Cochrane for Clinicians

Putting Evidence into Practice

Opioid Therapy for Chronic Noncancer Pain

DEAN A. SEEHUSEN, LTC, MC, USA, *Evans Army Community Hospital, Fort Carson, Colorado*

The Cochrane Abstract on the next page is a summary of a review from the Cochrane Library. It is accompanied by an interpretation that will help clinicians put evidence into practice. Dr. Seehusen presents a clinical scenario and question based on the Cochrane Abstract, followed by an evidence-based answer and a critique of the review. The practice recommendations in this activity are available at http://www.cochrane.org/reviews/en/ab006605.html.

EB CME

This clinical content conforms to AAFP criteria for evidence-based continuing medical education (EB CME). See CME Quiz on page 23.

The series coordinator for *AFP* is Clarissa Kripke, MD, Department of Family and Community Medicine, University of California, San Francisco.

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

Clinical Scenario

A 42-year-old woman with a four-month history of low back pain after a fall at work presents requesting pain medication. She was once given oral opioids after a dental procedure with good results. She would like to try oral opioids for her back pain.

Clinical Question

Are opioids safe and effective in the management of chronic pain from causes other than cancer?

Evidence-Based Answer

Weak evidence suggests that opioids reduce chronic noncancer pain in some highly selected patients, although the effects on quality of life and functional status are unclear.[1] Many patients will discontinue opioids because of adverse effects or inadequate pain relief. (Strength of Recommendation = A, based on consistent, good-quality patient-oriented evidence)

Practice Pointers

There are as many as 75 million patient encounters for chronic pain in the United States annually,[2] and treating chronic pain costs nearly $100 billion annually.[3] The International Association for the Study of Pain defines chronic pain as pain lasting at least three months.[4] This Cochrane review focused only on noncancer causes of chronic pain.[1]

Most studies included in the analysis consisted of patients with back pain, osteoarthritis, or nonspecific causes of chronic noncancer pain. Other studies included patients with neuropathic pain, vertebral fractures, or trigeminal neuralgia. Most of the studies included in the analysis were open-label case series. The exact opioid preparation, dose, and route of administration varied widely in the included trials.

Discontinuation rates from adverse effects were high for all delivery modes, whereas discontinuation rates from insufficient pain relief were lower. These two rates combined show that substantial percentages of patients did not complete these study protocols. The patients were not followed beyond the duration of the studies to determine what their long-term outcomes were or if they eventually restarted opioid use. Discontinuation from adverse effects in the oral opioid studies was higher than in the transdermal or intrathecal studies. The rates of discontinuation for weak opioid preparations were lower than for stronger opioids (11.4 versus 31.1 percent, respectively).

Among the studies reporting addiction or abuse rates, only seven participants out of 2,613 (0.27 percent) developed addictive or abusive traits. It must be noted that most studies carefully screened for and excluded patients with addiction or abuse histories. It is reasonable to assume that the rate would be higher in the general population.

Four studies of oral opioids evaluated change in pain levels. Pooled analysis of pain relief from six to 7.5 months showed a standard mean difference (SMD) of 1.55 (95% confidence interval [CI], 0.85 to 2.25), which would be considered a medium to large effect. The authors therefore concluded that this represented a clinically significant amount of pain relief. Two studies reported the proportion of patients achieving at least a 50 percent reduction in pain. Pooled results showed that 44.3 percent (95% CI, 33.3 to 55.9 percent) of participants achieved at least a 50 percent reduction from baseline pain scores at 7.5 to 13 months. An insufficient number of studies of oral opioids looked at quality of life measures to make any conclusions.

Cochrane Abstract

Background: Opioid therapy for chronic noncancer pain is controversial because of concerns about long-term effectiveness and safety, particularly the risk of tolerance, dependence, or abuse.

Objectives: To assess safety, efficacy, and effectiveness of opioids taken long-term for chronic noncancer pain.

Search Strategy: The authors searched 10 bibliographic databases up to May 2009.

Selection Criteria: The authors searched for studies that: collected efficacy data on participants after at least six months of treatment; were full-text articles; did not include redundant data; were prospective; enrolled at least 10 participants; and reported data of participants who had chronic noncancer pain. Randomized controlled trials (RCTs) and pre-post case-series studies were included.

Data Collection and Analysis: Two review authors independently extracted safety and effectiveness data and settled discrepancies by consensus. They used random-effects meta-analyses to summarize data where appropriate, used the I2 statistic to quantify heterogeneity, and, where appropriate, explored heterogeneity using meta-regression. Several sensitivity analyses were performed to test the robustness of the results.

Main Results: The authors reviewed 26 studies with 27 treatment groups that enrolled a total of 4,893 participants. Twenty-five of the studies were case series or uncontrolled long-term trial continuations; the other was an RCT comparing two opioids. Opioids were administered orally (number of study treatment groups [k] = 12; n = 3,040), transdermally (k = 5; n = 1,628), or intrathecally (k = 10; n = 231). Many participants discontinued because of adverse effects (*oral*: 22.9 percent; 95% confidence interval [CI], 15.3 to 32.8 percent; *transdermal*: 12.1 percent; 95% CI, 4.9 to 27.0 percent; *intrathecal*: 8.9 percent; 95% CI, 4.0 to 26.1 percent) or insufficient pain relief (*oral*: 10.3 percent; 95% CI, 7.6 to 13.9 percent; *intrathecal*: 7.6 percent; 95% CI, 3.7 to 14.8 percent; *transdermal*: 5.8 percent; 95% CI, 4.2 to 7.9 percent).

Signs of opioid addiction were reported in 0.27 percent of participants in the studies that reported that outcome. All three modes of administration were associated with clinically significant reductions in pain, but the amount of pain relief varied among studies. Findings regarding quality of life and functional status were inconclusive because of an insufficient quantity of evidence for oral administration studies and inconclusive statistical findings for transdermal and intrathecal administration studies.

Authors' Conclusions: Many patients discontinue long-term opioid therapy (especially oral opioids) because of adverse events or insufficient pain relief; however, weak evidence suggests that patients who are able to continue opioids long-term experience clinically significant pain relief. Whether quality of life or functioning improves is inconclusive. Many minor adverse events (e.g., nausea, headache) occurred, but serious adverse events, including iatrogenic opioid addiction, were rare.

Two studies of transdermal opioids reported changes in pain scores. A wide difference in findings between the two studies prevented the authors from making conclusions about the effect size. However, both studies individually showed a statistically significant reduction in pain levels at six months. Conclusions could not be drawn about the proportion of patients with at least a 50 percent reduction in baseline pain levels. Three studies of transdermal opioids reported change in quality of life measures. Pooled analysis of mental subscales did not show a statistically significant difference (SMD = 0.78; 95% CI, –0.06 to 1.63). However, physical subscales showed a statistically significant difference with an SMD of 4.46 (95% CI, 1.23 to 7.68), which is a large clinical effect.

The evidence for pain relief was strongest for studies involving intrathecal opioids. Nine studies evaluated change from baseline pain levels. Pooled analysis showed an SMD of 2.01 (95% CI, 1.37 to 2.66) at six to 29 months. Importantly, all nine studies individually showed a highly statistically significant reduction in pain scores. Seven small studies reported the proportion of patients with at least a 50 percent reduction in baseline pain scores. Pooled analysis showed that 44.5 percent (95% CI, 27.2 to 63.2 percent) of patients had a reduction of at least 50 percent from baseline pain scores. Three studies of intrathecal opioids reported quality of life measures, but pooled analysis did not demonstrate a statistically significant benefit of intrathecal opioids.

The opinions and assertions contained herein are the private views of the author and are not to be construed as official or as reflecting the views of the U.S. Army Medical Department or the U.S. Army Service at large.

Address correspondence to Dean A. Seehusen, LTC, MC, USA, at dseehusen@msn.com. Reprints are not available from the author.

Author disclosure: Nothing to disclose.

REFERENCES

1. Noble M, Treadwell JR, Tregear SJ, et al. Long-term opioid management for chronic noncancer pain. *Cochrane Database Syst Rev.* 2010;(1):CD006605.
2. Schnitzer TJ. Non-NSAID pharmacologic treatment options for the management of chronic pain. *Am J Med.* 1998;105(1B):45S-52S.
3. Carter C, Goldfarb NI, Hartmann CW, et al. Chronic pain management in managed care organizations: a national survey of medical directors. *P T.* 2003;28(3):179-182, 184, 215.

4. Classification of chronic pain. Descriptions of chronic pain syndromes and definitions of pain terms. Prepared by the International Association for the Study of Pain, Subcommittee on Taxonomy. *Pain Suppl.* 1986;3:S1-S226.

Cochrane Briefs

Effectiveness of Antidepressants Compared with Placebo for Depression in Primary Care

Clinical Question

What is the effectiveness of antidepressants compared with placebo for the treatment of depression in primary care settings?

Evidence-Based Answer

Tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) are more effective than placebo for the treatment of depression in primary care settings. (Strength of Recommendation = A, based on consistent, good-quality patient-oriented evidence)

Practice Pointers

In patients with mild to moderate depression symptoms, there is little or no benefit of antidepressant medications compared with placebo. Medications are more beneficial in patients with severe depression.[1] This Cochrane review compared the effectiveness of antidepressant medications with placebo for patients with depression who were recruited from primary care practices. It included 14 randomized controlled trials of patients 18 to 65 years of age. Most trials reported short-term outcomes at four to six weeks; four trials had follow-up for 12 to 24 weeks. Most studies were sponsored by pharmaceutical companies.

Compared with placebo, TCAs showed greater improvement in depression scores and a greater clinical response to remission (number needed to treat [NNT] = 9; 95% confidence interval [CI], 6 to 16), assessed by primary care physicians or psychiatrists. The number needed to harm (NNH) ranged from 4 to 30 in participants taking TCAs who discontinued treatment because of adverse effects.

SSRIs showed a clinical benefit for improvement in depression scores (NNT = 7; 95% CI, 7 to 8). More patients in the SSRI group withdrew from trials because of adverse effects (relative risk [RR] = 2.05; 95% CI, 1.11 to 3.75; NNH = 20 to 90) compared with placebo, but fewer patients in the SSRI group withdrew because of treatment failure (RR = 0.51; 95% CI, 0.34 to 0.78). Other reviews have shown higher drop-out rates related to tolerability in participants taking SSRIs.

The American College of Physicians recommends that when physicians choose pharmacologic therapy to treat patients with acute major depression, they select second-generation antidepressants on the basis of adverse effect profiles, cost, and patient preference.[2] The Institute for Clinical Systems Improvement states that SSRIs—as well as venlafaxine (Effexor), duloxetine (Cymbalta), mirtazapine (Remeron), and bupropion (Wellbutrin)—are often chosen as first-line antidepressant treatment options because of the quality and quantity of published data for these medications; their relative tolerability of adverse effects compared with TCAs and monoamine oxidase inhibitors; and their overall relative safety.[3]

JANELLE GUIRGUIS-BLAKE, MD

Author disclosure: Nothing to disclose.

SOURCE: Arroll B, Elley CR, Fishman T, et al. Antidepressants versus placebo for depression in primary care. *Cochrane Database Syst Rev.* 2009;(3):CD007954.

REFERENCES

1. Fournier JC, DeRubeis RJ, Hollon SD, et al. Antidepressant drug effects and depression severity: a patient-level meta-analysis. *JAMA.* 2010;303(1):47-53.
2. Qaseem A, Snow V, Denberg TD, Forciea MA, Owens DK; Clinical Efficacy Subcommittee of American College of Physicians. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians [published correction appears in *Ann Intern Med.* 2009;150(2):148]. *Ann Intern Med.* 2008;149(10):725-733.
3. Institute for Clinical Systems Improvement. Health care guideline: major depression in adults in primary care. 12th ed. May 2009. http://www.icsi.org/depression_5/depression__major__in_adults_in_primary_care_3.html. Accessed May 11, 2010. ■