Draft Comparative Effectiveness Review

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Nonopioid Pharmacological Treatment for Chronic Pain

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Key Messages

Purpose of Review

This review evaluates the benefits and harms of nonopioid drugs in randomized controlled trials (RCTs) 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,
    - Anticonvulsants pregabalin, gabapentin, and oxcarbazepine show small improvements in pain and function in patients with diabetic peripheral neuropathy/post-herpetic neuralgia and fibromyalgia.
    - SNRI antidepressants duloxetine and/or milnacipran show small to moderate improvements in pain, function and quality of life in patients with diabetic peripheral neuropathy/post-herpetic neuralgia and fibromyalgia. Patients with low back pain had small improvements in pain and no improvement in function.
    - NSAIDs show small improvements in pain and function in patients with osteoarthritis and inflammatory arthritis. Acetaminophen did not result in improvements in pain and function in patients with osteoarthritis.
- In the short- and intermediate-term, limited evidence found memantine to moderately improve pain, function and quality of life in patients with fibromyalgia.
- For all conditions, evidence on long-term treatment effectiveness, comparative effectiveness, and quality of life is limited
- Small to moderate, dose-dependent, increases in withdrawal due to adverse events was found with TCAs, SNRIs duloxetine and milnacipran, pregabalin and gabapentin, and NSAIDs. Large increases seen with oxcarbazepine. NSAIDs have increased risk of serious GI and CV adverse events.

This report is based on research conducted by the XXXXX Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. XXX-20XX-XXXXX). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

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

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

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

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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: (EPC NAME) Evidence-based Practice Center (Contract Number: (CONTRACT NUMBER).

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

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

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

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

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Key Informants

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

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

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

Technical Expert Panel

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

Technical Experts must disclose any financial conflicts of interest greater than $5,000and 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 will be provided in the final 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 does not necessarily represent the views of individual reviewers.

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

The list of Peer Reviewers will be provided in the final report.

Nonopioid Pharmacological Treatment 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 the effects of 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 January 2019, reference lists, data request, and previous reviews.

Review methods. Randomized controlled trials (RCTs) of nonopioid pharmacological 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. 182 RCTs in 218 publications and 5 systematic reviews were included
In the short-term, anticonvulsants (pregabalin, gabapentin, and oxcarbazepine for neuropathic pain, pregabalin/gabapentin for neuropathic pain), SNRI antidepressants (duloxetine for neuropathic pain, fibromyalgia, osteoarthritis and low back pain, milnacipran for fibromyalgia), and NSAIDs (for osteoarthritis and inflammatory arthritis) were associated with mostly small improvements (e.g. 5 to 20 points on a 0-100 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, but was insufficient to draw conclusions for other drugs and conditions. In limited evidence (1 RCT) memantine moderately improved pain, function and quality of life in patients with fibromyalgia. While most comparisons of drugs and doses did not identify differences, diclofenac improved pain and function moderately more than celecoxib. In the intermediate-term, improvements seen in patients with fibromyalgia with memantine were maintained; 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 with oxcarbazepine and cannabis. Drug-specific adverse events were also increased frequently in the RCTs. 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), duloxetine (sedation),

diclofenac/naproxen (liver events), and cannabis (nausea, dizziness). Dose-reductions reduced the risk of some adverse events with SNRI antidepressants. Increased risk of major coronary events and serious GI events 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 months[1] 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 U.S. live with chronic pain garnering an estimated $560 billion in annual healthcare costs,[1] 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 in 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 which 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 non-opioid 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 was 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 pharmacological treatment for issues of chronic pain. Key questions focus on:

- 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 treatments 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?

Pharmacological interventions considered in this review include Oral agents specifically used to treat pain such as: NSAIDS, antidepressants SNRIs and 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 (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").[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 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 in January 2019 (from database inception, see Appendix A for full strategies). Reference lists of included systematic reviews were screened for includable studies. Prior to the final report, we will update these searches and incorporate any new eligible studies into the report

Inclusion and Exclusion Criteria and Study Selection

Criteria for study inclusion were developed prior to conducting our searches based on our Key Questions and PICOTS detailed in Appendix B. For all Key Questions, we included and focused on randomized controlled trials (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 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 ensure 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.

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." (See Appendix G). 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 were abstracted and dual-reviewed by independent investigators in multiple-parts. Data regarding general study characteristics such as demographics, pain condition, County of trial, and baseline pain scores were abstracted into forms as seen in Appendix E. For clarity, data used for meta-analysis were abstracted into separate forms, pooled and synthesized (Appendix F). 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 0-10 or 0-100 over other pain assessments (e.g., Western Ontario and McMaster Universities Osteoarthritis Index pain subscale). Primary pain response was defined as ≥30% improvement (reduction) in pain score. Secondary pain response criteria included >30% improvement (e.g., ≥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 0-10; 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 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.

Strength of the Body of Evidence

The strength of evidence (SOE) for each Key Question was rated for each clinical outcome (see PICOTS) 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, 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.

Table ES-1. 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 ES-2. Definitions of effect sizes

Small effect	• 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	• MD >1 to 2 points on a 0 to10-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	• MD >2 points on a 0 to10-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 TOO and an EPC Associate Editor will provide comments and editorial review. Following this, the peer-reviewed draft report will be posted on the AHRQ website for 4 weeks for public comment.

Results

Results are shown by Key Question and then by condition for efficacy. Harms results are organized by drug class. Search results and selection of studies are summarized in the literature flow diagram (Figure 2 of the main report). After dual review of full-text articles, 182 randomized controlled trials (RCTs; in 216 publications) were included in this review. In addition, we identified 5 systematic reviews that included 44 trials included in this review. Overall, 29 trials were rated poor-quality, 127 fair-quality, and 26 good-quality (Appendix G). Of the good- and fair-quality trials, 124 were classified as short-duration (3 months to <6 months), 20 medium-duration (6 months to <1 year), and 9 were long-duration (≥1 year). We included 32 RCTs in neuropathic pain, 23 RCTs in fibromyalgia, 61 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 (65.9%) 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 38 months. Participants reported a mean pain intensity of 4 on a scale of 0 to10. Industry was the leading provider of funding for trials (81%) while 17 trials (11%) did not report funding source.

Data abstraction of study characteristics and results, and quality assessment for good- and fair-quality studies are available in Appendixes E, F and G

Key Question 1. Benefits

In patients with neuropathic pain (mainly diabetic peripheral neuropathy and/or post-herpetic neuralgia), short-term RCT (n=33) of anticonvulsants (prodrug gabapentin enacarbil, pregabalin, and oxcarbazepine) found small improvement in pain, with no differences between drugs (SOE: Moderate). The antidepressant duloxetine resulted in small to moderate improvements in pain and small improvements in function and quality of life in patients with diabetic peripheral neuropathy (SOE: Low to Moderate). 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=23) show small short-term improvements in pain and function with SNRI antidepressants milnacipran and duloxetine and anticonvulsants pregabalin and gabapentin (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 (n=52 RCTs), treatment with nonsteroidal anti-inflammatory drugs (NSAIDs, 28 RCTs) in the short-term resulted in small improvements in pain and function (SOE: Moderate for pain, High for function). Topical diclofenac did not improve average pain severity, but led to a small increase in patients reporting response. Few differences were found between drugs. Duloxetine resulted in small improvement in pain severity, moderate improvement in pain response, and small improvements in function and quality of life (SOE: High). Acetaminophen showed small effects in the short-term, only at higher doses (SOE: Low). In patients with inflammatory arthritis (n=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 had moderate improvement in pain and small improvement in function with duloxetine (7 RCTs, SOE: Moderate).

Key Question 2. Harms

Across all classes, incidence of serious adverse event (SAEs) was low. Twenty-two trials evaluated harms of antidepressants. Antidepressants led to a moderate increase in withdrawal due to adverse event (WAE) in 22 short-term 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, and amitriptyline led to a moderate increase in reports of dry mouth (SOE: Moderate to Low).

Twenty-four trials evaluated harms in short-term treatment with anticonvulsants. Oxcarbazepine led to a large increased risk of WAEs. Pregabalin and gabapentin also led to small increased risk of WAEs, with pregabalin risk being greater with higher doses. Pregabalin and gabapentin resulted in moderate to 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)

Fifty-eight trials evaluated harms of NSAID treatment in the short-term. WAEs were increased, specifically with ibuprofen (large increase), diclofenac (moderate increase) and naproxen (small increase). The risk of any CV event was not significantly elevated for NSAIDs as a group, but diclofenac had a small increase in risk, particularly in the first six months, and with higher doses. The risk of major coronary events was elevated with diclofenac and celecoxib (moderately) and with ibuprofen (large increase). The risk of serious upper GI 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: Large increases were found in incidence of dizziness with oral dronabinol solution, and in WAEs, dizziness and nausea with THC/CBD 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, please see the full report for a detailed discussion of our key findings and strength of evidence (Appendix H). 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 (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 (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 findings are categorized in the paragraphs below according to pain condition. In Tables ES-3 through ES-12, the evidence is organized first by drug class, then pain condition and duration of study. 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 was not improved in post-herpetic neuralgia or quality of life in HIV- or diabetes-associated neuropathy. In patients with diabetic peripheral neuropathy, duloxetine resulted in small improvements in pain, small improvements in function, and quality of life. Capsaicin patch had a small effect on pain severity in post-herpetic neuralgia and HIV-related neuralgia, but no improvement in pain response. Limited evidence on cannabis (dronabinol oral solution, tetrahydrocannabinol/cannabidiol [THC/CBD] oral spray) showed inconsistent effects on pain (depending on the measure) in patients with multiple sclerosis-associated neuropathy or allodynia in the short- or intermediate-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 (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. The exception was that diclofenac moderately improved pain and function more than

celecoxib in the short-term. Evidence on topical diclofenac was inconclusive. The SNRI antidepressant duloxetine resulted in moderate effects on pain improvement and response, and small effects on 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 is inconsistent. Evidence on intermediate- and long-term outcomes is 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.

Adverse events categorized as "Serious" were not reported more often with nonopioid drugs than placebo in patients with chronic pain, except with oxcarbazepine in neuropathic pain (large effect) and with longer duration capsaicin patch (compared with shorter duration, moderate effect). Lower (40 mg) versus higher (60 mg) dose duloxetine resulted in a moderate reduction in incidence of serious adverse events. 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 (CV) 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 CV events between drugs. NSAIDs led to moderate to large increased risk of serious upper gastrointestinal (GI) 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 THC/CBD oral spray resulted in large increases in dizziness and nausea. Other adverse events of interest were not reported (cognitive effects, misuse, addiction, SUD).

KQ1 Effectiveness and Comparative Effectiveness of Nonopioid Drugs for Chronic Pain

Table ES-3. 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	**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
Neuropathic Pain	Duloxetine vs. Placebo	Small to Moderate ++	No evidence	No evidence	Small +	No evidence	No evidence	Small ++
Fibromyalgia	Duloxetine / Milnacipran vs. Placebo	Small ++	Small ++	No evidence	Small ++	None ++	MCS: Small ++ PCS: None ++	MCS: Small ++ PCS: None +
	Duloxetine vs. Duloxetine	No evidence	No evidence	None +	No evidence	No evidence	None +	No evidence
	Milnacipran vs. Milnacipran	No evidence	Insufficient	None +	No evidence	Insufficient	None +	No evidence
Osteoarthritis	Duloxetine vs. Placebo	Small +++	No evidence	No evidence	Small +++	No evidence	No evidence	Small +++
Low Back Pain	Duloxetine vs. Placebo	Small ++	No evidence	No evidence	None ++	No evidence	No evidence	None ++

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 ES-4. 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	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 ES-5. 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	None ++	None +	No evidence	No evidence	No evidence	No evidence	No evidence
Inflammatory Arthritis	NSAID vs. Placebo	Small ++	Small +	Large +	Small ++	Small +	None +	Insufficient
	Celecoxib vs. Celecoxib	None ++	No evidence	No evidence	None +	No evidence	No evidence	No evidence
	Meloxicam vs. Meloxicam	None +	No evidence	None +	None +	No evidence	None +	None +
	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 ES-6. 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
Neuropathic Pain	Cannabis	None +	None +	No evidence	No evidence	None +	No evidence
Fibromyalgia	Memantine	Moderate +	Moderate +	Moderate +	Moderate +	Moderate +	Moderate +
Fibromyalgia	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 ES-7. Harms of antidepressants versus placebo

Types of Adverse Events	**Milnacipran** Short- to intermediate-term Effect Size SOE	**Duloxetine** Short- to intermediate-term Effect Size SOE	**Amitriptyline** Short-term Effect Size SOE	**Amitriptyline** Intermediate-term Effect Size SOE
WAE	Moderate ++	Moderate ++	None +	None +
SAE	None +	None +	No evidence	No evidence
Nausea	Moderate ++	Large ++	NA	NA
Sedation	None +	Large ++	NA	NA
Serotonin Syndrome	No evidence	No evidence	No evidence	No evidence
Dry mouth	NA	NA	Moderate +	None +
Cardiac rhythm abnormalities	NA	NA	No evidence	No evidence
Urinary retention	NA	NA	No evidence	No evidence

NA = not applicable (i.e., specific AE 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 ES-8. Harms of antidepressant dose comparisons

Types of Adverse Events	**Milnacipran 100 vs. 200 mg/day** Intermediate-term Effect Size SOE	**Duloxetine 20 vs. 60 mg/day** Short-term Effect Size SOE	**Duloxetine 60 vs. 120 mg/day** Short-term Effect Size SOE	**Duloxetine 40 vs. 60 mg/day** Long-term Effect Size SOE	**Duloxetine 60 vs. 120 mg/day** Long-term Effect Size SOE
WAE	None +	None +	Small reduction +	None +	None +
SAE	None +	Insufficient	None +	Moderate reduction +	None +
Nausea	None +	None +	None +	None +	No evidence
Sedation	No evidence	None +	Moderate reduction +	None +	No evidence
Serotonin Syndrome	No evidence	No evidence	No evidence	No evidence	No evidence

NA = not applicable (i.e., specific AE 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 ES-9. Harms of anticonvulsants versus placebo and active comparator

Types of Adverse Events	**Pregabalin** Short-term Effect Size SOE	**Gabapentin enacarbil**[a] Short-term Effect Size SOE	**Gabapentin** Short-term Effect Size SOE	**Pregabalin vs. gabapentin enacarbil** Short-term Effect Size SOE	**Oxcarbazepine** Short-term Effect Size SOE
WAE	Moderate ++	Small +	Moderate +	Moderate +	Large +
SAE	None ++	None +	No evidence	No evidence	Large +
Blurred Vision	Large ++	None +	Large ++	No evidence	NA
Cognitive Effects	Large ++	None +	Large +	No evidence	No evidence
Dizziness	Large +	Moderate +	Moderate +	No evidence	NA
Peripheral Edema	Large ++	None +	Insufficient	No evidence	NA
Sedation	Large ++	Moderate +	Large +	No evidence	Moderate +
Weight Gain	Large ++	None +	Large +	No evidence	NA
Hyponatremia	NA	NA	NA	NA	None +

NA = not applicable (i.e., specific AE 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
[a] gabapentin enacarbil is a prodrug of gabapentin

Table ES-10. Harms of NSAIDs versus placebo and active comparators

Types of Adverse Events	**NSAID** Short-term Effect Size SOE	**Celecoxib** Short-term Effect Size SOE	**Diclofenac** Short-term Effect Size SOE	**Ibuprofen** Short-term Effect Size SOE	**Naproxen** Short-term Effect Size SOE	**Celecoxib vs. nsNSAID** Intermediate-term Effect Size SOE
WAE	Small-Large ++	None ++	Moderate ++	Large ++	Small ++	None ++
SAE	None +	None +	None +	None +	None +	None +
CV Events	None ++	None ++	Small ++	None ++	None ++	None ++
GI Events	None ++	None ++	None ++	None ++	None ++	Insufficient
Liver Dysfunction	None +	None +	Large +	None +	Large +	None +

CV = cardiovascular; GI = gastrointestinal; NA = not applicable (i.e., specific AE not applicable to 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 ES-11. SAE and WAEs of other drugs versus placebo and active comparator

Types of Adverse Events	**Capsaicin** Short-term Effect Size SOE	**Capsaicin 60-min vs. 30-min** Short-term Effect Size SOE	**Dronabinol** Short-term Effect Size SOE	**THC + CBD** Short-term Effect Size SOE
WAE	None ++	None +	None +	Large +
SAE	None ++	Moderate +	None +	None +

CBD = cannabidiol; 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 ES-12. Specific harms of cannabis versus placebo

Types of Adverse Events	**Dronabinol** Short-term Effect Size SOE	**THC + CBD** Short-term Effect Size SOE
Cognitive Effects	No evidence	No evidence
Hyperemesis	No evidence	No evidence
Nausea	None +	Large +
Sedation	Insufficient	No evidence
Dizziness	Large +	Large +

CBD = cannabidiol; THC = tetrahydrocannabinol; 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 ES-13. 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
	TCAs	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/day, 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 OA found an SMD for acetaminophen of 0.18, and we found the 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.[13] 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, on 0-10 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 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 (OR 1.61 to 2.33) while we found a moderate effect (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 (FDA) warnings, drug information texts). However, as Table ES-13 above indicates, our analyses on adverse events, are consistent with these other sources.

Table ES-13, above, 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 type of chronic pain. The reverse is true of NSAIDs in that the evidence is only applicable 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 153 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. 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 CV or GI effects with NSAIDs. Consideration of patient characteristics including co-morbidities, 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 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.[3,18] Our 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] U.S.-based estimates find that nearly 50 million adults live with 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 (NSAIDs), 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 co-morbidities.

Nationally, a concern regarding appropriate use, misuse, 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

effectiveness[10] and serious safety concerns[9] speaks to the need to consider alternative treatments to opioids. The 2016 Center for Disease Control and Prevention (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 & 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 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

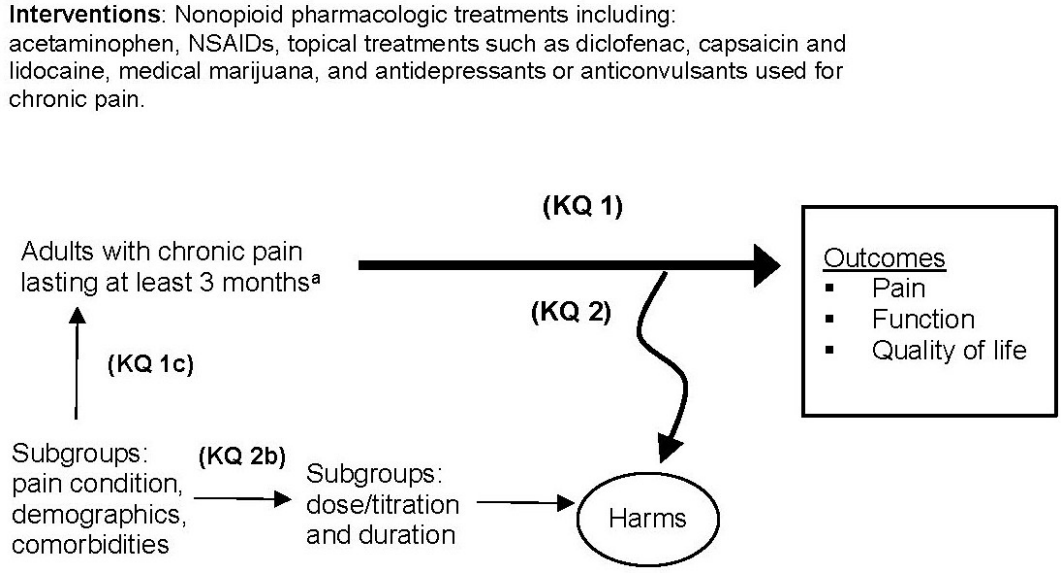
Key Question 2. Harms and Adverse Events

a. In patients with chronic pain, what are the risks of nonopioid pharmacologic agents for harms including overdose, misuse, dependence, SUD, 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) 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. Details of inclusion criteria are provided in the Methods.

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



KQ = Key Question
[a]Includes acute exacerbations of chronic pain, pregnant/breastfeeding women, and patients treated with opioids for opioid use disorder

Methods

This comparative effectiveness review (CER) follows the methods suggested in the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (hereafter "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 and a complete description is provided 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 (KQ) 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	• For all KQs: Adults (age ≥18 years) with chronic pain (pain lasting >3 months). • For KQs 1c, 2b Specific chronic pain populations: o Neuropathic o Musculoskeletal (e.g., low back pain, osteoarthritis) o Fibromyalgia (assessed using established criteria) o Sickle cell disease o Inflammatory arthritis (e.g., rheumatoid arthritis) o Chronic headache[a]	• 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	Nonopioid pharmacologic drugs for chronic pain: • Oral pharmacologic agents specifically used to treat chronic pain: o NSAIDs (e.g., celecoxib, diclofenac, ibuprofen) o Antidepressants SNRIs (i.e., duloxetine, milnacipran) and TCAs (e.g., amitriptyline) o Anticonvulsants: Carbamazepine, gabapentin, oxcarbazepine, pregabalin o 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	• 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	• For KQ 1a/b and 2a/b: Placebo • For KQ 1c and 2a/b: Another included nonopioid pharmacologic agent, dose, or treatment duration	• Nonpharmacologic treatment (comparison to nonopioids included in review of nonpharmacologic treatments) • Opioid treatment

PICOTS	Inclusion Criteria	Exclusion Criteria
Outcomes	• Pain, function, and quality of life using validated outcome measures. o 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). o Patient-reported pain assessments are prioritized. Pain response based on clinician assessments was also acceptable and noted where they are reported. o 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 SUD. • Key specific adverse events according to drug class (e.g., gastrointestinal and cardiovascular events, kidney and liver-related harms with NSAIDs).	• 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	• Randomized controlled trials • High-quality, recent systematic reviews that best match the scope of this review • English language publications	• 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

[a]Chronic headache defined as (International Classification of Headache Disorders, 3rd edition definition[22]):
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.[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. Prior to the final report, we will update these searches and incorporate any new eligible studies into the report.

Assessment of Methodological Risk of Bias of Individual Studies

We assessed the quality (or Risk of Bias) of included RCTs based on principles for appraisal as developed by the Cochrane Back and Neck Group,[23] and outlined in the *AHRQ EPC 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 re-assessed 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 Nonpharmacologic 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

Small effect	• 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	• MD >1 to 2 points on a 0 to10-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	• MD >2 points on a 0 to10-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 three studies reporting outcomes homogeneous enough to provide a meaningful combined estimate. The Profile Likelihood model was used, unless the model failed to converge where a DerSimonian and Laird model was used. Please see Appendix B for more details. 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. 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 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-US) 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

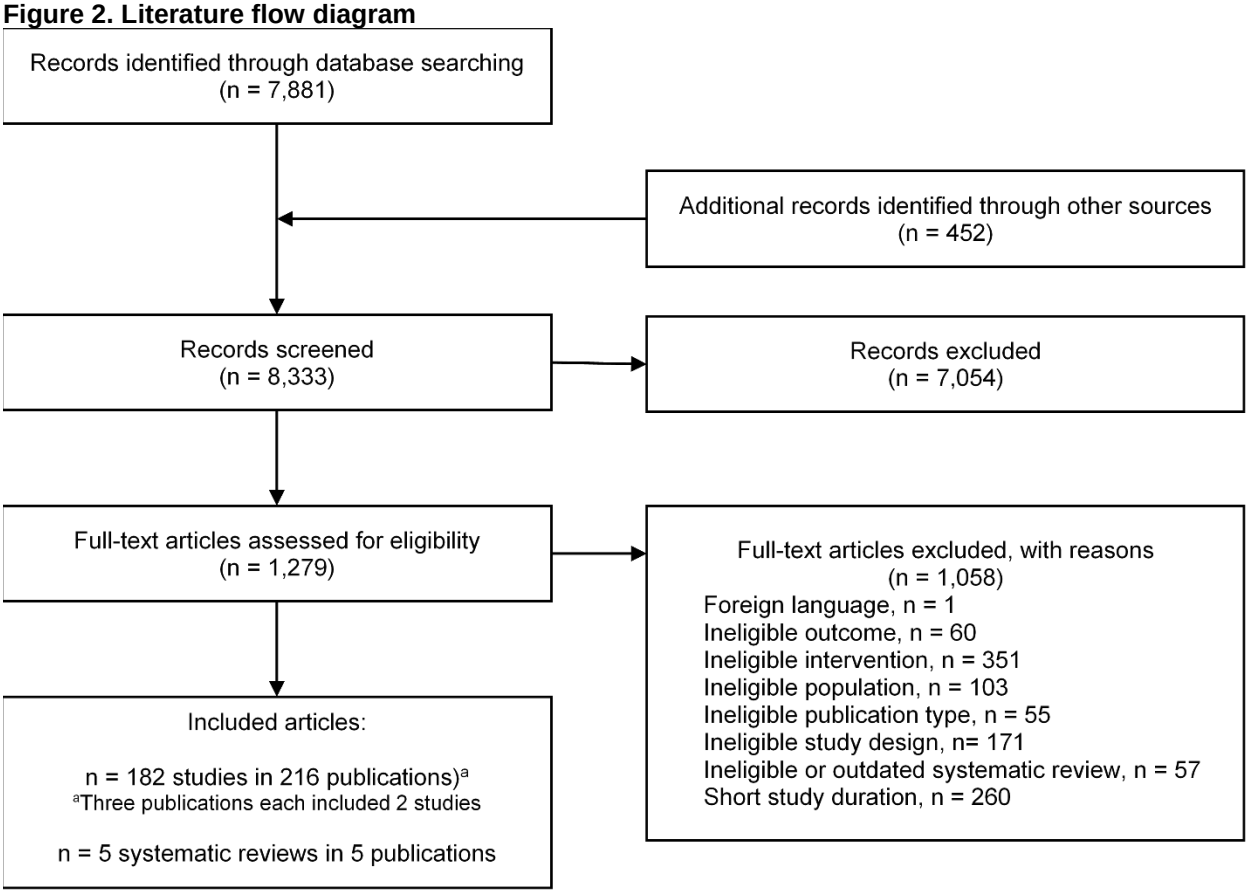
Experts in the field of chronic pain conditions will be invited to provide external peer review of this systematic review. Comments and editorial review will also be provided by the AHRQ Task Order Officer and an associate editor. The draft report will be posted on the AHRQ website for 4 weeks to elicit public comment. We will revise text as needed and address 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 8333 references were reviewed, including 7881 from electronic database searches and 452 from prior Evidence-based Practice Center (EPC) reports and reviewing studies included in other systematic reviews. After dual review of titles and abstracts, 1279 articles were selected for full-text review, of which 182 randomized controlled trials (RCTs) in 216 publications were include in this review. In addition, we identified 5 systematic reviews that included 44 of 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, 29 trials were rated poor-quality, 127 fair-quality, and 26 good-quality (Appendix G). Of the good- and fair-quality trials, 124 were classified as short-term (3 months to <6 months), 20 intermediate-term (6 months to <1 year), and 9 were long-term (≥1 year). We included 32 RCTs in neuropathic pain, 23 RCTs in fibromyalgia, 61 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 (65.9%) 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 38 months. Participants reported a mean pain severity of 4 on a scale of 0 to10. Industry was the leading provider of funding for trials (81%) while 17 trials (11%) did not report funding source. Data abstraction of study characteristics and results, and quality assessment for good- and fair-quality studies are available in Appendixes E, F and G.

Figure 2. Literature flow diagram



KQ 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 in patients with neuropathic pain (mainly diabetic peripheral neuropathy and/or postherpetic neuralgia; strength of evidence [SOE]: Moderate). Functional outcomes were not improved with gabapentin enacarbil in patients with post-herpetic 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 to moderate improvements in pain and quality of life outcomes (SOE: Moderate) and small improvements in function (SOE: Low) in diabetic peripheral neuropathy
- 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 39 publications) involving 9,539 patients evaluated nonopioid drugs to treat chronic neuropathic pain: 31 ***short-term*** (12 to 17 weeks) and 2 ***long-term*** trials (52 weeks). These included 21 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, 1 trial comparing multiple doses of topical capsaicin patch, 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 5 RCTs were rated poor quality (Appendix G).[58-62] 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.[58]

Studies were conducted most frequently in the U.S. (33%) and in Asia (18%); 21 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 (58%) and/or with

postherpetic neuralgia (18%). 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 43 percent (weighted mean) being female (range 0% to 73%) and 34 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 weight 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 4.4 years (range 0.4 to 10.1 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,[29,42,44,49,52,57] two trials enrolled patients with postherpetic neuralgia,[43,48] and one enrolled a mixed population of patients with either diabetic peripheral neuropathy or postherpetic neuralgia.[47] Five RCTs enrolled patients with other types of neuropathic pain; spinal cord injury (2 studies),[27,46] and one study each in patients with neuropathic pain associated with HIV,[51] stroke,[50] and trauma.[45] Study treatments were ***short-term*** (range 12 to 17 weeks) and involved flexible dose pregabalin (e.g., 150 mg/day to 600 mg/day based on response and tolerability),[27,29,44-46,50,51] or fixed dose pregabalin (e.g., 150 mg/day, 300 mg/day, 600 mg/day).[42,43,48,49,52] One study compared flexible dose pregabalin (150 mg/day to 600 mg/day) with fixed dose pregabalin (600 mg/day).[47]

A study of the prodrug gabapentin enacarbil in patients with postherpetic neuralgia randomized patients to 1200 mg/day, 2400 mg/day, 3600 mg/day or placebo, but combined data for the three drug arms after finding no difference in pain improvement between them.[38] A study of gabapentin enacarbil, pregabalin, and placebo in patients with diabetic peripheral neuropathy also combined data for the drug arms for similar reasons.[57]

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% reduction in mean pain score (risk ratio [RR] 1.28, 95% CI 1.12 to 1.51, I^2=73%) (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/day resulted in a numerically larger, statistically significant, reduction in pain and more patients achieving response than lower doses (Table 4).[42,43,49] Fixed dose pregabalin 600 mg/day and flexible dose pregabalin (150 mg to 600 mg/day) 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).[47] In the two trials of gabapentin enacarbil, there was little difference in pain score improvement among doses (Table 4).[38,57] 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)	Drug by Dose Interaction P-value
Pain Improvement 15 RCTs (n=4,832)	Pregabalin pooled 150 mg/day 300 mg/day 600 mg/day 150-600 mg/day 300-600 mg/day 450-600 mg/day Gabapentin pooled 1200 mg/day 2400 mg/day 3600 mg/day 1200-3600 mg/day	15 (4,832) 2 (375) 5 (1,035) 4 (735) 10 (2,963) 2 (511) 1 (375) 2 (725) 2 (384) 2 (353) 2 (418) 2 (725)	MD -0.63 (-0.92 to -0.36) MD -0.55 (-1.31 to 0.17) MD -0.36 (-0.89 to 0.17) MD -1.17 (-1.69 to -0.67) MD -0.75 (-1.13 to -0.39) MD -0.82 (-1.48 to -0.18) MD -0.02 (-0.39 to 0.35) MD -0.58 (-1.26 to 0.10) MD -0.66 (-1.21 to -0.08) MD -0.27 (-1.33 to 0.82) MD -0.74 (-1.50 to -0.01) MD -0.58 (-1.26 to 0.10)	0.90
Pain Response 15 RCTs (n=4,832)	Pregabalin pooled 150 mg/day 300 mg/day 600 mg/day 150-600 mg/day 300-600 mg/day 450-600 mg/day Gabapentin pooled 1200 mg/day 2400 mg/day 3600 mg/day 1200-3600 mg/day	15 (4,832) 2 (375) 5 (1,035) 4 (735) 10 (2,963) 2 (511) 1 (375) 2 (725) 2 (384) 2 (353) 2 (418) 2 (725)	RR 1.28 (1.09 to 1.54) RR 1.62 (0.71 to 4.00) RR 1.22 (0.90 to 1.77) RR 1.99 (1.42 to 2.87) RR 1.36 (1.14 to 1.71) RR 1.63 (1.15 to 2.26) RR 0.94 (0.77 to 1.16) RR 1.20 (0.94 to 1.57) RR 1.16 (0.88 to 1.53) RR 1.17 (0.72 to 1.84) RR 1.29 (1.01 to 1.66) RR 1.20 (0.94 to 1.57)	0.82

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/day, 2400 mg/day, 3600 mg/day) versus placebo (MD -0.23, 95% CI -0.70 to 0.23).[38] 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 (MD 0.24, 95% CI -0.07 to 0.54, I^2=58%) using the Euro Quality of Life (EQ-5D).[42,44,50] 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 (see Appendix H).[38,51,57] 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).[27,29,38,42-52,57]

Six RCTs of pregabalin,[27,29,44,46,50,51] one RCT of gabapentin enacarbil,[38] and one of both pregabalin and gabapentin enacarbil[57] found no ***short-term*** benefit on anxiety or depression as

assessed with the Hospital Anxiety and Depression Scale (Appendix H). 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 -0.85, 95% CI -1.39 to -0.45, I^2=0%, VAS 0-10 scale) (Appendix I).[40,41] Doses ranged from 300 mg/day to 1800 mg/day flexible dose in one trial and 600 mg/day, 1200 mg/day, or 1800 mg/day fixed dose in a second trial. Treatment with higher dose oxcarbazepine (1200 mg and 1800 mg/day) resulted in improved pain scores compared with placebo in one trial.[41] Pain response was also more likely with oxcarbazepine versus placebo (RR 1.33, 95% CI 0.97 to 1.93, I^2=0%) (Appendix I). This is moderate strength 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).[40] 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.[41]

Antidepressants, SNRI

Duloxetine

Six ***short-term*** (12 week) RCTs compared duloxetine with placebo at doses from 20 mg/day to 120 mg/day.[31,32,34-37] All patients had peripheral neuropathic pain from diabetes. One ***long-term*** (52 week), open label extension RCT compared duloxetine 40 mg/day with 60 mg/day.[33]

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).[31,32,34-37] Patients were also more likely to achieve response (≥30% improvement in pain in 5 RCTs, ≥50% in 1 RCT) with duloxetine compared with placebo (RR 1.43, 95% CI 1.24 to 1.69, I^2=47%), a moderate magnitude effect. A ***long-term*** RCT (N=257) found no differences between duloxetine 40 mg/day versus 60 mg/day in pain scores at 52 weeks (**Appendix H**).[33] 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 (standardized mean difference [SMD] -0.31, 95% CI -0.42 to -0.20, I^2=0%) (Appendix I).[31,32,34-37] A ***long-term*** extension RCT (N=257) found no difference in function (BPI Interference) between duloxetine 40 mg/day

versus 60 mg/day at 52 weeks,[33] (Appendix I) which was similar to the results at 12 weeks in another RCT.[31,32,34-37] This is low strength of evidence.

Quality of Life

Meta-analysis of three trials finds that duloxetine improved quality of life to a moderate degree as measured on the EQ-5D (MD 0.20, 95% CI 0.07 to 0.33, I^2=0%, 0-1 scale) (Appendix I).[31,34,36] 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.[31] Three RCTs examined changes in depression.[31,35,36] Using the Hamilton Rating Scale for Depression (HAMD), two RCTs found improvement in depression scores with 120 mg/day of duloxetine ($p \leq 0.05$),[31,36] while the third RCT found no improvement with either dose.[35] A ***long-term*** RCT (N=257) found no difference in sleep at 52 weeks between duloxetine 40 mg/day and 60 mg/day (Appendix I).[33]

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).[63] A ***long-term*** RCT (N=257) found no differences between duloxetine daily doses of 40 mg versus 60 mg in pain scores, function (BPI interference), or sleep at 52 weeks (Appendix I).[33]

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 sclerosis[28] or with allodynia[53] (Appendix F). The trials utilized oral dronabinol solution (mean 13 mg/day) and THC/CBD oromucosal spray (100 mL per spray, up to 24 sprays/day). One trial was rated good quality[28] and the other fair quality.[53] 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.[60]

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 $p=0.14$[53]). 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).[53] 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).[28,53] This is low strength of evidence (Appendix H).

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 neuropathy[30] or postherpetic neuralgia[26,54]

(Appendix F). A 0.04% topical capsaicin patch was used as a control. One trial was good-quality[26] 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).[26,30,54] Meta-analysis of pain response (≥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/day with placebo in patients with HIV-related neuropathy.[39] 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 vs. Gabapentin

Three ***short-term*** head-to-head RCTs (N=433) compared pregabalin (75 mg/day to 300 mg/day) with gabapentin (300 mg/day to 2,400 mg/day)[55,56] or gabapentin enacarbil (1200 mg/day to 3600 mg/day)[57] and found no difference between the drugs in pain relief,[55-57] function (BPI Interference),[57] quality of life (SF-36 physical component summary [PCS]/MCS),[57] or sleep interference (Appendix F).[56,57] This is low strength of evidence. Neuropathic pain was related to diabetic peripheral neuropathy[56,57] and peripheral nervy injury.[55,56]

Cross-class comparisons

Gabapentin vs. Pregabalin vs. Duloxetine

One fair-quality, ***short-term*** trial (N=152) compared gabapentin, pregabalin, and duloxetine in participants with diabetic peripheral neuropathy (Appendix F).[56] Gabapentin dose ranged from 300 to 1800, pregabalin 75 to 300, and duloxetine 20 to 120 mg/day. 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*** treatment.

- ***Short-term*** treatment with anticonvulsants was associated with small improvements in pain and function (SOE: Moderate), but not quality of life (SOE: Low). Subgroup analyses showed no effect of specific drug, dose, or study quality on these results. Small decreases in anxiety 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-three good- or fair-quality RCTs (in 33 publications) involving 10,844 patients meeting inclusion criteria evaluated nonopioid drugs to treat chronic pain in fibromyalgia.[52,64-84] All studies used criteria defined in 1990 by the American College of Rheumatology to identify patients with fibromyalgia.[85] Fifteen were ***short-term*** trials (range 12 to 16 weeks), 6 ***intermediate-term*** (26 to 28 weeks), and 2 ***long-term*** (each 52 weeks). These included 12 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 trial[72] and one other[76] assessed the tricyclic antidepressant (TCA) amitriptyline; the 15 other trials of antidepressants in fibromyalgia all used SNRIs. Five trials assessed anticonvulsants, and one the Alzheimer's drug memantine. Three RCTs met criteria for good quality,[79-81] 20 fair,[52,64-78,82-84] and 1 poor[86] (Appendix F). The poor-quality study was deemed to have high risk of bias due to high attrition and unclear randomization and blinding methods, and is not synthesized with the other evidence. Twelve studies (52%) were conducted in the U.S.[64-66,68,74,75,77,78,83,84,87] Most were funded by industry (87%, 20 of 23).

The weighted mean age of enrolled patients across studies was 49 years, a mean of 94 percent were female, and a mean of 12 percent were nonwhite. Across the RCTs, the mean baseline pain severity (standardized to a 0-10 scale) was 6.6 (range 6.0 to 7.6). Duration of pain was reported in 8 of 23 studies; less than a year in three, while in the other 5 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: 7 were of milnacipran, 8 of duloxetine, and 1 of amitriptyline.[64,65,67-70,74-76,78,79,84,88-90] Most were ***short-term*** studies, 4 were ***intermediate-term***,[73,78,83,87] and 2 were ***long-term***.[71,74] Pain was reported in all studies, and function in all but one, with moderate-strength evidence for pooled comparisons of SNRI antidepressants to placebo. Ten studies reported quality of life, with low to moderate SOE for pooled results (Appendix I and Appendix H).

Pain

Short-term results from 11 trials showed a small reduction in pain with an SNRI antidepressant compared with placebo (0-10 scale, MD -0.60, 95% CI -0.81 to -0.45, I^2=28.2%).

Three studies showed similar ***intermediate-term*** results (0-10 scale, MD -0.70, 95% CI -1.03 to -0.37, 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% 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.

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.[64,65,67,69,73] Two trials[79,84] stratified results and found that patients without baseline depression had a better response to SNRI than to placebo. However, these 2 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)[76] 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 study[67] 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 -0.25, 95% CI -0.33 to -0.18, I^2=28.6%), 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%). 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 0.20, 95% CI 0.13 to 0.29, I^2=19.5%). ***Intermediate-term*** changes in the MCS reported in two trials were similar (SMD 0.20, 95% CI 0.03 to 0.39, 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 well-being. Subgroup analyses did not show effects of specific drug or dose on these results.

Other Outcomes

Short-term antidepressant treatment for fibromyalgia in improvement in depression symptoms, based on meta-analysis of nine RCTs of SNRIs duloxetine or milnacipran (SMD -0.19, 95% CI -0.28 to -0.13; I^2=13.8%).[64,65,67-70,75,79,84] Most trials used the Beck Depression Index (BDI) or BDI-II to assess symptoms; one reported the HAMD,[65] and one the FIQ depression subscale.[84] Seven trials also measured anxiety, using several different

instruments.[64,67-70,79,84] Meta-analysis did not show a statistically significant effect of SNRI antidepressants on anxiety, and there was substantial heterogeneity across studies (SMD -0.08, 95% CI -0.23 to 0.03, I^2=55.9%).

Dose Comparisons

Two fair-quality ***intermediate-*** or ***long-term*** studies compared different doses of milnacipran, and a third ***long-term*** study compared 60 mg and 120 mg/day 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/day or 200 mg/day of milnacipran.[87] 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/day and -29.1 for 200 mg/day), 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/day,[71] 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% 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/day did not find differences in effects on pain. Function improved slightly for patients taking 60 mg/day, while it deteriorated in those taking 120 mg/day (FIQ total score, range not reported [NR], change from baseline: -0.69 vs. 3.49, $p \leq 0.05$), however on a 0-100 scale this difference is below the threshold for a small magnitude of effect for this report[74] (low strength of evidence).

Anticonvulsants

Five ***short-term*** RCTs (in 6 publications, N=2,891) compared an anticonvulsant to placebo in patients with fibromyalgia.[66,77,80,82,91,92] One study met criteria for good quality,[80] with the remainder being fair quality. One trial used gabapentin,[66] and the remaining trials used pregabalin. Pain and function outcomes were reported in all studies, and the strength of this evidence was moderate; one study provided low-strength evidence on quality of life (Appendix I and Appendix H).

Pain

In the ***short-term***, anticonvulsants were associated with a small reduction in pain, based on meta-analysis of five RCTs (0-10 scale, MD -0.60, 95% CI -0.86 to -0.36, I^2=33.3%). The proportion responding to anticonvulsants was also higher (41% vs. 29%, RR 1.41, 95% CI 1.25 to 1.62, I^2=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. This is moderate strength of evidence. One of the five trials assessed baseline depression as a subgroup, but found no statistically significant interaction with treatment in effects on pain.[82]

Function

Function as measured by the FIQ (range 0-80 or 0-100) improved with anticonvulsant treatment across five ***short-term*** trials, but the difference compared with placebo was small (SMD -0.20, 95% CI -0.33 to -0.11, I^2=0%). Subgroup analyses did not show significant effects of specific drug, pregabalin dose, or study quality. This is moderate strength of evidence.

Quality of Life

One ***short-term*** study reported the effect of anticonvulsants on quality of life, a fair-quality trial comparing pregabalin to placebo in 745 fibromyalgia patients.[52] Results showed no change in the SF-36 (MCS or PCS) for any dose (300 mg, 450 mg, or 600 mg/day), or for all doses combined compared with placebo. This is low strength of evidence.

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 three 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 six 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).[81,93] This evidence is low strength.

Cross-class Comparisons

A fair-quality RCT (N=208) compared the tricyclic antidepressant amitriptyline, the muscle relaxant cyclobenzaprine, and placebo for six months in fibromyalgia.[72] Both ***short-term*** (3 month) and ***intermediate-term*** (6 month) results were reported. There were no differences at either time point for outcomes in pain, function, or a composite response measure including pain, sleep, fatigue, and global assessments. This is low strength evidence.

Osteoarthritis

Key Points:

- Oral nonsteroidal anti-inflammatory drugs (NSAIDs) improve 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. Evidence on topical diclofenac was mixed, with no effect on improvement in pain in the ***short-term***, a small increase in the pain response rate, and serious heterogeneity in function results (SOE Moderate for pain, quality of life (QoL), High for response and function).
- The serotonin and norepinephrine reuptake inhibitor (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 suggests that pain and function improve to a small degree at higher doses (3900 mg-4000 mg/day), 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-two fair- and good-quality RCTs (in 61 publications) involving 22,341 patients meeting inclusion criteria evaluated nonopioid drugs to treat chronic pain in osteoarthritis; 44 ***short-term*** (12 to 24 weeks), 7 ***intermediate-term*** (26 weeks), and 1 ***long-term*** (52 weeks). These included 41 placebo-controlled trials (7 of duloxetine, 4 of acetaminophen, 4 of topical diclofenac, and 26 of oral NSAIDs), 6 trials comparing multiple doses, 3 comparing different formulations of diclofenac (2 comparing oral and topical, 1 comparing oral formulations), 15 head-to-head trials comparing various NSAIDs, and 2 making cross-class comparisons (some trials included more than one of these categories). Fifteen RCTs met criteria for good quality,[94-107] 7 were poor quality,[108-114] and the remainder (37) were fair quality (Appendix G). Most studies were conducted in the U.S. (22 RCTs) and were funded by industry (87%).

Studies included patients with osteoarthritis, but with varying and often unclear criteria for establishing the diagnosis. Mean age of enrolled patients ranged from 58 to 72 (weighted mean 63 years), a weighted mean of 68 percent were female, and a weighted mean of 24 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 56 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-eight RCTs (in 30 publications; N=16,541) compared at least one NSAID versus placebo in patients with OA (5 had more than 2 treatment arms)[97,99-102,104,105,115-135] Fifteen included the selective cyclooxygenase (COX)-2 inhibitor celecoxib (100 mg to 400 mg/day), while 19 included non-selective NSAIDs (7 of naproxen 1000 mg/day, 5 of meloxicam 3.75 mg to 15 mg/day, 3 of ibuprofen 2400 mg/day, 3 of diclofenac 100 mg to 150 mg/day, and 1 of diclofenac submicron 70 mg and 105 mg/day). All of the RCTs evaluated pain at 12 to 13 weeks (***short-term***), with one also evaluating at 26 weeks (***intermediate-term***).[124] Pain and function outcomes were reported in all studies, but quality of life only in three.[119,125,135] The strength of evidence for NSAIDs on improvement in pain and quality of life is moderate, and for pain response and improvement in function is high.

Pain

In the ***short-term***, NSAIDs resulted in a small reduction in pain, based on meta-analysis of 27 RCTs (MD -0.71, 95% CI -0.82 to -0.61, I^2=27%, 0-10 scale) (Appendix I). Similarly, the proportion responding to NSAIDs was significantly greater than placebo (12 RCTs, 60% vs. 47%, RR 1.23, 95% CI 1.17 to 1.31, I^2=24%) (Appendix I). At ***intermediate-term*** followup, celecoxib 200 mg/day also resulted in a small improvement in pain (MD -0.60, 95% CI -1.01 to -0.19, 0-10 scale).[124] 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 -0.55, 95% CI -0.66 to -0.43, 0-10 scale).

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=22%), 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).[124] 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=0.044), but the magnitude of the effect was still in the range of a small effect (Table 5).

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 is 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.[136] There was not a meaningful change in the Mental Component Score (MD 0.61, 95% CI -0.50 to 1.79).

Table 5. NSAID subgroup analyses

Outcome	Variable	Subgroup	N Studies (sample size)	Effect Size (95% CI)	Interaction P-value
Pain Improvement	Pain location	Knee Hip Knee/Hip	14 (7,352) 3 (2,617) 9 (2,854)	MD -0.55 (-0.66 to -0.43) MD -0.88 (-1.12 to -0.62) MD -0.93 (-1.10 to -0.76)	0.002
Function	Study quality	Good Fair	9 (4,491) 19 (8,947)	SMD -0.26 (-0.33 to -0.18) SMD -0.35 (-0.41 to -0.30)	0.04

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

Other Outcomes

Sleep improved in the ***short-term*** in one study of celecoxib 200 mg/day (other arms included tramadol).[119] 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/day reported that subgroup analyses of age, gender, race, and ethnicity were consistent with the overall findings.[135] 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,[97,98] but two others not finding a linear relationship.[128,135] 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.[98,128] 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). Separate meta-analysis of two RCTs (N=399) comparing celecoxib 400 mg/day with celecoxib 200 mg/day did not find a difference between doses in improvement in pain (MD 0.36, 95% CI -0.07 to 0.80, I^2=0%) or function (MD 0.02, 95% CI -0.14 to 0.18).

Topical NSAIDs: Diclofenac

Four ***short-term*** trials (N=1,551) 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.[95,105,137,138] 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 only slightly greater improvement in pain than vehicle, not reaching the level of a small improvement defined for this report (4 RCTs, MD -0.50, 95% CI -0.88 to -0.12, I^2=0%). Based on meta-analysis of two RCTs, topical diclofenac resulted in a small magnitude of response to treatment, based on the OARSI criteria (68% vs. 45%, RR 1.28, 95% CI 1.09 to 1.58, I^2=0%; Appendix I).[137-139] 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%).[137] 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 versus 62 to 64 years), and somewhat lower function scores (38 versus 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 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,[101,115,140] two of topical versus oral diclofenac, and two of nabumetone versus naproxen provided data for meta-analyses. Nine RCTs compared one NSAID to another which could not be pooled in meta-analyses, with six ***short-term*** (N=2022),[98,127,141-144] two ***intermediate-term*** (N=921),[145,146] and one ***long-term*** (N=925).[147] 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 non-combinable 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/day, but no effect over meloxicam 7 mg or 15 mg/day.[98,127] 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/day) 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.[141,144] 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).[145,146] In the ***long-term***, one RCT found no significant differences between celecoxib and diclofenac at 12 months of treatment.[147]

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/day) 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).[127] Another RCT found no difference in improvement in function between meloxicam 7 mg or 15 mg/day and diclofenac, but diclofenac had a small improvement over the 3.75 mg/day dose of meloxicam.[98] 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).[145,146]

Antidepressants: SNRI's

Duloxetine

Duloxetine was the only antidepressant with studies in OA patients that met inclusion criteria. All six included studies (N=1,574, 9 publications) were ***short-term***.[96,107,148-152] Pain was reported in all studies, function in three, and quality of life in three, but none report 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).[96,107,148-150,152] 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% improvement for a definition of response. Subgroup analyses of pain location (knee versus hip or knee), dose (60 mg versus 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 -0.1, I^2=27%), using the WOMAC function subscale (3 RCTs), and the BPI Interference subscale (2 RCTs). Subgroup analyses of pain location (knee versus hip or knee), dose (60 mg versus 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 versus 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 ($p<0.001$).[149]

Other Outcomes

Sleep was improved with duloxetine 60 mg/day 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.[107,149] Changes in depression and anxiety scales were reported in one study, with no improvement over placebo seen.[96]

Subpopulations

Three studies reported subgroup analyses according to age, with one finding no effect of age,[149] 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.[96,107] Subgroup analyses of gender, race, and baseline pain scores were not significant.[96,149] 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 =1,237) and one ***intermediate-term*** study compared acetaminophen (1950 mg to 4000 mg/day) with placebo in patients with OA.[128,153-155] 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/day, 1950 mg/day, and placebo, respectively; p-value for 3900 mg/day versus placebo =0.012).[153] Comparisons of 1950 mg/day 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.[154]

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/day (WOMAC function subscale, LSM change from baseline -24.2, -19.0, and -18.2 for 3900 mg/day, 1950 mg/day, and placebo, respectively; p-value for 3900 mg/day versus placebo =0.016).[153] Comparisons of 1950 mg/day 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.[154]

Subpopulations

None of the four RCTs included 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.[128] 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.[111]

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.[128] A very small study of diclofenac 150 mg/day and acetaminophen 4000 mg/day found diclofenac to be superior

in both pain and function improvement.[128] 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/day (MD -2.7, 95% CI -3.5 to -1.9) and duloxetine 60 mg/day (-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.[106]

Inflammatory Arthritis

Key Points:

- In the ***short-term***, oral NSAIDs resulted in small improvements in pain severity, pain response, and function 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: Low). 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: Insufficient). 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)[156-187] evaluated nonopioid drugs to treat chronic pain due to inflammatory arthritis. One trial met criteria for good quality[156] and 19 were fair quality.[157-176] 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.[177-187] (Appendix G). The 20 good- and fair-quality RCTs included 7,654 patients, with 15 studies (in 16 publications) of rheumatoid arthritis (RA) (N=5,835)[158,159,161-171,173,175,176] and 5 studies of ankylosing spondylitis (AS) (N=1,819).[156,157,160,172,174] Nineteen trials evaluated various NSAIDs and one trial[165] evaluated a TCA drug. Sixteen trials (12 in RA; 4 in AS) were ***short-term*** (12 to 24 weeks); 3 trials in RA were ***intermediate-term*** (26 weeks); and 1 trial in AS was ***long-term*** (52 weeks). Eleven placebo-controlled trials (8 in RA; 3 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. Twelve trials included head-to-head comparisons of various NSAIDs: celecoxib vs. diclofenac; celecoxib vs. naproxen; diclofenac vs. etodolac; diclofenac vs. meloxicam; etodolac vs. naproxen; meloxicam vs. naproxen; and nabumetone vs. naproxen.

The good- and fair-quality studies were most often conducted in Europe (50%) and the U.S. (40%); 25 percent were conducted in 4 or more countries. Of the 14 good- and fair-quality trials that reported the funding source, all but one (93%) 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 63 percent (range 22% to 87%, 18 trials). The race of participants was reported in only six trials, with a weighted mean proportion of nonwhite participants of 12 percent (range 0.3% to 26%, 6 trials). The weighted mean baseline pain level 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 121 months (range 23 to 147 months, 15 trials). Complete descriptions of included study characteristics are in Appendix E. Results of meta-analyses, including forest plots and subgroups analyses, are in Appendix I.

Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

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).[156-164,167,168,171,173,176] Similarly, the proportion of patients responding to treatment with NSAIDs was significantly higher than for placebo, with a small combined effect size (46% vs. 33%, RR 1.46, 95% CI 1.32 to 1.68, 6 trials, Appendix I).[156-158,164,171,173,176] These two meta-analyses combined studies of celecoxib,[157,173,176] diclofenac,[163] etodolac,[167,168] meloxicam,[163] and naproxen.[156-158,164,171,173,176] 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/day 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).[164] At ***long-term*** followup in a single trial (N=365), meloxicam 15 to 22.5 mg/day 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).[160] The strength of evidence for NSAIDs on pain reduction and pain response in the ***intermediate-term*** 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 no difference for pain response, but a significant difference for reduction in pain. In this subgroup analysis, studies of patients with AS found a significantly greater reduction in pain (MD -2.02, 95% CI -2.96 to -1.07, I^2=0%, 0-10 scale) compared with studies of patients 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). In addition, comparisons between different doses of celecoxib (200 mg/day vs. 400 mg/day)[157,172-174] and meloxicam (7.5 mg/day vs. 15 mg/day vs. 22.5 mg/day)[160,163] found no meaningful differences between doses for pain reduction or pain response.

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,[157,173,176] diclofenac,[163] meloxicam,[163] and naproxen (Appendix I).[156-158,164,171,173,176] At ***intermediate-term*** followup in a single trial (N=563), naproxen 1000 mg/day resulted in a small improvement in function compared with placebo (MD -0.18, 95% CI -0.35 to -0.02, 0-3 scale).[164] At ***long-term*** followup in a single trial (N=365), meloxicam 15 to 22.5 mg/day did not improve function compared with placebo (MD 0.63, 95% CI 0.85 to 0.40, 0-40 scale).[160] 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/day vs. 200 mg/day),[157,172-174] and meloxicam (7.5 mg/day vs. 15 mg/day vs. 22.5 mg/day)[160,163] found no meaningful differences in function between doses.

Quality of Life

At ***short-term*** followup in one trial (N=55), naproxen 1000 mg/day 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).[156] 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/day, 400 mg/day, and 800 mg/day) and for naproxen 1000 mg/day.[173] 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/day and 800 mg/day) for the PCS (MD = 3.4 and 3.5, respectively, 0-100 scale) and one dose of celecoxib (400 mg/day) for the MCS (MD 3.5, 0-100 scale) were slightly higher than the 3-point MCID recommended for use with the SF-36,[136] 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***.[173] 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/day (MD 10.3, p<0.05) and small for celecoxib 200 mg/day, celecoxib 800 mg/day, and naproxen 1000 mg/day (MD 8.1, 7.5, and 8.4, respectively; p<0.05). Although each dose of celecoxib and naproxen was 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/day, which was not statistically significant. At ***long-term*** followup in another trial (N=365), meloxicam 15 mg/day and 22.5 mg/day were associated with large

improvements in sleep disturbance due to pain compared with placebo (MD -26% and -35%, respectively, p<0.05).[160]

Head-to-Head Comparisons of NSAIDs

Three ***short-term***, fair-quality RCTs of celecoxib versus diclofenac,[162,172,174] two of celecoxib versus naproxen,[157,173] and two of nabumetone versus naproxen[161,169] 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,[170] diclofenac versus meloxicam,[163] and etodolac versus naproxen,[159] and ***intermediate-term*** comparisons of meloxicam versus naproxen[175] and nabumetone versus naproxen.[166]

Pain

In ***short-term*** followup, no meaningful difference in pain improvement was found between any two NSAIDs, including: celecoxib versus diclofenac (3 trials),[162,172,174] celecoxib versus naproxen (2 trials),[157,173] diclofenac versus etodolac (1 trial),[170] diclofenac versus meloxicam (1 trial), [163] etodolac versus naproxen (1 trial),[159] and nabumetone versus naproxen (2 trials)[161,169] (Appendix I). In ***intermediate-term*** followup, no difference in pain improvement was found between meloxicam versus naproxen (1 trial) nor nabumetone versus naproxen (1 trial).[166,175] Similarly, in ***short-term*** followup, no difference was found in pain response between celecoxib versus diclofenac (3 trials)[162,172,174] or celecoxib versus naproxen (2 trials).[157,173] 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),[162,172,174] celecoxib versus naproxen (2 trials),[157,173] diclofenac versus etodolac (1 trial),[170] diclofenac versus meloxicam (1 trial), [163] and nabumetone versus naproxen (2 trials)[161,169] (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/day to 800 mg/day) and naproxen 1000 mg/day, as measured by the SF-36 PCS the MCS.[173] 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/day and placebo for pain improvement (MD 0.12, p=not significant, 0-4 scale).[165] 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 improvement in function did not meet the threshold for a small improvement, based on pooled analysis of three trials (SOE: Moderate).
- In the ***short-term***, in patients with low-back pain evidence on the desipramine (a TCA) and gabapentin was insufficient to draw conclusions, based on one RCT each.
- 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 involving 1,838 patients meeting inclusion criteria evaluated nonopioid drugs to treat chronic low back pain (Appendix E).[188-194] Six were ***short-term*** studies (12 to 14 weeks) and one was ***intermediate-term*** (6 months).[194] Six were placebo-controlled trials,[188-193] two of which compared multiple doses of desipramine and/or duloxetine, and one head-to-head trial compari*g* amitriptyline and pregabalin.[194] Two RCTs met criteria for good-quality,[191,194] and the other five RCTs were fair-quality. Two studies were conducted in the United States,[188,189] two studies were multinational,[192,193] and one each was conducted in Australia,[194] India,[190] and Japan.[191] Three studies were government-funded[188,189,194] and three were industry-funded;[191-193] one did not report the funding source.[190]

Mean age of enrolled patients ranged from 42 to 56 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 ranged from 5 to 7 on a 0-10 VAS.[190-193] In the remaining three trials, two reported baseline pain of 9 on a 0-20 VAS,[188,189] and one reported baseline pain of 40 on a 0-100 VAS.[194] 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,[191,193,194] and 42 on the Oswestry Disability Index (ODI) scale in one trial;[190] baseline function/disability was unclear or not reported in the remaining three trials.[188,189,192] Complete descriptions of included study characteristics are in Appendix E.

Antidepressants: SNRI's

Duloxetine

Duloxetine versus placebo was assessed in one good- and two fair-quality, ***short-term*** RCTs (N=1,263) (Appendix E).[191-193] Duloxetine dose ranged from 20 to 120 mg/day. 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).[191-193] 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/day 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.[192]

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). 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.[191-193] 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/day.[193] 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).[188] 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 ng/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 insufficeint to draw conclusons, due to study quality, unknwn consistency, and imprecison.

One good-quality, ***intermediate-term*** trial (N=146) comparing amitriptyline 25 mg/day 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).[194] 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/day with placebo in patients with radicular and non-radicular back pain (Appendix E).[189] 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 clinial global impression of change (CGI-C; 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 insufficeint to draw conclusons, due to study quality, unknwn consistency, and imprecison.

Cross-class Comparisons

Pregabalin versus amitriptyline

One ***short-term*** trial (N=200) compared pregabalin 600 mg/day versus amitriptyline 50 mg/day in patients with low back pain (Appendix E).[190] After 14 weeks, although both groups improved signficantly, 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 to75 mg/day 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,[195-197] but two were rated poor-quality due to unclear randomization processes, differences at baseline in patient characteristics, and lack of blinding.[196,197] One of these RCTs (N=41) compared pregabalin with placebo in patients with "chronic unilateral cervicogenic headache,"[196] and the other (N=53) compared TCAs (amitriptyline or nortriptyline) with placebo, stress management, or a combination in patients with "chronic tension-type headache".[197]

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."[195] Mean age of enrolled patients was 38 years, 56 percent were female and at baseline, mean 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 three 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.

KQ 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, SUD), 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-term***, antidepressants (SNRIs duloxetine and milnacipran, TCAs amitriptyline and desipramine) did not increase reports of SAEs, and differences were not found between drugs or most doses (SOE: Low). Antidepressants (mainly SNRIs duloxetine and milnacipran) led to moderate increases in risk of WAE in the ***short-*** and

intermediate term (SOE: Moderate). Increasing dose of duloxetine and desipramine may lead to greater 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/day resulted in lower risk than 120 mg/day (SOE: Low).
- TCA specific harms: amitriptyline led to a moderate increase in reports of dry mouth (SOE: Low). Other adverse events of interest were not reported or not different to placebo.

Detailed Assessment

Thirty-two good- or fair-quality placebo-controlled trials (in 43 publications)[31,32,34-37,63-65,67-69,71,73-76,78,79,83,84,88-90,94,107,149-152,165,188,191-195,198-203] involving 12,064 patients meeting inclusion criteria evaluated antidepressants to treat chronic pain; 27 were ***short-term*** and three ***intermediate-term*** studies.[73,78,83] The large majority of evidence was for SNRIs, either milnacipran or duloxetine, with 27 trials including 11,477 participants, with five RCTs of TCAs (N=587).[76,165,188,194,195] Four trials met criteria for good quality.[79,96,107,191] Fibromyalgia was the patient population in 13 trials, neuropathic pain in 6, osteoarthritis in 5, low back pain in 4, and one each in 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)

SAEs were infrequent, and meta-analysis of 20 ***short-term*** trials found no difference in events between patients treated with antidepressants (mainly SNRIs duloxetine and milnacipran) and those given placebo (1.8% vs. 1.9%, RR 0.92, 95% CI 0.67 to 1.26, I^2=0%). Subgroup analyses by pain population, study quality, drug class (SNRI versus TCA), specific drug, and dose comparison within a single drug (duloxetine or milnacipran) 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 evidence. Evidence on SAEs of TCAs was limited, with one trial of five reporting this outcome.

Meta-analysis of various doses of duloxetine in four ***short-term*** trials showed no difference in SAEs between 60 mg and 120 mg/day doses (2.4% vs. 2.6%, RR 0.91, 95% CI 0.36 to 2.26, I^2=0%). A single ***long-term*** trial comparing 40 mg and 60 mg/day of duloxetine found substantially higher rates for both doses than those seen in the ***short-term*** trials, but half as many SAEs with the lower dose (8.5% vs. 17%, RR 0.50, 95% CI 0.25 to 0.97). These findings are low strength of evidence. One ***intermediate-term*** study of milnacipran 100 mg vs. 200 mg/day[78] and a ***long-term*** study of duloxetine 60 mg vs. 120 mg/day[74] could not be pooled with other results; each found no difference in incidence of SAEs and were low strength of evidence. A small (N=175) ***short-term*** study of duloxetine 20 mg vs. 60 mg/day[192] was insufficient to draw conclusions due to imprecision and unknown consistency.

Withdrawals due to adverse events (WAEs)

There was a moderate increase in WAEs with antidepressants (mainly SNRIs duloxetine and milnacipran) in 27 ***short-term*** studies (15.3% vs. 7.5%, RR 1.97, 95% CI 1.70 to 2.30, I^2=17%), and in three ***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 evidence. Subgroup analyses of pain population, study quality, drug class (SNRIs versus TCAs), specific drug, or dose comparisons of a single drug (duloxetine or amitriptyline) did not significantly alter these results. A good-quality ***intermediate-term*** RCT in patients with chronic low back pain (N=146) compared 25 mg/day of amitriptyline to 1 mg/day benztropine mesylate as an active placebo, and was not combined with the placebo-controlled RCTs.[194] There was no difference in the incidence of WAEs between groups in this study (RR 1.03, 95% CI 0.43 to 2.44) and this evidence is low strength.

In evaluating the effect of dose, meta-analysis of five ***short-term*** trials of duloxetine 60 mg and 120 mg/day found a small decrease in WAEs with the lower dose (14% vs. 19%, RR 0.72, 95% CI 0.53 to 0.94, I^2=0%; Appendix I). This is low strength evidence. A single ***short-term*** RCT of desipramine, which based treatment on plasma concentrations of desipramine, found significant increases in risk of WAEs with increasing dose (18% low concentration, 35% medium concentration, 44% high concentration versus 4% with placebo).[188] Meta-analysis analysis of two ***intermediate-term*** trials did not show a statistically significant difference in WAEs between milnacipran doses of 100 mg and 200 mg/day (19% vs. 25%, RR 0.74, 95% CI 0.53 to 1.10, I^2=0%), although the analysis of milnacipran dose in our overall meta-analysis was significant (p=0.003). Because of this inconsistency, we consider this evidence insufficient to draw conclusions. Two ***long-term*** RCTs of duloxetine found no difference in incidence of WAEs with various doses of duloxetine.[33,74] These findings are low strength of evidence. A single small ***long-term*** RCT of milnacipran doses (100 mg, 150 mg, and 200 mg/day) was insufficient to draw conclusions.

Specific Adverse Events

SNRIs

Nausea

SNRI antidepressants duloxetine and milnacipran resulted in increased incidence of nausea. Meta-analysis of three RCTs, two ***short-term*** and one ***intermediate-term***, showed a moderate increase in incidence of nausea in patients treated with milnacipran compared with those given placebo (34% vs. 17%, RR 1.87, 95% CI 1.59 to 2.29, I^2=0%; Appendix I). Treatment with duloxetine was associated with a large increase in nausea based on meta-analysis of 18 trials (21% vs. 5.6%, RR 3.24, 95% CI 2.74 to 4.03, I^2=4%; Appendix I). This is moderate strength of evidence. Meta-analyses of four ***short-term*** trials comparing 20 mg, 60 mg, and 120 mg/day of duloxetine and meta-analysis of two ***intermediate-term*** trials comparing 100 mg/day and 200 mg/day of milnacipran did not show differences in incidence of nausea. Similarly, a single ***long-term*** RCT of duloxetine 40 mg and 60 mg/day did not find a difference in incidence of nausea (RR 1.08, 95% CI 0.53 to 2.17). These findings are low strength of evidence.

Sedation

Combining reports of sedation or somnolence in 16 RCTs (14 ***short-term***, 2 ***intermediate-term***; N = 6,039) of the SNRI duloxetine showed a large increased incidence of sedation compared with placebo (12% vs. 4.4%, RR 2.68, 95% CI 2.19 to 3.28, I^2=0%). This is moderate strength of evidence. Sedation was not reported with other antidepressants. Duloxetine given at

60 mg compared with 120 mg/day was associated with a moderate reduction in sedation, based on meta-analysis of four ***short-term*** trials (8.9% vs. 15%, RR 0.62, 95% CI 0.40 to 0.90, I^2=0%). One ***short-term*** trial of duloxetine 20 mg vs. 60 mg/day and a ***long-term*** trial of 40 mg vs. 60 mg/day found no difference in incidence of sedation. These findings are low strength of evidence.

Serotonin syndrome

We found no RCTs reporting episodes of serotonin syndrome.

TCAs

Dry Mouth

A moderate increase in the incidence of patients reporting dry mouth was found 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).[195] No other trial of a TCA reported dry mouth as an adverse event.

Serotonin syndrome

We found no RCTs reporting episodes of serotonin syndrome.

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 SAEs and WAEs (SOE: Low and Moderate, respectively). Pregabalin and gabapentin also led to small increased risk of WAEs, with pregabalin risk being greater with higher doses (SOE: Low).
- 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). The prodrug 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 for pregabalin, Low for gabapentin).
- While the incidence of hyponatremia was greater with oxcarbazepine than placebo, the difference was not significant (SOE: Low).

Detailed Assessment

Twenty-four RCTs provided evidence for harms in the ***short-term***: 17 RCTs provided information on SAEs, 24 RCTs provided data on WAEs, and all 24 RCTs provided evidence on specific adverse events. Three studies met criteria for being good-quality, the remainder were fair-quality. Seventeen trials were in patients with neuropathic pain, five in patients with fibromyalgia, and one each in patients with low back pain and sickle cell disease. Nineteen RCTs involved pregabalin, and two each involved gabapentin, the prodrug gabapentin enacarbil, and oxcarbazepine (one included both pregabalin and gabapentin enacarbil).[57] 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 (SAEs)

Meta-analysis of 17 RCTs (N=6,151) of patients with fibromyalgia (3 RCTs) and neuropathic pain (14 RCTs) did not find a significant increase in risk of having an SAE with an anticonvulsant (3.0% vs. 2.5%, RR 1.25, 95% CI 0.85 to 1.99, I^2=16%) in the ***short-term***. (Appendix I). Stratifying this analysis by specific drug indicated that only oxcarbazepine had a significantly increased, large magnitude, risk of SAEs (2 RCTs, 8.6% vs. 2.4%, RR 3.55, 95% CI 1.19 to 10.6). Subgroup analysis of drug dose did not alter the findings significantly. Stratifying the analyses by pain population, pregabalin was the only drug in the three fibromyalgia trials and pooled analysis limited to this population and drug did not find a significantly increased risk of SAEs (1.7% vs. 0.81%, RR 1.57, 95% CI 0.60 to 6.51, I^2=0%). In patients with neuropathic pain, there was no difference between active treatment and placebo in the likelihood of experiencing an SAE (3.6% vs. 2.9%, RR 1.20, 95% CI 0.77 to 2.06, I^2=16%). Evidence for pregabalin is moderate strength, evidence for gabapentin and oxcarbazepine is low strength.

Withdrawal due to adverse events (WAEs)

Meta-analysis of 24 RCTs (N=8,272) of patients treated for chronic pain in the ***short-term*** found a moderate increase in WAEs (16% vs. 7.3%, RR 1.88, 95% CI 1.57 to 2.24, I^2=11%) with anticonvulsants. These RCTs included four patient populations: neuropathic pain (17 RCTs), fibromyalgia (5 RCTs), low back pain (1 RCT), and sickle cell disease (1 RCT). Anticonvulsants led to significantly more WAEs in patients with fibromyalgia (5 RCTs, 21% vs. 8.7%, RR 2.09, 95% CI 1.66 to 2.68, I^2=0%) and neuropathic pain (17 RCTs, 13% vs. 6.2%, RR 1.79, 95% CI 1.40 to 2.34, I^2=28%). Stratifying this analysis by specific drug indicated increased WAEs with all of the drugs, with oxcarbazepine having the largest magnitude of effect (2 RCTs, 25.7% vs. 7.2%, RR 3.64, 95% CI 2.03 to 6.54, I^2=0%). The single studies of patients with low back pain (13% vs. 9.4%) and sickle cell disease (9.0% vs. 9.0%) did not result in significant differences in WAEs. In subgroup analyses, increasing pregabalin dose was significantly associated with greater withdrawal due to adverse events (interaction p=0.04, Table 6). Although the subgroup analyses were not significant for studies of oxcarbazepine or gabapentin, there were very few studies and the point estimates clearly increased with increasing doses of oxcarbazepine (RR's 1.61 with 600 mg/day, 3.41 with 1200 mg/day, and 6.07 with 1800 mg/day). No pattern was seen with gabapentin. Evidence for pregabalin is moderate strength, evidence for gabapentin and oxcarbazepine is low strength.

Table 6. Withdrawal due to adverse events (WAEs) according to pregabalin dose[a]

Outcome	Pregabalin Dose	N studies (sample size)	Relative Risk (95% CI)
Withdrawals due to Adverse Events (WAE)	150 mg/day	2 (375)	1.54 (0.57 to 4.25)
	300 mg/day	8 (2,513)	1.73 (1.36 to 2.21)
	450 mg/day	3 (1,113)	1.97 (1.46 to 2.67)
	600 mg/day	5 (1,469)	2.53 (1.80 to 3.72)
	150-600 mg/day	8 (2,050)	1.42 (1.00 to 2.16)
	300-450 mg/day	1 (501)	2.99 (1.37 to 6.52)
	300-600 mg/day	3 (577)	3.67 (2.05 to 6.66)
	450-600 mg/day	1 (375)	3.15 (0.33 to 30.0)

CI = confidence interval

[a] DerSimonian-Laird random effects model used, as the profile-likelihood models did not converge.

Specific Adverse Events

Nineteen RCTs provided data on included specific harms for pregabalin, two studies each provided data on gabapentin enacarbil, gabapentin, and oxcarbazepine (Appendix F). Risk of blurred vision, weight gain, and cognitive effects were increased with pregabalin and gabapentin (not reported in studies of oxcarbazepine); risk of sedation and peripheral edema were increased with pregabalin; risk of dizziness was increased with pregabalin, gabapentin enacarbil, and gabapentin. Hyponatremia was reported more frequently with oxcarbazepine than placebo, but the difference was not statistically significant; neutropenia was not reported. However, there were few studies of anticonvulsants other than pregabalin, and the strength of evidence varied accordingly (Table 7).

Table 7. Specific harms by anticonvulsant drug

Specific Harms	Drug N studies (n patients)	Incidence (Drug vs. Placebo)	Magnitude of Effect Relative Risk (95% CI)	SOE
Blurred vision	Pregabalin 7 (3,266)	6.5% vs. 1.4%	**Large 4.15 (2.17 to 7.95)**	Moderate
	Gabapentin enacarbil 2 (725)	2.5% vs. 2.3%	No significant effect 1.28 (0.11 to 15.4)	Low
	Gabapentin 2 (258)	18.5% vs. 3.1%	**Large 5.83 (2.11 to 16.1)**	Low
Dizziness	Pregabalin 19 (6,883)	27.8% vs. 7.2%	**Large 3.46 (3.03 to 3.96)**	Moderate
	Gabapentin enacarbil 2 (725)	19.2% vs. 9.8%	**Moderate 1.82 (1.17 to 2.82)**	Low
	Gabapentin 2 (258)	33.1% vs. 16.4%	**Moderate 1.93 (1.22 to 3.06)**	Low
Peripheral edema	Pregabalin 17 (6,344)	9.9% vs. 4.4%	**Large 2.54 (1.87 to 3.45)**	Moderate
	Gabapentin enacarbil 2 (725)	5.9% vs. 4.7%	No significant effect 1.25 (0.62 to 2.51)	Low
	Gabapentin 1 (150)	16.0% vs. 8.0%	No significant effect 2.00 (0.79 to 5.05)	Insufficient
Weight gain	Pregabalin 15 (5,851)	10.5% vs. 1.9%	**Large 4.56 (3.28 to 6.32)**	Moderate
	Gabapentin enacarbil 2 (725)	3.5% vs. 0.9%	No significant effect 3.69 (0.86 to 15.8)	Low
	Gabapentin 2 (258)	9.2% vs. 0.8%	**Large 7.66 (1.42 to 41.2)**	Low
Cognitive effects	Pregabalin 8 (3,761)	5.1% vs. 1.2%	**Large 3.56 (2.09 to 6.08)**	Moderate
	Gabapentin enacarbil 1 (354)	1.7% vs. 1.7%	No significant effect 1.03 (0.19 to 5.52)	Low

Specific Harms	Drug N studies (n patients)	Incidence (Drug vs. Placebo)	Magnitude of Effect Relative Risk (95% CI)	SOE
	Gabapentin 1 (208)	16.4% vs. 0.6%	**Large** **25.0 (3.25 to 193.1)**	Low
Sedation	Pregabalin 18 (6,813)	18.5% vs. 5.8%	**Large** **3.15 (2.65 to 3.73)**	Moderate
	Gabapentin enacarbil 2 (725)	10.8% vs. 6.0%	No significant effect 1.69 (0.95 to 3.02)	Low
	Gabapentin 2 (258)	30.0% vs. 10.9%	No significant effect 3.00 (0.92 to 9.77)	Low
	Oxcarbazepine 2 (490)	9.0% vs. 6.6%	No significant effect 1.97 (0.16 to 24.1)	Low
Hyponatremia	Oxcarbazepine 1 (344)	2.4% vs. 0.0%	No significant effect 4.57 (0.26 to 80.3)	Low

CI = confidence interval; SOE = strength of evidence; vs. = versus

NSAIDs

Key Points

- In the ***short-term***, NSAIDs led to a small increase in WAEs, specifically ibuprofen (large increase), diclofenac (moderate increase) and naproxen (small increase) (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 (CV) 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-term***, there was not a difference between drugs in CV events (SOE: Moderate).
- In the ***short-term***, NSAIDs led to moderate (diclofenac), and large (ibuprofen, naproxen) increased risk of serious upper gastrointestinal (GI) events (largely bleeding), particularly in the first 6 months of treatment (SOE: Moderate). Evidence on celecoxib versus nonselective NSAIDs was mixed and inconclusive.
- 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-five RCTs (in 118 publications) and three systematic reviews (SR's)[204-206] provided evidence on harms of NSAIDs. Thirteen trials met criteria for good quality,[95,97-105,156,207-211] 21 were poor quality,[108-114,177-187,212-218] and the remainder (61) were fair quality[115-128,130-135,137,138,140-147,157,158,160-164,166,167,169-176,219-242] (Appendix G). 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 are not synthesized with the other evidence. Of the good- and fair-quality RCTs involving 88,733 patients, 58 were ***short-term*** (12 to 24 weeks), 11 were ***intermediate-term*** (26 weeks), and 5 ***long-term*** (52 to 156 weeks). These included 45 placebo-controlled trials (17 of celecoxib 100 to 400 mg/day, 7 of diclofenac 70 to 150 mg/day, 5 of ibuprofen 2400 mg/day, 4 of meloxicam 3.75 to 22.5 mg/day, 15 of naproxen 1000 mg/day, and 4 of topical diclofenac 1%-1.5%), 11 comparing various doses of a single NSAID, and 35 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 (25) and were funded by industry (84%). Mean age of enrolled patients ranged from 30 to 72 year (weighted mean 61.5 years), 67 percent were female, and 17 percent were nonwhite. Two trials were conducted in older adults with mean age of 71 and 72 years.[143,147]

Two included SRs were good quality, [204,205] one evaluated CV and serious GI harms using a mix of individual patient data (IPD) and published tabular data meta-analysis of 639 RCTs of at least 4-weeks duration published through 2001.[204] The other good-quality SR evaluated celecoxib in patients with OA, and included analyses of harms versus placebo and other NSIADs.[205] The fair-quality SR evaluating hepatic harms of NSAIDs included 64 RCTs of patients with OA or RA with duration of at least 4-weeks, published through 2004.[206]

Adverse events for NSAIDs selected for this review were WAE, SAEs, CV events (CV mortality, nonfatal myocardial infarction [MI], nonfatal stroke), serious GI events such as GI 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 (SAEs)

Based on meta-analysis of 32 ***short-term*** RCTs (N=3,986), there was no increased risk of overall SAEs with NSAIDs (RR 0.97, 95% CI 0.80 to 1.25, 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 not statically significant and analysis for interaction was also not statistically significant. This is low strength of evidence. A recent Cochrane review of celecoxib 200 mg/day 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.[205]

Withdrawals due to adverse events (WAEs)

Based on meta-analysis of 51 ***short-term*** RCTs (N=21,766), WAEs were increased to a small degree with NSAIDs (RR 1.44, 95% CI 1.24 to 1.67, I^2=44%; 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 1.76, 95% CI 1.19 to 2.82), a large increase with ibuprofen (5 RCTs, RR 2.06, 95% CI 1.52 to 2.77), and a small increase with naproxen (14 RCTs, RR 1.48, 95% CI 1.21 to1.82), while celecoxib (16 RCTs, RR 1.11, 95% CI 0.84 to 1.45) and meloxicam (2 RCTs, RR 1.12, 95% CI 0.19 to 5.77) had no clear increased risk (p-value for interaction=0.00). A recent Cochrane review of celecoxib 200 mg/day 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 WAEs (rated moderate quality evidence by the authors).

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 SR of 639 RCTs evaluated cardiovascular harms using a combination of individual patient data and standard meta-analysis.[204] 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 with 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 risks[204]

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; RR = risk ratio

[a]Nonfatal myocardial infarction (MI), coronary death, MI or chronic heart failure death, nonfatal stroke, stroke death, any stroke, other vascular death

[b]Nonfatal MI, coronary death, MI or CHD death

[c]99% CI calculated due to multiple comparisons

A recent Cochrane review of celecoxib 200 mg/day 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), did not find significant increased risk of cardiovascular events with celecoxib versus placebo, or nonselective NSAIDs.[205] This evidence was rated very low quality by the review authors.

In the ***intermediate-term***, a large, good-quality RCT (N=24,081) evaluated cardiovascular harms in patients treated for OA or RA with celecoxib (mean 209 mg/day), ibuprofen (mean 2045 mg/day), and naproxen (mean 852 mg/day).[231] 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. Evidence on cardiovascular harms of NSAIDs is moderate strength.

Serious gastrointestinal (GI) adverse events

A good-quality SR of 639 RCTs using a combination of individual patient data and standard meta-analysis found increased risk of serious GI events with NSAIDs in the ***short-term***.[204] The analyses combined data on four selective COX-2 inhibitor drugs ("coxibs"), although the authors report that their analyses found no evidence of a difference in effect according to the specific coxib used. This analysis found moderate to large increased risk of serious upper GI harms (defined as perforation, obstruction, or bleeding) with NSAIDs: (rate ratios [95% CI]) coxibs 1.81 (1.17 to 2.81); diclofenac 1.89 (1.16 to 3.09), ibuprofen 3.97 (2.22 to 7.10), and naproxen 4.22 (2.71 to 6.56) compared with placebo. It is noted that most of these complications were GI bleeds, that 2% were fatal, and that the findings were not affected by lower or higher risk at baseline for GI events. The risk was greater in the first 6 months (rate ratio [99% CI]) for coxibs 2.55 (1.49 to 4.35), diclofenac 3.93 (2.16 to 7.13), ibuprofen 5.73 (3.24 to 10.14), and naproxen 6.31 (3.81 to 10.44). Our meta-analyses of 12 RCTs meeting eligibility for this review are mostly

consistent with these findings (Table 9), with the exception of the finding on coxibs. Our analysis limited to celecoxib (200 mg/day, 3 RCTs), and did not find an increased risk of GI events in the ***short-term***. The findings for other NSAIDs were similar to the IPD meta-analysis findings, except that our estimate for naproxen was lower than the IPD analysis estimate. In our analysis the GI events were peptic ulcer bleeds or GI hemorrhage. Subgroup analysis did not indicate a difference based on the patient having OA or RA. This evidence is moderate strength.

Comparing the selective COX-2 inhibitor celecoxib with nonselective NSAIDs as a group, evidence is mixed. Meta-analysis of three celecoxib versus placebo RCTs (N=1877) resulted in a nonsignificant risk of serious GI events (8% vs. 7%, RR 1.02, 95% CI 0.47 to 1.56, 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 GI events (13% vs. 3%, RR 4.29, 95% CI 2.75 to 6.93, I^2=46%), suggesting increased risk with nonselective NSAIDs. These estimates were significantly different to each other (p-value for interaction <0.001). A recent Cochrane review analyzed four RCTs (N=1,755) directly comparing celecoxib versus any nonselective NSAID in patients with OA with GI perforation, obstruction, or bleeding.[205] Their analysis found no difference between celecoxib and nonselective NSAIDs or placebo (Peto Odds Ratio 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. Because the evidence is conflicting, it is insufficient to draw conclusions about the risk of serious GI events with celecoxib versus nonselective NSAIDs.

Table 9. Risk of serious gastrointestinal events with NSAIDs versus placebo

Drug	Meta-analysis of studies eligible for this review Relative Risk (95% CI, I^2) N RCTs, N Patients	Individual Patient Data Meta-Analysis[204] Relative Risk (95% CI)
Coxibs	1.02 (0.47 to 1.56, I^2=0%) 3 RCTs, N=1877	1.81 (1.17 to 2.81)
Diclofenac	3.8 (1.21 to 9.11.I^2=0%) 2 RCTs, N=780,	1.89 (1.16 to 3.09)
Ibuprofen	3.80 (2.69 to 5.37.I^2=0%) 3 RCTs, N=1614,	3.97 (2.22 to 7.10)
Meloxicam	1.65 (0.19 to 14.04, I^2=NA) 1 RCT, N=713	--
Naproxen	2.62 (0.68 to 9.75, I^2=0%) 3 RCTs, N=1341	4.22 (2.71 to 6.56)
Non-selective (combined)	4.29 (2.75 to 6.93, I^2=46%) 9 RCTs, N=4,448	--

CI = confidence interval; RCT = randomized controlled trial

Hepatic

A fair-quality SR 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.[206] This SR 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/day) 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 0.00% (95% CI 0.00% to 0.08%) with placebo. One liver-related hospitalization and one liver-related death occurred, both with naproxen. A more recent SR with no criteria for study duration or population, but a composite outcome for hepatic injury came to similar findings.[243] This evidence is low strength.

Renal

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

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 small 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, SUD).

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***.[153-155] 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 2 trials, each of which had a mean proportion of nonwhite participants of 18 percent.[153,155] The strength of evidence for all outcomes was low.

Serious adverse events (SAEs)

At ***short-term*** followup, meta-analysis of two RCTs (N=1023) found a higher incidence of SAEs with acetaminophen than placebo, an effect that was not statistically significant (2.4% vs. 0.9%, RR 2.58, 95% CI 0.85 to 7.79, I^2=0%).[153,155] One trial (N=318) found no meaningful difference in SAEs between 1950 mg/day versus 3900 mg/day of acetaminophen (1.9% vs. 1.9%, RR 1.01, 95% CI 0.21 to 4.94).[153] 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).[154]

Withdrawals due to adverse event (WAEs)

Acetaminophen did not result in an increase in WAEs compared with placebo in the ***short***- (2 RCTs, N=1,023) or ***intermediate-term*** (1 RCT, N=212). At ***short-term*** followup, meta-analysis of two RCTs (N=1023) 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%).[153,155] One trial (N=318) found no meaningful difference in WAEs between 1950 mg/day and 3900 mg/day of acetaminophen (6.3% vs. 5.0%, RR 1.27, 95% CI 0.51 to 3.12).[153] 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 0.57 to 2.92).[154]

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).[26,30,54] 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.[54] One trial was rated as good-quality[26] and two were rated as fair-quality.[30,54] 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 is moderate; evidence for dose comparisons is low strength.

Serious Adverse events (SAEs)

At ***short-term*** followup, meta-analysis of two RCTs (N=557) found a greater proportion of SAEs reported in patients treated with capsaicin patch compared with placebo; an effect that was not statistically significant (5.5% vs. 2.4%, RR 1.90, 95% CI 0.58 to 13.88).[26,54] 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).[30]

Withdrawals due to adverse event (WAEs)

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 0.13 to 8.45, 2 trials).[26,30] 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).[30]

Specific adverse events

Based on meta-analysis of three ***short-term*** RCTs, capsaicin patch resulted in a small increased risk of erythema (59% vs. 45%, RR 1.30, 95% CI 1.30 to 1.67, I^2=0%) and a large increased risk of pain (62% vs. 26%, RR 2.27, 95% CI 1.81 to 2.84, I^2=0%, 3 trials) at the application site. This evidence is moderate strength. There was not a difference between groups in pruritus (6% vs. 3%, RR 1.70, 95% CI 0.93 to 3.36, I^2=0%, 3 trials).[26,30,54] This evidence is low strength.

Cannabis

Cannabis (including derivatives and synthetic cannabinoids) was compared with placebo in two ***short-term*** trials (N=486)[28,53] (Appendix F). The trials utilized oral dronabinol solution (mean 13 mg/day) and THC/CBD oromucosal spray (100 mL per spray, up to 24 sprays/day). One trial was rated good-quality[28] and the other fair-quality.[53] 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.[60] 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 (17.5% vs. 8.5%, calculated RR 4.70, 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 or 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).[53] The strength of this evidence is low. Other adverse events of interest were not reported (cognitive effects, misuse, addiction, SUD).

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.[111] This evidence is insufficient to draw conclusions.

Skeletal Muscle Relaxants

A fair-quality, ***short-term*** (6-month) RCT of fibromyalgia patients (N=208) compared amitriptyline, the skeletal muscle relaxant cyclobenzaprine, and placebo.[72] 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.[39,81] 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.[39]A good-quality, ***intermediate-term*** (6-months) 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 and effect size definitions are summarized in Tables 10 to 20 and in Appendix H (the Strength of Evidence tables). 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, small improvements in function, and 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, but no improvement in pain response. 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 improve 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. Evidence on topical diclofenac was inconclusive. The SNRI antidepressant duloxetine resulted in moderate effects on pain improvement and response, and small effects on 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 is inconsistent. Evidence on intermediate- and long-term outcomes is 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 (CV) 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 CV events between drugs. NSAIDs led to moderate to large increased risk of serious upper gastrointestinal (GI) 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 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 [SUD]).

Table 10. Definitions of effect sizes

Small effect	• 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	• MD >1 to 2 points on a 0 to10-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	• MD >2 points on a 0 to10-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

Table 11. KQ1 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	**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
Neuropathic Pain	Duloxetine vs. Placebo	Small ++	No evidence	No evidence	Small +	No evidence	No evidence	Moderate ++
Fibromyalgia	Duloxetine / Milnacipran vs. Placebo	Small ++	Small ++	No evidence	Small ++	None ++	MCS: Small ++ PCS: None ++	MCS: Small ++ PCS: None +
	Duloxetine vs. Duloxetine	No evidence	No evidence	None +	No evidence	No evidence	None +	No evidence
	Milnacipran vs. Milnacipran	No evidence	Insufficient	None +	No evidence	Insufficient	None +	No evidence
Osteoarthritis	Duloxetine vs. Placebo	Small +++	No evidence	No evidence	Small +++	No evidence	No evidence	Small +++
Low Back Pain	Duloxetine vs. Placebo	Small ++	No evidence	No evidence	None ++	No evidence	No evidence	None ++

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 12. KQ2 Harms and Adverse Events of Nonopioid Drugs for Chronic Pain: Harms of antidepressants versus placebo

Types of Adverse Events	**Milnacipran** Short- to intermediate-term Effect Size SOE	**Duloxetine** Short- to intermediate-term Effect Size SOE	**Amitriptyline** Short-term Effect Size SOE	**Amitriptyline** Intermediate-term Effect Size SOE
WAE	Moderate ++	Moderate ++	None +	None +
SAE	None +	None +	No evidence	No evidence
Nausea	Moderate ++	Large ++	NA	NA
Sedation	None +	Large ++	NA	NA
Serotonin Syndrome	No evidence	No evidence	No evidence	No evidence
Dry mouth	NA	NA	Moderate +	None +
Cardiac Rhythm Abnormalities	NA	NA	No evidence	No evidence
Urinary Retention	NA	NA	No evidence	No evidence

NA = not applicable (i.e., specific AE 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 13. KQ2 Harms and Adverse Events of Nonopioid Drugs for Chronic Pain: Harms of antidepressant dose comparisons

Types of Adverse Events	**Milnacipran 100 vs. 200 mg/day** Intermediate-term Effect Size SOE	**Duloxetine 20 vs. 60 mg/day** Short-term Effect Size SOE	**Duloxetine 60 vs. 120 mg/day** Short-term Effect Size SOE	**Duloxetine 40 vs. 60 mg/day** Long-term Effect Size SOE	**Duloxetine 60 vs. 120 mg/day** Long-term Effect Size SOE
WAE	None +	None +	Small reduction +	None +	None +
SAE	None +	Insufficient	None +	Moderate reduction +	None +
Nausea	None +	None +	None +	None +	No evidence
Sedation	No evidence	None +	Moderate reduction +	None +	No evidence
Serotonin Syndrome	No evidence	No evidence	No evidence	No evidence	No evidence

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 14. KQ1 Effectiveness and Comparative Effectiveness of Nonopioid Drugs for Chronic Pain: 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	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 15. KQ2 Harms and Adverse Events of Nonopioid Drugs for Chronic Pain: Harms of anticonvulsants versus placebo and active comparator

Types of Adverse Events	**Pregabalin** Short-term Effect Size SOE	**Gabapentin enacarbil**[a] Short-term Effect Size SOE	**Gabapentin** Short-term Effect Size SOE	**Pregabalin vs. gabapentin enacarbil** Short-term Effect Size SOE	**Oxcarbazepine** Short-term Effect Size SOE
WAE	Moderate ++	Small +	Moderate +	Moderate +	Large +
SAE	None ++	None +	No evidence	No evidence	Large +
Blurred Vision	Large ++	None +	Large ++	No evidence	NA
Cognitive Effects	Large ++	None +	Large +	No evidence	No evidence
Dizziness	Large +	Moderate +	Moderate +	No evidence	NA
Peripheral Edema	Large ++	None +	Insufficient	No evidence	NA
Sedation	Large ++	Moderate +	Large +	No evidence	Moderate +
Weight Gain	Large ++	None +	Large +	No evidence	NA
Hyponatremia	NA	NA	NA	NA	None +

NA = not applicable (i.e., specific AE 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
[a] Gabapentin enacarbil is a prodrug of gabapentin

Table 16. KQ1 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	None ++	No evidence	No evidence	None +	No evidence	No evidence	No evidence
Inflammatory Arthritis	NSAID vs. Placebo	Small ++	Small +	Large +	Small ++	Small +	None +	Insufficient
	Celecoxib vs. Celecoxib	None ++	No evidence	No evidence	None +	No evidence	No evidence	No evidence
	Meloxicam vs. Meloxicam	None +	No evidence	None +	None +	No evidence	None +	None +
	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 17. KQ2 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	**Celecoxib** Short-term Effect Size SOE	**Diclofenac** Short-term Effect Size SOE	**Ibuprofen** Short-term Effect Size SOE	**Naproxen** Short-term Effect Size SOE	**Celecoxib vs. nsNSAID** Intermediate-term Effect Size SOE
WAE	Small-Large ++	None ++	Moderate ++	Large ++	Small ++	None ++
SAE	None +	None +	None +	None +	None +	None +
CV Events	None ++	None ++	Small ++	None ++	None ++	None ++
GI Events	None ++	None ++	None ++	None ++	None ++	Insufficient
Liver Dysfunction	None +	None +	Large +	None +	Large +	None +

CV = cardiovascular; GI = gastrointestinal; 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 18. KQ1 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
Neuropathic Pain	Capsaicin Patch	None ++	No evidence	No evidence	No evidence	No evidence
Neuropathic Pain	Cannabis	None +	No evidence	None +	No evidence	None +
Fibromyalgia	Memantine	Moderate +	Moderate +	Moderate +	Moderate +	Moderate +
Fibromyalgia	Cyclobenzaprine	No evidence	None +	No evidence	Insufficient	No evidence
Osteoarthritis	Acetaminophen	None +	None +	None +	None +	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 19. KQ2 Harms and Adverse Events of Nonopioid Drugs for Chronic Pain: SAE and WAEs of other drugs versus placebo and active comparator

Types of Adverse Events	**Capsaicin** Short-term Effect Size SOE	**Capsaicin 60-min vs. 30-min** Short-term Effect Size SOE	**Dronabinol** Short-term Effect Size SOE	**THC + CBD** Short-term Effect Size SOE
WAE	None ++	None +	None +	Large +
SAE	None ++	Moderate +	None +	None +

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

Table 20. KQ2 Harms and Adverse Events of Nonopioid Drugs for Chronic Pain: Specific harms of cannabis versus placebo

Types of Adverse Events	**Dronabinol** Short-term Effect Size SOE	**THC + CBD** Short-term Effect Size SOE
Cognitive Effects	No evidence	No evidence
Hyperemesis	No evidence	No evidence
Nausea	None +	Large +
Sedation	Insufficient	No evidence
Dizziness	Large +	Large +

CBD = cannabidiol; SOE = strength of evidence; THC = tetrahydrocannabinol
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.[244] 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, on 0-10 scale).[245] 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).[246] 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.[247,248]

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 (FDA) warnings, drug information texts). However, as Table 21 below indicates, our analyses on adverse events are consistent with these other sources.

Table 21, below, 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 21. 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
	TCAs	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[249]
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%[250]
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.[251,252]
Other	**Acetaminophen**	Hepatotoxicity	Not reported in included RCTs	Increased risk with chronic use of >3gms/day, effects often occur early in treatment; dose-adjustment if hepatic or renal dysfunction[253,254]
	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[255]
	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,[256,257] 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).[258] 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.[259]

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 female, 34 percent nonwhite, mean baseline pain of 6 to 7 (on a 0-10 scale), and a duration of pain for 4 years. Fibromyalgia patients were younger, mean 49 years, most (94%) were female, and only 12 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 3 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 153 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.[247,248] 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 Decisionmaking

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.[13,260] 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 health care 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 21 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 SUD, or withdrawal symptoms associated with gabapentin or pregabalin, non-liver related harms of acetaminophen, and harms of drugs in older adults found in studies in other indications (not chronic pain).[261-264] The effects of co-prescribing gabapentin with opioids is not within the scope of this report, but is addressed in the related report on opioid use in chronic pain.[247] 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 U.S., as identified using Center for Medicare & Medicaid Services (CMS) 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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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	Center for Disease Control and Prevention
CER	Comparative Effectiveness Review
CGI	Clinical Global Impressions
cGRP	calcitonin Gene-Related Peptide
CI	Confidence Interval
CMS	Center for Medicare & Medicaid Services
CONSORT	Consolidated Standards of Reporting Trials
COX-2	Cyclooxygenase-2
CV	Cardiovascular
DDS	Descriptor Differential Scale
DMARD	Disease-Modifying Atirheumatic 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

Acronym or Abbreviation	Definition
MHAQ	Modified Health Assessment Questionnaire
MI	Myocardial Infarction
NA	Not Applicable
NMDA	*N*-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