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Opioids for osteoarthritis? Weighing benefits and risks

A Cochrane Musculoskeletal Group review

Untreated pain is a major public health problem, but concerns about opioid misuse remain. This evidence-based look at when—or whether—opioids are indicated for OA patients will help you achieve the right balance.

Osteoarthritis (OA) affects nearly 27 million Americans, or about 12% of US adults.[1] As the average age of the population increases, the prevalence and burden of this debilitating disorder continue to rise.[2]

The American College of Rheumatology (ACR)'s guidelines for the medical management of OA of the hip and knee, last updated in 2000,[3] focus on controlling pain and improving function and health-related quality of life while minimizing the toxic effects of therapy. The guidelines recommend tramadol—an atypical opioid with 2 distinct mechanisms of action[4]—for moderate-to-severe pain in OA patients who either have contraindications to COX-2 inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs) or have failed to respond to previous oral therapy. Patients with severe pain who don't respond to or are unable to tolerate tramadol may be candidates for more traditional opioid therapy, the guidelines indicate.[3]

In recent years, however, the use (and abuse) of opioids has skyrocketed. Between 1997 and 2007, US per capita retail purchases of hydrocodone and oxycodone increased 4-fold and 9-fold, respectively.[5] In a similar time frame (1996-2006), the number of deaths from opioid overdose more than tripled, going from 4000 to 13,800 annually.[6] Not surprisingly, the use of narcotics for noncancer pain remains controversial.[7,8] But inadequately treated pain continues to be a serious public health problem, as well.[9]

In 2006 and 2009, respectively, the Cochrane Collaboration published systematic

How this series can help you

This is the third in a series of articles based on the findings of the Cochrane Musculoskeletal Group (CMSG). One of the largest groups in the Cochrane Collaboration, the CMSG synthesizes the results of clinical trials to determine whether interventions for the prevention, treatment, and rehabilitation of musculoskeletal disorders are safe and effective. In this installment, the reviewers use detailed analysis, as well as a case study, to bring their findings to the attention of family physicians in a practical, clinically relevant context.

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The data highlight the importance of making patients aware that the risks of opioids (including tramadol) for OA treatment may outweigh the benefits.

reviews of tramadol (for OA in any joint)[10] and other oral and transdermal opioids (for OA of the hip or knee).[11] The reviewers' findings, presented here along with data from more recent trials, can help ensure that you prescribe opioids for patients with OA only when their use is clinically appropriate and evidence-based. We've also included a case study (see page 211), so you can assess your knowledge and clinical skills.

Tramadol produces modest results—or none at all

The tramadol review[10] included 11 randomized controlled trials (RCTs) with a total of 1019 participants who took tramadol or tramadol/acetaminophen (paracetamol) and 920 controls. In 6 of the 11 studies, the controls received placebo; the remaining 5 trials used "active controls," with the control group for each RCT receiving a different analgesic. (To learn more about the methodology, see "How the reviews were conducted" on page 210.)

Placebo-controlled trials. Compared with patients on placebo, those receiving tramadol had an average absolute reduction in pain of 8.5 mm on a 0-100 mm visual analog scale (VAS) (95% confidence interval [CI], -12.05 to -4.9). That small benefit, however, did not reach the level defined as the minimal perceptible clinical improvement—a reduction of 9.7 mm on Western Ontario and McMaster Universities (WOMAC)'s OA pain subscale.[12]

Active-controlled trials. In the 5 RCTs comparing tramadol with another active agent, tramadol proved to be no better than the control drug. In fact, in a study of tramadol vs acetaminophen, 500 mg acetaminophen 3 times a day provided more pain relief than 50 mg tramadol 3 times a day.[13] Although this was a small (N=20), short-term (7-day) study, this finding is notable because participants took less than the usual acetaminophen dose of 1 g up to 4 times a day.

Nor was tramadol superior to the agents it was compared with in the 4 other active-controlled trials—dihydrocodeine,[14] dextropropoxyphene,[15] pentazocine,[16] and diclofenac[17]—in reducing pain intensity. It is important to keep in mind, however, that in each of these studies, both the quantity and quality of the evidence was limited. (Two studies did not use numerical scales,[14,16] for example; all had methodological issues; and none lasted longer than 28 days.)

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TABLE 1

Tramadol and other opioids for OA pain: NNT and NNH

Treatment	NNT	NNH
Tramadol[10]	6	5
Opioids (overall)[11]	25	12

NNH, number needed to harm; NNT, number needed to treat; OA, osteoarthritis.

The American College of Rheumatology recommends tramadol for moderate-to-severe OA pain in patients who have contraindications or haven't responded to COX-2-specific inhibitors and NSAIDs.

A modest boost in well-being

The reviewers measured function in 2 ways, focusing on both global improvement and improvement in physical function.

Global assessment. For the global assessment, the reviewers defined a treatment response as achieving at least a moderate improvement. By that standard, tramadol may improve overall well-being more than placebo. In the placebo-controlled trials, the number needed to treat (NNT) to elicit one treatment response was 6.

Three of the trials with active controls included global/functional assessments, and the results—bearing in mind the reduced quality and quantity of the evidence—were mixed. In a comparison of tramadol with dextropropoxyphene, tramadol increased the likelihood of moderate improvement by 38% (relative risk, 1.38 (95% CI, 1.15-1.67).[10] In a trial of tramadol vs pentazocine, tramadol was more effective in reducing the duration of morning stiffness (by about 10 minutes), but not its severity. Tramadol was comparable with pentazocine in the 7 other measures of OA and function.[16] In the tramadol-diclofenac study, both drugs were equally effective.[17]

Physical function. Four of the 6 placebo-controlled tramadol studies included in the Cochrane review used the WOMAC Index score, which included the physical function subscale. The tramadol group had a larger reduction in the score than the placebo group, by 0.34 mm (95% CI, -0.49 to -0.19). While this was equivalent to an 8.5% relative reduction in mean baseline score, it is still small compared with the minimal perceptible clinical improvement level of 9.3 mm on a 0-100 scale needed for the WOMAC physical function subscale. A similar improvement was reported for those taking tramadol compared with diclofenac—the only one of the active-controlled studies to report on physical function.[17]

Other opioids relieve pain, improve function—but how much?

The review of oral and transdermal opioids for OA[11] encompassed 10 trials, with a total of 1541 patients receiving opioids and 727 on placebo. The opioids used in the trials were codeine, oxycodone, oxymorphone, morphine, and transdermal fentanyl. (For more details, see "How the reviews were conducted" on page 210.)

Pain. The trials included in the review used a variety of scales to measure pain, so the reviewers gauged results by the proportion of patients responding to treatment. Response was defined as a 50% improvement in pain score.

In the overall analysis, 35% of patients taking opioids responded to treatment, vs 31% of those on placebo—or 4 more patients in 100. That represents an NNT of 25. (A subgroup analysis did not demonstrate any significant differences in effect size among the opioids tested. In addition, the effect size was similar regardless of the potency of the opioid or the administration route.)

Function. Seven of the 10 trials (1794 participants, including both the treatment groups and controls) used validated function scores to measure physical function after 4 weeks of treatment. Here, too, the reviewers defined a treatment response as a 50% improvement in score.

Their finding? Opioids had a greater effect on function compared with placebo, equaling 0.7 on a WOMAC disability scale of 1 to 10. This means that about 3 more patients in 100 responded to treatment with opioids vs placebo—an NNT of 30.

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TABLE 2

Tramadol for OA: Post-review RCTs are consistent with meta-analysis

Study duration (N)	Intervention groups	Primary outcome measures	Improvement in			Adverse effects
			Pain	Global assessment	Function	
Gana*[20] 12 wk (1020)	Tramadol ER 100 mg 200 mg 300 mg 400 mg Placebo	WOMAC OA index (pain and physical function subscales) 100-mm VAS: Subject global disease	Treatment groups, 35% Placebo, 25%	Treatment groups, 32%-36% Placebo, 24%	Treatment groups, 31%-33% Placebo, 22%	**≥1 AE** Treatment groups, 71%-84% Placebo, 56% **Withdrawals due to AEs** Treatment groups, 20%-30% Placebo, 10%
Delemos*[21] 12 wk (1001)	Tramadol ER 100 mg 200 mg 300 mg Celecoxib 200 mg Placebo	WOMAC OA index (pain and physical function subscales) 100-mm VAS: Subject global disease	Tramadol, 27%-39% Celecoxib, 45% Placebo, 32%	Tramadol, 28%-40% Celecoxib, 44% Placebo, 30%	Tramadol, 26%-35% Celecoxib, 43% Placebo, 28%	**≥1 AE** Tramadol, 63%-75% Celecoxib, 60% Placebo, 60% **Withdrawals due to AEs** Tramadol, 12%-31% Celecoxib,10% Placebo, 8%
Burch†[22] 12 wk (646)	Tramadol (Contramid OAD) 100 mg titrating to 300 mg Placebo	Pain intensity (11-point numerical scale) Physician/patient global impressions of change (7-point scale)	Treatment group, 40% Placebo, 33%	Treatment group, 80% Placebo, 69%	NA	**AEs** *Treatment group:* Nausea, 15.3%; constipation, 14.1%; dizziness/vertigo, 9.7%; somnolence, 6.7% *Placebo:* Nausea, 5.6%; constipation, 4.2%; dizziness/vertigo, 3.7%; somnolence, 3.7% **Withdrawals due to AEs** Treatment group, 10% Placebo, 5%
Beaulieu*[19] 6 wk (128)	Tramadol CR 200 mg titrating to 400 mg Diclofenac SR 75 mg titrating to 150 mg	WOMAC OA index (pain and physical function subscales) 100-mm VAS: Pain intensity Subject global disease Physician/patient global impressions of change (7-point scale)	Both groups, ~29%	Tramadol, 67%‡ Diclofenac, 54%‡	Tramadol, 29%‡ Diclofenac, 29%‡	**Withdrawals due to AEs** Tramadol, 16% Diclofenac, 15%

*Hip or knee osteoarthritis.

†Knee osteoarthritis.

‡Not statistically significant.

AEs, adverse events; CR, controlled release; ER, extended release; NA, not assessed; OA, osteoarthritis; OAD, once a day; RCTs, randomized controlled trials; SR, sustained release; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities.

How the reviews were conducted

The Cochrane Musculoskeletal Group conducted a review of tramadol and a review of other oral opioids and transdermal fentanyl for the treatment of osteoarthritis (OA). Both reviews featured pain, function, and safety as primary outcomes. The tramadol review included randomized controlled trials (RCTs) for OA in any joint, while the oral and transdermal opioid review included randomized and quasi-randomized trials of treatment for OA of the hip or knee. Other parameters follow:

The tramadol review included 11 RCTs, with a total of 1019 participants receiving either tramadol alone or tramadol/acetaminophen (paracetamol) and 920 controls. In 6 of the 11 studies, the controls received placebo; the remaining 5 studies featured "active control." That is, the control groups received acetaminophen 500 mg 3 times daily, diclofenac (25-50 mg up to 3 times daily on demand), dihydrocodeine 60 mg twice daily, dextropropoxyphene 100 mg 3 times daily, or pentazocine 50 mg 4 times per day. Because each of these agents was used in only one trial, the reviewers could not reach definitive conclusions about tramadol's performance relative to other medications. The average number of participants in the tramadol and control groups was 91 and 80, respectively. The average length of follow-up was 35 days.

The 11 RCTs included in this review used a variety of pain scales to assess the results of tramadol, active control medications, and placebo. For comparative purposes, the reviewers pooled the results from studies that used numerical scales (0 to 100 and 0 to 10) to assess pain intensity. As a reference, we have used 9.7 and 9.3, respectively, determined by other researchers to be the minimal perceptible clinical improvements on the Western Ontario and McMaster Universities (WOMAC) pain and physical function 0-100 mm visual analog scales.[12]

The review of oral and transdermal opioids included 10 studies, with a total of 1541 patients receiving opioids and 727 receiving placebo.[17] There were 3 trials of codeine (in 2 of the 3, a simple analgesic [acetaminophen 3000 mg/d or ibuprofen 1200 mg/d] was co-administered to both the treatment and control groups); other opioids included in the trials were oxycodone (4 trials), oxymorphone (2 trials), morphine (1 trial), and transdermal fentanyl (1 trial).

But what about safety?

Opioids, including tramadol, are associated with adverse events (AEs), which may be minor or major. To determine when, or whether, the benefits outweigh the risks for treating patients with OA, both reviews reported on AEs and the number of participants who stopped taking the drug because of AEs.

AEs limit tramadol's usefulness

While tramadol was more effective than placebo at reducing pain intensity, relieving symptoms, and improving function, the benefits were small—with an overall NNT of 6 (**TABLE 1**). This is similar to acetaminophen (NNT, 4-16),[18] but with a greater downside.

Minor AEs. Four placebo-controlled trials reported on minor AEs.[19-22] Those most commonly reported by patients taking tramadol were nausea, vomiting, dizziness, constipation, somnolence, tiredness, and headache.

Overall, 39% of those who received tramadol experienced minor AEs, compared with 18% of patients receiving placebo—an NNH of 5.[10] Thus, tramadol's NNH for minor AEs is equivalent to its NNT for pain relief. In active-controlled studies, there was a higher risk of minor AEs in those receiving tramadol compared with diclofenac or dextropropoxyphene, but a lower risk compared with those taking pentazocine.[10]

Major AEs. An analysis of the placebo-controlled trials revealed that 21% of those who received tramadol had major AEs—defined as an event that resulted in cessation of treatment—compared with 8% of those taking placebo. By this measure, the NNH was 8: One in 8 patients stopped taking tramadol because of a major AE.[10]

Among the active-controlled trials, participants taking tramadol were more likely to report a major AE compared with those

How would you treat this patient?

CASE ▶ Carol J, an active 72-year-old, was diagnosed with OA in her right hip 5 years ago. Now she reports that the pain is getting progressively worse, making it harder and harder to turn over in bed at night or get in and out of the car. The pain is particularly bad at night, Carol says, and she's had interrupted sleep for months. The patient has taken acetaminophen for the pain since her OA diagnosis, but now finds the analgesic is ineffective, even at the maximum dose of 4 g per day.

Carol has hypertension, which was difficult to manage until she began taking a combination ACE inhibitor/diuretic. She also has moderate renal impairment and mild chronic obstructive pulmonary disease, which limits her exercise tolerance. Nonetheless, she continues to smoke. The patient lives with and cares for her husband, who has Alzheimer's disease, and worries about her ability to continue to care for him.

What are her treatment options?

Full-dose acetaminophen is no longer helping Carol, and NSAIDs are contraindicated because she takes an ACE inhibitor/diuretic and has moderate renal impairment. Increasing exercise will be a challenge. You strongly encourage her to stop smoking, emphasizing that this is particularly important to reduce the risk involved with any future joint replacement surgery.

Oral dosing options for the patient include:

- prescribing tramadol, starting with a low-dose immediate-release formulation taken one hour before bedtime (The controlled-release formulation is not advisable, given her age and renal function.) *or*
- adding a traditional opioid, eg, codeine 30 to 60 mg every 6 hours as needed, to her regular acetaminophen regimen.

Codeine and hydrocodone are available in combination preparations with acetaminophen, which may be convenient for some patients. However, hydrocodone was not one of the opioids tested in the trials included in the Cochrane reviews, and evidence of its use in OA is lacking.

Intra-articular corticosteroid injection, performed under imaging guidance, is another option for Carol. You explain that although there have been no studies of intra-articular corticosteroid injections for OA of the hip, these are used occasionally and may provide short-term symptom relief.[7]

You emphasize that surgery is likely to give her the best long-term outcome. In view of the patient's circumstances and the need to care for her husband, however, you prescribe tramadol 50 mg at night. (Because of Carol's age, renal impairment, and the possible adverse effects, it's wise to start with a low dose and titrate upwards.) You warn her of the risks associated with opioids and advise her to alert your office staff if she experiences any adverse effects.

Before the patient leaves, you arrange an orthopedic consult and schedule a return visit for the following week. At your urging, she agrees to look into respite options for her husband.

One in 8 patients stopped taking tramadol because of a major adverse event.

receiving either diclofenac or dextropropoxyphene (NNH=5), but less likely compared with patients taking pentazocine. In a trial that compared tramadol alone with paracetamol, 2 out of 10 in the tramadol group discontinued treatment; none in the paracetamol group did.[13]

Post-review RCTs provide further evidence

We identified 4 double-blind RCTs of tramadol for the treatment of OA that were of at least 6 weeks' duration,[19-22] published after the 2006 review. The results of these studies (**TABLE 2**) were broadly consistent with those

of the systematic review. Two of the 4 studies had active controls, with one comparing tramadol with diclofenac[19] and the other with celecoxib.[21] Tramadol and diclofenac were found to be equally effective; celecoxib appeared to be superior in terms of pain relief, global improvement, and physical function, but no statistical comparisons were reported.

Oral and transdermal opioids: Pain relief but high risk

Among the patients with OA of the hip or knee—the study population for the review of oral and transdermal opioids—all the opioids tested were more effective than placebo. The benefits, however, were small to moderate, and were offset by large increases in the risk of AEs and a high dropout rate.

Four of the 10 trials reported the number of patients experiencing any AE: 23% of those taking opioids vs 15% of patients on placebo.[11] This represents an NNH of 12 (**TABLE 1**). All 10 trials reported the number of patients who withdrew due to AEs. Those receiving opioids were 4 times as likely to withdraw due to AEs, compared with those taking placebo. The NNH to cause one additional withdrawal was 19 (95% CI, 13-29).

In the opioid review—which included trials of 4 oral opioids and transdermal fentanyl—the effect size was similar, regardless of analgesic potency or administration route.

Bottom line

The data highlight both the limited role of opioids (including tramadol) in OA treatment and—when they are being considered for this patient population—the importance of making patients aware that the risks may outweigh the benefits. Used judiciously and with adequate patient counseling, tramadol may be an option when COX-2-specific inhibitors and NSAIDs fail or cannot be tolerated. Although the small-to-moderate benefits of non-tramadol opioids are generally outweighed by large increases in the risk of AEs, their use may be considered for severe OA pain if tramadol is ineffective or causes intolerable AEs. **JFP**

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