

# Cochrane for Clinicians

*Putting Evidence into Practice*

These are summaries of reviews from the Cochrane Library.

This series is coordinated by Corey D. Fogleman, MD, Assistant Medical Editor.

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**CME** This clinical content conforms to AAFP criteria for continuing medical education (CME). See CME Quiz Questions on page 284.

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## Controlled-Release Oxycodone for Neuropathic Pain and Fibromyalgia in Adults

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### Clinical Question

Is controlled-release (CR) oxycodone (Oxycontin) a safe and effective treatment for chronic neuropathic pain and fibromyalgia?

### Evidence-Based Answer

Oxycodone CR has limited effectiveness for the treatment of diabetic neuropathy or postherpetic neuralgia. Evidence is lacking regarding treatment benefit for other neuropathic pain syndromes or fibromyalgia. Adverse effects of oxycodone CR therapy are common. (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

### Practice Pointers

Chronic neuropathic pain and fibromyalgia are estimated to affect 10% of adults older than 30 years.<sup>1</sup> Neuropathic pain is classically difficult to treat, requiring a multidisciplinary approach with pharmacologic, physical, and mental health interventions. Even with a multifaceted approach, few patients achieve appreciable pain relief (i.e., at least a 50% reduction in pain intensity), typically achieving 10% to 25% more relief than with placebo.<sup>2</sup> Although opioid agonists are commonly used for the management of postoperative, posttraumatic, and cancer-related pain, their effectiveness in neuropathic pain syndromes is unclear.

This Cochrane review is one of a series exploring medications to treat neuropathic pain and fibromyalgia, and specifically looks at the effectiveness of oxycodone CR for these pain syndromes. Study arms included treatment groups using oxycodone in any dose and by any route compared with placebo or an active comparator. Participants

were adults 18 years or older with one or more of a range of chronic neuropathic pain conditions. Primary outcome measures were patient-reported percentage in pain intensity reduction, and secondary outcomes included adverse effects and withdrawals from studies because of adverse effects or lack of effectiveness.

Of 2,583 reports identified, three studies involving 254 participants met inclusion criteria. These studies tested oxycodone CR in diabetic neuropathy or postherpetic neuralgia. No studies were found that used oxycodone CR to treat fibromyalgia. Oral oxycodone CR was used in all three studies, all used a placebo group, and one used an active placebo group arm (benztropine). All studies had one or more sources of major bias.

None of the studies reported that participants had a 50% reduction in pain or felt “much improved” while taking oxycodone CR. One study reported a 30% reduction in pain in the oxycodone CR group. Outcomes regarding significant pain relief and high patient satisfaction with oxycodone CR were derived from third-tier data, meaning they had a small number of participants, bias present, and/or limited clinical usefulness of outcomes.

Adverse effects were more common in the treatment arms than in the placebo groups. At least one adverse effect was reported by 86% of persons in the oxycodone CR groups compared with 63% in the placebo groups. Somnolence, dizziness, and constipation were the most commonly reported adverse effects. Of those taking oxycodone CR, 11% withdrew from the study because of adverse effects compared with 6.4% in the placebo groups. However, 1.1% of those in the oxycodone CR groups withdrew from the study because of a lack of treatment effectiveness vs. 11% of those in the placebo group. The number needed to harm for participants taking oxycodone CR compared with placebo is 4.3 (95% confidence interval, 3.1 to 7.0).

Current guidelines for the treatment of neuropathic pain recommend opioid agonists as second-line agents only after first-line agents such as antidepressants, gabapentin (Neurontin), pregabalin (Lyrica), or topical lidocaine have failed.<sup>3</sup> Although all treatment for chronic pain should be individualized to the patient, there is no compelling evidence that oxycodone CR improves neuropathic pain from diabetic neuropathy or postherpetic neuralgia, and it should not be considered first-line treatment for these conditions.

SOURCE: Gaskell H, Moore RA, Derry S, Stannard C. Oxycodone for neuropathic pain and fibromyalgia in adults. *Cochrane Database Syst Rev.* 2014;(6):CD010692.

The practice recommendations in this activity are available at <http://summaries.cochrane.org/CD010692>.

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

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## Risk of Venous Thromboembolism with Use of Combined Oral Contraceptives

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### Clinical Question

Which combined oral contraceptives carry the greatest risk of venous thromboembolism (VTE)?

### Evidence-Based Answer

All combined oral contraceptives increase VTE risk. The risk is greater for those containing desogestrel, drospirenone, gestodene

(not available in the United States), and cyproterone acetate (not available in the United States) when compared with levonorgestrel. All combined oral contraceptives are effective in preventing pregnancy. (Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

### Practice Pointers

The first combined oral contraceptives debuted in 1960 and are now used by 17% of women 15 to 44 years of age. In the United States, more women use combined oral contraceptives than any other contraceptive method.<sup>1</sup> However, studies have demonstrated an up to fourfold increase in the risk of VTE among combined oral contraceptive users compared with nonusers (pregnancy carries a slightly greater than fourfold risk).<sup>2,3</sup> Over time, the hormone formulations and dosages of combined oral contraceptives have changed in an effort to decrease thrombotic risk. The authors of this review looked at studies featuring multiple combined oral contraceptive formulations and dosages to determine the relative risk associated with each.

This Cochrane review included nine cohort and 17 case-control studies. The authors found no pertinent randomized controlled trials. Only five studies objectively confirmed VTE in all study patients, raising concern that ascertainment bias influenced the outcomes of the other studies. The absolute risk of VTE in nonusers was 0.19 to 0.37 per 1,000 woman-years. The risk of VTE with combined oral contraceptive use (15 studies) was 3.5 times greater than with nonuse (95% confidence interval [CI], 2.9 to 4.3).

Compared with that of nonusers, the risk of VTE was 3.2 times greater (95% CI, 2.0 to 5.1) with first-generation progestins, 2.8 times greater (95% CI, 2.0 to 4.1) with second-generation progestins, and 3.8 times greater (95% CI, 2.7 to 5.4) with third-generation progestins. This corresponds to absolute risk increases of 0.61 to 1.18 per 1,000 woman-years for first-generation progestins, 0.55 to 1.04 per 1,000 woman-years for second-generation progestins, and 0.72 to 1.41 per 1,000 woman-years for third-generation progestins. Risk of VTE was similar

among the third- and fourth-generation progestins desogestrel, drospirenone, gestodene, and cyproterone acetate, each of which carried a risk of VTE that was 50% to 80% higher than that associated with the second-generation progestin levonorgestrel.

The Centers for Disease Control and Prevention (CDC) recommends against combined oral contraceptive use in those who smoke more than 15 cigarettes per day, who have a blood pressure equal to or greater than 160 mm Hg systolic or 100 mm Hg diastolic, or who have multiple risk factors for or a history of vascular disease. Likewise, the CDC strongly recommends against the use of combined oral contraceptives in those who have a history of VTE or known thrombophilia.<sup>4</sup>

All women should be counseled on the risk of VTE with combined oral contraceptive use vs. the risk of VTE in pregnancy (1.4%; 95% CI, 1.0% to 1.8%).<sup>5</sup> As much as possible, physicians should try to use lower-dose hormone formulations to decrease the risk of VTE. Based on this review, levonorgestrel has a lower risk than desogestrel, drospirenone, gestodene, or cyproterone acetate.

SOURCE: de Bastos M, Stegeman BH, Rosendaal FR, et al. Combined oral contraceptives: venous thrombosis. *Cochrane Database Syst Rev*. 2014;(3):CD010813.

The practice recommendations in this activity are available at <http://summaries.cochrane.org/CD010813>.

The views expressed here are those of the author and do not necessarily reflect those of the U.S. Army or the Department of Defense.

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