Draft Comparative Effectiveness Review

Number xx

Opioid Treatments for Chronic Pain

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Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
5600 Fishers Lane
Rockville, MD 20857
www.ahrq.gov

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Prepared by:
To be added for final version.

Investigators:
To be added for final version.

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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 follow up, 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, though 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 XXXXX Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. XXX-20XX-XXXXX). 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.

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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 Center 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 Number: (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.

Gopal Khanna, M.B.A
Director
Agency for Healthcare Research and Quality

Arlene S. Bierman, M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Center Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Suchitra Iyer, Ph.D.
Task Order Officer
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

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The authors gratefully acknowledge the following individuals for their contributions to this project: To be added for final version.

Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants will be provided in the final report.

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.

The list of Technical Experts who reviewed the report will be added for the final version.

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

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 non-financial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential non-financial conflicts of interest identified.

The list of Peer Reviewers who reviewed the report will be added for the final version.

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 upon 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 January 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. 113 randomized controlled trials (RCTs), 38 observational studies, and 7 studies of predictive accuracy were included; 133 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 versus 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 report published in 2015[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 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 131 studies were added from this update to the 27 included in the prior AHRQ report, for a total of 158 studies. Summary strength of evidence (SOE) tables were updated based on evidence from the prior AHRQ report and new evidence identified for this update.

The prior AHRQ report did not conduct 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 vs. 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 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 +++	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	Small +	Insufficient evidence	Small +	Small +	Small +	Small +	Small +	Small +	Small +

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

Table iii summarizes other evidence reviewed for this update, showing the number of studies included for each topic in the prior 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 prior 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 prior 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 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 prior 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 prior 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	2015 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	5 observational studies (N=38,750)	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
Opioid + cannabis vs. opioid	Pain, function, opioid discontinuation, opioid dose	Not addressed	1 observational study (N=1514)	No association	Low*
Opioid + benzodiazepine vs. opioid	Overdose	Not addressed	3 observational studies (N=140,002)	Opioid + benzodiazepine associated with increased risk	Low*
Opioid + gabapentinoid vs. opioid	Overdose	Not addressed	3 observational studies (N=799,013)	Opioid + gabapentinoid associated with increased risk	Low*
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	--	--
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‡

Intervention	Outcome	2015 AHRQ report	2019 update	Main findings	Strength of evidence
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	--	--
Scheduled, continuous vs. as-needed dosing	All	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
Opioid rotation vs. maintenance of current opioid therapy	All	No studies	No studies	--	--
Strategies for treating acute exacerbations of chronic pain	Pain (immediate)	5 RCTs (N=802)	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	--	--
Tapering off opioids vs. continuation of opioids	Pain, function	1 RCT (N=10)	1 RCT (N=34)	No difference	Low†
	Opioid dose	No studies	1RCT (N=34)	Taper associated with lower dose	Low†
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†
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

Intervention	Outcome	2015 AHRQ report	2019 update	Main findings	Strength of evidence
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†
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†
Brief Risk Interview	Diagnostic accuracy	No studies	3 studies (N=577)	Sensitivity 0.73 to 0.83 Specificity: 0.43 to 0.88	Low*
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*
	All-cause mortality, opioid poisoning deaths	No studies	1 nonrandomized study (N=1985)	No difference	Low*
Prescription opioid use disorder: Taper vs. maintenance	Drug use	No studies	1 RCT (N=113)	Buprenorphine taper inferior to maintenance	Low*
Prescription opioid use disorder: Buprenorphine vs. methadone	Drug use, pain function	No studies	1 RCT (N=54)	No differences	Low*

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 *Not addressed in the prior AHRQ report; VA=Veterans Affairs Department; vs.=versus.

†The SOE was insufficient in the prior AHRQ report

‡The SOE was low in the prior AHRQ report

Evidence Summary:
Opioid Treatment for Chronic Pain

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.[4] 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.[5] This increase was accompanied by marked increases in rates of opioid use disorder and drug overdose mortality[5-7] involving prescription opioids. From 1999 to 2014, over 165,000 people died from overdose related to prescription opioids in the United States,[8] with an estimated 17,087 prescription opioid overdose deaths in 2016.[5] In October 2017, the U.S. Department of Health and Human Services declared a nationwide public health emergency regarding the opioid crisis.[9]

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.[1] The review addressed the risks and benefits of opioids for chronic pain, dosing strategies, and risk assessment and risk mitigation strategies. The 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 AHRQ comparative effectiveness review and a subsequent update[8] 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.[8,10] 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).[8] 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.[11]

Rationale for This Review

The purpose of this review is to update the prior AHRQ report [1] on opioids for chronic pain. This update includes new evidence for questions covered in the prior 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[12] and nonopioid pharmacological treatments.[13]

Scope and Key Questions

This Comparative Effectiveness Review focused on opioid treatments with short-term (1 to <6 months), intermediate-term followup (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. Opioids versus placebo or no opioid therapy for outcomes related to pain, function, and quality of life

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 type 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. Opioids versus nonopioid therapies on outcomes related to pain, function, and quality of life

d. Opioids plus nonopioid interventions versus opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used

Key Question 2. Harms and Adverse Events

a. 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 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., are there differences between pure opioid agonists and 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. Risks of opioids versus nonopioid therapies on: (1) opioid use disorder, abuse, or misuse; (2) overdose; and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and mental health harms

d. Risks of opioids plus nonopioid interventions versus opioids or nonopioid interventions alone on: (1) opioid use disorder, abuse, or misuse; (2) overdose; and (3) other harms, including gastrointestinal-related harms, falls, fractures, motor vehicle accidents, endocrinological harms, infections, cardiovascular events, cognitive harms, and mental health harms

Key Question 3. Dosing Strategies

a. 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. 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. 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. 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. 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. Opioid dose escalation versus dose maintenance or use of dose thresholds on outcomes related to pain, function, and quality of life

g. Opioid rotation versus maintenance of current opioid therapy on outcomes related to pain, function, and quality of life; and doses of opioids used

h. Different strategies for treating acute exacerbations of chronic pain on outcomes related to pain, function, and quality of life

i. 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. different tapering protocols and strategies on measures related to pain, function, quality of life, opiate withdrawal symptoms, and likelihood of opioid cessation

k. different opioid dosages and durations of therapy for outcomes related to pain, function, and quality of life; risk of opioid use disorder, abuse, or misuse; and overdose

Key Question 4. Risk Assessment and Risk Mitigation Strategies

a. Accuracy of instruments and tests for predicting risk of opioid use disorder, abuse, or misuse; and overdose

b. Risk prediction instruments and tests on outcomes related to opioid use disorder, abuse, or misuse; and overdose

c. 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. 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?

Note: 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 Agency for Healthcare Research & Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[14] See the review protocol (https://effectivehealthcare.ahrq.gov/topics/opioids-chronic-pain/protocol) and the full report of the review for additional details.

Review Protocol

A multidisciplinary Technical Expert Panel (TEP) 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 January 2019. Searches were conducted from January 2014 for key questions addressed in the prior AHRQ report (searches conducted through August 2014). For questions or areas not covered by the prior review, searches were conducted from database inception. Reference lists of included systematic reviews were screened for additional studies and relevant references from the prior 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 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 Appendixes 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,[15] cohort and other observational studies of interventions were evaluated using criteria developed by the U.S. Preventive Services Task Force,[9] and studies of diagnostic accuracy were assessed using Quality Assessment of Diagnostic Accuracy Studies – Version 2 (QUADAS-2).[16] These criteria were used in conjunction with the approach recommended in the AHRQ Methods Guide.[17] Studies were rated as "good," "fair," or "poor". The quality ratings of studies included in the prior 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.[18] 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).

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.[8] 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.

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[19] 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).[17] 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[20] and an earlier AHRQ comparative effectiveness review on treatments for low back pain.[21] 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 analogue 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 analogue 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.[22] \

Grading the Strength of Evidence

The overall SOE 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.[17] Summary strength of evidence tables were updated based on all the evidence, from the prior AHRQ report and this updated review.

Peer Review and Public Commentary

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

Results

Results of Literature Searches

We included 113 randomized controlled trials, 38 observational studies, and seven studies of diagnostic accuracy of opioid risk prediction instruments to address four Key Questions and two Contextual Questions. 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. Effectiveness of opioid therapy vs. placebo or no opioid therapy for outcomes related to pain, function, and quality of life?	• Opioids were associated with a small mean improvement vs. placebo in pain intensity at short-term followup (70 trials, N=19,486, SOE: high). • Opioids were associated with increased likelihood vs. placebo of experiencing a pain response at short-term followup (43 trials, N=12,351, SOE: high). • Opioids were associated with a small mean improvement vs. placebo in function at short-term followup (43 trials, N=12,297, 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 (22 trials, N=7875, SOE: high). • No difference between opioids vs. placebo in mean improvement on SF-36 measures of mental health status at short-term followup (20 trials, N=7456, SOE: high) • Opioids were associated with a small mean improvement vs. placebo in sleep quality at short-term followup (24 trials, N=6590, 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 nociceptive pain (49 trials, N=16,849) (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. Comparative effectiveness of opioids vs. nonopioid therapies on outcomes related to pain, function, and quality of life?	• No differences between opioids vs. nonopioids in mean improvement in pain (12 trials, N=1879) or likelihood of a pain response at short-term followup (11 trials, N=2646) at short-term followup (SOE: moderate). • There were no differences between opioids vs. nonopioids in mean improvement in function at short-term followup (9 trials, N=1694, 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 (6 trials, N=1454), 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.
1d. Comparative effectiveness of opioids plus nonopioid interventions vs. opioids or nonopioid interventions alone on outcomes related to pain, function, quality of life, and doses of opioids used?	• No differences between an opioid plus nonopioid vs. a nonopioid alone in mean improvement in pain at short-term followup (5 trials, N=325), likelihood of a pain response (3 trials, N=462), function (3 trials, N=246), or other outcomes (SOE: low for all outcomes). • 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. a nonopioid 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).

Key Question[a]	Summary of Findings
2a. Risks of opioids vs. placebo or no opioid on: (1) substance misuse, substance use disorder, and related outcomes; (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?	• Opioids were associated with increased risk of withdrawal due to adverse events vs. placebo at short-term followup (60 trials, N=19,864, SOE: high). • There was no difference between opioids vs. placebo in risk of serious adverse events at short-term followup (37 trials, N=13,030, 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). • There was no association between opioids vs. placebo and risk of headache 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). • Five 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 >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 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. Comparative risks of opioids vs. nonopioid therapies on: (1) substance misuse, substance use disorder, and related outcomes; (2) overdose; and (3) other harms?	• Opioids were associated with increased risk of withdrawal due to adverse events (10 trials, N=3289), somnolence (10 trials, N=3029), nausea (10 trials, N=3029), constipation (10 trials, N=3029), vomiting (5 trials, N=2536), dizziness (10 trials, N=3029), pruritus (5 trials, N=2577, and headache (7 trials, N=2683) vs. a nonopioid at short-term followup (SOE: high).
2d. Comparative risks of opioids plus nonopioid interventions vs. opioids or nonopioid interventions alone?	• An opioid plus nonopioid was associated with increased risk of withdrawal due to adverse events (5 trials, N=404), nausea (5 trials, N=330), constipation (5 trials, N=330), and somnolence (5 trials, N=330) vs. a nonopioid alone at short-term followup. Effects on risk of dizziness were not statistically significant (5 trials, N=330) (SOE: low for dizziness, moderate for other outcomes). • No differences between an opioid plus nonopioid vs. an opioid alone in risk of withdrawal due to adverse events (5 trials, N=782), nausea (5 trials, N=585), constipation (6 trials, N=860), or somnolence (5 trials, N=860) vs. an opioid alone at short-term followup.

Key Question[a]	Summary of Findings
3b.Comparative effectiveness of 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.Comparative effectiveness of 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 withdrawal 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 withdrawals 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. Comparative effectiveness of 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 withdrawal due to opioid misuse, but opioid doses were similar (52 vs. 40 mg MED /day at the end of the trial) (SOE: low).
3h. Comparative effectiveness of 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. Effects of decreasing opioid doses or of 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. Comparative effectiveness of 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. Comparative effectiveness of 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. Effectiveness of 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. Comparative effectiveness of 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; ORT = Opioid Risk Tool; 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 two 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?

Discussion

Key Findings and Strength of Evidence

This report updates the prior AHRQ report. The key findings, including SOE ratings, are summarized in Tables A and B and reflect the combined evidence from the prior AHRQ report and this update. 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 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 prior 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.[23] New observational studies were consistent with the prior AHRQ report in finding an association between use of prescription opioids and risk of addiction,[24] overdose,[24] fractures,[25-27] falls[26,28] and cardiovascular events;[29] a new study also found an association between opioid use and risk of all-cause mortality.[29] New observational studies were also consistent with the prior AHRQ report in finding associations between higher doses of opioids and risks of overdose, addiction, and endocrinological adverse events;[24,25,28-31] new studies also found an association between higher dose and increased risk of incident or refractory depression.[32,33] 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[34-36] or benzodiazepines[37-39] and increased risk of overdose, with most pronounced risk occurring soon after initiation of these medications.

This update also expanded upon the prior 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 prior 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).[40] 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.[29,41,42] 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 prior AHRQ report, which found highly inconsistent estimates of diagnostic accuracy, methodological limitations and few studies of risk assessment instruments other than the ORT and 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.[43] 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.[3] 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.[44] 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 FDA 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[8] 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 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 (≥12 months) followup.[12] The review addressed the risks and benefits of opioids for chronic pain, dosing strategies, and risk assessment and risk mitigation strategies. The 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 AHRQ comparative effectiveness review 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 prior AHRQ report [12] on opioids for chronic pain, given the ongoing magnitude of the opioid crisis, the low quality of evidence in the prior 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 prior 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 prior AHRQ report by addressing shorter-term (1 to 12 month) 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 prior 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 nonpharmacologic 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 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., are there differences between pure opioid agonists and 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?

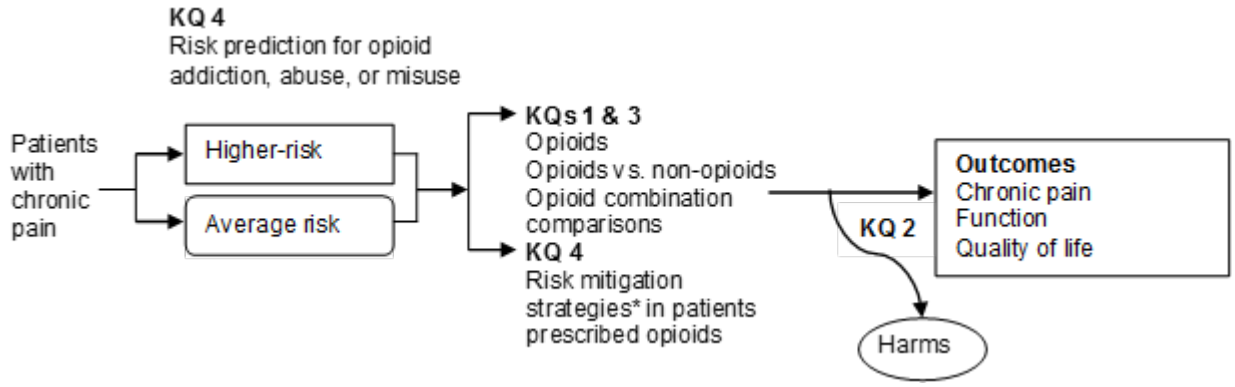
Contextual Questions

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?

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

Analytic Framework

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 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 published on the AHRQ web site (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®, Embase®, PsycINFO®, Cochrane CENTRAL, and Cochrane Database of Systematic Reviews in January 2019 (see **Appendix A** for full strategies). Searches were conducted from January 2014 for key questions addressed in the prior AHRQ report (searches conducted through August 2014). For questions or areas not covered by the prior review, searches were conducted from database inception. Reference lists of included systematic reviews were screened for additional studies and relevant references from the prior 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. Prior to the final report, searches will be updated and new eligible studies incorporated into the report.

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 (for specific questions or subquestions) persons with acute exacerbations of chronic pain, 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 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 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 crashes, 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). KQ 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	KQ 1a-c, 2a-c: Long- or short-acting opioids (including partial agonists and dual mechanism agents KQ 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]) KQ 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	KQ 1a, 1b and 2a, 2b: Placebo or no opioid therapy KQ 1c and 2c: Nonopioid therapies (pharmacologic or nonpharmarmacologic [noninvasive]) KQ 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 to nonopioids included in review of nonpharmacologic treatments) • Opioid treatment
Outcomes	Pain, function, and quality of life Mood, sleep Doses of opioids used (KQ 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 KQ: Randomized controlled trials KQ 1 and 2: Cohort and case-control studies for long-term (≥1 year) outcomes KQ 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 prior 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), 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 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 agonist, partial agonist (buprenorphine), or mixed (dual mechanism; tramadol or tapentadol) and opioid doses were converted to mg 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.

All study 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**). Randomized trials 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 prior AHRQ report were reviewed to insure 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 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.[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, MDs based on the original scale were also pooled separately for the most commonly utilized measures.

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[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 or visual analogue 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 analogue 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.[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 strength of evidence 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 strength of evidence 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 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, country), 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

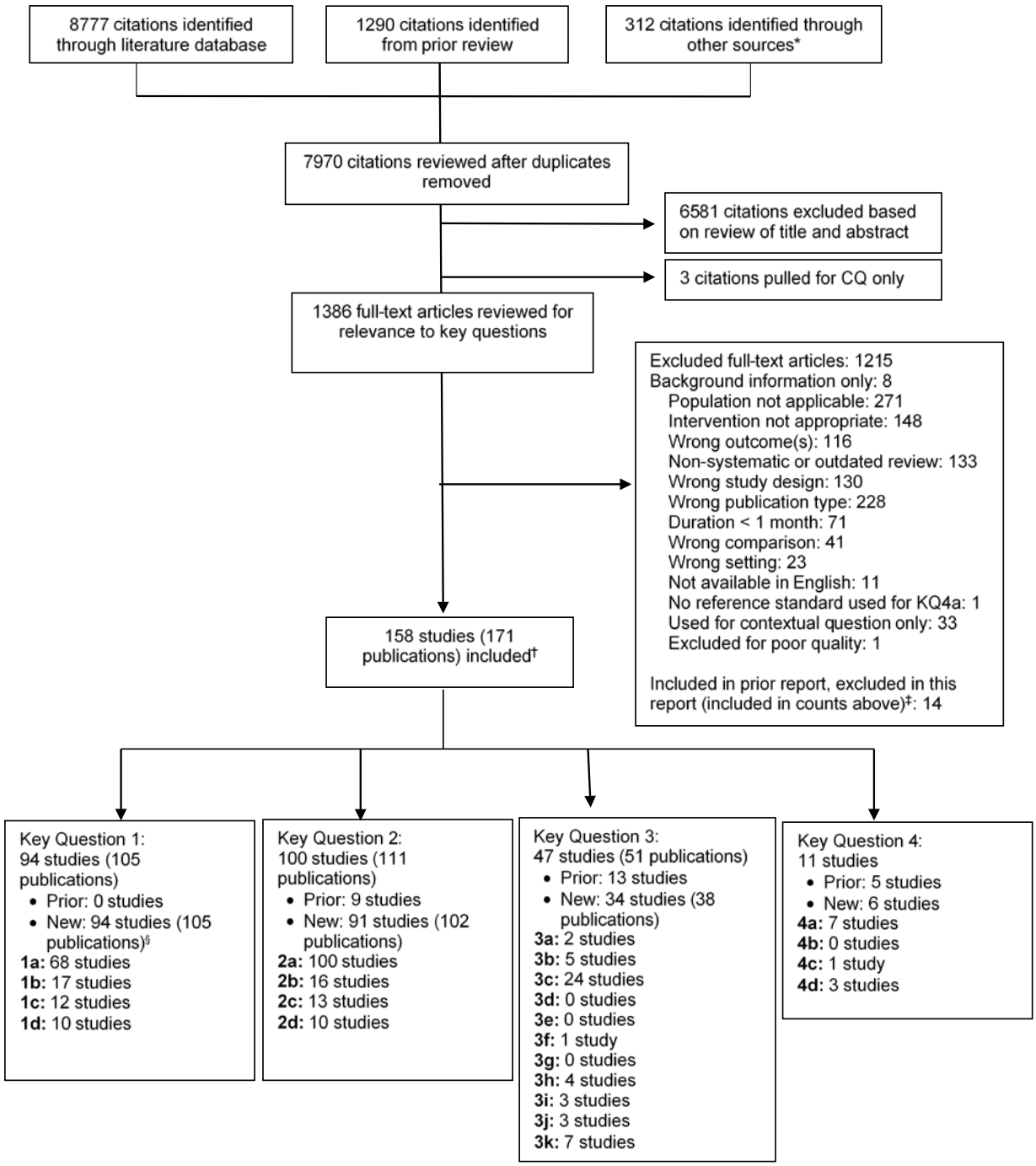
Experts will be invited to provide external peer review of this systematic review; AHRQ and an associate editor will also provide comments. In addition, the draft report will be posted on the AHRQ website for 4 weeks to for public comment. Comments will be reviewed and used to inform revisions to the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

Results

Results of Literature Search

A total of 7970 references from electronic database searches and reference lists were reviewed; from these, 1386 full-text papers were evaluated for inclusion, including 41 included in the prior AHRQ report. After review of full-text papers 1215 articles were excluded, including 14 from the prior 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 113 RCTs, 38 observational studies, and seven studies of diagnostic accuracy of opioid risk prediction instruments were included (**Figure 2 and Appendix F**). Of these, 27 studies were included in the prior AHRQ report and 131 studies were added for this update. Most (116) 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. The diagram indicates the numbers of abstracts and full text articles reviewed for inclusion and subsequently included or excluded.



*Other sources include reference lists of relevant articles, studies, and systematic reviews, suggestions from reviewers, etc.
†158 studies in 171 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

- Opioids were associated with a small mean improvement versus placebo in pain intensity at short-term followup (70 trials, N=19,486, mean difference -0.80 point on a 0 to 10 scale, 95% confidence interval [CI], -0.94 to -0.67, I^2=72%) (SOE: high).
- Opioids were associated with increased likelihood versus placebo of experiencing a pain response at short-term followup (43 trials, N=12,351, RR 1.35, 95% CI, 1.24 to 1.49, I^2=82%; 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 (43 trials, N=12,297, SMD -0.22, 95% CI, -0.28 to -0.16, I^2=54%) (SOE: high).
- Opioids were associated with a mean improvement below the threshold for small versus placebo in SF-36 measures of physical health status at short-term followup (22 trials, N=7875, mean difference 1.65 points on a 0 to 100 scale, 95% CI, 1.09 to 2.18, I^2=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 (20 trials, N=7456, -0.52 point on a 0 to 100 scale, 95% CI, -1.45 to 0.41, I^2=64%) (SOE: high)
- Opioids were associated with a small mean improvement versus placebo in sleep quality at short-term followup (24 trials, N=6590, SMD -0.25, 95% CI, -0.33 to -0.19, I^2=0%) (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, I^2=40%) (SOE: moderate).

Intermediate- and Long-Term

- 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%, absolute risk difference [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-two randomized trials compared opioids versus placebo for chronic pain (**Table 2**).[50-125] Sample sizes ranged from 7 to 806 (total N=20,372). None of the trials were included in the prior 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; 32 trials followed patients for less than 3 months and 39 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 50 trials. The duration of pain ranged from 6.8 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,[51,54,76,77,81,84,88,99,100,104,107,108,110,111,123-126] seven trials to opioid-experienced patients,[68,70,72,73,83,91,98,115] and 36 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] 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 four trials in Asia. The opioid type was a pure opioid agonist in 39 trials, partial agonist (buprenorphine) in eight trials, and mixed agent (tramadol or tapentadol) in 25 trials. The mean opioid dose ranged from 12 mg to 186 mg MED/day; in 15 trials the mean dose was less than 50 mg MED/day, in 26 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	Control
Afilalo, 2010[50] International Fair	1030	1. No 2. No 3. Yes	1: Osteoarthritis of knee 2: NR 3: NR 4: NR	Age: 58 (mean) 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	Placebo
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 (0 to100 VAS)	Age: 66 Female: 67% White: NR	Fentanyl patch 25 to 50 mcg/hour (mean 15.1 mcg/hour); 36 mg MED 12 weeks	Placebo
Arai, 2015[51] Japan Poor	163	1. Yes 2. No 3. Yes	1: Post-herpetic neuralgia, complex regional pain syndrome, or chronic postop pain 2: 46.5 3: No 4: 28.9 (0 to100 VAS)	Age: 67 Female: 49% White: NR	Fentanyl patch 25 to 50 mcg/hour (mean 18.6 mcg/hour); 45 mg MED 12 weeks	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	Control
Babul, 2004[52] USA Fair	246	1: No 2: No 3: Yes	1: Osteoarthritis 2: 154.9 (mean) 3: Mixed 4: 76.9 (0 to 100 VAS)	Age: 61.4 (mean) Female: 62% White: 82%	Tramadol SR 200 to 400 mg (mean 276 mg); 55 mg MED 12 weeks	Placebo
Boureau, 2003[53] France Good	127	1: No 2: No 3: Yes	1: Postherpetic neuralgia 2: 6.8 (mean) 3: Mixed 4: 60.5 (0 to100 VAS)	Age: 67 (mean) Female: 71% White: NR	Tramadol 100 to 400 mg (mean 276 mg); 55 mg MED 6 weeks	Placebo
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	Placebo
Burch, 2007[55] International Good	646	1: Yes 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: 7.2 (0 to 10 VAS)	Age: 62 (mean) Female: 63% White: 85%	Tramadol SR 200 to300 mg (mean 275 mg); 55 mg MED 12 weeks	Placebo
Buynak, 2010[56] USA Fair	981	1: No 2: No 3: Yes	1: Low back pain 2: NR 3: Mixed 4: 7.5 (0 to 10 NRS)	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	Placebo
Caldwell, 1999[57] USA Fair	70	1: Yes 2: No 3: Yes	1: Osteoarthritis 2: NR 3: NR 4: NR	Age: 57.5 (mean) Female: 61% White: NR	Oxycodone SR 20 to 60 mg (mean 40 mg); 60 mg MED 4 weeks	Placebo
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 (mean) Female: 62% White: 84%	Morphine SR (qd or bd) 30 mg; 30 mg MED 4 weeks	Placebo
Christoph, 2017[59] Germany Fair	252	1: No 2: No 3: Yes	1: Low back pain 2: 124.8 3: Mixed 4: 7.2 (0 to 10 NRS)	Age: 58 Female: 61% White: 99.6%	Tapentadol SR 400 mg; 160 mg MED 14 weeks	Placebo
Chu, 2012[60] USA Fair	139	1: No 2: No 3: No	1: Low back pain 2: NR 3: Mixed 4: 49.8 (0 to 100 VAS)	Age: 45 Female: 44% White: 65%	Morphine SR 30 to 120 mg (mean 78 mg); 78 mg MED 4.5 weeks	Placebo
Cloutier, 2013[61] Canada Fair	83	1: No 2: Yes 3: Yes	1: Low back pain 2: 165.6 3: Mixed 4: 61.4 (0 to 100 VAS)	Age: 51 Female: 50% White: NR	Oxycodone SR + Naloxone 20 to 80 mg (mean 36 mg); 54 mg MED 4 weeks	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	Control
Delemos, 2011[62] USA Fair	808	1: No 2: No 3: Yes	1: Osteoarthritis 2: 97.2 (mean) 3: Mixed 4: 302.1 (WOMAC pain 0 to 500)	Age: 60 (mean) Female: 63% White: 81%	Tramadol SR 100, 200, or 300 mg (mean 200 mg); 40 mg MED 12 weeks	Placebo
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 (mean) Female: 62% White: NR	Tramadol SR 100, 200, or 300 mg (mean 201 mg); 40 mg MED 12 weeks	Placebo
Fleischmann, 2001[64] USA Poor	129	1: No 2: No 3: Yes	1: Osteoarthritis 2: 7.9 (mean) 3: NR 4: 2.8 (0 to 4 NRS)	Age: 63 (mean) Female: 62% White: 91%	Tramadol 200 to 400 mg (mean NR); 60 mg MED 12 weeks	Placebo
Friedmann, 2011[65] USA Fair	412	1: Yes 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: 5.3 (0 to 10 NRS)	Age: 58 Female: 70% White: 82%	Oxycodone SR 40 mg (mean 27.5 mg); 41 mg MED 12 weeks	Placebo
Gilron, 2005[67] Canada Fair	1020	1: No 2: No 3: Yes	1: Osteoarthritis 2: 93.6 (mean) 3: Mixed 4: 69.1 (0 to 100 VAS)	Age: 58 (mean) Female: 62% White: 78%	Tramadol SR 100 to 400 mg; 50 mg MED 12 weeks	Placebo
Gilron, 2005[67] Canada Fair	57	1: No 2: Yes 3: No	1: Diabetic neuropathy 2: 54.7 (mean) 3: Mixed 4: 5.0 (0 to 10 VAS)	Age: 56 (median) Female: 44% White: 98%	Morphine Up to 120 mg (mean 45 mg); 45 mg MED 5 weeks	Lorazepam (active placebo)
Gimbel, 2003[69] USA Fair	159	1: No 2: No 3: Yes	1: Diabetic neuropathy 2: NR 3: Mixed 4: 6.8 (0 to 10 VAS)	Age: 59 (mean) Female: 48% White: 84%	Oxycodone SR 10 to 120 mg (mean 37 mg); 56 mg MED 6 weeks	Placebo
Gimbel, 2016[68] USA Fair	511	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Yes 4: 2.9 (0 to 10 NRS)	Age: 54 (mean) Female: 55% White: 77%	Buprenorphine buccal 300 to 1800 mcg (mean 1320 mcg); NA 12 weeks	Placebo
Gordon, 2010[70] Canada Fair	78	1: No 2: Yes 3: Yes	1: Low back pain 2: 154.8 (mean) 3: Yes 4: 60.9 (0 to 100 VAS)	Age: 51 (mean) Female: 60% White: NR	Buprenorphine patch 10 to 30 mcg/hour (mean 30 mcg/hour); NA 4 weeks	Placebo
Gordon, 2010[71] Canada Fair	79	1: No 2: Yes 3: Yes	1: Low back pain 2: 169.2 (mean) 3: NR 4: 61.4 (0 to 100 VAS)	Age: 55 (mean) Female: 47% White: NR	Buprenorphine 5 to 20 mcg/hour (mean 15.5 mcg/hour); NA 4 weeks	Placebo
Hale, 2007[73] USA Fair	143	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Yes 4: 23.0 (0 to 100 VAS)	Age: 47 (mean) Female: 45% White: 87%	Oxymorphone SR Mean 80 mg; 120 mg MED 12 weeks	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	Control
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 (0 to 10 NRS)	Age: 49 (mean) Female: 50% White: 85%	Hydromorphone SR 12 to 64 mg (mean 37.3 mg); 186 mg MED 12 weeks	Placebo
Hale, 2015[75] USA Good	371	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Mixed 4: 3.4 (0 to 10 NRS)	Age: 52 Female: 51% White: 71%	Hydrocodone SR 60 to 180 mg (mean 100 mg); 120 mg MED 12 weeks	Placebo
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 (0 to 10 NRS)	Age: 53 Female: NR White: 75%	Hydrocodone SR 30 to 180 mg (mean NR); NR 12 weeks	Placebo
Hanna, 2008[76] UK Good	338	1: No 2: No 3: Yes	1: Diabetic neuropathy 2: NR 3: No 4: 6.4 (0 to 10 NRS)	Age: 60 (mean) Female: 36% White: 99%	Oxycodone SR NR; NR 12 weeks	Placebo
Harati, 1998[77] USA Fair	131	1: No 2: No 3: Yes	1: Diabetic neuropathy 2: NR 3: Yes 4: 2.6 (0 to 10)	Age: 59 (mean) Female: 40% White: NR	Tramadol Up to 400 mg (mean 210 mg); 42 mg MED 6 weeks	Placebo
Huse, 2001[78] Germany Poor	12	1: No 2: Yes 3: Yes	1: Phantom limb pain 2: 197.9 (mean) 3: NR 4: 4.65 (0 to 10 VAS)	Age: 51 (mean) Female: 17% White: NR	Morphine SR 70 to 300 mg (mean NR); 185 mg MED 4 weeks	Placebo
Katz, 2007[81] USA Fair	205	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: No 4: 19.1 (0 to 100 VAS)	Age: 50 (mean) Female: 53% White: 90%	Oxymorphone SR Mean 39.2 mg; 118 mg MED 12 weeks	Placebo
Katz, 2010[79] USA Fair	344	1: Yes 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: 3.2 (0 to 10 NRS)	Age: 54 (mean) Female: 58% White: 72%	Morphine SR 20 to 160 mg (mean 43.5); 44 mg MED 12 weeks	Placebo
Katz, 2015[80] USA Fair	389	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Mixed 4: 3.0 (0 to 10 NRS)	Age: 50 Female: 53% White: 71%	Oxycodone SR 40 to 160 mg (mean 78 mg); 117 mg MED 12 weeks	Placebo
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 (0 to 10 NRS)	Age: 53 (median) Female: 45% White: NR	Morphine SR Up to 90 mg (mean 62 mg); 62 mg MED 7 weeks	Placebo
Langford, 2006[83] Europe Fair	416	1: No 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Yes 4: 73.2 (0 to100 VAS)	Age: 66 (mean) Female: 64% White: NR	Fentanyl 25 to 100 mg (Mean 43.9 mcg/hour); 105 mg MED 6 weeks	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	Control
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	Placebo
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 (mean) Female: 72% White: 93%	Oxycodone SR 20 to 120 mg (mean 44 mg); 66 mg MED 13 weeks	Placebo
Matsumoto, 2005[86] USA Fair	491	1: No 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: NR	Age: 62 (mean) Female: 61% White: 86%	Oxymorphone SR 40 to 80 mg; 180 mg MED 4 weeks	Placebo
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	Placebo
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	Placebo
Moulin, 1996[89] Canada Poor	61	1: No 2: Yes 3: Yes	1: Mixed (primarily musculoskeletal) 2: 49.2 (mean) 3: Mixed 4: NR	Age: 40.4 (mean) Female: 59% White: NR	Morphine Up to 120 mg (mean 83.5 mg); 84 mg MED 6 weeks	Benztropine (active placebo)
Munera, 2010[90] USA Fair	315	1: No 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: 8.2 (0 to10 NRS)	Age: 61 (mean) Female: 67% White: 85%	Buprenorphine patch 5 to 20 mcg/hour (mean NR); NA 4 weeks	Placebo
Niesters, 2014[92] The Netherlands Good	25	1: No 2: No 3: Yes	1: Diabetic neuropathy 2: 72 (median) 3: Mixed 4: 7.8 (0 to 10 NRS)	Age: 78 (median) Female: 42% White: NR	Tapentadol SR 200 titrated to 500 mg (mean 433 mg); 173 mg MED 4 weeks	Placebo
Norrbrink, 2009[93] Sweden Fair	36	1: No 2: No 3: No	1: Neuropathic pain after spinal cord injury 2: 175.2 (mean) 3: NR 4: Median 3 vs. 5 (0 to 10 NRS)	Age: 51 (mean) Female: 20% White: NR	Tramadol 150 to 400 mg (median 250 mg); 50 mg MED 4 weeks	Placebo
Peloso, 2000[94] Canada Fair	103	1: No 2: No 3: Yes	1: Osteoarthritis 2: 10.3 (mean) 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	Placebo
Raja, 2002[95] USA Fair	76	1: No 2: Yes 3: No	1: Postherpetic neuralgia 2: 32.3 (mean) 3: Mixed 4: NR	Age: 71 (mean) Female: 55% White: 88%	Morphine SR Up to 240 mg (mean 91 mg); 91 mg MED 8 weeks	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	Control
Rauck, 2013[96] USA Poor	990	1: No 2: No 3: Yes	1: Osteoarthritis 2: NR 3: Mixed 4: 7.4 (0 to 10 NRS)	Age: 60 Female: 64% White: 88%	Hydromorphone SR 8 to 16 mg (mean 12 mg); 60 mg MED 14 weeks	Placebo
Rauck, 2014[98] USA Poor	302	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Yes 4: 3.1 (0 to 10 NRS)	Age: 51 Female: 55% White: 80%	Hydrocodone SR 40 to 200 mg (mean 119 mg); 143 mg MED 12 weeks	Placebo
Rauck, 2015[97] USA Fair	281	1: Yes 2: No 3: Yes	1: Low back pain 2: 149 3: NR 4: 3.0 (0 to 10 NRS)	Age: 50 Female: 56% White: 73%	Oxycodone SR + Naltrexone 20 to 160 mg (mean 64 mg); 96 mg MED 12 weeks	Placebo
Rauck, 2016[99] USA Fair	461	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: No 4: 7.2 (0 to 10 NRS)	Age: 50 Female: 62% White: 70%	Buprenorphine buccal 300 to 900 mcg (mean 660 mcg); NR 12 weeks	Placebo
Russell, 2000[100] USA Fair	69	1: Yes 2: No 3: Yes	1: Fibromyalgia 2: 56.4 (mean) 3: No 4: NR	Age: 49 Female: 94% White: 81%	Tramadol 50 to 400 mg (mean NR); 45 mg MED 6 weeks	Placebo
Schnitzer, 2000[101] USA Poor	254	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: NR 4: NR	Age: 41 (mean) Female: 50% White: 93%	Tramadol 200 to 400 mg (mean NR); 60 mg MED 4 weeks	Placebo
Schwartz, 2011[102] USA Fair	395	1: Yes 2: No 3: Yes	1: Diabetic neuropathy 2: 70.1 3: Mixed 4: 3.5 (0 to 10 NRS)	Age: 60 Female: 40% White: 70%	Tapentadol SR 100 to 250 mg (mean NR); 70 mg MED 12 weeks	Placebo
Serrie, 2017[103] Europe Fair	990	1: No 2: No 3: Yes	1: Knee pain 2: NR 3: Mixed 4: 7.3 (0 to 10 NRS)	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	Placebo
Simpson, 2016[104] Australia Fair	186	1: No 2: No 3: Yes	1: Diabetic neuropathy 2: NR 3: No 4: 5.8 (0 to 10 NRS)	Age: 63 Female: 33% White: 94%	Buprenorphine patch 5 to 40 mcg/hour (mean 20 mcg/hour); NR 12 weeks	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	Control
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	Placebo
Sindrup, 2012[105] Denmark, Germany Fair	64	1: No 2: Yes 3: Yes	1: Polyneuropathy 2: NR 3: NR 4: 6.0 (0 to 10 NRS)	Age: 58 Female: 31% White: NR	Tramadol SR 100 to 400 mg (mean NR); 50 mg MED 4 weeks	Placebo
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 (0 to 10 NRS)	Age: 49 Female: 55% White: 70%	Buprenorphine patch 10 or 20 mcg/hour (mean NR); NR 12 weeks	Placebo
Thorne, 2008[109] Canada Fair	116	1: No 2: Yes 3: Yes	1: Osteoarthritis 2: 99.6 (mean) 3: Mixed 4: 50.8 (0 to 100 VAS)	Age: 61 (mean) Female: 55% White: NR	Tramadol SR 150 to 400 mg (mean 340 mg); 68 mg MED 4 weeks	Placebo
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 (0 to 10 NRS)	Age: NR Female: NR White: NR	Tapentadol SR 50 to500 mg (mean 237 mg); 95 mg MED 12 weeks	Placebo
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 (0 to 10 NRS)	Age: NR Female: NR White: NR	Tapentadol SR 50 to 500 mg (mean 274 mg); 110 mg MED 12 weeks	Placebo
Trenkwalder, 2015[111] Poland Fair	202	1: No 2: No 3: Yes	1: Parkinson's disease 2: 40.8 3: No 4: 7.3 (0 to 10 NRS)	Age: 67 Female: 48% White: NR	Oxycodone SR + Naloxone Oxycodone 10 to 40 mg (mean 19 mg) + Naloxone 5-20 mg; 28 mg MED 16 weeks	Placebo
Uberall, 2012[112] Germany Fair	240	1: No 2: No 3: Yes	1: Low back pain 2: 74.1 3: Mixed 4: 6.0 (0 to 10 NRS)	Age: 58 Female: 58% White: 98%	Tramadol SR 200 mg; 40 mg MED 4 weeks	Placebo
Vinik, 2014[113] USA Fair	318	1: Yes 2: No 3: Yes	1: Diabetic neuropathy 2: NR 3: Mixed 4: 3.6 (0 to 10 NRS)	Age: 59 Female: 41% White: 81%	Tapentadol SR 200 to 500 mg (mean NR); 140 mg MED 12 weeks	Placebo
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	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	Control
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 (mean) Female: 62% White: NR	Oxycodone SR / Oxycodone SR + Naloxone 20 or 40 mg / 20 or 40 mg + 10 or 20 mg; 45 mg MED 12 weeks	Placebo
Vorsanger, 2008[117] USA Fair	386	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Mixed 4: 29.0 (0 to 100 VAS)	Age: 48 (mean) Female: 50% White: 84%	Tramadol SR 200 to 300 mg; 50 mg MED 12 weeks	Placebo
Watson, 1998[118] Canada Fair	50	1: No 2: Yes 3: Yes	1: Postherpetic neuralgia 2: 31 (mean) 3: NR 4: NR	Age: 70 (mean) Female: 58% White: NR	Oxycodone 20 to 60 mg (mean 45 mg); 68 mg MED 4 weeks	Placebo
Watson, 2003[119] Canada Fair	45	1: No 2: Yes 3: Yes	1: Diabetic neuropathy 2: NR 3: NR 4: 67 (0 to 100 VAS)	Age: 63 (mean) Female: 47% White: NR	Oxycodone SR 20 to 80 mg (mean 40 mg); 60 mg MED 4 weeks	Placebo
Webster, 2006[120] USA Fair	307	1: No 2: No 3: NR	1: Low back pain 2: NR 3: Mixed 4: 7.6 (0 to10 VAS)	Age: 48 (mean) Female: 61% White: NR	Oxycodone 10 to 80 mg (mean 39 mg); 58 mg MED 6 weeks	Placebo
Wen, 2015[121] USA Fair	588	1: Yes 2: No 3: Yes	1: Low back pain 2: NR 3: Mixed 4: 7.4 (0 to 10 NRS)	Age: 49 Female: 57% White: 68%	Hydrocodone SR 20 to 120 mg (mean NR); 84 mg MED 12 weeks	Placebo
Wu, 2008[122] USA Fair	60	1: No 2: Yes 3: No	1: Postamputation pain 2: 51.3 3: NR 4: 6.8 (0 to 10 NRS)	Age: 71 Female: 22% White: 85%	Morphine SR 30 to 180 mg (mean 112 mg); 112 mg MED 6 weeks	Placebo

Abbreviations: bd=twice a day; BPI=Brief Pain Inventory**;** MED=morphine equivalent dose; NA=not applicable; NR=not reported; NRS=Numeric Rating Scale; qd=once a day; SR=sustained release; VAS=Visual Analogue Scale; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

Five trials were rated good-quality,[53,55,75,76,92] 54 trials fair-quality,[50,52,54,56-63,65-74,77,79-83,85-87,90,91,93-95,97,99,100,102-105,107-109,111-128] 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 24 trials used an EERW;[51,55,57,65,68,72-75,79-81,91,97-102,107,108,113,115,116,121,123-128] 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**).[129]

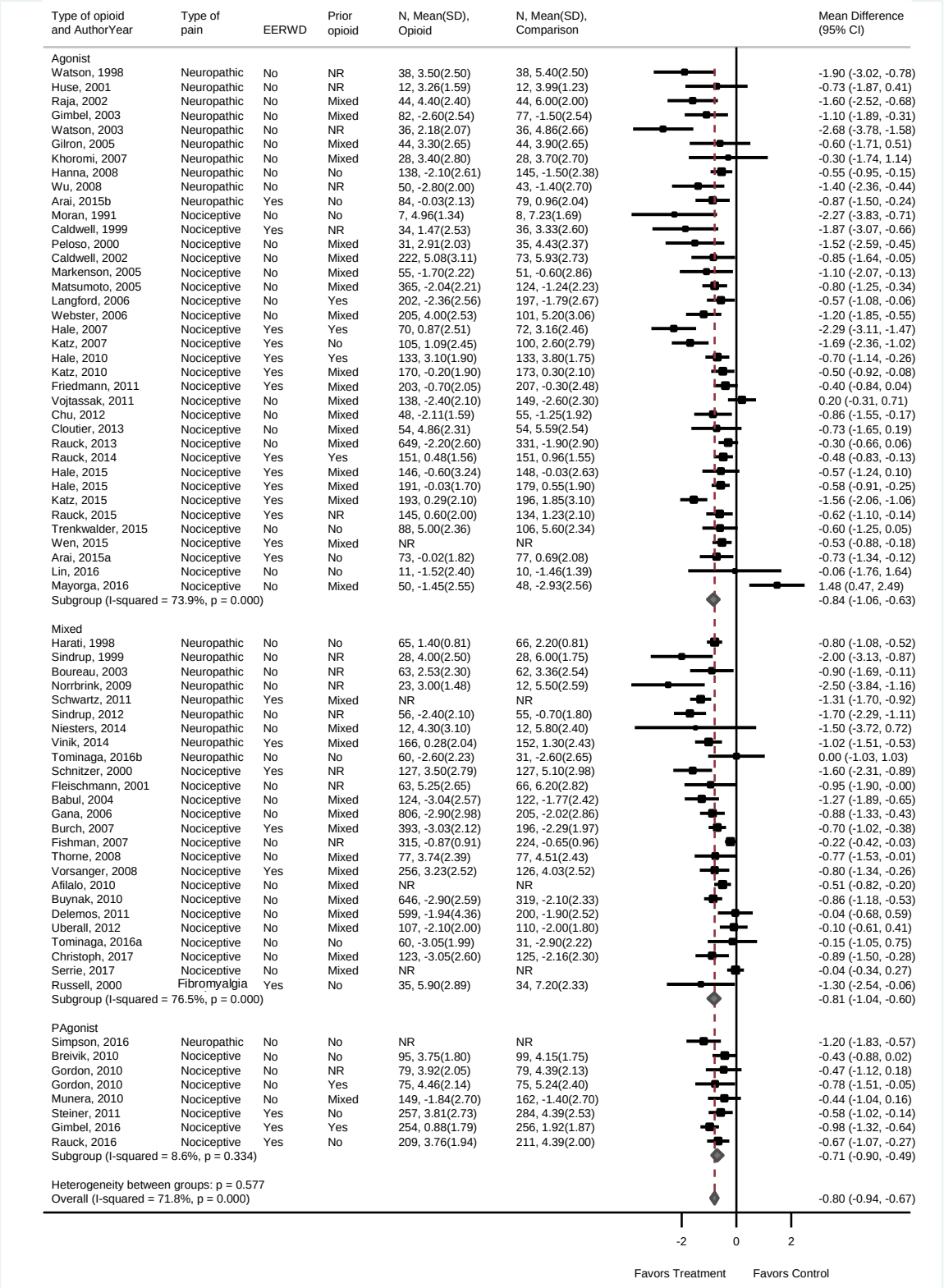
Detailed Synthesis

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 (70 trials, N=19,486, mean difference -0.80 point on a 0 to 10 scale, 95% CI, -0.94 to -0.67, I^2=72%; **Figure 3, Table 3**)[50-88,90,92-114,117-122] 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 (48 trials, N=15,212, mean difference -0.67, 95% CI, -0.82 to -0.52, I^2=74%), with a difference of 0.45 point (p for interaction=0.001). There were no interactions between trial quality (p for interaction=0.88), industry funding (p for interaction=0.43), geographic region (p for interaction=0.68), or use of EERW design (p for interaction=0.28) and effects on pain (**Table 4**). However, when the analysis was restricted to trials published in or after 2007, effects on pain were larger in trials that used an EERW design (20 trials, N=7048, mean difference -0.82, 95% CI, -1.01 to -0.66, I^2=63%)[51,55,65,68,72-75,79-81,91,97-99,102,107,108,113,117,121,123-128] 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 0.30 point (p for interaction=0.04). 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 (57 trials, N=18,525, mean difference -0.74, 95% CI, -0.87 to -0.61, I^2=71%);[50-60,62-66,69,72,73,76,77,79,81,83-88,90-94,96-98,100-104,107,108,110-114,116,117,120,121,123-126] the difference in pooled estimates was 0.45 point (p for interaction=0.03).

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



Note: Nociceptive pain refers to musculoskeletal conditions

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 200-500 mg (mean 350 mg) 1b: Oxycodone SR 40 to 100 mg (mean 70 mg) 2: Placebo	0 to 10 NRS 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) 1a: Difference -0.27 (95% CI, -0.42 to -0.13) (ANCOVA) 1b: Difference -0.17 (95% CI, -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	0 to 100 VAS 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 post-op pain	1: Fentanyl patch 25 to 50 mcg/hour (mean 18.6 mcg/hour) 2: Placebo	0 to 100 VAS 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	0 to 100 VAS 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	0 to 100 VAS 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	0 to 10 NRS 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	0 to 10 NRS 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 Pain 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	0 to 3 categorical scale, 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) 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 2: Placebo	0 to 10 NRS, 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	0 to 100 VAS, 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	0 to 100 VAS, mean (SD) 1: 48.6 (23.1) 2: 55.9 (25.4)	NR	Pain Disability Index (0 to 70, 70=worse function), mean (SD) 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	0 to 4 NRS, mean (SD) 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), mean (SD) 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	0 to 10 NRS, 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 (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	0 to 100 VAS, mean (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	0 to 10 VAS (McGill Pain Questionnaire), mean (SD) 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)	Brief Pain Inventory general activity (0 to 10), mean (SD) 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	0 to 10 NRS, mean change (SD) 1: -2.6 (0.28) 2: -1.5 (0.29) (ANCOVA)	NR	Brief Pain Inventory Physical function score (0 to 10, 10=worst function), 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	0 to 10 NRS 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	0 to 100 VAS, mean (SD) 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

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)
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	0 to 100 VAS, mean (SD) 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), mean (SD) 1: 2.3 (0.9) 2: 2.4 (1.0)	NR
Hale, 2007[73] USA Fair	1: 12 weeks 2: 143 3: Low back pain	1: Oxymorphone SR (mean 80 mg) 2: Placebo	0 to 100 VAS 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	0 to 10 NRS, mean (SD) 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), mean (SD) 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	0 to 10 NRS 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	0 to 10 NRS, 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	0 to 10 NRS 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)	0 to 10, mean (SD) 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	0 to 10 VAS, mean (SD) 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	0 to 100 VAS 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

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, 2010[79] USA Fair	1: 12 weeks 2: 344 3: Osteoarthritis	1: Morphine SR 20 to 160 mg (mean 43.5 mg) 2: Placebo	0 to 10 NRS, 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
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	0 to 10 NRS 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
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	0 to 10 NRS 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, mean (SD) 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	0 to 100 VAS, mean (SD) 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	0 to 10 NRS, 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	Brief Pain Inventory 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)	Brief Pain Inventory, 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 40-80 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 40-100 mg (mean NR) 2: Placebo	0 to 10 NRS, 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), mean (SD) 1: -1.34 (2.69) 2: -2.99 (2.70)	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)
Moran, 1991[88] UK Poor	1: 5 weeks 2: 20 3: Rheumatoid arthritis	1: CR Morphine 20 to 120 mg (mean NR) 2: Placebo	0 to 100 VAS (followup only), mean (SD) 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), mean (SD) 1: 2.3 (0.6) 2: 2.3 (0.6)	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	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 5-20 mcg/hour (mean NR) 2: Placebo	0 to 10 NRS, 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	0 to 10 NRS, mean (SD) 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	0 to 10 NRS, 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), mean (SD) 1: 145.4 (101.3) 2: 221.3 (118.7)	NR	WOMAC physical function (0 to 1700), mean (SD) 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	0 to 10 NRS, mean (SD) 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	0 to 10 NRS, 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

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, 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	0 to 10 NRS, mean (SD) 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	0 to 10 NRS 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
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	0 to 10 NRS 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 50-400 mg (mean NR) 2: Placebo	0 to 10 VAS, mean (SD) 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), mean (SD) 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 200-400 mg (mean NR) 2: Placebo	0 to 10 VAS, mean (SD) 1: 3.5 (2.79) 2: 5.1 (2.98)	NR	Roland Disability Questionnaire (0 to 24), mean (SD) 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 100-250 mg (mean NR) 2: Placebo	0 to 10 NRS 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 200-500 mg (mean 315 mg) 1b: Oxycodone SR 40-100 mg (mean 54 mg) 2: Placebo	0 to 10 NRS 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 5-40 mcg/hour (mean 20 mcg/hour) 2: Placebo	0 to 10 NRS 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)	Brief Pain Inventory General Activity (0 to 10), mean change (SD) 1: -1.85 (2.96) 2: -1.89 (2.79) (generalized linear mixed model)	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)
Sindrup, 1999[106] Denmark Poor	1: 4 weeks 2: 45 3: Polyneuropathy	1: Tramadol up to 400 mg (mean 364 mg) 2: Placebo	0 to 10 NRS, 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	0 to 10 NRS Difference -1.7 (SE 0.3) (No adjustment)	≥30% improvement in pain intensity 1: 50% (32/64) 2: 17.2% (11/64)	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	0 to 10 NRS 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)	Brief Pain Inventory Interference (0 to 10), mean (SD) 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	0 to 100 VAS, mean (SD) 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), mean (SD) 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	0 to 10 NRS, 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	0 to 10 NRS, 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	0 to 10 NRS 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	0 to 10 NRS, 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

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)
Vinik, 2014[113] USA Fair	1: 12 weeks 2: 318 3: Diabetic neuropathy	1: Tapentadol SR 200-500 mg (mean NR) 2: Placebo	0 to 10 NRS, 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)	Brief Pain Inventory 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	Brief Pain Inventory 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
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	0 to 10 NRS, improved vs. placebo (p=0.008), data not reported	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	0 to 100 VAS, mean (SD) 1: 32.3 (25.2) 2: 40.3 (25.2)	NR	Roland Morris Disability Index (0 to 24), mean (SD) 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	0 to 100 VAS, mean (SD) 1: 35 (25) 2: 54 (25)	NR	0 to 3 categorical scale (3=more disability), mean (SD) 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	0 to 100 VAS, mean (SD) 1: 21.8 (20.7) 2: 48.6 (26.6)	NR	Pain Disability Index (0 to 70, 70=total disability), mean (SD) 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	0 to 10 NRS, mean (SD) 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	0 to 10 NRS 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, Brief Pain Inventory Short Form--no differences, data 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: Placebo	0 to 10 NRS, 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; CI=confidence interval; IR=immediate release; NR=not reported; NRS=numeric rating scale; qd=once a day; RDQ=Roland-Morris Disability Questionnaire; SR=sustained release; UK=United Kingdom; USA=United States of America; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

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	-0.80 (-0.94 to -0.67)	72%	70 (19,486)	--	-0.22 (-0.28 to -0.16)	54%	43 (12,297)	--
Opioid type: Opioid agonist	-0.84 (-1.06 to -0.63)	74%	37 (8375)	0.93	-0.19 (-0.30 to -0.10)	59%	23 (5239)	0.70
Partial agonist	-0.71 (-0.90 to -0.49)	8.6%	8 (2470)	--	-0.25 (-0.46 to -0.03)	70%	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	-0.68 (-0.82 to -0.55)	69%	49 (16,849)	**0.003**	-0.21 (-0.28 to -0.14)	62%	33 (11,189)	0.85
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	-0.84 (-0.97 to -0.71)	69%	64 (17,535)	--‡	-0.38 (-0.44 to -0.32)	68%	34 (9522)	--‡
3 to 6 months	-0.30 (-0.83 to 0.23)	78%	8 (2243)	--	-0.13 (-0.40 to 0.13)	75%	6 (1502)	0.001
Trial quality: Good	-0.64 (-0.84 to -0.45)	0%	5 (1391)	0.88	0.06 (-0.14 to 0.27)	--	1 (382)	0.26
Fair	-0.83 (-0.99 to -0.67)	76%	53 (15,819)	--	-0.23 (-0.30 to -0.17)	56%	37 (10,445)	--
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)	**0.005**	-0.15 (-0.35 to -0.03)	25%	7 (1948)	0.28
50-90	-1.10 (-1.35 to -0.88)	59%	25 (6141)	--	-0.26 (-0.35 to -0.19)	0%	17 (3979)	--
>90	-0.73 (-0.91 to -0.55)	71%	31 (9597)	--	-0.18 (-0.29 to -0.07)	73%	19 (6370)	--
EERW design	-0.88 (-1.07 to -0.71)	64%	23 (7441)	0.28	-0.22 (-0.34 to -0.09)	70%	12 (3904)	0.94
Non-EERW	-0.75 (-0.94 to -0.58)	73%	47 (12,045)	--	-0.21 (-0.28 to -0.15)	33%	31 (8393)	--
EERW, 2007 or after	-0.82 (-1.01 to -0.66)	63%	20 (7048)	**0.04**	-0.22 (-0.37 to -0.07)	76%	10 (3581)	0.48
Non-EERW	-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	-0.74 (-0.87 to -0.61)	71%	57 (18,525)	--	-0.21 (-0.28 to -0.14)	62%	34 (11,457)	--

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†
Opioid status: Naïve	-0.73 (-0.92 to -0.57)	0%	15 (2754)	0.06	-0.26 (-0.50 to 0.02)	66%	6 (1199)	0.52
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%	35 (12,942)	--	-0.18 (-0.25 to -0.12)	39%	27 (8971)	--
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	-0.67 (-0.82 to -0.52)	74%	48 (15,212)	--	-0.18 (-0.27 to -0.10)	67%	26 (8642)	--
Region: USA or Canada	-0.84 (-0.99 to -0.70)	69%	50 (14,643)	0.68	-0.22 (-0.30 to -0.15)	59%	34 (10,191)	0.39
Europe or Australia	-0.82 (-1.27 to -0.44)	80%	14 (3078)	--	-0.15 (-0.27 to -0.05)	0%	8 (1798)	--
Asia	-0.59 (-0.96 to -0.07)	0%	4 (495)	--	No studies	--	--	--
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 (-0.92 to -0.64)	73%	62 (18,696)	0.43	-0.21 (-0.27 to -0.14)	57%	38 (11,927)	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)	--

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

*Negative values indicate improvement in pain or function

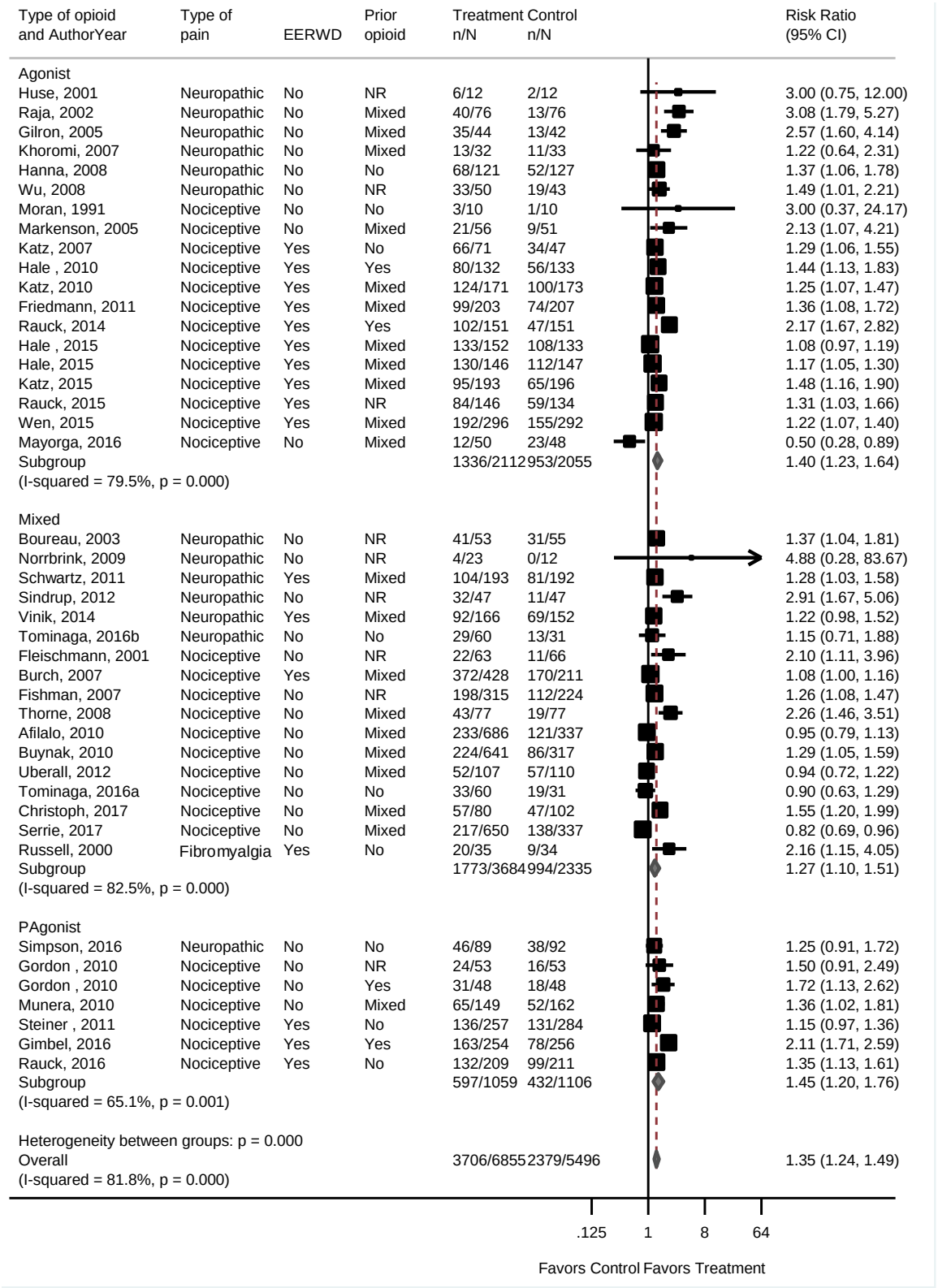
†p value is for interaction

‡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 (43 trials, N=12,351, RR 1.35, 95% CI, 1.24 to 1.49, I^2=82%; 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, three trials used other numerical thresholds (>25%,[78] ≥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 (31 trials, N=10,662, RR 1.29, 95% CI, 1.17 to 1.43, 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 likelihood of experiencing improvement in pain (9 trials, N=870, RR 1.99, 95% CI, 1.60 to 2.52, I^2=25%) than parallel group trials (34 trials, N=11,481, RR 1.27, 95% CI, 1.17 to 1.38, I^2=78%; 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 (35 trials, N=11,656, RR 1.28, 95% CI, 1.18 to 1.40, I^2=80%; p for interaction=0.002), and trials that reported industry funding (38 trials, N=11,920, RR 1.31, 95% CI, 1.21 to 1.44, I^2=80%) 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=0.52), use of an EERW design (p for interaction=0.88), or geographic region (p for interaction=0.17) and effects on likelihood of 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 (43 trials, N=13,022, RR 1.36, 95% CI, 1.24 to 1.50, I^2=81%). Findings were also similar when pain response was defined as 50 percent or more improvement or greater than 5-point improvement on a 0 to 10 scale in pain (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



Note: Nociceptive pain refers to musculoskeletal conditions

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

Analysis	Pain, RR (95% CI)	I^2	Number of trials (N)	p*
All trials[†]	1.35 (1.24 to 1.49)	82%	43 (12,351)	--
Opioid type: Opioid agonist	1.40 (1.23 to 1.64)	80%	19 (4167)	0.49
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)	85%	29 (10,402)	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)	80%	39 (10,946)	--
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)	0.52
Fair	1.36 (1.24 to 1.52)	80%	33 (10414)	--
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)	0.53
50-90	1.50 (1.23 to 1.99)	78%	11 (2324)	--
>90	1.31 (1.17 to 1.47)	82%	26 (8362)	--
EERW design	1.33 (1.21 to 1.48)	80%	17 (6156)	0.88
Non-EERW	1.39 (1.19 to 1.65)	79%	26 (8075)	--
EERW, 2007 or after	1.32 (1.20 to 1.46)	80%	16 (6087)	0.46
Non-EERW	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)	78%	34 (11,481)	--
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 (1.11 to 1.45)	87%	21 (7991)	--
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	1.28 (1.18 to 1.40)	80%	35 (11,656)	--
Region: USA or Canada	1.41 (1.29 to 1.56)	74%	30 (8659)	0.17
Europe or Australia	1.35 (1.01 to 2.02)	79%	9 (1848)	--
Asia	0.98 (0.69 to 1.47)	0%	2 (182)	--
Multiple[‡]	1.06 (0.90 to 1.16)	0%	2 (1662)	--
Industry funding: Yes	1.31 (1.21 to 1.44)	80%	38 (11,920)	**0.03**
No industry funding	1.99 (1.29 to 3.16)	41%	5 (431)	--
Numerical scale	1.29 (1.17 to 1.43)	85%	31 (10,662)	**0.03**
Categorical scale	1.60 (1.39 to 1.95)	18%	12 (311)	--
All trials, missing=non-responder	1.36 (1.24 to 1.50)	81%	43 (13,022)	--
>50% improvement or >5 point improvement on 0 to 10 scale	1.31 (1.18 to 1.47)	70%	26 (9485)	--

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

[‡]USA/Canada and Europe/Australia

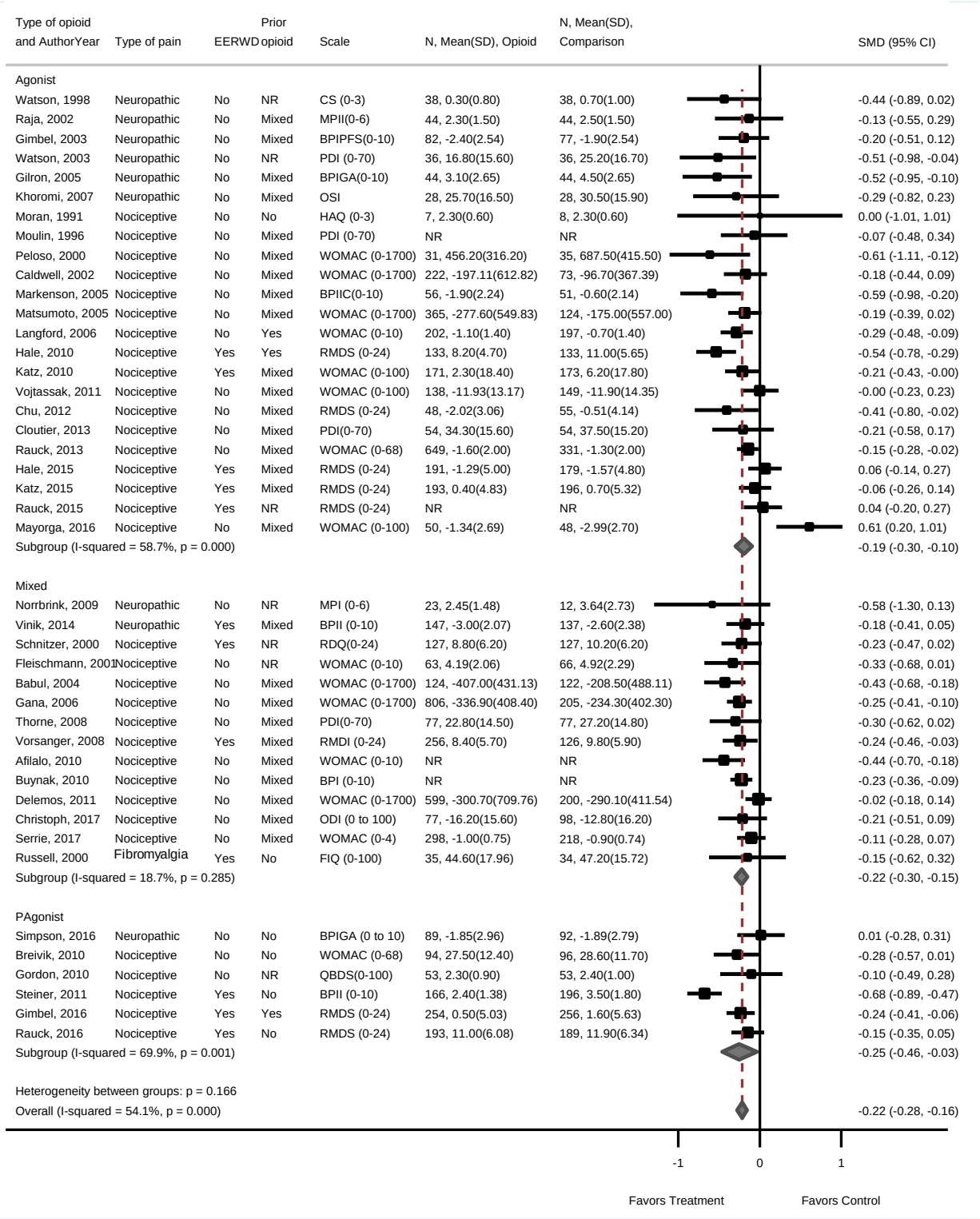
Function

Opioids were associated with a small mean improvement versus placebo in function measured at short-term (1 to <6 months) followup (43 trials, N=12,351, SMD -0.22, 95% CI, -0.28 to -0.16, I^2=54%; **Figure 5, Table 3**). Measures of function varied; the most commonly utilized measures were the BPI (7 trials, N=2146, mean difference -0.72 point on a 0 to 10 scale, 95% CI, -1.08 to -0.36, I^2=46%),[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 RDQ for low back pain (9 trials, N=2948, mean difference -0.92 point on a 0 to 24 scale, 95% CI, -1.61 to -0.28, I^2=60%).[60,68,72,75,80,97,99,101,117] There were no interactions between trial quality (p for interaction=0.26), use of an EERW design (p for interaction=0.94 overall and 0.48 when restricted to trials published in or after 2007), geographic setting (p for interaction=0.39), publication before or after 2007 (p for interaction=0.09), use of crossover design (p for interaction=0.48), or receipt of 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 Roland-Morris Disability Questionnaire 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



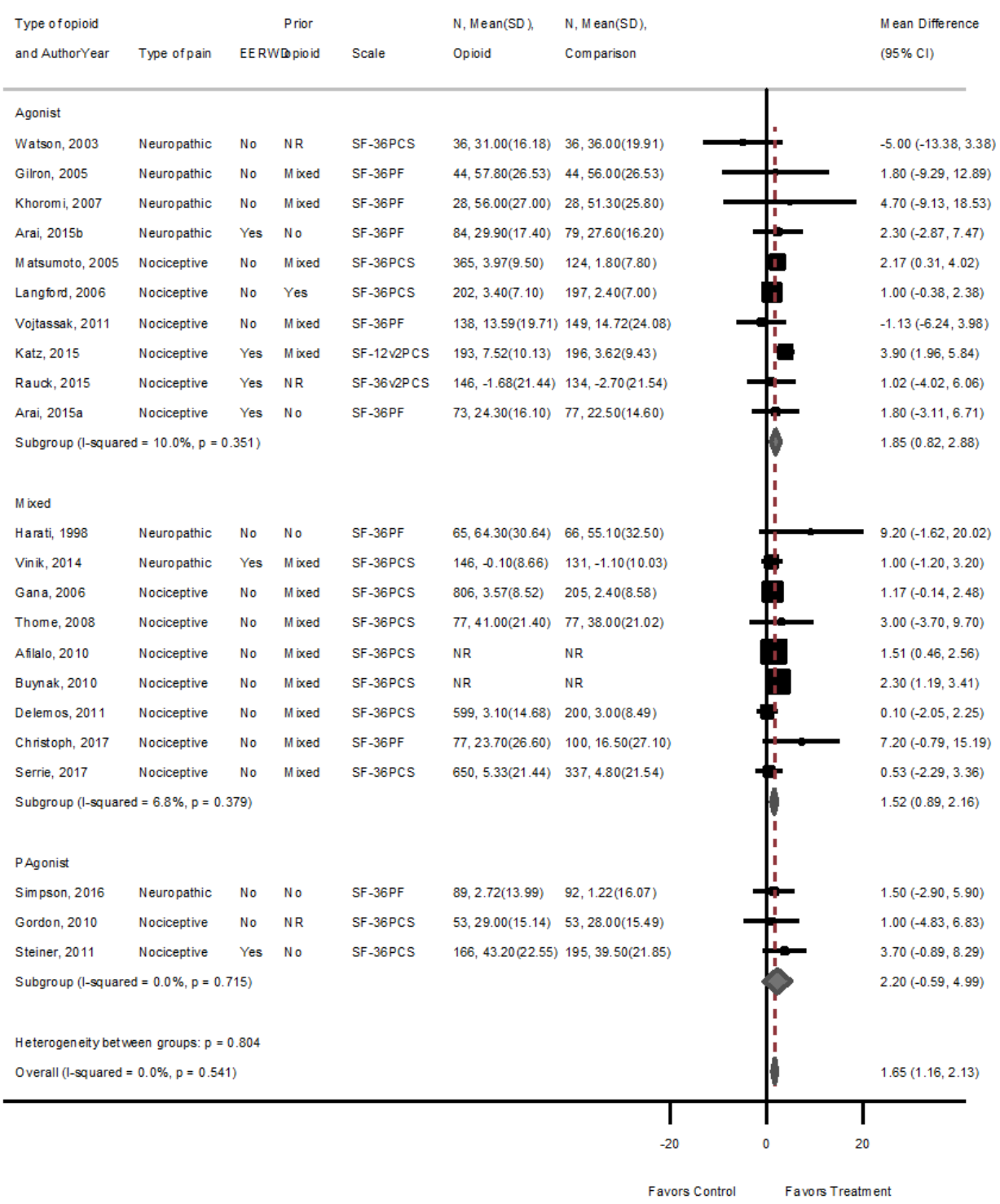
Note: Nociceptive pain refers to musculoskeletal conditions

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 (Physical Component Summary or Physical Function Subscale) at short-term (1 to <6 months) followup (22 trials, N=7875, mean difference 1.65 points, 95% CI, 1.09 to 2.18, 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] There was no difference between opioids versus placebo on SF-36 measures of mental health status (Mental Component Summary, Mental Health Subscale, or Role Emotional Subscale) (20 trials, N=7456, mean difference -0.52 point on a 0 to 100 scale, 95% CI, -1.45 to 0.41, I^2=64%).[50,51,56,59,62,66,67,71,80,82,83,86,97,103,104,107-109,113,119] 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 receipt of 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 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-3L.[111]

Figure 6. Meta-analysis of improvement in mean SF-36 PCS subscale for opioids versus placebo



Note: Nociceptive pain refers to musculoskeletal conditions

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 post-operative 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 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	Beck Depression Inventory (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)	Brief Pain Inventory, sleep (0 to 10, 10=pain completely interferes) 1: 1.6 (0.4) 2: 3.4 (0.4)	Beck Depression Inventory (0 to 63, 63=more severe depression) 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 (SD 0.24) 2: -0.5 (SD 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, total (0 to 500, 500=worse sleep) 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 (0 to 100, higher=better) 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)	Beck Depression Inventory (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
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	Beck Depression Inventory 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	Brief Pain Inventory, sleep (0 to 10, 10=pain completely interferes) 1: -2.8 (0.4) 2: -0.9 (0.4) (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	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

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*
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
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)	Beck Depression Inventory (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

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*
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
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)	Beck Depression Inventory-II total score (0 to 63) 1: -1.79 (7.64) 2: -3.93 (6.01) (generalized linear mixed)

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*
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
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

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*
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
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=Becky Depression Scale; 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 Analogue 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	1.65 (1.09 to 2.18)	0%	22 (7875)	--	-0.52 (-1.45 to 0.41)	64%	20 (7456)	--
Opioid type: Opioid agonist	1.84 (0.35 to 3.07)	10%	10 (2373)	0.79	-1.90 (-2.93 to -0.70)	0%	9 (2086)	0.14
Partial agonist	2.20 (-0.82 to 5.13)	0%	3 (648)	--	0.23 (-4.91 to 4.61)	71%	3 (648)	--
Mixed mechanism	1.54 (0.82 to 2.15)	6.8%	9 (4854)	--	-0.01 (-1.12 to 1.26)	73%	8 (4722)	--
Pain type: Musculoskeletal	1.68 (1.07 to 2.29)	5.4%	15 (6907)	0.67	-0.70 (-1.57 to 0.22)	62%	14 (6619)	0.48
Neuropathic	1.26 (-0.53 to 3.29)	0%	7 (968)	--	-0.15 (-3.48 to 2.74)	63%	6 (837)	--
Fibromyalgia	No studies	--	--	--	No studies	--	--	--
Followup: 1 to 3 months	1.66 (1.09 to 2.22)	0%	20 (6711)	--	-0.50 (-1.52 to 0.49)	66%	18 (6293)	--
3 to 6 months	2.78 (-3.40 to 8.95)	58%	2 (1164)	--	-1.04 (-3.47 to 3.18)	0%	2 (1163)	--
Trial quality: Good	No studies	--	--	0.83	No studies	--	--	--
Fair	1.64 (1.06 to 2.19)	3.2%	20 (7562)	--	-0.51 (-1.54 (0.52)	67%	18 (7143)	0.96
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 2.35)	0%	6 (1618)	0.24	-0.20 (-0.40 to 0.00)	0%	4 (1200)	0.80
50-90	1.03 (-0.13 to 2.18)	0%	5 (2280)	--	0.29 (-2.97 to 2.02)	42%	4 (1293)	--
>90	1.90 (1.34 to 2.46)	0%	11 (3977)	--	-0.76 (-2.07 to 0.56)	73%	12 (4963)	--
EERW design	2.48 (0.73 to 4.06)	0%	6 (1620)	0.15	0.19 (-2.10 to 2.42)	78%%	6 (1620)	0.27
Non-EERW	1.49 (0.89 to 2.02)	0%	16 (6255)	--	-0.78 (-1.64 to -0.16)	51%	14 (5836)	--
EERW, 2007 or after	2.48 (0.73 to 4.06)	12.5%	6 (1620)	0.26	0.19 (-2.10 to 2.42)	78%	6 (1620)	0.40
Non-EERW	1.61 (0.60 to 2.32)	0%	10 (4065)	--	-0.70 (-1.67 to 0.20)	46%	9 (3777)	--
Crossover design	0.81 (-3.00 to 4.55)	0%	5 (476)	0.65	-0.13 (-3.80 to 3.54)	40%	5 (476)	0.77
Parallel group	1.66 (1.11 to 2.22)	5.2%	17 (7399)	--	-0.56 (-1.55 to 0.41)	69%	15 (6980)	--
Opioid status: Naïve	2.64 (0.32 to 5.02)	0%	5 (986)	0.52	0.13 (-3.15 to 2.94)	62%	4 (855)	0.62
Experienced	1.00 (-0.38 to 2.38)	--	1 (399)	--	-2.00 (-6.73 to 2.73)	--	1 (399)	--
Mixed	1.73 (1.03 to 2.38)	11%	13 (6032)	--	-0.38 (-1.49 to 0.84)	71%	12 (5744)	--
Not reported	-0.02 (-4.52 to 3.61)	0%	3 (458)	--	-1.82 (-5.13 to 0.99)	0%	3 (458)	--
Publication: Prior to 2007	1.82 (1.01 to 2.55)	5.4%	6 (2190)	0.35	-1.05 (-3.24 to 0.90)	62%	5 (2059)	0.46
In or after 2007	1.30 (0.43 to 2.25)	0%	16 (5685)	--	-0.32 (-1.42 to 0.79)	66%	15 (5397)	--
Region: USA or Canada	1.87 (0.99 to 2.72)	11%	14 (4850)	0.70	-0.04 (-1.35 to 1.24)	66%	13 (4719)	0.48
Europe or Australia	0.98 (-0.29 to 2.30)	0%	5 (2031)	--	-1.61 (-3.10 to -0.09)	0%	4 (1743)	--
Asia	2.04 (-2.04 to 6.13)	0%	2 (313)	--	-0.59 (-3.27 to 2.08)	0%	2 (313)	--
Multiple‡	1.51 (-0.70 to 3.72)	--	1 (681)	--	-2.08 (-4.49 to 0.34)	--	1 (681)	--
Industry funding: Yes	1.64 (1.08 to 2.18)	2.6%	20 (7731)	0.77	-0.58 (-1.53 to 0.34)	66%	18 (7312)	0.30
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; MD = mean difference; N=total sample size

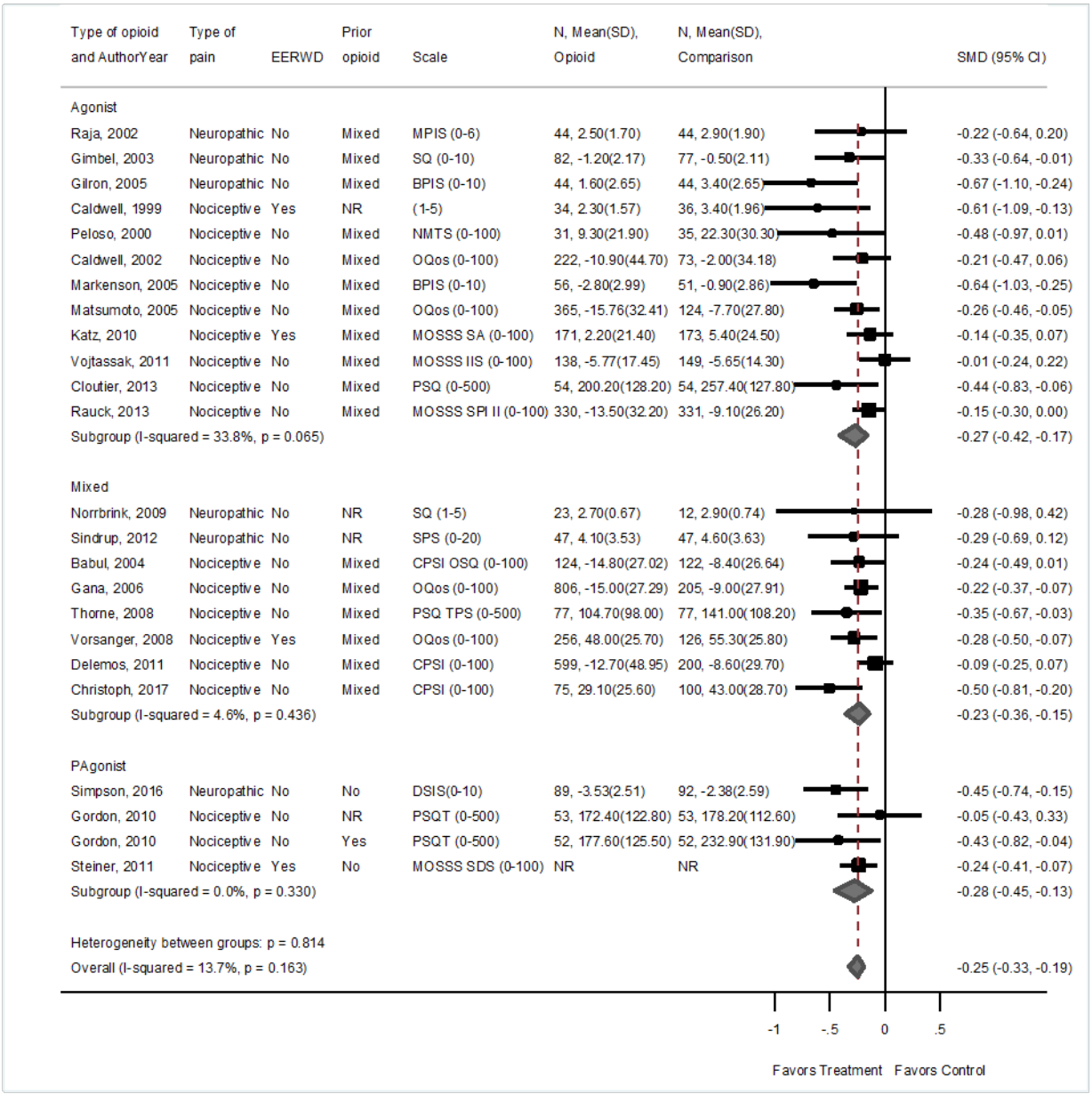
*Positive results indicate improved health status

[†]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 (24 trials, N=6590, SMD -0.25, 95% CI, -0.33 to -0.19, I^2=0%; **Figure 7, Table 6**).[52,57-59,61,62,66,67,69-71,79,85,86,93-96,104,105,107-109,114,117] 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] and 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] There were no interactions between trial quality (p for interaction=0.30), use of an EERW design (p for interaction=0.92), publication prior to or after 2007 (p for interaction=0.18), geographic region (p for interaction=0.78), use of a crossover design (p for interaction=0.21), or receipt of industry funding (p for interaction=0.28) 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



Note: Nociceptive pain refers to musculoskeletal conditions

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 (-0.33 to -0.19)	0%	24 (6590)	--	0.00 (-0.22 to 0.18)	40%	8 (1079)	--
Opioid type: Opioid agonist	-0.27 (-0.42 to -0.17)	34%	12 (2762)	0.93	-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)	0.3%	18 (5945)	0.10	-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 (-0.33 to -0.19)	0%	24 (6590)	--	-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	--	--	0.30	No studies	--	--	--
Fair	-0.26 (-0.34 to -0.20)	16%	23 (5929)	--	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)	0.15	-0.03 (-0.30 to 0.31)	0%	2 (538)	0.13
50-90	-0.26 (-0.38 to -0.19)	0%	11 (3027)	--	-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 (-0.38 to -0.13)	0%	4 (1337)	0.92	-0.12 (-0.33 to 0.09)	--	1 (344)	0.67
Non-EERW	-0.26 (-0.36 to -0.19)	26%	20 (5253)	--	0.02 (-0.26 to 0.23)	41%	7 (735)	--
EERW, 2007 or after	-0.22 (-0.34 to -0.10)	0%	3 (1267)	0.92	-0.12 (-0.33 to 0.09)	--	1 (181)	0.73
Non-EERW	-0.24 (-0.38 to -0.13)	38%	11 (2704)	--	0.03 (-0.35 to 0.29)	41%	5 (559)	--
Crossover design	-0.34 (-0.50 to -0.19)	0%	7 (742)	0.21	-0.05 (-0.33 to 0.24)	5.8%	4 (325)	0.80
Parallel group	-0.23 (-0.31 to -0.17)	5.9%	17 (5848)	--	0.02 (-0.42 to 0.33)	55%	4 (754)	--
Opioid status: Naïve	-0.29 (-0.57 to -0.10)	0%	2 (722)	0.80	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	-0.24 (-0.33 to -0.17)	15%	17 (5459)	--	-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)	0.18	0.00 (-0.64 to 0.63)	34%	2 (176)	0.96
In or after 2007	-0.22 (-0.32 to -0.15)	17%	14 (3971)	--	0.00 (-0.28 to 0.21)	42%	6 (903)	--
Region: USA or Canada	-0.24 (-0.31 to -0.18)	0%	19 (5818)	0.78	-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	No studies	--	--	--	No studies	--	--	--
Multiple‡	No studies	--	--	--	No studies	--	--	--
Industry funding: Yes	-0.24 (-0.32 to -0.18)	8.4%	21 (6379)	0.28	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; SMD= standardized mean difference; EERW=enriched enrollment randomized withdrawal; N= total sample size

*Negative results indicate improved sleep or depression

†p value for interaction

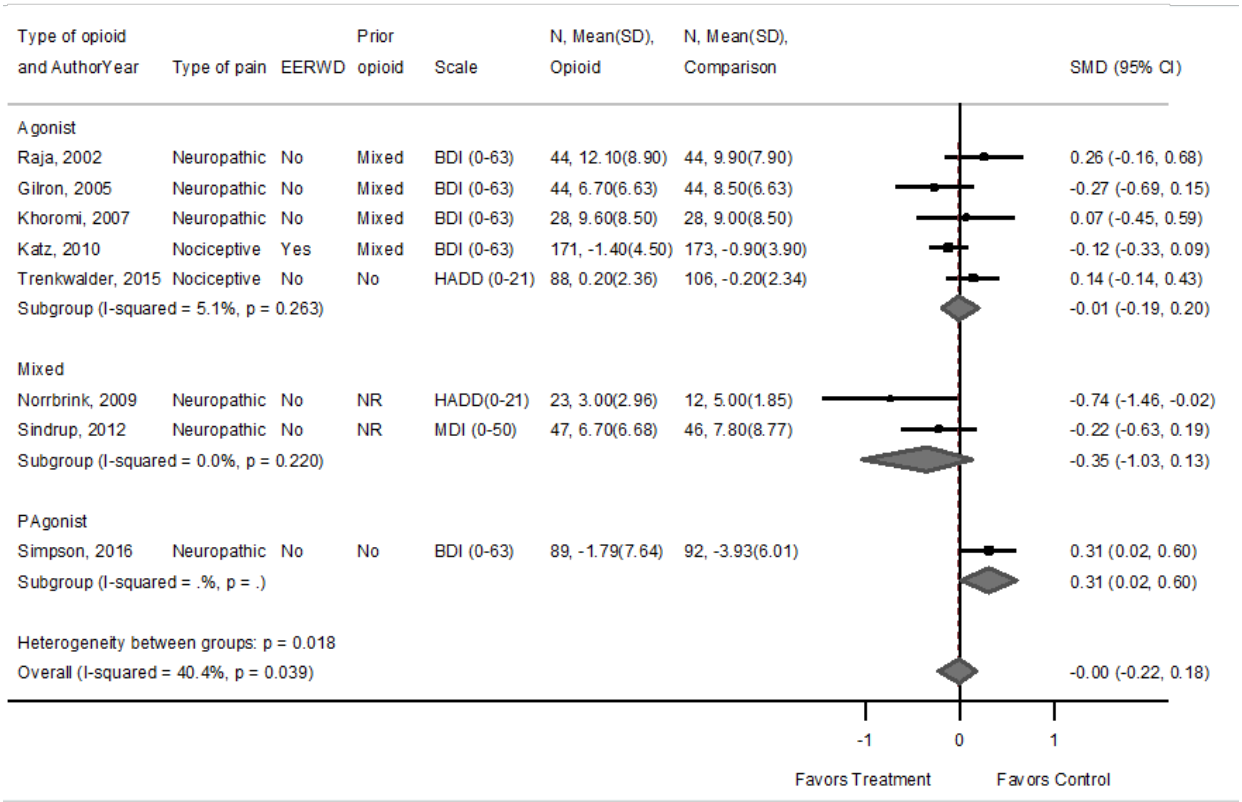
‡USA/Canada and Europe/Australia

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 0.08 point on a 0 to 21 scale, 95% CI, -3.87 to 2.26, 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=0.73), geographic region (p for interaction=0.87), use of a crossover design (p for interaction=0.80), or receipt of 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 measures of depression for opioids versus placebo



Note: Nociceptive pain refers to musculoskeletal conditions

Intermediate (6 to <12 month) 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 versus propensity score-matched patients not prescribed opioids (**Appendix Tables H-1 and H-2**).[129] 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.

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 point on a 0 to 10 scale (p for interaction=0.003) (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 (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 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 (24 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 (49 trials, N=16,849, mean difference -0.68 point, 95% CI, -0.82 to -0.55, I^2=69%),[50-52,54-66,68,70-75,79-81,83-88,90,91,94,96-99,101,103,107-112,114,116,117,120,121,123-128] with a difference of about 0.5 point (p for interaction=0.003). 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).[66,80,102,116,121,127] 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-seven placebo-controlled trials evaluated an 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 9 trials. There were no interactions between type of opioid (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).[50,56,103,130-134] 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 percent to 23 percent, for constipation from 10 percent to 18 percent, for nausea from -4 percent to 17 percent, and for vomiting from 6 percent 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.[135-137] Two trials (N=415) found no differences between transdermal buprenorphine versus sustained-release tramadol in mean improvement in pain or sleep.[135,136] 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.[137]

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 (12 trials, N=1879, mean difference -0.18 on a 0 to 10 scale, 95% CI, -0.52 to 0.14, I^2=53%) or likelihood of a pain response (11 trials, N=2646, RR 1.06, 95% CI, 0.88 to 1.32, I^2=75%) at short-term followup (SOE: moderate).
- There were no differences between opioids versus nonopioids in mean improvement in function at short-term followup (9 trials, N=1694, SMD 0.05, 95% CI, -0.10 to 0.17, I^2=12%) (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 -0.1[2], I2=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 (6 trials, N=1454, SMD 0.01, 95% CI, -0.14 to 0.12, I^2=0%), anxiety (3 trials, N=414, SMD 0.00, 95% CI, -0.62 to 0.36, I^2=0%), 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

Fourteen trials compared opioids versus nonopioids for chronic pain (**Table 9**).[62,67,82,95,122,138-145] Sample sizes ranged from 28 to 809 (total N=3348). None of the trials was included in the prior 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[142] (published subsequent to the prior AHRQ report). In the trials that were less than 6 months in duration, nine trials followed patients for less than 3 months and two trials followed patients for 3 to 6 months. The nonopioid was an non-steroidal anti-inflammatory drug (NSAID) in six trials, an antiemetic in one trial,[122] an antiarrhythmic drug in one trial,[139]and an antidepressant in three trials.[82,95,140] The opioid type was a pure opioid agonist in seven trials and mixed agent (tramadol or tapentadol) in five trials. The mean opioid dose ranged from 14 to 112 mg MED/day. The pain type was neuropathic in five trials and musculoskeletal in seven 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 on a scale of 10 to 70.8 on a 0 to 100 scale. Seven trials did not report whether they enrolled patients with a history of mental health comorbidities and the other seven excluded patients with mental health comorbidites or those with serious mental health comorbidities;[62,67,82,95,122,139,141] all trials excluded patients with a history of opioid or substance use disorder or active substance use disorder. One trial[142] excluded patients receiving daily or near-daily opioids, eight trials enrolled mixed populations of opioid-naïve and experienced patients, five trials did not describe prior opioid experience, and no trial restricted the sample to opioid-experienced patients. All trials were conducted in the United States, Canada, or Europe.

One trial[142] was rated good-quality, 12 trials fair-quality, and one trial[141] 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. Six trials used a crossover design and none used an EERW; the remainder used a parallel group non-EERW randomized trial design. All trials except for four[82,95,122,142] 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[138] 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[139] UK Fair	96	1: No 2: Yes 3: Yes	1: Neuropathic pain 2: 76.4 3: Mixed 4: 69.6 (0 to 100 VAS)	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)
Gilron, 2015[140] Canada Fair	52	1: No 2: Yes 3: Yes	1: Peripheral neuropathic pain 2: 73.2 3: Mixed 4: 5.3 (0 to 10 NRS)	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 (SD 5)	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)
Jamison, 1998[141] USA Poor	36	1: No 2: No 3: Yes	1: Back pain 2: 79.1 3: NR 4: 1a -67.2 (0 to 100 VAS) 1b -70.8 (0 to 100 VAS)	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 (0 to 10 NRS)	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)

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
Krebs, 2018[142] 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)	Age: 58.2 Female: 13% White: 86%	Mixed opioids Stepped therapy (mean 21 mg); 21 mg MED 52 weeks	Nonopioids, stepped therapy, tramadol at 3rd step (mean 1 mg)
O'Donnell, 2009a[143] 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; 40 mg MED 6 weeks	Celecoxib 400 mg
O'Donnell, 2009b[143] 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; 40 mg MED 6 weeks	Celecoxib 400 mg
Pavelka, 1998[144] Czech Republic and Germany Fair	60	1: No 2: Yes 3: Yes	1: Osteoarthritis 2: NR 3: NR 4: NR	Age: NR (range 44-85) 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 (0 to 10 NRS)	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[145] 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 9 mg; 42 mg MED 13 weeks	Ketamine 90 mg
Wu, 2008[122] USA Fair	60	1: No 2: Yes 3: No	1: Postamputation pain 2: 51.3 3: NR 4: 6.7 (0 to 10 NRS)	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)

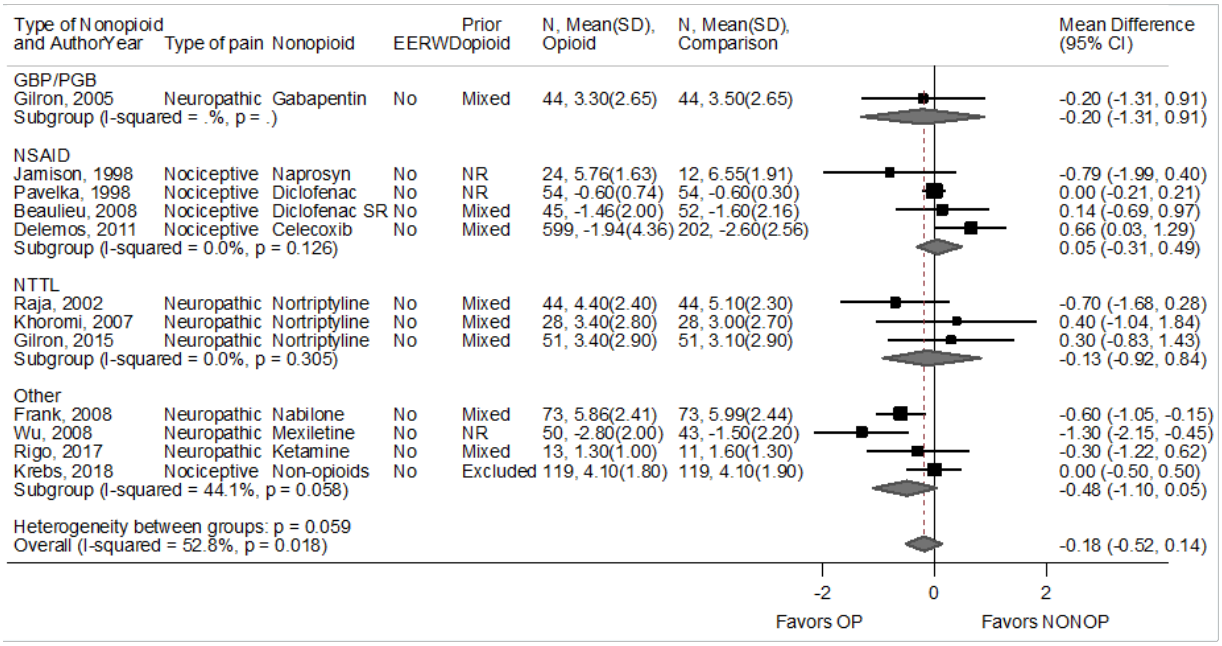
Abbreviations: BPI=Brief Pain Inventory; IR=immediate release; MED=morphine equivalent dose; NR=not reported; NRS=Numeric Rating Scale; SD=sustained release; SR=sustained release; VAS=Visual Analogue Scale; WOMAC=The Western Ontario and McMaster Universities Osteoarthritis Index

Detailed Synthesis

Short-Term (1 to <6 month) Outcomes

There was no difference between opioids versus nonopioids in mean improvement in pain at short-term followup (12 trials, N=1879, mean difference -0.18 on a 0 to 10 scale, 95% CI, -0.52 to 0.14, I^2=53%; **Figure 9, Table 10**).[62,67,82,95,122,138-142,144,145] There was no interaction between the type of nonopioid and effects on mean pain intensity (p for interaction=0.44). For NSAIDs (4 trials, N=1042), the mean difference was 0.05 (95% CI, -0.31 to 0.49, I^2=0%) and for nortriptyline (3 trials, N=246), the mean difference was -0.13 (95% CI, -0.92 to 0.84, 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 (7 trials, N=597, mean difference -0.52, 95% CI, -0.84 to -0.06, 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 0.56 point (p for interaction=0.02). 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



Note: Nociceptive pain refers to musculoskeletal condition

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[138] 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 0-500 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	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[139] 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)	0 to 100 VAS 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
Gilron, 2015[140] 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)	0 to 10 NRS 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)	0 to 10 VAS (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)	
Jamison, 1998[141] USA Poor	1: 16 weeks 2: 36 3: Back pain	1: Oxycodone IR 5 to 20 mg 2: Naproxen up to 100 mg (mean NR)	0 to 100 VAS 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
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)	0 to 10 NRS 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 1: 25.7 (16.5) 2: 27.5 (16.7)	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)
Krebs, 2018[142] 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 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[143] USA Fair	1: 6 weeks 2: 796 3: Low back pain	1: Tramadol IR 200 mg 2: Celecoxib 400 mg	NR	≥30% improvement in pain intensity 1: 50% (194/389) 2: 63% (254/402)	NR	NR
O'Donnell, 2009b[143] USA Fair	1: 6 weeks 2: 802 3: Low back pain	1: Tramadol IR 200 mg 2: Celecoxib 400 mg	NR	≥30% improvement in pain intensity 1: 55% (218/396) 2: 64% (254/396)	NR	NR
Pavelka, 1998[144] 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)	0 to 10 NRS 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[145] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic	1: Methadone 9 mg 2: Ketamine 90 mg	0 to 10 VAS 1: 13 (1.3) 2: 1.6 (1.3)	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)	0 to 10 NRS 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; CR=controlled release; IR=immediate release; NR=not reported; NRS=numeric rating scale; SR=sustained release; UK=United Kingdom; USA=United States of America; WOMAC=Western Ontario and McMaster Universities Osteoarthritis Index

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	-0.18 (-0.52 to 0.14)	53%	12 (1877)	--	0.05 (-0.10 to 0.17)	12%	9 (1614)	--
Nonopioid: Gabapentinoid	-0.20 (-1.31 to 0.91)	--	1 (88)	0.44	0.04 (-0.38 to 0.46)	--	1 (88)	0.62
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)	53%	4 (501)		-0.09 (-0.34 to 0.17)	--	1 (238)	--
Pain type: Other/mixed	0.04 (-0.18 to 0.34)	0%	5 (1280)	0.02	0.06 (-0.15 to 0.22)	20%	5 (1280)	0.69
Neuropathic	-0.52 (-0.84 to -0.06)	0%	7 (597)	--	0.00 (-0.22 to 0.22)	0%	4 (334)	--
Trial quality: Good	0.00 (-0.50 to 0.50)	--	1 (238)	0.68	-0.09 (-0.34 to 0.17)	--	1 (238)	0.64
Fair	-0.17 (-0.56 to 0.21)	58%	10 (1603)	--	0.10 (-0.10 to 0.21)	1.8%	7 (1340)	--
Poor	-0.79 (-1.99 to 0.40)	--	1 (36)	--	0.04 (-0.66 to 0.73)	--	1 (36)	--
Opioid dose (mg MED/day): <50	-0.11 (-0.49 to 0.24)	47%	7 (1441)	0.08	0.06 (-0.16 to 0.22)	21%	5 (1271)	0.77
50-90	0.23 (-0.39 to 0.89)	0%	3 (255)	--	0.06 (-0.21 to 0.31)	0%	3 (255)	--
>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)	0.23	-0.03 (-0.22 to 0.16)	0%	5 (442)	0.37
Parallel group	0.09 (-0.43 to 0.48)	6.5%	5 (1196)	--	0.09 (-0.14 to 0.27)	14%	4 (1172)	
Opioid status: Naïve	0.00 (-0.50 to 0.50)	--	1 (238)	0.52	-0.09 (-0.34 to 0.17)	--	1 (238)	0.32
Experienced	No studies	--	--	--	No studies	--	--	--
Mixed	-0.08 (-0.50 to 0.36)	40%	8 (1402)	--	0.12 (-0.07 to 0.24)	0%	6 (1232)	--
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)	0.64	-0.06 (-0.28 to 0.16)	0%	4 (334)	0.31
In or after 2007	-0.13 (-0.59 to 0.36)	59%	8 (1557)	--	0.09 (-0.10 to 0.23)	11%	5 (1292)	--
Industry funding: Yes	-0.04 (-0.49 to 0.42)	56%	6 (1290)	0.32	0.14 (-0.06 to 0.26)	0%	5 (470)	0.11
No industry funding	-0.37 (-0.89 to 0.13)	29%	6 (587)	--	-0.07 (-0.26 to 0.11)	0%	4 (1144)	--

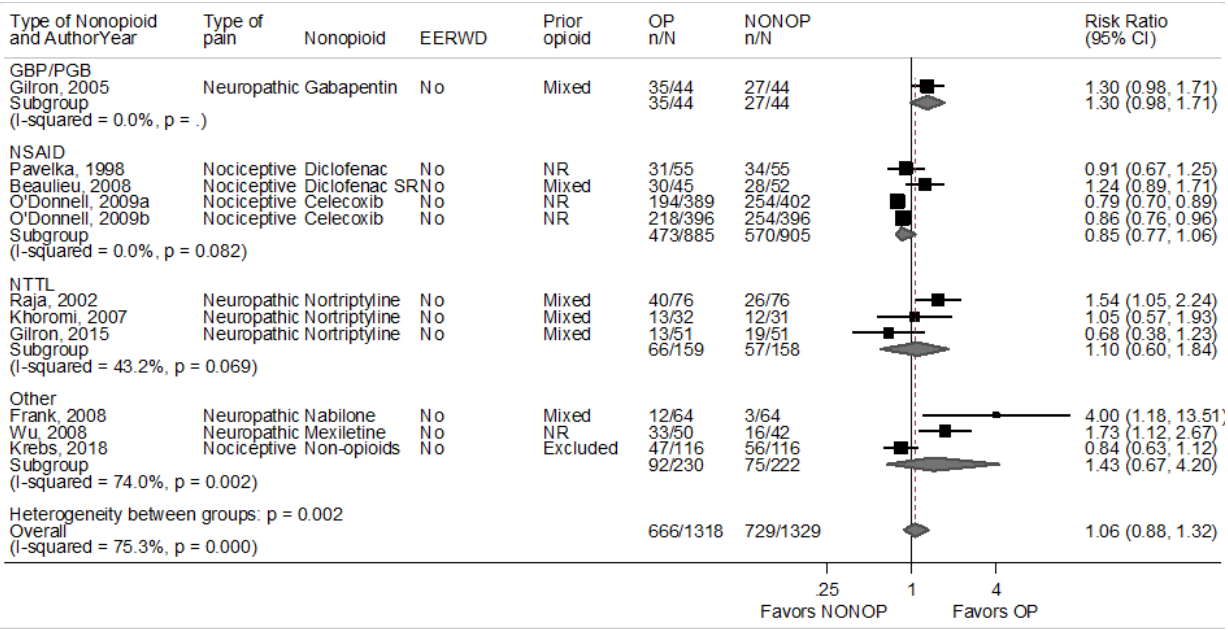
Abbreviations: CI=confidence interval; MD = mean difference; MED=morphine equivalent dose; N=total sample size; NSAIDs=non-steroidal anti-inflammatory drugs; SMD=standard mean difference

*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 (11 trials, N=2646, RR 1.06, 95% CI, 0.88 to 1.32, I^2=75%; **Figure 10, Table 10**).[67,82,95,122,138-140,142-144] There was no interaction between nonopioid type or other factors and likelihood of pain response (**Table 12**).

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



Note: Nociceptive pain refers to musculoskeletal condition

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

Analysis	Pain, RR (95% CI)	I^2	Number of trials (N)	p*
Opioid vs. nonopioid				
All trials[†]	1.06 (0.88 to 1.32)	75%	11 (2647)	--
Nonopioid type: NSAID	0.85 (0.77 to 1.06)	0%	4 (1790)	0.64
Gabapentinoid	1.30 (0.98 to 1.71)	--	1 (88)	--
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	1.21 (0.91 to 1.70)	57%	7 (857)	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)	0.47
Fair	1.09 (0.89 to 1.39)	77%	10 (2415)	--
Poor	No studies	--	--	--
Opioid dose (mg MED/day): <50	0.91 (0.79 to 1.18)	57%	6 (2141)	0.12
50-90	1.07 (0.66 to 1.47)	0%	3 (262)	--
>90	1.62 (1.16 to 2.28)	0%	2 (244)	--
Crossover design	1.23 (0.94 to 1.68)	47%	7 (735)	0.10
Parallel group	0.85 (0.77 to 1.03)	0%	4 (1912)	--
All trials, missing=nonresponder	1.06 (0.87 to 1.35)	77%	11 (3097)	--
Opioid plus nonopioid vs. nonopioid				
All trials	1.15 (0.83 to 1.54)	0%	3 (462)	--

Analysis	Pain, RR (95% CI)	I^2	Number of trials (N)	p*
Nonopioid type: Gabapentinoid	1.09 (0.72 to 1.61)	17%	2 (147)	0.27
Nortriptyline	1.52 (1.03 to 2.28)	0%	2 (161)	--
Acetaminophen	0.58 (0.28 to 1.19)	--	1 (154)	--
Opioid dose (mg MED/day): <50	1.09 (0.71 to 1.57)	38%	4 (360)	0.58
50-90	1.42 (0.91 to 2.21)	--	1 (102)	--
Opioid plus nonopioid vs. opioid				
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)	--
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)	--

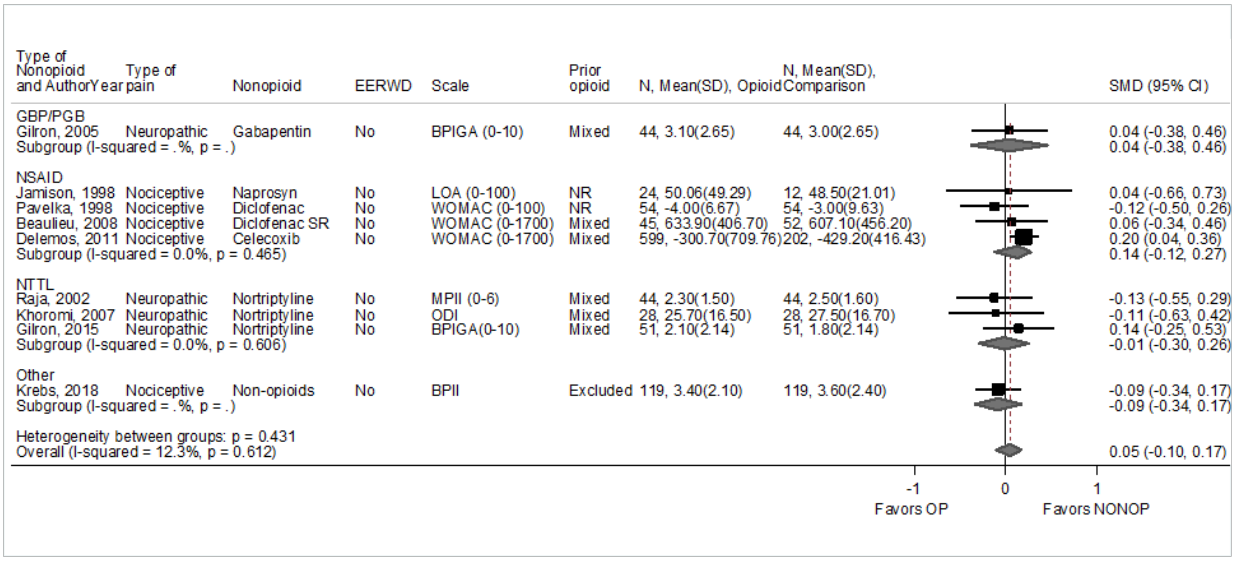
Abbreviations: CI=confidence interval; RR=risk ratio; N=number of trials; NSAID=nonsteroidal anti-inflammatory drug; MED=morphine equivalent dose

*p value for interaction

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

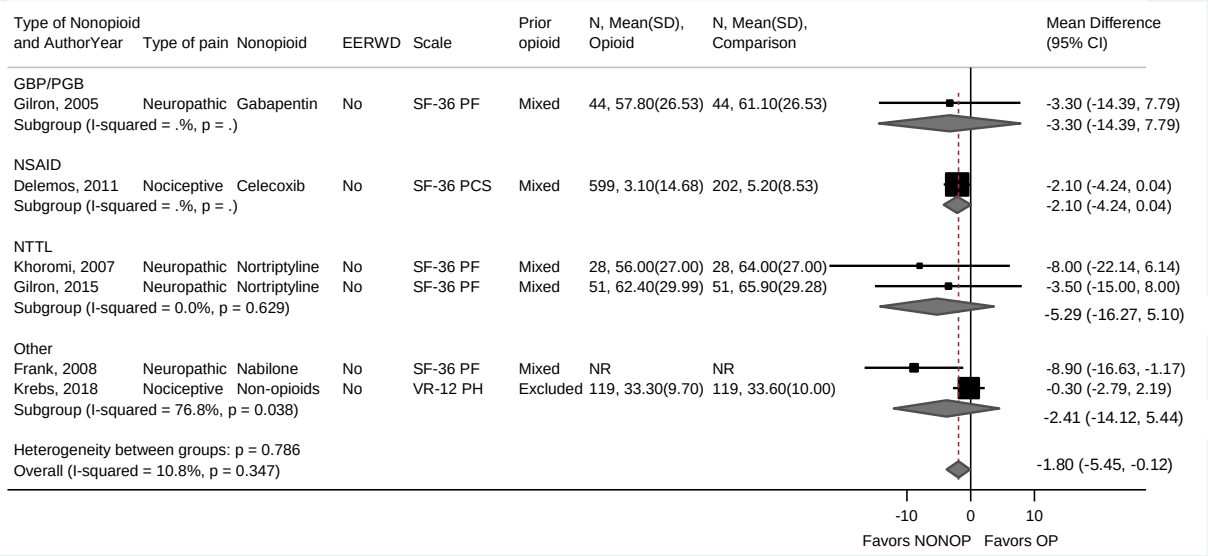
There were no differences between opioids versus nonopioids in mean improvement in function at short-term followup (9 trials, N=1694, SMD 0.05, 95% CI, -0.10 to 0.17, I^2=12%; **Figure 11, Table 10**).[62,67,82,95,138,140-142,144] Opioids were associated with greater improvement than nonopioids in SF-36 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**).[62,67,82,139,140,142] 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**),[62,67,82,139,140,142] sleep (6 trials, N=1454, SMD 0.01, 95% CI, -0.14 to 0.12, I^2=0%; **Figure 14, Table 13**),[62,67,95,138,139,142] anxiety (3 trials, N=414, SMD 0.00, 95% CI, -0.62 to 0.36, I^2=9%; **Figure 15, Table 13**),[139,141,142] or depression (7 trials, N=748, SMD 0.05, 95%% CI, -0.09 to 0.22, I^2=0%; **Figure 16, Table 13**).[67,82,95,139-142] 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



Note: Nociceptive pain refers to musculoskeletal condition

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



Note: Nociceptive pain refers to musculoskeletal condition

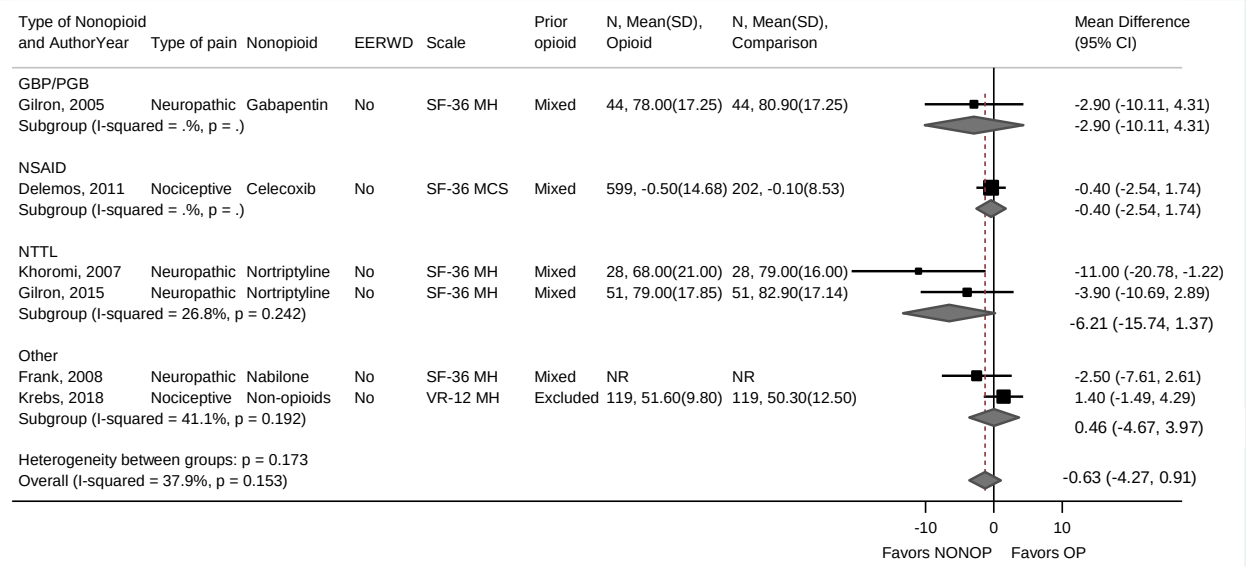
Table 13. Quality of life, sleep, and mental health outcomes for opioids versus nonopioids

Study, year	1: Duration of followup 2: Total patients randomized 3: Pain condition	1: Opioid 2: Control	Quality of life*	Sleep*	Mental Health Outcomes*
Beaulieu, 2008 [138] 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	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), mean (SD) 1: Change -12.7 (2.0) 2: Change -16.4 (2.1) (ANCOVA)	NR
Frank, 2008 [139] 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)
Gilron, 2015 [140] 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	Beck Depression Inventory 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)	Brief Pain Inventory, sleep (0 to 10, 10=pain completely interferes) 1: 1.6 (0.4) 2: 1.5 (0.4)	NR
Jamison, 1998[141] 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	Beck Depression Inventory 1: 9.6 (8.5) 2: 7.3 (7.1)

Study, year	1: Duration of followup 2: Total patients randomized 3: Pain condition	1: Opioid 2: Control	Quality of life*	Sleep*	Mental Health Outcomes*
Krebs, 2018 [146] 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[143] USA Fair	1: 6 weeks 2: 796 3: Low back pain	1: Tramadol IR 200 mg 2: Celecoxib 400 mg	NR	NR	NR
O'Donnell, 2009b[143] USA Fair	1: 6 weeks 2: 802 3: Low back pain	1: Tramadol IR 200 mg 2: Celecoxib 400 mg	NR	NR	NR
Pavelka, 1998[144] 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)	Beck Depression Inventory (0 to 63) 1: 12.1 (8.9) 2: 10.0 (7.6)
Rigo, 2017 [145] 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 30-180 mg (mean 112 mg) 2: Mexiletine 150-1200 mg (mean 933 mg)	NR	NR	NR

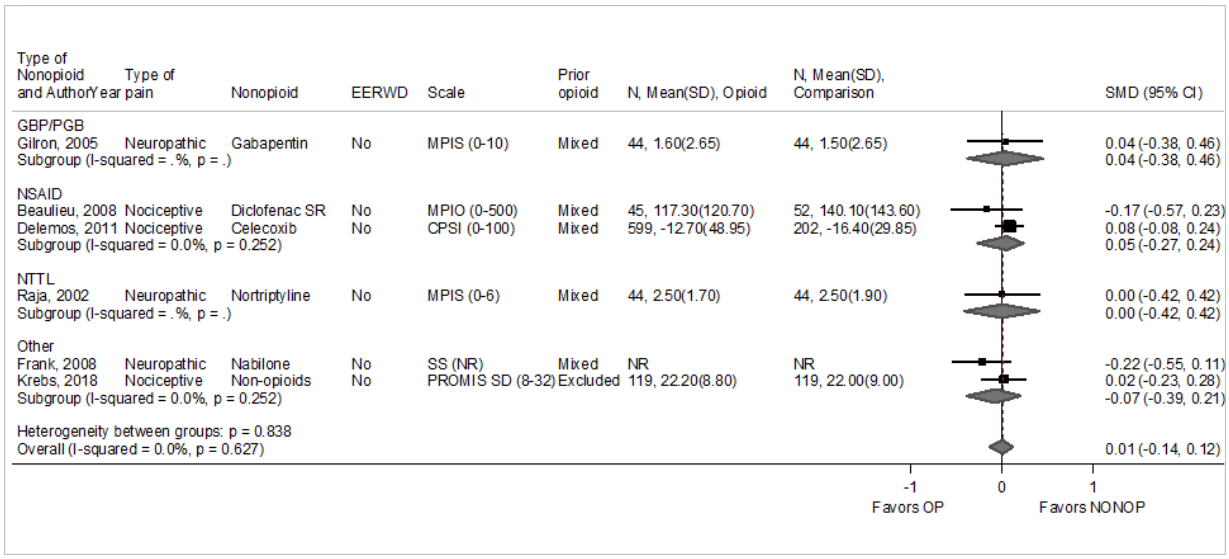
Abbreviations: ANCOVA=analysis of covariance; CR=controlled release; CI=confidence interval; HAD=Hospital Anxiety and Depression Scale; NR=not reported; PROMIS=Patient-Reported Outcomes Measurement Information System; PHQ-8=Personal Health Questionnaire-8; SF-36 MCS= Short Form-36 Mental Component Summary; 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



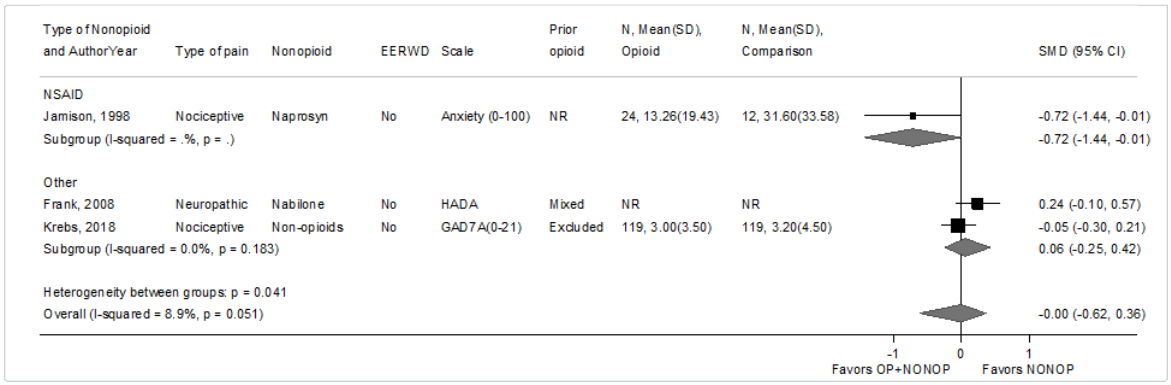
Note: Nociceptive pain refers to musculoskeletal condition

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



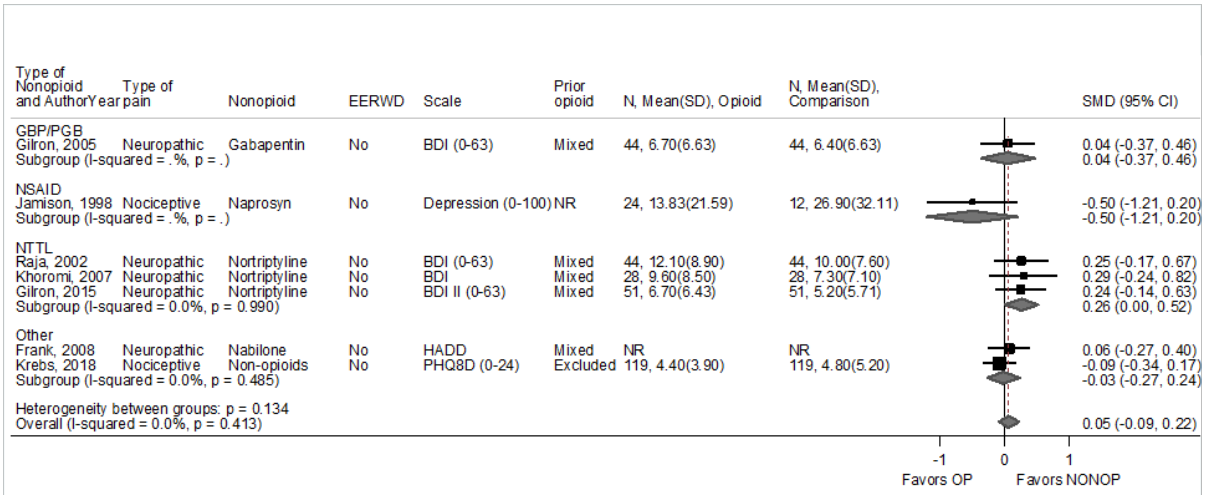
Note: Nociceptive pain refers to musculoskeletal condition

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



Note: Nociceptive pain refers to musculoskeletal condition

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



Note: Nociceptive pain refers to musculoskeletal condition

Long-Term (≥1 year) Outcomes

One RCT of opioids versus nonopioids evaluated outcomes at one year.[142] 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**).[142]

Doses of Opioids Used

Evidence on thow effects of opioids versus nonopioids varied according on 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.[142] 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 (5 trials, N=325, mean difference 0.00 on a 0 to 10 scale, 95% CI, -0.67 to 0.68, I^2=16%), likelihood of a pain response (3 trials, N=462, RR 1.15, 95% CI, 0.83 to 1.54, I^2=31%), function (3 trials, N=246, SMD -0.05, 95% CI, -0.31 to 0.21, I^2=0%), or other outcomes (SOE: low).

Description of Included Studies

Seven trials compared an opioid plus nonopioid versus nonopioid for chronic pain.[67,82,140,145,147-149] Sample sizes ranged from 28 to 62 (total N=516). None of the trials were included in the prior AHRQ report, which was restricted to trials with 1 year or more followup. The duration of followup was less than6 months in all trials; six trials followed patients for less than 3 months and one trial followed patients for 3 to 6 months. The nonopioid was nortriptyline in three trials, gabapentin in one trial, pregabalin in one trial, 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 all 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 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[145] (**Table 14**).

Five trials were rated fair-quality[67,82,140,145,149] and two were rated poor-quality (**Appendix Table G-1**).[147,148] 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[147] Italy Poor	409	1: No 2: No 3: NR	1: Mixed neuropathic pain 2: NR 3: Mixed 4: 169 (SD 7.43) vs. 106 (SD 7.51)	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 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[140] 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[148] 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; 1 mg MED 4 weeks	Acetaminophen 3000 mg
Rigo, 2017[145] 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; 42 mg MED 13 weeks	Ketamine 90 mg
Zin, 2010[149] 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: MED=morphine equivalent dose; NR=Not reported; SD=standard deviation; SR=sustained release

*Mean, unless otherwise noted

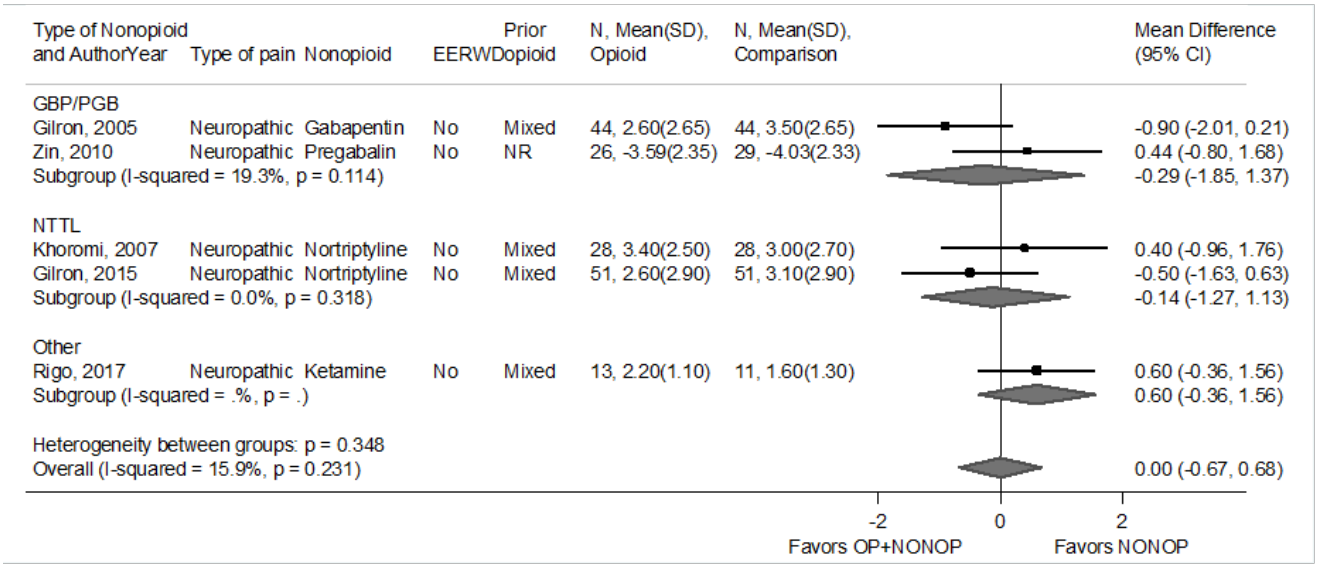
Detailed Synthesis

Short-Term (1 to <6 month) Outcomes

There was no difference between an opioid plus nonopioid versus a nonopioid alone in mean improvement in pain at short-term followup (5 trials, N=325, mean difference 0.00 on a 0 to 10 scale, 95% CI, -0.67 to 0.68, I^2=16%; **Figure 17 Table 15**),[67,82,140,145,149] likelihood of a pain response (5 trials, N=462, RR 1.15, 95% CI, 0.83 to 1.54, I^2=31%; **Figure 18 Table 15**),[67,82,140,148,149] or function (3 trials, N=246, SMD -0.05, 95% CI, -0.31 to 0.21, I^2=0%; **Figure 19, Table 15**).[67,82,140] 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 16**)[67,82,140,149] or mental (**Figure 21, Table 16**),[67,82,140,149] health status, sleep (**Figure 22, Table 16**),[67,149] or depression (**Figure 23, Table 16**),[67,82,140] though analyses were limited by small numbers of trials. There were no interactions between nonopioid type and effects on any outcome (**Tables 12 and 17**); all trials evaluated 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



Note: Nociceptive pain refers to musculoskeletal condition

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

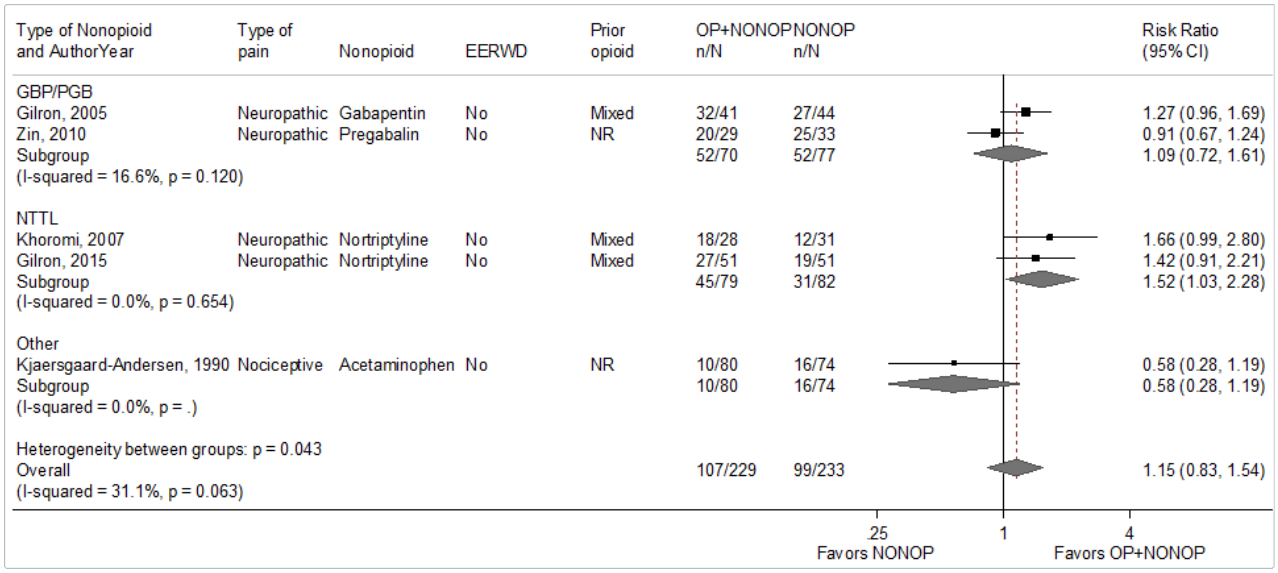
Study, year Country Quality	1: Duration of followup 2: Total patients randomized 3: Pain condition	1: Opioid + nonopioid 2: Nonopioid	Pain* (continuous)	Pain (dichotomous)	Function* (continuous)
Gatti, 2009[147] Italy Poor	1: 13 weeks 2: 409 3: Mixed neuropathic pain	1: Oxycodone SR (mean 36 mg) + pregabalin (mean142 mg) 2: Pregabalin (mean 289 mg)	0 to 10 NRS 1: 1.49 (NR) 2: 3.04 (NR)	Treatment "effective" or "very effective" 1: 1: 91.1% (154/169) 2: <20% (NR)	Brief Pain Inventory, 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)	0 to 10 VAS 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)	Brief Pain Inventory Interference? (0 to 10) 1: 2.9 (0.4) 2: 3.0 (0.4)
Gilron, 2015[140] 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)	0 to 10 NRS 1: 2.6 (2.9) 2: 3.1 (2.9)	Improvement in pain ≥30% 1: 52.9% (27/51) 2: 37/2% (19/51)	Brief Pain Inventory, 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)	0 to 10 NRS 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 1: 27.4 (15) 2: 27.5 (17)
Kjaersgaard-Andersen, 1990[148] Denmark Poor	1: 4 weeks 2: 158 3: Osteoarthritis	1: Codeine 180 mg + acetaminophen 3000 mg 2: Acetaminophen 3000 mg	NR	Slight or no pain 1: 12.5% (10/80) 2: 21.6% (16/74)	NR
Rigo, 2017 [145] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic pain	1: Methadone 9 mg + ketamine 90 mg 2: Ketamine 90 mg	NR	NR	NR
Zin, 2010 [149] 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)	0 to 10 cm VAS 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: CI=confidence interval; NR=not reported; NRS=numeric rating scale; SF-36 MCS= Short Form-36 Mental Component Summary; SF-36 PCS=Short Form-36 Physical Component Summary; SR=sustained release; VAS=Visual Analogue Scale

*Means (SD), unless otherwise reported

Note: No studies reported function (dichotomous)

Figure 18. Meta-analysis of likelihood of experiencing a pain response for opioids plus nonopioids versus nonopioids



Note: Nociceptive pain refers to musculoskeletal condition

Figure 19. Meta-analysis of improvement in mean function measures for opioids plus nonopioids versus nonopioids

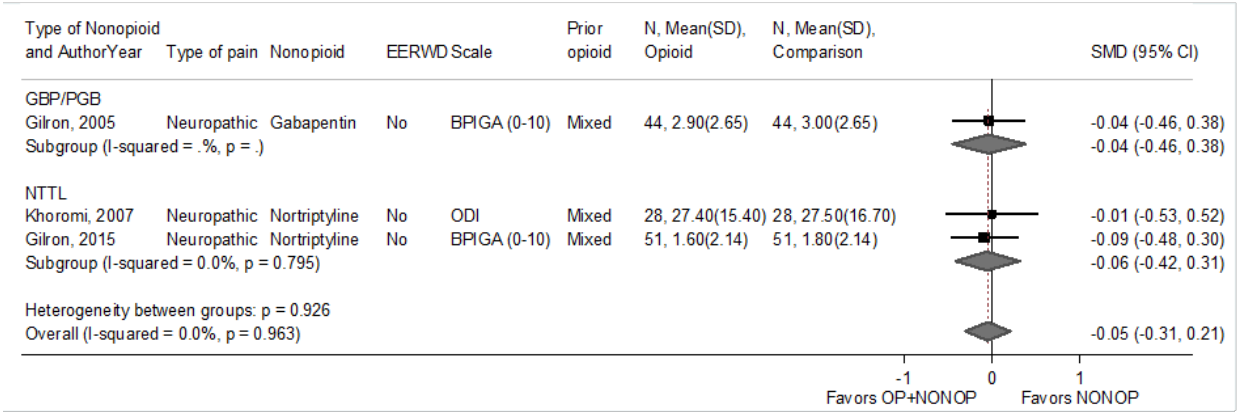


Figure 20. Meta-analysis of improvement in mean SF-36 physical function measures for opioids plus nonopioids versus nonopioids

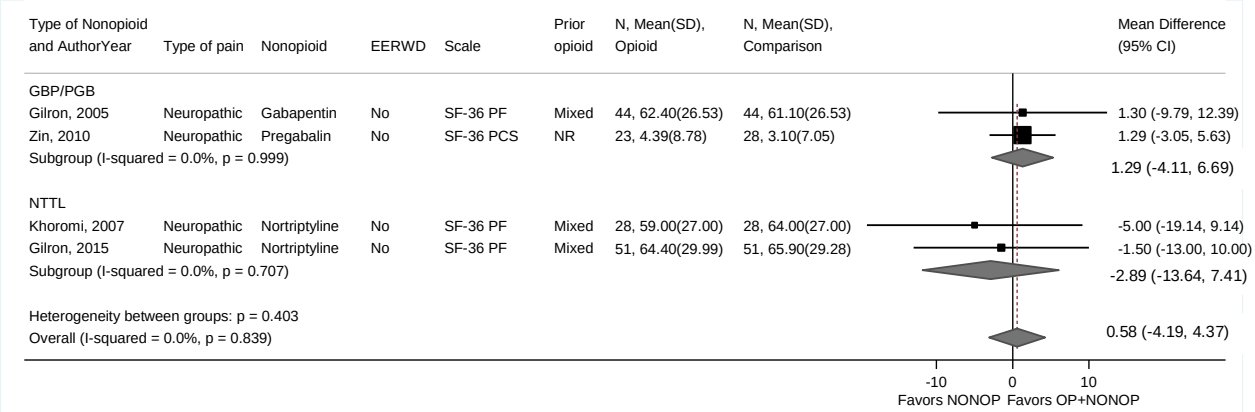


Table 16. Quality of life, sleep, and mental health outcomes for opioids plus nonopioids versus nonopioids

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[147] Italy Poor	1: 13 weeks 2: 409 3: Mixed neuropathic pain	1: Oxycodone SR (mean 36 mg) + pregabalin (mean142 mg) 2: Pregabalin (mean 289 mg)	NR	NR	Brief Pain Inventory, sleep (0 to 10) 1: 2.22 (NR) 2: 2.29 (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)	Brief Pain Inventory sleep (0 to 10, 10=pain complete interferes) 1: 1.1 (0.4) 2: 1.5 (0.4)	Beck Depression Inventory (0 to 63, 63=more severe depression) 1: 6 (1) 2: 6.4 (1)
Gilron, 2015[140] 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	Beck Depression Inventory 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	Beck Depression Inventory 1: 6 (5) 2: 7.3 (7.1)
Kjaersgaard-Andersen, 1990[148] Denmark Poor	1: 4 weeks 2: 158 3: Osteoarthritis	1: Codeine 180 mg + acetaminophen 3000 mg 2: Acetaminophen 3000 mg	NR	NR	NR

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*
Rigo, 2017 [145] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic pain	1: Methadone 9 mg + ketamine 90 mg 2: Ketamine 90 mg	NR	NR	NR
Zin, 2010 [149] 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 (0 10 VAS, 10=cannot sleep at all due to pain) Difference -1.11 (CI, NR)	NR

Abbreviations: CI, = 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 Analogue Scale

*Means (SD), unless otherwise reported

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

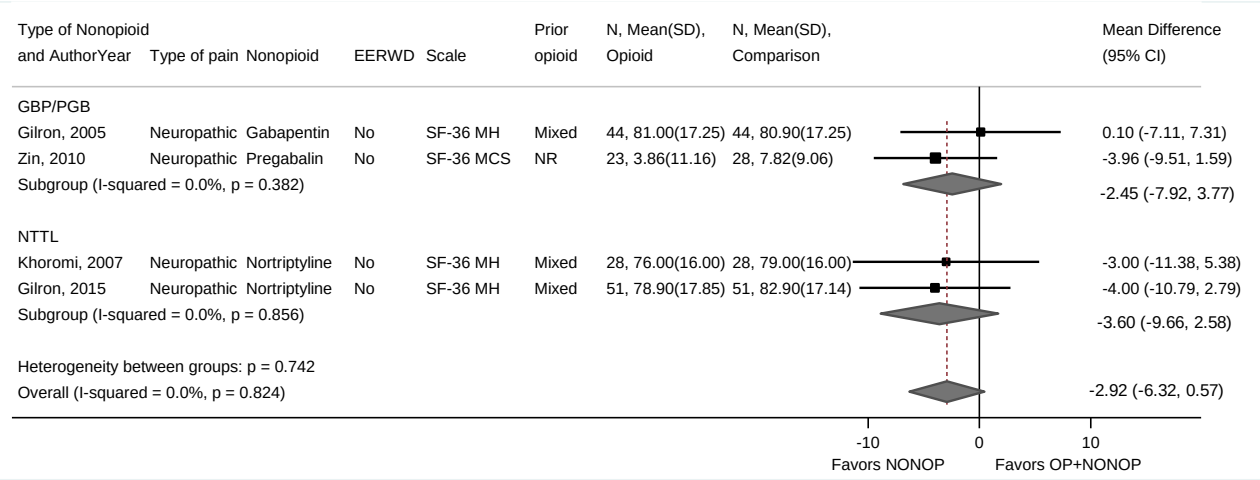


Figure 22. Meta-analysis of improvement in mean in sleep measures for opioids plus nonopioids versus nonopioids

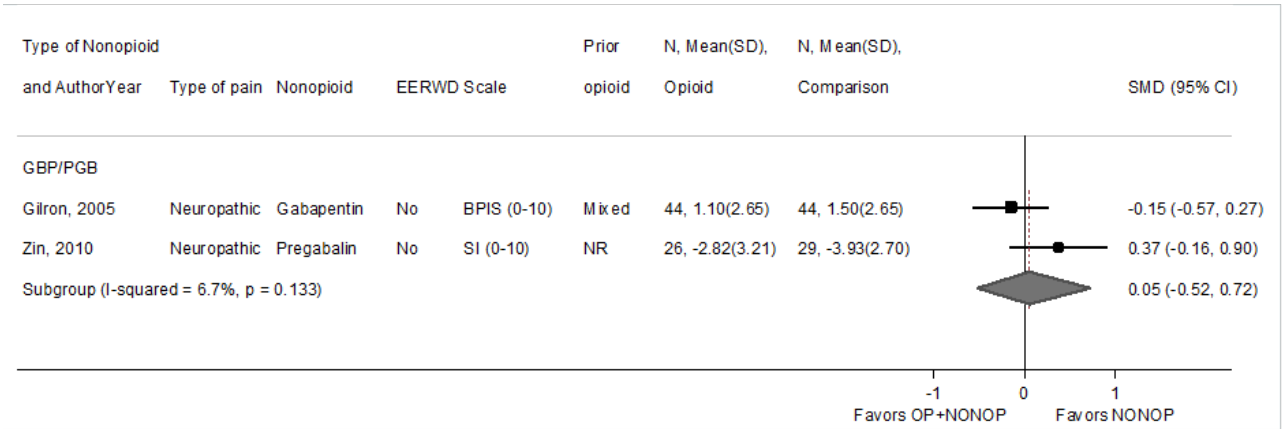


Figure 23. Meta-analysis of improvement in mean in depression measures for opioids plus nonopioids versus nonopioids

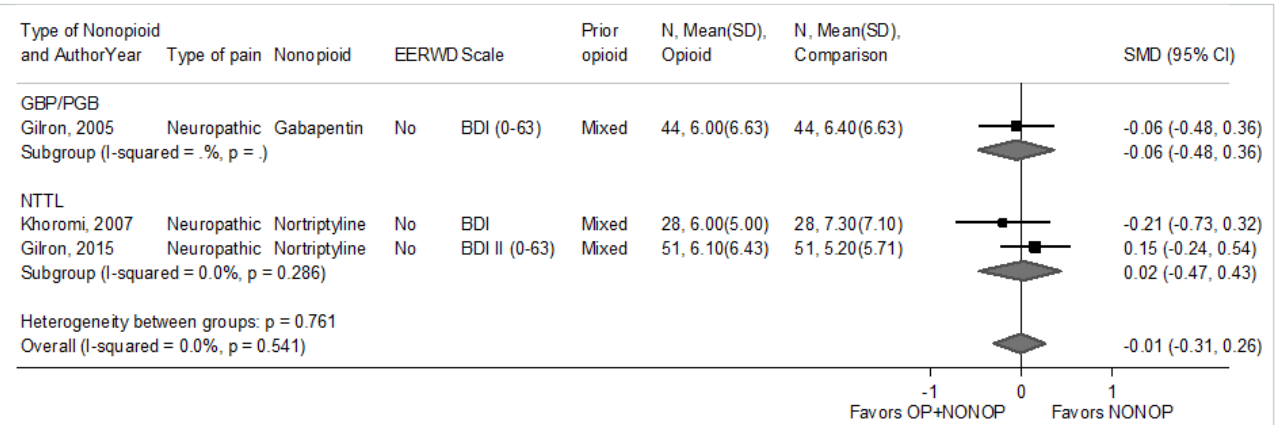


Table 17. Pooled analyses of improvment in mean pain and and function measures for opioids plus nonopioids versus nonopioids

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	0.00 (-0.67 to 0.68)	16%	5 (330)	--	-0.05 (-0.31 to 0.21)	0%	3 (246)	--
Nonopioid: Gabapentinoid	-0.29 (-1.85 to 1.37)	19%	2 (148)	0.68	-0.04 (-0.46 to 0.38)	--	1 (88)	0.94
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	0.00 (-0.67 to 0.68)	16%	5 (330)	--	-0.05 (-0.31 to 0.21)	0%	3 (246)	--
Pain type: Neuropathic	0.00 (-0.67 to 0.68)	16%	5 (330)	**--**	-0.05 (-0.31 to 0.21)	0%	3 (246)	--
Trial quality: Good	No studies	--	--	--	No studies	--	--	--
Fair	0.00 (-0.67 to 0.68)	16%	5 (330)	--	-0.05 (-0.31 to 0.21)	0%	3 (246)	--
Poor	No studies	--	--	--	No studies	--	--	--
Opioid dose (mg MED/day): <50	0.13 (-0.68 to 0.94)	18%	4 (228)	0.50	-0.03 (-0.40 to 0.35)	0%	2 (144)	0.84
50-90	-0.50 (-1.63 to 0.63)	--	1 (102)	--	-0.09 (-0.48 to 0.30)	--	1 (102)	--
>90	No studies	--	--	**--**	No studies	--	--	--
Crossover design	-0.43 (-1.22 to 0.47)	0%	3 (249)	0.16	-0.05 (-0.31 to 0.21)	0%	3 (246)	--
Parallel group	0.54 (-0.36 to 1.41)	0%	2 (81)	--	No studies	--	--	--

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, I2=0%) (SOE: low)
- There were no statistically significant differences between an opioid plus nonopioid versus a nonopioid alone in likelihood of a pain response (5 trials, N=831, RR 1.19, 95% CI, 0.97 to 1.68) or mean improvement in function (4 trials, N=521, SMD -0.25, 95% CI, -0.49 to 0.09, I2=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 18**).[67,82,140,145,147,150] None of the trials were included in the prior 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 409 (total N=914). Two trials evaluated morphine SR plus nortriptyline,[82,140] and one trial each evaluated methadone plus ketamine,[145] morphine plus gabapentin,[67] oxycodone SR plus pregabalin,[147] and tapentadol SR plus pregabalin.[150] 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 percent 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[67,82,140,145,150] and one poor-quality[147] (**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;[67,82,140] the remainder used a parallel group non-EERW randomized trial design. Two trials reported industry funding.[67,150]

Table 18. 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[150] 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[147] Italy Poor	409	1: No 2: No 3: NR	1: Mixed neuropathic pain 2: NR 3: Mixed 4: 169 (SD 7.43) vs. 106 (SD 7.51)	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[140] 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[145] 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 13 weeks	Methadone 9 mg

Abbreviations: MED=morphine equivalent dose; NR=Not reported; SR=sustained release

*Mean (SD), unless otherwise noted

Detailed Synthesis

Short-Term (1 to <?6 month) 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 (5 trials, N=623, mean difference -0.40, 95% CI, -0.72 to -0.07, I^2=0%; **Figure 24, Table 19**) versus an opioid alone.[67,82,140,147,150] 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). Results were similar for likelihood of a pain response (5 trials, N=831, RR 1.19, 95% CI, 0.97 to 1.68; **Figure 25, Table 19**).[67,82,140,147,150] 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 19**),[67,82,140,147] with no interaction with nonopioid type. 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 20**)[67,82,140,150] or mental (**Figure 28 Table 20**)[67,82,140,150] health status, sleep (**Figure 29 Table 20**),[67,147] anxiety (**Figure 30, Table 20**),[150] or depression (**Figure 31, Table 20**),[67,82,140,150] 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=0%), 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 12 and 21**). 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

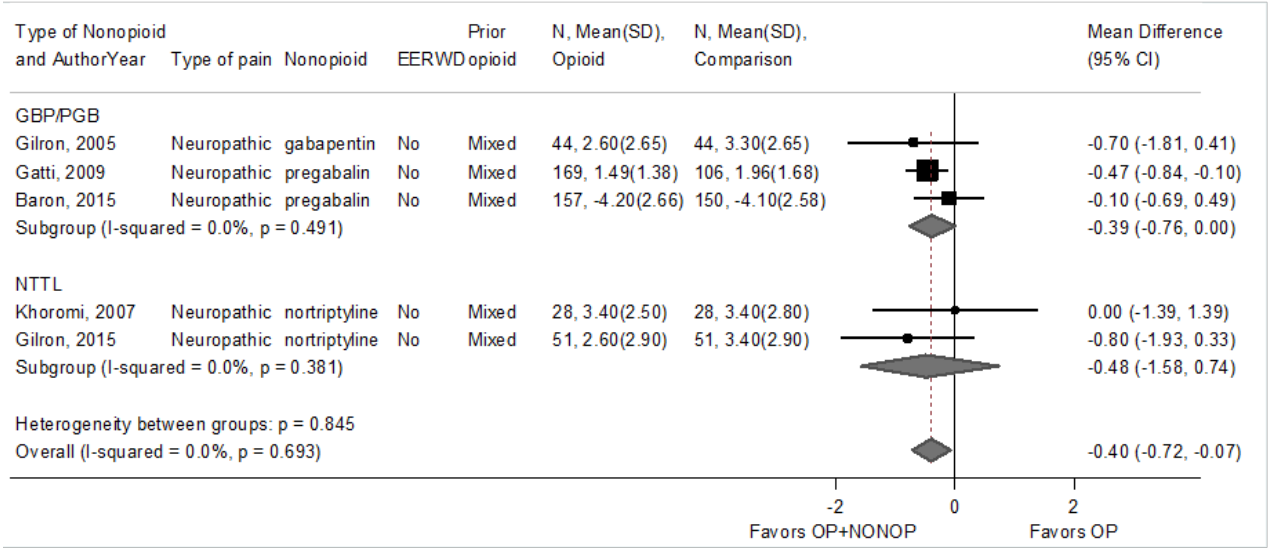


Table 19. Pain and function results for opioids plus nonopioids versus opioids

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[150] 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)	0 to 10 NRS 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[147] Italy Poor	1: 13 weeks 2: 409 3: Mixed neuropathic pain	1: Oxycodone SR (mean 36 mg) + pregabalin (mean142 mg) 2: Oxycodone SR (mean 46 mg)	0 to 10 NRS 1: 1.49 (NR) 2: 1.96 (NR)	Treatment "effective" or "very effective" 1: 91.1% (154/169) 2: 95.3% (101/106)	Brief Pain Inventory, 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)	0 to 10 VAS (McGil Pain Questionnaire) 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)	Brief Pain Inventory general activity (0 to 10) 1: 2.9 (0.4) 2: 3.1 (0.4)
Gilron, 2015[140] 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)	0 to 10 NRS 1: 2.6 (2.9) 2: 3.4 (2.9)	Improvement in pain ≥30% 1: 52.9% (27/51) 2: 25.5% (13/51)	Brief Pain Inventory, 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)	0 to 10 NRS 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 1: 27.4 (15.4) 2: 25.7 (16.5)
Rigo, 2017[145] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic	1: Methadone 9 mg + ketamine 90 mg 2: Methadone 9 mg	0 to 10 VAS 1: 13 (2.2) 2: 13 (1.3)	NR	NR

Abbreviations: NR=not reported; NRS=numeric rating scale; SR=sustained release; VAS=Visual Analogue Scale

*Means (SD), unless otherwise reported

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

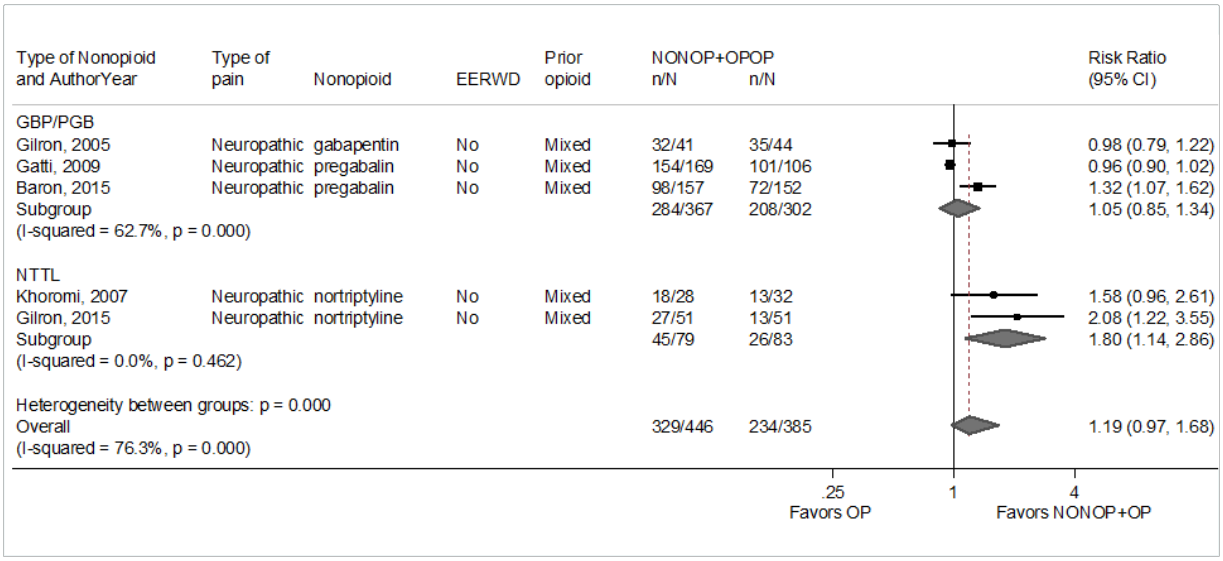


Figure 26. Meta-analysis of improvement in mean function measures for opioids plus nonopioids versus opioids

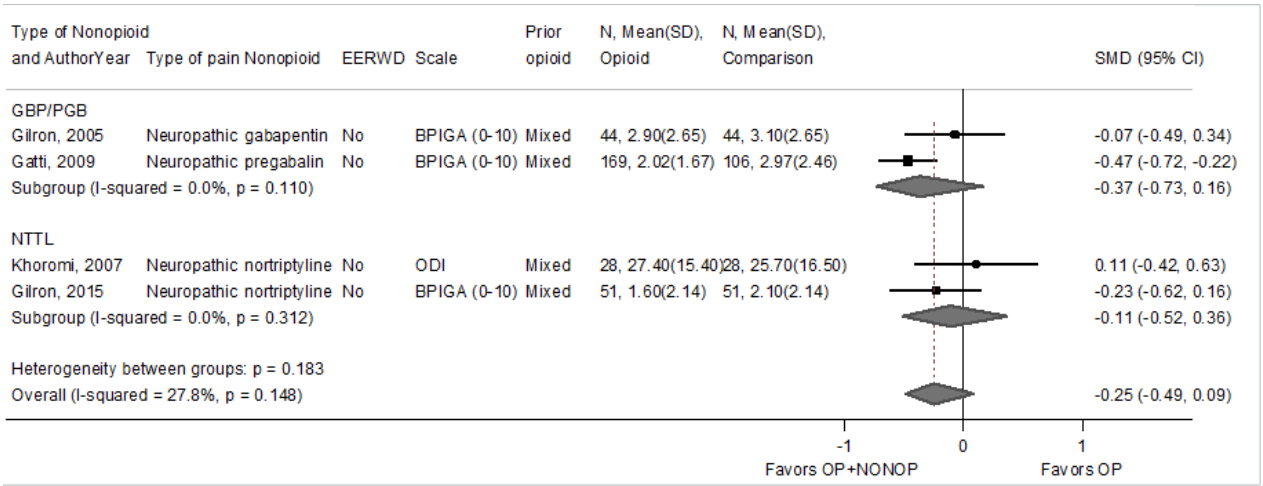


Figure 27. Meta-analysis of improvement in mean SF-36 physical function measures for opioids plus nonopioids versus nonopioids

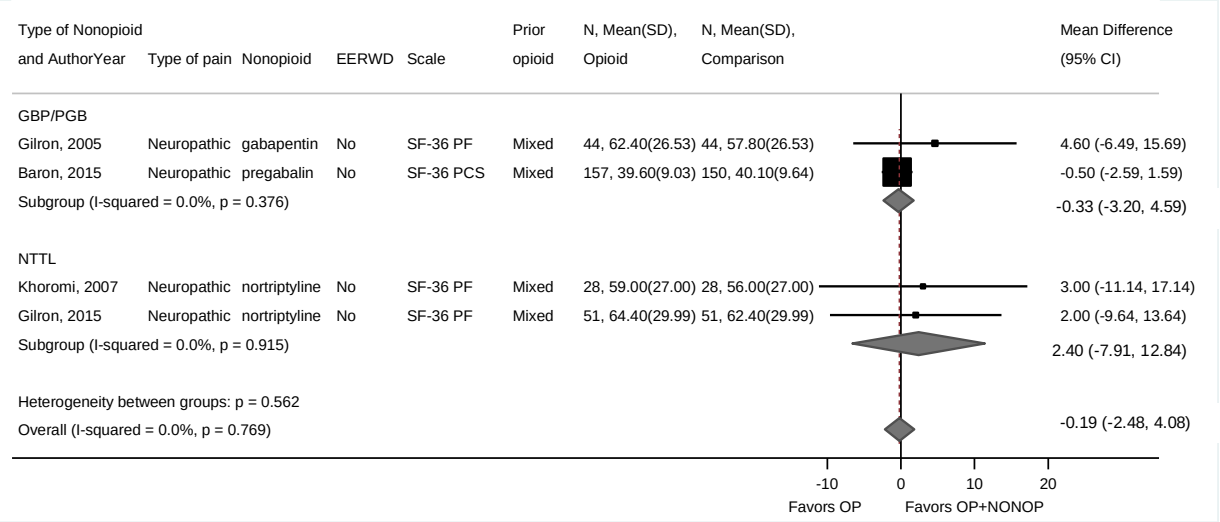


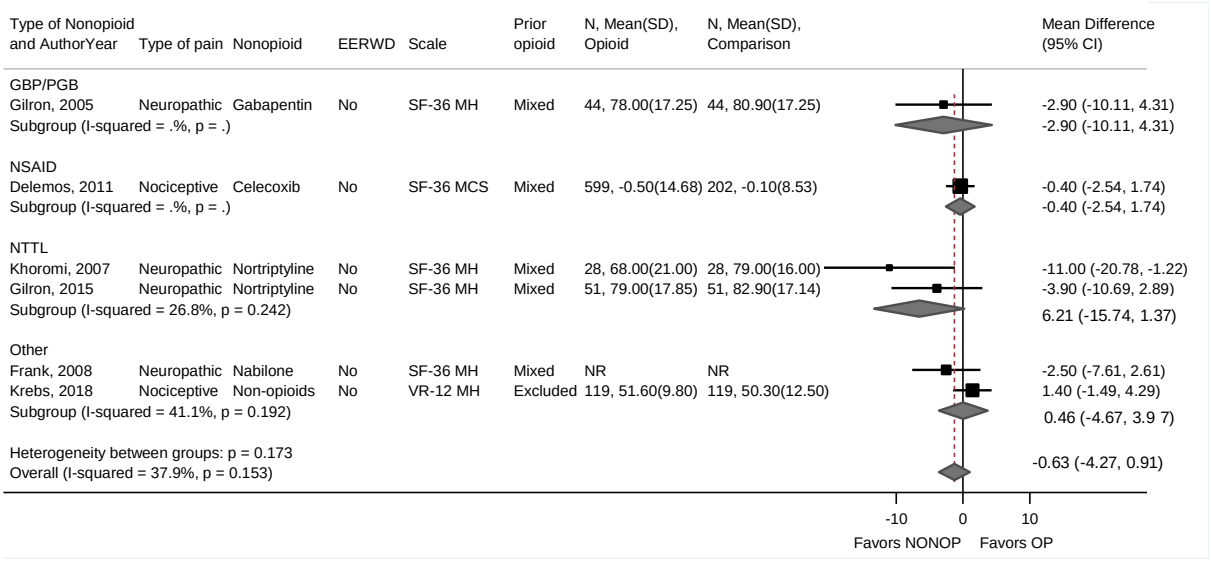
Table 20. Quality of life, sleep, and mental health outcomes for opioids plus nonopioids versus opioids

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[150] 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)	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[147] Italy Poor	1: 13 weeks 2: 409 3: Mixed neuropathic pain	1: Oxycodone SR (mean 36 mg) + pregabalin (mean142 mg) 2: Oxycodone SR (mean 46 mg)	NR	NR	Brief Pain Inventory, 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, 10=pain completely interferes) 1: 1.1 (0.4) 2: 1.6 (0.4)	BDI (0 to 63, 63=more severe depression) 1: 6 (1) 2: 6.7 (1)

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*
Gilron, 2015[140] 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 1: 6 (5) 2: 9.6 (8.5)
Rigo, 2017[145] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic	1: Methadone 9 mg + ketamine 90 mg 2: Methadone 9 mg	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 (SD), unless otherwise reported

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



Note: Nociceptive pain refers to musculoskeletal condition

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

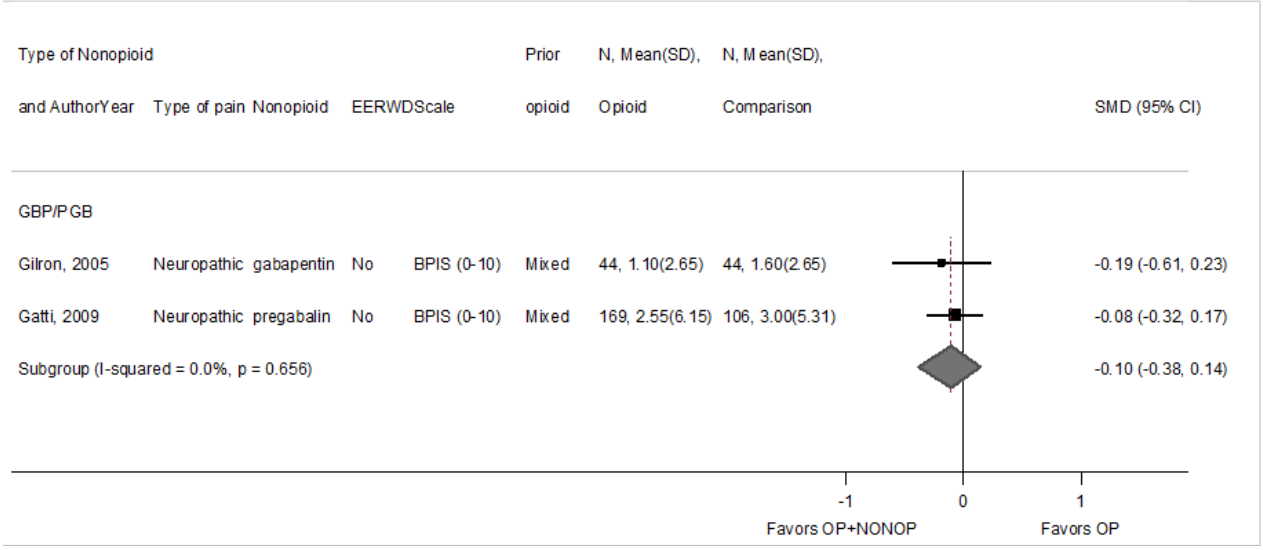


Figure 30. Meta-analysis of improvement in mean anxiety measures for opioids plus nonopioids versus opioids

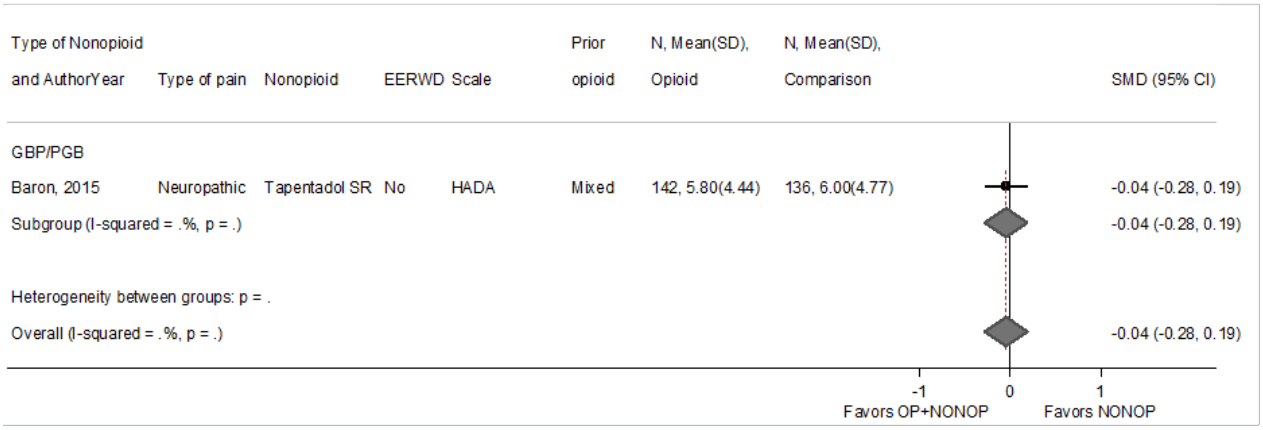


Figure 31. Meta-analysis of improvement in mean depression measures for opioids plus nonopioids versus opioids

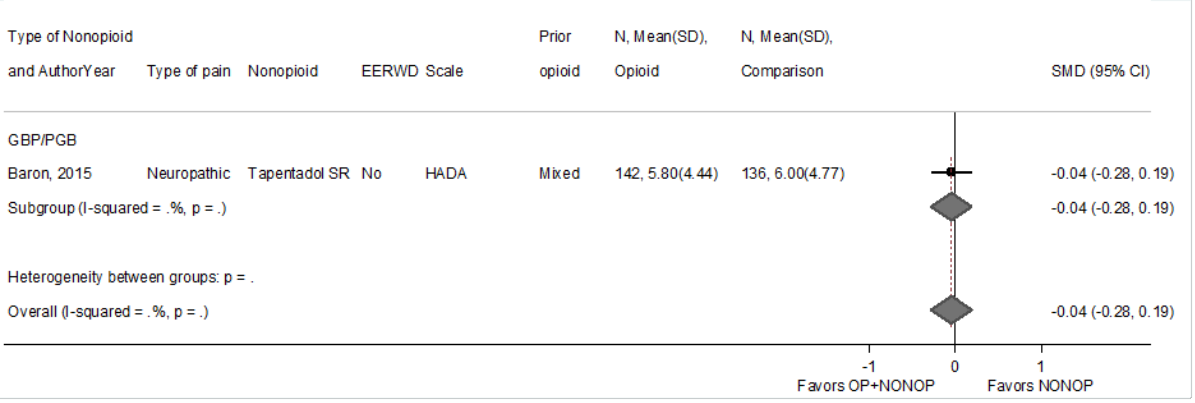


Table 21. Pooled analysis of improvement in mean pain and function measures for opioids plus nonopioids versus opioids

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	-0.40 (-0.72 to -0.07)	0%	5 (828)	--	-0.25 (-0.49 to 0.09)	28%	4 (521)	--
Nonopioid: Gabapentinoid	-0.39 (-0.76 to 0.00)	0%	3 (670)	0.86	-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	-0.40 (-0.72 to -0.07)	0%	5 (828)	--	-0.25 (-0.49 to 0.09)	28%	4 (521)	--
Pain type: Neuropathic	-0.40 (-0.72 to -0.07)	0%	5 (828)	--	-0.25 (-0.49 to 0.09)	28%	4 (521)	--
Trial quality: Fair	-0.30 (-0.88 to 0.16)	0%	4 (553)	0.60	-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	-0.43 (-1.48 to 0.74)	0%	2 (144)	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)	0.64	-0.10 (-0.36 to 0.19)	0%	3 (246)	0.17
Parallel group	-0.37 (-0.76 to 0.15)	0%	2 (582)	--	-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

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.[67,82,140,147] 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.[67,140,147] 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**).[151,152] 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).[151] 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).[152] 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 (60 trials, N=19,864, RR 2.26, 95% CI, 1.87 to 2.75, 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 (37 trials, N=13,030, RR 1.21, 95% CI, 0.87 to 1.71, I^2=37%) (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).
- 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%) (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).
- Five 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 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).[153-165]

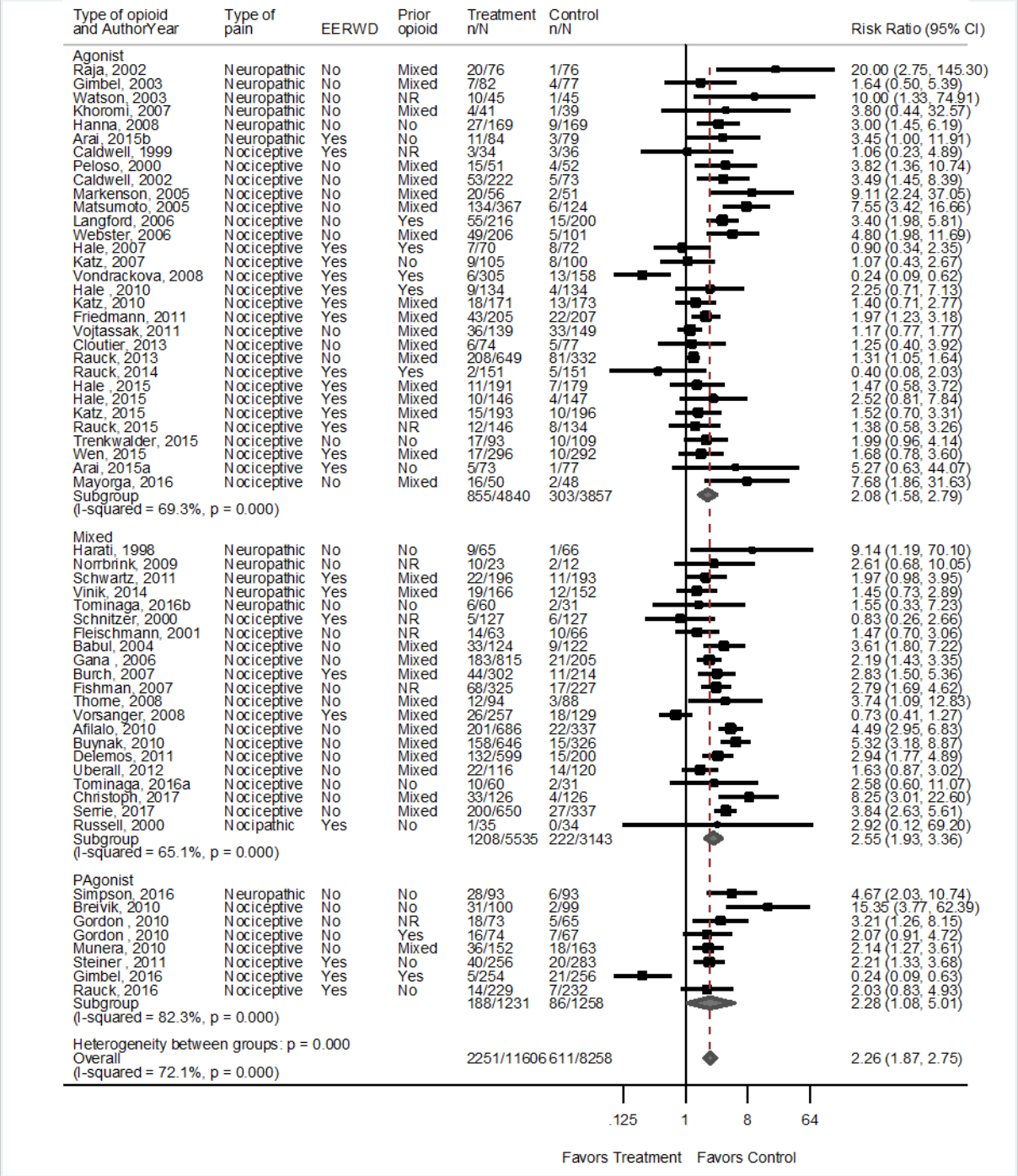
Detailed Synthesis

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 (60 trials, N=19,864, RR 2.26, 95% CI, 1.87 to 2.75, I^2=72%; ARD 10%, 95% CI, 7% to 12%; **Figure 32, Table 22**).[50-52,54-59,61-66,68-77,79-83,85-87,90,93-104,107-115,117,119-121] Trials that utilized an EERW design reported a lower risk of withdrawal due to adverse events (24 trials, N=7781, RR 1.35, 95% CI, 1.01 to 1.79, I^2=56%) 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 (44 trials, N=15,825, RR 2.03, 95% CI, 1.63 to 2.53, 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 23**).

There was no difference between opioids versus placebo in risk of serious adverse events (37 trials, N=13,030, RR 1.21, 95% CI, 0.87 to 1.71, I^2=37%).[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] Serious adverse events were generally not well defined by the trials. No interactions observed were observed in stratified analyses (**Table 23**).

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



Note: Nociceptive pain refers to musculoskeletal condition

Table 22. Summary table of adverse events for opioids versus placebo

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
Afilalo, 2010[50] International 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

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
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	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
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 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

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
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
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)
Fleischmann, 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)
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	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 3: Pain condition	1: Opioid 2: Control	Discontinuation due to adverse events	Serious adverse events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
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	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 3: Pain condition	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 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	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 30-180 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 3: Pain condition	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
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
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

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
Markenson, 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)
Matsumoto, 2005[86] USA Fair	1: 4 weeks 2: 491 3: Osteoarthritis	1a: Oxymorphone SR 40-80 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- 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 Poor	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
Munera, 2010[90] USA Fair	1: 4 weeks 2: 315 3: Osteoarthritis	1: Buprenorphine patch 5-20 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)

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
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)	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)
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)

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
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 50-400 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 200-400 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 100-250 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
Serrie, 2017[103] Europe Fair	1: 15 weeks 2: 990 3: Knee pain	1a: Tapentadol SR 200-500 mg (mean 315 mg) 1b: Oxycodone SR 40-100 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)

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
Simpson, 2016[104] Australia Fair	1: 12 weeks 2: 186 3: Diabetic neuropathy	1: Buprenorphine patch 5-40 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] Denmark, 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
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)
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	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

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
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	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
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	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 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 200-500 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
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

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
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	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
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	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 20-60 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)
Webster, 2006[120] USA Fair	1: 6 weeks 2: 307 3: Low back pain	1: Oxycodone 10-80 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 20-120 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

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 30-180 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; UK=United Kingdom; USA=United States of America

Table 23. 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	2.26 (1.87 to 2.75)	72%	60 (19864)	--	1.21 (0.87 to 1.71)	37%	37 (13030)	--	2.97 (2.44 to 3.66)	48%	52 (17458)	--
Opioid type: Opioid agonist	2.08 (1.58 to 2.79)	69%	31 (8697)	0.67	1.39 (0.99 to 1.97)	0%	21 (6075)	0.52	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	2.15 (1.72 to 2.68)	77%	47 (17663)	0.49	1.14 (0.79 to 1.67)	38%	32 (12074)	0.35	3.09 (2.48 to 3.91)	47%	40 (15748)	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 (0.12-69.20)	--	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)	0.28	2.81 (1.33 to 5.69)	5.0%	3 (1351)	0.97
Fair	2.39 (1.92 to 3.00)	74%	49 (16479)	--	1.09 (0.76 to 1.60)	36%	31 (11145)	--	3.00 (2.37 to 3.87)	56%	43 (14329)	--
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)	0.54	1.30 (0.77 to 2.27)	0%	8 (2573)	0.63	2.62 (1.55 to 4.74)	55%	13 (3936)	0.18
50-90	1.99 (1.49 to 2.78)	57%	18 (5690)	**--**	1.54 (0.58 to 3.44)	30%	10 (2837)	--	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 (1.01 to 1.79)	56%	24 (7781)	**<0.005**	1.56 (1.05 to 2.30)	0%	17 (5966)	0.18	2.10 (1.38 to 3.30)	5.5%	17 (5944)	0.12
Non-EERW	3.06 (2.50 to 3.81)	62%	36 (11983)	--	1.00 (0.59 to 1.70)	50%	20 (7064)	--	3.21 (2.58 to 4.11)	56%	35 (11514)	--
EERW, 2007 or after	1.38 (1.01 to 1.86)	61%	21 (7488)	**0.001**	1.56 (1.05 to 2.30)	0%	17 (5966)	0.11	2.10 (1.38 to 3.30)	5.5%	17 (5944)	0.08
Non-EERW	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)	0.27	1.16 (0.21 to 5.06)	37%	6 (781)	0.93	1.98 (1.36 to 3.32)	24%	9 (1090)	0.07
Parallel group	2.19 (1.79 to 2.69)	75%	53 (18930)	--	1.20 (0.85 to 1.72)	38%	31 (12249)	--	3.23 (2.61 to 4.05)	43%	43 (16368)	--

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*
Opioid naïve	2.59 (1.96 to 3.90)	0%	13 (2825)	**0.01**	1.40 (0.84 to 2.34)	0%	8 (2104)	0.76	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	2.52 (2.02 to 3.20)	72%	32 (13249)	--	1.19 (0.72 to 2.04)	54%	19 (8226)	--	3.12 (2.49 to 4.04)	46%	29 (11972)	--
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)	--
Published 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)	0.51	3.07 (1.98 to 5.15)	72%	13 (3593)	0.93
In or after 2007	2.03 (1.63 to 2.53)	74%	44 (15825)	--	1.17 (0.84 to 1.66)	36%	33 (12612)	--	2.96 (2.39 to 3.71)	27%	39 (13865)	--
Region: USA or Canada	2.12 (1.72 to 2.62)	65%	44 (14566)	0.68	1.51 (1.06 to 2.12)	0%	26 (8990)	0.28	3.08 (2.40 to 4.06)	53%	38 (12505)	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	2.78 (1.29 to 6.00)	0%	4 (495)	--	2.15 (0.56 to 12.63)	0%	2 (308)	--	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	2.19 (1.80 to 2.67)	73%	56 (19290)	0.27	1.21 (0.87 to 1.71)	37%	37 (13030)	--	3.15 (2.54 to 3.95)	42%	46 (16728)	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)	--

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

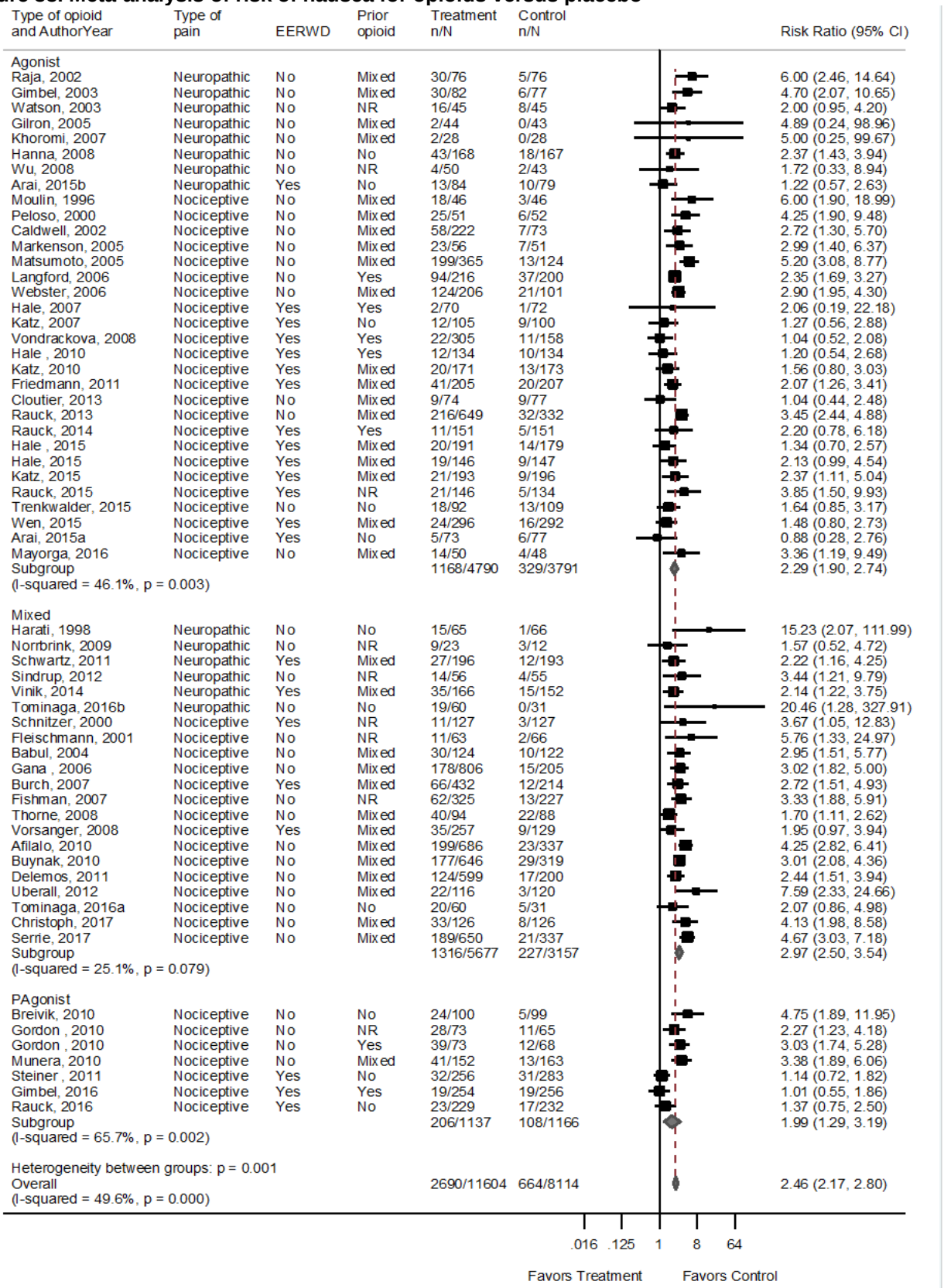
*p for interaction

†USA/Canada and Europe/Australia

Gastrointestinal Adverse Events

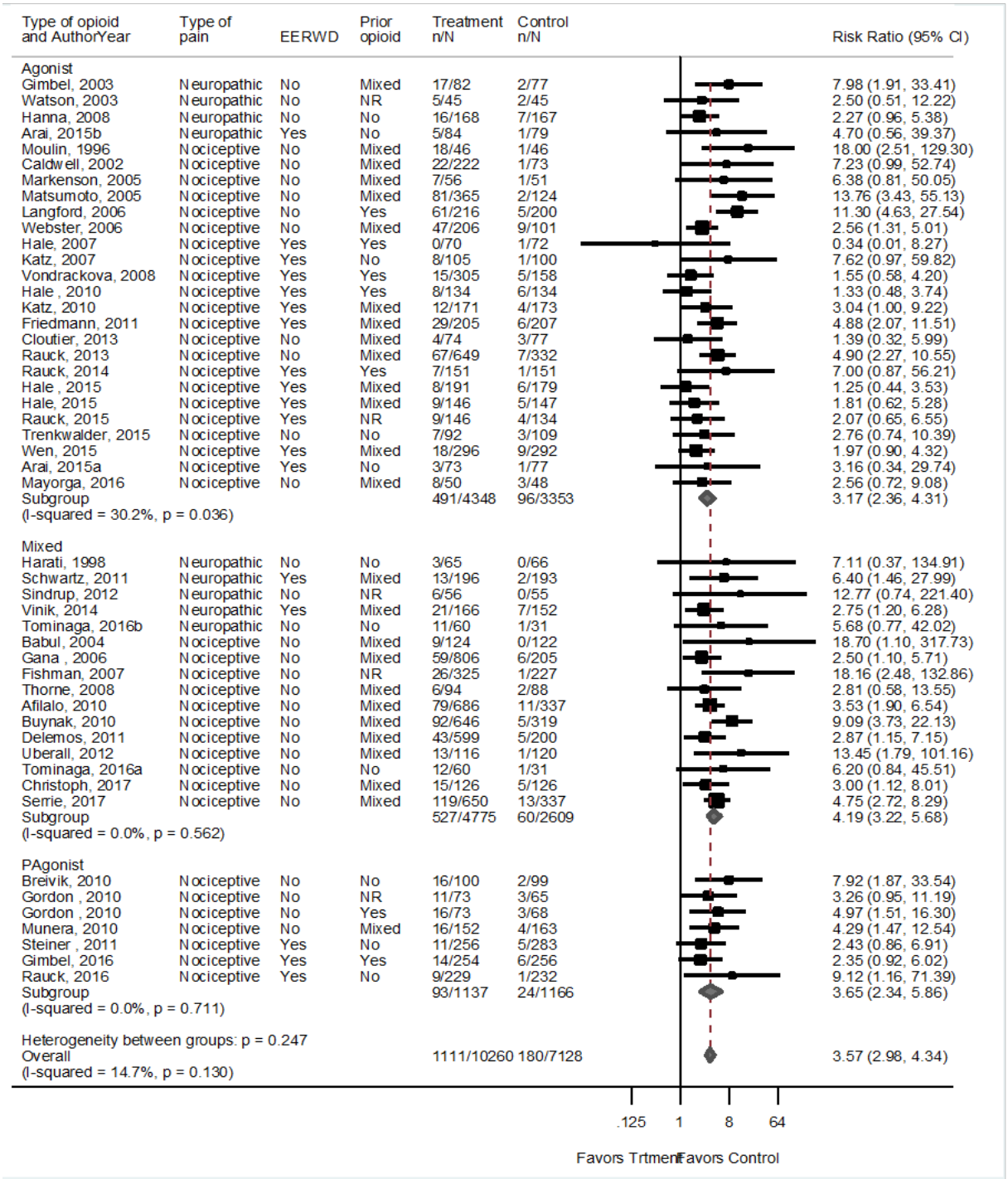
Opioids were associated with increased risk of nausea (60 trials, N=19,718, RR 2.46, 95% CI, 2.17 to 2.80, I^2=50%; ARD 14%, 95% CI, 11% to 17%, **Figure 33, Table 22**),[50-52,54-56,58,59,61-77,79-83,85-90,93-99,101-103,105,107-113,117,119-122] vomiting (49 trials, N=17,388, RR 3.57, 95% CI, 2.98 to 4.34, I^2=15%; ARD 7%, 95% CI, 6% to 9%, **Figure 34, Table 22**),[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 22**)[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 24**).

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



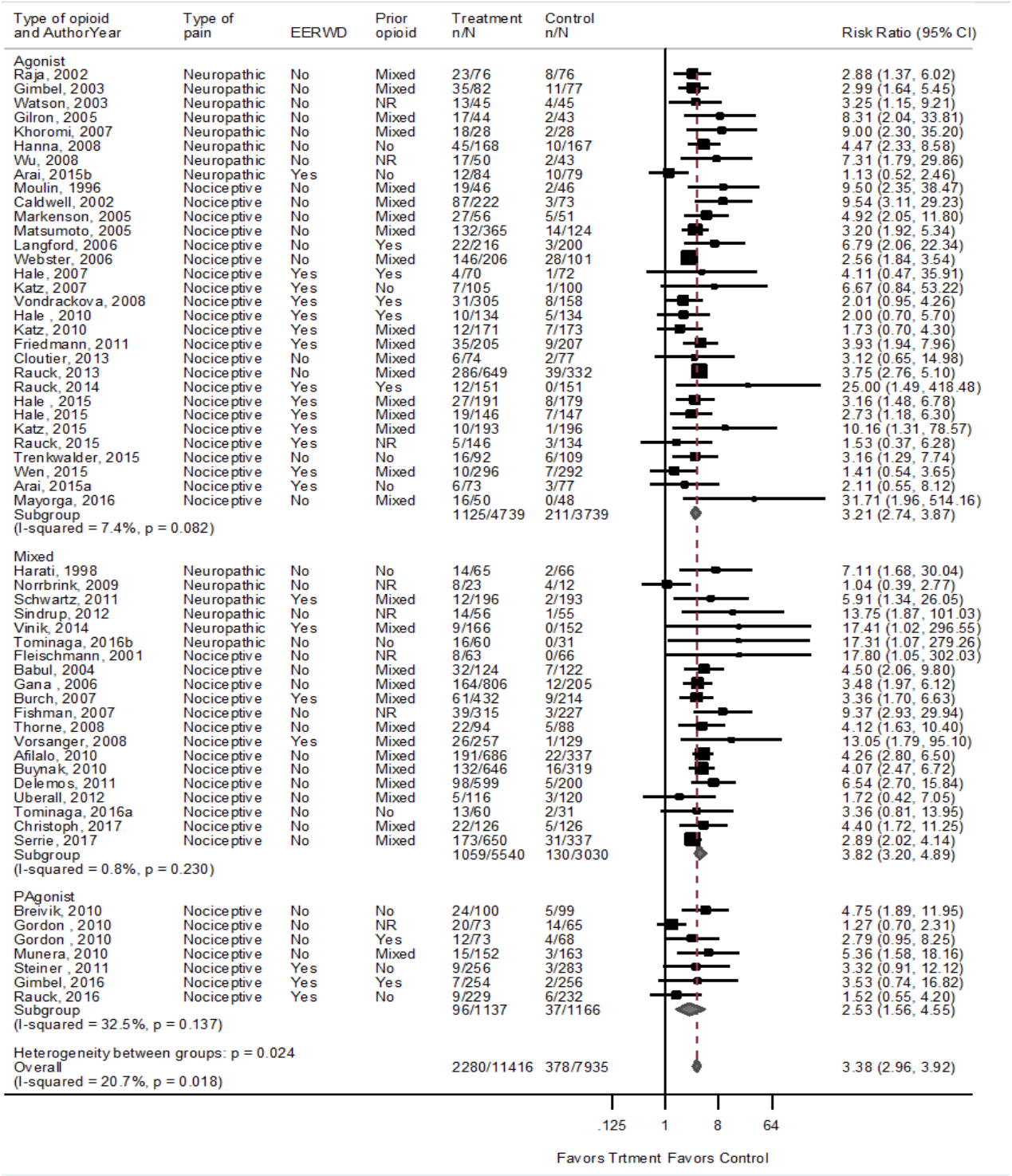
Note: Nociceptive pain refers to musculoskeletal condition

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



Note: Nociceptive pain refers to musculoskeletal condition

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



Note: Nociceptive pain refers to musculoskeletal condition

Table 24. 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 (19718)	--	3.57 (2.98 to 4.34)	15	49 (17388)	--	3.38 (2.96 to 3.92)	21%	58 (19351)	--
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 (17508)	0.64	3.57 (2.91 to 4.43)	21	40 (15601)	0.89	3.34 (2.93 to 3.88)	13%	44 (17141)	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 (16114)	--	3.58 (2.94 to 4.41)	14	40 (14813)	--	3.36 (2.90 to 3.98)	21%	47 (16001)	--
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	3.06 (2.70 to 3.48)	24%	38 (11846)	--	4.33 (3.50 to 5.54)	7.3	31 (11191)	--	3.69 (3.17 to 4.47)	24%	37 (11733)	--
EERW, 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	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 (18425)	--	3.57 (2.94 to 4.40)	18	42 (16483)	--	3.35 (2.96 to 3.83)	6.2%	47 (18058)	--
Opioid 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 (13228)	--	3.62 (2.94 to 4.53)	5.0	26 (11409)	--	3.51 (3.12 to 4.07)	0.4%	32 (13125)	--
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)	--
Published 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 (15650)	--	3.30 (2.72 to 3.97)	3.2	38 (14045)	--	3.24 (2.73 to 3.90)	30%	44 (15640)	--
Region: USA or Canada	2.41 (2.10 to 2.77)	43%	45 (14654)	0.25	3.27 (2.68 to 4.10)	6.6	36 (13005)	0.52	3.54 (3.04 to 4.26)	19%	43 (14287)	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	2.43 (2.13 to 2.78)	51%	54 (18988)	0.73	3.64 (3.01 to 4.44)	16	48 (17081)	--	3.43 (3.00 to 3.99)	15%	52 (18621)	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)	--

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

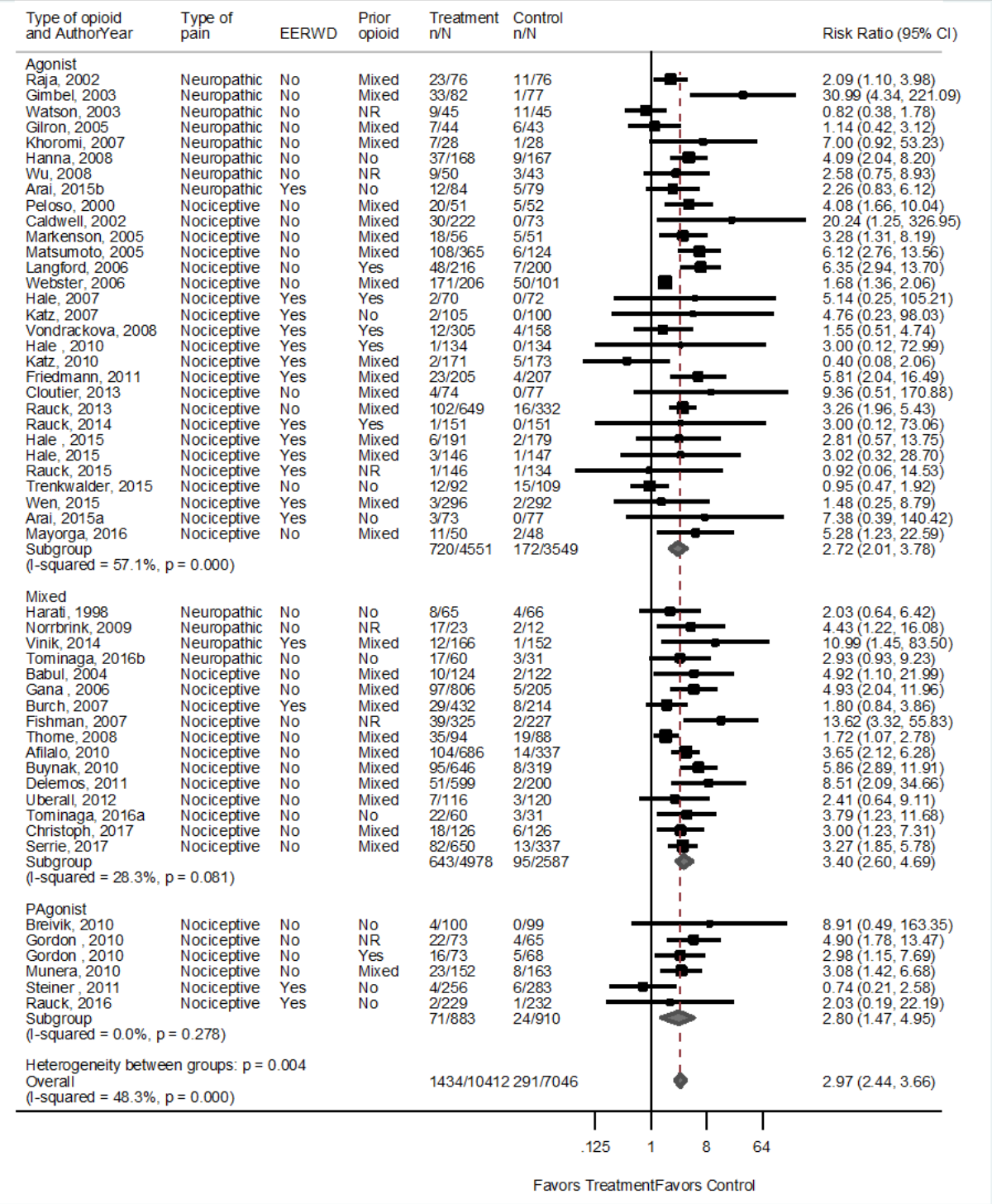
*p for interaction

†USA/Canada and Europe/Australia

Other Short-Term Adverse Events

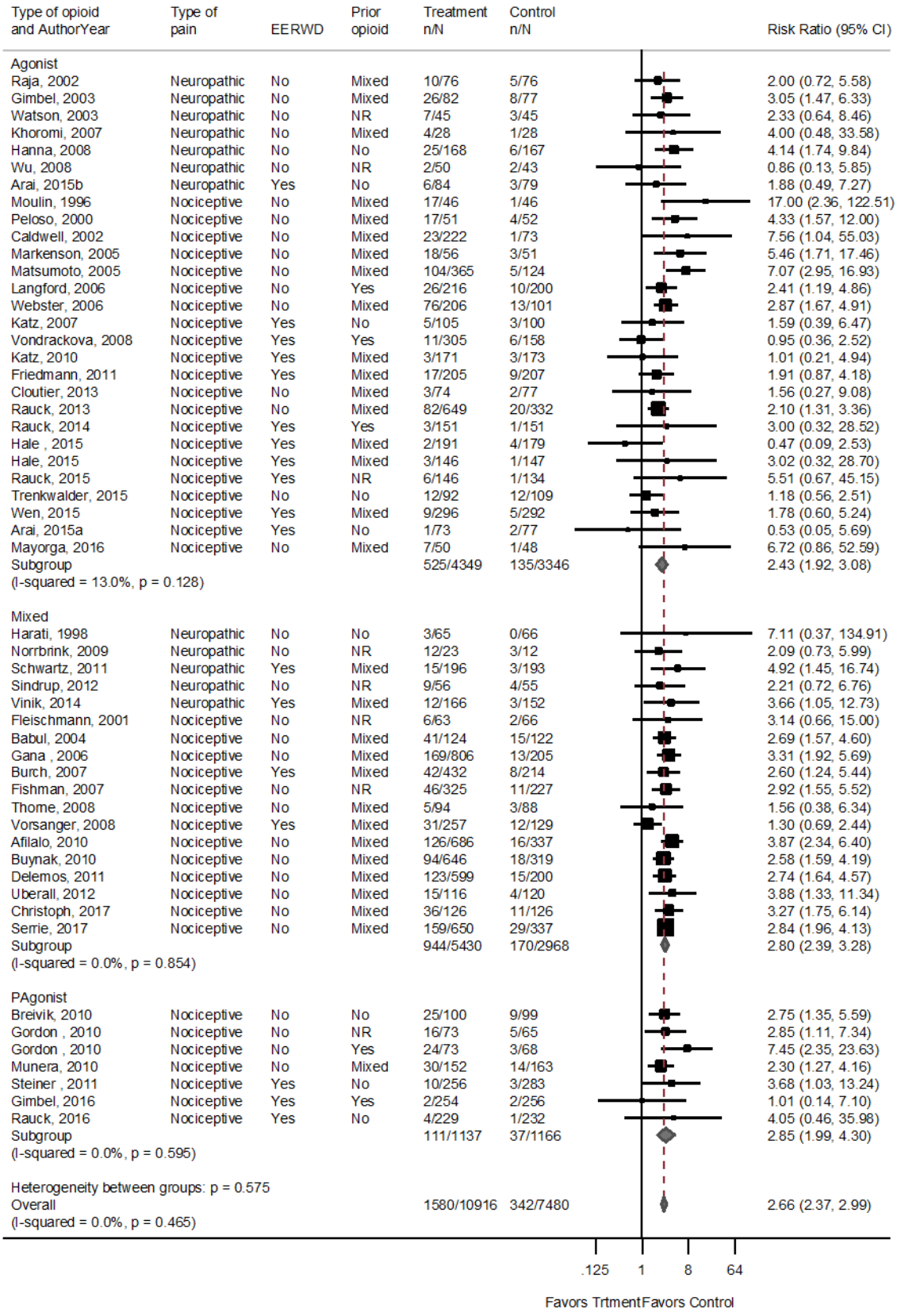
Opioids were associated with increased risk of somnolence (52 trials, N=17,458, RR 2.97, 95% CI, 2.44 to 3.66, I^2=48%; ARD 9%, 95% CI, 7% to 12%; **Figure 36, Table 22**),[50-52,54-56,58,59,61-63,65-67,69-77,79,81-83,85-87,90,93-99,103,107-113,115,119-122] dizziness (53 trials, N=18,396, RR 2.66, 95% CI, 2.37 to 2.99, I^2=0%; ARD 8%, 95% CI, 6% to 10%; **Figure 37, Table 22**),[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 22**)[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 25**). 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 22**).[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



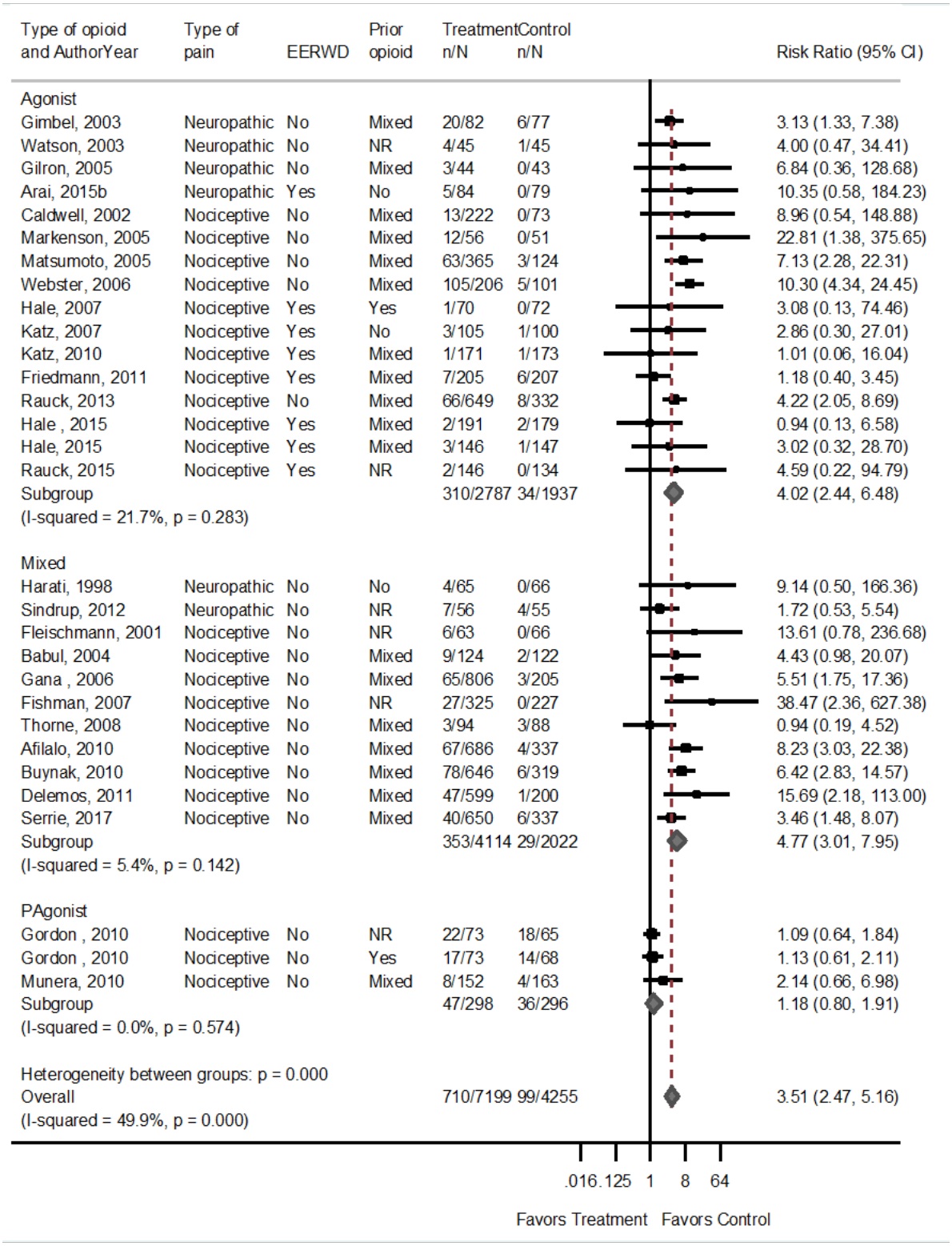
Note: Nociceptive pain refers to musculoskeletal condition

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



Note: Nociceptive pain refers to musculoskeletal condition

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



Note: Nociceptive pain refers to musculoskeletal condition

Table 25. 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 (18396)	--	1.06 (0.95 to 1.17)	0%	48 (17405)	--	3.51 (2.47 to 5.16)	50%	30 (11454)	--
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 (16364)	0.76	1.06 (0.95 to 1.19)	0%	39 (15729)	0.64	3.56 (2.37 to 5.52)	57%	24 (10713)	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 (15228)	--	1.04 (0.92 to 1.17)	3.3%	41 (14884)	--	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	2.87 (2.53 to 3.26)	0%	35 (11577)	--	1.08 (0.96 to 1.22)	0.1%	29 (10731)	--	3.95 (2.66 to 6.17)	58%	22 (9245)	--
EERW, 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	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 (17190)	--	1.05 (0.93 to 1.16)	0%	41 (16600)	--	4.66 (3.38 to 6.47)	13%	24 (10705)	--
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

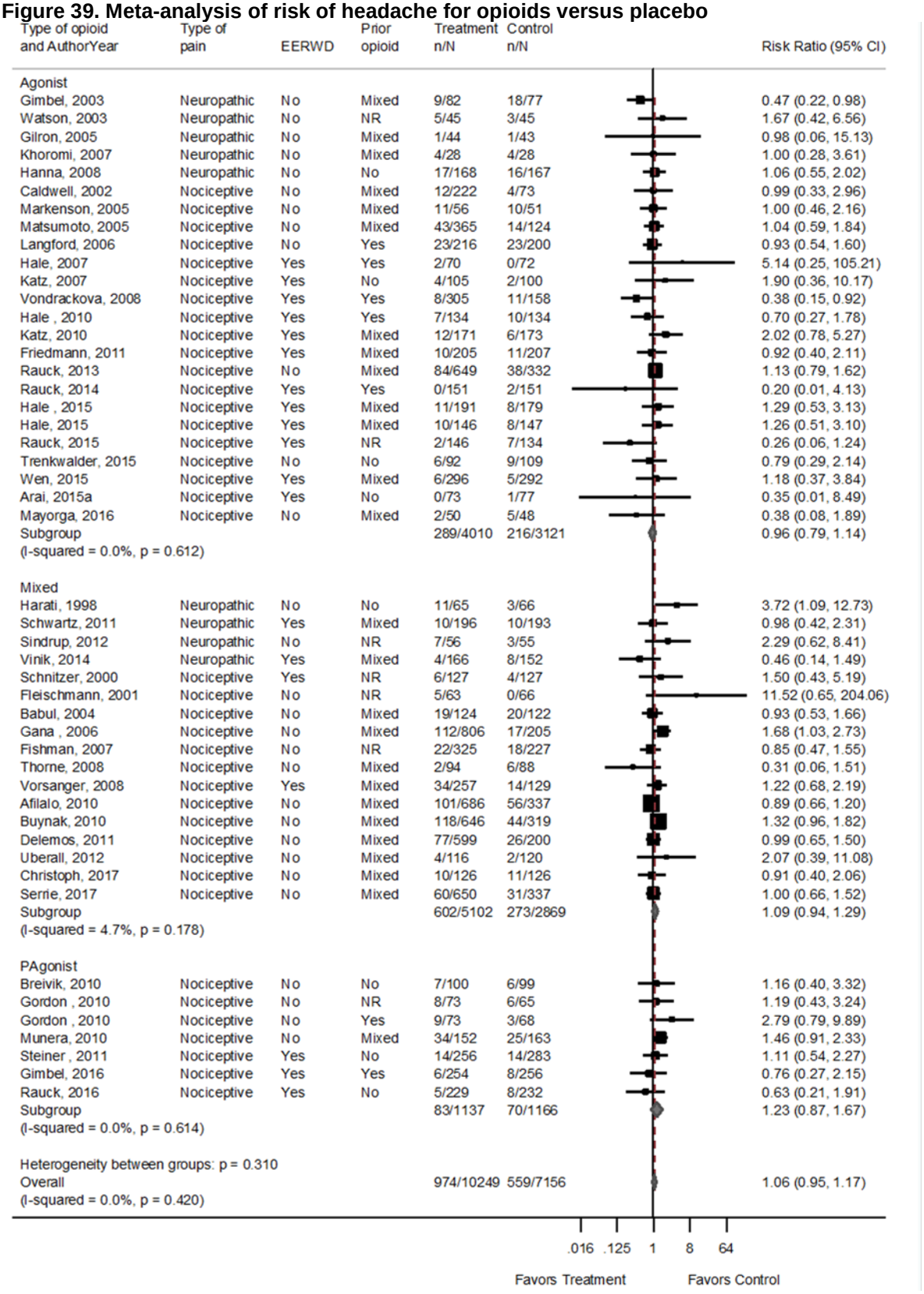
Analysis	Dizziness (95% CI)	I^2	# of trials (N)	p*	Headache (95% CI)	I^2	# of trials (N)	p*	Pruritus (95% CI)	I^2	# of trials (N)	p*
Experienced	2.25 (0.93 to 5.40)	39%	5 (1832)	--	0.82 (0.50 to 1.42)	0%	7 (2242)	--	1.17 (0.49 to 4.08)	0%	2 (283)	--
Mixed	2.76 (2.42 to 3.15)	0%	31 (12752)	--	1.08 (0.95 to 1.21)	0%	26 (11388)	--	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
In or after 2007	2.48 (2.13 to 2.84)	0%	39 (14669)	--	1.04 (0.92 to 1.17)	0%	36 (13991)	--	2.65 (1.72 to 4.25)	53%	19 (8403)	--
Region: USA or Canada	2.70 (2.34 to 3.13)	0%	40 (13514)	0.37	1.12 (0.98 to 1.26)	0%	38 (13367)	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 (17753)	0.64	1.06 (0.95 to 1.17)	0%	46 (17262)	0.92	3.23 (2.27 to 4.78)	46%	28 (11060)	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; N= total sample size

*p for interaction

†USA/Canada and Europe/Australia

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



Note: Nociceptive pain refers to musculoskeletal condition

Opioid Use Disorder, Dependence, and Related Outcomes

The prior AHRQ report included one fair-quality retrospective study that evaluated risk of opioid use disorder (defined as opioid abuse or dependence based on 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**).[158] 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: 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**).[153] 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 (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 prior 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 health care system.[157] 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).[153]

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**).[164] 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 prior 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**);[161,165] 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).[165] 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).[161] 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.

Three new cohort studies[154,159,162] (sample sizes ranged from 2902 to 7447, total N=14,580) evaluated the association between opioid use versus nonuse and fractures and three new cohort studies[153,159,163] evaluated the association between opioid use versus nonuse and risk of falls (one study[159] evaluated both outcomes). Sample sizes ranged from 2902 to 17310 (total N=24,443).[153] The average age of patients in the studies ranged from 60 to 80 years. One study[159] only evaluated men and in the other two 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 hazard ratio [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.[159] 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).[163] 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).[154] 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.

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).[159] 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).[162] 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).[153] 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).[153]

Cardiovascular Events

The prior 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**).[155,160] 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.[155] 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).[160] 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).[164] 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 prior 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**).[156] In a cross-sectional analysis of men with back pain (n=11,327) in an integrated health care 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]).[153]

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 >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 23-25**). 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.[142]

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).[142]

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 23-25**). 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 prior 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**).[158] Based on International Classification of Disease – Ninth Version (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).[153]

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**).[157,166,167] Two studies[157,166] were included in the prior AHRQ report and one new study[167] 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[166,167] 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 prior 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).[166] 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).[157] 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.[167] 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).[153]

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**).[164] 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.

Fracture and Falls

A fair-quality cohort study included in the prior 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**).[165]

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.[154,163] 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 ($p<0.0001$).[154] 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.[163] 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 prior 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.[161] 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).[154]

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.[153] 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 prior 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**).[155] 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 prior 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**).[168] 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 prior 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**).[156] 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).[169] 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).[170] 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).[153]

Depression

No study in the prior 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.[171] 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).[172] 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.

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 23-25**).

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)[173] (**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 26**, **Appendix Tables H-18 and H-19**).[174-176] 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[174] 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)[175] 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 26. Observational studies of opioid and benzodiazepine co-prescribing

Author, year Study design Duration	Sample	Interventions, N	Results	Quality
Dunn, 2010[157] 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[175] 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[176] 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**).[177-179] 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 (2,683 total cases) found exposure to gabapentin (adjusted OR 1.49, 95% CI, 1.18 to 1.88)[177] and pregabalin (OR 1.68, 95% CI, 1.19 to 2.36)[178] 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).[177] 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.[178]

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).[179] 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.[151] 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

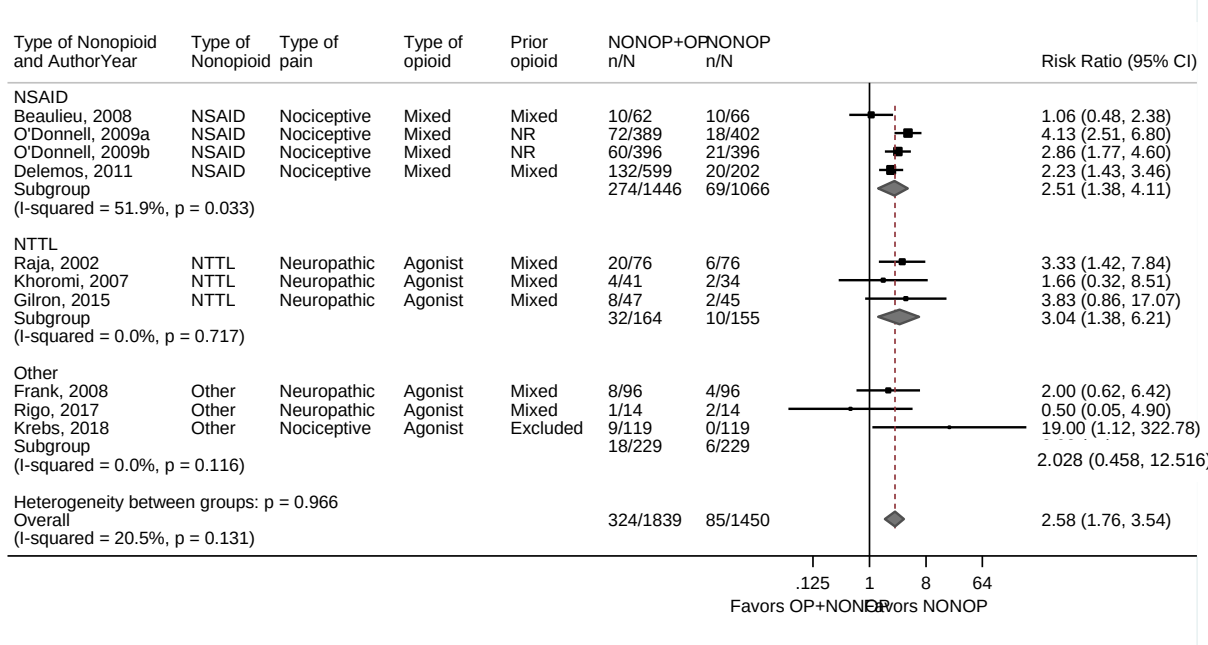
- Opioids were associated with increased risk of discontinuation due to adverse events (10 trials, N=3289, RR 2.58, 95% CI, 1.76 to 3.54, I2=20%; ARD 10%, 95% CI, 6% to 12%) somnolence (10 trials, N=3029, RR 2.68, 95% CI, 2.03 to 3.58, I2=0%; ARD 8%, 95% CI, 6% to 17%), nausea (10 trials, N=3029, RR 2.67, 95% CI, 1.97 to 3.94, I2=7.8%; ARD 11%, 95% CI, 6% to 16%), constipation (10 trials, N=3029, RR 3.63, 95% CI, 2.47 to 6.15, I2=0%; ARD 20%, 95% CI, 11% to 30%), vomiting (5 trials, N=2536, RR 4.50, 95% CI, 2.75 to 7.22, I2=0%; ARD 6%, 95% CI, 5% to 8%), dizziness (10 trials, N=3029, RR 1.87, 95% CI, 1.22 to 2.51, I2=21%; ARD 5%, 95% CI, 1% to 9%), pruritus (5 trials, N=2577, RR 4.22, 95% CI, 2.45 to 8.20, I2=0%; ARD 5%, 95% CI, 4% to 7%), and headache (7 trials, N=2683, RR 1.36, 95% CI, 1.09 to 1.74, I2=0%, ARD 3%, 95% CI, 1% to 5%) versus a nonopioid at short-term followup (SOE: high).

Detailed Synthesis

Opioids were associated with increased risk of discontinuation due to adverse events (10 trials, N=3289, RR 2.58, 95% CI, 1.76 to 3.54, I^2=20%; ARD 10%, 95% CI, 6% to 12%; **Figure 40**),[62,82,95,138-140,142,143,145] nausea (10 trials, N=3029, RR 2.67, 95% CI, 1.97 to 3.94, I^2=7.8%; ARD 11%, 95% CI, 6% to 16%; **Figure 41**),[62,67,82,95,122,138,140,143,145] vomiting (5 trials, N=2536, RR 4.50, 95% CI, 2.75 to 7.22, I^2=0%; ARD 6%, 95% CI, 5% to 8%; **Figure 42**),[62,138,143,145] constipation (10 trials, N=3029, RR 3.63, 95% CI, 2.47 to 6.15, I^2=34%; ARD 20%, 95% CI, 11% to 30%; **Figure 43**),[62,67,82,95,122,138,140,143,145] somnolence (10 trials, N=3029, RR 2.68, 95% CI, 2.03 to 3.58, I^2=0%; ARD 8%, 95% CI, 6% to 17%; **Figure 44**),[62,67,82,95,122,138,140,143,145] dizziness (10 trials, N=3029, RR 1.87, 95% CI, 1.22 to 2.51, I^2=21%; ARD 5%, 95% CI, 1% to 9%; **Figure 45**),[62,67,82,95,122,138,140,143,145] 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 46**),[62,67,140,143] and headache (7 trials, N=2683, RR 1.36, 95% CI, 1.09 to 1.74, I^2=0%, ARD 3%, 95% CI, 1% to 5%; **Figure 47**)[62,67,82,138,143,145] versus a nonopioid at short-term followup (**Table 27**). The estimate for serious adverse events (4 trials, N=1949, RR 0.63, 95% CI, 0.08 to 4.87; **Figure 48**)[138,142,143] was imprecise. 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[142] were rated fair-quality (**Tables 28 and 29**).

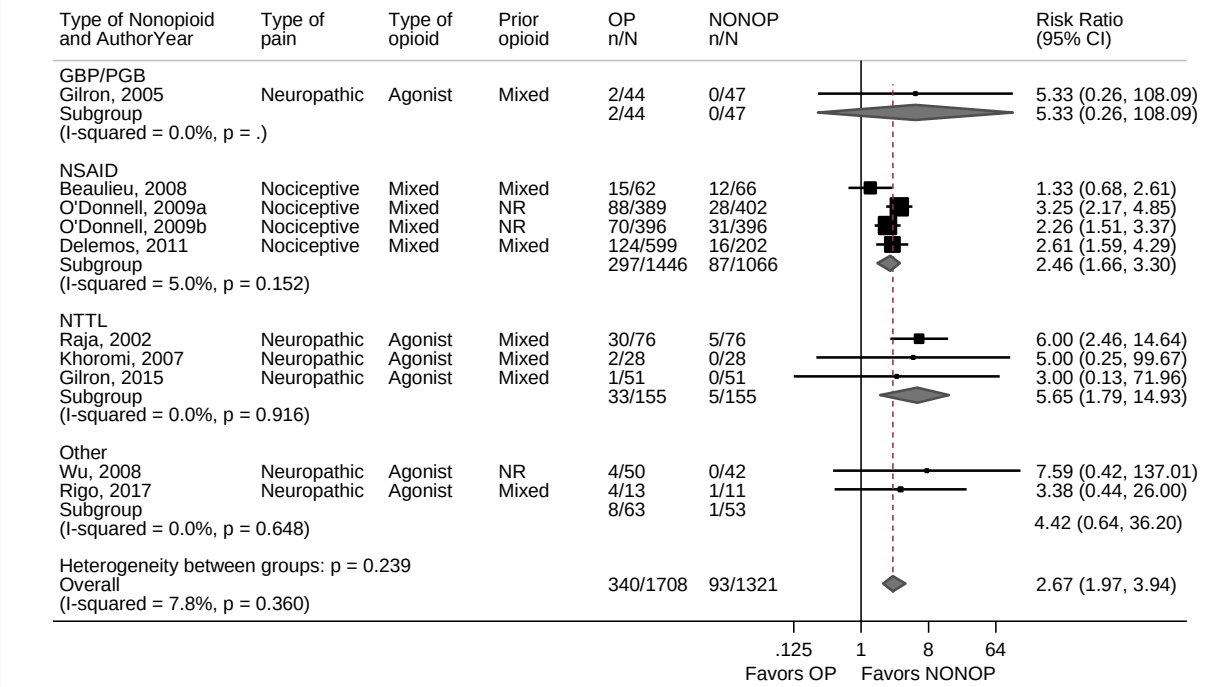
No study evaluated the association between an opioid plus nonopioid versus a nonopioid alone and risk of overdose or opioid use disorder and related outcomes.

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



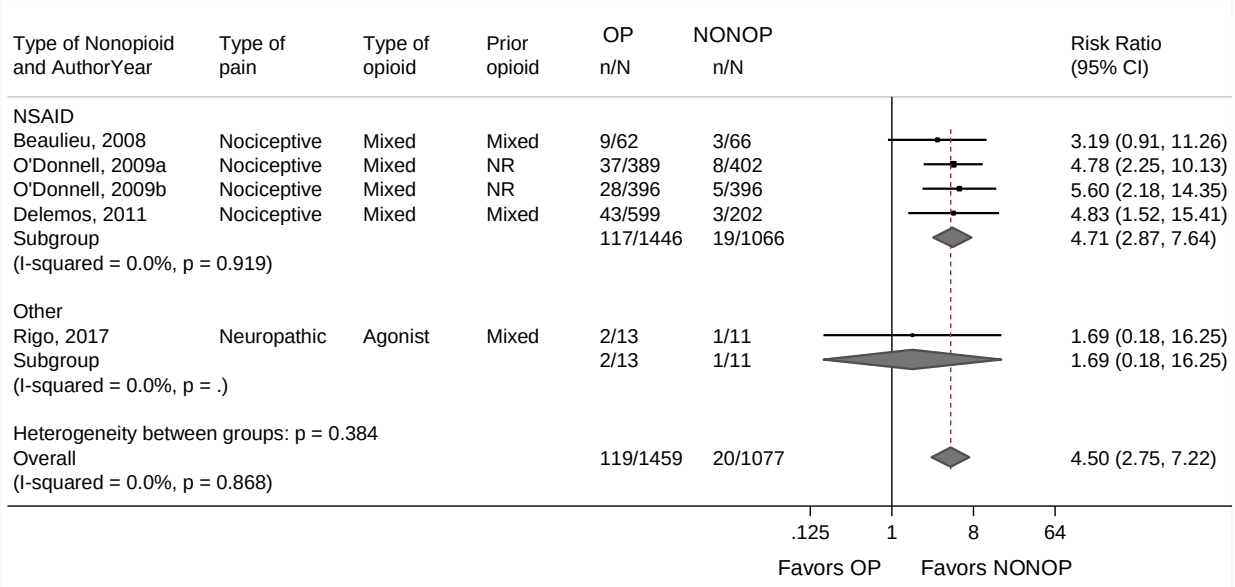
Note: Nociceptive pain refers to musculoskeletal condition

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



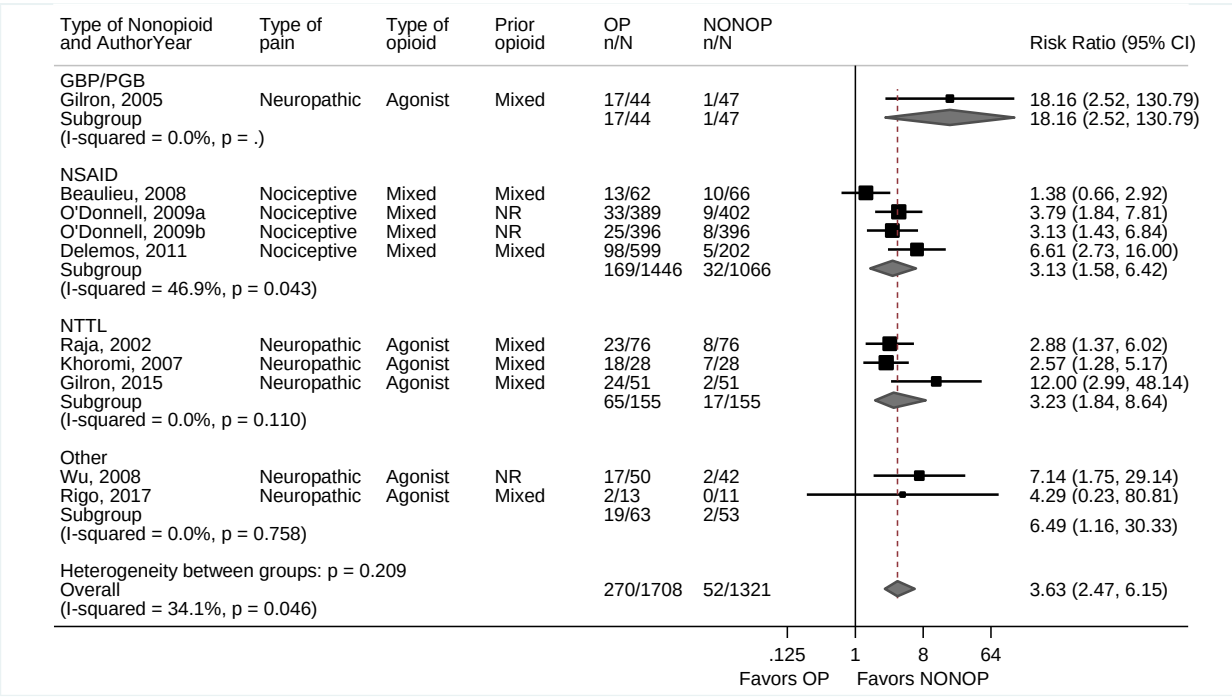
Note: Nociceptive pain refers to musculoskeletal condition

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



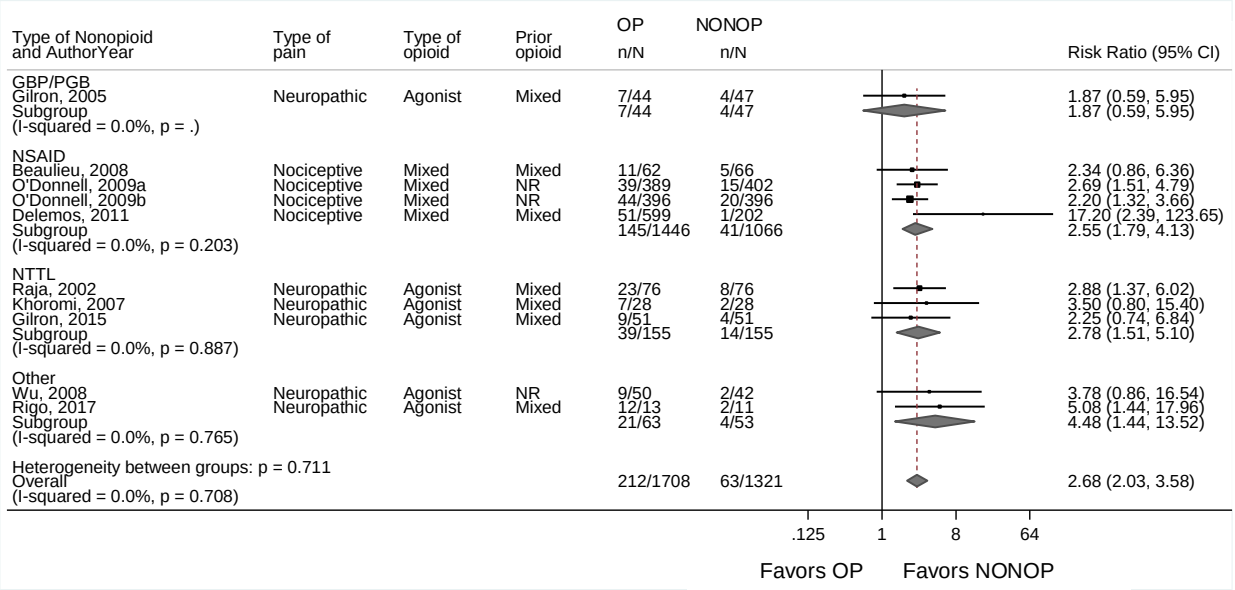
Note: Nociceptive pain refers to musculoskeletal condition

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



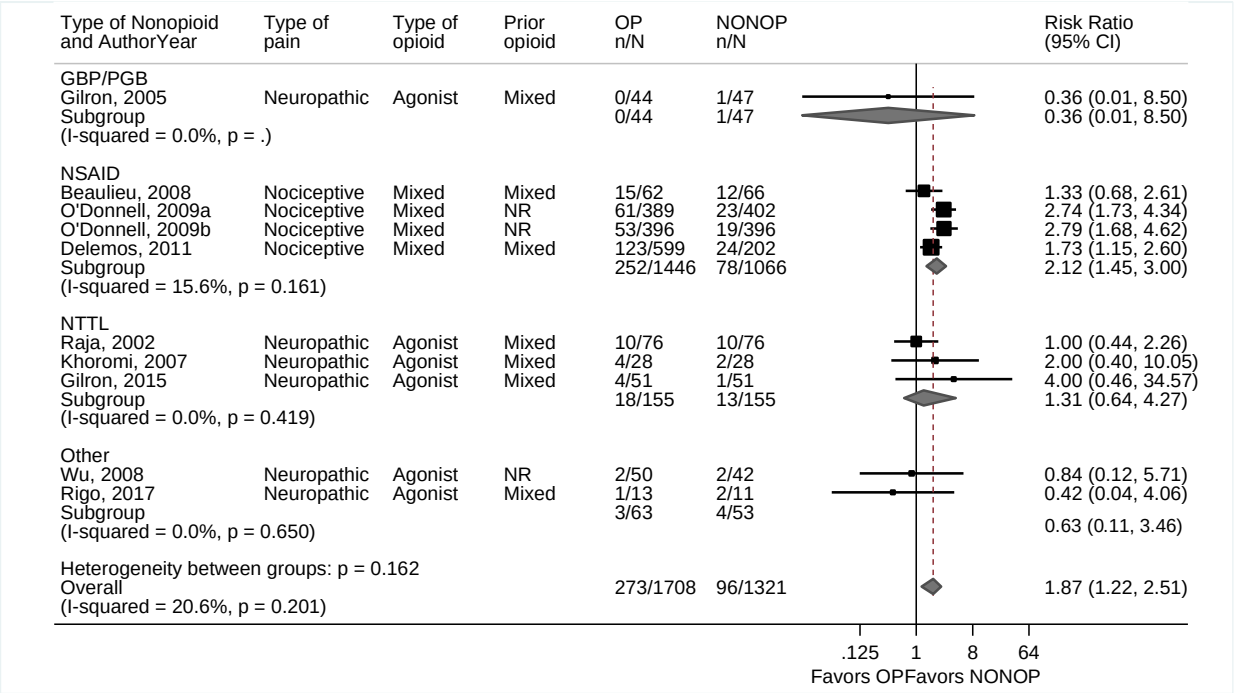
Note: Nociceptive pain refers to musculoskeletal condition

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



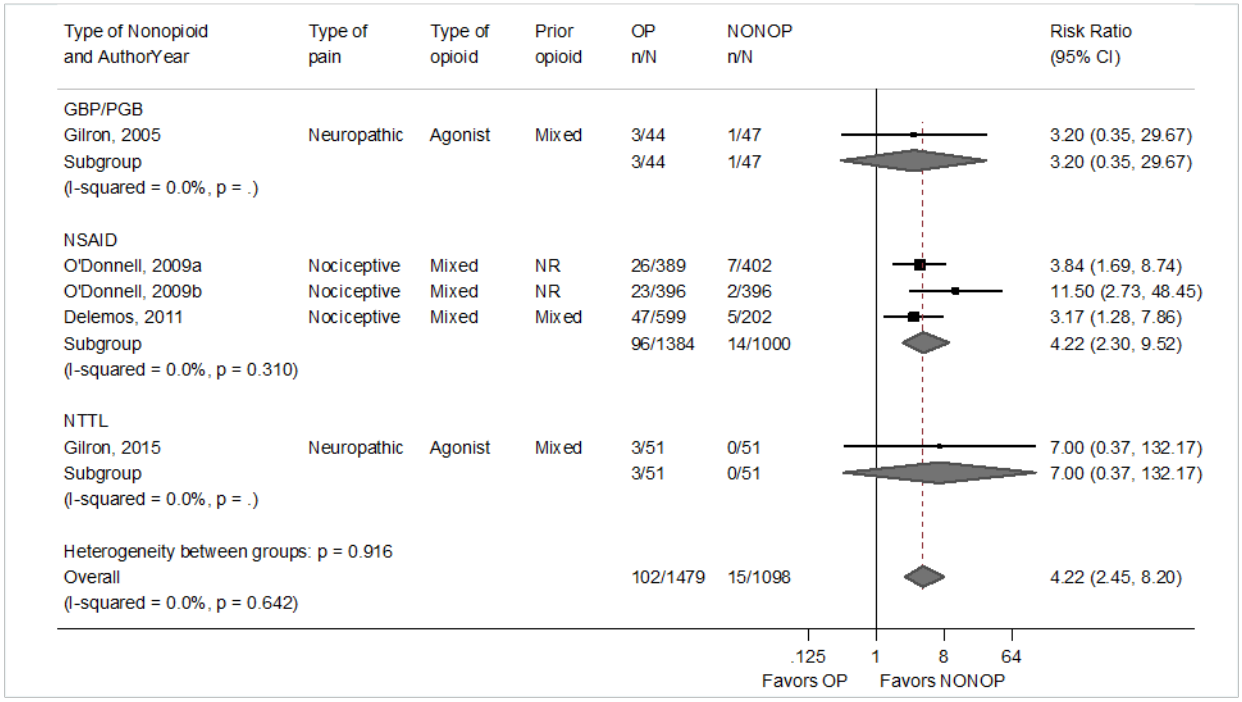
Note: Nociceptive pain refers to musculoskeletal condition

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



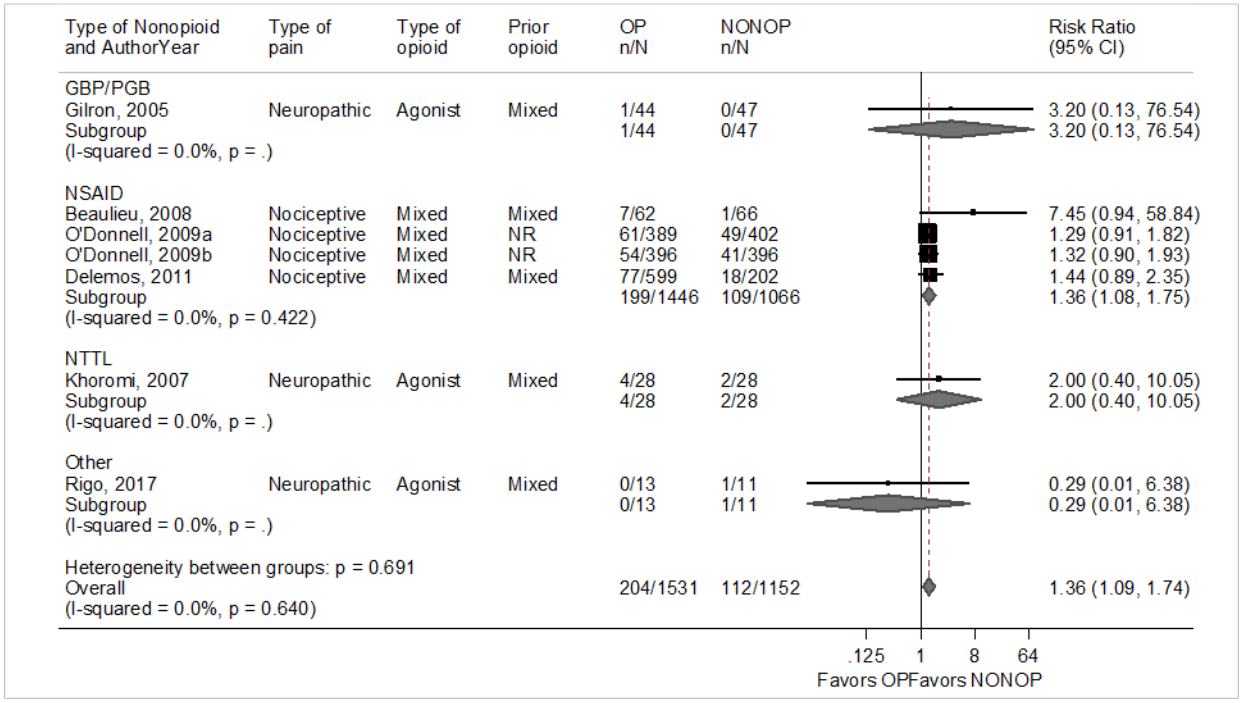
Note: Nociceptive pain refers to musculoskeletal condition

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



Note: Nociceptive pain refers to musculoskeletal condition

Figure 47. Meta-analysis of risk of headache for opioids versus nonopioids



Note: Nociceptive pain refers to musculoskeletal condition

Table 27. Summary table of adverse events for opioids versus nonopioids

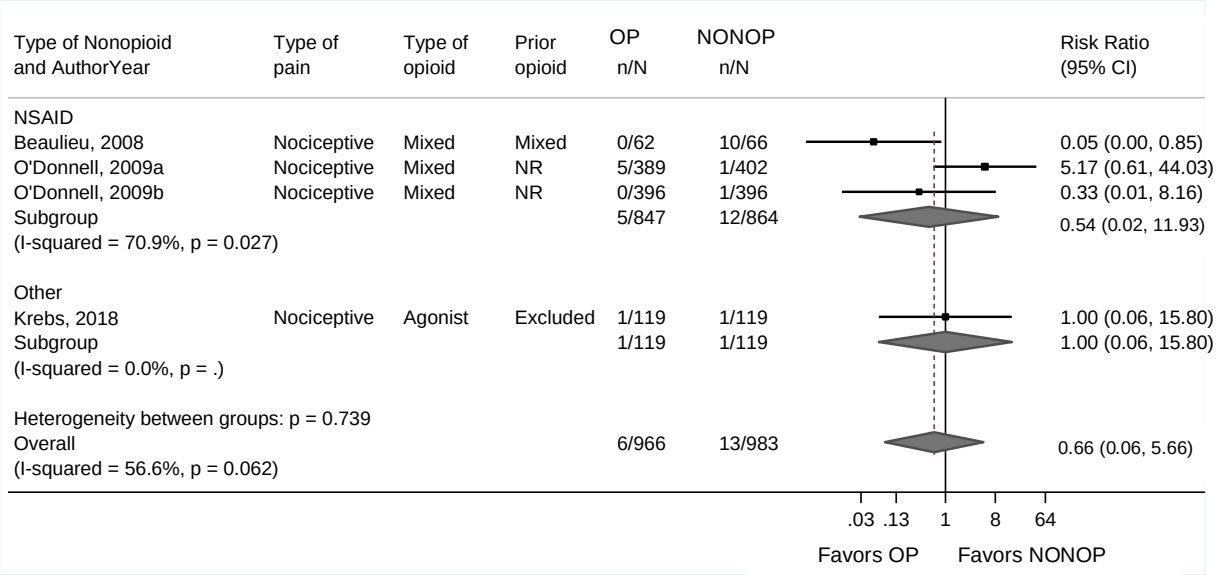
Study, year Country Year	1: Duration of followup 2: Total patients randomized 3: Pain condition	1: Opioid 2: Control	Discontinuation due to adverse events	Serious adverse events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pr
Beaulieu, 2008[138] Canada Fair	1: 8 weeks 2: 129 3: Osteoarthritis	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)	NI
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: (4 2: (5
Frank, 2008[139] 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	NI
Gilron, 2015[140] 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: (3 2: (0
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	NI

Study, year Country Year	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	Pr
Jamison, 1998[141] 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: 2:
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)	NI
Krebs, 2018[142] 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	NI
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	NI
O'Donnell, 2009a[143] USA Fair	1: 6 weeks 2: 796 3: Low back pain	1: Tramadol IR 200 mg 2: Celecoxib 400 mg	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: (2 2: (7
O'Donnell, 2009b[143] USA Fair	1: 6 weeks 2: 802 3: Low back pain	1: Tramadol IR 200 mg 2: Celecoxib 400 mg	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: (2 2: (2

Study, year Country Year	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	Pr
Pavelka, 1998[144] 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	NI
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)	NI
Rigo, 2017 [145] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic	1: Methadone 9 mg 2: Ketamine 90 mg	NR	NR	NR	NR	NR	NR	NR	NR	NI
Wu, 2008[122] USA Fair	1: 6 weeks 2: 60 3:Postamputation pain	1: Morphine SR 30-180 mg (mean 112 mg) 2: Mexiletine 150-1200 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)	NI

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

Figure 48. Meta-analysis of risk of serious adverse events for opioids versus nonopioids



Note: Nociceptive pain refers to musculoskeletal condition

Table 28. 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	2.58 (1.76 to 3.54)	20%	10 (3289)	--	2.68 (2.03 to 3.58)	0%	10 (3029)	0%
Nonopioid type: NSAID	2.51 (1.38 to 4.11)	52%	4 (2512)	0.88	2.55 (1.79 to 4.13)	0%	4 (2512)	0.68
• **Gabapentinoid**	No studies	--	--	--	1.87 (0.59 to 5.95)	--	1 (91)	--
• **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)	52%	3 (458)	--	4.48 (1.44 to 13.52)	0%	2 (116)	--
Opioid type: Opioid agonist	2.67 (1.44 to 4.67)	0%	6 (777)	0.91	2.91 (1.85 to 4.57)	0%	6 (517)	0.66
• **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)	0.83	2.55 (1.79 to 4.13)	0%	4 (2512)	0.66
• **Neuropathic**	2.47 (1.24 to 4.35)	0%	5 (539)	--	2.91 (1.85 to 4.57)	0%	6 (517)	--
Trial quality: Good	19.00 (1.12 to 322.78)	--	1 (238)	0.21	No studies	--	--	--
• **Fair**	2.52 (1.68 to 3.44)	23%	9 (3051)	--	2.68 (2.03 to 3.58)	0%	10 (3029)	0%
Opioid dose (mg MED/day): <50	2.83 (1.92 to 4.00)	3.6%	6 (2842)	0.35	2.64 (1.87 to 4.45)	0%	5 (2499)	0.14
• **50-90**	1.46 (0.70 to 4.35)	0%	3 (295)	--	2.50 (1.27 to 5.07)	0%	3 (286)	--

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*
• **>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 (663)	0.85	2.68 (1.65 to 4.35)	0%	5 (493)	0.99
• **Parallel group**	2.49 (1.37 to 4.07)	43%	6 (2778)	--	2.68 (1.91 to 4.46)	0%	5 (2536)	--

Abbreviations: CI=confidence interval; MED=morphine equivalent dose; N= total sample size
*p for interaction

Table 29. 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	2.67 (1.97 to 3.94)	7.8%	10 (3029)	--	3.63 (2.47 to 6.15)	34%	10 (3029)	--	1.87 (1.22 to 2.51)	21%	10 (3029)	--
Nonopioid type: NSAID	2.46 (1.66 to 3.30)	5.0%	4 (2512)	0.37	3.13 (1.58 to 6.42)	47%	4 (2512)	0.47	2.12 (1.45 to 3.00)	16%	4 (2512)	0.31
• **Gabapentinoid**	5.33 (0.26 to 108.09)	--	1 (91)	--	18.16 (2.52-130.79)	--	1 (91)	--	0.36 (0.01 to 8.50)	--	1 (91)	--
• **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	5.38 (2.42 to 11.15)	0%	6 (517)	0.09	4.23 (2.48 to 10.81)	21%	6 (517)	0.42	1.10 (0.58 to 2.15)	0%	6 (517)	0.11
• **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)	0.09	3.13 (1.58 to 6.42)	47%	4 (2512)	0.42	2.12 (1.45 to 3.00)	16%	4 (2512)	0.11
• **Neuropathic**	5.38 (2.42 to 11.15)	0%	6 (517)	--	4.23 (2.48 to 10.81)	21%	6 (517)	--	1.10 (0.58 to 2.15)	0%	6 (517)	--
Trial quality: Fair	2.67 (1.97 to 3.94)	7.8%	10 (3029)	--	3.63 (2.47 to 6.15)	34%	10 (3029)	--	1.87 (1.22 to 2.51)	21%	10 (3029)	--
Opioid dose (mg MED/day): <50	2.70 (2.06 to 3.60)	0%	5 (2499)	0.12	4.43 (2.83 to 8.09)	0%	5 (2499)	0.57	2.20 (1.39 to 3.08)	3.7%	5 (2499)	0.21
• **50-90**	1.46 (0.69 to 5.38)	0%	3 (286)	--	2.82 (0.90 to 12.14)	60%	3 (286)	--	1.53 (0.81 to 3.98)	0%	3 (286)	--
• **>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)	0.08	4.31 (2.43 to 11.96)	28%	5 (493)	0.43	1.18 (0.62 to 2.55)	0%	5 (493)	0.19
• **Parallel group**	2.48 (1.71 to 3.29)	2.1%	5 (2536)	--	3.16 (1.68 to 6.25)	39%	5 (2536)	--	2.07 (1.35 to 2.86)	14%	5 (2536)	--

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

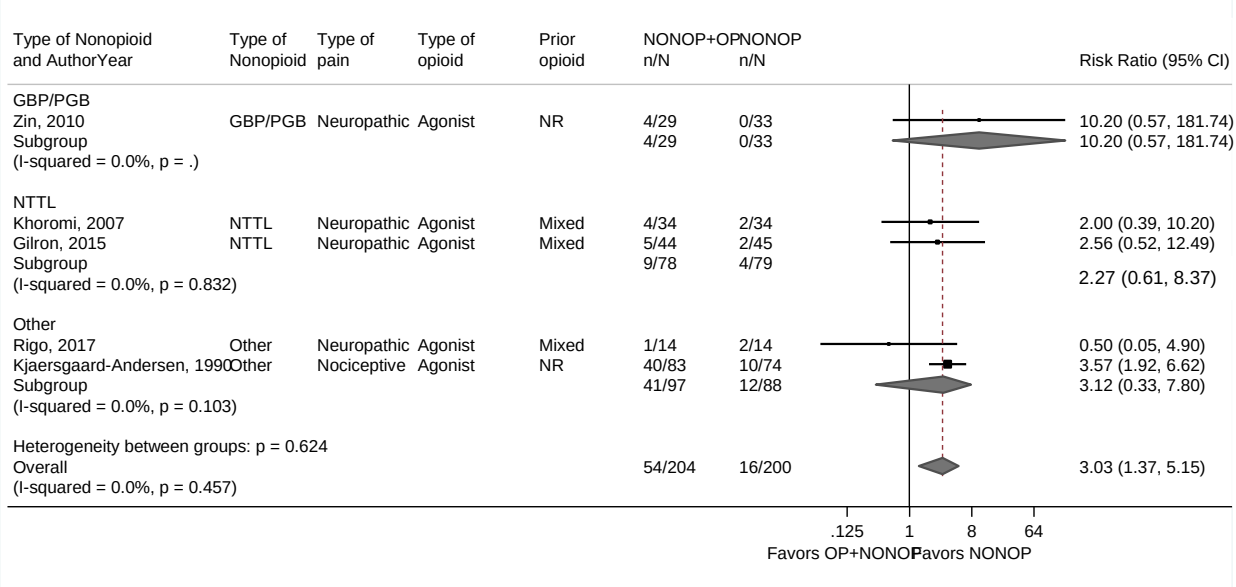
- An opioid plus nonopioid was associated with increased risk of discontinuation due to adverse events (5 trials, N=404, RR 3.03, 95% CI, 1.37 to 5.15, I^2=0%; ARD 12%, 95% CI, -3% to 26%), nausea (5 trials, N=330, RR 2.18, 95% CI, 1.16 to 6.49, I^2=0%; ARD 7%%, 95% CI, 2% to 12%), constipation (5 trials, N=330, RR 3.23, 95% CI, 2.10 to 7.57, I^2=0%; ARD 29%, 95% CI, 14% to 45%), and somnolence (5 trials, 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 dizziness were not statistically significant (5 trials, N=330, RR 1.38, 95% CI, 0.56 to 2.11, I^2=0%) (SOE: low for dizziness, moderate for other outcomes).

Detailed Synthesis

An opioid plus nonopioid was associated with increased risk of discontinuation due to adverse events (5 trials, N=404, RR 3.03, 95% CI, 1.37 to 5.15, I^2=0%; ARD 12%, 95% CI, -3% to 26%; **Figure 49**),[82,140,145,148,149] 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 50**),[67,82,140,145,149] constipation (5 trials, N=330, RR 3.23, 95% CI, 2.10 to 7.57, I^2=0%; ARD 29%, 95% CI, 14% to 45%; **Figure 51**),[67,82,140,145,149]and somnolence (5 trials, N=330, RR 2.44, 95% CI, 1.32 to 4.52, I^2=0%; ARD 11%, 95% CI, 4% to 17%; **Figure 52**),[67,82,140,145,149] versus a nonopioid alone at short-term followup (**Table 30**). Effects on risk of dizziness were not statistically significant (5 trials, N=330, RR 1.38, 95% CI, 0.56 to 2.11, I^2=0%; **Figure 53**).[67,82,140,145,149] Estimates for serious adverse events (1 trial, n=62, RR 0.38, 95% CI, 0.02 to 8.93),[149] headache (3 trials, N=137, RR 1.18, 95% CI, 0.42 to 3.00, I^2=0%),[82,145,149] vomiting (2 trials, N=81, RR 1.68, 95% CI, 0.43 to 6.56, I^2=0%),[145,149] and pruritus (2 trials, N=148, RR 3.49, 95% CI, 0.32 to 37.88, I^2=31%)[67,149] were imprecise. 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 31 and 32**). All trials were rated fair-quality, evaluated patients with neuropathic pain, and evaluated an opioid agonist.

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 discontinuation due to adverse events for opioids plus nonopioids versus nonopioids



Note: Nociceptive pain refers to musculoskeletal condition

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

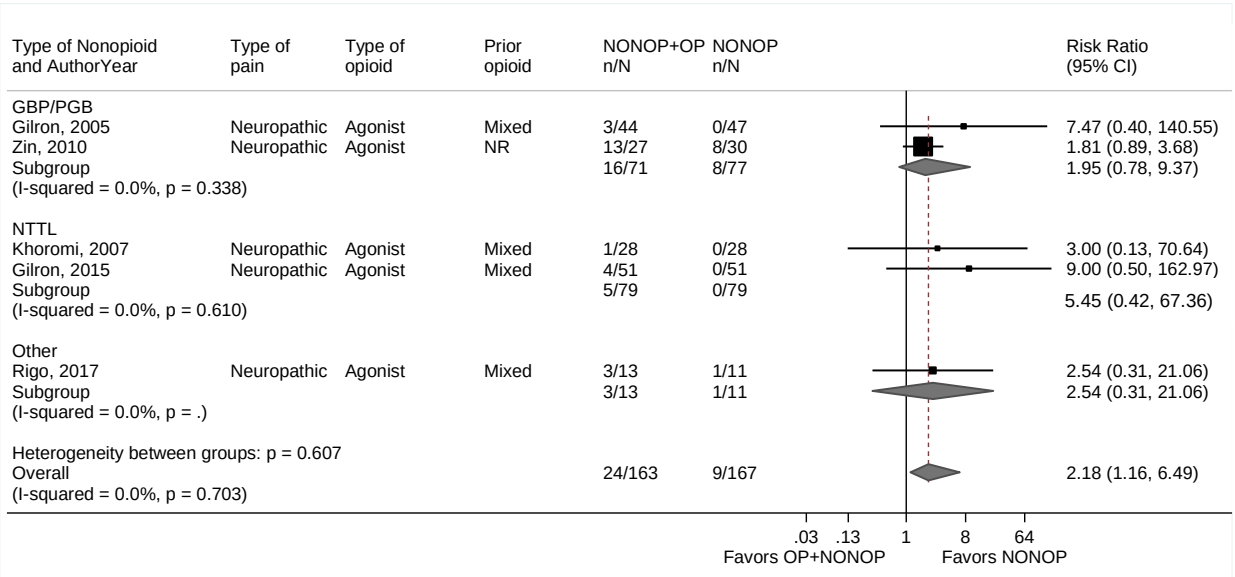


Figure 51. Meta-analysis of risk of constipation for opioids plus nonopioids versus nonopioids

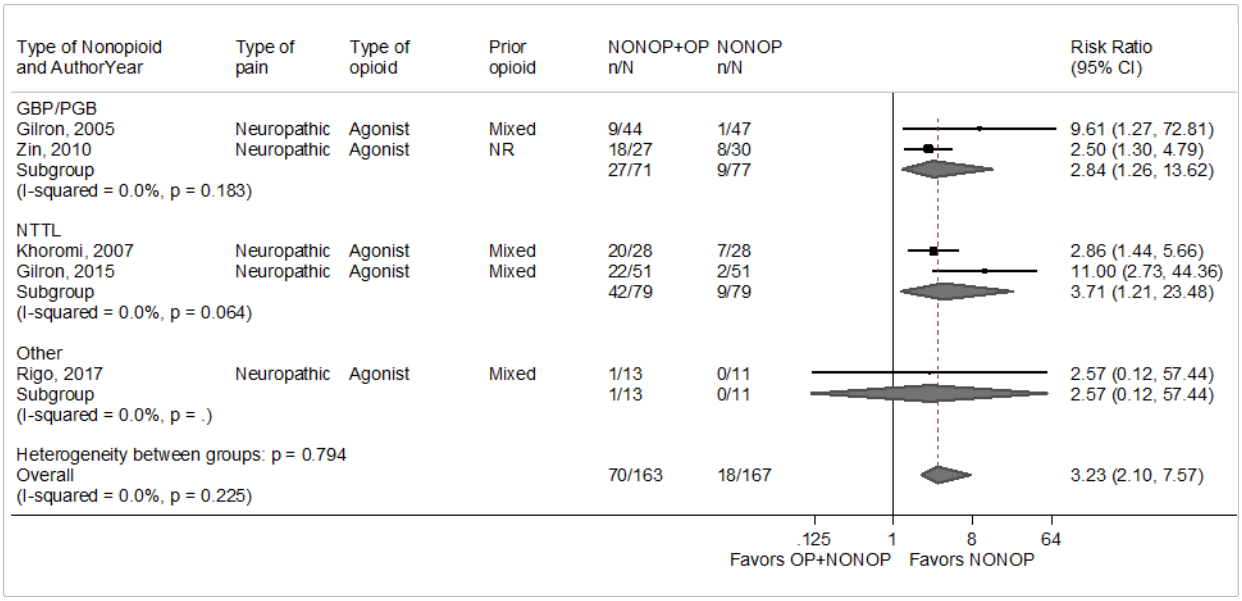


Figure 52. Meta-analysis of risk of somnolence for opioids plus nonopioids versus nonopioids

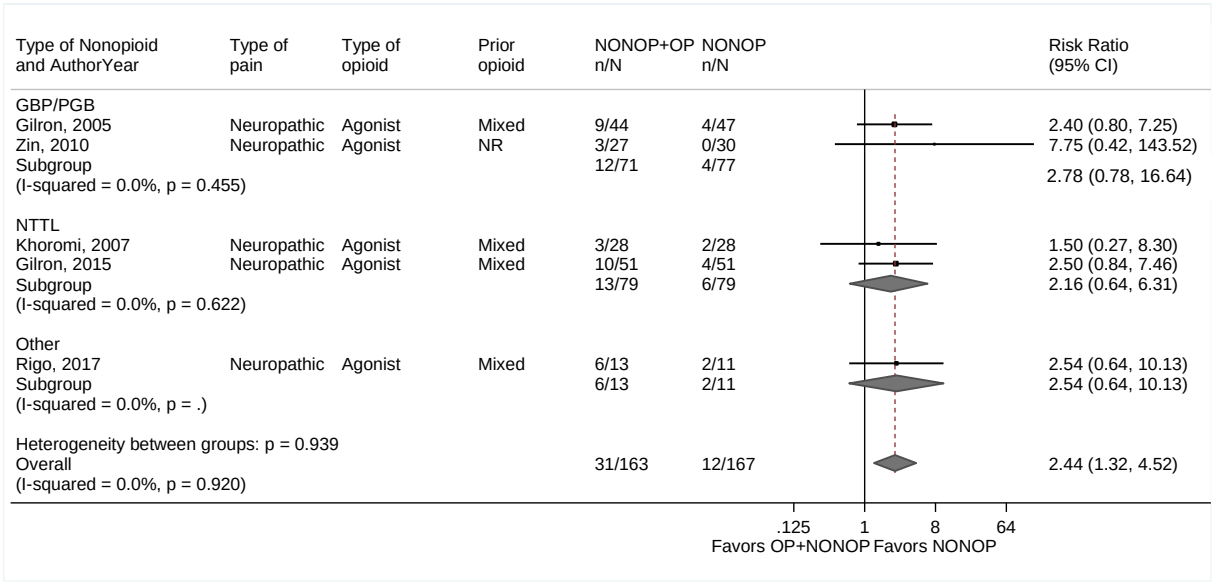


Table 30. Summary table of adverse events for opioids plus nonopioids versus nonopioids

Study, year Country Quality	1: Duration of followup 2: Total patients randomized 3: Pain condition	1: Opioid + nonopioid 2: Nonopioid	Discontinuation due to adverse events	Serious adverse events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
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[140] 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[148] Denmark Poor	1: 4 weeks 2: 158 3: Osteoarthritis	1: Codeine 180 mg + acetaminophen 3000 mg 2: Acetaminophen 3000 mg	1: 48.2% (40/83) 2: 13.5% (10/74)	NR	NR	NR	NR	NR	NR	NR	NR
Rigo, 2017 [145] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic pain	1: Methadone 9 mg + ketamine 90 mg 2: Ketamine 90 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 + nonopioid 2: Nonopioid	Discontinuation due to adverse events	Serious adverse events	Nausea	Vomiting	Constipation	Dizziness	Headache	Somnolence	Pruritus
Zin, 2010[149] 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

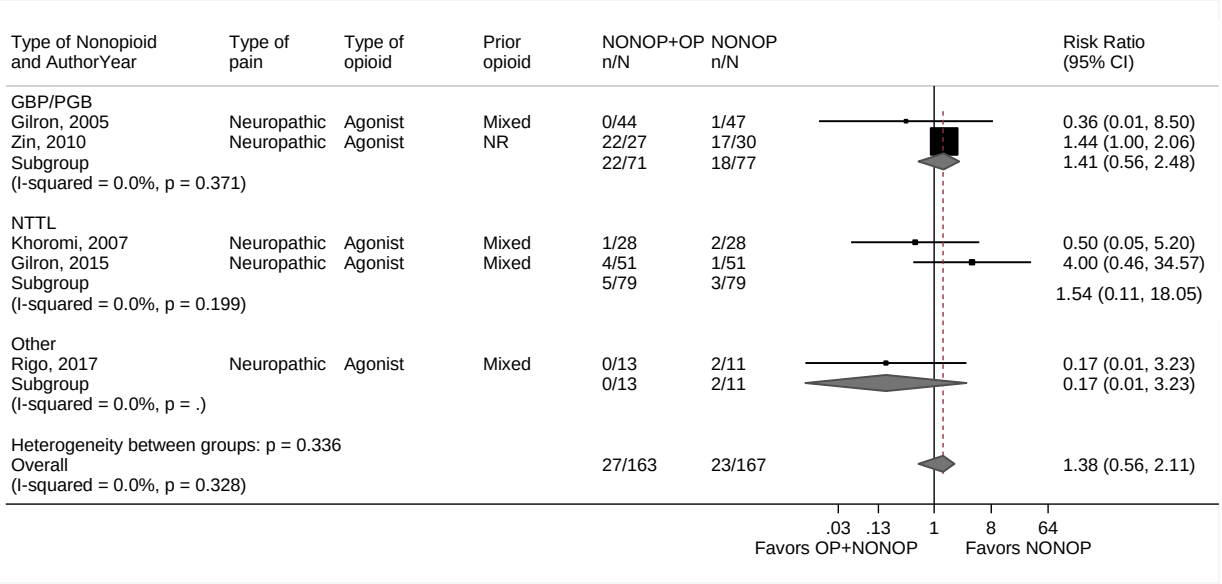


Table 31. Pooled analyses of risk of discontinuation due to adverse events and somnolence for opioids plus nonopioids versus nonopioids

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	3.03 (1.37 to 5.15)	0%	5 (404)	--	2.44 (1.32 to 4.52)	0%	5 (330)	--
Nonopioid type: Gabapentinoid	10.20 (0.57 to 181.74)	--	1 (62)	0.72	2.78 (0.78 to 16.64)	0%	2 (148)	0.94
• **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	3.03 (1.37 to 5.15)	0%	5 (404)	--	2.44 (1.32 to 4.52)	0%	5 (330)	--
Pain type: Musculoskeletal	3.57 (1.92 to 6.62)	--	1 (157)	0.41				
• **Neuropathic**	3.03 (1.37 to 5.15)	0%	5 (404)	--	2.44 (1.32 to 4.52)	0%	5 (330)	--
Trial quality: Fair	3.03 (1.37 to 5.15)	0%	5 (404)	0.41	2.44 (1.32 to 4.52)	0%	5 (330)	--
• **Poor**	3.57 (1.92 to 6.62)	--	1 (157)	--				
Opioid dose (mg MED/day): <50	3.10 (1.12 to 5.68)	0%	4 (315)	0.85	2.54 (1.13 to 5.24)	0%	4 (228)	0.96
• **50-90**	2.56 (0.52 to 12.49)	--	1 (89)	--	2.50 (0.84 to 7.46)	--	1 (102)	--
Crossover design	2.27 (0.61 to 8.37)	0%	2 (157)	0.63	2.25 (1.05 to 4.64)	0%	3 (249)	0.69
• **Parallel group**	3.27 (0.85 to 7.87)	0%	3 (247)	--	3.12 (0.70 to 21.58)	0%	2 (81)	--

Abbreviations: CI=confidence interval; MED=morphine equivalent dose; N= total sample size
*p for interaction

Table 32. 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)	--	3.23 (2.10 to 7.57)	0%	5 (330)	--	1.38 (0.56 to 2.11)	0%	5 (330)	--
Nonopioid type: Gabapentinoid	1.95 (0.78 to 9.37)	0%	2 (148)	0.71	2.84 (1.26 to 13.62)	0%	2 (148)	--	1.41 (0.56 to 2.48)	0%	2 (148)	0.56
• **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)	--	3.23 (2.10 to 7.57)	0%	5 (330)	--	1.38 (0.56 to 2.11)	0%	5 (330)	--
Pain type: Neuropathic	2.18 (1.16 to 6.49)	0%	5 (330)	--	3.23 (2.10 to 7.57)	0%	5 (330)	--	1.38 (0.56 to 2.11)	0%	5 (330)	--
Trial quality: Fair	2.18 (1.16 to 6.49)	0%	5 (330)	--	3.23 (2.10 to 7.57)	0%	5 (330)	--	1.38 (0.56 to.11)	0%	5 (330)	--
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)	0.17	1.34 (0.30 to 1.99)	0%	4 (228)	0.34
• **50-90**	9.00 (0.50 to 162.97)	--	1 (102)	--	11.00 (2.73 to 44.36)	--	1 (102)	--	4.00 (0.46 to 34.57)	--	1 (102)	--
Crossover design	6.07 (1.01 to 35.62)	0%	3 (249)	0.30	4.52 (1.89 to 19.36)	18%	3 (249)	0.41	1.15 (0.15 to 6.38)	0%	3 (249)	0.92
• **Parallel group**	1.87 (0.77 to 5.19)	0%	2 (81)	--	2.50 (0.91 to 6.97)	0%	2 (81)	--	1.39 (0.34 to 2.35)	0%	2 (81)	--

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 (5 trials, N=860, RR 0.74, 95% CI, 0.40 to 1.30, I^2=51%) 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**),[82,140,145,147,150] nausea (5 trials, N=585, RR 0.98, 95% CI, 0.57 to 1.84, I^2=0%; **Figure 55**),[67,82,140,145,150] constipation (6 trials, N=860, RR 0.91, 95% CI, 0.67 to 1.13, I^2=0%; **Figure 56**),[67,82,140,145,147,150] or somnolence (5 trials, N=860, RR 0.74, 95% CI, 0.40 to 1.30, I^2=51%; **Figure 57**),[67,82,140,145,147,150] versus an opioid alone at short-term followup (**Table 33**). Some estimates favored the opioid plus nonopioid combination, possibly due to lower average opioid doses used (see KQ 1d). Estimates for serious adverse events (1 trial, n=313, RR 0.58, 95% CI, 0.14 to 2.39),[150] dizziness (5 trials, N=772, RR 1.22, 95% CI, 0.23 to 1.99, I^2=0%; **Figure 58**),[82,140,145,147,150] headache (3 trials, N=457, RR 1.12, 95% CI, 0.46 to 2.25, I^2=0%; **Figure 59**),[67,82,150] vomiting (2 trials, N=339, RR 1.68 , 95% CI, 0.34 to 8.19, I^2=0%; **Figure 60**),[145,150] and pruritus (2 trials, N=190, RR 0.25, 95% CI, 0.03 to 1.91, I^2=0%; **Figure 61**)[67,140] 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 34**).

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 nonopiois versus opioids

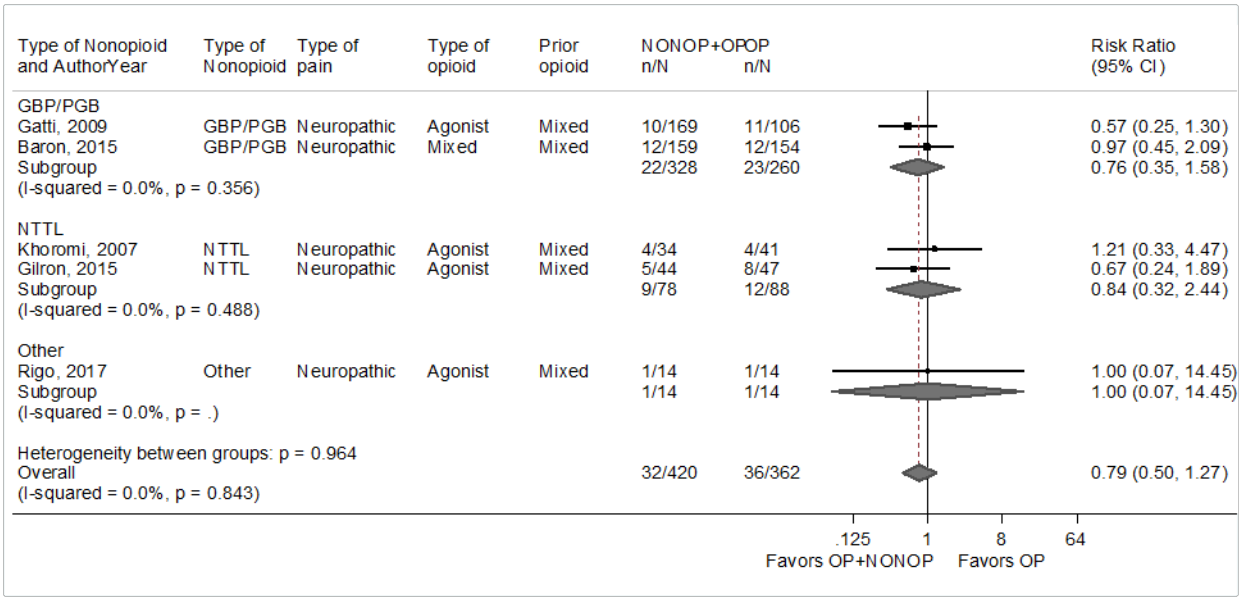


Figure 55. Meta-analysis of risk of nausea for opioids plus nonopioids versus opioids

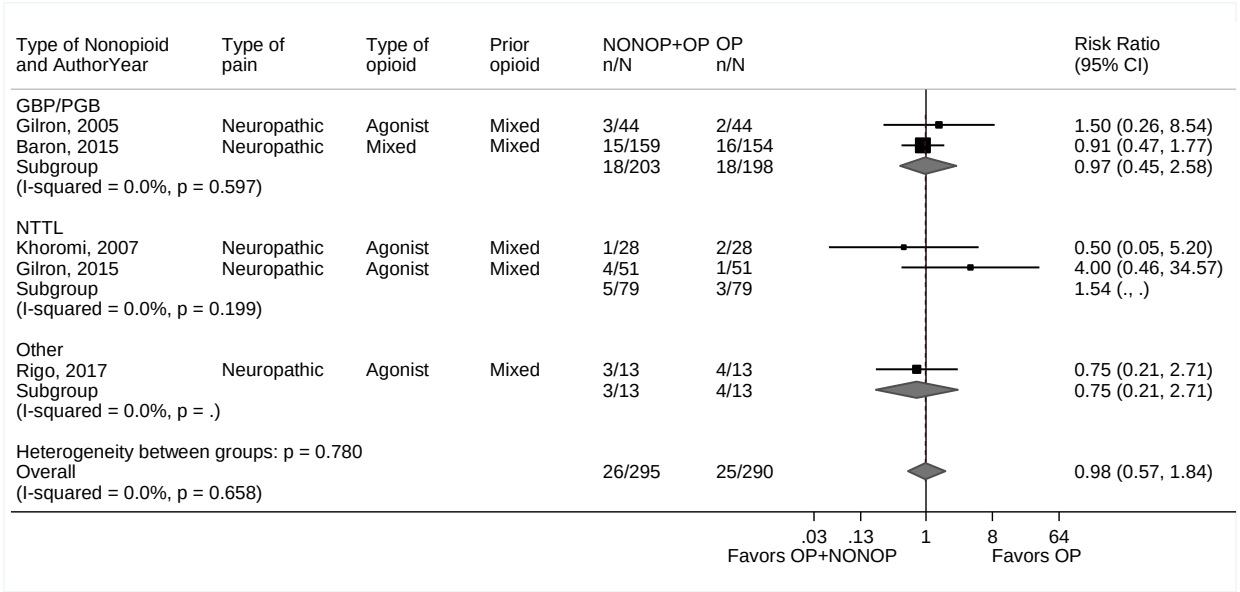


Figure 56. Meta-analysis of risk of constipation for opioids plus nonopioids versus opioids

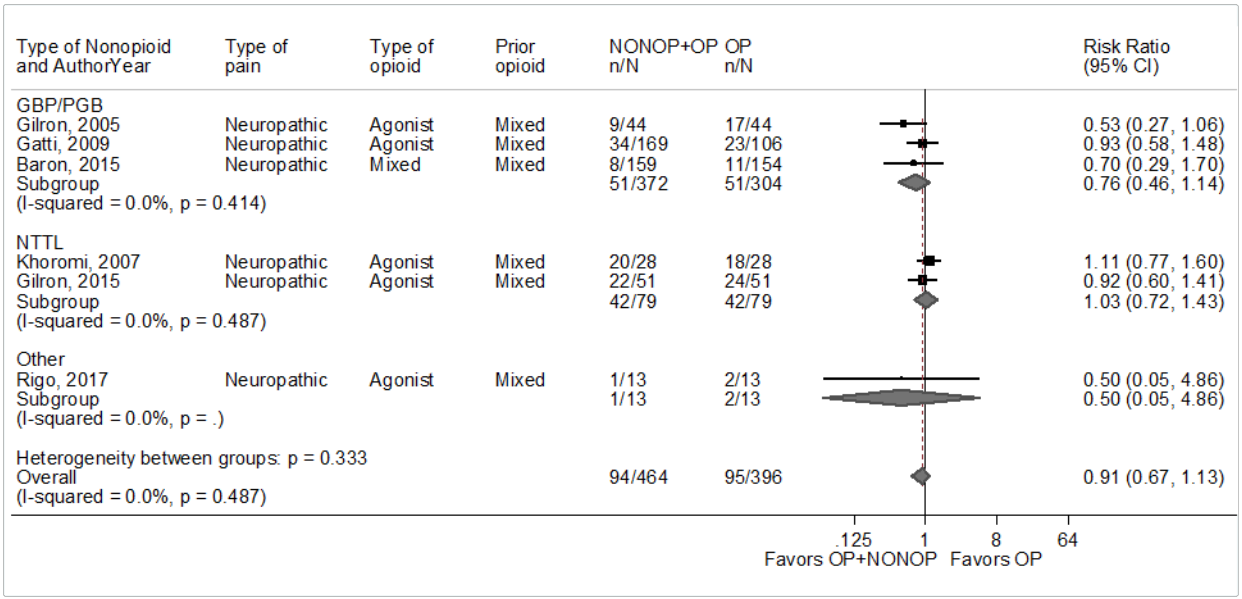


Figure 57. Meta-analysis of risk of somnolence for opioids plus nonopioids versus opioids

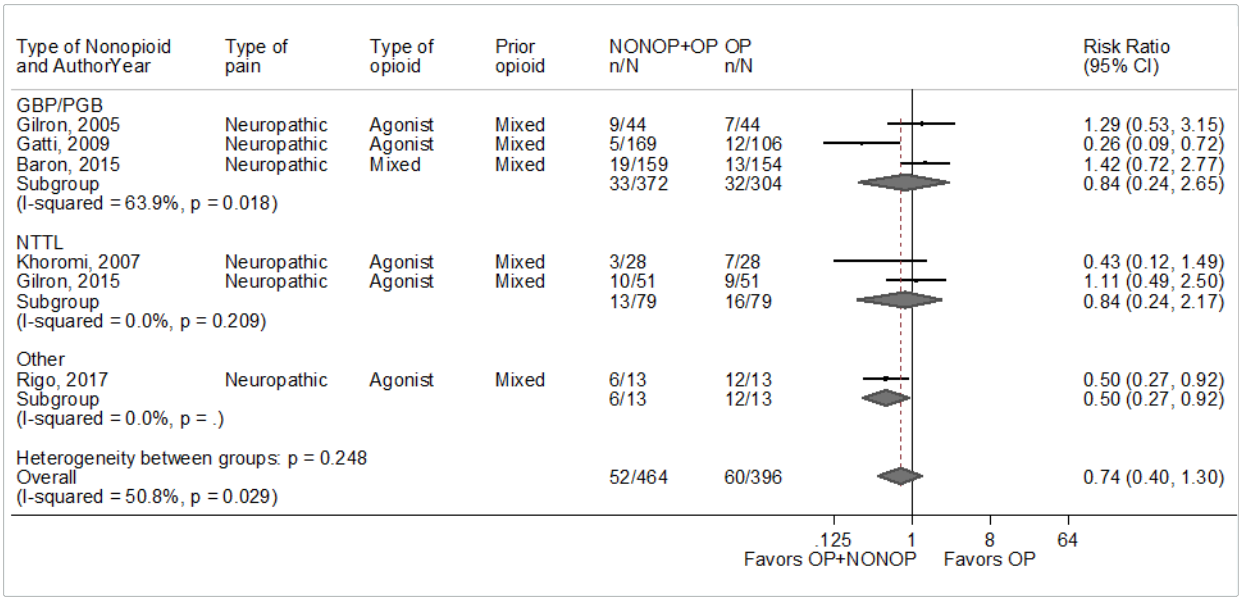


Table 33. Summary table of adverse events for opioids plus nonopioids versus opioids

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[150] 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[147] Italy Poor	1: 13 weeks 2: 409 3: Mixed neuropathic pain	1: Oxycodone SR (mean 36 mg) + pregabalin (mean142 mg) 2: Oxycodone SR (mean 46 mg)	NR	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: 2.9% (5/169) 2: 11.3% (12/106)
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[140] 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[145] Brazil Fair	1: 13 weeks 2: 28 3: Neuropathic	1: Methadone 9 mg + ketamine 90 mg 2: Methadone 9 mg	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 (SD), unless otherwise reported

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

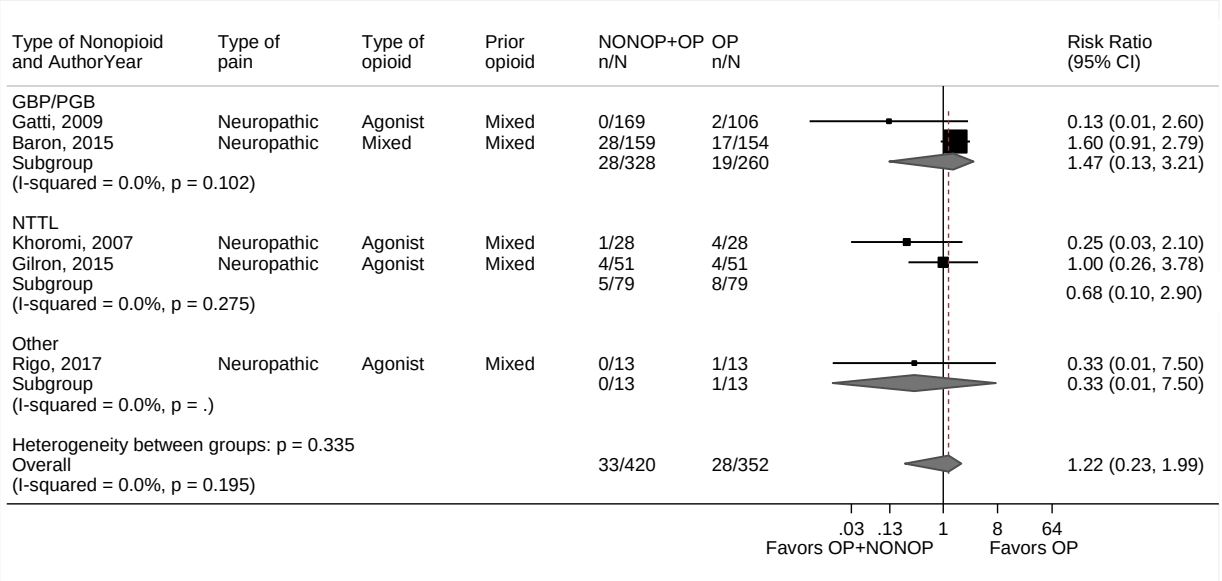


Figure 59. Meta-analysis of risk of headache for opioids plus nonopioids versus opioids

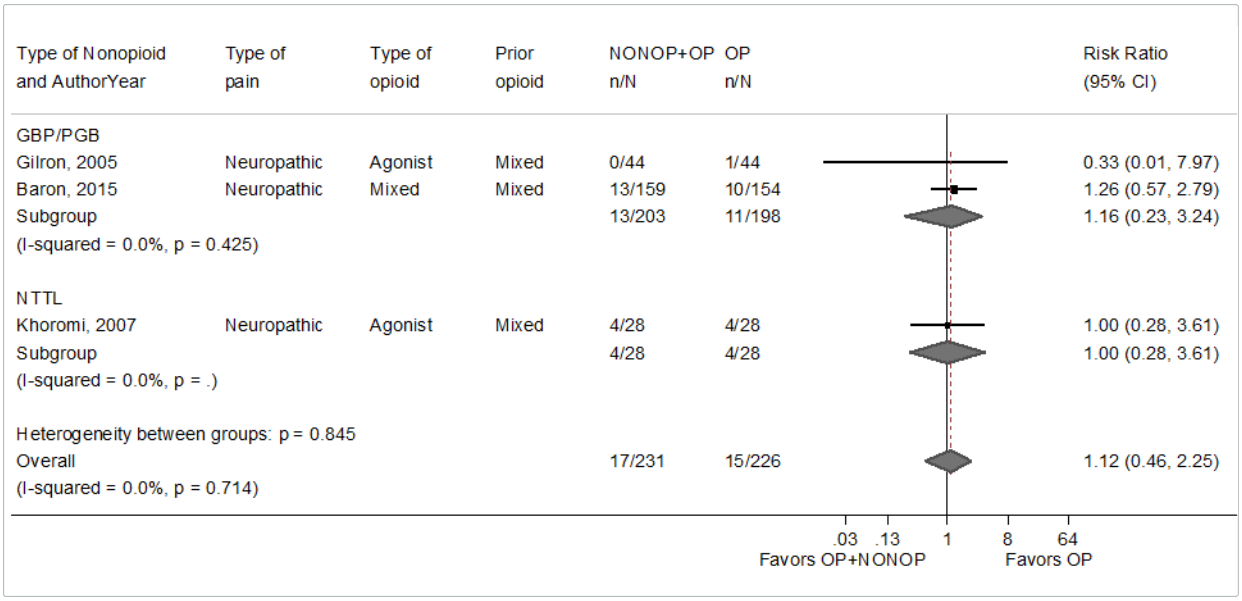


Figure 60. Meta-analysis of risk of vomiting for opioids plus nonopioids versus opioids

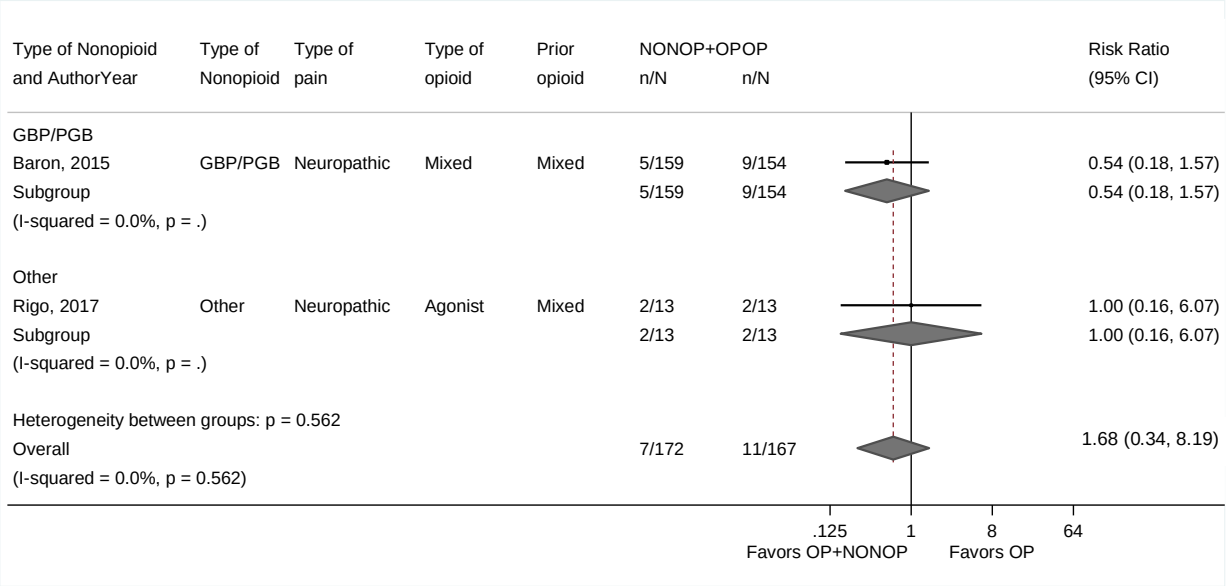


Figure 61. Meta-analysis of risk of pruritus for opioids plus nonopioids versus opioids

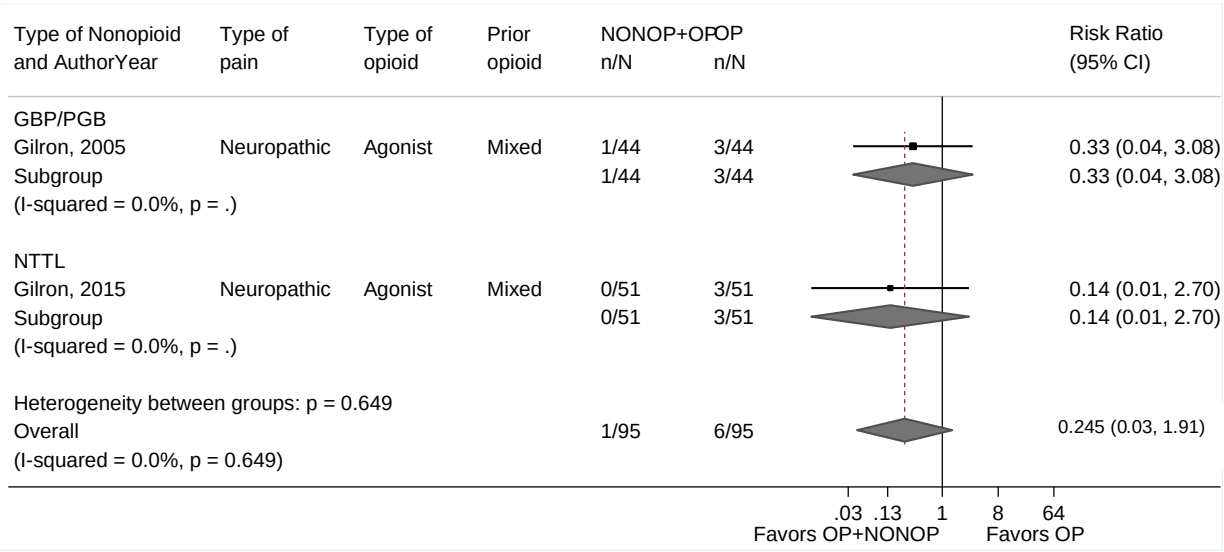


Table 34. Pooled analyses of risk of discontinuation due to adverse events and somnolence for opioids plus nonopioids versus opioids

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)	--	0.74 (0.40 to 1.30)	51%	6 (860)	--
Nonopioid type: Gabapentinoid	0.76 (0.35 to 1.58)	0%	2 (588)	0.96	0.84 (0.24 to 2.65)	64%	3 (676)	0.87
• **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	0.63 (0.33 to 1.16)	37%	5 (547)	0.28
• **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)	--	0.74 (0.40 to 1.30)	51%	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)	0.15
• **Poor**	0.57 (0.25 to 1.30)	--	1 (275)	--	0.26 (0.09 to 0.72)	--	1 (275)	--
Opioid dose (mg MED/day): <50	1.16 (0.26 to 4.97)	0%	2 (103)	0.44	0.64 (0.31 to 1.41)	4.8%	3 (170)	0.61
• **50-90**	0.61 (0.29 to 1.30)	0%	2 (366)	--	0.58 (0.10 to 3.10)	58%	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)	0.53
• **Parallel group**	0.77 (0.39 to 1.51)	0%	3 (616)	--	0.61 (0.20 to 1.73)	67%	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 prior 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 prior AHRQ report included two fair-quality, 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**).[141,180] 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.[180] 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.[141] 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 prior 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[108,141,181-183] (**Table 35; 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),[181] one trial compared sustained-release versus immediate-release dihydrocodeine (doses 120 to 240 mg/day),[182] one trial compared transdermal buprenorphine (7-day patch at 5 or 20 mcg/hour) versus oral immediate-release oxycodone (40 mg/day),[108,183] 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).[141] 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.

All of the trials were rated fair-quality (**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;[108,183] the remainder were parallel group randomized trials without enriched enrollment. All trials except one[182] 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[184] (**Appendix Table G-2, H-25, and H-26**).

Table 35. 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[181] 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[141] 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)	Fair
Pedersen, 2014[182] 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[183] 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, 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.[181,182] 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).[184] 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 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);[50,56,130,131,134] 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[185-189] (SOE: low)
- Three trials (N=957) compared transdermal fentanyl versus long-acting morphine.[190-192] Two trials reported no differences in pain or other outcomes.[191,192] 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 36; Appendix Tables H-27 and H-28**).[50,56,86,130,131,134-137,185-191,193-196] Sample sizes ranged from 18 to 1121 (total N=7356). Three trials were included in the prior AHRQ report, which was restricted to trials with 1 year or more followup.[134,137,191] One of the trials in the prior AHRQ report compared transdermal fentanyl versus sustained-release morphine,[191] one trial compared sustained-release tapentadol versus sustained-release oxycodone,[134] and one compared transdermal buprenorphine versus transdermal fentanyl.[137] The duration of followup in all of the new trials was 6 months or less;[50,56,86,130,131,135,136,185-190,192-195] 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 mg to 240 mg MED/day. The pain type was musculoskeletal in nine trials,[50,56,86,134-136,186-189,192,194,195] neuropathic in one trial,[130,131] and musculoskeletal in five trials.[137,185,190,191,193] 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,[137,186,187] two trials to opioid-experienced patients,[188,189,192] and seven trials enrolled mixed populations of opioid-naïve and experienced patients;[56,130,131,134,135,185,190,193-195] five trials did not describe prior opioid experience.[50,86,136,191] Fifteen trials were conducted in the United States, Canada, Europe, or Australia; and one trial in China.

One trial was rated good-quality,[136] 14 trials fair-quality,[50,56,86,130,131,134,135,185-195] and one trial poor-quality[137] (**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[190,192] and two trials used an EERW design;[186,187,194,195] the remainder used a parallel group non-EERW randomized trial design. All trials except one[137] reported industry funding.

The prior 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.[197,198] 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.[199,200]

Table 36. 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[190] 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[191] 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)[130,131] 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[193] 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[199] 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[195] 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[132] and Vorsanger, 2010[133] 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[197] 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[135] 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[198] 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[136] 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[137] 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[185] 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[192] 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[186,187] 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[200] 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[188,189] 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[134] 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),[50,56,130,131,134] morphine (3 trials, N=1405),[185-189] hydromorphone (2 trials, N=652),[193-195] 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).[50,56,130,131,134] 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.[185-189] Two trials[193-195] 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.[190-192] Two trials reported no differences in pain or other outcomes.[191,192] 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.[190] 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%).[190,191]

Three trials compared transdermal buprenorphine versus another long-acting opioid.[135-137] Two trials (N=415) found no differences between transdermal buprenorphine versus sustained-release tramadol in mean improvement in pain or sleep.[135,136] 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.[137]

The prior 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.[197] 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).[198]

Two new cohort studies compared risks of different opioids in Medicaid patients in the same state. One study[199] (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[200] (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 prior 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 37; Appendix Table G-1 and H-31**).[201] The trial enrolled Veterans Affairs patients with primarily musculoskeletal chronic (>6 months) pain.[201] 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 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 37. Trial of opioid dose escalation versus dose maintenance

Author, year Study design Duration	Sample	Interventions, N	Results	Quality
Naliboff, 2011[201] 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.

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 prior AHRQ report included two good-quality placebo-controlled, randomized trials (n=77 and 79) of buccal fentanyl[202,203] and two good-quality head-to-head trials (n=183 and 137) of buccal fentanyl versus oral opioids[204,205] for exacerbations of chronic noncancer pain of various etiologies (**Table 38, Appendix Table G-1, H-32, and H-33**). 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.[202] 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 ($p<0.0001$).[203]

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).[204,205] The pain condition in most patients in both trials was back or neck pain, osteoarthritis, fibromyalgia, traumatic injury, or complex regional pain syndrome.

Table 38. 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[204] 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[203] 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[202] 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[205] 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 prior 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 prior AHRQ report compared tapering versus continuation of opioid therapy in patients with chronic pain (**Table 39; Appendix Tables H-34 and H-35**).[146,206,207] 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.[206] 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;[207] one trial evaluated a buprenorphine taper following inpatient induction;[206] and one trial performed a scheduled taper of 10 percent per week (10 weeks to discontinuation) with clonidine for management of withdrawal symptoms.[146] The duration of followup ranged from 22 weeks to 6 months. Two trials[206,207] were conducted in the U.S. and one trial[146] in Europe.

One trial was rated fair-quality[207] and two trials were rated poor-quality (**Appendix Table G-1**).[146,206] 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.[207] 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.[146] 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.[206]

Other data 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));[207] the trial of buprenorphine taper[206] reported one discontinuation due to relapse, with no other adverse events reported. Suicidality or suicide events were not described in any of the trials.

Table 39. Trials of effects of decreasing opioid doses or of tapering off opioids

Author, year Study design Duration	Sample	Interventions, N	Results	Quality
Blondell, 2010[206] 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
Kurita, 2018[146] 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

Author, year Study design Duration	Sample	Interventions, N	Results	Quality
Sullivan, 2017[207] 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 prior 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.[47,208] 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.[208] 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 40; Appendix Tables H-36 and H-37**).

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 40; Appendix Tables H-36 and H-37**).[209] 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.[210] 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 40. Trials of effects of different tapering protocols and strategies

Author, year Study design Duration	Sample	Interventions, N	Results	Quality
Hooten, 2015[209] 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[208] 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=0.005) 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 (64 trials, N=17,243, mean difference -0.84 on a 0 to 10 scale, 95% CI -0.97 to -0.71, 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

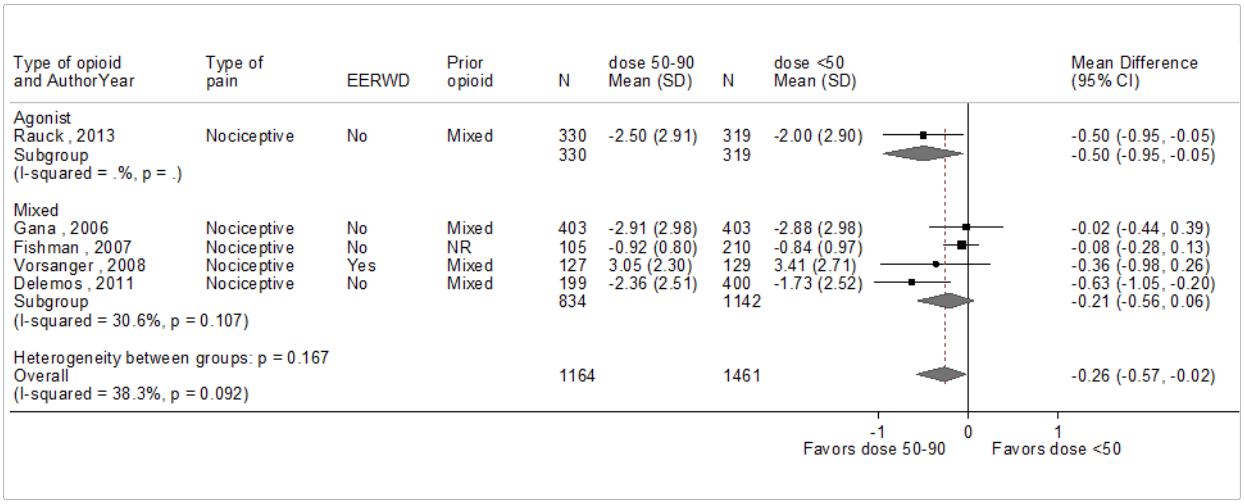
Seven trials directly compared effects of different opioid doses.[62,63,66,86,96,117,211] Sample sizes ranged from 81 to 815 (total N=3091). None of the trials were included in the prior AHRQ report, which was restricted to trials with 1 year or more followup. The duration of followup was 6 months or 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 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.[211] 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 years 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[211] reported industry funding.

Detailed Synthesis

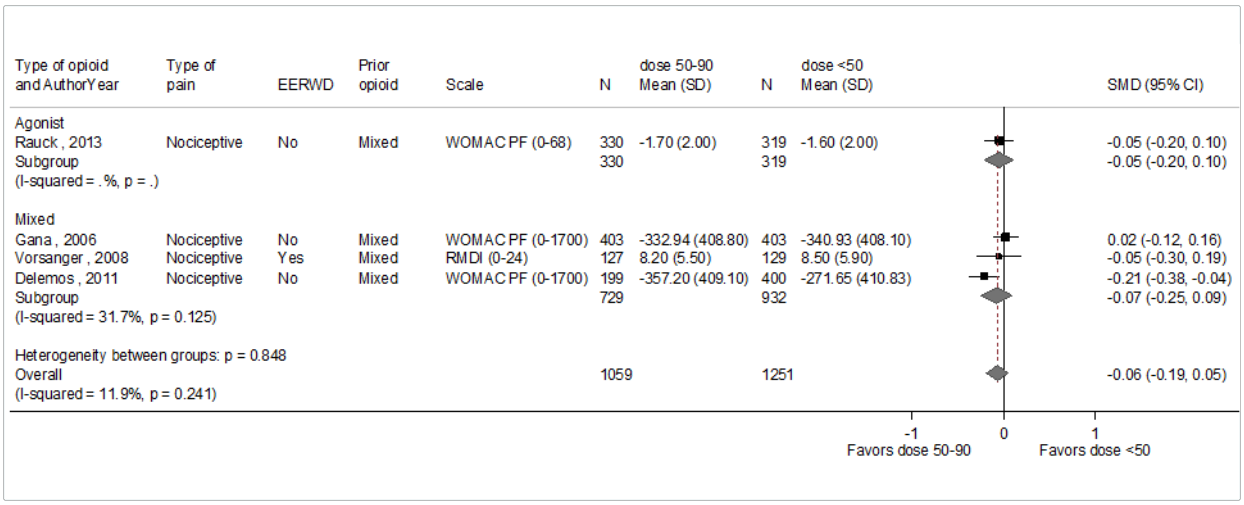
In trials that directly compared different opioid doses, 50 to 90 mg MED/day was associated with a mean improvement in pain versus less than 50 mg MED/day; however, the difference was below the threshold for a small effect (5 trials, N=2625, mean difference -0.26, 95% CI, -0.57 to -0.02, I^2=38%; **Figure 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[211] of greater than 90 mg versus 50 to 90 mg MED/day (n=57, mean difference -1.13, 95% CI, -2.46 to 0.20) and one trial[86] of greater than 90 mg versus less than 50 mg MED/day (n=365, mean difference -0.44, 95% CI, -0.96 to 0.08), effects on pain favored the higher dose, but were not statistically significant. 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 in pain measures for different opioid doses



Note: Nociceptive pain refers to musculoskeletal condition

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

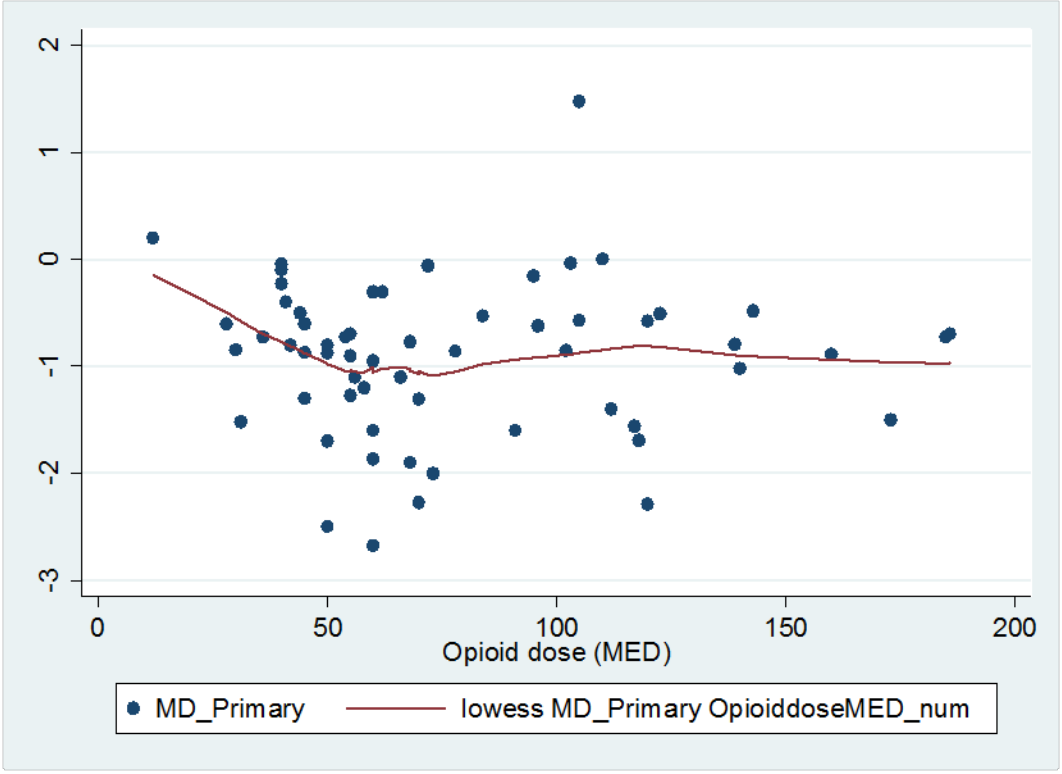


Note: Nociceptive pain refers to musculoskeletal condition

A meta-regression of placebo-controlled trials (k=60) found no association between opioid dose (mean mg MED/day) and pain intensity (p=0.79; **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=0.005) 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, -1.10 (25 trials, N=6141, 95% CI, -1.35 to -0.88, I^2=59%) 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 1.50, p for interaction=0.53; **Table 5**).

In analyses of placebo-controlled trials, effects on mean improvement in pain were larger at 1 to 3 months (64 trials, N=17,243, mean difference -0.84 on a 0 to 10 scale, 95% CI, -0.97 to -0.71, 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 -0.54 point (**Table 4**). A similar pattern was observed for likelihood of a pain response (39 trials, N=10,946, RR 1.35, 95% CI, 1.24 to 1.48, I^2=80% 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 (64 trials, N=17,243, SMD -0.38, 95% CI, -0.44 to -0.32, I^2=68% 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



Key Question 4a. In patients with chronic pain being considered for opioid therapy, what is the accuracy of instruments for predicting risk of opioid overdose, addiction, abuse, or misuse?

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 prior 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 prior 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 prior 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 41 and 42; Appendix Tables G-5, H38, and H-39**).[212-218] Sample sizes ranged from 48 to 257 (total N=1228). Four studies[212,213,217,218] were included in the prior AHRQ report and three studies[214-216] were added for this update. Six studies (three new) evaluated the ORT,[213-218] one study the SOAPP Version 1,[212,217] four studies (three new) the SOAPP-R,[213-216] one study the DIRE Score,[217] three studies (all new) the BRI,[214-216] and one new study the BRQ.[216] The mean age of participants ranged from 43 to 55 years and the proportion female ranged from 33 percent 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,[213-216] 12 months in one study,[218] a mean of 3.8 months in one study,[217] and was not reported in one study.[212] 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,[212,215,216,218] two studies were retrospective,[213,217] and in one study[214] it was unclear if the design was prospective or retrospective.

Four studies[212,213,216,218] were rated fair-quality and three studies[214,215,217] 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) [214], only evaluated cases (persons with opioid misuse or abuse)[217], or did not clearly enroll a consecutive sample.[214,217] 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.[214]

Table 41. Studies of risk assessment instruments

Author year	Population, N	Risk assessment instrument	Method of administration	Reference standard
Akbik, 2006[212]	n=155 Mean age (SD): 43 years (9.6) Female sex: 33% Race: 86% White, other races not reported Pain: 39% back pain	SOAPP (scale 0 to 56; high risk ≥8)	Self-report	Positive urine drug test
Jones, 2012[213] (Study 2)	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 (scale 0 to 25; high risk ≥8) PMQ (scale 0 to 104; high risk ≥30) SOAPP-R (scale 0 to 24; high risk ≥18) Clinician assessment	Self-report (SOAPP-R, ORT, PMQ); clinician interview	Opioid discontinuation due to abuse
Moore, 2009[217]	n=48 Mean age (SD): 44 years (11) Female sex: 60% Race not reported Pain not reported	SOAPP (scale 0 to 56; high risk ≥8) DIRE (scale 7 to 21; high-risk ≤13) ORT (scale 0 to 26; high risk ≥8) Clinician assessment	Self-report (SOAPP, DIRE, ORT); clinician interview	Opioid discontinuation due to abuse*
Webster, 2005[218]	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 (scale 0 to 25; high risk ≥8)	Self-report	Documentation in medical record of aberrant behavior during followup
Jones, 2013[214]	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 (scale 0 to 26; high risk ≥8) SOAPP-R (scale 0 to 24; high risk ≥18)	Self-report (ORT, SOAPP-R); clinician interview (BRI)	Documentation of aberrant behavior during followup
Jones, 2014[215]	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 (scale 0 to 26; high risk ≥4) SOAPP-R (scale 0 to 24; high risk ≥18)	Self-report (ORT, SOAPP-R); clinician interview (BRI)	Documentation of aberrant behavior during followup

Author year	Population, N	Risk assessment instrument	Method of administration	Reference standard
Jones, 2015[216]	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 (scale 0 to 24; high risk ≥3) ORT (scale 0 to 26; high risk ≥4) SOAPP-R (scale 0 to 24; 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 42. 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[217]	Score <14: 0.17	Not calculable*	Not calculable*	Not calculable*	Not calculable*
ORT	Jones, 2012[213]	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[217]	Score ≥4: 0.45	Not calculable*	Not calculable*	Not calculable*	Not calculable*
	Webster, 2005[218]	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[214]	Score ≥4: 0.58† (NR)	Score ≥4: 0.54† (NR)	Score ≥4: 1.26	Score ≥4: 0.78	NR
	Jones, 2014[215]	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[216]	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[213]	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
SOAPP-R	Jones, 2012[213]	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[214]	Score >17: 0.53 (NR)	Score >17: 0.62 (NR)	High risk 1.39	High risk: 0.76	NR
	Jones, 2014[215]	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[216]	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[217]	Score >6: 0.73 (NR)	Not calculable*	Not calculable*	Not calculable*	Not calculable
	Akbik, 2006[212]	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[214]	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[215]	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

Scale	Studies	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	AUROC
	Jones, 2015[216]	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[216]	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.[218] 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 42**).[218]

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.[213-218] Three studies[213,217,218] were included in the prior AHRQ report and three studies[214-216] 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)[213-218] and specificity ranged from 0.16 to 0.88 (5 studies).[213-216,218] 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.[213,215,216] The highest sensitivity (0.99) and lowest specificity (0.19) were reported in the initial study reporting the ORT.[218] Inconsistency remained present when the initial study was excluded (sensitivity 0.20 to 0.75 and specificity 0.54 to 0.88),[213-217] when findings were restricted to the three fair-quality studies (sensitivity 0.20 to 0.99 and specificity 0.16 to 0.88),[213,216,218] or when findings were restricted to the three new studies (sensitivity 0.32 to 0.75 and specificity 0.54 to 0.86).[214-216]

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

The SOAPP Version 1 instrument is a 14-item, patient self-report instrument.[219] 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 42**).[219]

Two studies (N=203) included in the prior AHRQ report evaluated the accuracy of the SOAPP Version 1 instrument administered prior to initiation of opioid therapy for predicting misuse or abuse.[212,217] 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.[212] 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.[217] 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.[219] 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 42**).[219]

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.[213-216] One study[213] was included in the prior AHRQ report and three studies[214-216] 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[213,215,216] 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).[214-216] 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.[213,216]

Four studies directly compared the predictive accuracy of the SOAPP-R and the ORT.[213-216] There was no consistent pattern indicating higher accuracy with one instrument compared with the other. AUROC estimates were very similar in two studies[213,216] and the ORT was associated with a higher AUROC than the SOAPP-R in a third study[215] (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).[214]

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

The DIRE Score is a 7-item clinician-rated instrument.[220] 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 prior AHRQ report.[217] 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 42**). 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.[221] 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 prior AHRQ report.[213] 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 42**). 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.[214] 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.[214-216] None of the studies were included in the prior 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 42**).[215,216] In one fair-quality study, the sensitivity was 0.79, the specificity was 0.51, and the AUROC was 0.65.[216]

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).[215] 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).[216] 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.[214]

Brief Risk Questionnaire (BRQ)

The BRQ is a 12-item patient self-report instrument derived from the BRI.[216] 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.[216] 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 42**).

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[222] co-prescription (**Appendix Table G-2 and H-40**). 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 misuse, opioid use disorder, overdose, pain, function, and 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 prior 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 prior AHRQ report evaluated effects of different treatment strategies in patients with opioid use disorder related to prescription opioids[196,206,223] (**Appendix Table G-1, H-41, and H-42**). Two trials compared buprenorphine maintenance versus taper, but one trial[223] excluded patients receiving opioids for pain and the other was a small trial[206] 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.[196]

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]).[223] 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.[206] 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[196] 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,[224] to predict[225] or identify [226]prescription medication misuse or opioid use disorder, and to discuss these issues with their patients.[226,227] Clinicians reported favorable beliefs and attitudes about effects of opioids on pain and quality of life; however,[228] 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,[229,230] urine drug testing,[231] and opioid treatment agreements;[232] administrative and logistical barriers were noted.[233]

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.[234] 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.[235] One study found that patients with chronic pain emphasized effectiveness of goal setting for increasing

motivation and functioning.[234] Patients on higher doses reported reliance on opioids despite ambivalence about their benefits;[236] reliance was not dependent on the degree of pain reduction, reported problems, concerns, side effects, or perceived helpfulness.[237]

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.[238] Sixty-seven percent were aware of the 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.[239] 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.[240] 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.[241] 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.[242] 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.[243] 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;[244] $55.7 billion for abuse, dependence (i.e., opioid use disorder), and misuse of prescription opioids;[245] and $20.4 billion for opioid-related overdoses.[246] In 2012, total expenses for outpatient prescription opioids were estimated at $9.0 billion, an increase of 120 percent from 2002.[247] 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.[248] 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.[249]

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 health care and substance abuse treatment costs.[250] 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.[251] 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.[252]

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.[253] 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.[254] A recent U.K. analysis found buprenorphine and methadone maintenance therapy both to be highly cost-effective[255] 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.[256]

Discussion

Key Findings and Strength of Evidence

The key findings of this review are summarized in **Tables 43 and 44** and the summary of evidence (SOE) table (**Appendix I)**. This review updates findings from the prior 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 prior 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 43. Efficacy of opioid treatments for chronic pain: function and pain outcomes

Intervention A vs. B	**Function** *Short-term* Effect size SOE	**Function** *Intermediate-term* Effect size SOE	**Function** *Long-term* Effect size SOE	**Pain** *Short-term* Effect size SOE	**Pain** *Intermediate-term* Effect size SOE	**Pain** *Long-term* 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 44. 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 +++	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	Small +	Insufficient evidence	Small +	Small +	Small +	Small +	Small +	Small +	Small +

Effect size: None orsmall, moderate, or large increase in risk for intervention A
SOE: + = low, ++ = moderate, +++ = high
Abbreviations: AE=adverse effects; SOE=strength of evidence

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 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). Although these are less than proposed minimum clinically important differences,[32] assessing MDs may obscure larger benefits experienced by some patients, since effects are averaged with patients who experience no benefit.[257,258] 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 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 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 EERW design.[259] In an EERW 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 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.[260] 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 prior 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% CI, 13 to 38%) and rates of addiction ranged from 8 to 12 percent (range, 95% CI, 3 to 17%).[261]

Evidence on short-term outcomes does not address the practice of long-term use of opioids and associated benefits and harms. As in the prior 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.[129] New observational studies were consistent with the prior AHRQ report in finding an association between use of prescription opioids and risk of addiction,[153] overdose,[153] fractures,[154,159,162] falls[159,163] and cardiovascular events;[164] a new study also found an association between opioid use and risk of all-cause mortality.[164] New observational studies were also consistent with the prior AHRQ report in finding associations between higher doses of opioids and risks of overdose, addiction, and endocrinological adverse events;[153,154,163,164,167,170] new studies also found an association between higher dose and increased risk of incident or refractory depression.[171,172] 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[177-179] or benzodiazepines[174-176] 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 prior 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. Although there were no interactions between nonopioid type and effects on any outcomes, subgroup analyses by nonopioid type 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 evaluated outcomes at 1 year.[142] 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, though findings were based on only five 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 on 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 prior 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).[201] 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.[164,197,198] 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 prior 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.[262]

New evidence on the accuracy of risk prediction instruments was consistent with the prior AHRQ report, which found highly inconsistent estimates of diagnostic accuracy, methodological limitations and few studies of risk assessment instruments other than the ORT and 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.[222] 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.[207] 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.[146,206] 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.[209] 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.[210] The FDA recently issued a warning on not discontinuing long-term opioid therapy abruptly.[263] 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.[223] 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,[196] and another small trial was terminated early because all patients randomized to a buprenorphine taper switched to maintenance or had a relapse.[206]

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.[264] 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,[74,85,119,122,138,142-145,147] 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.[265]

Like our review, other systematic reviews of opioid therapy for chronic pain also found no long-term, placebo-controlled randomized trials.[264,266,267] 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.[268] 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.[269]

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.[270] 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.[271] A systematic review of tapering found limited evidence that tapering or dose reductions may be associated with improved outcomes in patients prescribed opioids.[272] 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.[271] 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 trials might be greater and harms lower than seen in actual clinical practice.[267,273] 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.[48,202-205]

Implications for Clinical and Policy Decisionmaking

Our review has implications for clinical and policy decisionmaking. Findings of this review, with expansion of scope to include short-term trials, support the recommendation in the 2016 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.[274]

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.[275] 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.[16,276] 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 prior 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).[277-279]

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. 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 on how Validated measures are needed to better understand how underlying pain mechanisms (e.g., nociceptive, neuropathic, and nociplastic)[20] 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.[280] 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,[281] 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]).[282] 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.[283] 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.

Abbreviations and Acronyms

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 randomization withdraw
FDA	U.S. Food and Drug Administration
HR	Hazard ratio
ICD-9	International c
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 analogue scale
VHA	Veterans Health Administration

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