Cochrane for Clinicians

Putting Evidence into Practice

Opioid Antagonists for the Treatment of Alcohol Dependence

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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. Drs. Yancey and Lumbad present 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/ab001867.html.

EB CME

This clinical content conforms to AAFP criteria for evidence-based continuing medical education (EB CME). See CME Quiz on page 983.

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Clinical Scenario

A 45-year-old man comes to your office for evaluation after an arrest for driving under the influence of alcohol. He is concerned about his alcohol dependence, and is interested in medical help to quit drinking. You wonder if an opioid antagonist could help him abstain from alcohol.

Clinical Question

Do opioid antagonists help patients with alcohol dependence to stop drinking?

Evidence-Based Answer

Although it does not improve overall alcohol abstinence rates, the oral formulation of the opioid antagonist naltrexone (Revia) is moderately effective in decreasing the amount and frequency of alcohol consumption in patients with alcohol dependence.[1] (Strength of Recommendation: C, based on consensus, disease-oriented evidence, usual practice, expert opinion, or case series.)

Practice Pointers

Alcohol dependence is a disease with cognitive, behavioral, and physiologic symptoms in persons who continue to drink despite significant alcohol-related problems. Symptoms often include tolerance, withdrawal, and other physical and social impairments.[2] Because opioid receptors likely play a role in mediating the pleasant effects of alcohol, the opioid antagonists naltrexone and nalmefene (not available in the United States) have been studied as potential treatments for alcohol dependence.[3]

This Cochrane review examined 50 randomized controlled trials to determine whether the use of opioid antagonists could help patients with alcohol dependence to stop drinking or drink less.[1] The review included studies examining nalmefene and the oral and injectable (Vivitrol) formulations of naltrexone. Both agents in all formulations were compared with placebo; oral naltrexone also was compared with other medications, including acamprosate (Campral), aripiprazole (Abilify), nefazodone, and topiramate (Topamax). Combinations of oral naltrexone with acamprosate, ondansetron (Zofran), and sertraline (Zoloft) also were compared with placebo. Study participants were older than 18 years and had diagnosed alcohol abuse, alcohol dependence, or both. Most studies excluded persons with major psychiatric comorbidities and those who used illicit drugs. Most studies also provided concurrent psychosocial treatment to all participants. The primary end points were rates of return to heavy drinking, return to any drinking, and percentage of drinking days.

Compared with placebo, oral naltrexone reduced the risk of return to heavy drinking by 83 percent (relative risk [RR] = 0.17; 95% confidence interval [CI], 0.10 to 0.24) and reduced the number of drinking days by 4 percent (mean difference [MD] = –3.89; 95% CI, –5.75 to –2.04). In addition, naltrexone reduced heavy drinking days by 3 percent (MD = –3.25; 95% CI, –5.51 to –0.99) and reduced alcohol consumption by 11 g (0.39 oz) on drinking days (MD = –10.83; 95% CI, –19.69 to –1.97). There was no statistically significant difference in return to any drinking (RR = 0.96; 95% CI, 0.92 to 1.00).

Adverse effects were more common with naltrexone than placebo. These included gastrointestinal effects (e.g., abdominal pain, decreased appetite, nausea, vomiting), as well as neurologic effects (e.g., drowsiness, fatigue, insomnia, weakness,

Cochrane Abstract

Background: Alcohol dependence belongs to the globally leading health risk factors. Therapeutic success of psychosocial programs for relapse prevention is moderate and could be increased by an adjuvant treatment with the opioid antagonists naltrexone and nalmefene (not available in the United States).

Objectives: To determine the effectiveness and tolerability of opioid antagonists in the treatment of alcohol dependence.

Search Strategy: We searched the Cochrane Drugs and Alcohol Group (CDAG) Specialized Register, PubMed, EMBASE, and CINAHL in January 2010, and asked manufacturers and researchers for unpublished trials.

Selection Criteria: All double-blind randomized controlled trials that compare the effects of naltrexone or nalmefene with placebo or active control on drinking-related outcomes.

Data Collection and Analysis: Two authors independently extracted outcome data. Trial quality was assessed by one author and cross-checked by a second author.

Main Results: Based on a total of 50 randomized controlled trials with 7,793 patients, naltrexone reduced the risk of heavy drinking to 83 percent of the risk in the placebo group (relative risk [RR] = 0.17; 95% confidence interval [CI], 0.10 to 0.24) and decreased drinking days by about 4 percent (mean difference [MD] = −3.89; 95% CI, −5.75 to −2.04). Significant effects were also demonstrated for the secondary outcomes of the review, including heavy drinking days (MD = −3.25; 95% CI, −5.51 to −0.99), consumed amount of alcohol (MD = −10.83; 95% CI, −19.69 to −1.97), and γ-glutamyltransferase levels (MD = −0.37; 95% CI, −18.99 to −1.75), whereas the effects on return to any drinking (RR = 0.96; 95% CI, 0.92 to 1.00) missed statistical significance. Adverse effects of naltrexone were mainly gastrointestinal problems (e.g., nausea; risk difference [RD] = 0.10; 95% CI, 0.07 to 0.13) and sedative effects (e.g., daytime sleepiness; RD = 0.09; 95% CI, 0.05 to 0.14). Based on a limited study sample, effects of injectable naltrexone and nalmefene missed statistical significance. Effects of industry-sponsored studies (RR = 0.90; 95% CI, 0.78 to 1.05) did not significantly differ from those of nonprofit-funded trials (RR = 0.84; 95% CI, 0.77 to 0.91), and the linear regression test did not indicate publication bias (*P* = .765).

Authors' Conclusions: Naltrexone appears to be an effective and safe strategy in alcoholism treatment. Even though the sizes of treatment effects might appear moderate in their magnitudes, these should be valued against the background of the relapsing nature of alcoholism and the limited therapeutic options currently available for its treatment.

somnolence, lethargy, blurred vision, decreased libido, dizziness, depression, nightmares, daytime sleepiness).

There are no established guidelines on the appropriate length of naltrexone treatment for alcohol dependence. One study recommends oral naltrexone for at least three months. If it is not successful in helping the patient remain abstinent, a longer course or higher dosage of oral naltrexone, or changing to the injectable form, may be considered.[3]

Physicians treating patients who use illicit intravenous drugs have been hopeful that using an injectable extended-release formulation of naltrexone would improve compliance. In a small subgroup analysis of injectable naltrexone, there was no statistically significant difference in the risk of return to any drinking (RR = 0.92; 95% CI, 0.84 to 1.00) or in the percentage of heavy drinking days (MD = −3.05; 95% CI, −8.46 to 2.35). There was a statistically significant 9 percent reduction in days of any drinking (MD = −8.54; 95% CI, −15.77 to −1.31).[1]

In another Cochrane review, the glutamate antagonist acamprosate was found to provide moderate benefit for maintaining abstinence from alcohol use in those who are dependent.[4] In the Cochrane review on opioid antagonists, three clinical trials comparing naltrexone with acamprosate found no statistical difference in return to any drinking (RR = 0.97; 95% CI, 0.91 to 1.04), number of drinking days (MD = 3.06; 95% CI, −7.42 to 13.53), or risk of return to heavy drinking (RR = 0.96; 95% CI, 0.87 to 1.06).[1] Adverse effect profiles differed. Naltrexone was associated with significantly more nausea (risk difference [RD] = 0.08; 95% CI, 0.03 to 0.13) and somnolence (RD = 0.07; 95% CI, 0.01 to 0.13), whereas acamprosate was associated with more diarrhea (RD = −0.27; 95% CI, −0.34 to −0.20). Individual trials analyzing naltrexone versus aripiprazole, nefazodone, and topiramate showed no medication to be statistically superior to naltrexone.

When the combination of naltrexone and acamprosate was compared with naltrexone alone, there was no statistical difference in return to heavy drinking (RR = 0.97; 95% CI, 0.75 to 1.26), any drinking (RR = 0.88; 95% CI, 0.61 to 1.28), or drinking days (MD = −1.10; 95% CI, −5.21 to 3.01). Combined treatment was associated with more diarrhea (RD = 0.37; 95% CI, 0.10 to 0.65) and more nausea (RD = 0.09; 95% CI, 0.14 to 0.26).

Three randomized trials compared nalmefene with placebo. No statistically significant difference was noted in return to heavy drinking, return to any drinking,

reduction in drinking days, or amount of alcohol consumed. Nausea, dizziness, and insomnia were more common with nalmefene use.

Opioid antagonists modestly decrease alcohol consumption in patients with alcohol dependence, although they do not increase the likelihood that patients will stop drinking entirely. Given the lack of other more effective treatments for alcohol dependence, naltrexone is a useful adjunct to psychosocial treatment.

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

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Cochrane Briefs

Cognitive Interventions for Improving Cognitive Function

Clinical Question

Do cognitive interventions improve cognitive function in healthy older adults and older adults with mild cognitive impairments?

Evidence-Based Answer

Compared with no treatment, cognitive interventions improved cognitive performance in healthy older adults and older adults with mild cognitive impairments. However, there is inadequate evidence to determine which aspects of these interventions are effective.

(Strength of Recommendation: B, based on inconsistent or limited-quality patient-oriented evidence.)

Practice Pointers

Cognition may decline with increasing age. Mild cognitive impairment is defined as cognitive changes that are greater than expected for a person's age but not severe enough to meet criteria for dementia. Nonrandomized studies suggest that cognitive interventions may improve cognitive function in older adults. These interventions include activities such as problem-solving training, mnemonic training, and guided imagery.

The authors systematically reviewed literature from 1970 to 2007 that examined the effect of cognitive training on domains of cognitive functioning (i.e., memory, executive function, attention, and speed). Data from 24 randomized controlled trials with 2,229 participants were pooled according to measures of cognitive functioning, improvement, sustainability, and transfer of training effects. Time devoted to training ranged from six to 135 hours over a period of one day to one year. Studies included varying forms of individual and group-based interventions.

Adults with and without mild cognitive impairments who were randomized to receive cognitive training had statistically significant improvement in the areas of immediate and delayed verbal recall compared with persons who did not receive treatment. However, these improvements did not exceed those observed in persons randomized to active control groups, which included interventions such as discussion groups and physical training.

There are currently no guidelines specifically for cognitive training for adults older than 60 years. Although this review found improvement with different forms of active training, more research is needed to define optimal training design and the amount of training time needed.

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