Cochrane for Clinicians

Putting Evidence Into Practice

Osteoarthritis of the Hip and Knee: Can Antidepressants Help?

Kento Sonoda, MD, AAHIVS, Saint Louis University, Saint Louis, Missouri

Author disclosure: No relevant financial relationships.

Clinical Question

Are antidepressants safe and effective for the treatment of hip and knee osteoarthritis (OA)?

Evidence-Based Answer

Antidepressants provide a 50% or greater pain reduction in patients with hip and knee OA compared with placebo (number needed to treat [NNT] = 6; 95% CI, 4 to 11). (Strength of Recommendation [SOR]: A, consistent, good-quality patient-oriented evidence.) Antidepressants cause more adverse effects (number needed to harm [NNH] = 7; 95% CI, 5 to 11) compared with placebo.[1] (SOR: A, consistent, good-quality patient-oriented evidence.)

Practice Pointers

The estimated worldwide prevalence of OA of the hips and knees is 0.85% and 3.8%, respectively.[2] OA can lead to pain that affects physical and social function and mood, and it can be a financial burden. Although nonsteroidal anti-inflammatory drugs and intra-articular injection combined with nonpharmacologic interventions (e.g., structured exercise, weight loss) are commonly used to relieve pain, most patients are not satisfied with their pain control.[3,4] Antidepressants may inhibit sensory transmission in nociceptive fibers of the spinal cord through serotonin and norepinephrine reuptake inhibition.[5] The authors of the review sought to determine if antidepressants improve outcomes in people with hip or knee OA compared with placebo.

The Cochrane review included nine double-blind randomized controlled trials with a total of 2,122 adult patients.[1] Participants 40 years or older who had knee and hip OA were recruited in the United States, Canada, Europe, Asia, and New Zealand. The review included only placebo-controlled trials with or without nonsteroidal anti-inflammatory drugs. Antidepressants included serotonin-norepinephrine reuptake inhibitors (duloxetine [Cymbalta], 60 to 120 mg; milnacipran [Savella], 200 mg), selective serotonin reuptake inhibitors (fluvoxamine, 150 mg), and tricyclic antidepressants (nortriptyline, 25 to 100 mg). Duration of the trials ranged from 10 to 14 weeks. Individuals with prior joint prostheses or concurrent psychiatric disorders (e.g., depression, anxiety, mania) were not included. Primary outcomes were pain at eight to 16 weeks (on a scale of 0 to 10 points, with 0 = no pain), responder rate (defined as a 50% or greater reduction in 24-hour mean pain level), physical function (total score on the Western Ontario and McMaster Universities Arthritis Index on a scale of 0 to 100, with 0 = best function), quality of life (score on the EuroQol 5-Dimension scale of −0.11 to 1, with 1 = perfect health), adverse effects, and study withdrawals due to adverse effects.

Compared with placebo, antidepressants provided slight and clinically unimportant pain relief at eight to 16 weeks (mean difference [MD] = −0.59; 95% CI, −0.88 to −0.31; nine trials; n = 2,038; high-certainty evidence). Antidepressants yielded an increased responder rate (NNT = 6; 95% CI, 4 to 11; six trials; n = 1,904; high-certainty evidence) compared with placebo. Another analysis revealed that antidepressants slightly improved physical function (MD = −5.65; 95% CI, −7.08 to −4.23; six trials; n = 1,909; high-certainty evidence) and quality of life (MD = 0.04; 95% CI, 0.01 to 0.07; three trials; n = 815; moderate-certainty evidence) compared with placebo, but this effect has questionable clinical meaning.

Participants in the antidepressant group withdrew from a study due to adverse effects (NNH = 17; 95% CI, 10 to 35; six trials; n = 1,977; moderate-certainty evidence) more often than those taking placebo. Antidepressants also caused more adverse effects (NNH = 7; 95% CI, 5 to 11; nine trials; n = 2,101; high-certainty evidence) but did not increase serious adverse effects compared with placebo (low-certainty evidence).

Limitations of the review included extensive exclusion criteria regarding concurrent psychiatric conditions, underrepresentation of hip OA (only two out of nine trials included hip OA), and the use of antidepressants other than duloxetine (only one trial each used milnacipran, fluvoxamine, and nortriptyline). Six of the nine trials were funded by a pharmaceutical company (all six funded trials were for duloxetine).

Among the antidepressants included in the studies, duloxetine is the only medication approved by the U.S. Food and Drug Administration for the treatment of chronic musculoskeletal pain.[6] The recommended starting dosage

These are summaries of reviews from the Cochrane Library.

This series is coordinated by Corey D. Fogleman, MD, assistant medical editor.

A collection of Cochrane for Clinicians published in *AFP* is available at https://www.aafp.org/afp/cochrane.

CME This clinical content conforms to AAFP criteria for CME. See CME Quiz on page 575.

of duloxetine is 30 mg daily; the dosage can be titrated up to 60 mg daily.[6] Common adverse effects of duloxetine include nausea, constipation, xerostomia, dizziness, and fatigue. Although antidepressants may provide modest pain relief, their use is associated with more adverse effects compared with placebo; therefore, family physicians should carefully consider antidepressants as a treatment option for OA with usual care options. Further research is needed to better understand the clinically important effectiveness and safety of antidepressants in patients with OA and concurrent psychiatric disorders.

The practice recommendations in this activity are available at https://www.cochrane.org/CD012157.

References

1. Leaney AA, Lyttle JR, Segan J, et al. Antidepressants for hip and knee osteoarthritis. *Cochrane Database Syst Rev*. 2022;(10):CD012157.
2. Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 Study. *Ann Rheum Dis*. 2014;73(7):1323-1330.
3. Conaghan PG, Peloso PM, Everett SV, et al. Inadequate pain relief and large functional loss among patients with knee osteoarthritis: evidence from a prospective multinational longitudinal study of osteoarthritis real-world therapies. *Rheumatology (Oxford)*. 2015;54(2):270-277.
4. Katz JN, Arant KR, Loeser RF. Diagnosis and treatment of hip and knee osteoarthritis: a review. *JAMA*. 2021;325(6):568-578.
5. Shelton RC. Serotonin and norepinephrine reuptake inhibitors. *Handb Exp Pharmacol*. 2019;250:145-180.
6. U.S. Food and Drug Administration. Accessed April 21, 2023. https://www.fda.gov/food

Benefits and Harms of Systemic Corticosteroids for Radicular and Nonradicular Low Back Pain

Jeffrey C. Leggit, MD, CAQSM
Uniformed Services University of the Health Sciences, Bethesda, Maryland

Author disclosure: No relevant financial relationships.

Clinical Question

What are the benefits and harms of using systemic corticosteroids for the management of radicular and nonradicular low back pain or symptomatic spinal stenosis in adults?

Evidence-Based Answer

In patients with radicular low back pain, systemic corticosteroids increase the likelihood of improvement in function at short-term follow-up (absolute improvement = 19% better; 95% CI, 8% to 30% better). In adults with nonradicular low back pain, the use of systemic corticosteroids does not lead to a discernible effect on pain or function. Systemic corticosteroids are not beneficial in treating pain or function in those with spinal stenosis. A short course of systemic corticosteroids does not appear to cause harm.[1] (Strength of Recommendation: B, inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

Low back pain can be categorized by etiology as radicular (lumbar disc or nerve root abnormalities), nonradicular mechanical (a combination of muscle, ligament, tendon, or bony abnormalities not resulting from spinal stenosis or disc or nerve root abnormalities), symptomatic due to spinal stenosis (narrowing of the spinal canal from bony and/or soft tissue structures), or back pain secondary to rheumatologic, inflammatory, metabolic, or malignant conditions. Management of low back pain may be specific to etiology and guided by duration of symptoms: acute pain (less than four weeks), subacute pain (four to 12 weeks), or chronic pain (more than 12 weeks). The authors sought to determine the benefits and harms of systemic corticosteroids two to 12 weeks after administration for low back pain that was radicular, nonradicular mechanical, or symptomatic due to spinal stenosis.

The Cochrane review included 13 randomized controlled trials with a total of 1,047 participants, and sample sizes ranged from 29 to 269.[1] Nine trials evaluated participants with radicular low back pain. Of the nine trials, three evaluated participants with acute symptoms, two evaluated those with mixed acute and nonacute symptoms, one evaluated those with nonacute symptoms, and in three trials the duration of symptoms was unclear. Two trials studied participants with acute nonradicular low back pain. Two trials studied participants with spinal stenosis: one trial included patients with chronic symptoms whereas the other did not report the duration of symptoms. Radiologic confirmation of conditions was required in only two of the nine trials for radicular low back pain; radiologic confirmation was also required in both of the trials for spinal stenosis. Patient demographics were not consistently provided; however, in studies that reported this information, the median age of participants was 40 years in the radicular and nonradicular low

back pain trials and 58 years in the spinal stenosis trials. Corticosteroids were given as a one-time treatment or over the course of several days and were administered orally, intravenously, or intramuscularly; studies that evaluated epidural injections were excluded. Corticosteroid type, dosage, and length of treatment varied between studies. Total doses of prednisone equivalents ranged from 50 to 1,050 mg. Multiple scales were used to determine treatment effect.

There was no evidence that systemic corticosteroids improved pain or function in the short- or long-term in patients with nonradicular low back pain or spinal stenosis. Adverse effects were inconsistently reported but, in studies that included this information, no serious adverse effects were noted. Outcomes and adverse effects were not made more or less likely by the type of corticosteroid, route of administration, or dosing. Administration of a single dose vs. multi-day course of corticosteroids also did not make a difference in outcomes or adverse effects.

Updated guidelines from the U.S. Department of Veterans Affairs and U.S. Department of Defense (VA/DoD) and the North American Spine Society recommend against systemic corticosteroid administration for the treatment of low back pain because of poor evidence and possible adverse effects.[2,3] The VA/DoD guidelines apply to both radicular and nonradicular low back pain, whereas the North American Spine Society guidelines apply to low back pain without a neurologic defect or with radicular pain that does not travel beyond the knee. Family physicians may consider prescribing corticosteroids for improving function in patients with radicular low back pain but should discuss the relatively small benefit.

The practice recommendations in this activity are available at https://www.cochrane.org/CD012450.

The opinions and assertions contained herein are the private views of the author and are not to be construed as official or reflecting the views of the Uniformed Services University of the Health Sciences, U.S. Department of Defense, or U.S. government.

References

1. Chou R, Pinto RZ, Fu R, et al. Systemic corticosteroids for radicular and non-radicular low back pain. *Cochrane Database Syst Rev.* 2022;(10):CD012450.
2. U.S. Department of Veterans Affairs and U.S. Department of Defense. VA/DoD clinical practice guideline for the diagnosis and treatment of low back pain. 2022. Accessed December 15, 2022. https://www.healthquality.va.gov/guidelines/Pain/lbp/VADoDLBPCPGProviderSummaryFinal508.pdf
3. North American Spine Society. Evidence-based clinical guidelines for multidisciplinary spine care. Diagnosis and treatment of low back pain. 2020. Accessed December 15, 2022. https://www.spine.org/Portals/0/Documents/ResearchClinicalCare/Guidelines/LowBackPain.pdf ■