Comparative Effectiveness Review
Number 228

Nonopioid Pharmacologic Treatments for Chronic Pain

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 United States live with chronic pain, garnering an estimated $560 billion in annual healthcare costs[1,2] and contributing to the economic burden on the healthcare system.[2] Given the complexity of treating chronic pain and concerns regarding the safety and long-term effectiveness of opioids, there have been multiple initiatives in recent years to improve the evidence available to clinicians and patients for making treatment decisions. These initiatives, along with the recent publication of the evidence-based guideline on opioid use for chronic pain by the Centers for Disease Control and Prevention,[3] have prompted additional primary research on alternatives to opioids in managing chronic pain. There is a real need to fully understand the benefits and harms of nonopioid pharmacologic treatments for chronic pain. The most common forms of nonopioid pharmacologic treatment for pain are nonsteroidal anti-

Purpose of Review

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

Key Messages

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

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inflammatory drugs (NSAIDs), acetaminophen, topical formulations such as capsaicin, and drugs used for other conditions such as anticonvulsants and antidepressants that can be implemented for pain moderation. Evidence is needed on common chronic pain conditions, including neuropathic pain, fibromyalgia, inflammatory arthritis (e.g., rheumatoid arthritis), osteoarthritis, low back pain, chronic headache, and sickle cell disease, comparing nonopioid drugs to placebo, to each other, and comparing different doses and with adequate durations of treatment to reflect real-life situations.

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

Scope and Key Questions

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

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

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

Methods

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

Literature Search Strategy

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

Inclusion and Exclusion Criteria and Study Selection

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

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

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

Assessment of Methodological Risk of Bias of Individual Studies

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

Data Abstraction and Data Synthesis

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

We preferentially abstracted pain assessed with the visual analog scale (VAS) or numerical rating scale (NRS) on a scale of 0 to 10 or 0 to 100 over other pain assessments (e.g., Western Ontario and McMaster Universities Osteoarthritis Index pain subscale). Primary pain response was defined as ≥30 percent improvement (reduction) in pain score. Secondary pain response criteria included >30 percent improvement

(e.g., ≥50% improvement), condition-specific composite measure (e.g., American College of Rheumatology 20 criteria [ACR20], Assessment in Spondyloarthritis International Society 20 criteria [ASAS20]), and improvement in physician's clinical global impression of change. For quality of life outcome, we preferentially abstracted the EuroQoL-5 Dimensions (EQ-5D) over Short Form-36 (SF-36) physical and mental components summary scores (PCS and MCS), and synthesized the two scales separately.

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

Strength of the Body of Evidence

The strength of evidence (SOE) for each KQ was rated for each clinical outcome using the approach described in the AHRQ Methods Guide.[4] To ensure consistency and validity of the evaluation, the grades were reviewed by a second reviewer. The domains assessed were study limitations (low, medium, or high), consistency (consistent, inconsistent, or unknown/not applicable), directness (direct or indirect), precision (precise or imprecise), and publication bias (suspected or undetected). The SOE was assigned an overall grade of high, moderate, low, or insufficient (Table A), reflecting our confidence in the effect estimates (Table B) and whether the findings are stable. Evidence is found to be insufficient to draw conclusions when we have no evidence available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Table A. Description of the strength of evidence grades

Strength of Evidence	Description
High	Very confident that the effect estimate lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. Findings are stable, i.e., inclusion of additional studies would not change the conclusions.
Moderate	Moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	Limited confidence that the effect estimate lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies. Additional evidence is needed before concluding that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	No confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

Table B. Definitions of effect sizes

Effect Size	Definition
Small effect	• 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 Task Order Officer and an EPC Associate Editor also provided comments and editorial review. Following this, the peer-reviewed draft report was posted on the AHRQ website for 4 weeks for public comment.

Results

Results for efficacy are shown by KQ and then by condition. Harms results are organized by drug class. Search results and selection of studies are summarized in the literature flow diagram (Figure 2 of the full report). After dual review of full-text articles, 184 RCTs (in 217 publications) were included in this review. In addition, we identified 5 systematic reviews that included 47 trials included in this review. Overall, 30 trials were rated poor quality, 129 fair quality, and 25 good quality (Appendix G of the full report). Of the good- and fair-quality trials, 128 were classified as short duration (3 months to <6 months), 18 intermediate duration (6 months to <1 year), and 9 were long duration (≥1 year). We included 32 RCTs in neuropathic pain, 26 RCTs in fibromyalgia, 59 RCTs in osteoarthritis, 21 RCTs in inflammatory arthritis, 7 RCTs in low back pain, and 1 trial each in chronic headache and sickle cell disease. An additional 7 trials of mixed osteoarthritis and inflammatory arthritis patients were included for harms outcomes. Most study participants were female (66.7%) but proportion varied widely by condition with the highest seen in fibromyalgia trials. Mean age of participants was 59 years and mean pain duration was 7.9 years. Participants reported a weighted mean pain severity of 6 on a scale of 0 to10. Industry was the leading provider of funding for trials (82%) while 15 trials (10%) did not report funding source.

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

Key Question 1. Benefits

In patients with neuropathic pain (mainly diabetic peripheral neuropathy and/or post-herpetic neuralgia), short-term RCTs (n=31) of anticonvulsants (prodrug gabapentin enacarbil, pregabalin, and oxcarbazepine) found small improvement in pain, with no differences

between drugs (SOE: Low to insufficient). The antidepressant duloxetine resulted in small improvements in pain, function, and quality of life in patients with diabetic peripheral neuropathy (SOE: Moderate to low). Tetrahydrocannabinol (THC) and cannabidiol (CBD) oral spray had inconsistent effects on pain in patients with multiple sclerosis or with allodynia (SOE: Low). Improvements in pain with topical capsaicin were not significant or did not reach the level of a small effect (SOE: Moderate).

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

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

Key Question 2. Harms

Across all classes, incidence of serious adverse event (SAEs) was low. Forty good- or fair-quality trials evaluated harms of antidepressants. Antidepressants led to a moderate increase in withdrawal due to adverse events (WAE) in 27 short- and intermediate-term studies. SNRI antidepressants resulted in moderate to large increases in incidence of nausea (with no difference according to dose) and excessive sweating. Duloxetine resulted in a large, dose-dependent, increase in sedation (SOE: Moderate to Low).

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

Seventy-nine trials evaluated harms of NSAID treatment in the short term. WAEs were increased, specifically with ibuprofen and diclofenac (small increase) and naproxen (moderate increase). The risk of any cardiovascular event was not significantly elevated for NSAIDs as a group, but diclofenac had a small increase in risk, particularly in the first 6 months, and with higher doses. The risk of major coronary events was elevated with diclofenac and celecoxib (moderately) and with ibuprofen (large increase). There was no difference in cardiovascular events between celecoxib and

nonselective NSAIDs in the intermediate and long term (SOE: Moderate). The risk of serious upper gastrointestinal events was increased with diclofenac (moderately) and ibuprofen or naproxen (large increase), particularly in the first 6 months of treatment. In the intermediate term, large increases in incidence of hepatic harms were found with diclofenac and naproxen (SOE: Moderate to Low).

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

Discussion

Key Findings and Strength of Evidence

The key findings of this review and effect size definitions are summarized below (Tables C through K). (See the full report for a detailed discussion of our key findings and strength of evidence.) This review evaluated and synthesized the evidence on benefits and harms of nonopioid drugs in patients with chronic noncancer pain. The pain conditions included were neuropathic pain (diabetic peripheral neuropathy, post-herpetic neuralgia, other), fibromyalgia, osteoarthritis, inflammatory arthritis (rheumatoid arthritis or ankylosing spondylitis), spinal pain (neck or low back pain), chronic headache, and sickle cell disease. Drugs reviewed included antidepressants (SNRIs and TCAs), anticonvulsants (pregabalin, gabapentin, oxcarbazepine, and carbamazepine), NSAIDs, and other drugs such as acetaminophen, capsaicin, and cannabis. The findings are categorized in the paragraphs below according to pain condition. The magnitude of the findings and the strength of the evidence for each finding are categorized according to the methods described above. Interventions or comparisons for which all evidence was insufficient to draw conclusions are not included here.

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

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

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

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

the intermediate term, although the incidence is low, large increases in hepatic harms were seen with diclofenac and naproxen. Dronabinol oral solution resulted in a large increase in dizziness and tetrahydrocannabinol/cannabidiol oral spray resulted in large increases in dizziness and nausea. Other adverse events of interest were not reported (cognitive effects, misuse, addiction, substance use disorder).

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

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

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

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

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

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

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

QoL = quality of life; SOE = strength of evidence

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

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

[a] Gabapentin enacarbil is a prodrug of gabapentin

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

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

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

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

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

QoL = quality of life; SOE = strength of evidence
Effect size: none (i.e., no effect/no statistically significant effect), small, moderate, or large increased risk
SOE: + = low, ++ = moderate, +++ = high
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Table G. Harms of antidepressants versus placebo

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

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

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

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

Table H. Harms of anticonvulsants versus placebo and active comparator

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

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

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

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

Table I. Harms of NSAIDs versus placebo and active comparators

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

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

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

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

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

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

Table K. Summary of specific adverse events

Drug Class	Drug	Outcomes of Interest	Adverse Event Findings From RCTs in Chronic Pain (Magnitude of Effect)	Adverse Event Findings From Other Sources (to Address Missing Evidence)
Antidepressants	SNRIs	Nausea, sedation, serotonin syndrome	Nausea (moderate-to-large, no dose effect), sedation (duloxetine, dose-related), serotonin syndrome symptoms (large)	No missing outcomes
	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]

Table K. Summary of specific adverse events (continued)

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)
Other	Acetaminophen	Hepatotoxicity	Not reported in included RCTs	Increased risk with chronic use of >3gms daily, effects often occur early in treatment; dose-adjustment if hepatic or renal dysfunction[10,11]
	Cannabis	Addiction/dependence, cognitive effects, hyperemesis, nausea, sedation	Dizziness (large) Nausea (THC/CBD oral spray, large)	Hyperemesis syndrome: Case reports (not limited to medical uses), >1x/week for >2 years. Cognition: small negative impact with chronic use Addiction/dependence: not found[12]
	Capsaicin	Application site reactions	Pain (large), erythema (small) Greater with longer application	No missing outcomes

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

Findings in Relationship to What Is Already Known

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

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

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

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

Applicability

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

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

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

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

Implications and Conclusions

Our findings show that nonopioid drugs (mainly SNRI antidepressants, pregabalin/gabapentin, and NSAIDs) result in small to moderate improvements in pain and function in the short term in patients with specific types of chronic pain, with few

differences between drugs studied or doses of a drug. Drug class-specific adverse events can lead to withdrawal from treatment in some patients, and include serious cardiovascular or gastrointestinal effects with NSAIDs. Consideration of patient characteristics including comorbidities, is needed in selecting nonopioid drug treatments. These findings are mainly consistent with prior review findings, with our review finding smaller magnitude of effect in some cases.

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

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

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Full Report

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