (8/284), RR 1.52 (0.63 to 3.65) Application site pain: 5% (13/281) vs. 0, RR 27.29 (1.63 to 456.84) Application site ulcer: 1% (2/281) vs. 4% (11/284), RR 0.18 (0.04 to 0.82) Application site irritation: 3% (8/281) vs. 0, RR 17.18 (0.99 to 296.27) Discontinued during titration phase due to AEs: 11.3% (36/320) Discontinued during titration phase due to lack of efficacy: 7.5% (24/320) Discontinued during double-blind phase due to AEs: 1.6% (3/191)	Industry	Good
Portenoy, 2007	A vs. B Sum of pain intensity (0 to 10) differences from 5 to 60 minutes, mean (SE): 8.3 (0.66) vs. 3.6 (0.57), p<0.0001 BTP episodes with 'meaningful' pain reduction: 70% (289/413) vs. 30% (63/207), RR 2.30 (95% CI, 1.85 to 2.85), p<0.0001 BTP episodes with ≥33% reduction in pain intensity (0 to 10) after 30 minutes: 42% (172/413) vs. 18% (18/207), RR 4.79 (95% CI, 3.03 to 7.56), p<0.0001 BTP episodes with ≥50% reduction in pain intensity (0 to 10) after 30 minutes: 30% (122/413) vs. 13% (27/207), RR 2.26 (95% CI, 1.54 to 3.12), p<0.0001 BTP episodes with ≥33% reduction in pain intensity (0 to 10) after 120 minutes: 65% (269/413) vs. 28% (57/207), RR 2.36 (1.87 to 2.98), p<0.0001 BTP episodes with ≥50% reduction in pain intensity (0 to 10) after 120 minutes: 48% (198/413) vs. 16% (33/207), RR 3.01 (2.16 to 4.18), p<0.0001	All data reported only for buccal fentanyl Serious adverse events: 3% (2/77) Nausea: 1% Vomiting: 0% Dizziness: 4% Somnolence: 0% Dysgeusia: 8% Dry mouth: 4% Withdrawn due to adverse event: 1% (1/77)	Industry	Good

Author, Year	Results	Adverse Events and Discontinuation Due To Adverse Events	Funding Source	Quality
Simpson, 2007	A vs. B Sum pain intensity (0 to 10) differences from 5 to 60 minutes, mean (SE): 9.63 (0.75) vs. 5.73 (0.71), p<0.001 BTP episodes with 'meaningful' pain reduction: 69% vs. 36%, p<0.0001 BTP episodes with ≥50% reduction in pain intensity after 15 minutes: 12% vs. 5%, p<0.0001, p<0.0001 for each subsequent time point from 30 to 120 minutes Use of supplemental medication: 14% (59/432) vs. 36% (77/213), OR 0.28 (95% CI, 0.18 to 0.42)	All data reported only for buccal fentanyl: Nausea: 0% Vomiting: 0% Dizziness: 1% Somnolence: 1% Application site AE: 8% (8/103) during open-label dose titration Discontinued early: 2.5% (2/79) Discontinuation due to AEs during open-label dose titration phase: 12% (12/103) Discontinuation due to AEs during double-blind phase: 2.5% (2/79)	Industry	Good
Webster, 2013	A vs. B Pain intensity (0 to 10) difference at 15 minutes, mean (SD): 0.88 (1.20) vs. 0.76 (1.13), p<0.001 Pain relief (0 to 10) at 15 minutes: 38% vs. 34%, p<0.05 Meaningful pain relief within 15 minutes: 17% vs. 16%, p=NS Meaningful pain relief within 30 minutes: 46% vs. 38%, p<0.01	A vs. B Any AE: 18% (25/138) vs. 14% (20/142); RR 1.29 (95% CI, 0.75 to 2.20)	Industry	Good

Abbreviations: BTP=breakthrough pain; CI=confidence interval; MED=morphine equivalent dose; NR=not relevant; OR=odds ratio; RCT=randomized controlled trial; RR=relative risk; SD=standard deviation; SE=standard error; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-35. Key Question 3i: Trials of decreasing opioid doses or of tapering off opioids versus continuation of opioids – study characteristics

Author, Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup
Blondell, 2010	Open-label, RCT 6 months	Setting not describe, USA	Men and women aged ≥18 years with well documented chronic non-cancer pain and self-identified addiction to prescription opioids referred by physicians associated with study site program	Potential participants asked to stop taking all opioid medications evening prior to hospitalization for stabilization; following admission, patients given 4 mg buprenorphine sublingually after withdrawal signs and increased by 2 mg every 2 hours until withdrawal improved. Goal was to reduce pain in 24 to 48 hours on stable dose of buprenorphine/naloxone 2 mg/0.5 mg 3 to 4 times daily. A. Steady dose buprenoprhine at time of hospital discharge to be continued for entire 6 month followup; patients during first 4 weeks were permitted to increase dose to 16 mg/day; participants could opt out and switch to tapering protocol B. Tapering doses of buprenorphine over 4 months, then all opioids to be discontinued for 2 months-permitted to increase starting dose up to 16 mg; also permitted to opt out of tapering protocol and initiate steady dose schedule during the 4 month of followup	Mean (SD) age, years: 44 (6.4) vs. 46 (14.6) Female: 50% White: 92% History of alcohol use only: 33% History of alcohol and drug abuse: 33% Prior SUD treatment: 42%	Screened: 12 Enrolled: 12 1 drop out of study 1 relapsed to illicit drug use and lost to followup
Kurita, 2018	Open-label, parallel-group RCT 6 months	Single center outpatient multidisciplinary pain clinic International (Denmark)	Patients on waiting list to pain center aged ≥18 years, ≥7 years schooling, pain duration ≥6 months, treatment with oral opioids >3 months, and daily opioid dose ≥60 mg oral MED	Phase 1 (all patients) - Multidisciplinary pain team aimed at stable opioid dose levels and regular and clockwise use of sustained release opioids Phase 2: A. Taper off intervention consisted of reduction of 10% of daily opioid dose every week until discontinuation of opioid treatment for up to 6 months. clonidine for opioid withdrawal symptom management (n=15) B. Maintained on the same treatment from Phase 1 for next 6 months (n=20)	A vs. B Mean (SD) age, years: 56.3 (9.2) vs. 50.6 (14.4) Female: 40% vs. 75%, p=0.04 Race: NR Mean (SD) opioid use duration, years: 9.9 (7.1) vs. 6.6 (4.7) Mean opioid dose, MED/day: 367.4 vs. 220.8 Mean pain duration, years: 15.1 vs. 11.4 Mean years of education: 10.9 vs. 12.0 PHQ-9 score ≥10: 61% vs. 53%	Screened: 274 Eligible: NR Enrolled 75 in phase 1 Randomized: 35 Analyzed: 30 (at 4th week) Loss to followup: 5

Author, Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup
Sullivan, 2017	RCT 22 weeks	Single center Outpatient clinic United States	Patients with chronic noncancer pain on opioid recruited through clinician referrals and advertisements who were willing to taper opioid dose by ≥50%	A. 22-week outpatient tapering support including psychiatric consultation and 30 minute weekly visits with physician assistant for motivational interviewing and pain self-management training (n=18) B. Usual management for pain including opioid prescriptions, with no restrictions other than avoiding buprenorphine (n=17)	A vs. B Mean age, years: 54.4 (overall) Female: 67% vs. 77% White: 72% vs. 94% Black: 5.6% vs. 0% Asian: 11% vs. 5.6% Other race/ethnicity: 11% vs. 0% Mean opioid use duration: 10.2 years (overall) Mean opioid dose, MED/day: 207.2 vs. 245.2 Mean pain duration: 13.8 years (overall) College graduate, graduate, or professional school: 44% vs. 29% PHQ-9 score ≥10: 61% vs. 53% Mean (SD) BPI pain severity (0 to 10): 5.68 (1.36) vs. 6.26 (1.49) Mean (SD) BPI interference (0 to 10): 6.03 (1.88) vs. 6.60 (2.36) Mean (SD) PODS, opioid problems (0 to 32): 12.72 (10.97) vs. 12.00 (10.47)	Screened: 144 Eligible: 76 Enrolled: 35 Analyzed: 31 completed 22 week followup

Abbreviations: BPI=Brief Pain Inventory; MED=morphine equivalent dose; NR=not reported; PHQ=Patient Health Questionnaire; PODS=Prescribed Opioids Difficulties Scale; RCT=randomized controlled trial; SD=standard deviation; SUD=substance use disorder; USA=United States of America; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-36. Key Question 3i: Trials of decreasing opioid doses or of tapering off opioids versus continuation of opioids - study results

Author Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Blondell, 2010	Mean stable dose of buprenorphine: 7.5 mg/day at hospital discharge; 9.8 mg/day at 4 weeks Study terminated early because none of the 6 participants in tapering dose arm could complete the 6-month protocol -5 switched to stable dose arm (2 in month 1; 1 in month 2; 1 in month 3; 1 in month 4) -1 was admitted to inpatient unit after relapse after 2nd month (terminated due to ethical reasons) In the stable dose arm, 5 completed 6-month protocol and 1 withdrew due to cost of medication. (0/6 vs. 5/6 completed, p=0.015) At 6 month followup: 10 participants completed 5 and 5; 8 receiving opioid replacement therapy, 6 reported improved pain control and physical functioning.	1 discontinued due to relapse; no other reported events	National Institute on Alcohol Abuse and Alcoholism, Donald W. Reynolds Foundation	Poor
Kurita, 2018	A vs. B Mean (SD) opioid dose, MED/day: 230.6 (142.6) vs. 345.8 (273.3), p=0.23 at 2 to 3 weeks; 226.6 (144.4) vs. 300.8 (238.5), p=0.446 at 4 to 6 weeks Mean (SD) sleep, minutes: 380 (146) vs. 212 (96), p=0.09 at 2 to 3 weeks; 360 (121) vs. 353 (169), p=0.718 at 4 to 6 weeks Mean (SD) average pain: 6.3 (1.6) vs. 5.4 (2.3), p=0.245 at 2 to 3 weeks; 6.5 (1.4) vs. 6.3 (2.0), p=1.0 Mean (SD) pain now: 6.3 (2.2) vs. 5.4 (2.3), p=0.245 at 2 to 3 weeks; 6.5 (1.4) vs. 5.1 (2.0), p=0.09 at 4 to 6 weeks Mean (SD) anxiety: 6.9 (3.7) vs. 6.6 (4.3), p=0.65 at 2 to 3 weeks; 6.7 (4.0) vs. 6.3 (3.6), p=0.96 at 4 to 6 weeks Mean (SD) depression: 5.0 (4.7) vs. 5.0 (3.3), p=0.65 at 2 to 3 weeks; 6.4 (4.7) vs. 6.0 (3.7), p=0.856 at 4 to 6 weeks	Not reported	Rigshospitalet, Denmark	Poor

Author Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Sullivan, 2017	A vs. B Mean opioid dose, MED/day: 111.9 vs. 169.8 at 22 weeks, adjusted difference -42.95 (95% CI, -92.4 to 6.6); 99.51 vs. 138.2 at 34 weeks, adjusted difference -26.7 (95% CI, -83 to 29.6) Mean opioid dose, change from baseline: -43% vs. -19% at week 22, adjusted difference -25% (95% CI, -52% to 2%); -52% vs. -31% at 34 weeks, adjusted difference - 22% (95% CI, -52% to 8%) Mean BPI pain severity (0 to 10): 4.72 vs. 5.77 at 22 weeks, adjusted difference -0.68 (95% CI, -2.01 to 0.64), 4.67 vs. 6.16 at 34 weeks, adjusted difference -0.91 (95% CI, -2.30 to 0.48) Mean BPI interference (0 to 10): 4.55 vs. 6.38 at 22 weeks, adjusted difference -1.39 (95% CI, -2.01 to 0.64); 4.49 vs. 6.05 at 34 weeks, adjusted difference -1.21 (95% CI, -2.43 to 0.02) Mean PODS Opioid Problems (0 to 32): 2.94 vs. 7.53 at 22 weeks, adjusted difference -4.90 (95% CI, -8.40 to - 0.80); 3.44 vs. 9.25 at 34 weeks, adjusted difference - 4.74 (95% CI, -1.13 to 0.64) Mean PODS Opioid Concerns (0 to 32): 10.00 vs. 11.47 at 22 weeks, adjusted difference 0.16 (95% CI, -3.74 to 4.06); 10.00 vs. 10.75 at 34 weeks, adjusted difference 1.62 (95% CI, -3.27 to 6.51) Mean Insomnia Severity Index (0 to 28): 12.44 vs. 16.80 at 22 weeks, adjusted difference -3.13 (95% CI, -7.22 to 0.96); 13.38 vs. 15.50 at 34 weeks, adjusted difference - 1.19 (95% CI, -5.49 to 3.11) Mean PHQ-9: 8.88 vs. 11.27 at 22 weeks, adjusted difference -2.21 (95% CI, -6.62 to 2.21); 9.00 vs. 11.13 at 34 weeks, adjusted difference -1.89 (95% CI, -6.23 to 2.44) Mean GAD-7: 5.94 vs. 9.07 at 22 weeks, adjusted difference -2.73 (95% CI, -5.99 to 0.53); 6.00 vs. 8.75 at 34 weeks, adjusted difference -2.39 (95% CI, -5.79 to 1.01)	Discontinuation due to adverse events: 5.6% (1/18) vs. 0% (0/17)	National Institute of Drug Abuse	Fair

Abbreviations: BPI=Brief Pain Inventory; CI=confidence interval; GAD=generalized anxiety disorder; MED=morphine equivalent dose; PHQ=Patient Health Questionnaire; PODSSD=Prescription Opioid Difficulties Scale; standard deviation; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-37. Key Question 3i: Cohort study of decreasing opioid doses or of tapering off opioids versus continuation of opioids – study characteristics

Author, Year	Type of Study, Setting	Eligibility Criteria	Comparison Groups	Population Characteristics	Method For Assessing Outcomes and Confounders	Enrolled Analyzed Loss to Followup
James, 2019	Retrospective cohort study of primary care clinic based opioid registry in Seattle, WA	Pain condition: Mixed Age: ≥18 years Pain severity: Not specified Psychiatric disease: Included Substance use: Included Prior opioid use: Not specified	A. Continued on opioids B. Discontinued opioid use	A vs. B Aged 18 to 39 years: 5.7% vs. 8.7% Aged 40 to 49 years: 15.4% vs. 22.1% Aged 50 to 59 years: 50.5% vs. 43.05% Aged >59 years: 28.9% vs. 26.2% Female: 48.2% vs. 43.9% Pain duration: Not reported Back/spine pain: 82.5% vs. 77.3% Pain in extremity: 86.8% vs. 79.4% Abdominal pain: 37.7% vs. 32.8% Chronic wounds: 14.5% vs. 14.2% Neuropathic pain or headache: 38.6% vs. 34.3% Prescribed opioid dose range: 120 to 359 mg MED/day	Frequencies were calculated for each category of reasons for opioid discontinuation. Cox proportional hazard models adjusting for age and race were used to determine associations between discontinuation of opioid and all-cause mortality and between discontinuation of opioid and death due to overdose.	A vs. B Enrolled: 572 Analyzed: 572 (228 vs. 344)

Abbreviations: MED=morphine equivalent dose; vs.=versus; WA=Washington.
See Appendix F. Included Studies for full citations

Table H-38. Key Question 3i: Cohort study of decreasing opioid doses or of tapering off opioids versus continuation of opioids – study results

Author, Year	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
James, 2019	Age, sex	A vs. B Risk of overdose death: 1.8% vs. 4.9%, adjusted HR 2.94 (95% CI 1.01 to 8.61) Risk of overall mortality adjusted HR: 1.35 (95% CI 0.92 to 1.98)	The National Center for Advancing Translational Sciences of the National Institutes of Health and the Division of General Internal Medicine at the University of Washington	Poor

Abbreviations: CI=confidence interval; HR=hazard ratio.
See Appendix F. Included Studies for full citations

Table H-39. Key Question 3j. Trials of different opioid tapering protocols and strategies – study characteristics

Author Year	Study Design Duration	Setting Country	Eligibility Criteria	Interventions	Sample Characteristics	Screened Eligible Enrolled Analyzed Loss to Followup
Hooten, 2015	Single blinded placebo controlled pilot trial for 15 days	Interdisciplinary pain clinic, academic medical center, USA	Patients recruited at time of admission to ITP from June 2011 to May 2012 who were ≥21 years, on ≥60 mg/day MED, noncancer chronic pain of >6 months duration Exclusion criteria included current use of varenicline, history of major CVD, pulmonary or surgical/psychiatric condition	A. Varenicline B. Placebo Both groups were detoxed from opioids using a taper schedule with goal of eliminating opioids at conclusion of ITP.	A vs. B Median (IQR) age, years: 49.0 (36.0 to 60) vs. 46.0 (29.0 to 53) Female: 14% vs. 36% Mean BMI: 24.7 vs. 33.1 White: 100% vs. 100% Mean years of education: 14 vs. 16 Mean pain duration, years: 7 vs. 5 Median (IQR) opioid dose, MED: 135 (90 to 180) vs. 75 (60 to 142.5); p>0.1 Median (IQR) MPI pain severity: 50.6 (45.3 to 55.9) vs. 53.3 (47.9 to 61.2) Mean CES-D: 31 (24 to 37) vs. 30 (17 to 25)	Screened: NR Eligible: NR Randomized: 21 (10 vs. 11) Completers: 7 vs. 11
Tennant, 1982	Non-randomized clinical trial 3 to 18 months	Single center Outpatient clinic United States	Patients on opioids who volunteered for outpatient treatment for withdrawing opioids	A: Detoxification/ counseling: Detoxification over 3 weeks with methadone, propoxyphene, clonidine, diphenoxylate, or sedative-hypnotics, followed by weekly psychotherapeutic counseling B: Detoxification/ maintenance: Detoxification as above, with maintenance on opioid if detoxification unsuccessful	A vs. B Mean age, years: 33 vs. 44 Female: 48% vs. 52% Nonwhite race: 19% vs. 14% Duration of opioid use, years: 7.2 vs. 9.2 Proportion with chronic pain: 62% vs. 71% Back/spine disorder: 24% vs. 19% Use of codeine: 67% vs. 48%	Screened: NR Eligible: NR Enrolled: 42 (21 vs. 21) Analyzed: 42
Mark, 2019	Retrospective cohort Medicaid beneficiaries, USA		≥2 prescription opioid fills on separate days for a total combined supply of ≥15 days, aged 18 to 64 years, have used prescription opioids for ≥90 consecutive days at a daily dose of ≥120 mg MED/day, without a diagnosis of cancer	Cox proportional hazard model used	Mean (SD) age, years: 47 (10) Female: 49% Used ≥120 mg MED/day for 613 days Median days using opioids at high dose: 510 Primary or secondary substance use disorder: 60% Mood disorder: 27% Anxiety disorder: 25%	494

Abbreviations: BMI=body mass index; CES-D=Center for Epidemiologic Studies Depression Scale; CVD=cardiovascular disease; IQR=interquartile range: ITP=interdisciplinary treatment program; MED=morphine equivalent dose; MPI=Multidimensional Pain Inventory; NR=not reported; SD=standard deviation; USA=United States of America; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-40. Key Question 3j: Trials of different opioid tapering Pprotocols and strategies – study results

Author Year	Results	Adverse Events and Discontinuation Due to Adverse Events	Funding Source	Quality
Hooten, 2015	A vs. B Median (IQR) duration of opioid taper, days: 18 (14 to 19) vs. 15 (14 to 17) Median (IQR) MPI dismissal: 34.6 (24 to 53.3) vs. 41.3 (34.0 to 43.9) Median (IQR) change from baseline MPI: 16.0 (2.7 to 21.3) vs. 12.0 (6.6 to 23.3), between group p=NS Median (IQR) CES dismissal: 10.0 (6.0 to 14.0) vs. 12.0 (9.0 to 16.0) change: 21(10-32) vs. 18(0-28), p=NS Median (IQR) value of regression coefficient withdrawal symptoms: -0.116 (-0.248 to 0.025) vs. 0.086 (-0.264 to 0.332), p=0.258	No adverse events reported in both groups.	Mayo foundation	Fair
Tennant, 1982	A vs. B Proportion remaining in treatment past 3 weeks: 24% (5/21) vs. 95% (20/21) Abstinent after 90 days: 10% (2/21) vs. 19% (4/21)	NR	NR	Poor
Mark, 2019	Age, sex, opioid prescription drug use patterns, whether the member was started on medications to treat opioid use disorder after the tapering start date, physical diagnosis, mental health, and substance use disorder diagnosis	86% discontinued filling prescription opioids within 21 days 5% discontinued filling prescription opioids in >90 days 49% had an opioid related adverse event	RTI International	Fair

Abbreviations: IQR=interquartile range; MPI=Multidimensional Pain Inventory; NR=not reported; NS=not significant; RTI=Research Triangle Institute; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-41 Key Question 4a: Prospective studies on use of screening instruments to predict the risk of aberrant drug-related behaviors - study characteristics

Author, Year	Study Design Duration	Eligibility Criteria	Population Characteristics	N	Instrument	Method of Administration	Reference Standard
Akbik, 2006	Prospective cohort Duration unclear	Chronic pain patients attending 1 of 2 pain clinics	Mean (SD) age, years: 43 (9.6) Female: 33% White: 86%, other races not reported Back pain: 39%	155 (with reference standard, of 397 enrolled)	SOAPP (Version 1)	Self-report	Positive urine screening
Jones, 2012 (Study 2)	Retrospective cohort 6 months	Consecutive pain clinic patients being evaluated for risk of opioid addiction prior to opioid initiation	Mean (SD) age, years: 48 (13) Female: 56% White: 96%, other races not reported Low back pain: 45% Arthritis or fibromyalgia: 21% Joint paint: 14% Pelvic or abdominal pain: 10% Neck or upper back pain: 7%	263	ORT PMQ SOAPP-R Clinician assessment	Self-report; clinician interview	Subsequent opioid discontinuation due to abuse
Jones, 2013	Cohort, unclear if prospective 6 months	Chronic pain patients referred to a pain clinic	Mean (range) age, years: 50 (22 to 91) Female: 58% Race not reported Back pain: 60% Neck pain: 18%	196	BRI ORT SOAPP-R	Self-report (ORT, SOAPP-R); clinician interview (BRI)	Documentation of aberrant behavior during followup
Jones, 2014	Prospective cohort 6 months	Chronic pain patients referred to a pain clinic	Mean (range) age, years: NR (19 to 85); 32% 40 to 49 years of age Female: 67% White: 80% Back pain: 44% Neck pain: 26% Headache: 13%	124 (includes 49 patients who did not receive opioids)	BRI ORT SOAPP-R	Self-report (ORT, SOAPP-R); clinician interview (BRI)	Documentation of aberrant behavior during followup
Jones, 2015	Prospective cohort 6 months	Chronic pain patients referred to a pain clinic	Mean (range) age, years: 55 (21 to 82) Female: 49% White: 96% Back pain: 43% Neck pain: 19% Joint pain: 12% Arm or leg pain: 7% Abdominal pain: 4%	257	BRI ORT SOAPP-R BRQ	Self-report (BRQ, ORT, SOAPP-R); clinician interview (BRI)	Documentation of aberrant behavior during followup
Moore, 2009	Retrospective cohort Mean 3.8 months	New adult patients at a pain clinic	Mean (SD) age, years: 44 (11) Female: 60% Race not reported Pain not reported	48	SOAPP (Version 1) DIRE ORT Clinician assessment	Self-report (SOAPP, DIRE, ORT); clinician interview	Subsequent opioid discontinuation due to abuse

Author, Year	Study Design Duration	Eligibility Criteria	Population Characteristics	N	Instrument	Method of Administration	Reference Standard
Webster, 2005	Prospective cohort 12 months	New chronic pain patients at a pain clinic	Mean (SD) age, years: 44 (13) Female: 58% Race not reported Back pain: 45% Head pain: 18% Neuropathic pain: 16% Musculoskeletal pain: 16% Visceral pain: 5%	185	ORT	Self-report	Documentation of aberrant behavior during followup

Abbreviations: BRI=Brief Risk Interview; BRQ=Brief Risk Questionnaire; DIRE=Diagnosis, Intractability, Risk, Efficacy score; ORT=Opioid Risk Tool; PMQ=Pain Medication Questionnaire; SD=standard deviation; SOAPP=Screener and Opioid Assessment for Patients with Pain; SOAPP-R= Screener and Opioid Assessment for Patients with Pain-Revised; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-42. Key Question 4a: Prospective studies on use of screening instruments to predict the risk of aberrant drug-related behaviors - study results

Author, Year	True Positives (n)	False Positives (n)	True Negatives (n)	False Negatives (n)	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	AUROC	Quality
Akbik, 2006	SOAPP score ≥8: 30	SOAPP score ≥8: 59	SOAPP score ≥8: 37	SOAPP score ≥8: 14	SOAPP score ≥8: 0.68 (95% CI, 0.52 to 0.81)	SOAPP score ≥8: 0.39 (95% CI, 0.29 to 0.49)	SOAPP score ≥8: 1.11 (95% CI, 0.86 to 1.43)	SOAPP score ≥8: 0.83 (95% CI, 0.52 to 1.31)	Not reported	Fair
Jones, 2012 (Study 2)	ORT score >4: 8 PMQ score >30: 13 SOAPP-R score >17: 20 Clinician assessment of high-risk: 27	ORT score >4: 19 PMQ score >30: 41 SOAPP-R score >17: 65 Clinician assessment of high-risk: 57	ORT score >4: 142 PMQ score >30: 134 SOAPP-R score >17: Clinician assessment of high-risk: 84	ORT score >4: 33 PMQ score >30: 25 SOAPP-R score >17: Clinician assessment of high-risk: 11	ORT score >4: 0.20 (95% CI, 0.15 to 0.27) PMQ score >30: 0.34 (95% CI, 0.20 to 0.51) SOAPP-R score >17: 0.39 (95% CI, 0.26 to 0.54) Clinician assessment of high-risk: 0.71 (95% CI, 0.54 to 0.84)	ORT score >4: 0.88 (95% CI, 0.82 to 0.93) PMQ score >30: 0.77 (95% CI, 0.69 to 0.80) SOAPP-R score >17: 0.69 (95% CI, 0.63 to 0.75) Clinician assessment of high-risk: 0.60 (95% CI, 0.51 to 0.68)	ORT score >4: 1.65 (95% CI, 0.78 to 3.51) PMQ score >30: 1.46 (95% CI, 0.87 to 2.45) SOAPP-R score >17: 1.27 (95% CI, 0.86 to 1.90) Clinician assessment of high-risk: 1.76 (95% CI, 1.32 to 2.34)	ORT score >4: 0.91 (95% CI, 0.78 to 1.06) PMQ score >30: 0.86 (95% CI, 0.68 to 1.08) SOAPP-R score >17: 0.88 (95% CI, 0.70 to 1.10) Clinician assessment of high-risk: 0.49 (95% CI, 0.29 to 0.81)	ORT 0.53 PMQ 0.57 SOAPP-R 0.54	Fair
Jones, 2013	Not reported	Not reported	Not reported	Not reported	BRI rating high risk (medium to very high): 0.73 ORT score ≥4: 0.58 (also reported as 0.48) SOAPP-R score >17: 0.53	BRI rating high risk: 0.43 ORT score ≥4: 0.54 (also reported as 0.57) SOAPP-R score >17: 0.62	BRI high risk: 1.28 ORT score ≥4: 1.26 SOAPP-R high risk: 1.39	BRI high risk: 0.63 ORT score ≥4: 0.78 SOAPP-R high risk: 0.76	Not reported	Poor
Jones, 2014	BRI high risk (rating medium to very high): 10 ORT score ≥4: 9 SOAPP-R score >17: 3	BRI high risk: 13 ORT score ≥4: 16 SOAPP-R score >17: 30	BRI high risk: 99 ORT score ≥4: 96 SOAPP-R score >17: 82	BRI high risk: 2 ORT score ≥4: 3 SOAPP-R score >17: 9	BRI high risk: 0.83 (95% CI, 0.52 to 0.98) ORT score ≥4: 0.75 (95% CI, 0.43 to 0.95) SOAPP-R score >17: 0.25 (95% CI, 0.055 to 0.57)	BRI high risk: 0.88 (95% CI, 0.81 to 0.94) ORT score ≥4: 0.86 (95% CI, 0.78 to 0.92) SOAPP-R score >17: 0.73 (95% CI, 0.64 to 0.81)	BRI high risk: 7.18 (95% CI, 4.06 to 12.70) ORT score ≥4: 5.25 (95% CI, 3.00 to 9.18) SOAPP-R score >17: 0.93 (95% CI, 0.33 to 2.61)	BRI high risk: 0.19 (95% CI, 0.05 to 0.67) ORT score ≥4: 0.29 (95% CI, 0.11 to 0.78) SOAPP-R score >17: 1.02 (95% CI, 0.73 to 1.45)	BRI: 0.93 ORT: 0.74 SOAPP-R: 0.52	Poor

Author, Year	True Positives (n)	False Positives (n)	True Negatives (n)	False Negatives (n)	Sensitivity	Specificity	Positive Likelihood Ratio	Negative Likelihood Ratio	AUROC	Quality
Jones, 2015	BRI high risk (rating medium to very high): 59 ORT score ≥4: 24 SOAPP-R score >17: 25 BRQ score ≥3: 60	BRQ score ≥3: 107 ORT score ≥4: 33 SOAPP-R score >17: 42 BRI high risk: 89	BRI high risk: 93 ORT score ≥4: 149 SOAPP-R score >17: 140 BRQ score ≥3: 75	BRI high risk: 16 ORT score ≥4: 51 SOAPP-R score >17: 50 BRQ score ≥3: 15	BRI high risk: 0.79 (95% CI, 0.68 to 0.87) ORT score ≥4: 0.32 (95% CI, 0.22 to 0.44) SOAPP-R score >17: 0.33 (95% CI, 0.23 to 0.45) BRQ score ≥3: 0.80 (95% CI, 0.69 to 0.88)	BRI high risk: 0.51 (95% CI, 0.44 to 0.59) ORT score ≥4: 0.82 (95% CI, 0.75 to 0.87) SOAPP-R score >17: 0.77 (95% CI, 0.70 to 0.83) BRQ score ≥3: 0.41 (95% CI, 0.34 to 0.49)	BRI high risk: 1.61 (95% CI, 1.33 to 1.94) ORT score ≥4: 1.76 (95% CI, 1.12 to 2.77) SOAPP-R score >17: 1.44 (95% CI, 0.95 to 2.19) BRQ score ≥3: 1.36 (95% CI, 1.15 to 1.61)	BRI high risk: 0.42 (95% CI, 0.26 to 0.66) ORT score ≥4: 0.83 (95% CI, 0.70 to 0.98) SOAPP-R score >17: 0.87 (95% CI, 0.72 to 1.04) BRQ score ≥3: 0.49 (95% CI, 0.30 to 0.79)	BRI: 0.65 ORT: 0.57 SOAPP-R: 0.55 BRQ: 0.61	Fair
Moore, 2009	SOAPP: 35 DIRE: 8 ORT: 21 Clinical interview: 37	Not calculable	Not calculable	SOAPP: 13 DIRE: 40 ORT: 27 Clinical interview: 11	SOAPP score ≥6: 0.73 DIRE score <14: 0.17 ORT score >4: 0.45 Clinical interview assessment medium or high risk: 0.77	Not reported	Not reported	Not reported	Not reported	Poor
Webster, 2005	ORT score 1 to 3 (low risk): 1 ORT score 4 to 7 (moderate risk): 35 ORT score ≥8 (high risk): 40	ORT score 1 to 3 (low risk): 17 ORT score 4 to 7 (moderate risk): 88 ORT score high (≥8): 4	ORT score 1 to 3 (low risk): 92 ORT score 4 to 7 (moderate risk): 21 ORT score high (≥8): 105	ORT score 1 to 3 (low risk): 75 ORT score 4 to 7 (moderate risk): 41 ORT score high (≥8): 36	ORT score ≥4: 0.99 (95% CI, 0.92 to 0.999)	ORT score ≥4: 0.16 (95% CI, 0.10 to 0.24)	ORT score ≥4: 1.17 (95% CI, 1.07 to 1.27) ORT score 1 to 3 (low risk): 0.08 (95% CI, 0.01 to 0.62) ORT score 4 to 7 (moderate risk): 0.57 (95% CI, 0.44 to 0.74) ORT score ≥8 (high risk): 14.34 (95% CI, 5.35 to 38)	ORT score ≥4: 0.08 (95% CI, 0.01 to 0.65)	Not reported	Fair

Abbreviations: AUROC=area under the receiver operator curve; BRI=Brief Risk Interview; BRQ=Brief Risk Questionnaire; CI=confidence interval; DIRE=Diagnosis, Intractability, Risk, Efficacy score; ORT=Opioid Risk Tool; PMQ=Pain Medication Questionnaire; SD=standard deviation; SOAPP=Screener and Opioid Assessment for Patients with Pain; SOAPP-R= Screener and Opioid Assessment for Patients with Pain-Revised.

See Appendix F. Included Studies for full citations

Table H-43. Key Question 4c: Study of co-prescription of naloxone in persons prescribed opioids for chronic pain – study characteristics and results

Author, Year	Type of Study, Setting	Eligibility criteria	Comparison Groups	Sample Characteristics	Method For Assessing Outcomes and Confounders	Enrolled Analyzed Loss to Followup	Adjusted Variables For Statistical Analysis	Main Results	Funding Source	Quality
Coffin, 2016	Retrospective cohort 6 primary care clinics in San Francisco, USA	Pain condition: Not specified Age: ≥18 years Pain severity: Not specified Psychiatric disorder: Not specified Substance use: Not specified Prior opioid use: Yes	A. Co-prescribed naloxone B. Not co-prescribed naloxone	A vs. B Mean (SD) age, years: 55.7 (10.7) vs. 57.3 (10.8) Female: 42% vs. 41% White: 35.3% vs. 27.5% Black: 44.5% vs. 50.7% Hispanic: 11.9% vs. 14.3% Other race: 8.3% vs. 7.4% Median opioid dose: 53 mg MED/day (range: 2 to 4200)	Multivariable Poisson regression model was used for the monthly number of opioid related ED visits, using an offset to account for days of exposure in each month. The model used GEE with exchangeable working correlation and robust SEs to account for clustering by patient, as well as over dispersion.	Enrolled: 1985 (759 vs. 1226) Analyzed: 1985 (759 vs. 1226) Loss to followup: Not reported	The model adjusted for age, race/ethnicity, sex, MED at baseline, history of any opioid-related ED visit between January 1, 2012 and December 31, 2012, and clinic.	A vs. B, RR (95% CI) All-cause mortality: 2.5% (19/759) vs. 3.3% (40/1226), RR 0.77 (0.45 to 1.31) Opioid poisoning deaths: 0.3% (2/759) vs. 0.2% (3/1226), RR 1.08 (0.18 to 6.4) Opioid related ED visits per month, IRR (95% CI): 0.94 (0.89 to 0.998), p=0.044; 6% reduction Opioid related ED visits per month 6 months after given prescription, IRR (95% CI): 0.53 (0.34 to 0.83), p=0.005; 47% reduction Opioid related ED visits per month 1 year after given prescription, IRR (95% CI): 0.37 (0.22 to 0.64), p<0.001; 63% reduction	NIH	Fair

Abbreviations: CI=confidence interval; ED=emergency department; GEE=generalized estimating equation; MED=morphine equivalent dose; NIH=National Institutes of Health; RR=risk ratio; SD=standard deviation; SE=standard error; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-44. Key Question 4d: Studies of treatment strategies for managing patients with opioid use disorder related to prescription opioids - study characteristics

Author, Year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample Characteristics	Screened Eligible Randomized Analyzed
Blondell, 2010	Open-label, RCT 6 months	Setting not described, USA	Men and women aged ≥18 years with well documented chronic non-cancer pain and self-identified addiction to prescription opioids referred by physicians associated with study site program	Potential participants asked to stop taking all opioid medications evening prior to hospitalization for stabilization; following admission, patients given 4 mg buprenorphine sublingually after opiate withdrawal signs and increased by 2 mg every 2 hours until withdrawal improved. Goal was to reduce pain in 24 to 48 hours on stable dose of buprenorphine/naloxone 2 mg/0.5 mg 3 to 4 times daily. A. Steady dose buprenorphine at time of hospital discharge to be continued for entire 6 month followup; patients during first 4 weeks were permitted to increase dose to 16 mg/day; participants could opt out and switch to tapering protocol B. Tapering doses of buprenorphine over 4 months, then all opioids to be discontinued for 2 months-permitted to increase starting dose up to 16 mg; also permitted to opt out of tapering protocol and initiate steady dose schedule during the 4 month of followup	Mean (SD) age, years: 44 (6.4) vs. 46 (14.6) Female: 50% White: 92% History of alcohol use only: 33% History of alcohol and drug abuse: 33% Prior SUD treatment: 42%	Screened: 12 Enrolled: 12 1 drop out of study 1 relapsed to illicit drug use and lost to followup
Fiellin, 2014	Open-label RCT 14 weeks	Primary care center of Yale-New Haven Hospital, USA	Pain condition: Mixed Age: Not specified Pain severity: Not specified Psychiatric disease: Excluded Substance use: Excluded Prior opioid use: Yes, dose not specified	A. Buprenorphine taper (target dose of 16 mg/day) B. Buprenorphine maintenance	A vs. B Mean (95% CI) age, years: 30.3 (28.0 to 32.6) vs. 30.5 (27.9 to 33.1) Female: 40% vs. 50% White: 98% vs. 93% Hispanic: 7% vs. 7% Mean (95% CI) duration of opioid dependence, years: 4.5 (3.3 to 5.6) vs. 4.9 (3.7 to 6.0)	Screened: NR Eligible: NR Randomized: 113 (57 vs. 56) Analyzed: 113 (57 vs. 56)

Author, Year	Study design Duration	Setting Country	Eligibility criteria	Interventions	Sample Characteristics	Screened Eligible Randomized Analyzed
Neumann, 2013	RCT 6 months	Unclear, USA	Pain condition: Pain related to the spine or a large joint Age: ≥18 years Pain severity: Not specified Psychiatric disease: Excluded Substance use: Not specified Prior opioid use: Yes, but dose not specified	A. Buprenorphine (4 to 16 mg/day) + naloxone (1 to 4 mg/day) sublingually. B. Methadone oral tablets (10 to 60 mg/day), 1 to 4 doses daily	A vs. B Mean (SD) age, years: 39.0 (10.9) vs. 37.7 (8.6) Female: 34.6% vs. 57.1% White: 76.9% vs. 92.9% Mean (SD) pain score: 5.9 (2.1) vs. 6.9 (1.4) Mean (SD) functioning score: 4.4 (2.0) vs. 5.6 (1.7) Mean (SD) age of onset of opioid use, years: 31.2 (11.2) vs. 28.0 (6.5) Positive urine for opiates: 38.5% vs. 35.7%	Screened: 170 Eligible: NR Randomized: 54 (26 vs. 28) Analyzed: 26 (13 vs. 13)

Abbreviations: CI=confidence interval; NR=not reported; SD=standard deviation; SUD=substance use disorder; USA=United States of America; vs.=versus.

See Appendix F. Included Studies for full citations

Table H-45. Key Question 4d: Studies of treatment strategies for managing patients with opioid use disorder related to prescription opioids – study results

Author, Year	Results	Adverse Events and Discontinuation Due To Adverse Events	Funding Source	Quality
Blondell, 2010	Mean stable dose of buprenorphine: 7.5 mg/day at hospital discharge; 9.8 mg/day at 4 weeks Study terminated early because none of the 6 participants in tapering dose arm could complete the 6-month protocol -5 switched to stable dose arm (2 in month 1; 1 in month 2; 1 in month 3; 1 in month 4) -1 was admitted to inpatient unit after relapse after 2nd month (terminated due to ethical reasons) In the stable dose arm, 5 completed 6-month protocol and 1 withdrew due to cost of medication. (0/6 vs. 5/6 completed, p=0.015) At 6 month followup: 10 participants completed 5 and 5; 8 receiving opioid replacement therapy, 6 reported improved pain control and physical functioning.	1 discontinued due to relapse; no other reported events	National Institute on Alcohol Abuse and Alcoholism, Donald W. Reynolds Foundation	Poor
Fiellin, 2014	A vs. B Urine samples negative for opioids: 35.2% (95% CI, 26.2% to 44.2%) vs. 53.2% (95% CI, 44.3% to 62.05%) Mean (95% CI) days per week of illicit opioid use during last 7 weeks of trial once they were no longer receiving buprenorphine: 1.27 (0.60 to 1.94) vs. 0.47 (0.19 to 0.74) Mean (95% CI) maximum consecutive weeks of opioid abstinence: 2.70 (1.72 to 3.75) vs. 5.20 (4.16 to 6.20) Relapse with protective transfer: 28% vs. 5%, p=0.001	A vs. B Discontinued study: 89% vs. 34%, p<0.001	National Institute on Drug Abuse	Fair
Neumann, 2013	A vs. B, change from baseline at 24 weeks Pain (0 to 10), mean (SD): 87.4% (33.4) vs. 88.6% (24.5) Function (0 to 10), mean (SD): 121.9% (63.9) vs. 113.8% (62.5)	A vs. B Any self-reported side effect: 61.5% (8/13) vs. 69.2% (9/13); OR, 1.125 (95% CI, 0.209 to 6.046) Others of interest: NR	Government	Fair

Abbreviations: CI=confidence interval; NR=not reported; OR=odds ratio; SD=standard deviation; vs.=versus.

See Appendix F. Included Studies for full citations

Appendix I. Strength of Evidence

Table I-1. Strength of evidence and key findings*

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings† (95% CI)	SOE
Opioid vs. placebo or no opioid therapy	Pain (short-term)	71 RCTs (continuous); 44 RCTs (dichotomous)	19,616 (continuous); 12,481 (dichotomous)	Direct	Precise	Low	Consistent	MD -0.79 (-0.93 to -0.67); RR 1.35 (1.24 to 1.48)	High‡
	Function (short-term)	44 RCTs	12,427	Direct	Precise	Low	Consistent	SMD -0.22 (-0.28 to -0.16)	High‡
	SF-36 physical (short-term)	23 RCTs	8005	Direct	Precise	Low	Consistent	MD 1.64 (1.10 to 2.17)	High‡
	SF-36 mental (short-term)	21 RCTs	7586	Direct	Precise	Low	Consistent	MD -0.48 (-1.39 to 0.44)	High‡
	Sleep quality (short-term)	25 RCTs	6720	Direct	Precise	Low	Consistent	SMD -0.25 (-0.32 to -0.19)	Moderate‡, §
	Depression (short-term)	8 RCTs	1079	Direct	Imprecise	Low	Consistent	SMD 0.00 (-0.22 to 0.18)	Moderate‡
	Anxiety (short-term)	2 RCTs	229	Direct	Imprecise	Moderate	Consistent	MD 0.60 (-3.58 to 1.82)	Low‡
	Pain and function (long-term)	1 cohort study	529	Direct	Precise	Moderate	Unknown	No differences at 2 years	Low‡
	Discontinuation due to AEs	61 RCTs	19,994	Direct	Precise	Low	Consistent	RR 2.25 (1.86 to 2.73)	High‡
	Serious AEs	38 RCTs	13,160	Direct	Imprecise	Low	Consistent	RR 1.23 (0.88 to 1.74)	Moderate‡
	Nausea	60 RCTs	19,718	Direct	Precise	Low	Consistent	RR 2.46 (2.17 to 2.80)	High‡
	Vomiting	49 RCTs	17,388	Direct	Precise	Low	Consistent	RR 3.57 (2.98 to 4.34)	High‡
	Constipation	58 RCTs	19,351	Direct	Precise	Low	Consistent	RR 3.38 (2.96 to 3.92)	High‡
	Dizziness	53 RCTs	18,396	Direct	Precise	Low	Consistent	RR 2.66 (2.37 to 2.99)	High‡
	Headache	48 RCTs	17,405	Direct	Precise	Low	Consistent	RR 1.06 (0.95 to 1.17)	High‡
	Somnolence	52 RCTs	17,458	Direct	Precise	Low	Consistent	RR 2.97 (2.44 to 3.66)	High‡
	Pruritus	30 RCTs	11,454	Direct	Precise	Low	Consistent	RR 3.51 (2.47 to 5.16)	High‡

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings[†] (95% CI)	SOE
Opioid vs. placebo or no opioid therapy, continued	Opioid abuse, dependence, or addiction	2 cohort studies	666,780	Direct	Precise	Moderate	Consistent	Opioids associated with increased risk	Low
	Overdose	2 cohort studies	108,080	Direct	Precise	Moderate	Consistent	Opioids associated with increased risk	Low
	All-cause mortality	1 cohort study	22,912	Direct	Precise	Moderate	Unknown	Opioids associated with increased risk	Low
	Fracture	6 observational studies	48,250	Direct	Precise	Moderate	Consistent	Opioids associated with increased risk	Low
	Cardiovascular events	3 cohort studies	505,626	Direct	Precise	Moderate	Consistent	Opioids associated with increased risk	Low
	Endocrinological harms	1 cross-sectional analysis	11,327	Direct	Precise	Moderate	Unknown	Unable to determine	Insufficient
Opioids vs. nonopioids	Pain (short-term)	14 RCTs (continuous); 12 RCTs (dichotomous)	2195 (continuous); 2887 (dichotomous)	Direct	Precise	Moderate	Inconsistent	MD -0.29 (-0.61 to 0.03); RR 1.28 (0.90 to 1.85)	Moderate[‡]
	Function (short-term)	11 RCTs	2010	Direct	Precise	Moderate	Consistent	SMD 0.00 (-0.14 to 0.12)	High[‡]
	SF-36 physical (short-term)	6 RCTs	1423	Direct	Imprecise	Moderate	Consistent	MD -1.80 (-5.45 to -0.12)	Moderate[‡]
	SF-36 mental (short-term)	6 RCTs	1427	Direct	Precise	Moderate	Consistent	MD -0.63 (-4.27 to 0.91)	Moderate[‡]
	Sleep quality (short-term)	7 RCTs	1694	Direct	Precise	Moderate	Consistent	SMD 0.02 (-0.10 to 0.12)	Moderate[‡]
	Depression (short-term)	7 RCTs	748	Direct	Imprecise	Moderate	Consistent	SMD 0.05 (-0.09 to 0.22)	Moderate[‡]
	Anxiety (short-term)	3 RCTs	414	Direct	Imprecise	Moderate	Consistent	SMD 0.00 (-0.62 to 0.36)	Low[‡]
	Discontinuation due to AEs	12 RCTs	3637	Direct	Precise	Low	Inconsistent	RR 2.18 (1.48 to 3.08)	Moderate[‡]
	Serious AEs	4 RCTs	1949	Direct	Imprecise	Low	Consistent	RR 0.63 (0.06 to 5.66)	Moderate[‡]
	Nausea	11 RCTs	3137	Direct	Precise	Low	Consistent	RR 2.77 (2.09 to 4.18)	High[‡]
	Vomiting	6 RCTs	2644	Direct	Precise	Low	Consistent	RR 4.62 (2.94 to 7.24)	High[‡]
	Constipation	12 RCTs	3377	Direct	Precise	Low	Inconsistent	RR 2.92 (1.80 to 5.21)	Moderate[‡]

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings† (95% CI)	SOE
Opioids vs. nonopioids, continued	Dizziness	12 RCTs	3377	Direct	Imprecise	Low	Inconsistent	RR 1.33 (0.78 to 2.05)‖ • NSAID: 2.12 (1.45 to 3.00) • Gabapentinoid: 0.60 (0.15 to 1.09) • Nortriptyline: 1.31 (0.64 to 4.27)	Low‡
	Headache	8 RCTs	2791	Direct	Precise	Low	Consistent	RR 1.35 (1.08 to 1.70)	High‡
	Somnolence	12 RCTs	3377	Direct	Precise	Low	Inconsistent	RR 2.11 (1.39 to 3.47)	Moderate‡
	Pruritus	5 RCTs	2577	Direct	Precise	Low	Consistent	RR 4.22 (2.45 to 8.20)	High‡
	Opioid abuse, dependence, or addiction	No studies	--	--	--	--	--	--	--
	Overdose	No studies	--	--	--	--	--	--	--
	All-cause mortality	No studies	--	--	--	--	--	--	--
	Fracture	No studies	--	--	--	--	--	--	--
	Cardiovascular events	No Studies	--	--	--	--	--	--	--
	Endocrinological harms	No studies	--	--	--	--	--	--	--
Opioid + nonopioid vs. nonopioid	Pain (short-term)	6 RCTs (continuous); 6 RCTs (dichotomous)	628 (continuous); 765 (dichotomous)	Direct	Imprecise	Moderate	Consistent	MD -0.36 (-1.14 to 0.53); RR 1.46 (0.76 to 2.74)	Low‡
	Function (short-term)	4 RCTs	549	Direct	Imprecise	Moderate	Consistent	SMD -0.26 (-0.63 to 0.17)	Low‡
	SF-36 physical (short-term)	4 RCTs	297	Direct	Imprecise	Moderate	Consistent	SMD 0.58 (-4.19 to 4.37)	Low‡
	SF-36 mental (short-term)	4 RCTs	297	Direct	Imprecise	Moderate	Consistent	SMD -2.92 (-6.30 to 0.46)	Low‡
	Sleep quality (short-term)	3 RCTs	446	Direct	Imprecise	Moderate	Consistent	SMD 0.01 (-0.21 to 0.29)	Low‡
	Depression (short-term)	3 RCTs	246	Direct	Imprecise	Moderate	Consistent	SMD -0.01 (-0.31 to 0.26)	Low‡

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings† (95% CI)	SOE
Opioid + nonopioid vs. nonopioid, continued	Anxiety (short-term)	No studies	--	--	--	--	--	--	--
	Discontinuation due to AEs	6 RCTs	707	Direct	Imprecise	Moderate	Consistent	RR 1.99 (0.89 to 4.26)	Low‡
	Serious AEs	1 RCT	62	Direct	Imprecise	Moderate	Unable to assess	RR 0.38 (0.02 to 8.93)	Insufficient‡
	Nausea	5 RCTs	330	Direct	Precise	Moderate	Consistent	RR 2.18 (1.16 to 6.49)	Moderate‡
	Vomiting	2 RCTs	81	Direct	Imprecise	Moderate	Consistent	RR 1.68 (0.43 to 6.56)	Low‡
	Constipation	6 RCTs	633	Direct	Precise	Moderate	Consistent¶	RR 2.74 (1.28 to 7.44)	Moderate‡
	Dizziness	6 RCTs	633	Direct	Imprecise	Moderate	Consistent	RR 1.30 (0.12 to 2.09)	Low‡
	Headache	3 RCTs	137	Direct	Imprecise	Moderate	Consistent	RR 1.18 (0.42 to 3.00)	Low‡
	Somnolence	6 RCTs	663	Direct	Precise**	Moderate	Consistent¶	RR 1.39 (0.41 to 5.25); excluding poor quality trial RR 2.44 (1.32 to 4.52)	Moderate‡
	Pruritus	2 RCTs	148	Direct	Imprecise	Moderate	Consistent	RR 3.49 (0.32 to 37.88)	Low‡
	Opioid abuse, dependence, or addiction	No studies	--	--	--	--	--	--	--
	Overdose	No studies	--	--	--	--	--	--	--
	All-cause mortality	No studies	--	--	--	--	--	--	--
	Fracture	No studies	--	--	--	--	--	--	--
	Cardiovascular events	No studies	--	--	--	--	--	--	--
	Endocrinological harms	No studies	--	--	--	--	--	--	--
Opioid + nonopioid vs. opioid alone	Pain (short-term)	6 RCTs (continuous); 5 RCTs (dichotomous)	854 (continuous); 831 (dichotomous)	Direct	Imprecise	Moderate	Consistent	MD -0.18 (-0.72 to -0.36); RR 1.19 (0.97 to 1.68)	Low‡
	Function	4 RCTs	521	Direct	Imprecise	Moderate	Consistent	SMD -0.25 (-0.49 to 0.09)	Low‡
	SF-36 physical (short-term)	4 RCTs	553	Direct	Imprecise	Moderate	Consistent	SMD -0.19 (-2.48 to 4.08)	Low‡

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings† (95% CI)	SOE
Opioid + non-opioid vs. opioid alone, continued	SF-36 mental (short-term)	6 RCTs	1381	Direct	Imprecise	Moderate	Consistent	SMD 5.73 (-0.26 to 13.84)	Low‡
	Sleep quality (short-term)	2 RCTs	363	Direct	Imprecise	Moderate	Consistent	SMD -0.11 (-0.39 to 0.14)	Low‡
	Depression (short-term)	4 RCTs	524	Direct	Imprecise	Moderate	Consistent	SMD -0.18 (-0.37 to -0.01)	Low‡
	Anxiety (short-term)	1 RCT	278	Direct	Imprecise	Moderate	Consistent	SMD -0.04 (-0.28 to 0.19)	Insufficient‡
	Discontinuation due to AEs	5 RCTs	782	Direct	Imprecise	Moderate	Consistent	RR 0.79 (0.50 to 1.27)	Low‡
	Serious AEs	1 RCT	313	Direct	Imprecise	Moderate	Consistent	RR 0.58 (0.14 to 2.39)	Insufficient‡
	Nausea	5 RCTs	585	Direct	Imprecise	Moderate	Consistent	RR 0.98 (0.57 to 1.84)	Low‡
	Vomiting	2 RCTs	339	Direct	Imprecise	Moderate	Consistent	RR 1.68 (0.34 to 8.19)	Low‡
	Constipation	6 RCTs	860	Direct	Imprecise	Moderate	Consistent	RR 0.91 (0.67 to 1.13)	Low‡
	Dizziness	5 RCTs	772	Direct	Imprecise	Moderate	Consistent	RR 1.22 (0.23 to 1.99)	Low‡
	Headache	3 RCTs	457	Direct	Imprecise	Moderate	Consistent	RR 1.12 (0.46 to 2.25)	Low‡
	Somnolence	6 RCTs	860	Direct	Imprecise	Moderate	Inconsistent	RR 0.72 (0.35 to 1.33)	Low‡
	Pruritus	2 RCTs	190	Direct	Imprecise	Moderate	Consistent	RR 0.25 (0.03 to 1.91)	Low‡
	Opioid abuse, dependence, or addiction	No studies	--	--	--	--	--	--	--
	Overdose	No studies	--	--	--	--	--	--	--
	All-cause mortality	No studies	--	--	--	--	--	--	--
	Fracture	No studies	--	--	--	--	--	--	--
	Cardiovascular events	No studies	--	--	--	--	--	--	--
	Endocrinological harms	No studies	--	--	--	--	--	--	--
Opioid + cannabis vs. opioid	Pain, function, opioid discontinuation, opioid dose	1 observational study	1514	Direct	Imprecise	Moderate	Unable to assess	No association	Low‡

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings† (95% CI)	SOE
Opioid + benzodiazepine vs. opioid	Overdose	3 observational studies	140,002	Direct	Precise	Moderate	Consistent	Opioid + benzodiazepine associated with increased risk	Low‡
Opioid + gabapentinoid vs. opioid	Overdose	3 observational studies	799,013	Direct	Precise	Moderate	Consistent	Opioid + gabapentinoid associated with increased risk	Low‡
Methods for initiating and titrating opioids	Pain	2 RCTs	81	Direct	Imprecise	Moderate	Consistent	Unable to assess	Insufficient
Methods for initiating and titrating opioids, continued	Opioid use disorder or related outcomes	No studies	--	--	--	--	--	--	--
Short-acting vs. long-acting opioids	Pain, function	2 RCTs compared short- vs. long-acting of same opioid	184	Direct	Imprecise	Moderate	Consistent	No differences	Low††
	Overdose	1 cohort study	840,606	Direct	Precise	Moderate	Unknown	Long-acting associated with increased risk	Low‡‡
Long-acting opioid vs. a different long-acting opioid	Pain, function, and other effectiveness outcomes	16 RCTs	7356	Direct	Precise	Moderate	Inconsistent	No patterns showing differential effectiveness, with some differences in opioid dosing between arms	Moderate††
	Overdose	4 cohort studies	193,166	Direct	Precise	Moderate	Inconsistent	Methadone associated with increased risk vs. morphine in 2 studies of Medicaid patients and decreased risk in 1 study of VA patients	Low††
Short + long-acting opioid vs. long-acting opioid alone	All	No studies	--	--	--	--	--	--	--

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings† (95% CI)	SOE
Scheduled, continuous vs. as-needed dosing	All	No studies	--	--	--	--	--	--	--
Opioid dose escalation vs. dose maintenance	Pain, function	1 RCT	140	Direct	Imprecise	Moderate	Unknown	No differences; doses were similar in the 2 arms	Low
	Opioid withdrawal due to misuse	1 RCT	140	Direct	Imprecise	Moderate	Unknown	No difference	Low
Opioid rotation vs. maintenance of current opioid therapy	All	No studies	--	--	--	--	--	--	--
Strategies for treating acute exacerbations of chronic pain	Pain (immediate)	4 RCTs	476	Direct	Precise	Low	Consistent	Buccal fentanyl more effective than placebo or oral opioid for immediate pain relief	Moderate
	Longer-term outcomes, addiction, abuse	No studies	--	--	--	--	--	--	--
Tapering off opioids vs. continuation of opioids	Pain, function	1 RCT	34	Direct	Imprecise	Moderate	Unknown	No differences	Low††
	Opioid dose	1 RCT	34	Direct	Imprecise	Moderate	Unknown	Taper associated with lower dose	Low††
Tapering protocols and strategies	Pain, tapering completion, opioid withdrawal symptoms	1 RCT	21	Direct	Imprecise	Moderate	Unknown	Varenicline associated with no differences vs. placebo as an adjunct to tapering	Low††
	Opioid-related emergency department visit	1 cohort study	494	Direct	Imprecise	Moderate	Unknown	Each additional week to discontinuation associated with 7% reduction in risk	Low
Opioid Risk Tool	Diagnostic accuracy	6 studies	1025	Direct	Precise	Moderate	Inconsistent	Sensitivity: 0.20 to 0.99 Specificity: 0.16 to 0.88	Low††

Intervention	Outcomes	Number of Studies	Number of Subjects	Directness	Precision	Study Limitations	Consistency	Findings[†] (95% CI)	SOE
SOAPP Version 1	Diagnostic accuracy	2 studies	203	Direct	Imprecise	High	Consistent	Sensitivity: 0.68 and 0.73 Specificity: 0.38	Low
SOAPP-R	Diagnostic accuracy	4 studies	840	Direct	Precise	Moderate	Inconsistent	Sensitivity: 0.25 to 0.53 Specificity: 0.62 to 0.77	Low[††]
Brief Risk Interview	Diagnostic accuracy	3 studies	577	Direct	Precise	High	Inconsistent	Sensitivity 0.73 to 0.83 Specificity: 0.43 to 0.88	Low[‡]
Naloxone co-prescription	Emergency department visits	1 nonrandomized study	1985	Direct	Precise	Moderate	Unknown	Naloxone associated with decreased risk of emergency department visits vs. no naloxone	Low[‡]
	All-cause mortality, opioid poisoning deaths	1 nonrandomized study	1985	Direct	Imprecise	Moderate	Unknown	No difference	Low[‡]
Prescription opioid use disorder: Taper vs. maintenance	Drug use	1 RCT	113	Indirect	Precise	Moderate	Unknown	Buprenorphine taper inferior to maintenance	Low[‡]
Prescription opioid use disorder: Buprenorphine vs. methadone	Drug use, pain function	1 RCT	54	Indirect	Imprecise	Moderate	Unknown	No differences	Low[‡]

Abbreviations: AE=adverse events; CI=confidence interval; MD=mean difference; RCT=randomized controlled trial; RR=risk ratio; SMD=standard mean difference; SOE=strength of evidence; SOAPP= Screening and Opioid Assessment for Patients with Pain; SOAPP-R= Screening and Opioid Assessment for Patients with Pain-Revised Version; VA=Veterans Affairs Department; vs.=versus.

*Reporting bias was undetected for all key questions/outcomes

[†]Mean differences for pain are reported on a 0 to 10 scale and for SF-36 measures are reported on a 0 to 100 scale

[‡] Not addressed in the 2014 AHRQ publication

[§]Graded down for potential reporting bias

[|]p for nteraction by nonopioid type=0.03 (I think it was 0.03, but please double-check)

[¶]Not downgraded for inconsistency because statistical heterogeneity was eliminated by exclusion of poor-quality trial, with similar pooled estimate

**Not downgraded for precision based on the pooled estimate after excluding a poor-quality trial

[††]The SOE was insufficient in the 2014 AHRQ publication

[‡‡]The SOE was low in the 2014 AHRQ publication