

Pharmacotherapy for Adults With Alcohol Use Disorder in Outpatient Settings: Systematic Review

Executive Summary



Main Points

- This review updates a prior review of pharmacotherapy for alcohol use disorder published in 2014.¹
- Evidence for the use of oral naltrexone at the 50 mg dose had moderate strength of evidence across multiple outcomes, as well as relative ease of use as a once-daily oral medication and a number needed to treat for preventing return to any drinking of 18 and a number needed to treat to prevent return to heavy drinking of 11.
- The prior report found uncertain benefit for injectable naltrexone, but the addition of a new randomized controlled trial conducted in a population experiencing homelessness resulted in positive outcomes for a reduction in drinking days and in heavy drinking days, resulting in low strength of evidence.
- Acamprosate and topiramate have evidence for benefit with moderate strength of evidence. Treatment decisions could be affected by ease of use (e.g., the need to take multiple pills over the course of a day), the side effect profile, and potential for contraindications. The number needed to treat for preventing return to any drinking for acamprosate was 11.
- Since the last report, the addition of 11 new studies of baclofen have demonstrated low strength of evidence for reducing return to any drinking and studies of gabapentin demonstrated low strength of evidence for reducing return to any drinking and return to heavy drinking.
- No new eligible studies were found for disulfiram. Relatively limited evidence from well-controlled trials does not adequately support the efficacy of disulfiram compared with placebo for preventing return to any drinking or for other alcohol consumption outcomes. Our concluding assessment of this drug remains the same as the prior 2014 review.
- Because there are too few studies, very little evidence exists to evaluate the effectiveness of treatment with medications for alcohol use disorder among specific populations or in primary care settings.



Background and Purpose

Unhealthy alcohol use is the third leading preventable cause of death in the United States, accounting for more than 140,000 deaths annually.² Data from the 2020 National Survey on Drug Use and Health suggest that more than 28.3 million Americans 12 years of age or older met *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition³ criteria for alcohol use disorder in the past year.^{4,5} Only 0.9 percent of Americans who reported an alcohol use disorder in the past year received any medication assisted alcohol use disorder treatment, with 1 percent prescribed an approved medication as part of treatment, despite evidence of effectiveness for some pharmacotherapies.⁶

In 2014, the Agency for Healthcare Research and Quality Effective Healthcare Program published a systematic review of pharmacologic treatment for alcohol use disorder, which is the basis for this updated review.¹ Since the 2014 report on medications for alcohol use disorder, the literature has grown and a synthesis that incorporates new evidence could improve estimates of the benefits and harms of medications for alcohol use disorder, thus, optimizing clinical decision making. By improving clinical decision making, an updated review could potentially improve the health and welfare of persons with alcohol use disorder.



Methods

We used systematic review approaches in the Agency for Healthcare Research and Quality Evidence-based Practice Center Guidance to assess the evidence for our Key Questions. We reviewed studies for three medications with Food and Drug Administration approval for alcohol use disorder (including naltrexone, which has two formulations) and six medications that are currently used off-label in the United States. Eligibility criteria for studies for each Key Question are described in the full report. We searched multiple databases and the gray literature using publication dates from November 1, 2012, through September 9, 2022. When possible, we conducted quantitative analyses using random-effects models to estimate pooled effects.⁷ For continuous outcomes (e.g., scales for symptom reduction), we used weighted mean differences. For binary outcomes, we calculated risk ratios between groups. We included all studies in the main analyses and conducted sensitivity analyses without studies rated as high or unclear risk of bias. We graded strength of evidence based on the guidance established for the Evidence-based Practice Center program.⁸



Results

We included 118 studies (156 articles) in our review. Among these, 81 studies (106 articles) were included in the 2014 report and 37 studies (50 articles) are new to this update. Key Question 1 included 111 studies, Key Question 2 included 31 studies, Key Question 3 included 99 studies, Key Question 4 included 1 study, and Key Question 5 included 9 studies.

There was one new trial for acamprosate, five new trials for naltrexone (1 of which was for injectable naltrexone), and no new studies of disulfiram. In addition, there were 11 new trials to this update for baclofen and 7 new trials for topiramate, and a small number of studies reported on some drugs for which there previously were no trials or only 1 trial (e.g., 5 new trials of varenicline, 4 new trials of gabapentin, 2 new trials of ondansetron, 2 new trials of prazosin). No new eligible studies provided head-to-head comparisons.

Key Question 1: Efficacy and Comparative Effectiveness for Improving Consumption Outcomes. Naltrexone had moderate strength of evidence for reducing return to any drinking, return to heavy drinking, percent drinking days, and percent heavy drinking days at the 50 mg oral dose. Of note, the prior report found no benefit for injectable naltrexone, but the addition of a new randomized controlled trial conducted in a population experiencing homelessness resulted in positive outcomes for a reduction in drinking days and in heavy drinking days, resulting in low strength of evidence. Acamprosate had moderate strength of evidence for a significant reduction in return to any drinking and reduction in drinking days. Topiramate demonstrated moderate strength of evidence for percent drinking days, percent heavy drinking days and drinks per drinking day. Other medications that demonstrated low strength of evidence for benefit in at least one consumption outcome included baclofen (return to any drinking) and gabapentin (return to any drinking and return to heavy drinking). As reported in the prior report, relatively limited evidence from well-controlled trials does not adequately support the efficacy of disulfiram compared with placebo for preventing return to any drinking or for other alcohol consumption outcomes.

Key Question 2: Health Outcomes. As in the prior report, few studies measured health outcomes so most medications had insufficient strength of evidence. We did find low strength of evidence for no difference in quality of life measures for baclofen based on two studies, and in the topiramate studies, we found low strength of evidence for no effect on injuries or quality of life measures.

Key Question 3: Harms. Collection of adverse events data was notably inconsistent across studies. In particular, although some studies reported all adverse events, others only reported them in the situation where they differed by medication or placebo arm or where there were higher numbers of affected participants (e.g., 5% or more). Serious harms were rarely reported, but some minor harms such as diarrhea and dizziness were common. Compared with placebo, study participants treated with acamprosate were more likely to experience anxiety and diarrhea. Trials of naltrexone found higher likelihood of dizziness, insomnia, nausea, and vomiting. Baclofen studies reported an increased likelihood of dizziness, drowsiness, numbness, and sleepiness. Trials of topiramate reported increased risks of many adverse events, including paresthesias, taste abnormalities, anorexia, difficulty with concentration/attention, nervousness, dizziness, pruritis, psychomotor slowing, and weight loss. Varenicline was associated with higher rates of nausea, and gabapentin with cognitive dysfunction and dizziness. Neither ondansetron nor prazosin had adequate data to assess harms. In head-to-head studies, patients treated with acamprosate had a slightly lower risk of headache and vomiting than those treated with naltrexone. For most serious harms, there was insufficient data to determine comparative rates of adverse events.

Key Question 4: Evidence From Primary Care Settings. We found no new evidence on the use of alcohol use disorder medications in primary care settings; thus, evidence continues to be scant. One trial (N=100) that recruited participants primarily by advertisement in two family medicine settings in the United States found no significant treatment effect when comparing acamprosate with placebo.⁹

Key Question 5: Subgroups: We did not find any convincing evidence that any medication is more or less effective (compared with each other) for men or women, older adults, young adults, persons who smoke, or those with co-occurring disorders in head-to-head studies.



Major Changes Since the Previous Report

We largely attempted to maintain the approach taken in the original review in this update, with some exceptions. As before, we included all medications with Food and Drug Administration indications for alcohol use disorder (acamprosate, naltrexone [both oral and injectable] and disulfiram). With the help of our technical expert panel, we limited drugs with off-label uses to those that are currently in use in the United States (baclofen, gabapentin, ondansetron, topiramate, varenicline, and prazosin). Therefore, some drugs reviewed as emerging therapies and some only available outside the United States (e.g., nalmefene) may have been in the original review but not in the current update. We also eliminated a Key Question on pharmacogenomics that was in the original review. In terms of results, our assessment of the effects of those drugs with Food and Drug Administration approval for alcohol use disorder treatment remained essentially the same with a few more studies available to add to the evidence base. What is new in this update is the addition of evidence related to several medications used off-label for treatment. In particular, baclofen and gabapentin have new studies that provide low strength of evidence for benefit in some outcomes. Although there are a number of studies of varenicline, strength of evidence is low for no effect across all outcomes.



Limitations

There are limitations associated with both our review methods and the literature itself. We included only medications currently in use in the United States and we did not examine nonpharmacologic interventions. We excluded trials that had less than 12 weeks of follow up from the time of medication initiation; because longitudinal studies have found that shorter treatment periods may yield misleading conclusions about treatment efficacy, we do not consider this a significant limitation.^{10, 11} We combined studies that included populations with a dual diagnosis (e.g., alcohol dependence and depression) and those that did not have a dual diagnosis in the meta-analyses. We did not examine data on subgroups in placebo-controlled trials because we were attempting to answer a comparative question regarding relative effectiveness for different medications by subgroup. The biggest limitations of the evidence base were a lack of direct evidence on health outcomes, limited and varying reporting on harms, a lack of trials conducted in

primary care settings, and scant head-to-head evidence on differences for population subgroups.



Implications and Conclusions

Oral naltrexone (50 mg) had moderate strength of evidence across multiple outcomes and relative ease of use as a once-daily oral medication. Acamprosate and topiramate also have evidence of benefit. Topiramate has a less desirable side effect profile, and both are less convenient to take, with multiple doses per day. Acamprosate is contraindicated in patients with severe renal impairment. Injectable naltrexone has low strength of evidence for reduction in drinking days and heavy drinking days. To some degree, treatment decisions may be driven by desired outcomes. For example, acamprosate has evidence for effectiveness in abstinence outcomes, whereas topiramate only has evidence for reduction of heavy drinking. Regardless, decisions about treatment should be made collaboratively between the patient and the clinician with considerations for desired outcomes, tolerance of side effects, contraindications, and the potential to adhere to the medication regimen.

Currently, there is insufficient evidence on the direct impact of medications on health outcomes. Engaging patients to ensure that outcomes are patient centered and meet a range of patient needs also will benefit the field. Very little evidence exists to evaluate the effectiveness of the use of medications for alcohol use disorder among specific populations.

Finally, only one study was carried out in primary care. There are too few studies to assess the efficacy of medications in this setting or to characterize differences between specialty outpatient clinics and primary care populations. Although medication efficacy does not depend on setting, there may be meaningful differences with regard to population or availability of concomitant therapies. Given the increasing numbers of patients with alcohol use disorder, it is likely that primary care providers will be essential to any treatment strategy. Understanding best approaches to using pharmacotherapy for treatment in primary care is an area worthy of specific study.



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Full Report

McPheeters M, O'Connor EA, Riley S, Kennedy SM, Voisin C, Kuznacic K, Coffey CP, Edlund M, Bobashev G, Jonas DE. Pharmacotherapy for Adults With Alcohol Use Disorder in Outpatient Settings: Systematic Review. Comparative Effectiveness Review No. 262. (Prepared by the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center under Contract No. 75Q80120D00007.) AHRQ Publication No. 23(24)-EHC011. Rockville, MD: Agency for Healthcare Research and Quality; November 2023. DOI: <https://doi.org/10.23970/AHRQEPCCER262>. Posted final reports are located on the Effective Health Care Program [search page](#).

