Implementing AHRQ Effective Health Care Reviews

Helping Clinicians Make Better Treatment Choices

Nonopioid Pharmacologic Treatments for Chronic Pain

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Key Clinical Issue

What are the effects of nonopioid drugs on pain, function, and quality of life in patients with specific types of chronic pain, and what are the adverse events related to these drugs?

Evidence-Based Answer

People with chronic neuropathic pain and fibromyalgia reported small short-term improvements in pain and function with certain anticonvulsants and moderate short-term improvement with certain antidepressants. (Strength of Recommendation [SOR]: B, based on inconsistent or limited-quality patient-oriented evidence.) Nonsteroidal anti-inflammatory drugs (NSAIDs) produced small short-term improvements in pain and function in patients with inflammatory arthritis and osteoarthritis. (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.) Memantine and serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressants were beneficial in the intermediate term for treating fibromyalgia. (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.) SNRIs were also beneficial for treating low back pain. (SOR: B, based on inconsistent or limited-quality patient-oriented evidence.) Evidence was insufficient to draw conclusions about long-term effects of any treatments.[1]

Practice Pointers

Chronic pain is defined by the International Association for the Study of Pain as ongoing or recurrent pain that lasts beyond the usual course of acute illness or injury or more than three to six months and adversely affects well-being.[2] A simpler definition is pain that persists past normal healing time.[3] Management options include nonopioid pharmacologic treatments, nonpharmacologic therapy, and opioids. The Centers for Disease Control and Prevention's 2016 guidelines state that when benefits outweigh risks, nonopioid pharmacologic therapies are preferred and should be combined with nonpharmacologic therapy to reduce chronic pain and improve function.[4]

The Agency for Healthcare Research and Quality (AHRQ) review focused on seven common chronic pain conditions (neuropathic pain, fibromyalgia, osteoarthritis, inflammatory arthritis, low back pain, chronic headache, and sickle cell

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to produce evidence to improve health care and to make sure the evidence is understood and used. A key clinical question based on the AHRQ Effective Health Care Program systematic review of the literature is presented, followed by an evidence-based answer based on the review. AHRQ's summary is accompanied by an interpretation by an *AFP* author that will help guide clinicians in making treatment decisions. For the full review, go to https://effectivehealthcare.ahrq.gov/sites/default/files/pdf/nonopioid-chronic-pain.pdf.

This series is coordinated by Kenny Lin, MD, MPH, deputy editor.

A collection of Implementing AHRQ Effective Health Care Reviews published in *AFP* is available at https://www.aafp.org/afp/ahrq.

CME **This clinical content** conforms to AAFP criteria for CME. See CME Quiz on page 521.

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disease) and assessed the effectiveness of common nonopioid medications on the primary outcomes of pain, function, and quality of life, as well as adverse events related to these medications. The review included oral agents, topical agents, and medical cannabis.

CLINICAL BOTTOM LINE

Effect of Certain Drugs in Placebo-Controlled and Head-to-Head Trials

Condition	Drug	Short-term pain	Intermediate-term pain	Long-term pain
Antidepressants				
Neuropathic pain	Duloxetine vs. placebo	Moderate ●●○	No evidence	—
Fibromyalgia	Duloxetine/milnacipran vs. placebo	Small ●●○	Small ●●○	
Osteoarthritis	Duloxetine vs. placebo	Small ●●●	No evidence	
Low back pain	Duloxetine vs. placebo	Small ●●○	No evidence	
	Amitriptyline vs. placebo	No evidence	None ●○○	
	Amitriptyline vs. pregabalin	Small ●○○	No evidence	
Anticonvulsants				
Neuropathic pain	Pregabalin/gabapentin vs. placebo	Small ●●○	—	—
	Oxcarbazepine vs. placebo	Small ●●○		
	Pregabalin vs. gabapentin	Insufficient evidence		
	Pregabalin vs. gabapentin enacarbil	None ●○○		
Fibromyalgia	Pregabalin/gabapentin vs. placebo	Small ●●○		
NSAIDs				
Osteoarthritis	NSAID vs. placebo	Small ●●○	No evidence	No evidence
	Diclofenac vs. celecoxib	Moderate ●○○	No evidence	No evidence
	NSAID vs. NSAID	None ●○○	None ●○○	None ●○○
	Topical diclofenac vs. placebo	Small ●●○	No evidence	No evidence
Inflammatory arthritis	NSAID vs. placebo	Small/moderate ●●○	Small ●○○	Large ●○○
	Celecoxib vs. diclofenac	None ●●○	No evidence	No evidence
	Celecoxib vs. naproxen	None ●○○	No evidence	No evidence
	Diclofenac vs. meloxicam	None ●○○	No evidence	No evidence
	Meloxicam vs. naproxen	No evidence	None ●○○	No evidence
	Nabumetone vs. naproxen	None ●○○	None ●○○	No evidence
Other drugs				
Neuropathic pain	Capsaicin patch	None ●●○	No evidence	—
	Cannabis	None ●○○	No evidence	
Fibromyalgia	Memantine	No evidence	Moderate ●○○	
	Cyclobenzaprine	No evidence	None ●○○	
Osteoarthritis	Acetaminophen	None ●○○	None ●○○	

Strength of evidence scale

●●● **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. 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.

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Treatment outcomes were analyzed at three to six months (short term), six to 12 months (intermediate term), and 12 months or later (long term). The review included 25 randomized controlled trials rated as good quality, 129 rated as fair quality, and 30 rated as poor quality. Meta-analyses

Short-term function	Intermediate-term function	Long-term function	Short-term quality of life	Intermediate-term quality of life
Small ●○○	No evidence	—	Small ●●○	No evidence
Small ●●○	None ●●○		Small/none* ●●○	Small ●●○
Small ●●●	No evidence		Small ●●●	No evidence
None ●●○	No evidence		None ●●○	No evidence
No evidence	None ●○○		No evidence	No evidence
None ●○○	No evidence		No evidence	No evidence
None ●○○	—	—	None ●○○	—
No evidence			None ●○○	
No evidence			No evidence	
None ●○○			None ●○○	
Small ●●○			None ●●○	
Small ●●●	No evidence	No evidence	None ●●○	—
Moderate ●○○	No evidence	No evidence	No evidence	
None ●○○	None ●○○	No evidence	No evidence	
None ●○○	No evidence	No evidence	No evidence	
Small ●●○	Small ●○○	None ●○○	Insufficient evidence	—
None ●●○	No evidence	No evidence	No evidence	
None ●○○	No evidence	No evidence	None ●○○	
None ●○○	No evidence	No evidence	No evidence	
No evidence	No evidence	No evidence	No evidence	
None ●○○	No evidence	No evidence	No evidence	
No evidence	No evidence	—	No evidence	No evidence
None ●○○	No evidence		None ●○○	No evidence
No evidence	Moderate ●○○		No evidence	Moderate ●○○
No evidence	Insufficient evidence		No evidence	No evidence
None ●○○	None ●○○		No evidence	No evidence

Note: Pain outcomes were standardized to a scale of 0 to 10, with effect size defined as small (0.5 to 1 point), moderate (> 1 to 2 points), or large (> 2 points).

NSAIDs = nonsteroidal anti-inflammatory drugs.

*—Small effect on mental component score, and no effect on physical component score.

Adapted from McDonagh MS, Selph SS, Buckley DI, et al. Nonopioid pharmacologic treatments for chronic pain. Comparative effectiveness review no. 228. (Prepared by the Pacific Northwest Evidence-Based Practice Center under Contract No. 290-2015-00009-I.) AHRQ publication no. 20-EHC010. Rockville, Md.; Agency for Healthcare Research and Quality; April 2020. Accessed June 21, 2020. https://effectivehealthcare.ahrq.gov/sites/default/files/nonopioid-chronic-pain-summary.pdf

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were conducted when possible. The mean age of the participants was 59 years, and two-thirds of participants were women. Mean pain duration was 7.9 years, with a mean pain severity of 6 out of 10. Pain outcomes were standardized to a scale of 0 to 10, with effect size defined as small (0.5 to 1 point), moderate (more than 1 to 2 points), or large (more than 2 points). Inferences for function were limited by the heterogeneous measures used across studies.

For neuropathic pain (mainly diabetic peripheral neuropathy and postherpetic neuralgia), the anticonvulsants gabapentin, pregabalin, and oxcarbazepine produced small improvements in pain in the short term compared with placebo. The SNRI duloxetine resulted in moderate improvements in short-term pain and small improvements in short-term function and quality of life compared with placebo for people with diabetic peripheral neuropathy. Tricyclic antidepressants, capsaicin patch, and medical cannabis had no clear effects.

The AHRQ review found that treatment with memantine resulted in moderate intermediate-term improvements in pain, function, and quality of life for fibromyalgia. Treatment with the SNRIs duloxetine and milnacipran resulted in small short- and intermediate-term improvements in pain, with small short-term improvement in function compared with placebo. The anticonvulsants pregabalin and gabapentin showed short-term improvements in pain and function compared with placebo, but not quality of life. Cyclobenzaprine and tricyclic antidepressants had no clear effects.

For patients with osteoarthritis, duloxetine resulted in a small improvement in short-term pain response, function, and quality of life compared with placebo. NSAIDs resulted in small improvements in pain and function in the short term, particularly in patients with knee pain and those with higher baseline pain severity. Notable differences between NSAIDs were that oral diclofenac improved pain and function moderately compared with celecoxib in the short term, but intermediate-term pain effects were maintained with celecoxib, and topical diclofenac showed a small improvement in short-term pain but no change in function. Acetaminophen did not improve pain, function, or quality of life in this patient population.

For those with rheumatoid arthritis or ankylosing spondylitis, short-term treatment with NSAIDs resulted in small to moderate improvements in pain and function compared with placebo. For patients with low back pain, use of duloxetine was associated with a small short-term improvement in pain compared with placebo.

Study withdrawal because of adverse events increased with anticonvulsants, antidepressants, cannabidiol oral spray, and NSAIDs. Pregabalin and gabapentin both resulted in moderate to large increases in cognitive effects (4.8%), dizziness (25.6%), and weight gain (10.1%); pregabalin also resulted in large increases in the risk of sedation (17%) and peripheral edema (8.8%). Sedation was reported in a dose-dependent manner with duloxetine (11%). Moderate to large increases in nausea (25%) and excessive sweating (22%) occurred with SNRIs as a class. Oral cannabidiols resulted in large increases in dizziness (20%), and oral spray solutions caused significant dizziness (39%) and nausea (17%). Capsaicin had increased risk of application site pain (61%) and erythema (58%). Acetaminophen did not increase withdrawal because of adverse events.

NSAIDs had mixed results regarding adverse events. There was no increased risk of overall serious adverse events. As a class, withdrawal because of adverse events increased to a small degree (relative risk [RR] = 1.30; 95% CI, 1.14 to 1.49). NSAIDs did not have a significant increased risk of cardiovascular events overall; however, there was a short-term increased risk of major coronary events. The risk was moderate for diclofenac (RR = 1.70; 95% CI, 1.19 to 2.41) and celecoxib (RR = 1.76; 95% CI, 1.31 to 2.37) and highest for ibuprofen (RR = 2.22; 95% CI, 1.10 to 4.48). NSAIDs exhibited moderate short- and long-term increases in serious gastrointestinal adverse events.

The AHRQ review reinforces, as well as calls into question, several current practices. For fibromyalgia, a previous *American Family Physician* (*AFP*) article recommended prescribing cyclobenzaprine to decrease pain; however, in this AHRQ review, cyclobenzaprine had no effect on pain in the short term.[5] For neuropathic pain, another *AFP* review supports using gabapentin and pregabalin as first-line treatments.[6] For osteoarthritis, a previous *AFP* article recommended acetaminophen as first-line therapy, followed by NSAIDs and SNRIs,[7] but this review found acetaminophen to be ineffective. The American Academy of Family Physicians (AAFP) endorses the American College of Physicians' 2017 clinical

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practice guideline on treating low back pain, which recommends NSAIDs or skeletal muscle relaxants followed by tramadol or duloxetine for patients who do not tolerate or respond to NSAIDs.[8,9] The AHRQ review supports the effectiveness of duloxetine in this patient population while also highlighting the dose-dependent risk of sedation.

A 2019 AAFP position paper acknowledged the limited, mixed evidence regarding cannabinoids for chronic pain.[10] A recent systematic review and meta-analysis found low to moderate strength of evidence that inhaled, oral, and oromucosal formulations of cannabinoids produce small reductions in pain intensity for chronic noncancer pain.[11] In light of these findings, more research is needed to clarify and strengthen current practice recommendations around nonopioid pharmacologic treatments for chronic pain.

Editor's Note: *American Family Physician* SOR ratings are different from the AHRQ Strength of Evidence ratings.

The views expressed in this article are those of the authors and do not reflect the official policy of the U.S. Army Medical Department, Department of the Army, Department of Defense, or the U.S. government.

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