



Comparative Effectiveness Review
Number 228

Nonopioid Pharmacologic Treatments for Chronic Pain



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Prepared by:

Pacific Northwest Evidence-based Practice Center
Portland, OR

Investigators:

Marian S. McDonagh, Pharm.D.
Shelley S. Selph, M.D., M.P.H.
David I. Buckley, M.D., M.P.H.
Rebecca S. Holmes, M.D., M.S.
Kimberly Mauer, M.D.
Shaun Ramirez, M.P.H.
Frances C. Hsu, M.S.
Tracy Dana, M.L.S.
Rochelle Fu, Ph.D.
Roger Chou, M.D.

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Key Messages

Purpose of Review

Evaluate the benefits and harms of nonopioid drugs in randomized controlled trials of patients with specific types of chronic pain, considering the effects on pain, function, quality of life, and adverse events.

Key Messages

- In the short term, improvement in pain and function was small with specific anticonvulsants, moderate with specific antidepressants in diabetic peripheral neuropathy/post-herpetic neuralgia and fibromyalgia, and small with nonsteroidal anti-inflammatory drugs (NSAIDs) in osteoarthritis and inflammatory arthritis.
- In the intermediate term, evidence was limited, with evidence of benefit for memantine in fibromyalgia and for serotonin norepinephrine reuptake inhibitor (SNRI) antidepressants in low back pain and fibromyalgia.
- In the long term, evidence was too limited to draw conclusions. In general, evidence on quality of life was limited and no treatment achieved a large improvement in pain or function.
- Small to moderate, dose-dependent increases in withdrawal due to adverse events were found with SNRIs duloxetine and milnacipran, anticonvulsants pregabalin and gabapentin, and NSAIDs. Large increases were seen with oxcarbazepine. NSAIDs have increased risk of serious gastrointestinal, liver dysfunction, and cardiovascular adverse events.

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

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

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

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. The Centers for Disease Control and Prevention requested this report from the EPC Program at AHRQ. AHRQ assigned this report to the following EPC: Pacific Northwest Evidence-based Practice Center (Contract No. 290-2015-00009-I).

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

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

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

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

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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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 provided input to this report follows:

Daniel Clauw, M.D.*
Professor, Anesthesiology, Rheumatology,
and Psychiatry
University of Michigan
Ann Arbor, MI

Christopher Goodman, M.D.*
Clinical Assistant Professor of Internal
Medicine
University of South Carolina School of
Medicine
Columbia, SC

Sharon Hertz, M.D.
Division Director, Office of Neuroscience
Division of Anesthesia, Addiction Medicine,
and Pain Medicine
U.S. Food and Drug Administration
Beltsville, MD

Jennifer Kawi, Ph.D., M.S.N., A.P.R.N.,
F.N.P.-B.C.*

Associate Professor, School of Nursing
University of Nevada, Las Vegas
Las Vegas, NV

Kurt Kroenke, M.D., M.A.C.P.*
Professor of Medicine, Indiana University
School of Medicine and Regenstrief Institute
Indianapolis, IN

Michelle Matthews, Pharm.D., B.C.A.C.P,
C.P.E, FASHP
Vice Chair, Department of Pharmacy
Practice
Massachusetts College of Pharmacy and
Health Sciences
Boston, MA

Mark Wallace, M.D.
Chair, Division of Pain Medicine
University of California, San Diego
San Diego, CA

*Provided input on Draft Report

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

The list of Peer Reviewers follows:

Wendy L. Bennett, M.D., M.P.H.
Associate Professor of Medicine
Division of General Internal Medicine
Core Faculty, The Welch Center for
Prevention, Epidemiology and Clinical
Research
Johns Hopkins School of Medicine
Baltimore, MD

Haitao Chu, Ph.D., M.D.
Professor, Division of Biostatistics
University of Minnesota
Minneapolis, MN

James Rathmell, M.D.
Chair, Department of Anesthesia
Brigham and Women's Hospital
Boston, MA

Barbara St. Marie, Ph.D, A.G.P.C.N.P.,
FAAN.P
Assistant Professor, College of Nursing
University of Iowa
Iowa City, IA

Jasvinder Singh, M.D., M.P.H
Endowed Professor, Musculoskeletal
Outcomes Research, Division of Clinical
Immunology and Rheumatology
Professor of Medicine and Epidemiology,
University of Alabama at Birmingham
Director, Gout Clinic
Staff Physician, University of Alabama
Health Services Foundation,
Birmingham Veterans Affairs Medical
Center
Birmingham, AL

Nonopioid Pharmacologic Treatments for Chronic Pain

Structured Abstract

Objectives. To evaluate the effectiveness and comparative effectiveness of nonopioid pharmacologic agents in patients with specific types of chronic pain, considering effects on pain, function, quality of life, and adverse events.

Data sources. Electronic databases (Ovid[®] MEDLINE[®], Embase[®], PsycINFO[®], CINAHL[®], Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews) through September 10, 2019, reference lists, data requests, and previous reviews.

Review methods. Randomized controlled trials (RCTs) of nonopioid pharmacologic agents in patients with chronic pain were selected using predefined criteria and dual review. This review focused on seven common chronic pain conditions (neuropathic pain, fibromyalgia, osteoarthritis, inflammatory arthritis, low back pain, chronic headache, sickle cell disease), with effects analyzed at short term (1 to <6 months following treatment completion), intermediate term (≥ 6 to <12 months), and long term (≥ 12 months). Magnitude of effects were described as small, moderate, or large using previously defined criteria, and strength of evidence was assessed. Meta-analyses were conducted where data allowed, stratified by duration within each intervention type, using random effects models. We evaluated effect modification through subgroup and sensitivity analyses, including specific drug, dose, study quality, and pain type.

Results. We included 185 RCTs in 221 publications and 5 systematic reviews.

In the short term, anticonvulsants (pregabalin, gabapentin, and oxcarbazepine for neuropathic pain, pregabalin/gabapentin for fibromyalgia), serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants (duloxetine for neuropathic pain, fibromyalgia, osteoarthritis, and low back pain, milnacipran for fibromyalgia), and nonsteroidal anti-inflammatory drugs (NSAIDs) (for osteoarthritis and inflammatory arthritis) were associated with mostly small improvements (e.g., 5 to 20 points on a 0 to 100 scale) in pain and function. Function was not found to be improved with duloxetine for low back pain or pregabalin/gabapentin for neuropathic pain. Moderate improvement in quality of life was seen with duloxetine in patients with neuropathic pain, and small improvements in patients with osteoarthritis, but evidence was insufficient to draw conclusions for other drugs and conditions. While most comparisons of drugs and doses did not identify differences, diclofenac improved pain and function moderately more than celecoxib. In the intermediate term, limited evidence (1 RCT) showed memantine moderately improved pain, function, and quality of life in patients with fibromyalgia; improvements in pain, but not function, were maintained in the intermediate term with duloxetine and milnacipran for fibromyalgia. Other drugs studied, including acetaminophen (osteoarthritis), capsaicin (neuropathic pain), cannabis (neuropathic pain), amitriptyline (fibromyalgia, neuropathic pain), and cyclobenzaprine (fibromyalgia) had no clear effects. Withdrawal from study due to adverse events was significantly increased with nonopioid drugs, with the greatest increase over placebo seen with cannabis. Large increases in risk of adverse events were seen with pregabalin (blurred vision, cognitive effects, dizziness, peripheral edema, sedation, and weight gain), gabapentin (blurred vision, cognitive effects, sedation, weight gain), and cannabis (nausea, dizziness). Dose

reductions reduced the risk of some adverse events with SNRI antidepressants. In the short term small increases in risk of major coronary events and moderate increases in serious gastrointestinal events (both short and long term) were found with NSAIDs.

Conclusions. In the short term, small improvements in pain and/or function were seen with SNRI antidepressants for neuropathic pain, fibromyalgia, osteoarthritis, and low back pain; pregabalin/gabapentin for neuropathic pain and fibromyalgia; oxcarbazepine for neuropathic pain; and NSAIDs for osteoarthritis and inflammatory arthritis. Improvement in function was not found with duloxetine for low back pain and pregabalin/gabapentin for neuropathic pain. Intermediate- and long-term outcomes were mostly not assessed. Increased incidence of drug class-specific adverse events led to withdrawal from treatment in some patients, suggesting that careful consideration of patient characteristics is needed in selecting nonopioid drug treatments.

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Evidence Summary

Introduction

Chronic pain is typically defined as pain lasting 3 to 6 months¹ and can be the result of a wide array of issues, including underlying medical conditions or disease, inflammation of injured tissue, and neuropathic pain (which involves a lesion or disease of the somatosensory nervous system). Nearly 50 million adults in the United States live with chronic pain, garnering an estimated \$560 billion in annual healthcare costs^{1,2} and contributing to the economic burden on the healthcare system.² Given the complexity of treating chronic pain and concerns regarding the safety and long-term effectiveness of opioids, there have been multiple initiatives in recent years to improve the evidence available to clinicians and patients for making treatment decisions. These initiatives, along with the recent publication of the evidence-based guideline on opioid use for chronic pain by the Centers for Disease Control and Prevention,³ have prompted additional primary research on alternatives to opioids in managing chronic pain. There is a real need to fully understand the benefits and harms of nonopioid pharmacologic treatments for chronic pain. The most common forms of nonopioid pharmacologic treatment for pain are nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, topical formulations such as capsaicin, and drugs used for other conditions such as anticonvulsants and antidepressants that can be implemented for pain moderation. Evidence is needed on common chronic pain conditions, including neuropathic pain, fibromyalgia, inflammatory arthritis (e.g., rheumatoid arthritis), osteoarthritis, low back pain, chronic headache, and sickle cell disease, comparing nonopioid drugs to placebo, to each other, and comparing different doses and with adequate durations of treatment to reflect real-life situations.

The purpose of this review is to evaluate the benefits and harms of nonopioid drugs in randomized controlled trials (RCTs) of patients with chronic pain, considering the effects on pain, function, quality of life, and adverse events.

Scope and Key Questions

This Comparative Effectiveness Review focused on nonopioid pharmacologic treatments for issues of chronic pain. Key Questions (KQs) focus on the following.

- KQ1. Effectiveness and comparative effectiveness:
 - Of nonopioid pharmacologic agents versus placebo and versus other nonopioid pharmacologic agents.
 - For outcomes related to pain, function, and quality of life.
 - For treatment durations of 3 to 6 months (short-term), 6 to 12 months (intermediate), and ≥ 12 months (long-term).
 - How does this vary by pain condition, demographics, comorbidities, dose, duration, and titration?
- KQ2. Harms and adverse events:
 - What are the risks of nonopioid pharmacologic agents for harms including overdose, misuse, dependence, withdrawals due to adverse events, and serious adverse events, and specific adverse events?
 - How do these vary by pain condition, demographics, comorbidities, dose, duration, and titration?

Pharmacologic interventions considered in this review include oral agents specifically used to treat pain such as NSAIDs, antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), anticonvulsants, acetaminophen, and muscle relaxants, and memantine. Some commonly used topical agents were included in this review, including diclofenac, capsaicin, and lidocaine. Medical cannabis is a broad category and was included in this study in all of its various forms.

Methods

This Comparative Effectiveness Review follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter “AHRQ Methods Guide”).⁴ All methods were determined *a priori*, and a protocol was published on the AHRQ website (<https://effectivehealthcare.ahrq.gov/topics/nonopioid-chronic-pain/protocol>) and on the PROSPERO systematic reviews registry (registration no. CRD42019134249). Below is a summary of the specific methods used in this review, and a complete description is provided in Appendix B.

Literature Search Strategy

We conducted electronic searches in Ovid[®] MEDLINE[®], Embase[®], PsycINFO[®], CINAHL[®], Cochrane CENTRAL, and Cochrane Database of Systematic Reviews through September 10, 2019 (from database inception; see Appendix A for full strategies). Reference lists of included systematic reviews were screened for includable studies. Manufacturers of included drugs submitted potential relevant studies to include in this review using the Federal Register notification.

Inclusion and Exclusion Criteria and Study Selection

Criteria for study inclusion were developed prior to conducting our searches based on our KQs and the population, interventions, comparators, outcomes, timing, setting, and study design (PICOTS) detailed in Appendix B. For all KQs, we included and focused on RCTs with at least 3 months’ duration. We recognized that by definition, chronic pain requires treatments that are effective in the long term, and short-term benefits may not persist. This duration threshold is similar to the duration used in the prior AHRQ systematic review on nonpharmacologic interventions for chronic pain,⁵ which included studies with greater than 1 month of followup after the end of treatment, with most studies involving 6 to 8 weeks of treatment. The Evidence-based Practice Center (EPC) evaluated the availability and quality of studies with 3 to 6 months duration and found adequate evidence, thus we did not include studies with shorter durations. However, existing systematic reviews were reviewed to summarize evidence where possible.

We evaluated the persistence of benefits or harms by evaluating the three periods identified in the KQs (3 to 6 months, 6 to 12 months, and ≥ 12 months). We used existing systematic reviews primarily to screen their included studies to ensure we identified all relevant studies for this review. In the case where a systematic review is recent enough to cover the majority of the available evidence, and evaluates a cohesive group of interventions, outcomes and time frames included here, we included the review as the primary evidence and supplemented with any newer or excluded studies.

We restricted to English-language articles, but reviewed English-language abstracts of non-English language articles to identify studies that would otherwise meet inclusion criteria, in order to assess for the likelihood of language bias.

Assessment of Methodological Risk of Bias of Individual Studies

Study quality was independently assessed by two researchers using the predefined criteria below and based on methods recommended in the AHRQ Methods Guide.⁴ Studies were rated as “good,” “fair,” or “poor” (Appendix G of the full report). Studies rated “good” are considered to have the least risk of bias, and their results are considered valid. Studies rated “fair” are susceptible to some bias, though not enough to invalidate the results. Studies rated “poor” have significant flaws that imply biases of various types that may invalidate the results. We did not exclude studies rated as being poor in quality *a priori*, but poor-quality studies were considered to be less reliable than higher-quality studies when synthesizing the evidence, particularly if discrepancies between studies were present.

Data Abstraction and Data Synthesis

Data regarding general study characteristics, such as demographics, pain condition, country of trial, and baseline pain scores, were abstracted and dual-reviewed by independent investigators (Appendix E of the full report). For clarity, data used for meta-analysis were abstracted into separate forms, pooled, and synthesized (Appendix F of the full report). Methods for abstracting data for synthesis are detailed next. Data from studies included in a systematic review that met our inclusion criteria were abstracted from the published article with missing data supplemented by systematic reviews.

We preferentially abstracted pain assessed with the visual analog scale (VAS) or numerical rating scale (NRS) on a scale of 0 to 10 or 0 to 100 over other pain assessments (e.g., Western Ontario and McMaster Universities Osteoarthritis Index pain subscale). Primary pain response was defined as ≥ 30 percent improvement (reduction) in pain score. Secondary pain response criteria included >30 percent improvement (e.g., $\geq 50\%$ improvement), condition-specific composite measure (e.g., American College of Rheumatology 20 criteria [ACR20], Assessment in Spondyloarthritis International Society 20 criteria [ASAS20]), and improvement in physician’s clinical global impression of change. For quality of life outcome, we preferentially abstracted the EuroQoL-5 Dimensions (EQ-5D) over Short Form-36 (SF-36) physical and mental components summary scores (PCS and MCS), and synthesized the two scales separately.

Pain outcomes were standardized to a scale of 0 to 10; standardized mean differences (SMD) were calculated for other outcomes (e.g., function, quality of life) unless all pertinent studies assessed the outcome using the same scale. Studies with multiple nonopioid arms 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. When reported, adjusted mean difference from analysis of covariance model or other appropriate regression models was used if reported by the study, followed by difference in change score and followup score.

Strength of the Body of Evidence

The strength of evidence (SOE) for each KQ was rated for each clinical outcome using the approach described in the AHRQ Methods Guide.⁴ To ensure consistency and validity of the evaluation, the grades were reviewed by a second reviewer. The domains assessed were study

limitations (low, medium, or high), consistency (consistent, inconsistent, or unknown/not applicable), directness (direct or indirect), precision (precise or imprecise), and publication bias (suspected or undetected). The SOE was assigned an overall grade of high, moderate, low, or insufficient (Table A), reflecting our confidence in the effect estimates (Table B) and whether the findings are stable. Evidence is found to be insufficient to draw conclusions when we have no evidence available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Table A. Description of the strength of evidence grades

Strength of Evidence	Description
High	Very confident that the effect estimate lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. Findings are stable, i.e., inclusion of additional studies would not change the conclusions.
Moderate	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	Limited confidence that the effect estimate lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies. Additional evidence is needed before concluding that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	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.

Table B. Definitions of effect sizes

Effect Size	Definition
Small effect	<ul style="list-style-type: none"> • MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale • SMD 0.2 to 0.5 • RR/OR 1.2 to 1.4
Moderate effect	<ul style="list-style-type: none"> • MD >1 to 2 points on a 0 to 10-point scale, >10 to 20 points on a 0 to 100-point scale • SMD >0.5 to 0.8 • RR/OR 1.5 to 1.9
Large effect	<ul style="list-style-type: none"> • MD >2 points on a 0 to 10-point scale, >20 points on a 0 to 100-point scale • SMD >0.8 • RR/OR ≥2.0

MD = mean difference; OR = odds ratio; RR = relative risk; SMD = standardized mean difference

Peer Review and Public Commentary

Peer reviewers with expertise in primary care and management of the included chronic pain conditions were invited to provide written comments to the draft report. The AHRQ Task Order Officer and an EPC Associate Editor also provided comments and editorial review. Following this, the peer-reviewed draft report was posted on the AHRQ website for 4 weeks for public comment.

Results

Results for efficacy are shown by KQ and then by condition. Harms results are organized by drug class. Search results and selection of studies are summarized in the literature flow diagram (Figure 2 of the full report). After dual review of full-text articles, 184 RCTs (in 217 publications) were included in this review. In addition, we identified 5 systematic reviews that included 47 trials included in this review. Overall, 30 trials were rated poor quality, 129 fair quality, and 25 good quality (Appendix G of the full report). Of the good- and fair-quality trials,

128 were classified as short duration (3 months to <6 months), 18 intermediate duration (6 months to <1 year), and 9 were long duration (≥ 1 year). We included 32 RCTs in neuropathic pain, 26 RCTs in fibromyalgia, 59 RCTs in osteoarthritis, 21 RCTs in inflammatory arthritis, 7 RCTs in low back pain, and 1 trial each in chronic headache and sickle cell disease. An additional 7 trials of mixed osteoarthritis and inflammatory arthritis patients were included for harms outcomes. Most study participants were female (66.7%) but proportion varied widely by condition with the highest seen in fibromyalgia trials. Mean age of participants was 59 years and mean pain duration was 7.9 years. Participants reported a weighted mean pain severity of 6 on a scale of 0 to 10. Industry was the leading provider of funding for trials (82%) while 15 trials (10%) did not report funding source.

Data abstraction of study characteristics and results, and quality assessment for good- and fair-quality studies is available in Appendixes E, F, and G of the full report.

Key Question 1. Benefits

In patients with neuropathic pain (mainly diabetic peripheral neuropathy and/or post-herpetic neuralgia), short-term RCTs (n=31) of anticonvulsants (prodrug gabapentin enacarbil, pregabalin, and oxcarbazepine) found small improvement in pain, with no differences between drugs (SOE: Low to insufficient). The antidepressant duloxetine resulted in small improvements in pain, function, and quality of life in patients with diabetic peripheral neuropathy (SOE: Moderate to low). Tetrahydrocannabinol (THC) and cannabidiol (CBD) oral spray had inconsistent effects on pain in patients with multiple sclerosis or with allodynia (SOE: Low). Improvements in pain with topical capsaicin were not significant or did not reach the level of a small effect (SOE: Moderate).

In patients with fibromyalgia, RCTs (n=24) show small short-term and intermediate-term improvements in pain and quality of life (function only short-term) with SNRI antidepressants milnacipran and duloxetine. Anticonvulsants pregabalin and gabapentin show short-term improvements in pain and function but not quality of life (SOE: Moderate). Dose comparisons did not find differences in pain results. Short and intermediate-term treatment with memantine resulted in moderate improvements in pain, function, and quality of life compared with placebo (SOE: Low).

In patients with osteoarthritis, treatment with nonsteroidal anti-inflammatory drugs (NSAIDs, k=26 RCTs) in the short term (k=44 RCTs) resulted in small improvements in pain and function (SOE: Moderate for pain, High for function). Topical diclofenac led to a small improvement in average pain severity and patients reporting response. Few differences were found between drugs. Duloxetine resulted in a small improvement in pain severity, moderate improvement in pain response, and small improvements in function and quality of life (SOE: High). Acetaminophen did not show improvements in pain or function, across all doses (SOE: Low). In patients with inflammatory arthritis (k=30 RCTs), NSAIDs resulted in small improvements in pain and function (SOE: Moderate). Differences were not found between drugs or doses. Patients with low-back pain (k=7 RCTs) had small improvement in pain and response, but improvements in function and quality of life did not meet the threshold for small improvement with duloxetine (SOE: Moderate).

Key Question 2. Harms

Across all classes, incidence of serious adverse event (SAEs) was low. Forty good- or fair-quality trials evaluated harms of antidepressants. Antidepressants led to a moderate increase in

withdrawal due to adverse events (WAE) in 27 short- and intermediate-term studies. SNRI antidepressants resulted in moderate to large increases in incidence of nausea (with no difference according to dose) and excessive sweating. Duloxetine resulted in a large, dose-dependent, increase in sedation (SOE: Moderate to Low).

Thirty-two trials evaluated harms in short-term treatment with anticonvulsants. Oxcarbazepine led to a large increased risk of WAEs. Pregabalin and gabapentin also led to a small increased risk of WAEs, with pregabalin risk being greater with higher doses. Pregabalin and gabapentin resulted in large increases in blurred vision, dizziness, weight gain, and cognitive effects (e.g., confusion). Gabapentin enacarbil may have lower risk of blurred vision, weight gain or cognitive effects. Additionally, pregabalin resulted in large increases in risk of peripheral edema and sedation (SOE: Moderate to Low).

Seventy-nine trials evaluated harms of NSAID treatment in the short term. WAEs were increased, specifically with ibuprofen and diclofenac (small increase) and naproxen (moderate increase). The risk of any cardiovascular event was not significantly elevated for NSAIDs as a group, but diclofenac had a small increase in risk, particularly in the first 6 months, and with higher doses. The risk of major coronary events was elevated with diclofenac and celecoxib (moderately) and with ibuprofen (large increase). There was no difference in cardiovascular events between celecoxib and nonselective NSAIDs in the intermediate and long term (SOE: Moderate). The risk of serious upper gastrointestinal events was increased with diclofenac (moderately) and ibuprofen or naproxen (large increase), particularly in the first 6 months of treatment. In the intermediate term, large increases in incidence of hepatic harms were found with diclofenac and naproxen (SOE: Moderate to Low).

In the short or intermediate term, acetaminophen did not increase WAEs (3 RCTs, SOE: Low). In the short term (3 RCTs), capsaicin 8 percent topical patch 60 minute application led to a moderate increase in SAEs compared with 30 minutes. Capsaicin resulted in a large increased risk of application site pain and a small increased risk of erythema (SOE: Moderate and Low). Cannabis showed large increases in incidence of dizziness with oral dronabinol solution, and in WAEs, dizziness, and nausea with tetrahydrocannabinol/cannabidiol oral spray (2 RCTs, SOE: Low).

Discussion

Key Findings and Strength of Evidence

The key findings of this review and effect size definitions are summarized below (Tables C through K). (See the full report for a detailed discussion of our key findings and strength of evidence.) This review evaluated and synthesized the evidence on benefits and harms of nonopioid drugs in patients with chronic noncancer pain. The pain conditions included were neuropathic pain (diabetic peripheral neuropathy, post-herpetic neuralgia, other), fibromyalgia, osteoarthritis, inflammatory arthritis (rheumatoid arthritis or ankylosing spondylitis), spinal pain (neck or low back pain), chronic headache, and sickle cell disease. Drugs reviewed included antidepressants (SNRIs and TCAs), anticonvulsants (pregabalin, gabapentin, oxcarbazepine, and carbamazepine), NSAIDs, and other drugs such as acetaminophen, capsaicin, and cannabis. The findings are categorized in the paragraphs below according to pain condition. The magnitude of the findings and the strength of the evidence for each finding are categorized according to the

methods described above. Interventions or comparisons for which all evidence was insufficient to draw conclusions are not included here.

In patients with neuropathic pain, in the short term, the anticonvulsant drugs gabapentin, pregabalin, and oxcarbazepine provided small improvement in pain outcomes in patients with diabetic peripheral neuropathy/post-herpetic neuralgia. Function did not improve with gabapentin and quality of life showed no improvements with the three anticonvulsant drugs. In patients with diabetic peripheral neuropathy, duloxetine resulted in small improvements in pain, function, and quality of life. Capsaicin patch had effects on pain severity short of small-effect in post-herpetic neuralgia and HIV-related neuralgia, and showed no improvement in pain response. Limited evidence on cannabis (dronabinol oral solution, tetrahydrocannabinol/cannabidiol oral spray) showed inconsistent effects on pain (depending on the measure) in patients with multiple sclerosis-associated neuropathy or allodynia in the short term, and no effect on function or quality of life in the short term,

In patients with fibromyalgia, in the short and intermediate term, SNRI antidepressants duloxetine and milnacipran resulted in small improvements in pain. Function improved to a small degree in the short term, but not in the intermediate term. Short-term treatment with the anticonvulsants pregabalin and gabapentin results in small improvements in pain and function, but not quality of life. Subgroup analyses showed no effect of specific drug, dose, or study quality on these results. Short- and intermediate-term treatment with memantine resulted in moderate improvements in pain, function, and quality of life. Evidence for cyclobenzaprine showed no effect on pain in the short term.

Oral NSAIDs improve pain and function in patients with osteoarthritis to a small degree in the short term, with evidence indicating these effects are maintained in the intermediate term for celecoxib. Subgroup analyses indicated that studies of patients with knee pain only and those of good quality had smaller effects, while patients with more severe pain at baseline experienced greater reduction in pain. Direct comparisons of NSAIDs with each other found few differences between drugs in pain or function in osteoarthritis patients in the short, intermediate, or long term. The exception was that diclofenac moderately improved pain and function more than celecoxib in the short term. Topical diclofenac showed small improvement in pain in the short term. The SNRI antidepressant duloxetine resulted in moderate improvement in pain response, and small effects on pain improvement, function, and quality of life. Subgroup analyses found that pain improvement was greater in older patients (>65 years) and patients with knee osteoarthritis. Acetaminophen did not improve pain significantly in the short or intermediate term. In patients with rheumatoid arthritis or ankylosing spondylitis, short-term treatment with oral NSAIDs resulted in small improvements in pain severity and function, and moderate improvements on pain response, but evidence on quality of life was inconsistent. Evidence on intermediate- and long-term outcomes was limited to one trial each, with improvements in pain but not function. Comparisons of different doses or between different NSAIDs did not find important differences. Subgroup analyses of specific drug, dose, year of publication, type of inflammatory arthritis, and study quality did not alter the findings meaningfully. The TCA amitriptyline did not improve pain severity. Evidence in patients with chronic headache or sickle cell disease was too limited to draw conclusions.

Adverse events categorized as “serious” were more often not reported with nonopioid drugs than placebo in patients with chronic pain, the exception being in neuropathic pain with longer duration capsaicin patch (compared with shorter duration, moderate effect). Withdrawal due to adverse events was increased with anticonvulsants, antidepressants (both moderately), NSAIDs

(to a small degree), and cannabidiol oral spray (ranging from a small increase to large increases). SNRI antidepressants resulted in increased reports of nausea (dose did not alter these findings). Duloxetine also resulted in increased sedation, but lower doses did reduce the risk. Amitriptyline led to a moderate increase in reports of dry mouth, but other adverse events of interest were not reported or not different to placebo. There were no reports of serotonin syndrome in any included RCT of antidepressants. In the short term, pregabalin and gabapentin resulted in moderate to large increases in blurred vision, dizziness, weight gain, sedation, and cognitive effects (e.g., confusion). A prodrug of gabapentin, gabapentin enacarbil may have lower risk of blurred vision, weight gain, or cognitive effects. Additionally, pregabalin resulted in large increases in risk of peripheral edema and sedation. In the short term, the risk of any cardiovascular event was not significantly elevated for NSAIDs as a group, although there was a small increase in risk with diclofenac, particularly within the first 6 months, and with higher doses; risk was increased to a similar degree with ibuprofen and celecoxib but did not reach statistical significance. Although the absolute risk is low, there was a moderate relative increased risk of major coronary events with diclofenac and celecoxib and a large increase with ibuprofen. In the intermediate and long term, there was not a difference in cardiovascular events between drugs. In the short term, NSAIDs led to moderate to large increased risk of serious upper gastrointestinal events (largely bleeding), particularly in the first 6 months of treatment. In the intermediate term, although the incidence is low, large increases in hepatic harms were seen with diclofenac and naproxen. Dronabinol oral solution resulted in a large increase in dizziness and tetrahydrocannabinol/cannabidiol oral spray resulted in large increases in dizziness and nausea. Other adverse events of interest were not reported (cognitive effects, misuse, addiction, substance use disorder).

Table C. Effects of antidepressants in placebo-controlled and head-to-head trials

Condition	Drug	Pain Short Term Effect Size SOE	Pain Intermediate Term Effect Size SOE	Function Short Term Effect Size SOE	Function Intermediate Term Effect Size SOE	QoL Short Term Effect Size SOE	QoL Intermediate Term Effect Size SOE
Neuropathic pain	Duloxetine vs. placebo	Moderate ++	No evidence	Small +	No evidence	Small ++	No evidence
Fibromyalgia	Duloxetine/milnacipran vs. placebo	Small ++	Small ++	Small ++	None ++	MCS: Small ++ PCS: None ++	Small ++
Osteoarthritis	Duloxetine vs. placebo	Small +++	No evidence	Small +++	No evidence	Small +++	No evidence
Low back pain	Duloxetine vs. placebo	Small ++	No evidence	None ++	No evidence	None ++	No evidence
	Amitriptyline vs. placebo	No evidence	None +	No evidence	None +	No evidence	No evidence
	Amitriptyline vs. pregabalin	Small +	No evidence	None +	No evidence	No evidence	No evidence

QoL = quality of life; SOE = strength of evidence; MCS = Mental Component Score; PCS = Physical Component Score

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk

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

Table D. Effects of anticonvulsants in placebo-controlled and head-to-head trials

Condition	Drug	Pain Short Term Effect Size SOE	Function Short Term Effect Size SOE	QoL Short Term Effect Size SOE
Neuropathic pain	Pregabalin/gabapentin vs. placebo	Small ++	None +	None +
	Oxcarbazepine vs. placebo	Small ++	No evidence	None +
	Pregabalin vs. gabapentin	Insufficient	No evidence	No evidence
	Pregabalin vs. gabapentin enacarbil ^a	None +	None +	None +
Fibromyalgia	Pregabalin / gabapentin vs. placebo	Small ++	Small ++	None ++

QoL = quality of life; SOE = strength of evidence

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large

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

^a Gabapentin enacarbil is a prodrug of gabapentin

Table E. Effects of NSAIDs in placebo-controlled and head-to-head trials

Condition	Drug	Pain Short Term Effect Size SOE	Pain Intermediate Term Effect Size SOE	Pain Long Term Effect Size SOE	Function Short Term Effect Size SOE	Function Intermediate Term Effect Size SOE	Function Long Term Effect Size SOE	QoL Short Term Effect Size SOE
Osteoarthritis	NSAID vs. placebo	Small ++	No evidence	No evidence	Small +++	No evidence	No evidence	None ++
	Diclofenac vs. celecoxib	Moderate +	No evidence	No evidence	Moderate +	No evidence	No evidence	No evidence
	NSAID vs. NSAID	None +	None +	None +	None +	None +	No evidence	No evidence
	Topical diclofenac vs. placebo	Small ++	No evidence	No evidence	None +	No evidence	No evidence	No evidence
Inflammatory arthritis	NSAID vs. placebo	Small/Moderate ++	Small +	Large +	Small ++	Small +	None +	Insufficient
	Celecoxib vs. diclofenac	None ++	No evidence	No evidence	None ++	No evidence	No evidence	No evidence
	Celecoxib vs. naproxen	None +	No evidence	No evidence	None +	No evidence	No evidence	None +
	Diclofenac vs. meloxicam	None +	No evidence	No evidence	None +	No evidence	No evidence	No evidence
	Meloxicam vs. naproxen	No evidence	None +	No evidence	No evidence	No evidence	No evidence	No evidence
	Nabumetone vs. naproxen	None +	None +	No evidence	None +	No evidence	No evidence	No evidence

NSAID = nonsteroidal anti-inflammatory drug; QoL = quality of life; SOE = strength of evidence
 Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk
 SOE: + = low, ++ = moderate, +++ = high

Table F. Effects of other drugs in placebo-controlled trials

Condition	Drug	Pain Short Term Effect Size SOE	Pain Intermediate Term Effect Size SOE	Function Short Term Effect Size SOE	Function Intermediate Term Effect Size SOE	QoL Short Term Effect Size SOE	QoL Intermediate Term Effect Size SOE
Neuropathic pain	Capsaicin patch	None ++	No evidence	No evidence	No evidence	No evidence	No evidence
	Cannabis	None +	No evidence	None +	No evidence	None +	No evidence
Fibromyalgia	Memantine	No evidence	Moderate +	No evidence	Moderate +	No evidence	Moderate +
	Cyclobenzaprine	No evidence	None +	No evidence	Insufficient	No evidence	No evidence
Osteoarthritis	Acetaminophen	None +	None +	None +	None +	No evidence	No evidence

QoL = quality of life; SOE = strength of evidence

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk

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

KQ2 Harms and Adverse Events of Nonopioid Drugs for Chronic Pain

Table G. Harms of antidepressants versus placebo

Types of Adverse Events	SNRIs (duloxetine/milnacipran)	SNRIs (duloxetine/milnacipran)	TCA's	TCA's
	Short Term Effect Size SOE	Intermediate Term Effect Size SOE	Short Term Effect Size SOE	Intermediate Term Effect Size SOE
WAE	Moderate ++	Moderate ++	None +	Insufficient
SAE	None +	None +	No evidence	No evidence
Cognitive effects	None +	No evidence	No evidence	No evidence
Nausea	Large ++	Moderate +	NA	NA
Sedation	Large ++	Large +	NA	NA
Serotonin syndrome	No evidence	No evidence	No evidence	No evidence
Dry mouth	NA	NA	Insufficient	No evidence
Cardiac rhythm abnormalities	NA	NA	No evidence	No evidence
Urinary retention	NA	NA	No evidence	No evidence

NA = not applicable (i.e., specific adverse event not applicable to drug); SAE = serious adverse event; SNRI = serotonin-norepinephrine reuptake inhibitor; SOE = strength of evidence; TCA = tricyclic antidepressant; WAE = withdrawal due to adverse event
 Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk
 SOE: += low, ++ = moderate, +++ = high

Table H. Harms of anticonvulsants versus placebo and active comparator

Types of Adverse Events	Pregabalin/Gabapentin Short Term Effect Size SOE	Oxcarbazepine Short Term Effect Size SOE
WAE	Moderate ++	Large +
SAE	None +	None +
Blurred vision	Large +	NA
Cognitive effects	Large +	No evidence
Dizziness	Large ++	NA
Peripheral edema	Large ++	NA
Sedation	Large ++	None +
Weight gain	Large ++	NA
Hyponatremia	NA	None +

NA = not applicable (i.e., specific adverse event not applicable to drug); SAE = serious adverse event; SOE = strength of evidence; WAE = withdrawal due to adverse event
 Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk
 SOE: + = low, ++ = moderate, +++ = high

Table I. Harms of NSAIDs versus placebo and active comparators

Types of Adverse Events	NSAID Short Term Effect Size SOE	NSAID Intermediate Term Effect Size SOE	NSAID Long Term Effect Size SOE	Topical Diclofenac Versus Placebo Short Term Effect Size SOE	nsNSAID Versus Celecoxib Intermediate Term Effect Size SOE	nsNSAID Versus Celecoxib Long Term Effect Size SOE
WAE	Small ++	None +	Insufficient	None +	No evidence	No evidence
SAE	None +	Insufficient	No evidence	None +	No evidence	No evidence
Cardiovascular events	Small ++	No evidence	No evidence	No evidence	None ++	None ++
Gastrointestinal events	Moderate +/++	No evidence	No evidence	No evidence	Moderate +	No evidence
Liver dysfunction	Large +	No evidence	No evidence	No evidence	No evidence	No evidence

NA = not applicable (i.e., specific AE not applicable to drug); NS = nonsteroidal anti-inflammatory drug; nsNSAID = nonselective nonsteroidal anti-inflammatory drug; SAE = serious adverse event; SOE = strength of evidence; WAE = withdrawal due to adverse event

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk

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

Table J. SAEs and WAEs of other drugs versus placebo and active comparator

Types of Adverse Events	Capsaicin Short Term Effect Size SOE	Dronabinol Short Term Effect Size SOE	THC + CBD Short Term Effect Size SOE	Acetaminophen Short Term Effect Size SOE	Acetaminophen Intermediate Term Effect Size SOE	Cyclobenzaprine Intermediate Term Effect Size SOE
WAE	None ++	None +	Large +	None +	None +	None +
SAE	None ++	None +	None +	None +	None +	No evidence
Application site erythema	Moderate ++	NA	NA	NA	NA	NA
Application site pain	Large ++	NA	NA	NA	NA	NA
Application site pruritus	None ++	NA	NA	NA	NA	NA
Cognitive effects	NA	No evidence	No evidence	NA	NA	NA
Hyperemesis	NA	No evidence	No evidence	NA	NA	NA
Nausea	NA	None +	Large +	NA	NA	NA
Sedation	NA	No evidence	Insufficient	NA	NA	Insufficient
Dizziness	NA	Large +	Large +	NA	NA	Insufficient

CBD = cannabidiol; NA = not applicable; THC = tetrahydrocannabinol; SAE = serious adverse event; SOE = strength of evidence; WAE = withdrawal due to adverse event

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk

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

Table K. Summary of specific adverse events

Drug Class	Drug	Outcomes of Interest	Adverse Event Findings From RCTs in Chronic Pain (Magnitude of Effect)	Adverse Event Findings From Other Sources (to Address Missing Evidence)
Antidepressants	SNRIs	Nausea, sedation, serotonin syndrome	Nausea (moderate-to-large, no dose effect), sedation (duloxetine, dose-related), serotonin syndrome symptoms (large)	No missing outcomes
	TCA s	Cardiac rhythm abnormalities, dry mouth, urinary retention, weight gain, serotonin syndrome	Dry mouth (moderate)	Cardiac arrhythmias and sinus tachycardia: increases with higher dose and pre-existing risk Urinary retention: no estimate found Weight gain: 2-2.5kg over 3 months Serotonin syndrome: very rare ⁶
Antiepileptic drugs	Pregabalin, gabapentin	Blurred vision, cognitive effects, dizziness, peripheral edema, sedation, weight gain	Blurred vision, dizziness, weight gain, and cognitive effects (moderate to large, lower with the prodrug gabapentin enacarbil) Peripheral edema (large with pregabalin)	No missing outcomes
	Oxcarbazepine	Cognitive effects, hyponatremia, and sedation	Hyponatremia – 1 RCT, no increased risk	Significant hyponatremia: 2.5%, occurs in first 3 months. Cognitive effects: 7-11% Somnolence: 35% ⁷
NSAIDs	Oral NSAIDs	CV, GI, renal, and hepatic Events	Short term: Increased CV risk - diclofenac (small, dose-dependent); increased coronary events - diclofenac, celecoxib (moderate), ibuprofen (large); Increased GI events – diclofenac (moderate), ibuprofen, naproxen (large); Intermediate term: Differences in CV risk unclear; Increased hepatic harms- diclofenac, naproxen (large, low incidence)	Renal: Increased risk (moderate to large), higher in older patients and those with chronic kidney disease (evidence from observational studies, includes short-term use) No difference found between NSAIDs. ^{8,9}
Other	Acetaminophen	Hepatotoxicity	Not reported in included RCTs	Increased risk with chronic use of >3gms daily, effects often occur early in treatment; dose-adjustment if hepatic or renal dysfunction ^{10,11}
	Cannabis	Addiction/dependence, cognitive effects, hyperemesis, nausea, sedation	Dizziness (large) Nausea (THC/CBD oral spray, large)	Hyperemesis syndrome: Case reports (not limited to medical uses), >1x/week for >2 years. Cognition: small negative impact with chronic use Addiction/dependence: not found ¹²
	Capsaicin	Application site reactions	Pain (large), erythema (small) Greater with longer application	No missing outcomes

CBD = cannabidiol; CV = cardiovascular; GI = gastrointestinal; kg = kilogram; NSAIDs = nonsteroidal anti-inflammatory drugs; RCTs = randomized controlled trials; SNRIs = serotonin-norepinephrine reuptake inhibitor; TCAs = tricyclic antidepressants; THC = tetrahydrocannabinol

Findings in Relationship to What Is Already Known

This systematic review combines evidence across multiple pain conditions and multiple drug classes in a way that prior reviews have not. Prior reviews generally had dissimilar scope (e.g., limited to a single condition and/or drug class, included drugs or populations not included here), included very short duration studies (<12 weeks), did not classify results according to treatment duration, and did not categorize effect sizes (small, moderate, large). Although our review includes more recent studies, other reviews of individual drugs, drug classes, or pain conditions have reviewed some of the evidence included here, and where comparisons of our results and prior findings are possible, they are generally consistent. For example, a 2015 systematic review with network meta-analysis of acetaminophen, NSAIDs, and injectable drugs for knee osteoarthritis found an SMD for acetaminophen of 0.18, and we found the mean difference (MD, 0 to 10 scale) was 0.34. Both are less than a small magnitude of effect according to our system, and the prior review noted that the effect did not reach clinical significance in their system.¹³ Findings for NSAIDs were similar to ours, and our subgroup analysis of only knee osteoarthritis was also in a similar range of magnitude of effect to their findings. The exception was that they found a moderate-size effect with diclofenac, while our subgroup analysis of specific drug was not significant. For neuropathic pain, a 2017 systematic review of only diabetic peripheral neuropathy found duloxetine to have large effect (SMD -1.33), but when we added another study the magnitude was reduced to small (MD -0.79, 0 to 10 scale).¹⁴ This review and ours had similar findings for pregabalin (small effect). Both reviews found that the effect of gabapentin was not significant, but the effect was moderate in the older review, while in ours the effect was small after incorporating additional studies. In fibromyalgia, a 2016 systematic review with a network meta-analysis found a large magnitude of effect in pain response with SNRI antidepressants (odds ratio [OR] 1.61 to 2.33) while we found a moderate effect (relative risk [RR] 1.29 to 1.36), and the prior review found a moderate effect with pregabalin (OR 1.68) while we found a small effect with pregabalin and gabapentin combined (RR 1.41).¹⁵ Differences in magnitude could be due to the addition of 15 studies in our report, reporting relative risks rather than odds ratios, and using direct comparisons rather than network analysis. Our findings regarding the effects of nonopioid drugs on pain and function are also consistent with two related systematic reviews on opioids and nonpharmacologic treatments for chronic pain, which found similar small effects.^{16,17}

In terms of evidence on the harms of the drugs included, because many of the drugs have been available for decades (e.g., acetaminophen), were initially approved for other indications (e.g., antidepressants and anticonvulsants), or primarily studied in acute pain and short-term treatment (e.g., acetaminophen, topical lidocaine), our findings on adverse events are not comprehensive relative to other, non-systematic review sources (e.g., product labels, large observational studies, Food and Drug Administration warnings, drug information texts). However, as Table K indicates, our analyses on adverse events are consistent with these other sources.

Table K provides a summary of the evidence on adverse events of interest that were identified in RCTs of patients with chronic pain meeting inclusion criteria for this review. Because the scope of this review focused on a specific patient population (chronic pain with specific conditions), a specific study design (RCTs), and study duration (12 weeks or more), it is unlikely that all important evidence on harms of these drugs would be identified. Where included evidence did not adequately address the prioritized harms, information from other sources is summarized. The evidence from other sources may have unclear applicability to patients with

chronic pain, who may use these drugs for longer periods of time, possibly at higher doses, and who may be older (in some cases) or have more comorbidities than patients providing data for these sources.

Applicability

The applicability of the evidence-base for nonopioid drugs to treat chronic pain varies according to the pain population and intervention studied. In terms of patient populations studied, the participants were generally typical for each pain condition (with the possible exception of chronic headache). Because our definition of chronic headache was broad, and our criteria for treatments excluded use of nonopioids for prophylaxis, the result was a single, older, study of amitriptyline in patients with “chronic tension-type headache.” Headache classification has changed over the years such that the evidence identified may not be highly applicable to current patients or treatment strategies. While some RCTs excluded patients with mental illness, most did not report on baseline characteristics in relation to mental health, prior use of opioids, substance use disorder, etc.

Similarly, the specific interventions studied varied according to the pain condition. The medications studied in patients with neuropathic pain (predominantly peripheral diabetic neuropathy) and fibromyalgia were most often antidepressants (primarily duloxetine) and anticonvulsants (primarily pregabalin), with some evaluations of other categories such as capsaicin and cannabis in neuropathic pain and memantine in both conditions. In contrast, osteoarthritis and inflammatory arthritis studies involved primarily NSAIDs. In patients with osteoarthritis, a small number of studies evaluated topical diclofenac, duloxetine, and acetaminophen. As a result, we have little or no information on how some interventions that were found effective in one pain condition may affect another pain condition. An example is that the evidence on pregabalin and gabapentin is applicable mainly to patients with specific types of neuropathic pain and fibromyalgia; but not applicable to patients with osteoarthritis or rheumatoid arthritis, or other types of chronic pain. The reverse is true of NSAIDs in that the evidence is restricted to osteoarthritis or rheumatoid arthritis/ankylosing spondylitis. The use of comedications was rarely reported; acetaminophen use as a rescue medication in trials of NSAIDs was the only comedication reported. As such, it is unclear how applicable this evidence is to patients using comedications, including intermittent use of over-the-counter medications.

For all pain conditions, the most common comparator in the RCTs was placebo (117 out of 154 RCTs of good or fair quality), with limited head-to-head comparisons, especially across classes (7 RCTs). The most common head-to-head comparison was among different NSAIDs in patients with osteoarthritis (15 RCTs). The specific outcomes assessed in the included RCTs also varied according to the pain condition studied. The outcomes reported here apply mostly to the short term—12 to 24 months of treatment. The applicability of the study settings is very unclear, as few studies reported setting characteristics.

All of these elements affect how applicable the findings of this review are to a specific patient. The results apply mostly to addressing whether a drug is effective and/or harmful in comparison to no treatment, but less applicable to selecting among nonopioid treatments. However, the evidence base does provide some information on dose comparisons, such as higher and lower doses of SNRI antidepressants, pregabalin and gabapentin anticonvulsants, and some of the NSAIDs, where our analyses found little differences in efficacy, and a few cases of lower risk of adverse events with lower doses of antidepressants.

Implications and Conclusions

Our findings show that nonopioid drugs (mainly SNRI antidepressants, pregabalin/gabapentin, and NSAIDs) result in small to moderate improvements in pain and function in the short term in patients with specific types of chronic pain, with few differences between drugs studied or doses of a drug. Drug class-specific adverse events can lead to withdrawal from treatment in some patients, and include serious cardiovascular or gastrointestinal effects with NSAIDs. Consideration of patient characteristics including comorbidities, is needed in selecting nonopioid drug treatments. These findings are mainly consistent with prior review findings, with our review finding smaller magnitude of effect in some cases.

Recent guidelines from the Centers for Disease Control and Prevention in the United States and the Canadian Guideline for Opioid Use in Chronic Non-Cancer Pain recommend nonopioid treatment as the preferred treatment for chronic pain.^{3,18} This review provides evidence that can be used to update these clinical practice guidelines on treating the specific, common, chronic pain conditions and can inform guideline producers on the balance of benefits and harms, in the short, intermediate, and longer term. Our report also reviewed evidence that may help inform decisions regarding prioritization of nonopioid drug therapies by clinicians and patients when selecting therapy.

Our ability to evaluate harms of included nonopioid drugs may have been limited by restricting the evidence to RCTs and to studies of patients with chronic pain, specifically. Restricting to studies of at least 12 weeks' duration may have limited the evidence for certain treatments (e.g., cannabis and topical agents) and favored interventions commonly studied in clinical trials, the majority coming from industry funding. In addition, the number of studies identified on chronic headache and sickle cell disease was low. Evidence on long-term treatment (>12 months) and for quality of life outcomes was sparse.

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Background and Objectives

Understanding Chronic Pain

Chronic pain is typically defined as pain lasting at least 3 to 6 months or that which persists past the time for normal tissue healing.¹ From a strictly biological perspective, pain is activation of the sensory nervous system's nociceptive and hypothalamic-pituitary-adrenal axis,² and has been described as an aversive sensory and emotional experience typically caused by, or resembling that caused by, actual or potential tissue injury.³ Adding to the complexity of chronic pain are its diverse origins and the subjective experience of a sufferer.⁴ Chronic pain can be the result of several issues ranging from a potential underlying medical condition or disease to inflammation of injured tissue, to neuropathic pain involving a lesion or disease of the somatosensory nervous system. The manner in which pain is experienced is more than simply the biological output of an underlying issue. Attitudes, emotional disposition, and belief systems can shape the experience of pain.¹ It is also heavily influenced by extrinsic psychosocial and socioeconomic factors and thus the biopsychosocial impact of chronic pain on the individual is as complex and varied as the condition itself. The physical deficits associated with chronic pain lead to reductions in function (disabilities) and quality of life, and increased medical costs. Psychological and social effects are also common and can manifest in a number of ways, including depression, anxiety, and an inability to fulfill social roles with family, friends, and employers.¹ The Centers for Disease Control and Prevention (CDC) estimates that 20.4 percent of U.S. adults in 2016 had chronic pain, contributing to population morbidity and mortality and adding to the economic burden of the healthcare system.⁵ Annual healthcare costs due to chronic pain are estimated above \$560 billion, with 2008 costs to federal and state governments alone reaching \$99 billion.¹

Chronic Pain Management

Pain management is a dynamic process of care for an individual, with a goal of alleviating pain and dysfunction.⁶ Understanding pain from the biopsychosocial perspective, its management should be multimodal. The National Pain Strategy (NPS) report recommended a population-based approach which draws upon current scientific evidence.⁶ Self-management is often considered an important first step to alleviating chronic pain.¹ While there exist numerous pharmacologic and nonpharmacologic interventions for the treatment of chronic pain, the overview below focuses on pharmacologic treatments.

The most common forms of pharmacologic treatment for pain include opioids, nonsteroidal anti-inflammatory drugs, acetaminophen, topical formulations of drugs such as lidocaine, and other drugs such as antiseizure/anticonvulsant medications and antidepressants that are used for moderating pain. Cannabis has also been used to treat chronic pain. Pharmacologic treatments can be used individually (monotherapy) or in combination, taking into consideration potential side effects and contraindications based on the patient's comorbidities.

Nationally, a concern regarding the appropriate use, misuse, and diversion of opioids, and development of substance use disorder (SUD) when opioids are used to treat chronic pain has been the subject of numerous scientific and news reports. Opioid prescriptions for chronic pain have increased substantially in the past 20 years; the number of opioid prescriptions dispensed rose from 76 million in 1999 to over 215 million in 2011, with approximately 35 percent of all opioid overdose deaths in 2017 being attributed to prescription medications.^{6,7} However,

evidence shows only modest short-term benefits.⁸⁻¹² Lack of evidence on long-term effectiveness¹⁰ and serious safety concerns⁹ speaks to the need to consider alternative treatments to opioids. The 2016 CDC Guideline for Prescribing Opioids for Chronic Pain recommended that nonopioid therapy is preferred for the treatment of chronic pain.¹³ To support, update, and expand such guidelines, synthesis of the current state of the science is required to guide clinicians and inform health policy.

Rationale for Evidence Review and What This Review Adds

The 2010 Patient Protection and Affordable Care Act mandated the Department of Health and Human Services to contract with the Institute of Medicine (IOM, now the National Academy of Medicine) to assess the state of the science on pain research, care, and education, and formulate recommendations in these key areas.^{1,6} Recommendations outlined in the 2011 IOM report have spawned a number of national initiatives to address gaps related to understanding the complexities of pain assessment and management, including the creation of the NPS under the oversight of the Interagency Pain Research Coordinating Committee (IPRCC), and creation of a federal portfolio of existing pain research to help inform additional research needs on pain. Concerns regarding the use of opioids for management of chronic pain are outlined in both the IOM report and the NPS. These initiatives, along with the recent publication of the evidence-based guideline on opioid use for chronic pain by the CDC,¹³ have prompted additional primary research on alternatives to opioids in managing chronic pain.

Given the complexity of treating chronic pain and concerns regarding the safety and long-term effectiveness of opioids, there is a need for a comprehensive understanding of the benefits and harms of nonopioid pharmacologic treatments for chronic pain. While there have been numerous systematic reviews on nonopioid drugs in chronic pain populations,¹⁴⁻²⁰ many are outdated, focused on a single pain condition or a single drug/drug class, or reported on limited outcomes. An updated analysis that includes the main pain conditions and treatments is essential to respond to the current need to provide guidance on the use of nonopioid treatments in chronic pain.

The purpose of this report is to evaluate the effectiveness and comparative effectiveness of nonopioid pharmacologic agents, considering the effects on pain, function, quality of life, and adverse events. This review is one of three concurrent systematic reviews on treating chronic pain; other reviews address noninvasive nonpharmacologic treatments and opioids.

Key Questions

Key Question 1. Effectiveness and Comparative Effectiveness

- a. In patients with chronic pain, what is the effectiveness of nonopioid pharmacologic agents versus placebo for outcomes related to pain, function, and quality of life after short-term treatment duration (3 to 6 months), intermediate-term treatment duration (6 to 12 months), and long-term treatment duration (≥ 12 months)?
- b. In patients with chronic pain, what is the comparative effectiveness of nonopioid pharmacologic agents compared to other nonopioid pharmacologic agents for outcomes related to pain, function, and

quality of life after short-term treatment duration (3 to 6 months), intermediate-term treatment duration (6 to 12 months), and long-term treatment duration (≥ 12 months)?

- c. How does effectiveness or comparative effectiveness vary depending on: (1) the specific type or cause of pain, (2) patient demographics, (3) patient comorbidities, (4) dose of medication used, (5) duration of treatment, and (6) dose titration, including tapering?

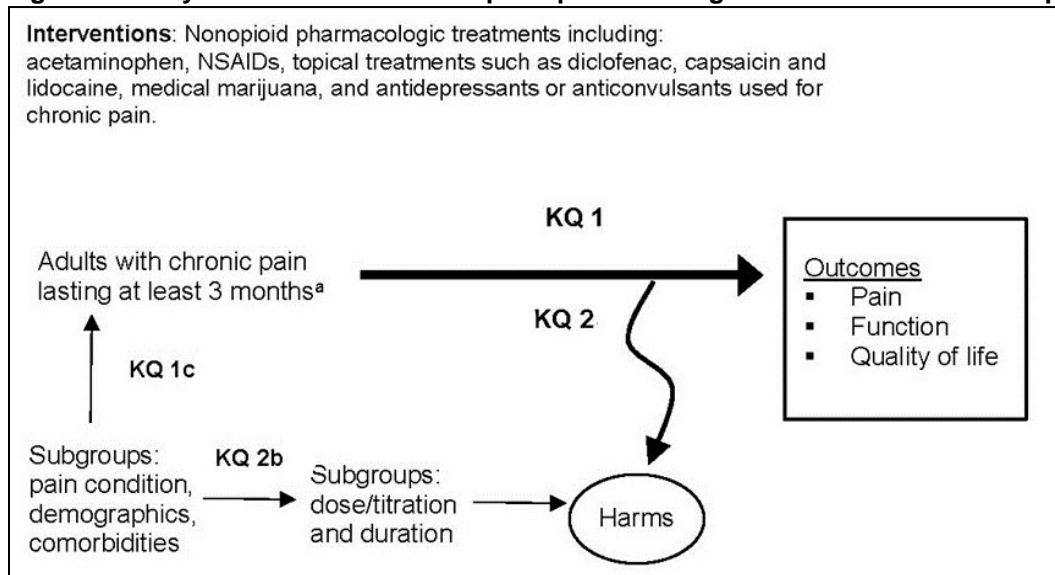
Key Question 2. Harms and Adverse Events

- a. In patients with chronic pain, what are the risks of nonopioid pharmacologic agents for harms, including overdose, misuse, dependence, substance use disorder, withdrawals due to adverse events, serious adverse events (including falls, fractures, motor vehicle accidents), and specific adverse events, according to drug class?
- b. How do harms vary depending on: (1) the specific type or cause of pain, (2) patient demographics, (3) patient comorbidities, (4) dose of medication used, (5) duration of treatment, and (6) dose titration, including tapering?

Analytic Framework

The analytic framework (Figure 1) graphically describes the relationship between the Key Questions and the outcomes for this review. Inclusion criteria are provided in the Methods.

Figure 1. Analytic framework for nonopioid pharmacologic treatments for chronic pain



KQ = Key Question; NSAID = nonsteroidal anti-inflammatory drug

^a Includes acute exacerbations of chronic pain, pregnant/breastfeeding women, and patients treated with opioids for opioid use disorder

Methods

This Comparative Effectiveness Review follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter “AHRQ Methods Guide”).²¹ All methods were determined *a priori*, and a protocol was published on the AHRQ website (<https://effectivehealthcare.ahrq.gov/topics/nonopioid-chronic-pain/protocol>) and on PROSPERO systematic reviews registry (Registration No. CRD42019134249). Below is a summary of the specific methods used in this review. Appendix A presents the literature search strategy, and a detailed description of methods appears in Appendix B.

Criteria for Inclusion/Exclusion of Studies in the Review

The criteria for inclusion and exclusion of studies for this systematic review are based on the Key Questions and are described in Table 1. (See Appendix B for complete details.)

Table 1. PICOTS: Inclusion and exclusion criteria

PICOTS	Inclusion Criteria	Exclusion Criteria
Populations and Conditions	<ul style="list-style-type: none"> For all KQs: Adults (age ≥18 years) with chronic pain (pain lasting >3 months). For KQs 1c, 2b specific chronic pain populations: <ul style="list-style-type: none"> Neuropathic Musculoskeletal (e.g., low back pain, osteoarthritis) Fibromyalgia (assessed using established criteria) Sickle cell disease Inflammatory arthritis (e.g., rheumatoid arthritis) Chronic headache^a 	<ul style="list-style-type: none"> Pain at the end of life (life expectancy ≤6 months) Acute pain (<8 weeks duration), including sickle cell crisis Pain due to active malignancy (e.g., tumor-related pain while receiving active treatment to reduce tumor size) Episodic migraine Undefined mixed pain conditions
Interventions	<p>Nonopioid pharmacologic drugs for chronic pain:</p> <ul style="list-style-type: none"> Oral pharmacologic agents specifically used to treat chronic pain: <ul style="list-style-type: none"> NSAIDs (e.g., celecoxib, diclofenac, ibuprofen) Antidepressants SNRIs (i.e., duloxetine, milnacipran) and TCAs (e.g., amitriptyline) Anticonvulsants: Carbamazepine, gabapentin, oxcarbazepine, pregabalin Other: Acetaminophen, muscle relaxants (e.g., cyclobenzaprine, diazepam), memantine Topical agents (diclofenac, capsaicin, and lidocaine) Medical cannabis in all forms, including phytocannabinoids and synthetic cannabinoids 	<ul style="list-style-type: none"> Injectable preparations, including biologic drugs, corticosteroids, etc. Other antidepressants (e.g., SSRIs, MAOIs) Other antiepileptics (e.g., topiramate, lamotrigine, levetiracetam, phenytoin) Drugs used for migraine prophylaxis (e.g., verapamil, beta-blockers) or treating acute migraine (e.g., triptans) Salicylates (topical and oral) Topical menthol preparations Disease-modifying drugs for rheumatoid arthritis (DMARDs, e.g., methotrexate)
Comparators	<ul style="list-style-type: none"> For KQ 1a/b and 2a/b: Placebo For KQ 1c and 2a/b: Another included nonopioid pharmacologic agent, dose, or treatment duration 	<ul style="list-style-type: none"> Nonpharmacologic treatment (comparison to nonopioids included in review of nonpharmacologic treatments) Opioid treatment

PICOTS	Inclusion Criteria	Exclusion Criteria
Outcomes	<ul style="list-style-type: none"> • Pain, function, and quality of life using validated outcome measures. <ul style="list-style-type: none"> ○ Pain severity is the assessment of improvement in pain from baseline as a continuous measure. Pain response is the dichotomous assessment whether patients' improvement meet an established threshold (e.g., 30% improvement). ○ Patient-reported pain assessments are prioritized. Pain response based on clinician assessments was also acceptable and noted where they are reported. ○ Secondary outcomes include mood, sleep, and global assessments using validated scales. • All drug classes: Withdrawal from treatment due to adverse events (any adverse event, not specifically symptoms of withdrawal from an opioid or other drug), incidence of serious adverse events, overdose, misuse, addiction, and development of substance use disorder. • Key specific adverse events according to drug class (e.g., gastrointestinal and cardiovascular events, kidney and liver-related harms with NSAIDs). 	<ul style="list-style-type: none"> • Intermediate outcomes (e.g., pharmacokinetics/pharmacodynamics, drug-drug interactions, dose conversions) • Indirect measurement of pain (e.g., quantitative sensory testing).
Timing	Short- (3 to <6 months), intermediate- (6 to <12 months), and long-term (≥12 months) treatment duration	Studies or outcomes reported with <3-month duration of treatment
Setting	Outpatient settings (e.g., primary care, pain clinics, emergency rooms, urgent care clinics)	Addiction treatment settings, inpatient settings
Study Design	<ul style="list-style-type: none"> • Randomized controlled trials • High-quality, recent systematic reviews that best match the scope of this review • English language publications 	<ul style="list-style-type: none"> • Observational studies • Outdated/out of scope systematic reviews • Non-English language publications

DMARDs = disease-modifying antirheumatic drug; KQ = Key Question; MAOI = monoamine oxidase inhibitor; NSAID = nonsteroidal anti-inflammatory drug; PICOTS = populations, interventions, comparators, outcomes, timing, setting, study design; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant

^aChronic headache defined as (International Classification of Headache Disorders, 3rd edition definition²²): Primary headaches attributed to the headache condition itself, not caused by another disease or medical condition. Chronic headache is defined as 15 or more days each month for at least 12 weeks or history of headache more than 180 days a year.

Literature Search

We conducted electronic searches in Ovid[®] MEDLINE[®], Embase[®], PsycINFO[®], CINAHL[®], Cochrane CENTRAL, and Cochrane Database of Systematic Reviews through September 10, 2019 (from database inception, see Appendix A for full strategies). Reference lists of included systematic reviews were screened for includable studies. Manufacturers of included drugs submitted potential relevant studies to include in this review using the Federal Register notification. We screened citations identified through our searched using the pre-established criteria above to determine eligibility for full-text review, with any citation deemed not relevant by one reviewer screened by a second reviewer.²¹ 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.

Assessment of Methodological Risk of Bias of Individual Studies

We assessed the quality (or risk of bias) of included randomized controlled trials (RCTs) based on principles for appraisal as developed by the Cochrane Back and Neck Group,²³ and outlined in the AHRQ Methods Guide chapter “Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions”.^{21,24} Based on the risk of bias assessment, each included study was rated as “good,” “fair,” or “poor” quality. Assessments of RCTs included in good-quality systematic reviews that we included here were reviewed by a single reviewer, with the exception that any rated poor quality or high risk of bias were reassessed by our team using dual review.

Data Synthesis

Data were qualitatively summarized in tables. The magnitude of effects for pain, function, and quality of life were classified using the system in the 2018 AHRQ Noninvasive Nonpharmacological Treatment for Chronic Pain review (Table 2).²⁵ Mean differences are based on a 0–10 scale, unless otherwise noted.

Table 2. Definitions of effect sizes

Effect Size	Definition
Small effect	<ul style="list-style-type: none"> • MD 0.5 to 1.0 points on a 0 to 10-point scale, 5 to 10 points on a 0 to 100-point scale • SMD 0.2 to 0.5 • RR/OR 1.2 to 1.4
Moderate effect	<ul style="list-style-type: none"> • MD >1 to 2 points on a 0 to 10-point scale, >10 to 20 points on a 0 to 100-point scale • SMD >0.5 to 0.8 • RR/OR 1.5 to 1.9
Large effect	<ul style="list-style-type: none"> • MD >2 points on a 0 to 10-point scale, >20 points on a 0 to 100-point scale • SMD >0.8 • RR/OR ≥2.0

MD = mean difference; OR = odds ratio; RR = relative risk; SMD = standardized mean difference

Meta-analyses, using random effects model, were conducted to summarize data and obtain more precise estimates where there were at least two studies reporting outcomes homogeneous enough to provide a meaningful combined estimate. The Profile Likelihood model was used, unless the model failed to converge, then a DerSimonian and Laird model was used. To determine whether meta-analysis was meaningfully performed, we considered the quality of the studies and the heterogeneity among studies in design, patient population, interventions, and outcomes, and conducted sensitivity analyses. Poor-quality studies were not pooled with other studies. The Key Questions were designed to assess the comparative effectiveness and harms by patient demographics, comorbidities, pain types, treatment dosing strategies, and durations; we conducted subgroup and sensitivity analyses to explore the impact of these variables. In comparisons with placebo, we combined various dosing arms and drugs within the same pharmacologic class, exploring differences based on these factors in subgroup analyses. In meta-analysis findings below, I^2 stands for Inconsistency (0% to 100%), reflecting statistical heterogeneity. See Appendix B for additional details on data synthesis.

Grading the Strength of Evidence for Major Comparisons and Outcomes

The strength of evidence (SOE) was rated for priority clinical outcomes (pain, function, quality of life) for each pain condition-treatment pair, using the approach described in the AHRQ Methods Guide.²¹ To ensure consistency and validity of the evaluation, the grades were reviewed by a second reviewer. The domains assessed were study limitations (low, medium, or high), consistency (consistent, inconsistent, or unknown/not applicable), directness (direct or indirect), precision (precise or imprecise), and publication bias (suspected or undetected). The SOE was assigned an overall grade of high, moderate, low, or insufficient, reflecting our confidence in the effect estimates and whether the findings are stable (Table 3). Evidence is found to be insufficient to draw conclusions when we have no evidence available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Table 3. Description of the strength of evidence grades

Strength of Evidence	Description
High	Very confident that the effect estimate lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. Findings are stable, i.e., inclusion of additional studies would not change the conclusions.
Moderate	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	Limited confidence that the effect estimate lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies. Additional evidence is needed before concluding that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	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 of the bodies of evidence were assessed by examining the characteristics of the populations, interventions, comparators, outcomes, timing, setting, and study design (PICOTS) elements, such as patient population characteristics (e.g., demographic characteristics, duration or severity of pain, underlying pain condition, presence of medical co-morbidities), clinical settings (e.g., primary care, specialty setting), or countries (e.g., non-U.S.) in which the studies are performed. These characteristics indicate to whom the results are directly applicable; applicability to patients, interventions, outcomes, etc. outside of these may be limited and results may differ.

Peer Review and Public Commentary

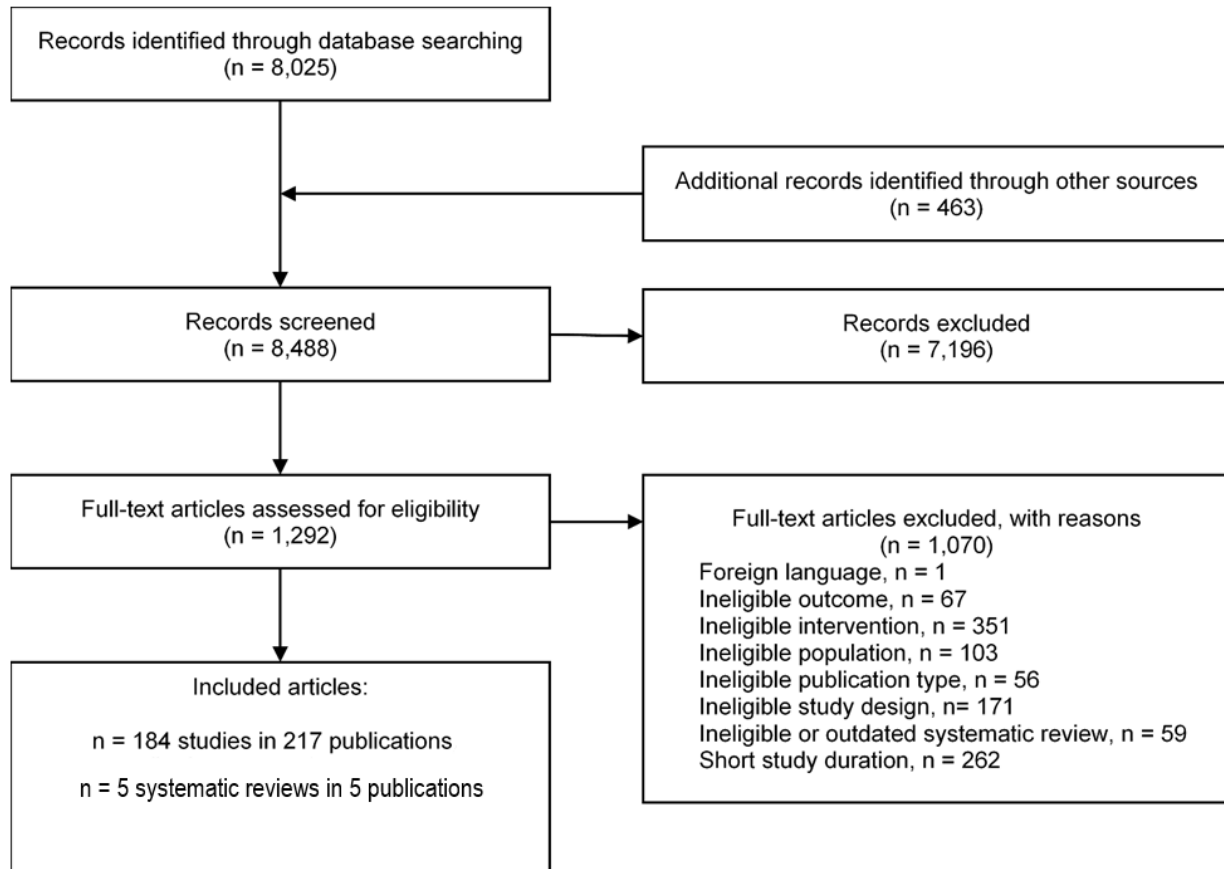
Experts in the field of chronic pain conditions were invited to provide external peer review of this systematic review. Comments and editorial review were also provided by the AHRQ Task Order Officer and an associate editor. The draft report was posted on the AHRQ website for 4 weeks to elicit public comment. In response to reviewers' comments, we revised text as needed and addressed all relevant reviewer comments in an associated disposition of comments report with the authors' individual responses. This report will be posted after the publication of the final comparative effectiveness review on AHRQ's website.

Results

Results of Literature Search

A total of 8,488 references were reviewed, including 8,025 from electronic database searches and 463 from reviewing studies included in prior Evidence-based Practice Center reports and other systematic reviews. After dual review of titles and abstracts, 1,292 articles were selected for full-text review, of which 184 randomized controlled trials (RCTs) in 217 publications were included in this review (Appendix C) and 1,070 were excluded (Appendix D). In addition, we identified 5 systematic reviews that included 47 of the trials included in this review. Search results and selection of studies are summarized in the literature flow diagram (Figure 2). Results are shown by Key Question and then by condition for efficacy. Harms results are organized by drug class. Overall, 30 trials were rated poor quality, 129 fair quality, and 25 good quality. Of the good- and fair-quality trials, 128 were classified as short term (3 months to <6 months), 18 intermediate term (6 months to <1 year), and 8 were long term (≥ 1 year). We included 32 RCTs in neuropathic pain, 26 RCTs in fibromyalgia, 59 RCTs in osteoarthritis, 21 RCTs in inflammatory arthritis, 7 RCTs in low back pain, and 1 trial each in chronic headache and sickle cell disease. An additional seven trials of mixed osteoarthritis and inflammatory arthritis patients were included for harms outcomes. Most study participants were female (66.7%) but proportion varied widely by condition with the highest seen in fibromyalgia trials. The median age of participants was 59 years and mean pain duration was 7.9 years. Participants reported a weighted mean pain severity of 6 on a scale of 0 to 10. Industry was the leading provider of funding for trials (82%) while 15 trials (10%) did not report funding source. Data abstraction of study characteristics and results for good- and fair-quality studies, and quality assessment for all included studies, are available in Appendixes E, F, and G. Strength of evidence (SOE) grades for priority clinical outcomes (pain, function, quality of life) for each pain condition-treatment pair appear in Appendix H. Results of meta-analyses, including forest plots and subgroup analyses, appear in Appendix I.

Figure 2. Literature flow diagram



Key Question 1: Effectiveness and Comparative Effectiveness

Neuropathic Pain

Key Points

- In the *short term*, the anticonvulsant drugs pregabalin, the prodrug gabapentin enacarbil, and oxcarbazepine provided small improvement in pain (SOE: Moderate) and pain response (SOE: Moderate and Low) in patients with neuropathic pain mainly diabetic peripheral neuropathy and/or postherpetic neuralgia. Functional outcomes were not improved with gabapentin enacarbil in patients with postherpetic neuralgia, and quality of life was not improved with pregabalin, gabapentin enacarbil, or oxcarbazepine (SOE: Low).
- In the *short term*, the serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant duloxetine resulted in small improvements in pain, function, and quality of life in diabetic peripheral neuropathy (SOE: Moderate for pain and quality of life, Low for function).
- In the *short term*, topical capsaicin patch resulted in improvements in pain severity that did not reach the level of a small effect, and pain response was not significantly better

than placebo in patients with postherpetic neuralgia and with HIV-associated neuropathy (SOE: Moderate).

- In the *short term*, cannabis (dronabinol oral solution, tetrahydrocannabinol/cannabidiol [THC/CBD] oral spray) had no effect on pain severity in multiple sclerosis or allodynia, but THC/CBD oral spray improved pain response to a moderate degree in patients with allodynia. Function and quality of life were not improved (SOE: Low).
- Comparisons of pregabalin with gabapentin (diabetic peripheral neuropathy and peripheral nerve injury), either drug with duloxetine (diabetic peripheral neuropathy), and memantine with placebo (HIV-related neuropathy) did not find significant differences (SOE: Low to insufficient).

Detailed Assessment

Thirty-two good- and fair-quality RCTs (in 36 publications) involving 9,392 patients evaluated nonopioid drugs to treat chronic neuropathic pain: 31 *short-term* (12 to 17 weeks) and 1 *long-term* trials (52 weeks). These included 29 placebo-controlled trials, 5 trials comparing multiple doses of duloxetine, 4 trials comparing multiple doses of pregabalin, 2 trials comparing multiple doses of the prodrug gabapentin enacarbil (with higher blood levels for longer periods than gabapentin), 1 trial comparing multiple doses of oxcarbazepine, and 3 head-to-head trials (gabapentin vs. pregabalin; gabapentin vs. pregabalin vs. duloxetine; and gabapentin enacarbil vs. pregabalin). Four trials met criteria for good quality,²⁶⁻²⁹ 28 trials met criteria for fair quality,³⁰⁻⁵⁷ and 6 RCTs were rated poor quality (Appendix G).⁵⁸⁻⁶³ The poor-quality studies were deemed to have high risk of bias due to unclear randomization and allocation concealment techniques, baseline differences between randomized groups, lack of blinding, and high attrition. One of the poor-quality studies was the only RCT of carbamazepine found for this review.⁶¹

Studies were conducted most frequently in the United States (25%) and in Asia (19%); 34 percent were conducted in 4 or more countries. Most trials were funded by industry (91%). The majority of studies enrolled patients with painful diabetic peripheral neuropathy (53%) and/or with postherpetic neuralgia (16%). Other conditions included neuropathic pain associated with HIV, spinal cord injury, peripheral nerve injury, stroke, and multiple sclerosis. Weighted mean age of enrolled participants across trials was 58 years (range 25 to 71 years) with 41 percent (weighted mean) being female (range 0% to 73%) and 41 percent (weighted mean) nonwhite (range 0% to 100%). Weighted mean baseline pain score was 6.2 (0-10 numeric rating scale [NRS], range 5.3 to 7.0, 26 trials) and the weighted mean visual analog scale (VAS) pain score was 70 (0-100, range 61 to 73, 4 trials). Few studies reported baseline function or quality of life. Weighted mean duration of neuropathic pain was 3.9 years (range 0.25 to 10.2 years, 26 trials). Complete descriptions of included study characteristics are in Appendix E.

Anticonvulsants

Pregabalin and Gabapentin

Fourteen RCTs compared pregabalin with placebo: six trials enrolled patients with diabetic peripheral neuropathy,^{30,39,44,45,50,51} one trial enrolled patients with postherpetic neuralgia,⁵² and one enrolled a mixed population of patients with either diabetic peripheral neuropathy or postherpetic neuralgia.³⁵ Six RCTs enrolled patients with other types of neuropathic pain: spinal cord injury (2 studies),^{27,48} HIV (2 studies),^{29,49} and one study each in patients with neuropathic pain associated with stroke,⁴¹ and trauma.⁴² Study treatments were *short term* (range 12 to 17

weeks) and involved flexible-dose pregabalin (e.g., 150 mg to 600 mg daily based on response and tolerability),^{29,35,39,41,42,48,49} or fixed-dose pregabalin (e.g., 150 mg, 300 mg, 600 mg daily).^{27,30,45,50-52} One study compared flexible-dose pregabalin (150 mg to 600 mg daily) with fixed-dose pregabalin (600 mg daily).³⁵

A study of the prodrug gabapentin enacarbil in patients with postherpetic neuralgia randomized patients to 1200 mg, 2400 mg, 3600 mg daily, or placebo, but combined data for the three drug arms after finding no difference in pain improvement between them.⁵⁷ A study of gabapentin enacarbil, pregabalin, and placebo in patients with diabetic peripheral neuropathy also combined data for the drug arms for similar reasons.⁴⁴

Pain

In the *short term*, meta-analysis of 15 trials found a small reduction in pain with pregabalin/gabapentin enacarbil compared with placebo (N=4,832, mean difference [MD] -0.61, 95% confidence interval [CI] -0.87 to -0.36, $I^2=72%$, 0-10 scale; Appendix I). Treatment with pregabalin/gabapentin enacarbil also resulted in more patients achieving at least a 30 percent reduction in mean pain score (risk ratio [RR] 1.27, 95% CI 1.12 to 1.50, $I^2=72%$; Appendix I). Subgroup analyses on pain etiology, study drug, and trial quality did not alter these findings meaningfully (Appendix I).

Although the subgroup analysis of dose was not statistically significant, pregabalin 600 mg daily resulted in a numerically larger, statistically significant, reduction in pain and more patients achieving response than lower doses (Table 4).^{45,51,52} Fixed-dose pregabalin 600 mg daily and flexible-dose pregabalin (150 mg to 600 mg daily) did not differ in the proportion who achieved response ($\geq 30%$ decrease in pain score; 66.4% vs. 59.0%, RR 1.13, 95% CI 0.94 to 1.36).³⁵ In the two trials of gabapentin enacarbil, there was little difference in pain score improvement among doses (Table 4).^{44,57} These findings are moderate strength of evidence.

Table 4. Pregabalin/gabapentin pain improvement dose analysis

Outcome Sample Size	Drug Dose	N Studies (Sample Size)	Effect Size (95% CI)	Treatment by Drug Interaction p-value		
Pain improvement 15 RCTs (n=4,576)	Pregabalin pooled	14 (3,971)	MD -0.61 (-0.87 to -0.36)	0.90		
	150 mg daily	2 (374)	MD -0.55 (-1.31 to 0.17)			
	300 mg daily	5 (1,035)	MD -0.36 (-0.89 to 0.17)			
	600 mg daily	4 (725)	MD -1.17 (-1.69 to -0.67)			
	150-600 mg daily	10 (2,715)	MD -0.75 (-1.13 to -0.39)			
	300-600 mg daily	2 (572)	MD -0.82 (-1.48 to -0.18)			
	450-600 mg daily	1 (373)	MD -0.02 (-0.39 to 0.35)			
	Gabapentin pooled	2 (725)	MD -0.58 (-1.26 to 0.10)			
	1200 mg daily	2 (384)	MD -0.66 (-1.21 to -0.08)			
	2400 mg daily	2 (353)	MD -0.27 (-1.33 to 0.82)			
	3600 mg daily	2 (418)	MD -0.74 (-1.50 to -0.01)			
	1200-3600 mg daily	2 (725)	MD -0.58 (-1.26 to 0.10)			
	Pain response 15 RCTs (n=4,576)	Pregabalin pooled	14 (3,971)		RR 1.28 (1.09 to 1.54)	0.82
		150 mg daily	2 (369)		RR 1.57 (0.74 to 3.58)	
300 mg daily		5 (1,029)	RR 1.21 (0.89 to 1.73)			
600 mg daily		4 (719)	RR 1.93 (1.38 to 2.79)			
150-600 mg daily		10 (2,876)	RR 1.35 (1.13 to 1.68)			
300-600 mg daily		2 (572)	RR 1.63 (1.15 to 2.26)			
450-600 mg daily		1 (373)	RR 0.94 (0.77 to 1.16)			
Gabapentin pooled		2 (725)	RR 1.20 (0.94 to 1.57)			
1200 mg daily		2 (384)	RR 1.16 (0.88 to 1.53)			
2400 mg daily		2 (353)	RR 1.17 (0.72 to 1.84)			
3600 mg daily		2 (418)	RR 1.29 (1.01 to 1.66)			
1200-3600 mg daily		2 (725)	RR 1.20 (0.94 to 1.57)			

CI = confidence interval; MD = mean difference; RCTs = randomized controlled trials; RR = relative risk

Function

One *short-term* trial of gabapentin enacarbil (N=371) examined function using the Brief Pain Inventory (BPI) Interference scale in patients with postherpetic neuralgia and found no difference in function between pooled gabapentin enacarbil doses (1200 mg, 2400 mg, 3600 mg daily) versus placebo (MD -0.23, 95% CI -0.70 to 0.23).⁵⁷ This is low strength of evidence.

Quality of Life

In the *short term*, three fair-quality pregabalin trials in patients with diabetic peripheral neuropathic pain found that treatment with pregabalin did not improve quality of life scores (standardized mean difference [SMD] 0.24, 95% CI -0.07 to 0.54, $I^2=58%$) using the Euro Quality of Life (EQ-5D).^{39,41,51} Similarly, two RCTs of pregabalin (one each in diabetic peripheral neuropathy and HIV) and one of gabapentin enacarbil (in postherpetic neuralgia) found no difference between the drugs and placebo using the Short Form-36 (SF-36) scale (Appendix I).^{44,49,57} Subgroup analyses on study drug and drug dose did not show significant effects. This is low strength of evidence.

Other Outcomes

In the *short term*, meta-analysis of all RCTs of pregabalin and gabapentin enacarbil for neuropathic pain found a small magnitude of improvement in sleep compared with placebo (MD -0.65, 95% CI -0.89 to -0.41, $I^2=70%$, 0-10 scale; Appendix I).^{27,29,30,35,39,41,42,44,45,48-52,57}

Six RCTs of pregabalin,^{27,29,39,41,48,49} one RCT of gabapentin enacarbil,⁵⁷ and one of both pregabalin and gabapentin enacarbil⁴⁴ found no *short-term* benefit on anxiety or depression as assessed with the Hospital Anxiety and Depression Scale (HADS; Appendix I). Subgroup analyses based on etiology of pain showed no significant effects for sleep, anxiety, or depression.

Oxcarbazepine

Pain

In the *short term*, in patients with diabetic peripheral neuropathic pain, oxcarbazepine resulted in a small improvement in pain severity (2 RCTs, N=493, MD -0.89, 95% CI -1.50 to -0.37, $I^2=0\%$, VAS 0-10 scale; Appendix I).^{31,34} Doses ranged from 300 mg to 1800 mg daily flexible dose in one trial and 600 mg, 1200 mg, or 1800 mg daily fixed dose in a second trial. This is moderate strength of evidence. Treatment with higher dose oxcarbazepine (1200 mg and 1800 mg daily) resulted in improved pain scores compared with placebo in one trial.³¹ A greater proportion of patients treated with oxcarbazepine achieved a greater than 30 percent improvement in pain response than patients given placebo (45.6% vs. 28.9%, $p=0.028$).³⁴ This is low strength of evidence.

Quality of Life

In patients with diabetic peripheral neuropathic pain, oxcarbazepine did not consistently improve quality of life, as measured on the SF-36 scale. Both trials reported similar SF-36 scale scores with oxcarbazepine and placebo, though one trial noted a statistically significant difference between groups in SF-36 mental component summary (MCS) scores (47.2 versus 50.2, $p=0.03$).³⁴ This is low strength evidence.

Other Outcomes

One trial reported a lower incidence of sleep disruption due to pain in the oxcarbazepine group ($p=0.02$), while the other trial found no difference between groups in sleep.³¹

Antidepressants, SNRI

Duloxetine

Six *short-term* (12 week) RCTs compared duloxetine with placebo at doses from 20 mg to 120 mg daily.^{36-38,43,54,56} All patients had peripheral neuropathic pain from diabetes. One *long-term* (52-week), open-label extension RCT compared duloxetine 40 mg daily with 60 mg daily.⁵⁵

Pain

Pooled analysis of the six *short-term* trials found a small magnitude reduction in pain with duloxetine versus placebo (MD -0.79, 95% CI -1.10 to -0.49, $I^2=43\%$, 0-10 scale; Appendix I).^{36-38,43,54,56} Patients were also more likely to achieve response ($\geq 30\%$ improvement in pain in 5 RCTs, $\geq 50\%$ in 1 RCT) with duloxetine compared with placebo (RR 1.39, 95% CI 1.22 to 1.62, $I^2=39\%$), a small magnitude effect. A *long-term* RCT (N=257) found that duloxetine 40 mg daily versus 60 mg daily produced similar reductions in pain at 52 weeks.⁵⁵ This is moderate strength of evidence.

Function

In the *short term*, based on a meta-analysis of six trials, function as assessed by the BPI Interference scale was improved to a small degree with duloxetine (SMD -0.31, 95% CI -0.42 to -0.20, $I^2=0\%$; Appendix I).^{36-38,43,54,56} A *long-term* extension RCT (N=257) found no difference in function (BPI Interference) between duloxetine 40 mg daily versus 60 mg daily at 52 weeks,⁵⁵ which was similar to the results at 12 weeks in another RCT.^{36-38,43,54,56} This is low strength of evidence.

Quality of Life

Meta-analysis of three trials finds that duloxetine improved quality of life to a small degree as measured on the EQ-5D (MD 0.22, 95% CI 0.05 to 0.38, $I^2=0\%$, 0-1 scale; Appendix I).^{37,38,54} This is moderate strength of evidence.

Other Outcomes

In the *short term*, one trial (N=457) reported no difference in change from baseline on the Beck Anxiety Inventory (BAI) for duloxetine at daily doses of 20 mg, 60 mg, and 120 mg versus placebo.³⁸ Three RCTs examined changes in depression symptoms as measured by the Hamilton Rating Scale for Depression (HAM-D) and the Beck Depression Inventory (BDI) scales.^{38,43,54} Meta-analysis did not identify a significant difference between placebo and duloxetine (SMD -0.07, 95% CI -0.34 to 0.20, $I^2=44\%$; Appendix I).

In the *short term*, meta-analysis based on five RCTs (N=2,478) found that sleep interference on the BDI subscale was improved more with duloxetine (40, 60 or 120 mg daily) than placebo, but the difference was very small (MD -0.60, 95% CI -0.86 to -0.34, $I^2=0\%$, 0-10 scale).^{36,37,43,54,56} A *long-term* RCT (N=257) found no difference in sleep at 52 weeks between duloxetine 40 mg daily and 60 mg daily.⁵⁵

Subgroups

A post-hoc analysis of three *short-term* RCTs in patients with diabetic peripheral neuropathic pain stratified patients based on age (<65 years, ≥65 years) and found no differences between the older subgroup and the younger subgroup on pain response (30% and 50% reductions in pain) and function (BPI interference; Appendix I).^{55,64}

Other Drugs

Cannabis

Cannabis (including derivatives and synthetic cannabinoids) was compared with placebo in two *short-term* trials (N=486) in those with neuropathic pain related to multiple sclerosis²⁸ or with allodynia⁴⁷ (Appendix E). The trials utilized oral dronabinol solution (mean 13 mg daily) and THC/CBD oromucosal spray (100 mL per spray, up to 24 sprays daily). One trial was rated good quality²⁸ and the other fair quality.⁴⁷ A third trial was rated poor quality due to unclear randomization and allocation concealment, between-group differences at baseline, and high rates of attrition; results from that trial are not included here.⁶²

Both studies reported that change in mean pain score (NRS 0-10) from baseline to followup were similar for cannabis and placebo ($p=0.68$ ²⁸ and $p=0.14$ ⁴⁷). Despite this, the trial of THC/CBD, conducted in a population with allodynia, found a moderate magnitude of effect on response (a ≥30% reduction in pain). Response was more likely with cannabis than placebo (28% vs. 16%; RR 1.70, 95% CI 1.04 to 2.78).⁴⁷ Response was not reported in the other trial.

There was no difference between treatment groups in measures of function (1 trial), quality of life (2 trials), or sleep (1 trial).^{28,47} This is low strength of evidence.

Capsaicin

Three *short-term* trials (N=1,519) assessed the effect of an 8% topical capsaicin patch applied for either 30 or 60 minutes on HIV-related neuropathy³² or postherpetic neuralgia^{26,53} (Appendix F). A 0.04% topical capsaicin patch was used as a control. One trial was good-quality²⁶ and the other trials were fair quality.

Pooled analysis found that while topical capsaicin improved pain severity in the *short term* (MD -0.33, 95% CI -0.60 to -0.004, $I^2=0\%$, 0-10 scale), the difference was less than a small magnitude as defined for this report (Appendix I).^{26,32,53} Meta-analysis of pain response ($\geq 30\%$ reduction in pain) resulted in a small, nonsignificant effect (RR 1.17, 95% CI 0.98 to 1.37, $I^2=0\%$; Appendix I). Subgroup analyses of the impact of study quality and type of neuropathic pain did not alter these results meaningfully. This is moderate strength of evidence.

Memantine

A small *short-term*, fair-quality trial (N=45) compared the effect of memantine up to 40 mg daily with placebo in patients with HIV-related neuropathy.⁴⁶ After 16 weeks of treatment, memantine and placebo were associated with similar reductions in pain scores (mean change -1.82 [standard deviation (SD) 2.77] vs. -2.36 [SD 3.35], $p=0.87$, 1-10 scale). Due to study limitations, including size, lack of other studies, and imprecise estimates, this evidence is insufficient to draw conclusions.

Head-to-Head Comparisons

Pregabalin Versus Gabapentin

Three *short-term* head-to-head RCTs (N=433) compared pregabalin (75 mg to 300 mg daily) with gabapentin (300 mg to 2,400 mg daily)^{33,40} or gabapentin enacarbil (1200 mg to 3600 mg daily)⁴⁴ and found no difference between the drugs in pain relief,^{33,40,44} function (BPI Interference),⁴⁴ quality of life (SF-36 physical component summary [PCS]/MCS),⁴⁴ or sleep interference (Appendix E).^{33,44} This is low strength of evidence. Neuropathic pain was related to diabetic peripheral neuropathy^{33,44} and peripheral nerve injury.^{33,40}

Cross-Class Comparisons

Gabapentin Versus Pregabalin Versus Duloxetine

One fair-quality, *short-term* trial (N=152) compared gabapentin, pregabalin, and duloxetine in participants with diabetic peripheral neuropathy (Appendix E).³³ Gabapentin dose ranged from 300 to 1800, pregabalin 75 to 300, and duloxetine 20 to 120 mg daily. At baseline, mean pain score was 61 (VAS scale 0-100). After 12 weeks of treatment, mean pain scores were reduced with all three interventions, ranging from 26.5 to 35.2, with no difference between groups (p =not reported). There was also no difference between groups in sleep interference score (scale 0-10; range 2.84 to 3.99). Due to study limitations, including size, lack of other studies, and imprecise estimates, this evidence is insufficient to draw conclusions.

Fibromyalgia

Key Points

- In the *short* and *intermediate term*, SNRI antidepressants resulted in small improvements in pain. Function improved to a small degree in the *short term*, but not in the *intermediate term*. Based on the SF-36 MCS, quality of life improved to a small degree in the *short* and *intermediate term*, but no effect was seen on the PCS. (SOE Moderate for all, but Low for *intermediate-term* PCS). There was a small decrease in depression with *short-term* duloxetine treatment.
- *Short-term* treatment with anticonvulsants was associated with small improvements in pain and function, but not quality of life (SOE: Moderate). Subgroup analyses showed no effect of specific drug, dose, or study quality on these results. Small improvements in sleep were also seen.
- *Short-* and *intermediate-term* treatment with memantine resulted in moderate improvements in pain, function, and quality of life compared with placebo (SOE: Low).

Detailed Assessment

Twenty-six good- or fair-quality RCTs (in 32 publications) involving 12,744 patients meeting inclusion criteria evaluated nonopioid drugs to treat chronic pain in fibromyalgia.⁶⁵⁻⁹⁴ All studies used criteria defined in 1990 by the American College of Rheumatology (ACR) to identify patients with fibromyalgia;⁹⁵ three studies in one publication⁷⁴ also required patients to meet 2010 ACR criteria. Eighteen were *short-term* trials (range 12 to 16 weeks), six *intermediate-term* (26 to 28 weeks), and two *long-term* (each 52 weeks). These included 15 placebo-controlled trials; 3 trials comparing multiple doses of the SNRIs milnacipran or duloxetine, and 7 trials that included both placebo and dose comparisons for a single included drug. One additional trial had a head-to-head design, comparing cyclobenzaprine and amitriptyline, with a third arm comparing each drug to placebo. That trial⁷⁸ and one other⁸⁵ assessed the tricyclic antidepressant (TCA) amitriptyline; the 15 other trials of antidepressants in fibromyalgia all used SNRIs. Eight trials assessed anticonvulsants, and one the Alzheimer's drug memantine. Three RCTs met criteria for good quality,⁸⁸⁻⁹⁰ 23 fair,^{65-67,69,71,72,74-81,84-87,92-94} and 1 poor⁹⁶ (Appendix G). The poor-quality study was deemed to have high risk of bias due to high attrition and unclear randomization and blinding methods, and was not synthesized with the other evidence. Thirteen studies (52%) were conducted in the United States.^{65-67,69,71,72,80,81,84,86,87,93,94} Most were funded by industry (88%, 23 of 26). One publication⁹⁷ on fibromyalgia treatment in pregnancy did not meet inclusion criteria as a systematic review because it did not assess the quality of included studies or synthesize their results. The studies reviewed also did not meet our criteria for design (many were observational or case reports) or duration (up to 9 weeks).

The weighted mean age of enrolled patients across our 26 included studies was 49 years, a mean of 94 percent of patients were female, and a mean of 15 percent were nonwhite. Across the RCTs, the mean baseline pain severity (standardized to a 0-10 scale) was 6.7 (range 6.0 to 7.6). Duration of pain was reported in 11 of 26 studies; it was less than a year in three, while in the other eight it ranged from 5 to 13 years. The percent of participants with comorbid depression was reported in nine studies, with a weighted average across studies of 21 percent. Complete descriptions of included study characteristics are in Appendix E.

Antidepressants

Sixteen RCTs (in 20 publications) assessed antidepressants to treat fibromyalgia, with comparisons to placebo and/or between doses: seven were of milnacipran, eight of duloxetine, and one of amitriptyline.^{65,66,68-71,73,75-77,79-81,83-86,88,93,94} Most were *short-term* studies, four were *intermediate-term*,^{79,84,86,93} and two were *long-term*.^{76,80} Pain was reported in all studies, and function in all but one, with moderate-strength evidence for pooled comparisons of SNRI antidepressants with placebo. Ten studies reported quality of life, with low to moderate SOE for pooled results (Appendix H and Appendix I).

Pain

Short-term results from 11 trials showed a small reduction in pain with an SNRI antidepressant compared with placebo (0-10 scale, MD -0.59, 95% CI -0.80 to -0.43, $I^2=26\%$). Three studies showed similar *intermediate-term* results (0-10 scale, MD -0.67, 95% CI -0.99 to -0.34, $I^2=0\%$). The proportion responding was also greater with SNRIs than placebo in the *short term*; 40 percent of patients given SNRIs had at least a 30 percent reduction in pain, compared with 31 percent of those given placebo (RR 1.36, 95% CI 1.26 to 1.46, $I^2=0\%$). *Intermediate-term* response rates were also higher with treatment than placebo (34% vs. 28%, RR 1.29, 95% CI 1.08 to 1.52, $I^2=0\%$). Pooled subgroup analyses by specific drug (duloxetine or milnacipran), dose, and study quality showed no change in the effect of treatment on pain. This is moderate strength evidence.

Many individual trials also reported effects of baseline depression on pain response, but none found a statistically significant interaction between depression and treatment in effects on pain.^{66,69,71,75,79} Two trials^{88,94} stratified results and found that patients without baseline depression had a better response to SNRI than to placebo. However, these two trials did not assess whether the difference in response between patients with and without depression was statistically significant.

One fair-quality, *short-term* trial (N=87)⁸⁵ randomized female patients with fibromyalgia to the tricyclic antidepressant amitriptyline or placebo. Patients assigned to amitriptyline had better response to treatment according to physicians' global assessments (74% vs. 49%, $p=0.017$), and lower pain severity at the 12-week endpoint (VAS 0-10, 4.5 vs. 5.2) than placebo. Using a VAS 0-10 scale, sleep problems were also rated lower at endpoint with amitriptyline than placebo (3.6 vs. 4.8), and the change from baseline was significant only with amitriptyline. This evidence is insufficient due to small sample size (imprecision), study limitations, and unknown consistency.

Function

Most studies of antidepressants in fibromyalgia measured function using the Fibromyalgia Impact Scale (FIQ, range either 0-80 or 0-100); one study⁶⁶ used the BPI Interference score (0-10). Pooled analysis of *short-term* results from 11 studies showed a small effect of SNRI antidepressants on function compared with placebo (SMD -0.24, 95% CI -0.32 to -0.17, $I^2=22\%$), while *intermediate-term* results from 3 studies showed an effect less than that defined as small for this report (SMD -0.13, 95% CI -0.24 to -0.02, $I^2=0\%$). This is moderate strength evidence. Subgroup analyses by specific drug, dose, and study quality did not alter these results.

Quality of Life

Eight fair-quality trials reported effects of 3 to 12 months' SNRI treatment on quality of life. *Short-term* treatment with duloxetine or milnacipran was associated with small improvements in the SF-36 MCS (0-100 or not reported; SMD 0.19, 95% CI 0.13 to 0.27, $I^2=12\%$). *Intermediate-*

term changes in the MCS reported in three trials were similar (SMD 0.18, 95% CI 0.08 to 0.30, $I^2=0\%$). SF-36 PCS scores also improved with **short-term** treatment, but the difference was not clinically important as defined in this report, and **intermediate-term** treatment had no effect on physical wellbeing. Subgroup analyses did not show effects of specific drug or dose on these results. This is moderate strength evidence, except for intermediate-term results for the SF-36 PCS scale, which is low strength.

Other Outcomes

In the **short term**, SNRI antidepressants duloxetine and milnacipran improved depression symptoms in patients with fibromyalgia, but to a very small degree, based on meta-analysis of 10 RCTs that measured depression using the BDI, BDI-II, FIQ depression subscale, or HAM-D (SMD -0.17, 95% CI -0.24 to -0.12, $I^2=0\%$).^{65,66,69,71,75,77,81,86,88,94} Subgroup analyses by drug showed that only duloxetine had a clinically important effect on depression (SMD -0.28, 95% CI -0.38 to -0.18, $I^2=0\%$). Seven **short-term** trials also measured anxiety, using several different instruments.^{65,66,69,75,77,88,94} Meta-analysis did not show a statistically significant effect and there was substantial heterogeneity across studies (SMD -0.08, 95% CI -0.23 to 0.03, $I^2=56\%$). Seven **short-term** trials measured effects on sleep using a variety of instruments.^{66,71,77,81,86,88,94} Meta-analysis found that milnacipran showed no effect on sleep (SMD 0.01, 95% CI -0.16 to 0.08, $I^2=0\%$), and that duloxetine improved sleep compared with placebo, but the effect did was very small (SMD -0.18, 95% CI -0.33 to -0.05, $I^2=0\%$).

Dose Comparisons

Two fair-quality **intermediate-** or **long-term** studies compared different doses of milnacipran,^{76,84} and a third **long-term** study⁸⁰ compared 60 mg and 120 mg daily of duloxetine. In the **intermediate term** (28 weeks), fibromyalgia patients treated with placebo in an earlier “lead-in” study (N=129) were re-randomized to either 100 mg or 200 mg daily of milnacipran.⁸⁴ Although pain decreased from **lead-in** study baseline to the end of the extension study with both milnacipran doses (VAS 0-100: -25.7 for 100 mg daily and -29.1 for 200 mg daily), the difference (-3.4 on a 0-100 scale) was below the threshold for a small effect for this report. Effects on physical function did not differ between doses. This evidence is insufficient to draw conclusions due to small sample size (imprecision), unknown consistency, and study limitations. The study also showed little or no difference between doses in effects on depression and sleep. In the **long term** (52 weeks), a similarly designed study (N=270) re-randomized patients given placebo in a **lead-in** study to milnacipran 100 mg, 150 mg, or 200 mg daily,⁷⁶ and did not show differences between doses in pain (VAS 0-100, change from extension baseline range -11.6 to -15.3), function, or quality of life, or a composite response measure including 30 percent improvement in pain and patient global impressions. This is low strength of evidence. Effects on sleep were also similar across doses (VAS 0-100, change from extension baseline range -6.6 to -13.6).

A **long-term** study (N=307) of the SNRI duloxetine 60 mg or 120 mg daily did not find differences in effects on pain.⁸⁰ Function improved slightly for patients taking 60 mg daily, while it deteriorated in those taking 120 mg daily (FIQ total score, range not reported [NR], change from baseline: -0.69 vs. 3.49, $p<0.05$), however on a 0-100 scale this difference is below the threshold for a small magnitude of effect for this report (low strength of evidence).⁸⁰ Improvements in sleep were greater with 60 mg than 120 mg of duloxetine, though the magnitude of effect was small (mean change in BPI sleep interference score of -1.16 vs. -0.23 on a scale of 1 to 10, $p<0.01$).

Anticonvulsants

Eight *short-term* RCTs (in 7 publications, N=4,821) compared an anticonvulsant to placebo in patients with fibromyalgia.^{67,72,74,82,87,89,92} One study met criteria for good quality,⁸⁹ with the remainder being fair quality. One trial used gabapentin⁶⁷ and the remaining trials used pregabalin. Pain and function outcomes were reported in all studies, and three studies provided evidence on quality of life; the strength of evidence on all outcomes was moderate. (Appendix H and Appendix I).

Pain

In the *short term*, anticonvulsants were associated with a small reduction in pain, based on meta-analysis of eight RCTs (0-10 scale, MD -0.57, 95% CI -0.75 to -0.40, I²=30%). The proportion responding to anticonvulsants was also higher (41% vs. 32%, RR 1.30, 95% CI 1.20 to 1.43, I²=0%). Analyses of specific drug, pregabalin dose, and study quality did not alter results, with small but statistically significant pain reductions (and higher response rates) seen in each subgroup. One of the five trials assessed baseline depression as a subgroup, but found no statistically significant interaction with treatment in effects on pain.⁹²

Function

Function as measured by the FIQ (range 0-80 or 0-100) improved with anticonvulsant treatment across eight *short-term* trials, but the difference compared with placebo was small (SMD -0.22, 95% CI -0.29 to -0.15, I²=0%). Subgroup analyses did not show significant effects of specific drug, pregabalin dose, or study quality.

Quality of Life

Four *short-term* fair quality RCTs of pregabalin (in 2 publications) reported the effect of anticonvulsants on quality of life.^{72,74} Results showed statistically significant improvements in the SF-36 with treatment, but differences were less than that defined as small for this report (SMD 0.13 for MCS and 0.17 for PCS). One study⁷² tested three doses of pregabalin (300 mg, 450 mg, or 600 mg daily), but did not show differences in effects on quality of life.

Other Outcomes

Short-term pregabalin treatment improved depression symptoms measured by HADS-D, based on meta-analysis of five trials in three publications, but the effect was not clinically important (SMD -0.11, 95% CI -0.18 to -0.03, I²=0%).^{72,74,89} Effects on anxiety symptoms were similar in the same studies (HADS-A, SMD -0.11, 95% CI -0.25 to -0.02, I²=0%). Seven studies in five publications measured sleep with various instruments, and found small improvements in sleep with *short-term* pregabalin compared with placebo (SMD -0.33, 95% CI -0.40 to -0.25, I²=13%).^{72,74,87,89,92}

Other Drug Classes

Memantine

A good-quality, 6-month RCT (N=63) randomized fibromyalgia patients to memantine, an N-Methyl-D-aspartic acid (NMDA) receptor antagonist approved for Alzheimer's dementia, or to placebo. Pain, function, and quality of life all improved moderately more with memantine than placebo. At 3 months (*short term*), results showed lower pain scores (VAS 0-10 scale, 5.06 vs. 6.85, p=0.001), lower disability scores, (FIQ 0-10 scale, 49.91 vs. 59.67, p=0.011), and better

quality of life (EQ-5D 0-100 scale, 58.06 vs. 43.43, $p=0.003$) with memantine than placebo. Similar *intermediate-term* improvements were seen at 6 months (pain severity, VAS 0-10 scale 4.87 vs. 7.01, $p=0.001$; FIQ 0-10 scale, 50.02 vs. 69.57, $p<0.001$; EQ-5D quality of life scale 0-100, 60.48 vs. 43.75, $p=0.001$).^{90,91} This evidence is low strength. Memantine had no effect on anxiety at 3 or 6 months, but treatment reduced symptoms of depression at both time points (HADS-D 0 to 21 scale, 7.87 vs. 10.46 at 6 months, $p=0.002$).

Cross-Class Comparisons

A fair-quality RCT (N=208) compared the tricyclic antidepressant amitriptyline, the muscle relaxant cyclobenzaprine, and placebo for 6 months in fibromyalgia.⁷⁸ Both *short-term* (3-month) and *intermediate-term* (6-month) results were reported (treatment was for 24 weeks, but outcomes reported at 6 months). There were no differences at either time point for outcomes, pain, function, or a composite response measure including pain, sleep, fatigue, and global assessments. This is low strength evidence. No differences between treated groups and placebo were seen for depression, anxiety, or sleep at 3 or 6 months.

Osteoarthritis

Key Points

- Oral nonsteroidal anti-inflammatory drugs (NSAIDs) improved pain and function in patients with osteoarthritis (OA) to a small degree in the *short term*, with evidence indicating these effects are maintained in the *intermediate term* with celecoxib. Subgroup analyses indicated that studies of only patients with knee pain and those of good quality had smaller effects, while patients with more severe pain at baseline experienced greater reduction in pain. (SOE: Moderate for pain, quality of life, High for response and function).
- In the *short term*, topical diclofenac improved pain severity and response to a small degree (SOE: Moderate). There was no effect on improvement in function, but there was serious inconsistency among studies (SOE: Low).
- The SNRI antidepressant duloxetine resulted in small improvement in pain severity, moderate improvement in pain response, and small improvements in function and quality of life in OA patients in the *short term*. Subgroup analyses found that older patients (>65 years) had better effects on pain, and studies of only patients with knee OA had larger effects on pain (SOE: High).
- Acetaminophen did not significantly improve pain or function in the *short* or *intermediate term*, across all doses (SOE: Low). Evidence from a single *short-term* study suggested that pain and function improve to a small degree at higher doses (3900 mg to 4000 mg daily), but was insufficient to draw conclusions.
- Direct comparisons of NSAIDs with each other found few differences between drugs in pain or function in OA patients in the *short, intermediate, or long term* (SOE: Low). Cross-class comparisons were limited (3 RCTs) and insufficient to draw conclusions.

Detailed Assessment

Fifty-one fair- and good-quality RCTs (in 57 publications) involving 22,052 patients meeting inclusion criteria evaluated nonopioid drugs to treat chronic pain in osteoarthritis; 44 were *short term* (12 to 24 weeks), 6 *intermediate term* (26 weeks), and 1 *long term* (52 weeks). These

included 40 placebo-controlled trials (8 of duloxetine, 4 of acetaminophen, 4 of topical diclofenac, and 26 of oral NSAIDs), 5 trials comparing multiple doses, 3 comparing different formulations of diclofenac (2 comparing oral and topical, 1 comparing oral formulations), 13 head-to-head trials comparing various NSAIDs, and 3 making cross-class comparisons (some trials included more than one of these categories). Fourteen RCTs met criteria for good quality,⁹⁸⁻¹¹⁰ seven were poor quality,¹¹¹⁻¹¹⁷ and the remainder (37) were fair quality (Appendix G). Most studies were conducted in the United States (22 RCTs) and were funded by industry (84%).

Studies included patients with osteoarthritis, but with varying and often unclear criteria for establishing the diagnosis. Mean age of enrolled patients ranged from 54 to 72 (weighted mean 63 years), a weighted mean of 68 percent were female, and a weighted mean of 14 percent were nonwhite. Across the RCTs, baseline pain severity ranged from 50 to 78 on a 0-100 VAS. Duration of pain was reported in 53 percent of trials, with a mean duration ranging from <1 year to 12 years. At baseline, function/disability ranged from 63 to 72 on a VAS scale, and 27 to 37 out of 68 on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function subscale. Complete descriptions of included study characteristics are in Appendix E. Results of meta-analyses, including forest plots and subgroup analyses, can be found in Appendix I.

Oral NSAIDs

Twenty-seven RCTs (in 28 publications; N=13,808) compared at least one NSAID versus placebo in patients with OA (5 had more than 2 treatment arms).^{101,103-108,118-138} Fifteen included the selective cyclooxygenase (COX)-2 inhibitor celecoxib (100 mg to 400 mg daily), while 14 included nonselective NSAIDs (7 of naproxen 1000 mg daily, 2 of meloxicam 3.75 mg to 15 mg daily, 2 of ibuprofen 2400 mg daily, 3 of diclofenac 100 mg to 150 mg daily, and 1 of diclofenac submicron 70 mg and 105 mg daily). All of the RCTs evaluated pain at 12 to 13 weeks (*short term*), with one also evaluating at 26 weeks (*intermediate term*).¹³¹ Pain and function outcomes were reported in all studies, but quality of life only in three.^{125,127,132} The strength of evidence for NSAIDs on improvement in pain and quality of life is moderate, and for pain response and function is high.

Pain

In the *short term*, NSAIDs resulted in a small reduction in pain, based on meta-analysis of 27 RCTs (MD -0.73, 95% CI -0.84 to -0.62, $I^2=27%$, 0-10 scale; Appendix I). Similarly, the proportion responding to NSAIDs was significantly greater than placebo (15 RCTs, 56% vs. 46%, RR 1.23, 95% CI 1.18 to 1.31, $I^2=0%$; Appendix I). At *intermediate-term* followup, celecoxib 200 mg daily also resulted in a small improvement in pain (MD -0.63, 95% CI -1.10 to -0.16, 0-10 scale), and a nonsignificant increase in response (RR 1.13, 95% CI 0.94 to 1.35).¹³¹ Subgroup analyses of specific drug, dose (celecoxib), year of publication (≤ 2000 , ≥ 2001), study quality (good and fair), and criteria used for response (30% improvement, 50% improvement, Osteoarthritis Research Society International [OARSI]), did not alter the findings meaningfully, with no significant interactions found. Subgroup analyses of location of pain (hip, knee, either) was not significant for response, but was significant for improvement in pain ($p=0.0021$). In this subgroup analysis, studies that enrolled only patients with knee pain had a smaller pooled improvement in pain (MD -0.57, 95% CI -0.71 to -0.46, 0-10 scale). Publication bias (small study bias) is possible, with the Egger's test being significant, but the funnel plot appearing balanced (Appendix I).

Function

In the *short term*, NSAIDs resulted in a small improvement in function, based on meta-analysis of 28 RCTs (SMD -0.32, 95% CI -0.37 to -0.28, $I^2=24\%$), using mostly the WOMAC function subscale (Appendix I). At *intermediate-term* followup in one study, a similar improvement was maintained (SMD -0.25, 95% CI -0.47 to -0.04).¹³¹ Subgroup analyses by specific drug, dose (celecoxib, diclofenac), location of pain (hip, knee, either), and year of publication (≤ 2000 , ≥ 2001) did not alter the findings meaningfully, with no significant interactions found. Good-quality studies found a smaller effect size (-0.35 for fair-quality studies, -0.26 for good-quality studies, p-value for interaction=0.052), but the magnitude of the effect was still in the range of a small effect (Table 5). Tests for publication bias (small-study bias) were not significant; evidence of this bias was not found (see funnel plot and Egger's test result, Appendix I).

Table 5. NSAID subgroup analyses

Outcome	Variable	Subgroup	N Studies (Sample Size)	Effect Size (95% CI)	Interaction p-value
Pain improvement	Pain location	Knee	14 (7,352)	MD -0.57 (-0.71 to -0.46)	0.0035
		Hip	4 (2,617)	MD -0.88 (-1.12 to -0.62)	
		Knee/Hip	9 (3,509)	MD -0.94 (-1.11 to -0.77)	
Function	Study quality	Good	8 (4,212)	SMD -0.26 (-0.34 to -0.18)	0.05
		Fair	19 (9,261)	SMD -0.35 (-0.41 to -0.30)	

CI = confidence interval; MD = mean difference; NSAID = nonsteroidal anti-inflammatory drug; SMD = standardized mean difference

Quality of Life

In the *short term*, NSAIDs improved quality of life as measured by the SF-36 PCS (MD 2.95, 95% CI 1.79 to 4.18), but the difference was less than a small effect as defined for this report and also less than the 3-point minimal clinically important difference (MCID) used in OA studies.¹³⁹ There was not a meaningful change in the MCS (MD 0.61, 95% CI -0.50 to 1.79).

Other Outcomes

Sleep improved in the *short term* in one study of celecoxib 200 mg daily (other arms included tramadol).¹²⁵ Using the Chronic Pain Sleep Inventory (0-100 VAS), patients on celecoxib improved by 16.4 points (2.1 standard error of the mean [SEM]) compared with 8.6 (2.1 SEM) with placebo (analysis of covariance [ANCOVA] p-value across 5 study arms = 0.027, with the largest improvement in the celecoxib group).

Subpopulations

One study of naproxen 1000 mg daily reported that subgroup analyses of age, gender, race, and ethnicity were consistent with the overall findings.¹³² Four studies analyzed impact of baseline pain, with two finding that improvement in pain with was greatest in patients whose pain was greater at baseline and least in those whose pain was lowest at baseline,^{101,102} but two others not finding a linear relationship.^{122,132} Two studies found that patients who had used or were using an NSAID prior to study enrollment responded better than those who had or were not.^{102,122} Because sample sizes varied and not all analyses were pre-planned, these findings are considered preliminary.

Based on the meta-analyses reported above, results of subgroup analyses on study quality, specific drug and dose, year of publication, and definition of pain response did not show statistically significant effects (Appendix I). As noted, subgroup analysis of improvement in pain

by location of pain was significant, and improvement in function by study quality was significant (Appendix I).

Topical NSAIDs: Diclofenac

Four *short-term* trials (N=1,541) evaluated topical formulations (2 of 1% gel, 2 of 1.5% solution) of diclofenac, used four times a day, compared with vehicle in patients with knee OA.^{99,108,140,141} Pain and function were reported in all four RCTs, with pain response also reported in two.

Pain

In the *short term*, topical diclofenac resulted in a small improvement in pain over vehicle (4 RCTs, MD -0.58, 95% CI -0.81 to -0.35, $I^2=0\%$). Based on meta-analysis of three RCTs, topical diclofenac resulted in a small magnitude of response to treatment, based on the OARSI criteria (65% vs. 53%, RR 1.20, 95% CI 1.09 to 1.38, $I^2=0\%$; Appendix I).¹⁴⁰⁻¹⁴² The strength of this evidence is moderate.

Function

In the *short term*, based on meta-analysis of four RCTs, topical diclofenac did not improve function in patients with knee OA pain (WOMAC function subscale 0-68; MD -0.51, 95% CI -1.06 to 0.04). However, one of the studies found a significant benefit favoring diclofenac, and the meta-analysis has high heterogeneity ($I^2=94\%$).¹⁴⁰ All of the studies used the same scale to measure function (WOMAC, 0-68). There were only small differences in baseline characteristics; this study had slightly younger patients (59 years vs. 62 to 64 years), and somewhat lower function scores (38 vs. 42 out of 68). Statistical heterogeneity was not found in analysis of pain (above) and other differences that may explain the heterogeneity were not identified, so the strength of this evidence is low.

Subpopulations

Subgroup analyses of age, gender, race or ethnicity, pain location, and dose were not conducted by individual studies or in our analyses (due to lack of variability).

Head-to-Head Comparisons of NSAIDs

Three RCTs of celecoxib versus naproxen,^{105,120,143} two of topical versus oral diclofenac,^{108,144} and two of nabumetone versus naproxen^{145,146} provided data for meta-analyses. Nine RCTs compared one NSAID to another, which could not be pooled in meta-analyses, with four *short-term* (N=2022),^{102,137,147,148} two *intermediate-term* (N=921),^{149,150} and one *long-term* (N=925).¹⁵¹ The most common comparator was diclofenac, with eight RCTs making comparisons with celecoxib (2), nabumetone (2), ibuprofen (1), meloxicam (2, multiple doses), and one comparing different formulations of diclofenac. All studies reported on pain, four studies reported on function, and none reported on quality of life. The strength of this evidence is low for all outcomes in this group of noncombinable studies.

Pain

In the *short term*, diclofenac resulted in moderate improvement over celecoxib (MD -12.2, 95% CI -22.1 to -2.2) and small improvement over meloxicam 3.75 mg daily, but no effect over meloxicam 7 mg or 15 mg daily.^{102,137} Pain improvement was not found to be different between NSAIDs for the remainder of comparisons. Meta-analyses of celecoxib and naproxen (3 RCTs,

N=1,013, MD -0.37, 95% CI -0.76 to 0.03, $I^2=0\%$) and of oral diclofenac (100 mg and 150 mg daily) versus topical diclofenac 1.5% (2 RCTs, N=909, MD -0.27, 95% CI -0.63 to 0.10, $I^2=0\%$) and single studies of diclofenac and nabumetone, ibuprofen, different formulations of diclofenac or between ibuprofen and nabumetone did not find differences in pain between drugs. In two studies, the proportion of patients with response to treatment was not found different between ibuprofen and nabumetone or between dispersible and enteric coated diclofenac formulations.^{147,152} In the *intermediate term*, two studies found improvement in pain and response to treatment to not be different between celecoxib and naproxen (1 study) or between meloxicam and diclofenac (1 study).^{149,150} In the *long term*, one RCT found no significant differences between celecoxib and diclofenac at 12 months of treatment.¹⁵¹

Function

In the *short term*, meta-analysis of three RCTs (N=1,013) of celecoxib and naproxen did not find a difference in improvement in function, (MD -0.02, 95% CI -0.21 to 0.16, $I^2=16\%$), and a meta-analysis of two RCTs (N=909) of oral diclofenac (100 mg and 150 mg daily) versus topical diclofenac 1.5% found a small difference that was on the border of being statistically significant (MD -0.18, 95% CI -0.34 to 0.00, $I^2=0\%$, $p=0.50$). A single RCT found that diclofenac had a moderate improvement in function over celecoxib when categorized as improved, no change, or worse (RR 2.06, 95% CI 1.37 to 3.08).¹³⁷ Another RCT found no difference in improvement in function between meloxicam 7 mg or 15 mg daily and diclofenac, but diclofenac had a small improvement over the 3.75 mg daily dose of meloxicam.¹⁰² In the *intermediate term*, two studies found improvement in function to not be different between celecoxib and naproxen (1 study) or between meloxicam and diclofenac (1 study).^{149,150}

Antidepressants: SNRIs

Duloxetine

Duloxetine was the only antidepressant with studies in OA patients that met inclusion criteria. All six included studies (N=1,575, 8 publications) were *short term*.^{98,100,110,153-157} Pain was reported in all studies, function in five, and quality of life in three, but none reported other secondary measures eligible for this review (e.g., sleep, depression). SOE for duloxetine versus placebo was high for pain, function outcomes, and quality of life.

Pain

In the *short term*, duloxetine resulted in a small reduction in pain, based on meta-analysis of 6 RCTs (MD -0.75, 95% CI -1.05 to -0.53, $I^2=15\%$, 0-10 scale).^{100,110,153,156-158} Similarly, duloxetine resulted in a moderate improvement in the proportion responding to treatment (4 RCTs, 65% vs. 47%, RR 1.37, 95% CI 1.24 to 1.52, $I^2=0\%$); in this set all RCTs used 30 percent improvement for a definition of response. Subgroup analyses of pain location (knee vs. hip or knee), dose (60 mg vs. 60 to 120 mg daily), and study quality (good or fair) did not alter the findings meaningfully, with no significant interactions found.

Function

In the *short term*, duloxetine resulted in a small improvement in function, based on meta-analysis of five RCTs (SMD -0.27, 95% CI -0.41 to -0.12, $I^2=27\%$), using the WOMAC function subscale (3 RCTs), and the BPI Interference subscale (2 RCTs).^{98,100,110,153,157}

Subgroup analyses of pain location (knee vs. hip or knee), dose (60 mg vs. 60 to 120 mg daily), and study quality (good or fair) did not alter the findings meaningfully, with no significant interactions found.

Quality of Life

In the *short term*, duloxetine resulted in a small improvement in quality of life, based on meta-analysis of two RCTs (MD 0.05, 95% CI 0.02 to 0.08, $I^2=0\%$), using the EQ-5D. Subgroup analyses of pain location (knee vs. hip or knee), dose (60 mg vs. 60 to 120 mg daily), and study quality (good or fair) did not alter the findings meaningfully, with no significant interactions found. A third fair-quality study reported the SF-36 PCS, with mean change from baseline of 7.8 (standard error [SE] 0.85) with duloxetine and 4.41 (SE 0.81) with placebo ($p<0.001$).¹⁵³

Other Outcomes

Sleep was improved with duloxetine 60 mg daily in two studies, based on BDI sleep interference subscale, but the clinical meaning of the magnitude of difference seen (-0.46 and -0.22) is unclear.^{110,153} Changes in depression and anxiety scales were reported in one study, with no improvement over placebo seen.¹⁰⁰

Subpopulations

Three studies reported subgroup analyses according to age, with one finding no effect of age,¹⁵³ but two that analyzed age according to categories of <65 years and ≥ 65 years found that a significant effect of duloxetine on pain was found in older patients, while the effect was similar to placebo in younger patients.^{100,110} Subgroup analyses of gender, race, and baseline pain scores were not significant.^{100,153} Based on the meta-analyses reported above, results of subgroup analyses on location of pain, study quality and dose did not show statistically significant effects for any outcome, although pain outcomes were better in studies of only patients with knee pain than in studies with a mix of patients with knee or hip pain (See Appendix I).

Acetaminophen

Three *short-term* RCTs (N =1,107) and one *intermediate-term* study compared acetaminophen (1950 mg to 4000 mg daily) with placebo in patients with OA.^{122,159-161} Pain and function outcomes were reported in all studies. The strength of evidence for acetaminophen is low for all outcomes.

Pain

In the *short term*, acetaminophen did not impact pain significantly (MD -0.34, 95% CI -0.66 to 0.03, $I^2=0\%$) based on meta-analysis of three trials (Appendix I). One of these RCTs included two doses of acetaminophen and found that, compared with placebo, pain improved significantly more with the higher dose (WOMAC pain subscale, least squares mean [LSM] change from baseline -25.9, -22.5, -19.8 for 3900 mg daily, 1950 mg daily, and placebo, respectively; p-value for 3900 mg daily versus placebo=0.012).¹⁵⁹ Comparisons of 1950 mg daily with placebo were reported as not statistically significant. In the *intermediate term*, a single trial (N=212) also found no difference between acetaminophen and placebo in pain improvement (WOMAC pain subscale), or in the proportion of patients responding to treatment, using the OARSI criteria for response.¹⁶⁰

Function

In the *short term*, acetaminophen did not impact function (SMD -0.14, 95% CI -0.29 to 0.04, $I^2=0\%$) significantly based on meta-analysis of three trials (Appendix I). Similar to the findings on the impact of dose on pain, in a single RCT function was improved significantly with 3900 mg daily (WOMAC function subscale, LSM change from baseline -24.2, -19.0, and -18.2 for 3900 mg daily, 1950 mg daily, and placebo, respectively; p-value for 3900 mg daily versus placebo=0.016).¹⁵⁹ Comparisons of 1950 mg daily with placebo were reported as not statistically significant. In the *intermediate term*, a single trial (N=212) found a slightly greater improvement in function with acetaminophen on the WOMAC function subscale (0-100; MD -3.7, 95% CI -6.9 to -0.5), but the difference was less than the magnitude of effect defined as small for this report.¹⁶⁰

Subpopulations

None of the four included RCTs conducted subgroup analyses by age, gender, race, or ethnicity. One evaluated baseline pain, but did not report results for acetaminophen other than to note that it was not different to placebo.¹²² Subgroup analyses could not be conducted based on study quality (all were fair) or on pain location (2 were knee, 1 was mixed knee/hip).

Topical Lidocaine

A single *short-term* study of lidocaine 5% patch compared with celecoxib in patients with knee OA (N=143) was poor-quality (unclear allocation concealment, no blinding, high attrition: 46%), and terminated early due to the withdrawal of celecoxib from the market at that time.¹¹⁴

Cross-Class Comparisons

Evidence from two small, *short-term* RCTs comparing drugs across classes was insufficient to draw conclusions due to serious imprecision and inconsistency. One small (N= 85) *short-term*, fair-quality RCT compared diclofenac with acetaminophen over 12 weeks.¹²² A very small study of diclofenac 150 mg daily and acetaminophen 4000 mg daily found diclofenac to be superior in both pain and function improvement.¹²² In a small (N=65), good-quality RCT of patients with OA of the hand taking acetaminophen or an NSAID at baseline, pregabalin 1300 mg daily (MD -2.7, 95% CI -3.5 to -1.9) and duloxetine 60 mg daily (-2.3, 95% CI -3.8 to -0.9) improved pain to a similar degree (NRS 0-10 scale), but a statistical comparison was not made.¹⁰⁹

Inflammatory Arthritis

Key Points

- In the *short term*, oral NSAIDs resulted in small improvements in pain severity and function, and moderate improvement in pain response compared with placebo (SOE: Moderate). Evidence on quality of life is inconsistent, with one trial finding a moderate effect and one trial finding no effect (SOE: Insufficient). Evidence on *intermediate-term* outcomes is limited to one trial of naproxen, finding small improvements in pain severity and pain response and no improvement in function (SOE: Low). Evidence on *long-term* outcomes is limited to one trial of meloxicam, finding large improvements in pain severity and pain response and no improvement in function (SOE: Low).

- Subgroup analyses of specific drug, dose, year of publication, type of inflammatory arthritis, and study quality did not alter the findings meaningfully.
- Comparisons of different doses of various NSAIDs and comparisons of different NSAIDs with one another found no meaningful differences in effectiveness for pain improvement, pain response, function, or quality of life (SOE: Low to Insufficient).
- The tricyclic antidepressant amitriptyline resulted in no improvement in pain severity compared with placebo in one trial (SOE: Low).

Detailed Assessment

Thirty RCTs (in 32 publications) evaluated nonopioid drugs to treat chronic pain due to inflammatory arthritis.¹⁶²⁻¹⁹³ One trial met criteria for good quality¹⁷¹ and 19 were fair quality.^{162,164,165,167,169,170,172,173,177-179,183-186,188,189,191,192} An additional 10 trials (in 11 publications) were rated as poor quality – deemed to have high risk of bias due to unclear randomization and allocation concealment techniques, baseline differences between randomized groups, lack of blinding, and/or high attrition – and are not synthesized with the other evidence (Appendix G).^{163,166,168,174-176,180,182,187,190} The 20 good- and fair-quality RCTs included 7,708 patients, with 15 studies (in 16 publications) of rheumatoid arthritis (RA) (N=6,218)^{164,165,169,170,172,173,177-179,183-185,189,192,194} and 6 studies of ankylosing spondylitis (AS) (N=1,869).^{162,167,171,186,188,191} Twenty trials evaluated various NSAIDs and one trial¹⁷⁷ evaluated a TCA drug. Eighteen trials (13 in RA; 5 in AS) were *short term* (12 to 24 weeks); 2 trials in RA were *intermediate term* (26 weeks); and 1 trial in AS was *long term* (52 weeks). Thirteen placebo-controlled trials (9 in RA; 4 in AS) evaluated five different NSAIDs (celecoxib, diclofenac, etodolac, meloxicam, and naproxen) and one TCA (amitriptyline). Four trials (1 in RA; 3 in AS) compared multiple doses of celecoxib and two trials (1 in RA; 1 in AS) compared multiple doses of meloxicam. Ten trials included head-to-head comparisons of various NSAIDs: celecoxib vs. diclofenac; celecoxib vs. naproxen; diclofenac vs. etodolac; etodolac vs. naproxen; meloxicam vs. naproxen; and nabumetone vs. naproxen.

The good- and fair-quality studies were most often conducted in Europe (25%) and the United States (35%); 30 percent were conducted in 4 or more countries. Of the 16 good- and fair-quality trials that reported the funding source, all but two (88%) were funded by industry. The weighted mean age of enrolled participants across trials was 52 years (range 30 to 58 years, 19 trials), with a weighted mean proportion of female participants of 64 percent (range 22% to 87%, 18 trials). The race of participants was reported in eight trials, with a weighted mean proportion of nonwhite participants of 19 percent (range 0.3% to 50%). The weighted mean baseline pain severity was 65 (VAS scale 0-100, range 46 to 72, 9 trials). Six trials reported baseline pain using a variety of other measures and six trials did not report baseline pain. Fourteen trials reported mean baseline functional ability using a variety of measures, including Bath Ankylosing Spondylitis Functional Index (BASFI) 100-point scale (weighted mean = 50, range 47 to 52, 2 trials), BASFI 10-point scale (weighted mean = 4, 2 trials), American Rheumatoid Association (ARA) Functional Class (weighted means: ARA I: 25%, ARA II: 59%, ARA III: 17%, 3 trials), and the Modified Health Assessment Questionnaire (MHAQ; weighted mean = 1.12, 2 trials). The weighted mean duration of pain at baseline was 122 months (range 61 to 147 months, 15 trials). Complete descriptions of included study characteristics are in Appendix E. Results of meta-analyses, including forest plots and subgroup analyses, are in Appendix I.

Nonsteroidal Anti-Inflammatory Drugs

Placebo-Controlled Trials

Pain

At *short-term* followup, NSAIDs resulted in a small, statistically significant, reduction in pain compared with placebo, based on meta-analysis of nine RCTs (MD -0.97, 95% CI -1.33 to -0.74, $I^2=39\%$, 0-10 scale; Appendix I).^{162,164,165,167,169-173,178,179,185,189,193} Similarly, the proportion of patients responding to treatment with NSAIDs was significantly higher than for placebo, with a moderate combined effect size (45% vs. 32%, RR 1.58, 95% CI 1.34 to 2.06, 7 RCTs, $I^2=52\%$; Appendix I).^{162,164,171,173,185,189,193} These two meta-analyses combined studies of celecoxib,^{162,189,193} diclofenac,¹⁷² etodolac,^{178,179} meloxicam,¹⁷² and naproxen.^{162,164,171,173,185,189,193} The strength of evidence for NSAIDs on pain reduction and pain response in the *short term* is moderate. At *intermediate-term* followup in a single trial (N=563), naproxen 1000 mg daily was associated with greater reduction in pain compared with placebo (MD -0.53, 95% CI -0.93 to -0.13, 0-10 scale) and a higher proportion responding to treatment (42% vs. 32%, RR 1.28, 95% CI 1.03 to 1.60).¹⁷³ At *long-term* followup in a single trial (N=365), meloxicam 15 to 22.5 mg daily was associated with a large and statistically significant greater reduction in pain compared with placebo (MD -2.10, 95% CI -2.72 to -1.48, 0-10 scale) and a significantly higher proportion responding to treatment (48% vs. 16%, RR 3.05, 95% CI 1.98 to 4.71).¹⁶⁷ The strength of evidence for NSAIDs on pain reduction and pain response in the *intermediate* and *long term* is low.

Subgroup analyses of specific drug, dose (celecoxib), year of publication (≤ 2000 , ≥ 2001), and study quality (good and fair) did not alter the findings meaningfully, with no significant interactions found (Appendix I). Subgroup analysis of type of inflammatory arthritis (RA vs. AS) found improvement in pain was significantly greater in patients with AS (MD -2.02, 95% CI -2.96 to -1.07, $I^2=0\%$, 0-10 scale), compared with those with RA (MD -0.88, 95% CI -1.12 to -0.65, $I^2=39\%$, 0-10 scale), with a statistically significant test for interaction ($p=0.03$; Appendix I). Pain response was also greater (RR 2.27, 95% CI 1.72 to 3.84, $I^2=0\%$) in AS patients than in RA patients (RR 1.41, 95% CI 1.25 to 1.61) with a significant test for interaction ($p=0.03$). In addition, comparisons between different doses of celecoxib (200 mg daily vs. 400 mg daily)^{162,188,189,191} and meloxicam (7.5 mg daily vs. 15 mg daily vs. 22.5 mg daily)^{167,172} found no meaningful differences between doses for pain reduction or pain response (Appendix I).

Function

At *short-term* followup, NSAIDs resulted in a small, statistically significant, improvement in function compared with placebo, based on meta-analysis of seven RCTs (SMD -0.34, 95% CI -0.51 to -0.20, $I^2=67\%$), using the BASFI and the Health Assessment Questionnaire (HAQ). The meta-analysis combined studies of celecoxib,^{162,189,193} diclofenac,¹⁷² meloxicam,¹⁷² and naproxen (Appendix I).^{162,164,171,173,185,189,193} At *intermediate-term* followup in a single trial (N=563), naproxen 1000 mg daily resulted in a small improvement in function compared with placebo (MD -0.18, 95% CI -0.35 to -0.02, 0-3 scale).¹⁷³ At *long-term* followup in a single trial (N=365), meloxicam 15 to 22.5 mg daily did not improve function compared with placebo (MD -0.63, 95% CI -0.85 to -0.40, 0-40 scale).¹⁶⁷ The strength of evidence for NSAIDs on function in the *short term* is moderate; and for the *intermediate term* and *long term* it is low.

Subgroup analyses of specific drug, dose (celecoxib), year of publication (< 2000 , > 2001), type of inflammatory arthritis (RA vs. AS), and study quality (good and fair) did not alter the

findings meaningfully, with no significant interactions found. In addition, comparisons between different doses of celecoxib (400 mg daily vs. 200 mg daily),^{162,188,189,191} and meloxicam (7.5 mg daily vs. 15 mg daily vs. 22.5 mg daily)^{167,172} found no meaningful differences in function between doses.

Quality of Life

At *short-term* followup in one trial (N=55), naproxen 1000 mg daily was associated with moderate improvement in quality of life compared with placebo, as measured by the Ankylosing Spondylitis Quality of Life (ASQoL) scale (MD -2.9, p=0.04, 0-18 scale).¹⁷¹ Another *short-term* trial in patients with RA (N=1,148) found improvement in quality of life, as measured by the SF-36 PCS and MCS, for each of three different doses of celecoxib (200 mg, 400 mg, and 800 mg daily) and for naproxen 1000 mg daily.¹⁸⁹ However, the effect sizes for the PCS (MD range: 1.6 to 3.5, p<0.01, 0-100 scale) and for the MCS (MD range: 2.5 to 3.5, p<0.05, 0-100 scale) were all less than a small effect as defined for this report. The mean differences for two doses of celecoxib (400 mg daily and 800 mg daily) for the PCS (MD = 3.4 and 3.5, respectively, 0-100 scale) and one dose of celecoxib (400 mg daily) for the MCS (MD 3.5, 0-100 scale) were slightly higher than the 3-point MCID recommended for use with the SF-36,¹³⁹ while the mean differences for naproxen and the other doses of celecoxib were less than the MCID. This evidence is insufficient to draw conclusions about quality of life, given the inconsistency in findings.

Other Outcomes

One trial (N=1,148) assessed changes in depression and/or anxiety, using the “role emotional” and “mental health” domains of the SF-36 in the *short term*.¹⁸⁹ Three different doses of celecoxib and one dose of naproxen were associated with improvement in “role emotional” scores compared with placebo. The effect size was moderate for celecoxib 400 mg daily (MD 10.3, p<0.05) and small for celecoxib 200 mg daily, celecoxib 800 mg daily, and naproxen 1000 mg daily (MD 8.1, 7.5, and 8.4, respectively; p<0.05). Although each dose of celecoxib and naproxen were also associated with improvement in “mental health” scores, all effect sizes were less than small as defined for this report (MD range: 2.8 to 4.6), with p<0.05 for each dose except for celecoxib 400 mg daily, which was not statistically significant. At *long-term* followup in another trial (N=365), meloxicam 15 mg daily and 22.5 mg daily were associated with large improvements in sleep disturbance due to pain compared with placebo (MD -26% and -35%, respectively, p<0.05).¹⁶⁷

Head-to-Head Comparisons of NSAIDs

Three *short-term*, fair-quality RCTs of celecoxib versus diclofenac,^{170,188,191} two of celecoxib versus naproxen,^{162,189} and two of nabumetone versus naproxen^{169,183} provided data for meta-analyses. Five additional fair-quality RCTs, which could not be pooled in meta-analyses, compared one NSAID with another. These included *short-term* comparisons of diclofenac versus etodolac,¹⁸⁴ diclofenac versus meloxicam,¹⁷² and etodolac versus naproxen,¹⁶⁵ and *intermediate-term* comparisons of meloxicam versus naproxen¹⁹² and nabumetone versus naproxen.¹⁹⁵

Pain

In *short-term* followup, no meaningful difference in pain improvement was found between any two NSAIDs, including: celecoxib versus diclofenac (3 trials),^{170,188,191} celecoxib versus naproxen (2 trials),^{162,189} diclofenac versus etodolac (1 trial),¹⁸⁴ diclofenac versus meloxicam (1

trial),¹⁷² etodolac versus naproxen (1 trial),¹⁶⁵ and nabumetone versus naproxen (2 trials)^{169,183} (Appendix I). In *intermediate-term* followup, difference in pain improvement was not found between meloxicam versus naproxen (1 trial) or nabumetone versus naproxen (1 trial).^{192,195} Similarly, in *short-term* followup, no difference was found in pain response between celecoxib versus diclofenac (3 trials)^{170,188,191} or celecoxib versus naproxen (2 trials).^{162,189} In the meta-analyses of celecoxib, subgroup analyses by year of publication (<2000, >2001) and type of inflammatory arthritis (RA vs. AS) did not alter the findings meaningfully. This evidence is low strength, except for the small, single study comparisons of etodolac and diclofenac or naproxen, which was insufficient to draw conclusions.

Function

In *short-term* followup, no meaningful difference in function was found between any two NSAIDs, including: celecoxib versus diclofenac (3 trials),^{170,188,191} celecoxib versus naproxen (2 trials),^{162,189} diclofenac versus etodolac (1 trial),¹⁸⁴ diclofenac versus meloxicam (1 trial),¹⁷² and nabumetone versus naproxen (2 trials)^{169,183} (Appendix I). In the meta-analyses of celecoxib, subgroup analyses by year of publication (<2000, >2001) and type of inflammatory arthritis (RA vs. AS) did not alter the findings meaningfully. This evidence is low strength, except for the small, single study comparison of etodolac and diclofenac, which was insufficient to draw conclusions.

Quality of Life

In *short-term* followup in one trial (N=917), no meaningful difference in quality of life was found between celecoxib (200 mg to 800 mg daily) and naproxen 1000 mg daily, as measured by the SF-36 PCS the MCS.¹⁸⁹ This evidence is low strength.

Antidepressants

Pain

In *short-term* followup in one fair-quality trial (N=36), there was no meaningful difference between amitriptyline 50 mg to 75 mg daily and placebo for pain improvement (MD 0.12, p=not significant, 0-4 scale).¹⁷⁷ The study did not assess pain response, function, or quality of life. This evidence was insufficient to draw conclusions due to study limitations and size.

Low Back Pain/Neck Pain

Key Points

- In patients with low back pain, *short-term* duloxetine use resulted in a small improvement in pain severity and response, but the improvements in function and quality of life did not meet the threshold for a small improvement, based on pooled analysis of three trials (SOE: Moderate).
- In the *intermediate term*, a single study of amitriptyline found no improvement in pain or function in patients with low back pain (SOE: Low).

Detailed Assessment

Seven RCTs (in 9 publications) involving 1,838 patients meeting inclusion criteria evaluated nonopioid drugs to treat chronic low back pain (Appendix E).¹⁹⁶⁻²⁰⁴ Six were *short-term* studies

(12 to 14 weeks) and one was *intermediate-term* (6 months).²⁰⁴ Six were placebo-controlled trials,¹⁹⁶⁻²⁰¹ two of which compared multiple doses of desipramine and/or duloxetine, and one head-to-head trial comparing amitriptyline and pregabalin.²⁰⁴ Two RCTs met criteria for good quality,^{199,204} and the other five RCTs were fair quality. Two studies were conducted in the United States,^{196,197} two studies were multinational,^{200,201} and one each was conducted in Australia,²⁰⁴ India,¹⁹⁸ and Japan.¹⁹⁹ Three studies were government-funded^{196,197,204} and three were industry-funded;¹⁹⁹⁻²⁰¹ one did not report the funding source.¹⁹⁸

Mean age of enrolled patients ranged from 42 to 59 years and 23 to 61 percent were female. In four studies reporting race, less than 30 percent of participants were nonwhite. Four RCTs reported baseline pain severity ranging from 5 to 7 on a 0-10 VAS.¹⁹⁸⁻²⁰¹ In the remaining three trials, two reported baseline pain of 9 on a 0-20 VAS,^{196,197} and one reported baseline pain of 40 on a 0-100 VAS.²⁰⁴ Duration of pain across all studies ranged from 35 to 204 months (median 120). At baseline, function/disability ranged from 8 to 9 on the Roland Morris Disability Questionnaire (RMDQ) in three trials,^{199,201,204} and 42 on the Oswestry Disability Index (ODI) scale in one trial;¹⁹⁸ baseline function/disability was unclear or not reported in the remaining three trials.^{196,197,200} Complete descriptions of included study characteristics are in Appendix E.

Antidepressants: SNRIs

Duloxetine

Duloxetine versus placebo was assessed in one good- and two fair-quality, *short-term* RCTs (N=1,491) (Appendix E).¹⁹⁹⁻²⁰¹ Duloxetine dose ranged from 20 to 120 mg daily. Pain, function, and quality of life were reported in all three publications. Strength of evidence for duloxetine versus placebo was moderate for pain, function outcomes, and quality of life.

Pain

In the *short term*, duloxetine resulted in a small reduction in pain, based on meta-analysis of three RCTs (BPI Pain Scale 0-10; MD -0.50, 95% CI -0.71 to -0.29, $I^2=0\%$; Appendix I).¹⁹⁹⁻²⁰¹ Similarly, the proportion responding to duloxetine was significantly greater than placebo (RR 1.25, 95% CI 1.11 to 1.40, $I^2=0\%$). Sensitivity analysis of study quality did not alter the findings meaningfully. Estimates were similar when stratified according to dose of duloxetine, though 20 mg daily was not associated with improvement in pain (MD 0.08, 95% CI -0.66 to 0.82) or proportion responding to duloxetine (RR 0.95, 95% CI 0.65 to 1.38) based on one trial.²⁰⁰

Function

In the *short term*, duloxetine resulted in improvement in function that was below the threshold for a small magnitude of effect for this report, based on meta-analysis of three RCTs (BPI Interference Scale; MD -0.36, 95% CI -0.73 to -0.04, $I^2=34\%$; Appendix I).¹⁹⁹⁻²⁰¹ Sensitivity analysis of study quality did not alter the findings meaningfully, though only one study was good quality and the estimate was imprecise. Results were also consistent when stratified according to dose of duloxetine.

Quality of Life

Three *short-term* RCTs reported the effect of duloxetine on quality of life.¹⁹⁹⁻²⁰¹ All three trials reported small improvement in quality of life with duloxetine, but the effect estimate was only statistically significant in one trial that used a dose of 60 mg daily.²⁰¹ When pooled, the effect of duloxetine on quality of life was not statistically significant (SMD 0.18, 95% CI -0.03

to 0.39, $I^2=38\%$; Appendix I). Results were consistent when studies were stratified according to study quality and dose of duloxetine.

Tricyclic Antidepressants

One *short-term* fair-quality trial (N=78) compared desipramine with placebo (Appendix E).¹⁹⁶ Desipramine dose was not reported, rather the study focused on the effect of low (<60 mg/ml) or high (>60 ng/ml) plasma concentrations of desipramine. After 12 weeks of treatment, Descriptor Differential Scale (DDS) scores (scale 0-20) were not significantly different between all desipramine concentrations (6.0) and placebo (6.8) groups (MD -0.80, 95% CI -2.64 to 1.04). Desipramine less than 60 mg/ml was more effective than placebo at reducing pain ($p=0.05$) with no such effect for higher plasma levels of desipramine. The proportion responding (>75% reduction in pain) was similar for desipramine and placebo (23% vs. 18%, RR 1.28, 95% CI 0.43 to 3.85), though low plasma concentration desipramine was associated with greater response than placebo (37% vs. 18%, RR 2.03, 95% CI 0.70 to 5.87). Evidence on other outcomes for all desipramine concentrations was not reported, but low concentration desipramine improved function relative to placebo, based on RMDQ score (mean 2.3 vs. 4.1, $p=0.05$). This evidence is insufficient to draw conclusions, due to study quality, unknown consistency, and imprecision.

One good-quality, *intermediate-term* trial (N=146) comparing amitriptyline 25 mg daily with placebo found a mean difference in pain score of -7.81 (VAS 0-100 scale) between groups after 6 months treatment; this difference was not statistically significant (95% CI -15.7 to 0.10).²⁰⁴ The mean difference (-0.98) between groups in function, measured using the RMDQ scale (0-24), also showed a nonsignificant effect favoring amitriptyline (95% CI -2.42 to 0.46). This evidence is low strength.

Anticonvulsants

Gabapentin

A *short-term*, fair-quality trial (N=108) meeting inclusion criteria compared gabapentin up to 3600 mg daily with placebo in patients with radicular and nonradicular back pain (Appendix E).¹⁹⁷ After 12 weeks, both gabapentin and placebo were associated with similar reduction in DDS pain scores compared with baseline ($p=0.42$) and with similar proportions responding to treatment (36% vs. 36%, $p=1.00$). Similar proportions of patients in both groups were rated as having at least “minimal improvement” on the physician-rated Clinical Global Impression of Change (37% vs. 33%, $p=0.95$). Quality of life, based on BDI-II scores, were also not different between groups following treatment ($p=0.52$). This evidence is insufficient to draw conclusions due to study quality, unknown consistency, and imprecision.

Cross-Class Comparisons

Pregabalin Versus Amitriptyline

One *short-term* trial (N=200) compared pregabalin 600 mg daily versus amitriptyline 50 mg daily in patients with low back pain (Appendix E).¹⁹⁸ After 14 weeks, although both groups improved significantly, a small greater improvement was seen with amitriptyline (-3.9 on VAS) compared with pregabalin (-2.9 on VAS, $p=0.03$). The proportion of patients responding to treatment (>50% improvement in VAS score) was also significantly higher with amitriptyline (57%) than pregabalin (39%; RR 1.46, 95% CI 1.08 to 1.97). Both interventions similarly

improved function based on ODI scale score, with no difference between groups ($p=0.09$). This evidence is low strength.

Chronic Headache

Key Points

- Evidence from a single fair-quality RCT (N=197) did not find differences between amitriptyline 50 to 75 mg daily and placebo in patients with “chronic tension-type headache” (SOE: Low).

Detailed Assessment

Although the classification of headache has changed over time, in order to capture any evidence relevant to treating chronic headache pain and being consistent with other similar reports,^{10,25} we defined chronic headache broadly using the International Headache Society 2013 definition: headache frequency of at least 15 days per month over a period of at least 6 months or headache more than 180 days per year.²² No other requirement was made in terms of defining chronic headache, although all the other inclusion criteria applied (e.g., 12 weeks duration minimum). Using this definition, three RCTs were found,²⁰⁵⁻²⁰⁷ but two were rated poor quality due to unclear randomization processes, differences at baseline in patient characteristics, and lack of blinding.^{206,207} One of these RCTs (N=41) compared pregabalin with placebo in patients with “chronic unilateral cervicogenic headache,”²⁰⁶ and the other (N=53) compared TCAs (amitriptyline or nortriptyline) with placebo, stress management, or a combination in patients with “chronic tension-type headache.”²⁰⁷

The fair-quality RCT (N=197) compared treatment with amitriptyline and placebo (and a drug studied in Germany, amitriptylinoxide—not reported here) in patients with “chronic tension-type headache.”²⁰⁵ Mean age of enrolled patients was 38 years, 56 percent were female, and mean baseline pain severity was 3.7 on a VAS of 0-8. Dosing was adjusted for tolerability and ranged from 50 to 75 mg of amitriptyline per day. In the *short term* (24 weeks), headache pain severity decreased in both amitriptyline and placebo groups (reduction of 0.9 with amitriptyline and 1.7 with placebo, on a scale of 0-8, no statistical analysis presented). Similarly, response (defined as 50% reduction in duration and frequency of headache in weeks 13-16) was not different between groups (22.4% vs. 21.9%, calculated RR 1.024, 95% CI 0.54 to 1.95). This is low strength of evidence.

Sickle-Cell Disease

Key Points

- Evidence from a single pilot study was insufficient to draw conclusions on the effect of pregabalin given over 3 months in patients with sickle cell disease and ongoing pain.

Detailed Assessment

A single fair-quality pilot study (N=22) compared pregabalin with placebo in patients with sickle cell disease and a history of pain that was not well controlled; at least a score of 4 on a 0-10 scale and requiring intermittent NSAIDs, acetaminophen, or opioids. Mean age of participants was 33 years, 73 percent were female, and nearly all were nonwhite (95% African American). Mean pain score at baseline for pregabalin group was 3.8 versus 4.8 for placebo on the Average

Pain Intensity (API) 0-10 scale; other pain measures showed similar differences at baseline. Mean SF-36 PCS at baseline was 64.3. Dosing of pregabalin was flexible based on tolerability with a range of 75 to 600 mg daily, given for 3 months. In the *short term*, pregabalin led to a small reduction in API score (pregabalin -1.1, placebo -0.5 on a scale of 0-10), but was not statistically significant given the small sample size. Differences on three other pain measures (the composite pain index, neuropathic pain symptom index, and the Leeds Assessment of Neuropathic Signs and Symptoms) were small and sometimes favored placebo. No difference was reported in SF-36 scores between groups. Due to the very small size, no corroborating evidence, and study limitations (e.g. differences in pain scores at baseline), this evidence is insufficient to draw conclusions.

Key Question 2: Harms and Comparative Harms of Nonopioid Drugs for Chronic Pain

We evaluated the harms of nonopioid drugs in patients with chronic pain, including (for comparison purposes) adverse events associated with opioid use (e.g., overdose, misuse, dependence, substance use disorder), over-arching adverse event outcomes that can be assessed across classes (i.e., withdrawals due to adverse events [WAE], and serious adverse events [SAE]), and adverse events that are specific to individual drug classes. We evaluated the impact of type of pain, patient demographics and comorbidities, and dose and duration of treatment. The evidence is limited to RCTs and systematic reviews of these drugs in patients with chronic pain, and is organized by drug classes.

Antidepressants

Key Points

- In the *short* and *intermediate term*, SNRI antidepressants (duloxetine and milnacipran) did not increase reports of SAEs (SOE: Low) but led to a moderate increase in risk of WAE (SOE: Moderate). In the *short term*, TCAs (amitriptyline and desipramine) did not increase the risk of WAE (SOE: Low).
- SNRI specific harms: in the *short* and *intermediate term*, reports of nausea were significantly increased with milnacipran (moderate increase) and duloxetine (large increase; SOE: Moderate). Dose did not affect the findings (SOE: Low). A large increase in sedation was reported with duloxetine in the *short term* (SOE: Moderate); 60 mg daily resulted in lower risk than 120 mg daily (SOE: Low). In the *short term*, cognitive adverse events were not significantly more frequent with SNRIs (SOE: Low).
- TCA specific harms: TCAs did not significantly increase the risk WAE (SOE: Low). Evidence on other adverse events of interest was not available or insufficient.

Detailed Assessment

Forty good- or fair-quality placebo-controlled trials (in 50 publications)^{33,36-38,43,54-56,64-66,68-71,73,75-77,79-81,83-86,88,93,94,98,100,109,110,153-157,177,196,198-205,208,209} involving 13,943 patients meeting inclusion criteria evaluated antidepressants to treat chronic pain; 32 were *short-term* studies, 5 *intermediate-term*,^{79,84,86,93,204} and 3 *long-term*.^{55,76,80} The large majority of evidence was for SNRIs, either milnacipran or duloxetine, with 34 trials including 13,156 participants, with 6 RCTs of TCAs (N=787).^{85,177,196,198,204,205} Seven trials met criteria for good

quality.^{88,98,100,109,110,199,204} The patient population in 16 trials was fibromyalgia, 8 trials neuropathic pain, 8 trials osteoarthritis, 6 trials low back pain, and 1 trial each of rheumatoid arthritis and chronic headache. The specific adverse events of interest included nausea and sedation for SNRIs, cardiac rhythm abnormalities, dry mouth, urinary retention, and weight gain for TCAs, and cognitive effects and serotonin syndrome for both drug classes.

Serious Adverse Events

SAEs were infrequent; meta-analysis of 19 *short-term* trials of SNRI antidepressants (duloxetine and milnacipran) did not find a significant difference compared with placebo (1.5% vs. 1.6%, RR 0.88, 95% CI 0.62 to 1.24, $I^2=0\%$).^{36,37,43,54,56,65,66,71,75,77,81,88,100,110,153,157,199-201} Subgroup analyses by pain population, study quality, specific drug, and dose within a single drug did not alter these results significantly. Two *intermediate-term* trials of SNRIs duloxetine or milnacipran also found no difference in the incidence of SAEs compared with placebo (2.2% vs. 2.6%, RR 0.86, 95% CI 0.35 to 2.24, $I^2=0\%$). These findings are low strength of evidence. Evidence on SAEs of TCAs was limited, with one trial of five reporting this outcome.

Withdrawals Due to Adverse Events

There was a moderate increase in WAEs with antidepressants (duloxetine and milnacipran) in 24 *short-term* studies (15.2% vs. 7.5%, RR 1.99, 95% CI 1.71 to 2.35, $I^2=18\%$), and in 3 *intermediate-term* studies (21.9% vs. 11.4%, RR 1.83, 95% CI 1.23 to 2.61, $I^2=4\%$). These findings are moderate strength of evidence. Subgroup analyses of pain population, study quality, or specific drug (duloxetine or milnacipran) did not significantly alter these results. Higher doses of duloxetine (60 mg or 120 mg daily) and milnacipran (200 mg daily) resulted in significant increased risk of WAE (relative risks great than 2.0), while lower doses (20 mg and 40 mg daily of duloxetine, 100 mg daily of milnacipran) did not reach statistical significance and had lower relative risks (less than 2.0).

The risk of WAE with a TCA (amitriptyline or desipramine) was not significantly increased over placebo in the *short term* (5 RCTs, N=478, 19% vs. 10%, RR 1.49, 95% CI 0.89 to 3.01, $I^2=0\%$) or the *intermediate term* (1 RCT, N=126, 8% vs. 5%, RR 1.75 95% CI 0.38 to 8.06; Appendix I). The evidence in the *short term* is low strength, but the *intermediate-term* evidence is insufficient.

Subgroup analysis by study quality did not alter the findings. Analysis by specific drug found the risk with amitriptyline similar to the overall meta-analysis result (4 RCTs, N=400), and the risk with desipramine, based on a single small study (N=78), significantly increased (RR 8.50, 95% CI 1.20 to 60.41).

Specific Adverse Events

SNRIs

Nausea

In the *short term*, 19 RCTs of SNRI antidepressants duloxetine and milnacipran (N=8,929) resulted in a large increased incidence of nausea (25% vs. 9%, RR 3.10, 95% CI 2.50 to 4.06, $I^2=60\%$; Appendix I).^{36-38,54,56,65,66,71,75,77,81,88,100,110,153,157,199-201} This is moderate strength of evidence. Subgroup analyses by pain population, dose, and study quality did not alter these findings. Analysis by specific drug showed that duloxetine (16 RCTs, N=5,803) has a significantly greater risk of nausea (20% vs. 4.8%, RR 3.57, 95% CI 2.97 to 4.50, $I^2=0\%$;

Appendix I) than milnacipran (3 RCTs, N=3,098, RR 1.90, 95% CI 1.64 to 2.29, $I^2=0\%$, p-value for interaction=0.00). In the *intermediate term*, 3 RCTs (N=1,738) found a moderate increased risk of nausea (33% vs. 15%, RR 1.98, 95% CI 1.57 to 2.82, $I^2=0\%$).^{79,86,93} This is low-strength evidence.

Sedation

In the *short term*, 16 RCTs (N=5,831) of the SNRI duloxetine showed a large increased incidence of sedation compared with placebo (12% vs. 4.6%, RR 2.46, 95% CI 2.00 to 3.01, $I^2=0\%$).^{36-38,54,56,66,71,75,88,100,110,153,157,199-201} This is moderate strength of evidence. In the *intermediate term*, 2 RCTs (N=850) found a large increased risk of sedation with duloxetine (11% vs. 2.6%, RR 3.51, 95% CI 1.46 to 11.05, $I^2=0\%$).^{79,93} This is low-strength evidence. Subgroup analyses of pain population and study quality did not alter these findings. Analyses by dose found significant increased risk and higher relative risks with 60 mg and 120 mg daily than with lower doses (20 mg and 30 mg daily).

Cognitive Effects

Only two *short-term* RCTs of SNRI antidepressants reported cognitive adverse events, with the pooled estimate not reaching statistical significance (0.8% vs. 0%, RR 3.24, 95% CI 0.26 to 40.17, $I^2=0\%$). This is low strength evidence.

Serotonin Syndrome

We found no RCTs reporting episodes of serotonin syndrome.

TCA

Dry Mouth

Significantly more patients reported dry mouth with the TCA amitriptyline in a *short-term* RCT (N=131) of patients with chronic tension-type headache (51% vs. 28%, RR 1.80, 95% CI 1.14 to 2.85).²⁰⁵ No other trial of a TCA reported dry mouth as an adverse event, and this evidence is insufficient to draw conclusions.

Other Specific Adverse Events

No adverse events of interest, including cardiac rhythm abnormalities, were reported in the included studies.

Anticonvulsants

Key Points

- In the *short term*, oxcarbazepine led to a large increased risk of WAEs (SOE: Low).
- In the *short term*, pregabalin/gabapentin resulted in large increases in blurred vision, dizziness, weight gain, and cognitive effects (e.g., confusion).
- While the incidences of hyponatremia and sedation were greater with oxcarbazepine than placebo, the differences were not significant (SOE: Low).

Detailed Assessment

Twenty-eight RCTs provided evidence for harms in the *short term*: 21 RCTs provided information on SAEs, all 28 RCTs provide evidence on WAE, and 27 RCTs provided evidence

on specific adverse events. Four studies met criteria for being good quality^{27,29,89,109} and the remainder were fair quality. Seventeen trials were of patients with neuropathic pain, eight of patients with fibromyalgia, one each of patients with low back pain, osteoarthritis, and sickle cell disease. Twenty-three RCTs involved pregabalin, and two each involved gabapentin, the prodrug gabapentin enacarbil, and oxcarbazepine (one included both pregabalin and gabapentin enacarbil).⁴⁴ For this drug class, specific adverse events of interest included blurred vision, cognitive effects, dizziness, peripheral edema, sedation, weight gain for pregabalin, gabapentin, and gabapentin enacarbil, and cognitive effects, hyponatremia, neutropenia, and sedation for oxcarbazepine (there were no studies of carbamazepine).

Serious Adverse Events

Meta-analysis of 19 RCTs (N=7,982) of patients with fibromyalgia (6 RCTs) and neuropathic pain (13 RCTs) did not find a significant increase in risk of having an SAE with an anticonvulsant in the *short term* (2.3% vs. 2.5%, RR 0.90, 95% CI 0.90 to 1.30, I²=0%; Appendix I). Subgroup analyses by pain condition, specific drug, dose, and study quality did not alter these results. In the *short term*, oxcarbazepine did not significantly increase the risk of serious adverse events (2 RCTs, N=493, 8.9% vs. 4.8%, RR 1.82, 95% CI 0.74 to 5.05, I²=0%). This evidence is low strength.

Withdrawal Due to Adverse Events

Meta-analysis of 26 RCTs (N=9,754) of patients treated for chronic pain in the *short term* found a moderate increase in WAEs (14% vs. 7.0%, RR 1.73, 95% CI 1.48 to 2.01, I²=5%) with pregabalin/gabapentin. Subgroup analyses by pain condition, specific drug, dose, and study quality did not alter these results. This evidence is moderate strength. In the *short term*, oxcarbazepine led to a large increase in the risk of WAEs (2 RCTs, N=493, 26% vs. 7%, RR 3.64, 95% CI 1.86 to 7.12, I²=0%). This is evidence is low strength.

Specific Adverse Events

Pregabalin/Gabapentin

Twenty-five RCTs provided data on specific harms of pregabalin and gabapentin.^{27,29,30,35,39,41,42,44,45,48-52,57,67,72,74,87,89,92,109,197} There were large increases in the risk of blurred vision, cognitive effects, dizziness, peripheral edema, sedation, and weight gain (Table 6). This evidence is low to moderate strength.

Table 6. Specific harms of pregabalin/gabapentin

Specific Harms	N Studies (n Patients)	Incidence	Relative Risk (95% CI)	Magnitude of Effect Strength of Evidence
Cognitive effects	8 (N=3,801)	4.8% vs. 1.3%	RR 3.15 (1.86 to 5.51)	Large effect Low
Dizziness	25 (N=9,696)	25.6% vs. 7.4%	RR 2.97 (2.53 to 3.50)	Large effect Moderate
Peripheral edema	22 (N=9,005)	8.8% vs. 3.7%	RR 2.32 (1.80 to 3.09)	Large effect Moderate
Sedation	24 (N=9,652)	17% vs. 5.4%	RR 3.03 (2.62 to 3.67)	Large effect Moderate
Weight gain	21 (N=8,620)	10.1% vs. 2.8%	RR 3.57 (2.77 to 4.91)	Large effect Moderate

CI = confidence interval; RR = relative risk

Oxcarbazepine

Two RCTs (N=490) provided evidence on sedation and hyponatremia.^{31,34} While the incidence of each was greater in the oxcarbazepine group, and the relative risks reflected large increased risk, the differences compared with placebo was not statistically significant. This is low-strength evidence (Table 7).

Table 7. Specific harms of oxcarbazepine

Specific Harms	N Studies (n Patients)	Incidence	Relative Risk (95% CI)	Magnitude of Effect Strength of Evidence
Sedation	2 (N=490)	8.6% vs. 3.0%	RR 3.13 (0.74 to 16.08)	No effect Low
Hyponatremia	2 (N=490)	2.8% vs. 0.0%	RR 5.93 (0.55 to 63.8)	No effect Low

CI = confidence interval; RR = relative risk

NSAIDs

Key Points

- In the *short term*, NSAIDs led to a small increase in WAEs, with ibuprofen, diclofenac, and naproxen having moderately-increased risk (SOE: Moderate). Reports of SAEs were not increased with NSAIDs and differences were not found between celecoxib and nonselective NSAIDs in SAEs or WAEs (SOE: Low).
- In the *short term*, the risk of any cardiovascular event was not significantly elevated for NSAIDs as a group, although there was a small increase in risk with diclofenac, particularly within the first 6 months, and with higher doses. There was a moderate increased risk of major coronary events with diclofenac and celecoxib and a large increase with ibuprofen. In the *intermediate* and *long term*, there was not a difference in cardiovascular events between celecoxib and nonselective NSAIDs (SOE: Moderate).
- In the *short term*, nonselective NSAIDs led to moderate to large increased risk of serious upper gastrointestinal events (largely bleeding), particularly in the first 6 months of treatment (SOE: Moderate). In the *short-term*, evidence on celecoxib versus nonselective NSAIDs was mixed and inconclusive; in the *intermediate term*, nonselective NSAIDs had a moderately greater risk of serious gastrointestinal events than celecoxib (SOE: Low).
- In the *intermediate term*, although the incidence was low, large increases in hepatic harms were seen with diclofenac and naproxen (SOE: Low). No evidence on renal harms met inclusion criteria.

Detailed Assessment

Ninety-six RCTs (in 114 publications) and three systematic reviews²¹⁰⁻²¹² provided evidence on harms of NSAIDs. Twelve trials (in 16 publications) met criteria for good quality,^{99,101-108,124,171,213-216} 21 were poor quality (in 25 publications),^{111-117,163,166,168,174-176,180-182,187,190,217-223} and the remainder (63 trials in 74 publications) were fair quality (Appendix G).^{118-123,125-138,140,141,143-152,162-165,167,169,170,172,173,178,179,183-186,188,189,191-194,224-245} The poor-quality trials were deemed to have high risk of bias due to unclear randomization methods, important differences at baseline, and large amounts of missing data, and were not synthesized with the other evidence. Of the good- and fair-quality RCTs involving 89,063 patients, 60 were *short term* (12 to 24 weeks), 10 were *intermediate term* (26 weeks), and 5 *long term* (52 to 156 weeks). These

included 46 placebo-controlled trials (17 of celecoxib 100 to 400 mg daily, 6 of diclofenac 70 to 150 mg daily, 5 of ibuprofen 2400 mg daily, 4 of meloxicam 3.75 to 22.5 mg daily, 16 of naproxen 1000 mg daily, and 4 of topical diclofenac 1% to 1.5%), 12 comparing various doses of a single NSAID, and 36 RCTs making head-to-head comparisons of NSAIDs (some trials included more than one of these categories). Most studies were conducted in the United States (37) and were funded by industry (83%). Mean age of enrolled patients ranged from 30 to 72 years (weighted mean 61.8 years), 67 percent were female, and 18 percent were nonwhite. Two trials were conducted in older adults with mean age of 71 and 72 years.^{148,151}

Two included systematic reviews were good quality.^{210,211} One evaluated cardiovascular and serious gastrointestinal harms using a mix of individual patient data (IPD) and published tabular data meta-analysis of 639 RCTs with a duration of at least 4 weeks and was published through 2001.²¹⁰ The other good-quality systematic review evaluated celecoxib in patients with OA, and included analyses of harms versus placebo and other NSAIDs.²¹¹ The fair-quality systematic review evaluating hepatic harms of NSAIDs included 64 RCTs of patients with OA or RA with duration of at least 4 weeks, and was published through 2004.²¹²

Adverse events for NSAIDs selected for this review were WAE, SAEs, cardiovascular events (cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke), serious gastrointestinal events such as gastrointestinal bleeding or perforated ulcers, and renal or hepatic events. Results of meta-analyses of data from these trials, including Forest plots and subgroup analyses, can be found in Appendix I.

Serious Adverse Events

Based on meta-analysis of 23 *short-term* RCTs (N=13,082), there was no increased risk of overall SAEs with NSAIDs (RR 0.96, 95% CI 0.72 to 1.29, $I^2=0\%$; Appendix I). Stratified analyses by subgroups indicated numerically greater risk in patients with RA, with ibuprofen and naproxen, and in good-quality studies, although it was not statically significant and analysis for interaction was also not statistically significant. This is low strength of evidence. In the *intermediate term*, a single RCT (N=563) did not find an increased risk of SAEs with naproxen (RR 0.51, 95% CI 0.05 to 5.58), but this evidence was insufficient to draw conclusions. A recent Cochrane review of celecoxib 200 mg daily versus any nonselective NSAID or placebo in patients with OA found that compared with nonselective NSAIDs (9 RCTs, 6 versus naproxen, 3 versus diclofenac) or placebo (32 RCTs), there were no significant differences in the incidence of SAEs, although the authors rated this evidence as very low quality.²¹¹ Based on two RCTs (N=912), there was not a significant increase in SAEs with topical diclofenac compared with placebo (RR 1.03, 95% CI 0.29 to 27.01, $I^2=0\%$).^{99,140} This evidence is low strength.

Withdrawals Due to Adverse Events

Based on meta-analysis of 38 *short-term* RCTs (N=20,060), WAEs were increased to a small degree with NSAIDs (RR 1.30, 95% CI 1.14 to 1.49, $I^2=13\%$; Appendix I). This is moderate strength of evidence. Stratified analysis by population (RA or OA) or study quality did not meaningfully alter these results. However, the analysis by specific drug varied significantly; a moderate increase with diclofenac (6 RCTs, RR 1.71, 95% CI 1.22 to 2.65), ibuprofen (5 RCTs, RR 1.96, 95% CI 1.42 to 2.69), and naproxen (15 RCTs, RR 1.50, 95% CI 1.23 to 1.84), while celecoxib (16 RCTs, RR 1.05, 95% CI 0.86 to 1.24) and meloxicam (3 RCTs, RR 1.16, 95% CI 0.51 to 2.32) had no clear increased risk (p-value for interaction=0.01). Two *intermediate-term* RCTs (N=941)^{131,173} and one *long-term* RCT (N=365)¹⁶⁷ did not find significantly increased risk

of WAE. This evidence is low strength and insufficient, respectively. A recent Cochrane review of celecoxib 200 mg daily versus any nonselective NSAID or placebo in patients with OA found that compared with nonselective NSAIDs (9 RCTs, 6 vs. naproxen, 3 vs. diclofenac) or placebo (32 RCTs), there were no significant differences in the incidence of WAEs (rated moderate quality evidence by the authors).²¹¹ Based on four RCTs (N=1,549), there was not a significant increase in WAEs with topical diclofenac compared with placebo (RR 1.03, 95% CI 0.29 to 27.01, I²=0%).^{99,108,140,141} This is low strength of evidence.

Cardiovascular Adverse Events

Evidence on cardiovascular risks of NSAIDs comes from a large number of RCTs, some with specific intent to study these harms. A good-quality systematic review of 639 RCTs evaluated cardiovascular harms using a combination of individual patient data and standard meta-analysis.²¹⁰ The analyses combined data on four selective COX-2 inhibitor drugs (“coxibs”). This review found an increased risk in major vascular events with a coxib and diclofenac, and increased risk of vascular death with coxibs (Table 8). Major coronary events were increased with coxibs, diclofenac, and ibuprofen, and increased risk of hospitalization for heart failure was found with all NSAIDs. This analysis found that baseline risk did not alter the findings, that there may be increased risk of major vascular events in the first 6 months of treatment with diclofenac (but no evidence of increased risk over longer treatment periods for any NSAID or coxib studied), and that across the drugs higher doses were associated with greater risk.

Table 8. Individual patient data meta-analysis of NSAID cardiovascular risks²¹⁰

Event	Diclofenac Adjusted RR (95% CI)	Ibuprofen Adjusted RR (95% CI)	Naproxen Adjusted RR (95% CI)	Coxibs Adjusted RR (95% CI)
Major vascular events ^a	1.41 (1.12 to 1.78)	1.44 (0.89 to 2.33)	0.93 (0.69 to 1.27)	1.37 (1.14 to 1.66) Celecoxib 1.36 (1.00 to 1.84)
Vascular mortality	1.65 (0.95 to 2.85)	1.90 (0.56 to 6.41)	1.08 (0.48 to 2.47)	1.58 (1.00 to 2.49) ^c
Major coronary events ^b	1.70 (1.19 to 2.41)	2.22 (1.10 to 4.48)	0.84 (0.52 to 1.35)	1.76 (1.31 to 2.37)
Heart failure (hospitalization)	1.85 (1.17 to 2.94)	2.59 (1.19 to 5.20)	1.87 (1.10 to 3.16)	2.28 (1.62 to 3.20)

CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug; RR = risk ratio

^a Nonfatal myocardial infarction, coronary death, myocardial infarction or chronic heart failure death, nonfatal stroke, stroke death, any stroke, other vascular death

^b Nonfatal myocardial infarction, coronary death, myocardial infarction or coronary heart disease death

^c 99% CI calculated due to multiple comparisons

In the *intermediate term*, three RCTs compared the risk for cardiovascular events with celecoxib and nonselective NSAIDs, with none finding a significant difference. A large, good-quality RCT (N=24,081) evaluated cardiovascular harms in patients treated for OA or RA with celecoxib (mean 209 mg daily), ibuprofen (mean 2045 mg daily), and naproxen (mean 852 mg daily).²³⁶ Using a noninferiority analysis (on-treatment analysis), the incidence of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was 1.7 percent with celecoxib, 1.9 percent with ibuprofen, and 1.8 percent with naproxen, with p<0.001 for noninferiority between drugs. The second fair-quality RCT (N=916) also enrolled patients 60 years and older with OA and randomized to celecoxib or diclofenac (50 mg twice daily) and was included in a Cochrane review.^{151,211} This study also did not find a significant difference in cardiovascular events between the drugs (odds ratio [OR] 0.47, 95% CI 0.17 to 1.25). A third fair-quality RCT

(N=8,067) reported on adjudicated cardiovascular events, but did not conduct analyses comparing the event rates. The rate was very similar between celecoxib (0.4%) and nonselective NSAIDs (0.3%).²²⁶ This is moderate-strength evidence.

In the *long term*, a large good-quality RCT (N=7297) randomized patients with OA or RA who were under the age of 60 years, had no known cardiovascular disease, and who were currently taking a nonselective NSAID, to celecoxib or continuing their nonselective NSAID. At followup (median 3 years), there was not a significant difference in the incidence of hospitalization for nonfatal myocardial infarction or other biomarker positive acute coronary syndrome, nonfatal stroke, or cardiovascular death (hazard ratio [HR] 1.12, 95% CI 0.81 to 1.55).²³⁴ This study was designed as a noninferiority study, and noninferiority (equivalence) was achieved. This evidence is moderate strength.

Serious Gastrointestinal Adverse Events

In the *short term*, both study-level meta-analyses, and a published combination of individual patient data and standard meta-analysis found increased risk of serious gastrointestinal events with NSAIDs, with magnitude of risk varying by specific drug. A good-quality systematic review of 639 RCTs using a combination of individual patient data and standard meta-analysis found moderate to large increased risk of serious upper gastrointestinal harms compared with placebo (Table 9).²¹⁰ The analyses combined data on four selective COX-2 inhibitor drugs (“coxibs”), and the authors reported no evidence of a difference in effect according to the specific coxib used. Most of the events were gastrointestinal bleeds, 2 percent were fatal, and the findings were not affected by lower or higher risk at baseline for gastrointestinal events. The risk was greater in the first 6 months for coxibs (RR 2.55, 99% CI 1.49 to 4.35), diclofenac (RR 3.93, 99% CI 2.16 to 7.13), ibuprofen (RR 5.73, 99% CI 3.24 to 10.14), and naproxen (RR 6.31, 99% CI 3.81 to 10.44).

Our meta-analyses of study-level data from 13 RCTs are mostly consistent with these findings (Table 9),^{101,104,107,126,129,162,172,189,194,229,232,233,241} with the main difference being that our analysis did not find celecoxib to have increased risk. Subgroup analyses did not indicate a difference based on the patient having OA or RA, study quality, or NSAID dose. This evidence is low strength due to high heterogeneity ($I^2=73%$, Appendix I).

Table 9. Risk of serious gastrointestinal events by NSAID drug versus placebo

Drug	Meta-Analysis of Study-Level Events Relative Risk (95% CI, I^2)	Magnitude of Effect	Individual Patient Data Meta-Analysis ²¹⁰ Relative Risk (95% CI)	Magnitude of Effect
Coxibs	1.04 (0.67 to 1.54, $I^2=0%$) 4 RCTs, ^{101,107,126} N=4,399	None	1.81 (1.17 to 2.81)	Moderate
Diclofenac	3.07 (1.18 to 8.86, $I^2=0%$) 2 RCTs, ^{172,194} N=723,	Large	1.89 (1.16 to 3.09)	Moderate
Ibuprofen	3.60 (2.27 to 6.19, $I^2=0%$) 3 RCTs, ^{229,233,241} N=1,486	Large	3.97 (2.22 to 7.10)	Large
Meloxicam	1.65 (0.19 to 14.04, $I^2=NA$) 1 RCT, ¹⁶⁷ N=713	Moderate	No data	No data
Naproxen	6.02 (2.80 to 12.91, $I^2=44%$) 6 RCTs, ^{104,129,162,189,194,232} N=2,097	Large	4.22 (2.71 to 6.56)	Large

CI = confidence interval; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial

Comparing the selective COX-2 inhibitor celecoxib with nonselective NSAIDs as a group, evidence is mixed. In the *short term*, a Cochrane review analyzed four RCTs (N=1,755) directly

comparing celecoxib versus any nonselective NSAID in patients with OA with gastrointestinal perforation, obstruction, or bleeding.²¹¹ Their analysis found no difference between celecoxib and nonselective NSAIDs or placebo (OR 0.61, 95% CI 0.15 to 2.43, $I^2=38\%$). The authors rated this evidence as very low quality due to few events, concerns over missing data, and study limitations. Our meta-analysis of four *short-term* celecoxib versus placebo RCTs (N=4,399) resulted in a nonsignificant risk of serious gastrointestinal events (7.5% vs. 6.7%, RR 1.04, 95% CI 0.67 to 1.54, $I^2=0\%$) compared with the pooled analysis of diclofenac, ibuprofen, naproxen, and meloxicam (9 RCTs, N=4,448), which found a large increased risk of serious gastrointestinal events (13% vs. 3%, RR 4.29, 95% CI 2.75 to 6.93, $I^2=46\%$). These estimates were significantly different to each other (p-value for interaction <0.001). Because the evidence is inconsistent and imprecise, it is insufficient to draw conclusions. Finally, one additional fair-quality, *intermediate-term* RCT randomized 8,067 patients with OA to celecoxib or any nonselective NSAID for 6 months.²²⁶ Doses could be adjusted, and patients could switch nonselective NSAIDs. Nonselective NSAIDs had a moderately greater risk of clinically important gastrointestinal events than celecoxib (OR 1.82, 95% CI 1.31 to 2.55). This evidence is low strength.

Hepatic Adverse Events

A fair-quality systematic review evaluated the hepatic harms of NSAIDs (specifically diclofenac, naproxen, ibuprofen, meloxicam, celecoxib, rofecoxib, and valdecoxib) in RCTs of patients with OA or RA with duration of at least 4-weeks, published through 2004.²¹² This systematic review included 64 RCTs, primarily in patients with OA, and most were 6 months or longer in duration. Diclofenac was found to have a large increased incidence of elevated liver enzymes (aminotransferases more than three times the upper limit of normal) than placebo (3.55%, 95% CI 3.12 to 4.03 vs. 0.29%, 95% CI 0.17 to 0.51). Diclofenac also resulted in a large increase in liver-related discontinuations from treatment (2.17%, 95% CI 1.78 to 2.64) than placebo (0.08%, 95% CI 0.02 to 0.29). Liver enzyme elevations and liver-related discontinuations with diclofenac were elevated more with greater dose (>100 mg daily) and duration of treatment (>13 weeks). Liver-related SAEs were infrequent, but naproxen resulted the highest incidence (0.06%, 95% CI 0.02 to 0.15) compared with placebo (0.00%, 95% CI 0.00 to 0.08). One liver-related hospitalization and one liver-related death occurred, both with naproxen. A more recent systematic review with no criteria for study duration or population, but a composite outcome for hepatic injury, came to similar findings.²⁴⁶ This evidence is low strength.

Renal Adverse Events

No included study meeting inclusion criteria reported events of renal dysfunction or renal failure.

Pruritus

Three RCTs (N=1,129) reported on the incidence of pruritus with topical diclofenac, with the increase in risk not reaching statistical significance (1.22% vs. 0.18%, RR 3.84, 95% CI 0.82 to 18.09, $I^2=0\%$).^{108,140,141}

Other Drugs

Key Points

- In the *short* or *intermediate term*, acetaminophen was not found to increase SAEs or WAEs, and no differences were found between doses (SOE: Low). No evidence on hepatic harms was found in studies eligible for this review.
- In the *short term*, capsaicin 8% topical patch did not increase risk of SAEs or WAEs compared with an active placebo patch, but longer application duration (60 minutes) led to a moderate increase in SAEs compared with shorter duration (30 minutes). Capsaicin patch resulted in a large increased risk of application site pain and a moderate increased risk of erythema (no impact on pruritus) (SOE: Moderate for placebo comparisons; Low for dose comparisons).
- Cannabis: dronabinol oral solution did not increase SAEs, WAEs, or nausea, but dronabinol resulted in a large increase in dizziness. Oral THC/CBD spray resulted in large increases in WAEs, dizziness, and nausea, but no increase in SAEs or sedation (SOE: Low). Other adverse events of interest were not reported (cognitive effects, misuse, addiction, substance use disorder).

Detailed Assessment

Acetaminophen

In patients with chronic pain due to OA, three fair-quality RCTs (N=1,235) reported on adverse events from acetaminophen compared with placebo—two *short-term* and one *intermediate-term*.¹⁵⁹⁻¹⁶¹ These trials were industry funded and conducted in the United States, Spain, and Portugal. The weighted mean age of participants was 62 years (range 62 to 64 years), and the weighted mean proportion of female participants was 73 percent (range 67% to 86%). The race of participants was reported in two trials, each of which had a mean proportion of nonwhite participants of 18 percent.^{159,161} The strength of evidence for all outcomes is low.

Serious Adverse Events

At *short-term* followup, meta-analysis of two RCTs (N=1,023) found a higher incidence of SAEs with acetaminophen than placebo, an effect that was not statistically significant (2.4% vs. 0.9%, RR 2.57, 95% CI 0.60 to 10.8, $I^2=0\%$).^{159,161} One trial (N=318) found no meaningful difference in SAEs between 1950 mg daily versus 3900 mg daily of acetaminophen (1.9% vs. 1.9%, RR 1.01, 95% CI 0.21 to 4.94).¹⁵⁹ At *intermediate-term* followup in a single trial (N=212), there was no meaningful difference in SAEs between acetaminophen and placebo (4.6% vs. 4.8%, RR 0.96, 95% CI 0.29 to 3.23).¹⁶⁰

Withdrawals Due to Adverse Events

Acetaminophen did not result in an increase in WAEs compared with placebo in the *short* or *intermediate term*. At *short-term* followup, meta-analysis of two RCTs (N=1,023) found no meaningful difference in WAEs between acetaminophen and placebo (7.4% vs. 7.1%, RR 1.14, 95% CI 0.67 to 1.95, $I^2=0\%$).^{159,161} One trial (N=318) found no meaningful difference in WAEs between 1950 mg and 3900 mg daily of acetaminophen (6.3% vs. 5.0%, RR 1.27, 95% CI 0.51 to 3.12).¹⁵⁹ At *intermediate-term* followup in a single trial (N=212), acetaminophen was

associated with a slightly greater proportion of WAEs compared with placebo, a difference that was not statistically significant (11.1% vs. 8.7%, RR 1.28, 95% CI 0.56 to 2.92).¹⁶⁰

Hepatic Events

No evidence was found in studies eligible for this review.

Topical Capsaicin

In patients with chronic neuropathic pain, three *short-term* RCTs (N=1,051) reported on adverse events from capsaicin 8% topical patch compared with active placebo (0.04% patch).^{26,32,53} These RCTs were industry funded and conducted in the United States, Canada, the United Kingdom, and Australia; one trial did not report where it was conducted.⁵³ One trial was rated as good quality²⁶ and two were rated as fair quality.^{32,53} The weighted mean age of participants was 61 years (range 50 to 71 years), the weighted mean proportion of female participants was 34 percent (range 13% to 54%), and the weighted mean proportion of nonwhite participants was 20 percent (range 8% to 30%). The strength of evidence for all outcomes compared with placebo was moderate; evidence for dose comparisons is low.

Serious Adverse Events

At *short-term* followup, meta-analysis of three RCTs (N=1,051) found a greater proportion of SAEs reported in patients treated with capsaicin patch compared with placebo, an effect that was not statistically significant (5.6% vs. 3.6%, RR 1.32, 95% CI 0.71 to 3.47).^{26,32,53} One of these RCTs (N=332) compared two different durations of application of a capsaicin patch – 60 minutes versus 30 minutes – and found the 60-minute application to result in a moderately increased risk of SAEs (24% vs. 11.4%, RR 1.76, 95% CI 1.11 to 2.80).³²

Withdrawals Due to Adverse Events

At *short-term* followup, meta-analysis of two RCTs (N=896) found no difference in WAEs between capsaicin patch and placebo (0.4% vs. 0.3%, RR 1.04, 95% CI 0.08 to 17.1).^{26,32} One of these RCTs (N=332) compared two different durations of application of a capsaicin patch – 60 minutes versus 30 minutes – and found no significant difference in WAEs (0.6% vs. 0.0%, RR 3.04, 95% CI 0.13 to 74.00).³²

Specific Adverse Events

Based on meta-analysis of three *short-term* RCTs, capsaicin patch resulted in a moderate increased risk of erythema (58% vs. 45%, RR 1.46, 95% CI 1.29 to 1.66, I²=0%). There was a large increase in pain at the application site with capsaicin (61% vs. 26%, RR 2.26, 95% CI 1.81 to 2.82, I²=0%). There was not a difference between groups in pruritus (6.1% vs. 3.4%, RR 1.70, 95% CI 0.92 to 3.35, I²=0%).^{26,32,53}

Cannabis

Cannabis (including derivatives and synthetic cannabinoids) was compared with placebo in two *short-term* trials (N=486).^{28,47} The trials utilized oral dronabinol solution (mean 13 mg daily) and THC/CBD oromucosal spray (100 mL per spray, up to 24 sprays daily). One trial was rated good quality²⁸ and the other fair quality.⁴⁷ A third trial was rated poor quality due to unclear randomization and allocation concealment, between-group differences at baseline, and high rates of attrition; results from that trial are not included here.⁶² The adverse event profiles for the two different formulations varied and are reported separately.

In a good-quality study (N=240) there was no difference between dronabinol oral solution and placebo in the incidence of SAEs, WAEs, or nausea, but dronabinol had a large effect on the incidence of dizziness (20% vs. 4.3%, calculated RR 4.68, 95% CI 1.85 to 11.8).²⁸ In a fair-quality study (N=246), there was no difference between an oral spray with THC/CBD compared with placebo in SAEs or the incidence of sedation, but there were large differences in the incidence of WAEs (19% vs. 6%, calculated RR 3.16, 95% CI 1.41 to 7.06), dizziness (39% vs. 9%, calculated RR 4.55, 95% CI 2.48 to 8.32) and nausea (17% vs. 8%, calculated RR 2.25, 95% CI 1.8 to 4.70).⁴⁷ The strength of this evidence is low. Other adverse events of interest were not reported (cognitive effects, misuse, addiction, substance use disorder).

Topical Lidocaine

A single *short-term* study of lidocaine 5% patch compared with celecoxib in patients with knee OA (N=143) was poor quality (unclear allocation concealment, no blinding, high attrition; 46%), and stopped early due to the withdrawal of celecoxib from the market at that time.¹¹⁴ This evidence is insufficient to draw conclusions.

Skeletal Muscle Relaxants

A fair-quality, *intermediate-term* (6-month) RCT of fibromyalgia patients (N=208) compared amitriptyline, the skeletal muscle relaxant cyclobenzaprine, and placebo.⁷⁸ Thirteen of 82 patients (16%) assigned to cyclobenzaprine withdrew from study due to adverse events, compared with 2 of 42 patients (5%) taking placebo. Serious adverse events were not reported. Somnolence was the reason for discontinuing in three patients (3.7%) with cyclobenzaprine, versus one patient (2.4%) with placebo. Dizziness was reported in five (6.1%) and one patient (2.4%), respectively. Additional patients withdrew due to abdominal pain (3 patients, 3.7%), rash, and headache (1 patient each, 1.2%) with cyclobenzaprine. Due to study limitations, unknown consistency and limited events (imprecision), this evidence was insufficient to draw conclusions regarding adverse event outcomes.

Memantine

Two small RCTs included memantine, an NMDA receptor antagonist approved for Alzheimer's dementia, compared with placebo.^{46,90} A *short-term* fair-quality RCT (N=45) in patients with HIV-related neuropathy did not report adverse events in a specific way, noting only that there were no differences seen.⁴⁶ A good-quality, *intermediate-term* (6-month) RCT (N=63) in patients with fibromyalgia also poorly reported adverse events. Two of 31 patients assigned to memantine (6%) compared with 1 of 32 (3%) withdrew from the study due to adverse events, and it was reported that there were no serious adverse events. Dizziness occurred in eight patients on memantine (25.8%) versus four patients on placebo (12.5%). Sedation (drowsiness) was reported in no patients taking memantine, and two taking placebo (6%). None of these findings were statistically significantly different. This evidence was insufficient to draw conclusions as the studies were small (very imprecise findings) with unknown consistency or publication bias.

Discussion

Key Findings and Strength of Evidence

The key findings of this review are summarized in Tables 10 to 17 and in Appendix H. (See Table 2 for definitions of effect sizes and Table 3 for descriptions of strength of evidence grades.) This review evaluates and synthesizes the evidence on benefits and harms of nonopioid drugs in patients with chronic noncancer pain. The pain conditions included were neuropathic pain, fibromyalgia, osteoarthritis, inflammatory arthritis, low back pain, chronic headache, and sickle cell disease. Drugs reviewed included antidepressants (serotonin-norepinephrine reuptake inhibitors [SNRIs] and tricyclic antidepressants [TCAs]), anticonvulsants (pregabalin, gabapentin, oxcarbazepine, and carbamazepine), nonsteroidal anti-inflammatory drugs (NSAIDs), and other drugs such as acetaminophen, capsaicin, and cannabis. The review included randomized controlled trials (RCTs) of at least 3 months duration, and categorizes findings according to duration of study, magnitude of the findings, and the strength of the evidence for each finding. Interventions or comparisons for which all evidence was insufficient to draw conclusions are not included in the tables below, but details can be found in the report results (above).

In patients with neuropathic pain, in the short term, the anticonvulsant drugs gabapentin, pregabalin, and oxcarbazepine provided small improvement in pain outcomes in patients with diabetic peripheral neuropathy/postherpetic neuralgia, but not function in postherpetic neuralgia or quality of life in HIV- or diabetes-associated neuropathy. In patients with diabetic peripheral neuropathy, duloxetine resulted in small improvements in pain, function, quality of life. Capsaicin patch did not have improvements in pain severity or response that were both significant and reached the level of a small effect in postherpetic neuralgia and HIV-related neuralgia. Cannabis (dronabinol oral solution, tetrahydrocannabinol/cannabidiol [THC/CBD] oral spray) had no effect on pain severity in multiple sclerosis-associated neuropathy or allodynia, but THC/CBD oral spray improved pain response to a moderate degree in patients with allodynia. Differences in pain improvement was not seen between drugs.

In patients with fibromyalgia, in the short and intermediate term, antidepressants resulted in small improvements in pain and mixed findings on quality of life. Function improved to a small degree in the short term, but not in the intermediate term. Short-term treatment with anticonvulsants (pregabalin and gabapentin) is associated with small improvements in pain and function, but not quality of life. Subgroup analyses showed no effect of specific drug, dose, or study quality on these results. Intermediate-term treatment with memantine resulted in moderate improvements in pain, function, and quality of life compared with placebo.

Oral NSAIDs improved pain and function in patients with osteoarthritis (OA) to a small degree in the short term, with evidence indicating these effects are maintained in the intermediate term for celecoxib. Subgroup analyses indicated that studies of only patients with knee pain and those of good quality had smaller effects, while patients with more severe pain at baseline experienced greater reduction in pain. Direct comparisons of NSAIDs with each other found few differences between drugs in pain or function in OA patients in the short, intermediate, or long term. Small improvements were seen in pain severity and response with topical diclofenac, but not function. The SNRI antidepressant duloxetine resulted in moderate effects on pain response, and small effects on pain severity, function, and quality of life. Subgroup analyses found that pain improvement was greater in older patients (>65 years) and patients with knee osteoarthritis. Acetaminophen did not improve pain significantly in the short or intermediate term. In patients

with rheumatoid arthritis or ankylosing spondylitis, short-term treatment with oral NSAIDs resulted in small improvements in pain severity, pain response, and function, but evidence on quality of life was inconsistent. Evidence on intermediate- and long-term outcomes was limited to one trial each, with improvements in pain but not function. Comparisons of different doses or between different NSAIDs did not find important differences. Subgroup analyses of specific drug, dose, year of publication, type of inflammatory arthritis, and study quality did not alter the findings meaningfully. The TCA amitriptyline did not improve pain outcomes. Evidence in patients with chronic headache or sickle cell disease was too limited to draw conclusions.

Serious adverse events were not reported more often with nonopioid drugs than placebo in patients with chronic pain, with the exception of oxcarbazepine and with longer duration capsaicin patch (compared with shorter duration). Withdrawal due to adverse events was increased significantly with anticonvulsants, antidepressants, NSAIDs, and cannabis oral spray, ranging from a small increase to large increases. SNRI antidepressants resulted in increased reports of nausea (dose did not alter these findings). Duloxetine also resulted in increased sedation, but lower doses did reduce the risk. Amitriptyline led to a moderate increase in reports of dry mouth, but other adverse events of interest were not reported or not different to placebo. There were no reports of serotonin syndrome in any included RCT of antidepressants. In the short term, pregabalin and gabapentin resulted in moderate to large increases in blurred vision, dizziness, weight gain, and cognitive effects (e.g., confusion). As a prodrug of gabapentin, gabapentin enacarbil may have lower risk of blurred vision, weight gain, or cognitive effects. Additionally, pregabalin resulted in large increases in risk of peripheral edema and sedation. In the short term, the risk of any cardiovascular event was not significantly elevated for NSAIDs as a group, although there was a small increase in risk with diclofenac, particularly within the first 6 months, and with higher doses; risk was increased to a similar degree with ibuprofen and celecoxib but did not reach statistical significance. Although the absolute risk is low, there was a moderate relative increased risk of major coronary events with diclofenac and celecoxib, and a large increase with ibuprofen. In the intermediate term, there was not a difference in cardiovascular events between drugs. NSAIDs led to moderate to large increased risk of serious upper gastrointestinal events (largely bleeding), particularly in the first 6 months of treatment. In the intermediate term, although the incidence was low, large increases in hepatic harms were seen with diclofenac and naproxen. Dronabinol oral solution resulted in a large increase in dizziness and THC/CBD oral spray resulted in large increases in dizziness and nausea. Other adverse events of interest were not reported (cognitive effects, misuse, addiction, substance use disorder).

Table 10. Key Question 1 – Effectiveness and comparative effectiveness of nonopioid drugs for chronic pain: effects of antidepressants in placebo-controlled and head-to-head trials

Condition	Drug	Pain Short Term Effect Size SOE	Pain Intermediate Term Effect Size SOE	Function Short Term Effect Size SOE	Function Intermediate Term Effect Size SOE	QoL Short Term Effect Size SOE	QoL Intermediate Term Effect Size SOE
Neuropathic pain	Duloxetine vs. placebo	Small ++	No evidence	Small +	No evidence	Small ++	No evidence
Fibromyalgia	Duloxetine/milnacipran vs. placebo	Small ++	Small ++	Small ++	None ++	MCS: Small ++ PCS: None ++	Small ++
Osteoarthritis	Duloxetine vs. placebo	Small +++	No evidence	Small +++	No evidence	Small +++	No evidence
Low back pain	Duloxetine vs. placebo	Small ++	No evidence	None ++	No evidence	None ++	No evidence
	Amitriptyline vs. placebo	No evidence	None +	No evidence	None +	No evidence	No evidence
	Amitriptyline vs. pregabalin	Small +	No evidence	None +	No evidence	No evidence	No evidence

QoL = quality of life; SOE = strength of evidence

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk

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

Table 11. Key Question 2 – Harms and adverse events of nonopioid drugs for chronic pain: harms of antidepressants versus placebo

Types of Adverse Events	SNRIs (Duloxetine/Milnacipran)	SNRIs (Duloxetine/Milnacipran)	TCAs	TCAs
	Short Term Effect Size SOE	Intermediate Term Effect Size SOE	Short Term Effect Size SOE	Intermediate Term Effect Size SOE
WAE	Moderate ++	Moderate ++	None +	Insufficient
SAE	None +	None +	No evidence	No evidence
Cognitive effects	None +	No evidence	No evidence	No evidence
Nausea	Large ++	Moderate +	NA	NA
Sedation	Large ++	Large +	NA	NA
Serotonin syndrome	No evidence	No evidence	No evidence	No evidence
Dry mouth	NA	NA	Insufficient	No evidence
Cardiac rhythm abnormalities	NA	NA	No evidence	No evidence
Urinary retention	NA	NA	No evidence	No evidence

NA = not applicable (i.e., specific adverse event not applicable to drug); SAE = serious adverse event; SOE = strength of evidence; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; WAE = withdrawal due to adverse event

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk

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

Table 12. Key Question 1 – Effectiveness and comparative effectiveness of nonopioid drugs for chronic pain: effects of anticonvulsants in placebo-controlled and head-to-head trials

Condition	Drug	Pain	Function	QoL
		Short Term Effect Size SOE	Short Term Effect Size SOE	Short Term Effect Size SOE
Neuropathic pain	Pregabalin / Gabapentin vs. Placebo	Small ++	None +	None +
	Oxcarbazepine vs. Placebo	Small ++	No evidence	None +
	Pregabalin vs. Gabapentin	Insufficient	No evidence	No evidence
	Pregabalin vs. Gabapentin Enacarbil ^a	None +	None +	None +
Fibromyalgia	Pregabalin / Gabapentin vs. Placebo	Small ++	Small ++	None ++

QoL = quality of life; SOE = strength of evidence

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large. SOE: + = low, ++ = moderate, +++ = high.

^aGabapentin enacarbil is a prodrug of gabapentin.

Table 13. Key Question 2 – Harms and adverse events of nonopioid drugs for chronic pain: harms of anticonvulsants versus placebo and active comparator

Types of Adverse Events	Pregabalin/Gabapentin Short Term Effect Size SOE	Oxcarbazepine Short Term Effect Size SOE
WAE	Moderate ++	Large +
SAE	None +	None +
Blurred vision	Large +	NA
Cognitive effects	Large +	No evidence
Dizziness	Large ++	NA
Peripheral edema	Large ++	NA
Sedation	Large ++	None +
Weight gain	Large ++	NA
Hyponatremia	NA	None +

NA = not applicable (i.e., specific adverse event not applicable to drug); SAE = serious adverse event; SOE = strength of evidence; WAE = withdrawal due to adverse event

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk

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

^aGabapentin enacarbil is a prodrug of gabapentin.

Table 14. Key Question 1 – Effectiveness and comparative effectiveness of nonopioid drugs for chronic pain: effects of NSAIDs in placebo-controlled and head-to-head trials

Condition	Drug	Pain Short Term Effect Size SOE	Pain Intermediate Term Effect Size SOE	Pain Long Term Effect Size SOE	Function Short Term Effect Size SOE	Function Intermediate Term Effect Size SOE	Function Long Term Effect Size SOE	QoL Short Term Effect Size SOE
Osteoarthritis	NSAID vs. placebo	Small ++	No evidence	No evidence	Small +++	No evidence	No evidence	None ++
	Diclofenac vs. celecoxib	Moderate +	No evidence	No evidence	Moderate +	No evidence	No evidence	No evidence
	NSAID vs. NSAID	None +	None +	None +	None +	None +	No evidence	No evidence
	Topical diclofenac vs. placebo	Small ++	No evidence	No evidence	None +	No evidence	No evidence	No evidence
Inflammatory arthritis	NSAID vs. placebo	Small/Moderate ++	Small +	Large +	Small ++	Small +	None +	Insufficient
	Celecoxib vs. diclofenac	None ++	No evidence	No evidence	None ++	No evidence	No evidence	No evidence
	Celecoxib vs. naproxen	None +	No evidence	No evidence	None +	No evidence	No evidence	None +
	Diclofenac vs. meloxicam	None +	No evidence	No evidence	None +	No evidence	No evidence	No evidence
	Meloxicam vs. naproxen	No evidence	None +	No evidence	No evidence	No evidence	No evidence	No evidence
	Nabumetone vs. naproxen	None +	None +	No evidence	None +	No evidence	No evidence	No evidence

NSAID = nonsteroidal anti-inflammatory drug; QoL = quality of life; SOE = strength of evidence
 Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk
 SOE: + = low, ++ = moderate, +++ = high

Table 15. Key Question 2 – Harms and adverse events of nonopioid drugs for chronic pain: harms of NSAIDs versus placebo and active comparators

Types of Adverse Events	NSAID Short Term Effect Size SOE	NSAID Intermediate Term Effect Size SOE	NSAID Long Term Effect Size SOE	Topical Diclofenac vs. Placebo Short Term Effect Size SOE	nsNSAID vs. Celecoxib Intermediate Term Effect Size SOE	nsNSAID vs. Celecoxib Long Term Effect Size SOE
WAE	Small ++	None +	Insufficient	None +	No evidence	No evidence
SAE	None +	Insufficient	No evidence	None +	No evidence	No evidence
Cardiovascular events	Small ++	No evidence	No evidence	No evidence	None ++	None ++
Gastrointestinal events	Moderate +/++	No evidence	No evidence	No evidence	Moderate +	No evidence
Liver dysfunction	Large +	No evidence	No evidence	No evidence	No evidence	No evidence

NSAID = nonsteroidal anti-inflammatory drug; nsNSAID = nonselective nonsteroidal anti-inflammatory drug; SAE = serious adverse event; SOE = strength of evidence; WAE = withdrawal due to adverse event

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk

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

Table 16. Key Question 1 – Effectiveness and comparative effectiveness of nonopioid drugs for chronic pain: effects of other drugs in placebo-controlled trials

Condition	Drug	Pain Short Term Effect Size SOE	Pain Intermediate Term Effect Size SOE	Function Short Term Effect Size SOE	Function Intermediate Term Effect Size SOE	QoL Short Term Effect Size SOE	QoL Intermediate Term Effect Size SOE
Neuropathic pain	Capsaicin patch	None ++	No evidence	No evidence	No evidence	No evidence	No evidence
	Cannabis	None +	No evidence	None +	No evidence	None +	No evidence
Fibromyalgia	Memantine	No evidence	Moderate +	No evidence	Moderate +	No evidence	Moderate +
	Cyclobenzaprine	No evidence	None +	No evidence	Insufficient	No evidence	No evidence
Osteoarthritis	Acetaminophen	None +	None +	None +	None +	No evidence	No evidence

QoL = quality of life; SOE = strength of evidence

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk

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

Table 17. Key Question 2 - Harms and adverse events of nonopioid drugs for chronic pain: harms of other drugs versus placebo

Types of Adverse Events	Capsaicin Short Term Effect Size SOE	Dronabinol Short Term Effect Size SOE	THC + CBD Short Term Effect Size SOE	Acetaminophen Short Term Effect Size SOE	Acetaminophen Intermediate Term Effect Size SOE	Cyclobenzaprine Intermediate Term Effect Size SOE
WAE	None ++	None +	Large +	None +	None +	None +
SAE	None ++	None +	None +	None +	None +	No evidence
Application site erythema	Moderate ++	NA	NA	NA	NA	NA
Application site pain	Large ++	NA	NA	NA	NA	NA
Application site pruritus	None ++	NA	NA	NA	NA	NA
Cognitive effects	NA	No evidence	No evidence	NA	NA	NA
Hyperemesis	NA	No evidence	No evidence	NA	NA	NA
Nausea	NA	None +	Large +	NA	NA	NA
Sedation	NA	No evidence	Insufficient	NA	NA	Insufficient
Dizziness	NA	Large +	Large +	NA	NA	Insufficient

CBD = cannabidiol; SAE = serious adverse event; SOE = strength of evidence; THC = tetrahydrocannabinol; WAE = withdrawal due to adverse event

Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk

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

Findings in Relationship to What Is Already Known

This systematic review combines evidence across multiple pain conditions and multiple drug classes in a way that prior reviews have not. Prior reviews generally had dissimilar scope (e.g., limited to a single condition and/or drug class, included drugs or populations not included here), included very short duration studies (<12 weeks), did not classify results according to treatment duration, and did not categorize effect sizes (small, moderate, large). Although our review includes more recent studies, other reviews of individual drugs, drug classes, or pain conditions have reviewed some of the evidence included here, and where comparisons of our results and prior findings are possible, they are generally consistent. For example, a 2015 systematic review with network meta-analysis of acetaminophen, NSAIDs, and injectable drugs for knee OA found a standardized mean difference (SMD) for acetaminophen of 0.18, and we found the mean difference (MD, 0-10 scale) was 0.34. Both are less than a small magnitude of effect according to our system, and the prior review noted that the effect did not reach clinical significance in their system.²⁴⁷ Findings for NSAIDs were similar to ours, and our subgroup analysis of only knee OA was also in a similar range of magnitude of effect to their findings. The exception was that they found a moderate-size effect with diclofenac, while our subgroup analysis of specific drug was not significant. For neuropathic pain, a 2017 systematic review of only diabetic peripheral neuropathy found duloxetine to have large effect (SMD -1.33), but when we added another study the magnitude was reduced to small (MD -0.79, 0-10 scale).²⁴⁸ This review and ours had similar findings for pregabalin (small effect). Both reviews found that the effect of gabapentin was not significant, but the effect was moderate in the older review, while our effect was small after incorporating additional studies. In fibromyalgia, a 2016 systematic review with a network meta-analysis found a large magnitude of effect in pain response with SNRI antidepressants (odds ratio [OR] 1.61 to 2.33) while we found a moderate effect (relative risk [RR] 1.29 to 1.36), and the prior review found a moderate effect with pregabalin (OR 1.68) while we found a small effect with pregabalin and gabapentin combined (RR 1.41).²⁴⁹ Differences in magnitude could be due to the addition of 15 studies in our report, reporting relative risks rather than odds ratios, and using direct comparisons rather than network analysis. Our findings regarding the effects of nonopioid drugs on pain and function are also consistent with two related systematic reviews on opioids and nonpharmacologic treatments for chronic pain, which found similar small effects.^{250,251}

In terms of evidence on the harms of the drugs included, because many of the drugs have been available for decades (e.g., acetaminophen), were initially approved for other indications (e.g., antidepressants and anticonvulsants), or primarily studied in acute pain and short-term treatment (e.g., acetaminophen, topical lidocaine), our findings on adverse events are not comprehensive relative to other, nonsystematic review sources (e.g., product labels, large observational studies, U.S. Food and Drug Administration [FDA] warnings, drug information texts). However, as Table 18 indicates, our analyses on adverse events are consistent with these other sources.

Table 18 provides a summary of the evidence on adverse events of interest that were identified in RCTs of patients with chronic pain meeting inclusion criteria for this review. Because the scope of this review focused on a specific patient population (chronic pain with specific conditions), a specific study design (RCTs), and study duration (12 weeks or more), it is unlikely that all important evidence on harms of these drugs would be identified. Where included evidence did not adequately address the prioritized harms, information from other sources is summarized. The evidence from other sources may have unclear applicability to patients with

chronic pain, who may use these drugs for longer periods of time, possibly at higher doses, and who may be older (in some cases) or have more comorbidities than patients providing data for these sources.

Table 18. Summary of specific adverse events

Drug Class	Drug	Outcomes of Interest	Adverse Event Findings From RCTs in Chronic Pain (Magnitude of Effect)	Adverse Event Findings From Other Sources (To Address Missing Evidence)
Antidepressants	SNRIs	Nausea, sedation, serotonin syndrome	Nausea (moderate-to-large, no dose effect), sedation (duloxetine, dose-related), serotonin syndrome symptoms (large)	No missing outcomes
	TCA s	Cardiac rhythm abnormalities, dry mouth, urinary retention, weight gain, serotonin syndrome	Dry mouth (moderate)	Cardiac arrhythmias and sinus tachycardia: increases with higher dose and pre-existing risk Urinary retention: no estimate found Weight gain: 2-2.5kg over 3 months Serotonin syndrome: very rare ²⁵²
Antiepileptic drugs	Pregabalin, gabapentin	Blurred vision, cognitive effects, dizziness, peripheral edema, sedation, weight gain	Blurred vision, dizziness, weight gain, and cognitive effects (moderate to large, lower with the prodrug gabapentin enacarbil) Peripheral edema (large with pregabalin)	No missing outcomes
	Oxcarbazepine	Cognitive effects, hyponatremia, and sedation	Hyponatremia – 1 RCT, no increased risk	Significant hyponatremia: 2.5%, occurs in first 3 months. Cognitive effects: 7-11% Somnolence: 35% ²⁵³
NSAIDs	Oral NSAIDs	CV, GI, renal, and hepatic events	Short term: Increased CV risk - diclofenac (small, dose-dependent); increased coronary events - diclofenac, celecoxib (moderate), ibuprofen (large); Increased GI events – diclofenac (moderate), ibuprofen, naproxen (large); Intermediate term: Differences in CV risk unclear; Increased hepatic harms- diclofenac, naproxen (large, low incidence)	Renal: Increased risk (moderate to large), higher in older patients and those with chronic kidney disease (evidence from observational studies, includes short-term use) No difference found between NSAIDs. ^{254,255}
Other	Acetaminophen	Hepatotoxicity	Not reported in included RCTs	Increased risk with chronic use of >3gms daily, effects often occur early in treatment; dose-adjustment if hepatic or renal dysfunction ^{256,257}
	Cannabis	Addiction/dependence, cognitive effects, hyperemesis, nausea, sedation	Dizziness (large) Nausea (THC/CBD oral spray, large)	Hyperemesis syndrome: Case reports (not limited to medical uses), >1x/week for >2 years. Cognition: small negative impact with chronic use Addiction/dependence: not found ²⁵⁸
	Capsaicin	Application site reactions	Pain (large), erythema (small) Greater with longer application	No missing outcomes

CBD = cannabidiol; CV = cardiovascular; GI = gastrointestinal; kg = kilogram; NSAIDs = nonsteroidal anti-inflammatory drugs; RCTs = randomized controlled trials; SNRIs = serotonin-norepinephrine reuptake inhibitor; TCAs = tricyclic antidepressants; THC = tetrahydrocannabinol

In relation to existing guidelines relating to treating chronic pain, our review findings differ in some respects. While the 2016 Center for Disease Control and Prevention (CDC) *Guideline for Prescribing Opioids for Chronic Pain* recommends nonopioid therapy for the treatment of chronic pain, specific recommendations were not within the scope of the guideline.¹³ Prior guidelines that made specific recommendations on nonopioid treatments commonly recommended acetaminophen among the first-line treatments,^{259,260} while our review findings do not demonstrate that acetaminophen provided adequate pain relief to qualify as a small effect size. Similarly, guidelines on treating fibromyalgia recommended drugs we found to have insufficient evidence of effectiveness or to have inadequate pain relief (e.g., cyclobenzaprine, amitriptyline -although some are weak/low-level recommendations), and are either missing some drugs included in our review that have evidence of small or moderate effects (e.g., milnacipran) or recommended a class of drugs for which we found disparate results for specific drugs in the class (anticonvulsants).²⁶¹ While guidelines on treating neuropathic pain do recommend drugs found effective in this review, they also include recommendations for medications not found to have evidence of effectiveness.²⁶²

Applicability

The applicability of the evidence base for nonopioid drugs to treat chronic pain varies according to the pain population and intervention studied. In terms of patient populations studied, the participants were generally typical for each pain condition (with the possible exception of chronic headache). For example, the mean age of participants with neuropathic pain was 58, most had painful diabetic peripheral neuropathy, 43 percent were female, and 34 percent were nonwhite and had a mean baseline pain of 6 to 7 (on a 0-10 scale) and a 4-year duration of pain. Fibromyalgia patients were younger, with a mean of 49 years, most (94%) were female, and only 15 percent were nonwhite. Mean baseline pain was again 6 to 7 (on a 0-10 scale), with duration of pain ranging from less than a year in three RCTs, and 5 to 13 years in the rest. In osteoarthritis and inflammatory arthritis, mean age was 63 and 52 years, 68 percent and 63 percent were female, 24 percent and 12 percent were nonwhite, respectively. Mean baseline pain was 63 to 72 (osteoarthritis) and 65 (inflammatory arthritis) on a 0-100 visual analog scale (VAS), and duration of pain was typically not reported for patients with osteoarthritis, but a mean of 10 years was reported for inflammatory arthritis patients studied. Twenty-five percent of patients in the section on inflammatory arthritis had ankylosing spondylitis. Although there were few RCTs of patients with low back pain, mean age was 49 years, 42 percent were female, and 30 percent were nonwhite. Across 7 RCTs, baseline pain was lower than in other pain conditions, with a mean of 5 on a 0-10 scale, and a median duration of 10 years. Because our definition of chronic headache was broad, and our criteria for treatments excluded use of nonopioids for prophylaxis, the result was a single, older, study of amitriptyline in patients with “chronic tension-type headache.” Headache classification has changed over the years such that the evidence identified may not be highly applicable to current patients or treatment strategies. While some RCTs excluded patients with mental illness, most did not report on baseline characteristics in relation to mental health, prior use of opioids, substance use disorder, etc.

Similarly, the specific interventions studied varied according to the pain condition. The medications studied in patients with neuropathic pain and fibromyalgia were most often antidepressants (primarily duloxetine) and anticonvulsants (primarily pregabalin), with some evaluations of other categories such as capsaicin and cannabis in neuropathic pain and memantine in both conditions. In contrast, osteoarthritis and inflammatory arthritis studies

involved primarily NSAIDs. In patients with osteoarthritis, a small number of studies evaluated topical diclofenac, duloxetine, and acetaminophen. As a result, we have little or no information on how some interventions that were found effective in one pain condition may work in another pain condition. An example is that the evidence on pregabalin and gabapentin is applicable mainly to patients with specific types of neuropathic pain and fibromyalgia, but not applicable to patients with osteoarthritis or rheumatoid arthritis, or other type of chronic pain. The reverse is true of NSAIDs in that the evidence is restricted to osteoarthritis or rheumatoid arthritis/ankylosing spondylitis. The use of co-medications was rarely reported; acetaminophen use as a rescue medication in trials of NSAIDs was the only co-medication reported. As such, it is unclear how applicable this evidence is to patients using co-medications, including intermittent use of over-the-counter medications.

For all pain conditions, the most common comparator in the RCTs was placebo (114 out of 154 RCTs of good or fair quality), with limited head-to-head comparisons, especially across classes (7 RCTs). The most common head-to-head comparison was among different NSAIDs in patients with osteoarthritis (36 RCTs). The specific outcomes assessed in the included RCTs also varied according to the pain condition studied. Specific pain and function measures developed for specific conditions were used, for example the Fibromyalgia Impact Scale (FIQ) in fibromyalgia, the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) in osteoarthritis, and the American College of Rheumatology (ACR) criteria for swollen and painful joints in rheumatoid arthritis. In our analyses, these were standardized where studies reported outcomes with scales of differing directions, ranges, etc. Other outcomes also varied according to pain condition, for example, sleep was reported most often for neuropathic pain, and depression was reported most often in studies of patients with fibromyalgia. To facilitate interpretation of results across trials and interventions, we categorized the magnitude of effects for function and pain outcomes using the system described in the Methods and used in two related systematic reviews.^{250,251} Using this system, beneficial effects identified were generally in the small or moderate range. We recognize that effects that we classified as small (e.g., 0.5 to 1.0 points on a 0 to 10 scale for pain or function) may be below some proposed thresholds for minimum clinically important differences for some measures and that there is variability across individual patients regarding what may constitute a clinically important effect, which is influenced by a number of factors such as preferences, duration and type of chronic pain, baseline symptom severity, harms, and costs. However, our classification provides some consistent and objective benchmarks to assess magnitude of smaller effects across trials and interventions. Interpretation of clinically important differences in mean change for continuous variables is challenging. If data were provided, we also evaluated the proportion of patients who experienced a clinically important improvement in pain or function (primarily at least a 30% improvement from baseline). This provides valuable insight regarding clinically important improvement. The outcomes reported here apply mostly to the short term – 12 to 24 months of treatment. The applicability of the study settings is very unclear, as few studies reported setting characteristics. It was not apparent that the setting was specifically in pain clinics, but given the study design (RCT) and the high proportion with industry funding (>80%), it is likely that the setting was tertiary care clinics.

All of these elements affect how applicable the findings of this review are to a given, specific, patient. The evidence is less applicable to patients older than early 70's, those with severe pain, nonwhite patients, and for most conditions, patients with more recent onset of pain. The results apply mostly to addressing whether a drug is effective and/or harmful in comparison

to no treatment, but less applicable to selecting among nonopioid treatments. However, the evidence base does provide some information on dose comparisons, such as higher and lower doses of SNRI antidepressants, pregabalin and gabapentin anticonvulsants, and some of the NSAIDs, where our analyses found little differences in efficacy, and a few cases of lower risk of adverse events with lower doses of antidepressants.

Implications for Clinical and Policy Decision Making

Recent guidelines from the CDC in the United States and the Canadian Guideline for Opioid Use in Chronic Non-Cancer Pain recommend nonopioid treatment as the preferred treatment for chronic pain.^{13,263} As noted above, many clinical practice guidelines recommend nonopioid treatments that may not provide adequate pain relief or improve functioning, while there are alternatives available. Our review provides evidence that can be used to update these clinical practice guidelines on treating the specific, common, chronic pain conditions included in this review. Given the need to offer nonopioid options to patients with chronic pain, especially in patients who wish to avoid an opioid, have or are at risk of developing opioid use disorder, this evidence is timely. Importantly, our review can inform guideline producers on the balance of benefits and harms, in the short, intermediate, and longer term.

Our report reviewed evidence that may also help inform decisions regarding prioritization of nonopioid drug therapies by clinicians and patients when selecting therapy. The evidence reviewed here may also help inform healthcare policy (including reimbursement policy) related to coverage of these nonopioid treatments, and inform policy decisions regarding funding priorities for future research.

Limitations of the Review Process

Limitations of our review process include that we excluded non-English language publications, and study results published only as abstract. We had limited ability to assess publication bias (small sample size bias), as most of our meta-analyses included fewer than 10 studies. We did not search clinical trial registries to identify unpublished trial results, but referred to study results reported in ClinicalTrials.gov when variance data were not reported in the trial publication. Another limitation was that we restricted inclusion to RCTs, limited to monotherapy, and limited the trials to those with at least 12 weeks of treatment. We could have missed effects reported only in shorter-term trials. This may have affected some older drugs (e.g., acetaminophen) more than others. Excluding observational studies may have meant not identifying serious harms of included drugs, or getting more precise estimates on these harms. We included information on such harms from other sources in Table 18 to complement our findings. For some of the drugs, there may be emerging concerns that were not prioritized here, such as misuse of, development of substance use disorder, or withdrawal symptoms associated with gabapentin or pregabalin, nonliver related harms of acetaminophen, and harms of drugs in older adults found in studies in other indications (not chronic pain).²⁶⁴⁻²⁶⁷ The effects of coprescribing gabapentin with opioids is not within the scope of this report, but is addressed in the related report on opioid use in chronic pain.²⁵⁰ We did not have access to individual patient data, which limited our ability to evaluate subgroup effects. Some meta-analyses were based on two or three trials; findings based on such meta-analyses must be interpreted with caution.

We did not include trials of patients with chronic pain conditions other than those specified. Our definition of chronic headache was broad, and may not align with currently used definitions of headache. Additionally, we excluded studies of prophylaxis of headache, which use many of

the same drugs included in this review. Using these criteria, we included only one RCT, which did not find amitriptyline effective in reducing pain in “chronic tension-type headache.” Therefore, our review is not adequate to address treatment of chronic forms of headache, which are now typically treated with medications such as onabotulinum toxin therapy, calcitonin gene-related peptide (cGRP) antibody therapies, and cGRP receptor ligand blockers. We limited our analysis of NSAIDs to the nine most commonly prescribed in the United States, as identified using Centers for Medicare & Medicaid Services data from 2018. We excluded combination therapies such as two included drugs (e.g., an NSAID plus and antidepressant). We also excluded specifically the combination of an NSAID and a proton-pump inhibitor. Given that most studies compared active drugs to placebo, we could have performed network meta-analyses to provide more information on how the drugs compare to each other. We did not perform such analyses due to time and resource limitations and concerns over validity of such analyses leading to a preference for direct comparisons.

Limitations of the Evidence Base

Important limitations of the evidence base include the small number of studies overall in most of the pain conditions, the small number of studies of individual drugs, and few studies of direct comparisons among the drugs. Most evidence on head-to-head comparisons of specific drugs is limited to one or two trials, making this evidence base not helpful in choosing among the nonopioid drug treatments. To address this latter limitation, we combined studies of within classes for meta-analyses compared with placebo. The clear majority (>80%) of the trials were sponsored by industry, which might limit the evidence by increasing the likelihood of publication and/or other forms of bias. An unusually large proportion of the trials were poor-quality (16%), largely due to poor reporting and reflecting that many studies were published prior to established guidance on reporting standards for RCTs. Since more of the studies of NSAIDs were older, and we were able to conduct meta-analyses of these studies, we evaluated the effect in studies published prior to 2000 versus those published later (after adoption of the CONSORT guidance), but did not find a significant interaction. Most studies (82%) were short term (3 to <6 months), while only 13 percent were intermediate term (6 to <12 months), and 6 percent were long term (≥ 12 months). Sample sizes of RCTs ranged from small (<200) to medium (<2000), but for some conditions/treatments the sample size was extremely small (e.g., an RCT of amitriptyline in sickle cell disease, N=22).

Although the mean age of the populations studied is consistent with the age range of each pain condition, the evidence may be limited in not including a larger age range, or studies exclusively of older patients. Relatively few trials reported on the race of participants, and the evidence from trials that did report on race is limited to a largely White/Caucasian population. Assessment of primary outcomes were limited by trials that did not report on baseline pain or baseline function. Similarly, a very small proportion of trials (10%) reported on quality of life and when reported, there was lack of consistency in the measures used, which limited our ability to combine results and draw conclusions. Inferences on effects for function are also limited by the heterogeneous variety of measures used for that outcome.

A major limitation of the evidence base is the inadequate reporting on harms for most of the included drugs, other than the NSAIDs. For example, cognitive effects were prioritized as an adverse event outcome of interest for multiple drug classes, but reporting varied widely (reported as confusion, “thinking abnormal,” euphoric mood, disturbance in attention, etc.) leaving us to make decisions about which of these reflect cognition and should be combined. Specific serious

harms were rarely reported in the included trials, in part because the trials were too short or too small to identify them, or because they were not specifically sought out.

Research Gaps

Although there are many studies included in this review, important gaps remain and future research should address these to better inform clinicians, patients, guideline developers and policymakers on the use of nonopioid pharmacologic treatments for chronic pain. Important gaps in the available research include a relative lack of:

- Comparative effectiveness trials – those that evaluate intermediate- and long-term treatment duration, long-term health outcomes (including quality of life), and make direct comparisons among key interventions both within- and across-classes;
- Good quality/low risk of bias studies – many trials suffered from poor reporting (e.g., unclear randomization and allocation concealment techniques), baseline differences between randomized groups, lack of blinding, and high attrition;
- Trials in older patients to better understand possible age-related difference in treatment effect and in patients of nonwhite race;
- Consistent use of recognized standard measures of pain and function to facilitate comparisons across trials;
- More trials in patients with chronic headache, low back pain, and sickle cell disease

Conclusions

Nonopioid drugs (mainly SNRI antidepressants, pregabalin/gabapentin, and NSAIDs) resulted in small to moderate improvements in pain and function outcomes in patients with specific types of noncancer chronic pain in the short term, with few differences between drugs in a class or doses of a drug. Evidence on intermediate- and long-term effects on pain, function, and quality of life is limited. Increased incidence of drug class-specific adverse events lead to withdrawal from treatment in some patients, suggesting that careful consideration of patient characteristics is needed in selecting nonopioid drug treatments. Additional research is needed on longer-term followup, quality of life, direct comparisons of nonopioid drugs, and in older patients, nonwhite patients, and patients with more severe pain and with comorbidities

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266. McCrae JC, Morrison EE, MacIntyre IM, et al. Long-term adverse effects of paracetamol - a review. *Br J Clin Pharmacol.* 2018 Oct;84(10):2218-30. doi: 10.1111/bcp.13656. PMID: 29863746.
267. Roberts E, Delgado Nunes V, Buckner S, et al. Paracetamol: not as safe as we thought? A systematic literature review of observational studies. *Ann Rheum Dis.* 2016;75(3):552-9. doi: 10.1136/annrheumdis-2014-206914. PMID: 25732175.

Abbreviations and Acronyms

Acronym or Abbreviation	Definition
ACR	American College of Rheumatology
AHRQ	Agency for Healthcare Research and Quality
ANCOVA	Analysis of Covariance
API	Average pain intensity
ARA	American Rheumatism Association
AS	Ankylosing spondylitis
ASQoL	Ankylosing Spondylitis Quality of Life
BAI	Beck Anxiety Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BDI	Beck Depression Inventory
BID	Twice daily
BPI	Brief Pain Inventory
CBD	Cannabidiol
CDC	Centers for Disease Control and Prevention
CER	Comparative Effectiveness Review
cGRP	calcitonin Gene-Related Peptide
CI	Confidence interval
CMS	Centers for Medicare & Medicaid Services
CONSORT	Consolidated Standards of Reporting Trials
COX-2	Cyclooxygenase-2
CV	Cardiovascular
DDS	Descriptor Differential Scale
DMARD	Disease-Modifying Antirheumatic Drug
EPC	Evidence-based Practice Center
EQ-5D	Euro Quality of Life five-dimension
FDA	Food and Drug Administration
FIQ	Fibromyalgia Impact Questionnaire
GI	Gastrointestinal
HAMD	Hamilton Rating Scale for Depression
HAQ	Health Assessment Questionnaire
IOM	Institute of Medicine
IPD	Individual Patient Data
IPRCC	Interagency Pain Research Coordinating Committee
KQ	Key Question
LSM	Least squares mean
MAOI	Monoamine Oxidase Inhibitor
MCID	Minimal Clinically Important Difference
MD	Mean difference
MHAQ	Modified Health Assessment Questionnaire
MI	Myocardial infarction

Acronym or Abbreviation	Definition
NA	Not applicable
NMDA	<i>N</i> -Methyl-D-aspartic acid
NPS	National Pain Strategy
NR	Not reported
NRS	Numeric rating scale
NSAID	Nonsteroidal anti-inflammatory drug
OA	Osteoarthritis
OARSI	Osteoarthritis Research Society International
ODI	Oswestry Disability Index
PICOTS	Population, Intervention, Comparison, Outcome, Time, Setting, Study design
PROSPERO	International Prospective Register of Systematic Reviews
QoL	Quality of life
RA	Rheumatoid arthritis
RCT	Randomized controlled trial
RMDQ (RDQ)	Roland-Morris Disability Questionnaire
RR	Relative risk; risk ratio
SAE	Serious adverse event
SD	Standard deviation
SE	Standard error
SEM	Standard error of the mean
SF-36 (MCS, PCS)	Short Form-36 (Mental Component Summary, Physical Component Summary)
SMD	Standardized mean difference
SNRI	Serotonin-norepinephrine reuptake inhibitor
SOE	Strength of evidence
SR	Systematic review
SSRI	Selective serotonin reuptake inhibitor
TCA	Tricyclic antidepressant
THC	Tetrahydrocannabinol
TID	Three times daily
US	United States
VAS	Visual analog scale
WAE	Withdrawal due to adverse event
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Appendix A. Literature Search Strategies

Randomized Controlled Trials

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

- 1 (celecoxib or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or meclufenamate or "mefenamic acid" or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or salsalate or sulindac or tenoxicam or "tiaprofenic acid" or tolmetin).ab,kw,sh,ti.
- 2 (carbamazepine or gabapentin or oxcarbazepine or pregabalin).ab,kw,sh,ti.
- 3 (desvenlafaxine or duloxetine or levomilnacipran or milnacipran or venlafaxine).ab,kw,sh,ti.
- 4 (amitriptyline or desipramine or doxepin or imipramine or nortriptyline or alprazolam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flurazepam or lorazepam or oxazepam or temazepam or triazolam or baclofen or carisoprodol or cyclobenzaprine or metaxalone or methocarbamol or tizanidine).ab,kw,sh,ti.
- 5 (acetaminophen or paracetamol or capsaicin or methocarbamol or cannabis or marijuana or cannabidiol or phytocannabinoid* or dronabinol or nabilone or memantine).ab,kw,sh,ti.
- 6 (topical adj2 lidocaine).ab,kw,ti.
- 7 or/1-6
- 8 exp Neuralgia/
- 9 Fibromyalgia/
- 10 exp Anemia, Sickle Cell/
- 11 Headache/
- 12 exp Headache Disorders/
- 13 Musculoskeletal Pain/
- 14 exp Osteoarthritis/
- 15 Low Back Pain/
- 16 Neck Pain/
- 17 exp Arthritis, Rheumatoid/
- 18 Spondylitis, Ankylosing/
- 19 ("ankylosing spondylitis" or "neuropathic pain" or neuralgia or neuropathy or fibromyalgia or "sickle cell" or headache or "musculoskeletal pain" or osteoarthritis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis").ab,kw,ti.
- 20 or/8-19
- 21 7 and 20
- 22 randomized controlled trial.pt.
- 23 controlled clinical trial.pt.
- 24 clinical trials as topic.sh.
- 25 (random* or trial or placebo).ti,ab.
- 26 clinical trials as topic.sh.
- 27 exp animals/ not humans.sh.
- 28 or/22-26
- 29 28 not 27
- 30 21 and 29

- 31 limit 21 to randomized controlled trial
- 32 30 or 31
- 33 limit 32 to (english language and humans)

Database: EBM Reviews - Cochrane Central Register of Controlled Trials

- 1 (celecoxib or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or meclufenamate or "mefenamic acid" or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or salsalate or sulindac or tenoxicam or "tiaprofenic acid" or tolmetin).ab,kw,sh,ti.
- 2 (carbamazepine or gabapentin or oxcarbazepine or pregabalin).ab,kw,sh,ti.
- 3 (desvenlafaxine or duloxetine or levomilnacipran or milnacipran or venlafaxine).ab,kw,sh,ti.
- 4 (amitriptyline or desipramine or doxepin or imipramine or nortriptyline or alprazolam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flurazepam or lorazepam or oxazepam or temazepam or triazolam or baclofen or carisoprodol or cyclobenzaprine or metaxalone or methocarbamol or tizanidine).ab,kw,sh,ti.
- 5 (acetaminophen or paracetamol or capsaicin or methocarbamol or cannabis or marijuana or cannabidiol or phytocannabinoid* or dronabinol or nabilone or memantine).ab,kw,sh,ti.
- 6 (topical adj2 lidocaine).ab,kw,ti.
- 7 or/1-6
- 8 exp Neuralgia/
- 9 Fibromyalgia/
- 10 exp Anemia, Sickle Cell/
- 11 Headache/
- 12 exp Headache Disorders/
- 13 Musculoskeletal Pain/
- 14 exp Osteoarthritis/
- 15 Low Back Pain/
- 16 Neck Pain/
- 17 exp Arthritis, Rheumatoid/
- 18 Spondylitis, Ankylosing/
- 19 ("ankylosing spondylitis" or "neuropathic pain" or neuralgia or neuropathy or fibromyalgia or "sickle cell" or headache or "musculoskeletal pain" or osteoarthritis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis").ab,kw,ti.
- 20 or/8-19
- 21 7 and 20
- 22 21 not acute.ti.
- 23 limit 22 to english language

Database: PsycINFO

- 1 (celecoxib or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or meclufenamate or "mefenamic acid" or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or salsalate or sulindac or tenoxicam or "tiaprofenic acid" or tolmetin).ab,kw,sh,ti.
- 2 (carbamazepine or gabapentin or oxcarbazepine or pregabalin).ab,kw,sh,ti.
- 3 (desvenlafaxine or duloxetine or levomilnacipran or milnacipran or venlafaxine).ab,kw,sh,ti.

- 4 (amitriptyline or desipramine or doxepin or imipramine or nortriptyline or alprazolam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flurazepam or lorazepam or oxazepam or temazepam or triazolam or baclofen or carisoprodol or cyclobenzaprine or metaxalone or methocarboamol or tizanidine).ab,kw,sh,ti.
- 5 (acetaminophen or paracetamol or capsaicin or methocarbamol or cannabis or marijuana or cannabidiol or phytocannabinoid* or dronabinol or nabilone or memantine).ab,kw,sh,ti.
- 6 (topical adj2 lidocaine).ab,kw,ti.
- 7 or/1-6
- 8 exp NEURALGIA/
- 9 exp chronic pain/
- 10 exp headache/
- 11 exp Back Pain/
- 12 sickle cell disease/
- 13 exp ARTHRITIS/
- 14 fibromyalgia/
- 15 ("ankylosing spondylitis" or "neuropathic pain" or neuralgia or neuropathy or fibromyalgia or "sickle cell" or headache or "musculoskeletal pain" or osteoarthritis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis").ab,hw,ti.
- 16 or/8-15
- 17 7 and 16
- 18 17 and (random* or control* or trial).ti,ab.
- 19 limit 18 to english language

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(celecoxib:ti OR diclofenac:ti OR diflunisal:ti OR etodolac:ti OR fenoprofen:ti OR flurbiprofen:ti OR ibuprofen:ti OR indomethacin:ti OR ketoprofen:ti OR ketorolac:ti OR meclofenamate:ti OR 'mefenamic acid':ti OR meloxicam:ti OR nabumetone:ti OR naproxen:ti OR oxaprozin:ti OR piroxicam:ti OR salsalate:ti OR sulindac:ti OR tenoxicam:ti OR 'tiaprofenic acid':ti OR tolmetin:ti OR celecoxib:ab OR diclofenac:ab OR diflunisal:ab OR etodolac:ab OR fenoprofen:ab OR flurbiprofen:ab OR ibuprofen:ab OR indomethacin:ab OR ketoprofen:ab OR ketorolac:ab OR meclofenamate:ab OR 'mefenamic acid':ab OR meloxicam:ab OR nabumetone:ab OR naproxen:ab OR oxaprozin:ab OR piroxicam:ab OR salsalate:ab OR sulindac:ab OR tenoxicam:ab OR 'tiaprofenic acid':ab OR tolmetin:ab OR carbamazepine:ti OR gabapentin:ti OR oxcarbazepine:ti OR pregabalin:ti OR carbamazepine:ab OR gabapentin:ab OR oxcarbazepine:ab OR pregabalin:ab OR desvenlafaxine:ti OR duloxetine:ti OR levomilnacipran:ti OR milnacipran:ti OR venlafaxine:ti OR desvenlafaxine:ab OR duloxetine:ab OR levomilnacipran:ab OR milnacipran:ab OR venlafaxine:ab OR amitriptyline:ti OR desipramine:ti OR doxepin:ti OR imipramine:ti OR nortriptyline:ti OR amitriptyline:ab OR desipramine:ab OR doxepin:ab OR imipramine:ab OR nortriptyline:ab OR alprazolam:ti OR chlordiazepoxide:ti OR clobazam:ti OR clonazepam:ti OR clorazepate:ti OR diazepam:ti OR estazolam:ti OR flurazepam:ti OR lorazepam:ti OR oxazepam:ti OR temazepam:ti OR triazolam:ti OR baclofen:ti OR carisoprodol:ti OR cyclobenzaprine:ti OR metaxalone:ti OR methocarboamol:ti OR tizanidine:ti OR alprazolam:ab OR chlordiazepoxide:ab OR clobazam:ab OR clonazepam:ab OR clorazepate:ab OR diazepam:ab OR estazolam:ab OR flurazepam:ab OR lorazepam:ab OR oxazepam:ab OR temazepam:ab OR triazolam:ab OR baclofen:ab OR carisoprodol:ab OR cyclobenzaprine:ab OR metaxalone:ab OR methocarboamol:ab OR

tizanidine:ab OR acetaminophen:ti OR paracetamol:ti OR acetaminophen:ab OR paracetamol:ab OR capsaicin:ti OR capsaicin:ab OR methocarbamol:ti OR methocarbamol:ab OR marijuana:ti OR cannabidiol:ti OR phytocannabinoid:ti OR dronabinol:ti OR nabilone:ti OR marijuana:ab OR cannabidiol:ab OR phytocannabinoid:ab OR dronabinol:ab OR nabilone:ab OR memantine:ti OR memantine:ab OR (lidocaine:ti AND topical) OR (lidocaine:ab AND topical)) AND ('neuropathic pain':ti OR fibromyalgia:ti OR 'sickle cell':ti OR headache:ti OR 'musculoskeletal pain':ti OR osteoarthritis:ti OR 'low back pain':ti OR 'neck pain':ti OR 'inflammatory pain':ti OR 'rheumatoid arthritis':ti OR 'neuropathic pain':ab OR fibromyalgia:ab OR 'sickle cell':ab OR headache:ab OR 'musculoskeletal pain':ab OR osteoarthritis:ab OR 'low back pain':ab OR 'neck pain':ab OR 'inflammatory pain':ab OR 'rheumatoid arthritis':ab) AND ('clinical trial'/de OR 'randomized controlled trial'/de OR 'randomization'/de OR 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/de OR 'placebo'/de OR 'prospective study'/de OR ('randomized controlled' NEXT/1 trial*) OR rct OR 'randomly allocated' OR 'allocated randomly' OR 'random allocation' OR (allocated NEAR/2 random) OR (single NEXT/1 blind*) OR (double NEXT/1 blind*) OR ((treble OR triple) NEAR/1 blind*) OR placebo*) AND [humans]/lim AND [english]/lim AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Systematic Reviews

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

- 1 (celecoxib or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or meclizolam or "mefenamic acid" or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or salsalate or sulindac or tenoxicam or "tiaprofenic acid" or tolmetin).ab,kw,sh,ti.
- 2 (carbamazepine or gabapentin or oxcarbazepine or pregabalin).ab,kw,sh,ti.
- 3 (desvenlafaxine or duloxetine or levomilnacipran or milnacipran or venlafaxine).ab,kw,sh,ti.
- 4 (amitriptyline or desipramine or doxepin or imipramine or nortriptyline or alprazolam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flurazepam or lorazepam or oxazepam or temazepam or triazolam or baclofen or carisoprodol or cyclobenzaprine or metaxalone or methocarbamol or tizanidine).ab,kw,sh,ti.
- 5 (acetaminophen or paracetamol or capsaicin or methocarbamol or cannabis or marijuana or cannabidiol or phytocannabinoid* or dronabinol or nabilone or memantine).ab,kw,sh,ti.
- 6 (topical adj2 lidocaine).ab,kw,ti.
- 7 or/1-6
- 8 exp Neuralgia/
- 9 Fibromyalgia/
- 10 exp Anemia, Sickle Cell/
- 11 Headache/
- 12 exp Headache Disorders/
- 13 Musculoskeletal Pain/
- 14 exp Osteoarthritis/
- 15 Low Back Pain/
- 16 Neck Pain/
- 17 exp Arthritis, Rheumatoid/

- 18 ("ankylosing spondylitis" or "neuropathic pain" or neuralgia or neuropathy or fibromyalgia or "sickle cell" or headache or "musculoskeletal pain" or osteoarthritis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis").ab,kw,ti.
- 19 or/8-18
- 20 7 and 19
- 21 meta-analysis.pt.
- 22 meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
- 23 ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
- 24 ((quantitative adj3 (review* or overview* or syntheses*)) or (research adj3 (integrati* or overview*))).ti,ab.
- 25 ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
- 26 (data syntheses* or data extraction* or data abstraction*).ti,ab.
- 27 (handsearch* or hand search*).ti,ab.
- 28 (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
- 29 (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
- 30 (meta regression* or metaregression*).ti,ab.
- 31 (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
- 32 (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
- 33 (cochrane or (health adj2 technology assessment) or evidence report).jw.
- 34 (meta-analysis or systematic review).ti,ab.
- 35 (comparative adj3 (efficacy or effectiveness)).ti,ab.
- 36 (outcomes research or relative effectiveness).ti,ab.
- 37 ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
- 38 or/21-37
- 39 20 and 38
- 40 limit 20 to (meta analysis or systematic reviews)
- 41 39 or 40
- 42 limit 41 to yr="2008 -Current"
- 43 limit 42 to english language

Database: EBM Reviews - Cochrane Database of Systematic Reviews

- 1 (celecoxib or diclofenac or diflunisal or etodolac or fenoprofen or flurbiprofen or ibuprofen or indomethacin or ketoprofen or ketorolac or meclufenamate or "mefenamic acid" or meloxicam or nabumetone or naproxen or oxaprozin or piroxicam or salsalate or sulindac or tenoxicam or "tiaprofenic acid" or tolmetin).ab,ti.
- 2 (brivaracetam or carbamazepine or divalproex or "eslicarbazepine acetate" or ethotoin or gabapentin or lacosamide or lamotrigine or levetiracetam or oxcarbazepine or perampanel or phenytoin or pregabalin or tiagabine or topiramate or "valproic acid" or zonisamide).ab,ti.

- 3 (bupropion or citalopram or desvenlafaxine or duloxetine or escitalopram or fluoxetine or fluvoxamine or levomilnacipran or mirtazapine or nefazodone or paroxetine or sertraline or trazodone or venlafaxine or vilazodone or vortioxetine).ab,ti.
- 4 (amitriptyline or desipramine or imipramine or nortriptyline or baclofen or carisoprodol or cyclobenzaprine or metaxalone or methocarbamol or tizanidine or alprazolam or chlordiazepoxide or clobazam or clonazepam or clorazepate or diazepam or estazolam or flurazepam or lorazepam or oxazepam or temazepam or triazolam).ab,ti.
- 5 (acetaminophen or paracetamol or capsaicin or methocarbamol or cannabis or marijuana or cannabidiol or phytocannabinoid* or dronabinol or nabilone or memantine).ab,ti.
- 6 (topical adj2 lidocaine).ab,ti.
- 7 or/1-6
- 8 ("ankylosing spondylitis" or "neuropathic pain" or neuralgia or neuropathy or fibromyalgia or "sickle cell" or headache or "musculoskeletal pain" or osteoarthritis or "low back pain" or "neck pain" or "inflammatory pain" or "rheumatoid arthritis").ab,ti.
- 9 7 and 8

Elsevier Embase

(celecoxib:ti OR diclofenac:ti OR diflunisal:ti OR etodolac:ti OR fenoprofen:ti OR flurbiprofen:ti OR ibuprofen:ti OR indomethacin:ti OR ketoprofen:ti OR ketorolac:ti OR meclofenamate:ti OR 'mefenamic acid':ti OR meloxicam:ti OR nabumetone:ti OR naproxen:ti OR oxaprozin:ti OR piroxicam:ti OR salsalate:ti OR sulindac:ti OR tenoxicam:ti OR 'tiaprofenic acid':ti OR tolmetin:ti OR celecoxib:ab OR diclofenac:ab OR diflunisal:ab OR etodolac:ab OR fenoprofen:ab OR flurbiprofen:ab OR ibuprofen:ab OR indomethacin:ab OR ketoprofen:ab OR ketorolac:ab OR meclofenamate:ab OR 'mefenamic acid':ab OR meloxicam:ab OR nabumetone:ab OR naproxen:ab OR oxaprozin:ab OR piroxicam:ab OR salsalate:ab OR sulindac:ab OR tenoxicam:ab OR 'tiaprofenic acid':ab OR tolmetin:ab OR carbamazepine:ti OR gabapentin:ti OR oxcarbazepine:ti OR pregabalin:ti OR carbamazepine:ab OR gabapentin:ab OR oxcarbazepine:ab OR pregabalin:ab OR desvenlafaxine:ti OR duloxetine:ti OR levomilnacipran:ti OR milnacipran:ti OR venlafaxine:ti OR desvenlafaxine:ab OR duloxetine:ab OR levomilnacipran:ab OR milnacipran:ab OR venlafaxine:ab OR amitriptyline:ti OR desipramine:ti OR doxepin:ti OR imipramine:ti OR nortriptyline:ti OR amitriptyline:ab OR desipramine:ab OR doxepin:ab OR imipramine:ab OR nortriptyline:ab OR alprazolam:ti OR chlordiazepoxide:ti OR clobazam:ti OR clonazepam:ti OR clorazepate:ti OR diazepam:ti OR estazolam:ti OR flurazepam:ti OR lorazepam:ti OR oxazepam:ti OR temazepam:ti OR triazolam:ti OR baclofen:ti OR carisoprodol:ti OR cyclobenzaprine:ti OR metaxalone:ti OR methocarbamol:ti OR tizanidine:ti OR alprazolam:ab OR chlordiazepoxide:ab OR clobazam:ab OR clonazepam:ab OR clorazepate:ab OR diazepam:ab OR estazolam:ab OR flurazepam:ab OR lorazepam:ab OR oxazepam:ab OR temazepam:ab OR triazolam:ab OR baclofen:ab OR carisoprodol:ab OR cyclobenzaprine:ab OR metaxalone:ab OR methocarbamol:ab OR tizanidine:ab OR acetaminophen:ti OR paracetamol:ti OR acetaminophen:ab OR paracetamol:ab OR capsaicin:ti OR capsaicin:ab OR methocarbamol:ti OR methocarbamol:ab OR marijuana:ti OR cannabidiol:ti OR phytocannabinoid:ti OR dronabinol:ti OR nabilone:ti OR marijuana:ab OR cannabidiol:ab OR phytocannabinoid:ab OR dronabinol:ab OR nabilone:ab OR memantine:ti OR memantine:ab OR (lidocaine:ti AND topical) OR (lidocaine:ab AND topical)) AND ('neuropathic pain':ti OR fibromyalgia:ti OR 'sickle cell':ti OR headache:ti OR 'musculoskeletal pain':ti OR osteoarthritis:ti OR 'low back pain':ti OR 'neck pain':ti OR 'inflammatory pain':ti OR

'rheumatoid arthritis':ti OR 'neuropathic pain':ab OR fibromyalgia:ab OR 'sickle cell':ab OR headache:ab OR 'musculoskeletal pain':ab OR osteoarthritis:ab OR 'low back pain':ab OR 'neck pain':ab OR 'inflammatory pain':ab OR 'rheumatoid arthritis':ab) AND ('systematic review' OR 'meta analysis') AND (2008:py OR 2009:py OR 2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py OR 2015:py OR 2016:py OR 2017:py OR 2018:py) AND [embase]/lim NOT ([embase]/lim AND [medline]/lim

Appendix B. Methods

Citations for Appendix B references appear in Appendix J.

This Comparative Effectiveness Review (CER) follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter “AHRQ Methods Guide”).¹ All methods were determined *a priori*, and a protocol was published on the AHRQ website (<https://effectivehealthcare.ahrq.gov/topics/nonopioid-chronic-pain/protocol>) and on PROSPERO systematic reviews registry (registration no. CRD42019134249).

Key Questions

Key Question 1. Effectiveness and Comparative Effectiveness

- a. In patients with chronic pain, what is the effectiveness of nonopioid pharmacologic agents versus placebo for outcomes related to pain, function, and quality of life, after short-term treatment duration (3 to 6 months), intermediate-term treatment duration (6 to 12 months), and long-term treatment duration (≥ 12 months)?
- b. In patients with chronic pain, what is the comparative effectiveness of nonopioid pharmacologic agents compared to other nonopioid pharmacologic agents for outcomes related to pain, function, and quality of life, after short-term treatment duration (3 to 6 months), intermediate-term treatment duration (6 to 12 months), and long-term treatment duration (≥ 12 months)?
- c. How does effectiveness or comparative effectiveness vary depending on: (1) the specific type or cause of pain, (2) patient demographics, (3) patient comorbidities, (4) the dose of medication used, (5) the duration of treatment, and (6) dose titration, including tapering.

Key Question 2. Harms and Adverse Events

- a. In patients with chronic pain, what are the risks of nonopioid pharmacologic agents for harms including overdose, misuse, dependence, withdrawals due to adverse events, and serious adverse events (including falls, fractures, motor vehicle accidents), and specific adverse events, according to drug class?
- b. How do harms vary depending on: (1) the specific type or cause of pain, (2) patient demographics, (3) patient comorbidities, (4) the dose of medication used, (5) the duration of treatment, and (6) dose titration, including tapering.

Criteria for Inclusion/Exclusion of Studies in the Review

Population(s):

- For all Key Questions (KQs): Adults (age ≥ 18 years) with various types of chronic pain (defined as pain lasting >3 months), including patients with acute exacerbations of chronic pain, pregnant/breastfeeding women, and patients with opioid use disorder
- For KQs 1c, 2b: Subgroups of the above patient populations as defined by specific pain condition (neuropathic pain, musculoskeletal pain, fibromyalgia, inflammatory arthritis,

and chronic headache), patient demographics (e.g., age, race, ethnicity, and sex), comorbidities and degree of nociplasticity/central sensitization.

Interventions:

- Oral pharmacologic agents: nonsteroidal anti-inflammatory drugs, acetaminophen, muscle relaxants (including benzodiazepines), antidepressants, and anticonvulsants
- Topical pharmacologic agents: diclofenac, capsaicin, and lidocaine
- Medical cannabis (any formulation)

Comparators:

- For KQ 1a/c and KQ2: Placebo (effectiveness)
- For KQ 1b/c and KQ2: Another included nonopioid pharmacologic agent, different doses, or treatment durations (comparative effectiveness)

Outcomes:

- KQ 1: Pain (intensity, severity, bothersomeness), function (physical disability, activity limitations, activity interference, work function), and quality of life (including depression)
 - Only validated scales for assessments of pain, function, and quality of life
- KQ 2: For all drug classes: overdose, misuse, dependence, withdrawals due to adverse events, and serious adverse events. Specific adverse events for each drug class, such as gastrointestinal events, cardiovascular events, and liver or kidney-related harms for nonsteroidal anti-inflammatory drugs; weight gain, sedation, and cognitive effects for gabapentin and pregabalin, etc.

Timing:

- Short-term treatment duration (3 to 6 months), intermediate-term treatment duration (6 to 12 months), and long-term treatment duration (≥ 12 months)
- We will assess available literature to ensure that adequate evidence exists from studies of ≥ 3 months' treatment duration. If adequate evidence is not available for this shorter-duration, we will consider adding shorter-duration studies. If high-quality systematic reviews are available covering the scope of the review for shorter duration studies, we will summarize these in this case.

Settings:

- Outpatient settings (e.g., primary care, pain clinics, other specialty clinics)

Table B-1. PICOTS: Inclusion and exclusion criteria

PICOTS	Inclusion Criteria	Exclusion Criteria
Populations and Conditions	<ul style="list-style-type: none"> • For all KQs: Adults (age ≥18 years) with chronic pain (pain lasting >3 months). • For KQs 1b, 2b Specific chronic pain populations: <ul style="list-style-type: none"> • Neuropathic • Musculoskeletal (e.g. low back pain, osteoarthritis) • Fibromyalgia (assessed using established criteria) • Sickle cell disease • Inflammatory arthritis (e.g., rheumatoid arthritis) • Chronic headache^a 	<ul style="list-style-type: none"> • Pain at the end of life (life expectancy ≤6 months) • Acute pain (<8 weeks duration), including sickle cell crisis • Pain due to active malignancy (e.g. tumor-related pain while receiving active treatment to reduce tumor size) • Episodic migraine • Undefined mixed pain conditions
Interventions	<p>Nonopioid pharmacologic drugs for chronic pain:</p> <ul style="list-style-type: none"> • Oral pharmacologic agents specifically used to treat chronic pain: <ul style="list-style-type: none"> • NSAIDs (e.g., celecoxib, diclofenac, ibuprofen) • Antidepressants SNRIs (i.e., duloxetine, milnacipran) and TCAs (e.g., amitriptyline) • Anticonvulsants: carbamazepine, gabapentin, oxcarbazepine, pregabalin • Other: Acetaminophen, muscle relaxants (e.g., cyclobenzaprine, diazepam), memantine • Topical agents (diclofenac, capsaicin, and lidocaine) • Medical cannabis in all forms, including phytocannabinoids and synthetic cannabinoids 	<ul style="list-style-type: none"> • Injectable preparations, including biologic drugs, corticosteroids, etc. • Other antidepressants (e.g. SSRIs, MAOIs) • Other antiepileptics (e.g. topiramate, lamotrigine, levetiracetam, phenytoin) • Drugs used for migraine prophylaxis (e.g., verapamil, beta-blockers) or treating acute migraine (e.g., triptans) • Salicylates (topical and oral) • Topical menthol preparations • Disease-modifying drugs for rheumatoid arthritis (DMARDs, e.g. methotrexate)
Comparators	<ul style="list-style-type: none"> • For KQ 1a/b and 2a/b: Placebo • For KQ 1c and 2a/b: Another included nonopioid pharmacologic agent, dose, or treatment duration 	<ul style="list-style-type: none"> • Nonpharmacologic treatment (comparison to nonopioids included in review of nonpharmacologic treatments) • Opioid treatment
Outcomes	<ul style="list-style-type: none"> • Pain, function, and quality of life using validated outcome measures. <ul style="list-style-type: none"> • Pain severity is the measure of improvement in pain from baseline, as a continuous measure. Pain response is a categorical value (yes/no) of significant improvement, e.g. 30% improvement on a 0-100 scale. • Pain assessments are patient-reported. Clinician assessments were also acceptable, and noted where they are reported. • Secondary outcomes include mood, sleep, and global assessments using validated scales • All drug classes: Withdrawal from treatment due to adverse events (any adverse event, not specifically symptoms of withdrawal from an opioid or other drug), incidence of serious adverse events, overdose, misuse, addiction, development of SUD. • Key specific adverse events according to drug class (e.g., gastrointestinal and cardiovascular events, kidney and liver-related harms with NSAIDs). 	<ul style="list-style-type: none"> • Intermediate outcomes (e.g., pharmacokinetics/pharmacodynamics, drug-drug interactions, dose conversions) • Indirect measurement of pain, e.g. quantitative sensory testing.
Timing	<ul style="list-style-type: none"> • Short- (3 to 6 months), intermediate- (6 to 12 months), and long-term (≥12 months) treatment duration 	<ul style="list-style-type: none"> • Studies or outcomes reported with <3-month duration of treatment
Setting	<ul style="list-style-type: none"> • Outpatient settings (e.g., primary care, pain clinics, emergency rooms, urgent care clinics) 	<ul style="list-style-type: none"> • Addiction treatment settings, inpatient settings

PICOTS	Inclusion Criteria	Exclusion Criteria
Study Design	<ul style="list-style-type: none"> • Randomized controlled trials • High-quality, recent systematic reviews that best match the scope of this review • English language publications 	<ul style="list-style-type: none"> • Observational studies • Outdated/out of scope systematic reviews • Non-English language publications

CBD = cannabidiol; KQ = Key Question; MAOI = monoamine oxidase inhibitor; NSAID = nonsteroidal anti-inflammatory drug; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant; THC = tetrahydrocannabinol

^aChronic headache defined as (International Classification of Headache Disorders, 3rd edition definition²):

Primary headaches attributed to the headache condition itself, not caused by another disease or medical condition. Chronic headache is defined as 15 or more days each month for at least 12 weeks or history of headache more than 180 days a year.

Literature Search

We conducted electronic searches in Ovid[®] MEDLINE[®], Embase[®], PsycINFO[®], CINAHL[®], Cochrane CENTRAL, and Cochrane Database of Systematic Reviews in January 2019 (from database inception, see Appendix A for full strategies). Reference lists of included systematic reviews were screened for includable studies. Manufacturers of included drugs submitted potential relevant studies to include in this review using a Federal Register notification. We screened citations identified through our searched using the pre-established criteria above to determine eligibility for full-text review, with any citation deemed not relevant by one reviewer screened by a second reviewer.¹ 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, we will update these searches and incorporate any new eligible studies into the report.

Study Design

For all Key Questions, we included and focused on randomized controlled trials (RCTs) with at least 3 months duration to maintain a manageable scope for this review, recognizing that by definition, chronic pain requires treatments that are effective in the long term, and short-term benefits may not persist. This duration threshold is similar to the duration used in the prior AHRQ systematic review on nonpharmacologic interventions for chronic pain,³ which included studies with greater than 1 month of followup after the end of treatment, with most studies involving 6 to 8 weeks of treatment. The Evidence-based Practice Center (EPC) evaluated the availability and quality of studies with 3 to 6 months duration to determine if an evaluation of studies with shorter durations was needed. It was deemed that adequate evidence was found in this window of duration and thus we did not include studies with shorter durations. However, existing systematic reviews to summarize evidence where possible.

We evaluated the persistence of benefits or harms by evaluating the three periods identified in the Key Questions (3 to 6 months, 6 to 12 months, and ≥ 12 months). We used existing systematic reviews primarily to screen their included studies to insure we have identified all relevant studies for this review. In the case where a systematic review is recent enough to cover the majority of the available evidence, and evaluates a cohesive group of interventions, outcomes and time frames included here, we included the review as the primary evidence and supplement with any newer or excluded studies.

Non-English Language Studies

We restricted to English-language articles, but reviewed English-language abstracts of non-English language articles to identify studies that would otherwise meet inclusion criteria, in order to assess for the likelihood of language bias.

Data Abstraction and Data Management

For studies meeting inclusion criteria, data were abstracted and dual-reviewed by independent investigators in multiple-parts. Data regarding general study characteristics were abstracted into forms as seen in Appendix E. Information abstracted in these evidence tables included author, year of publication, country, study quality, pain condition, age, sex, race/ethnicity, duration of chronic pain, severity of pain and function at baseline, presence of psychiatric, total randomized and analyzed, intervention characteristics (including the specific drug class and dose), duration of treatment, and funding source. For clarity, data used for meta-analysis were abstracted into separate forms, pooled and synthesized (Appendix F). Methods regarding abstracting data for synthesis are detailed below. Data from studies included in a systematic review that met our inclusion criteria were abstracted from the published article with missing data supplemented by systematic reviews.

Effectiveness and comparative effectiveness data were organized by pain condition with effects on pain abstracted as mean difference in pain intensity (continuous) and pain improvement (dichotomous) based on meeting specified thresholds (“pain response”). Pain conditions were categorized as neuropathic (diabetic peripheral neuropathy, post-herpetic neuralgia, other), fibromyalgia, osteoarthritis, inflammatory arthritis (e.g., rheumatoid arthritis or ankylosing spondylitis), spinal pain (neck or low-back pain), sickle cell disease, or chronic headache. We preferentially abstracted pain assessed with the visual analog scale (VAS) or numerical rating scale (NRS) on a scale of 0-10 or 0-100 over other pain assessments (e.g., Western Ontario and McMaster Universities Osteoarthritis Index pain subscale). Mean differences in effects on pain from baseline to followup, unadjusted differences in change from baseline, and differences (both within- and between-group) in followup scores were abstracted for meta-analysis. Primary pain response was defined as $\geq 30\%$ improvement (reduction) in pain score. Secondary pain response criteria included $>30\%$ improvement (e.g., $\geq 50\%$ improvement), condition-specific composite measure (e.g., American College of Rheumatology 20 criteria [ACR20], Assessment in Spondyloarthritis International Society 20 criteria [ASAS20]), and improvement in physician’s clinical global impression of change. For quality of life outcome, we preferentially abstracted the EuroQoL-5 Dimensions (EQ-5D) over Short Form-36 (SF-36) physical and mental components summary scores (PCS and MCS), and synthesized the two scales separately.

Effects on harms were organized by drug class and based on the proportion of patients experiencing adverse events. Generalized adverse events (e.g., serious adverse events, withdrawal due to adverse events, overdose and misuse), were abstracted for all classes of drugs. In addition, harms specific to each drug class were abstracted when available but limited to the items found in Table B-1. While the scope of this review limited the number of harms we could capture and report for each drug we recognize that other adverse events specific to an individual drug class do exist. For more information on these please refer to Table 21 in the main text. Nonopioid drugs considered in this review were categorized as, anticonvulsant drugs, benzodiazepines, nonsteroidal anti-inflammatory drugs (NSAIDs), skeletal muscle relaxants,

antidepressants (e.g., SNRIs and Tricyclics), topical drugs (e.g., lidocaine or capsaicin), acetaminophen, memantine, and all forms of cannabis.

Table B-2. Harms

Drug(s)/Drug Class	Harms by Drug Class
All drugs	Withdrawal due to adverse events, serious adverse events, overdose, misuse, and dependence
Serotonin-norepinephrine reuptake inhibitor antidepressants	Cognitive effects, nausea, sedation
Tricyclic antidepressants	Cardiac rhythm abnormalities, cognitive effects, dry mouth, urinary retention, weight gain
Pregabalin/gabapentin anticonvulsants	Blurred vision, cognitive effects, dizziness, peripheral edema, sedation, weight gain
Oxcarbazepine/carbamazepine anticonvulsants	Cognitive effects, hyponatremia, neutropenia, sedation
NSAIDs	CV events, GI, liver dysfunction, renal dysfunction
Skeletal muscle relaxants	Dry mouth, sedation, urinary retention
Acetaminophen	Liver toxicity
Memantine	Cardiac rhythm abnormalities, cognitive effects, dizziness, sedation
Topical (any)	Application site reactions
Topical lidocaine	Cardiotoxicity, cognitive effects
Topical diclofenac	CV events, GI, liver dysfunction, renal dysfunction
Cannabis	Addiction/dependence, cognitive effects, hyperemesis, nausea, sedation

Assessment of Methodological Risk of Bias of Individual Studies

Risk of bias was used to assess the quality of included RCTs based on principles for appraisal as developed by the Cochrane Back and Neck Group,⁴ and outlined in the *AHRQ EPC Methods Guide* chapter “Assessing the Risk of Bias of Individual Studies When Comparing Medical Interventions”.^{1,5} Given the risk of bias assessment, each included study was rated as “good,” “fair,” or “poor” quality. Assessments of RCTs included in good-quality systematic reviews that we included here were reviewed by a single reviewer, with the exception that any rated poor quality or high risk of bias were re-assessed by our team using dual review.

Studies rated “good” are considered to have the least risk of bias, and their results are considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates and clear reporting of dropouts; appropriate means for preventing bias; and appropriate measurement of outcomes.

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 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 will 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 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 least as likely to reflect flaws in the study design as the true difference between the compared interventions. We did not exclude studies

rated as being poor in quality a priori, but poor-quality studies were considered to be less reliable than higher-quality studies when synthesizing the evidence, particularly if discrepancies between studies were present.

Data Analysis and Synthesis

Data were synthesized qualitatively (e.g., ranges and descriptive analysis) and quantitatively using meta-analysis where appropriate. Results are organized by Key Question (i.e., Effectiveness and Comparative Effectiveness and Harms and Adverse Events). Subquestions are then organized by pain condition and again by intervention within that condition (e.g., Osteoarthritis, duloxetine vs. placebo). Outcomes for effectiveness and comparative effectiveness were pain, function, and quality of life given treatment durations of 1 to <6 months (short term), 6 to 12 months (intermediate term), and more than 12 months (long term) (≥ 12 months).

Using Stata©/IC 12.1 (StatsCorp, College Station, TX), meta-analyses were conducted using the profile-likelihood model^{6,7} or Dersimonian-Laird model,⁸ when profile-likelihood model did not converge. Statistical heterogeneity among studies was assessed using the standard Cochran's chi-square test and the I^2 statistic.⁹ Pooled mean differences (MD) or standardized mean differences (SMD) were calculated for continuous pain assessment, function, quality of life, anxiety, depression, and sleep disturbances. Pooled relative risks (RR) were calculated for pain response and harms (e.g., withdrawals due to adverse events, serious adverse events). In addition, we performed subgroup and sensitivity analyses based on specific drug, drug dose, pain condition (e.g., rheumatoid arthritis vs. ankylosing spondylitis, diabetic polyneuropathy vs. postherpetic neuralgia vs. other neuropathic pain, osteoarthritis of the knee vs. hip vs. knee/hip vs. all sites), study quality (good or fair), and publication year (≤ 2000 or ≥ 2001). For analyses with more than 10 studies that were sufficiently homogeneous with regard to populations, interventions, and outcomes, publication bias was assessed using Funnel plot. Meta-analyses of harms outcomes included all treatment duration and were stratified by pain condition.

Pain outcomes were standardized to a scale of 0-10; SMD was calculated for other outcomes (e.g., function, quality of life) unless all pertinent studies assessed the outcome using the same scale. Studies with multiple nonopioid arms 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. When reported, adjusted MD from analysis of covariance model or other appropriate regression models was used if reported by the study, followed by difference in change score and followup score. Below lists hierarchical order for calculating missing standard deviations (SD):

- For followup score, missing SD was imputed by assuming constant coefficient of variation across included studies.
- For change score, it is not appropriate to assume constant coefficient of variation to impute missing SD given variability in treatment effects among studies. Instead,
 - If baseline mean and SD were available, we imputed followup SD assuming constant coefficient of variation and calculated SD for change score assuming $\rho = 0.5$
 - If baseline mean was available and SD was not, we imputed followup SD assuming constant coefficient of variation and used it as change score SD (This is equivalent to assuming the same baseline and followup SD, and calculating SD for change score assuming $\rho = 0.5$.)

- If both baseline mean and SD were not available, we imputed change score SD as the average of follow up SD of other studies for the same outcome.
- The imputed values were based on all available data from the same outcome, which did not appear to vary much by type of pain or opioid.
- If the study publication was missing crucial data (e.g., SD, standard error [SE], change score), we searched www.ClinicalTrials.gov and abstracted the data when available.

Grading the Strength of Evidence for Major Comparisons and Outcomes

Regardless of whether evidence was synthesized quantitatively or qualitatively, the strength of evidence (SOE) was assessed for priority clinical outcomes (pain, function, quality of life) on each pain condition-treatment pair, using the approach described in the *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.¹ To ensure consistency and validity of the evaluation, the grades were reviewed by a second reviewer. The domains assessed were study limitations (low, medium, or high), consistency (consistent, inconsistent, or unknown/not applicable), directness (direct or indirect), precision (precise or imprecise), and publication bias (suspected or undetected). Details of how each domain was assessed can be found in the AHRQ guidance. In general, study limitations were determined by the quality or risk of bias rating of the majority of studies reporting a given outcome. Consistency was evaluated based on the consistency of the point estimates (direction and magnitude) in a body of evidence, and the I^2 statistic if a meta-analysis was conducted. Directness was determined based on the comparison, population, and outcome being those that were identified in the Key Questions. Precision was determined first based on whether the body of evidence met the optimal information size (OIS) for a given outcome, and then based on interpretation of the 95% confidence intervals. For precision, we followed the guidance of the GRADE organization. The SOE was assigned an overall grade of high, moderate, low, or insufficient, reflecting our confidence in the effect estimates and whether the findings are stable. Evidence is found to be insufficient to draw conclusions when we have no evidence available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion. A definition of the SOE grades is as follows:

- High - Very confident that the effect estimate lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. Findings are stable, i.e., inclusion of additional studies would not change the conclusions.
- Moderate - 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 - Limited confidence that the effect estimate lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies. Additional evidence is needed before concluding that the findings are stable or that the estimate of effect is close to the true effect.
- Insufficient - 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.

Appendix C. Included Studies

1. Abou-Raya S, Abou-Raya A, Helmii M. Duloxetine for the management of pain in older adults with knee osteoarthritis: randomised placebo-controlled trial. *Age Ageing*. 2012 Sep;41(5):646-52. doi: 10.1093/ageing/afs072. PMID: 22743149.
2. Allen R, Sharma U, Barlas S. Clinical experience with desvenlafaxine in treatment of patients with fibromyalgia syndrome. *Clin Pharmacol Drug Dev*. 2017 May;6(3):224-33. doi: 10.1002/cpdd.271. PMID: 27139158.
3. Altman R, Hochberg M, Gibofsky A, et al. Efficacy and safety of low-dose SoluMatrix meloxicam in the treatment of osteoarthritis pain: a 12-week, phase 3 study. *Curr Med Res Opin*. 2015 Dec;31(12):2331-43. doi: 10.1185/03007995.2015.1112772. PMID: 26503347.
4. Altman RD, Zinsenheim JR, Temple AR, et al. Three-month efficacy and safety of acetaminophen extended-release for osteoarthritis pain of the hip or knee: a randomized, double-blind, placebo-controlled study. *Osteoarthritis Cartilage*. 2007 Apr;15(4):454-61. doi: 10.1016/j.joca.2006.10.008. PMID: 17142063.
5. Andelman SY. Etodolac, aspirin, and placebo in patients with degenerative joint disease: a twelve-week study. *Clin Ther*. 1983;5(6):651-61. PMID: 6226358.
6. Arezzo JC, Rosenstock J, Lamoreaux L, et al. Efficacy and safety of pregabalin 600 mg/d for treating painful diabetic peripheral neuropathy: a double-blind placebo-controlled trial. *BMC Neurol*. 2008 Sep 16;8(33):doi: 10.1186/1471-2377-8-33. PMID: 18796160.
7. Arnold L, Gendreau R, Palmer R, et al. Efficacy and safety of milnacipran 100 mg/day in patients with fibromyalgia: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum*. 2010b Sep;62(9):2745-56. doi: 10.1002/art.27559. PMID: 20496365.
8. Arnold LM, Clauw D, Wang F, et al. Flexible dosed duloxetine in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. *J Rheumatol*. 2010a Dec;37(12):2578-86. doi: 10.3899/jrheum.100365. PMID: 20843911.
9. Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum*. 2007a Apr;56(4):1336-44. doi: 10.1002/art.22457. PMID: 17393438.
10. Arnold LM, Hudson JI, Wang F, et al. Comparisons of the efficacy and safety of duloxetine for the treatment of fibromyalgia in patients with versus without major depressive disorder. *Clin J Pain*. 2009 Jul-Aug;25(6):461-8. doi: 10.1097/AJP.0b013e318197d4e4. PMID: 19542792.
11. Arnold LM, Lu Y, Crofford LJ, et al. A double-blind, multicenter trial comparing duloxetine with placebo in the treatment of fibromyalgia patients with or without major depressive disorder. *Arthritis Rheum*. 2004 Sep;50(9):2974-84. doi: 10.1002/art.20485. PMID: 15457467.
12. Arnold LM, Palmer RH, Gendreau RM, et al. Relationships among pain, depressed mood, and global status in fibromyalgia patients: post hoc analyses of a randomized, placebo-controlled trial of milnacipran. *Psychosomatics*. 2012b Jul-Aug;53(4):371-9. doi: 10.1016/j.psych.2012.02.005. PMID: 22677218.
13. Arnold LM, Rosen A, Pritchett YL, et al. A randomized, double-blind, placebo-controlled trial of duloxetine in the treatment of women with fibromyalgia with or without major depressive disorder. *Pain*. 2005 Dec 15;119(1-3):5-15. doi: 10.1016/j.pain.2005.06.031. PMID: 16298061.

14. Arnold LM, Russell IJ, Diri EW, et al. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. *J Pain*. 2008 Sep;9(9):792-805. doi: 10.1016/j.jpain.2008.03.013. PMID: 18524684.
15. Arnold LM, Wang F, Ahl J, et al. Improvement in multiple dimensions of fatigue in patients with fibromyalgia treated with duloxetine: secondary analysis of a randomized, placebo-controlled trial. *Arthritis Res Ther*. 2011 Jun 13;13(3):R86. doi: 10.1186/ar3359. PMID: 21668963.
16. Arnold LM, Whitaker S, Hsu C, et al. Efficacy and safety of mirogabalin for the treatment of fibromyalgia: results from three 13-week randomized, double-blind, placebo-and active-controlled, parallel-group studies and a 52-week open-label extension study. *Curr Med Res Opin*. 2019 Jul 9:1-11. doi: 10.1080/03007995.2019.1629757. PMID: 31284771.
17. Arnold LM, Zhang S, Pangallo BA. Efficacy and safety of duloxetine 30 mg/d in patients with fibromyalgia: a randomized, double-blind, placebo-controlled study. *Clin J Pain*. 2012a Nov-Dec;28(9):775-81. doi: 10.1097/AJP.0b013e3182510295. PMID: 22971669.
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21. Baerwald C, Verdecchia P, Duquesroix B, et al. Efficacy, safety, and effects on blood pressure of naproxen 750 mg twice daily compared with placebo and naproxen 500 mg twice daily in patients with osteoarthritis of the hip: a randomized, double-blind, parallel-group, multicenter study. *Arthritis Rheum*. 2010 Dec;62(12):3635-44. doi: 10.1002/art.27694. PMID: 20722026.
22. Bakshi R, Ezzet N, Frey L, et al. Efficacy and tolerability of diclofenac dispersible in painful osteoarthritis. *Clin Rheumatol*. 1993 Mar;12(1):57-61. PMID: 7682167.
23. Baraf HS, Gold MS, Clark MB, et al. Safety and efficacy of topical diclofenac sodium 1% gel in knee osteoarthritis: a randomized controlled trial. *Phys Sportsmed*. 2010 Jun;38(2):19-28. doi: 10.3810/psm.2010.06.1779. PMID: 20631460.
24. Barkhuizen A, Steinfeld S, Robbins J, et al. Celecoxib is efficacious and well tolerated in treating signs and symptoms of ankylosing spondylitis. *J Rheumatol*. 2006 Sep;33(9):1805-12. PMID: 16960941.
25. Barthel HR, Haselwood D, Longley S, 3rd, et al. Randomized controlled trial of diclofenac sodium gel in knee osteoarthritis.[Erratum appears in *Semin Arthritis Rheum*. 2010 Aug;40(1):95]. *Semin Arthritis Rheum*. 2009 Dec;39(3):203-12. doi: <https://dx.doi.org/10.1016/j.semarthrit.2009.09.002>. PMID: 19932833.
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220. Zhang L, Rainka M, Freeman R, et al. A randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of gabapentin enacarbil in subjects with neuropathic pain associated with postherpetic neuralgia (PXN110748). *J Pain.* 2013 Jun;14(6):590-603. doi: 10.1016/j.jpain.2013.01.768. PMID: 23602345.
221. Zhao SZ, Fiechtner JI, Tindall EA, et al. Evaluation of health-related quality of life of rheumatoid arthritis patients treated with celecoxib. *Arthritis Care Res (Hoboken).* 2000 Apr;13(2):112-21. doi: 10.1002/1529-0131%28200004%2913:2%3C112::AID-ANR5%3E3.0.CO;2-L. PMID: 14635284.
222. Zhao SZ, McMillen JI, Markenson JA, et al. Evaluation of the functional status aspects of health-related quality of life of patients with osteoarthritis treated with celecoxib. *Pharmacotherapy.* 1999 Nov;19(11):1269-78. PMID: 10555933.

Appendix D. Excluded Studies

Table D-1. Key to exclusion codes

Exclusion Code	Exclusion Reason
1	Included primary or secondary publication
2	Foreign language
3	Ineligible intervention (including comparator)
4	Ineligible population
5	Ineligible publication type
6	Ineligible study design
7	Study not obtainable
8	Outdated or ineligible systematic review
9	Study duration <12 weeks

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| <p>1. Duloxetine effective for fibromyalgia in some women. <i>J Fam Pract.</i> 2006 May;55(5):382. PMID: 16722009. Exclusion: 5</p> | <p>7. Ahern MJ, Wetherall M, Leslie A, et al. A comparison of ketoprofen SR and sulindac in the elderly with rheumatoid arthritis. <i>Br J Clin Pract.</i> 1992 Winter;46(4):229-33. PMID: 1290729. Exclusion: 3</p> |
| <p>2. Accardo S, Seriola B, Samanta E, et al. Controlled-release naproxen in rheumatoid arthritis. <i>Curr Ther Res Clin Exp.</i> 1991;49(6):936-42. Exclusion: 3</p> | <p>8. Ahmed M, Aamir R, Jishi Z, et al. The effects of milnacipran on sleep disturbance in fibromyalgia: a randomized, double-blind, placebo-controlled, two-way crossover study. <i>J Clin Sleep Med.</i> 2016 Jan;12(1):79-86. doi: 10.5664/jcsm.5400. PMID: 26414990. Exclusion: 9</p> |
| <p>3. Acevedo E, Castaneda O, Ugaz M, et al. Tolerability profiles of rofecoxib (Vioxx) and Arthrotec. A comparison of six weeks treatment in patients with osteoarthritis. <i>Scand J Rheumatol.</i> 2001;30(1):19-24. doi: 10.1080/030097401750065274 PMID: 11252687. Exclusion: 3</p> | <p>9. Aicher B, Peil H, Peil B, et al. Pain measurement: Visual Analogue Scale (VAS) and Verbal Rating Scale (VRS) in clinical trials with OTC analgesics in headache. <i>Cephalalgia.</i> 2012 Feb;32(3):185-97. doi: 10.1177/0333102411430856. PMID: 22332207. Exclusion: 3</p> |
| <p>4. Admani AK, Verma S. A study of sulindac versus ibuprofen in elderly patients with osteoarthritis. <i>Curr Med Res Opin.</i> 1983;8(5):315-20. doi: 10.1185/03007998309112390. PMID: 6839797. Exclusion: 3</p> | <p>10. Al MJ, Maniadakis N, Grijseels EW, et al. Costs and effects of various analgesic treatments for patients with rheumatoid arthritis and osteoarthritis in the Netherlands. <i>Value Health.</i> 2008 Jul-Aug;11(4):589-99. doi: 10.1111/j.1524-4733.2007.00303.x. PMID: 18194404. Exclusion: 6</p> |
| <p>5. Agrawal N, Van Kerckhove HE, Erhardt LJ, et al. Misoprostol coadministered with diclofenac for prevention of gastroduodenal ulcers. A one-year study. <i>Dig Dis Sci.</i> 1995 May;40(5):1125-31. doi: 10.1007/BF02064210. PMID: 7729275. Exclusion: 3</p> | <p>11. Alballa S, Al-Arfaj H, Al-Sugair S, et al. Randomized, double-blind, short-term trial of nabumetone versus diclofenac in osteoarthritis of the knee. <i>Curr Ther Res Clin Exp.</i> 1992;52(4):581-6. doi: 10.1016/S0011-393X(05)80465-5. Exclusion: 10</p> |
| <p>6. Agrawal NM, Roth S, Graham DY, et al. Misoprostol compared with sucralfate in the prevention of nonsteroidal anti-inflammatory drug-induced gastric ulcer. A randomized, controlled trial. <i>Ann Intern Med.</i> 1991 Aug 1;115(3):195-200. doi: 10.7326/0003-4819-115-3-195. PMID: 1905501. Exclusion: 3</p> | |

12. Alballa S, AlNasser A, AlArfaj H, et al. A randomized double-blind short-term trial of tenoxicam versus piroxicam in osteoarthritis of the knee. *Curr Ther Res Clin Exp*. 1990;47(3):591-6. Exclusion: 10
13. Alcock J, Jones E, Rust P, et al. Controlled trial of imipramine for chronic low back pain. *J Fam Pract*. 1982 May;14(5):841-6. PMID: 6210751. Exclusion: 9
14. Alda M, Luciano JV, Andres E, et al. Effectiveness of cognitive behaviour therapy for the treatment of catastrophisation in patients with fibromyalgia: a randomised controlled trial. *Arthritis Res Ther*. 2011;13(5):R173. doi: 10.1186/ar3496. PMID: 22018333. Exclusion: 3
15. Aldrete JA, Aldrete VT, Williams SK, et al. Reduction of neuropathic pain in patients with arachnoiditis: crossover study of gabapentin versus phenytoin. *Pain digest*. 2000;10(2):64-7. Exclusion: 6
16. Alexander SJ. Clinical experience with naproxen in rheumatoid arthritis. *Arch Intern Med*. 1975 Nov;135(11):1429-35. PMID: 1103765. Exclusion: 6
17. Alharbi GS, Chen LC, Knaggs R. Efficacy of anticonvulsant, antidepressant and opioid in treating neuropathic pain - A systematic review and meta-analysis. *Pharmacoepidemiol Drug Saf*. 2016;25(Suppl 3):583-4. doi: 10.1002/pds.4070. Exclusion: 8
18. Alho A, Jaer O, Slungaard U, et al. Piroxicam and naproxen in patients with osteoarthritis of the hip waiting for total hip replacement. *Clin Rheumatol*. 1988 Jun;7(2):208-13. PMID: 3046826. Exclusion: 9
19. al-Quorain AA, Satti MB, Marwah S, et al. Non-steroidal anti-inflammatory drug-induced gastropathy: a comparative endoscopic and histopathological evaluation of the effects of tenoxicam and diclofenac. *J Int Med Res*. 1993 Mar-Apr;21(2):89-97. doi: 10.1177/030006059302100204. PMID: 8243794. Exclusion: 2
20. Al-Sharkawi MS. A multicentre study of diclofenac sodium slow-release (Voltaren Retard) in the treatment of rheumatic disorders in the Kingdom of Saudi Arabia. *J Int Med Res*. 1984;12(4):244-9. doi: 10.1177/030006058401200404. PMID: 6381168. Exclusion: 6
21. Altman RD, Dreiser R-L, Fisher CL, et al. Diclofenac sodium gel in patients with primary hand osteoarthritis: a randomized, double-blind, placebo-controlled trial. *J Rheumatol*. 2009 Sep;36(9):1991-9. doi: 10.3899/jrheum.081316. PMID: 19648310. Exclusion: 9
22. Altman RD, Moskowitz R. Intraarticular sodium hyaluronate (Hyalgan) in the treatment of patients with osteoarthritis of the knee: a randomized clinical trial. Hyalgan Study Group.[Erratum appears in *J Rheumatol* 1999 May;26(5):1216]. *J Rheumatol*. 1998 Nov;25(11):2203-12. PMID: 9818665. Exclusion: 3
23. Altman RD, Strand V, Hochberg MC, et al. Low-dose SoluMatrix diclofenac in the treatment of osteoarthritis: a 1-year, open-label, phase III safety study. *Postgrad Med*. 2015 Jun;127(5):517-28. doi: 10.1080/00325481.2015.1040716. PMID: 25913498. Exclusion: 6
24. Amante CM. Randomized comparative study on programmed released ketoprofen vs. piroxicam in the treatment of rheumatoid arthritis. *Philippine Journal of Internal Medicine*. 1988;26(2):69-73. Exclusion: 3
25. Ambanelli U, Nervetti A, Colombo B, et al. Piroxicam-beta-cyclodextrin in the treatment of rheumatic diseases: a prospective study. *Curr Ther Res Clin Exp*. 1990;48(1):58-68. Exclusion: 3
26. Ambanelli U, Nervetti A, Colombo B, et al. β -cyclodextrin-piroxicam in the treatment of rheumatic diseases: a prospective study. *J Drug Development*. 1991;4(1):55-66. Exclusion: 3
27. Ammitzboll F. Fenbufen and indomethacin in the treatment of rheumatoid arthritis. A comparative double-blind, crossover study. *Scand J Rheumatol Suppl*. 1979(23):5-10. PMID: 373083. Exclusion: 3

28. Anderberg UM, Marteinsdottir I, von Knorring L. Citalopram in patients with fibromyalgia--a randomized, double-blind, placebo-controlled study. *Eur J Pain*. 2000;4(1):27-35. doi: 10.1053/eujp.1999.0148. PMID: 10833553. Exclusion: 3
29. Anderson JA, Lee P, Webb J, et al. Evaluation of the therapeutic potential of ketoprofen in rheumatoid arthritis. *Curr Med Res Opin*. 1974;2(4):189-97. doi: 10.1185/03007997409112306. PMID: 4601567. Exclusion: 3
30. Anderson JJ, Firschein HE, Meenan RF. Sensitivity of a health status measure to short-term clinical changes in arthritis. *Arthritis Rheum*. 1989 Jul;32(7):844-50. PMID: 2665756. Exclusion: 6
31. Andrew A, Rodda B, Verhaest L, et al. Diflunisal: six-month experience in osteoarthritis. *Br J Clin Pharmacol*. 1977 Feb;4 Suppl 1:45S-52S. doi: 10.1111/j.1365-2125.1977.tb04514.x. PMID: 328034. Exclusion: 3
32. Anonymous. Clinical evaluation of ketoprofen in rheumatoid arthritis--early phase II study by multi-clinical trial. New drug research group. *Ryumachi*. 1973 Jul;13(3):256-60. PMID: 4755623. Exclusion: 9
33. Anonymous. Migraine treated with an antihistamine-analgesic combination. *Practitioner*. 1973 Sep;211(263):357-61. PMID: 4148490. Exclusion: 3
34. Anonymous. The simultaneous assessment of four nonsteroidal antiinflammatory drugs in rheumatoid arthritis using a simple and rapid trial design. Australasia Multicentre Trial Group. *J Rheumatol*. 1980 Nov-Dec;7(6):857-64. PMID: 7009858. Exclusion: 6
35. Anonymous. Piroxicam vs indomethacin: a double blind multicenter comparative study in osteoarthritis. A Canadian Multicenter Study. *J Rheumatol*. 1985 Apr;12(2):328-36. PMID: 3897535. Exclusion: 3
36. Anonymous. A double blind comparison of piroxicam and enteric coated ASA in rheumatoid arthritis. A cooperative multicenter Canadian trial. *J Rheumatol*. 1985 Feb;12(1):68-77. PMID: 3884806. Exclusion: 3
37. Anonymous. Nabumetone: new preparation. Just another NSAID. *Prescrire Int*. 2000 Apr;9(46):43-6. PMID: 11503785. Exclusion: 5
38. Ansell BM, Carter ME, Gumpel JM, et al. Clinical studies with tolmetin: open study and a double-blind cross-over comparison with aspirin in rheumatoid arthritis. *Rheumatol Rehabil*. 1978 Aug;17(3):150-4. PMID: 360360. Exclusion: 9
39. Anthony M, Lance JW. Indomethacin in migraine. *Med J Aust*. 1968 Jan 13;1(2):56-7. PMID: 4867513. Exclusion: 4
40. Arai Y-CP, Matsubara T, Shimo K, et al. Low-dose gabapentin as useful adjuvant to opioids for neuropathic cancer pain when combined with low-dose imipramine. *J Anesth*. 2010 Jun;24(3):407-10. doi: 10.1007/s00540-010-0913-6 PMID: 20217150. Exclusion: 6
41. Argoff CE. Review of current guidelines on the care of postherpetic neuralgia. *Postgrad Med*. 2011 Sep;123(5):134-42. doi: 10.3810/pgm.2011.09.2469. PMID: 21904096. Exclusion: 6
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43. Armstrong DG, Chappell AS, Le TK, et al. Duloxetine for the management of diabetic peripheral neuropathic pain: evaluation of functional outcomes.[Erratum appears in *Pain Med*. 2007 Nov-Dec;8(8):690]. *Pain Med*. 2007 Jul-Aug;8(5):410-8. doi: 10.1111/j.1526-4637.2007.00276.x. PMID: 17661854. Exclusion: 6
44. Arnold LM. Duloxetine and other antidepressants in the treatment of patients with fibromyalgia. *Pain Med*. 2007 Sep;8(Suppl 2):S63-74. doi: 10.1111/j.1526-4637.2006.00178.x. PMID: 17714117. Exclusion: 6

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46. Arnold LM, Arsenault P, Huffman C, et al. Once daily controlled-release pregabalin in the treatment of patients with fibromyalgia: a phase III, double-blind, randomized withdrawal, placebo-controlled study.[Erratum appears in *Curr Med Res Opin.* 2017 Apr;33(4):795-796; PMID: 28276874]. *Curr Med Res Opin.* 2014 Oct;30(10):2069-83. doi: 10.1185/03007995.2014.928275. PMID: 24867298. Exclusion: 6
47. Arnold LM, Bateman L, Palmer RH, et al. Preliminary experience using milnacipran in patients with juvenile fibromyalgia: lessons from a clinical trial program. *Pediatr Rheumatol Online J.* 2015 Jun 26;13:27. doi: 10.1186/s12969-015-0025-9. PMID: 26112278. Exclusion: 4
48. Arnold LM, Choy E, Clauw DJ, et al. An evidence-based review of pregabalin for the treatment of fibromyalgia. *Curr Med Res Opin.* 2018 Aug;34(8):1397-409. doi: 10.1080/03007995.2018.1450743. PMID: 29519159. Exclusion: 8
49. Arnold LM, Crofford LJ, Martin SA, et al. The effect of anxiety and depression on improvements in pain in a randomized, controlled trial of pregabalin for treatment of fibromyalgia. *Pain Med.* 2007 Nov-Dec;8(8):633-8. doi: 10.1111/j.1526-4637.2007.00332.x. PMID: 18028041. Exclusion: 9
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52. Arnold LM, Pritchett YL, D'Souza DN, et al. Duloxetine for the treatment of fibromyalgia in women: pooled results from two randomized, placebo-controlled clinical trials. *J Womens Health (Larchmt).* 2007 Oct;16(8):1145-56. doi: 10.1089/jwh.2006.0213. PMID: 17937567. Exclusion: 6
53. Arnold LM, Sarzi-Puttini P, Arsenault P, et al. Efficacy and safety of pregabalin in patients with fibromyalgia and comorbid depression taking concurrent antidepressant medication: a randomized, placebo-controlled study. *J Rheumatol.* 2015 Jul;42(7):1237-44. doi: 10.3899/jrheum.141196. PMID: 26034150. Exclusion: 9
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56. Atalay H, Solak Y, Biyik Z, et al. Cross-over, open-label trial of the effects of gabapentin versus pregabalin on painful peripheral neuropathy and health-related quality of life in haemodialysis patients. *Clin Drug Investig.* 2013 Jun;33(6):401-8. doi: 10.1007/s40261-013-0080-2. PMID: 23572323. Exclusion: 9
57. Ataoglu S, Ataoglu A, Erdogan F, et al. Comparison of paroxetine, amitriptyline in the treatment of fibromyalgia. *Turk J Med Sci.* 1997;27(6):535-9. Exclusion: 3

58. Atkinson M, Germain G, Lee P. The efficacy and safety of sulindac (400 mg vs 600 mg daily) in rheumatoid arthritis. A Canadian multicentre study. *J Rheumatol*. 1988 Jun;15(6):1001-4. PMID: 3047380. Exclusion: 9
59. Atra E, Metz CA, Brown BL, et al. Flurbiprofen versus diclofenac for the treatment of osteoarthritis of the knee. *DICP*. 1990 Oct;24(10):920-3. PMID: 2244403. Exclusion: 9
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61. Aylward M, Maddock J, Lewis PA, et al. Mefenamic acid and diclofenac sodium in osteoarthritis of the weight bearing joints: a double blind comparison. *Br J Clin Pract*. 1985 Apr;39(4):135-9. PMID: 3893502. Exclusion: 3
62. Aylward M, Maddock J, Parker RJ, et al. Evaluation of tolmetin in the treatment of arthritis: open and controlled double-blind studies. *Curr Med Res Opin*. 1976;4(2):158-69. doi: 10.1185/03007997609109297. PMID: 776539. Exclusion: 6
63. Aylward M, Parker RJ, Holly F, et al. Long-term study of indomethacin and alclofenac in treatment of rheumatoid arthritis. *Br Med J*. 1975 Apr 5;2(5961):7-9. doi: 10.1136/bmj.2.5961.7. PMID: 236805. Exclusion: 3
64. Backonja M, Beydoun A, Edwards KR, et al. Gabapentin for the symptomatic treatment of painful neuropathy in patients with diabetes mellitus: a randomized controlled trial. *JAMA*. 1998 Dec 2;280(21):1831-6. doi: 10.1001/jama.280.21.1831. PMID: 9846777. Exclusion: 9
65. Backonja MM. Gabapentin monotherapy for the symptomatic treatment of painful neuropathy: a multicenter, double-blind, placebo-controlled trial in patients with diabetes mellitus. *Epilepsia*. 1999;40 Suppl 6:S57-9; discussion S73-4. doi: 10.1111/j.1528-1157.1999.tb00934.x. PMID: 10530684. Exclusion: 9
66. Bacon PA. Safety profile of etodolac in the elderly population. *Eur J Rheumatol Inflamm*. 1994;14(1):19-22. PMID: 7744124. Exclusion: 5
67. Bacon PA, Davies J, Ring FJ. Benoxaprofen--dose-range studies using quantitative thermography. *J Rheumatol Suppl*. 1980;6:48-53. PMID: 6993672. Exclusion: 3
68. Baer PA, Thomas LM, Shainhouse Z. Treatment of osteoarthritis of the knee with a topical diclofenac solution: a randomised controlled, 6-week trial [ISRCTN53366886]. *BMC Musculoskelet Disord*. 2005 Aug 8;6(44)doi: 10.1186/1471-2474-6-44. PMID: 16086839. Exclusion: 9
69. Bahous I. Double-blind multicentre, between patients comparison of two different doses of indoprofen and one of indomethacin in osteoarthritis. *Eur J Rheumatol Inflamm*. 1981;4(1):118-25. PMID: 7042355. Exclusion: 3
70. Bain LS, el-Ghobarey AF, Collins RM, et al. Tolmetin: an evaluation of a new preparation in the treatment of rheumatoid arthritis. *Br J Clin Pract*. 1975 Aug;29(8):208-10. PMID: 1100086. Exclusion: 3
71. Bakshi R. Comparative efficacy and tolerability of two diclofenac formulations in the treatment of painful osteoarthritis. *Br J Clin Pract*. 1996 Sep;50(6):294-7. PMID: 8983316. Exclusion: 3
72. Balme HW, Wojtulewski JA, Huskisson EC. Clinical experience with tolmetin sodium. *Curr Med Res Opin*. 1980;7(2):127-30. doi: 10.1185/03007998009112039. PMID: 7002482. Exclusion: 5
73. Banerjee M, Pal S, Bhattacharya B, et al. A comparative study of efficacy and safety of gabapentin versus amitriptyline as coanalgesics in patients receiving opioid analgesics for neuropathic pain in malignancy. *Indian J Pharmacol*. 2013 Jul-Aug;45(4):334-8. doi: 10.4103/0253-7613.115000. PMID: 24014906. Exclusion: 4
74. Bank J. A comparative study of amitriptyline and fluvoxamine in migraine prophylaxis. *Headache*. 1994 Sep;34(8):476-8. PMID: 7960733. Exclusion: 3

75. Bannuru RR, Schmid CH, Kent DM, et al. Comparative effectiveness of pharmacologic interventions for knee osteoarthritis: a systematic review and network meta-analysis. *Ann Intern Med.* 2015 Jan 06;162(1):46-54. doi: 10.7326/M14-1231. PMID: 25560713. Exclusion: 8
76. Bannwarth B. Safety of the nonselective NSAID nabumetone : focus on gastrointestinal tolerability. *Drug Saf.* 2008;31(6):485-503. doi: 10.2165/00002018-200831060-00004. PMID: 18484783. Exclusion: 8
77. Bansal D, Bhansali A, Hota D, et al. Amitriptyline vs. pregabalin in painful diabetic neuropathy: a randomized double blind clinical trial. *Diabet Med.* 2009 Oct;26(10):1019-26. doi: 10.1111/j.1464-5491.2009.02806.x. PMID: 19900234. Exclusion: 9
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79. Baraf HSB, Fuentealba C, Greenwald M, et al. Tolerability and effectiveness of etoricoxib compared to diclofenac sodium in patients with osteoarthritis: a randomized controlled study (EDGE trial). *Arthritis Rheum.* 2004;50(9):S346-7. Exclusion: 3
80. Barnard-Jones K, Davies RW, Lalla O, et al. Mefenamic acid versus ibuprofen in osteoarthritis--a double-blind cross-over study. *Br J Clin Pract.* 1986 Dec;40(12):528-31. PMID: 3307863. Exclusion: 9
81. Baron R, Mayoral V, Leijon G, et al. 5% lidocaine medicated plaster versus pregabalin in post-herpetic neuralgia and diabetic polyneuropathy: an open-label, non-inferiority two-stage RCT study. *Curr Med Res Opin.* 2009 Jul;25(7):1663-76. doi: 10.1185/03007990903047880. PMID: 19485723. Exclusion: 9
82. Baron R, Mayoral V, Leijon G, et al. Efficacy and safety of combination therapy with 5% lidocaine medicated plaster and pregabalin in post-herpetic neuralgia and diabetic polyneuropathy. *Curr Med Res Opin.* 2009 Jul;25(7):1677-87. doi: 10.1185/03007990903048078. PMID: 19480610. Exclusion: 9
83. Barraclough DR, Lenaghan E, Muirden KD. A comparison of flurbiprofen and aspirin in the treatment of rheumatoid arthritis. *Med J Aust.* 1974 Dec 28;2(26):925-7. PMID: 4616159. Exclusion: 3
84. Battagliotti CA, Baetti EA. Clinical, double-blind long-term study of tenoxicam 20 mg (Ro 12-0068) versus piroxicam 20 mg in patients with gonarthrosis. *Eur J Rheumatol Inflamm.* 1987;9(2):74-6. PMID: 3329112. Exclusion: 3
85. Baumgartner H, Hohmeister R, Blumenberg-Novoselac N. An observer-blind crossover study to compare the efficacies of flurbiprofen, indomethacin and naproxen given orally and rectally in the relief of night pain and morning stiffness due to rheumatoid arthritis. *J Int Med Res.* 1988 May-Jun;16(3):189-96. doi: 10.1177/030006058801600304. PMID: 2457523. Exclusion: 3
86. Bayley TR, Haslock I. Night medication in rheumatoid arthritis. *J R Coll Gen Pract.* 1976 Aug;26(169):591-4. PMID: 787518. Exclusion: 4
87. Bedaiwi MK, Sari I, Wallis D, et al. Clinical Efficacy of Celecoxib Compared to Acetaminophen in Chronic Nonspecific Low Back Pain: Results of a Randomized Controlled Trial. *Arthritis Care Res (Hoboken).* 2016 Jun;68(6):845-52. doi: 10.1002/acr.22753. PMID: 26474041. Exclusion: 9
88. Beesdo K, Hartford J, Russell J, et al. The short- and long-term effect of duloxetine on painful physical symptoms in patients with generalized anxiety disorder: results from three clinical trials. *J Anxiety Disord.* 2009 Dec;23(8):1064-71. doi: 10.1016/j.janxdis.2009.07.008. PMID: 19643572. Exclusion: 4

89. Beghi E. The use of anticonvulsants in neurological conditions other than epilepsy: A review of the evidence from randomized controlled trials. *CNS Drugs*. 1999;11(1):61-82. Exclusion: 6
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91. Bellamy N, Bensen WG, Beaulieu A, et al. A multicenter study of nabumetone and diclofenac SR in patients with osteoarthritis. *J Rheumatol*. 1995 May;22(5):915-20. PMID: 8587082. Exclusion: 2
92. Bellamy N, Buchanan WW, Goldsmith CH, et al. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*. 1988 Dec;15(12):1833-40. PMID: 3068365. Exclusion: 3
93. Bellamy N, Wells G, Campbell J. Relationship between severity and clinical importance of symptoms in osteoarthritis. *Clin Rheumatol*. 1991 Jun;10(2):138-43. PMID: 1914413. Exclusion: 9
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Appendix E. Study Characteristics Evidence Tables

Shown in associated Excel[®] files.

Appendix F. Meta-Analysis Evidence Tables

Shown in associated Excel files.

Appendix G. Quality Assessment

Shown in associated Excel file.

Appendix H. Strength of Evidence Tables

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Efficacy

Table H-1. Neuropathic pain - placebo controlled trials

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	15 (N=4,832) ¹⁰⁻²⁴	Fair	Direct	Consistent	Precise	Undetected	Small effect (NRS) Pregabalin/gabapentin vs. placebo MD -0.61 (-0.87 to -0.36), I ² =72%	Moderate
		2 (N=493) ^{25,26}	Fair	Direct	Consistent	Imprecise	Unknown	Small effect (VAS) Oxcarbazepine vs. placebo MD -0.89 (-1.50 to -0.37), I ² =0%	Moderate
		6 (N=2,082) ²⁷⁻³²	Fair	Direct	Consistent	Precise	Unknown	Small effect (NRS) Duloxetine vs. placebo MD -0.79 (-1.10 to -0.49), I ² =43%	Moderate
		2 (N=486) ^{33,34}	Fair	Direct	Consistent	Imprecise	Unknown	No effect (NRS) Cannabis vs. placebo no difference between groups (p=0.68 and 0.14)	Low
		3 (N=1,519) ³⁵⁻³⁷	Fair	Direct	Consistent	Precise	Unknown	No effect (NRS) Capsaicin vs. Placebo MD -0.33 (-0.60 to -0.004), I ² =0%	Moderate
		1 (N=45) ³⁸	Fair	Direct	Unknown	Imprecise	Unknown	VAS Memantine vs. placebo mean change 1.82 (SD 2.77) vs. -2.36 (SD 3.35), p=0.87	Insufficient
Pain Response^c (Dichotomous)	Short	15 (N=4,576) ¹⁰⁻²⁴	Fair	Direct	Consistent	Imprecise	Undetected	Small effect (≥30%) Pregabalin/gabapentin vs. placebo RR 1.27 (1.12 to 1.50), I ² =72%	Moderate
		1 (N=144) ^{25,26}	Fair	Direct	Unknown	Imprecise	Unknown	Small effect Oxcarbazepine vs. placebo 45.6% vs. 28.9%, p=0.028	Low

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
		6 (N=2,075) ²⁷⁻³²	Fair	Direct	Consistent	Imprecise	Unknown	Small effect (≥30%) Duloxetine vs. placebo RR 1.39 (1.22 to 1.62), I ² =39%	Moderate
		1 (N=246) ³⁴	Fair	Direct	Unknown	Imprecise	Unknown	Moderate effect Cannabis vs. placebo 28% vs. 16%; RR 1.70 (1.04 to 2.78), p=0.03	Low
		3 (N=1,519) ³⁵⁻³⁷	Fair	Direct	Consistent	Precise	Unknown	No effect Capsaicin vs. placebo RR 1.17 (0.98 to 1.37), I ² =0%	Moderate
Function	Short	1 (N=371) ²⁴	Fair	Direct	Unknown	Imprecise	Unknown	No effect BPI Interference Gabapentin enacarbil vs. placebo MD -0.23 (-0.70 to 0.23)	Low
		6 (N=2,082) ²⁷⁻³²	Fair	Direct	Consistent	Imprecise	Unknown	Small effect (BPI Interference) Duloxetine vs. placebo SMD -0.31 (-0.42 to -0.20), I ² =0%	Low
		1 (N=303) ³⁴	Fair	Direct	Unknown	Imprecise	Unknown	No effect (BPI) Cannabis vs. placebo p=0.18	Low
Quality of Life	Short	3 (N=1,015) ^{13,14,22} 3 (N=1,400) ^{16,19,24} 3 (N=1,400) ^{16,19,24}	Fair	Direct	Consistent	Imprecise	Unknown	No effect (EQ-5D) Pregabalin/gabapentin vs. placebo SMD 0.24 (-0.07 to 0.54), I ² =58% (SF-36 MCS) Pregabalin/gabapentin vs. placebo MD 0.22 (-1.93 to 2.37) (SF-36 PCS) Pregabalin/gabapentin vs. placebo MD 0.80 (-0.29 to 2.07)	Low

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
		2 (N=493) ^{25,26}	Fair	Direct	Inconsistent	Precise	Unknown	(SF-36 MCS) Oxcarbazepine vs. placebo 47.2 vs. 50.2; p=0.03 (1 trial); No difference for other SF-36 scales	Low
		3 (N=9,444) ^{27,29,31}	Fair	Direct	Consistent	Precise	Unknown	Small effect (EQ-5D) Duloxetine vs. placebo MD 0.22 (0.05 to 0.38), I ² =0%	Moderate
		2 (N=486) ^{33,34}	Fair	Direct	Consistent	Imprecise	Unknown	No effect (EQ-5D) Cannabis vs. placebo p=0.62 (SF-36) Cannabis vs. placebo p=not significant	Low

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

^c Pain Response main findings, percentages represent threshold for Pain Response

BPI = Brief Pain Inventory; CI = confidence interval; EQ-5D = EuroQol five dimensions; MCS = mental component score; MD = mean difference; NRS = numeric rating scale; PCS = physical component score; RR = risk ratio; SD = standard deviation; SF-36 = Short Form-36; SMD = standard mean difference; VAS = visual analogue scale

Table H-2. Neuropathic pain - cross-class comparisons

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	1 (N=152) ³⁹	Fair	Direct	Unknown	Imprecise	Unknown	(VAS) Gabapentin vs. duloxetine No difference between groups (p=not reported)	Insufficient

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

VAS = visual analogue scale

Table H-3. Neuropathic pain - head-to-head comparisons

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	1 (N=301) ¹⁶	Fair	Direct	Unknown	Imprecise	Unknown	No effect (NRS) Pregabalin vs. gabapentin enacarbil (p-values NR)	Low
		2 (N=132) ^{39,40}	Fair	Direct	Unknown	Imprecise	Unknown	(VAS) Pregabalin vs. gabapentin (p-value NR)	Insufficient
Function	Short	1 (N=301) ¹⁶	Fair	Direct	Unknown	Imprecise	Unknown	No effect (BPI Interference) Pregabalin vs. gabapentin enacarbil (p-values NR)	Low
Quality of Life	Short	1 (N=301) ¹⁶	Fair	Direct	Unknown	Imprecise	Unknown	No differences between Pregabalin vs. gabapentin enacarbil (p-values NR)	Low

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

BPI = Brief Pain Inventory; MCS = mental component score; NR = not reported; NRS = numeric rating scale; PCS = physical component score; SF-36 = Short Form-36; VAS = visual analogue scale

Table H-4. Fibromyalgia - antidepressants

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	11 (N=5,936) <small>d,41-51</small>	Fair	Direct	Consistent	Precise	Undetected	Small effect (0-10 scale) Antidepressants vs. placebo MD -0.59 (-0.80 to -0.43), I ² =26%	Moderate
		1 (N=87) ⁵²	Fair	Direct	Unknown	Imprecise	Unknown	(VAS 0-10) Amitriptyline vs. placebo MD -0.7 (Endpoint VAS 4.5 vs. 5.2, p=NR)	Insufficient
	Intermediate	3 (N=1,357) <small>d,45,46,53</small>	Fair	Direct	Consistent	Precise	Unknown	Small effect (0-10 scale) Antidepressants vs. placebo MD -0.67 (-0.99 to -0.34), I ² =0%	Moderate
Pain Response^c (Dichotomous)	Short	10 (N=5,853) <small>d,41-44,46-51</small>	Fair	Direct	Consistent	Precise	Undetected	Small effect (≥30%) Antidepressants vs. placebo RR 1.36 (1.26 to 1.46), I ² =0%	Moderate
		1 (N=87) ⁵²	Fair	Direct	Unknown	Imprecise	Unknown	(Physician's global assessment) Amitriptyline vs. placebo 74% vs. 49%, p=0.017	Insufficient
	Intermediate	3 (N=1,715) <small>d,45,46,53</small>	Fair	Direct	Consistent	Precise	Unknown	Small effect (≥30%) Antidepressants vs. placebo RR 1.29 (1.08 to 1.52), I ² =0%	Moderate
Function	Short	11 (N=6,240) <small>d,41-51</small>	Fair	Direct	Consistent	Precise	Undetected	Small effect Antidepressants vs. placebo SMD -0.24 (-0.32 to -0.17), I ² =22%	Moderate
	Intermediate	3 (N=1,724) <small>d,45,46,53</small>	Fair	Direct	Consistent	Precise	Unknown	No effect Antidepressants vs. placebo SMD -0.13 (-0.24 to -0.02), I ² =0%	Moderate
Quality of Life	Short	8 (N=5,487) <small>e,,41,43,45-50</small>	Fair	Direct	Consistent	Precise	Undetected	Small effect (SF-36 MCS or PCS, 0-100) Antidepressants vs. placebo MCS: SMD 0.19 (0.13 to 0.27), I ² =12% PCS: SMD 0.16 (0.10 to 0.22), I ² =0%	Moderate

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
	Intermediate	3 (N=1,716) <small>e,45,46,53</small>	Fair	Direct	Consistent	Precise	Unknown	Small effect (SF-36 MCS or PCS, 0-100) Antidepressants vs. placebo MCS: SMD 0.18 (0.08 to 0.30), I ² =0% PCS: SMD 0.07 (-0.10 to 0.24), I ² =0%	Moderate

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

^c Pain Response main findings, percentages represent threshold for Pain Response

^d Russell 2008 and Mease 2009 included both short-term and intermediate-term time points, and n's are included in both totals

^e Russell 2008 included both short-term and intermediate-term time points, and n's are included in both totals

BPI = brief pain inventory; CI = confidence interval; MCS = mental component score; MD = mean difference; NR = not reported; PCS = physical component score; SD = standard deviation; SE = standard error; SEM = standard error of the mean; SF-36 = Short Form-36; SMD = standard mean difference

Table H-5. Fibromyalgia - anticonvulsants

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	8 (N=4,747) ⁵⁴⁻⁵⁹	Fair	Direct	Consistent	Precise	Undetected	Small effect (0-10 scale) MD -0.57 (-0.75 to -0.40), I ² =30%	Moderate
Pain Response^c (Dichotomous)	Short	8 (N=4,773) ⁵⁴⁻⁵⁹	Fair	Direct	Consistent	Precise	Undetected	Small effect (≥30%) RR 1.30 (1.20 to 1.43), I ² =0%	Moderate
Function	Short	8 (N=4,740) ⁵⁴⁻⁵⁹	Fair	Direct	Consistent	Precise	Undetected	Small effect (FIQ 0-80 or 0-100) SMD -0.22 (-0.29 to -0.15), I ² =0%	Moderate
Quality of Life	Short	4 (N=2,520) ^{55,56}	Fair	Direct	Consistent	Precise	Unknown	No effect (SF-36 MCS or PCS, 0-100) Pregabalin vs. placebo MCS: SMD 0.13 (0.04 to 0.22), I ² =0% PCS: SMD 0.17 (0.04 to 0.31), I ² =39%	Moderate

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

^c Pain Response main findings, percentages represent threshold for Pain Response

CI = confidence interval; FIQ = Fibromyalgia Impact Questionnaire; MCS = mental component score; MD = mean difference; PCS = physical component score; RR = risk ratio; SMD = standard mean difference; SF-36 = short form 36

Table H-6. Fibromyalgia - memantine and cross-class comparisons

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size	Strength of Evidence Grade
Pain Improvement (Continuous)	Intermediate	1 (N=63) ⁶⁰	Good	Direct	Unknown	Imprecise	Unknown	Moderate effect (VAS, 0-10) Memantine vs. placebo: 4.87 vs. 7.01, p=0.001	Low
		1 (N=208) ⁶¹	Fair	Direct	Unknown	Imprecise	Unknown	No effect (MPQ present pain intensity, range NR) Cyclobenzaprine vs. amitriptyline vs. placebo 2.11 (SD 0.93, p<0.001 vs. baseline) vs. 2.17 (SD 1.02, p<0.001 vs. baseline) vs. 2.47 (SD 0.97, p<0.05 vs. baseline)	Low
Function	Intermediate	1 (N=63) ⁶⁰	Good	Direct	Unknown	Imprecise	Unknown	Moderate effect (FIQ, range NR) Memantine vs. placebo 50.02 vs. 69.57, p<0.001	Low
		1 (N=208) ⁶¹	Fair	Direct	Unknown	Imprecise	Unknown	Magnitude of effect uncertain (HAQ, range NR) Cyclobenzaprine vs. amitriptyline vs. placebo 0.53 (SD 0.40) vs. 0.60 (SD 0.49) vs. 0.70 (SD 0.65)	Insufficient
Quality of Life	Intermediate	1 (N=63) ⁶⁰	Good	Direct	Unknown	Imprecise	Unknown	Moderate effect (EQ-5D, 0-100) Memantine vs. placebo 60.48 vs. 43.75, Cohen's d -1.09, p=0.001	Low

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

EQ-5D = EuroQol five dimensions; FIQ = Fibromyalgia Impact Questionnaire; HAQ = Health Assessment Questionnaire; MPQ = McGill Pain Questionnaire; NR = not reported; SD = standard deviation; VAS = visual analogue scale

Table H-7. Osteoarthritis – oral NSAIDs vs. placebo

Outcome	Duration	Number of Studies (n participants) ^a	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	27 (N=13,478) ⁶²⁻⁸⁶	Fair	Direct	Consistent	Precise	Possible	Small effect (NRS 0-10) MD -0.73 (-0.84 to -0.62), I ² =27%	Moderate
Pain Response^c (Dichotomous)	Short	15 (N=8,253) ^{62-65,67,68,70-72,75,79,80,82}	Fair	Direct	Consistent	Precise	Undetected	Small effect RR 1.23 (1.18 to 1.31), I ² =0%	High
Function	Short	28 (N=13,473) ⁶²⁻⁸⁶	Fair	Direct	Consistent	Precise	Undetected	Small effect (WOMAC, LI) SMD -0.32 (-0.37 to -0.28), I ² =24%	High
Quality of Life	Short	3 (N=1,027) ^{69,71,81}	Fair	Direct	Consistent	Imprecise	Unknown	No effect (SF-36 MCS or PCS) MCS: MD 0.61 (-0.50 to 1.79) PCS: MD 2.95 (1.79 to 4.18)	Moderate

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

^c Pain Response main findings, percentages represent threshold for Pain Response

CI = confidence interval; LI = Lequesne Index; MD = mean difference; NRS = numeric rating scale; RR = risk ratio; SMD = standard mean difference; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Table H-8. Osteoarthritis - topical diclofenac vs. placebo

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	4 (N=1,541) ^{83,87-89}	Fair	Direct	Consistent	Precise	Unknown	Small effect (WOMAC) MD -0.58 (-0.81 to -0.35), I ² =0%	Moderate
Pain Response^c (Dichotomous)	Short	3 (N=1,232) ⁸⁷⁻⁸⁹	Good	Direct	Consistent	Imprecise	Unknown	Small effect RR 1.20 (1.09 to 1.38), I ² =0%	Moderate
Function	Short	4 (N=1,538) ^{83,87-89}	Fair	Direct	Inconsistent	Precise	Unknown	No effect (WOMAC) MD -0.51 (-1.06 to 0.04), I ² =94%	Low

^a Study references are in Appendix J.

^b Study Quality, poor-quality studies not synthesized

^c Pain Response main findings, percentages represent threshold for Pain Response

CI = confidence interval; MD = mean difference; RR = risk ratio; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Table H-9. Osteoarthritis - oral NSAIDs: head-to-head comparisons

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	4 (N=1,313) <small>86,90-92</small>	Fair	Direct	Consistent	Imprecise	Unknown	Moderate effect (VAS, WOMAC pain Subscale) Diclofenac vs. celecoxib MD -12.2 (2.2 to 22.1) Small effect Diclofenac vs. 3.75 mg/d meloxicam No effect 7 mg vs. 15 mg No effect with other comparisons	Low
	Intermediate	1 (N=586) ⁹³	Fair	Direct	Consistent	Imprecise	Unknown	No effect (VAS, WOMAC pain subscale) Celecoxib vs. naproxen	Low
	Long	1 (N=916) ⁹⁴	Fair	Direct	Unknown	Precise	Unknown	No significant differences between groups at endpoint (VAS) Celecoxib vs. diclofenac	Low
Pain Response^c (Dichotomous)	Short	2 (N=849) ^{86,92}	Fair	Direct	Consistent	Imprecise	Unknown	No effect Diclofenac dispersible vs. enteric coated: RR 0.82 (0.73 to 1.09) Ibuprofen vs. nabumetone: RR 1.2 (0.88 to 1.66)	Low
	Intermediate	1 (N=586) ⁹³	Fair	Direct	Consistent	Imprecise	Unknown	No effect Celecoxib vs. naproxen	Low
Function	Short	2 (N=301) ^{86,92}	Fair	Direct	Consistent	Imprecise	Unknown	Moderate effect (WOMAC 0-68) Diclofenac vs. celecoxib RR 2.06 (1.37 to 3.08) No effect: Diclofenac vs. meloxicam 7 or 15 mg/d, but small effect over meloxicam 3.75 mg/d	Low
	Intermediate	2 (N=921) ^{93,95}	Fair	Direct	Consistent	Imprecise	Unknown	No effect (WOMAC) Celecoxib vs. naproxen Meloxicam vs. diclofenac	Low

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

^c Pain Response main findings, percentages represent threshold for Pain Response

CI = confidence interval; MD = mean difference; RR = risk ratio; VAS = visual analogue scale; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Table H-10. Osteoarthritis - antidepressants: duloxetine vs. placebo

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	6 (N=1,508) ⁹⁶⁻¹⁰¹	Good	Direct	Consistent	Precise	Unknown	Small effect (0 to 10 scale) MD -0.75 (-1.05 to -0.53), I ² =15%	High
Pain Response^c (Dichotomous)	Short	4 (N=1,247) ^{97,98,100,101}	Good	Direct	Consistent	Precise	Unknown	Moderate effect RR 1.37 (1.24 to 1.52), I ² =0%	High
Function	Short	5 (N=1,480) ^{96-98,100,101}	Good	Direct	Consistent	Precise	Unknown	Small effect (WOMAC, BPI) SMD -0.27 (-0.41 to -0.12), I ² =27%	High
Quality of Life	Short	2 (N=570) ^{98,100}	Good	Direct	Consistent	Precise	Unknown	Small effect (EQ-5D, 0 to 1 scale) MD 0.05 (0.02 to 0.08), I ² =0%	High

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

^c Pain Response main findings, percentages represent threshold for Pain Response

BPI = brief pain inventory; EQ-5D = EuroQol five dimensions; MD = mean difference; RR = risk ratio; SMD = standardized mean difference; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Table H-11. Osteoarthritis - acetaminophen vs. placebo

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	3 (N=1,082) ^{66,102,103}	Fair	Direct	Consistent	Imprecise	Unknown	No effect MD -0.34 (-0.66 to 0.03), I ² =0%	Low
	Intermediate	1 (N=212) ¹⁰⁴	Fair	Direct	Unknown	Imprecise	Unknown	No effect (WOMAC subscale) MD -0.30 (-0.77 to 0.17)	Low
Pain Response^c (Dichotomous)	Intermediate	1 (N=212) ¹⁰⁴	Fair	Direct	Unknown	Imprecise	Unknown	No effect (OARSI-A criteria) RR 1.58 (1.00 to 2.49), p=0.051	Low
Function	Short	3 (N=1,081) ^{66,102,103}	Fair	Direct	Consistent	Imprecise	Unknown	No effect (WOMAC) SMD -0.14 (-0.29 to 0.04), I ² =0%	Low
	Intermediate	1 (N=212) ¹⁰⁴	Fair	Direct	Unknown	Imprecise	Unknown	No effect (< small) (WOMAC, 1 to 100) MD -3.7 (-6.9 to -0.5)	Low

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

^cPain Response main findings, percentages represent threshold for Pain Response

MD = mean difference; OARSI = Osteoarthritis Research Society International; SMD = standardized mean difference; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Table H-12. Osteoarthritis - anticonvulsants vs. antidepressants: duloxetine vs. pregabalin

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	1 (N=65) ¹⁰⁵	Good	Direct	Unknown	Imprecise	Unknown	(NRS scale, 0 to 10): Pregabalin 300 mg/d: -2.7 (-3.5 to -1.9) vs. duloxetine 60 mg/d: -2.3 (-3.8 to -0.9) vs. placebo: -0.9 (-2.0 to 0.2); Pregabalin vs. placebo = 0.023 and 0.19	Insufficient
Function	Short	1 (N=65) ¹⁰⁵	Good	Direct	Unknown	Imprecise	Unknown	(AUSCAN Function scale, 0 to 900): Pregabalin 300 mg/d: -46.4 (-341.7 to -151.0) vs. duloxetine 60 mg/d: -101.8 (-248.4 to -44.7) vs. placebo: -67.3 (-156.4 to -21.8); Pregabalin vs. placebo = 0.009 and >0.05	Insufficient

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

AUSCAN = Australian Canadian osteoarthritis hand index; CI = confidence interval; NRS = numeric rating scale

Table H-13. Osteoarthritis - acetaminophen vs. NSAIDs

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	1 (N=85) ⁶⁶	Fair	Direct	Inconsistent	Imprecise	Unknown	(WOMAC) Diclofenac 150 mg/d vs. acetaminophen 4000 mg/d; diclofenac shows greater pain improvement (-53.9 vs. -23.8 WOMAC; p=0.003)	Insufficient
Function	Short	1 (N=25) ⁶⁶	Fair	Direct	Unknown	Imprecise	Unknown	(WOMAC) Diclofenac 150 mg/d vs. acetaminophen 4000 mg/d; diclofenac shows greater function improvement (-163.0 vs. -41.8 WOMAC; p<0.001)	Insufficient

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Table H-14. Inflammatory arthritis – oral NSAIDS vs. placebo

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	9 (N=4,543) ¹⁰⁶⁻¹¹⁴	Fair	Direct	Consistent	Precise	Undetected	Small effect (0 to 10 scale) MD -0.97 (-1.33 to -0.74), I ² =39%	Moderate
	Intermediate	1 (N=563) ¹¹⁰	Fair	Direct	Unknown	Precise	Unknown	Small effect (0 to 10 scale) Naproxen 1000 mg/d MD -0.53 (-0.93 to -0.13)	Low
	Long	1 (N=365) ¹¹⁵	Fair	Direct	Unknown	Precise	Unknown	Large effect (0 to 10 scale) Meloxicam 15-22.5 mg/d MD -2.10 (-2.72 to -1.48)	Low
Pain Response ^c (Dichotomous)	Short	7 (N=3,434) ^{106-108,110,113,114,116}	Fair	Direct	Consistent	Precise	Unknown	Moderate effect (ACR 20; ASAS 20) RR 1.58 (1.34 to 2.06), I ² =52%	Moderate
	Intermediate	1 (N=563) ¹¹⁰	Fair	Direct	Unknown	Precise	Unknown	Small effect (ACR 20) Naproxen 1000 mg/d: RR 1.28 (1.03 to 1.60)	Low
	Long	1 (N=365) ¹¹⁵	Fair	Direct	Unknown	Precise	Unknown	Large effect (≥ 50%) Meloxicam 15- 22.5 mg/d: RR 3.05 (1.98 to 4.71)	Low
Function	Short	7 (N=4,284) ^{106-110,113,114}	Fair	Direct	Consistent	Precise	Undetected	Small effect (HAQ; BASFI) SMD -0.34 (-0.51 to -0.20), I ² =67%	Moderate
	Intermediate	1 (N=563) ¹¹⁰	Fair	Direct	Unknown	Precise	Unknown	Small effect (HAQ-DI, 0-3) Naproxen 1000 mg/d: MD -0.18 (-0.35 to -0.02)	Low
	Long	1 (N=365) ¹¹⁵	Fair	Direct	Unknown	Precise	Unknown	No effect (ASFI ¹¹⁷ , 0-40) Meloxicam 15-22.5 mg/d: MD -0.63 (-0.85 to -0.40)	Low
Quality of Life	Short	2 (N=1,204) ^{108,114}	Fair	Direct	Inconsistent	Imprecise	Unknown	(ASQoL, 0 to 18) Naproxen 1000 mg/d: MD -2.9; p=0.04 (SF-36 PCS and MCS) Celecoxib 200-800 mg/d or Naproxen 1000 mg/d	Insufficient

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

^c Pain Response main findings, percentages represent threshold for Pain Response

ACR = American College of Rheumatology; ASAS = Assessment of SpondyloArthritis international Society; ASFI = Ankylosing Spondylitis Functional Index; ASQoL = Ankylosing Spondylitis Quality of Life; BASFI = Bath Ankylosing Spondylitis Functional Index; HAQ = Health Assessment Questionnaire; MCS = mental component score; MD = mean difference; PCS = physical component score; RR = risk ratio; SMD = standardized mean difference

Table H-15. Inflammatory arthritis – oral NSAIDs: head-to-head comparisons

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	3 (N=1,453) ¹¹⁸⁻¹²⁰	Fair	Direct	Consistent	Precise	Unknown	No effect (0-10 scale) Celecoxib 200-400 mg/d vs. diclofenac 150 mg/d: NS	Moderate
		2 (N=1,132) ^{106,114}	Fair	Direct	Consistent	Imprecise	Unknown	No effect (0-10 scale) Celecoxib 200-400 mg/d vs. naproxen 1000 mg/d: NS	Low
		1 (N=103) ¹²¹	Fair	Direct	Unknown	Imprecise	Unknown	(Non-visual scale, 1-5) Diclofenac vs. etodolac	Insufficient
		1 (N=717) ¹⁰⁹	Fair	Direct	Unknown	Imprecise	Unknown	No effect (VAS, 0-100) Diclofenac vs. meloxicam	Low
		1 (N=39) ¹²²	Fair	Direct	Unknown	Imprecise	Unknown	(Non-visual scale, 1-5) Etodolac vs. naproxen	Insufficient
		2 (N=621) ^{123,124}	Fair	Direct	Consistent	Precise	Unknown	No effect (0-10 scale) Nabumetone 2000 mg/d vs. naproxen 1000 mg/d: NS	Low
	Intermediate	1 (N=379) ¹²⁵	Fair	Direct	Unknown	Precise	Unknown	No effect (VAS, 0-100) Meloxicam vs. naproxen	Low
		1 (N=47) ¹²⁶	Fair	Direct	Unknown	Imprecise	Unknown	No effect (% better, %same, %worse) Nabumetone vs. naproxen	Low
Pain Response^c (Dichotomous)	Short	3 (N=1,443) ¹¹⁸⁻¹²⁰	Fair	Direct	Consistent	Precise	Unknown	No effect (ACR 20; ASAS 20) Celecoxib 200-400 mg/d vs. diclofenac 150 mg/d: NS	Moderate
		2 (N=1,133) ^{106,114}	Fair	Direct	Inconsistent	Imprecise	Unknown	No effect (ACR 20; ASAS 20) Celecoxib 200-400 mg/d vs. naproxen 1000 mg/d: NS	Low
		1 (N=344) ¹²⁴	Fair	Direct	Unknown	Imprecise	Unknown	No effect (Pt global assess, % improved) Nabumetone 2000 mg/d vs. naproxen 1000 mg/d: NS	Low
Function	Short	3 (N=1,448) ¹¹⁸⁻¹²⁰	Fair	Direct	Consistent	Precise	Unknown	No effect (mHAQ; BASFI) Celecoxib 200-400 mg/d vs. diclofenac 150 mg/d: NS	Moderate

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size	Strength of Evidence Grade
		2 (N=1,373) ^{106,114}	Fair	Direct	Consistent	Imprecise	Unknown	No effect (HAQ; BASFI) Celecoxib 200-400 mg/d vs. naproxen 1000 mg/d: NS	Low
		1 (N=103) ¹²¹	Fair	Direct	Unknown	Imprecise	Unknown	(Non-visual scale, 1-4) Diclofenac vs. etodolac	Insufficient
		1 (N=717) ¹⁰⁹	Fair	Direct	Unknown	Imprecise	Unknown	No effect (mHAQ, max 3) Diclofenac vs. meloxicam	Low
		1 (N=346) ¹²⁴	Fair	Direct	Unknown	Imprecise	Unknown	No effect (ACR class) Nabumetone 2000 mg/d vs. naproxen 1000 mg/d: NS	Low
Quality of Life	Short	1 (N=917) ¹¹⁴	Fair	Direct	Unknown	Precise	Unknown	No effect (SF-36 PCS and MCS) Celecoxib vs. naproxen	Low

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

^c Pain Response main findings, percentages represent threshold for Pain Response

ACR = American College of Rheumatology; ASAS = Assessment of SpondyloArthritis international Society; BASFI = Bath Ankylosing Spondylitis Functional Index; (m)HAQ = (modified) Health Assessment Questionnaire; MCS = mental component score; NS = not significant; PCS = physical component score; SF-36 = Short Form-36; SMD = standardized mean difference; VAS = visual analogue score

Table H-46. Inflammatory arthritis – antidepressants: placebo controlled trials

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	1 (N=36) ¹²⁷	Fair	Direct	Unknown	Imprecise	Unknown	(Non-visual scale, 0-4) Amitriptyline 50-75 mg/d	Insufficient

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

Table H-17. Low back pain – antidepressants and anticonvulsants: placebo controlled trials

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	3 (N=1,491) ¹²⁸⁻¹³⁰	Fair	Direct	Consistent	Precise	Unknown	Small effect (BPI Pain Scale) Duloxetine vs. placebo MD -0.50 (-0.71 to -0.29), I ² =0%	Moderate
		1 (N=78) ¹³¹	Fair	Direct	Unknown	Imprecise	Unknown	(DDS, 0-20) Despiramine vs. placebo MD -0.80 (-2.64 to 1.04)	Insufficient
		1 (N=86) ¹³¹	Fair	Direct	Unknown	Imprecise	Unknown	(DDS, 0-20) Fluoxetine vs. placebo MD 0.70 (-1.40 to 2.80)	Insufficient
		1 (N=108) ¹³²	Fair	Direct	Unknown	Imprecise	Unknown	(DDS, 0-20) Gabapentin vs. placebo p=0.42	Insufficient
	Intermediate	1 (N=146) ¹³³	Good	Direct	Unknown	Imprecise	Unknown	No effect (VAS) Amitriptyline vs. placebo MD -7.81 (-15.7 to 0.10)	Low
Pain Response^c (Dichotomous)	Short	3 (N=1,235) ¹²⁸⁻¹³⁰	Fair	Direct	Consistent	Imprecise	Unknown	Small effect Duloxetine vs. placebo RR 1.25 (1.11 to 1.40), I ² =0%	Low
Function	Short	3 (N=1,214) ¹²⁸⁻¹³⁰	Fair	Direct	Consistent	Precise	Unknown	No effect (BPI Interference Scale) Duloxetine vs. placebo MD -0.36 (-0.73 to -0.04), I ² =34%	Moderate
		1 (N=78) ¹³¹	Fair	Direct	Unknown	Imprecise	Unknown	(RMDQ score) Despiramine vs. placebo 2.3 vs. 4.1, p=0.05 (Physician-rated CGI) Despiramine vs. placebo 5.9 vs. 4.8, p=0.003	Insufficient
		1 (N=108) ¹³²	Fair	Direct	Unknown	Imprecise	Unknown	(CGI-C "minimal improvement") Gabapentin vs. placebo 37% vs. 33%, p=0.95	Insufficient
	Intermediate	1 (N=146) ¹³³	Good	Direct	Unknown	Imprecise	Unknown	No effect (RMDQ) Amitriptyline vs. placebo MD -0.98 (-2.42 to 0.46)	Low
Quality of Life	Short	3 (N=1,198) ¹²⁸⁻¹³⁰	Fair	Direct	Consistent	Precise	Unknown	No effect Duloxetine vs. placebo SMD 0.18 (-0.03 to 0.39), I ² =38%	Moderate

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
		1 (N=108) ¹³²	Fair	Direct	Unknown	Imprecise	Unknown	(BDI-II) Gabapentin vs. placebo p=0.52	Insufficient

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

^c Pain Response main findings, percentages represent threshold for Pain Response

BDI-II = Beck Depression Inventory-II; BPI = brief pain inventory; CGI = clinical global impression scale; CI = confidence interval; DDS = Descriptor Differential Scale; MD = mean difference; RMDQ = Roland-Morris Disability Questionnaire; SMD = standard mean difference; VAS = visual analogue scale

Table H-18. Low back pain - antidepressants: head-to-head trials

Outcome	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size	Strength of Evidence Grade
Pain Improvement (Continuous)	Short	1 (N=200) ¹³⁴	Fair	Direct	Unknown	Imprecise	Unknown	Small effect (VAS) Amitriptyline vs. pregabalin Mean change from baseline: 2.9 vs. 3.9, p=0.03	Low
Function	Short	1 (N=200) ¹³⁴	Fair	Direct	Unknown	Imprecise	Unknown	No effect (ODI) Amitriptyline vs. pregabalin Mean change from baseline: p=0.09	Low

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

ODI = Oswestry Disability Index; VAS = visual analogue scale;

Harms

Table H-19. Adverse events - antidepressants

Adverse Effect	Comparison	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
SAE	SNRI Antidepressants vs. Placebo	Short	19 (N=8,832) ^{28-32,42,43,47-51,97,98,100,101,128-130}	Fair	Direct	Consistent	Imprecise	Undetected	No effect RR 0.88 (0.62 to 1.24), I ² =0%	Low
		Intermediate	2 (N=1,218) ^{46,53}	Fair	Direct	Consistent	Imprecise	Unknown	No effect RR 0.86 (0.35 to 2.24), I ² =0%	Low
WAE	SNRI Antidepressants vs. Placebo	Short	24 (N=9,971) ^{27-32,41-44,47-51,96-98,100,101,105,128-130}	Fair	Direct	Consistent	Precise	Undetected	Moderate effect RR 1.99 (1.71 to 2.35), I ² =18%	Moderate
		Intermediate	3 (N=1,738) ^{45,46,53}	Fair	Direct	Consistent	Precise	Unknown	Moderate effect RR 1.83 (1.23 to 2.61), I ² =4%	Moderate
	TCA Antidepressants vs. placebo	Short	5 (N=478) ^{52,127,131,133,135}	Fair	Direct	Consistent	Imprecise	Unknown	No effect RR 1.49 (0.89 to 3.01)	Low
		Intermediate	1 (N=126) ⁶¹	Far	Direct	Unknown	Imprecise	Unknown	RR 1.75 (0.38 to 8.06)	Insufficient
Nausea	SNRI Antidepressants vs. Placebo	Short	19 (N=8,929) ^{27-29,31,32,42,43,47-51,97,98,100,101,128-130}	Fair	Direct	Consistent	Precise	Undetected	Large effect RR 3.10 (2.50 to 4.06), I ² =60%	Moderate
		Intermediate	3 (N=1,738) ^{45,46,53}	Fair	Direct	Consistent	Imprecise	Unknown	Moderate effect RR 1.98 (1.57 to 2.82), I ² =0%	Low
Sedation	SNRI Duloxetine vs. Placebo	Short	16 (N=5,831) ^{27-29,31,32,42,47,50,51,97,98,100,101,128-130}	Fair	Direct	Consistent	Precise	Undetected	Large effect RR 2.46 (2.00 to 3.01), I ² =0%	Moderate
		Intermediate	2 (N=850) ^{45,53}	Fair	Direct	Consistent	Imprecise	Unknown	Large effect RR 3.51 (1.46 to 11.05), I ² =0%	Low
Dry Mouth	TCA Antidepressants vs Placebo	Short	1 (N=131) ¹³⁵	Fair	Direct	Unknown	Imprecise	Unknown	RR 1.80, (1.14 to 2.85)	Insufficient
Cognitive effects	SNRI Antidepressants vs. Placebo	Short	2 (N=805) ^{129,130}	Fair	Direct	Consistent	Imprecise	Unknown	No effect RR 3.24 (0.26 to 40.17), I ² =0	Low

^a Study references are in Appendix J.

^b Study Quality; poor quality studies not synthesized

CI = confidence interval; RR = risk ratio; SAE = serious adverse event; SNRI = serotonin-norepinephrine reuptake inhibitor; TCA = tricyclic antidepressant; WAE = withdrawal due to adverse event

Table H-20. Adverse events – anticonvulsants

Adverse Effect	Comparison	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study = Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
SAE	Oxcarbazepine vs. Placebo	Short	2 (N=493) ^{25,26}	Fair	Direct	Consistent	Imprecise	Unknown	No effect 8.9% vs. 4.8% RR 1.82 (0.74 to 5.05), I ² =0%	Low
	Pregabalin/Gabapentin vs. Placebo	Short	19 (N=7,982) ^{10-19,21,22,24,55,56,58,59}	Fair	Direct	Consistent	Imprecise	Undetected	No effect 2.3% vs. 2.5% RR 0.90 (0.63 to 1.30), I ² =0%	Low
WAE	Oxcarbazepine vs. Placebo	Short	2 (N=493) ^{25,26}	Fair	Direct	Consistent	Imprecise	Unknown	Large effect 25.7% vs. 7.2% RR 3.64 (1.86 to 7.12), I ² =0%	Low
	Pregabalin/Gabapentin vs. Placebo	Short	26 (N=9,754) ^{10-24,54-59,105,132,136}	Fair	Direct	Consistent	Precise	Undetected	Moderate effect 14.4% vs. 7.0% RR 1.73, (1.48 to 2.01), I ² =5%	Moderate
Blurred Vision	Pregabalin/Gabapentin vs. Placebo	Short	12 (N=5,127) 11,16,18,23,24,54-59,132	Fair	Direct	Consistent	Imprecise	Undetected	Large effect 5.8% vs. 1.4% RR 3.79 (2.20 to 7.19), I ² =29%	Low
Cognitive Effects	Pregabalin/Gabapentin vs. Placebo	Short	8 (N=3,801) 15,16,18,23,55,57,58,132	Fair	Direct	Consistent	Imprecise	Undetected	Large effect 4.8% vs. 1.3% RR 3.15 (1.86 to 5.51), I ² =0%	Low
Dizziness	Pregabalin/Gabapentin vs. Placebo	Short	25 (N=9,696) ^{10-24,54-59,105,132}	Fair	Direct	Consistent	Precise	Undetected	Large effect 25.6% vs. 7.4% RR 2.97 (2.53 to 3.50), I ² =31%	Moderate
Peripheral Edema	Pregabalin/Gabapentin vs. Placebo	Short	22 (N=9,005) ^{10-14,16-24,54-59}	Fair	Direct	Consistent	Precise	Undetected	Large effect 8.8% vs. 3.7% RR 2.32 (1.80 to 3.09), I ² =26%	Moderate
Sedation	Pregabalin/Gabapentin vs. Placebo	Short	24 (N=9,652) ^{10-24,54-59,132}	Fair	Direct	Consistent	Precise	Undetected	Large effect 17% vs. 5.4% RR 3.03 (2.62 to 3.67), I ² =0%	Moderate
	Oxcarbazepine vs. Placebo	Short	2 (N=490) ^{25,26}	Fair	Direct	Consistent	Imprecise	Unknown	No effect 8.6% vs. 3.0% RR 3.13 (0.74 to 16.08), I ² =0%	Low

Adverse Effect	Comparison	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study = Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
Weight Gain	Pregabalin/Gabapentin vs. Placebo	Short	21 (N=8,620) ^{10-14,16,18,19,22-24,54-59,105,132}	Fair	Direct	Consistent	Precise	Undetected	Large effect 10.1% vs. 2.8% RR 3.57 (2.77 to 4.91), I ² =7%	Moderate
Hyponatremia	Oxcarbazepine vs. Placebo	Short	2 (N=490) ^{25,26}	Fair	Direct	Consistent	Imprecise	Unknown	No effect 2.8% vs. 0.0% RR 5.93 (0.55 to 63.8), I ² =0%	Low

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

CI = confidence interval; RR = risk ratio; SAE = serious adverse event; WAE = withdrawal due to adverse event

Table H-21. Adverse events – NSAIDs

Adverse Effect	Comparison	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
SAE	NSAIDs vs. Placebo	Short	23 (N=13,082) ^{63-65,68,70-72,75,76,78,80-82,84,85,106,107,109,113,114,137}	Fair	Direct	Consistent	Imprecise	Undetected	No effect RR 0.96 (0.72 to 1.29), I ² =0%	Low
		Intermediate	1 (N=563) ¹¹⁰	Fair	Direct	Unknown	Imprecise	Unknown	RR 0.51 (0.05 to 5.58)	Insufficient
	Topical diclofenac vs placebo	Short	2 (N=912) ^{87,88}	Fair	Direct	Consistent	Imprecise	Unknown	No effect RR 1.03 (0.29 to 27.01), I ² =0%	Low
WAE	NSAIDs vs. Placebo	Short	38 (N=20,060) ^{62-78,80-86,106-109,113,114,116,137-141}	Fair	Direct	Consistent	Precise	Undetected	Small effect RR 1.30 (1.14 to 1.49), I ² =13%	Moderate
		Intermediate	2 (N=941) ^{79,110}	Fair	Direct	Consistent	Imprecise	Unknown	No effect RR 1.59 (0.89 to 3.08), I ² =0%	Low
		Long	1 (N=365) ¹¹⁵	Fair	Direct	Unknown	Imprecise	Unknown	RR 1.59 (0.81 to 3.12)	Insufficient
	Topical diclofenac vs placebo	Short	4 (N=1,549) ^{83,87-89}	Fair	Direct	Consistent	Imprecise	Unknown	No effect RR 1.03 (0.29 to 27.01), I ² =0%	Low

Adverse Effect	Comparison	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
CV Events	NSAIDs vs. Placebo	Short	1 SR (639 RCTs, unclear N patients) ¹⁴²	Fair	Direct	Consistent	Precise	Unknown	Small effect Diclofenac RR 1.41 (1.12 to 1.78) No effect Ibuprofen RR 1.44 (0.89 to 2.33) Naproxen RR 0.93 (0.69 to 1.27) Celecoxib RR 1.36 (1.00 to 1.84)	Moderate
	Celecoxib vs. nonselective NSAIDs	Intermediate	3 RCTs (N=33,064) ^{94,143,144}	Fair	Direct	Consistent	Precise	Unknown	No effect Cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke: celecoxib 1.7%; ibuprofen 1.9%; naproxen 1.8% (p<0.001 for noninferiority between drugs)	Moderate
		Long	1 RCT (N=7,297) ¹⁴⁵	Good	Direct	Unknown	Precise	Unknown	No effect Hospitalization for non-fatal MI or other biomarker positive acute coronary syndrome, non-fatal stroke or CV death hazard ratio 1.12 (0.81 to 1.55)	Moderate
Serious GI Events	NSAIDs vs. Placebo	Short	1 SR (639 RCTs, unclear N patients), ¹⁴² 13 RCTs (N=7,262) <small>67,70,73,76,80,106,109,114,137-141</small>	Fair	Direct	Consistent/ Inconsistent	Precise	Undetected	Moderate effect EPC meta-analysis NSAIDs vs. placebo RR 3.04 (1.73 to 5.11), I ² =73% IPD meta-analysis coxibs RR 1.81 (1.17 to 2.81); Diclofenac RR 1.89 (1.16 to 3.09); Ibuprofen RR 3.97 (2.22 to 7.10); Naproxen RR 4.22 (2.71 to 6.56); Celecoxib vs. placebo: 1.02 (0.47 to 1.56; 3 RCTs, N=1,877), I ² = 0%	Moderate (non-selectives) Low (celecoxib)

Adverse Effect	Comparison	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
	Coxibs (celecoxib) vs. nonselective NSAIDs	Short	1 SR (639 RCTs, unclear N patients) ¹⁴² ; 13 RCTs (N=7,262) ^{67,70,73,76,80,106,109,114,137-141}	Fair	Direct and Indirect	Inconsistent	Imprecise	Undetected	No clear effect SR (4 RCTs, N=1,755) OR 0.61 (0.15 to 2.43), I ² =38% Placebo trials: Celecoxib RR 1.04 (0.67 to 1.54), I ² =0% Nonselective NSAIDs RR 4.29 (2.75 to 6.93), I ² =46%; p<0.001 for interaction	Insufficient
		Intermediate	1 RCT (N=8,067) ¹⁴⁶	Fair	Direct	Unknown	Precise	Unknown	Moderate effect OR 1.82 (1.31 to 2.55)	Low
Serious Hepatic Events	NSAIDs vs. Placebo	Intermediate	1 SR (64 RCTs) ¹⁴⁷	Fair	Direct	Unclear	Imprecise	Unknown	Large effect Aminotransferase >3x upper limit of normal: Diclofenac 3.55% (3.12% to 4.03%) vs. 0.29% (0.17% to 0.51%) Large effect Liver-related discontinuations: Diclofenac 2.17% (1.78% to 2.64%) vs. 0.08% (0.02% to 0.29%) No effect Liver-related SAE: Naproxen 0.06% (0.02% to 0.15%) vs. 0.00% (0.00% to 0.08%)	Low

^a Study references are in Appendix J.

^b Study Quality: poor quality studies not synthesized

CI = confidence interval; CV = cardiovascular; GI = gastrointestinal; IPD = individual patient data; NSAIDs = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial; RR = risk ratio; SAE = serious adverse event; SR = systematic review; WAE = withdrawal due to adverse event

Table H-22. Adverse events - acetaminophen vs. placebo

	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
SAE	Short	2 (N=1,023) ^{102,103}	Fair	Direct	Consistent	Imprecise	Unknown	No effect RR 2.57 (0.60 to 10.8); I ² =0%	Low
	Intermediate	1 (N=212) ¹⁰⁴	Fair	Direct	Unknown	Imprecise	Unknown	No effect RR 0.96 (0.29 to 3.23)	Low
WAE	Short	2 (N=1,023) ^{102,103}	Fair	Direct	Consistent	Imprecise	Unknown	No effect RR 1.14 (0.67 to 1.95); I ² =0%	Low

	Duration	Number of Studies ^a (n) participants	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
	Intermediate	1 (N=212) ¹⁰⁴	Fair	Direct	Unknown	Imprecise	Unknown	No effect RR 1.28 (0.56 to 2.92)	Low

^a Study references are in Appendix J.

^b Study Quality; poor quality studies not synthesized

SAE = serious adverse event; WAE = withdrawal due to adverse event; RR = risk ratio

Table H-53. Adverse events - capsaicin vs. placebo

	Duration	Number of Studies ^a (n) participants	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
SAE	Short	3 (N=1,051) ³⁵⁻³⁷	Good	Direct	Consistent	Imprecise	Unknown	No effect RR 1.32 (0.71 to 3.47), I ² =0%	Moderate
WAE	Short	2 (N=896) ^{35,36}	Good	Direct	Consistent	Imprecise	Unknown	No effect RR 1.04 (0.08 to 17.1), I ² =0%	Moderate
Application Site Erythema	Short	3 (N=1,051) ³⁵⁻³⁷	Good	Direct	Consistent	Imprecise	Unknown	Moderate effect RR 1.46 (1.29 to 1.66) , I ² =0%	Moderate
Application Site Pain	Short	3 (N=1,051) ³⁵⁻³⁷	Good	Direct	Consistent	Imprecise	Unknown	Large effect RR 2.26 (1.61 to 2.82) , I ² =0%	Moderate
Application Site Pruritus	Short	3 (N=1,051) ³⁵⁻³⁷	Good	Direct	Consistent	Imprecise	Unknown	No effect RR 1.70 (0.92 to 3.35) , I ² =0%	Moderate

^a Study references are in Appendix J.

^b Study Quality; poor quality studies not synthesized

SAE = serious adverse event; WAE = withdrawal due to adverse event; RR = risk ratio

Table H-24. Adverse events - cannabis vs. placebo

Adverse Event	Cannabis type	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
SAE	Dronabinol 7.5-15mg/d	Short	1 (N=240) ³³	Good	Direct	Unknown	Imprecise	Unknown	No effect 13.7% vs. 8.9% RR 1.58 (0.75 to 3.30)	Low
	THC 2.7m/microL + CBD 2.5gm/microL	Short	1 (N=246) ³⁴	Fair	Direct	Unknown	Imprecise	Unknown	No effect 8% vs. 5% RR 1.54 (0.58 to 4.10)	Low
WAE	Dronabinol 7.5-15mg/d	Short	1 (N=240) ³³	Good	Direct	Unknown	Imprecise	Unknown	No effect 14.5% vs. 14.0% RR 1.05 (0.56 to 1.96)	Low
	THC 2.7m/microL + CBD 2.5gm/microL	Short	1 (N=246) ³⁴	Fair	Direct	Unknown	Imprecise	Unknown	Large effect 19% vs. 6% RR 3.16 (1.41 to 7.06)	Low
Dizziness	Dronabinol 7.5-15mg/d	Short	1 (N=240) ³³	Good	Direct	Unknown	Imprecise	Unknown	Large effect 20% vs. 4.3% RR 4.68 (1.85 to 11.8)	Low
	THC 2.7m/microL + CBD 2.5gm/microL	Short	1 (N=246) ³⁴	Fair	Direct	Unknown	Imprecise	Unknown	Large effect 39% vs. 9% RR 4.55 (2.48 to 8.32)	Low
Nausea	Dronabinol 7.5-15mg/d	Short	1 (N=240) ³³	Good	Direct	Unknown	Imprecise	Unknown	No effect 4.2% vs. 6.8% RR 1.39 (0.40 to 4.80)	Low
	THC 2.7m/microL + CBD 2.5gm/microL	Short	1 (N=246) ³⁴	Fair	Direct	Unknown	Imprecise	Unknown	Large effect 17% vs. 8% RR 2.25 (1.8 to 4.70)	Low
Sedation	THC 2.7m/microL + CBD 2.5gm/microL	Short	1 (N=246) ³⁴	Fair	Direct	Unknown	Imprecise	Unknown	3% vs. 0% RR 8.30 (0.45 to 152.58)	Insufficient

^a Study references are in Appendix J.

^b Study Quality; poor quality studies not synthesized

SAE = serious adverse event; WAE = withdrawal due to adverse event; RR = risk ratio; min = minute; THC = tetrahydrocannabinol; CBD = Cannabidiol

Table H-25. Adverse events - skeletal muscle relaxants

Adverse Effect	Comparison	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
WAE	Cyclobenzaprine vs. Placebo	Intermediate	1 (N=208) ⁶¹	Fair	Direct	Unknown	Imprecise	Unknown	No effect 16% vs. 5%; p=0.20 RR 2.82 (0.65 to 12.1)	Low
	Cyclobenzaprine vs. Amitriptyline	Intermediate	1 (N=208) ⁶¹	Fair	Direct	Unknown	Imprecise	Unknown	No effect 16% vs. 8% RR 2.25 (0.82 to 6.20)	Low
Dizziness	Cyclobenzaprine vs. Placebo	Intermediate	1 (N=208) ⁶¹	Fair	Direct	Unknown	Imprecise	Unknown	6.1% vs. 2.4%; p=0.38 RR 2.56 (0.31 to 21.22)	Insufficient
	Cyclobenzaprine vs. Amitriptyline	Intermediate	1 (N=208) ⁶¹	Fair	Direct	Unknown	Imprecise	Unknown	61.1% vs. 0% RR 11.27 (0.63 to 200.53)	Insufficient
Sedation	Cyclobenzaprine vs. Placebo	Intermediate	1 (N=208) ⁶¹	Fair	Direct	Unknown	Imprecise	Unknown	3.7% vs. 2.4%; p=0.23 RR 2.00 (0.23 to 17.34)	Insufficient
	Cyclobenzaprine vs. Amitriptyline	Intermediate	1 (N=208) ⁶¹	Fair	Direct	Unknown	Imprecise	Unknown	3.7% vs. 4.8% RR 1.30 (0.30 to 5.64)	Insufficient

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

WAE = withdrawal due to adverse event

Table H-26. Adverse events – memantine vs. placebo

Adverse Effect	Comparison	Duration	Number of Studies ^a (n participants)	Study Quality ^b	Directness	Consistency (1 study= Unknown)	Precision	Publication Bias	Main Findings Effect Size (95% CI)	Strength of Evidence Grade
SAE	Neuropathic Pain	Short	1 (N=45) ³⁸	Fair	Direct	Unknown	Imprecise	Unknown	Reported as “no differences”	Insufficient
	Fibromyalgia	Medium	1 (N=63) ⁶⁰	Good	Direct	Unknown	Imprecise	Unknown	Reported as “no serious adverse events”	Insufficient
WAE	Neuropathic Pain	Short	1 (N=45) ³⁸	Fair	Direct	Unknown	Imprecise	Unknown	Reported as “no differences”	Insufficient
	Fibromyalgia	Medium	1 (N=63) ⁶⁰	Good	Direct	Unknown	Imprecise	Unknown	6% vs. 3%; p=0.55	Insufficient
Dizziness	Fibromyalgia	Medium	1 (N=63) ⁶⁰	Good	Direct	Unknown	Imprecise	Unknown	25.8% vs. 12.5%; RR 2.06 (0.69 to 6.16), p=0.22	Insufficient
Sedation	Fibromyalgia	Medium	1 (N=63) ⁶⁰	Good	Direct	Unknown	Imprecise	Unknown	0% vs. 6%; RR 0.21 (0.01 to 4.13), p=0.30	Insufficient

^a Study references are in Appendix J.

^b Study Quality: poor-quality studies not synthesized

CI = confidence interval; RR = risk ratio; SAE = serious adverse event; WAE = withdrawal due to adverse event

Appendix I. Forest Plots

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Table I-1. Pregabalin and gabapentin pain outcomes subgroup analyses

Outcome Sample Size	Variable	Subgroup	N studies (sample size)	Effect Size (95% CI)	Interaction p-value
Pain Improvement 15 RCTs (n=4,832)	Pain type	DPN	7 (2,424)	MD -0.45 (-0.71 to -0.22)	0.2087
		PHN	2 (747)	MD -1.04 (-1.55 to -0.54)	
		DPN/PHN	1 (338)	MD -1.30 (-1.78 to -0.81)	
		Other	5 (1,478)	MD -0.49 (-1.07 to 0.04)	
	Pregabalin Dose	Pregabalin pooled	15 (4,832)	MD -0.63 (-0.92 to -0.36)	0.8967 ^a
150 mg/day		2 (375)	MD -0.55 (-1.31 to 0.17)		
300 mg/day		5 (1,035)	MD -0.36 (-0.89 to 0.17)		
600 mg/day		4 (735)	MD -1.17 (-1.69 to -0.67)		
150-600 mg/day		10 (2,963)	MD -0.75 (-1.13 to -0.39)		
300-600 mg/day		2 (511)	MD -0.82 (-1.48 to -0.18)		
450-600 mg/day		1 (375)	MD -0.02 (-0.39 to 0.35)		
Gabapentin enacarbil Dose		Gabapentin pooled	2 (725)	MD -0.58 (-1.26 to 0.10)	
		1200 mg/day	2 (384)	MD -0.66 (-1.21 to -0.08)	
		2400 mg/day	2 (353)	MD -0.27 (-1.33 to 0.82)	
	3600 mg/day	2 (418)	MD -0.74 (-1.50 to -0.01)		
1200-3600 mg/day	2 (725)	MD -0.58 (-1.26 to 0.10)			
Study quality	Good	2 (509)	MD -0.51 (-1.04 to 0.08)	0.7095	
Fair	13 (4,323)	MD -0.63 (-0.93 to -0.35)			
Pain Response 15 RCTs (n=4,832)	Pain type	DPN	7 (2,178)	RR 1.15 (1.04 to 1.38)	0.3636
		PHN	2 (737)	RR 1.80 (0.82 to 4.37)	
		DPN/PHN	1 (338)	RR 1.70 (1.22 to 2.36)	
		Other	5 (1,323)	RR 1.15 (0.93 to 1.65)	
	Pregabalin Dose	Pregabalin pooled	15 (4,832)	RR 1.28 (1.09 to 1.54)	0.8149 ^a
150 mg/day		2 (375)	RR 1.62 (0.71 to 4.00)		
300 mg/day		5 (1,035)	RR 1.22 (0.90 to 1.77)		
600 mg/day		4 (735)	RR 1.99 (1.42 to 2.87)		
150-600 mg/day		10 (2,963)	RR 1.36 (1.14 to 1.71)		
300-600 mg/day		2 (511)	RR 1.63 (1.15 to 2.26)		
450-600 mg/day		1 (375)	RR 0.94 (0.77 to 1.16)		
Gabapentin enacarbil Dose		Gabapentin pooled	2 (725)	RR 1.20 (0.94 to 1.57)	
		1200 mg/day	2 (384)	RR 1.16 (0.88 to 1.53)	
		2400 mg/day	2 (353)	RR 1.17 (0.72 to 1.84)	
	3600 mg/day	2 (418)	RR 1.29 (1.01 to 1.66)		
1200-3600 mg/day	2 (725)	RR 1.20 (0.94 to 1.57)			
Study quality	Good	2 (509)	RR 1.13 (0.78 to 1.84)	0.6690	
Fair	13 (4,067)	RR 1.31 (1.12 to 1.58)			

^a p-value for interaction with study drug

DPN = diabetic peripheral neuropathy; MD = mean difference; PHN = postherpetic neuralgia; RCT = randomized controlled trial; RR = relative risk

Table I-2. Duloxetine in NPP subgroup analyses

Outcome Sample Size	Variable	Subgroup	N studies (sample size)	Effect Size (95% CI)
Pain Improvement	Duloxetine Dose	Duloxetine pooled	6 (2,082)	MD -0.79 (-1.10 to -0.49)
		20 mg/day	1 (230)	MD -0.45 (-1.05 to 0.15)
		40 mg/day	1 (252)	MD -0.80 (-1.38 to -0.22)
		60 mg/day	5 (1,328)	MD -0.85 (-1.22 to -0.54)
		120 mg/day	3 (675)	MD -1.16 (-1.64 to -0.76)
		20-120 mg/day	1 (457)	MD -0.90 (-1.40 to -0.41)
		40-60 mg/day	1 (338)	MD -0.86 (-1.32 to -0.40)
		60-120 mg/day	3 (889)	MD -0.88 (-1.52 to -0.24)
Pain Response	Duloxetine Dose	Duloxetine pooled	6 (2,082)	RR 1.43 (1.24 to 1.69)
		20 mg/day	1 (230)	RR 1.59 (1.08 to 2.33)
		40 mg/day	1 (252)	RR 1.57 (1.18 to 2.07)
		60 mg/day	5 (1,328)	RR 1.50 (1.31 to 1.80)
		120 mg/day	3 (675)	RR 1.64 (1.37 to 2.02)
		20-120 mg/day	1 (457)	RR 1.83 (1.31 to 2.56)
		40-60 mg/day	1 (338)	RR 1.62 (1.27 to 2.07)
		60-120 mg/day	3 (889)	RR 1.38 (1.09 to 1.79)
Function (Brief Pain Inventory- Interference)	Duloxetine Dose	Duloxetine pooled	6 (2,082)	SMD -0.31 (-0.42 to -0.20)
		20 mg/day	1 (230)	SMD 0.00 (-0.26 to 0.26)
		40 mg/day	1 (252)	SMD -0.18 (-0.44 to 0.08)
		60 mg/day	5 (1,328)	SMD -0.34 (-0.45 to -0.22)
		120 mg/day	3 (675)	SMD -0.46 (-0.65 to -0.27)
		20-120 mg/day	1 (457)	SMD -0.22 (-0.43 to -0.00)
		40-60 mg/day	1 (338)	SMD -0.20 (-0.41 to 0.01)
		60-120 mg/day	3 (889)	SMD -0.39 (-0.58 to -0.17)
Quality of Life (Euro Quality of Life-5D)	Duloxetine Dose	Duloxetine pooled	4 (1,404)	MD 0.20 (0.07 to 0.33)
		20 mg/day	1 (457)	MD 0.10 (-0.17 to 0.37)
		60 mg/day	2 (791)	MD 0.29 (0.06 to 0.52)
		120 mg/day	2 (791)	MD 0.29 (0.06 to 0.53)
		60-120 mg/day	3 (1,006)	MD 0.22 (0.05 to 0.38)

Table I-3. Duloxetine subgroup analyses

Outcome Sample Size	Variable	Subgroup	SMD (95% CI) ^a	Interaction p-value
Pain Improvement 5 RCTs (n=1,535)	Pain location	Knee	-0.90 (-1.21 to -0.66)	0.129
		Knee/Hip	-0.50 (-0.80 to -0.20)	
	Study quality	Good	-0.93 (-1.37 to -0.63)	0.197
		Fair	-0.57 (-1.00 to -0.25)	
Pain Response 4 RCTs (n=1,274)	Pain location	Knee	1.41 (1.24 to 1.61)	0.457
		Knee/Hip	1.28 (1.08 to 1.52)	
	Study quality	Good	1.38 (1.16 to 1.64)	0.862
		Fair:	1.36 (1.13 to 1.69)	
Function 5 RCTs (n=1,535)	Pain location	Knee	-0.26 (-0.45 to -0.06)	0.819
		Knee/Hip	-0.31 (-0.21 to -0.10)	
	Study quality	Good	-0.26 (-0.53 to 0.02)	0.889
		Fair	-0.29 (-0.47 to -0.10)	
Dose	60mg/day	-0.28 (-0.54 to -0.01)	0.876	
	60-120mg/day	-0.25 (-0.46 to -0.05)		

^a Response outcome is a relative risk (RR)

Neuropathic Pain

Figure I-1. Neuropathic pain—pain pregabalin and gabapentin plot

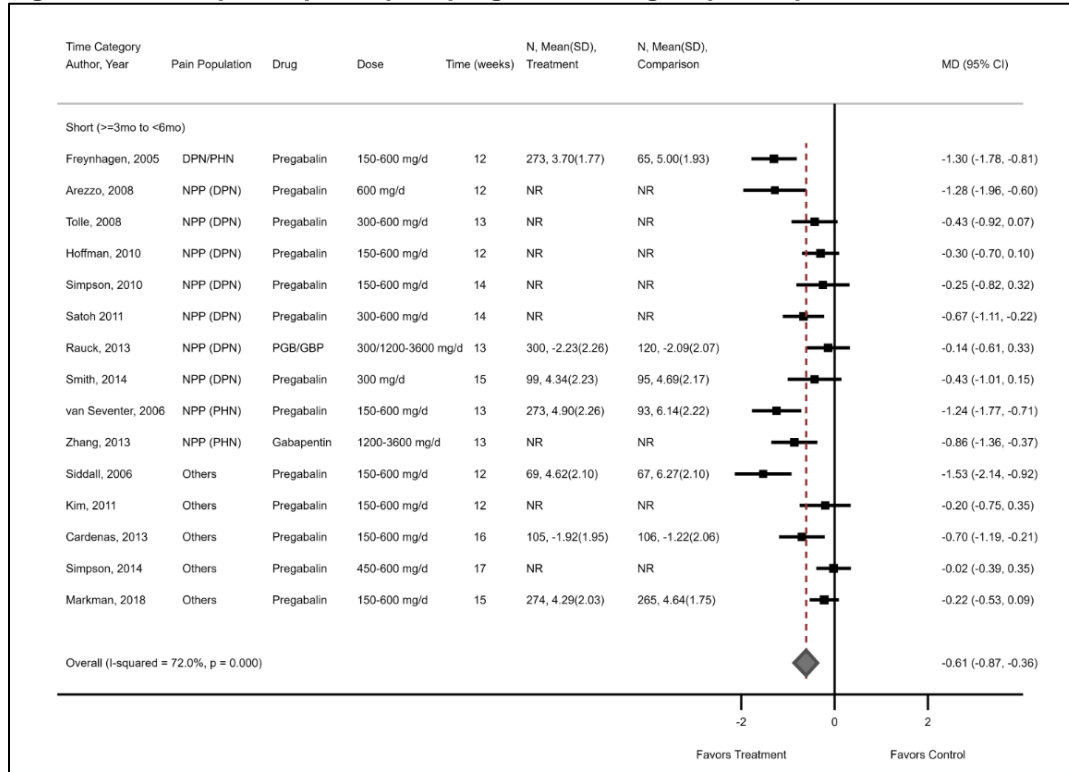


Figure I-2. Neuropathic pain—pain oxcarbazepine plot

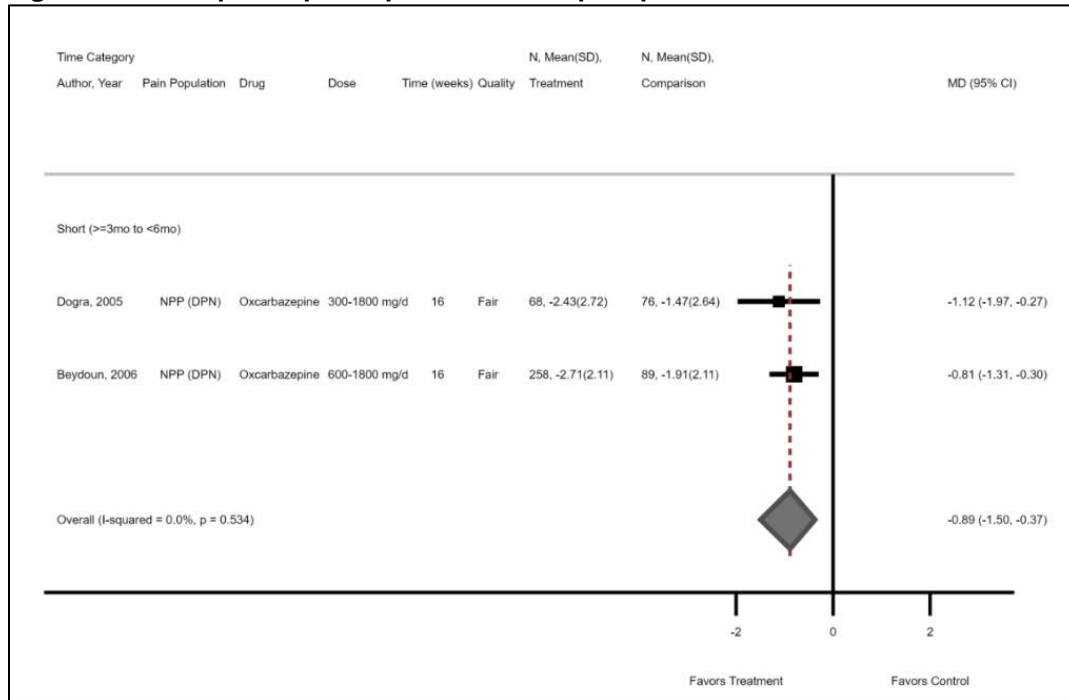


Figure I-3. Neuropathic pain—pain SNRI plot

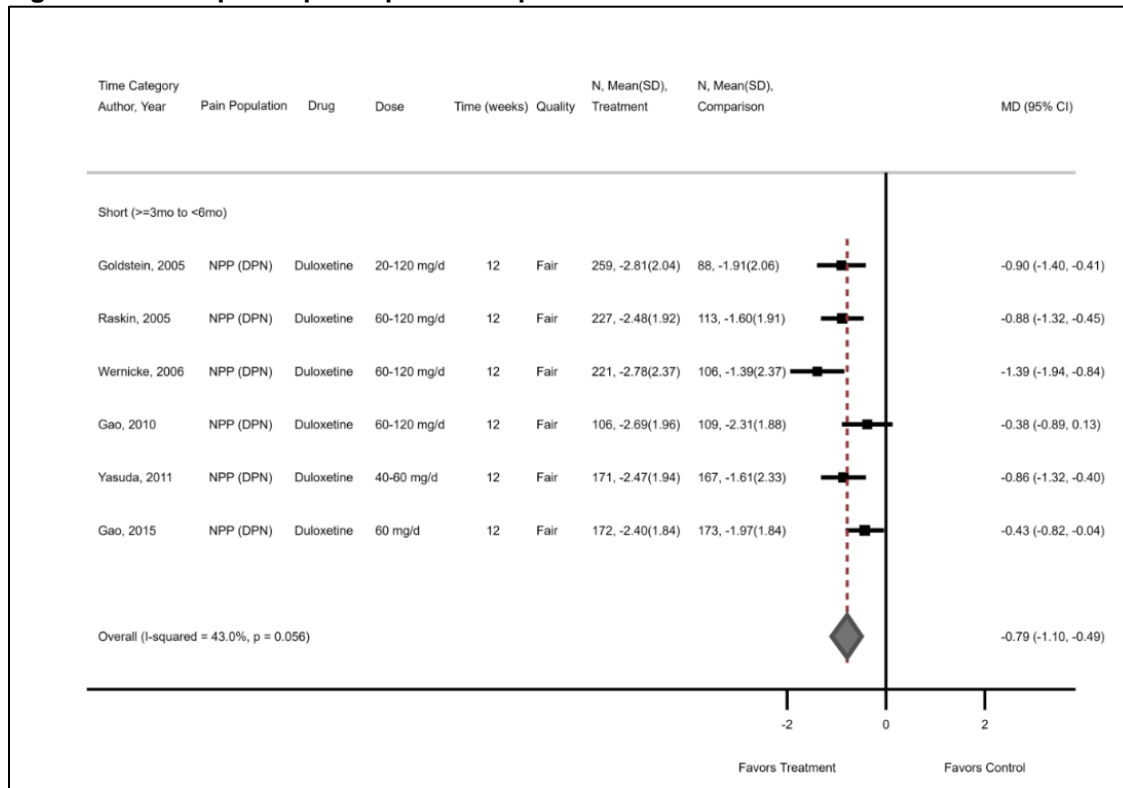


Figure I-4. Neuropathic pain—pain capsaicin plot

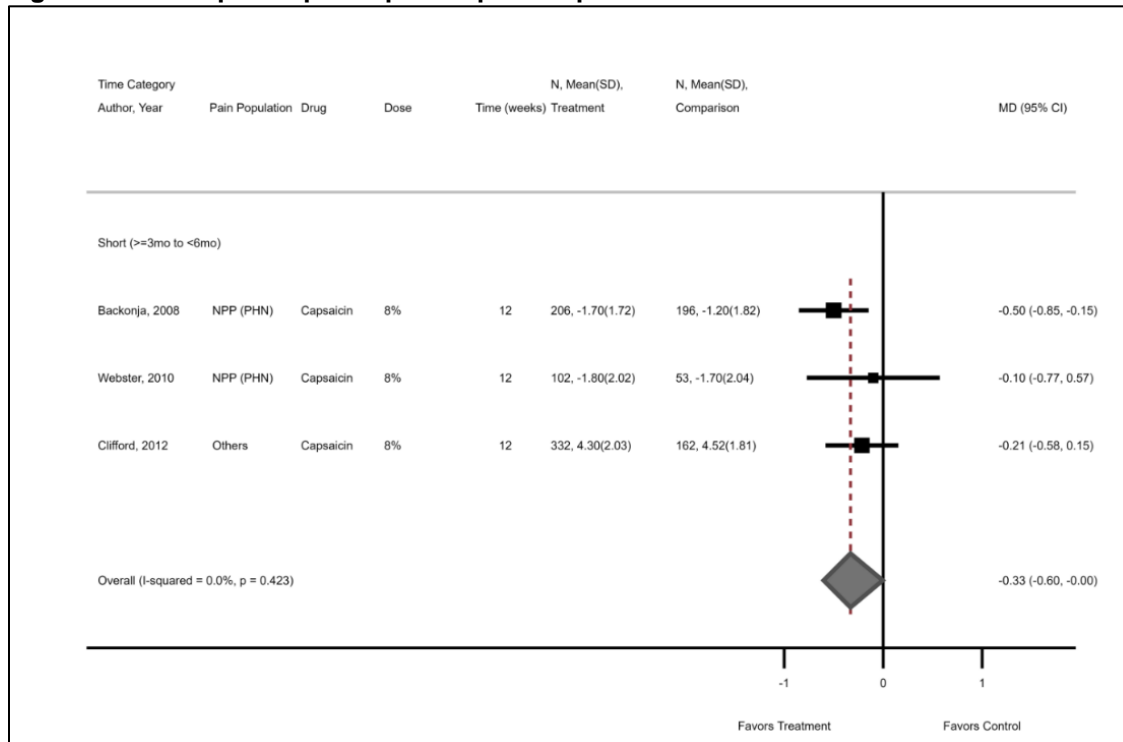


Figure I-5. Neuropathic pain—pain response pregabalin and gabapentin plot

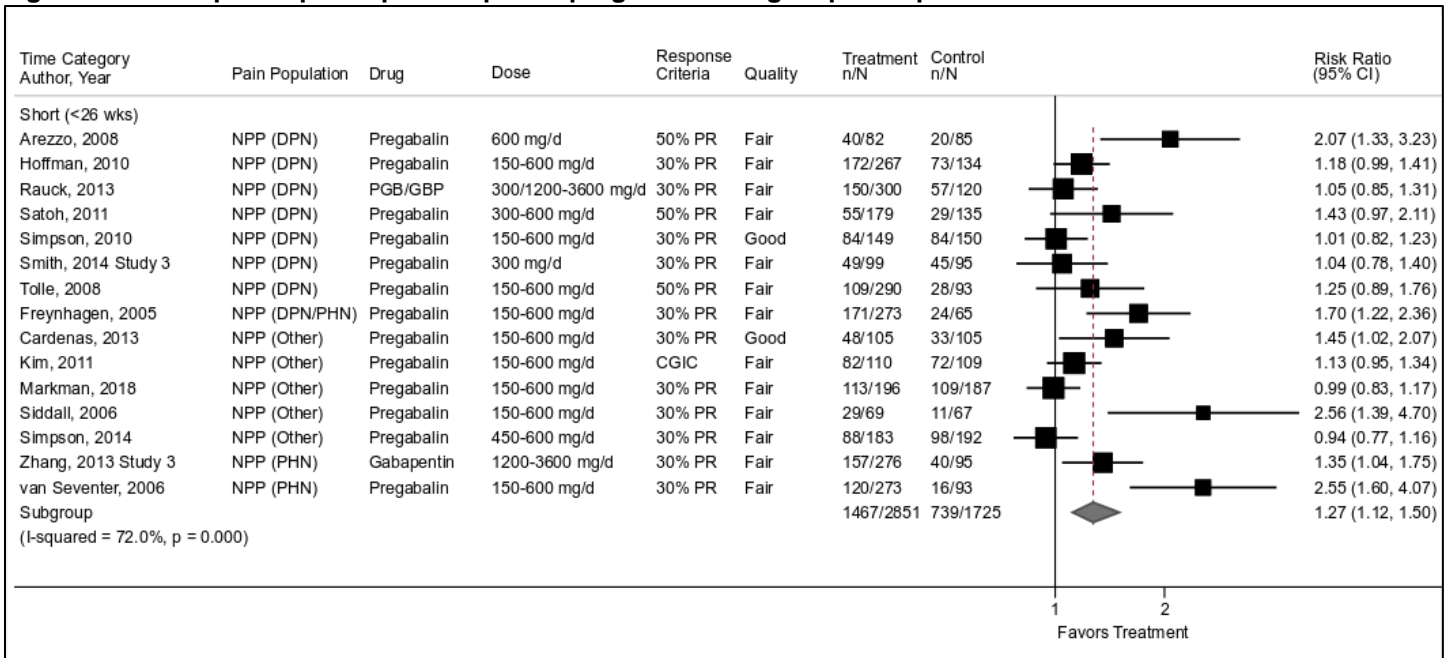


Figure I-6. Neuropathic pain—pain response SNRI plot

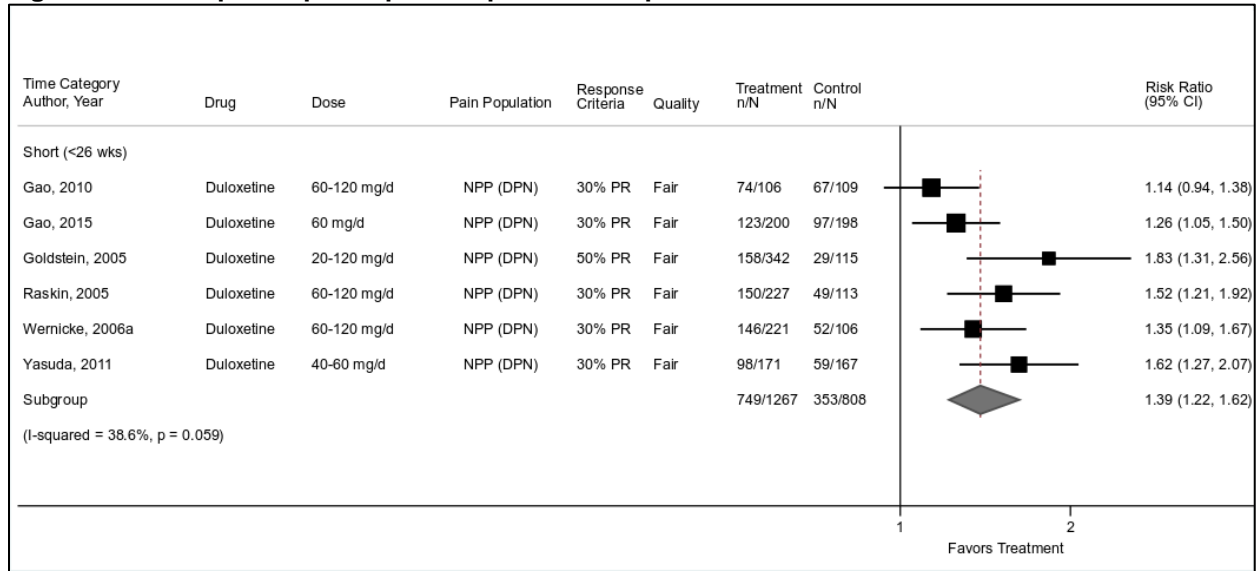


Figure I-7. Neuropathic pain—pain response capsaicin plot

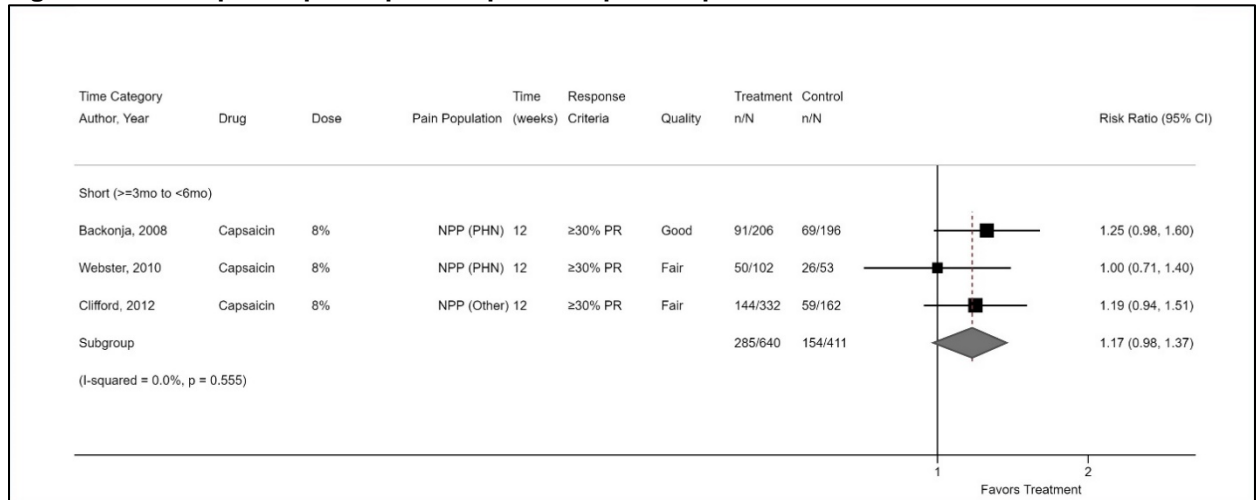


Figure I-8. Neuropathic pain—function pregabalin and gabapentin plot

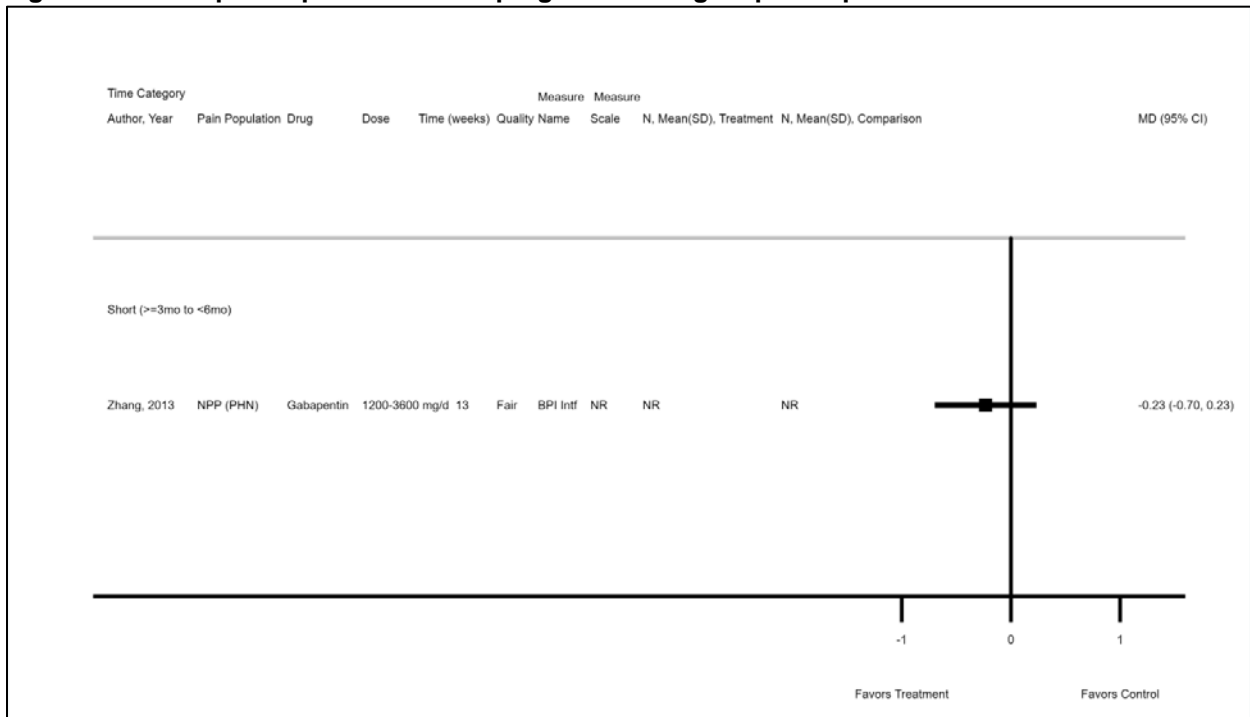


Figure I-9. Neuropathic pain—function SNRI plot

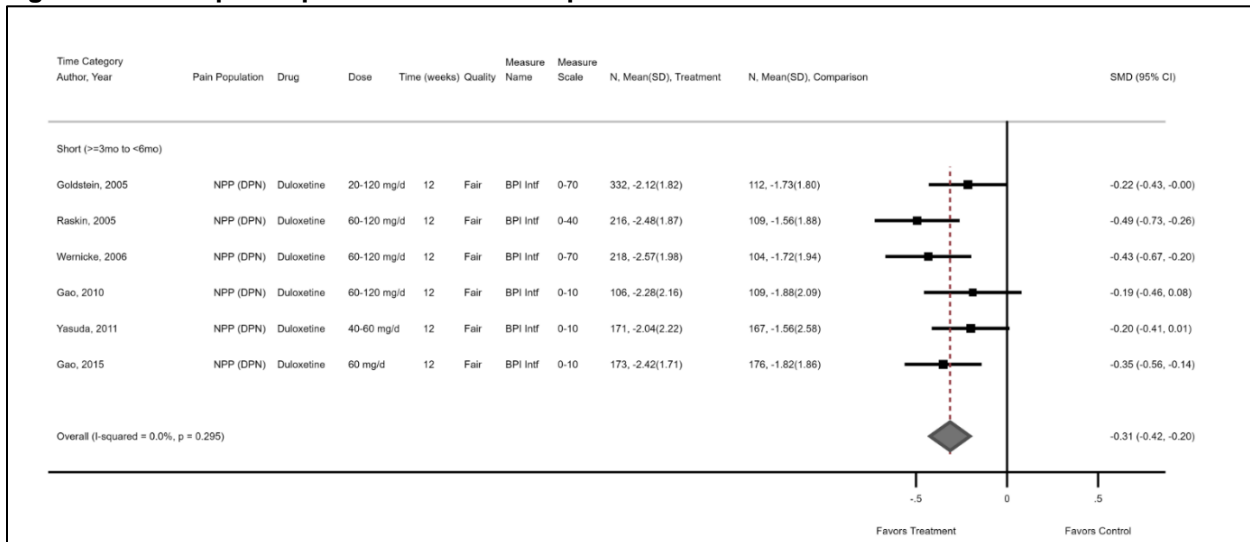


Figure I-10. Neuropathic pain—quality of life pregabalin and gabapentin EQ-5D plot

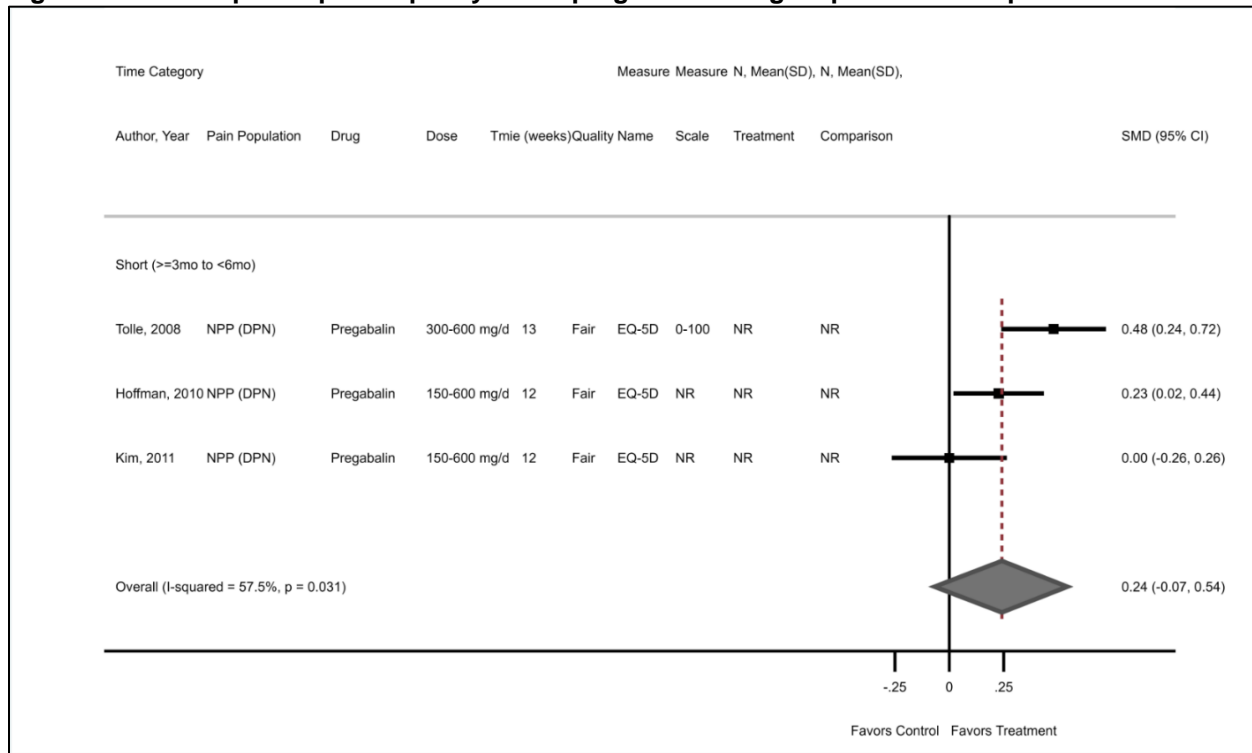


Figure I-11. Neuropathic pain—quality of life pregabalin and gabapentin SF-36 PCS plot

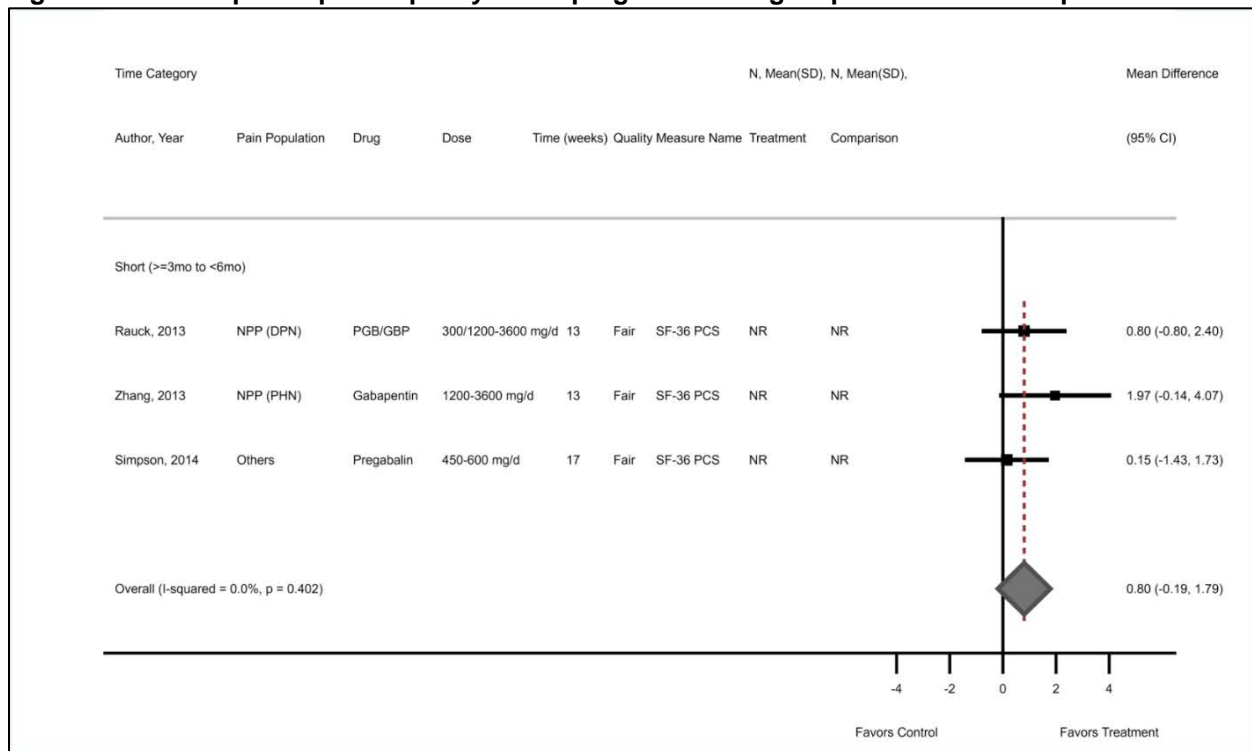


Figure I-12. Neuropathic pain—quality of life pregabalin and gabapentin SF-36 MCS plot

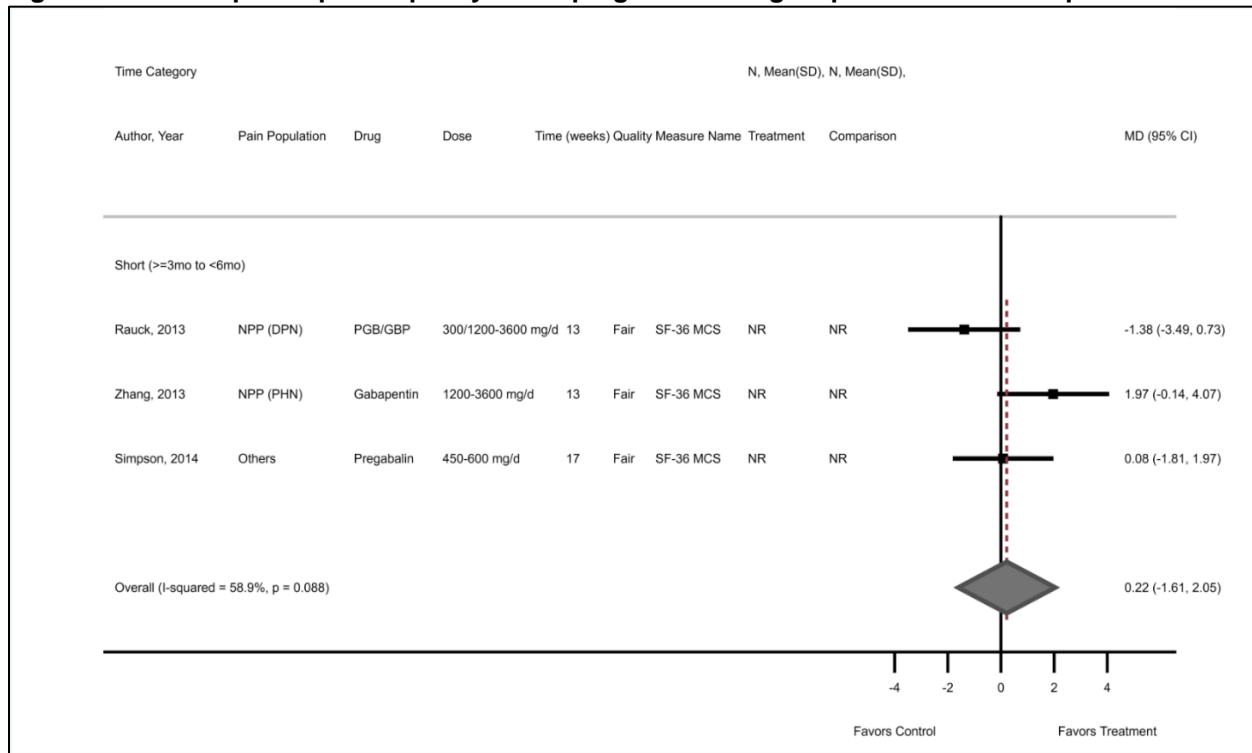


Figure I-13. Neuropathic pain—quality of life SNRI plot

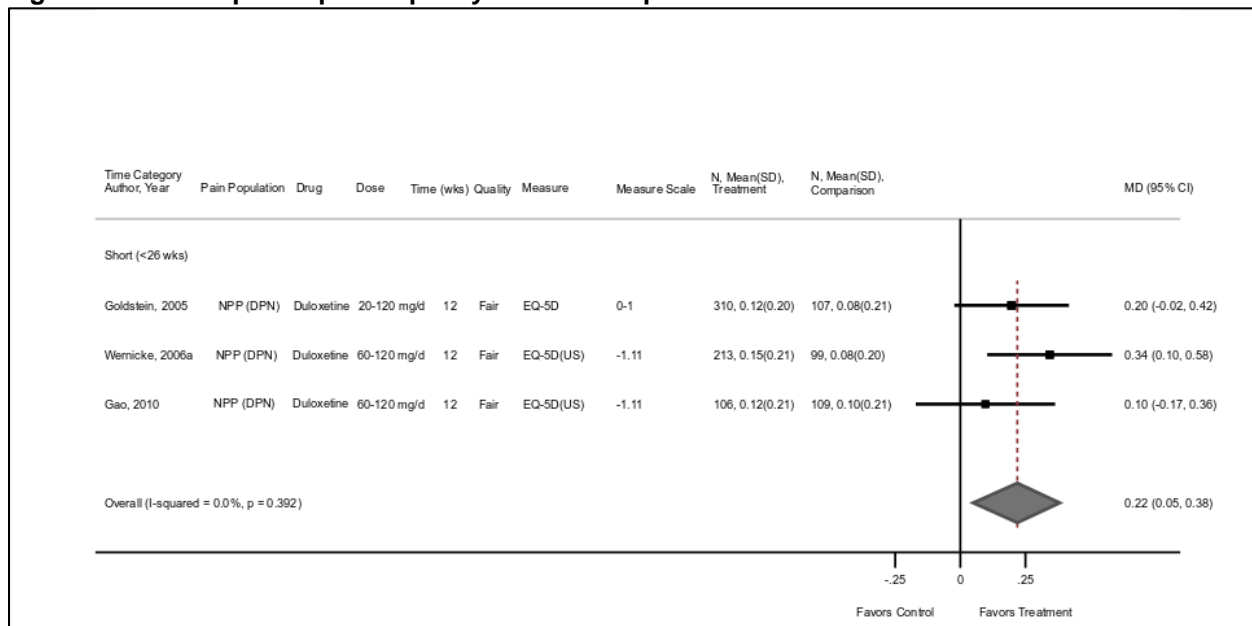


Figure I-14. Neuropathic pain—anxiety pregabalin and gabapentin plot

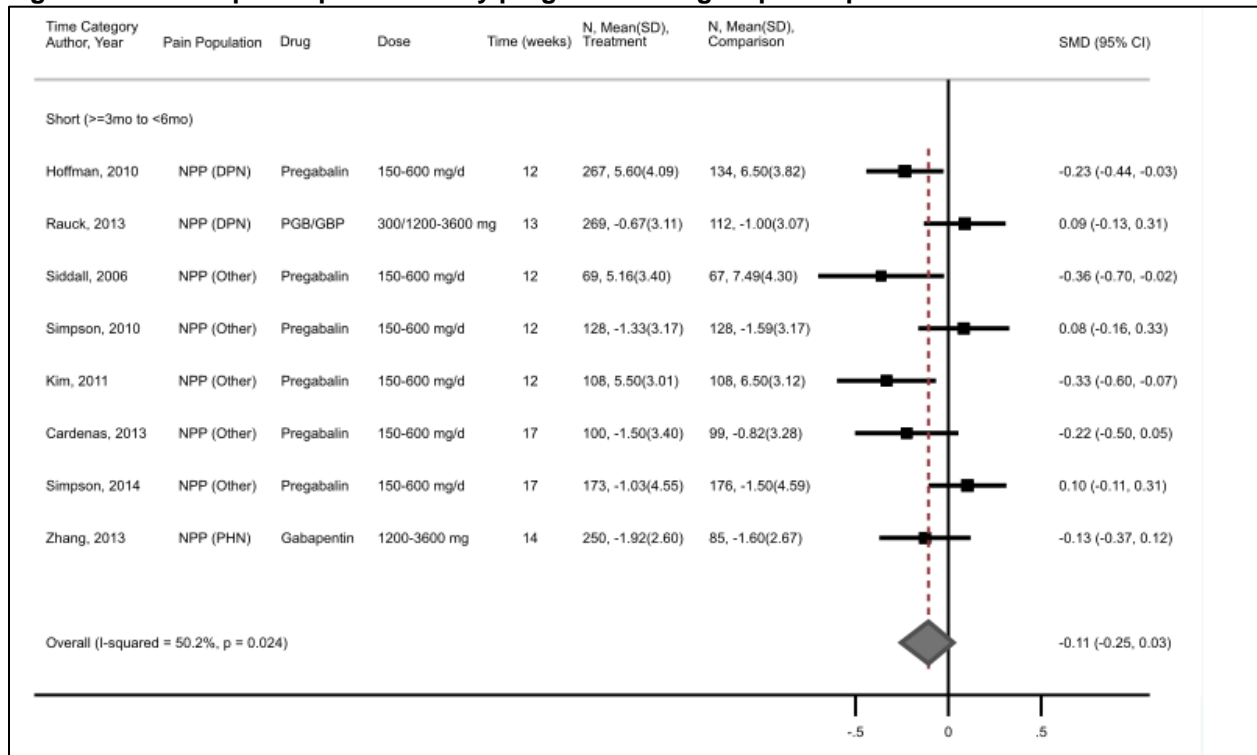


Figure I-15. Neuropathic pain—depression pregabalin and gabapentin plot

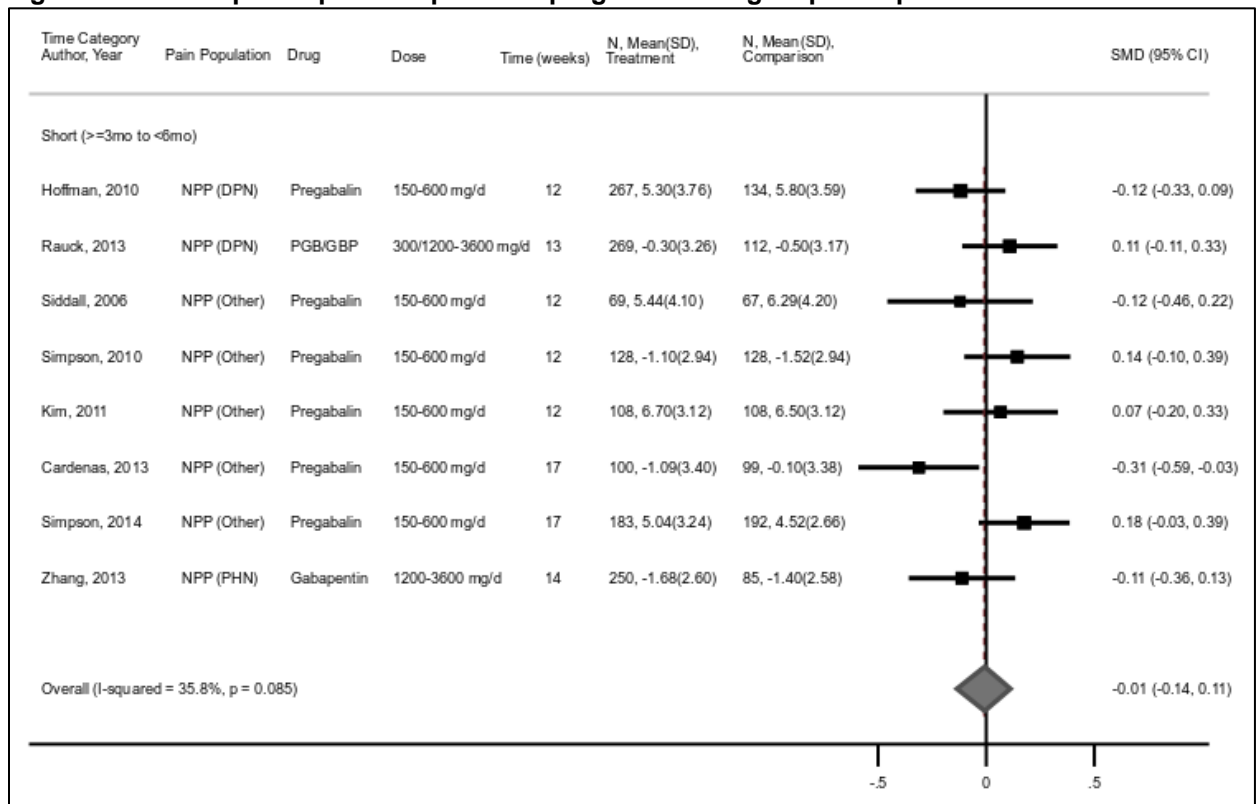


Figure I-16. Neuropathic pain—depression SNRI plot

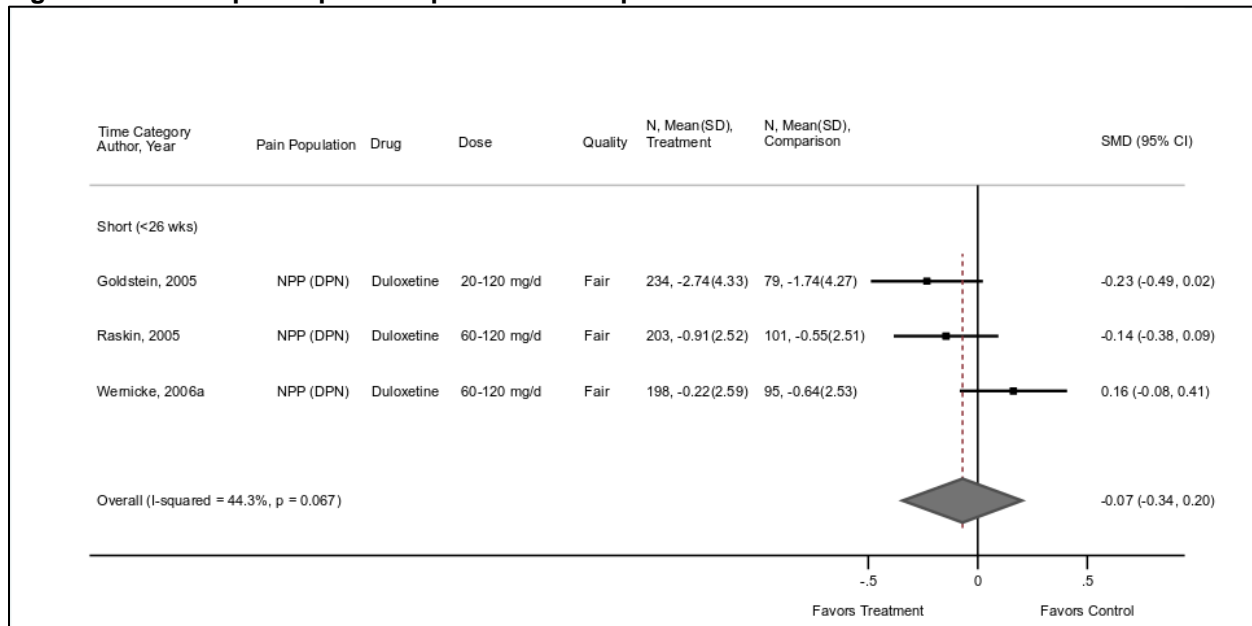
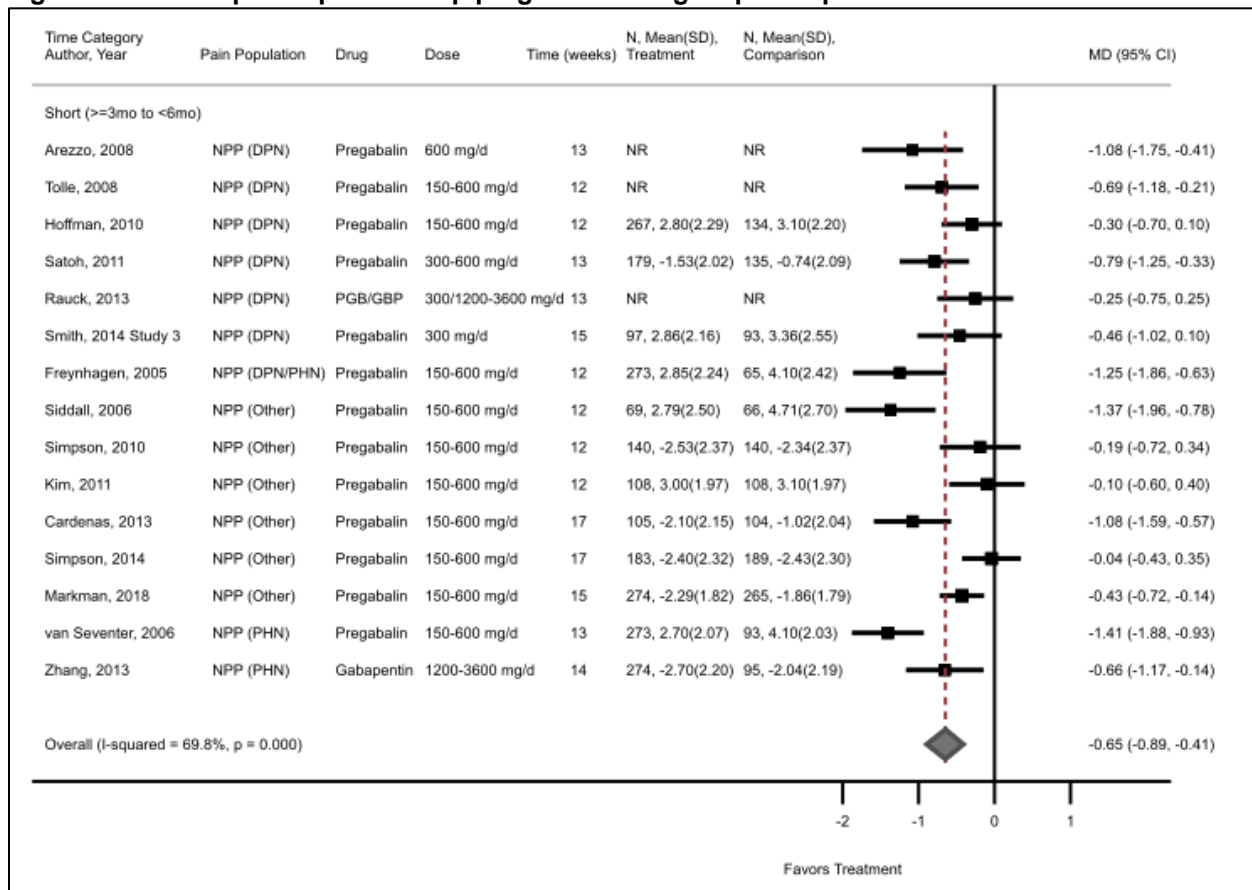


Figure I-17. Neuropathic pain—sleep pregabalin and gabapentin plot



Fibromyalgia

Figure I-18. Fibromyalgia—pain pregabalin and gabapentin plot

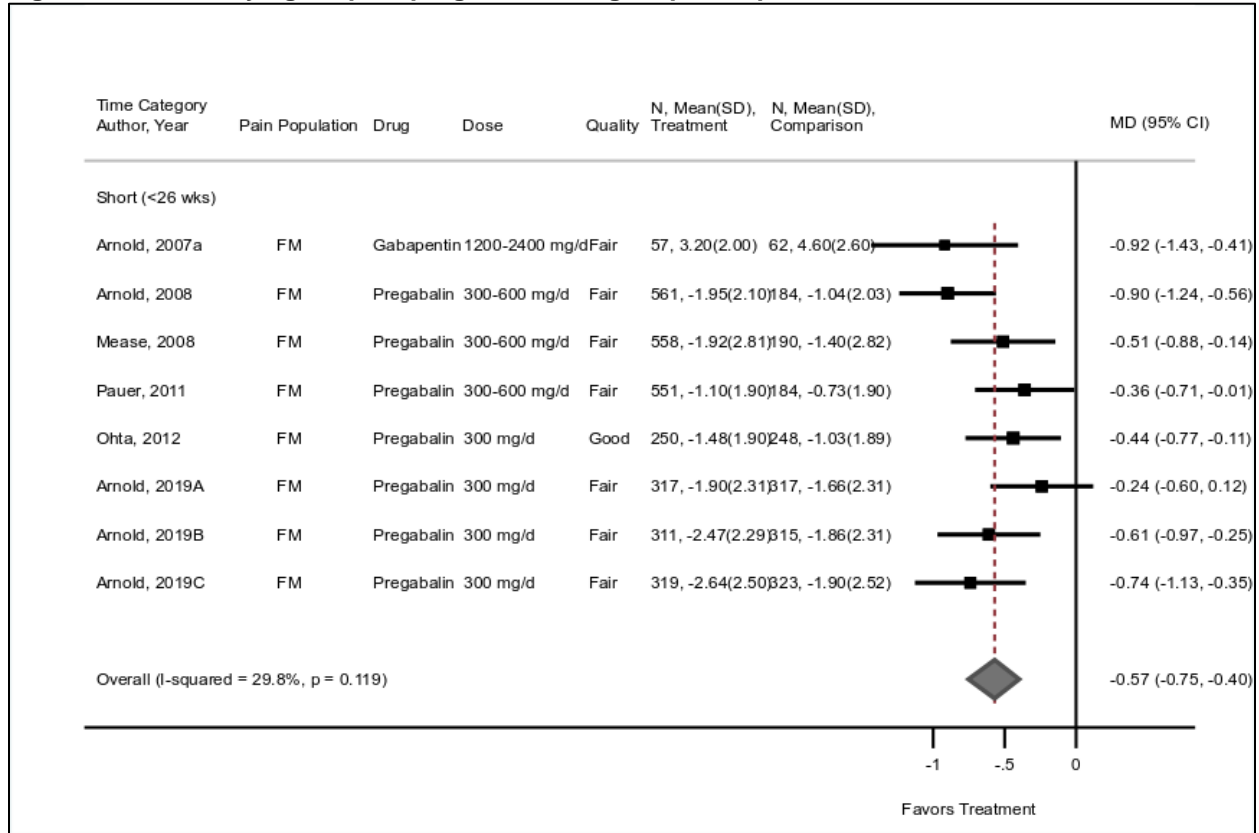


Figure I-19. Fibromyalgia—pain SNRI plot

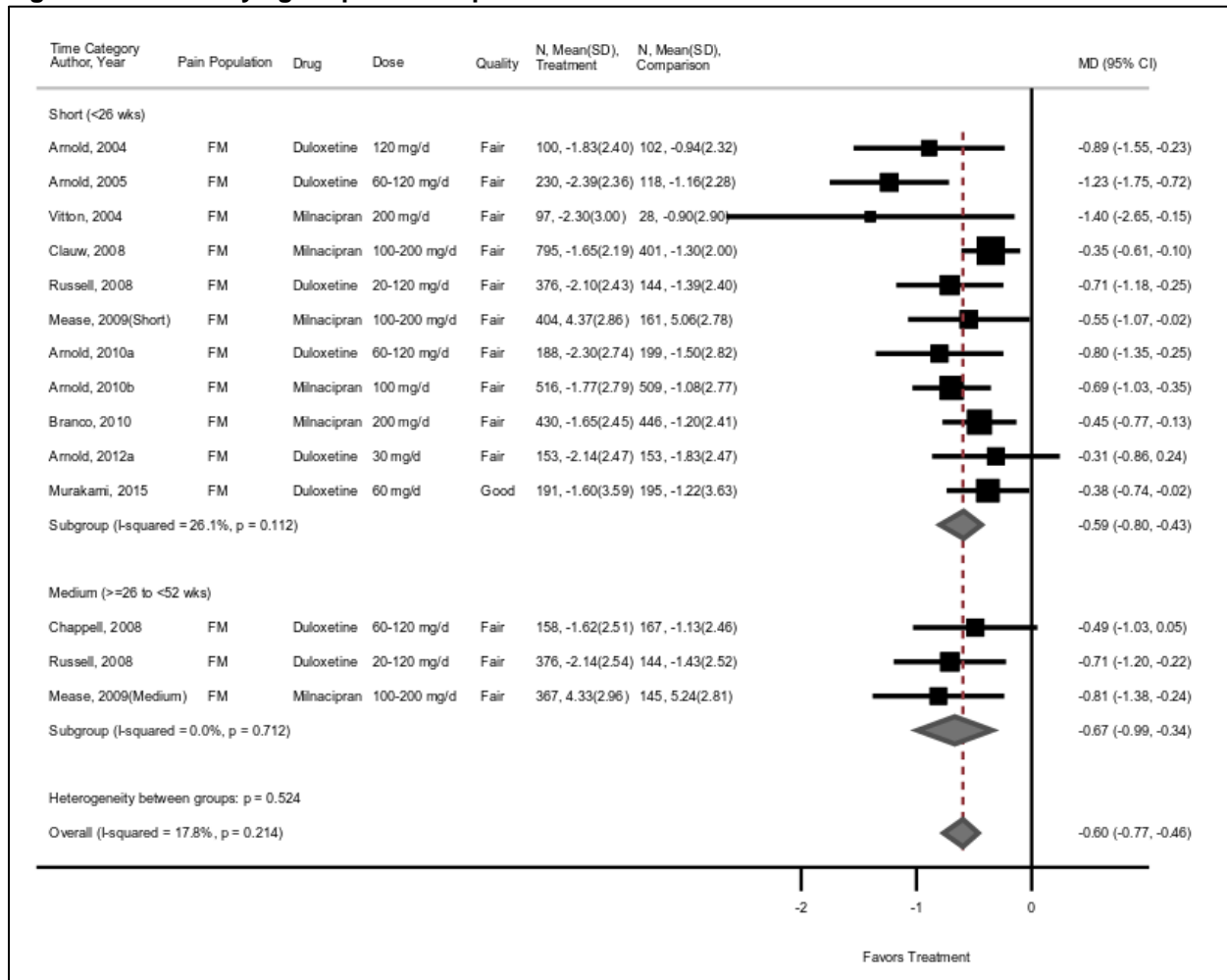


Figure I-20. Fibromyalgia—pain response pregabalin and gabapentin plot

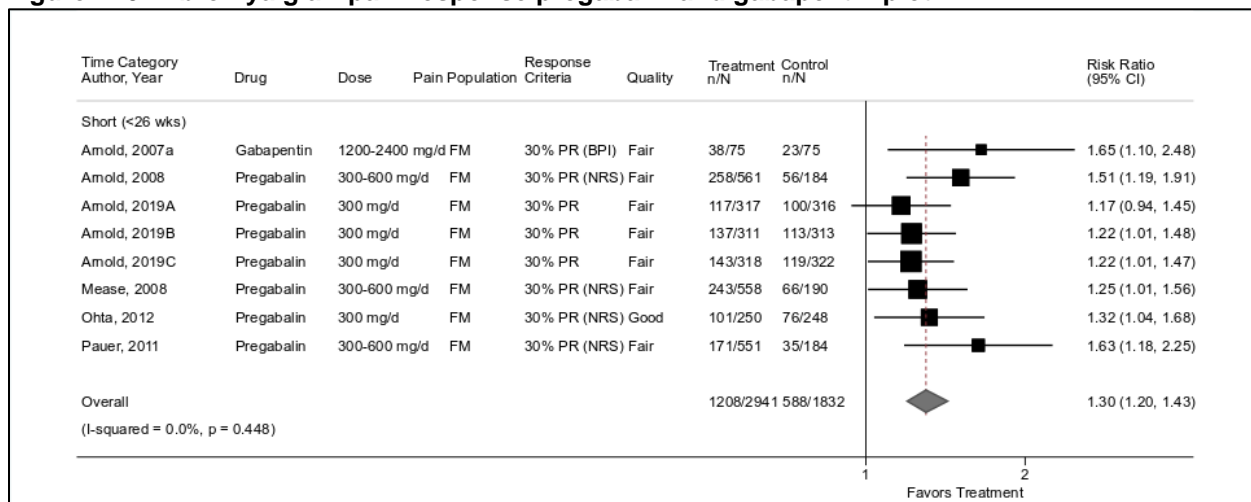


Figure I-21. Fibromyalgia—pain response SNRI plot

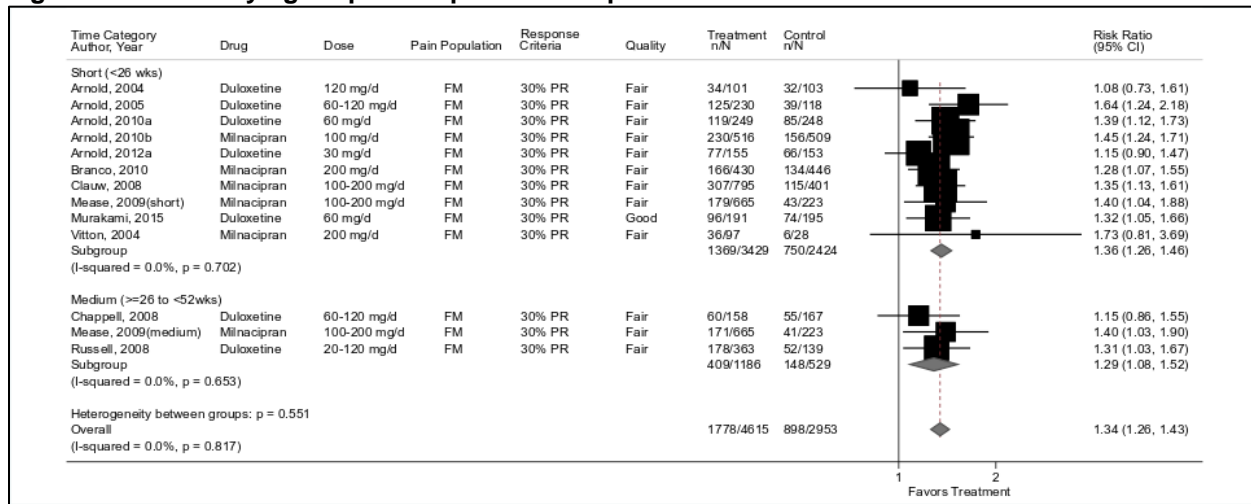


Figure I-22. Fibromyalgia—function pregabalin and gabapentin plot

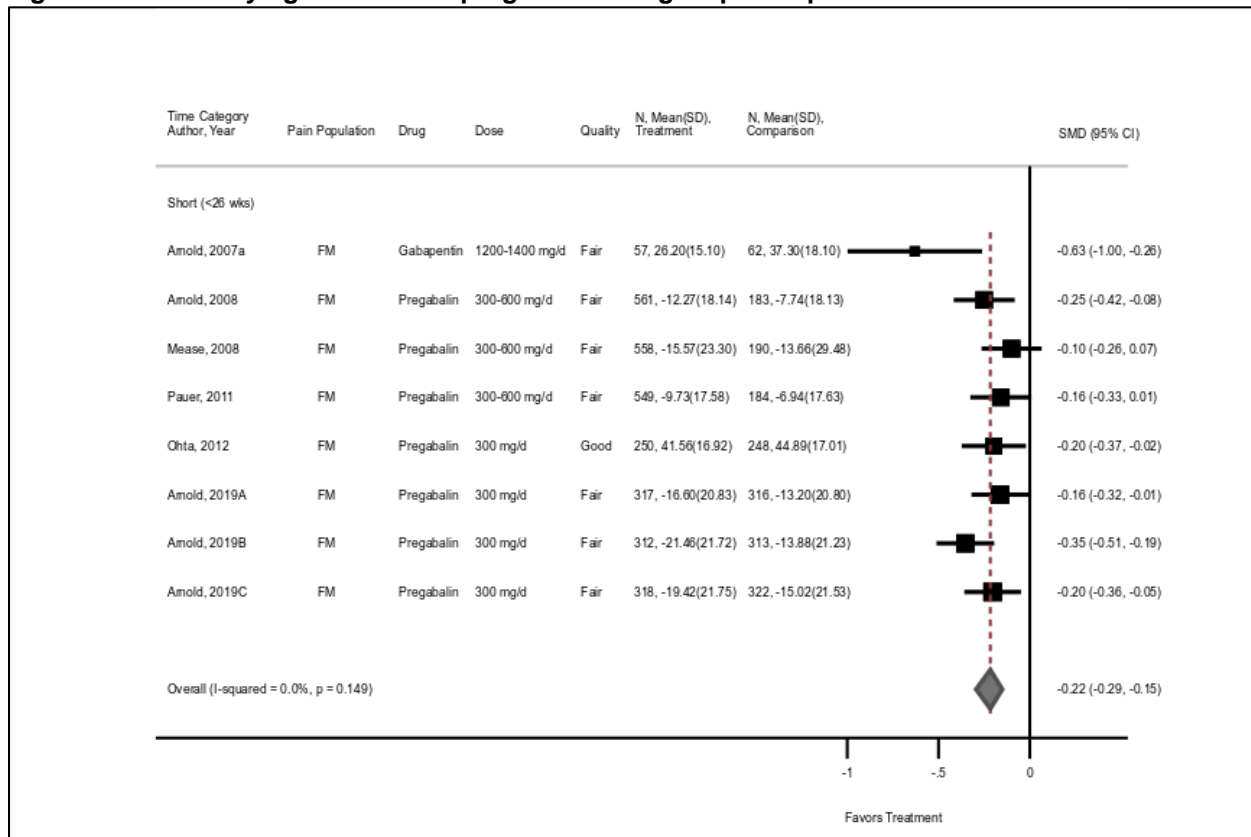


Figure I-24. Fibromyalgia—quality of life pregabalin and gabapentin plot

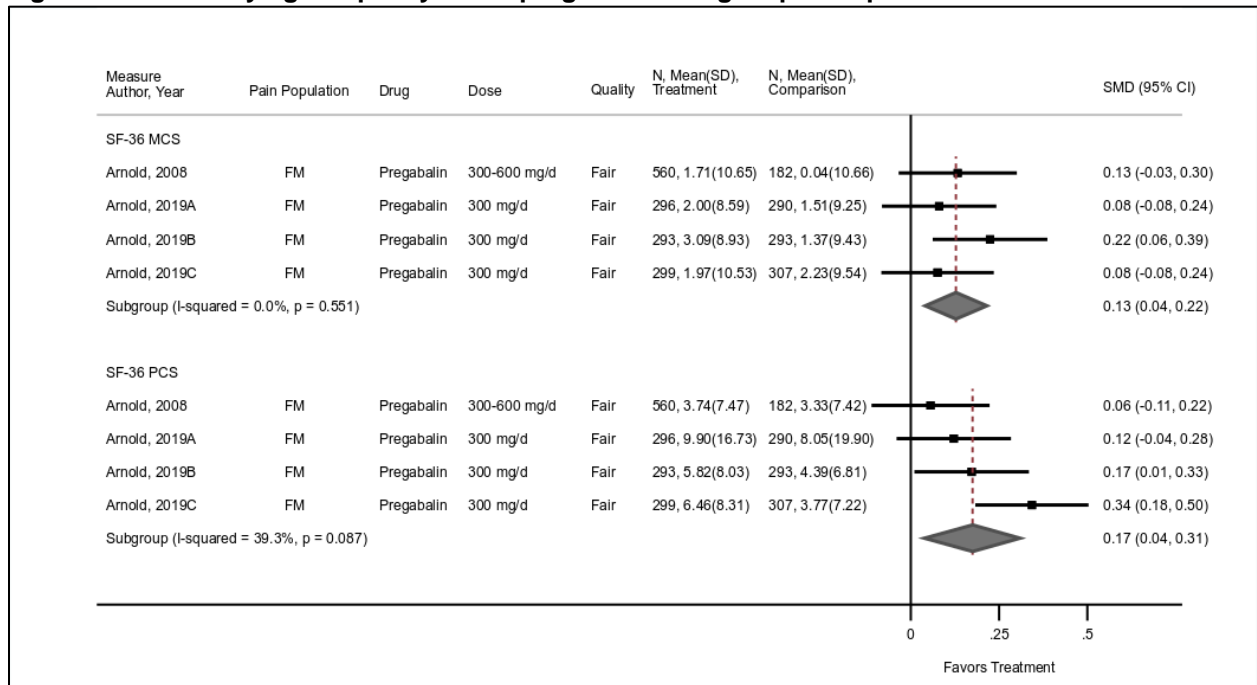


Figure I-25. Fibromyalgia—quality of life SNRI SF-36 PCS plot

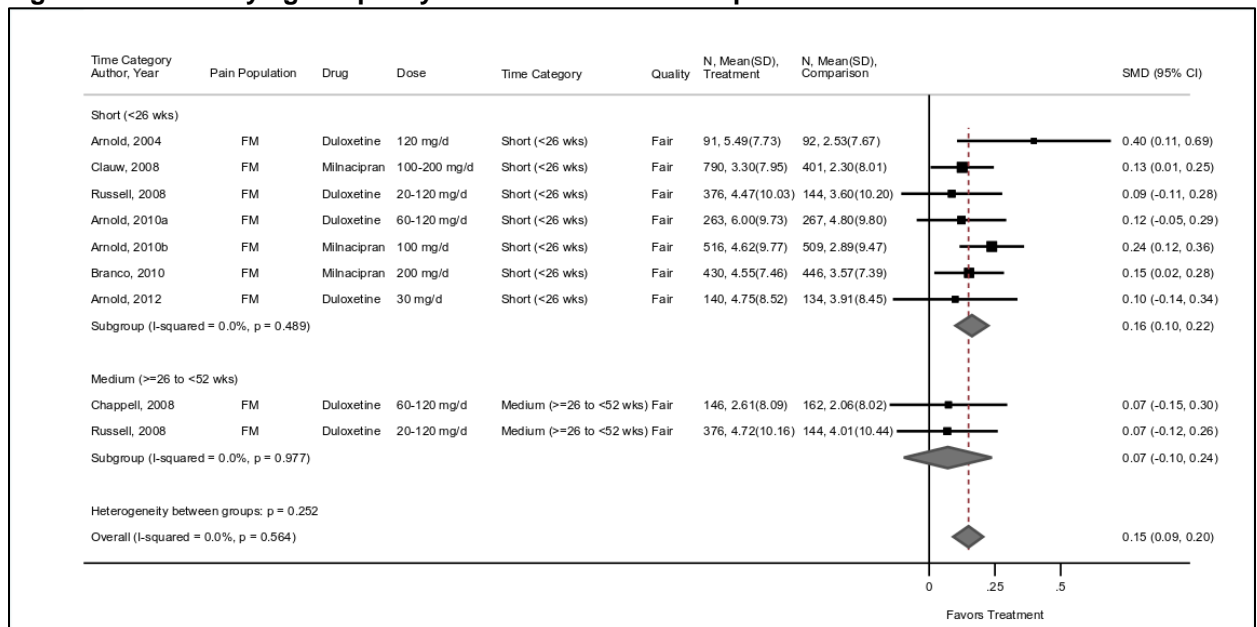


Figure I-26. Fibromyalgia—quality of life SNRI SF-36 MCS plot

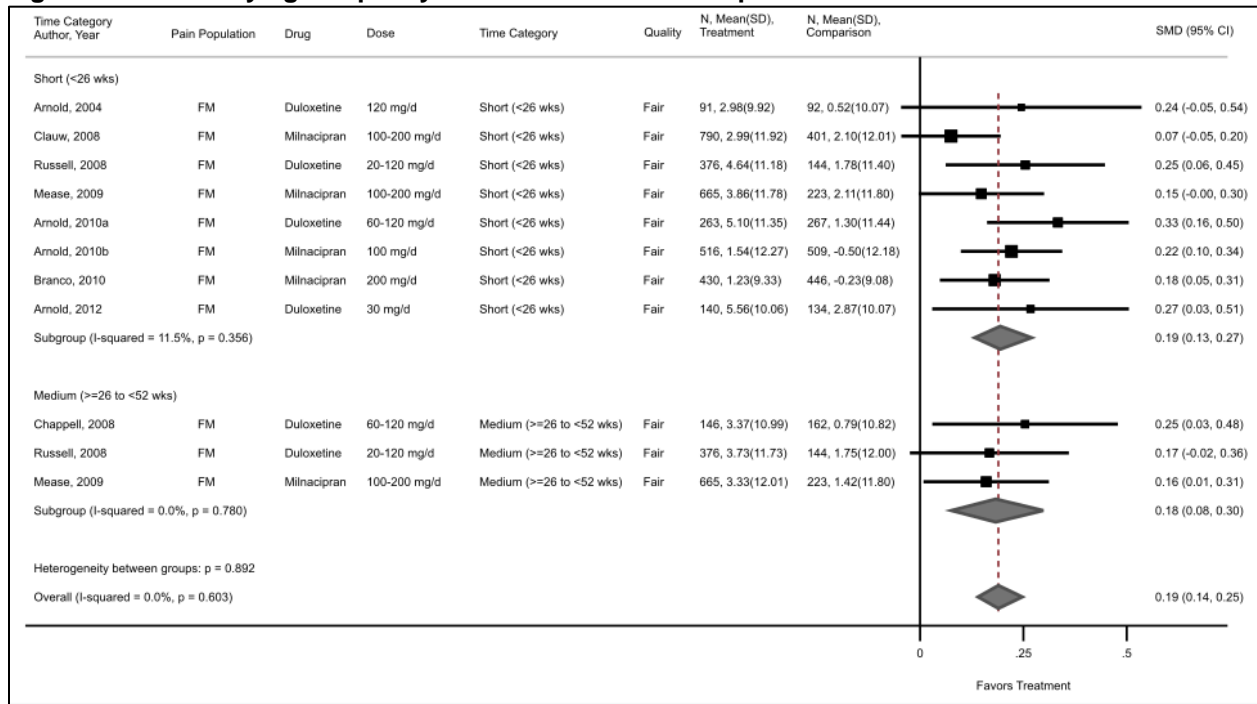


Figure I-27. Fibromyalgia—anxiety pregabalin and gabapentin plot

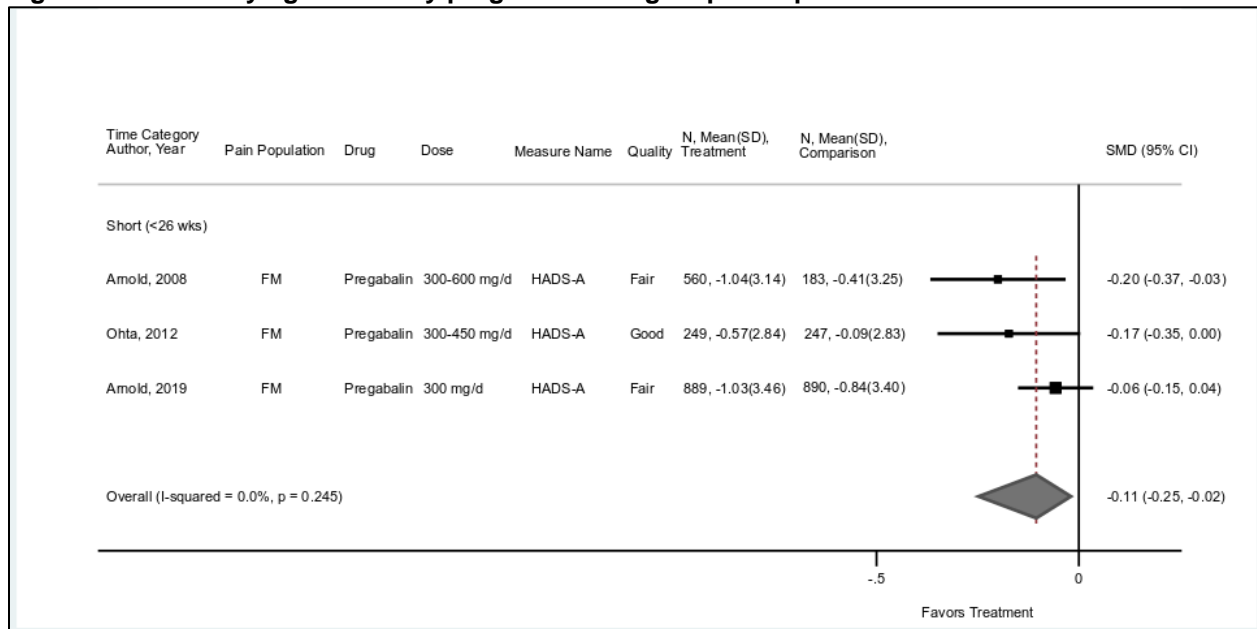


Figure I-28. Fibromyalgia—anxiety SNRI plot

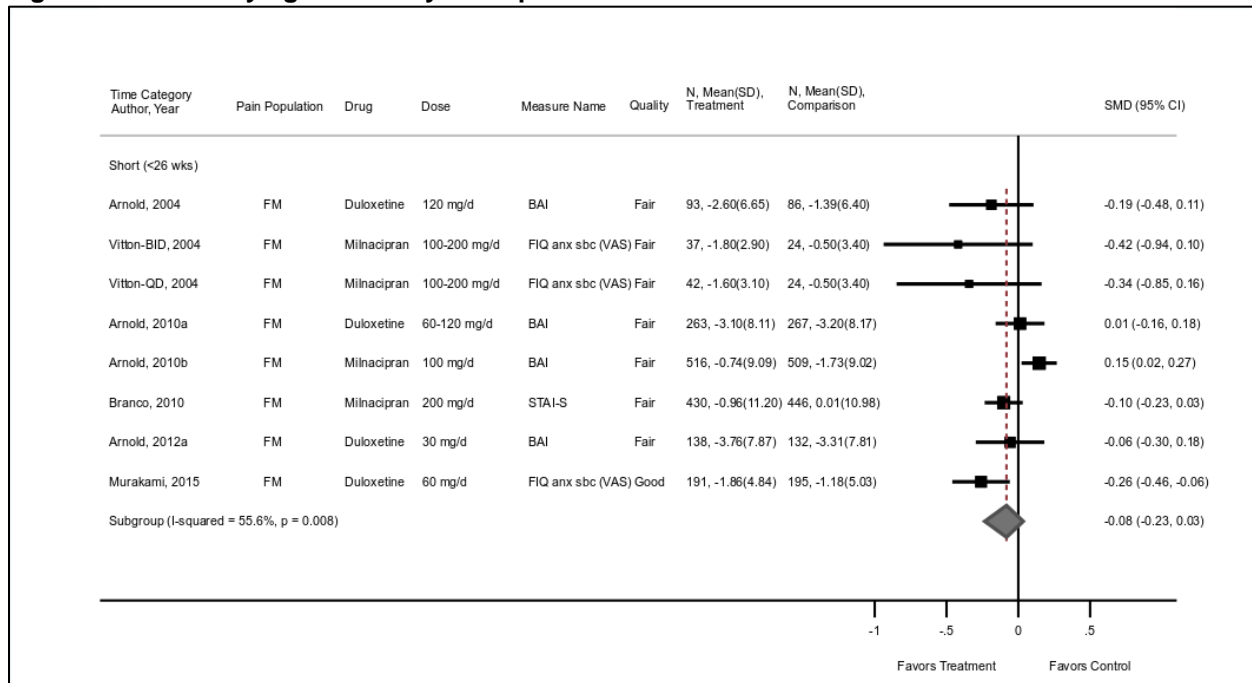


Figure I-29. Fibromyalgia—depression pregabalin and gabapentin plot

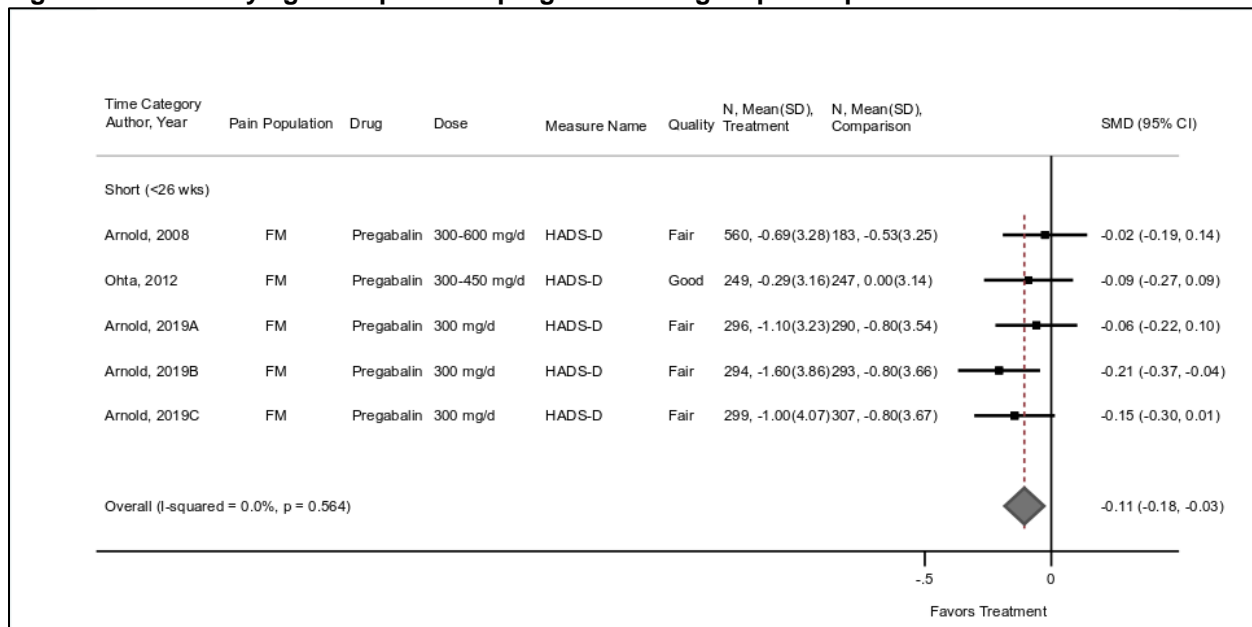


Figure I-30. Fibromyalgia—depression SNRI plot

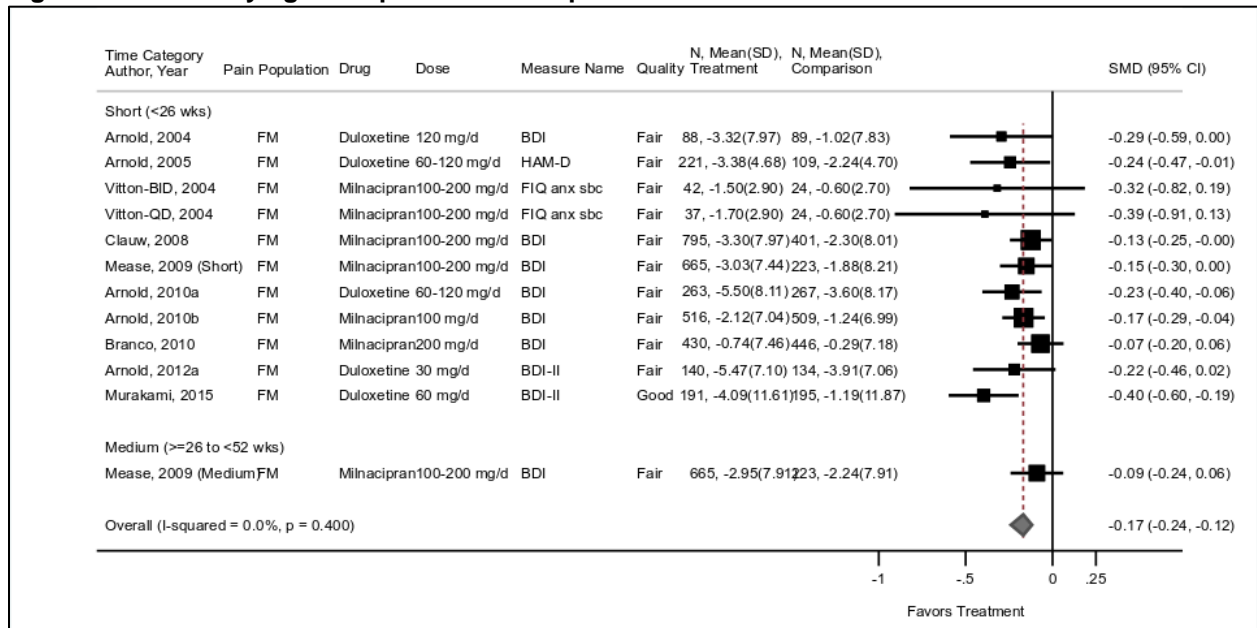


Figure I-31. Fibromyalgia—sleep pregabalin and gabapentin plot

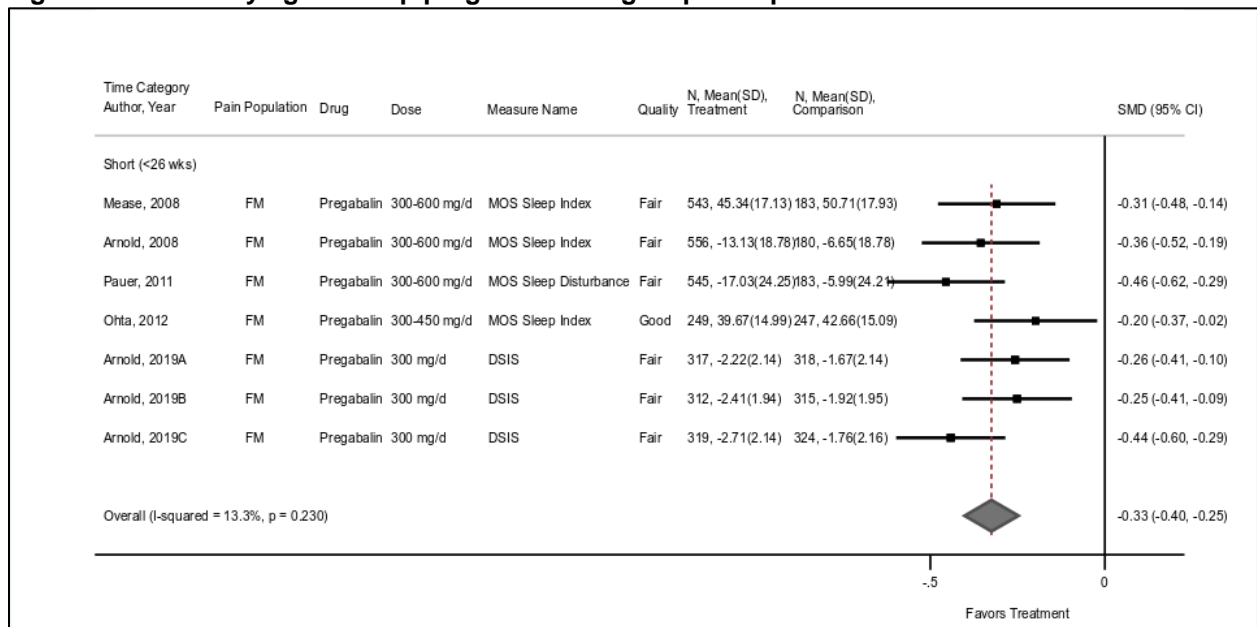
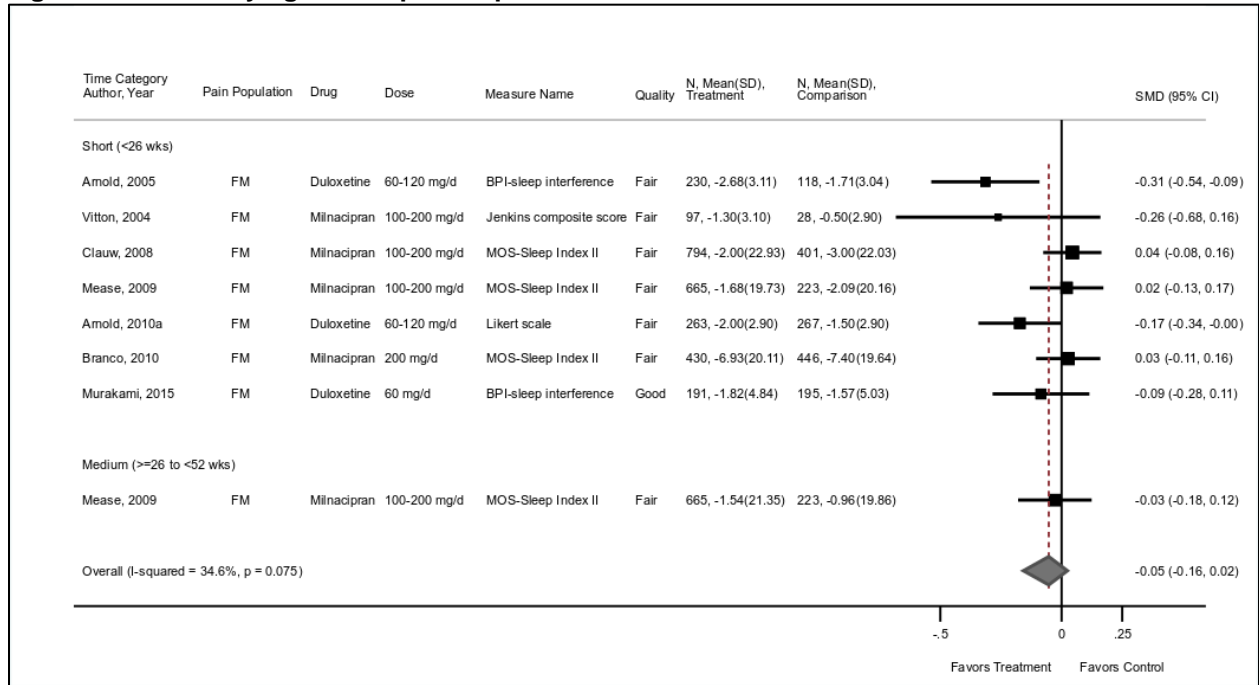


Figure I-32. Fibromyalgia—sleep SNRI plot



Osteoarthritis

Figure I-33. Osteoarthritis—pain NSAID plot

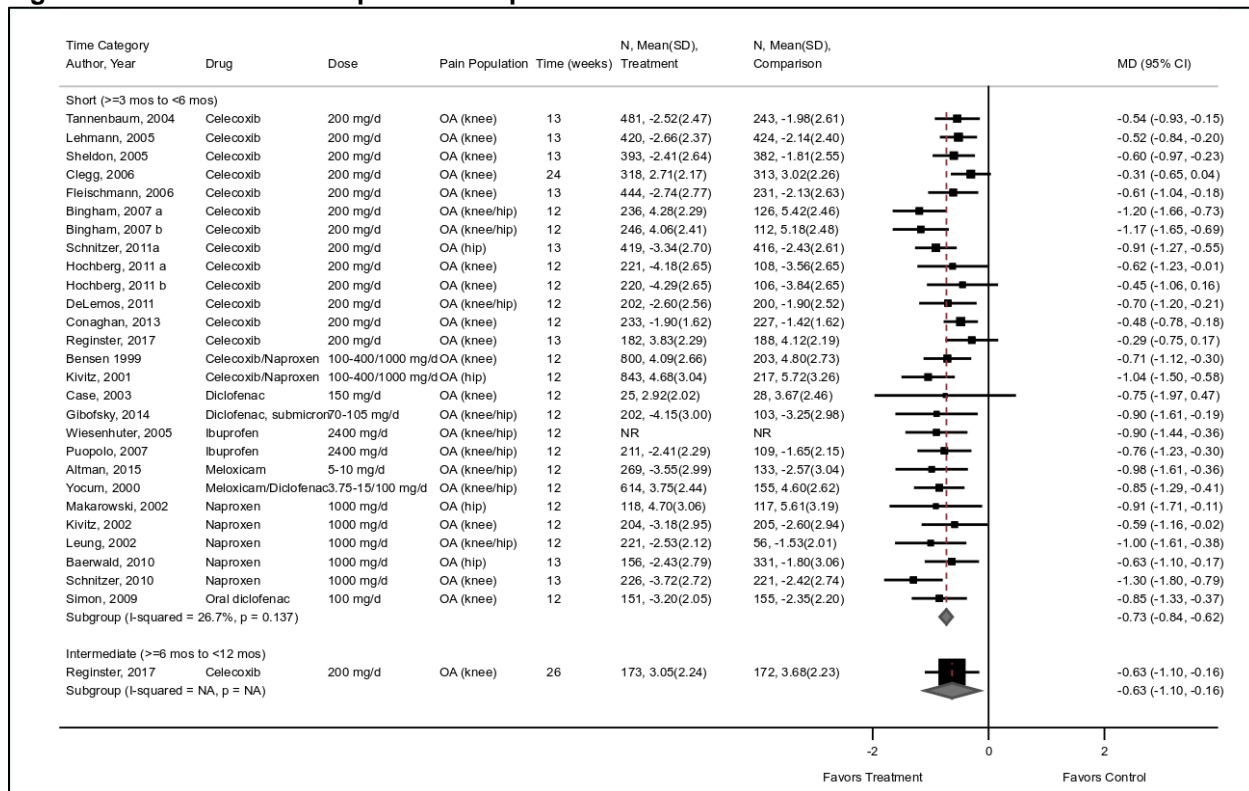


Figure I-34. Osteoarthritis—pain NSAID topical diclofenac plot

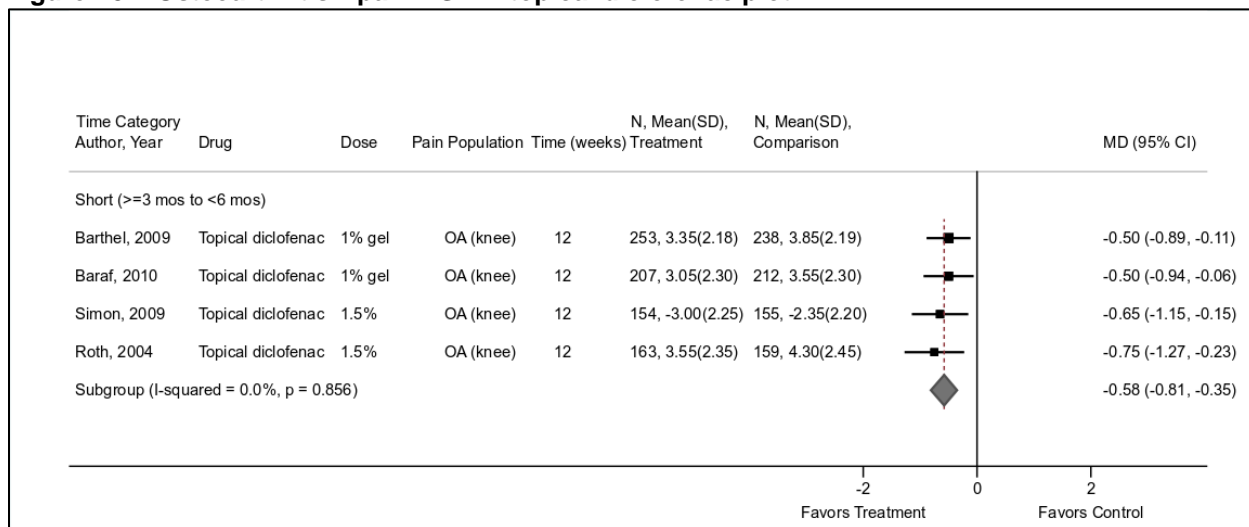


Figure I-35. Osteoarthritis—pain SNRI plot

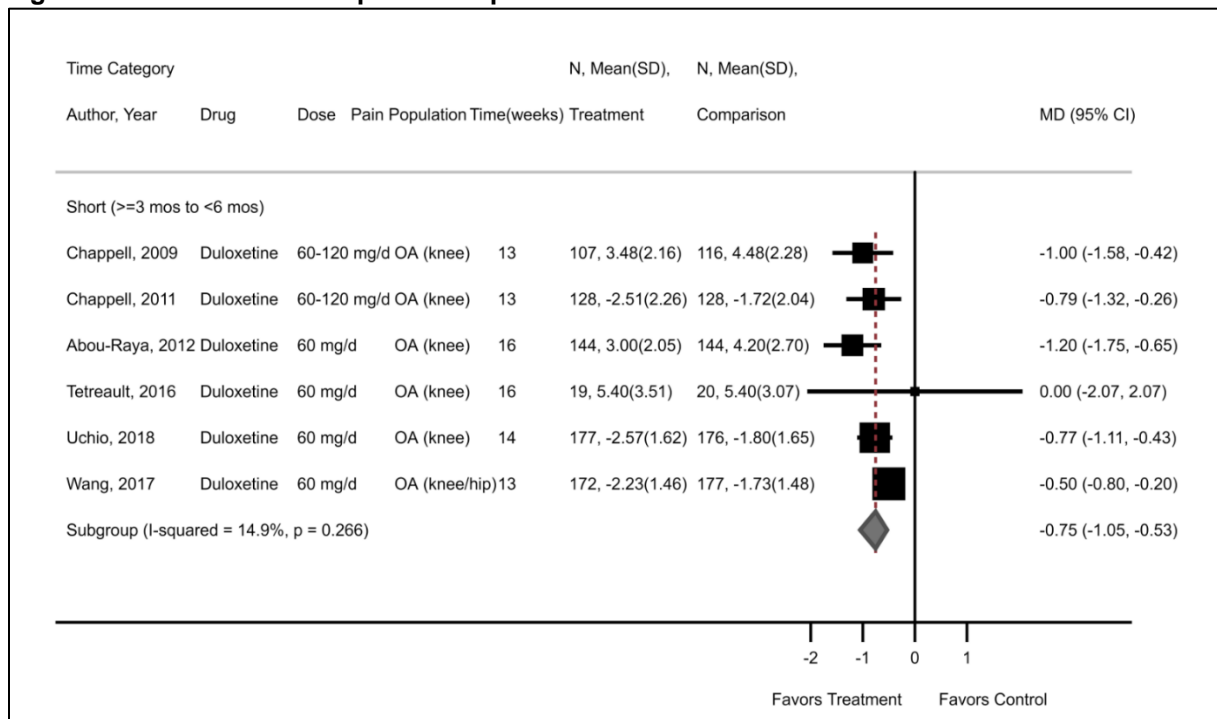


Figure I-36. Osteoarthritis—pain acetaminophen plot

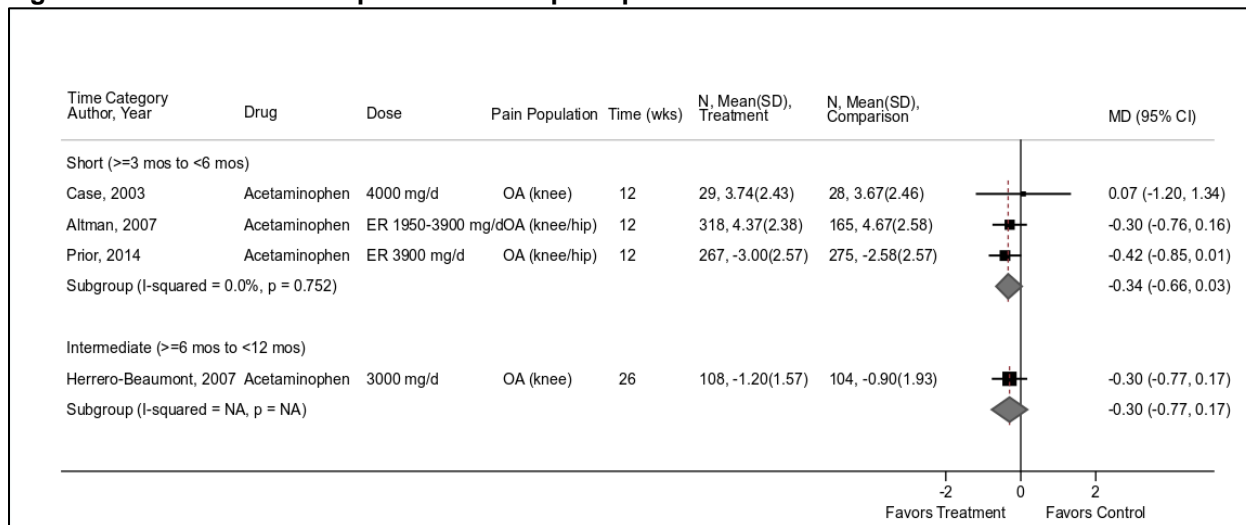


Figure I-37. Osteoarthritis—pain response NSAID plot

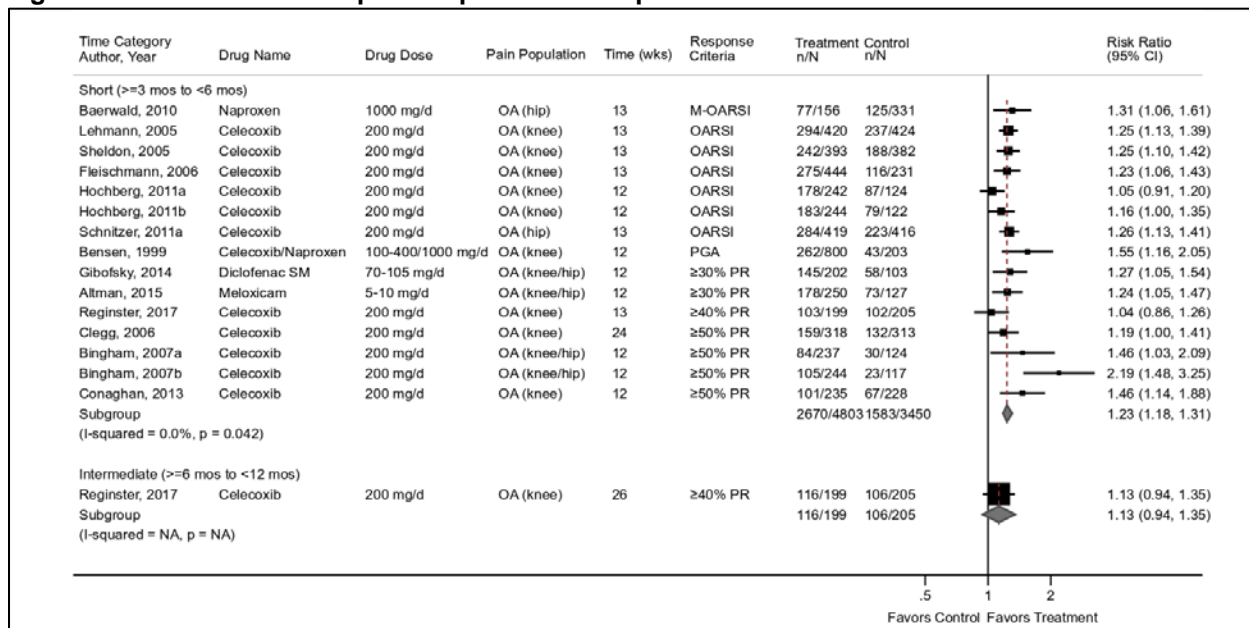


Figure I-38. Osteoarthritis—pain response NSAID topical diclofenac plot

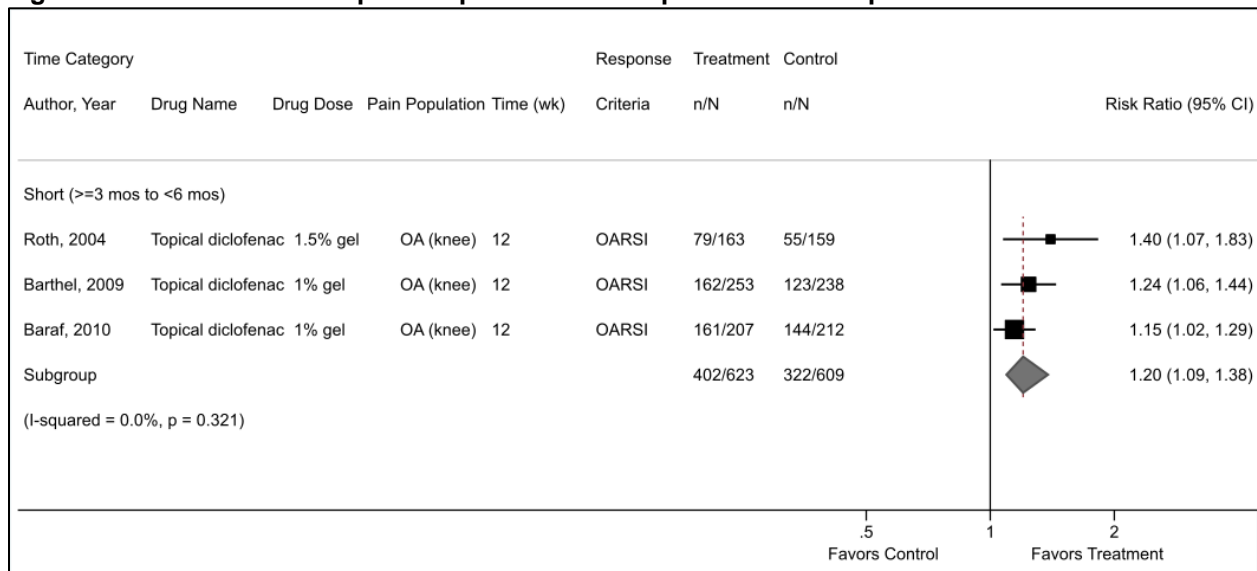


Figure I-39. Osteoarthritis—pain response SNRI plot

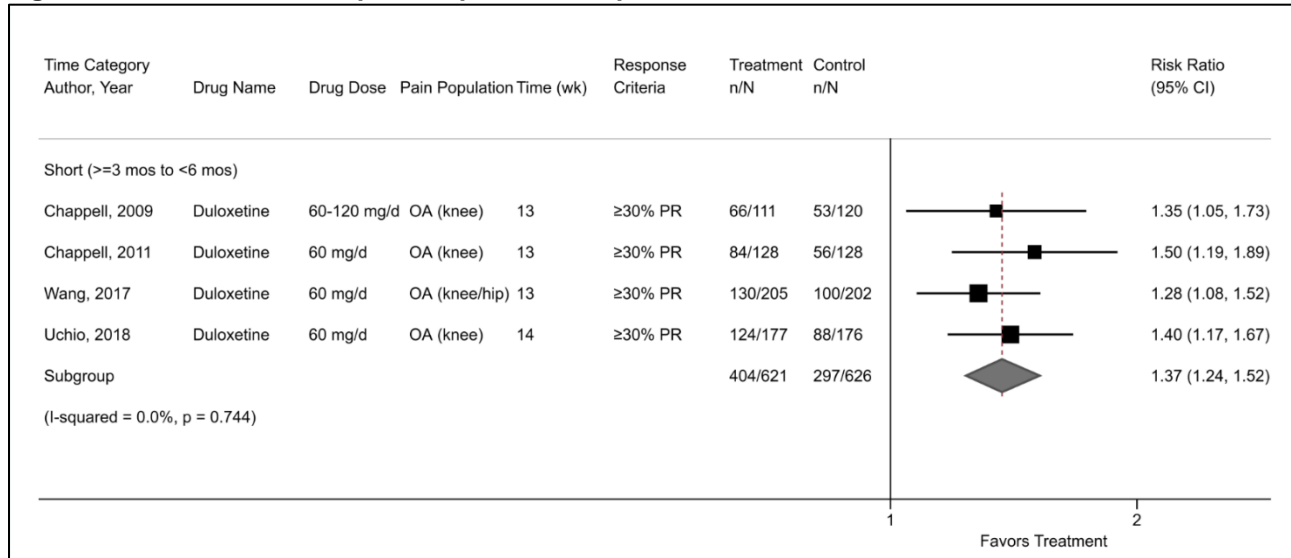


Figure I-40. Osteoarthritis—function NSAID plot

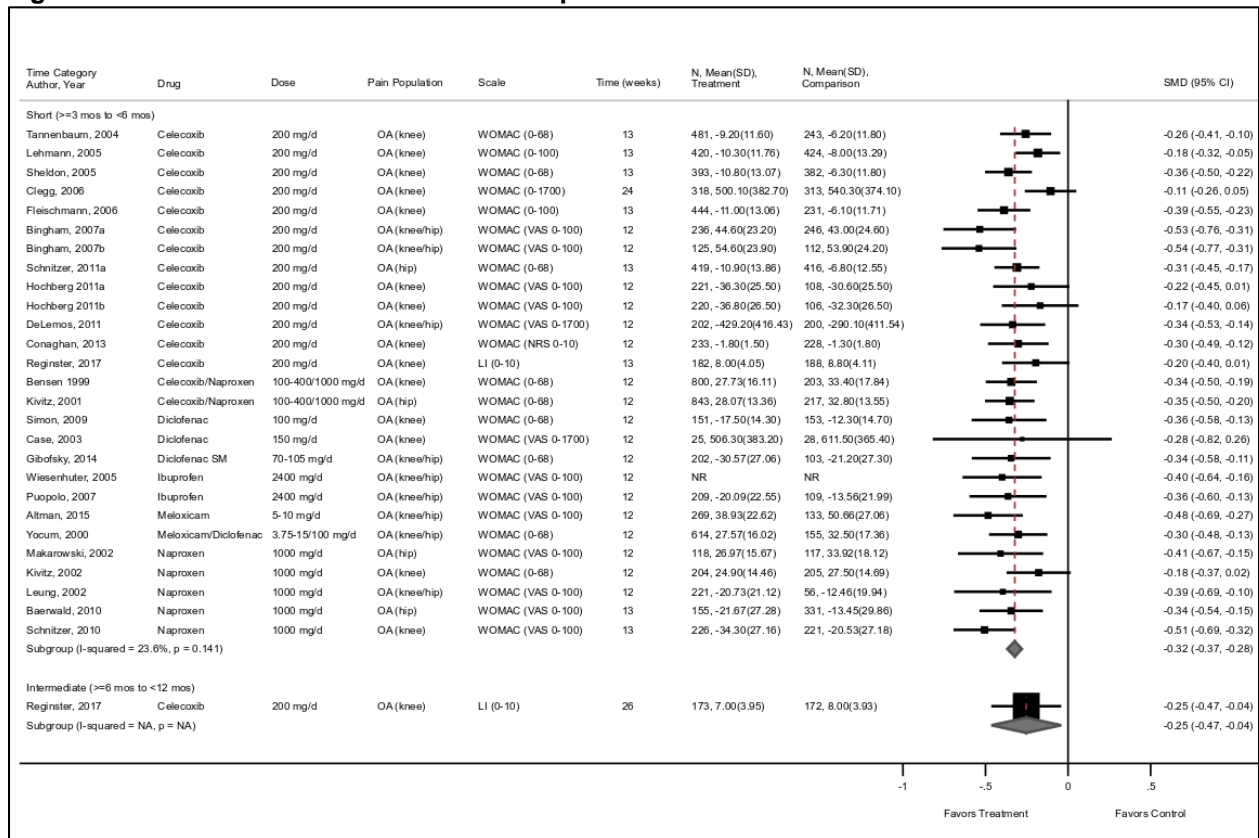


Figure I-41. Osteoarthritis—function topical diclofenac plot

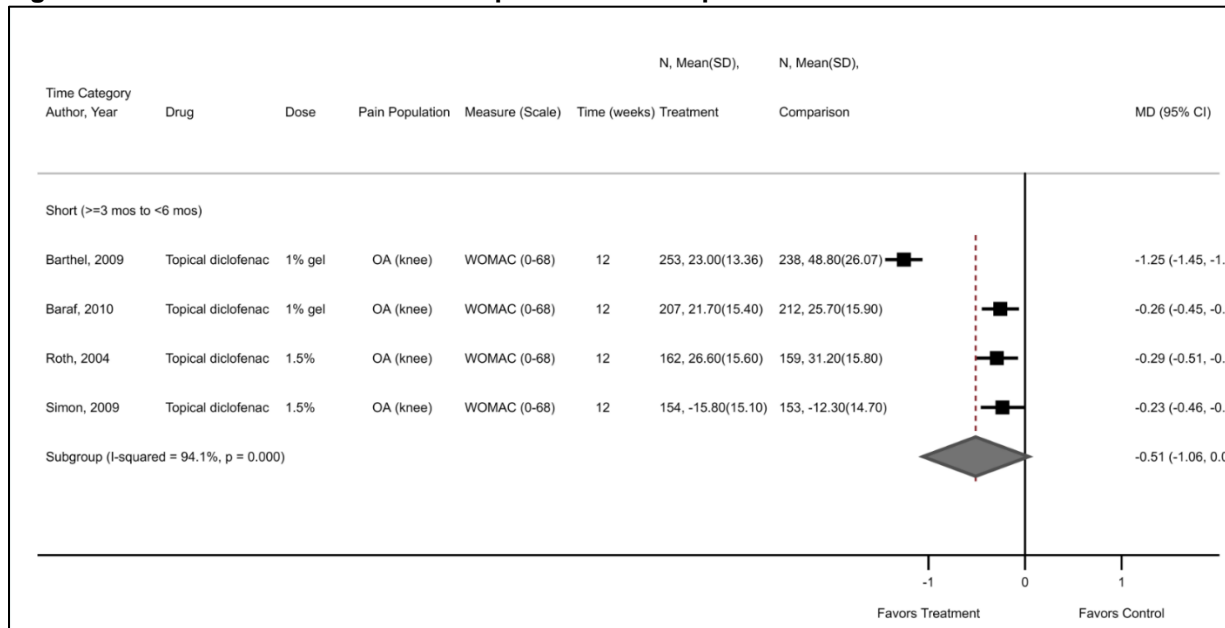


Figure I-42. Osteoarthritis—function SNRI plot

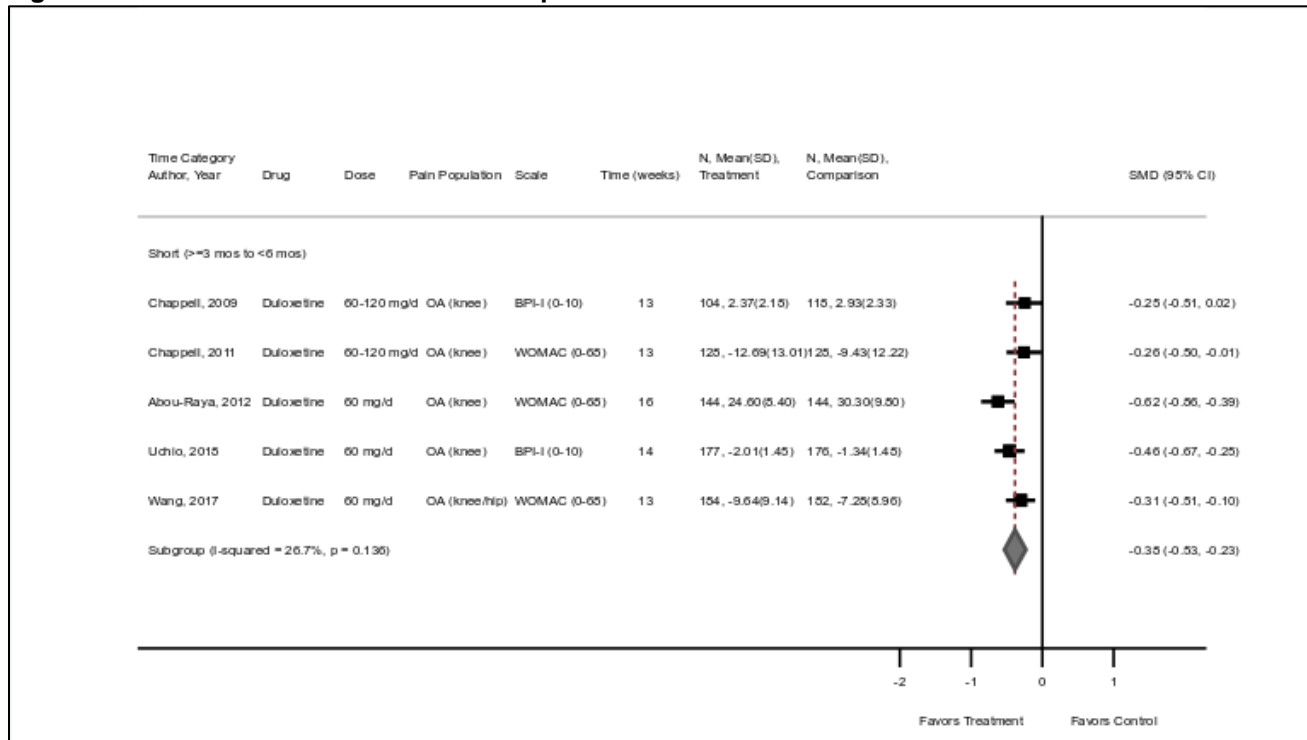


Figure I-43. Osteoarthritis—function acetaminophen plot

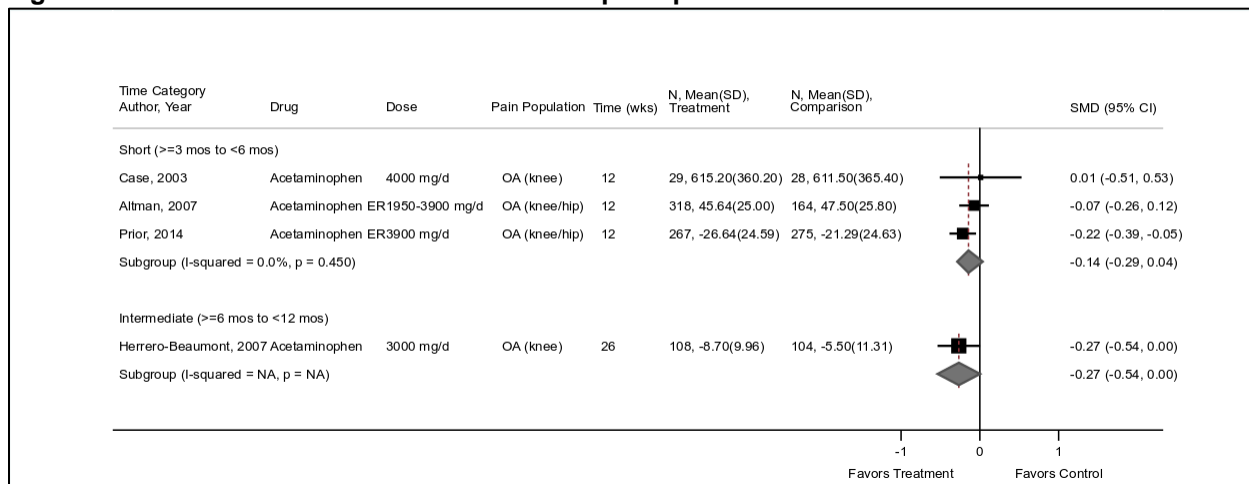


Figure I-44. Osteoarthritis—quality of life NSAID plot

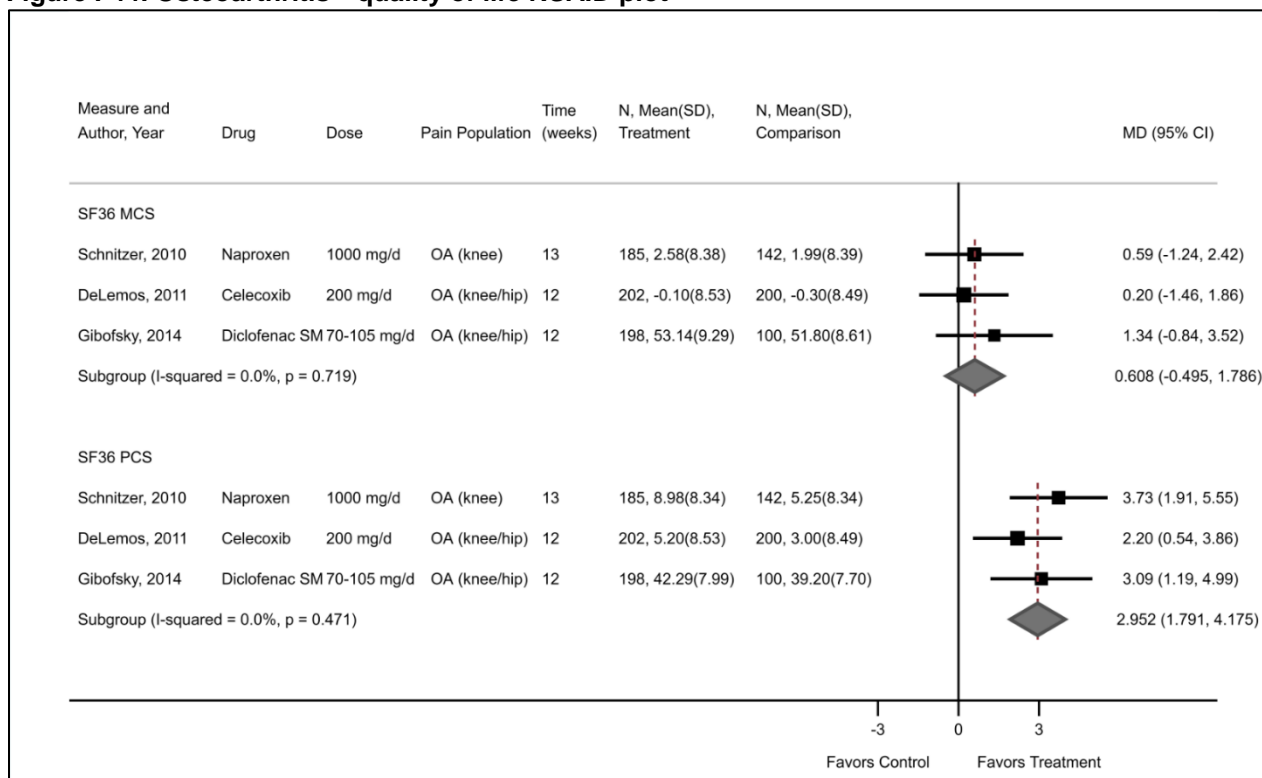


Figure I-45. Osteoarthritis—quality of life SNRI plot

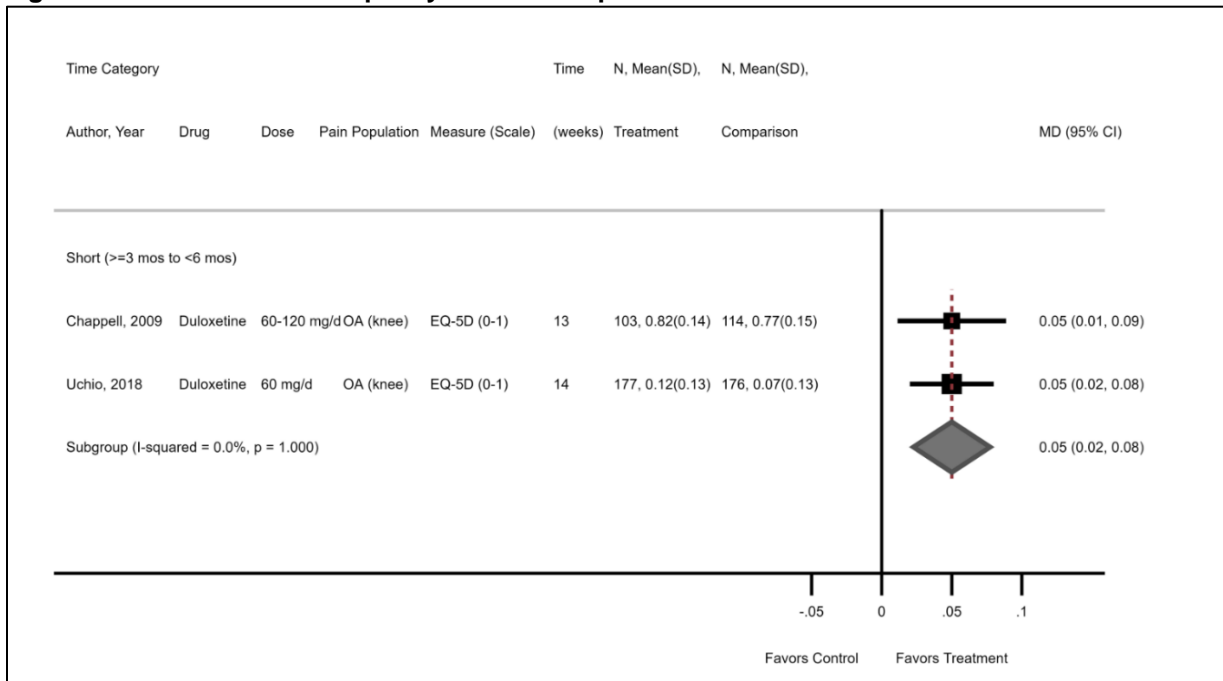
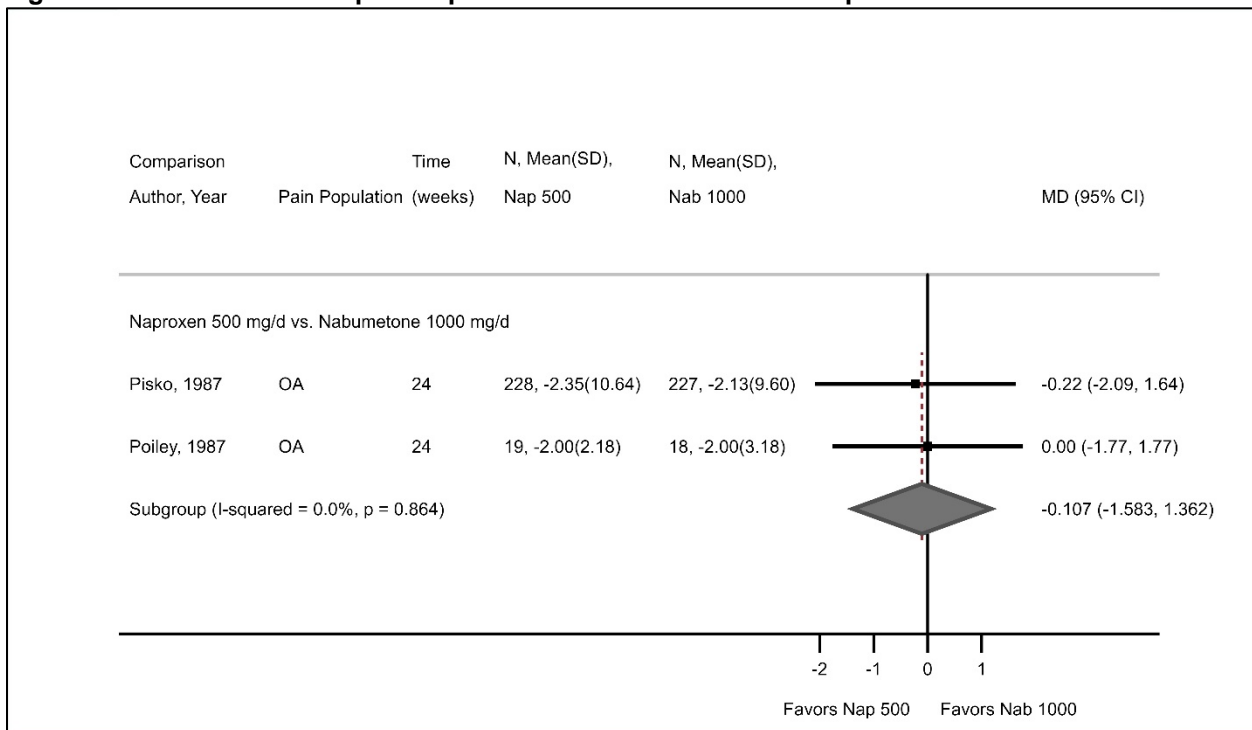


Figure I-46. Osteoarthritis—pain naproxen vs. nabumetone NSAID plot



Inflammatory Arthritis

Figure I-47. Inflammatory arthritis—pain NSAID plot

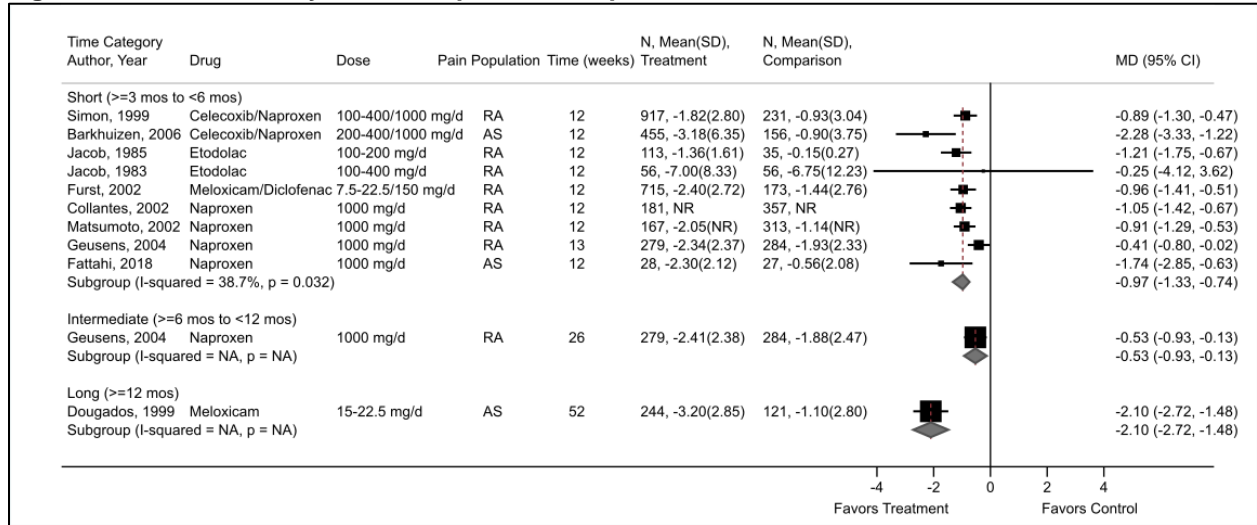


Figure I-48. Inflammatory arthritis—pain response NSAID plot

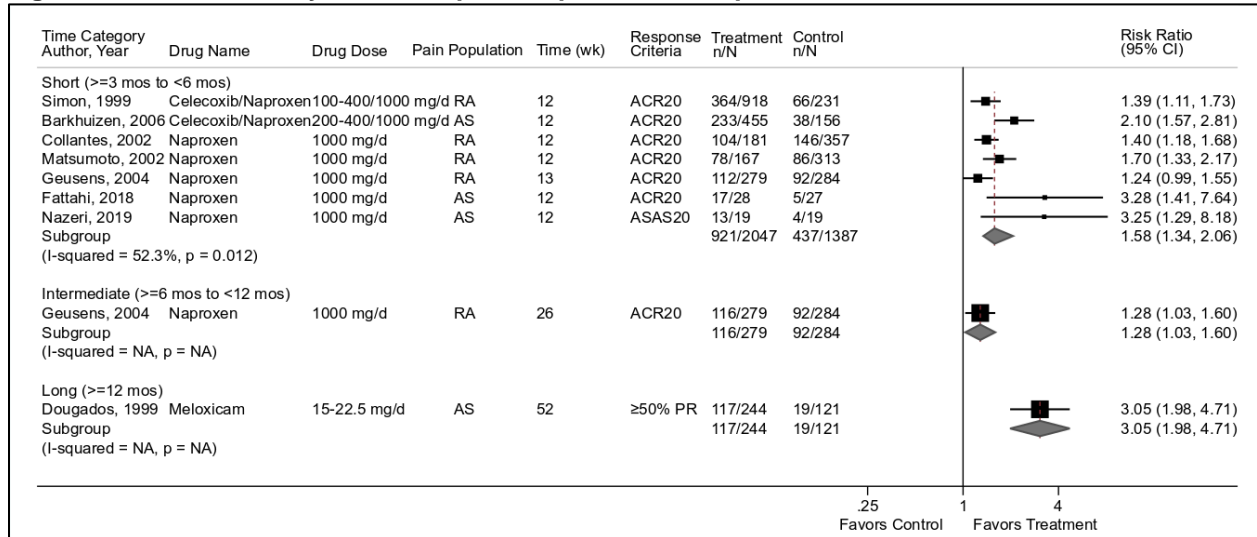


Figure I-49. Inflammatory arthritis—function NSAID plot

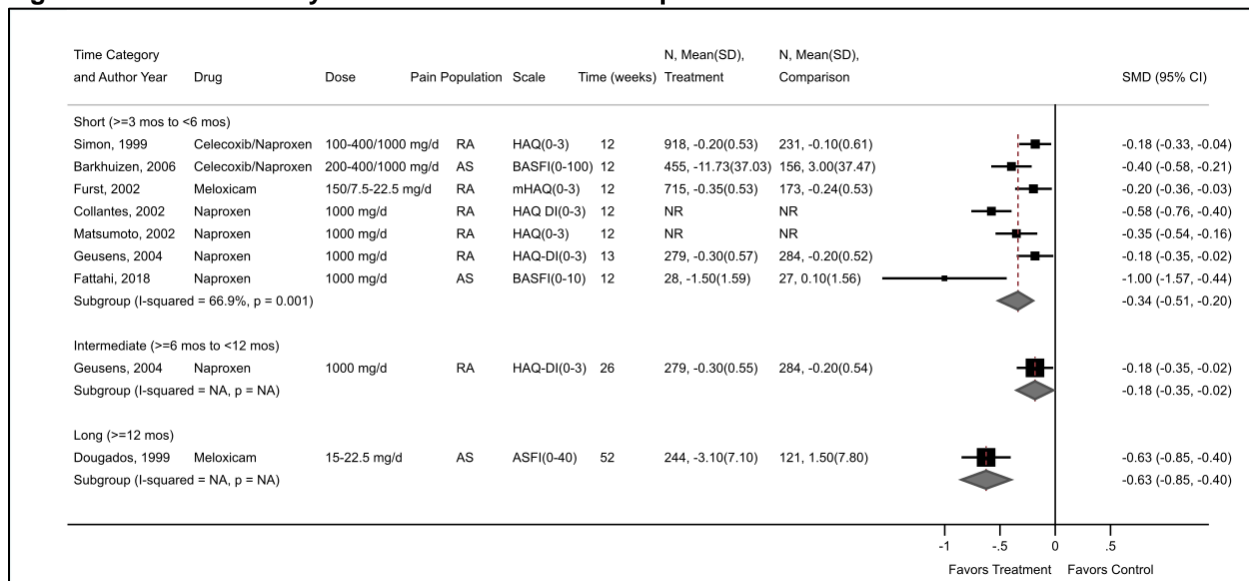


Figure I-50. Inflammatory arthritis—pain celecoxib 200 mg/d vs. naproxen plot

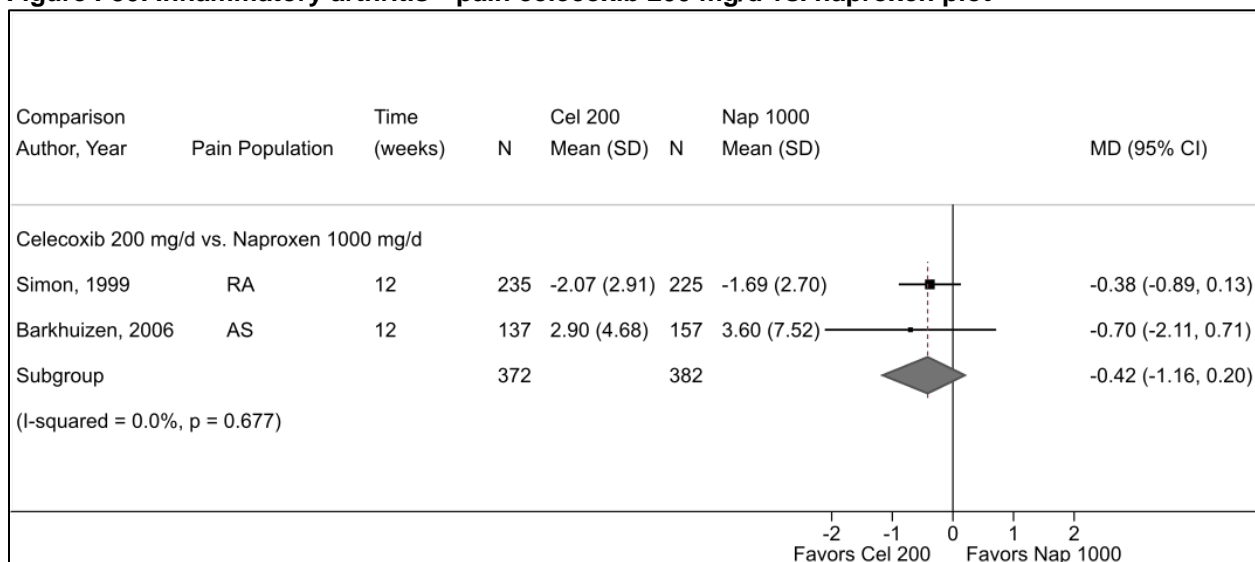


Figure I-51. Inflammatory arthritis—pain celecoxib 400 mg/d vs. naproxen plot

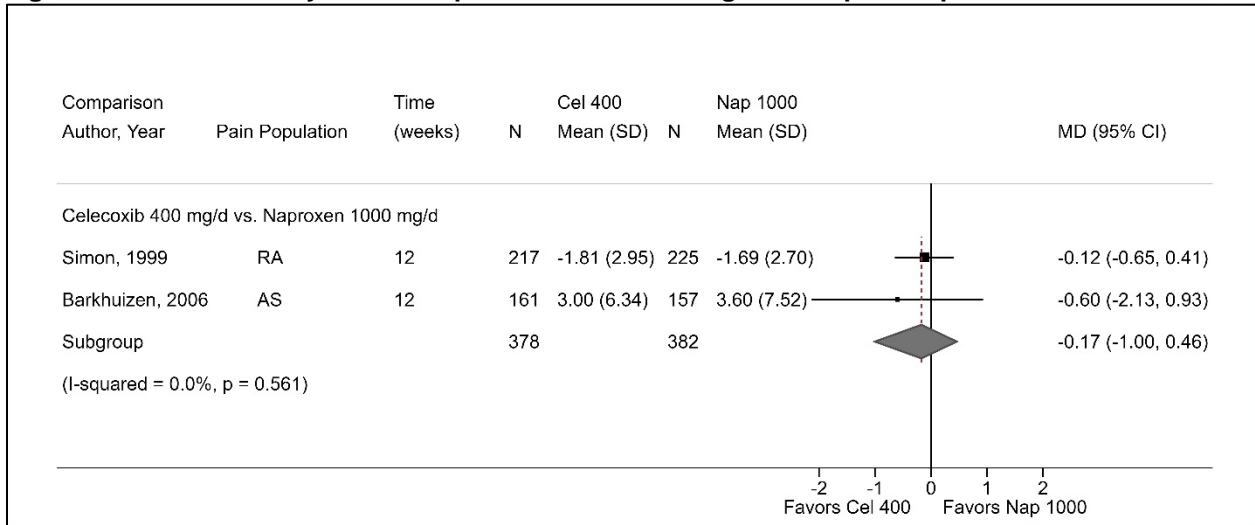


Figure I-52. Inflammatory arthritis—pain diclofenac vs. celecoxib 200 mg/d plot

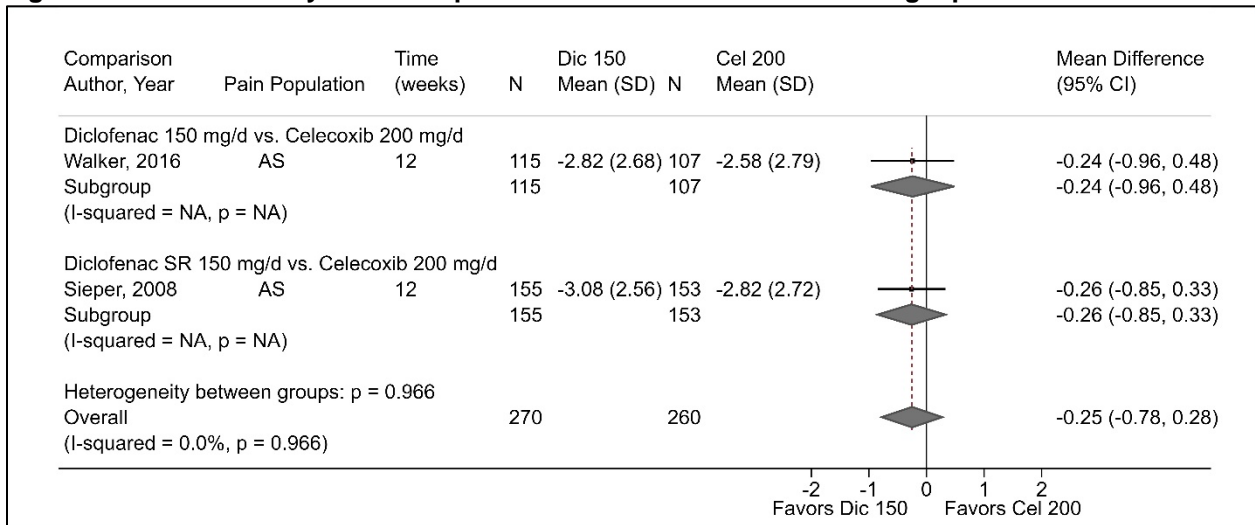


Figure I-53. Inflammatory arthritis—pain diclofenac vs. celecoxib 400 mg/d plot

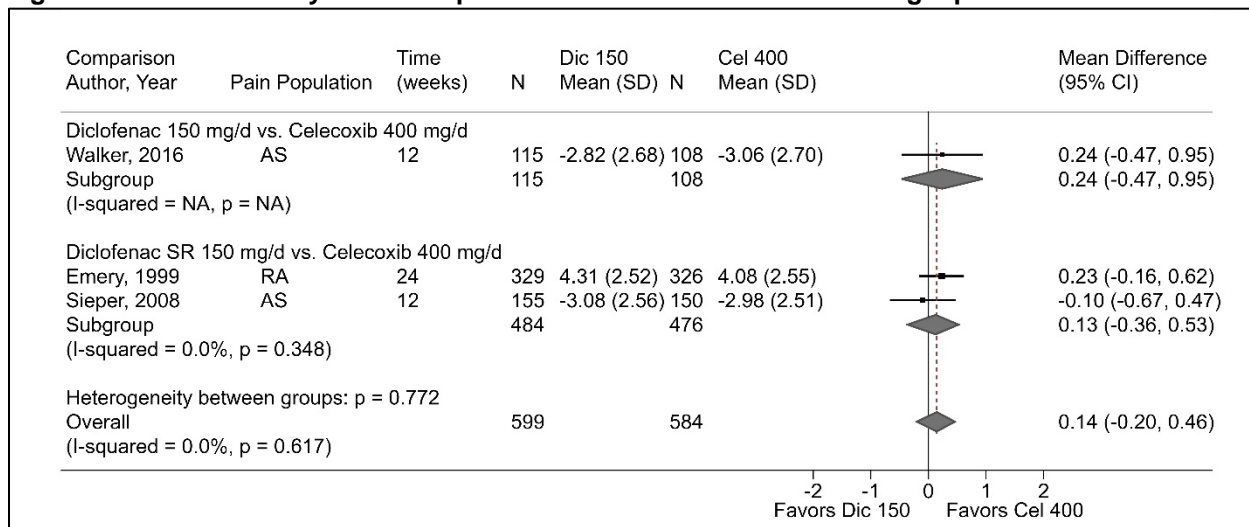


Figure I-54. Inflammatory arthritis—pain naproxen vs. nabumetone plot

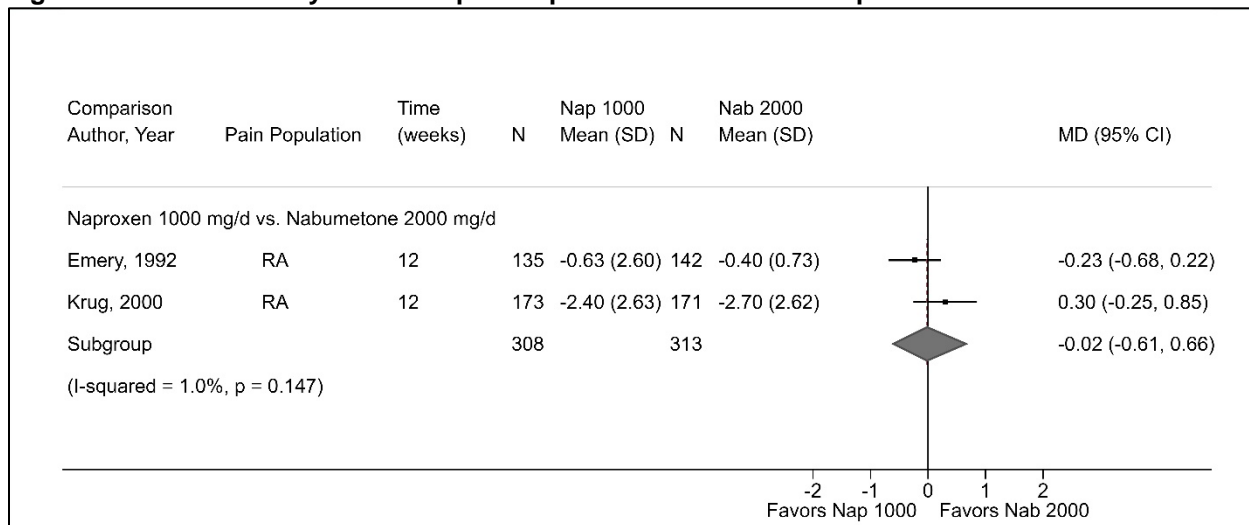


Figure I-55. Inflammatory arthritis—pain response celecoxib 200 mg/d vs. naproxen plot

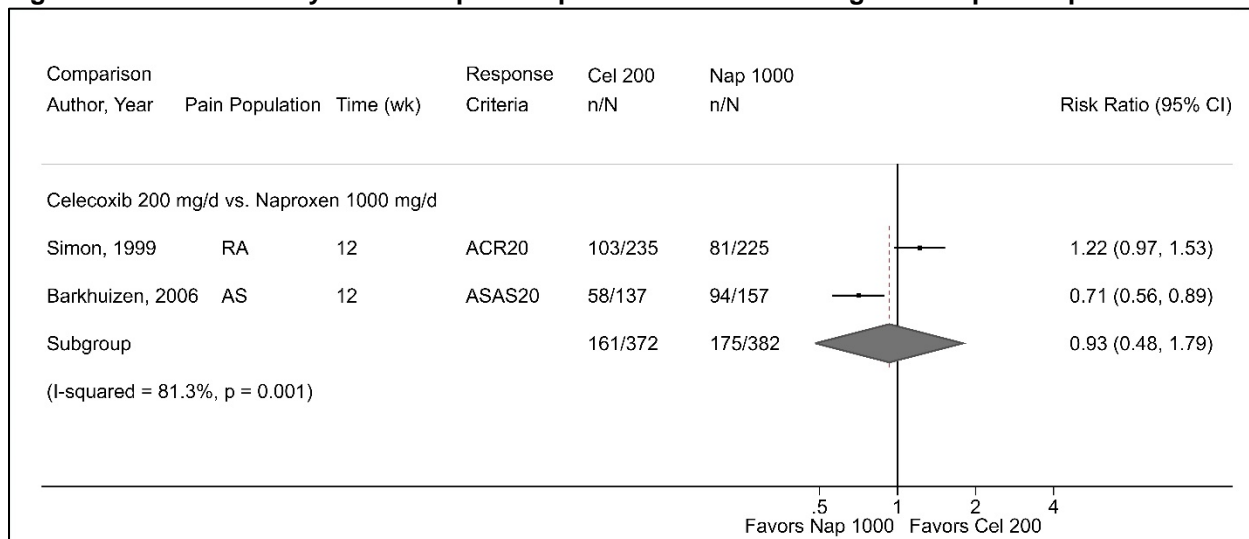


Figure I-56. Inflammatory arthritis—pain response celecoxib 400 mg/d vs. naproxen plot

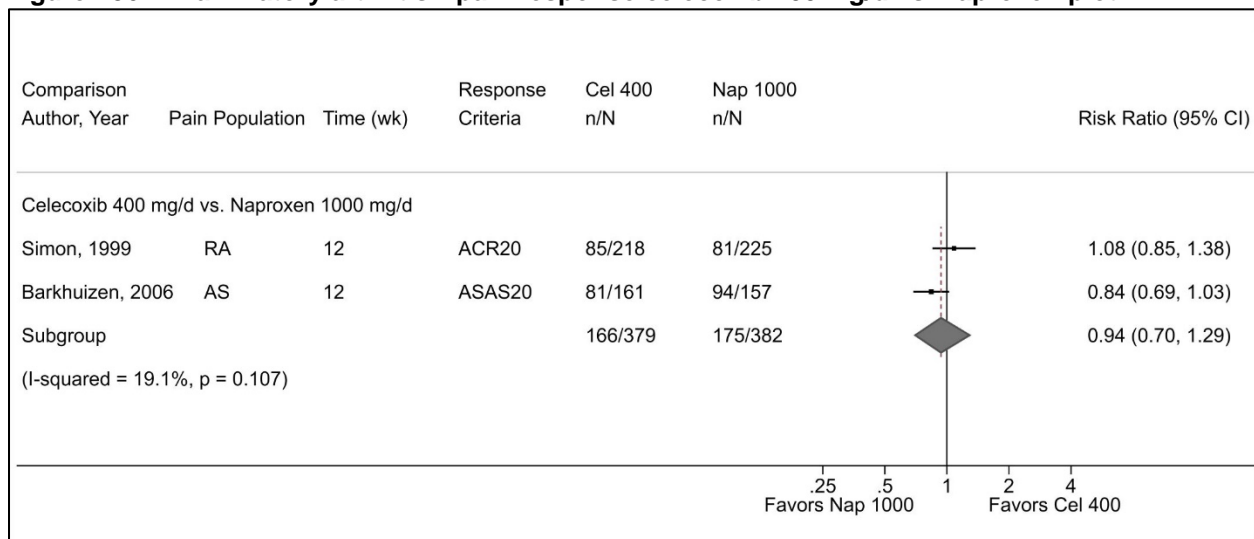


Figure I-57. Inflammatory arthritis—pain response diclofenac vs celecoxib 200 mg/d plot

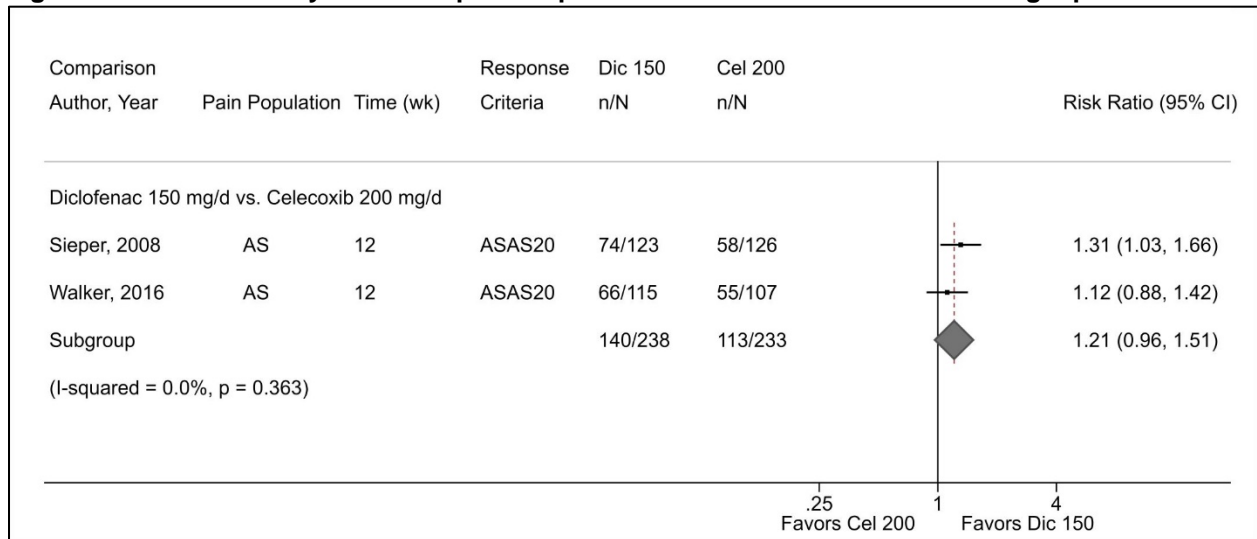


Figure I-58. Inflammatory arthritis—function celecoxib 200 mg/d vs. naproxen plot

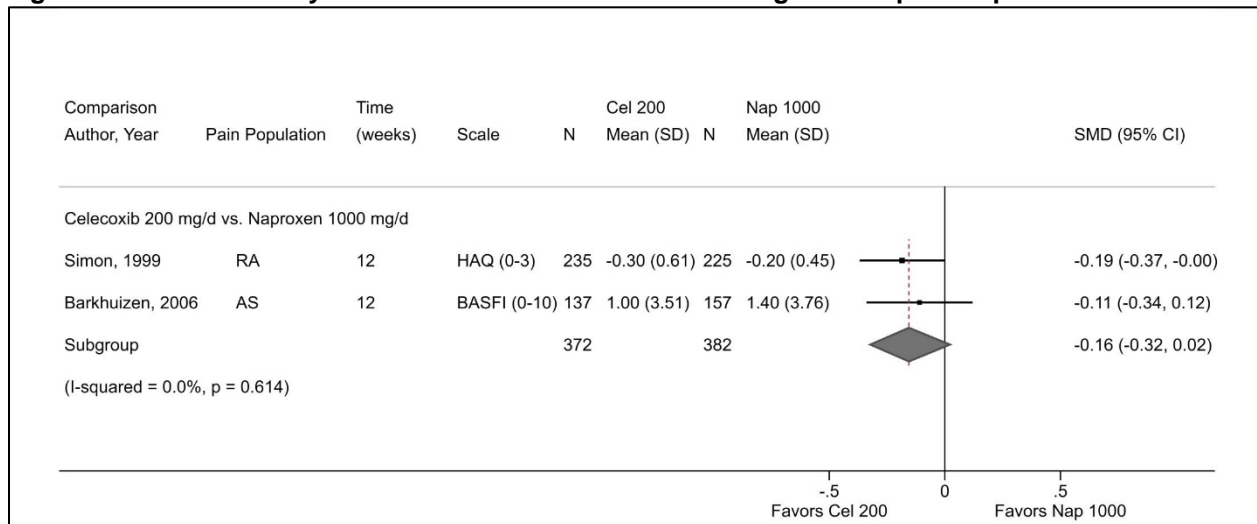


Figure I-59. Inflammatory arthritis—function celecoxib 400 mg/d vs. naproxen plot

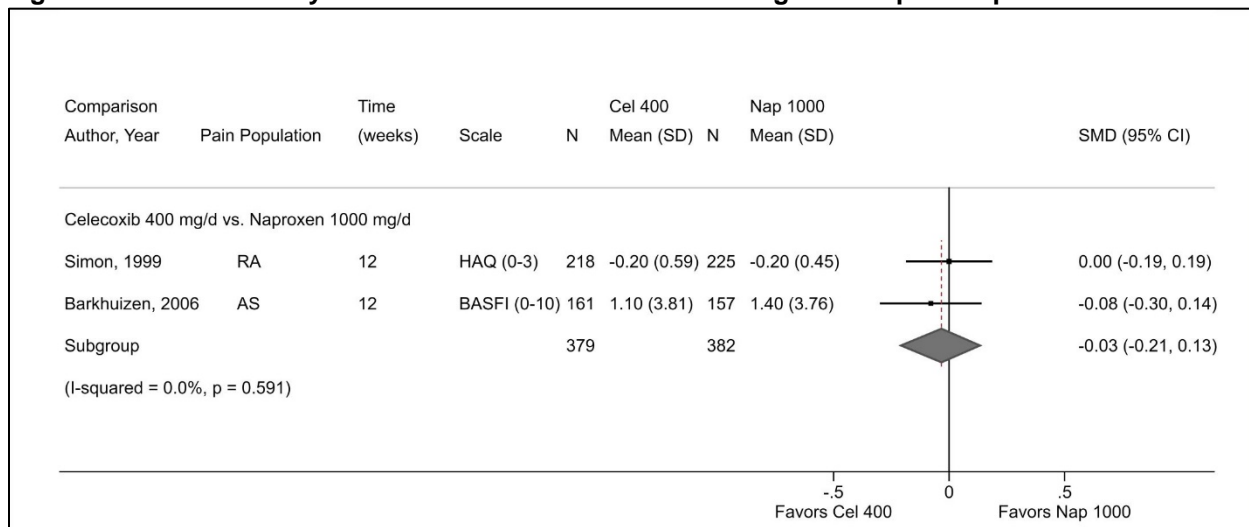


Figure I-60. Inflammatory arthritis—function diclofenac vs. celecoxib 200 mg/d plot

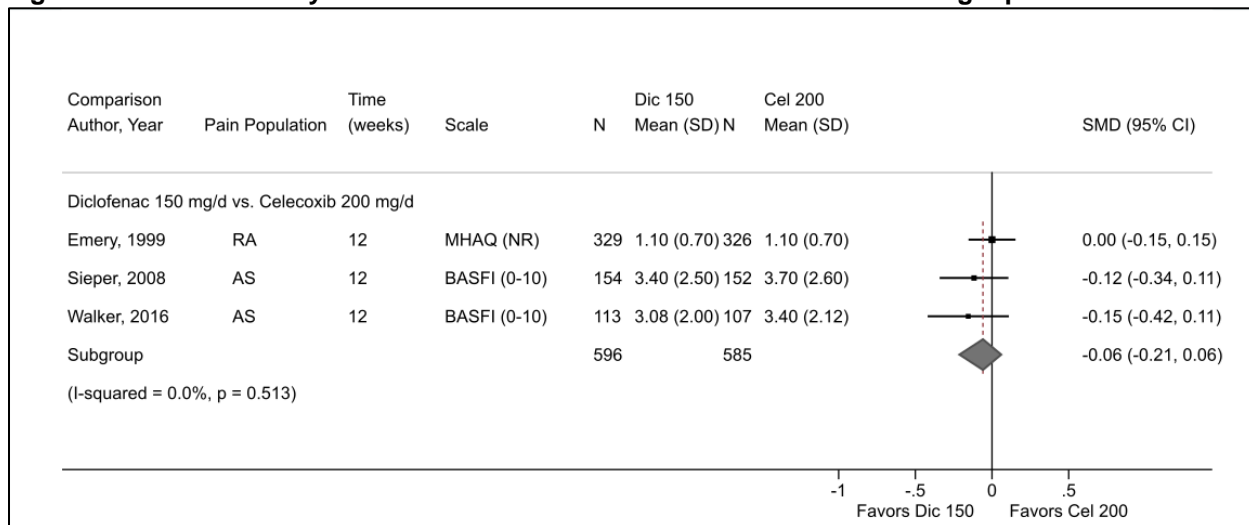


Figure I-61. Inflammatory arthritis—function diclofenac vs. celecoxib 400 mg/d plot

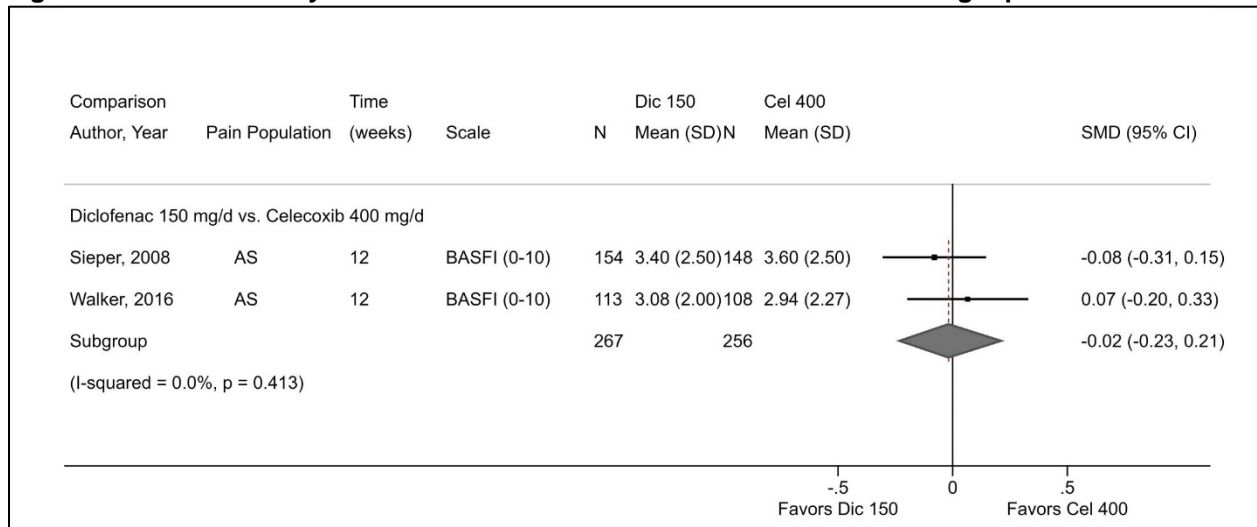
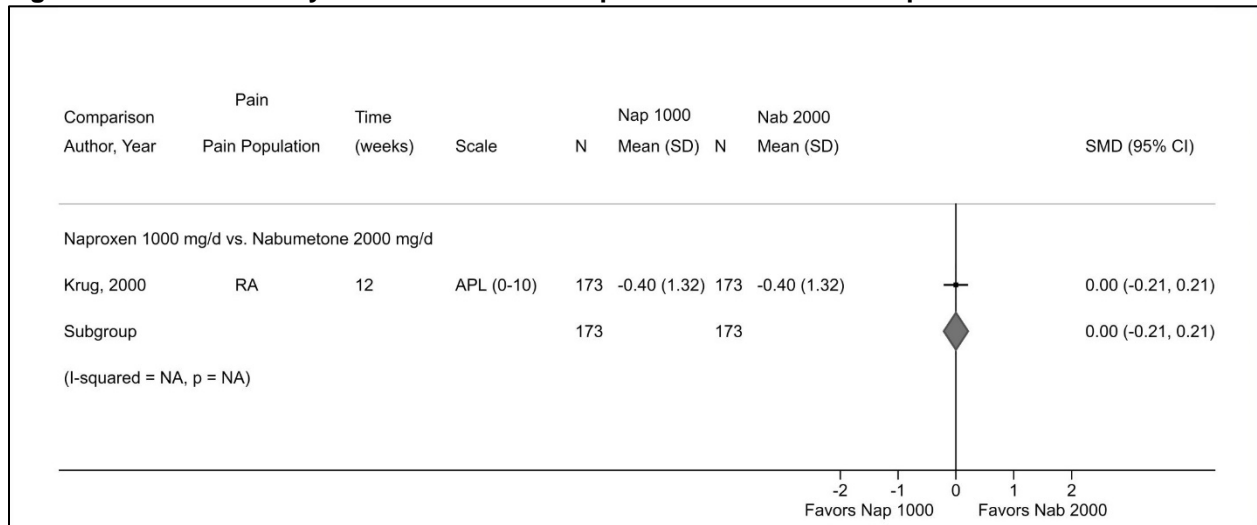


Figure I-62. Inflammatory arthritis—function naproxen vs. nabumetone plot



Low Back Pain

Figure I-63. Low back pain—pain SNRI plot

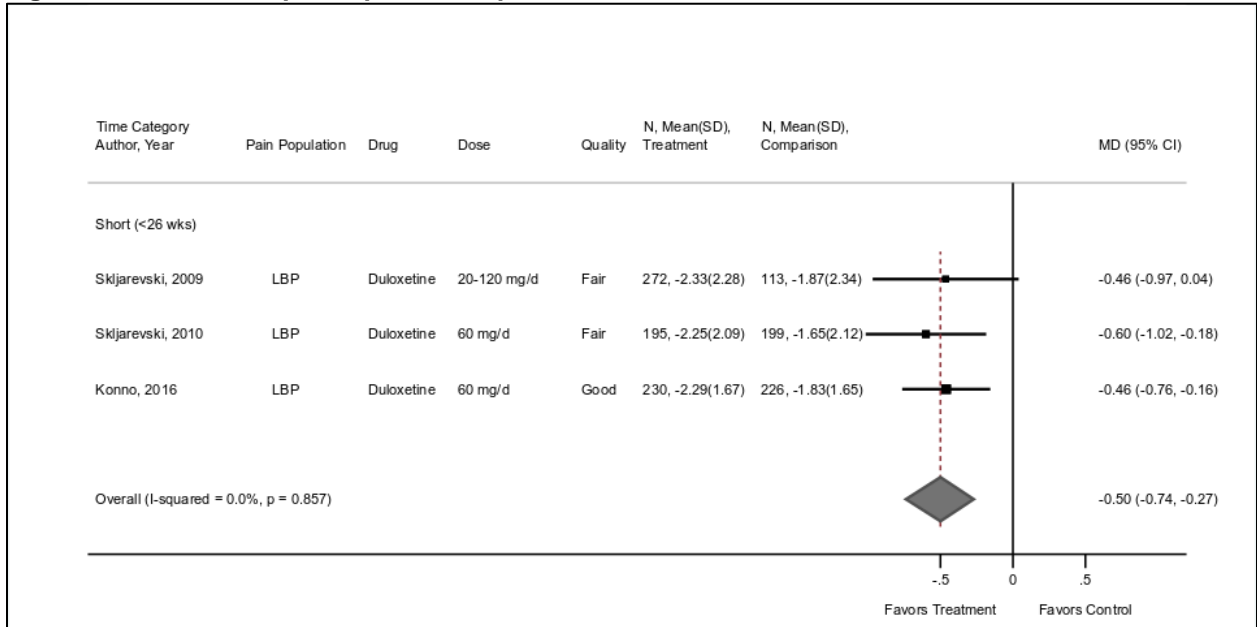


Figure I-64. Low back pain—pain response SNRI plot

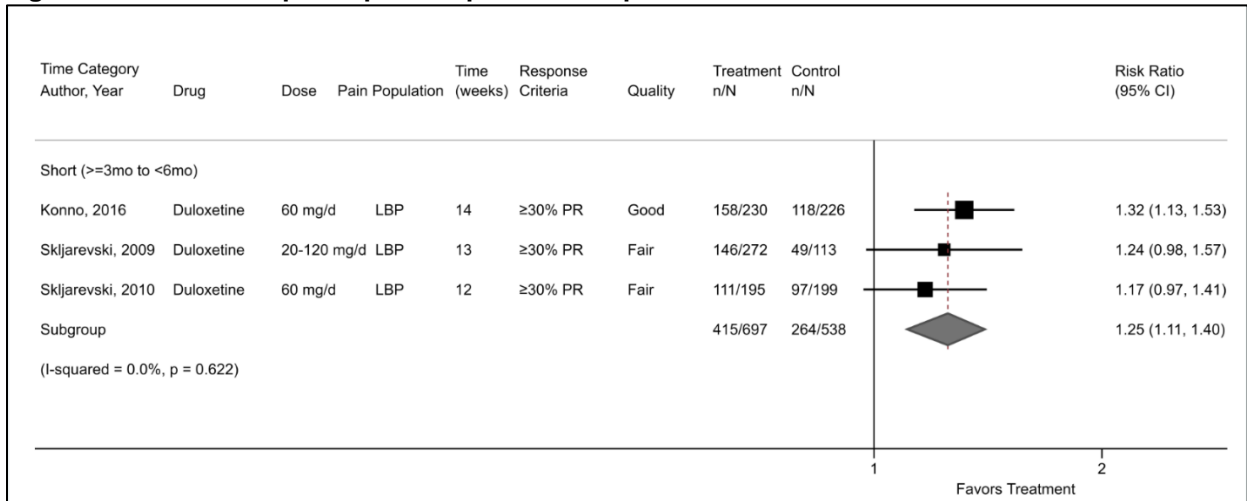


Figure I-65. Low back pain—function SNRI plot

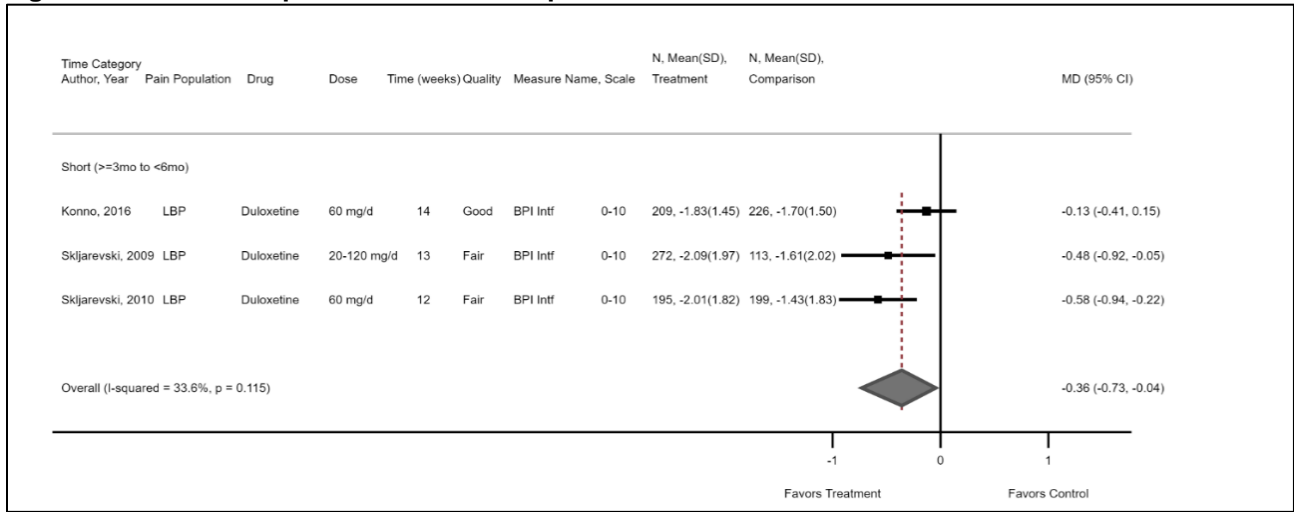
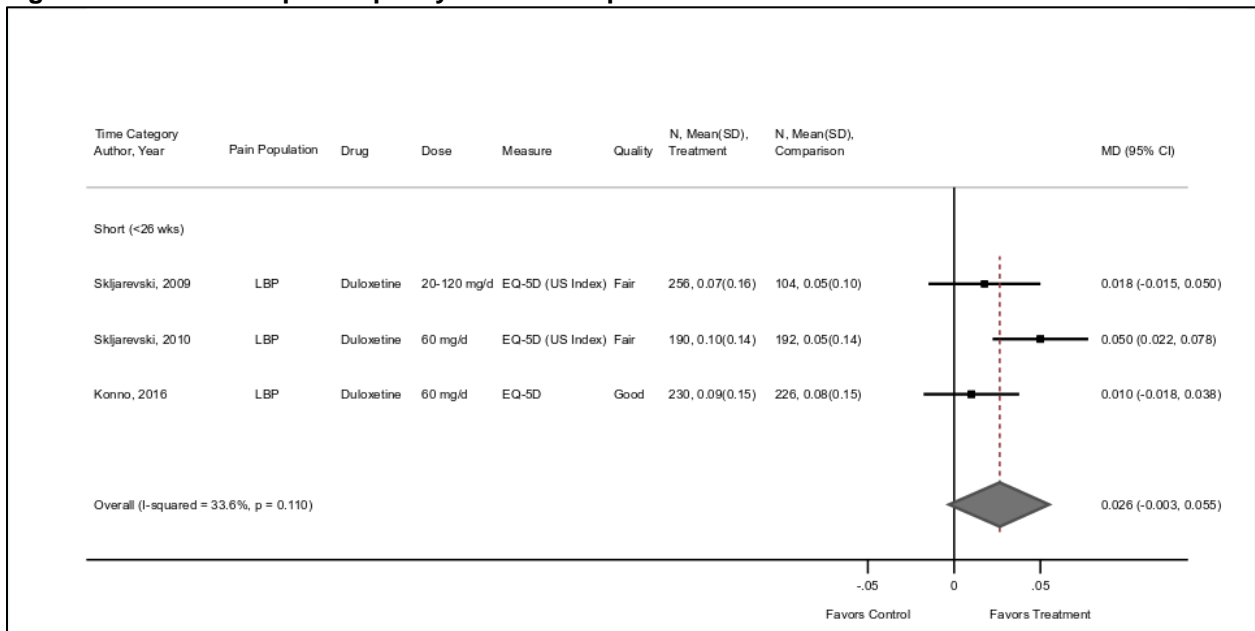


Figure I-66. Low back pain—quality of life SNRI plot



Adverse Events

Figure I-67. Antidepressants—SNRI withdrawals due to adverse events plot

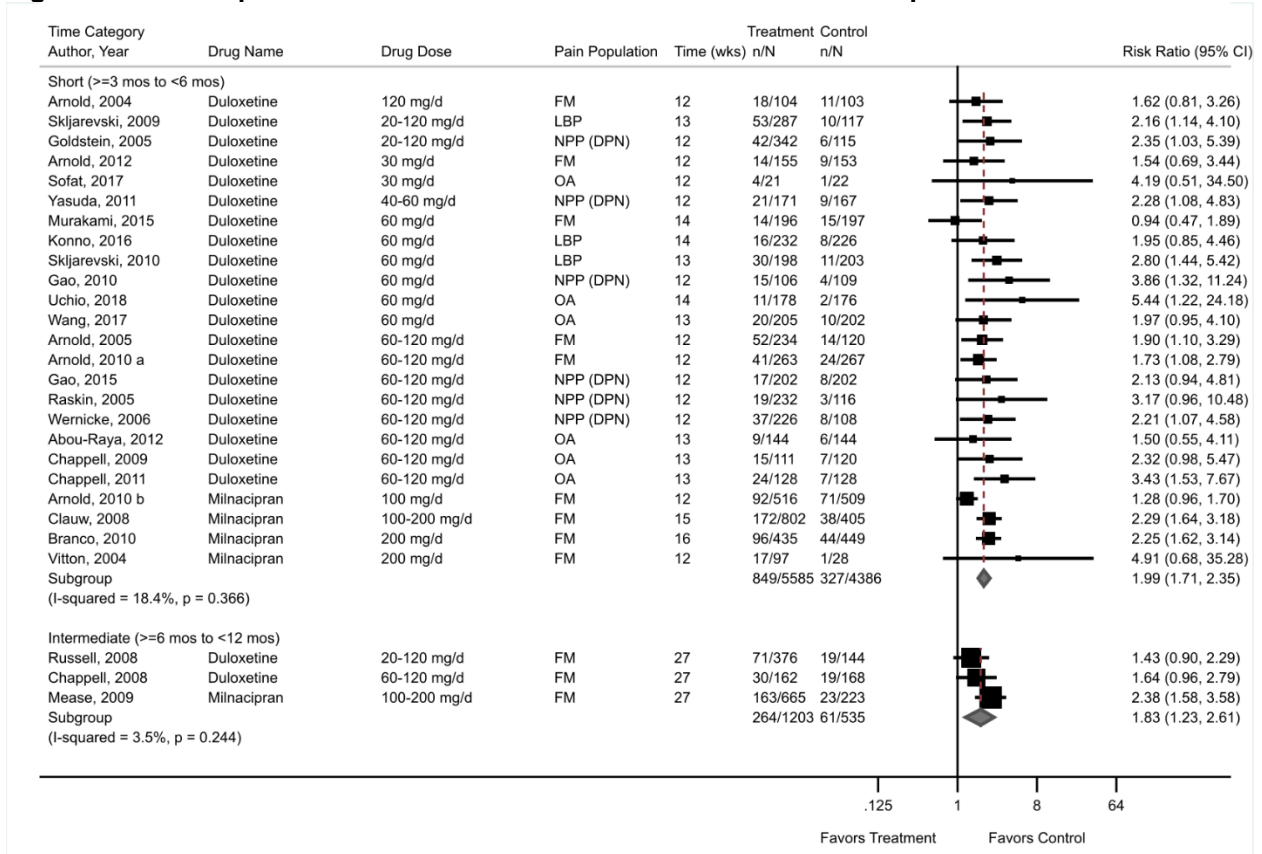


Figure I-68. Antidepressants—SNRI serious adverse events plot

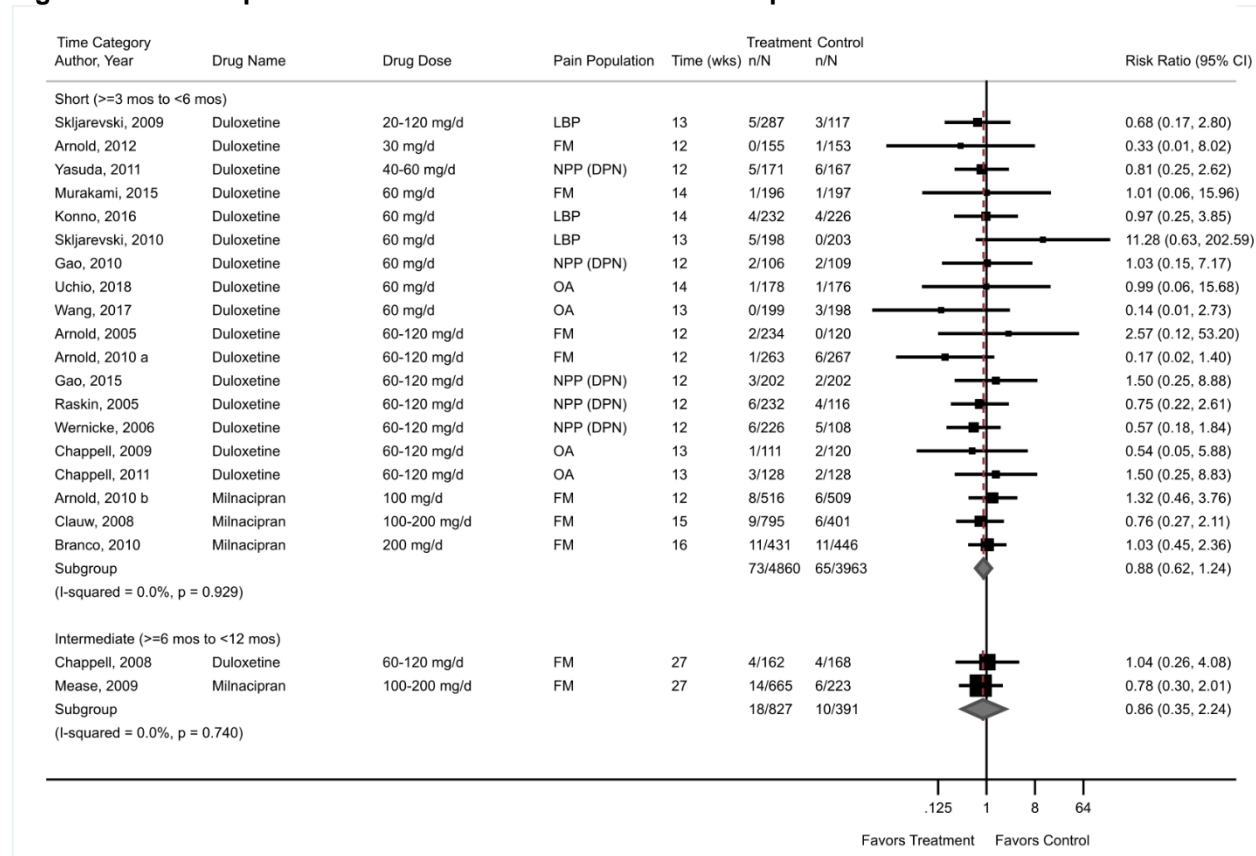


Figure I-69. Antidepressants—SNRI adverse cognitive effects plot

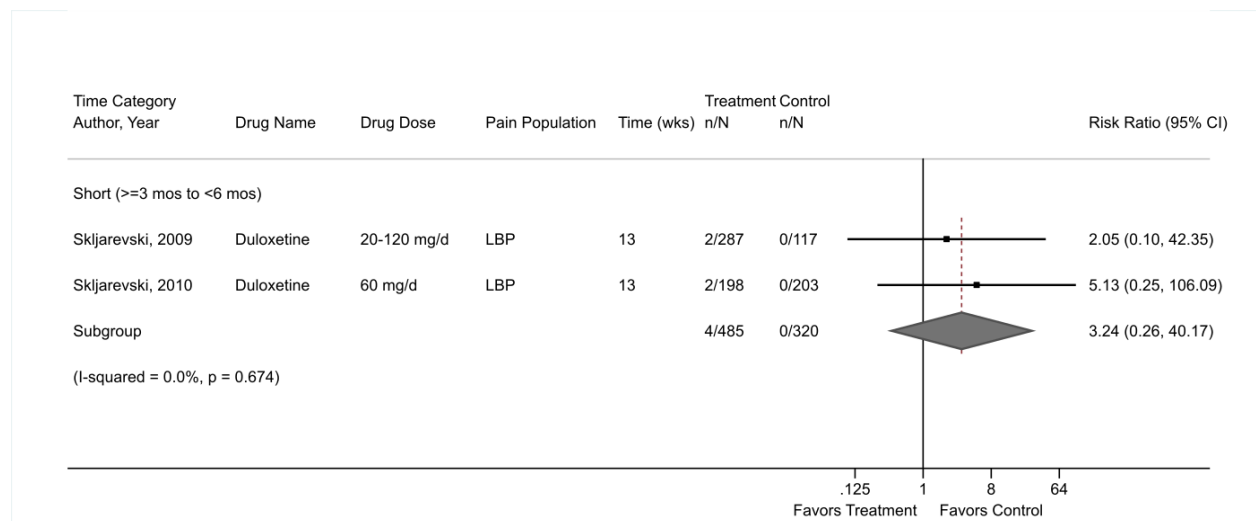


Figure I-70. Antidepressants—SNRI nausea plot

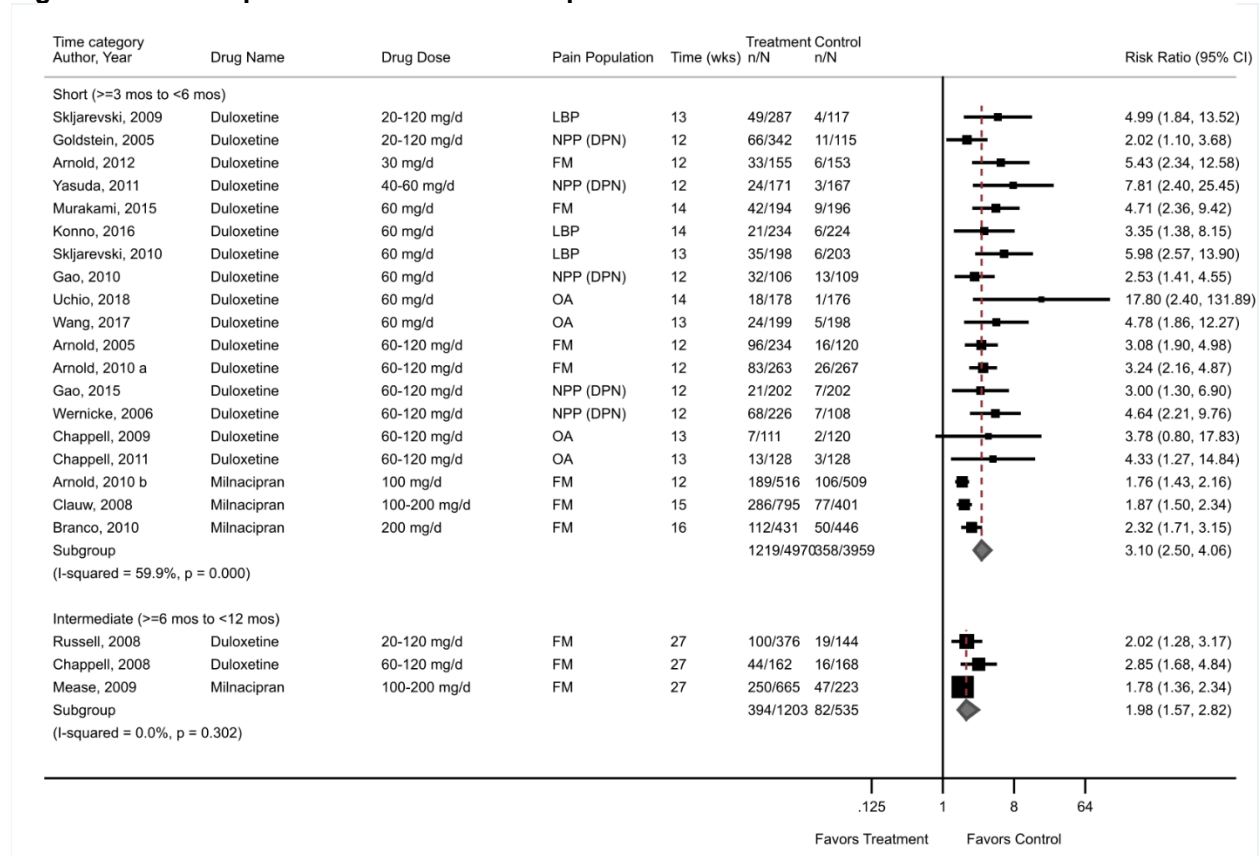


Figure I-71. Antidepressants—SNRI sedation plot

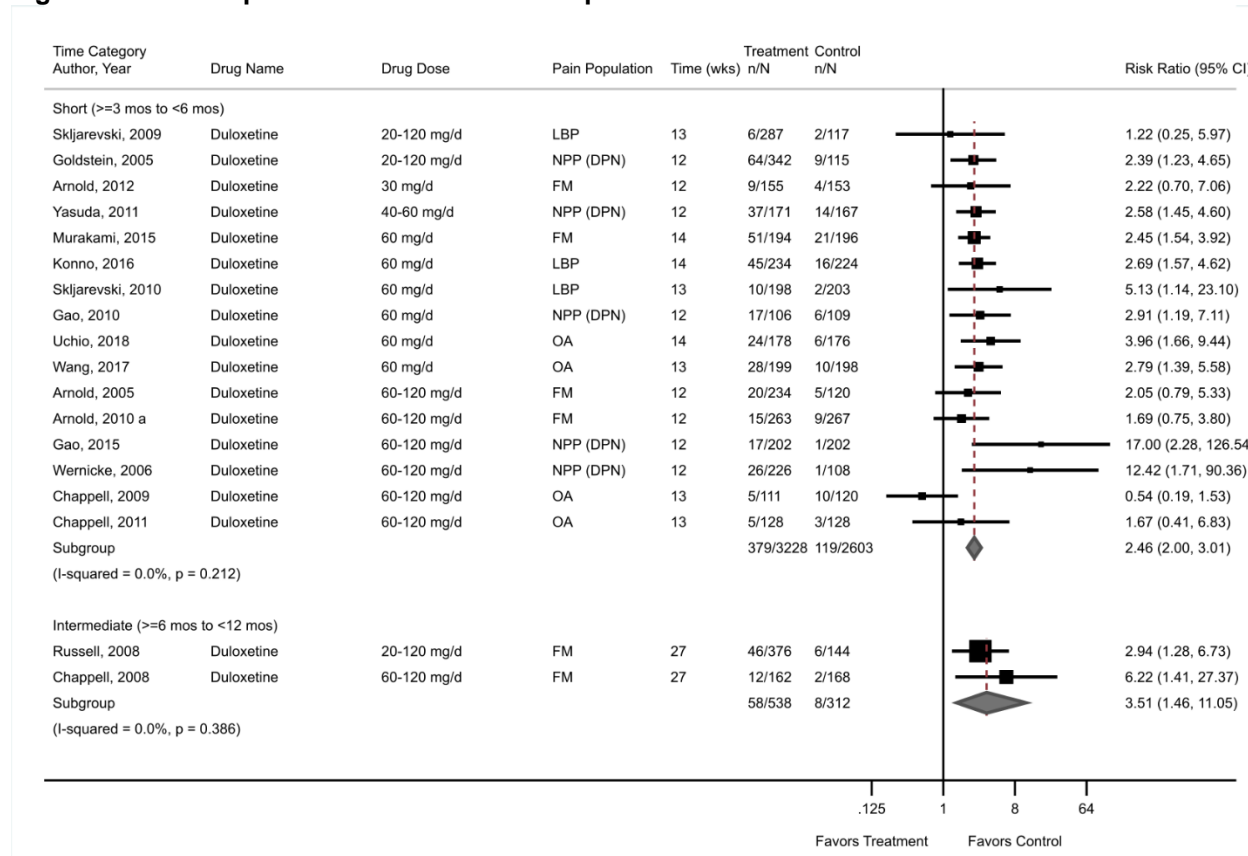


Figure I-72. Antidepressants—TCA withdrawals due to adverse events plot

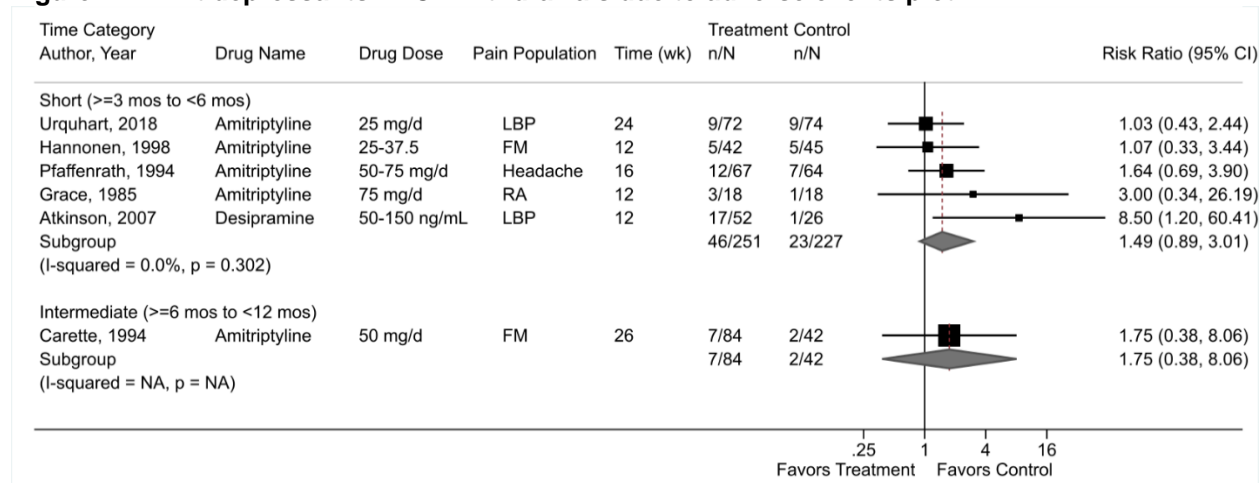


Figure I-73. Anticonvulsants—pregabalin and gabapentin withdrawals due to adverse events plot

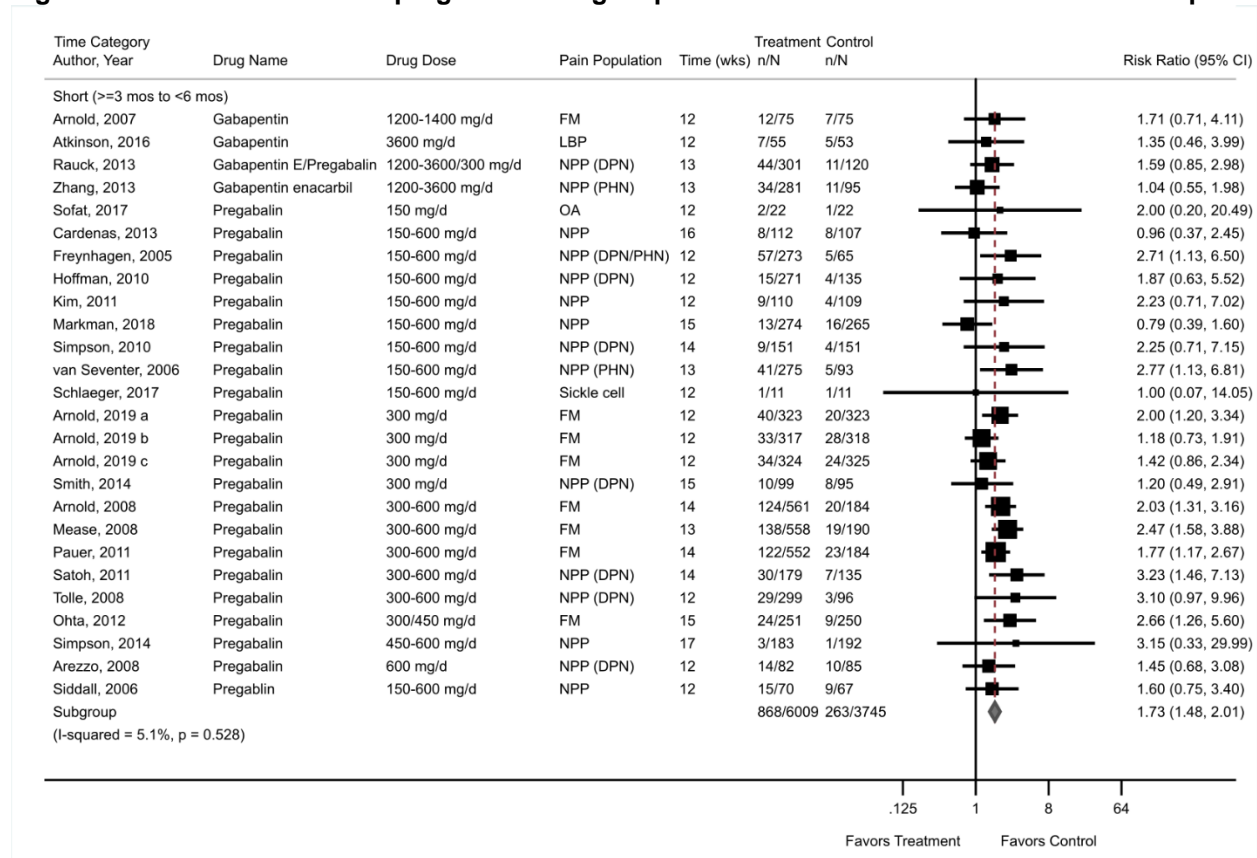


Figure I-74. Anticonvulsants—pregabalin and gabapentin serious adverse events plot

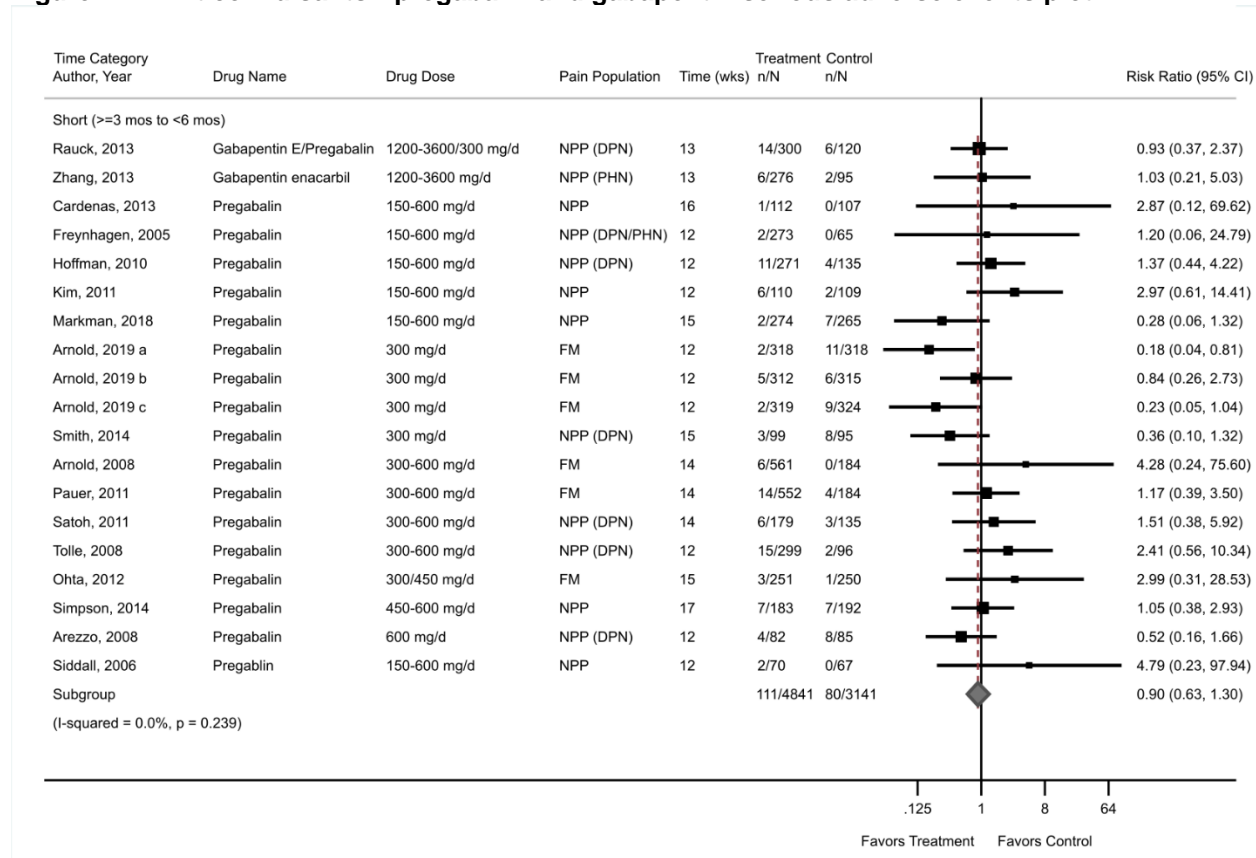


Figure I-75. Anticonvulsants—pregabalin and gabapentin blurred vision plot

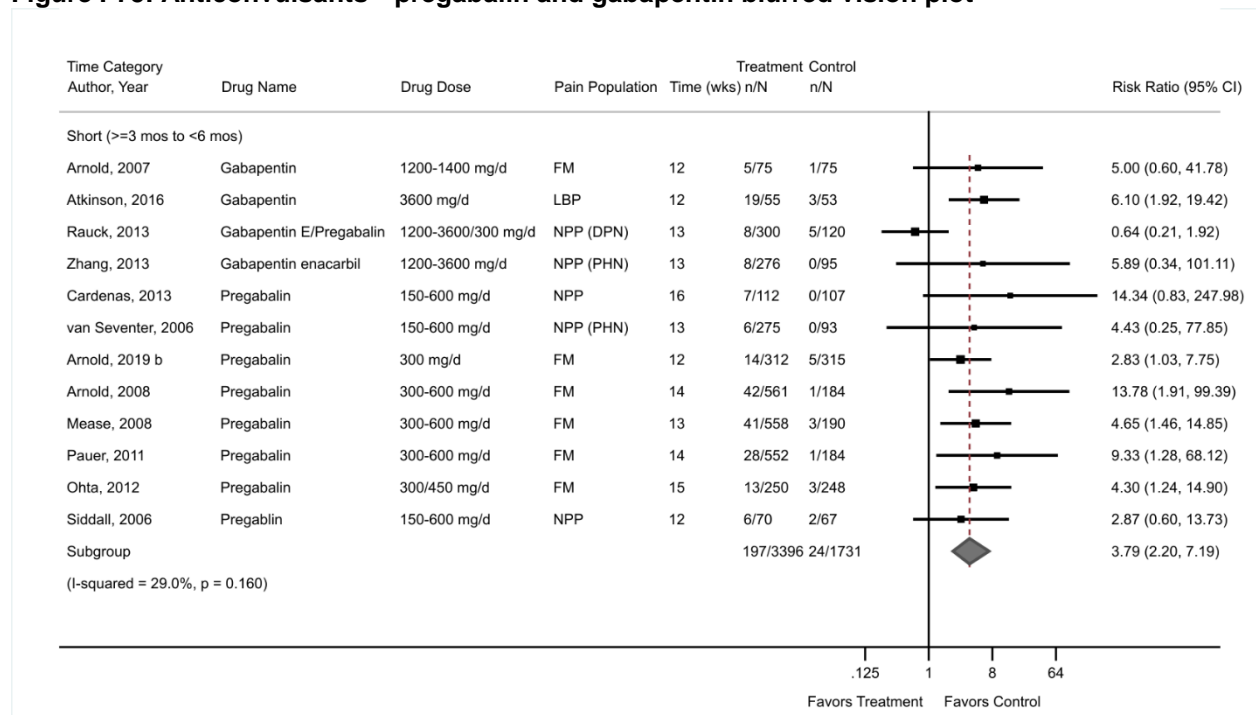


Figure I-76. Anticonvulsants—pregabalin and gabapentin adverse cognitive effects plot

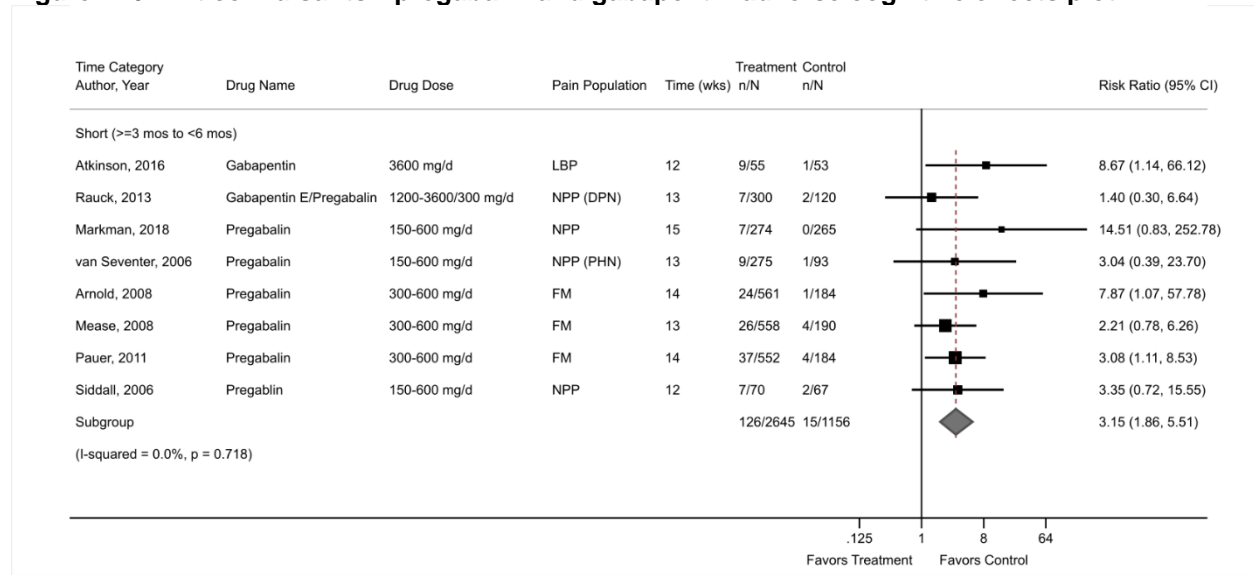


Figure I-77. Anticonvulsants—pregabalin and gabapentin dizziness plot

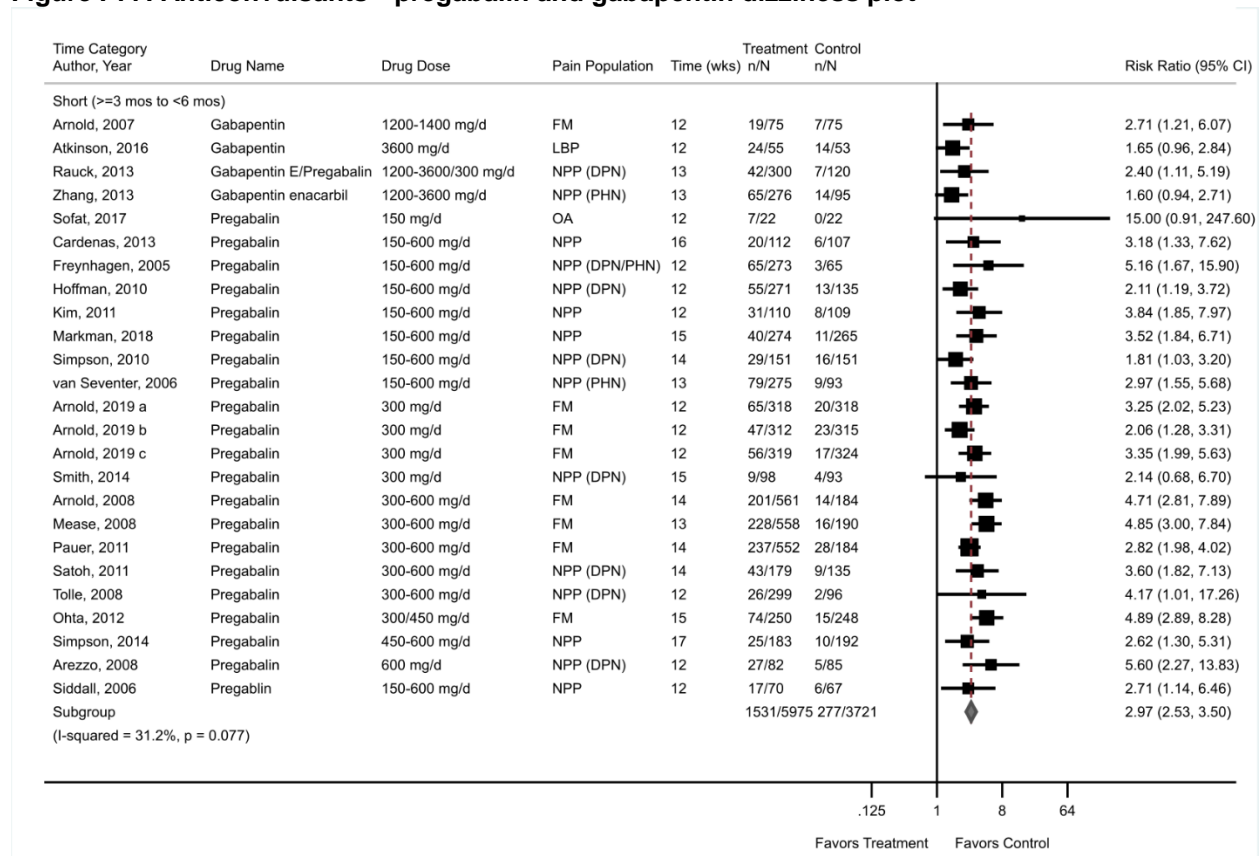


Figure I-78. Anticonvulsants—pregabalin and gabapentin peripheral edema plot

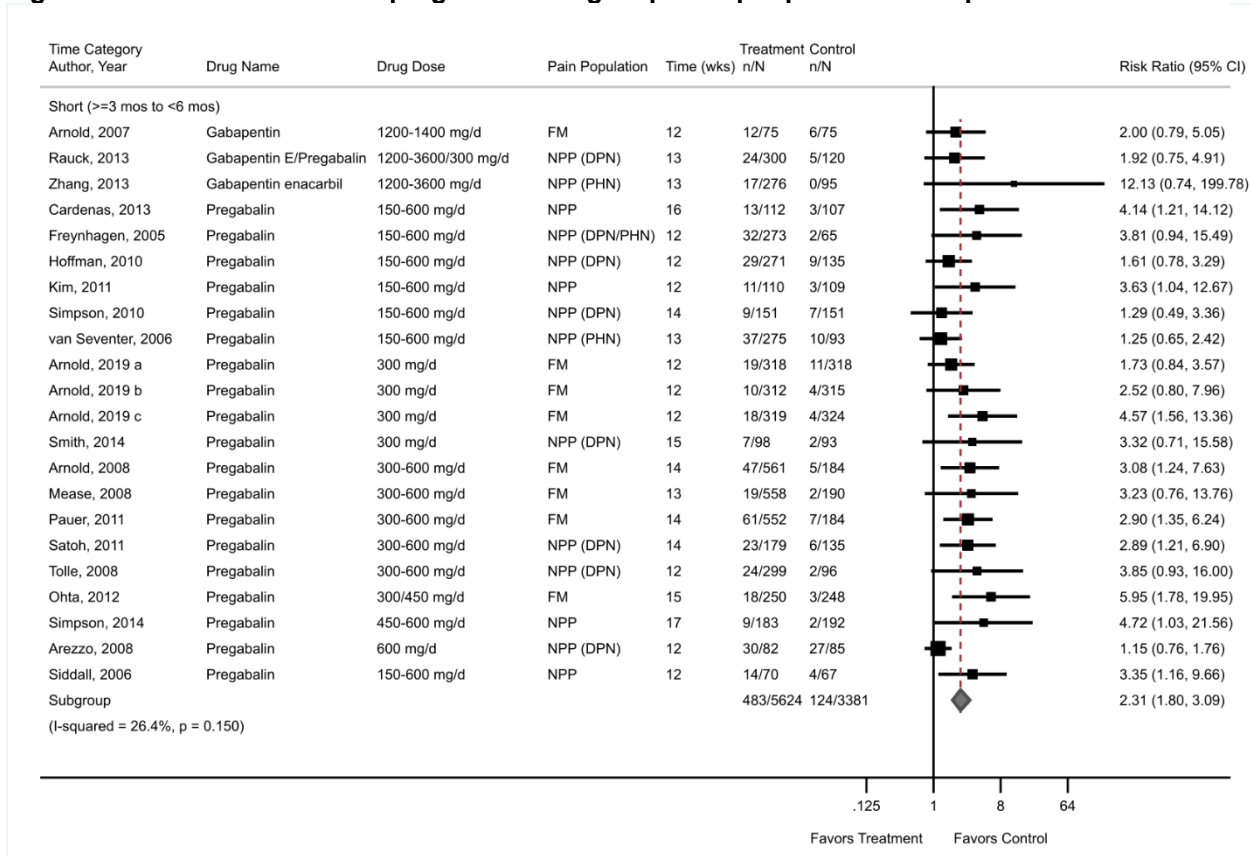


Figure I-79. Anticonvulsants—pregabalin and gabapentin sedation plot

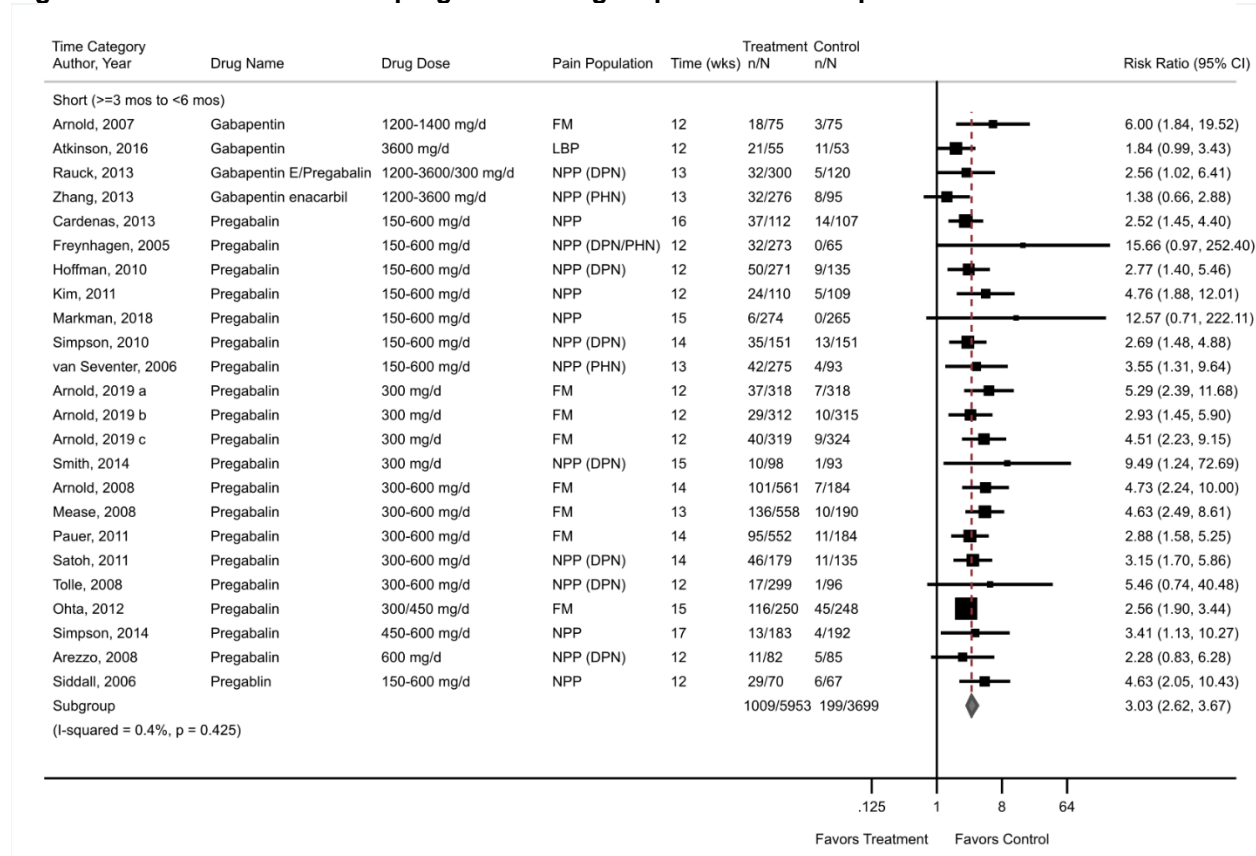


Figure I-80. Anticonvulsants—pregabalin and gabapentin weight gain plot

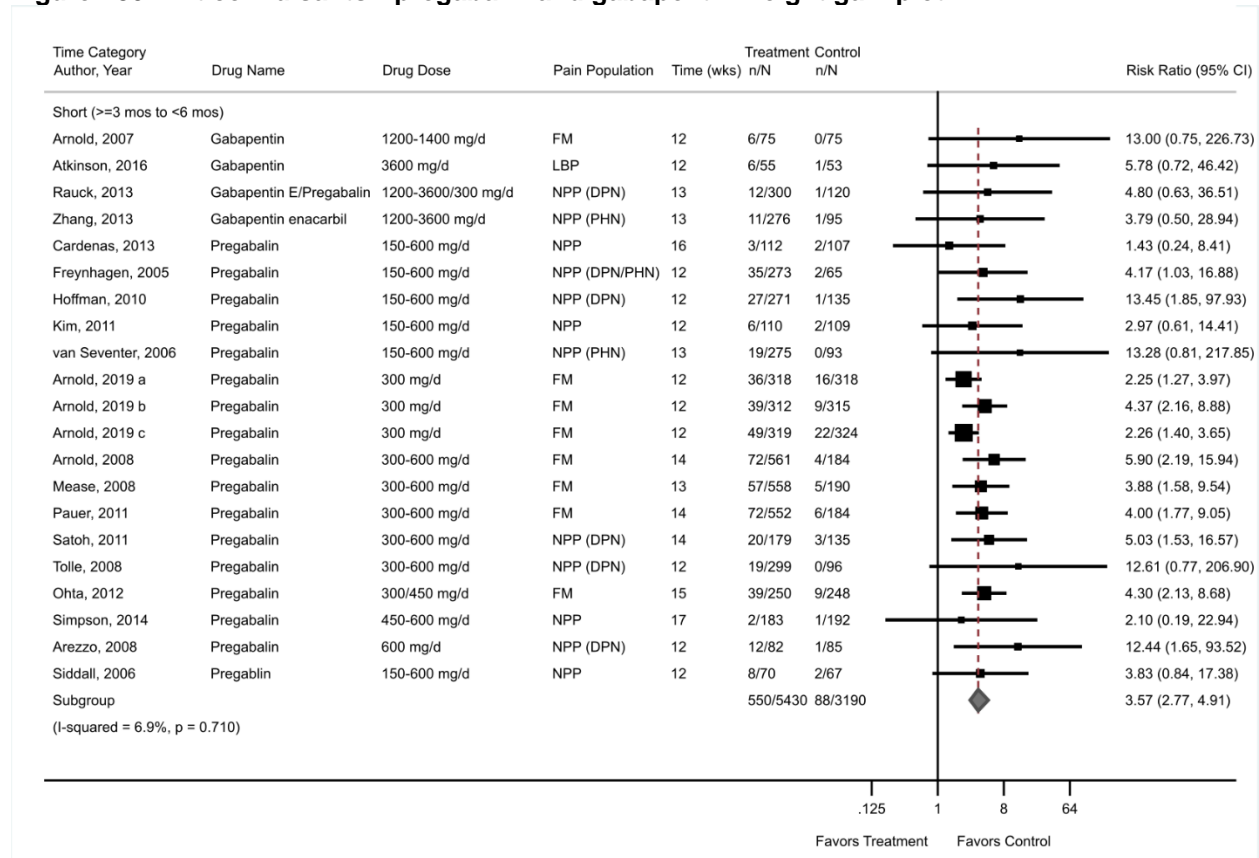


Figure I-81. Anticonvulsants—oxcarbazepine withdrawals due to adverse events plot

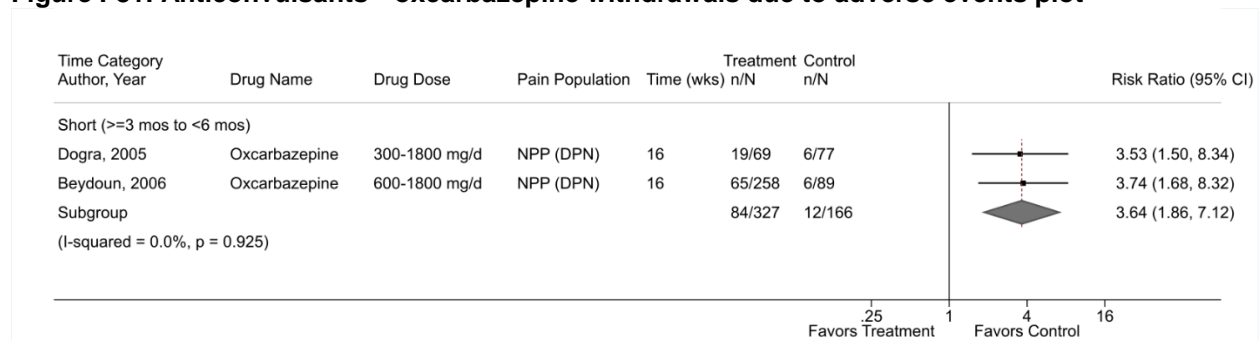


Figure I-82. Anticonvulsants—oxcarbazepine serious adverse events plot

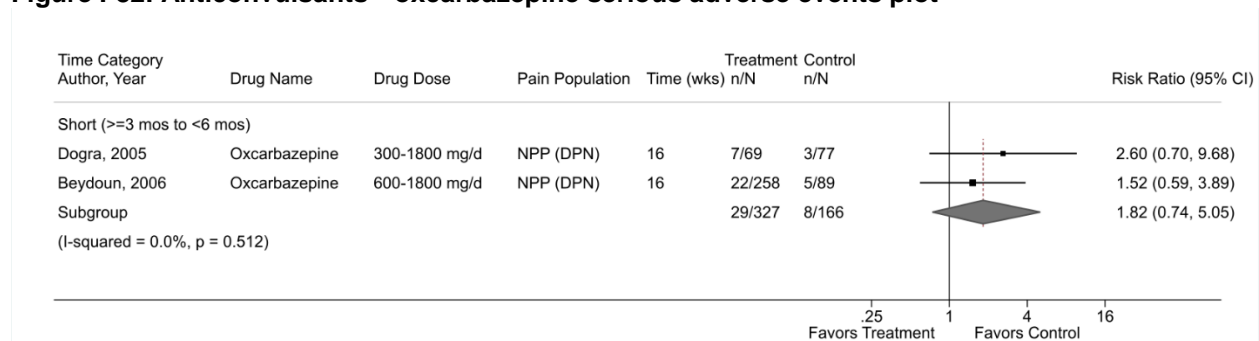


Figure I-83. Anticonvulsants—oxcarbazepine hyponatremia plot

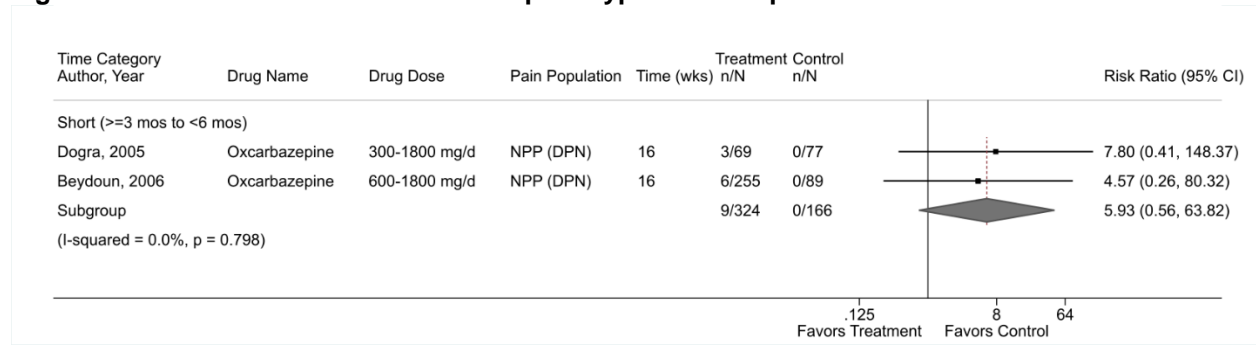


Figure I-84. Anticonvulsants—oxcarbazepine sedation plot

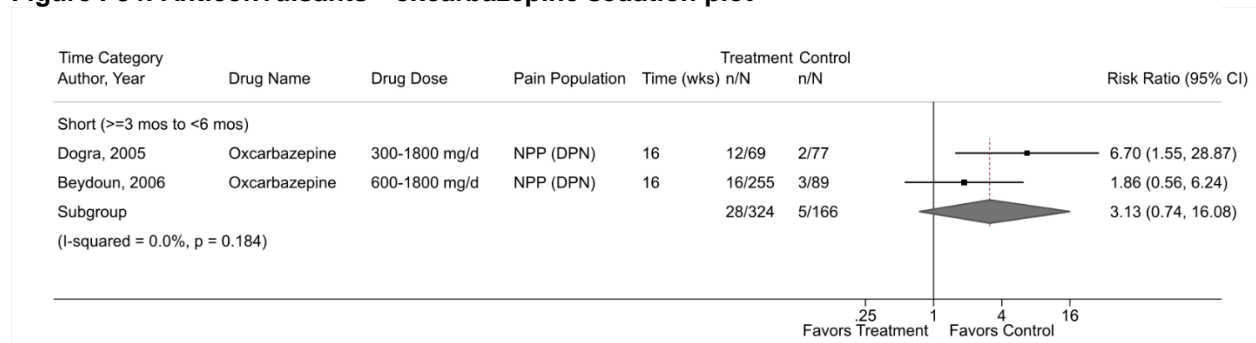


Figure I-85. NSAIDs—oral NSAIDs withdrawals due to adverse events plot

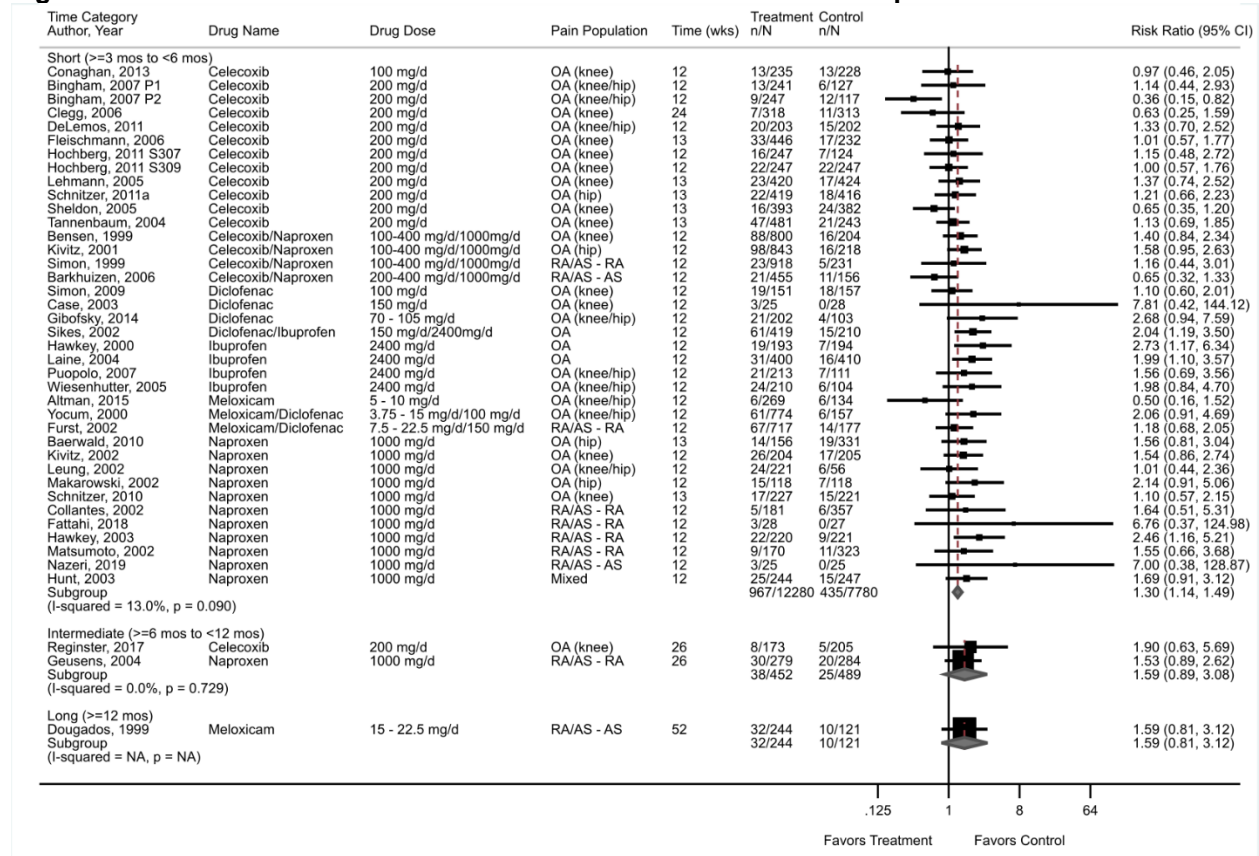


Figure I-86. NSAIDs—oral NSAIDs serious adverse events plot

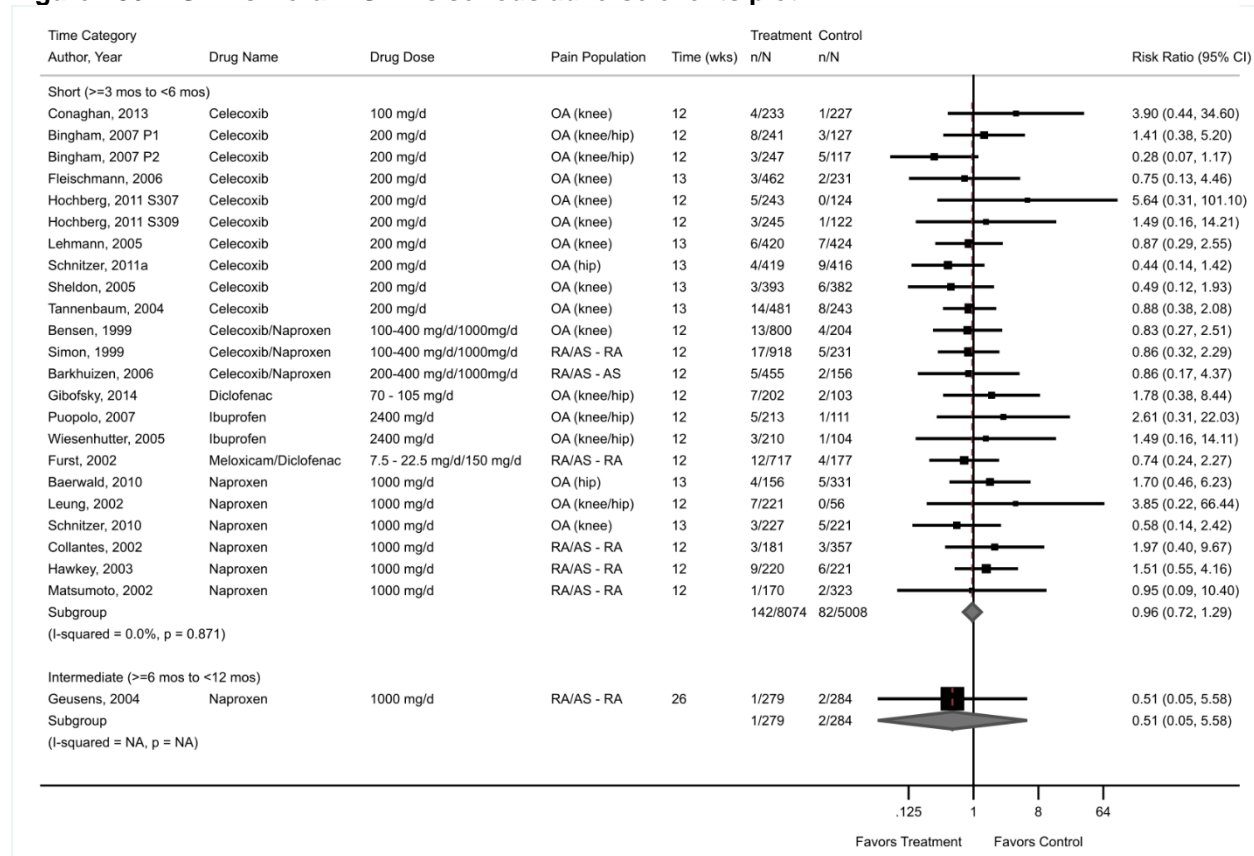


Figure I-87. NSAIDs—oral NSAIDs serious gastrointestinal events plot

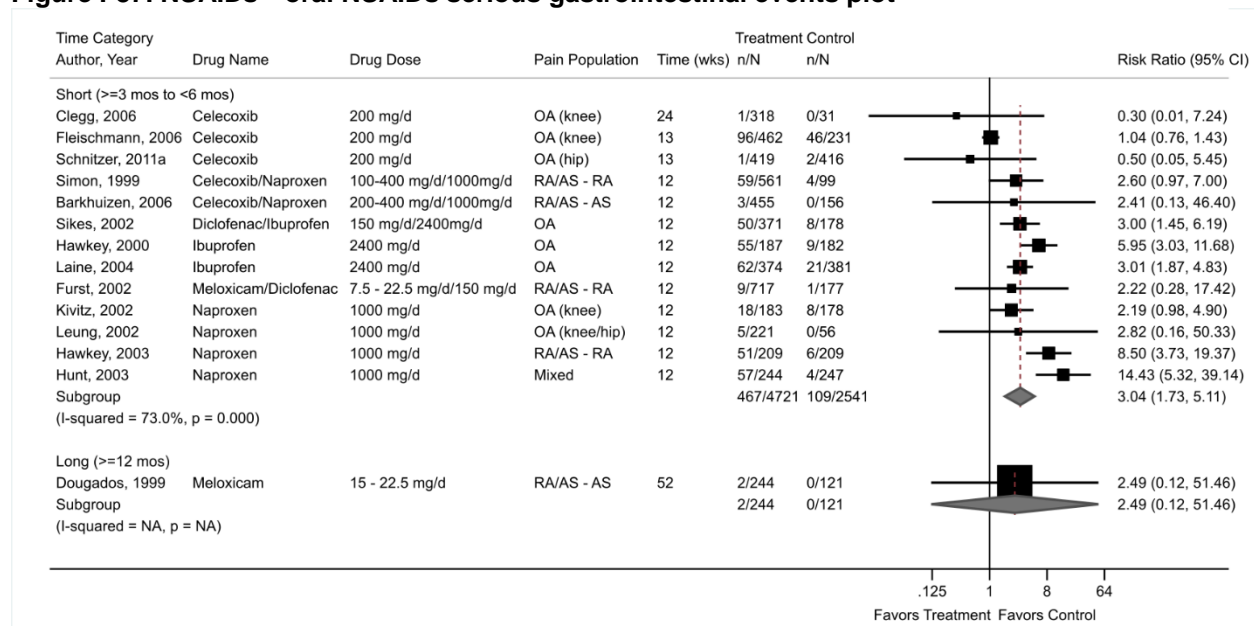


Figure I-88. NSAIDs—topical diclofenac withdrawals due to adverse events plot

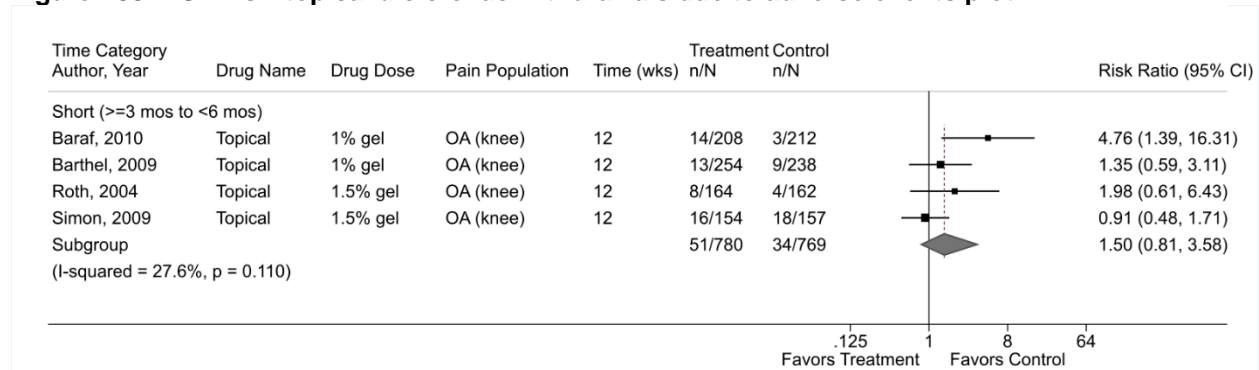


Figure I-89. NSAIDs—topical diclofenac serious adverse events plot

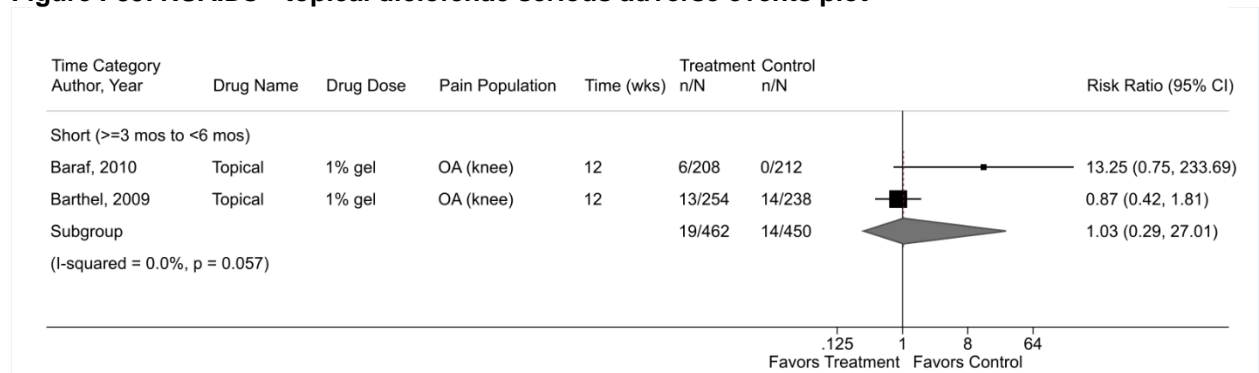


Figure I-90. NSAIDs—topical diclofenac application site pruritus plot

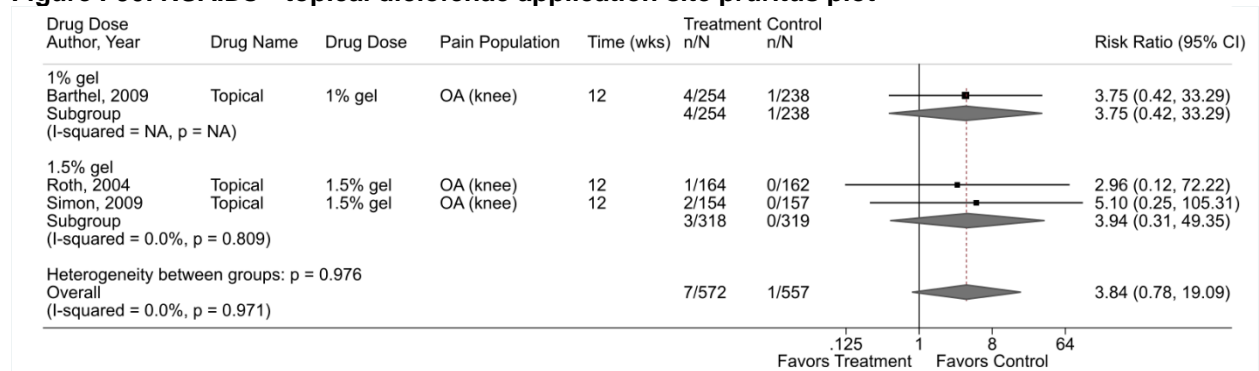


Figure I-91. Acetaminophen—withdrawals due to adverse events plot

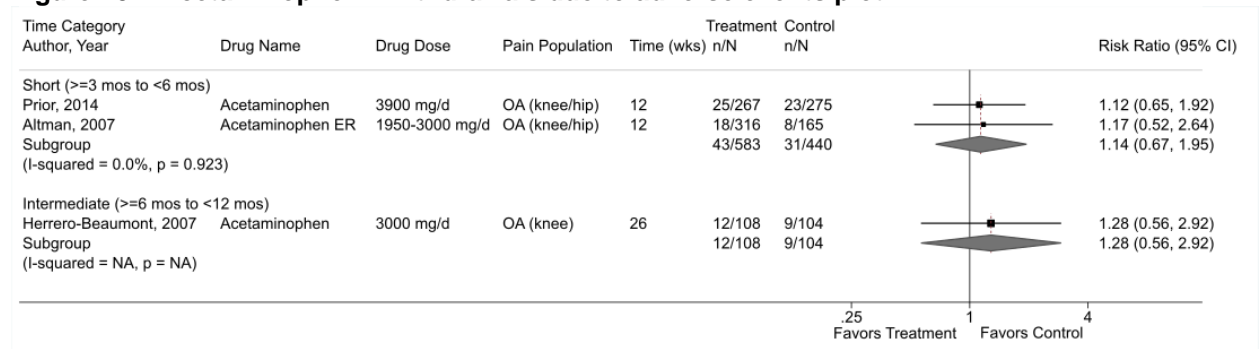


Figure I-92. Acetaminophen—serious adverse events plot



Figure I-93. Capsaicin patch—withdrawals due to adverse events plot

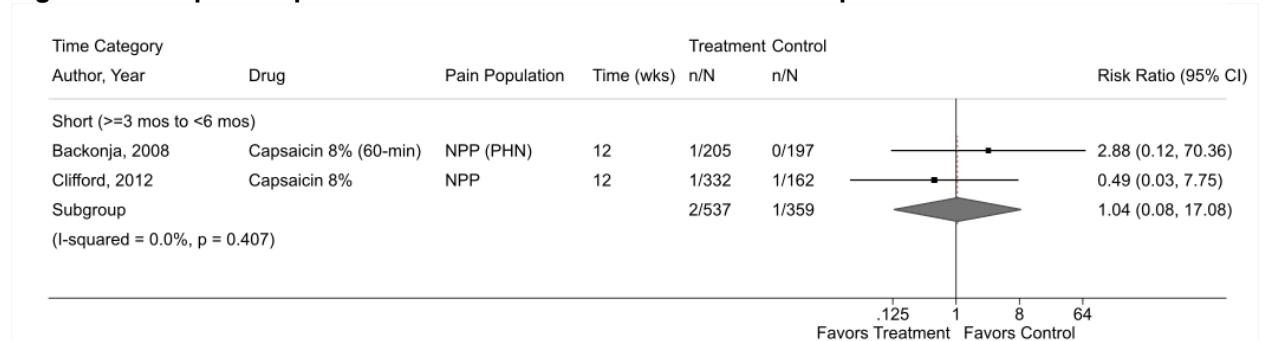


Figure I-94. Capsaicin patch—application site erythema plot

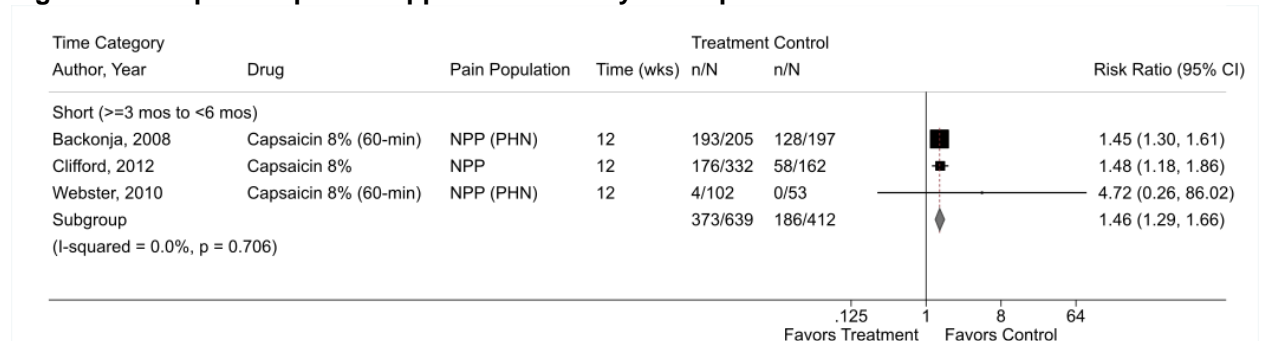


Figure I-95. Capsaicin patch—application site pain plot

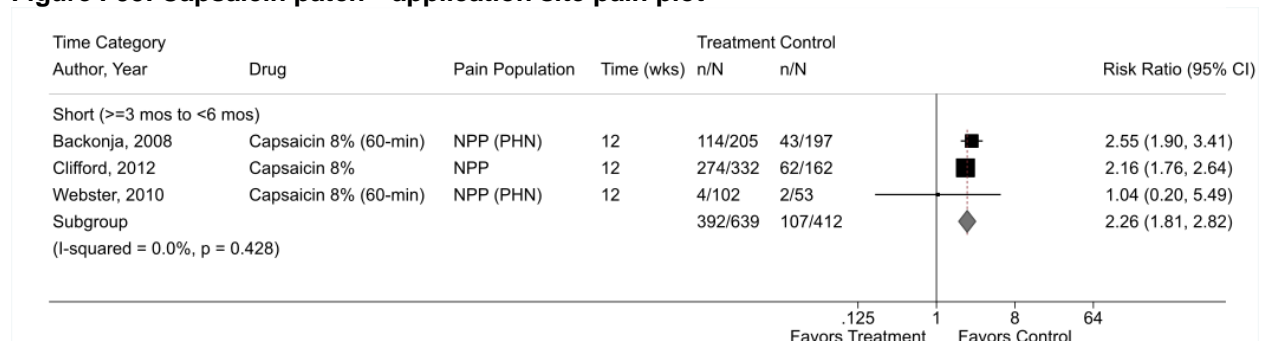
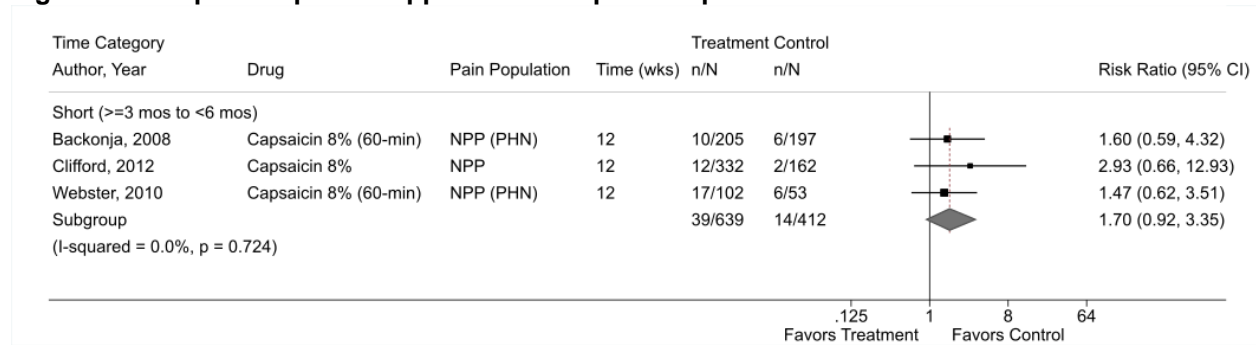
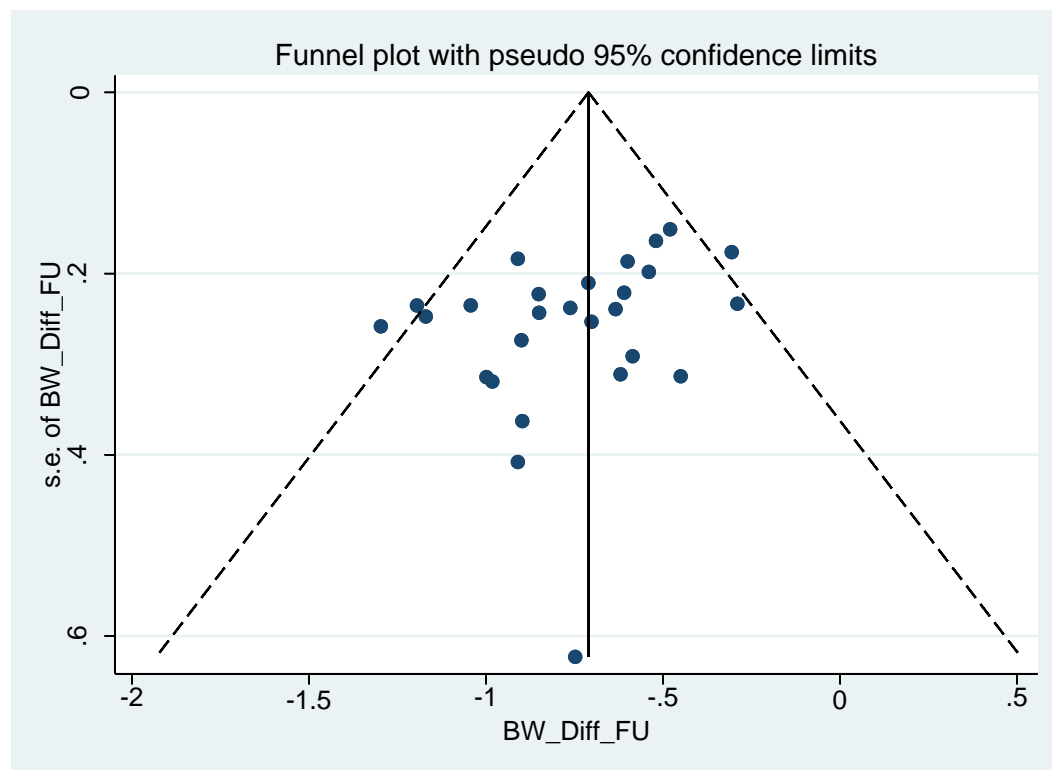


Figure I-96. Capsaicin patch—application site pruritus plot



Publication Bias

Figure I-97. Osteoarthritis – Egger’s test for publication bias



Appendix J. Appendix References

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