Comparative Effectiveness Review
Number 262

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

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None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of healthcare in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new healthcare technologies and strategies.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see https://effectivehealthcare.ahrq.gov/about/epc/evidence-synthesis.

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the website (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

If you have comments on this systematic review, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicting opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $5,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

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Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers. AHRQ may also seek comments from other Federal agencies when appropriate.

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

Abstract

Background. Unhealthy alcohol use is the third leading preventable cause of death in the United States, accounting for more than 140,000 deaths annually. Only 0.9 percent of Americans who reported having alcohol use disorder (AUD) in the past year indicated they received medication-assisted AUD treatment.

Methods. We updated a 2014 Agency for Healthcare Research and Quality (AHRQ) report on pharmacotherapy for AUD treatment, following AHRQ Evidence-based Practice Center Guidance. We assessed efficacy and comparative effectiveness of specific medications for improving consumption outcomes (Key Question [KQ] 1) and health outcomes (KQ 2). We assessed harms (KQ 3) and sought to identify evidence for the use of pharmacotherapy to treat AUD in primary care (KQ 4) and among subgroups (KQ 5). When possible, we conducted quantitative analyses using random-effects models to estimate pooled effects. When quantitative analyses could not be conducted, we used qualitative approaches.

Results. We included 118 studies (156 articles) in our review, which included 81 studies (106 articles) from the 2014 review and 37 studies (50 articles) published since then. Studies generally included counseling co-interventions in all study groups, and the benefits observed reflect the added benefit of medications beyond those of counseling and placebo. Oral naltrexone at the 50 mg dosage had moderate strength of evidence (SOE) for reducing return to any drinking, return to heavy drinking, percent drinking days, and percent heavy drinking days. The addition of a new randomized controlled trial of injectable naltrexone conducted in a population experiencing homelessness resulted in positive outcomes for a reduction in drinking days and heavy drinking days with low SOE. Acamprosate had moderate SOE for a significant reduction in return to any drinking and reduction in drinking days. Topiramate had moderate SOE for several outcomes as well, but with greater side effects. Two other medications demonstrated low SOE for benefit in at least one consumption outcome—baclofen (reduced return to any drinking) and gabapentin (reduced return to drinking and to heavy drinking). With no new studies on disulfiram, there remains inadequate evidence for efficacy compared to placebo for preventing return to any drinking or for other alcohol consumption outcomes. No new eligible studies provided head-to-head comparisons.

Conclusions. Oral naltrexone at the 50 mg dose had moderate strength of evidence across multiple outcomes and relative ease of use as a once-daily oral medication. Acamprosate and topiramate also have moderate evidence of benefit with a less desirable side effect profile (topiramate) and a higher pill burden (acamprosate). Clinicians and patients may want to consider which treatment outcomes are most important when choosing among the medications. Current data are largely insufficient for understanding health outcomes. Finally, there is relatively little research to assess the use of medications for AUD among subgroups (9 studies) or in primary care settings (1 study).

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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 edition[3] 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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1. Introduction

1.1 Background

Alcohol use disorder (AUD) is relatively common in developed countries.[1, 2] Estimates of lifetime prevalence are greater than 20 percent, and men are twice as likely as women to have AUD.[1, 3-5] Unhealthy alcohol use is the third leading preventable cause of death in the United States, accounting for more than 140,000 deaths annually.[6] Data from the 2020 National Survey on Drug Use and Health (NSDUH) suggest that more than 28.3 million Americans 12 years of age or older met *Diagnostic and Statistical Manual of Mental Disorders,* fifth edition (DSM-5) criteria for AUD in the past year.[7, 8] This is significantly higher than in 2019, likely due to differences between the 2019 and 2020 surveys and the COVID-19 pandemic.[7, 8] In 2021, 29.5 million people reported having AUD. In that same year, 2.6 million received treatment for AUD regardless of past-year use. Of these, 15.1 percent received medication assisted treatment in the past year for alcohol use. Among the 29.5 million people with a past-year AUD, 0.9 percent or 265,000 people received medication assisted treatment.[9,10]

Definitions of unhealthy alcohol use (sometimes termed alcohol misuse)[11] continue to evolve, as our knowledge base grows. Unhealthy alcohol use ranges from risky alcohol use (without AUD) to severe AUD. While the current standard criteria used for diagnosis of AUD are from the *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition, Text Revision (DSM-5-TR),[12] the inclusion criteria for unhealthy alcohol use severity differ across studies, particularly because criteria have evolved over time (Table 1).

Table 1. Definitions of unhealthy alcohol use (sometimes previously referred to as alcohol misuse)

Term	Definition
Alcohol use disorder (DSM-5-TR)[12]	A problematic pattern of alcohol use leading to clinically significant impairment or distress, as manifested by at least two of the following, occurring within a 12-month period: Alcohol is often taken in larger amounts or over a longer period than was intended. (1) There is a persistent desire or unsuccessful efforts to cut down or control alcohol use. (2) A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects. (3) Craving, or a strong desire or urge to use alcohol. (4) Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, home, or school. (5) Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol. (6) Important social, occupational, or recreational activities are given up or reduced because of alcohol use. (7) Recurrent alcohol use in situations in which it is physically hazardous. (8) Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol. (9) Tolerance as defined by either of the following: a. A need for markedly increased amounts of alcohol to achieve the intoxication or desired effect. b. A markedly diminished effect with continued use of the same amount of alcohol. (10) Withdrawal, as manifested by either of the following: a. The characteristic withdrawal symptoms for alcohol. b. Alcohol (or a closely related substance, such as a benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

1. Introduction

Term	Definition
Alcohol use disorder (DSM-5-TR)[12] (continued)	Severity: Mild: 2-3 symptoms Moderate: 4-5 symptoms Severe: 6 or more symptoms
Risky or hazardous use	Consumption of alcohol above recommended daily, weekly, or per-occasion amounts.[13] Consumption levels that increase the risk for health consequences.
Harmful use[14, 15]	A pattern of drinking that is causing damage to health. The damage may be either physical (e.g., liver damage) or mental/social (e.g., alcohol-induced depression).
Alcohol abuse (from DSM-IV)[16]	A. A maladaptive pattern of alcohol use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period: (1) Recurrent alcohol use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to alcohol use; alcohol-related absences, suspensions, or expulsions from school; neglect of children or household); (2) Recurrent alcohol use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired); (3) Recurrent alcohol-related legal problems (e.g., arrests for alcohol-related disorderly conduct); or (4) Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol (e.g., arguments with spouse about consequences of intoxication, physical fights). B. The symptoms have never met the criteria for alcohol dependence.
Alcohol dependence from DSM-IV[16] (alcoholism, alcohol addiction)	A maladaptive pattern of alcohol use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period: (1) Tolerance (2) Withdrawal (3) Alcohol is often taken in larger amounts or over a longer period than was intended; (4) There is a persistent desire or unsuccessful efforts to cut down or control alcohol use; (5) A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects; (6) Important social, occupational, or recreational activities are given up or reduced because of alcohol use; *or* (7) Alcohol use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol (e.g., continued drinking despite recognition that an ulcer was made worse by alcohol consumption).

DSM-5-TR = *Diagnostic and Statistical Manual of Mental Disorders,* Fifth Edition, Text Revision , DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition.

AUD causes substantial morbidity and mortality.[17, 18] Between 1999 and 2017, deaths related to alcohol increased 50 percent.[19] The Centers for Disease Control and Prevention estimates that more than 140,000 individuals die annually from excessive alcohol use, and 1 in 10 deaths among working age individuals are due to excessive alcohol use.[6] On average, these deaths result in 26 years of lost life.[6] AUD is associated with several diseases, including but not limited to, hypertension, heart disease, stroke, cognitive impairment, sleep problems, depression, anxiety, peripheral neuropathy, gastritis and gastric ulcers, liver disease including cirrhosis, pancreatitis, osteoporosis, anemia, fetal alcohol spectrum disorders, and several types of cancer.[1, 20] Excessive alcohol consumption is also a major factor in homicide, suicide, motor vehicle accidents and deaths, sexual violence, domestic violence, and drownings.[21] In addition, AUD complicates the assessment and treatment of other medical and psychiatric problems.[1] Furthermore, during the COVID-19 pandemic, researchers at RTI International found significant increases between

February and April 2020 in overall (+29%), excessive (+20%), and binge (+21%) drinking, suggesting that the need for treatment has increased.[22]

1.1.1 Treatments for Alcohol Use Disorder

Treatments for AUD continue to evolve as research on the effectiveness of various treatments is published and include a range of medications and behavioral approaches. Treatment may be delivered via intensive outpatient programs using group or individual counseling, addiction treatment centers, or general outpatient care.

The goals of treatment can range from abstinence to reducing alcohol use or harms related to alcohol use. Although abstinence has traditionally been cited as a predominant goal in much of the treatment literature, awareness has grown over the past 15 to 20 years that outcomes related to reduced alcohol consumption are clinically meaningful and important to patients. Some studies indicate that less than 10 percent of those with AUD are able to achieve long periods of reduced alcohol consumption.[23-27] As a result, research has used a broader array of outcomes to measure the effectiveness of treatment, which can be subsumed under the concept of tertiary prevention.[28] They include number of drinking or nondrinking days or heavy drinking episodes, physical health, healthcare costs, and psychosocial functioning. Research using non-abstinent outcomes provides evidence for the effectiveness of treatment for AUD. Miller et al.[29] analyzed seven large multisite trials. They found that whereas, in aggregate, about 25 percent of individuals maintained sobriety over 1 year, the remaining non-abstinent individuals showed substantial decreases in drinking days (from 63% pretreatment to 25% post-treatment) and a mean 57 percent decrease in drinks per drinking day. Thus, even in the presence of small gains in abstinence there can be reductions in alcohol use that may be meaningful to patients and potentially affect health and other outcomes.

Treatment outcomes can be affected by many factors, including but not limited to the following: (1) AUD severity; (2) co-occurring conditions, including physical and mental health disorders that make treatment more challenging; (3) type of treatment, which can include multiple psychosocial interventions and several pharmacotherapies; (4) pathway to treatment, ranging from voluntary care seeking to legally mandated treatment; (5) patient desires and preferences; (6) stigma; and (7) lack of access to treatment. This complexity contributes to variance in treatment outcomes and makes it difficult to identify a single best treatment across all patients.

1.1.2 Pharmacological Interventions for Alcohol Use Disorder

This review focuses on the effectiveness of pharmacotherapy for AUD in the outpatient setting, including for the reduction of alcohol consumption as well as for achieving abstinence. Current use of pharmacotherapy is low, despite evidence of effectiveness for some medications. Medications for AUD may hold a Food and Drug Administration (FDA) indication for AUD or may be FDA approved for other indications and used off-label to treat AUD. This review covers the four medications with FDA indications for AUD and several other medications that have been studied and are used off-label in the United States.

From the 1950s until the early 1990s, AUD pharmacotherapy consisted only of disulfiram, which produces significant physical symptoms, such as nausea, emesis, and tachycardia, within 12 hours of alcohol consumption. Anticipatory fear of this response acts as a deterrent to consuming alcohol. Its effectiveness requires a high degree of patient motivation and adherence, thereby limiting its overall usefulness for many patients. Since the 1990s, two oral

medications—naltrexone and acamprosate—and one long-acting intramuscular formulation of naltrexone have been approved by FDA for AUD. These medications were originally approved for people with alcohol dependence, generally after withdrawing from alcohol and together with psychological intervention.[2] Table 2 describes the medications available in the United States that are FDA approved for treatment of AUD, their mechanism of action, and dosing. A small group of additional medications are used off-label and have been studied for AUD treatment with some positive results. Table 3 describes the medications commonly used (off-label) for AUD that are included in this review.

Table 2. FDA-approved medications for treating adults with AUD

Generic Drug Name	Mechanism	Usual Dosing
Acamprosate	The exact mechanism of action is unclear but acamprosate is thought to antagonize glutamatergic N-methyl-D-aspartate receptors and lead to increased activation of the GABA type A receptors. [30-32]	666 mg 3 times per day (note: renal dose adjustment to 333 mg 3 times per day if CrCl is 30 to 50 milliliter/minute; and contraindicated if CrCl <30 milliliter/minute)
Disulfiram	A thiuram derivative that blocks the oxidation of alcohol by aldehyde dehydrogenase. When taken concomitantly with alcohol, there is an increase in serum acetaldehyde levels.[33]	250 to 500 mg per day
Naltrexone oral	Acts as a competitive antagonist at opioid receptor sites and has the highest affinity for mu receptors. Endogenous opioids are involved in modulating the expression of alcohol's reinforcing effects. Naltrexone also modifies the hypothalamic-pituitary-adrenal axis to suppress alcohol consumption.[34]	50 to 100 mg per day
Naltrexone long-acting intramuscular injectable	Acts as a competitive antagonist at opioid receptor sites, showing the highest affinity for mu receptors. Endogenous opioids are involved in modulating the expression of alcohol's reinforcing effects. Naltrexone also modifies the hypothalamic-pituitary-adrenal axis to suppress alcohol consumption.[34]	380 mg per month

AUD = alcohol use disorder; CrCl = creatinine clearance; FDA = Food and Drug Administration, GABA = gamma-aminobutyric acid; mg = milligram.

Table 3. Medications commonly used off-label in the United States for adults with AUD

Drug	Drug Class
Baclofen	Muscle relaxant
Gabapentin	Anticonvulsant/anxiolytic/analgesic
Ondansetron	Antinausea
Prazosin	Antihypertensive
Topiramate	Anti convulsants/mood stabilizers
Varenicline	Nicotinic receptor partial agonist

AUD = alcohol use disorder.

1.1.3 Existing Guidance and Evidence Reviews

In 2011, the United Kingdom's National Institute for Clinical Excellence released clinical guidelines on the identification and treatment of people with alcohol dependence and harmful alcohol use.[2] The guidelines, which focused on AUD treatment more broadly, include the following recommendations: (1) after a successful detoxification for people with moderate or severe alcohol dependence, to consider offering acamprosate or oral naltrexone in combination with an individual psychological intervention (cognitive behavioral therapies, behavioral therapies, or social network and environment-based therapies) focused specifically on unhealthy

alcohol use; (2) to consider offering disulfiram in combination with a psychological intervention to service users who have a goal of abstinence but for whom acamprosate and oral naltrexone are not suitable or who prefer disulfiram and understand the relative risks of taking the drug; and (3) to have specialist and competent staff administer pharmacological interventions.

In 2014, the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program published a systematic review of pharmacologic treatment for AUD, which is the basis for this updated review.[35] The review included data from 135 studies, reported in 167 papers. Both acamprosate and naltrexone demonstrated effectiveness, with the number needed to treat (NNT) to prevent one person from returning to any drinking of 12 to 20, respectively. NNT for preventing one person from returning to heavy drinking was 20 for oral naltrexone at 50 mg per day. Injectable naltrexone was not associated with a benefit for return to any or heavy drinking, but there was a reduction in heavy drinking days, although the strength of the evidence was low. Since acamprosate did not show a benefit for the outcome of heavy drinking, no NNT was calculated for that outcome specifically. For disulfiram, there was weak evidence suggesting a benefit in some patients with excellent adherence, based on a subgroup analysis in one trial.

That review also examined a number of medications used off-label that are available in the United States and found moderate evidence at the time supporting the efficacy of topiramate. There was insufficient direct evidence to support benefits of pharmacologic treatment for improving health outcomes, rather than alcohol use outcomes.

The American Psychiatric Association (APA) recommends naltrexone or acamprosate as first-line therapy for patients with moderate to severe AUD.[36] Disulfiram, topiramate, and gabapentin may be second-line options depending on the patient's goals, comorbidities, and lack of response or tolerance to first-line medications. The APA recommends against the use of antidepressants or benzodiazepines for treating AUD and against pharmacological treatment during pregnancy or breastfeeding except in certain circumstances. Naltrexone may also be used to treat a patient with AUD and a co-occurring opioid use disorder if the patient wishes to abstain from opioid use and can do so for 10 days before initiating naltrexone treatment.

The Department of Veterans Affairs and Department of Defense updated guideline[37] includes "strong" recommendations for oral naltrexone or topiramate and "weak" recommendations for acamprosate and disulfiram as first-line AUD pharmacotherapy for patients with moderate to severe AUD. These should be offered in combination with addiction-focused counseling.

1.2 Purpose and Scope of the Systematic Review

Since the 2014 AHRQ report on medications for AUD, the literature has grown, and a synthesis that incorporates new evidence could improve estimates of the benefits and harms of medications for AUD and could, therefore, optimize clinical decision making. There are new data for several relevant medications, outcomes beyond abstinence, and treatment of AUD with pharmacotherapy in the outpatient setting. By improving clinical decision making, an updated review could potentially improve the health and welfare of persons with AUD.

The scope of this review includes efficacy and comparative effectiveness studies of pharmacotherapies used for AUD in the United States, either with an FDA indication or off-label.

2. Methods

2.1 Review Approach

The methods for this systematic review followed the Agency for Healthcare Research and Quality (AHRQ) *Methods Guide for Effectiveness and Comparative Effectiveness Reviews* (available at https://effectivehealthcare.ahrq.gov/topics/cer-methods-guide/overview). This systematic review also reports in accordance with the Preferred Items for Reporting in Systematic Reviews and Meta-Analyses (PRISMA).[38]

This topic is an update to a report published in 2014.[35] We revised the analytic framework, Key Questions (KQs), and inclusion/exclusion criteria in the form of PICOTS (populations, interventions, comparators, outcomes, timing, settings). We worked with a Technical Expert Panel (TEP) to update the review protocol. The TEP consisted of a distinguished group of six scientists and clinicians, including individuals with experience in addiction medicine, psychiatry, pharmacotherapy, and patient experiences. TEP members participated in a conference call and discussions through email to review the scope, analytic framework, KQs, and PICOTS and provided input on the data analysis plan. A list of TEP members is included in the front matter of this report.

We largely maintained the approach of the 2014 review in this update, with some exceptions. As before, we included all medications with Food and Drug Administration indications for alcohol use disorder (AUD)—acamprosate, naltrexone (both oral and injectable) and disulfiram. With the help of the TEP, we limited drugs with off-label uses to those that are currently in use off-label for AUD in the United States (baclofen, gabapentin, ondansetron, topiramate, varenicline, and prazosin). Therefore, some drugs in the original review are not in the update (amitriptyline, aripiprazole, atomoxetine, buspirone, citalopram, desipramine, escitalopram, fluoxetine, fluvoxamine, imipramine, nalmefene, olanzapine, paroxetine, quetiapine, sertraline, valproate, viloxazine). We also eliminated a KQ on pharmacogenomics that was in the original review.

The draft protocol was posted for public comment on AHRQ's Effective Health Care website from April 18, 2022, to June 17, 2022. Most comments provided suggestions for studies to include in the review. No changes were made based on public review. The protocol was registered with Prospero (CRD42022324376). Additional details on methods are reported in Appendix A.

2.1.1 Key Questions

The KQs for this update are the same questions that were addressed in the 2014 review with the exception of removing the prior KQ 6 on pharmacogenomics.

KQ 1a. Which medications are efficacious for improving consumption outcomes for adults with alcohol use disorder in outpatient settings?

KQ 1b. How do medications for adults with alcohol use disorder compare for improving consumption outcomes in outpatient settings?

KQ 2a. Which medications are efficacious for improving health outcomes (including functioning and quality of life outcomes) for adults with alcohol use disorder in outpatient settings?

KQ 2b. How do medications for adults with alcohol use disorder compare for improving health outcomes (including functioning and quality of life outcomes) in outpatient settings?

KQ 3a. What adverse effects are associated with medications for adults with alcohol use disorder in outpatient settings?

KQ 3b. How do medications for adults with alcohol use disorder compare for adverse effects in outpatient settings?

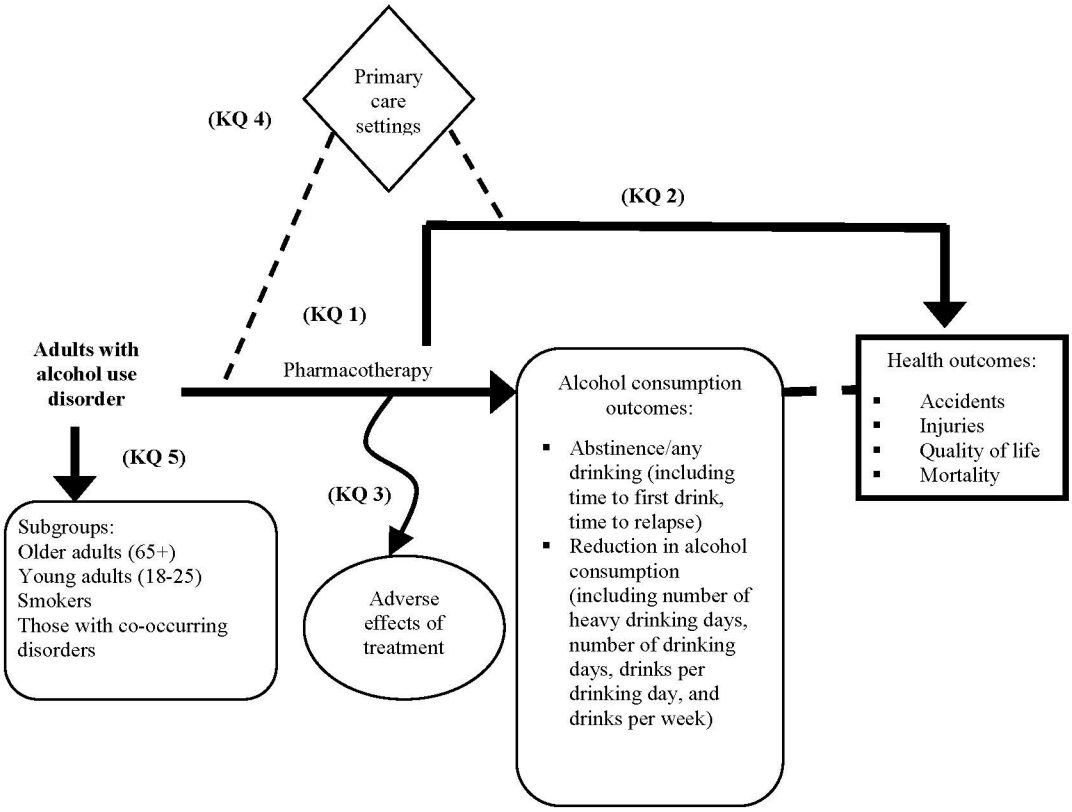
KQ 4. Are medications for treating adults with alcohol use disorder effective in primary care settings?

KQ 5. Are any of the medications more or less effective than other medications for older adults, young adults, persons who smoke, or those with co-occurring disorders?

2.1.2 Analytic Framework

We developed an analytic framework to guide the systematic review process (Figure 1).

Figure 1. Analytic framework for pharmacotherapy for adults with alcohol use disorder in outpatient settings



KQ = Key Question.

2.2 Study Selection

Included papers from the prior review were assessed to ensure that they were still relevant and excluded if they were related to a drug no longer in the update, had an outcome or study design not included, or were related to the KQ that was eliminated on genetics.

Two trained members of the research team independently reviewed each title and abstract (identified through searches) against our eligibility criteria. Studies marked for possible inclusion by either reviewer underwent a full-text review. For titles or abstracts that lacked adequate information to determine eligibility, we retrieved and reviewed the full text. Two trained members of the research team independently reviewed each full-text article and determined eligibility based on the criteria described above. If the reviewers disagreed, they resolved conflicts by discussion and consensus or by consulting a third, senior member of the team. We recorded the principal reason that each excluded full-text publication did not satisfy the eligibility criteria (Appendix B). All results in both review stages were tracked in an EndNote database.

2.2.1 Literature Search Strategy

To identify articles relevant to each KQ, we searched PubMed®, the Cochrane Library, the Cochrane Central Trials Registry, PsycINFO®, CINAHL®, and Embase®. The full search strategy is presented in Appendix A. We used either Medical Subject Headings (MeSH) or major

headings as search terms when available or keywords when appropriate, focusing on terms to describe the relevant populations and interventions of interest. We reviewed our search strategy with the TEP and incorporated their input. Searches were run by an experienced information scientist serving as the Evidence-based Practice Center (EPC) librarian and were peer-reviewed by another information scientist/EPC librarian.

We limited the electronic searches to English-language studies, adults (18 years of age or older), and human-only studies. Sources were searched from November 1, 2012, to September 9, 2022. The search dates were selected to be 6 months before the search dates of the previous AHRQ Effective Health Care (EHC) report.[35] To identify relevant articles published before our searches, we relied on the previous AHRQ EHC report that covered the literature going back to January 1, 1970.[35]

We manually searched reference lists of pertinent reviews, trials, and background articles on this topic to look for any relevant citations that our searches might have missed. We also reviewed references suggested by peer and public reviewers. We imported all citations into an EndNote® X9 (Thomson Reuters, New York, NY) electronic database.

We also searched for unpublished studies relevant to this review using ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform.

In cases in which relevant information was unclear or not reported, we contacted authors to get additional or unpublished information. When successful, this information was included in the findings.

Since September 9, 2022, ongoing surveillance was conducted through article alerts and additional searches of PubMed were conducted on August 14, 2023, to identify studies published in the interim that may affect the conclusions or understanding of the evidence; those searches did not identify any new studies for inclusion in the review.

2.2.2 Inclusion and Exclusion Criteria

We developed eligibility (inclusion and exclusion) criteria with respect to PICOTS and study designs and durations for each KQ (Table A-15). We largely maintained the PICOTS of the 2014 report but limited included interventions to drugs approved by the Food and Drug Administration for AUD and drugs that are currently in use off label in the United States. Appendix A lists detailed inclusion and exclusion criteria, organized by population, intervention, comparator, outcome, timing, setting, and study design. We included randomized controlled trials conducted in outpatient settings among adults with AUD that compared an eligible pharmacotherapy to placebo or another pharmacotherapy and reported eligible alcohol consumption outcomes, health outcomes, or harms. Harms of medications were extracted from studies of populations with AUD that focused on AUD-related outcomes.

2.3 Data Extraction

For each included study, one investigator extracted information about design, population, intervention, and outcomes, and a second investigator reviewed the information for completeness and accuracy.

2.4 Risk-of-Bias Assessment of Individual Studies

To assess the risk of bias (internal validity) of studies for major outcomes of interest, we used predefined criteria based on guidance from the AHRQ *Methods Guide for Effectiveness and*

Comparative Effectiveness Reviews.[39] In the previous report, we assessed selection bias, confounding, performance bias, detection bias, and attrition bias; we included questions about adequacy of randomization, allocation concealment, similarity of groups at baseline, blinding, attrition, whether intent to treat analysis was used, methods of handling missing data, and fidelity.[35] We rated the studies as low, medium, high, or unclear risk of bias.[40] In the current report, we assessed the risk of bias of included studies with Cochrane RoB 2.0[41] per current guidance, which focuses on the same issues as the previous guidance, including allocation sequence, baseline similarities, concealment, and approaches to analyses and could be appropriately mapped to the approach used in the original report.

2.5 Data Synthesis and Analysis

We conducted quantitative synthesis using meta-analyses of outcomes reported by multiple studies that were sufficiently homogeneous to justify combining their results. When quantitative synthesis was not appropriate (e.g., because of clinical heterogeneity, insufficient numbers of similar studies, or insufficiency or variation in outcome reporting), we synthesized the data qualitatively. Additional details are provided in Appendix A.

2.6 Grading the Strength of the Body of Evidence

We graded strength of evidence (SOE) based on the guidance established for the EPC program.[42] Developed to grade the overall strength of a body of evidence, this approach incorporates four key domains: risk of bias (includes study design and aggregate quality), consistency, directness, and precision of the evidence. It also considers optional domains, such as a dose-response association, plausible confounding that would decrease the observed effect, strength of association (magnitude of effect), and publication bias. Table 4 defines the grades of evidence that we assigned.

Table 4. Definitions of the grades of overall strength of evidence

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Source: Owens et al., 2010[42]

Two reviewers assessed each domain for each key outcome and determined an overall SOE grade based on domain ratings. We generally required consistent, direct, precise evidence from studies with aggregate low risk of bias to give high SOE grades. An unfavorable assessment for any one of the four key domains (i.e., inconsistency, indirectness, imprecision, or medium aggregate risk of bias) typically resulted in downgrading to moderate SOE. Two unfavorable assessments typically resulted in downgrading to low SOE. We allowed reviewers to include the optional domains listed above (e.g., dose-response association, publication bias) if relevant and to upgrade or downgrade the SOE for those domains if appropriate. In the event of disagreements on the domain or overall grade, they resolved differences by consensus discussion or by consulting with a third, experienced EPC investigator.

We graded the SOE for the following outcomes: return to any drinking, return to heavy drinking, drinking days, heavy drinking days, drinks per drinking day, accidents, injuries, quality of life or function, mortality, and adverse events.

2.7 Applicability

We assessed applicability of the evidence following guidance from the *Methods Guide for Comparative Effectiveness Reviews*.[43] We used the PICOTS framework to explore factors that affect applicability. Some factors identified a priori that may limit the applicability of evidence include the age, sex, and race or ethnicity of enrolled populations; smoking status of enrolled populations; co-occurring disorders of enrolled populations; setting; type of provider prescribing the treatment; and source of subject recruitment. Regarding the source of subject recruitment, studies of participants recruited via advertisements may enroll people that have less severe disorders and may be less applicable to patients with more severe forms of alcohol use disorder.

2.8 Peer Review and Public Commentary

Experts in addiction medicine, development of AUD treatments, and psychopharmacology and individuals representing stakeholder and user communities were invited to provide external peer review of this systematic review; AHRQ, and an associate editor also provided comments. The draft report was posted on the AHRQ website for 4 weeks to elicit public comment (from November 7, 2022, to December 7, 2022). We addressed all reviewer comments, revising the text as appropriate. A disposition of comments table of peer and public comments will be posted on the EHC website 3 months after the Agency posts the final systematic review.

3. Results

Results of our searches are described in Appendix B. We included 118 studies described in 156 publications. Additional details describing the included studies are provided in the relevant sections of this results chapter.

Risk-of-bias assessments of included studies are reported in Appendix C. Appendix D includes tables showing our assessments for each domain and the resulting strength of evidence (SOE) grades for each outcome, organized by Key Question (KQ) and intervention/comparison pair. Forest plots of meta-analyses are presented in Appendix E. Appendix F is the reference list for the appendixes.

3.1 Key Question 1. Efficacy and Comparative Effectiveness for Improving Consumption Outcomes

For this KQ, we describe the characteristics of included trials and then results for alcohol consumption outcomes (return to any drinking, return to heavy drinking, drinking days, heavy drinking days, drinks per drinking day).

Negative effect sizes indicate lower alcohol consumption with medication use compared with placebo. Positive effect sizes indicate higher consumption with medication use compared with placebo. Studies typically included psychosocial co-interventions in both arms; thus, effect sizes reflect the added benefits of medications beyond those of psychosocial interventions.

3.1.1 Key Points

- We found moderate SOE that both acamprosate and naltrexone reduced the risk of return to any drinking and reduced the number of drinking days. However, naltrexone also had a moderate SOE for reducing return to heavy drinking and number of heavy drinking days.
- Percent drinking days, percent heavy drinking days, and drinks per drinking day all had moderate SOE for improvement with topiramate use.
- With no new additional studies, 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.
- The strength of evidence was low for improvement in return to any drinking for baclofen compared with placebo.
- We found low SOE that gabapentin was associated with a statistically significant reduction in return to any drinking and to heavy drinking.
- We found low SOE that varenicline demonstrated no benefit across all drinking outcomes. Ondansetron had low SOE for no reduction for a single outcome (drinking days), and insufficient evidence for all other outcomes and evidence was insufficient for any outcomes for prazosin.
- There were no new head-to-head trials. In the prior review, a meta-analysis of four head-to-head randomized controlled trials (RCTs) comparing acamprosate with naltrexone,[44-47] all rated as low risk of bias, found no statistically significant difference between the two medications for improvement in alcohol consumption outcomes.

3.1.2 Detailed Synthesis: Placebo-Controlled Trials of Medications for Treating Alcohol Dependence Approved by the Food and Drug Administration (FDA)

3.1.2.1 Acamprosate

3.1.2.1.1 Characteristics of Trials

Table B-1 summarizes characteristics of the 23 trials meeting our inclusion criteria.[44-66] Only one trial was new to this update.[54] The majority were parallel two-arm trials comparing acamprosate with placebo. Doses ranged from 1,000 to 3,000 mg per day; 1,998 mg per day (divided into 3 doses) was the most frequently used dose. Duration of treatment ranged from 12 to 52 weeks; most (19 trials) treated participants for 12 to 26 weeks;[44-49, 51-57, 59-62, 64, 66] 4 trials treated participants for longer periods, 48 to 52 weeks.[47, 50, 58, 63, 65] Followup to 1 year or longer was available for 8 trials.[44, 50, 52, 58, 61, 63, 65, 66]

The majority were conducted in Europe (16 trials);[45, 47, 50-53, 55, 56, 58, 59, 61, 63-66] 4 were conducted in the United States,[44, 49, 57, 62]1 in Brazil,[48] 1 in Japan,[54] and 1 in Australia.[46] Recruitment methods varied, with trials typically identifying patients through treatment programs (e.g., inpatient detoxification, outpatient treatment), advertisements, referrals, or some combination of those.

Mean age was very similar across trials, usually in the early to mid-40s. All participants met criteria for alcohol dependence in 22 trials; 1 trial did not report the percent with alcohol dependence, but most participants likely had alcohol dependence, based on having an average of 15 drinks per drinking day and 6 drinking days per week.[46] Most studies did not report information on race; 1 U.S.-based trial of persons with schizophrenia spectrum disorders as well as alcohol dependence reported enrolling a majority (65%) of participants who were not White; 61 percent of participants were Black and 4 percent were of Puerto Rican descent.[62] Most trials enrolled between 11 and 36 percent females; 1 trial enrolled all males,[48] and 1 did not report information on sex.[60] Just 4 trials reported information on smoking history at baseline; those trials had 46 to 81 percent persons who smoke enrolled.[44, 46, 57, 67]

The majority of trials either did not report information about how many participants had co-occurring psychiatric conditions or excluded participants with other psychiatric disorders; one trial enrolled participants with alcohol dependence and schizophrenia spectrum disorders.[62] Trials often included or encouraged psychological or psychosocial co-interventions.

3.1.2.1.2 Summary of Findings

We found moderate SOE that acamprosate reduced the risk of return to any drinking and the percentage of drinking days compared with placebo, but that it did not have an impact on return to heavy drinking. Primary meta-analysis results for these three alcohol use outcomes are shown in Table 5 and figures are shown in Figures E-1 to E-3. Although statistical significance was mixed among the included studies, pooled results showed that acamprosate was associated with a 12 percent relative reduction in the likelihood of returning to any drinking (risk ratio [RR], 0.88; 95% confidence interval [CI], 0.83 to 0.93). Acamprosate was also associated with an 8.3 percentage point reduction in the percentage of drinking days (weighted mean difference [WMD], -8.3; 95% CI, -12.2 to -4.4). However, there was no impact on the percentage of people

returning to heavy drinking (RR, 0.99; 95% CI, 0.94 to 1.05; moderate SOE). Effect sizes did not differ by risk-of-bias rating or duration of treatment (up to 1 year). Evidence was insufficient for all heavy drinking days and drinks per drinking day. See Table D-1 for SOE ratings for all drinking and health outcomes.

Table 5. Meta-analysis results for alcohol use outcomes among placebo-controlled trials of acamprosate

Outcome	No. RCTs	N	Effect	95% CI	I^2, %	Range of Post-Treatment Means or %, Placebo	Range of Post-Treatment Means or %, Treatment
Return to any drinking	20	6,380	RR, 0.88	0.83 to 0.93	77.6	60.0% to 95.7%	37.5% to 96.2%
Return to heavy drinking	7	2,496	RR, 0.99	0.94 to 1.05	0.0	45.8% to 82.9%	41.9% to 85.1%
Percentage drinking days	14	4,916	WMD, -8.3	-12.2 to -4.4	67.5	9 to 79	12.7 to 66.0

CI = confidence interval; No. = number; N = sample size; RCT = randomized controlled trial; RR = risk ratio; WMD = weighted mean difference.

3.1.2.1.3 Return to Any Drinking

We found moderate SOE that acamprosate reduced the likelihood of return to any drinking. Twenty of the 23 trials reported sufficient data for meta-analysis.[44-46, 48-61, 63-65] All but two studies[49, 57] had point estimates trending in favor of acamprosate. The meta-analysis found a 12 percent relative reduction in the likelihood of any alcohol use during followup (RR, 0.88; 95% CI, 0.83 to 0.93). Although the statistical heterogeneity was fairly high, findings were largely consistent in finding an effect in the direction of benefit, and the pooled result was reasonably precise. No differences in effect were observed when stratifying by risk-of-bias or treatment duration, but studies conducted in the United States tended to have smaller effect sizes. None of the three studies conducted in the United States showed a benefit for acamprosate.[44, 49, 57] Trials conducted in the United States all recruited patients largely through advertisements, while trials in other countries tended to recruit from treatment settings and often from inpatient settings.

3.1.2.1.4 Return to Heavy Drinking

There was moderate SOE that acamprosate had no impact on the likelihood of returning to heavy drinking. Seven trials reported on this outcome, and none of them showed an improvement with acamprosate use compared with placebo.[44-47, 51, 57, 66] The meta-analysis found no significant difference between acamprosate and placebo (RR, 0.99; 95% CI, 0.94 to 1.05).

3.1.2.1.5 Drinking Days

We found moderate SOE that patients treated with acamprosate had a smaller percentage of drinking days than those treated with placebo (WMD, -8.3; 95% CI, -12.2 to -4.4). Four of the 14 trials that contributed data were conducted in the United States.[44, 49, 57, 62] Stratifying the meta-analysis by U.S. and non-U.S. studies found no benefit for the four U.S.-based trials (WMD, -1.8; 95% CI, -5.3 to 1.8) but found that patients treated with acamprosate had 11.2 percent fewer drinking days than those treated with placebo for trials conducted in other countries (WMD, -11.2; 95% CI, -15.8 to -6.6). As above, trials conducted in the United States recruited through advertising rather than treatment settings so that may have resulted in differences in patient characteristics. Although there was a tendency for trials with longer duration of treatment to show more benefit, stratified analysis did not suggest an association

between treatment duration and effect size. In addition, U.S.-based trials tended to have short duration, so any apparent association with duration of treatment cannot be disentangled from other study characteristics.

3.1.2.1.6 Heavy Drinking Days

Two trials reported data for heavy drinking days, both conducted in the United States[49, 62] Neither found that acamprosate reduced the percentage of heavy drinking days (medium risk-of-bias trial: WMD, -2.6; 95% CI, -11.4 to 6.2; high risk-of-bias trial: WMD, 1.9; 95% CI, -6.9 to 10.7).

3.1.2.1.7 Drinks per Drinking Day

Two trials reported data for drinks per drinking days, both conducted in the United States[46, 62] Neither found that acamprosate reduced the percentage of heavy drinking days (low risk-of-bias trial: WMD, 0.4; 95% CI, -1.8 to 2.6; high risk-of-bias trial: WMD, 1.8; 95% CI, -3.5 to 7.1).

3.1.2.2 Disulfiram

3.1.2.2.1 Characteristics of Trials

The updated search did not identify any new studies of disulfiram that were eligible. Table B-2 summarizes characteristics of the four trials meeting our inclusion criteria.[68-71] All four were conducted in Veterans Affairs (VA) medical centers. Three compared disulfiram with placebo or riboflavin (which was intended as placebo);[68-70] one compared disulfiram with naltrexone, placebo, and the combination of naltrexone and disulfiram.[71] Doses for the intended active disulfiram arms were the same (250 mg per day) in all four trials.[68-71] Two of the four trials were rated as high risk of bias, either primarily for high risk of attrition bias and inadequate handling of missing data[70] or primarily for high risk of ascertainment bias.[71] Two were rated as medium risk of bias.[68, 69] See Appendix C for details.

Duration of treatment ranged from 12 to 52 weeks. Three of the four trials followed participants for 9 to 12 months.[68-70] All four were conducted in the United States.[68-71] Mean age was very similar across trials, ranging from 39 to 47 years. All participants likely met criteria for alcohol dependence. Very few female participants were enrolled (0 to 3% in the 3 trials reporting). None of the trials reported information on smoking history at baseline. One trial enrolled participants with alcoholism who were also in methadone maintenance programs.[70] Another enrolled participants with co-occurring psychiatric disorders.[71] Neither of the trials rated as medium risk of bias reported information on how many participants had co-occurring psychiatric conditions.[68, 69]

3.1.2.2.2 Summary of Findings

With no new studies added to the prior report, there was again low SOE that disulfiram is not associated with a reduction in return to any drinking (RR, 1.03; 95% CI, 0.90 to 1.17). There was insufficient SOE that disulfiram was associated with a change in drinking days.

3.1.2.2.3 Return to Any Drinking

Three of the four trials reported data.[68, 69, 71] The meta-analysis found no statistically significant difference between disulfiram 250 mg per day and disulfiram 1 mg per day or placebo (RR, 1.03; 95% CI, 0.90 to 1.17). Both medium risk-of-bias studies found point estimates

favoring placebo/disulfiram 1 mg, but differences between groups were not statistically significant.[68, 69]

The meta-analysis found no statistically significant difference between disulfiram 250 mg per day and riboflavin (i.e., no disulfiram) (RR, 0.95; 95% CI, 0.88 to 1.04). Both medium risk-of-bias studies found point estimates favoring disulfiram 250 mg per day, but differences between groups were not statistically significant.[68, 69]

The largest trial (N=605)[69] reported a significant relationship between adherence and complete abstinence in all groups (disulfiram 250 mg, disulfiram 1 mg, and no disulfiram/riboflavin). The other trial assessed as medium risk of bias similarly reported that complete abstinence correlated significantly with adherence.[68]

3.1.2.2.4 Drinking Days

Both medium risk-of-bias trials reported some information about the percentage of drinking days.[68, 69] The smaller trial (N=128) reported no statistically significant differences among the three groups in percentage of drinking days (31% vs. 32% vs. 37%, for disulfiram 500/250, disulfiram 1, and riboflavin, respectively, p not reported]).[68] The larger trial (N=605) reported this outcome only for the subset of participants who drank and had a complete set of assessment interviews (N=162). It found that patients among this subset treated with disulfiram reported fewer drinking days than those given disulfiram 1 mg or those given riboflavin (49% vs. 75.4% vs. 86.5%, respectively, p=0.05).[69]

3.1.2.3 Naltrexone

3.1.2.3.1 Characteristics of Trials

Table B-3 summarizes characteristics of the 49 trials meeting our inclusion criteria,[44-47, 71-115] of which 5 were new for this update.[80-83, 112] Less than half were parallel two-arm trials comparing naltrexone with placebo; most had three or more study arms. Seven trials evaluated long-acting, injectable naltrexone at doses from 150 to 400 mg per month.[73, 80, 82, 85, 90, 92, 112] Forty-two administered oral naltrexone[44-47, 71, 72, 74-79, 81, 83, 84, 86-89, 91, 93-111, 113-115]: 33 trials used a dose of 50 mg per day,[45-47, 71, 72, 74-79, 81, 84, 86-89, 91, 93-97, 99, 101-104, 107, 110, 113-115] 7 used 100 mg per day,[44, 83, 98, 100, 105, 108, 111] 1 used 150 mg per day,[109] and 1 used 100 mg on Mondays and Wednesdays and 150 mg on Fridays (weekly average of 50 mg per day).[106] Duration of treatment ranged from 12 to 52 weeks; most (40 trials) treated participants for 12 to 17 weeks;[44-47, 71-75, 77-81, 84, 86, 87, 89-93, 95, 96, 98-104, 106-111, 113-115] 9 trials included treatment with naltrexone for longer periods—24 to 52 weeks.[76, 82, 83, 85, 88, 94, 97, 105, 112] Two of the latter groups included comparisons of different treatment durations for 50 mg per day, either comparing 12 versus 24 weeks[97] or comparing 12 versus 52 weeks.[94]

The majority were conducted in the United States only (32 trials);[44, 71, 74, 75, 78, 80-83, 85, 91-94, 97-100, 102-115] 8 were conducted in Europe;[45, 47, 73, 76, 79, 86-88] 3 in Australia;[46, 95, 101] 2 in Brazil;[77, 84] 1 multinational (United States, France, and the Netherlands);[90] and 1 each in Singapore,[96] Iran,[72] and Taiwan.[89] Recruitment methods varied, with trials typically identifying patients through treatment programs (e.g., inpatient detoxification, outpatient treatment), advertisements, referrals, or some combination of those.

Mean age was very similar across trials, usually in the 40s (38 trials)[44-47, 71-81, 83, 85, 86, 88-90, 92-98, 100-105, 107, 108, 112, 115] or 30s (6 trials);[91, 99, 109-111, 113] 3 trials did not report mean age,[84, 87, 114] and 2 trials enrolled participants with mean ages in their 50s.[82, 106] All participants met criteria for

alcohol dependence in the vast majority of trials. Fourteen of 49 trials enrolled a majority of non-White participants (60% to 100%).[80-83, 89, 96, 103, 106, 109-114] Most trials enrolled a third or fewer females; 2 trials enrolled all women.[82, 102] Just 11 trials reported information on smoking history at baseline, with most of those reporting a majority of persons who smoke (55% to 77%) enrolled in those trials[44, 46, 77, 78, 80, 81, 94, 103, 115, 116] and 2 reporting a minority (17% and 47%).[85, 108]

Ten trials reported enrolling all or a majority of participants with co-occurring psychiatric disorders, including bipolar disorder,[78] schizophrenia or schizoaffective disorder,[107] cocaine use disorder,[109-111] depression,[108] another Axis I disorder,[71] posttraumatic stress disorder (PTSD),[83, 117] or any comorbid psychiatric disorder.[91] Trials generally included or encouraged psychological or psychosocial co-interventions.

Of the five trials that were added in this update,[80-83, 112] two provided data that could be included in meta-analyses for effectiveness on the outcome of drinking days.[80, 83] One of those[83] studied the 100 mg dosage and included participants receiving intensive therapy for PTSD who were required to undergo medical detoxfication prior to the study. The other studied the injectable formulation in a population experiencing homelessness.[80]

3.1.2.3.2 Summary of Findings

We found moderate SOE that naltrexone compared with placebo reduced the risk of return to any drinking and return to heavy drinking and that it reduced the percent drinking days and percent heavy drinking days. We found low SOE that naltrexone compared with placebo reduced the number of drinks per drinking day (Table D-3). Primary meta-analysis results for the most common 50 mg oral dose, for the 100 mg dose and for injectable naltrexone are presented in Tables 6 through 8 below, SOE ratings in Tables D-4 to D-6, and additional meta-analysis results are shown in Appendix E.

The majority of studies examined the 50 mg dose (Table 6), and analysis of that dosage demonstrated a relative reduction in return to any drinking of 7 percent (RR, 0.93; 95% CI, 0.87 to 1.00; moderate SOE). Neither the 100 mg dose (3 RCTs) (Table 7) nor the injectable modality (2 RCTs) (Table 8) demonstrated a significant decrease in return to any drinking in the meta-analyses (low SOE).

The effect on return to heavy drinking also was significant only in the 50 mg group (RR, 0.85; 95% CI, 0.77 to 0.94; moderate SOE). However, there were very few studies assessing either the 100 mg dosage (2 RCTs) or injectable (2 RCTs); we found low SOE for both for no benefit.

Naltrexone 50 mg had a significant effect on percent drinking days (WMD, -5.10; 95% CI, -7.16 to -3.04; moderate SOE) and percent heavy drinking days (WMD, -4.26; 95% CI -7.61 to -0.91; moderate SOE). Similar effects were seen for both 100 mg and injectable naltrexone (low SOE). Of note, the prior report found no benefit for injectable naltrexone, but the addition of a new RCT conducted in a population experiencing homelessness resulted in positive outcomes for this reduction in drinking days and in heavy drinking days.

3.1 Key Question 1. Efficacy and Comparative Effectiveness for Improving Consumption Outcomes

Table 6. Meta-analysis results for alcohol use outcomes among placebo-controlled trials of oral naltrexone, 50 mg

Outcome	No. RCTs	N	Effect	95 CI %	I^2, %	Range of Post-Treatment Means or %, Placebo	Range of Post-Treatment Means or %, Treatment
Return to any drinking	16	2,347	RR, 0.93	0.87 to 1.00	40.7	34.4 to 95.2	28.6 to 98.2
Return to heavy drinking	23	3,149	RR, 0.81	0.72 to 0.90	58.7	15.0 to 93.5	7.9 to 94.6
Percent drinking days	18	2,063	WMD, -5.10	-7.16 to -3.04	39.1	10.0 to 53.3	5 to 99
Percent heavy drinking days	7	624	WMD, -4.26	-7.61 to -0.91	68.9	2.7 to 49.2	1.2 to 41.7

CI = confidence interval; No. = number; N = sample size; RCT = randomized controlled trial; RR = risk ratio; WMD = weighted mean difference.

Table 7. Meta-analysis results for alcohol use outcomes among placebo-controlled trials of oral naltrexone, 100 mg

Outcome	No. RCTs	N	Effect	95 CI %	I^2, %	Range of Post-Treatment Means or %, Placebo	Range of Post-Treatment Means or %, Treatment
Return to any drinking	3	946	RR, 0.97	0.91 to 1.03	0.0	76.9 to 82.2	78.0 to 79.6
Return to heavy drinking	2	858	RR, 0.93	0.84 to 1.01	0.0	63.3 to 73.1	60.8 to 67.0
Percent drinking days	3	1.023	WMD, -4.99	-9.49 to -0.49	31.1	18.7 to 45.7	15.15 to 37.1
Percent heavy drinking days	2	423	WMD, -3.07	-5.84 to -0.30	0.0	8.9 to 11.2	5.0 to 9.2

CI = confidence interval; No. = number; N = sample size; RCT = randomized controlled trial; RR = risk ratio; WMD = weighted mean difference.

Table 8. Meta-analysis results for alcohol use outcomes among placebo-controlled trials of naltrexone, injectable

Outcome	No. RCTs	N	Effect	95% CI	I^2, %	Range of Post-Treatment Means or %, Placebo	Range of Post-Treatment Means or %, Treatment
Return to any drinking	2	939	0.96	0.90 to 1.03	54.4	89.8 to 94.7	82.3 to 93.5
Return to heavy drinking	2	615	1.00	0.82 to 1.21	66.4	52.7 to 84.1	59.2 to 77.2
Percent drinking days	2	467	WMD, -4.99	-9.49 to -0.49	31.1	18.7 to 45.7	15.2 to 37.1
Percent heavy drinking days	3	956	WMD, -4.68	-8.63 to -0.73	0.0	25.0 to 30.1	12.0 to 26.7

CI = confidence interval; No. = number; N = sample size; RCT = randomized controlled trial; WMD = weighted mean difference.

3.1.2.3.3 Return to Any Drinking

The meta-analysis found that participants in the naltrexone arms were slightly less likely to return to any drinking than those receiving placebo. Stratifying by dose and delivery method found similar effect sizes for 50 mg per day orally (RR, 0.93; 95% CI, 0.87 to 1.00), 100 mg per day orally (RR, 0.97; 95% CI, 0.91 to 1.03), and injectable naltrexone (RR, 0.96; 95% CI, 0.90 to 1.03).

3.1.2.3.4 Return to Heavy Drinking

Pooled results indicated that participants taking naltrexone had a 14 percent relative reduction in the likelihood of returning to heavy drinking than those taking placebo (RR, 0.86;

95% CI, 0.80 to 0.93). Excluding high risk-of-bias studies resulted in a relative risk reduction of 11 percent (RR, 0.89; 95% CI, 0.83 to 0.96). There was no indication the effect size was associated with whether the study was conducted in the United States or duration of treatment. When limited to studies conducted in the United States, there was a 12 percent relative reduction in the risk of return to heavy drinking (RR, 0.88; 95% CI, 0.81 to 0.94).

Stratifying by dose and delivery method found that only the 50 mg dose demonstrated a statistically significant effect with a relative reduction of 15 percent (RR, 0.81; 95% CI, 0.72 to 0.90) compared with no significant effect in either the 100 mg dose (RR, 0.93; 95% CI, 0.84 to 1.01) or the injectable (RR, 1.00; 95% CI, 0.82 to 1.21). Both the 100 mg dose and the injectable had few studies (3 each), however, and CIs overlapped for all three dose categories.

3.1.2.3.5 Drinking Days

Participants treated with naltrexone had 4.5 percent fewer drinking days than those treated with placebo (WMD, -4.5; 95% CI, -6.3 to -2.8). All point estimates (of the individual studies) favored naltrexone over placebo. There was no difference in effect size when stratifying the meta-analysis by U.S. and non-U.S. studies (p=0.99).

The most robust findings were for 50 mg per day (WMD, -5.4; 95% CI, -7.5 to -3.2), used by 15 of the 21 trials included in the meta-analysis. The pooled analysis of the two studies of injectable naltrexone also found benefit at a similar effect size (WMD, 4.99; 95% CI, -9.49 to -0.49**).** Of note, the prior report found no benefit for injectable naltrexone, but the addition of a new RCT conducted in a population experiencing homelessness resulted in positive outcomes for the reduction in drinking days.

3.1.2.3.6 Heavy Drinking Days

Participants treated with 50 mg naltrexone had 4.26 fewer heavy drinking days than those treated with placebo (WMD -4.26. 95% CI, -7.61 to -0.91). Results for 100 mg naltrexone (WMD – 3.07; 95% CI, -5.84 to -0.30) and injectable naltrexone (WMD -4.68; 95% CI, -8.68 to -0.73) were similar.

3.1.2.3.7 Drinks per Drinking Day

Participants treated with 50 mg naltrexone had 0.85 percent fewer drinks per drinking day than those treated with placebo (WMD, -0.85; 95% CI, -1.44 to -0.26). Stratifying the meta-analysis by U.S. and non-U.S. studies found similar effect sizes for U.S.- and non-U.S.-based trials.

3.1.3 Detailed Synthesis: Placebo-Controlled Trials of Medications Used Off-Label or Those Under Investigation

3.1.3.1 Baclofen

3.1.3.1.1 Characteristics of Trials

We included 13 trials comparing baclofen with placebo for 12 to 52 weeks (Table B-4).[118-130] Two of the 13 trials were included in the previous report; the rest are new.[118, 120] Mean age ranged from 43 to 57 years. All participants met criteria for alcohol use disorder (AUD) in 12 of the 13 trials; 1 trial reported that 93 percent of participants met criteria for AUD.[130] One trial enrolled only men;[118] the other 12 ranged from 2 to 55 percent women. Only 5 trials reported

information on smoking history at baseline, with 31 to 100 percent persons who smoke enrolled in those trials.[121, 124, 125, 127, 129] Most of the trials did not report information about race or ethnicity of the included participants. Three included trials limited participants to specific populations with both AUD and an additional health condition: liver cirrhosis (n=84),[118] veterans with chronic hepatitis C (n=180),[122] or nicotine dependence (n=30).[124]

Baclofen doses ranged from 30 mg per day up to 300 mg per day. The most common dose was 30 mg per day, evaluated by seven trials.[118-122, 125, 126] Two trials evaluated 50 mg per day.[123, 128] One trial each evaluated 60 mg per day,[126] 75 mg per day,[125] and 90 mg per day.[121] One trial each evaluated titrating (as tolerated and based on response) up to target doses of 150 mg per day,[119] 180 mg per day,[129] 270 mg per day,[127] and 300 mg per day.[130] All but one[130] of the trials offered a medical management intervention that included manual-driven, supportive counseling to promote adherence to the medication regimen and reduction in alcohol use or a similar program of psychosocial support.

3.1.3.1.2 Summary of Findings

Overall, five of the included trials reported some results favoring baclofen,[118, 121, 125, 127, 130] seven of the included trials did not,[119, 120, 122, 123, 126, 128, 129] and one small (n=30) trial rated as high risk of bias reported some outcomes significantly favoring baclofen and some significantly favoring placebo.[124] The most commonly reported outcomes were return to any drinking and percent heavy drinking days. Primary meta-analysis results for the most commonly reported alcohol use outcomes are shown in Table 9. The SOE was low for improvement in return to any drinking for baclofen compared with placebo. For all other alcohol consumption outcomes, SOE was low for no benefit, and the main analyses did not reveal a statistically significant difference between baclofen and placebo. We did not find a clear dose-response pattern across the included trials. For example, in the meta-analysis for return to any drinking, two of the trials assessing a dose of 30 mg per day reported a statistically significant difference favoring baclofen,[118, 125] and two of the trials assessing a dose of 30 mg per day reported no difference;[119, 122] likewise, two of the trials assessing higher doses (75 mg and titration up to 270 mg) reported a statistically significant difference favoring baclofen,[125, 127] and two of the trials assessing higher doses (up to 150 mg daily and 180 mg daily) reported no difference.[119, 129] See Table D-7 for SOE grades for all consumption and health outcomes for baclofen compared with placebo.

There were not enough trials to conduct adequate sensitivity analyses; however, there was no apparent pattern indicating that high risk of bias was associated with larger or smaller effect sizes for alcohol consumption outcomes, except for the outcome of percent drinking days. For that outcome, pooled analysis removing the one study rated as high risk of bias (and for which we had concerns about reporting errors) showed a statistically significant benefit for baclofen compared with placebo (pooled RR -9.90; 95% CI, -18.93 to -0.87).

Table 9. Summary of meta-analysis results for alcohol use outcomes among placebo-controlled trials of baclofen

Outcome	No. RCTs	N	Effect	95% CI	I^2, %	Range of Post-Treatment Means or %, Placebo	Range of Post-Treatment Means or %, Treatment
Return to any drinking	6	883	RR, 0.83	0.70, 0.98	76.0	53.2 to 89.9	28.6 to 92.4
Return to heavy drinking	2	319	RR, 0.92	0.80, 1.06	0.0	46.8 to 84.3	48.4 to 74.7

3.1 Key Question 1. Efficacy and Comparative Effectiveness for Improving Consumption Outcomes

Outcome	No. RCTs	N	Effect	95% CI	I^2, %	Range of Post-Treatment Means or %, Placebo	Range of Post-Treatment Means or %, Treatment
Percent drinking days	5	714	WMD, -5.55[a]	-18.79, 7.69	87.5	29.4 to 68.9	46.0 to 67.7
Percent heavy drinking days	7	760	WMD, -2.16	-7.34, 3.02	99.8	2.5 to 39.8	1.6 to 42.0
Drinks/drinking day	2	146	WMD, 0.85	-2.23, 3.93	65.7	2.8 to 7.5	4.7 to 8.8

[a] Sensitivity analysis removing the one study rated as high risk of bias showed a statistically significant benefit for baclofen compared with placebo, pooled RR -9.90 (95% CI, - 18.93 to -0.87)

CI = confidence interval; No. = number; N = sample size; RCT = randomized controlled trial; RR = risk ratio; WMD = weighted mean difference.

3.1.3.1.3 Return to Any Drinking

Eight trials reported on return to any drinking.[118-120, 122, 123, 125, 127, 129] Of those, six provided sufficient data to be combined in meta-analysis.[118, 119, 122, 125, 127, 129] The meta-analysis found that baclofen was associated with a reduced risk of returning to any drinking (RR, 0.83; 95% CI, 0.70 to 0.98). The two RCTs that could not be included in the meta-analysis had a combined 112 participants; both reported that there was not a significant difference between baclofen and placebo.[120, 123]

3.1.3.1.4 Return to Heavy Drinking

Four trials reported on return to heavy drinking.[118-120, 122] Three of the four RCTs found no statistically significant difference between baclofen and placebo for return to heavy drinking. Of the four included trials, two reported sufficient data to pool.[119, 122] The pooled risk was not significantly different between baclofen and placebo (RR, 0.92; 95% CI, 0.80 to 1.06). The two RCTs that could not be included in the meta-analysis had a combined 164 participants; one of those reported a significant reduction with baclofen (data NR, figure only, p=0.0062),[118] and one reported no significant difference between groups (hazard ratio, 0.924; p=0.76).[120]

3.1.3.1.5 Drinking Days

Six trials reported on drinking days or reported sufficient information to allow for calculation of the percentage of drinking days.[120-122, 124, 125, 130] Of those, three trials reported a statistically significant result favoring baclofen,[121, 125, 130] and three did not.[120, 122, 124] Of the six trials, five contributed data to the meta-analysis. The meta-analysis found no statistically significant difference in the percentage of drinking days (WMD -5.55; 95% CI, -18.79 to 7.69). Sensitivity analysis removing the one study rated as high risk of bias (and for which we had concerns about reporting errors) showed a statistically significant benefit for baclofen compared with placebo (pooled RR -9.90; 95% CI, -18.93 to -0.87). The one trial that was not represented in the meta-analysis had 120 participants and did not report sufficient data to include in the meta-analysis.[121] It reported a lower percentage of drinking days for those treated with baclofen 90 mg daily than those taking placebo (41% vs. 53%, p=0.028) but no difference between those treated with baclofen 30 mg daily and those treated with placebo (52% vs. 53%).

3.1.3.1.6 Heavy Drinking Days

Nine trials reported on heavy drinking days.[120, 121, 123-126, 128-130] Study effects were very heterogeneous, ranging from favoring baclofen to favoring placebo. Seven of the nine studies

contributed data to the meta-analysis.[120, 121, 123-126, 128-130] The meta-analysis found no statistically significant difference between baclofen and placebo for the percentage of heavy drinking days (WMD, -2.21; 95% CI, -8.85 to 4.42). Two RCTs were not represented in the meta-analysis.[123, 129] Specifically, a trial with 320 participants did not report sufficient data to include in the meta-analysis,[129] and a trial with 32 participants did not show up in the meta-analysis because both study groups achieved zero heavy drinking days.[123] Both trials reported no significant difference between groups.

3.1.3.3.1.7 Drinks per Drinking Day

Two trials reported on drinks per drinking day.[125, 126] Both trials compared two doses of baclofen (either 30 mg and 60 mg or 30 mg and 75 mg) with placebo. Three of the four study arms demonstrated no reduction in drinks per drinking day with baclofen use (WMD range, +1.3 [95% CI, –2.7 to 5.4] to +3.0 [-1.1 to 7.2]), and one demonstrated a small benefit (WMD, -2.8; 95% CI, -5.6 to -0.1). Pooling the data for all four comparisons yielded no statistically significant difference between baclofen and placebo for change in the number of drinks per drinking days (WMD, 0.85; 95% CI, -2.23 to 3.93; 2 RCTs making 4 comparisons, N=146).

3.1.3.2 Gabapentin

3.1.3.2.1 Characteristics of Trials

We included four trials comparing gabapentin with placebo for 12 to 28 weeks (Table B-5). All of the trials were newly identified for this update. Three trials were conducted in the United States[131-133] and one in Thailand.[134] Mean age of participants ranged from 43 to 50 years. Two studies required a diagnosis of AUD,[131, 132] and two required alcohol dependence.[133, 134] The percentage of women in each trial ranged from 9 to 43 percent. Only two trials reported information on smoking history at baseline, with 31 to 43 percent persons who smoke enrolled in those trials, and both were conducted in the United States.[131, 132]

One trial, conducted in Thailand, did not report any information on race or ethnicity.[134] In the three trials that did report race at baseline, most of the participants were White, ranging from 67 to 94 percent White in the individual studies.[131-133] One study was limited to people with co-occurring PTSD (N=26).[131]

Gabapentin doses ranged from 300 to 1,800 mg per day. One trial also compared a dose of 900 mg per day to a dose of 1,800 mg per day.[133] All four trials explicitly described flexible dosing, based on individuals' balance of efficacy and side effects. Three of the studies also offered some type of psychosocial support including medical management (typically offered in weekly 15- to 20-minute sessions), a weekly module, or guided counseling.[131-133] One study did not offer any structured psychotherapy. All of the patients in that study were provided trazodone at a dose of 50 mg nightly in addition to a folic acid and vitamin B supplement for the duration of the study.[134]

3.1.3.2.2 Summary of Findings

Three trials each reported return to any drinking and return to heavy drinking, which had sufficient evidence for pooling. Quantitative results are shown in Table 10. We found low SOE that gabapentin was associated with a statistically significant reduction in return to any drinking given that two of the three studies did show benefit (RR, 0.92; 95% CI, 0.83 to 1.02; 2 of 3 studies showed a significant benefit). We found low SOE for a 10 percent relative reduction in

return to heavy drinking (RR, 0.90; 95% CI, 0.82 to 0.98), although none of the three studies reported a significant benefit for this outcome individually. We found low SOE for heavy drinking days and drinks per drinking day and insufficient SOE for drinking days; none of these outcomes had sufficient data for meta-analysis (Table D-8).

Table 10. Meta-analysis results for alcohol use outcomes among placebo-controlled trials of gabapentin

Outcome	No. RCTs	N	RR or WMD	95% CI	I^2, %	Range of n/N % or Mean, Placebo	Range of n/N% or Mean, Treatment
Return to any drinking	3	522	0.92	0.83 to 1.02	61.2	88.2 to 95.9	79.5 to 88.4
Return to heavy drinking	3	522	0.90	0.82 to 0.98	0	77.6 to 87.0	63.4 to 75.9
Percent heavy drinking days	1	338	-3.40	-4.28 to -2.52	100	46.5	43.1
Drinks/drinking day	1	338	0.2	-0.91 to 1.31	0	3.9	4.1

CI = confidence interval; mg = milligram; N = sample size; RCT= randomized controlled trial; RR=risk ratio; WMD = weighted mean difference.

3.1.3.2.3 Return to Any Drinking

We found low SOE that gabapentin reduced return to any drinking compared with placebo. Three trials rated as medium risk of bias[131-133] reported data on return to any drinking. The meta-analysis combining these trials did not find a significant difference in return to any drinking for patients treated with gabapentin compared with placebo (RR, 0.92; 95% CI, 0.83 to 1.02); however, two of the three trials reporting this outcome did find a reduced likelihood of return to drinking with gabapentin use.

3.1.3.2.4 Return to Heavy Drinking

Three trials rated as medium risk of bias[131-133] reported this outcome. All three trials were included in the meta-analysis. Although none of the individual trials found significant between-group differences for this outcome, there was low SOE from pooled analysis of a 10 percent relative reduction in return to heavy drinking for patients treated with gabapentin compared with placebo (RR, 0.90; 95% CI, 0.82 to 0.98).

3.1.3.2.5 Drinking Days

Evidence for a reduction in drinking days was insufficient, with no statistically significant difference in drinking days (p=0.2) reported in one trial conducted in Thailand that was rated as high risk of bias.[134] Falk (2019)[132] and Mason (2014)[133] reported measures of drinks per week that could not be pooled in meta-analysis (Table 11).

Table 11. Drinks per week reported among placebo-controlled trials that could not be included in meta-analysis of gabapentin

Study	Country	Population	N	Weeks	Specific Outcome	Results
Falk, 2019 [132]	U.S.	AUD	338	26	Drinks/week, mean	GAB XR: 23.1 Placebo: 21.4 p=0.545
Mason, 2014 [133]	U.S.	Alcohol dependence	150	12	Change in drinks/ week, mean	GAB 900 mg: -2.2 GAB 1,800 mg:-6.7 Placebo: -5.3 GAB 900 mg p=0.20 GAB 1,800 mg p<0.001

AUD = alcohol use disorder; GAB = gabapentin; mg = milligram; N = sample size; U.S. = United States; XR = extended release.

3.1.3.2.6 Heavy Drinking Days

There was low SOE for a reduction in heavy drinking days when treated with gabapentin compared with placebo, based on three studies (Table 12).[132-134] One study[132] found gabapentin reduced heavy drinking days by 3.4% (46.5% vs. 43.1%; WMD, -3.40; 95% CI, -4.28 to -2.52), whereas another study[134] showed gabapentin had a lower percentage of heavy drinking days in a week compared with placebo with a reduction from 100% to 88% with gabapentin use (incident rate ratio, 0.88; 95% CI, 0.81 to 0.96; p<0.005). The third study[133] found a linear decrease in the average number of days of heavy drinking per week with higher doses of gabapentin (p<0.001).

Table 12. Heavy drinking days results that could not be included in meta-analysis among placebo-controlled trials of gabapentin and gabapentin XR

Study	Country	Population	N	Weeks	Specific Outcome	Results
Falk, 2019[132]	U.S.	AUD	338	26	Percentage of heavy drinking days	GAB XR: 46.5% Placebo: 43.1% p=0.397
Mason, 2014[133]	U.S.	Alcohol dependence	150	12	Heavy drinking days/week, Mean	GAB 900 mg: 1.8 GAB 1,800 mg: 2.0 Placebo: NR GAB 900 mg p<0.001 GAB 1,800 mg p<0.001
Chompookham, 2018[134]	Thailand	Alcohol dependence	112	12	Percentage of heavy drinking days	GAB:12% Placebo: NR p<0.005

AUD = alcohol use disorder; GAB = gabapentin; mg = milligram; N = sample size; NR = not reported; U.S. = United States; XR = extended release.

3.1.3.2.7 Drinks per Drinking Day

Two trials reported data on drinks per drinking day.[131, 132] Both were U.S. based and found no difference in drinks per drinking day (Table 13). The SOE was low because of risk of bias and imprecision.

Table 13. Drinks per drinking day results that could not be included in meta-analysis among placebo-controlled trials of gabapentin and gabapentin XR

Study	Country	Population	N	Weeks	Specific Outcome	Results
Falk, 2019[132]	U.S.	AUD	338	26	Drinks per drinking day, mean	GAB XR: 4.1 Placebo: 3.9 p=0.641
Anton, 2020[131]	U.S.	AUD	90	16	Drinks per drinking day, mean	GAB: 8.1 Placebo: 7.9 p=0.79

AUD = alcohol use disorder; GAB = gabapentin; N = sample size; U.S. = United States; XR = extended release.

3.1.3.3 Ondansetron

3.1.3.3.1 Characteristics of Trials

Table B-6 summarizes characteristics of the three trials meeting our inclusion criteria.[135-137] One study (n=95) was conducted in the United States, with participants recruited through a variety of methods, including media advertising, flyers, and medical records searches.[137] This study randomized participants to 0.66 mg/day of ondansetron or placebo, and all participants also

received Brief Behavioral Compliance Enhancement Treatment. They only included people who were of European or African American descent (63% and 37%, respectively), stratifying randomization by site, race, sex, and whether they had a genotype believed to be responsive to ondansetron.

The second study was new to this update.[136] One was conducted at a single university in Brazil and compared ondansetron 16 mg/day with placebo among men with alcohol dependence. All participants (N=102) received a standardized brief cognitive behavioral intervention. Forty-five percent were multiracial, 33 percent were White, and 22 percent were Black. Patients were enrolled as outpatients in a substance abuse treatment program at the university; 64 percent were persons who smoke. This study was rated as high risk of bias mainly because of very high attrition; 58 percent of those randomized to the placebo group and 42 percent taking ondansetron dropped out of the study.[135]

The third study (N=70) was conducted in the United States and was limited to persons with co-occurring early-onset AUD (onset prior to age 25) and bipolar or related disorders (bipolar disorder I, II, or NOS); schizoaffective disorder (bipolar type); cyclothymia disorder; or major depressive disorder with mixed features. The dose was similar to the U.S. study, titrating up to 1 mg/day after 4 weeks.[136] In this study, 51 percent of participants were Black, 26 percent were White, 13 percent were Hispanic, 9 percent were Asian or Pacific Islander, and 1 percent were Native American.

3.1.3.3.2 Summary of Findings

Ondansetron was not associated with reductions in percent drinking days (low SOE), heavy drinking days (insufficient SOE), or drinks per drinking day (insufficient SOE). The findings were mixed for heavy drinking days, and we considered evidence to be insufficient to determine whether ondansetron reduced heavy drinking days. The high risk of bias study conducted in Brazil found a small difference in the percent of heavy drinking days (8% of days with ondansetron vs. 12% with placebo, p=0.02),[135] but differences were not statistically significant in either of the two lower-dose studies, where findings trended in opposite directions.[136, 137]

3.1.3.3.3 Drinking Days

Neither study reporting this outcome found a statistically significant improvement in percent drinking with ondansetron.[135, 136] In the trial conducted in Brazil, participants treated with ondansetron drank on a mean of 22 percent of days; patients treated with placebo drank on 33 percent of days (p=0.40). In the trial limited to people with bipolar and related disorders, patients treated with ondansetron drank on a mean of 48 percent of days; patients treated with placebo drank on 67 percent of days (p=0.10).

3.1.3.3.4 Heavy Drinking Days

In the study conducted in the United States, mean heavy drinking days per week was 1.24 times higher among ondansetron users (95% CI, 0.95 to 1.62), although the likelihood of having no heavy drinking days during followup trended in the direction favoring ondansetron (odds ratio, 1.49; 95% CI, 0.79 to 2.84).[137] In the Brazilian study, participants treated with ondansetron drank heavily (>5 drinks) on a mean of 8 percent of days; those treated with placebo drank heavily on 12 percent of days (p=0.02).[135] However, the difference between groups was not statistically significant in the trial among people with bipolar and related disorders (34% of days with ondansetron vs. 44% with placebo, p=0.44).[136]

3.1.3.3.5 Drinks per Drinking Day

None of the studies found a statistically significant group difference in drinks per drinking day. The trial conducted in the United States found that the ondansetron group averaged 0.48 more drinks per drinking day (95% CI, -0.35 to 1.31).[137] The trial limited to people with bipolar and related disorders found no reduction in drinks per drinking day with ondansetron.[136] Patients treated with ondansetron drank a mean (standard deviation [SD]) 4.1 (4.1) drinks per drinking day compared with 4.9 (4.1) drinks per drinking day in the placebo group (p=0.11). The trial conducted in Brazil reported a related outcome of average drinks per day across the entire observation period and reported no benefit of ondansetron (mean [SD], 0.7 [0.2] with ondansetron vs. 1.1 [0.3] with placebo; p=0.22).[135]

3.1.3.4 Prazosin

3.1.3.4.1 Characteristics of Trials

Two placebo-controlled trials[138, 139] reported on the effect of prazosin on AUD-related outcomes; both were new to this update (Table B-7). Both were conducted at VA medical centers in the United States, using a daily dosage of 16 mg over 12 weeks. The populations were similar, with average ages in the 40s, with majority male patients. Participants in both studies had medical management concurrent with treatment with prazosin.

The focus of the first trial[138, 140] was on the treatment of persons with both PTSD and alcohol dependence. Most (94%) of the participants were male, and approximately 80% were White. Participants were recruited primarily from clinicians in the PTSD and substance treatment programs at the VA and met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria for both PTSD and AUD, reporting at least one episode of heavy drinking per week in the past 14 days. Participants were randomized into a prazosin group or placebo with prazosin titrated over the first 2 weeks starting at 2 mg per day up to 16 mg per day.

The second[139] was a trial rated as high risk of bias that focused on AUD and excluded any participants with PTSD. Approximately 80 percent of the participants in this study were male, and 44 percent were White. This study also followed a 2-week titration period, and data were collected daily via interactive voice response by telephone.

3.1.3.4.2 Summary of Findings

With only two studies in different populations, one of which had high risk of bias, SOE was insufficient for all outcomes. Neither study showed any significant group difference in any outcome.

3.1.3.4.3 Return to Any Drinking

Although all drinking outcomes showed improvement over the study period in both groups, there were no differences by treatment group in return to any drinking (p=0.26) in the one study that reported on this outcome.[138, 140]

3.1.3.4.3 Drinking Days

Number of drinking days over 90 days decreased in both groups in the study of patients with comorbid PTSD from a baseline of 47.0 (SD 29.9) to 11.0 (SD 18.9) in the prazosin group and baseline of 43.1 (SD 27.8) to 9.2 (SD 16.6) in the placebo group; the difference between groups was not significant (p=0.59).[138, 140]

In the second study that excluded participants with PTSD, drinking days per week were reduced by 0.4 in the treatment group, from 3.2 to 2.8 and by 0.5 in the placebo group, from 2.8 to 2.3 (p=0.94).[139]

3.1.3.4.4 Heavy Drinking Days

Number of heavy drinking days over 90 days decreased in both groups in the study of patients with comorbid PTSD from a baseline of 41.3 (SD 29.3) to 7.2 (SD 13.8) in the prazosin group and baseline of 39.5 (SD 28.2) to 6.0 (SD 12.6) in the placebo group; the difference between groups was not significant (p=0.65).[138, 140]

Heavy drinking days per week in the study that excluded patients with PTSD were reduced by 0.8 in the treatment group, from 1.8 to 1.0, and by 0.3 in the placebo group, from 1.5 to 1.2. Although the number of heavy drinking days decreased more rapidly in the prazosin group than placebo, at the end of treatment, the number of heavy drinking days did not differ (p=0.56).[139]

3.1.3.4.5 Drinks per Drinking Day

In the study of patients with PTSD, drinks per drinking day decreased from 17.3 (SD 10.7) to 4.4 (SD 5.7) in the treatment group and from 21.9 (SD 13.2) to 6.9 (SD 9.1) in the placebo group (p=0.25).[138, 140] In the second study, change in drinks per week at completion did not differ between the groups (p=0.94), although the authors noted that the prazosin group experienced a more rapid decline to the end point between weeks 3 and 12.[139]

3.1.3.5 Topiramate

3.1.3.5.1 Characteristics of Trials

We included 11 trials comparing topiramate with placebo for 12 to 26 weeks (Table B-8).[141-147] Eight trials were conducted in the United States,[141-144, 146-149] and 1 each in Spain,[150] Brazil,[77] and Thailand.[145] Four of these were included in the previous report,[77, 148, 149, 151] and seven are newly identified.[141-147] Mean age ranged from 41 to 51 years. All participants met criteria for AUD in 12 of the 13 trials, and 1 trial reported that 92 percent of participants met criteria for alcohol dependence but based inclusion on alcohol use quantity rather than on having AUD diagnosis.[143] Three trials enrolled only men;[77, 145, 151] the other 8 ranged from 6 to 42 percent women. Only 2 trials reported information on smoking history at baseline, with 66 to 80 percent persons who smoke enrolled in those trials, conducted in Spain[151] and Brazil, respectively.[77]

Most of the included participants were White, ranging from 17 percent to 100 percent White in the individual studies; only three studies included more that 40 percent of participants who were not White.[141, 142, 146] These studies with higher representation of participants who were not White were limited to specific populations: people with PTSD,[141] with co-occurring cocaine use disorder,[142] and with mild traumatic brain injuries.[146] Among these three studies, Black, Hispanic, and multiracial groups were most commonly represented. In total, four studies were limited to populations with specific comorbid medical conditions, including PTSD (N=30),[141] cocaine use disorder (N=170),[142] mild traumatic brain injury (N=32),[146] and bipolar disorder (N=12).[147]

Topiramate doses were typically 200 to 300 mg per day. Four studies explicitly described flexible dosing, based on individuals' balance of efficacy and side effects.[77, 146, 148, 149] One trial examined a dose of 150 mg per day in a small trial of adults with bipolar disorder.[147] Most of the included trials also offered a medical management intervention that included manual-driven,

low-intensity supportive counseling to promote adherence to the medication regimen and reduction in alcohol use (typically offered in weekly 20- to 30-minute sessions) or a similar program of psychosocial support.

3.1.3.5.2 Summary of Findings

The most commonly reported outcomes were percent drinking days, percent heavy drinking days, and drinks per drinking day, which all had moderate SOE for improvement with topiramate use. Primary meta-analysis results for these three alcohol use outcomes are shown in Table 14. Although statistical significance was mixed among the included studies, pooled results showed that topiramate was associated with a 7.2 percentage point reduction in percent drinking days (WMD, -7.2; 95% CI, -14.3 to -0.1), a 6.2 percentage point reduction in percent heavy drinking days (WMD, -6.2; 95% CI, -10.9 to -1.4), and 2.0 fewer drinks per drinking day (WMD, -2.0; 95% CI, -3.1 to -1.0) after 12 weeks. There were not enough trials to conduct stratified analyses; however, there was no apparent pattern indicating that high risk of bias was associated with larger or smaller effect sizes for any of these outcomes. Evidence was insufficient SOE for return to any drinking and return to heavy drinking. See Table D-11 for SOE ratings for all drinking and health outcomes.

Table 14. Meta-analysis results for alcohol use outcomes among placebo-controlled trials of topiramate

Outcome	No. RCTs	N	WMD	95% CI	I^2, %	Range of Post-Treatment Means, Placebo	Range of Post-Treatment Means, Topiramate
Percent drinking days	4	570	-7.2	-14.3 to -0.1	46	6.4 to 70.9	5.5 to 62.4
Percent heavy drinking days	5	720	-6.2	-10.9 to -1.4	16	5.3 to 51.8	2.3 to 43.8
Drinks/drinking day	6	752	-2.0	-3.1 to -1.0	33	4.0 to 8.8	1.2 to 6.5

CI = confidence interval; No. = number; N = sample size; RCT = randomized controlled trial; WMD = weighted mean difference.

3.1.3.5.3 Return to Any Drinking

Just one trial reported this outcome—a trial conducted in Brazil that was rated as high risk of bias.[77] It reported that fewer patients treated with topiramate returned to any drinking than with placebo (28/52 patients [53.8%] vs. 39/54 [72.2%]).

3.1.3.5.4 Return to Heavy Drinking

One trial reported this outcome—the trial conducted in the United States was limited to persons with cocaine use disorder (N=170) and rated as being at high risk of bias.[142] This study found no difference between groups, with 10 percent reporting a return to heavy drinking among participants taking topiramate and 14 percent among those taking placebo (p=0.42).

3.1.3.5.5 Drinking Days

Eight studies[141-146, 148, 151] reported on drinking days, but only four[141, 145, 148, 151] could be combined in the meta-analysis. The four trials that could be combined reported percent of days in which the participants drank any alcohol. Two of these three trials were conducted in the United States and were rated as low risk of bias, one in a general population of people with AUD (N=371)[148] and one limited to people with comorbid PTSD (N= 30).[141] The other two trials

included in the meta-analysis were conducted in Spain (N=63)[151] and Thailand (N=106)[145] among general populations of people with AUD, both rated as high risk of bias.

Meta-analysis combining four trials (N=570) found a lower percentage of drinking days for patients treated with topiramate than for those who received placebo (WMD, -7.2; 95% CI, -14.3 to -0.1).The larger U.S.-based trial in a general population of people with AUD found an 8.5 percentage point lower percent of drinking days for patients treated with topiramate than for those who received placebo (WMD, -8.5; 95% CI, -15.9 to -1.1).[148] This finding is consistent with the findings of the previous review (WMD, -9.7; 95% CI, -16.4 to -3.1), which included only two trials. The remaining four trials that were not included in the meta-analysis reported mixed findings on drinking days or related outcomes (Table 15). Two U.S.-based trials reported statistically significant improvement with topiramate during the active treatment period (N=170[144] and 138[143]) in general populations. However, a combined analysis of these two trials demonstrated that the benefit disappeared after medication use had ended (p=1.0 at both 3- and 6-month post-treatment followups).[152] The other two trials found no differences between groups in U.S.-based trials among people with cocaine use disorder[142] and mild traumatic brain injuries.[146]

Table 15. Drinking days results that could not be included in meta-analysis among placebo-controlled trials of topiramate

Study	Country	Population	N	Weeks	Specific Outcome	Results
Kampman, 2013[142]	U.S.	AUD+ Cocaine use disorder	170	13	Percent of drinking days, Mean	TOP: 16% Placebo: 20% p=0.13
Kranzler, 2021 [144]	U.S.	AUD	170	12	Drinking days/ week, Mean	TOP: ~4.8 Placebo: ~5.3 p=0.03 (estimated from a figure)
Kranzler, 2014[143]	U.S.	AUD	138	12	Days abstinent/ week, Mean	TOP: ~2.5 Placebo: ~1.5 p=0.03 (estimated from a figure)
Pennington, 2020[146]	U.S.	AUD+ Mild TBI	32	12	Drinking days/ week, Mean (SD)	TOP: 2.2 (1.8) Placebo: 1.6 (2.1) p=0.50

AUD = alcohol use disorder; N = sample size; SD = standard deviation; TBI = traumatic brain injury; TOP = topiramate; U.S. = United States.

3.1.3.5.6 Heavy Drinking Days

Nine of the trials reported this outcome.[141-145, 147-149, 151] However, only five, which all reported the percent of heavy drinking days in the study observation period, could be combined in a meta-analysis.[141, 145, 148, 149, 151] Three of these included in the meta-analysis were conducted in the United States[141, 148, 149] (combined N=551) and the others in Spain[151] and Thailand.[145] One of these was limited to veterans with PTSD (N=30).[141] The meta-analysis found a lower percentage of heavy drinking days for patients treated with topiramate than for those who received placebo (WMD, -6.2; 95% CI, -10.9 to -1.4). The pooled effect is smaller than the effect from the previous review, which only included three trials (WMD, -12.5; 95% CI, -17.9 to -7.2) but retained statistical significance. Findings also indicated greater benefit with topiramate in two of the four trials that were not included in the meta-analysis (Table 16), both of which were conducted in the United States (N=170[144] and 138[143]). However, a combined analysis of these two trials demonstrated that the benefit disappeared after medication use had ended (p=0.95 at 3-month post-treatment followup, p=0.64 at 6-month followup).[152] The remaining two trials found

no benefit among 170 adults with comorbid cocaine use disorder rated as high risk of bias[142] and no reporting on group differences in small study of 12 persons with bipolar disorder.[147]

Table 16. Heavy drinking days results with insufficient data to include in meta-analysis among placebo-controlled trials of topiramate

Study	Country	Population	N	Weeks	Specific Outcome	Results
Kampman, 2013[142]	U.S.	Cocaine use disorder	170	13	Percent of heavy drinking days	TOP: 10% Placebo: 16% p=0.42
Kranzler, 2021[144]	U.S.	General	170	12	Heavy drinking days/ week, Mean	TOP: ~2.1 Placebo: ~3.1 p<0.01 (estimated from a figure)
Kranzler, 2014[143]	U.S.	General	138	12	Heavy drinking days/ week, Mean	TOP: ~1.5 Placebo: ~2.5 p=0.03 (estimated from a figure)
Sylvia, 2016 [147]	U.S.	Bipolar disorder	12	12	Drinking days/ week, Mean (SD)	TOP: 2.4 (0.8) Placebo: 2.4 (3.0) p NR

N = sample size; NR = not reported; SD = standard deviation; TOP = topiramate; U.S. = United States.

3.1.3.5.7 Drinks per Drinking Day

Seven of the trials reported drinks per drinking day.[141, 142, 145, 146, 148, 149, 151] Six of the trials could be combined in meta-analysis.[141, 145, 146, 148, 149, 151] The meta-analysis found that topiramate was associated with a reduction in drinks per drinking day (WMD, -2.0; 95% CI, -3.1 to -1.0). The pooled effect is similar to that in the previous review, which included only three trials (WMD, -1.2; 95% CI, -1.8 to -0.6). The one trial that could not be included in the meta-analysis was a U.S.-based trial among persons with cocaine use disorder (N=170). This study found that topiramate did not differ from placebo in the effect on drinks/drinking day (mean [standard error (SE)], 5.2 [0.6] with topiramate vs. 6.1 [0.6] with placebo, p=0.45).

3.1.3.6 Varenicline

3.1.3.6.1 Characteristics of Trials

Table B-9 summarizes characteristics of the six trials meeting our inclusion criteria.[153-158] Five of the six trials[154-157, 158] were new to this update. Four of the six were conducted in the United States,[153, 155, 156, 158] one was conducted in Germany,[157] and one in Sweden.[154] Mean age ranged from 39 to 55. Participants in the studies were predominantly male, with females making up 15 percent to 38 percent of the participants. Three of the six studies provided data on race, including 0 percent non-White in the study in Sweden,[154] 9 percent in one U.S. study,[155] and 62 percent in another U.S. study.[156]

Three of the studies included populations with 100 percent persons who smoke[155-157] with the other studies including 39 percent persons who smoke,[153] 42 percent persons who smoke,[158] and 53 percent persons who smoke.[154] Only one provided stratified outcomes data by smoking status,[158] although one tested for an interaction with smoking and found none.[153]

Four of the studies explicitly described co-interventions, including brief behavioral counseling;[155] medical management based on the COMBINE approach;[156] a weekly individual, manual-guided medical management approach;[158] or a computerized self-help program.[153] One study[157] focused on a population that had undergone detoxification and expressed a desire to completely abstain from alcohol. None of the studies provided data on co-occurring conditions.

3.1 Key Question 1. Efficacy and Comparative Effectiveness for Improving Consumption Outcomes

All studies had a treatment period of around 12 weeks, except one[156] in which the treatment period was 16 weeks.

Only one study (from the previous report) was rated as low risk of bias,[153] while three of the newer studies were rated as medium risk of bias,[154, 156, 158] and two were rated as high risk of bias.[155, 157]

Results for all studies are summarized below by outcomes. Forest plots for meta-analyzed data are found in Figure E-26. The prior report, based on one study,[153] found no effect of varenicline on return to any drinking, return to heavy drinking, or drinking days but did report a beneficial effect on heavy drinking days and drinks per drinking day.

3.1.3.6.2 Summary of Findings

We found low SOE that varenicline demonstrated no benefit across all drinking outcomes (Table D-12).

3.1.3.6.3 Return to Any Drinking

With two studies reporting return to any drinking, we found low SOE for no benefit. One study had low risk of bias[153] and found no difference between varenicline-treated patients and placebo-treated patients (97.9% vs. 98%, respectively; p=0.81). One small study[158] also reported no difference in return to any drinking (p=0.8) in the meta-analysis (Table 17).

Table 17. Return to any drinking results that could not be included in meta-analysis among placebo-controlled trials of varenicline

Study	Country	Population	N	Weeks	Specific Outcome	Results
Litten, 2013[153]	U.S.	AUD	200	12	Percentage of participants without abstinent days	VAR: 97.9% Placebo: 98% p=0.81
Peblani, 2013[158]	U.S.	AUD	40	12	Presence/absence of alcohol use	p=0.8

AUD = alcohol use disorder; N = sample size; U.S. = United States; VAR = varenicline.

3.1.3.6.4 Return to Heavy Drinking

The same two studies that reported on return to any drinking provided data on return to heavy drinking, and again we found low SOE for no benefit. The one low risk-of-bias study from the original report found no significant difference between groups (92.7% vs. 95%, respectively; p=0.50).[153] The additional small study (N=40) found no significant effect (p=0.16) for varenicline on the outcome in the meta-analysis (Table 18).

Table 18. Return to heavy drinking results that could not be included in meta-analysis among placebo-controlled trials of varenicline

Study	Country	Population	N	Weeks	Specific Outcome	Results
Litten, 2013[153]	U.S.	AUD	200	12	Return to HDD	VAR: 92.7% Placebo: 95.0% p=0.50
Peblani, 2013[158]	USA	AUD	40	12	Return to HDD	p=0.16

AUD = alcohol use disorder; HDD = heavy drinking days; N = sample size; U.S. = United States; VAR = varenicline.

3.1.3.6.5 Drinking Days

We found low SOE for no effect on drinking days of varenicline versus placebo. Five studies reported no effect of varenicline on drinking days, defined either as number of drinking days or a percentage (Table 19). In the previous review, one low risk-of-bias study found no difference

between varenicline-treated patients and placebo-treated patients on percent of drinking days (60.0% vs. 64.4%, respectively; p=0.29) at the end of treatment.[153] In the update, two medium risk-of-bias studies found similar effects (70% vs. 66%, p=0.13[154] and p=0.67 for no group effects for weekly days of alcohol use[158]).

Two additional studies rated as high risk of bias also reported no significant effect on the number of drinking days. One study reported a reduction in drinking days in a treatment group of 3.3 versus 2.3 in the placebo group; overall treatment effect was -0.9 (95% CI, -4.1 to 2.2).[155] The other of these[157] reported 27 percent drinking days in the varenicline group compared with 22 percent in the placebo group (p=0.58). This study differed from other outpatient studies in that participants had just undergone detoxification and were required to exhibit a desire to abstain completely. Participants were instructed to entirely abstain from alcohol, and only three of 15 individuals in the treatment group and none in the placebo group completed treatment.[157]

Table 19. Drinking days results that could not be included in meta-analysis among placebo-controlled trials of varenicline

Study	Country	Population	N	Weeks	Specific Outcome	Results
Litten, 2013 [153]	U.S.	AUD	200	12	% drinking days	VAR: 60% Placebo: 64.4% p=0.29
Bejczy, 2015[154]	Sweden	AUD	171	12	% drinking days	VAR: 70% Placebo: 66% p=0.13
Plebani, 2013[158]	U.S.	AUD	40	12	Weekly days of alcohol use	p=0.67
Hurt, 2018 [155]	U.S.	AUD	33	12	Change in number of drinking days from baseline	VAR: -3.3 Placebo: -2.3 -0.9 (95% CI: -4.1 – 2.2)
Pfeifer, 2019[157]	Germany	AUD; just completed detoxification	28	12	% drinking days	VAR: 27% Placebo: 22% p=0.58

AUD = alcohol use disorder; CI = confidence interval; N = sample size; U.S. = United States; VAR = varenicline.

3.1.3.6.6 Heavy Drinking Days

All six studies (5 of them new) reported data for heavy drinking days either as a percentage of heavy drinking days[153, 154, 156, 157] or number of heavy drinking days (Table 20).[155, 158] With one study with low risk of bias reporting a benefit[153] and five with mixed risk of bias reporting no effect, we found low SOE for no benefit in this outcome.[154-158]

The one study in the original report found that varenicline-treated patients reported a lower percentage of heavy drinking days compared with placebo-treated patients (37.9% vs. 48.4%, respectively; p=0.03). Among the newer studies, none found an effect on heavy drinking days. One reported the percentage of heavy drinking days and found no difference by group (51% vs. 49%, p=0.73), with the treatment group reporting a higher percentage of heavy drinking days than the placebo group.[154] Another study[156] presented mean change in log transformed drinking days from a linear mixed model and found no difference (p=0.08) between varenicline (least squares estimate [LSE]:1.60 [SE: 0.20]) and placebo (LSE: 1.77 [SE: 0.20]). This study reported a significant interaction by sex, with men reporting a greater decrease than women (p=0.3), although the number of women in the study was small. The third new study reporting percentage of heavy drinking days included only two of 15 participants who completed the study in the treatment group and reported no effect.[157]

The two studies that measured number of heavy drinking days also found no group differences. The medium risk-of-bias study reported that the varenicline-treated group had slightly lower numbers of drinking days but that the difference was nonsignificant in their model (p=0.10).[158] The high risk-of-bias study also found no group difference, with mean (SD) 7.9 (8.3) heavy drinking days in the varenicline group and 9.1 (7.2) in the placebo group for a difference of -1.3 days (95% CI, -4.7 to 2.1).[155]

Table 20. Heavy drinking days results that could not be included in meta-analysis among placebo-controlled trials of varenicline

Study	Country	Population	N	Weeks	Specific Outcome	Results
Litten, 2013[153]	U.S.	AUD	200	12	% HDD	VAR: 37.9% Placebo: 48.4% p=0.03
Bejczy, 2015[154]	Sweden	AUD	171	12	% HDD	VAR: 51% Placebo: 49% p=0.73
O'Malley, 2017[156]	U.S.	AUD	131	12	Log transformed mean (SE) change in %HDD from baseline	VAR: 1.69 (0.20) Placebo: 1.77 (0.20) p=0.80
Peblani, 2013[158]	U.S.	AUD	40	12	% HDD	p=0.10
Hurt, 2018[155]	U.S.	AUD	33	12	Mean (SD) HDD	VAR: 7.9 (8.3) Placebo: 9.1 (7.2) -1.3 (95% CI, -4.7 to 2.1)
Pfeifer, 2019[157]	Germany	AUD, just completed detoxification	28	12	% HDD	No effect

AUD = alcohol use disorder; CI = confidence interval; HDD = heavy drinking days; N = sample size; SD = standard deviation; SE = standard error; U.S. = United States; VAR = varenicline.

3.1.3.6.7 Drinks per Drinking Day

We found low SOE for no effect on drinks per drinking day based on four studies reporting on this outcome.[153-155, 157] One low risk-of-bias study found that varenicline-treated patients reported fewer drinks per drinking day compared with placebo-treated patients (5.8 vs. 6.8; p=0.03). A second, small (N=33) high risk-of-bias study reported a greater reduction in drinks per drinking day by -2.8 (90% CI, -6.6 to -1.0) at the end of the treatment period, with mean numbers of drinks per drinking day of 5.7 (3.9) in the varenicline group and 9.0 (5.3) in the placebo group after 12 weeks.[155]

Two additional studies reported no effect. One had medium risk of bias[154] and reported a mean number of drinks per drinking day at the end of treatment of 3.0 (95% CI, 1.93 to 4.08) in the varenicline group and 3.42 (95% CI, 2.51 to 4.34) in the placebo group (p=0.28). The final study[157] reported final mean (SD) drinks per drinking day of 11.4 (12.2) in the treatment group and 21.0 (11.9) in the placebo group (p=0.12).

Meta-analysis of these four studies did not find a statistically significant difference between varenicline and placebo (WMD, -1.40; 95% CI, -2.94 to 0.13).

3.1.4 Detailed Synthesis: Head-to-Head Trials

3.1.4.1 Acamprosate Versus Disulfiram

3.1.4.1.1 Characteristics of Trials

We found no studies meeting our inclusion criteria (insufficient SOE). Our searches did identify some studies comparing acamprosate with disulfiram that did not meet our inclusion criteria for this section because they were open-label studies.[159, 160]

3.1.4.2 Acamprosate Versus Naltrexone

3.1.4.2.1 Characteristics of Trials

No new studies in this update compared acamprosate with naltrexone. The 2014 review included four trials comparing acamprosate with naltrexone (Table B-10).[44] Three used 50 mg per day doses for naltrexone;[45-47] one used 100 mg per day.[44] Three used a 1,998 mg per day dose for acamprosate;[45-47] one used 3,000 mg per day.[44] One trial, COMBINE, was a multicenter nine-arm trial that compared eight groups of patients receiving medical management with 16 weeks of naltrexone (100 mg per day) or acamprosate (3,000 mg per day), both, and/or both placebos, with or without a combined behavioral intervention (CBI). The ninth group received CBI only and no drug or placebo.[44] Duration of treatment ranged from 12 to 16 weeks. One trial was conducted in the United States, two in Germany, and one in Australia. Mean age was in the mid-40s for all four trials. All participants met criteria for alcohol dependence in three trials; one trial did not report the percentage with alcohol dependence, but most participants likely had alcohol dependence.[46] Three studies did not report information on race; one trial reported enrolling 23 percent non-White participants.[44] The trials enrolled a similar percentage of women (23% to 31%). Two trials reported information on smoking history at baseline—one reported that 55 percent of pill-taking participants were persons who smoke;[44] one reported that 72 to 81 percent of participants were persons who smoke across study arms.[46] Trials included or encouraged psychological or psychosocial co-interventions.

3.1.4.2.2 Return to Any Drinking

The meta-analysis found no statistically significant difference between naltrexone and acamprosate (RR, 1.03; 95% CI, 0.96 to 1.10; moderate SOE).

3.1.4.2.3 Return to Heavy Drinking

The meta-analysis found no statistically significant difference between naltrexone and acamprosate (RR, 1.02; 95% CI, 0.93 to 1.11; moderate SOE).

3.1.4.2.4 Drinking Days

Two of the four trials reported sufficient data for meta-analysis for drinking days; neither found a statistically significant difference between treatments.[44, 46] The meta-analysis found no statistically significant difference between naltrexone and acamprosate (WMD, -2.98; 95% CI, -13.4 to 7.5; low SOE).

3.1.4.2.5 Heavy Drinking Days

The COMBINE study reported that analyses of alternative summary measures of drinking, including heavy drinking days per month were consistent with those for the co-primary end points (percentage of days abstinent from alcohol and time to first heavy drinking day), all showing a significant reduction with naltrexone compared to placebo, but not with acamprosate (insufficient SOE).

3.1.4.2.6 Drinks per Drinking Day

Two of the trials reported some information about drinks per drinking day, but not enough data for us to conduct quantitative synthesis (insufficient SOE). The trial conducted in Australia reported no statistically significant difference between acamprosate and naltrexone (mean [SD], 7.5 [6.1] versus 5.9 [6.1]; p not reported). The COMBINE study reported that analyses of alternative summary measures of drinking, including drinks per drinking day (p=0.03), were consistent with those for the co-primary end points (percentage of days abstinent from alcohol and time to first heavy drinking day), all showing a significant reduction with naltrexone, CBI or both compared to placebo.

3.1.4.3 Disulfiram Versus Naltrexone

3.1.4.3.1 Characteristics of Trials

We included one trial comparing disulfiram with naltrexone (Table B-11). It compared disulfiram, naltrexone, placebo, and the combination of disulfiram plus naltrexone for 12 weeks in VA outpatient settings. All participants met criteria for alcohol dependence and had co-occurring Axis I psychiatric disorders. Almost all participants were male. The trial did not report information on smoking history at baseline. The study used a double-blind design for the comparison between naltrexone and placebo but not for disulfiram (which was given open label). We rated the trial as high risk of bias for the comparison between disulfiram and naltrexone, primarily for high risk of ascertainment bias (see Appendix C for details; we rated it as medium risk of bias for naltrexone vs. placebo).

Other studies that did not meet our inclusion criteria for this section comparing disulfiram with naltrexone were either open-label studies[160-162] or were conducted in adolescents.[163]

3.1.4.3.2 Return to Any Drinking

The trial reported no statistically significant difference between disulfiram and naltrexone for number of participants achieving total abstinence (51 vs. 38, p=0.11, insufficient SOE).

3.1.4.3.3 Drinking Days

The trial reported no statistically significant difference between disulfiram and naltrexone for the percentage of days abstinent (96.6 vs. 95.4, p=0.55, insufficient SOE).

3.1.4.3.4 Heavy Drinking Days

The trial reported no statistically significant difference between disulfiram and naltrexone for the percentage of heavy drinking days (3.2 vs. 4, p=0.65; insufficient SOE).

3.1.5 Head-to-Head Trials Including Medications Used Off-Label or Those Under Investigation

3.1.5.1Topiramate Compared With Naltrexone

The only included trial, rated as high risk of bias, reported no significant differences between topiramate and naltrexone for percent of abstinent participants, cumulative abstinence duration, time to first return to any drinking, or heavy drinking weeks.[77] The trial was conducted in Brazil. Significantly more participants in the topiramate group participated in Alcoholics Anonymous than in the naltrexone group (19.2% vs. 4.1%, p=0.04). Across alcohol use outcomes, SOE was insufficient for the comparison between topiramate and naltrexone.[77]

3.2 Key Question 2. Health Outcomes

For this KQ, we describe the characteristics of included studies and then results for the included health outcomes (accidents, injuries, quality of life, function, and mortality).

3.2.1 Key Points

- We found insufficient to low SOE for measures of quality of life, function, accidents, and mortality across all medications.
- In the available studies, we found low SOE for no difference in quality of life and function measures for use of baclofen based on two studies, and in the topiramate studies, we see low SOE for no effect on injuries or quality of life measures.

3.2.2 Summary of Findings

As in the prior report, very few data are available on health outcomes; we found insufficient to low SOE for measures of quality of life, function, accidents, and mortality across all medications.

3.2.3 Detailed Synthesis: Placebo-Controlled Trials of FDA-Approved Medications for Treating Alcohol Dependence

3.2.3.1 Acamprosate

3.2.3.1.1 Characteristics of Trials

Ten placebo-controlled RCTs reported a health outcome, but only as a secondary outcome, and none were new to this update (Table B-12).[49, 50, 52, 56-58, 61, 63, 65, 164] Sample sizes ranged from 100 to 612 participants in acamprosate plus placebo arms. Duration of treatment ranged from 12 to 52 weeks. Followup to 1 year or longer was available for six trials.[52, 58, 61, 63, 65]

The mean age of patients ranged from 40 to 48. All patients enrolled in the trials had alcohol dependence. Two trials reported on race: 9 to 15 percent of patients were non-White.[49, 57] Females made up 18 to 38 percent of the patients across studies. Three trials[44, 49, 57] reported smoking status at baseline, from 44 percent to 55 percent.[44] No trials specified the percentage of patients who had a coexisting medical or psychiatric condition.

There was minor variation in the dosing of acamprosate across trials. Most studies used doses from 1,332 to 1,998 mg per day and determined dosing based on weight. Two studies included an arm that received 3,000 mg per day.[44, 57] Three studies commented on the use of other pharmacotherapy to address alcohol or comorbid psychiatric disorders.[50, 52, 58] One trial allowed the use of disulfiram on a voluntary basis.[50] Two other trials reported that 5 to 6 percent of patients in either treatment group were prescribed benzodiazepines,[52] and one trial allowed the use of "hypnotics, anxiolytics, or antidepressants" in either group.[58]

Three studies were conducted in the United States;[44, 49, 57] all others were conducted in European countries.[50, 52, 56, 58, 61, 63, 65] One study was conducted in a primary care setting;[49] most of the others were conducted in outpatient substance abuse or psychiatric treatment centers. The majority of trials recruited patients during or shortly after discharge from an inpatient substance abuse treatment center. Two U.S. trials recruited patients via newspaper advertisement[57] or a combination of advertisements and provider referrals.[49] One German trial recruited patients from outpatient substance abuse treatment centers.[63] The COMBINE study recruited patients by advertisement and referral from 11 academic centers.[44]

Eight trials were rated as low or medium risk of bias. One trial was rated as unclear risk of bias, primarily because of unclear handling of missing data and unclear masking of outcome assessors (see Appendix C for details).[56]

Overall, the SOE for accidents, injuries, quality of life, and mortality was insufficient for acamprosate, mainly because of having no data or very few events.

3.2.3.1.2 Accidents or Injuries

We identified one study, rated as unclear risk of bias, reporting that one patient in the placebo group died by "accident." No other details on the cause or nature of the accident were provided.[56]

3.2.3.1.3 Quality of Life or Function

The COMBINE study assessed quality of life using the World Health Organization Quality of Life (WHOQOL) and 12-item Short-Form Health Survey (SF-12v2) physical and mental health scores. Results were not presented for each treatment group separately.[165] These results are discussed in detail in the acamprosate versus naltrexone section (below). Briefly, no clinically significant differences were found across the eight combinations of pharmacological and behavioral treatments for quality of life for acamprosate compared with placebo.[165]

3.2.3.1.4 Mortality

Nine trials of acamprosate reported on mortality. Few deaths were reported; no study reported more than two deaths in any group. Table 21 shows the number of deaths in studies that reported deaths per study arm. In the COMBINE trial, the authors reported that one fatal serious adverse event was reported during the 16-week treatment phase. Investigators classified this death as being unrelated to the study medication. No details were provided on which group the death occurred in, the nature of the adverse event, or the cause of death.[44]

Table 21. Mortality reported in placebo-controlled trials of acamprosate[a]

Author, Year	Study Duration, Weeks	N (Cause) Deaths, Placebo Arm	N (Cause) Deaths, Treatment Arm
Berger, 2013[49]	12	0	0
Besson, 1998[50]	52	1 (cardiac arrest)	0
Geerlings, 1997[52]	26	0	0
Mason, 2006[57]	26	0	0
Paille, 1995[58]	51	2 (NR)	4 (NR)[b]
Poldrugo, 1997[61]	26	1 (NR)	0
Sass, 1996[63]	52	1 (suicide, by hanging)	1 (suicide, by hanging)
Whitworth, 1996[65]	26	1 (NR)	2 (NR)

[a] The table includes eight of the nine trials that reported on mortality. The other trial was the COMBINE trial (as described in the text, it did not report which group the death occurred in).

[b] The study reported two deaths in the arm receiving 1,300 mg daily and two deaths in the arm receiving 2,000 mg daily.

N = sample size; NR = not reported.

3.2.3.2. Naltrexone

3.2.3.2.1 Characteristics of Trials

Ten RCTs comparing naltrexone with placebo reported at least one health outcome of interest (Table B-13). One trial was new to this update.[80]All 10 trials were rated as low or medium risk of bias.[44, 71, 76, 80, 85, 100, 103, 107-109] Sample sizes ranged from 31 to 618 participants in the naltrexone plus placebo arms. Duration of treatment ranged from 12 to 26 weeks.

Mean age was similar across trials, ranging from 39 to 50. Two trials included only male patients;[100, 107] females made up 3 to 38 percent of patients in the other trials. One study did not report on the race of study participants;[76] most of the other trials enrolled a minority of non-White participants (17 to 35%) and two enrolled a majority (70 to 76%).[103, 109] Three studies provided information on smoking status; approximately half of participants in those trials were persons who smoke.[44, 85, 103] All trials enrolled a vast majority (93% or more) of patients with alcohol dependence. Three trials did not specifically include (or describe) whether study participants had any coexisting medical or psychiatric disorders.[76, 85, 109] One trial was conducted among men who have sex with men; 67 percent reported any other drug use and 15 percent had HIV.[100] One trial was conducted in a population of individuals experiencing homelessness.[80] Four trials were conducted among populations who all had a specific psychiatric comorbidity: one among patients with either schizophrenia or schizoaffective disorder,[107] one among patients with cocaine dependence,[109] one among patients with at least one other psychiatric (Axis I) disorder,[71] and one among patients with depression.[108]

One trial evaluated the efficacy of two doses of injectable naltrexone,[85] and the remainder randomized patients to oral naltrexone either at 50, 100,[100, 108, 165] or 150 mg per day.[109] Four trials described a specific behavioral or psychological co-intervention.[76, 85, 100, 108] The one new trial in this update included a specific behavioral harm-reduction intervention.[80] Two trials conducted among those with a psychiatric comorbidity specified that patients continued medical management and usual psychiatric care[71, 107] and one included cognitive behavioral therapy for depressed patients.[108] No specific co-intervention was described in the trial comparing naltrexone with placebo in patients with cocaine dependence.[109]

One trial was conducted in Sweden;[76] all others were conducted in the United States. Most were conducted at an outpatient substance abuse or mental health center; none were conducted in primary care settings.

Overall, the SOE for accidents, injuries, quality of life, and mortality was insufficient for naltrexone, mainly because of having no data or very few events.

3.2.3.2.2 Accidents or Injuries

None of the included trials systematically assessed accidents or injuries.

3.2.3.2.3 Quality of Life or Function

Five placebo-controlled trials of naltrexone measured quality of life or some aspect of function, each trial using a different measure.[80, 100, 165, 166] One trial conducted among men who have sex with men[100] measured quality of life at 13 weeks using the Short Inventory of Problems, an alcohol-specific quality of life measure used to assess negative consequences of drinking.[167] No differences between naltrexone and placebo in end-of-treatment scores were found when using a last observation carried forward method to impute missing data (mean difference between groups at 13 weeks was -1.7, $p<0.09$).[100]

One study comparing injectable naltrexone with placebo measured quality of life using the Medical Outcomes Study 36-item short-form health survey (SF-36).[166] Data were reported separately for the overall physical and overall mental health summary scores of the SF-36. The study found no significant difference on either scale at 24 weeks between the placebo group and the injectable naltrexone 190 mg per month group. Patients receiving naltrexone 380 mg per month had greater improvement on the mental health summary score than those receiving placebo at 24 weeks (8.2 vs. 6.2, $p=0.044$), but there was no difference in improvement found on the physical health summary score (0.2 vs. -0.1, $p=0.51$).[166]

The COMBINE study assessed quality of life using the WHOQOL and SF-12v2 physical and mental health scores. Results were not presented for each treatment group separately.[165] See the section below on acamprosate versus naltrexone for details on these results. Briefly, the results indicated that the eight combinations of pharmacological and behavioral treatments did not show clinically significant differential effects on quality of life for either scale.[165]

One placebo-controlled study of naltrexone 50 mg measured the Drinker Inventory of Consequences (DrInC) at 16 weeks.[103] The DrInC is a 50-item questionnaire designed to measure adverse consequences of alcohol abuse in five areas: interpersonal, physical, social, impulsive, and intrapersonal.[167] More patients in the placebo group reported one or more alcohol-related consequence than in the naltrexone group, as measured by the DrInC (76 vs. 45%, $p=0.02$).[103]

One new study measured physical and mental health quality of life using the Short Form-12 survey.[80] This study, which included only participants experiencing homelessness, combined behavioral harm reduction with medical treatment and reported no significant effect of naltrexone on quality of life outcomes, although measures improved in all groups.

3.2.3.2.4 Mortality

Seven placebo-controlled trials of naltrexone reported mortality rates; six of these found more than one death in each treatment group (Table 22). Three studies reported that there were no deaths in either group,[108, 109, 166] one study reported one death in each study arm without providing additional details,[71] and one study reported a death due to alcohol intoxication in the placebo group.[76] In the COMBINE trial, the authors reported that one fatal serious adverse event was reported during the 16-week treatment phase. Investigators classified this death as being unrelated to the study medication. No details were provided on which group the death occurred

in, the nature of the adverse event, or the cause of death.[44] Three deaths were reported in a new study in this update.[80] All occurred in a usual care arm; none occurred in the naltrexone plus harm reduction, placebo plus harm reduction, or harm reduction alone arms; therefore, the difference could not be attributed to the specific treatment. Deaths are not uncommon in this population with coexisting homelessness and AUD.

Table 22. Mortality reported in placebo-controlled trials of naltrexone[a]

Author, Year	Study Duration, Weeks	N (Cause) Deaths, Placebo Arm	N (Cause) Deaths, Treatment Arm
Collins, 2021[80]	12	3	0
Balldin, 2003[76]	24	1 (alcohol intoxication)	0
Petrakis, 2005[71]	12	1	1
Pettinati, 2008[109]	12	0	0
Pettinati, 2009[166]	24	0	0
Pettinati, 2010[108]	14	0	0

[a] The table includes six of the seven trials that reported on mortality. The other trial was the COMBINE trial (as described in the text, it did not report which group the death occurred in).

N = sample size.

3.2.4 Detailed Synthesis: Placebo-Controlled Trials Including Medications Used Off-Label or Those Under Investigation

3.2.4.1 Baclofen

3.2.4.1.1 Characteristics of Trials

The included trials were designed to assess alcohol consumption outcomes. None were primarily focused on health outcomes, although five trials reported some information about health outcomes.[122, 125, 127, 128, 130] All were new to this update. Of those, four reported the number of deaths in each study group,[122, 125, 127, 130] and two reported on quality of life outcomes.[128, 130] Overall, the SOE for accidents, injuries, and mortality was insufficient, mainly because of having no data or very few events. The SOE was low for quality of life, supporting no significant difference between baclofen and placebo.

3.2.4.1.2 Accidents or Injuries

None of the included trials systematically assessed accidents or injuries.

3.2.4.1.3 Quality of Life or Function

Both studies that reported on quality of life outcomes found no statistically significant difference between baclofen and placebo.[128, 130] One was a 12-week trial (n=64) of baclofen 50 mg daily with 52-week followup conducted in Israel,[128] and the other was a 52-week trial (n=320) of baclofen up to 300 mg daily conducted in France.[130] The trial conducted in Israel reported no difference between groups (p=0.99) at 12 weeks or at 52 weeks on the Quality of Life Enjoyment and Satisfaction Questionnaire (12 weeks, mean [SD]: baclofen vs. placebo 3.4 [0.7] vs. 3.6 [0.8]; 52 weeks: 3.4 [0.8] vs. 3.6 [0.7], respectively). The trial conducted in France reported no difference between groups at 52 weeks on the SF-36 physical functioning score (mean [SD]: 71 [21] vs. 73 [19], absolute difference [95% CI] 0.2 [-5.3 to 5.6]) or the SF-36 mental functioning score (59 [23] vs. 61 [25], absolute difference [95% CI] 1.0 [-5.7 to 7.7]).

3.2.4.1.4 Mortality

Of the four trials (with a total of 660 participants) that reported the number of deaths in each study group,[122, 125, 127, 130] two of them reported zero deaths in any participant at 12 or 24 weeks,[122, 127] one reported a single death in a participant treated with baclofen and zero deaths in the placebo group over 12 weeks,[125] and one trial that evaluated high-dose baclofen up to 300 mg per day reported death among 4.3 percent (7 out of 162 participants) of those treated with baclofen and 1.9 percent (3 out of 158) of those in the placebo group over 52 weeks (RR, 2.28; 95% CI, 0.60, 8.64).[130] Overall, the strength of the evidence on mortality was graded as insufficient because of very few total events but suggests a possible increased risk of mortality with high-dose baclofen.

3.2.4.2 Topiramate

3.2.4.2.1 Characteristics of Trials

Five of the previously described placebo-controlled trials for topiramate reported health outcomes; 4 were new to this update.[141, 143, 145, 147] Four were conducted in the United States,[141, 143, 144, 147, 148] and one in Thailand.[145] The study in Thailand only enrolled men; the remaining studies reported that 7 percent to 42 percent were women with no mention of other gender identities. Two studies were limited to people with comorbid conditions: PTSD[141] and bipolar disorder.[147]

We found low SOE for no effect of topiramate on either injuries or quality of life and insufficient SOE for all other health outcomes.

3.2.4.2.2 Accident or Injury

Two placebo-controlled trials of topiramate reported on injuries. We assessed the SOE as low that topiramate may help prevent injuries.[143, 148] In one U.S.-based study (N=371), topiramate was associated with a reduction in injuries (8/183 [4.4%] in the topiramate group vs. 22/188 [11.7%] in the placebo group (p=0.01). The other study, also conducted in the United States (N=170), found very similar event rates in the two groups (9/85 [10.6% with topiramate vs. 8/85 [9.4%] with placebo, p-value not reported).[143]

3.2.4.2.3 Quality of Life or Function

Two trials reported quality of life outcomes, neither of which was included in the previous review. Both were rated as being high risk of bias, and we rated the SOE as low for no impact of topiramate. One trial was conducted in a general population of patients with AUD in Thailand (N=106);[145] the other was conducted in the United States and limited to people with bipolar disorder (N=12).[147] The trial in Thailand found no group differences in either the mental and physical component scores of the SF-36 after 12 weeks. Mean (SD) scores at followup were 89.9 (9.5) with topiramate and 89.4 (13.2) with placebo for the physical component score (p=0.85); mental component scores were 84.0 (11.6) and 84.2 (14.0) for topiramate and placebo, respectively (p=0.92).

3.2.4.2.4 Mortality

Evidence was also insufficient to determine the effect of topiramate on mortality. Three placebo-controlled trials of topiramate reported no deaths among participants taking topiramate and one death in each of the placebo groups.[141, 145, 148]

3.2.4.3 Varenicline

3.2.4.3.1 Characteristics of Trials

Only one study provided data on quality of life or mortality for varenicline.[153] No studies new to this update of varenicline reported other health outcomes. This low risk of bias study was conducted in the United States in a population of men and women meeting Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR) criteria for alcohol dependence and included both persons who smoke and do not smoke. Overall, the SOE for accidents, injuries, quality of life, and mortality was insufficient for varenicline, mainly because of having no data or very few events.

3.2.4.3.2 Accidents or Injuries

None of the included trials systematically assessed accidents or injuries.

3.2.4.3.3 Quality of Life

The only study reporting quality of life was in the original report, which reported no difference in SF-12 mental (mean difference 0.7; p=0.55) or physical (mean difference 0.4; p=0.38) scores between varenicline-treated and placebo-treated patients.[153]

3.2.4.3.4 Mortality

During the 13-week treatment period, there was a shooting death in the varenicline arm and no deaths in the placebo arm reported in one study.[153]

3.2.5 Head-to-Head Trials Including FDA-Approved Medications

3.2.5.1 Characteristics of Trials

We identified three RCTs (Table B-14) that reported at least one health outcome of interest.[44, 71, 160] All were included in the 2014 report. Two of these were rated as high risk of bias for the head-to-head comparison—one three-arm study comparing naltrexone with disulfiram or placebo[71] and one four-arm open-label trial comparing acamprosate, disulfiram, and naltrexone.[160] Both trials had high risk of ascertainment bias; one did not adequately handle missing data for quality of life outcomes (see Appendix C for additional details about risk-of-bias ratings).

One study (COMBINE), rated as low risk of bias, reported mortality and quality of life. COMBINE is a multicenter nine-arm trial that compared eight groups of patients receiving medical management with 16 weeks of naltrexone (100 mg per day) or acamprosate (3,000 mg per day), both, or both placebos, with or without a CBI. The ninth group received CBI only and no drug or placebo. Mean age was 44 years; all patients met criteria for alcohol dependence.[44, 165] Overall, the SOE for accidents, injuries, quality of life, and mortality was insufficient for head-to-head comparisons due to lack of data or very few events.

3.2.5.2 Acamprosate Versus Naltrexone

3.2.5.2.1 Accidents or Injuries

None of the included trials systematically assessed accidents or injuries.

3.2.5.2.2 Quality of Life or Functional Status

The COMBINE study assessed quality of life using the WHOQOL and SF-12v2 physical and mental health scores. This study was included in the 2014 report. Results were not presented for each treatment group separately.[165] To analyze the treatment effects of specific pharmacological and behavior treatment combinations on quality of life, a mixed-effects general linear model was used to examine the main and interaction effects of three treatments (acamprosate, naltrexone, and CBIs) from baseline to 26 weeks and from baseline to 52 weeks (20 analyses of variance [ANOVAs] were conducted unadjusted and 20 were adjusted for percent heavy drinking days). The results indicated that the eight combinations of pharmacological and behavioral treatments did not show differential effects on quality of life for either scale. The only two significant effects reaching a p-value of <0.001 (to account for multiple tests) were the two-way interaction of naltrexone by CBI for the SF-12v2 physical health score at 52 weeks for both the adjusted and unadjusted analyses. The authors concluded that this suggests CBI and naltrexone combined have a greater effect than either alone for the SF-12v2 physical health scale; however, the difference between groups was no larger than 2.1 and unlikely to suggest a clinically meaningful difference (the 95% CI for the SF-12v2 physical health scale is 6.6).[165]

One study examining acamprosate versus naltrexone and rated as high risk of bias measured quality of life with the European Quality of Life Scale (EQ-5),[168] Koskenvuo Quality of Life Scale (KQL)[169] and Visual Analogue Scale (VAS).[170] Quality of life improved for both groups over the 52-week followup compared with baseline with no difference between groups.[160]

3.2.5.2.3 Mortality

In the COMBINE trial, the authors reported that one fatal serious adverse event was reported during the 16-week treatment phase; it was classified by investigators as not related to the study medication. No details were provided on which group the death occurred in, the nature of the adverse event, or the cause of death.[44, 165]

One study, rated as high risk of bias, reported that one person died by suicide and two persons drowned in the acamprosate group but reported no events in the naltrexone group.[160]

3.2.5.3 Acamprosate Versus Disulfiram

3.2.5.3.1 Accident or Injury

One study, included in the 2014 report and rated as high risk of bias, reported one traffic accident in the disulfiram group and none in the acamprosate group over 52 weeks.[160] No details of the event were described; the study coordinator determined that the event was not related to the study treatment.

3.2.5.3.2 Mortality

One study, rated as high risk of bias, reported that one person died by suicide and two persons drowned in the acamprosate group and reported no events in the disulfiram group.[160]

3.2.5.3.3 Quality of Life

In one study rated as high risk of bias, quality of life was measured with the EQ-5, KQL, and VAS. Quality of life improved for both groups over the 52-week followup compared with baseline with no difference between the acamprosate and disulfiram groups.[160]

3.2.5.4 Disulfiram Versus Naltrexone

3.2.5.4.1 Accident or Injury

One study, rated as high risk of bias, reported one traffic accident in the disulfiram group and no accidents or injuries in the naltrexone group.[160] No details of the event were described; the study coordinator determined that the event was not related to the study treatment.

3.2.5.4.2 Quality of Life

In one study rated as high risk of bias, quality of life was measured with the EQ-5, KQL, and VAS. Quality of life improved for both groups over the 52-week followup compared with baseline with no difference between the disulfiram and naltrexone groups.[160]

3.2.5.4.3 Mortality

In one study rated high risk of bias that compared disulfiram and naltrexone among patients with coexisting depression, one person died in the naltrexone group, and no deaths were reported in the disulfiram group.[71]

3.2.6 Head-to-Head Trials Including Medications Used Off-Label or Those Under Investigation

3.2.6.1 Topiramate Versus Naltrexone

3.2.6.1.1 Characteristics of Trials

We identified two head-to-head trials of off-label medications that measured an eligible health outcome (Table B-15).[171, 172] Both were included in the 2014 report compared topiramate with naltrexone. Sample size ranged from 102 to 182. All participants met criteria for alcohol dependence, the average age of participants was similar across trials (47 to 48), and females made up 15 percent of participants. The trials enrolled about a quarter of participants with personality disorders and did not report smoking rates.[171, 172] Both studies included a psychological co-intervention.

Two open-label RCTs compared topiramate 200 mg per day with naltrexone 50 mg per day.[171, 172] Both were conducted in Spain and were rated as high risk of bias.[171, 172] One study allowed titration of topiramate from 200 mg per day up to 300 to 400 mg per day based on continued alcohol consumption or craving.[171] Overall, the SOE for accidents, injuries, quality of life, and mortality was insufficient for comparisons of topiramate versus naltrexone due to lack of data or very few events.

3.2.6.1.2 Accidents or Injuries

None of the included trials systematically assessed accidents or injuries.

3.2.6.1.3 Quality of Life or Function

One unblinded study rated as high risk of bias used the World Health Organization Disability Assessment Schedule (WHODAS) to assess alcohol dependence–related disability at 3 and 6 months.[172] No significant changes were found in most domains of the WHODAS (personal, family, social), with two exceptions: patients taking topiramate had a lower disability score (i.e.,

better functioning) on the employment domain at 3 months followup (1.64 versus 2.2, p=0.047) and on the family domain at 6 months followup (0.58 vs. 1.05, p=0.035).[172] A similar study that adjusted topiramate doses based on continued alcohol intake or craving, found no difference between the topiramate and naltrexone groups on any of the WHODAS domains at 3 or 6 months.[171]

This same study measured quality of life using the EQ-5D at 3 and 6 months.[172] At 3 months, the topiramate group had a small but statistically significant greater improvement in quality of life compared with the naltrexone group (96.10 vs. 94.16, p=0.014); there was no difference between the two groups at 6 months.[172] A similar study that adjusted topiramate doses based on continued alcohol intake or craving, found that patients treated with topiramate had better quality of life at 3 months compared with naltrexone (96.88 vs. 95.21, p=0.014), but no statistically significant difference was found between the two groups at 6 months.[171]

3.2.6.1.4 Mortality

None of the included trials systematically assessed mortality.

3.3 Key Question 3. Adverse Effects of Medications

For this question, we evaluated trials included in KQs 1 and 2. In addition, we searched for nonrandomized controlled trials (non-RCTs), open-label trials, secondary analyses or subgroup analyses from trials, prospective cohort studies, and case-control studies comparing two or more of the medications of interest in which at least 50 events are reported. Throughout this KQ, we often describe risks of various adverse events—risks reported are RRs between intervention and control. Because the studies were not primarily focused on harms, the reporting of harms varied across studies significantly.

3.3.1 Key Points

- Adverse events were often not collected using standardized measures, and methods for systematically capturing adverse events were often not described.
- Serious harms were rarely reported, but some minor harms such as diarrhea and dizziness were common across drugs.
- 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.[148, 149]
- 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; the risk of withdrawals due to adverse events was not significantly different between the two drugs.

3.3.2 Summary of Findings

Adverse events were often not collected using standardized measures, and methods for systematically capturing adverse events were often not reported. Studies were generally not designed primarily to assess adverse events; the vast majority focused on alcohol consumption outcomes. Evidence for many potential adverse events was insufficient to determine whether the risk was increased or not, often primarily because of lack of precision. However, some minor harms, such as diarrhea and dizziness were common across drugs. For serious harms, there was insufficient data to determine comparative rates of adverse events. Most studies were limited to 6 months of followup or less, so very little is known about potential harms of long-term use. In addition, studies commonly excluded patients with comorbid medical conditions, so use of these medications in people with medical issues is not well understood. Withdrawals from studies due to adverse events were higher among participants taking naltrexone than placebo with moderate SOE (RR, 1.38; 95% CI 0.99 to 1.93) and among participants taking topiramate with low SOE (RR, 2.45; 95% CI 1.09 to 5.53). In head-to-head studies, the risk of withdrawals due to adverse events was not significantly different between acamprosate and naltrexone. No other differences were found in withdrawals due to adverse events for any other drugs.

3.3.3 Characteristics of Additional Included Studies Not Previously Described

The vast majority of the included RCTs are described in KQs 1 and 2, and we do not describe them again in this KQ. Seven studies not described in KQ 1 or 2 were eligible for inclusion in this KQ. All were included in the previous report. These included five open-label RCTs,[159, 161, 162, 171, 172] one single-blind RCT,[173] and one double-blind RCT.[164] Of those seven, five focused on comparisons of FDA-approved medications for AUD (Table B-16); the other two compared naltrexone with topiramate.[171, 172] All but one of the studies[164] were rated as high risk of bias, primarily because of concerns with selection bias, attrition bias, measurement bias, confounding, or selective outcome reporting bias (see Appendix C for details).

For the five studies not described elsewhere that focused on comparisons of medications with FDA indications for AUD, one compared acamprosate with naltrexone,[173] one was the multi-arm COMBINE pilot study,[164] two compared naltrexone with disulfiram,[161, 162] and one compared acamprosate with disulfiram.[159] Study duration ranged from 35 to 52 weeks. Two of the studies were conducted in India,[159, 161] one in the United States,[164] one in Spain,[173] and one in Italy.[162] For three trials, study participants were recruited as inpatients.[159, 161, 173] For the other trials, recruitment methods included advertisements, word of mouth, clinical referrals, and a press release.[162, 164] Mean age ranged from 38 to 47 years. Two of the studies included women.[162, 164] In one study,[159] all participants were non-White; one study enrolled 17 to 22 percent non-White participants;[164] race and ethnicity was not reported in the other three studies.[161, 162, 173]

3.3.4 Detailed Synthesis: Harms Reported in Placebo-Controlled Trials of Medications for Treating Alcohol Use Disorder

In this section, we consider harms associated with acamprosate, disulfiram, naltrexone, baclofen, gabapentin, ondansetron, prazosin, topiramate, and varenicline. Forest plots are shown in Appendix E. Insufficient data were available to conduct meta-analyses of results from studies

of disulfiram, ondansetron, and prazosin. Therefore, we described and summarized these qualitatively when possible.

3.3.4.1 Acamprosate

Table 23 summarizes the main results of the meta-analyses. Twenty-three studies compared acamprosate with placebo.[44, 46-52, 54-58, 60-65, 159, 160, 164, 173] The only statistically significant findings for harms from the meta-analyses were for anxiety (low SOE) and diarrhea (moderate SOE). Absolute rates of diarrhea were highly variable (range, 3% to 64% with acamprosate, 2% to 65% with placebo), but most studies trended in the direction of increased risk with acamprosate and some studies found much higher rates of diarrhea than with placebo (with absolute risks increased as much as 33%). Evidence was insufficient for cognitive dysfunction, suicide attempts or suicidal ideation, taste abnormalities, and vision changes, and it was low for no effect for dizziness, headache, insomnia, numbness, rash, vomiting, and study withdrawal due to adverse events.

Table 23. Results of meta-analyses and risk difference calculations for adverse events: acamprosate compared with placebo

Outcome	No. RCTs	N	RR	95% CI	I^2, %	Range of % With Event, Placebo	Range of % With Event, Treatment
Withdrawal due to adverse events	16	5,480	1.16	0.86 to 1.56	6.9	0.0 to 8.9	0.0 to 14.5
Anxiety	2	624	1.90	1.42 to 2.54	NA 0.0	0.0 to 18.5	8.3 to 34.9
Diarrhea	14	4,118	1.58	1.27 to 1.97	47.3	1.6 to 64.9	3.0 to 63.7
Dizziness	2	151	1.66	0.37 to 7.44	24.2	3.3 to 11.8	1.8 to 33.3
Headache	7	1,643	1.02	0.63 to 1.66	41.4	0.0 to 35.5	3.6 to 50.0
Insomnia	4	820	1.32	0.85 to 2.05	18.1	1.6 to 35.5	0.0 to 61.1
Nausea	8	1,828	1.08	0.84 to 1.37	0.0	0.0 to 47.1	0.8 to 23.8
Numbness	2	831	1.23	0.79 to 1.92	0.0	0.0 to 10.7	0.8 to 12.9
Rash	2	105	5.14	0.62 to 42.39	0.0	0.0 in both studies	6.1 to 11.1
Suicide attempts or suicidal ideation	3	1,173	0.86	0.17 to 4.27	0.0	0.0 to 9.1	0.0 to 0.7
Vomiting	5	1,840	1.33	0.74 to 2.38	31.9	0.8 to 17.6	0.0 to 11.1

Note: RRs > 1.0 indicate higher likelihood of the event with acamprosate use.

CI = confidence interval; N = number of trials or participants contributing data; NA = not applicable; RCT = randomized controlled trial; RR = risk ratio.

3.3.4.2 Disulfiram

Four included studies, all of which were included in the previous review, compared disulfiram with placebo or control.[68-71] One of these did not report results for adverse events.[68] The other three did not yield sufficient quantitative data to conduct meta-analyses. We found insufficient SOE for all harms.

One study of disulfiram compared with placebo in patients who were all taking methadone reported that "there were no deaths, serious adverse reactions, or illnesses that could be attributed to the combined use of the drugs [disulfiram and methadone]" (p. 852) but did not provide details about the incidence of specific adverse events in the study population.[70]

In another study, patients who received 250 mg per day of disulfiram reported "moderate or severe" drowsiness more often than those not given disulfiram (8% vs. 2%, p=0.03). There was

no significant difference in the incidence of drowsiness between the 250 and 1 mg per day disulfiram groups.[69] In this same study, disulfiram was discontinued by three patients in the 250 mg per day group and one patient in the 1 mg per day group because of increased serum alkaline phosphatase or aspartate aminotransferase. Psychiatric problems were observed in 11 patients with no statistically significant difference between the three groups.[69]

Results from a four-arm study comparing disulfiram combined with naltrexone, disulfiram combined with placebo, naltrexone alone, and placebo alone showed that patients on any study medication experienced aftertaste, blurred vision, confusion, constipation, drowsiness, dry mouth, loss of appetite, nausea, or tremors more often than patients who received placebo. There were no statistically significant between-group differences for other adverse events.[71] Six of the 14 serious adverse events reported in this study occurred in the disulfiram with placebo group (4 psychiatric hospitalizations—2 for a change in mental status and 2 for suicidal ideation, 1 cardiac event, and 1 hospitalization for acute axonal neuropathy) and three occurred in the placebo group (1 death, 1 drug and alcohol overdose, and 1 hospitalization for pneumonia).[71]

3.3.4.3 Naltrexone

Forty-three studies compared naltrexone with placebo.[44-47, 71-74, 77, 79-81, 83-88, 90-96, 99-107, 109, 111, 112, 114, 160-162, 164, 173] Four studies were new to this report.[80, 81, 83, 112] Table 24 presents the meta-analyses on harms for naltrexone compared with placebo. We found statistically significant increased risk with moderate SOE of study withdrawal due to adverse events, dizziness, nausea, and vomiting and low SOE for no effect on anxiety, diarrhea, rash, insomnia, vision changes, and headache. Sensitivity analyses and separate analyses by dose and administration did not change the results.

Table 24. Results of meta-analyses and risk difference calculations for adverse events: Naltrexone compared with placebo

Outcome	No. RCTs	N	RR	95% CI	I^2, %	Range of % With Event, Placebo	Range of % With Event, Treatment
Withdrawal due to adverse events	21	3,257	1.38	0.99 to 1.93	0.0	0.0 to 14.1	1.5 to 17.6
Anxiety	10	1,870	1.02	0.87 to 1.20	0.0	2.0 to 59.8	2.1 to 62.2
Diarrhea	14	2,755	1.10	0.83 to 1.46	26.1	0.0 to 60.0	0.0 to 55.6
Dizziness	19	3,271	1.99	1.47 to 2.69	6.9	0.0 to 20.6	2.9 to 34.8
Headache	24	4,093	0.98	0.86 to 1.12	11.5	1.0 to 63.4	1.0 to 62.5
Insomnia	13	2,224	1.28	1.01 to 1.64	0.0	2.1 to 38.9	0.0 to 35.3
Nausea	33	5,557	1.73	1.51 to 1.98	17.2	2.5 to 57.6	0.0 to 47.1
Numbness	2	226	0.97	0.68 to 1.38	0.0	3.7 to 50.0	2.0 to 49.2
Rash	5	522	0.69	0.15 to 3.23	46.7	0.0 to 37.5	2.0 to 20.0
Vomiting	13	2,861	1.53	1.23 to 1.91	0.0	0.0 to 25.6	0.7 to 23.4
Vision Changes	2	154	1.16	0.71 to 1.90	48.9	42.2 to 60.0	50 to 59.3

Note: Positive risk ratios favor placebo. Sensitivity analyses include studies rated as high risk of bias.

CI = confidence interval; N = number of trials or participants contributing data; RCT = randomized controlled trial; RR = risk ratio.

3.3.4.4 Baclofen

All 13 trials comparing baclofen with placebo reported some information on adverse effects.[118, 121, 125, 127, 130] Eleven of the trials were new to this report.[119-130] Table 25 summarizes the main results of the meta-analyses, and SOE summaries are shown in Table D-20. Overall, the meta-analyses did not find a statistically significant increase in most adverse effects, including

withdrawals due to adverse events, anxiety, cognitive dysfunction, diarrhea, headache, insomnia, nausea, rash, suicidal ideation or attempts, taste abnormalities, vision changes, or vomiting (all low SOE for no effect). However, the total number of events for many of these outcomes was relatively low, pooled results were often very imprecise, and larger samples may be needed to detect a small to moderate increase in risk. The pooled results indicate an increased risk in dizziness, sleepiness, drowsiness (all moderate SOE), and numbness (low SOE). Please see Section 3.2.2 for the assessment of the effect of baclofen on mortality.

Table 25. Summary of results of meta-analyses for adverse events: Baclofen compared with placebo

Outcome	No. RCTs	N	RR	95% CI	I^2, %	Range of % With Event, Placebo	Range of % With Event, Treatment
Withdrawal due to adverse events	6	931	1.40	0.83, 2.38	0.0	0.0 to 8.6	3.4 to 17.1
Anxiety	3	388	1.33	0.81, 2.17	0.0	6.7 to 13.2	0.0 to 19.1
Cognitive dysfunction	2	495	1.58	0.93, 2.70	0.0	3.1 to 15.2	5.7 to 23.0
Diarrhea	4	581	0.76	0.47, 1.22	33.5	10.7 to 53.3	3.6 to 60.0
Dizziness	13	1,231	1.89	1.40, 2.55	5.0	0.0 to 22.8	0.0 to 30.2
Drowsiness	7	937	1.46	1.15, 1.86	18.1	9.4 to 32.6	6.3 to 50.0
Fatigue	6	632	1.40	0.99, 1.98	0.0	2.4 to 25	0.0 to 46.4
Headache	8	941	1.29	0.96, 1.73	0.0	6.3 to 25.0	0.0 to 26.8
Insomnia	3	537	0.76	0.35, 1.66	53.5	7.1 to 30.8	0.0 to 38.9
Nausea	4	643	1.11	0.72, 1.72	9.0	0.0 to 23.9	7.1 to 16.3
Numbness	2	207	7.78	1.42, 42.56	0.0	0.0 to 1.1	7.1 to 12.6
Rash	5	475	0.88	0.43, 1.80	23.9	0.0 to 20.0	0.0 to 16.3
Sleepiness	2	235	1.81	1.11, 2.97	0.0	0.0 to 17.7	2.4 to 36.2
Taste abnormalities	2	495	2.28	0.45, 11.59	65.4	1.3 to 5.4	5.7 to 7.0
Vision changes	2	235	1.30	0.61, 2.79	0.0	7.1 to 9.8	10.3 to 17.9
Vomiting	2	495	0.97	0.50, 1.88	0.0	3.8 to 12.0	5.1 to 9.2

CI = confidence interval; N = number of trials or participants contributing data; RCT = randomized controlled trial; RR = risk ratio.

3.3.4.5 Gabapentin

All four trials comparing gabapentin with a placebo reported on adverse effects and all were new to this report.[131-134] Trials of gabapentin reported increased risk of cognitive dysfunction (low SOE), and dizziness (moderate SOE). There did not appear to be an increase in study withdrawal due to adverse events, diarrhea, headaches, insomnia, nausea, numbness/paresthesia, vomiting, or anxiety; however the SOE for all of these outcomes was rated as low. Table 26 summarizes the main results of the meta-analyses.

Table 26. Results of meta-analyses and risk difference calculations for adverse events: Gabapentin compared with placebo

Outcome	No. RCTs	N	RR	95% CI	I^2, %	Range of % With Event, Placebo	Range of % With Event, Treatment
Withdrawal due to adverse events	2	488	1.28	0.42 to 3.82	0.0	1.2 to 4.1	0.6 to 9.3
Cognitive dysfunction	1	104	2.76	1.51 to 5.06	0.2	5.7 to 17	5.9 to 25.5
Diarrhea	2	442	1.78	0.59 to 5.36	38.5	3.8 to 6	6.5 to 7.8
Dizziness	3	532	1.70	1.24 to 2.32	0.0	13.7 to 32.6	21.2 to 32.6
Headache	2	488	0.80	0.58 to 1.11	0.0	16.3 to 28.0	12.8 to 28.0
Insomnia	2	488	0.84	0.55 to 1.30	0.0	10.1 to 22.4	10.6 to 18.5
Nausea	2	442	0.83	0.47 to 1.45	0.0	5.7 to 13.7	3.9 to 10.0

Outcome	No. RCTs	N	RR	95% CI	I^2, %	Range of % With Event, Placebo	Range of % With Event, Treatment
Numbness/ tingling/ paresthesia	1	338	0.54	0.20 to 1.42	0.0	6.5	3.5
Suicidal ideation	1	338	0.33	0.01 to 8.03	0.0	0.6	0.0
Vision changes	1	104	5.44	1.51 to 19.63	0.0	5.7	15.7
Vomiting	2	442	1.64	0.77 to 3.47	0.0	4.8 to 5.7	3.9 to 8.8
Rash	1	338	0.17	0.04 to 0.76	0.0	7.7	1.2
Anxiety	1	338	1.98	0.82 to 4.77	0.0	4.2	8.2

CI = confidence interval; N = sample size; RCT = randomized controlled trial; RR=risk ratio.

3.3.4.6 Ondansetron

All three trials reported no statistically significant differences between groups in any specific adverse event or in the total number of people with any adverse effects. Two trials were new to the updated report.[136, 137] The U.S.-based trials reported no difference in the percentage of participants who reported at least one adverse event (87% in ondansetron group vs. 82% in the placebo group).[137] In the Brazilian study, 26 participants (52%) taking ondansetron experienced adverse effects compared with 26 (50%) taking placebo.[135] The study among people with bipolar and related disorders reported adverse effects in 13 (37%) participants taking ondansetron compared with 7 (20%) on placebo.[136] The Brazilian trial reported no group differences in somnolence (2.0% with ondansetron vs. 3.8% with placebo), headache (14.0% with ondansetron vs. 17.3%), dyspepsia (18.0% with ondansetron vs. 13.5%), or diarrhea (2.0% with ondansetron vs. 5.8%), with a difference of only 1 to 2 individuals between groups for each of these outcomes.[135] The other trial did not provide detailed numbers of events by group for other adverse outcomes.[136] Evidence was insufficient to determine adverse effects of ondansetron.

3.3.4.7 Prazosin

In the study that included only participants with PTSD (N=100), individuals on prazosin were more likely to report dizziness, but the difference was not significant. No other differences were reported.[138, 140] The second study (N=92), which excluded individuals with PTSD, reported that a higher percentage of participants in the treatment group experienced drowsiness (p=0.02), but that there were no significant differences in other adverse effects, including dizziness, light-headedness, headache, nausea, or palpitations.[139] Both studies were new to the updated report.[138, 139] Evidence was insufficient to determine adverse effects of prazosin.

3.3.4.8 Topiramate

All 11 trials comparing topiramate with a placebo reported on adverse effects.[77, 141-149, 151] Seven trials were new to this update.[141-147] Trials of topiramate reported increased risk of many adverse events, with strongest evidence (rated as moderate SOE) supporting increases in paresthesias, dizziness, taste abnormalities, and cognitive dysfunction. There was also low SOE for an increased risk of withdrawals due to adverse events and vision abnormalities. There did not appear to be increases in headache, diarrhea, insomnia, or nausea associated with topiramate use; however, these outcomes were all rated as low SOE. Table 27 summarizes the main results of the meta-analyses, and SOE summaries are shown in Table D-24.

Table 27. Results of meta-analyses and risk difference calculations for adverse events: Topiramate compared with placebo

Outcome	No. RCTs	N	RR	95% CI	I^2, %	Range of % With Event, Placebo	Range of % With Event, Treatment
Withdrawal due to adverse events	7	1042	2.45	1.09 to 5.53	38.4	0.0 to 14.3	1.2 to 20.0
Cognitive dysfunction	4	765	2.37	1.58 to 3.55	0.0	5.4 to 11.3	12.6 to 23.9
Diarrhea	5	864	1.27	0.86 to 1.87	0.0	5.6 to 18.8	1.9 to 28.6
Dizziness	4	782	2.29	1.39 to 3.78	0.0	1.9 to 10.7	0.0 to 28.0
Headache	5	955	1.02	0.71 to 1.45	26.0	0.0 to 31.9	3.8 to 24.7
Insomnia	3	696	1.29	0.88 to 1.88	0.0	5.6 to 16.0	9.6 to 19.1
Nausea	3	696	0.73	0.46 to 1.14	0.0	3.7 to 16.5	5.8 to 10.4
Numbness/tingling/ paresthesias	8	1292	3.08	2.11 to 4.49	47.0	1.9 to 29.4	0.0 to 57.3
Suicidal ideation	1	30	0.38	0.02 to 8.59	NA	6.3	0.0
Vision changes	2	200	2.01	0.98 to 4.11	0.0	8.2 to 18.8	20.0 to 21.4
Taste abnormalities	6	847	3.01	1.70 to 5.34	56.1	4.8 to 31.3	15.1 to 53.3

Note: Positive risk differences favor placebo. Sensitivity analyses included studies rated as high risk of bias.

CI = confidence interval; N = number of trials or participants contributing data; NA = not applicable; RCT = randomized controlled trial; RR = risk ratio.

3.3.4.9 Varenicline

Five trials comparing varenicline with placebo reported adverse events; all were new to this report.[153-157] Nausea was significantly more common in the varenicline group compared with placebo in a meta-analysis that included four studies and 522 participants (RR, 2.34; 95% CI, 1.38 to 3.97) with moderate SOE (Table 28). No other adverse effect was found to differ. We found low SOE for study withdrawals due to adverse events, anxiety, diarrhea, dizziness, headache, insomnia, and vomiting. Four studies reported significantly higher incidence of abnormal dreams in the treatment group.[153-156]

Studies generally excluded participants with any baseline suicidal ideation or attempts. Those studies specifically assessing suicidal ideation during the study found no differences between groups (insufficient SOE).[153, 155, 174] One study did report three serious adverse events in the varenicline group (psychiatric hospitalization for suicidal ideation, alcohol rehabilitation following suicidal behavior [trying to drink self to death] and hospitalization for blood pressure monitoring), and two serious events in the placebo group (psychiatric hospitalization within 30 days of treatment and hospitalization for an infection).[156]

Table 28. Results of meta-analyses and risk difference calculations for adverse events: Varenicline compared with placebo

Outcome	No. RCTs	N	RR	95% CI	I^2, %	Range of % With Event, Placebo	Range of % With Event, Treatment
Withdrawal due to adverse events	4	519	2.39	0.69 to 8.23	21.1	0.0 to 3.0	1.0 to 13.3
Anxiety	2	329	1.27	0.65 to 2.49	0.0	7.9 to 9.0	9.3 to 12.5
Diarrhea	3	502	0.69	0.35 to 1.37	23.6	8.4 to 14.9	3.9 to 11.3
Dizziness	2	329	1.98	0.95 to 4.13	0.0	5.9 to 6.0	11.3 to 12.5
Headache	3	502	1.12	0.78 to 1.47	0.0	14.5 to 29.7	22.1 to 26.8
Insomnia	3	502	1.26	0.76 to 2.09	0.0	3.6 to 13.4	5.2 to 15.6
Nausea	4	522	2.34	1.38 to 3.97	58.1	0.0 to 26.9	25.0 to 48.1
Rash	1	198	0.52	0.13 to 2.02	NA	5.9	3.1
Vomiting	2	329	0.99	0.51 to 1.94	3.1	9.9 to 10.4	6.3 to 12.4

Outcome	No. RCTs	N	RR	95% CI	I^2, %	Range of % With Event, Placebo	Range of % With Event, Treatment
Vision changes	1	131	2.09	0.40 to 11.04	NA	6.3	3.0
Taste abnormalities	1	131	0.63	0.16 to 2.52	NA	7.5	4.7

Note: Positive risk ratios favor placebo. Sensitivity analyses include studies rated as high risk of bias.

CI = confidence interval; N = number of trials or participants contributing data; NA = not applicable; RCT = randomized controlled trial; RR = risk ratio.

3.3.5 Detailed Synthesis: Head-to-Head Trials

3.3.5.1 Acamprosate Compared With Disulfiram

Both studies reporting results for adverse events for this comparison were rated as high risk of bias; both reported no statistically significant differences between the acamprosate and disulfiram groups.[159, 160]

One of the studies reported that six patients who received disulfiram experienced elevated alanine transaminase (ALT) levels. Subsequently, three of the patients discontinued the medication, and three continued to receive a half dose; ALT levels normalized within 2 to 3 weeks.[160] The most common adverse events reported in the study for patients treated with acamprosate were diarrhea and dermatological problems, and for patients treated with disulfiram tiredness and headache. Evidence was insufficient to determine whether adverse effects differed between acamprosate and disulfiram.

3.3.5.2 Acamprosate Compared With Naltrexone

We found seven studies comparing acamprosate with naltrexone and reporting adverse events.[44-46, 115, 160, 173, 175]

Table 29 summarizes the main results of the meta-analyses. The risks of nausea (low SOE), and vomiting (moderate SOE) were slightly higher for those treated with naltrexone in either the main analyses or in sensitivity analyses that included studies rated as high or unclear risk of bias. There was low SOE that study withdrawals due to adverse events, dizziness, and insomnia did not differ between groups, and SOE was insufficient for all other outcomes.

Table 29. Results of meta-analyses for adverse events: Acamprosate compared with naltrexone

Outcome	No. RCTs	N	RR	95% CI	I^2, %
Withdrawal due to adverse events	3	1,110	1.07	0.38 to 3.05	53.8
Diarrhea	5	993	1.90	1.35 to 2.68	28.7
Dizziness	3	306	0.67	0.11 to 4.04	75.3
Headache	4	463	0.52	0.22 to 1.22	62.7
Insomnia	2	144	1.36	0.73 to 2.53	0.0
Nausea	6	1,155	0.56	0.35 to 0.88	44.6
Vomiting	2	648	0.60	0.39 to 0.93	0.0

Note: Positive risk differences favor naltrexone. Table only includes rows for outcomes with sufficient data for meta-analyses.

CI = confidence interval; N = number of trials or participants contributing data; RCT = randomized controlled trial; RR = risk ratio.

3.3.5.3 Disulfiram Compared With Naltrexone

We found four studies comparing disulfiram with naltrexone and reporting on adverse events; all four were rated as high risk of bias.[71, 160-162] One of these reported no statistically significant difference in the incidence of adverse events between groups;[160] another stated that no serious adverse events occurred during the study and reported the incidence of adverse events only among those who withdrew because of adverse events.[162]
In one of the studies, nausea, drowsiness, abdominal pain, and diarrhea were more common among patients receiving naltrexone than among those receiving disulfiram, but statistical significance was not reported.[161]

A four-arm study comparing disulfiram combined with naltrexone, disulfiram combined with placebo, naltrexone alone, and placebo alone found that fever was more common in the disulfiram group than in the naltrexone group (p=0.03); nervousness (p=0.005) and restlessness (p=0.03) were more common in the naltrexone group than in the disulfiram group.[71] Evidence was insufficient to determine whether adverse effects differed between disulfiram and naltrexone.

3.4 Key Question 4. Evidence From Primary Care Settings

For this KQ, we describe the characteristics and outcomes of included studies that assessed if medications for treating adults with AUD were effective in primary care settings.

3.4.1 Key Points

- 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.[49]

3.4.2 Summary of Findings

We found no new evidence on the use of AUD medications in primary care settings; thus, evidence continues to be scant.

3.4.3 Characteristics of Included Trials

We identified one eligible trial, which was included in the 2014 report, conducted completely in primary care settings (Table B-17).[49] This study compared acamprosate 1,998 milligrams per day with placebo for 12 weeks and was based in two U.S. primary care clinics. Primary care providers also delivered a brief structured behavioral intervention. Mean age of patients was 48, 9 percent of patients were non-White, and almost 40 percent were female.

Several other published studies, including some in other sections of this report, may have implications for or some applicability to primary care settings, an issue addressed in the report Discussion.

3.4.4 Results for Consumption Outcomes

The trial conducted completely in primary care settings (N=100)[49] found no significant treatment effect of acamprosate on drinking days (RR, 1.15; 95% CI, 0.99 to 1.34) or heavy drinking days (RR, -2.60; 95% CI, -11.38 to 6.18).

3.5 Key Question 5. Subgroups

For this KQ, we describe the characteristics and outcomes of included studies that assessed if medications were more or less effective than other medications for older adults, young adults, persons who smoke, or those with co-occurring disorders.

3.5.1 Key Points

- 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.

3.5.2 Characteristics of Included Studies

Nine RCTs compared the effects of one of the included medications across populations of interest (Table B-18).[44-46, 71, 77, 108, 159, 161, 176] All nine trials were included in the 2014 report. Studies included FDA-approved (acamprosate, disulfiram, naltrexone) and non-FDA-approved (topiramate) medications. Treatment durations ranged from 12 weeks to 68 weeks. All studies reported concurrent psychiatric care, psychotherapy, or other psychosocial support. Studies were conducted in Australia,[46] Brazil,[77] Germany,[45, 177] and India[159, 161] in addition to the four in the United States.[44, 71, 108, 176]

Mean age ranged from 32 to 47, the reported percentage of non-White participants ranged from 23 to 100 percent, and the reported percentage of female participants ranged from 0 to 72 percent. In all of the studies, all participants had alcohol dependence. Smoking rates were high (55% to 81% of participants) in three studies;[46, 67, 77, 178, 179] all patients in one study[176] had cocaine dependence. Two studies included only participants with psychiatric comorbidities (Axis I disorders, depression, or PTSD).[71, 108, 180-182] Participants were recruited from the community as well as from outpatient and inpatient contacts. Three of these studies were rated low risk of bias, three were rated medium, and the rest were rated high risk of bias, primarily due to concerns with attrition bias, inadequate handling of missing data, or measurement bias (see Appendix C for details).

3.5.3 Sex

Three trials provided evidence about the effectiveness of medications by sex.[159, 161, 183]

Subgroup analyses from the COMBINE study,[183] the only study among this group rated as low risk of bias, found no significant association between sex and the impact of acamprosate or naltrexone treatment on percentage of days abstinent, time to heavy drinking, or percentage of heavy drinking days.

Two trials, both open-label trials limited to men and from the same group of investigators and rated as high risk of bias, found that naltrexone and topiramate had a greater effect than disulfiram, and disulfiram had a greater effect than acamprosate on reducing drinking for men.[159, 161]

3.5.4 Persons Who Smoke

Two studies provided evidence about the effectiveness of medications by smoking status. Subgroup analyses from the COMBINE study[67] found that persons who smoke who received naltrexone had more days abstinent (78% vs. 72%, p=0.004) and fewer heavy drinking days

(14% vs. 20%, p=0.003) than persons who smoke who received placebo. No data were reported on the effectiveness of acamprosate among persons who smoke—only that persons who smoke did not benefit differentially from acamprosate. Subgroup analyses from a trial comparing naltrexone, topiramate, and placebo found no association between the number of cigarettes smoked per day at the start of the trial and the effect of naltrexone or topiramate on any drinking outcomes.[77, 179]

4. Discussion

This report is an update of a prior systematic review published in 2014.[35, 184] The main changes between this and the prior review included removing medications not commonly used in the United States for alcohol use disorder (AUD) (amitriptyline, aripiprazole, atomoxetine, buspirone, citalopram, desipramine, escitalopram, fluoxetine, fluvoxamine, imipramine, nalmefene, olanzapine, paroxetine, quetiapine, sertraline, valproate, viloxazine) and the exclusion of a prior Key Question on the role of genetic testing in predicting outcomes.

4.1 Key Findings and Strength of Evidence

4.1.1 Efficacy and Comparative Effectiveness

As in the prior report, very few data were available on how health outcomes are affected by AUD medications. However, this report found many trials that evaluated consumption outcomes. Consumption outcomes related to AUD can range from complete abstinence (achieving it or maintaining it) to harm reduction, focusing on reducing alcohol use to improve functioning and health outcomes. Our report focused on five key consumption outcomes: return to any drinking, return to heavy drinking, drinking days, heavy drinking days, and drinks per drinking day. We found that several medications have at least low strength of evidence for benefit in some outcomes (Figure 2).

Figure 2. Summary of strength-of-evidence assessments for efficacy and health outcomes

Drug	Return to Any Drinking	Return to Heavy Drinking	Drinking Days	Heavy Drinking Days	Drinks per Drinking Day	QoL/ Function	Mortality
Acamprosate	▲▲	●●	▲▲	IE	IE	IE	IE
Disulfiram	●	IE	IE	IE	IE	IE	IE
Naltrexone 50 mg	▲▲	▲▲	▲▲	▲▲	▲	IE	IE
Naltrexone Inj	IE	IE	▲	▲	IE	IE	IE
Baclofen	▲	●	●	●	●	●	IE
Topiramate	IE	IE	▲▲	▲▲	▲▲	●	IE
Gabapentin	▲	▲	IE	●	●	IE	IE
Varenicline	●	●	●	●	●	IE	IE
Ondansetron	IE	IE	●	IE	IE	IE	IE
Prazosin	IE	IE	IE	IE	IE	IE	IE

▲ = Low SOE for benefit ▲▲ = Moderate SOE for benefit ● = Low SOE for no effect ●● = Moderate SOE for no effect
IE = Insufficient evidence **QoL** = Quality of life **SOE** = Strength of evidence

Among the drugs with Food and Drug Administration (FDA) approval for use in AUD, both acamprosate and naltrexone demonstrated moderate strength of evidence (SOE) for multiple outcomes (Table 30). Specifically, acamprosate had moderate SOE for a significant reduction in return to any drinking and reduction in drinking days; however, this was counterbalanced by our finding that it had no effect on return to heavy drinking (moderate SOE). Naltrexone had moderate SOE for reducing return to any drinking, return to heavy drinking, percent drinking

days, and percent heavy drinking days at the 50 mg oral dose, which was by far most commonly studied. Data were more sparse for the 100 mg and injectable doses; SOE was low or insufficient at these doses/formulations.

With the addition of a new study to this report, we found that injectable naltrexone demonstrates low SOE (the pooled analysis previously showed no effect) for a benefit at reducing drinking days and heavy drinking days. The new study[80] was conducted in a population of individuals experiencing homelessness, so this finding may have particular relevance for this vulnerable, difficult to treat population.

The updated search did not identify any new studies of disulfiram. 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. We found low SOE for no effect on a return to any drinking and insufficient SOE for all other outcomes (Table 30). However, some disulfiram trials did report fewer drinking days for participants who returned to any drinking and who had a complete set of assessment interviews and suggested that disulfiram may benefit some. Some clinicians have noted that their patients benefit from this treatment, and there are challenges with designing trials to adequately evaluate a medication with its unique deterrent mechanism. The available trials, however, do not establish efficacy; rather they may suggest that combination programs of counseling, support, and coaching along with disulfiram may work for motivated patients who are interested in taking disulfiram and in adhering to the medication. Four additional trials of disulfiram that were not eligible for this review (because of the trial design and comparison) have been published.[185-188] We have previously described these small trials (with 15 or fewer disulfiram-treated patients in each) and their limitations, including significant threats to internal validity and their inability to disentangle whether any benefits identified can be attributed to disulfiram as opposed to the benefits of counseling or therapeutic relationships.[189, 190]

Table 30. Summary of findings and strength of evidence for efficacy of FDA-approved medications for alcohol use disorder compared with placebo

Medication	Outcome	N Studies; N Participants	Results Effect Size (95% CI)[a]	NNT[b]	Strength of Evidence
ACA	Return to any drinking	20; 6,380	RR, 0.88 (0.83 to 0.93)	11	Moderate
	Return to heavy drinking	7; 2,496	RR, 0.99 (0.94 to 1.05)	NA	Moderate (NE)
	% DDs	14; 4,916	WMD, -8.3 (-12.2 to -4.4)	NA	Moderate
	% HDDs	2; 123	WMD, -3.4 (-6.45 to 5.86)	NA	Insufficient
	Drinks per DD	2; 139	WMD, 0.6 (-1.43 to 2.64)	NA	Insufficient
	Accidents or injuries	0;[c] 0	NA	NA	Insufficient
	QoL or function	1; 612	NSD	NA	Insufficient
	Mortality	8; 2,677	7 events (ACA) vs. 6 events (placebo)	NA	Insufficient
DIS	Return to any drinking	3; 492	RR, 1.03 (0.90 to 1.17)	NA	Low (NE)
	Return to heavy drinking	0; 0	NA	NA	Insufficient
	% DDs	2; 290	NSD	NA	Insufficient
	% HDDs	0; 0	NA	NA	Insufficient
	Drinks per DD	0; 0	NA	NA	Insufficient
	Accidents or injuries	0; 0	NA	NA	Insufficient
	QoL or function	0; 0	NA	NA	Insufficient
	Mortality	0; 0	NA	NA	Insufficient
NTX 50 mg oral	Return to any drinking	16; 2,347	RR, 0.93 (0.87 to 1.00)	18	Moderate

Medication	Outcome	N Studies; N Participants	Results Effect Size (95% CI)[a]	NNT[b]	Strength of Evidence
NTX 50 mg oral (continued)	Return to heavy drinking	23; 3,139	RR, 0.81 (0.72 to 0.90)	11	Moderate
	% DDs	15; 1,992	WMD, -5.1 (-7.16 to -3.04)	NA	Moderate
	% HDDs	7; 624	WMD, -4.3 (-7.60 to -0.91)	NA	Moderate
	Drinks per DD	9; 1,018	WMD, -0.49 (-0.92 to -0.06)	NA	Low
NTX 100 mg oral	Return to any drinking	3; 946	RR, 0.97 (0.91 to 1.03)	NA	Low (NE)
	Return to heavy drinking	2; 858	RR, 0.93 (0.84 to 1.01)	NA	Low (NE)
	% DDs	3; 1,023	WMD, -2.3 (-5.60 to 0.99)	NA	Low
	% HDDs	2; 423	WMD, -3.1 (-5.8 to -0.3)	NA	Low
	Drinks per DD	1; 240	WMD, 1.9 (-1.5 to 5.2)	NA	Insufficient
NTX injection	Return to any drinking	2; 939	RR, 0.96 (0.90 to 1.03)	NA	Low (NE)
	Return to heavy drinking	2; 615	RR, 1.00 (0.82 to 1.21)	NA	Low (NE)
	% DDs	2; 467	WMD, -4.99 (-9.49 to 0.49)	NA	Low
	% HDDs	3; 956	WMD, -4.68 (-8.63 to -0.73)	NA	Low
	Drinks per DD	0; 0	NA	NA	Insufficient
NTX (any dose)	Accidents or injuries	0; 0	NA	NA	Insufficient
	QoL or function	5; 1844	Some conflicting results[c]	NA	Insufficient
	Mortality	6; 1,738	1 event (NTX) vs. 2 events (placebo)	NA	Insufficient

[a] Negative effect sizes favor intervention over placebo/control.

[b] NA entry for numbers needed to treat (NNT) indicates that the relative risk (95% CI) was not statistically significant, so we did not calculate an NNT or that the effect measure was not one that allows direct calculation of NNT (e.g., WMD).

[c] One study rated as unclear risk of bias reported that one patient in the placebo group died by "accident." No other details on the cause or nature of the accident were provided.[56] That study also reported one injury in the acamprosate group and two in the placebo group. Another study, rated high risk of bias, reported a traffic accident in the acamprosate group.[160]

ACA = acamprosate; CI = confidence Interval; DD = drinking days; DIS = disulfiram; FDA = Food and Drug Administration; HDD = heavy drinking days; N = number; NA = not applicable; NE = no effect; NNT = number needed to treat; NSD = no significant different; NTX = naltrexone; QoL = quality of life; RR = risk ratio; vs. = versus; WMD = weighted mean difference.

Data also are newly available for several medications that are used off label to treat AUD (Table 31) with low to moderate SOE. Studies evaluating the use of topiramate for AUD demonstrated moderate SOE for significant reductions in percent drinking days, percent heavy drinking days, and drinks per drinking day, but low to insufficient evidence for other alcohol use outcomes.

Both baclofen and gabapentin demonstrated low SOE for benefit in at least one outcome, but no benefit for one or more other alcohol use outcomes. For baclofen, there were 11 new trials in addition to the 2 in the first report. Despite the added studies, the SOE was low or insufficient for all outcomes for baclofen compared with placebo. The outcome with the most evidence was return to any drinking, which we graded as low SOE due to imprecision of the effect estimate and inconsistency of results across studies. Although the previous report identified no studies of gabapentin, we found four trials that demonstrated low SOE for no benefit for, heavy drinking

days, and drinks per drinking day. We did find, however, low SOE for a benefit in reducing return to any drinking and return to heavy drinking.

There were also several drugs for which new trials suggest lack of effectiveness. Five additional studies were added to the one study in the original report for varenicline. Although the study in the original review reported a small benefit in some outcomes (drinking days and heavy drinking days), none of the newer studies demonstrated benefit in any outcomes; therefore, we found low SOE for no effect across all consumption outcomes. The previous report identified one study of ondansetron and no studies of prazosin. For ondansetron, there was one newly added study for a total of two studies. We found low SOE for no effect on heavy drinking days. For prazosin, there were two newly added studies, one of which we rated as high risk of bias, and SOE was insufficient for all outcomes.

Table 31. Summary of findings and strength of evidence for efficacy of medications used off label for alcohol use disorder compared with placebo

Medication	Outcome	N Studies; N Participants	Results Effect Size (95% CI)[a]	NNT[b]	Strength of Evidence
Baclofen	Return to any drinking	8; 995	RR, 0.83 (0.70 to 0.98)	NA	Low
	Return to heavy drinking	4; 483	RR, 0.92 (0.80 to 1.06)	NA	Low (NE)
	% DDs	5; 714	WMD –5.55 (-18.79 to 7.69)	NA	Low (NE)
	% HDDs	9; 1,112	WMD, -2.16 (-7.34 to 3.02)	NA	Low (NE)
	Drinks per DD	2; 146	WMD, 0.85 (-2.23 to 3.93)	NA	Low (NE)
	Accidents or injuries	0; 0	NA	NA	Insufficient
	QoL or function	2; 384	NSD	NA	Low (NE)
	Mortality	4; 660	8 BAC vs. 3 PLA	NA	Insufficient
Gabapentin	Return to any drinking	3; 522	RR, 0.92 (0.83 to 1.02)	NA	Low
	Return to heavy drinking	3; 522	RR, 0.90 (0.82 to 0.98)	NA	Low
	% DDs	1; 112	NSD	NA	Insufficient
	% HDDs	3; 600	NSD	NA	Low (NE)
	Drinks per DD	2; 428	NSD	NA	Low (NE)
	Accidents or injuries	0; 0	NA	NA	Insufficient
	QoL or function	0; 0	NA	NA	Insufficient
	Mortality	0; 0	NA	NA	Insufficient
Ondansetron	Return to any drinking	0; 0	NA	NA	Insufficient
	Return to heavy drinking	0; 0	NA	NA	Insufficient
	% DDs	2; 172	NSD	NA	Low (NE)
	% HDDs	2; 172	Diff in one study only	NA	Insufficient
	Drinks per DD	1; 70	NSD	NA	Insufficient
	Accidents or injuries	0; 0	NA	NA	Insufficient
	Mortality	0; 0	NA	NA	Insufficient
Prazosin	Return to any drinking	1; 96	NSD	NA	Insufficient
	Return to heavy drinking	0; 0	NA	NA	Insufficient
	% DDs	2; 188	NSD	NA	Insufficient
	% HDDs	2; 188	NSD	NA	Insufficient

Medication	Outcome	N Studies; N Participants	Results Effect Size (95% CI)[a]	NNT[b]	Strength of Evidence
	Drinks per DD	2; 188	NSD	NA	Insufficient
Topiramate	Return to any drinking	1; 106	TOP 53.8%, PLA 72.2%	NA	Insufficient
	Return to heavy drinking	1; 170	TOP 10%, PLA 14%	NA	Insufficient
	% DDs	8; 1080	WMD, -7.2 (-14.3 to -0.1)	NA	Moderate
	% HDDs	9; 1210	WMD, -6.2 (-10.9 to -1.4)	NA	Moderate
	Drinks per DD	7; 922	WMD, -2.0 (-3.1 to -1.0)	NA	Moderate
	Accidents or injuries	2; 541	Reduced risk	NA	Low
	QoL or function	2; 118	NSD	NA	Low (NE)
	Mortality	3; 507	NR	NA	Insufficient
Varenicline	Return to any drinking	2; 240	NSD	NA	Low (NE)
	Return to heavy drinking	2; 240	NSD	NA	Low (NE)
	% DDs	5; 472	Reduced in 1 study	NA	Low (NE)
	%HDDs	6; 603	Reduced in 1 study	NA	Low (NE)
	Drinks per DD	4; 432	WMD, -1.4 (-2.94 to 0.13)	NA	Low (NE)
	Accidents or injuries	0; 0	NA	NA	Insufficient
	QoL or function	1; 200	No difference in SF-12 mental (mean difference 0.7; p 0.55) or physical (mean difference 0.4; p=0.38) scores	NA	Insufficient
	Mortality	1; 200	1 vs. 0 deaths	NA	Insufficient

[a] Negative effect sizes favor intervention over placebo/control.

[b] NA entry for NNT indicates that the relative risk (95% CI) was not statistically significant, so we did not calculate an NNT or that the effect measure was not one that allows direct calculation of NNT (e.g., WMD).

BAC = baclofen; CI = confidence interval; DD, drinking day; HDD, heavy drinking day; N = number; NA = not applicable; NE = no effect; NNT = number needed to treat; NR = not reported; NSD = no significant difference; PLA = placebo; QoL = quality of life; RR = risk ratio; SF-12 = 12-item Short-Form Health Survey; TOP = topiramate; vs. = versus; WMD = weighted mean difference.

No new head-to-head studies were found for this update. In the prior review, a meta-analysis of four head-to-head randomized controlled trials comparing acamprosate with naltrexone,[44-47] all rated as low risk of bias, found no statistically significant difference between the two medications for improvement in alcohol use outcomes.

We found insufficient to low evidence for measures of quality of life and function, accidents, and mortality across all medications.

4.1.2 Harms From Included Studies

Adverse events were often not collected using standardized measures, and methods for systematically capturing adverse events were often not reported. Studies were generally not designed primarily to assess adverse events; the vast majority focused on alcohol use outcomes. Evidence for many potential adverse events was insufficient to determine whether the risk was increased or not, often primarily because of small sample size and resultant lack of precision (Figures 3 and 4).

4. Discussion

Figure 3. Summary of strength-of-evidence assessments for harms outcomes (Part 1)

Drug	Anxiety	Cognitive Dysfunc-tion	Diarrhea	Dizziness	Drowsi-ness	Fatigue	Headache	Insomnia
Acamprosate	●	IE	▲▲	●	NA	NA	●	●
Disulfiram	IE	IE	IE	IE	IE	NA	IE	IE
Naltrexone	●	IE	●	▲▲	NA	NA	●	●
Baclofen	●	●	●	▲▲	▲▲	●	●	●
Gabapentin	●	▲	●	▲▲	NA	NA	●	●
Topiramate	IE	▲▲	●	▲▲	NA	NA	●	●
Varenicline	●	IE	●	●	NA	NA	●	●

▲ = Low SOE for harm ▲▲ = Moderate SOE for harm ● = Low SOE for no effect ●● = Moderate SOE for no effect
IE = Insufficient evidence **NA** = Not assessed **SOE** = Strength of evidence

Figure 4. Summary of strength-of-evidence assessments for harms outcomes (Part 2)

Drug	Nausea	Numbness	Rash	Sleepi-ness	Suicide Attempts or Suicidal Ideation	Taste	Vision Changes	Vomiting	Withdraw-als due to AEs
Acamprosate	●●	●	●	NA	IE	IE	IE	●	●
Disulfiram	IE	IE	IE	NA	IE	IE	IE	IE	IE
Naltrexone	▲▲	IE	●	NA	IE	IE	●	▲▲	▲▲
Baclofen	●	▲	●	▲▲	●	●	●	●	●
Gabapentin	●	●	●	NA	IE	IE	IE	●	●
Topiramate	●	▲▲	IE	NA	IE	▲▲	▲	IE	▲
Varenicline	▲▲	NA	IE	NA	IE	IE	IE	●	●

▲ = Low SOE for harm ▲▲ = Moderate SOE for harm ● = Low SOE for no effect ●● = Moderate SOE for no effect
AE = Adverse event **IE** = Insufficient evidence **NA** = Not assessed **SOE** = Strength of evidence

Importantly, reporting of adverse events was notably inconsistent across studies, and this fact could affect the results presented here. 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.

Dizziness was the most common mild side effect, and was noted with naltrexone, baclofen, topiramate and gabapentin. In addition, gastrointestinal distress of some sort was higher for acamprosate (diarrhea), naltrexone (nausea and vomiting), and varenicline (nausea). Studies of baclofen also reported higher rates of 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. Gabapentin was associated 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 nausea and vomiting than those treated with naltrexone. Most studies were limited to 6 months of followup or less, so very little

is known about potential harms of long-term use. In addition, studies commonly excluded patients with comorbid medical conditions, so use of these medications in people with medical issues is not well understood.

4.1.3 Primary Care Settings

With increasing numbers of patients seeking care for AUD in primary care settings, understanding the effectiveness of medical interventions in these setting is important. Particularly in the United States, participants also are often recruited for studies from the community setting. It is possible that patients who present in primary care settings may have different distributions of baseline alcohol use measures as well as comorbidities. Barriers to prescribing medications for AUD in primary care may include lack of familiarity with the medications, lack of confidence in their effectiveness, or inability to provide suitable psychosocial co-interventions (e.g., due to competing demands or insufficient practice resources, personnel, or training). We found no new studies on the use of AUD 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.[49]

4.1.4 Subgroups

We did not find any convincing evidence that any medication is more or less effective for men versus women, older adults versus young adults, persons who smoke versus persons who do not smoke, or those with or without co-occurring disorders in head-to-head studies.

4.1.5 Findings in Relation to What Is Already Known

Our main findings are consistent with existing guidelines and systematic reviews.[35, 191-196] Some guidelines, including from the United Kingdom's National Institute for Clinical Evidence (2011)[2] and the American Psychiatric Association (2018),[36] recommend that naltrexone and/or acamprosate be considered as first-line treatment for patients with AUD in combination with addiction-focused counseling. The U.S. Department of Veterans Affairs guideline from 2021[37] lists naltrexone and topiramate as recommended first options if choosing to add pharmacotherapy as part of treatment, and then suggests that acamprosate or disulfiram be considered if the first options are ineffective or cannot be tolerated.[197]

4.1.6 Applicability

As in the prior report, most studies reported that all participants met criteria for alcohol dependence. The included literature used definitions from the *Diagnostic and Statistical Manual* version III (DSM-III) or DSM-IV. DSM-5 (2013) describes a single AUD category measured on a continuum from mild to severe and no longer has separate categories for alcohol abuse and dependence.[12] Using DSM-5 terminology, most participants in the included studies likely had moderate to severe AUD. Thus, applicability of our findings to people with mild AUD is uncertain. The mean age of participants was generally in the 40s, with very few studies enrolling slightly younger or older populations. Thus, it is uncertain whether the medications have similar efficacy for older (e.g., those age 65 years or older) or younger (e.g., in the 20s) subgroups as they have for patients enrolled in the trials. Given generally higher numbers of comorbidities

seen in older populations, this may be of concern. Most studies included low numbers of non-White participants or women, and none specified genders other than male or female.

Importantly, almost all studies included some sort of co-intervention, ranging from usual management to specific harm reduction or counseling approaches, so it is important to note that the benefits observed reflect a combination of medication and co-therapy relative to co-therapy alone.

Although the majority of included trials assessing the efficacy of acamprosate were conducted in Europe (16 of 23) and a minority were conducted in the United States (4 of 23), the opposite was true for naltrexone (32 of 49 in the United States and 8 of 49 in Europe). Further, the few studies of acamprosate conducted in the United States did not find that it demonstrated a benefit either for return to any drinking or return to heavy drinking. Trials conducted in the United States all recruited participants largely through advertisements, while trials in other countries tended to recruit from treatment settings and often from inpatient settings, where alcohol withdrawal may have abated and treatment may have been begun prior to discharge. Patients recruited to these trials in the United States may, therefore, represent a more general population and potentially one with a larger range of alcohol-related baseline data. Thus, the lack of efficacy in U.S.-based trials for acamprosate may be a reflection of differences in patient characteristics as well as differences in the healthcare systems.

Most studies required patients to abstain for at least a few days before initiating medication, and the medications are generally recommended for maintenance of abstinence. Acamprosate and injectable naltrexone are only approved for use in patients who have established abstinence, though the duration of required abstinence is not set. However, some studies enrolling patients who were not yet abstinent reported reduction in heavy drinking with naltrexone[85, 198] or acamprosate.[53]

4.1.7 Implications for Clinical and Policy Decision Making

Three medications (naltrexone, acamprosate and topiramate) had moderate SOE for some consumption outcomes, but they differ in terms of ease of use and side effect profiles. Oral naltrexone (50 mg) had moderate strength of evidence for benefit across multiple outcomes and relative ease of use as a once-daily oral medication. Acamprosate and topiramate also have evidence of benefit, but topiramate has a less desirable side effect profile and acamprosate may be less convenient to take. Injectable naltrexone has low SOE for reduction in drinking days and heavy drinking days. Baclofen had low SOE for benefit for return to any drinking. Gabapentin had low SOE for benefit for return to any drinking and return to heavy drinking. Decisions will be affected by ease of use, including the need to take multiple pills (acamprosate three times daily and topiramate twice daily) over the course of a day and the side-effect profile, which is greater with topiramate. Also, acamprosate and naltrexone can be initiated at therapeutic doses, while topiramate requires an upward titration. To some degree, decisions may also be driven by desired outcomes. For example, acamprosate has evidence for effectiveness in abstinence outcomes, while topiramate only does for harm reduction outcomes.

Regardless, decisions about treatment should be made collaboratively between the patient and the clinical provider with considerations for desired outcomes, tolerance of side effects, contraindications, and the potential to adhere to the medication regimen.

For example, acamprosate is typically dosed as two 333 mg tablets given 3 times daily, whereas oral naltrexone is one tablet given once daily, and injectable naltrexone is given once monthly. Acamprosate is contraindicated for people with severe renal impairment and requires

dose adjustments for moderate renal impairment. Oral naltrexone is contraindicated for patients with acute hepatitis or liver failure and for those currently using opioids or with anticipated need for opioids, and it can precipitate severe withdrawal for patients dependent on opioids (see Harms section above for injectable naltrexone contraindications). Trials of topiramate have reported a significantly increased risk of many adverse events, including difficulty with concentration/attention, paresthesias, taste abnormalities, anorexia, nervousness, dizziness, pruritis, psychomotor slowing, and weight loss.[148, 149]

Although we did not evaluate the effectiveness or comparative effectiveness of psychosocial interventions for AUD (e.g., cognitive behavioral therapy, 12-step programs, combined behavioral intervention), such interventions were often included in the pharmacotherapy studies. In order to fully understand how to design effective programs, decision makers should consult other sources to better understand the efficacy of psychosocial interventions.

Finally, given that effective medications for AUD have been underused,[199, 200] it is unlikely that these medications will deliver their full potential impact unless policies and programs are put into place to increase education and uptake.

4.1.8 Limitations of the Comparative Effectiveness Review Process

This review focused specifically on efficacy and comparative effectiveness of medications. We included only medications currently in use in the United States, whether they have a specific FDA indication for AUD or not. Reporting of previous and ongoing psychosocial interventions was variable across the included studies, and we were unable to determine whether participants actually received some co-interventions (e.g., Alcoholics Anonymous was recommended, but no information was reported about how many participants adhered to the recommendation).

We excluded trials that had less than 12 weeks of follow up from the time of medication initiation. But since longitudinal studies have found that shorter treatment periods may yield misleading conclusions about treatment efficacy we do not consider this a significant limitation.[201, 202] We combined studies that described including populations with a dual diagnosis (e.g., alcohol dependence and depression) and those that did not have a dual diagnosis in the meta-analyses.

For Key Question 5 (on subgroups), we did not review subgroup analyses from placebo-controlled trials. The question we aimed to answer was a comparative question. We were looking for direct evidence for whether any of the medications are more or less effective than other medications for certain subgroups. To be eligible, studies had to compare at least two medications. Multiple studies were placebo controlled and were in specific populations (e.g., HIV positive, post-traumatic stress disorder [PTSD], persons who smoke only) that were not eligible for this Key Question.

Finally, publication bias and selective reporting are potential limitations. Although we searched for unpublished studies and unpublished outcomes and did not find direct evidence of either of these biases, many of the included trials were published before the availability of trial registries (e.g., clinicaltrials.gov) that would allow for greater certainty in determining the potential for either type of bias.

4.1.9 Areas for Future Research

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.

We found insufficient direct evidence to determine whether medications are efficacious for improving health outcomes. Although evidence from epidemiologic literature consistently relates high average and heavy per-occasion alcohol use to an increased risk of health problems as noted in the introduction, it is challenging to estimate the magnitude of reduction in the risk of health problems that is derived from a reduction in consumption. For example, it is unclear how much benefit (for health outcomes) is derived from 10 percent fewer patients returning to any drinking, or from 8 percent fewer patients returning to heavy drinking. That said, with increasing numbers of individuals in the United States diagnosed with AUD, the potential effect is large.

Many of the included trials had methodological limitations introducing some risk of bias. The most common issue was high proportions of participants lost to followup. High attrition rates are not uncommon in studies of psychiatric conditions. Methods of handling missing data varied, and some trials did nothing to address missing data (i.e., only analyzing completers). However, many trials conducted true intention-to-treat analyses and used appropriate methods of handling missing data, such as imputing return to heavy drinking for participants lost to followup or multiple imputation. Where possible, we used data from intention-to-treat analyses.

Reporting of previous treatments and ongoing treatments (i.e., co-interventions) was variable across the included studies. We were often unable to determine whether participants had received any previous treatments for AUD.

4.1.10 Research Gaps

Although evidence continues to grow that some medications are effective for improving consumption outcomes, the preponderance of the data for benefit derives from research on two medications, acamprosate and naltrexone. There is a need for continued research on those medications for which there is promising data but few studies, including baclofen and gabapentin. New areas of research that were not a part of this review are emerging and appear promising, such as one recent study on psilocybin.[203] We expect the field to continue to grow.

Current data are largely insufficient for understanding health outcomes and long-term outcomes. Conducting longer studies or followup studies will be helpful for better understanding the implications of pharmacotherapy in AUD at both the individual and population levels. Engaging patients to ensure that outcomes are patient centered and meet a range of patient needs also will benefit the field.

To make a decision about what medication to pursue for given patients, clinicians and patients need to understand what medications are likely to be most beneficial for which patients. However, understanding the potential role of specific medications for important subpopulations is largely lacking. Many studies have very strict exclusion criteria that may exclude participants at greatest risk of some known harms or that reflect a broader patient population, thus providing a challenge for assessing applicability to typical AUD clinical care. There are particular gaps in studies of non-White participants, older adults, and women. No studies included recognition of gender identities other than male and female. With different risks for AUD, potentially differential risks of poor outcomes, and varying comorbidities, it is important that studies include the variety of patient populations that experience AUD. For example, given that risks of having AUD and of specific associated health outcomes may differ between men and women, it is important that future studies ensure that women are included.

Finally, only one study was carried out in primary care. Given the increasing numbers of patients with AUD, it is likely that many will seek care with primary care providers.

Understanding best approaches to using pharmacotherapy for treatment in primary care is an area worthy of specific study.

4.1.11 Conclusions

Oral naltrexone at 50 mg per day and acamprosate both have moderate strength of evidence for consumption related outcomes, although naltrexone had moderate SOE across a wider range of outcomes. Numbers needed to treat to prevent one person from returning to any drinking were 18 and 11, respectively. Moderate SOE evidence suggested that topiramate also reduces alcohol use and may be a valuable second-line medication. Among other medications used off label, both baclofen and gabapentin demonstrated efficacy with low SOE for improving some alcohol consumption outcomes.

The meta-analyses of head-to-head trials found no statistically significant difference between naltrexone and acamprosate for improvement in alcohol consumption outcomes (moderate SOE) in the small number of available head-to-head trials.

We found insufficient to low (for no effect) direct evidence to conclude whether medications for AUD are effective for improving health outcomes. There were too few studies to determine comparative effectiveness of medications for subgroups or whether effectiveness varies between the primary care and specialty outpatient settings.

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6. Abbreviations and Acronyms

ACA = acamprosate
AE = adverse event
ALD = alcoholic liver disease
ASI = Addiction Severity Index
AUD = alcohol use disorder
AUDIT = Alcohol Use Disorders Identification Test
BAC = baclofen
BBCET = brief behavioral compliance enhancement treatment
BPD = bipolar disorder
BRENDA = BRENDA is an acronym based on the components of the intervention: (B)iopsychosocial evaluation, (R)eport to the patient on assessment, (E)mpathic understanding of the patient's situation, (N)eeds collaboratively identified by the patient and treatment provider, (D)irect advice to the patient on how to meet those needs, (A)ssess reaction of the patient to advice and adjust as necessary for best care
BST = broad spectrum treatment
CB = cognitive behavioral
CBCST = cognitive behavioral coping skills therapy
CBI = combined behavioral intervention
CBT = cognitive behavioral therapy
CI = confidence interval
CM = contingency management
CND = cannot determine
COMBINE = Combined Pharmacotherapies and Behavioral Intervention
CS = coping skills
DBRCT = double blind randomized control trial
DC = drug counseling
DD = drinking days
DIS = disulfiram
DrInC = Drinker Inventory of Consequences
DSM-IV = Diagnostic and Statistical Manual of Mental Disorders version 4
FDA = Food and Drug Administration
GAB = gabapentin
GABA = gamma-aminobutyric acid
GAD = generalized anxiety disorder
GHB = γ-Hydroxybuteric acid
GP = general practitioner
HaRT-A = Harm Reduction Treatment for Alcohol
HDD = heavy drinking days
HIV = human immunodeficiency virus
IBT = integrative behavior therapy
IE = insufficient evidence
inj = injectable
ITT = intent to treat
KQ = Key Question

LOCF = last observation carried forward
MATCH = Matching Alcoholism Treatments to Client Heterogeneity
MBCST = modified behavioral self-control therapy
MCV = mean corpuscular volume
MDD = major depressive disorder
med = medium
MedDRA = Mental Dictionary for Regulatory Activities
MET = motivational enhancement therapy
mg = milligrams
MIRECC = Mental Illness Research, Education and Clinical Center
MM = medical management
N = sample size
NA = not applicable
NE = no effect
NNT = number needed to treat
No. = number
NOS = not otherwise specified
NR = no reported
NSD = no significant difference
NTX = naltrexone
OCD = obsessive-compulsive disorder
OCDS = Obsessive Compulsive Disorder Drinking Scale
OLRCT = open-label randomized controlled trial
OND = ondansetron
PLA = placebo
PRA = prazosin
PTSD = post-traumatic stress disorder
PUFA = polyunsaturated fatty acid
Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire
QoL = quality of life
RCT = randomized controlled trial
RIB = riboflavin
RoB = risk of bias
RPT = relapse prevention therapy
RR = risk ratio
Rx = Prescription
SADD = Short Alcohol Dependence Data
SAFTEE = Systematic Assessment for Treatment Emergent Events
SBRCT = single-blind randomized controlled trial
SD = standard deviation
SE = standard error
SERT = sertraline
SF-12 = 12-item Short-Form Health Survey
SF-36 = 36-Item Short Form Survey
SOE = strength of evidence
ST = supportive therapy

TAU = treatment as usual
TBI = traumatic brain injury
TLFB = timeline followback method
TOP = Topiramate
UK = United Kingdom
Unc = unclear
US = United States
VA = Veterans Affairs
VACS = Veterans Affairs Cooperative Study
VAMC = Veterans Administration Medical Center
VAR = varenicline
vs. = versus
WHOQOL = World Health Organization Quality of Life
WMD = weighted mean difference
XR = extended release

Appendix A. Methods

Details of Study Selection

Search Strategy

Search dates: October 1, 2013 to March 14, 2022
Original search: October 1, 2013 to February 11, 2022 or February 15, 2022
Patch searches adding varenicline and prazosin:
Varenicline and prazosin: October 1, 2013 to March 14, 2022
All other drugs: February 11, 2022 or February 15, 2022 to March 14, 2022
Bridge searches:
PubMed: November 1, 2012 to October 1, 2013 AND September 1, 2021 to September 9, 2022
All other databases: November 1, 2012 to October 1, 2013 AND September 1, 2021 to September 22, 2022

Table A-1. PubMed search, 2/11/2022

Search Number	Query	Results
1	"Alcohol-Related Disorders"[Mesh] OR Alcoholics[Mesh] OR "Alcoholism"[Mesh] OR "Alcohol Drinking" [MeSH] OR "alcohol abuse" OR "alcohol addiction*" OR "alcohol consumption" OR "alcohol depend*" OR "alcohol misuse" OR "alcohol problem*" OR alcoholism OR "alcohol use disorder*"[tw] OR ((drinking[tiab] OR drinker[tiab] OR drinkers[tiab]) AND alcohol*[tiab]) OR "harmful alcohol*" OR "harmful drink*" OR "problem drink*"	1,091,995
2	"Naltrexone"[Mesh] OR naltrexone OR ReVia OR Vivitrol	10,806
3	#1 AND #2	2,742
4	Acamprosate[Mesh] OR acamprosate OR Campral OR Disulfiram[Mesh] OR disulfiram OR disulphiram	5,314
5	#1 AND #4	3,457
6	Baclofen[Mesh] OR Baclofen OR "Baclofen S"[All Fields] OR Gabapentin[Mesh] OR Gabapentin OR Gabapentine OR "Gabapentin S"[All Fields] OR Ondansetron[Mesh] OR Ondansetron OR Topiramate[Mesh] OR Topiramate OR "Topiramate S"[All Fields]	25,277
7	#1 AND #6	2,488
8	#3 OR #5 OR #7	7,665
9	(#8 AND Humans[Mesh:NOEXP]) OR (#8 NOT Animals[Mesh:NOEXP])	5,574
10	Adult[Mesh] OR adult OR adults OR elderly	8,689,920
11	#9 AND #10	2,392

Search Number	Query	Results
12	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR preterm*	6,092,526
13	#9 NOT #12	4,828
14	#11 OR #13	5,349
15	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murine OR murinae	89,999,025
16	#14 NOT #15	4,083
17	("2013/10/11"[Date - Entry] : "3000"[Date - Entry]) OR ("2013/10/01"[Date - Publication] : "3000"[Date - Publication])	10,383,355
18	#16 AND #17 Filter: English	1,199
19	"Systematic Reviews as Topic"[Mesh] OR "systematic review"[subset] OR "systematic review"[ti] OR "meta-analysis"[pt] OR "meta-analysis"[ti] OR "systematic literature review"[ti] OR "this systematic review"[tw] OR ("systematic review"[tiab] AND review[pt]) OR "cochrane database syst rev"[ta] OR "umbrella review"[tiab] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta-synthesis"[tiab] OR "meta-syntheses"[tiab]	365,686
20	#18 AND #19	120
21	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]	532,652
22	#18 AND #21	891
23	"Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Organizational Case Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Seroepidemiologic Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR "comparative study"[pt] OR "compared"[tw] OR "case control"[tw] OR "multivariate"[tw] OR (cohort[all] OR (control[all] AND study[all]) OR (control[tw] AND group*[tw]) OR epidemiologic studies[mh] OR program[tw] OR clinical trial[pt] OR comparative stud*[all] OR evaluation studies[all] OR statistics as topic[mh] OR survey*[tw] OR follow-up*[all] OR time factors[all] OR ci[tw]) NOT (review[pt] OR meta analysis[pt] OR consensus[mh] OR guideline[pt] OR history[sh])	11,615,664

Search Number	Query	Results
24	#18 AND #23	683
25	#24 NOT #22	109

Table A-2. The Cochrane Library (Wiley), 2/11/2022

ID	Search	Hits
#1	[mh “Alcohol-Related Disorders”] OR [mh Alcoholics] OR [mh Alcoholism] OR [mh “Alcohol Drinking”] OR “alcohol abuse”:ti,ab,kw OR (“alcohol”:ti,ab,kw NEXT addiction*:ti,ab,kw) OR “alcohol consumption”:ti,ab,kw OR (“alcohol”:ti,ab,kw NEXT depend*:ti,ab,kw) OR “alcohol misuse”:ti,ab,kw OR (“alcohol”:ti,ab,kw NEXT problem*:ti,ab,kw) OR alcoholism:ti,ab,kw OR (“alcohol use”:ti,ab,kw NEXT disorder*:ti,ab,kw) OR ((drinking:ti,ab OR drinker:ti,ab OR drinkers:ti,ab) AND alcohol*:ti,ab) OR (“harmful”:ti,ab,kw NEXT alcohol*:ti,ab,kw) OR (“harmful”:ti,ab,kw NEXT drink*:ti,ab,kw) OR (“problem”:ti,ab,kw NEXT drink*:ti,ab,kw)	20792
#2	[mh Naltrexone] OR naltrexone OR ReVia OR Vivitrol	2705
#3	#1 AND #2	1031
#4	[mh Acamprosate] OR acamprosate OR Campral OR [mh Disulfiram] OR disulfiram OR disulphiram	661
#5	#1 AND #4	489
#6	[mh Baclofen] OR Baclofen OR “Baclofen S” OR [mh Gabapentin] OR Gabapentin OR Gabapentine OR “Gabapentin S” OR [mh Ondansetron] OR Ondansetron OR [mh Topiramate] OR Topiramate OR “Topiramate S”	8916
#7	#1 AND #6	544
#8	#3 OR #5 OR #7	1804
#9	[mh Adult] OR adult OR adults OR elderly	863876
#10	#8 AND #9	1049
#11	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR “school child”:ti,ab OR (“school” NEXT child*):ti,ab OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR [mh pediatrics] OR pediatric* OR paediatric* OR peadiatric* OR school:ti,ab OR school*:ti,ab OR prematur* OR preterm*	356349
#12	#8 NOT #11	1587
#13	#10 OR #12	1778
#14	address:pt OR autobiography:pt OR bibliography:pt OR biography:pt OR “case report”:ti,ab,kw OR “case reports”:ti,ab,kw OR “case series”:ti,ab,kw OR comment:pt OR “comment on” OR congress:pt OR dictionary:pt OR directory:pt OR editorial:pt OR festschrift:pt OR “historical article”:pt OR interview:pt OR lecture:pt OR “legal case”:pt OR legislation:pt OR letter:pt OR news:pt OR “newspaper article”:pt OR “patient education handout”:pt OR “periodical index”:pt OR rats:ti,ab,kw OR cow:ti,ab,kw OR cows:ti,ab,kw OR chicken:ti,ab,kw OR chickens:ti,ab,kw OR horse:ti,ab,kw OR horses:ti,ab,kw OR mice:ti,ab,kw OR mouse:ti,ab,kw OR bovine:ti,ab,kw OR sheep OR ovine OR murine OR murinae	58346
#15	#13 NOT #14	1665
#16	#15 Limited to Date added to CENTRAL trials database (Custom range: October 11, 2013 to February 11, 2022; and limited to year first published 2013-2022)	**696**

Table A-3. Cumulative Index to Nursing and Allied Health (CINAHL Plus with Full Text, Ebsco), 2/11/2022

[Used SR-Accelerator/Polygot Search module (SR-Accelerator) to convert syntax from PubMed strategy, then reviewed and edited by hand.]

#	Query	Limiters/Expanders	Results
S1	(MH "Alcohol-Related Disorders"+) OR (MH Alcoholics+) OR (MH Alcoholism+) OR (MH "Alcohol Drinking"+) OR "alcohol abuse" OR "alcohol addiction*" OR "alcohol consumption" OR "alcohol depend*" OR "alcohol misuse" OR "alcohol problem*" OR alcoholism OR "alcohol use disorder*" OR (((TI drinking OR AB drinking) OR (TI drinker OR AB drinker) OR (TI drinkers OR AB drinkers)) AND (TI alcohol* OR AB alcohol*)) OR "harmful alcohol*" OR "harmful drink*" OR "problem drink*"	Expanders - Apply equivalent subjects Search modes - Find all my search terms	64,442
S2	(MH Naltrexone+) OR naltrexone OR ReVia OR Vivitrol	Expanders - Apply equivalent subjects Search modes - Find all my search terms	2,934
S3	S1 AND S2	Expanders - Apply equivalent subjects Search modes - Find all my search terms	924
S4	(MH Acamprosate+) OR acamprosate OR Campral OR (MH Disulfiram+) OR disulfiram OR disulphiram	Expanders - Apply equivalent subjects Search modes - Find all my search terms	719
S5	S1 AND S4	Expanders - Apply equivalent subjects Search modes - Find all my search terms	535
S6	(MH Baclofen+) OR Baclofen OR "Baclofen S" OR (MH Gabapentin+) OR Gabapentin OR Gabapentine OR "Gabapentin S" OR (MH Ondansetron+) OR Ondansetron OR (MH Topiramate+) OR Topiramate OR "Topiramate S"	Expanders - Apply equivalent subjects Search modes - Find all my search terms	7,560
S7	S1 AND S6	Expanders - Apply equivalent subjects Search modes - Find all my search terms	489
S8	S3 OR S5 OR S7	Expanders - Apply equivalent subjects Search modes - Find all my search terms	1,551
S9	(MH Adult+) OR adult OR adults OR elderly	Expanders - Apply equivalent subjects Search modes - Find all my search terms	2,136,852
S10	S8 AND S9	Expanders - Apply equivalent subjects Search modes - Find all my search terms	531
S11	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR (TI "school child" OR AB "school child") OR (TI "school child*" OR AB "school child*") OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR (MH pediatrics+) OR pediatric* OR paediatric* OR peadiatric* OR (TI school OR AB school) OR (TI school* OR AB school*) OR prematur* OR preterm*	Expanders - Apply equivalent subjects Search modes - Find all my search terms	1,546,474
S12	S8 NOT S11	Expanders - Apply equivalent subjects Search modes - Find all my search terms	1,418

#	Query	Limiters/Expanders	Results
S13	S10 OR S12	Expanders - Apply equivalent subjects Search modes - Find all my search terms	1,516
S14	PT address OR PT autobiography OR PT bibliography OR PT biography OR "case report" OR "case reports" OR "case series" OR PT comment OR "comment on" OR PT congress OR PT dictionary OR PT directory OR PT editorial OR PT festschrift OR PT "historical article" OR PT interview OR PT lecture OR PT "legal case" OR PT legislation OR PT letter OR PT news OR PT "newspaper article" OR PT "patient education handout" OR PT "periodical index" OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae	Expanders - Apply equivalent subjects Search modes - Find all my search terms	1,077,401
S15	S13 NOT S14	Expanders - Apply equivalent subjects Search modes - Find all my search terms	1,264
S16	S15	Limiters - Published Date: 20131001-20221231 Expanders - Apply equivalent subjects Search modes - Find all my search terms	542
S17	S16	Limiters - English Language Expanders - Apply equivalent subjects Search modes - Find all my search terms	537
S18	(MH "Systematic Reviews as Topic"+) OR SB "systematic review" OR TI "systematic review" OR PT meta-analysis OR TI meta-analysis OR TI "systematic literature review" OR "this systematic review" OR ((TI "systematic review" OR AB "systematic review") AND PT review) OR (SO "cochrane database syst rev" OR ST "cochrane database syst rev" OR IB "cochrane database syst rev") OR (TI "umbrella review" OR AB "umbrella review") OR (TI meta-analysis OR AB meta-analysis) OR (TI meta-analyses OR AB meta-analyses) OR (TI meta-synthesis OR AB meta-synthesis) OR (TI meta-syntheses OR AB meta-syntheses)	Limiters - English Language Expanders - Apply equivalent subjects Search modes - Find all my search terms	188,472
S19	S17 AND S18	Expanders - Apply equivalent subjects Search modes - Find all my search terms	52
S20	PT "randomized controlled trial" OR PT "controlled clinical trial" OR (TI randomized OR AB randomized) OR (TI placebo OR AB placebo) OR (MW "drug therapy") OR (TI randomly OR AB randomly) OR (TI trial OR AB trial) OR (TI groups OR AB groups)	Expanders - Apply equivalent subjects Search modes - Find all my search terms	1,630,950
S21	S17 AND S20	Expanders - Apply equivalent subjects Search modes - Find all my search terms	452

#	Query	Limiters/Expanders	Results
S22	(MH “Case-Control Studies”+) OR (MH “Cohort Studies”+) OR (MH “Epidemiologic Studies”+) OR (MH “Cross-Sectional Studies”+) OR (MH “Organizational Case Studies”+) OR (MH “Cross-Over Studies”+) OR (MH “Follow-Up Studies”+) OR (MH “Seroepidemiologic Studies”+) OR PT “Evaluation Studies” OR PT “comparative study” OR compared OR “case control” OR multivariate OR (cohort OR (control AND study) OR (control AND group*) OR (MH “epidemiologic studies”+) OR program OR PT “clinical trial” OR “comparative stud*” OR “evaluation studies” OR (MH “statistics as topic”+) OR survey* OR follow-up* OR “time factors” OR ci) NOT (PT review OR PT “meta analysis” OR (MH consensus+) OR PT guideline OR MW “History”)	Expanders - Apply equivalent subjects Search modes - Find all my search terms	2,427,347
S22 (continued)			
S23	S17 AND S22	Expanders - Apply equivalent subjects Search modes - Find all my search terms	274
S24	S23 NOT S21	Expanders - Apply equivalent subjects Search modes - Find all my search terms	35

Table A-4. Embase (Embase.com), 2/15/2022

[Used SR-Accelerator/Polygot Search module (SR-Accelerator) to convert syntax from PubMed strategy, then reviewed and edited by hand.]

No	Query	Results
#1	'alcohol-related disorders'/exp OR 'alcohol-related disorders' OR 'alcoholics'/exp OR 'alcoholics' OR 'alcohol drinking'/exp OR 'alcohol drinking' OR 'alcohol abuse'/exp OR 'alcohol abuse' OR 'alcohol addiction*' OR 'alcohol consumption'/exp OR 'alcohol consumption' OR 'alcohol depend*' OR 'alcohol misuse'/exp OR 'alcohol misuse' OR 'alcohol problem*' OR 'alcoholism'/exp OR 'alcoholism' OR 'alcohol use disorder*' OR ((drinking.tw. OR drinker.tw. OR drinkers.tw.) AND alcohol*.tw.) OR 'harmful alcohol*' OR 'harmful drink*' OR 'problem drink*'	362,189
#2	'naltrexone'/exp OR naltrexone OR revia OR vivitrol	17,587
#3	#1 AND #2	4,765
#4	'acamprosate'/exp OR acamprosate OR campral OR 'disulfiram'/exp OR disulfiram OR disulphiram	11,736
#5	#1 AND #4	5,102
#6	'baclofen'/exp OR baclofen OR 'baclofen s' OR 'gabapentin'/exp OR gabapentin OR gabapentine OR 'gabapentin s' OR 'ondansetron'/exp OR ondansetron OR 'topiramate'/exp OR topiramate OR 'topiramate s'	88,597
#7	#1 AND #6	3,170
#8	#3 OR #5 OR #7	10,074
#9	#8 AND 'humans'/de OR (#8 NOT 'animals'/de)	10,056
#10	#9 AND ([adult]/lim OR [young adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)	3,017
#11	infan* OR newborn* OR 'newborn*' OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR 'school child':ti,ab OR 'school child*':ti,ab OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR 'pediatrics'/exp OR pediatric* OR paediatric* OR peadiatric* OR school:ti,ab OR school*:ti,ab OR prematur* OR preterm*	6,327,943
#12	#9 NOT #11	9,308
#13	#10 OR #12	9,599
#14	#13 AND ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it)	2,685
#15	#13 NOT #14	6,914
#16	'case report' OR 'case reports' OR 'case series' OR term:it OR 'comment on' OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae	7,097,172
#17	#15 NOT #16	5,509
#18	#15 NOT #16 AND [english]/lim	4,694
#19	#15 NOT #16 AND [english]/lim AND [11-10-2013]/sd NOT [01-01-2023]/sd AND [2013-2022]/py	1,610
#20	'systematic review'/exp OR 'systematic review (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'systematic literature review':ti,ab OR 'this systematic review':ti,ab OR 'umbrella review':ti,ab OR 'meta-analysis':ti,ab OR 'meta-analyses':ti,ab OR 'meta-synthesis':ti,ab OR 'meta-syntheses':ti,ab	559,425
#21	#19 AND #20	196

No	Query	Results
#22	'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'random allocation'/exp OR 'controlled trial'/exp OR 'control trial' OR (('control':ab,ti OR 'controlled':ab,ti) AND 'trial':ab,ti) OR 'drug therapy'/exp OR randomized:ti,ab OR placebo:ti,ab OR randomly:ti,ab OR trial:ti,ab OR groups:ti,ab	13,210,671
#23	#19 AND #22	1080
#24	('case-control studies'/exp OR 'cohort studies'/exp OR 'epidemiologic studies'/exp OR 'cross-sectional studies'/exp OR 'organizational case studies'/exp OR 'cross-over studies'/exp OR 'follow-up studies'/exp OR 'seroepidemiologic studies'/exp OR 'evaluation study'/exp OR 'comparative study'/exp OR compared:ti,ab,kw OR 'case control':ti,ab,kw OR multivariate:ti,ab,kw OR cohort OR (control AND study) OR (control AND group*) OR program:ti,ab,kw OR 'clinical trial'/exp OR 'comparative stud*' OR 'evaluation studies' OR 'statistics as topic'/exp OR survey*:ti,ab,kw OR 'follow up*' OR 'time factors' OR ci:ti,ab,kw) NOT ('review'/exp OR 'meta analysis'/exp OR 'consensus'/exp OR 'guideline'/exp OR 'history'/exp)	13,565,708
#25	#19 AND #24	787
#26	#25 NOT #23	155

Table A-5. PubMed patch search, 3/14/2022

Search Number	Query	Results
1	"Alcohol-Related Disorders"[Mesh] OR Alcoholics[Mesh] OR "Alcoholism"[Mesh] OR "Alcohol Drinking" [MeSH] OR "alcohol abuse"[tw] OR "alcohol addiction*"[tw] OR "alcohol consumption"[tw] OR "alcohol depend*"[tw] OR "alcohol misuse"[tw] OR "alcohol problem*"[tw] OR alcoholism[tw] OR "alcohol use disorder*"[tw] OR ((drinking[tiab] OR drinker[tiab] OR drinkers[tiab]) AND alcohol*[tiab]) OR "harmful alcohol*"[tw] OR "harmful drink*"[tw] OR "problem drink*"[tw]	219,860
2	"Varenicline"[Mesh] OR Chantix[tw] OR "Prazosin"[Mesh] or prazosin[tw]	10,237
3	#1 AND #2	191
4	(#3 AND Humans[Mesh:NOEXP]) OR (#3 NOT Animals[Mesh:NOEXP])	124
5	(#3 AND Humans[Mesh:NOEXP]) OR (#3 NOT Animals[Mesh:NOEXP]) Filter: English	120
6	Adult[Mesh] OR adult OR adults OR elderly	8,720,390
7	#5 AND #6	72
8	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR preterm*	6,117,863
9	#5 AND #8	20
10	#7 OR #9	75
11	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep OR ovine OR murine OR murinae	9,028,844
12	#10 NOT #11	68
13	("2013/10/11"[Date - Entry] : "3000"[Date - Entry]) OR ("2013/10/01"[Date - Publication] : "3000"[Date - Publication])	10,521,912
14	#12 AND #13	53
15	"Systematic Reviews as Topic"[Mesh] OR "systematic review"[subset] OR "systematic review"[ti] OR "meta-analysis"[pt] OR "meta-analysis"[ti] OR "systematic literature review"[ti] OR "this systematic review"[tw] OR ("systematic review"[tiab] AND review[pt]) OR "cochrane database syst rev"[ta] OR "umbrella review"[tiab] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta-synthesis"[tiab] OR "meta-syntheses"[tiab]	370,581
16	#14 AND #15	1
17	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]	5,362,639
18	#14 AND #17	51

Search Number	Query	Results
19	"Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Organizational Case Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Seroepidemiologic Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR "comparative study"[pt] OR "compared"[tw] OR "case control"[tw] OR "multivariate"[tw] OR (cohort[all] OR (control[all] AND study[all]) OR (control[tw] AND group*[tw]) OR epidemiologic studies[mh] OR program[tw] OR clinical trial[pt] OR comparative stud*[all] OR evaluation studies[all] OR statistics as topic[mh] OR survey*[tw] OR follow-up*[all] OR time factors[all] OR ci[tw]) NOT (review[pt] OR meta analysis[pt] OR consensus[mh] OR guideline[pt] OR history[sh])	11,674,694
20	#14 AND #19	47

Table A-6. Cochrane Library patch search, 3/14/2022

ID	Search	Hits
#1	[mh “Alcohol-Related Disorders”] OR [mh Alcoholics] OR [mh Alcoholism] OR [mh “Alcohol Drinking”] OR “alcohol abuse”:ti,ab,kw OR (“alcohol”:ti,ab,kw NEXT addiction*:ti,ab,kw) OR “alcohol consumption”:ti,ab,kw OR (“alcohol”:ti,ab,kw NEXT depend*:ti,ab,kw) OR “alcohol misuse”:ti,ab,kw OR (“alcohol”:ti,ab,kw NEXT problem*:ti,ab,kw) OR alcoholism:ti,ab,kw OR (“alcohol use”:ti,ab,kw NEXT disorder*:ti,ab,kw) OR ((drinking:ti,ab OR drinker:ti,ab OR drinkers:ti,ab) AND alcohol*:ti,ab) OR (“harmful”:ti,ab,kw NEXT alcohol*:ti,ab,kw) OR (“harmful”:ti,ab,kw NEXT drink*:ti,ab,kw) OR (“problem”:ti,ab,kw NEXT drink*:ti,ab,kw)	18493
#2	[mh “Varenicline”] OR Chantix:ti,ab,kw OR [mh “Prazosin”] or prazosin:ti,ab,kw	1475
#3	#1 AND #2	105
#4	[mh Adult] OR adult OR adults OR elderly	866616
#5	#3 AND #4	59
#6	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR “school child”:ti,ab OR (“school” NEXT child*):ti,ab OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR [mh pediatrics] OR pediatric* OR paediatric* OR peadiatric* OR school:ti,ab OR school*:ti,ab OR prematur* OR preterm*	359209
#7	#3 NOT #6	98
#8	#5 OR #7	104
#9	address:pt OR autobiography:pt OR bibliography:pt OR biography:pt OR “case report”:ti,ab,kw OR “case reports”:ti,ab,kw OR “case series”:ti,ab,kw OR comment:pt OR “comment on” OR congress:pt OR dictionary:pt OR directory:pt OR editorial:pt OR festschrift:pt OR “historical article”:pt OR interview:pt OR lecture:pt OR “legal case”:pt OR legislation:pt OR letter:pt OR news:pt OR “newspaper article”:pt OR “patient education handout”:pt OR “periodical index”:pt OR rats:ti,ab,kw OR cow:ti,ab,kw OR cows:ti,ab,kw OR chicken:ti,ab,kw OR chickens:ti,ab,kw OR horse:ti,ab,kw OR horses:ti,ab,kw OR mice:ti,ab,kw OR mouse:ti,ab,kw OR bovine:ti,ab,kw OR sheep OR ovine OR murine OR murinae	58739
#10	#8 NOT #9	103
#11	#10 Limited to Date added to CENTRAL trials database (Custom range: October 11, 2013 to February 11, 2022; and limited to year first published 2013-2022)	93

Table A-7. Cumulative Index to Nursing and Allied Health (CINAHL) Ebsco, patch search, 3/14/2022

#	Query	Limiters/Expanders	Results
1	(MH "Alcohol-Related Disorders"+) OR (MH Alcoholics+) OR (MH Alcoholism+) OR (MH "Alcohol Drinking"+) OR "alcohol abuse" OR "alcohol addiction*" OR "alcohol consumption" OR "alcohol depend*" OR "alcohol misuse" OR "alcohol problem*" OR alcoholism OR "alcohol use disorder*" OR (((TI drinking OR AB drinking) OR (TI drinker OR AB drinker) OR (TI drinkers OR AB drinkers)) AND (TI alcohol* OR AB alcohol*)) OR "harmful alcohol*" OR "harmful drink*" OR "problem drink*"	Expanders - Apply equivalent subjects Search modes - Find all my search terms	64,725
2	(MH "Varenicline") OR "chantix"	Expanders - Apply equivalent subjects Search modes - Find all my search terms	270
3	(MH "Prazosin") OR "prazocin"	Expanders - Apply equivalent subjects Search modes - Find all my search terms	417
4	S2 OR S3	Expanders - Apply equivalent subjects Search modes - Find all my search terms	686
5	S1 AND S4	Expanders - Apply equivalent subjects Search modes - Find all my search terms	66
6	(MH Adult+) OR adult OR adults OR elderly	Expanders - Apply equivalent subjects Search modes - Find all my search terms	2,145,031
7	S5 AND S6	Expanders - Apply equivalent subjects Search modes - Find all my search terms	16
8	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR (TI "school child" OR AB "school child") OR (TI "school child*" OR AB "school child*") OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR (MH pediatrics+) OR pediatric* OR paediatric* OR peadiatric* OR (TI school OR AB school) OR (TI school* OR AB school*) OR prematur* OR preterm*	Expanders - Apply equivalent subjects Search modes - Find all my search terms	1,552,852
9	S5 NOT S8	Expanders - Apply equivalent subjects Search modes - Find all my search terms	52
10	S7 OR S9	Expanders - Apply equivalent subjects Search modes - Find all my search terms	56
11	PT address OR PT autobiography OR PT bibliography OR PT biography OR "case report" OR "case reports" OR "case series" OR PT comment OR "comment on" OR PT congress OR PT dictionary OR PT directory OR PT editorial OR PT festschrift OR PT "historical article" OR PT interview OR PT lecture OR PT "legal case" OR PT legislation OR PT letter OR PT news OR PT "newspaper article" OR PT "patient education handout" OR PT "periodical index" OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae	Expanders - Apply equivalent subjects Search modes - Find all my search terms	1,081,136

#	Query	Limiters/Expanders	Results
12	S10 NOT S11	Expanders - Apply equivalent subjects Search modes - Find all my search terms	36
13	S12	Limiters - Published Date: 20131001-20221231; Language: English Expanders - Apply equivalent subjects Search modes - Find all my search terms	35
14	(MH "Systematic Reviews as Topic"+) OR SB "systematic review" OR TI "systematic review" OR PT meta-analysis OR TI meta-analysis OR TI "systematic literature review" OR "this systematic review" OR ((TI "systematic review" OR AB "systematic review") AND PT review) OR (SO "cochrane database syst rev" OR ST "cochrane database syst rev" OR IB "cochrane database syst rev") OR (TI "umbrella review" OR AB "umbrella review") OR (TI meta-analysis OR AB meta-analysis) OR (TI meta-analyses OR AB meta-analyses) OR (TI meta-synthesis OR AB meta-synthesis) OR (TI meta-syntheses OR AB meta-syntheses)	Limiters - Published Date: 20131001-20221231; Language: English Expanders - Apply equivalent subjects Search modes - Find all my search terms	139,065
15	S13 AND S14	Expanders - Apply equivalent subjects Search modes - Find all my search terms	1
16	PT "randomized controlled trial" OR PT "controlled clinical trial" OR (TI randomized OR AB randomized) OR (TI placebo OR AB placebo) OR (MW "drug therapy") OR (TI randomly OR AB randomly) OR (TI trial OR AB trial) OR (TI groups OR AB groups)	Expanders - Apply equivalent subjects Search modes - Find all my search terms	1,639,038
17	S13 AND S16	Expanders - Apply equivalent subjects Search modes - Find all my search terms	33
18	(MH "Case-Control Studies"+) OR (MH "Cohort Studies"+) OR (MH "Epidemiologic Studies"+) OR (MH "Cross-Sectional Studies"+) OR (MH "Organizational Case Studies"+) OR (MH "Cross-Over Studies"+) OR (MH "Follow-Up Studies"+) OR (MH "Seroepidemiologic Studies"+) OR PT "Evaluation Studies" OR PT "comparative study" OR compared OR "case control" OR multivariate OR (cohort OR (control AND study) OR (control AND group*) OR (MH "epidemiologic studies"+) OR program OR PT "clinical trial" OR "comparative stud*" OR "evaluation studies" OR (MH "statistics as topic"+) OR survey* OR follow-up* OR "time factors" OR ci) NOT (PT review OR PT "meta analysis" OR (MH consensus+) OR PT guideline OR MW "History")	Expanders - Apply equivalent subjects Search modes - Find all my search terms	2,439,334
19	S13 AND S18	Expanders - Apply equivalent subjects Search modes - Find all my search terms	18

Table A-8. Embase (Embase.com), patch search, 3/14/2022

No.	Query	Results
#1	'alcohol-related disorders'/exp OR 'alcohol-related disorders' OR 'alcoholics'/exp OR 'alcoholics' OR 'alcohol drinking'/exp OR 'alcohol drinking' OR 'alcohol abuse'/exp OR 'alcohol abuse' OR 'alcohol addiction*' OR 'alcohol consumption'/exp OR 'alcohol consumption' OR 'alcohol depend*' OR 'alcohol misuse'/exp OR 'alcohol misuse' OR 'alcohol problem*' OR 'alcoholism'/exp OR 'alcoholism' OR 'alcohol use disorder*' OR ((drinking.tw. OR drinker.tw. OR drinkers.tw.) AND alcohol*.tw.) OR 'harmful alcohol*' OR 'harmful drink*' OR 'problem drink*'	363,659
#2	'varenicline'/exp OR varenicline OR chantix OR 'prazosin'/exp OR prazosin	30,593
#3	#1 AND #2	950
#4	#3 AND 'humans'/de OR (#3 NOT 'animals'/de)	948
#5	#4 AND ([adult]/lim OR [young adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)	282
#6	infan* OR newborn* OR 'new born*' OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR 'school child':ti,ab OR 'school child*':ti,ab OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR 'pediatrics'/exp OR pediatric* OR paediatric* OR peadiatric* OR school:ti,ab OR school*:ti,ab OR prematur* OR preterm*	6,351,626
#7	#4 NOT #6	861
#8	#5 OR #7	886
#9	#8 NOT ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it)	586
#10	'case report' OR 'case reports' OR 'case series' OR term:it OR 'comment on' OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae	7,120,920
#11	#9 NOT #10	482
#12	#11 AND [english]/lim	466
#13	#12 AND [11-10-2013]/sd NOT [01-01-2023]/sd AND [2013-2022]/py	282
#14	'systematic review'/exp OR 'systematic review (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'systematic literature review':ti,ab OR 'this systematic review':ti,ab OR 'umbrella review':ti,ab OR 'meta-analysis':ti,ab OR 'meta-analyses':ti,ab OR 'meta-synthesis':ti,ab OR 'meta-syntheses':ti,ab	565,154
#15	#13 AND #14	35
#16	'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'random allocation'/exp OR 'controlled trial'/exp OR 'control trial' OR (('control':ab,ti OR 'controlled':ab,ti) AND 'trial':ab,ti) OR 'drug therapy'/exp OR randomized:ti,ab OR placebo:ti,ab OR randomly:ti,ab OR trial:ti,ab OR groups:ti,ab	13,281,654
#17	#13 AND #16	216
#18	('case-control studies'/exp OR 'cohort studies'/exp OR 'epidemiologic studies'/exp OR 'cross-sectional studies'/exp OR 'organizational case studies'/exp OR 'cross-over studies'/exp OR 'follow-up studies'/exp OR 'seroepidemiologic studies'/exp OR 'evaluation study'/exp OR 'comparative study'/exp OR compared:ti,ab,kw OR 'case control':ti,ab,kw OR multivariate:ti,ab,kw OR cohort OR (control AND study) OR (control AND group*) OR program:ti,ab,kw OR 'clinical trial'/exp OR 'comparative stud*' OR 'evaluation studies' OR 'statistics as topic'/exp OR survey*:ti,ab,kw OR 'follow up*' OR 'time factors' OR ci:ti,ab,kw) NOT ('review'/exp OR 'meta analysis'/exp OR 'consensus'/exp OR 'guideline'/exp OR 'history'/exp)	13,633,234
#19	#13 AND #18	135

Table A-9. APA PsycInfo (Ebsco), 3/14/2022

#	Query	Limiters/Expanders	Results
1	DE “Alcohol Abuse” OR DE “Alcohol Drinking Patterns” OR DE “Alcohol Use Disorder” OR DE “Alcoholism” OR “alcohol-related disorders” OR “alcohol abuse” OR “alcohol addiction” OR “alcohol consumption” OR “alcohol depend*” OR “alcohol misuse” OR “alcohol problem*” OR alcoholics OR alcoholism OR “alcohol use disorder* OR ((drinking OR drinker OR drinkers) AND alcohol*) OR “harmful alcohol*” OR “harmful drink*” OR “problem drink*”	Expanders - Apply equivalent subjects Search modes - Find all my search terms	115,290
2	Acamprosate OR Campral OR Disulfiram OR Disulfiram OR Disulphiram OR Baclofen OR Gabapentin OR Gabapentine OR Naltrexone OR Revia OR Vivitrol OR Ondansetron OR Topiramate OR Varenicline OR Chantix OR Prazosin	Expanders - Apply equivalent subjects Search modes - Find all my search terms	12,080
3	S1 AND S2	Expanders - Apply equivalent subjects Search modes - Find all my search terms	2,729
4	S3	Limiters - Published Date: 20131001-20221231; English; Language: English; Population Group: Human Expanders - Apply equivalent subjects Search modes - Find all my search terms	640
5	S4	Limiters - Age Groups: Adulthood (18 yrs & older), Aged (65 yrs & older), Very Old (85 yrs & older) Expanders - Apply equivalent subjects Search modes - Find all my search terms	465
6	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR preterm*	Expanders - Apply equivalent subjects Search modes - Find all my search terms	1,433,461
7	S4 NOT S6	Expanders - Apply equivalent subjects Search modes - Find all my search terms	561
8	S5 OR S7	Expanders - Apply equivalent subjects Search modes - Find all my search terms	622

#	Query	Limiters/Expanders	Results
9	DE “Autobiography” OR DE “Biography” OR DE “Case Report” OR DE “Newspapers” (DE “Biography” OR DE “Newspapers” OR TX “comment on” OR TW “case report*” OR TX “case series” OR TX congress OR TX dictionary OR TX directory OR TX editorial OR TX festschrift OR TX “legal case” OR TX legislation OR TX “patient education handout” OR TX “periodical index” OR TX rats OR TX cow OR TX cows OR TX chicken OR TX chickens OR TX horse OR TX horses OR TX mice OR TX mouse OR TX bovine OR TX sheep OR TX ovine OR TX murine OR TX murinae	Expanders - Apply equivalent subjects Search modes - Find all my search terms	543,567
10	S8 NOT S9	Expanders - Apply equivalent subjects Search modes - Find all my search terms	583
11	S10	Limiters - Methodology: -Systematic Review, META ANALYSIS, METASYNTHESIS Expanders - Apply equivalent subjects Search modes - Find all my search terms	45
12	DE “Randomized Controlled Trials” OR DE “Randomized Clinical Trials”) OR “controlled clinical trial” OR TI (randomized OR placebo OR “drug therapy” OR randomly OR trial OR groups) OR AB (“controlled clinical trial” OR randomized OR placebo OR “drug therapy” OR randomly OR trial OR groups)	Expanders - Apply equivalent subjects Search modes - Find all my search terms	1,399,509
13	S10 AND S12	Expanders - Apply equivalent subjects Search modes - Find all my search terms	406
14	“Case-Control Studies” OR DE “Cohort Analysis” OR “Epidemiologic Study” OR “Cross-Sectional Study” OR “Organizational Case Study” OR “Cross-Over Study” OR “Follow-Up Study” OR “Seroepidemiologic Study”[MeSH] OR “Evaluation Study” OR “comparative study” OR “compared” OR “case control” OR “multivariate” OR (cohort OR (control AND study) OR (control AND group*) OR program OR DE “Clinical Trials” OR “comparative stud*” OR survey* OR “follow-up*” OR “time factors”) NOT (DE “Literature Review” OR DE “Meta Analysis”)	Expanders - Apply equivalent subjects Search modes - Find all my search terms	1,875,314
15	S10 AND S14	Expanders - Apply equivalent subjects Search modes - Find all my search terms	350

Table A-10. PubMed Bridge Search, 9/9/2022

Search Number	Query	Results
1	"Alcohol-Related Disorders"[Mesh] OR Alcoholics[Mesh] OR "Alcoholism"[Mesh] OR "Alcohol Drinking" [MeSH] OR "alcohol abuse"[tw] OR "alcohol addiction*"[tw] OR "alcohol consumption"[tw] OR "alcohol depend*"[tw] OR "alcohol misuse"[tw] OR "alcohol problem*"[tw] OR alcoholism[tw] OR "alcohol use disorder*"[tw] OR ((drinking[tiab] OR drinker[tiab] OR drinkers[tiab]) AND alcohol*[tiab]) OR "harmful alcohol*"[tw] OR "harmful drink*"[tw] OR "problem drink*"[tw]	223,548
2	"Naltrexone"[Mesh] OR naltrexone OR ReVia OR Vivitrol	11,001
3	#1 AND #2	1,878
4	Acamprosate[Mesh] OR acamprosate OR Campral OR Disulfiram[Mesh] OR disulfiram OR disulphiram	5,435
5	#1 AND #4	2,506
6	Baclofen[Mesh] OR Baclofen OR "Baclofen S"[All Fields] OR Gabapentin[Mesh] OR Gabapentin OR Gabapentine OR "Gabapentin S"[All Fields] OR Ondansetron[Mesh] OR Ondansetron[tw] OR Topiramate[Mesh] OR Topiramate[tw] OR "Topiramate S"[All Fields] OR "Varenicline"[Mesh] OR varenicline[tw] OR Chantix[tw] OR "Prazosin"[Mesh] or prazosin[tw]	41,804
7	#1 AND #6	1,140
8	#3 OR #5 OR #7	4,710
9	(#8 AND Humans[Mesh:NOEXP]) OR (#8 NOT Animals[Mesh:NOEXP])	4,048
10	Adult[Mesh] OR adult OR adults OR elderly	8,830,352
11	#9 AND #10	1,747
12	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR preterm*	6,254,427
13	#9 NOT #12	3,558
14	#11 OR #13	3,920
15	address[pt] OR "autobiography"[pt] OR "bibliography"[pt] OR "biography"[pt] OR "case report"[tw] OR "case reports"[tw] OR "case series"[tw] OR "comment"[pt] OR "comment on"[All Fields] OR congress[pt] OR "dictionary"[pt] OR "directory"[pt] OR "editorial"[pt] OR "festschrift"[pt] OR "historical article"[pt] OR "interview"[pt] OR lecture[pt] OR "legal case"[pt] OR "legislation"[pt] OR letter[pt] OR "news"[pt] OR "newspaper article"[pt] OR "patient education handout"[pt] OR "periodical index"[pt] OR rats[tw] OR cow[tw] OR cows[tw] OR chicken[tw] OR chickens[tw] OR horse[tw] OR horses[tw] OR mice[tw] OR mouse[tw] OR bovine[tw] OR sheep[tw] OR ovine[tw] OR murine[tw] OR murinae[tw]	9,087,460
16	#14 NOT #15	3,031

Search Number	Query	Results
17	("2012/11/01"[Date - Entry] : "2013/10/01"[Date - Entry]) OR ("2012/11/01"[Date - Publication] : "2013/04/30"[Date - Publication]) OR ("2021/09/01"[Date - Entry] : "3000"[Date - Entry]) OR ("2021/09/01"[Date - Publication] : "3000"[Date - Publication])	2,903,269
18	#16 AND #17 Filter: English	209
19	"Systematic Reviews as Topic"[Mesh] OR "systematic review"[subset] OR "systematic review"[ti] OR "meta-analysis"[pt] OR "meta-analysis"[ti] OR "systematic literature review"[ti] OR "this systematic review"[tw] OR ("systematic review"[tiab] AND review[pt]) OR "cochrane database syst rev"[ta] OR "umbrella review"[tiab] OR "meta-analysis"[tiab] OR "meta-analyses"[tiab] OR "meta-synthesis"[tiab] OR "meta-syntheses"[tiab]	396,706
20	#18 AND #19	15
21	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]	5,527,773
22	#18 AND #21	166
23	"Case-Control Studies"[MeSH] OR "Cohort Studies"[MeSH] OR "Epidemiologic Studies"[MeSH] OR "Cross-Sectional Studies"[MeSH] OR "Organizational Case Studies"[MeSH] OR "Cross-Over Studies"[MeSH] OR "Follow-Up Studies"[MeSH] OR "Seroepidemiologic Studies"[MeSH] OR "Evaluation Studies"[Publication Type] OR "comparative study"[pt] OR "compared"[tw] OR "case control"[tw] OR "multivariate"[tw] OR (cohort[all] OR (control[all] AND study[all]) OR (control[tw] AND group*[tw]) OR epidemiologic studies[mh] OR program[tw] OR clinical trial[pt] OR comparative stud*[all] OR evaluation studies[all] OR statistics as topic[mh] OR survey*[tw] OR follow-up*[all] OR time factors[all] OR ci[tw]) NOT (review[pt] OR meta analysis[pt] OR consensus[mh] OR guideline[pt] OR history[sh])	11,993,042
24	#18 AND #23	125
25	#24 NOT #22	19

Table A-11. Cochrane Library bridge search, 9/22/2022

No.	Search	Results
#1	[mh "Alcohol-Related Disorders"] OR [mh Alcoholics] OR [mh Alcoholism] OR [mh "Alcohol Drinking"] OR "alcohol abuse":ti,ab,kw OR ("alcohol":ti,ab,kw NEXT addiction*:ti,ab,kw) OR "alcohol consumption":ti,ab,kw OR ("alcohol":ti,ab,kw NEXT depend*:ti,ab,kw) OR "alcohol misuse":ti,ab,kw OR ("alcohol":ti,ab,kw NEXT problem*:ti,ab,kw) OR alcoholism:ti,ab,kw OR ("alcohol use":ti,ab,kw NEXT disorder*:ti,ab,kw) OR ((drinking:ti,ab OR drinker:ti,ab OR drinkers:ti,ab) AND alcohol*:ti,ab) OR ("harmful":ti,ab,kw NEXT alcohol*:ti,ab,kw) OR ("harmful":ti,ab,kw NEXT drink*:ti,ab,kw) OR ("problem":ti,ab,kw NEXT drink*:ti,ab,kw)	18959
#2	[mh Naltrexone] OR naltrexone OR ReVia OR Vivitrol	2749
#3	#1 AND #2	911
#4	[mh Acamprosate] OR acamprosate OR Campral OR [mh Disulfiram] OR disulfiram OR disulphiram	667
#5	#1 AND #4	478
#6	[mh Baclofen] OR Baclofen OR "Baclofen S" OR [mh Gabapentin] OR Gabapentin OR Gabapentine OR "Gabapentin S" OR [mh Ondansetron] OR Ondansetron OR [mh Topiramate] OR Topiramate OR "Topiramate S" OR [mh "Varenicline"] OR varenicline:ti,ab,kw OR Chantix:ti,ab,kw OR [mh "Prazosin"] or prazosin:ti,ab,kw	11485
#7	#1 AND #6	686
#8	#3 OR #5 OR #7	1792
#9	[mh Adult] OR adult OR adults OR elderly	883429
#10	#8 AND #9	1016
#11	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR "school child":ti,ab OR ("school" NEXT child*):ti,ab OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR [mh pediatrics] OR pediatric* OR paediatric* OR peadiatric* OR school:ti,ab OR school*:ti,ab OR prematur* OR preterm*	368417
#12	#8 NOT #11	1612
#13	#10 OR #12	1767
#14	address:pt OR autobiography:pt OR bibliography:pt OR biography:pt OR "case report":ti,ab,kw OR "case reports":ti,ab,kw OR "case series":ti,ab,kw OR comment:pt OR "comment on" OR congress:pt OR dictionary:pt OR directory:pt OR editorial:pt OR festschrift:pt OR "historical article":pt OR interview:pt OR lecture:pt OR "legal case":pt OR legislation:pt OR letter:pt OR news:pt OR "newspaper article":pt OR "patient education handout":pt OR "periodical index":pt OR rats:ti,ab,kw OR cow:ti,ab,kw OR cows:ti,ab,kw OR chicken:ti,ab,kw OR chickens:ti,ab,kw OR horse:ti,ab,kw OR horses:ti,ab,kw OR mice:ti,ab,kw OR mouse:ti,ab,kw OR bovine:ti,ab,kw OR sheep OR ovine OR murine OR murinae	60543
#15	#13 NOT #14	1695

Table A-12. Cumulative Index to Nursing and Allied Health (CINAHL) Ebsco bridge search, 9/22/2022

#	Query	Results
S1	(MH "Alcohol-Related Disorders"+) OR (MH Alcoholics+) OR (MH Alcoholism+) OR (MH "Alcohol Drinking"+) OR "alcohol abuse" OR "alcohol addiction*" OR "alcohol consumption" OR "alcohol depend*" OR "alcohol misuse" OR "alcohol problem*" OR alcoholism OR "alcohol use disorder*" OR (((TI drinking OR AB drinking) OR (TI drinker OR AB drinker) OR (TI drinkers OR AB drinkers)) AND (TI alcohol* OR AB alcohol*)) OR "harmful alcohol*" OR "harmful drink*" OR "problem drink*"	66,411
S2	(MH Naltrexone+) OR naltrexone OR ReVia OR Vivitrol	3,040
S3	S1 AND S2	941
S4	(MH Acamprosate+) OR acamprosate OR Campral OR (MH Disulfiram+) OR disulfiram OR disulphiram	749
S5	S1 AND S4	554
S6	(MH Baclofen+) OR Baclofen OR "Baclofen S" OR (MH "Varenicline") OR "chantix" OR (MH "Prazosin") OR "prazosin" (MH Gabapentin+) OR Gabapentin OR Gabapentine OR "Gabapentin S" OR (MH Ondansetron+) OR Ondansetron OR (MH Topiramate+) OR Topiramate OR "Topiramate S" OR	8,464
S7	S1 AND S6	560
S8	S3 OR S5 OR S7	1,634
S9	(MH Adult+) OR adult OR adults OR elderly	2,191,504
S10	S8 AND S9	562
S11	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR (TI "school child" OR AB "school child") OR (TI "school child*" OR AB "school child*") OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR (MH pediatrics+) OR pediatric* OR paediatric* OR peadiatric* OR (TI school OR AB school) OR (TI school* OR AB school*) OR prematur* OR preterm*	1,596,521
S12	S8 NOT S11	1,494
S13	S10 OR S12	1,598
S14	PT address OR PT autobiography OR PT bibliography OR PT biography OR "case report" OR "case reports" OR "case series" OR PT comment OR "comment on" OR PT congress OR PT dictionary OR PT directory OR PT editorial OR PT festschrift OR PT "historical article" OR PT interview OR PT lecture OR PT "legal case" OR PT legislation OR PT letter OR PT news OR PT "newspaper article" OR PT "patient education handout" OR PT "periodical index" OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae	1,108,004
S15	S13 NOT S14	1,322
S16	S15 Limiters - Published Date: 20121101-20131031	66

#	Query	Results
S17	S15 Limiters - Published Date: 20210901-20220931	57
S18	S16 OR S17	123
S19	S18 Limiters - English Language	120
S20	(MH "Systematic Reviews as Topic"+) OR SB "systematic review" OR TI "systematic review" OR PT meta-analysis OR TI meta-analysis OR TI "systematic literature review" OR "this systematic review" OR ((TI "systematic review" OR AB "systematic review") AND PT review) OR (SO "cochrane database syst rev" OR ST "cochrane database syst rev" OR IB "cochrane database syst rev") OR (TI "umbrella review" OR AB "umbrella review") OR (TI meta-analysis OR AB meta-analysis) OR (TI meta-analyses OR AB meta-analyses) OR (TI meta-synthesis OR AB meta-synthesis) OR (TI meta-syntheses OR AB meta-syntheses)	207,773
S21	S19 AND S20	8
S22	PT "randomized controlled trial" OR PT "controlled clinical trial" OR (TI randomized OR AB randomized) OR (TI placebo OR AB placebo) OR (MW "drug therapy") OR (TI randomly OR AB randomly) OR (TI trial OR AB trial) OR (TI groups OR AB groups)	1,696,489
S23	S19 AND S22	100
S24	(MH "Case-Control Studies"+) OR (MH "Cohort Studies"+) OR (MH "Epidemiologic Studies"+) OR (MH "Cross-Sectional Studies"+) OR (MH "Organizational Case Studies"+) OR (MH "Cross-Over Studies"+) OR (MH "Follow-Up Studies"+) OR (MH "Seroepidemiologic Studies"+) OR PT "Evaluation Studies" OR PT "comparative study" OR compared OR "case control" OR multivariate OR (cohort OR (control AND study) OR (control AND group*) OR (MH "epidemiologic studies"+) OR program OR PT "clinical trial" OR "comparative stud*" OR "evaluation studies" OR (MH "statistics as topic"+) OR survey* OR follow-up* OR "time factors" OR ci) NOT (PT review OR PT "meta analysis" OR (MH consensus+) OR PT guideline OR MW "History")	2,523,490
S25	S19 AND S24	61
S26	S25 NOT S23	7

Table A-13. Embase (Embase.com) bridge search, 9/22/2022

No.	Query	Results
#1	'alcohol-related disorders'/exp OR 'alcohol-related disorders' OR 'alcoholics'/exp OR 'alcoholics' OR 'alcohol drinking'/exp OR 'alcohol drinking' OR 'alcohol abuse'/exp OR 'alcohol abuse' OR 'alcohol addiction*' OR 'alcohol consumption'/exp OR 'alcohol consumption' OR 'alcohol depend*' OR 'alcohol misuse'/exp OR 'alcohol misuse' OR 'alcohol problem*' OR 'alcoholism'/exp OR 'alcoholism' OR 'alcohol use disorder*' OR ((drinking.tw. OR drinker.tw. OR drinkers.tw.) AND alcohol*.tw.) OR 'harmful alcohol*' OR 'harmful drink*' OR 'problem drink*'	374,587
#2	'naltrexone'/exp OR naltrexone OR revia OR vivitrol	18,087
#3	#1 AND #2	4,865
#4	'acamprosate'/exp OR acamprosate OR campral OR 'disulfiram'/exp OR disulfiram OR disulphiram	12,026
#5	#1 AND #4	5,216
#6	'baclofen'/exp OR baclofen OR 'baclofen s' OR 'gabapentin'/exp OR gabapentin OR gabapentine OR 'gabapentin s' OR 'ondansetron'/exp OR ondansetron OR 'topiramate'/exp OR topiramate OR 'topiramate s' OR 'varenicline'/exp OR varenicline OR chantix OR 'prazosin'/exp OR prazosin	121,951
#7	#1 AND #6	4,097
#8	#3 OR #5 OR #7	10,982
#9	#8 AND 'humans'/de OR (#8 NOT 'animals'/de)	10,960
#10	#9 AND ([adult]/lim OR [young adult]/lim OR [middle aged]/lim OR [aged]/lim OR [very elderly]/lim)	3,410
#11	infan* OR newborn* OR 'new born*' OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR 'school child':ti,ab OR 'school child*':ti,ab OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR 'pediatrics'/exp OR pediatric* OR paediatric* OR peadiatric* OR school:ti,ab OR school*:ti,ab OR prematur* OR preterm*	6,518,472
#12	#9 NOT #11	10,116
#13	#10 OR #12	10,453
#14	#13 AND ('conference abstract'/it OR 'conference paper'/it OR 'conference review'/it OR 'editorial'/it OR 'letter'/it OR 'note'/it OR 'short survey'/it)	2,985
#15	#13 NOT #14	7,468
#16	'case report' OR 'case reports' OR 'case series' OR term:it OR 'comment on' OR rats OR cow OR cows OR chicken OR chickens OR horse OR horses OR mice OR mouse OR bovine OR sheep OR ovine OR murine OR murinae	7,293,876
#17	#15 NOT #16 AND [english]/lim	5,090
#18	#17 AND [11-01-2012]/sd NOT [11-01-2013]/sd	202
#19	#17 AND [2012-2013]/py	427
#20	#17 AND [11-01-2012]/sd NOT [11-01-2013]/sd	202
#21	#17 AND [2021-2022]/py	413
#22	#18 OR #19 OR #20 OR #21	863
#23	'systematic review'/exp OR 'systematic review (topic)'/exp OR 'meta analysis'/exp OR 'meta analysis (topic)'/exp OR 'systematic literature review':ti,ab OR 'this systematic review':ti,ab OR 'umbrella review':ti,ab OR 'meta-analysis':ti,ab OR 'meta-analyses':ti,ab OR 'meta-synthesis':ti,ab OR 'meta-syntheses':ti,ab	605,816
#24	#22 AND #23	93
#25	'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'random allocation'/exp OR 'controlled trial'/exp OR 'control trial' OR (('control':ab,ti OR 'controlled':ab,ti) AND 'trial':ab,ti) OR 'drug therapy'/exp OR randomized:ti,ab OR placebo:ti,ab OR randomly:ti,ab OR trial:ti,ab OR groups:ti,ab	13,774,075
#26	#22 AND #25	598

No.	Query	Results
#27	('case-control studies'/exp OR 'cohort studies'/exp OR 'epidemiologic studies'/exp OR 'cross-sectional studies'/exp OR 'organizational case studies'/exp OR 'cross-over studies'/exp OR 'follow-up studies'/exp OR 'seroepidemiologic studies'/exp OR 'evaluation study'/exp OR 'comparative study'/exp OR compared:ti,ab,kw OR 'case control':ti,ab,kw OR multivariate:ti,ab,kw OR cohort OR (control AND study) OR (control AND group*) OR program:ti,ab,kw OR 'clinical trial'/exp OR 'comparative stud*' OR 'evaluation studies' OR 'statistics as topic'/exp OR survey*:ti,ab,kw OR 'follow up*' OR 'time factors' OR ci:ti,ab,kw) NOT ('review'/exp OR 'meta analysis'/exp OR 'consensus'/exp OR 'guideline'/exp OR 'history'/exp)	14,099,132
#28	#22 AND #27	406
#29	#28 NOT #26	74

Table A-14. APA PsycInfo (Ebsco) bridge search, 9/22/2022

#	Query	Results
S1	DE "Alcohol Abuse" OR DE "Alcohol Drinking Patterns" OR DE "Alcohol Use Disorder" OR DE "Alcoholism" OR “alcohol-related disorders” OR "alcohol abuse" OR "alcohol addiction" OR "alcohol consumption" OR "alcohol depend*" OR "alcohol misuse" OR "alcohol problem*" OR alcoholics OR alcoholism OR "alcohol use disorder* OR ((drinking OR drinker OR drinkers) AND alcohol*) OR “harmful alcohol*" OR "harmful drink*" OR "problem drink*"	117,010
S2	Acamprosate OR Campral OR Disulfiram OR Disulfiram OR Disulphiram OR Baclofen OR Gabapentin OR Gabapentine OR Naltrexone OR Revia OR Vivitrol OR Ondansetron OR Topiramate OR Varenicline OR Chantix OR Prazosin	12,201
S3	S1 AND S2	2,752
S4	S3 Limiters - Published Date: 20121101-20131031	129
S5	S3 Limiters - Published Date: 20210901-20220931	59
S6	S4 OR S5	188
S7	S6 Limiters - English; Population Group: Human	145
S8	S7 Limiters - Age Groups: Adulthood (18 yrs & older), Aged (65 yrs & older), Very Old (85 yrs & older)	0
S9	S7 Limiters - Age Groups: Adulthood (18 yrs & older), Aged (65 yrs & older), Very Old (85 yrs & older)	95
S10	Infan* OR newborn* OR new-born* OR perinat* OR neonat* OR baby OR baby* OR babies OR toddler* OR minors OR minors* OR boy OR boys OR boyfriend OR boyhood OR girl* OR kid OR kids OR child OR child* OR children* OR schoolchild* OR schoolchild OR school child[tiab] OR school child*[tiab] OR adolescen* OR juvenil* OR youth* OR teen* OR under*age* OR pubescen* OR pediatrics[mh] OR pediatric* OR paediatric* OR peadiatric* OR school[tiab] OR school*[tiab] OR prematur* OR preterm* Limiters - Age Groups: Adulthood (18 yrs & older), Aged (65 yrs & older), Very Old (85 yrs & older)	566,306
S11	S8 NOT S10 Limiters - Age Groups: Adulthood (18 yrs & older), Aged (65 yrs & older), Very Old (85 yrs & older)	84
S12	S9 OR S11	95
S13	DE "Autobiography" OR DE "Biography" OR DE "Case Report" OR DE "Newspapers" (DE "Biography" OR DE "Newspapers" OR TX "comment on" OR TW "case report*" OR TX "case series" OR TX congress OR TX dictionary OR TX directory OR TX editorial OR TX festschrift OR TX "legal case" OR TX legislation OR TX "patient education handout" OR TX "periodical index" OR TX rats OR TX cow OR TX cows OR TX chicken OR TX chickens OR TX horse OR TX horses OR TX mice OR TX mouse OR TX bovine OR TX sheep OR TX ovine OR TX murine OR TX murinae	549,216
S14	S12 NOT S13	92

#	Query	Results
S15	S14 Limiters - Methodology: -Systematic Review, META ANALYSIS, METASYNTHESIS	2
S16	DE "Randomized Controlled Trials" OR DE "Randomized Clinical Trials") OR “controlled clinical trial” OR TI (randomized OR placebo OR "drug therapy" OR randomly OR trial OR groups) OR AB ("controlled clinical trial" OR randomized OR placebo OR "drug therapy" OR randomly OR trial OR groups)	1,162,681
S17	S14 AND S16	62
S18	"Case-Control Studies" OR DE “Cohort Analysis” OR "Epidemiologic Study” OR "Cross-Sectional Study" OR "Organizational Case Study" OR "Cross-Over Study” OR "Follow-Up Study" OR "Seroepidemiologic Study"[MeSH] OR "Evaluation Study" OR "comparative study" OR "compared" OR "case control" OR "multivariate" OR (cohort OR (control AND study) OR (control AND group*) OR program OR DE "Clinical Trials" OR “comparative stud*” OR survey* OR “follow-up*” OR “time factors”) NOT (DE “Literature Review” OR DE "Meta Analysis")	1,919,970
S19	S14 AND S18	59

Inclusion and Exclusion Criteria

Table A-15 lists inclusion and exclusion criteria.

Table A-15. Inclusion and exclusion criteria

Category	Inclusion	Exclusion
Population	Adults (age 18 years or older) with AUDs (as defined above in the Background section) For KQ 5, co-occurring disorders will include other mental health disorders (e.g., depression) and acute or chronic medical conditions (e.g., cirrhosis)	Children and adolescents under age 18 years
Geography	No limits	None
Time period	6 months before the date of the last update search for the previous review (10/11/2013) to the present; searches to be updated after the draft report goes out for peer review	None
Length of followup	At least 12 weeks of planned treatment in an outpatient setting	Less than 12 weeks
Settings	Outpatient healthcare settings	All other settings; inpatient settings
Interventions	Pharmacotherapy for relapse prevention and reduction of risky drinking. This includes medications approved by FDA for treating alcohol dependence: acamprosate, disulfiram, naltrexone (oral or injectable), and certain medications in use off-label that are available in the United States: baclofen, gabapentin, ondansetron, topiramate, prazosin, and varenicline. Studies evaluating pharmacotherapy that used co-interventions with other treatments for AUDs (e.g., behavioral counseling, cognitive behavioral therapy, motivational enhancement therapy, psychosocial treatments, or self-help such as 12-step programs [e.g., Alcoholics Anonymous]) will be eligible for inclusion, as long as they meet other inclusion/exclusion criteria.	Pharmacotherapy for alcohol withdrawal; any drugs not listed in the PICOTS above; combinations of medications (e.g., studies randomizing subjects to naltrexone plus ondansetron vs. placebo)
Comparators	Studies must compare one of the medications listed above with placebo or another eligible medication.	No comparison; nonconcordant historical controls
Outcomes	Consumption outcomes: abstinence/any drinking, rates of continuous abstinence, percentage of days abstinent, time to first drink/lapse, time to heavy drinking/relapse, reduction in alcohol consumption, number of heavy drinking days, percentage of subjects with no heavy drinking days, number of drinking days, drinks per drinking day, drinks per week Health outcomes: accidents, injuries, quality of life, function, mortality Adverse effects of intervention(s): withdrawals due to adverse events, nausea/vomiting, diarrhea, anorexia, palpitations, headache, dizziness, cognitive dysfunction, taste abnormalities, paresthesias (numbness, tingling), metabolic acidosis, glaucoma, vision changes, suicidal ideation, insomnia, anxiety, rash, tiredness, weakness, constipation	Craving; cue reactivity[a]
Publication language	English	All other languages[b]

Category	Inclusion	Exclusion
Admissible evidence (study design and other criteria)	Original research; eligible study designs include the following: For all KQs, we will include RCTs with masking of subjects and providers (i.e., double blind). For KQ 2b, we will also include head-to-head prospective cohort studies. For KQ 3 (focused on harms), nonserious harms will be extracted from the efficacy RCTs; serious harms will be extracted from non-RCTs, open-label trials, secondary analyses or subgroup analyses from trials, prospective cohort studies, and case-control studies comparing two or more of the medications of interest in which at least 50 events are reported. For KQ 5 (focused on subgroups), we will include RCTs and secondary analyses or subgroup analyses from RCTs comparing two or more of the medications of interest.	Case series Case reports Nonsystematic reviews Editorials Letters to the editor Studies with historical, rather than concurrent, control groups

[a]We excluded studies that only report craving and/or cue reactivity; we will include studies that report eligible outcomes in addition to craving and/or cue reactivity.

[b]Because of limited time and resources, we will include only studies published in English.

AUD = alcohol use disorder; FDA = Food and Drug Administration; KQ = Key Question; PICOTS = populations, interventions, comparators, outcomes, timing, and setting; RCT = randomized controlled trial; vs. = versus.

We imported all citations identified through searches and other sources into EndNote v.X9. Two independent reviewers screened the titles and abstracts of all citations based on the inclusion and exclusion criteria using DistillerSR. Studies included by either reviewer were retrieved for full-text screening. Two independent reviewers then screened the full-text version of eligible references. Discrepancies between the reviewers were resolved through discussions and consensus or consultation with a third reviewer. Excluded studies are listed in the Results Appendix.

Data Extraction

For new studies that met our inclusion criteria, we extracted important information in DistillerSR®. We designed, pilot-tested, and used structured data extraction forms to gather pertinent information from each article; this included characteristics of study populations, settings, interventions, comparators, study designs, and results. Trained reviewers extracted the relevant data from each newly included article. All data abstractions were reviewed for completeness and accuracy by a second member of the team. We recorded intention-to-treat (ITT) results if available rather than results limited to those who completed the full course of medication.

Risk of Bias Assessment

In general terms, studies categorized as low risk of bias imply high confidence that the results represent the true treatment effects. Studies with medium risk of bias are susceptible to some risk of bias but probably not enough to invalidate the results. Studies with a medium risk of bias did not meet all criteria required for low risk of bias. These studies had some flaws in design or execution (e.g., inadequate description of methods of randomization and allocation concealment), but they provided enough information to allow readers to determine that the flaws did not likely cause major bias. Missing information often led to ratings of medium as opposed

to low risk of bias. Studies assessed as high risk of bias have significant flaws stemming from serious errors in design, conduct, or analysis that may invalidate the results (e.g., high overall or differential attrition without appropriate handling of missing data).

Two independent reviewers assessed the risk of bias for each study; at least one of the two reviewers was always an experienced EPC investigator. Disagreements between the two reviewers were resolved by discussion and consensus or by a third member of the team. Appendix C details the criteria used for evaluating the risk of bias of all included studies and explains the rationale for high risk-of-bias ratings.

Data Synthesis and Analysis

We used random-effects models to estimate pooled effects.[1] For continuous outcomes (e.g., scales for symptom reduction), we used weighted mean differences (WMDs). For binary outcomes, we calculated risk ratios (RRs) between groups. We included studies rated as high or unclear risk of bias in our main analyses and conducted sensitivity analyses without studies rated as high or unclear risk of bias. For alcohol consumption outcomes, if studies reported consumption in grams, we used a conversion factor of 13.7 grams as equivalent to a standard drink.[2] All quantitative analyses were conducted using Stata® version 17.0 (StataCorp LP, College Station, TX).

We calculated the chi-squared statistic and the I^2 statistic to assess statistical heterogeneity in effects between studies.[3, 4] The importance of the observed value of I^2 depends on the magnitude and direction of effects and on the strength of evidence (SOE) for heterogeneity (e.g., p-value from the chi-squared test or a confidence interval for I^2). Whenever we include a meta-analysis with considerable statistical heterogeneity in this report, we attempt to provide an explanation for the heterogeneity, considering the magnitude and direction of effects.[5] We examined potential sources of heterogeneity by stratifying analyses by patient population or setting (e.g., U.S.-based trials compared with others, studies that enrolled a dual diagnosis population compared with those that did not), variation in interventions (i.e., dose and route of delivery), and duration of treatment.

Number needed to treat (NNT) was calculated as the reciprocal of the difference in absolute risk of an outcome with medication versus placebo. NNT was calculated for medications with moderate or high SOE for improving either of two outcomes: return to any drinking and return to heavy drinking. NNT was calculated based on the pooled RR from meta-analysis, applied to plausible control group rates for these outcomes. Plausible control group rates were estimated from the median control group rates for these outcomes among all included studies: 79 percent for return to any drinking and 61 percent for return to heavy drinking.

Grading the Strength of the Body of Evidence

We graded the SOE based on the Grading of Recommendations Assessment, Development and Evaluation (short GRADE) working group guidance[6] and guidance established for the Evidence-based Practice Center Program to grade the overall strength of a body of evidence.[7] This approach incorporates five key domains: risk of bias (includes study design and aggregate quality), consistency, directness, precision of the evidence, and reporting bias.

The domains listed above are reflected in an overall rating regarding the strength of the evidence of high, moderate, low, or insufficient.

- A high strength of evidence reflects high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- A moderate rating implies moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of the effect and may change the estimate.
- A low rating implies low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of the effect and is likely to change the estimate.
- An insufficient rating indicates that the evidence does not permit estimation of an effect because multiple domain ratings indicate weakness in the evidence base (i.e., the evidence base may comprise studies with limitations; be inconsistent, indirect, or imprecise; or be biased in reporting). When high risk-of-bias studies are likely to alter the judgment, we offer a strength-of-evidence grade that relies on the better quality evidence. When the signals from the evidence base are conflicting and we cannot attribute the differences to risk of bias alone, we assigned the grade as insufficient.
- We also note evidence bases where we found no eligible evidence based on our inclusion and exclusion criteria; evidence may be available from studies of other populations ineligible for this review, particularly in terms of side effects and other potential harms of medications.

Evidence bases consisting of RCTs begin with an overall rating of high; downgrading any domain (study limitations, precision, consistency, directness, and reporting bias) results in lower ratings. Evidence bases consisting of observational studies begin with a rating of low. They may be downgraded for the domains listed above. They may also be upgraded on three domains: dose-response association, plausible confounding that would decrease the observed effect, and strength of association (magnitude of effect).

Peer Review and Public Commentary

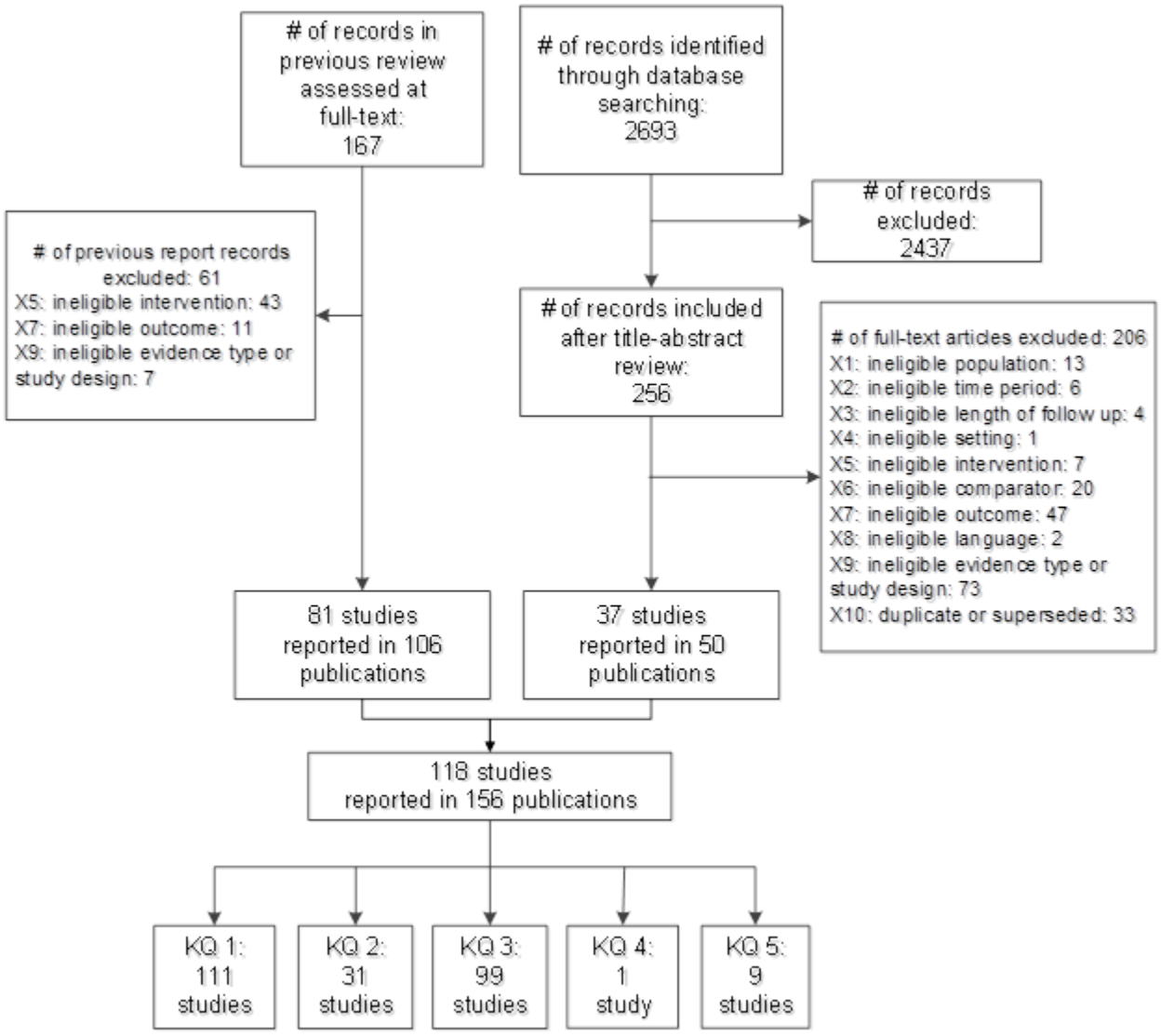
Experts in addiction medicine, development of alcohol use disorder (AUD) treatments, and psychopharmacology and individuals representing stakeholder and user communities were invited to provide external peer review of this systematic review; AHRQ and an associate editor also provided comments. The draft report was posted on the Agency for Healthcare Research and Quality (AHRQ) website for 4 weeks to elicit public comment (from November 7, 2022, to December 7, 2022). We addressed all reviewer comments, revising the text as appropriate. A disposition of comments table of peer and public comments will be posted on the Effective Healthcare Program (EHC) website 3 months after the Agency posts the final systematic review.

Appendix B. Results

Results of Literature Searches

The previous report included 167 records that were assessed at full text. Among those, 61 were excluded at full text: 43 for ineligible intervention, 11 for ineligible outcome, and 7 for ineligible evidence type or study design. Eighty-one studies reported in 106 publications were included from the previous report. Database searches identified 2,693 records. Among those, 2,437 records were excluded at title and abstract review and the remaining 256 records were included after title-abstract review. Among those, 206 were excluded at full-text review: 13 for ineligible population, 6 for ineligible time period, 4 for ineligible length of follow up, 1 for ineligible setting, 7 for ineligible intervention, 20 for ineligible comparator, 47 for ineligible outcome, 2 for ineligible language, 73 for ineligible evidence type or study design, and 33 for duplicate or superseded. Thirty-seven studies reported in 50 publications were included from the database search. In total, 118 studies reported in 156 publications were included. The final row of the flow diagram shows 111 studies were included for KQ 1, 31 were included for KQ 2, 99 studies were included for KQ 3, 1 study was included for KQ 4, and 9 were included studies for KQ 5.

Figure B-1. Literature flow diagram



Note: KQ counts are not mutually exclusive because studies could be included for multiple KQs.

KQ = Key Question.

Description of Included Studies

This section described the study characteristics of included studies by Key Question and drug.

Key Question 1

Table B-1. Characteristics of included double-blind randomized placebo-controlled trials of acamprosate

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Anton, 2006[8] Donovan, 2008[9] COMBINE	ACA 3,000 + CBI + MM (151) ACA 3,000 + MM (152) NTX 100 + CBI + MM (155) NTX 100 + MM (154) Placebo + CBI + MM (156) Placebo + MM (153)[a]	16 (68)	U.S.	11 U.S. academic sites	Ads, community resources, clinical referrals at 11 academic sites	44	23	31	NR	As randomized, community support group participation (like AA) encouraged	Low
Baltieri, 2004[10]	ACA 1,998 (40) Placebo (35)	12 (24)	Brazil	Outpatient	Patients seeking treatment at an outpatient clinic for treatment of drug dependence	18-60	NR	0	0	AA encouraged	Medium
Berger, 2013[11]	ACA 1,998 (51) Placebo (49)	12	U.S.	2 outpatient primary care clinics	Provider referral and ads	48	9	38	NR	Brief structured behavioral intervention from primary care physician	Medium
Besson, 1998[12]	ACA 1,300 to 1,998 (55) Placebo (55)	52 (108)	Switzerland	Outpatient; 3 psychiatric treatment centers	From inpatient treatment unit	42	NR	20	0	Routine counseling 100% Voluntary disulfiram 22-24%	Medium
Chick, 2000[13]	ACA 1,998 (289) Placebo (292)	24	U.K.	Outpatient	Recruited from treatment programs	43	NR	16	0	Usual psychosocial outpatient treatment program	Medium

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Geerlings, 1997[14]	ACA 1,332 to 1,998 (128) Placebo (134)	26 (52)	Belgium, the Netherlands, and Luxembourg	Outpatient substance abuse treatment centers	Recruited from detoxification patients in same centers	40-42	NR	24	NR	ACA: benzodiazepines 5% Placebo: benzodiazepines 6%	Medium
Gual, 2001[15]	ACA 1,998 (148) Placebo (148)	26	Spain	Outpatient, multicenter, hospitals	NR	41	NR	20 to 21	NR	NR	Medium
Higuchi, 2015[16]	ACA 1998 (163) Placebo (164)	24 (48)	Japan	Outpatient, 34 medical institutes	From inpatient treatment unit	52	NR	13	NR	Individual therapy, group therapy, and/or self-help group	Medium
Kiefer, 2003[17] Kiefer, 2004[18] Kiefer, 2005[19]	ACA 1,998 (40) NTX 50 (40) Placebo (40) ACA 1,998 + NTX 50 (40)	12	Germany	1 site, Hamburg outpatient	Inpatient withdrawal treatment	46	NR	26	0	Group therapy	Low
Lhuintre, 1985[20]	ACA 1,000 to 2,250 (42) Placebo (43)	13	France	Outpatient, methadone maintenance clinics	Recruited as inpatients within 48 hours of admission	40 to 43	NR	11	NR	Meprobamate for first month	High
Lhuintre, 1990[21]	ACA 1,332 (279) Placebo (290)	12	France	Outpatient, multicenter	Recruited within 48 hours of hospitalization for alcohol withdrawal	42 to 43	NR	18	NR	Psychotherapy allowed	Unclear
Mann, 2012[22] PREDICT	ACA 1,998 (172) NTX 50 (169) Placebo (86)	12	Germany	NR	Recruited from inpatient facilities of 5 academic medical centers plus 2 State-run psychiatric hospitals	45	NR	23	NR	Medical management	Medium

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Mason, 2006[23]	ACA 2,000 (258) ACA 3,000 (83) Placebo (260)	24 (32)	U.S.	21 outpatient clinics[b]	Primarily by newspaper ads	44 to 45	14 to 15	29 to 36	NR	Brief abstinence-oriented protocol-specific counseling and self-help materials	Low
Morley, 2006[24] Morley, 2010[25]	ACA 1,998 (55) NTX 50 (53) Placebo (61)	12	Australia	3 treatment centers with "medical care typically available at hospital-based drug and alcohol treatment services"	Patients who had attended an inpatient detoxification program, outpatient treatment or followup or who responded to live or print ads	45	NR	30	Severe concurrent illness (psychiatric or other)—NOS 3	All offered 4-6 sessions of manualized compliance therapy Uptake/attendance NR	Low
Paille, 1995[26]	ACA 1.3 g (188) ACA 2 g (173) Placebo (177)	52 (78)	France	NR[c]	Referral from alcohol specialist centers	43	NR	20	NR	Supportive psychotherapy 100% Hypnotics 6 to 7% Anxiolytics 8 to 12% Antidepressants 8 to 9%	Medium
Pelc, 1996[27]; Pelc, 1992[28]	ACA 1,332 to 1,998 (55) Placebo (47)	26	Belgium	Outpatient, multicenter	Post-inpatient detoxification	43	NR	31	NR	Supportive psychotherapy	High
Pelc, 1997[29]	ACA 1,332 (63) ACA 1,998 (63) Placebo (62)	13	Belgium, France	Outpatient, after inpatient detoxification	Inpatient referral	NR	NR	NR	NR	Counseling, social support when needed	Medium
Poldrugo, 1997[30]	ACA 1,332 to 1,998 (122) Placebo (124)	26 (52)	Italy	Inpatient for 1-2 weeks then outpatient, multicenter community-based alcohol rehabilitation program	From acute inpatient withdrawal treatment	43 to 45	NR	23 to 31	0	Community-based rehabilitation program with group sessions, alcohol education, community meetings	Medium

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Ralevski, 2011[31]; Ralevski, 2011[32]	ACA 1,998 (12) Placebo (11)	12	U.S.	Outpatient, university and VA health centers	From community and through referrals from treatment facilities at a university and a VA facility	51	65	17	Schizophrenia spectrum disorders 100	Weekly skills training that incorporated CB drug relapse prevention strategies	High
Sass, 1996[33]	ACA 1,332 to 1,998 (136) Placebo (136)	48 (96)	Germany	Psychiatric outpatient	Outpatient referral	41 to 42	NR	22	NR	Counseling/ psychotherapy	Medium
Tempesta, 2000[34]	ACA 1,998 (164) Placebo (166)	26 (39)	Italy	Outpatient	Recruited from outpatient internal medicine, neurology and addiction treatment programs	46	NR	17	0	Medical and behavioral counseling	Medium
Whitworth, 1996[35]	ACA 1,332 or 1,998 (224) Placebo (224)	52 (104)	Austria	Outpatient specialty	Inpatient recruitment	42	NR	21	NR	NR	Medium
Wolwer, 2011[36]	ACA 1,998 + IBT (124) ACA 1,998 + TAU (122)[d] Placebo + IBT (125)	24 (52)	Germany	Outpatient, 4 university hospitals 1 nonacademic clinic	Recruited after inpatient detoxification	46	NR	29	NR	NR	Medium

[a] Three additional treatment arms were included in COMBINE but were not relevant to our KQs: ACA + NTX + CBI + MM, ACA + NTX + MM, and CBI only (no pills).

[b] Clinics were affiliated with academic medical centers and had investigators experienced in alcoholism treatment.

[c] The article was not explicit about the setting, but patients received psychotherapy and psychiatric medication management suggesting a psychiatric outpatient setting.

[d] Treatment as usual, seen once per week in an individual setting.

Note: Age, Years is the mean age in years, unless otherwise stated. Co-interventions offered to 100% of the sample, unless otherwise stated.

AA = Alcoholics Anonymous; ACA = acamprosate; CB = cognitive behavioral; CBI = combined behavioral intervention; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; IBT = integrative behavior therapy; KQ = Key Question; mg = milligram; MM = medical management; N = sample size; NOS = not otherwise specified; NR = not reported; NTX = naltrexone; TAU = treatment as usual; Rx = prescription; U.K. = United Kingdom; U.S. = United States; VA = Veterans Administration.

Table B-2. Characteristics of included double-blind randomized placebo-controlled trials of disulfiram

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-Intervention	Risk of Bias
Fuller, 1979[37]	DIS 250 (43) DIS 1 (43) RIB 50 (42)	52	U.S.	Outpatient, VA hospital	Patients presenting to VA hospital requesting treatment for alcoholism or patients admitted for alcohol-related illness	43	61	0	NR	Counseling (unspecified)	Medium
Fuller, 1986[38]	DIS 250 (202) DIS 1 (204) RIB 50 (199)	52	U.S.	Outpatient, 9 VAMCs	Screened as inpatients in 7 centers and outpatients at 2	41 to 42	47	0	NR	Counseling (loosely defined) % NR	Medium
Ling, 1983[39]	DIS 250 (41) Placebo (41)	37	U.S.	Outpatient, VA	Unclear	39	NR	NR	Heroin use 80 Marijuana use 36 Other drug use 67 Depression 83 Moderate to high depression 50	Methadone	High
Petrakis, 2005[40] Ralevski, 2007[41] Petrakis, 2007[42] Petrakis, 2006[43] VA MIRECC	DIS 250 (66) NTX 50 (59) Placebo (64) NTX 50 + DIS 250 (65)	12	U.S.	Outpatient, VA	Recruited as outpatients or ad	47	26	3	Axis I disorder 100	Psychiatric treatment as usual	High for DIS vs. placebo

Note: Age, Years is the mean age in years, unless otherwise stated. Co-interventions offered to 100% of the sample, unless otherwise stated.

DIS = disulfiram; mg = milligram; MIRECC = Mental Illness Research, Education and Clinical Center; N = sample size; NR = not reported; NTX = naltrexone; RIB = riboflavin; U.S. = United States; VA = Veterans Affairs; VAMC = Veterans Administration Medical Center; vs. = versus.

Table B-3. Characteristics of included double-blind randomized placebo-controlled trials of naltrexone

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-Intervention	Risk of Bias
Ahmadi, 2002[44]; Ahmadi, 2004[45]	NTX 50 (58) Placebo (58)	12	Iran	Outpatient treatment	Self-referral	43	NR	0	NR	Individual counseling	Unclear
Anton, 1999[46]; Anton, 2001[47]	NTX 50 (68) Placebo (63)	12	U.S.	Outpatient academic research center	Ads, referrals for treatment seekers	41 to 44	11 to 18	27 to 31	0	CBT	Medium
Anton, 2005[48]	NTX 50 + CBT (39) NTX 50 + MET (41) Placebo + CBT (41) Placebo + MET (39)	12	U.S.	Outpatient	Ads, referred to clinical service	43 to 45	8 to 23	21 to 27	NR	CBT and MET as randomized	Medium
Anton, 2006[8] Donovan, 2008[49] COMBINE	ACA[a] 3,000 + CBI + MM (151) ACA 3,000 + MM (152) NTX 100 + CBI + MM (155) NTX 100 + MM (154) Placebo + CBI + MM (156) Placebo + MM (153)	16 (68)	U.S.	11 U.S. academic sites	Ads, community resources, clinical referrals at 11 academic sites	44	23	31	NR	As randomized; community support group participation (like AA) encouraged	Low
Anton, 2011[50]	NTX 50 (50) Placebo (50) NTX 50 + 6 weeks gabapentin, with 1,200 maximum dose (50)	16	U.S.	Outpatient	NR	43 to 47	13	18	NR	Used COMBINE's manual (CBT + MM + 12-step techniques)	Medium

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-Intervention	Risk of Bias
Balldin, 2003[51]	NTX 50 + CBT (25) NTX 50 +ST (31) Placebo + CBT (30) Placebo + ST (32)	26	Sweden	10 sites outpatient	Newspaper, outpatient treatment	48 to 51	NR	9 to 23	0	None	Low
Baltieri, 2008[52]; Baltieri, 2009[53]	TOP target 200, maximum 400 (52) NTX 50 (49) Placebo (54)	12	Brazil	Outpatient	NR	44 to 45	29	0	NR	Psychosocial	High
Brown, 2009[54]	NTX 50 (20) Placebo (23)	12	U.S.	Outpatient, university health center	Newspaper ads, physician referral, flyers and brochures at clinics	41	26	49	Bipolar (current depressed or mixed mood) 100 Cannabis abuse 21 Cocaine abuse 12 Amphetamine abuse 7	CBT	High
Chick, 2000[55]	NTX 50 (90) Placebo (85)	12	U.K.	Outpatient	From patients starting outpatient alcohol rehabilitation program	43	NR	25	0	"Usual psychosocial treatment program"	Medium
Collins, 2021[56] Collins, 2014[57]	Harm-reduction treatment for AUD + NTX 380 (74) Harm-reduction treatment for AUD + Placebo (78) Harm-reduction treatment for AUD (79) Usual care (77)	12	U.S.	Three community-based service sites (low-barrier shelters and housing programs)	From community-based service sites Snowball sampling later in trial	48	69	16	Polysubstance use in the past month: 78	Participants in the three active treatment groups (HaRT-A plus XR-NTX, HaRT-A plus placebo, and HaRT-A alone groups) attended five manualized HaRT-A sessions, delivered by study physicians or nurses	Medium

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-Intervention	Risk of Bias
Cook, 2019[58]	NTX 50 (96) Placebo (98)	16 (28)	U.S.	Outpatient, clinical and community-based settings	Brochures in clinical settings, contacting participants from previous research studies, and referral from other participants.	48	96	100	Any drug use 58 HIV 100	Medical management	Medium
Edelman, 2019[59]	NTX inj 380 + counseling (25) Placebo + counseling (26)	24 (52)	U.S.	Four HIV clinics	Ads, clinical referral, peer referral, chart review	51	84	29	HIV 100	Counseling	Medium
Foa, 2013[60] Kaczkurkin, 2016[61]	Prolonged exposure therapy + NTX 100 (40) Prolonged exposure therapy + placebo (40) Supportive counseling + NTX 100 (42) Supportive counseling + placebo (43)	24 (52)	U.S.	Outpatient, academic medical center and VA	Treatment-seeking patients recruiting through advertisements and professional referrals	43	70	35	PTSD 100	Prolonged exposure therapy 48% Supportive counseling 52%	Medium
Fogaca, 2011[62]	NTX 50 (20) Placebo (20) NTX 50 + PUFA (20) PUFA (20)	12	Brazil	Outpatient	Newspaper and radio ads	NR	NR	0	NR	None	High
Garbutt, 2005[63]; Pettinati, 2009[64]; Lucey, 2008[65]	NTX inj 380 every 4 weeks (208) NTX inj 190 every 4 weeks (210) Placebo (209)	26	U.S.	Inpatient and outpatient, private and VA	NR	45	17	32	NR	BRENDA[b] standardized ST	Medium
Gastpar, 2002[66]	NTX 50 (84) Placebo (87)	12	Germany	7 centers, outpatient	Outpatient and inpatient recruitment	43	0	28	0	Psychosocial treatment	Medium
Guardia, 2002[67]	NTX 50 (101) Placebo (101)	12	Spain	7 centers, outpatient	Recruited treatment-seeking patients	NR	NR	25	NR	Psychosocial	Medium

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-Intervention	Risk of Bias
Heinala, 2001[68]	NTX 50 daily for 12 weeks then targeted + CS (34) Placebo + CS (33) NTX 50 daily for 12 weeks then targeted + ST (29) Placebo + ST (25)	32	Finland	Outpatient	Ads	46	NR	29	0	None	High
Huang, 2005[69]	NTX 50 (20) Placebo (20)	14	Taiwan	Alcoholism treatment unit of an inpatient psychiatric hospital: 1 week inpatient, remainder outpatient	Recruited as inpatients after admission for detoxification	38 to 43	100	0	NR	Weekly individual psychotherapy sessions	High
Johnson, 2004[70]	NTX inj 400 every 28 days (25) Placebo inj (5)	17	U.S., France, the Nether-lands	4 centers; outpatient	NR	43	37	27	NR	Psychosocial support	High
Kiefer, 2003[17] Kiefer, 2004[18] Kiefer, 2005[71]	ACA 1,998 (40) NTX 50 (40) Placebo (40) ACA 1,998 + NTX 50 (40)	12	Germany	1 site, outpatient	Inpatient withdrawal treatment	46	NR	26	0	Group therapy	Low
Killeen, 2004[72]	NTX 50 + TAU (54) Placebo + TAU (43) TAU alone (48)	12	U.S.	Outpatient community substance abuse treatment center	Clinic treatment seekers	37	24	37	Comorbid psychiatric disorder 51 Additional substance use disorder 35	Several types and intensities	Medium
Kranzler, 2004[73]	NTX inj once a month 150 (185) Placebo inj (157)	12	U.S.	Outpatient	Ads, recruited as outpatients	44	17 to 18	33 to 37	NR	MET	Medium

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-Intervention	Risk of Bias
Kranzler, 2009[74]	NTX 50 targeted (38) NTX 50 once daily (45) Placebo targeted (39) Placebo once daily (41)	12	U.S.	Outpatient	Media ads, local provider referral	49	3	42	Drug use disorder <1 Social phobia 3 Antisocial personality disorder 3 Dysthymic disorder <1 Agoraphobia without panic disorder <1 OCD <1 GAD <1	Brief coping skills training	Medium
Krystal, 2001[75] VACS 425	NTX 50 for 12 months (209) NTX 50 for 3 months then placebo (209) Placebo (209)	12 or 52	U.S.	Multicenter, outpatient	VA clinics	49	37	3	0	12-step facilitation	Medium
Latt, 2002[76]	NTX 50 (56) Placebo (51)	12 (26)	Australia	4 hospitals, outpatient	NR	45	NR	30	0	No extensive psychosocial interventions	Medium
Lee, 2001[77]	NTX 50 (35) Placebo (18)	12	Singa-pore	Mixed: initially inpatient, discharged after 1 month from substance abuse treatment center	Direct recruitment from inpatient facility	45	≥88	0	NR	Intensive inpatient rehabilitation program, postdischarge therapy encouraged	High

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-Intervention	Risk of Bias
Longabaugh, 2009[78]	NTX 50 for 24 weeks + BST (36) NTX 50 for 12 weeks then placebo for 12 weeks + BST (35) NTX 50 for 24 weeks + MET (33) NTX 50 for 12 weeks then placebo for 12 weeks + MET (38)[c]	12-24 (72)	U.S.	Outpatient	Newspaper ads	44 to 46	6 to 14	33 to 43	NR	None[d]	Medium
Mann, 2012[22] PREDICT	ACA 1,998 (172) NTX 50 (169) Placebo (86)	12	Germany	NR	Recruited from inpatient facilities of 5 academic medical centers plus 2 State-run psychiatric hospitals	45	NR	23	NR	Medical management	Medium
Monterosso, 2001[79]	NTX 100 (121) Placebo (62)	12	U.S.	Outpatient	Ads	46	27	27	NR	BRENDA[b]	Medium
Monti, 2001[80]; Rohsenow, 2007[81]; Rohsenow, 2000[82]	NTX 50 (64) Placebo (64)	12 (52)	U.S.	2 weeks partial hospital (pre-medication); 52 weeks outpatient	Recruited from partial hospital program in an urban private psychiatric hospital	39	3	24	Cocaine use 23 Sedative use 8 Opiate use 4	Brief physician outpatient contacts (intensive therapy occurred prior to medication portion of trial)	Medium
Morgenstern, 2012[83]	NTX 100 + MBSCT (51) NTX 100 (51) Placebo + MBSCT (50) Placebo (48)	12	U.S.	NR	Ads, community outreach	40	26	0	HIV 15 Any drug use 67	BBCET	Medium

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-Intervention	Risk of Bias
Morley, 2006[24] Morley, 2010[84]	ACA 1,998 (55) NTX 50 (53) Placebo (61)	12	Australia	3 treatment centers with "medical care typically available at hospital-based drug and alcohol treatment services"	Patients who had attended an inpatient detoxification program, outpatient treatment, or followup or who responded to live or print ads	45	NR	30	Severe concurrent illness (psychiatric or other)– NOS 3	All offered 4 to 6 sessions of manualized compliance therapy Uptake/attendance NR	Low
Morris, 2001[85]	NTX 50 (55) Placebo (56)	12	Australia	Outpatient	Outpatient, self-referral	47	NR	0	PTSD 23 GAD 32 Panic disorder 4 MDD 6 BPD 1	Group psychoeducation and social support	Medium
O'Malley, 1992[86]; O'Malley, 1996[87]	NTX 50 + CS (29) NTX 50 + ST (23) Placebo + CS (25) Placebo + ST (27)	12 (38)	U.S.	Outpatient, university alcohol treatment unit	Ads and those seeking treatment at unit	41	7	26	NR	See arms	Medium
O'Malley, 2007[88]	NTX 50 (57) Placebo (50) Randomization stratified by presence of eating disorder	12	U.S.	University mental health center	Newspaper ads and patients seeking substance abuse treatment	40	11	100	Eating disorder 28	CBCST, based on manualized approach used in Project MATCH	Medium
O'Malley, 2008[89]	NTX 50 (34) Placebo (34) NTX 50 + SERT 100 (33)	16	U.S.	Outpatient	Direct community recruitment, health clinic referral, local ads	40	70	34	NR	Medical management	Medium
Oslin, 1997[90]	NTX 100 on Monday and Wednesday, 150 on Friday (21) Placebo (23)	12	U.S.	Outpatient substance abuse clinic and VAMC	From a VA hospital	58	64	NR	0	Group therapy and case manager	Medium

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-Intervention	Risk of Bias
Oslin, 2008[91]	NTX 100 + CBT (40) NTX 100 + BRENDA[b] (39) NTX 100 + doctor only (41) Placebo + CBT (40) Placebo + BRENDA[b] (40) Placebo + doctor only (40)	24	U.S.	Outpatient psychiatry clinic	Ads in local media	41	27	27	NR	None	Medium
Petrakis, 2004[92] Ralevski, 2006[93]	NTX 50 (16) Placebo (15)	12	U.S.	At least 3 outpatient centers—MIRECC clinics	Direct recruitment from participating centers	46	19	0	Schizophrenia or schizo-affective disorder 100	CBT + psychiatric TAU Neuroleptics 52% Benzodiazepines 16% Thymoleptics 39%	Medium
Petrakis, 2005[40] Ralevski, 2007[94] Petrakis, 2007[59] Petrakis, 2006[95] VA MIRECC DBRCT	DIS 250 (66) NTX 50 (59) Placebo (64) NTX 50 + DIS 250 (65)	12	U.S.	Outpatient VA	Recruited as outpatient or ads	47	26	3	Axis I disorder 100	Psychiatric TAU	Medium for NTX vs. placebo

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-Intervention	Risk of Bias
Springer, 2017[96]	NTX inj 380 (67) Placebo (33)	26	U.S.	Prerelease intervention administered in dept. of corrections Postrelease intervention is unclear	Recruited from department of corrections + postrelease transitional care	45	84	21	Opioid dependence (Screening) 22 Opioid Use Disorder (Diagnosis) 16 Cannabis Use Disorder 16 Cocaine use Disorder 60 HIV 100 Bipolar disorder 16 Major depressive disorder 14 PTSD 8 Panic disorder 7 Psychotic disorder 11	Medical management Referred to more intensive community-based counseling if perceived to be failing the program	Medium
Pettinati, 2008[97]	NTX 150 (82) Placebo (82) Subjects also randomized to either CBT or BRENDA[b] (2x2 design)[e]	12	U.S.	University-affiliated outpatient substance abuse treatment research facility	Those seeking treatment at the facility	39	76	29	Cocaine dependence 100	NR	Medium
Pettinati, 2010[98]	SERT 200 (40) NTX 100 (49) Placebo (39) SERT 200 + NTX 100 (42)	14	U.S.	Outpatient	Newspaper ads, referrals from local professional or friends/family	43	35	38	Depression 100	CBT	Medium

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-Intervention	Risk of Bias
Schmitz, 2004[99]	NTX 50 + RPT (20) NTX 50 + DC (20) Placebo + RPT (20) Placebo + DC (20)	12	U.S.	Outpatient	Ads	36	71	16	Cocaine dependence 100	RPT or DC as randomized	High
Schmitz, 2009[100]	NTX 100 + CBT (20) NTX 100 + CBT and CM (25) Placebo + CBT (27) Placebo + CBT and CM (14)	12	U.S.	Outpatient substance abuse clinic	Media ads	34	84 to 93	13	Cocaine use disorder 100	CBT	High
Volpicelli, 1995[101] Volpicelli, 1992[102]	NTX 50 (54) Placebo (45)[f]	12	U.S.	Substance abuse treatment unit of a VAMC	Patients in the substance abuse treatment program of a VAMC	NR	≥78	0	NR	Outpatient treatment program and group therapy	Unclear
Volpicelli, 1997[103]	NTX 50 (48) Placebo (49)	12	U.S.	Outpatient substance abuse treatment, university/VA treatment research center	Receiving outpatient treatment	38 to 39	60 to 65	18 to 26	NR	Counseling	Medium
ALK21-014, 2011[104]	NTX inj 380 every 4 weeks (152) Placebo (148)	12	Germany, Austria	Outpatient	NR	46	NR	20	NR	NR	Medium

[a] Three additional treatment arms were included in COMBINE but were not relevant to our Key Questions: ACA + NTX + CBI + MM, ACA + NTX + MM, and CBI only (no pills).

[b] BRENDA is a psychosocial program designed to enhance medication and treatment compliance. The approach has six components: biopsychosocial evaluation, giving the patient a report of findings from the evaluation, empathy, addressing patient needs, providing direct advice, and assessing patient reaction to advice and adjusting the treatment plan as needed.

[c] Ns are numbers analyzed; numbers randomized to each group NR. Total number randomized was 174.

[d] This study is not focused on NTX versus placebo comparison; it is a different design and has four arms, aiming to compare 12 versus 24 weeks of NTX and to compare MET versus BST (to determine whether the type of psychosocial treatment delivered in combination with duration of NTX may partially explain inconsistent findings regarding efficacy of NTX).

[e] Study stratified randomization by sex and reports the results overall and separately by sex.

[f] Data are from Volpicelli 1995,[101] which reported pooled results of 99 subjects. Data from a smaller subset (N=70) of this sample were reported in Volpicelli (1992).[102] For our data analyses, we used data from Volpicelli 1995 to use the larger, more complete sample and did not use data from Volpicelli (1992) to avoid double counting.

Note: Age, Years is the mean age in years, unless otherwise stated. Co-interventions offered to 100% of the sample, unless otherwise stated.

AA = Alcoholics Anonymous; ACA = acamprosate; AUD = alcohol use disorder; BBCET = brief behavioral compliance enhancement treatment; BPD = bipolar disorder; BRENDA = BRENDA is an acronym based on the components of the intervention: (B)iopsychosocial evaluation, (R)eport to the patient on assessment, (E)mpathic understanding of the patient's situation, (N)eeds collaboratively identified by the patient and treatment provider, (D)irect advice to the patient on how to meet those needs, (A)ssess reaction of the patient to advice and adjust as necessary for best care; BST = broad spectrum treatment; CBCST = cognitive behavioral coping skills therapy; CBI = combined behavioral intervention; CBT = cognitive behavioral therapy; CM = contingency management ; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; CS = coping skills; DBRCT = double-blind randomized control trial; DC = drug counseling; DIS = disulfiram; GAD = generalized anxiety disorder; HaRT-A = Harm Reduction Treatment for Alcohol; HIV = human immunodeficiency virus; inj = injectable; MATCH = Matching Alcoholism Treatments to Client Heterogeneity; MBSCT = modified behavioral self-control therapy; MDD = major depressive disorder; MET = motivational enhancement therapy; mg = milligram; MIRECC = Mental Illness Research, Education and Clinical Center; MM = medical management; N = sample size; NOS = not otherwise specified; NR = not reported; NTX = naltrexone; OCD = obsessive-compulsive disorder; PTSD = posttraumatic stress disorder; PUFA = polyunsaturated fatty acid; RPT = relapse prevention therapy; SERT = sertraline; ST = supportive therapy; TAU = treatment as usual; TOP = topiramate; U.K. = United Kingdom; U.S. = United States; VA = Veterans Affairs; VACS = Veterans Affairs Cooperative Study; VAMC = Veterans Administration Medical Center; vs. = versus; XR-NTX = extended release naltrexone.

Table B-4. Characteristics of included double-blind randomized placebo-controlled trials of baclofen

Author, Year	Arm Dose, mg/day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-Intervention	Risk of Bias
Addolorato, 2007[105]	BAC 30 (42) Placebo (42)	12	University treatment and research center	People contacting alcohol treatment unit	49	NR	0	Liver cirrhosis 100 Hepatitis B 15 Hepatitis C 29	Routine psychological support	Medium
Beraha, 2016[106]	BAC 30 (31) BAC up to 150, mean dose 93.6 (58) Placebo (62)	16	NR	From 2 inpatient and 3 outpatient treatment centers	45	NR	31	NR	Weekly outpatient group or individual sessions based on motivational therapy/ community reinforcement approach or Minnesota Model depending on recruitment site	Low
Garbutt, 2010[107]	BAC 30 (40) Placebo (40)	12	Outpatient	Newspaper and radio ads	49	4	45	NR	BRENDA	Medium
Garbutt, 2021[108]	BAC 90 (37) BAC 30 (43) Placebo (40)	16	Outpatient	Screening at outpatient clinic, advertising, and referrals	46	14	48	NR	Medical management	Medium
Hauser, 2017[109]	BAC 30 (88) Placebo (92)	12	4 VA medical centers	VA hepatology clinics	57	43	2	Chronic hepatitis C 100%	Manual-guided counseling	Low
Krupitskii, 2017[110]	BAC 50 (16) Placebo (16)	12	Narcology department at a research institute	NR	45	NR	19	NR	Weekly cognitive behavioral therapy	High
Leggio, 2015[111]	BAC 80 (15) Placebo (15)	12 (16)	Outpatient alcohol and addiction research center	Ads, referrals from other clinics, word of mouth	46	57	30	DSM-IV diagnosis of alcohol and nicotine co-dependence 100	Medical management based on COMBINE and modified to focus on alcohol and smoking	High

Author, Year	Arm Dose, mg/day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-Intervention	Risk of Bias
Morley, 2014[112]	BAC 30 (14) BAC 60 (14) Placebo (14)	12	Hospital-based outpatient drug and alcohol services	Provider referral from outpatient drug and alcohol unit	46	NR	55	NR	Structured psychotherapy for AUD (BRENDA)	Medium
Morley, 2018[113] Rombouts, 2019[114] BacALD	BAC 30 (36) BAC 75 (35) Placebo (33)	12	Outpatient, 3 hospital drug treatment sites	Ads, recruitment from participating hospitals, and flyers at local GP offices	48	NR	29	ALD (alcoholic liver disease) 56	Adherence therapy by trained psychologist	Low
Müller, 2015[115]	BAC 30 to 270 (28) Placebo (28)	20 (24)	Outpatient	Inpatient and outpatient departments at a university psychiatry and psychotherapy department, spontaneous referral at study site	46	NR	30	0	Standardized supportive therapy	Low
Ponizovsky, 2015[116]	BAC 50 (32) Placebo (32)	12 (52)	15 outpatient medical centers for alcohol dependence treatment	NR	43	NR	25	NR	Weekly psychosocial treatment for AUD following BRENDA principles	Medium
Reynaud, 2017[117] ALPADIR	BAC 180 (158) Placebo (162)	26 (30)	Outpatient	39 specialized hospital centers	49	NR	27	Anxiety 13 Depression 34	BRENDA sessions	Low
Rigal, 2020[118]	BAC up to 300 (162) Placebo (158)	52	50 private offices and 12 addiction centers	Outpatient settings	46 to 47 (median)	NR	30	Bipolar disorder 7 Attempted suicide 21 Behavioral addiction 7 Cannabis addiction 8 Cocaine addiction 1 Heroin addiction 0.5	Did not provide a standardized psychosocial co-intervention	Medium

Note: Age, Years is the mean age in years, unless otherwise stated. Co-interventions offered to 100% of the sample, unless otherwise stated.

ALD = alcoholic liver disease; AUD = alcohol use disorder; BAC = baclofen; BRENDA = BRENDA is an acronym based on the components of the intervention: (B)iopsychosocial evaluation, (R)eport to the patient on assessment, (E)mpathic understanding of the patient's situation, (N)eeds collaboratively identified by the patient and treatment provider, (D)irect advice to the patient on how to meet those needs, (A)ssess reaction of the patient to advice and adjust as necessary for best care; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DSM-IV = *Diagnostic and Statistical Manual of Mental Disorders* version 4; Gp= general practitioner; mg = milligram; N = sample size; NR = not reported; U.S. = United States; VA = Veterans Affairs.

Table B-5. Characteristics of included double-blind randomized placebo-controlled trials of gabapentin

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Follow-up)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Anton, 2020[119]	GAB 1200 (44) Placebo (46)	16	U.S., academic outpatient	Ads, recruited from community	50	6	23	PTSD 26	Medical management	Medium
Chompookham, 2018 [120]	GAB 300 (56) Placebo (56)	12 (24)	Thailand, outpatient	Recruited and screened from inpatient alcohol treatment in a hospital; all were discharged prior to study	43	NR	9	NR	None	High
Falk, 2019[121]	GAB XR 600 (170) Placebo (168)	26 (28)	U.S., 10 clinical academic sites	Ads from 10 academic sites	50	33	34	NR	Online behavioral platform (Take Control)	Medium
Mason, 2014[122]	Placebo (49) GAB 900 (54) GAB 1800 (47)	12 (24)	U.S., outpatient research institute	Print and Internet ads	45	19	43	NR	Counseling throughout study, referral to optional self-help groups and psychosocial therapies at study onset	Low

Note: Age, Years is the mean age in years, unless otherwise stated. Co-interventions offered to 100% of the sample, unless otherwise stated.

GAB= gabapentin; mg = milligram; N = sample size; NR = not reported; PTSD = posttraumatic stress disorder; Rx = prescription; U.S. = United States; XR= extended release.

Table B-6. Characteristics of included double-blind randomized placebo-controlled trials of ondansetron

Author, Year	Arm Dose, mg/day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Sene-viratne, 2022[123]	OND 0.66 (46) Placebo (49)	16 (20)	2 academic sites	Print, broadcast, internet advertisements, distribution of flyers at relevant clinical and nonclinical community sites, and by outreach to potentially eligible patients identified in medical record searches.	52	37	30	Depression 13 Anxiety 11	Brief Behavioral Compliance Enhancement Treatment (BBCET) (100%)	Medium
Corrêa Filho, 2013[124]	OND 16 (50) Placebo (52)	12	Outpatient	University-based outpatient substance abuse treatment center	43	67	0	NR	Standardized brief cognitive behavioral intervention	High
Brown, 2021[125]	OND 1 (35) Placebo (35)	12	Outpatient	NR	45	74	40	Bipolar and related disorders[a] 100	Medical management	Medium

Notes: Age (y) is the mean age in years, unless otherwise stated.

[a]Bipolar disorder I, II, or NOS; schizoaffective disorder (bipolar type); cyclothymia disorder; major depressive disorder with mixed features

mg = milligram; N = sample size; NOS = not otherwise specified; NR = not reported; OND = ondansetron; Rx = prescription.

Table B-7. Characteristics of included double-blind randomized placebo-controlled trials of prazosin

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Country	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Petrakis, 2016[126] Verplaeste, 2019[127]	PRA 16 (50) Placebo (46)	13	U.S.	Outpatient, VA medical center	Referral from clinicians in the substance abuse treatment programs and PTSD treatment programs, advertisements at the VA facilities and in the community	44	19	6	PTSD (100) Depression (39) Cocaine abuse (17) Marijuana abuse (12) Anxiety disorder (19)	Medical management	Medium
Simpson, 2018[128]	PRA 16 (48) Placebo (44)	12	U.S.	Outpatient, VA hospital	Clinical referrals, flyers, and advertisements in newspapers and on Craigslist	48	56	21	NR	Medical management	High

N = sample size; NR = not reported; PRA = prazosin; PTSD = posttraumatic stress disorder; VA = Veterans Affairs.

Table B-8. Characteristics of included double-blind randomized placebo-controlled trials of topiramate

Author, Year	Arm Dose, mg/day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Baltieri, 2008[52]; Baltieri, 2009[129]	TOP target 200, maximum 400 (52) NTX 50 (49) Placebo (54)	12	Brazil, outpatient	NR	44 to 45	29	0	NR	Psychosocial	High
Batki, 2014[130]	TOP 300 (14) Placebo (16)	12	Outpatient; VA medical center	VA Medical Center	50	47	7	Post-traumatic stress disorder 100	Medical management 100% Community-based rehab with structured living/group therapy 20%	Medium
Johnson, 2003[131] Ma, 2006[132]; Johnson, 2004[133]	TOP 25-300 (75) Placebo (75)	12	U.S.; 1 site; outpatient	Newspaper	41	36	28 to 40	0	None	Medium
Johnson, 2007[134] Johnson, 2008[135]	TOP 50-300, mean 171 (183) Placebo (188)	14	U.S.; 17 academic sites	From academic sites; by newspaper, radio, television ads	47 to 48	15	26 to 28	NR	BBCET	Low
Kampman, 2013[136]	TOP 300 (83) Placebo (87)	13	Outpatient; university treatment research center for clinic visits	Ads and referrals	44	83	21	Cocaine use disorder 100	Individual CBT relapse prevention therapy	High
Kranzler, 2021[137]	TOP 200 (85) Placebo (85)	12	Outpatient; Academic Treatment Center and VA	Ads, clinical referral, medical records screening	51	0	29	Depression 21 Anxiety Disorder 15	Medical management	Low
Kranzler, 2014 [138]	TOP 200 (67) Placebo (71)	12	Outpatient; 2 academic sites	Ads	51	12	38	Depression or Anxiety disorder 6	Medical management	Medium
Likhitsathian, 2013 [139]	TOP 300 (53) Placebo (53)	12	Outpatient (but initiated in inpatient treatment centers, <=14 days of discharge)	From inpatient treatment units	42	NR	0	Alcoholic cirrhosis 2 Hypertension 3 Peptic ulcer 4 Diabetes mellitus 4 MDD 3	Medical management	High
Pennington, 2020 [140]	TOP 284Mdn (15) Placebo (17)	12 (16)	Outpatient; VA health system	NR	46	51	6	Mild Traumatic Brain Injury 100	Medical Management	Low
Rubio, 2009[141]	TOP 250 (31) Placebo (32)[a]	12	Spain; outpatient	NR	42	NR	0	NR	Supportive group therapy offered	High

Author, Year	Arm Dose, mg/day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Sylvia, 2016 [142]	TOP 150 (5) Placebo (7)	12	Outpatient	From 2 bipolar research programs at two academic sites	44	0	42	Bipolar disorder 100	Behavioral compliance enhancement therapy at each visit	High

[a] Numbers entered are those analyzed; 76 total were randomized, but dropouts were not reported by arm.

Note: Age, Years is the mean age in years, unless otherwise stated. Co-interventions offered to 100% of the sample, unless otherwise stated.

BBCET = brief behavioral compliance enhancement treatment; CBT = cognitive behavioral therapy; MDD = major depressive disorder; mg = milligram; N = sample size; NR = not reported; NTX = naltrexone; PTSD = posttraumatic stress disorder; TOP = topiramate; VA = Veterans Affairs; U.S. = United States.

Table B-9. Characteristics of included double-blind randomized placebo-controlled trials of varenicline

Author, Year	Arm Dose, mg/day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% NonWhite	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Bejczy, 2015[143]	VAR 2 (86) Placebo (85)	12 (24)	Sweden, three outpatient university clinics	Ads	55	0	38	NR	NR	Medium
Hurt, 2018[144]	VAR 2 (16) Placebo (17)	12 (24)	U.S., outpatient	Radio advertisements (74.9%), word of mouth (10.7%), Internet postings (5.9%), flyers (3.2%), and television advertisements (3.7%)	39	9	36	NR	Brief behavioral counseling sessions	High
Litten, 2013[145] Falk, 2015[146] Fertig, 2015[147]	VAR 2 (99) Placebo (101)	13	U.S., 5 outpatient academic sites	Ads	45 to 46	30 to 38	27 to 32	NR	Required computerized self-help program	Low
O'Malley, 2018[148] Bold, 2019[149]	VAR 2 (64) Placebo (67)	16 (52)	U.S., two outpatient substance abuse treatment and research facilities	Print, radio, social media ads, and community outreach to healthcare professionals	43	62	30	NR	Medical management 9%	Medium
Pfeifer, 2019[150]	VAR 2 (15) Placebo (13)	12 (14)	Germany, academic medical center All inpatients were discharged from inpatient care between 2 and 7 days after randomization	Recruited in the psychiatric clinics and by public announcement	45	NR	14	NR	NR	High

Author, Year	Arm Dose, mg/day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% NonWhite	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Plebani, 2013[151]	VAR 2 (19) Placebo (21)	12	U.S., outpatient	Print ads	47	NR	15	NR	Weekly individual, manual-guided medical management	Medium

Notes: Age (y) is the mean age in years, unless otherwise stated.

mg = milligram; NR = not reported; Rx = prescription; U.S. = United States; VAR = varenicline.

Table B-10. Characteristics of double-blind head-to-head randomized controlled trials of acamprosate versus naltrexone

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Anton, 2006[8] Donovan, 2008[9] COMBINE	ACA 3,000 + CBI + MM (151) ACA 3,000 + MM (152) NTX 100 + CBI + MM (155) NTX 100 + MM (154) Placebo + CBI + MM (156) Placebo + MM (153)[a]	16 (68)	U.S., 11 academic sites	Ads, community resources, clinical referrals	44	23	31	NR	Community support group participation (like AA) encouraged	Low
Kiefer, 2003[17] Kiefer, 2004[18] Kiefer, 2005[19]	ACA 1,998 (40) NTX 50 (40) Placebo (40) ACA 1.998 + NTX 50 (40)	12	Germany,1 site in Hamburg, outpatient	From inpatient withdrawal treatment	46	NR	26	0	Group therapy	Low
Mann, 2012[22] PREDICT	ACA 1,998 (172) NTX 50 (169) Placebo (86)	12	Germany, NR	Recruited from inpatient facilities of 5 academic medical centers plus 2 State-run psychiatric hospitals	45	NR	23	NR	Medical management	Medium
Morley, 2006[24] Morley, 2010[25]	ACA 1,998 (55) NTX 50 (53) Placebo (61)	12	Australia, 3 treatment centers in Sydney	Patients who had attended an inpatient detoxification program, outpatient treatment, or followup, or who responded to live or print ads	45	NR	30	Severe concurrent illness (psychiatric or other)–NOS 3	All offered 4-6 sessions of manualized compliance therapy	Low

[a] Three additional treatment arms were included in COMBINE but were not relevant to our Key Questions: ACA + NTX + CBI + MM, ACA + NTX + MM, and CBI only (no pills).

Note: Age, Years is the mean age in years, unless otherwise stated. Co-interventions offered to 100% of the sample, unless otherwise stated.

AA = Alcoholics Anonymous; ACA = acamprosate; CBI = combined behavioral intervention; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; mg = milligram; MM = medical management; N = sample size; NOS = not otherwise specified; NR = not reported; NTX = naltrexone; Rx = prescription; U.S. = United States.

Table B-11. Characteristics of double-blind head-to-head randomized controlled trials of disulfiram versus naltrexone

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Petrakis, 2005[40] Ralevski, 2007[41] Petrakis, 2007[42] Petrakis, 2006[43] VA MIRECC	DIS 250 (66) NTX 50 (59) Placebo (64) NTX 50 + DIS 250 (65)	12	U.S., out-patient VA	Recruited as outpatients or by ads	47	26	3	Axis I disorder 100	Psychiatric treatment as usual	High[a]

[a] High risk of bias for disulfiram versus naltrexone; medium for naltrexone versus placebo.

Note: Age, Years is the mean age in years, unless otherwise stated. Co-interventions offered to 100% of the sample, unless otherwise stated.

DIS = disulfiram; mg = milligram; MIRECC = Mental Illness Research, Education and Clinical Center; N = sample size; NTX = naltrexone; Rx = prescription; U.S. = United States; VA = Veterans Affairs.

Key Question 2

Table B-12. Characteristics of included double-blind randomized placebo-controlled trials of acamprosate that reported a health outcome

Author, Year Trial Name Design	Arm Dose, mg/day (N)	Rx Duration, Weeks (Follow-up)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	Co-Intervention	Risk of Bias
Anton, 2006[8] Donovan, 2008[9] LoCastro, 2009[152] COMBINE	ACA 3,000 + CBI + MM (151) ACA 3,000 + MM (152) NTX 100 + CBI + MM (155) NTX 100 + MM (154) Placebo + CBI + MM (156) Placebo + MM (153)[a]	16 (68)	U.S., 11 academic sites	Ads, community resources, clinical referrals	44	23	31	As randomized; community support group participation (like AA) encouraged	Low
Berger, 2013[11]	ACA 1,998 (51) Placebo (49)	12	U.S., 2 outpatient primary care clinics	Provider referral and ads	48	9	38	Brief structured behavioral intervention from primary care physician	Medium
Besson, 1998[12]	ACA 1,300 to 1,998 (55) Placebo (55)	52 (108)	Switzerland, outpatient; 3 psychiatric treatment centers	From inpatient treatment unit	42	NR	20	Routine counseling 100% Voluntary disulfiram 22% to 24%	Medium
Geerlings, 1997[14]	ACA 1,332 to 1,998 (128) Placebo (134)	26 (52)	Belgium, the Netherlands, and Luxembourg, outpatient substance abuse treatment centers	Recruited from detoxification patients in same centers	40 to 42	NR	24	ACA: benzodiazepines 5% Placebo: benzodiazepines 6%	Medium
Lhuintre, 1990[21]	ACA 1,332 (279) Placebo (290)	12 (12)	France, outpatient substance abuse treatment centers	Inpatient treatment centers (30 centers across France)	42 to 43	NR	18	None	Unclear
Mason, 2006[23]	ACA 2,000 (258) ACA 3,000 (83) Placebo (260)	24 (32)	U.S., 21 outpatient clinics[b]	Primarily by newspaper ads	44 to 45	14 to 15	29 to 36	Brief abstinence-oriented protocol-specific counseling and self-help materials	Low
Paille, 1995[26]	ACA 1.3 g (188) ACA 2 g (173) Placebo (177)	52 (78)	France, NR[c]	Referral from alcohol specialist centers	43	NR	20	Supportive psychotherapy 100% Hypnotics 6 to 7% Anxiolytics 8 to 12% Antidepressants 8 to 9%	Medium
Poldrugo, 1997[30]	ACA 1,332 to 1,998 (122) Placebo (124)	26 (52)	Italy, inpatient for 1-2 weeks then outpatient; multicenter community-based alcohol rehabilitation program	From acute inpatient withdrawal treatment	43 to 45	NR	23 to 31	Community-based rehabilitation program with group sessions, alcohol education, community meetings	Medium

Author, Year Trial Name Design	Arm Dose, mg/day (N)	Rx Duration, Weeks (Fol-lowup)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	Co-Intervention	Risk of Bias
Sass, 1996[33]	ACA 1,332 to 1,998 (136) Placebo (136)	48 (96)	Germany, psychiatric outpatient	Outpatient referral	41 to 42	NR	22	Counseling/psychotherapy	Medium
Whitworth, 1996[35]	ACA 1,332 or 1,998 (224) Placebo (224)	52 (52)	Austria, outpatient specialty	Recruited after inpatient detoxification	42	NR	21	NR	Medium

[a] Three additional treatment arms were included in COMBINE but were not relevant to our Key Questions: ACA + NTX + CBI + MM, ACA + NTX + MM, and CBI only (no pills).

[b] Clinics were affiliated with academic medical centers and had investigators experienced in alcoholism treatment.

[c] The article was not explicit about the setting, but patients received psychotherapy and psychiatric medication management suggesting a psychiatric outpatient setting.

Note: Age, Years is the mean age in years, unless otherwise stated. Co-interventions offered to 100% of the sample, unless otherwise stated.

AA = Alcoholics Anonymous; ACA = acamprosate; CBI = combined behavioral intervention; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; mg = milligram; MM = medical management; N = sample size; NR = not reported; NTX = naltrexone; Rx = prescription; U.S. = United States

Table B-13. Characteristics of included double-blind randomized placebo-controlled trials of naltrexone that reported a health outcome

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Follow-up)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Anton, 2006[8] Donovan, 2008[49] LoCastro, 2009[153] COMBINE	ACA 3,000 + CBI + MM (151) ACA 3,000 + MM (152) NTX 100 + CBI + MM (155) NTX 100 + MM (154) Placebo + CBI + MM (156) Placebo + MM (153)[a]	16 (68)	U.S., 11 academic sites	Ads, community resources, clinical referrals at 11 academic sites	44	23	31	NR	As randomized; community support group participation (like AA) encouraged	Low
Balldin, 2003[51]	NTX 50 (56) Placebo (62)	26	Sweden, 10 sites outpatient	Ads, outpatient treatment center	48 to 51	NR	9 to 23	0	None	Low
Collins, 2021[56] Collins, 2014[57]	Harm-reduction treatment for AUD + NTX 380 (74) Harm-reduction treatment for AUD + Placebo (78) Harm-reduction treatment for AUD (79) Usual care (77)	12	U.S., three community-based service sites (low-barrier shelters and housing programs)	From community-based service sites Snowball sampling later in trial	48	69	16	Polysubstance use in the past month: 78	Participants in the three active treatment groups (HaRT-A plus XR-NTX, HaRT-A plus placebo, and HaRT-A alone groups) attended five, manualized HaRT-A sessions, delivered by study physicians or nurses	Medium
Garbutt, 2005[63] Pettinati, 2009[154]	NTX inj 380 every 4 weeks (208) NTX inj 190 every 4 weeks (210) Placebo (209)	26	U.S., inpatient and outpatient, private and VA	NR	45	17	32	NR	BRENDA standardized supportive therapy	Medium
Morgenstern, 2012[83]	NTX 100 + MBSCT (51) NTX 100 (51) Placebo + MBSCT (50) Placebo (48)	12	U.S., NR	Ads, community outreach	40	26	0	HIV: 15 Any drug use: 67	BBCET	Medium
O'Malley, 2008[89]	NTX 50 (34) Placebo (34) NTX 50 + SER 100 (33)	16	U.S., outpatient	Direct community recruitment, health clinic referral, local ads	40	70	34	NR	Medical Management	Medium

Author, Year Trial Name	Arm Dose, mg/day (N)	Rx Duration, Weeks (Follow-up)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Petrakis, 2004[92] Ralevski, 2006 Ralevski, 2006[93]	NTX 50 (16) Placebo (15)	12	U.S., at least 3 outpatient centers—MIRECC clinics	Direct recruitment from participating centers	46	19	0	Schizophrenia or schizoaffective disorder 100	CBT + psychiatric treatment as usual Neuroleptics 52% Benzodiazepines 16% Thymoleptics 39%	Medium
Petrakis, 2005[40] Ralevski, 2007[94] Petrakis, 2007[59] Petrakis, 2006[95] VA MIRECC	DIS 250 (66) NTX 50 (59) Placebo (64) NTX 50 + DIS 250 (65)	12	U.S., outpatient VA	Recruited as outpatients or ads	47	26	3	Axis I disorder 100	Psychiatric treatment as usual	Medium
Pettinati, 2008[97]	NTX 150 (82) Placebo (82) Subjects also randomized to either CBT or BRENDA (2x2 design)	12	U.S., university-affiliated outpatient substance abuse treatment research facility	Those seeking treatment at the facility	39	76	29	Cocaine dependence 100	NR	Medium
Pettinati, 2010[98]	SER 200 (40) NTX 100 (49) Placebo (39) SER 200 + NTX 100 (42)	14	U.S., outpatient	Newspaper ads, referrals from local professional or friends/family	43	35	38	Depression 100	CBT	Medium

[a] Three additional treatment arms were included in COMBINE but were not relevant to our Key Questions: ACA + NTX + CBI + MM, ACA + NTX + MM, and CBI only (no pills).

Note: Age, Years is the mean age in years, unless otherwise stated. Co-interventions offered to 100% of the sample, unless otherwise stated.

AA = Alcoholics Anonymous; ACA = acamprosate; AUD = alcohol use disorder; BBCET = brief behavioral compliance enhancement treatment; BRENDA = BRENDA is an acronym based on the components of the intervention: (B)iopsychosocial evaluation, (R)eport to the patient on assessment, (E)mpathic understanding of the patient's situation, (N)eeds collaboratively identified by the patient and treatment provider, (D)irect advice to the patient on how to meet those needs, (A)ssess reaction of the patient to advice and adjust as necessary for best care; CBI = combined behavioral intervention; CBT = cognitive behavioral therapy; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DIS = disulfiram; HaRT-A = Harm Reduction Treatment for Alcohol (HaRT-A) ; HIV = human immunodeficiency virus; inj = injection; mg = milligram; MBSCT = modified behavioral self-control therapy; MIRECC = Mental Illness Research, Education and Clinical Center; N = sample size; NR = not reported; NTX = naltrexone; SER = sertraline; U.S. = United States; VA = Veterans Affairs; XR-NTX = extended release naltrexone.

Table B-14. Characteristics of head-to-head randomized controlled trials including FDA-approved medications for treating alcohol dependence reporting a health outcome

Author, Year Trial Name Design	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	Co-Intervention	Risk of Bias
Anton, 2006[8] LoCastro, 2009[152] COMBINE DBRCT	ACA 3,000 + CBI + MM (151) ACA 3,000 + MM (152) NTX 100 + CBI + MM (155) NTX 100 + MM (154) Placebo + CBI + MM (156) Placebo + MM (153)[a]	68	U.S., 11 sites	Ads, community resources, clinical referrals at 11 academic sites	44	23	31	Community support group participation encouraged (e.g., AA)	Low
Laaksonen, 2008[155] OLRCT	ACA 1,998 or 1,333 (81) DIS 100 to 200 (81) NTX 50 (81)	Up to 52 (119)	Finland, 6 sites in 5 cities	Volunteers seeking outpatient treatment for alcohol problems	43	0	29	Manual-based CBT[b]	High for quality of life
Petrakis, 2005[40] Ralevski, 2007[41] Petrakis, 2007[42] Petrakis, 2006[43] VA MIRECC DBRCT	DIS 250 (66) NTX 50 (59) Placebo (64) NTX 50 + DIS 250 (65)	12	U.S., outpatient VA	Recruited as outpatients or via ads	47	26	3	Psychiatric treatment as usual	High for DIS vs. NTX

[a] Three additional treatment arms were included in COMBINE but were not relevant to our Key Questions: ACA + NTX + CBI + MM, ACA + NTX + MM, and CBI only (no pills).

[b] Co-intervention included a "Winning at last--defeating the drinking problem" booklet targeted to match medication goals (i.e., reduction in drinking or abstinence for ACA and NTX; abstinence for DIS).

Note: Age, Years is the mean age in years, unless otherwise stated. Co-interventions offered to 100% of the sample, unless otherwise stated.

AA = Alcoholics Anonymous; ACA = acamprosate; CBI = combined behavioral intervention; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DBRCT = double-blind randomized controlled trial; DIS = disulfiram; KQ = Key Question; mg = milligram; MIRECC = Mental Illness Research, Education and Clinical Center; MM = medical management; N = sample size; NTX = naltrexone; OLRCT = open-label randomized controlled trial; U.S. = United States; VA = Veterans Affairs.

Table B-15. Characteristics of head-to-head randomized controlled trials including medications used off-label or those under investigation

Author, Year Design	Arm Dose, mg/day (N)	Rx Duration, Weeks	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-Occurring Condition	Co-Intervention	Risk of Bias
Florez, 2008[156] OLRCT	TOP intended 200[a] (51) NTX 50 (51)	26	Spain, outpatient substance abuse clinic, referrals	Recruited when presenting for treatment	47	0	15	Personality disorders 27	Therapy based on Relapse Prevention Model	High
Florez, 2011[157] OLRCT	TOP 200 (91) NTX 50 (91)	26	Spain, outpatient substance abuse clinic, referrals	Recruited and screened when presenting for treatment	47 to 48	NR	15	Personality disorders 23	BRENDA 100% At least monthly meeting with psychiatrist	High

[a]Actual dosing: increased by 50 mg per day up to 300 or 400 mg based on consumption control or cravings.

Note: Age, Years is the mean age in years, unless otherwise stated. Co-interventions offered to 100% of the sample, unless otherwise stated.

BRENDA = BRENDA is an acronym based on the components of the intervention: (B)iopsychosocial evaluation, (R)eport to the patient on assessment, (E)mpathic understanding of the patient's situation, (N)eeds collaboratively identified by the patient and treatment provider, (D)irect advice to the patient on how to meet those needs, (A)ssess reaction of the patient to advice and adjust as necessary for best care; mg = milligram; N = sample size; NTX = naltrexone; OLRCT = open-label randomized controlled trial; TOP = topiramate; U.S. = United States.

Key Question 3

Table B-16. Characteristics of studies included for Key Question 3 that were not in Key Question 1 or 2

Author, Year Design	Arm Dose, mg/day (N)	Rx Duration, Weeks	Country Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Additional Condition	Co-Intervention	Risk of Bias
Anton, 2003[158] COMBINE pilot DBRCT	ACA 3,000 + CBI + MM (9) ACA 3,000 + MM (9) NTX 100 + CBI + MM (9) NTX 100 + MM (9) Placebo + CBI + MM (9) Placebo + MM (8)[a]	16	11 U.S. academic sites	Ads, community resources, clinical referrals at 11 academic sites	38 to 42	17 to 22	22 to 33	NR	As randomized	Med
De Sousa, 2005[159] OLRCT	ACA 1,998 (50) DIS 250 (50)	35	India, outpatient, private psychiatric hospital	Patients undergoing detoxification	42 to 43	100	0	NR	Weekly supportive group psychotherapy offered	High
De Sousa, 2004[154] OLRCT	DIS 250 (50) NTX 50 (50)	52	India, outpatient	Recruited as inpatients	43 to 47	NR	0	NR	Supportive group psychotherapy	High
Nava, 2006[160] OLRCT	GHB 50[b] (28) NTX 50 (24) DIS 200 (28)	52	Italy, outpatient	Advertisements, word of mouth, press release	38.5 to 42.7	NR	15	0	Cognitive behavioral therapy	High
Rubio, 2001[161] SBRCT	ACA 1,665-1,998 (80) NTX 50 (77)	52	Spain, outpatient	Patients presenting to hospital for detoxification	44	NR	0	0	Supportive group therapy weekly; weekly visits with a psychiatrist for 3 months, then biweekly until end of study	High

[a] Three additional treatment arms were included in COMBINE pilot study but were not relevant to our Key Questions: ACA + NTX + CBI + MM, ACA + NTX + MM, and CBI only (no pills).

[b] Dose is 50 mg per kg of body weight 3 times a day.

Notes: Age, Years is the mean age in years, unless otherwise stated.

The following studies also met the inclusion criteria but assessed harms of an off-label medication (compared with placebo) without evidence of efficacy or compared an off-label medication without evidence of efficacy with an FDA-approved medication and are therefore not described further in this Key Question: Florez, 2011,[157] and Florez, 2008.[156]

ACA = acamprosate; CBI = combined behavioral intervention; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DBRCT = double-blind randomized controlled trial; DIS = disulfiram; FDA = U.S. Food and Drug Administration; GHB = γ-Hydroxybuteric acid; med = medium; mg = milligram; MM = medical management; N = sample size; NR = not reported; NTX = naltrexone; OLRCT = open-label randomized controlled trial; SBRCT = single-blind randomized controlled trial; U.S. = United States.

Key Question 4

Table B-17. Characteristics of included randomized controlled trials of FDA-approved medications for treating alcohol dependence in primary care settings

Author, Year	Arm Dose, mg/day (N)	Rx Duration, Weeks (Followup)	Setting	Recruitment Method	Age, Years	% Non-White	% Female	% With Co-occurring Condition	Co-intervention	Risk of Bias
Berger, 2013[11]	ACA 1,998 (51) Placebo (49)	12	U.S., 2 primary care sites	Provider referral and ads	48	9	38	NR	Brief structured behavioral intervention from primary care physician	Medium

Note: Age, Years is the mean age in years, unless otherwise stated. Co-interventions offered to 100% of the sample, unless otherwise stated.

ACA = acamprosate; FDA = U.S. Food and Drug Administration; mg = milligram; N = sample size; NR = not reported; Rx = prescription; U.S. = United States.

Key Question 5

Table B-18. Characteristics of head-to-head medication studies that evaluated subgroups

Author, Year Trial Name Design	Arm Dose, mg/day (N)	Subgroup(s)	Rx Duration, Weeks	Setting	Age, Years	% Non-White	% Female	Co-Intervention	Risk of Bias
Anton, 2006[8] Greenfield, 2010[162] Fucito, 2012[163] COMBINE DBRCT	ACA 3,000 + CBI + MM (151) ACA 3,000 + MM (152) NTX 100 + CBI + MM (155) NTX 100 + MM (154) Placebo + CBI + MM (156) Placebo + MM (153)	Men/women, smokers	68	11 U.S. academic sites	44	23	31	As randomized; community support group participation (like AA) encouraged	Low
Baltieri, 2008[52]; Baltieri, 2009[129] NA DBRCT	TOP target 200, maximum 400 (52) NTX 50 (49) Placebo (54)	Smokers	12	Brazil, outpatient	44 to 45	29	0	Psychosocial	High
Carroll, 1993[164] NA OLRCT	DIS 250 (9) NTX 50 (9)	Cocaine dependence	12	U.S., outpatient substance abuse	32	39	72	Weekly individual psychotherapy	High
De Sousa, 2004[154] NA OLRCT	DIS 250 (50) NTX 50 (50)	Men	52	India, outpatient	43 to 47	NR	0	Supportive group psychotherapy	High
De Sousa, 2005[159] NA OLRCT	ACA 1,998 (50) DIS 250 (50)	Men	35	India, outpatient, private psychiatric hospital	42 to 43	100	0	Weekly supportive group psychotherapy offered	High
Kiefer, 2003[17] Kiefer, 2005[19] NA DBRCT	ACA 1,998 (40) NTX 50 (40) Placebo (40) ACA 1,998 + NTX 50 (40)	Somatic distress, depression, anxiety	12	Germany, 1 site, outpatient	46	NR	26	Group therapy	Low
Morley, 2006[24] Morley, 2010[25] NA DBRCT	ACA 1,998 (55) NTX 50 (53) Placebo (61)	Depression	12	Australia, 3 treatment centers with “medical care typically available at hospital-based drug and alcohol treatment services”	45	NR	30	All offered 4-6 sessions of manualized compliance therapy Uptake/ attendance NR	Low
Petrakis, 2005[40] Ralevski, 2007[41] Petrakis, 2007[42] Petrakis, 2006[43] VA MIRECC DBRCT	DIS 250 (66) NTX 50 (59) Placebo (64) NTX 50 + DIS 250 (65)	Axis I disorders	12	U.S., outpatient VA	47	26	3	Psychiatric treatment as usual	High for DIS vs. NTX

Author, Year Trial Name Design	Arm Dose, mg/day (N)	Subgroup(s)	Rx Dura-tion, Weeks	Setting	Age, Years	% Non-White	% Fe-male	Co-Intervention	Risk of Bias
Pettinati, 2010[98] NA DBRCT	SER 200 (40) NTX 100 (49) Placebo (39) SER 200 + NTX 100 (42)	Depression	14	U.S., outpatient	43	35	38	CBT	Medium

Note: Age, Years is the mean age in years, unless otherwise stated. Co-interventions offered to 100% of the sample, unless otherwise stated.

AA = Alcoholics Anonymous; ACA = acamprosate; CBI = combined behavioral intervention; CBT = cognitive behavioral therapy; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DBRCT = double-blind randomized controlled trial; DIS = disulfiram; mg = milligram; MIRECC = Mental Illness Research, Education and Clinical Center; MM = medical management; N = sample size; NA = not applicable; NR = not reported; NTX = naltrexone; OLRCT = open-label randomized controlled trial; PTSD = posttraumatic stress disorder; SER = sertraline; TOTOP = topiramate; vs. = versus; U.S. = United States; VA = Veterans Affairs.

Harms From Package Inserts

Naltrexone is contraindicated for patients with acute hepatitis or liver failure, those currently using opioids or with anticipated need for opioids, or those who have failed a naloxone challenge test.[165, 166] It can precipitate severe withdrawal for patients dependent on opioids.[165, 166] Precautions are listed in the package insert for other hepatic disease, renal impairment, and history of suicide attempts or depression. Patients should be advised to carry a wallet card to alert medical personnel because larger doses of opioids may be required, and respiratory depression may be deeper and more prolonged if opioid analgesia is needed. Common side effects include nausea, vomiting, decreased appetite, headache, dizziness, fatigue, somnolence, and anxiety. Injectable naltrexone can also cause injection-site reactions. The prescribing information for injectable naltrexone is somewhat different.[166] For example, additional adverse events associated with injectable naltrexone include eosinophilic pneumonia and there is a precaution regarding intramuscular injections for those with coagulation disorders.

Acamprosate is contraindicated for people with severe renal impairment (creatinine clearance 30 mL per minute or less) and requires dose adjustments for moderate renal impairment (creatinine clearance between 30 and 50 mL per minute). Precautions are listed to monitor for depression and suicidal ideation. Common side effects include diarrhea and somnolence.[167]

Disulfiram is contraindicated in patients currently receiving metronidazole, paraldehyde, alcohol-containing preparations or using alcohol.[168] The package insert also includes contraindications in patients with myocardial disease or coronary artery occlusion or psychoses. Precautions are listed for those with hypersensitivity to thiuram derivatives due to dermatitis, severe hepatitis, or hepatic failure. Use in comorbid conditions such as diabetes mellitus, hypothyroidism, epilepsy, cerebral damage, and nephritis is cautioned. Common side effects include drowsiness and bitter taste.

Gabapentin includes warnings for Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), angioedema, effects while operating heavy machinery, increased seizure risk with abrupt discontinuation, and suicidal ideation. A dose adjustment in renal impairment is necessary.[169] Common side effects include somnolence, fatigue, and dizziness.

Ondansetron is contraindicated with concomitant use of apomorphine due to reports of severe hypotension and loss of consciousness of unclear mechanism.[170] Precautions for ondansetron use include QT prolongation and Torsade de Pointes, serotonin syndrome, masking of progressive ileus or gastric distention. Also, the dissolving tablet preparation of ondansetron contains phenylalanine, which contributes to neurological damage in individuals with phenylketonuria. In severe hepatic impairment, an adjustment in total daily dose is necessary. Common adverse reactions include headache, fatigue, constipation, and diarrhea.

According to the package insert,[7] use of topiramate is cautioned in those with acute myopia and secondary angle closure glaucoma, oligohidrosis and hyperthermia, metabolic acidosis, and suicidal ideation.[171] Additional warnings exist for patients with hyperammonemia with concomitant valproic acid use, kidney stones, abrupt discontinuation of the medication, and pregnancy. Dose adjustments are required for renal impairment. The most common side effects are weight loss, paresthesia, fatigue, taste perversion, dizziness, and cognitive effects.

Varenicline's package insert includes warnings for angioedema, somnambulism, serious skin reactions, central nervous system depression leading to accidental injury when operating heavy machinery, and nausea.[172] Postmarketing reports of neuropsychiatric adverse effects such as changes in mood, psychosis, agitation, and suicidal ideation exist along with increased

intoxication effects with concurrent alcohol use. Other use precautions are for those with cardiovascular disease and seizure disorders. Dosage adjustment is required for those with severe renal impairment. Common side effects include nausea, abnormal dreams, constipation, flatulence, and vomiting.

Prazosin has a warning for syncope with sudden loss of consciousness.[173] Precautions for use exist as well, including Intraoperative Floppy Iris Syndrome, priapism, and angina. Common side effects include dizziness, headache, drowsiness, lack of energy, weakness, and palpitations.

Baclofen has a product warning for abrupt discontinuation of the medication, which may cause withdrawal.[174] Additional warnings include use in those with impaired renal function and history of stroke. A dose adjustment is recommended in severe renal impairment. Common side effects include drowsiness, dizziness, weakness, confusion, and nausea.

Excluded Studies

Exclusion Codes:

- X1: Ineligible population
- X2: Ineligible time period
- X3: Ineligible length of follow up
- X4: Ineligible setting
- X5: Ineligible intervention
- X6: Ineligible comparator
- X7: Ineligible outcome
- X8: Ineligible language
- X9: Treatment evidence type or study design
- X10: Duplicate or superseded

1. Safety and Efficacy of Nalmefene in Patients with Alcohol Dependence (SENSE). 2013. Exclusion Code: X5.
2. Study: Topiramate helps some heavy drinkers cut back. Alcoholism & Drug Abuse Weekly. 2014;26(8):6-. PMID: 104035702. Language: English. Entry Date: 20140228. Revision Date: 20150710. Publication Type: Journal Article. Exclusion Code: X9.
3. Topiramate effective for problem drinkers as well as dependent. Brown University Psychopharmacology Update. 2014;25(6):3-4. PMID: 103944902. Language: English. Entry Date: 20140520. Revision Date: 20150710. Publication Type: Journal Article. Journal Subset: Biomedical. Exclusion Code: X9.
4. Safety concern clouds outcome of baclofen study for alcohol dependence. Brown University Psychopharmacology Update. 2018;29(9):4-. doi: 10.1002/pu.30353. PMID: 131134730. Language: English. Entry Date: 20180817. Revision Date: 20190704. Publication Type: Article. Journal Subset: Biomedical. Exclusion Code: X10.
5. Drugs for alcohol use disorder. Med Lett Drugs Ther. 2021 Dec 13;63(1639):193-8. PMID: 35100235. Exclusion Code: X9.
6. Baclofen shows efficacy in alcohol use disorder, mainly at higher dose. Brown University Psychopharmacology Update. 2021;32(10):4-. doi: 10.1002/pu.30780. PMID: 152211613. Language: English. Entry Date: 20210907. Revision Date: 20210907. Publication Type: Article. Exclusion Code: X9.
7. Aldridge AP, Zarkin GA, Dowd WN, et al. The Relationship Between Reductions in WHO Risk Drinking Levels During Treatment and Subsequent Healthcare Costs for the ACTIVE Workgroup. J Addict Med. 2021 Dec 3. doi: 10.1097/adm.0000000000000925. PMID: 34864785. Exclusion Code: X7.
8. Anonymous. Erratum: reduction of alcohol drinking in young adults by naltrexone: a double-blind, placebo-controlled, randomized clinical trial of efficacy and safety (Journal of Clinical Psychiatry (2015) 76: 2 (e207-e213) DOI: 10.4088/JCP.13m08934). Journal of clinical psychiatry. 2018;79(5). PMID: CN-01923062. Exclusion Code: X3.
9. Anthenelli RM, Heffner JL, Bekman N, et al. Does topiramate prevent relapse to alcoholism in the context of smoking cessation treatment? Alcoholism: clinical and experimental research. 2015;39:75A. doi: 10.1111/acer.12741. PMID: CN-01088806. Exclusion Code: X9.

10. Anthenelli RM, Heffner JL, Wong E, et al. A Randomized Trial Evaluating Whether Topiramate Aids Smoking Cessation and Prevents Alcohol Relapse in Recovering Alcohol-Dependent Men. Alcohol Clin Exp Res. 2017 Jan;41(1):197-206. doi: 10.1111/acer.13279. PMID: 28029173. Exclusion Code: X1.

11. Anthenelli RM, Heffner JL, Wong E, et al. A randomized trial evaluating whether topiramate aids smoking cessation and prevents alcohol relapse in recovering alcohol-dependent men. Alcoholism: Clinical and Experimental Research. 2017;41(1):197-206. doi: 10.1111/acer.13279. PMID: 2017-00094-023. Exclusion Code: X10.

12. Anton R, Baros A, Latham P, et al. Naltrexone plus aripiprazole compared to naltrexone alone and placebo in the treatment of alcohol dependence - a double blind pilot study. Neuropsychopharmacology. 2011:Abstract no:S234. PMID: CN-00845465. Exclusion Code: X9.

13. Anton R, Book S, Voronin K, et al. OPRM1 ASP40 interacts with COMT val158met in predicting naltrexone response in an alcohol use disorder randomized clinical trial. Neuropsychopharmacology. 2017;43:S203-S4. doi: 10.1038/npp.2017.264. PMID: CN-01439296. Exclusion Code: X9.

14. Anton R, Latham P, Voronin K, et al. RCT of gabapentin for alcohol use disorder: response based on alcohol withdrawal history. Neuropsychopharmacology. 2019;44:208-9. doi: 10.1038/s41386-019-0545-y. PMID: CN-02119321. Exclusion Code: X9.

15. Anton RF, Book S, Latham P, et al. The effectof smoking on naltrexone efficacy: does OPRM1 asp40 allele status matter? Alcoholism: clinical and experimental research. Conference: 39th annual scientific meeting of the research society on alcoholism. New orleans, LA united states. Conference start: 20160625. Conference end: 20160629. Conference publication: (var.pagings). 2016;40:251A. doi: 10.1111/acer.13085. PMID: CN-01267388. Exclusion Code: X9.

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17. Anton RF, Latham P, Voronin K, et al. Randomized clinical trial of gabapentin for alcohol use disorder: influence of alcohol withdrawal and sleep history. Alcoholism: clinical and experimental research. 2021;45(SUPPL 1):52A-. doi: 10.1111/acer.14617. PMID: CN-02293670. Exclusion Code: X9.

18. Anton RF, Latham PK, Voronin KE, et al. Nicotine-Use/Smoking Is Associated with the Efficacy of Naltrexone in the Treatment of Alcohol Dependence. Alcohol Clin Exp Res. 2018 Apr;42(4):751-60. doi: 10.1111/acer.13601. PMID: 29431852. Exclusion Code: X9.

19. Anton RF, Oroszi G, O'Malley S, et al. An evaluation of mu-opioid receptor (OPRM1) as a predictor of naltrexone response in the treatment of alcohol dependence: results from the Combined Pharmacotherapies and Behavioral Interventions for Alcohol Dependence (COMBINE) study. Arch Gen Psychiatry. 2008 Feb;65(2):135-44. doi: 10.1001/archpsyc.65.2.135. PMID: 18250251. Exclusion Code: X7.

20. Anton RF, Pettinati H, Zweben A, et al. A multi-site dose ranging study of nalmefene in the treatment of alcohol dependence. J Clin Psychopharmacol. 2004 Aug;24(4):421-8. PMID: 15232334. Exclusion Code: X5.

21. Anton RF, Voronin KE, Book SW, et al. Opioid and Dopamine Genes Interact to Predict Naltrexone Response in a Randomized Alcohol Use Disorder Clinical Trial. Alcohol Clin Exp Res. 2020 Oct;44(10):2084-96. doi: 10.1111/acer.14431. PMID: 32772383. Exclusion Code: X7.

22. Arechiga G, Bonilla J, Mendoza I, et al. Naltrexone implants improve therapeutic adherence with multiple substance use disorder. Journal of addiction medicine. 2019;13(3):E13-. doi: 10.1097/ADM.0000000000000548. PMID: CN-01960998. Exclusion Code: X5.

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25. Arias AJ, Gelernter J, Gueorguieva R, et al. Pharmacogenetics of naltrexone and disulfiram in alcohol dependent, dually diagnosed veterans. Am J Addict. 2014 May-Jun;23(3):288-93. doi: 10.1111/j.1521-0391.2014.12102.x. PMID: 24724887. Exclusion Code: X9.

26. Bach P, Weil G, Pompili E, et al. Incubation of neural alcohol cue reactivity after withdrawal and its blockade by naltrexone. Addict Biol. 2020 Jan;25(1):e12717. doi: 10.1111/adb.12717. PMID: 30748046. Exclusion Code: X6.

27. Bajovic B, Zivkovic N, Djokic G, et al. Oxcarbazepine, topiramate and lamotrigine in the treatment of alcohol craving. European neuropsychopharmacology. 2012;22:S65-S6. PMID: CN-01034479. Exclusion Code: X7.

28. Batki S, Pennington D, Meyerhoff D, et al. Pharmacologic therapies for alcohol use disorder and PTSD. Alcoholism: clinical and experimental research. 2015;39:289A. doi: 10.1111/acer.12742. PMID: CN-01102525. Exclusion Code: X10.

29. Batki SL, Lasher BA, Metzler T, et al. Predictors of outcome in a pilot controlled trial of topiramate for alcohol dependence in veteranswith PTSD. Alcoholism: clinical and experimental research. 2013;37:17A. doi: 10.1111/acer.12162. PMID: CN-00974257. Exclusion Code: X10.

30. Batki SL, Pennington DL. Topiramate treatment for alcohol use disorder in veterans with mild traumatic brain injury: a pilot controlled clinical trial. Alcoholism: clinical and experimental research. 2017;Conference: 40th Annual Scientific Meeting of the Research Society on Alcoholism. United States. 41(pp 321A). doi: 10.1111/acer.13392. PMID: CN-01383609. Exclusion Code: X10.

31. Batki SL, Pennington DL, Lasher B, et al. Topiramate treatment for alcohol use disorder in veterans with mild traumatic brain injury: preliminary results of a pilot controlled clinical trial. Alcoholism: clinical and experimental research. 2016;40:162A. doi: 10.1111/acer.13084. PMID: CN-01167558. Exclusion Code: X7.

32. Batki SL, Pennington DL, Lasher BA, et al. Topiramate treatment of alcohol use disorder in veterans with PTSD: preliminary analysis of a controlled trial. Alcoholism: clinical and experimental research. 2020;44:158A-. doi: 10.1111/acer.14356. PMID: CN-02139093. Exclusion Code: X9.

33. Bence C, Cottencin O, Deheul S, et al. Baclofen-induced edema in alcohol use disorders. Journal of Clinical Pharmacology. 2014;54(4):478-81. doi: 10.1002/jcph.233. PMID: 104043746. Language: English. Entry Date: 20140320. Revision Date: 20200708. Publication Type: Journal Article. Exclusion Code: X6.

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39. Brady KT, Myrick H, Henderson S, et al. The use of divalproex in alcohol relapse prevention: a pilot study. Drug Alcohol Depend. 2002 Aug 1;67(3):323-30. PMID: 12127203. Exclusion Code: X5.

40. Brady KT, Sonne S, Anton RF, et al. Sertraline in the treatment of co-occurring alcohol dependence and posttraumatic stress disorder. Alcohol Clin Exp Res. 2005 Mar;29(3):395-401. PMID: 15770115. Exclusion Code: X5.

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Appendix C. Risk-of-Bias Assessments for Included Studies

Table C-1. Risk-of-bias assessment for RCTs of newly included studies

Author, Year	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall RoB	Comments
Anton, 2020[119]	Low	Low	Some concerns	Low	Low	Some concerns	None
Batki, 2014[130]	Some concerns	Low	Low	Low	Low	Some concerns	None
Bejczy, 2015[143]	Low	Low	Some concerns	Low	Low	Some concerns	None
Beraha, 2016[106]	Low	Low	Low	Low	Low	Low	None
Berger, 2013[11]	Low	Low	Some concerns	Low	Low	Some concerns	None
Brown, 2021[125]	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns	None
Chompookham, 2018[120]	Low	Some concerns	High	Low	Low	High	This study had an extremely low completion rate and analyzed completer data only.
Collins, 2021[56] Collins, 2014[57]	Low	Low	Some concerns	Low	Low	Some concerns	None
Cook, 2019[58]	Some concerns	Low	Low	Low	Low	Some concerns	None
Edelman, 2019[59]	Some concerns	Low	Some concerns	Low	Low	Some concerns	None
Falk, 2019[121]	Low	Low	Some concerns	Low	Low	Some concerns	None
Foa, 2013[60] Kaczkurkin, 2016[61]	Some concerns	Some concerns	Some concerns	Low	Low	Some concerns	None
Garbutt, 2021[108]	Some concerns	Low	Some concerns	Low	Low	Some concerns	None
Hauser, 2017[109]	Low	Low	Some concerns	Low	Low	Some concerns	None
Higuchi, 2015[16]	Low	Low	Some concerns	Low	Low	Some concerns	None
Hurt, 2018[144]	Some concerns	Some concerns	High	Low	Low	High	Small study with very high attrition in the placebo group, and not well balanced on marital status, education, and smoking quit attempt history at baseline.
Kampman, 2013[136]	Low	Low	High	Low	Low	High	Dropout was high across the study, with a significant difference in survival time by group.

Author, Year	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall RoB	Comments
Kranzler, 2021[137]	Low	Low	Low	Low	Low	Low	None
Kranzler, 2014[138] Kranzler, 2014[175] Feinn, 2016[176]	Low	Low	Some concerns	Low	Low	Some concerns	None
Krupitskii, 2017[110]	Low	High	High	Low	Low	High	High loss to followup and small sample size.
Leggio, 2015 [111]	High	Some concerns	Some concerns	Low	Low	High	None
Likhitsathian, 2013[139]	Low	Low	High	Low	Low	High	Very high attrition, 52% at 12w
Mason, 2014[122]	Low	Low	Low	Low	Low	Low	None
Morley, 2018 [113] Rombouts, 2019[114] BacALD	Low	Low	Low	Low	Low	Low	None
Morley, 2014[112]	Some concerns	Low	Some concerns	Low	Low	Some concerns	Concerns about the randomization and substantial loss to followup.
Müller, 2015[115]	Low	Low	Low	Low	Low	Low	None
O'Malley, 2018[148] Bold, 2019[149]	Low	Low	Some concerns	Low	Low	Some concerns	None
Pennington, 2020[140]	Low	Low	Low	Low	Low	Low	None
Petrakis, 2016[126] Verplaeste, 2019[127]	Low	Low	Some concerns	Low	Low	Some concerns	None
Pfeifer, 2019 [150]	Some concerns	Some concerns	High	Low	Low	High	This was a very small study with only 20% of the treatment group and none of the placebo group completing the trial.
Plebani, 2013[151]	Some concerns	Low	Low	Low	Low	Some concerns	None
Ponizovsky, 2015[116]	Some concerns	Low	Some concerns	Low	Low	Some concerns	None
Reynaud, 2017[117] ALPADIR	Low	Low	Low	Low	Low	Low	None

Author, Year	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Overall RoB	Comments
Rigal, 2020[118]	Low	Some concerns	Some concerns	Some concerns	Low	Some concerns	None
Simpson, 2018[128]	Low	Low	High	Low	Some concerns	High	Main concern is high and differential attrition, however multiple exploratory analyses left open the possibility of reporting bias.
Springer, 2017[96]	Low	Low	Some concerns	Low	Some concerns	Some concerns	None
Sylvia, 2016[142]	Some concerns	Some concerns	High	Low	Some concerns	High	Very high and differential attrition, very small sample

RCT = randomized controlled trial; RoB = risk of bias.

Table C-2. Risk of bias assessment for RCTs and related secondary/subgroup analyses included in the previous report

Author, Year Trial Name Design	Was Randomization Adequate?	Was Allocation Concealment Adequate?	Were Groups Similar at Baseline?	What Was the Overall Attrition?	What Was the Differential Attrition?	Did the Study Have Overall High Attrition or Differential Attrition Raising Concern for Bias?	Did the Study Have Cross-overs or Contamination Raising Concern for Bias?	Was Intervention Fidelity Adequate?
Addolorato, 2007[105] NA DBRCT	Yes	Yes	Yes	Loss to followup: 14% Total dropouts: 23%	Loss to followup: 9% Total dropouts: 17%	Yes, differential	No	NR/CND
Ahmadi, 2002[44]; Ahmadi, 2004[177] NA DBRCT	NR/CND	NR/CND	NR/CND (no data provided; per authors, groups were similar at baseline)	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND
ALK21-014[104] DBRCT	NR/CND	NR/CND	Yes	37% did not complete; all patients included in analysis	8%	Yes	No	NR/CND
Anton, 1999[46]; Anton, 2001[178] NA DBRCT	NR/CND	NR/CND	Yes	17 (but all but 2 subjects, 1.5%, had week 12 drinking data)	9	No	No	Yes
Anton, 2003[158] COMBINE pilot DBRCT	Yes	NR/CND	Yes	31% discontinued	11% to 20%	Yes	No	Yes
Anton, 2005[48] NA DBRCT	NR/CND	NR/CND	Yes	19% did not complete trial; 15% did not have complete; 12 week drinking data	9 to 11	No	No	Yes

Author, Year Trial Name Design	Was Randomization Adequate?	Was Allocation Concealment Adequate?	Were Groups Similar at Baseline?	What Was the Overall Attrition?	What Was the Differential Attrition?	Did the Study Have Overall High Attrition or Differential Attrition Raising Concern for Bias?	Did the Study Have Cross-overs or Contamination Raising Concern for Bias?	Was Intervention Fidelity Adequate?
Anton, 2006[8] Donovan, 2008[9] LoCastro, 2009[152] Greenfield, 2010[162] Fucito, 2012[163] COMBINE DBRCT	Yes	Yes	Yes	6 (16 wks) 18 (1 year)	7 (1 year)	No	No	Yes
Anton, 2011[50] NA DBRCT	NR/CND	NR/CND	Yes	3% had no drinking data; 35% did not complete treatment;12 to 18% provided drinking data for all 16 weeks	1% for no drinking data; 10% for not completing treatment; 6% for providing drinking data for all 16 weeks	No	No	NR/CND
Balldin, 2003[51] NA DBRCT	Yes	Yes	Yes	22% terminated the study early; 9% had missing drinking data	NR/CND	No	No	Yes
Baltieri, 2004[10] NA DBRCT	NR/CND	NR/CND	Yes	23	5	No	NR/CND	NR/CND
Baltieri, 2008[52]; Baltieri, 2009[129] NA DBRCT	Yes	Yes	Yes	45	4.3, 16.6, and 20.9 differences between each pair of groups	Yes	Yes	NR/CND
Berger, 2013[11] DBRCT	Yes	Yes	Yes, for most characteristics	19%	5%	No	No	Yes

Author, Year Trial Name Design	Was Randomization Adequate?	Was Allocation Concealment Adequate?	Were Groups Similar at Baseline?	What Was the Overall Attrition?	What Was the Differential Attrition?	Did the Study Have Overall High Attrition or Differential Attrition Raising Concern for Bias?	Did the Study Have Cross-overs or Contamination Raising Concern for Bias?	Was Intervention Fidelity Adequate?
Besson, 1998[12] NA DBRCT	NR/CND	NR/CND	Yes	30 at 90 days; 65 at 360 days	6 at 90 days; 0 at 360 days	No at 90 days; Yes by 360 days	Yes	NR/CND
Brown, 2009[54] NA DBRCT	NR/CND	NR/CND	Mixed	48	17	Yes	Yes	NR/CND
Carroll, 1993[164] NA OLRCT	NR/CND	NR/CND	NR/CND-study says groups were comparable, but data not presented.	67	22	Yes	No	Yes
Chick, 2000[13] NA DBRCT	NR/CND	NR/CND	Yes	16% not interviewed at end of medication phase; 32% lost to followup or missed many appointments; 65% did not complete 6-month study	5% for lost to followup or missed many appointments	No	No	Yes
Chick, 2000[55] NA DBRCT	NR/CND	NR/CND	Yes	19% lost to followup; 59% did not complete 12 weeks36	1% for lost to followup and for completing 12 weeks	Yes	No	Yes
Corrêa Filho, 2013[124] DBRCT	Yes	NR/CND	Yes	50%	16%	Yes	No	NR/CND
De Sousa, 2004[154] NA OLRCT	Yes	No	Yes	3	2	No	NR/CND	NR/CND

Author, Year Trial Name Design	Was Randomization Adequate?	Was Allocation Concealment Adequate?	Were Groups Similar at Baseline?	What Was the Overall Attrition?	What Was the Differential Attrition?	Did the Study Have Overall High Attrition or Differential Attrition Raising Concern for Bias?	Did the Study Have Cross-overs or Contamination Raising Concern for Bias?	Was Intervention Fidelity Adequate?
De Sousa, 2005[159] NA OLRCT	NR/CND	No	Yes	7	2	No	No	Yes
Florez, 2008[156] NA OLRCT	NR/CND	NR/CND	No	10	4	No	No	Yes
Florez, 2011[157] NA OLRCT	NR/CND	NR/CND	Yes	9	5	No	No	Yes
Fogaca, 2011[62] NA DBRCT	NR/CND	NR/CND	NR/CND	46	15% (between PUFAs group and NTX+PUFAs); 0% (between NTX and placebo groups as both were 45% attrition)	Yes	No	NR/CND
Fuller, 1979[37] NA DBRCT	Yes	NR/CND	NR/CND (no data provided; per authors, groups were similar at baseline)	2% for final assessment after 1 year; 18% for regular bimonthly and final assessments	NR/CND	No	No	Yes
Fuller, 1986[38] NA DBRCT	Yes	Yes	Yes	5	<5% across three groups	No	No	Yes
Garbutt, 2005[63] NA DBRCT	Yes	Yes	Yes	39% did not complete; 13% lost to followup	1%; 3%	Yes	NR/CND	NR/CND
Garbutt, 2010[107] NA DBRCT	Yes	NR/CND	Yes	24	8	No	No	NR/CND

Author, Year Trial Name Design	Was Randomization Adequate?	Was Allocation Concealment Adequate?	Were Groups Similar at Baseline?	What Was the Overall Attrition?	What Was the Differential Attrition?	Did the Study Have Overall High Attrition or Differential Attrition Raising Concern for Bias?	Did the Study Have Cross-overs or Contamination Raising Concern for Bias?	Was Intervention Fidelity Adequate?
Gastpar, 2002[66] NA DBRCT	NR/CND	NR/CND	Yes	36% did not complete (19% failed to return/lost to followup, 8% withdrew consent, 4% AEs, 1% protocol violations, 4% other reasons)	5	Yes	No	NR/CND
Geerlings, 1997[14] NA DBRCT	NR/CND	NR/CND	Yes	15% lost to followup; 64% did not complete the study (most common reason was relapse leading to hospitalization)	1% lost to followup; 10% for completing the study	No	No	Yes
Gual, 2001[15] NA DBRCT	NR/CND	NR/CND	Yes	16% lost to followup; 35% non-completers	4% lost to followup; 7% non-completers	No	No	Yes
Guardia, 2002[67] NA DBRCT	NR/CND	NR/CND	Yes	5% did not have assessable data; 26% dropout, treatment refusal, or other reasons for not completing; 41% total did not complete the study for any reason	0%; 7%; 2	Yes	Possible contamination due to allowed SSRIs	NR/CND
Heinala, 2001[68] NA DBRCT	NR/CND	NR/CND	NR/CND	32% did not complete study	NR/CND	Yes	NR/CND	NR/CND
Huang, 2005[69] NA DBRCT	NR/CND	NR/CND	Yes	No data for primary outcome: 20 Non-completers: 40	No data for primary outcome: 10% Non-completers: 10%	No	NR/CND	NR/CND

Author, Year Trial Name Design	Was Randomization Adequate?	Was Allocation Concealment Adequate?	Were Groups Similar at Baseline?	What Was the Overall Attrition?	What Was the Differential Attrition?	Did the Study Have Overall High Attrition or Differential Attrition Raising Concern for Bias?	Did the Study Have Cross-overs or Contamination Raising Concern for Bias?	Was Intervention Fidelity Adequate?
Johnson, 2003[131] Ma, 2006[132]; Johnson, 2004[133] NA DBRCT	Yes	NR/CND	Yes	35% did not complete; 5% not assessed for outcomes at all; unclear amount of missing data	9; 2; unclear for missing data	CND	No	NR/CND
Johnson, 2004[70] NA DBRCT	NR/CND	NR/CND	No	30	12	Yes	NR/CND	NR/CND
Johnson, 2007[134] Johnson, 2008[135] NA DBRCT	Yes	Yes	Yes	Loss to followup: 6% Non-completers: 31%	Loss to followup: 4% Non-completers: 15%	Yes	No	Yes
Kiefer, 2003[17] Kiefer, 2005[19] NA DBRCT	Yes	Yes	Yes, for most characteristics; Drug arms had slightly more severe problems on some alcohol measures	0 lost to followup; 11% dropout; 53% did not complete trial (most because of relapse)	0 for lost to followup; 40% for completion of trial (because 75% of the placebo group relapsed and did not complete)	No	No	NR/CND
Killeen, 2004[72] NA DBRCT	Yes	NR/CND	No	28	9	No	NR/CND	NR/CND
Kranzler, 2004[73] NA DBRCT	NR/CND	Yes	Yes	22	5	No	NR/CND	Yes
Kranzler, 2009[74] NA DBRCT	NR/CND	NR/CND	NR/CND	15	NR/CND	No	NR/CND	Yes

Author, Year Trial Name Design	Was Randomization Adequate?	Was Allocation Concealment Adequate?	Were Groups Similar at Baseline?	What Was the Overall Attrition?	What Was the Differential Attrition?	Did the Study Have Overall High Attrition or Differential Attrition Raising Concern for Bias?	Did the Study Have Cross-overs or Contamination Raising Concern for Bias?	Was Intervention Fidelity Adequate?
Krystal, 2001[75] VACS 425 DBRCT	NR/CND	NR/CND	Yes	27% did not complete; 22% did not have complete data and 10% did not have complete or partially complete data for drinking at week 13	NR/CND; 2%; 1%	No	No	NR/CND
Laaksonen, 2008[155] NA OLRCT	Yes	NR/CND	Yes for most variables; no for smoking	25% at 12 weeks (continuous med phase); 52% at 52 weeks (after targeted med phase)	7% at 12 weeks; 5% at 52 weeks	No at 12 weeks; Yes at 52 weeks	Np	Yes
Latt, 2002[76] NA DBRCT	Yes	NR/CND	Yes	31% lost to followup; 0% excluded from analyses	3%; 0%	Yes	No	NR/CND
Lee, 2001[77] NA DBRCT	NR/CND	NR/CND	Yes	66% did not complete 12 weeks; 26% did not have any drinking data	18%; 15%	Yes	No	Yes
Lhuintre, 1985[20] NA DBRCT	NR/CND	NR/CND	NR/CND; only age, ggt and MCV level reported	11% lost to followup; 18% did not complete	2% for lost to followup; 7% for did not complete	No	Yes	NR/CND
Lhuintre, 1990[21] NA DBRCT	NR/CND	NR/CND	Yes	37% dropouts	<1% dropouts	Yes	No	NR/CND
Ling, 1983[39] NA DBRCT	NR/CND	NR/CND	NR/CND	57% did not complete 12 week study; 55% lost to followup	3% for completion of study; 22% for lost to followup	Yes	No	NR/CND

Author, Year Trial Name Design	Was Randomization Adequate?	Was Allocation Concealment Adequate?	Were Groups Similar at Baseline?	What Was the Overall Attrition?	What Was the Differential Attrition?	Did the Study Have Overall High Attrition or Differential Attrition Raising Concern for Bias?	Did the Study Have Cross-overs or Contamination Raising Concern for Bias?	Was Intervention Fidelity Adequate?
Litten, 2013[145] DBRCT	Yes	NR/CND	Yes	10% discontinued completely; additional 5% discontinued medication but remained in study; 1% not included in analyses	8% overall	No	No	NR/CND
Longabaugh, 2009[78] NA DBRCT	Yes	NR/CND	No	18	NR/CND for the 4 groups; 0% for those receiving BST vs. MET	No	NR/CND	NR/CND
Mann, 2012[22] PREDICT DBRCT	Yes	NR/CND	Yes	34% discontinued; <1% not included in analyses	0% to 2%	Yes	No, since cross-overs were considered to have discontinued	Yes
Mason, 2006[23] NA DBRCT	Yes	Yes	Yes	Loss to followup: 13% Non-completers: 51%	Loss to followup: 6% Non-completers: 14%	No	No	Yes
Monterosso, 2001[79] NA DBRCT	NR/CND	NR/CND	NR/CND	17	NR/CND	No	No	Yes
Monti, 2001[80]; Rohsenow, 2007[179]; Rohsenow, 2000[82] NA DBRCT	NR/CND	NR/CND	NR/CND	9 to 13	NR/CND	No	No	Yes
Morgenstern, 2012[83] NA DBRCT	Yes	NR/CND	No, but relatively small differences	16% discontinued treatment; 7% were unavailable for followup.	4	No	No	Yes

Author, Year Trial Name Design	Was Randomization Adequate?	Was Allocation Concealment Adequate?	Were Groups Similar at Baseline?	What Was the Overall Attrition?	What Was the Differential Attrition?	Did the Study Have Overall High Attrition or Differential Attrition Raising Concern for Bias?	Did the Study Have Cross-overs or Contamination Raising Concern for Bias?	Was Intervention Fidelity Adequate?
Morley, 2006[24] Morley, 2010[25] NA DBRCT	Yes	NR/CND	Yes	Loss to followup or unwilling to continue: 12% Non-completers: 31%	Loss to followup or unwilling to continue: 5% Non-completers: 9%	No	NR/CND	Yes
Morris, 2001[85] NA DBRCT	NR/CND	NR/CND	No	36% did not complete; 20% dropout for reasons other than relapse	10%; 3%	No	No	NR/CND
Nava, 2006[160] NA OLRCT	Yes	NR/CND	Yes	31	17	Yes	NR/CND	CND
O'Malley, 1992[86]; O'Malley, 1996[180] NA DBRCT	NR/CND	NR/CND	No	35% did not complete; 7% were not included in analyses	8% for did not complete (NTX vs. placebo); 9.6% for inclusion in analyses (NTX vs. placebo)	No	No	Yes
O'Malley, 2007[88] NA DBRCT	NR/CND	NR/CND	Yes	23	1.2	No	No	NR/CND
O'Malley, 2008[89] NA DBRCT	NR/CND	NR/CND	Yes	33% did not complete; 25% unable to contact or declined further contact or moved	15	Yes	No	Yes
Oslin, 1997[90] NA DBRCT	NR/CND	NR/CND	Yes	39% did not complete; 20% with some missing data (lost to followup or dropped out)	10%; 7%	No	No	Yes

Author, Year Trial Name Design	Was Randomization Adequate?	Was Allocation Concealment Adequate?	Were Groups Similar at Baseline?	What Was the Overall Attrition?	What Was the Differential Attrition?	Did the Study Have Overall High Attrition or Differential Attrition Raising Concern for Bias?	Did the Study Have Cross-overs or Contamination Raising Concern for Bias?	Was Intervention Fidelity Adequate?
Oslin, 2008[91] NA DBRCT	NR/CND	NR/CND	No	23	5 (for all NTX vs. all placebo)	No	No	Yes
Paille, 1995[26] NA DBRCT	NR/CND	NR/CND	Yes	13.9% lost to followup; 56% did not complete 12 months (top reason was relapse)	2% for loss to followup	No	No	Yes
Pelc, 1996[27]; Pelc, 1992[28] DBRCT	NR/CND	NR/CND	Yes	45% lost to followup by day 90; 65% by day 180	17%; 21%	Yes	No	NR/CND
Pelc, 1997[29] NA DBRCT	NR/CND	NR/CND	NR/CND ("no statistical differences" was reported, but data not provided)	37% did not complete the study; 14% lost to followup	18% for not completing; 14.7% for lost to followup	No	No	Yes
Petrakis, 2004[92]; Ralevski, 2006[93] NA DBRCT	NR/CND	NR/CND	Yes	19	12	No	No	NR/CND
Petrakis, 2005[40] Ralevski, 2007 [41] Petrakis, 2007[42] Petrakis, 2006[43] VA MIRECC DBRCT	NR/CND	NR/CND	Yes for most characteristic; No for number of other psych meds	11% without 12-week outcome data	2 to 7	No	Yes: some concern for contamination from additional psychiatric medications	NR/CND

Author, Year Trial Name Design	Was Randomization Adequate?	Was Allocation Concealment Adequate?	Were Groups Similar at Baseline?	What Was the Overall Attrition?	What Was the Differential Attrition?	Did the Study Have Overall High Attrition or Differential Attrition Raising Concern for Bias?	Did the Study Have Cross-overs or Contamination Raising Concern for Bias?	Was Intervention Fidelity Adequate?
Pettinati, 2008[97] NA DBRCT	NR/CND	NR/CND	Yes	36% did not complete	10	Yes	No	Yes
Pettinati, 2010[98] NA DBRCT	Yes	NR/CND	Yes	43 (did not complete study, but just 3/170 subjects had no data for drinking outcomes)	6.5	Yes	No	Yes
Poldrugo, 1997[30] NA DBRCT Poldrugo, 1997[30] NA DBRCT (continued)	NR/CND	NR/CND	Yes	4% lost to followup; 55% did not complete 6 months (top reasons were severe relapse, non-compliance, and refusal to continue	0 for lost to followup; 15% for completing 6 months (most of difference accounted for by higher severe relapse rate in placebo group)	No	No	NR/CND
Ralevski, 2011[31] Ralevski, 2011[32] NA DBRCT	NR/CND	NR/CND	Yes, except all 4 women were randomized to the placebo group	35	NR/CND	Yes	No	NR/CND
Rubio, 2001[161] NA SBRCT	Yes	NA (open-label trial)	Yes	17	13	No	Yes	Yes
Rubio, 2009[141] NA DBRCT	NR/CND	NR/CND	Yes	17	2	No	No	NR/CND

Author, Year Trial Name Design	Was Randomization Adequate?	Was Allocation Concealment Adequate?	Were Groups Similar at Baseline?	What Was the Overall Attrition?	What Was the Differential Attrition?	Did the Study Have Overall High Attrition or Differential Attrition Raising Concern for Bias?	Did the Study Have Cross-overs or Contamination Raising Concern for Bias?	Was Intervention Fidelity Adequate?
Sass, 1996[33] NA DBRCT	NR/CND	Yes	Yes	20% lost to followup; 51% did not complete 48 weeks50	1.5% for lost to followup; 18% for completing	No	No	Yes
Schmitz, 2004[99] NA DBRCT	NR/CND	NR/CND	No	69% did not complete 12 weeks of treatment; lost to followup/missing data NR; mean sessions attended: 10.3	NR/CND	Yes	NR/CND	NR/CND
Schmitz, 2009[100] NA DBRCT	Yes	Yes	No	76% completed 12 weeks; 60% completed 6 weeks; lost to followup/missing data NR	NR (but median survival times before dropout were similar)	Yes	NR/CND	NR/CND
Tempesta, 2000[34] NA DBRCT	NR/CND	NR/CND	Yes, for most characteristic; not for previous treatment for alcoholism No (see comment)	26% did not complete; 9% for lost to followup	2%; 0% for lost to followup	No	No	Yes
Volpicelli, 1995[101] NA DBRCT	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND	NR/CND	No	Yes
Volpicelli, 1997[103] NR DBRCT	Yes	NR/CND	Yes	27% did not complete	0	No	No	NR/CND (for therapy co-intervention); Yes for medication

Author, Year Trial Name Design	Was Randomization Adequate?	Was Allocation Concealment Adequate?	Were Groups Similar at Baseline?	What Was the Overall Attrition?	What Was the Differential Attrition?	Did the Study Have Overall High Attrition or Differential Attrition Raising Concern for Bias?	Did the Study Have Cross-overs or Contamination Raising Concern for Bias?	Was Intervention Fidelity Adequate?
Whitworth, 1996[35] NA DBRCT	Yes	Yes	Yes	15% for loss to followup; 60% did not complete double-blind treatment	1.4% for lost to followup	No	No	Yes
Wolwer, 2011[36] NA DBRCT	NR/CND	Yes	Yes, except for fewer women in IBT + placebo group	~20 lost to followup; 55% did not complete (most due to relapse)	4	No	No	NR/CND

AE = adverse event; BST = broad spectrum treatment; CND = cannot determine; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DBRCT = double-blind randomized controlled trial; ESENSE/SENSE = Safety and Efficacy of Nalmefene in Patients With Alcohol Dependence; IBT = integrative behavior therapy; MCV = mean corpuscular volume; MET = motivational enhancement therapy; MIREC = Mental Illness Research, Education and Clinical Center; NA = not applicable; NR = not reported; NTX = naltrexone: OLRCT = open-label randomized controlled trial; PUFA = polyunsaturated fatty acid; RCT = randomized controlled trial; SBRCT = single-blind randomized controlled trial; VA = Veterans Affairs; VACS = Veterans Affairs Cooperative Study.

Table C-3. Continued risk of bias assessment for RCTs and related secondary/subgroup analyses from previous report

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Addolorato, 2007[105] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Medium	Some concern for attrition bias due to differential attrition, and because most subjects counted as relapses in the placebo group were those who dropped out or did not followup (accounted for 10/21 relapses) rather than those with actual outcome data confirming relapse
Ahmadi, 2002[44]; Ahmadi, 2004[177] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	NR/CND	Unclear	Unclear risk of bias due to limited reporting of methods; methods of randomization, allocation concealment, and handling of missing data NR; baseline characteristics of groups and loss-to-followup data NR. Primary outcome was abstinence (completers); those who relapsed were noncompleters. It is not clearly stated whether outcome data are available for all participants or whether those who were not available for followup were considered to be relapsed.
ALK21-014[104] DBRCT	NR/CND	Yes	Yes	Yes	Yes	Yes	NR/CND	Medium	All information came from clinicaltrials.gov; study not yet published
Anton, 1999[46]; Anton, 2001[178] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	None
Anton, 2003[158] COMBINE pilot DBRCT	No	Yes	Yes	Yes	Yes	Yes	NR/CND	Medium	None
Anton, 2005[48] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	NR/CND	Medium	Therapists were blind to drug assignment but not therapy type, and since the drug is our treatment of interest, we considered the care providers masked.

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Anton, 2006[8] Donovan, 2008[9] LoCastro, 2009[152] Greenfield, 2010 [162] Fucito, 2012 [163] COMBINE DBRCT	Yes	Yes to meds, no to psychosocial treatment	Yes	Yes	Yes	Yes	Yes	Low	None
Anton, 2011[50] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	No	No	Medium	Note on statistical methods and missing data: 4 postrandomizations excluded; missing data due to dropout censored, but very low percentage of subjects
Balldin, 2003[51] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	None
Baltieri, 2004[10] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	All missing data entered as nonabstinent; the ASI includes a field for "Alcohol-any use at all" allowing a reasonably valid and reliable ascertainment
Baltieri, 2008[52]; Baltieri, 2009[129] NA DBRCT	NR/CND	Yes	Yes	Yes	NR/CND	Yes	Yes	High	High risk of selection bias and confounding; high overall attrition (45% did not complete the 12-week study) and differential attrition; Concern for contamination as the groups had differences in rates of AA participation (the authors provide some adjusted analyses to attempt to address this); Those with insufficient adherence were dropped from the study; Some concern for measurement bias as the study did not report using TLFB method to ascertain drinking outcomes (used self-report to ascertain quantity and frequency, but further details of method NR)

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Berger, 2013[11] DBRCT Berger, 2013[11] DBRCT (continued)	Yes	Yes	Yes	Yes	Yes	Yes	No	Medium	Some baseline differences between groups for current tobacco use and previous alcohol treatment (although not statistically significant); nothing done to handle missing data; no data imputation was performed, but they had relatively little missing data (19% lost to followup) and it was nondifferential.
Besson, 1998[12] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Use of disulfiram (voluntary, not randomized) was allowed; randomization was stratified by disulfiram use. Missing data was assumed to be relapse.
Brown, 2009[54] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	No	No	High	High risk of selection bias and confounding; 7 out of 50 post-randomization exclusions; 48% of subjects did not complete the study; inadequate handling of missing data; Groups similar at baseline for demographics, but higher proportion of anticonvulsant, antidepressant, and sedative/hypnotic use in the naltrexone group; methods of randomization and allocation concealment NR; allowed adjustment of medications or addition of new medications raising some concern for contamination
Carroll, 1993[164] NA OLRCT	NR/CND	Yes	No	No	Yes	Yes	No	High	Very high rate of attrition; inadequate description of how missing data was handled.
Chick, 2000[13] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	None
Chick, 2000[55] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	None

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Corrêa Filho, 2013[124] DBRCT	NR/CND	Yes	Yes	Yes	Yes	Yes	Yes	High	Very high overall attrition (50%) and high differential attrition; methods of allocation concealment not reported
De Sousa, 2004[154] NA OLRCT	Yes	No	No	No	Yes	Yes	Drop-out considered relapse	High	No allocation concealment; no masking; open label trial
De Sousa, 2005[159] NA OLRCT	NR/CND	No	No	No	NR/CND	Yes	Yes	High	Methods of randomization (by the "qualified statistician") NR; no allocation concealment; High risk of ascertainment bias; no masking; Open-label trial comparing disulfiram and acamprosate; potentially had more effort to ensure adherence in the disulfiram group
Florez, 2008[156] NA OLRCT	Yes	No	No	No	Yes	Yes	Yes, for consumption and composite measure (assumed relapse); No, for quality of life measures and other outcomes (nothing done to handle missing data)	High	Open label; no masking; some baseline differences between groups that may bias results in favor of topiramate—including more nicotine addiction in the naltrexone group, higher proportions of family history of alcoholism, personality disorders, and higher alcohol intake; baseline means on some scales show trends toward worse scores for naltrexone (Fagerstrom, OCDS, most EuropASI subscales, EQ-5D); methods of randomization and allocation concealment NR

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Florez, 2011[157] NA OLRCT	Yes	NR/CND	No	No	Yes	Yes	NR/CND	High	Open-label trial of topiramate and naltrexone; no masking of patients, providers or outcome assessors; unclear method of randomization and allocation concealment; For missing data, they report assuming that subjects resumed heavy drinking, but not what was done for the quality of life outcomes that we would be interested in from this article (it's not eligible for our KQ 1b because it's open label)
Fogaca, 2011[62] NA DBRCT	NR/CND	NR/CND	Yes	Yes	NR/CND	No	No	High	High risk of attrition bias, completer's analysis (excluded 37/80 patients after randomization); methods of randomization and allocation concealment NR; unclear method of measurement for consumption outcomes
Fuller, 1979[37] NA DBRCT	No	Yes	Yes	Partially	Yes	Yes	NR/CND	Medium	Subjects receiving 250 or 1 mg doses of disulfiram were masked to the dose they received, but told they were receiving disulfiram (aim was to control for implied threat of the disulfiram-ethanol reaction); subjects receiving riboflavin were told they were not receiving disulfiram

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Fuller, 1986[38] NA DBRCT	No	Yes	Yes	Partially	Yes	Yes	No	Medium	Subjects receiving 250 or 1 mg doses of disulfiram were masked to the dose they received, but told they were receiving disulfiram (aim was to control for implied threat of the disulfiram-ethanol reaction); subjects receiving riboflavin were told they were being given a vitamin; missing data censored (if no interview obtained, they were considered to be abstinent until censored) and did not impute assumed lapse/relapse, but relatively little missing data.
Garbutt, 2005[63] NA DBRCT	See comment	Yes	Yes	Yes	Yes	Yes	No	Medium	64% received all 6 injections; 74% received at least 4 injections. Moderate risk of attrition bias due to dropouts, but nondifferential.
Garbutt, 2010[107] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	None
Gastpar, 2002[66] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	Medium	None
Geerlings, 1997[14] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Although his study had a high rate of non-completers, they have followup information for most of those subjects, and all subjects were considered to be nonabstinent for the period during which there was missing data.
Gual, 2001[15] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	None

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Guardia, 2002[67] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	No	Medium	Risk of attrition bias, but nondifferential; some were excluded post-randomization and not evaluated; apparently censored dropouts in the survival analysis.
Heinala, 2001[68] NA DBRCT	NR/CND	NR/CND	NR/CND	Yes	Yes	NR/CND	NR/CND	High	High risk of selection bias, attrition bias, and confounding. No description of randomization, allocation concealment, outcome assessor masking, or details of statistical methods. Methods section does not include any information on statistical analyses. Patient characteristics according to treatment group NR. High rate of overall attrition with no reporting of differential attrition and inadequate description of how missing data was handled.
Huang, 2005[69] NA DBRCT Huang, 2005[69] NA DBRCT (continued)	NR/CND	NR/CND	Yes	Yes	NR/CND	CND	CND	High	High risk of measurement bias and confounding; statistical methods don't report whether they used an ITT or completer's analysis; no description of approach to handling missing data; methods of randomization and allocation concealment NR; no description of ascertainment methods for drinking quantity and frequency; relatively few subjects with missing data because they interviewed those who did not complete the study visits and were able to determine that many of them relapsed, they ultimately had outcome data for 80% of subjects.

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Johnson, 2003[131] Ma, 2006[132]; Johnson, 2004[133] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	CND	Medium	No completely clear how much missing data for consumption outcomes there was; methods of handling missing data—used data reduction technique taking mean of weeks 1 through 12, weighted by number of study weeks completed with non-missing data; unclear how this would compare with imputing heavy drinking for missing data
Johnson, 2004[70] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	NR/CND	NR/CND	High	High risk of selection bias and confounding. Groups were not similar at baseline, with differences for sex and higher baseline heavy drinking days for the placebo group. Not surprising that groups were different at baseline in this small, pilot study with 25 NTX subjects and 5 placebo subjects. High attrition. Methods of statistical analyses and handling of missing data NR.

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Johnson, 2007[134] Johnson, 2008[135] NA DBRCT Johnson, 2007[134] Johnson, 2008[135] NA DBRCT (continued)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	High differential attrition, with 61.2% completing the trial in the topiramate group compared with 76.6% in the placebo group, but not concerned that introduces significant risk of bias because they have outcome information for most of the non-completers and imputed missing data with baseline values (which were all heavy drinking), so the analysis would be likely to underestimate the benefit of topiramate, if anything; also, few subjects were actually lost to followup; statistical analysis methods and approach to handling missing data were good.
Kiefer, 2003[17] Kiefer, 2005[19] NA DBRCT	NR/CND	Yes	Yes	Yes	Yes	Yes	Yes	Low	None
Killeen, 2004[72] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	NR/CND	Medium	None
Kranzler, 2004[73] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	None
Kranzler, 2009[74] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Methods of randomization and allocation concealment NR; unclear if outcome assessors were masked; very little baseline information reported to allow comparing the two groups at baseline

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Krystal, 2001[75] VACS 425 DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	Medium	Inadequate handling of missing data, but relatively low % without complete or partial data (10%) that were not included in the analyses, and nondifferential missing data.
Laaksonen, 2008[155] NA OLRCT Laaksonen, 2008[155] NA OLRCT (continued)	Yes for NTX and ACA during continuous phase; No for DIS (67.5%)	NR/CND	No	No	Yes	Yes for some outcomes; no for others (see comments)	No	High for quality of life/KQ 2 outcomes	Open-label trial; no masking; Quality of life outcomes were reported for the 52 week time point (with less than 50% of subjects reaching that time point); inadequate handling of missing data for AUDIT, SADD, QoL measures (per-protocol analysis including patients that completed the study); used ITT for primary outcomes (consumption outcomes) but study is not eligible for KQ 1 because it is open label.
Latt, 2002[76] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	NR/CND	Medium	Moderate risk of attrition bias; unclear how missing values were imputed for some analyses
Lee, 2001[77] NA DBRCT	NR/CND	NR/CND	Yes, but NTX and placebo pills not identical	Yes	Yes	No	No	High	High risk of selection bias and confounding; high rate of overall and differential attrition; inadequate handling of missing data; methods of randomization and allocation concealment NR; LOCF analysis used which included some, but not all non-completers

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Lhuintre, 1985[20] NA DBRCT	NR/CND	NR/CND	Yes	Yes	NR/CND	No	No	High	High risk of selection bias and confounding; medium to high risk of ascertainment bias; completers-only analysis (70/85 randomized subjects in the analysis); methods of randomization, allocation concealment, and consumption outcome assessment NR; inadequate handling of missing data; some concern for contamination because of the use of meprobamate; unable to assess similarity of groups at baseline
Lhuintre, 1990[21] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	NR/CND	NR/CND	Unclear	Unclear analytic methods and methods of handling missing data; some indications that this is a completers analysis, but unclear; 37% of study participants dropped out; although nondifferential attrition. Methods of randomization, allocation concealment, and masking of outcome assessors NR.
Ling, 1983[39] NA DBRCT	NR/CND	NR/CND	Yes	Yes	NR/CND	Yes	No for most outcomes; Yes for return to heavy drinking	High	High risk of selection bias and confounding, primarily due to attrition; very high overall and differential loss to followup; inadequate handling of missing data for most outcomes (e.g., completers analysis for everything in the Table); methods of randomization, allocation concealment, and masking outcome assessors NR; unclear whether consumption outcomes used valid and reliable measures (just reports that it was self-report, but no description of timeline follow back or other details).
Litten, 2013[145] DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Low	None

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Longabaugh, 2009[78] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	No	Medium	Moderate risk of selection bias and confounding; inadequate handling of missing data; Excluded 32/174 (18.4%) randomized subjects from analyses, although nondifferential; some baseline differences between the four groups for marital status, education, abstinent days and heavy drinking days in previous 90 days (possibly a result of not using the sample that was randomized, which may have undermined the randomization); methods of allocation concealment NR
Mann, 2012[22] PREDICT DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	High attrition and marginal adherence, but use of worst-case imputation
Mason, 2006[23] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	None
Monterosso, 2001[79] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	None
Monti, 2001[80]; Rohsenow, 2007[179]; Rohsenow, 2000[82] NA DBRCT	No	Yes	Yes	Yes	Yes	Yes	Yes	Medium	Rated on basis of medication part of the study (not the preceding psychological treatment part)
Morgenstern, 2012[83] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	Medium	None
Morley, 2006[24] Morley, 2010[25] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	None

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Morris, 2001[85] NA DBRCT	Yes	Yes	Yes	Yes	Yes	Yes	No	Medium	Some baseline differences, with NTX patients drinking 15 more drinks/wk than placebo; inadequate handling of missing data
Nava, 2006[160] NA OLRCT	CND	No	No	No	Yes	No	No	High	Completers analysis; inadequate handling of missing data; all patients who relapsed were excluded from the analyses; high overall and differential attrition; open-label trial with no masking
O'Malley, 1992[86]; O'Malley, 1996[180] NA DBRCT	Yes	Yes	Yes (to medication, not therapy)	Yes	Yes	Yes	Mixed	Medium	Subjects randomized to supportive therapy had more severe alcohol problems and drank more alcohol per occasion during baseline compared to those randomized to supportive psychotherapy; inadequate handling of missing data for some analyses; methods of randomization and allocation concealment NR.
O'Malley, 2007[88] NA DBRCT O'Malley, 2007[88] NA DBRCT (continued)	Yes, when calculation based on number of days in treatment	Yes	Yes	Yes	Yes	Yes	Yes	Medium	Methods of randomization and allocation concealment NR; our attrition calculations based on having complete timeline data
O'Malley, 2008[89] NA DBRCT	No	Yes	Yes	Yes	Yes	Yes	Yes	Medium	Methods of randomization and allocation concealment NR; 33% did not complete study; adherence was 59 to 67% across groups
Oslin, 1997[90] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	NR/CND	Medium	Unclear handling of missing data, but nondifferential missing data; methods of randomization and allocation concealment NR

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Oslin, 2008[91] NA DBRCT	No	Yes	Yes	Yes	Yes	Yes	Yes	Medium	Methods of randomization and allocation concealment NR; some baseline differences between groups (race), but analyses adjusted for age, race, gender, pretreatment percent of HDDs; only 50% adhered to medication across conditions
Paille, 1995[26] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Study counted those lost to followup as not abstinent.
Pelc, 1996[27]; Pelc, 1992[28] DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	High	High risk of selection bias and confounding, primarily due to potential attrition bias due to high overall (65% loss to followup) and high differential attrition; methods of randomization and allocation concealment NR
Pelc, 1997[29] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Slightly high differential loss to followup, but overall loss to followup was low and the higher loss to followup was in the placebo group, who also had higher rate of severe relapse
Petrakis, 2004[92]; Ralevski, 2006[93] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Methods of randomization and allocation concealment NR; some baseline differences between groups for drinking; low adherence; masking of outcome assessors NR
Petrakis, 2005[40] Ralevski, 2007[41] Petrakis, 2007[42] Petrakis, 2006[43] VA MIRECC DBRCT	Yes	NR/CND	Mixed (yes for NTX, no for DIS)	Mixed (yes for NTX, no for DIS)	Yes	Yes	NR/CND	Medium for NTX vs. pbo	For the DIS comparisons, high risk of ascertainment bias, with no masking; DIS was open-label.

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Pettinati, 2008[97] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	Methods of randomization and allocation concealment NR; moderate risk of selection bias due to attrition; <50% had adequate adherence (over 80%) to medication; unclear if outcome assessors were masked
Pettinati, 2010[98] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	No	Medium	Methods of allocation concealment and masking of outcome assessors NR; some risk of attrition bias; Did not impute anything for missing data, but 84.1% of patients provided drinking reports that were 100% complete, and analyses are time to event analyses
Poldrugo, 1997[30] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	None
Ralevski, 2011[31] Ralevski, 2011[32] NA DBRCT	No	NR/CND	Yes	Yes	Yes	NR/CND	NR/CND	High	High risk of attrition bias; some baseline differences in sex (all females in the placebo group) and very small sample size of 23; methods of randomization and allocation concealment NR; unclear how missing data was handled; no reporting of masking outcome assessors
Rubio, 2001[161] NA SBRCT	Yes	Yes	No	No	Yes	Yes	Yes	High	Significantly more patients in the acamprosate group were prescribed disulfiram during the course of the study.
Rubio, 2009[141] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	No	No	High	Completer's analysis (N=63 analyzed), not ITT; no approach to handling missing data; methods of randomization and allocation concealment and masking of outcome assessors NR
Sass, 1996[33] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	None

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Schmitz, 2004[99] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Restricted Maximum Likelihood	High	High risk of selection bias and confounding; high overall attrition, unclear differential attrition and missing data, methods of randomization, allocation concealment, and masking of outcome assessors NR; unclear why patients dropped out and if they were included in the analysis
Schmitz, 2009[100] NA DBRCT	No	Yes	Yes	Yes	Yes	Yes	No	High	High risk of selection bias, primarily due to attrition; only 40.5% of subjects completed at least 6 weeks of treatment and just 24% completed all 12 weeks; median followup prior to dropout was around 30 days; some baseline differences between groups for sex (lower percentage of males in the naltrexone+CBT+CM group); adherence ranged from 50 to 80%; missing data due to dropout were handled as missing (indicating that nothing was done for missing data due to dropout)
Tempesta, 2000[34] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	None
Volpicelli, 1995[101] NA DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	NR/CND	Unclear	Unclear risk of selection bias, confounding, and attrition bias. Baseline characteristics are not reported by treatment group. Inadequate description of handling of missing data. No information is provided regarding attrition or differential attrition. Methods of randomization, allocation concealment, and masking outcome assessors NR.

Author, Year Trial Name Design	Was Adherence to the Intervention Adequate?	Were Outcome Assessors Masked?[a]	Were Care Providers Masked?[a]	Were Patients Masked?[a]	Were Outcome Measures Equal, Valid, and Reliable?	Did the Study Use Acceptable Statistical Methods?	Was an Appropriate Method Used To Handle Missing Data?	Risk of Bias	Comments
Volpicelli, 1997[103] NR DBRCT	Yes	NR/CND	Yes	Yes	Yes	Yes	CND	Medium	None
Whitworth, 1996[35] NA DBRCT	NR/CND	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	None
Wolwer, 2011[36] NA DBRCT	No	NR/CND	Yes	Yes	Yes	Yes	Yes	Medium	None

[a] Masking refers to whether outcome assessors, providers, or patients were aware of the treatment arm to which the participant was assigned.

AA = Alcoholics Anonymous; ACA = acamprosate; ASI = Addiction Severity Index; AUDIT = Alcohol Use Disorders Identification Test ; CBT = cognitive behavior therapy; CM = contingency management; CND = cannot determine; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DBRCT = double-blind randomized controlled trial; DIS = ; EQ-5D = ; EuropASI = European Addiction Severity Index; HDD = heavy drinking day; ITT = intention to treat; KQ = Key question; LOCF = last observation carried forward; MIREC = Mental Illness Research, Education and Clinical Center; NA = not applicable; NR = not reported; NTX = naltrexone; OCDS = Obsessive Compulsive Disorder Drinking Scale; OLRCT = open-label randomized controlled trial; QoL = Quality of Life; RCT = randomized controlled trial; SADD = Short Alcohol Dependence Data; SBRCT = single-blind randomized controlled trial; TLFB = timeline followback method; VA = Veterans Affairs; VACS = Veterans Affairs Cooperative Study.

Table C-4. Additional risk-of-bias questions for RCTs and related secondary/subgroup analyses that report harms from previous report

Author, Year Trial Name Design	Were Harms Prespecified and Defined?	Were Ascertainment Techniques for Harms Adequately Described?	Were Ascertainment Techniques for Harms Equal, Valid and Reliable?	Was the Duration of Followup Adequate for Harms Assessment?	Risk of Bias	Comments
Ahmadi, 2002[44]; Ahmadi, 2004[177] NA DBRCT	No	No	NR/CND	Yes	Unclear	See comments for efficacy risk of bias assessment
ALK21-014[104] DBRCT	NR/CND	Yes	NR/CND	Yes	Medium	None
Anton, 1999[46]; Anton, 2001[178] NA DBRCT	No	Yes	Yes	Yes	Medium	None
Anton, 2003[158] COMBINE pilot DBRCT	Yes	Yes	Yes	Yes	Medium	SAFTEE assessments (method for systematic assessment of side effects in clinical trials) and lab tests (some of harms description is in other publications)
Balldin, 2003[51] NA DBRCT	No	Yes	Equal but not valid/reliable	Yes	Medium	None
Berger, 2013[11] DBRCT	No	No	NR/CND	Yes	Medium	Adverse events were coded using the Medical Dictionary for Regulatory Activities Version 14 (MedDRA, 2011); although harms were not prespecified, the outcome assessors were masked and any problems with ascertainment are likely nondifferential.
Besson, 1998[12] NA DBRCT	No	No	NR/CND	Yes	Medium	None
Chick, 2000[13] NA DBRCT	No	No	NR/CND	Yes	Medium	None
Chick, 2000[55] NA DBRCT	No	No	NR/CND	Yes	Medium	None
Corrêa Filho, 2013[124] DBRCT	No	Yes	Yes	Yes	High	See comments for assessment of efficacy; high risk of attrition bias; UKU Side Effect Rating Scale used at each visit for harms, but significant overall and differential attrition introduces high risk-of-bias.

Author, Year Trial Name Design	Were Harms Prespecified and Defined?	Were Ascertainment Techniques for Harms Adequately Described?	Were Ascertainment Techniques for Harms Equal, Valid and Reliable?	Was the Duration of Followup Adequate for Harms Assessment?	Risk of Bias	Comments
De Sousa, 2004[154] NA OLRCT	No	No	NR/CND	Yes	High	No allocation concealment; no masking; open label trial
De Sousa, 2005[159] NA OLRCT	No	No	NR/CND	Yes	High	Methods of randomization (by the "qualified statistician") NR; no allocation concealment; High risk of ascertainment bias; no masking; Open label trial comparing disulfiram and acamprosate; potentially had more effort to ensure adherence in the disulfiram group
Fuller, 1986[38] NA DBRCT	No	Yes	Yes	Yes	Medium	None
Garbutt, 2005[63] NA DBRCT	NR/CND	Yes	Yes	Yes	Medium	None
Gastpar, 2002[66] NA DBRCT	No	No	NR/CND	Yes	Medium	None
Geerlings, 1997[14] NA DBRCT	No	No	NR/CND	Yes	Medium	None
Gual, 2001[15] NA DBRCT	No	No	NR/CND	Yes	Medium	None
Guardia, 2002[67] NA DBRCT	No	No	NR/CND	Yes	Medium	None
Heinala, 2001[68] NA DBRCT	No	No	NR/CND	Yes	High	High risk of selection bias, attrition bias, and confounding. No description of randomization, allocation concealment, outcome assessor masking, or details of statistical methods. Methods section does not include any information on statistical analyses. Patient characteristics according to treatment group NR. High rate of overall attrition with no reporting of differential attrition and inadequate description of how missing data was handled.

Author, Year Trial Name Design	Were Harms Prespecified and Defined?	Were Ascertainment Techniques for Harms Adequately Described?	Were Ascertainment Techniques for Harms Equal, Valid and Reliable?	Was the Duration of Followup Adequate for Harms Assessment?	Risk of Bias	Comments
Johnson, 2003[131] Ma, 2006[132]; Johnson, 2004[133] NA DBRCT	Yes	Yes	Yes	Yes	Medium	See comments for efficacy assessment
Johnson, 2004[70] NA DBRCT	No	No	NR/CND	Yes	High	High risk of selection bias and confounding. Groups were not similar at baseline, with differences for sex and higher baseline heavy drinking days for the placebo group. Not surprising that groups were different at baseline in this small, pilot study with 25 NTX subjects and 5 placebo subjects. High attrition. Methods of statistical analyses and handling of missing data NR.
Kiefer, 2003[17] Kiefer, 2005[19] NA DBRCT	No	No	NR/CND	Yes	Medium	Ascertainment techniques for lab measures adequately described, but nothing reported for subjective AEs (e.g., fatigue, diarrhea, etc.)
Killeen, 2004[72] NA DBRCT	NR/CND	Yes	Yes	Yes	Medium	None
Kranzler, 2004[73] NA DBRCT	No	No	NR/CND	Yes	Medium	Very few details about harms data collection; specific harms were only reported if overall frequency >=10% or significant group difference
Krystal, 2001[75] VACS 425 DBRCT	NR/CND	No	NR/CND	Yes	Medium	None
Latt, 2002[76] NA DBRCT	No	Yes	NR/CND	Yes	Medium	None
Lee, 2001[77] NA DBRCT	No	No (a questionnaire was used, but not described)	NR/CND	Yes	High	High risk of selection bias and confounding; high rate of overall and differential attrition; inadequate handling of missing data; methods of randomization and allocation concealment NR; LOCF analysis used which included some, but not all non-completers

Author, Year Trial Name Design	Were Harms Prespecified and Defined?	Were Ascertainment Techniques for Harms Adequately Described?	Were Ascertainment Techniques for Harms Equal, Valid and Reliable?	Was the Duration of Followup Adequate for Harms Assessment?	Risk of Bias	Comments
Lhuintre, 1985[20] NA DBRCT Lhuintre, 1985[20] (continued)	No	No	NR/CND	Yes	High	High risk of selection bias and confounding; medium to high risk of ascertainment bias; completers-only analysis (70/85 randomized subjects in the analysis); methods of randomization, allocation concealment, and consumption outcome assessment NR; inadequate handling of missing data; some concern for contamination because of the use of meprobamate; unable to assess similarity of groups at baseline
Lhuintre, 1990[21] NA DBRCT	Yes	Yes	Yes	Yes	Medium	Used a 44-item questionnaire of somatic complaints; AEs assessment includes those who dropped out due to AEs (whereas it was unclear whether efficacy outcomes only included completers)
Ling, 1983[39] NA DBRCT	No	No	NR/CND	Yes	High	High risk of selection bias and confounding, primarily due to attrition; very high overall and differential loss to follow-up; inadequate handling of missing data for most outcomes (e.g., completers analysis for everything in the Table); methods of randomization, allocation concealment, and masking outcome assessors NR; unclear whether consumption outcomes used valid and reliable measures (just reports that it was self-report, but no description of timeline follow back or other details)
Litten, 2013[145] DBRCT	Mixed	Yes	Mixed	Yes	Medium	Psychiatric harms were prespecified and defined; other harms were assessed with an open-ended question.
Mann, 2012[22] PREDICT DBRCT	Yes	No	Yes	Yes	Medium	Side effects assessed with SAFTEE per methods paper
Mason, 2006[23] NA DBRCT	NR/CND	No	NR/CND	Yes	Medium	Only report that adverse drug events were assessed at every study visit by an open-ended question and coded with the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART)
Monti, 2001[80]; Rohsenow, 2007[179]; Rohsenow, 2000[82] NA DBRCT	NR/CND	Yes	NR/CND	Yes	Medium	Open-ended description of specific symptoms

Author, Year Trial Name Design	Were Harms Prespecified and Defined?	Were Ascertainment Techniques for Harms Adequately Described?	Were Ascertainment Techniques for Harms Equal, Valid and Reliable?	Was the Duration of Followup Adequate for Harms Assessment?	Risk of Bias	Comments
Morgenstern, 2012[83] NA DBRCT	NR/CND	NR/CND	NR/CND	Yes	High	Could not determine if harms were prespecified and defined, if ascertainment techniques were adequate, or if methods were valid and reliable
Morris, 2001[85] NA DBRCT	No	No	NR/CND	Yes	Medium	None
O'Malley, 1992[86]; O'Malley, 1996[180] NA DBRCT	No	No	NR/CND	Yes	Medium	None
Oslin, 1997[90] NA DBRCT	NR/CND	Yes	NR/CND	Yes	Medium	Harms prespecified, used checklist, but not clear if defined
Paille, 1995[26] NA DBRCT	No	Yes	Yes	Yes	Medium	None
Pelc, 1996[27]; Pelc, 1992[28] DBRCT	No	Yes	NR/CND	Yes	High	High risk of selection bias and confounding due to attrition bias. AEs prespecified (checklist used) but not defined. Harms rates only reported for AEs with >5% occurrence. With relatively small Ns, this could be an issue.
Pelc, 1997[29] NA DBRCT	No	Yes	Yes	Yes	Medium	None
Petrakis, 2004[92]; Ralevski, 2006[93] NA DBRCT	Yes	Yes	Yes	Yes	Medium	None
Petrakis, 2005[40] Ralevski, 2007 [41] Petrakis, 2007[42] Petrakis, 2006[43] VA MIRECC DBRCT	Yes	Yes	Yes	Yes	Medium for NTX vs. pbo;	Petrakis, 2005[40] Ralevski, 2007 [41] Petrakis, 2007[42] Petrakis, 2006[43] VA MIRECC DBRCT

Author, Year Trial Name Design	Were Harms Prespecified and Defined?	Were Ascertainment Techniques for Harms Adequately Described?	Were Ascertainment Techniques for Harms Equal, Valid and Reliable?	Was the Duration of Followup Adequate for Harms Assessment?	Risk of Bias	Comments
Poldrugo, 1997[30] NA DBRCT	NR/CND	No	NR/CND	Yes	Medium	Reports using a systematic questionnaire for evaluation of adverse events; details NR
Rubio, 2001[161] NA SBRCT	No	No	No	Yes	High	Significantly more patients in the acamprosate group were prescribed disulfiram during the course of the study.
Sass, 1996[33] NA DBRCT	No	No	NR/CND	Yes	Medium	None
Schmitz, 2004[99] NA DBRCT	NR/CND	Yes	NR/CND	Yes	High	Used preset list of harms, but not clear if those were defined. See comments for efficacy assessment; no usable harms data reported in results
Tempesta, 2000[34] NA DBRCT	No	No	Yes	Yes	Medium	Harms were not defined; recorded by spontaneous reporting and by a questionnaire, but it is unclear what the questionnaire asks.
Volpicelli, 1995[101] NA DBRCT	No	No	NR/CND	Yes	Unclear	See comments on efficacy assessment
Volpicelli, 1997[103] NR DBRCT	NR/CND	Yes	NR/CND	Yes	Medium	Used a side effects checklist, so harms were prespecified, but unclear if they were defined and how they were defined
Whitworth, 1996[35] NA DBRCT	Yes	Yes	NR/CND	Yes	Medium	Asked about 44 AEs (details of the list of 44 and their definitions NR) and rated for severity, and classified into one of seven categories

AE = adverse event; CND = cannot determine; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; DBRCT = double-blind randomized controlled trial; MedDRA = Mental Illness Research Education and Clinical Center; MIRECC = Mental Illness Research Education Clinical, Centers of Excellence, NA = not applicable; NR = not reported; NTX = naltrexone; OLRCT = open-label randomized controlled trial; RCT = randomized controlled trial; SAFTEE = Systematic Assessment for Treatment Emergent Events; SBRCT = single-blind randomized controlled trial; UKU = Udvalg for kliniske undersøgelser; VA = Veterans Affairs; VACS = Veterans Affairs Cooperative Study.

Appendix D. Strength-of-Evidence Assessments

KQ 1 and KQ 2

Table D-1. Acamprosate compared with placebo for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Return to any drinking	20; 6,380	Medium; RCTs	Consistent[a]	Direct	Precise	RR, 0.88 (0.83 to 0.93)	Moderate
Return to heavy drinking	7; 2,496	Low; RCTs	Consistent	Direct	Precise	RR, 0.99 (0.94 to 1.05)	Moderate[b]
Drinking days	14; 4,916	Medium; RCTs	Consistent	Direct	Precise	WMD, -8.3 (-12.2 to -4.4)	Moderate
Heavy drinking days	2; 123	Medium-high; RCT	Consistent	Direct	Imprecise	WMD, -0.34 (-6.45 to 5.86)	Insufficient
Drinks per drinking day	2; 139	Low-high; RCT	Consistent	Direct	Imprecise	No benefit WMD, 0.60 (-1.43 to 2.64)	Insufficient
Accidents	0[c]; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	1; 612	Low; RCT	Unknown	Direct	Unknown	NSD[d]	Insufficient
Mortality	8[e]; 2,677	Medium; RCTs	Unknown	Direct	Imprecise	7 (ACA) vs. 6 (PLA)	Insufficient

[a] Although there was considerable statistical heterogeneity, 18 of the 20 studies reported point estimates that favored acamprosate; differences were in magnitude of benefit.

[b] The relatively small number of studies reporting this outcome raises concern for potential reporting bias, hence the rating of moderate rather than high.

[c] The single study that reported this outcome was rated as unclear risk of bias. It reported that one patient in the placebo group died by "accident." No other details on the cause or nature of the accident were provided.[21]

[d] Results were not reported for each treatment group separately, but there were no clinically significant differences across treatment groups.

[e] One additional study reported a death but did not specify in which treatment group it occurred.[8]

ACA = acamprosate; CI = confidence interval; NA = not applicable; NSD = no significant difference; PLA = placebo; RCT = randomized controlled trial; RR = risk ratio; vs. = versus; WMD = weighted mean difference.

Table D-2. Disulfiram compared with control for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Return to any drinking	3; 622	Medium to High; RCTs	Inconsistent	Direct	Imprecise	RR, 1.03 (95% CI, 0.90 to 1.17)	Low
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	2; 290	Medium; RCTs	Inconsistent	Indirect[a]	Imprecise	1 study reported similar percentages and no significant difference; the other reported that DIS was favored among the subset of subjects who drank and had a complete set of assessment interviews (N=162/605 subjects), p=0.05	Insufficient
Heavy drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

[a] We considered this indirect because the larger study did not report the outcome for the randomized sample; it only reported this outcome for the subset (162/605) who drank and who had a complete set of assessment interviews.

CI = confidence interval; DIS = disulfiram; NA = not applicable; RR = risk ratio.

Table D-3. Naltrexone (any dose and delivery) compared with placebo for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Return to any drinking	25; 4,604	Medium; RCTs	Consistent	Direct	Precise	RR, 0.95 (0.92 to 0.99)	Moderate
Return to heavy drinking	27; 4,645	Medium; RCTs	Consistent	Direct	Precise	RR, 0.86 (0.80 to 0.93)	Moderate
Drinking days	24[a], 4,021	Medium; RCTs	Consistent	Direct	Precise	WMD, -4.51 (-6.26 to -2.77)	Moderate
Heavy drinking days	13; 2,167	Medium; RCTs	Consistent	Direct	Precise	WMD, -3.92 (-5.86 to -1.97)	Moderate
Drinks per drinking day	16; 2,011	Medium; RCTs	Consistent	Direct	Imprecise	WMD, -0.85 (-1.44 to -0.26)	Low
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life	5; 1,844	Medium; RCTs	Inconsistent	Direct	Imprecise	Unable to pool data, some conflicting results[b]	Insufficient
Mortality	6[c]; 1,738	Medium; RCTs	Unknown	Direct	Imprecise	1 (NTX) vs. 2 (PLA) 3 in usual care	Insufficient

[a] One study contained two treatment arms included in the meta-analysis.[60]

[b] Two studies found no significant difference between naltrexone- and placebo-treated subjects.[83, 152] One study reported that patients receiving injectable naltrexone 380 mg/month had greater improvement on the mental health summary score than those receiving placebo at 24 weeks (8.2 vs. 6.2, p=0.044).[181] One study measured alcohol-related consequences (with the DrInC) and reported that more subjects who received placebo (N=34) had ≥1 alcohol-related consequence than those who received naltrexone (N=34): 76% vs. 45%, p=0.02.[89]

[c] One additional study reported a death but did not specify in which treatment group it occurred.[8] One study reported 3 deaths in the usual-care arm, but none in the NTX and PLA arms.[56]

CI = confidence interval; DrInC = Drinker Inventory of Consequences; mg = milligram; NA = not applicable; NTX = naltrexone; PLA = placebo; RCT = randomized controlled trial; RR = risk ratio; vs. = versus; WMD = weighted mean difference.

Table D-4. Oral naltrexone (50 mg) compared with placebo for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Return to any drinking	16; 2,347	Medium; RCTs	Consistent	Direct	Precise	RR, 0.93 (0.87 to 1.00)	Moderate
Return to heavy drinking	21; 3, 149	Medium; RCTs	Consistent	Direct	Precise	RR, 0.81 (0.72 to 0.90)	Moderate
Drinking days	18; 2,063	Medium; RCTs	Consistent	Direct	Precise	WMD, -5.1 (-7.16 to -3.04)	Moderate
Heavy drinking days	7; 624	Medium to high; RCTs	Consistent	Direct	Precise	WMD, -4.26 (-7.61 to -0.91)	Moderate
Drinks per drinking day	9; 1,018	Medium; RCTs	Consistent	Direct	Imprecise	WMD, -0.49 (-0.92 to -0.06)	Low

CI = confidence interval; mg = milligram; RCT = randomized controlled trial; RR = risk ratio; WMD = weighted mean difference.

Table D-5. Oral naltrexone (100 mg) compared with placebo for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Return to any drinking	3; 946	Medium; RCTs	Consistent	Direct	Imprecise	RR, 0.97 (0.91 to 1.03)	Low
Return to heavy drinking	2; 858	Medium; RCTs	Consistent	Direct	Imprecise	RR, 0.93 (0.84 to 1.01)	Low
Drinking days	3; 1,023	Medium; RCTs	Consistent	Direct	Imprecise	WMD, -2.3 (-5.59 to 0.99)	Low
Heavy drinking days	2; 423	Medium; RCTs	Consistent	Direct	Imprecise	WMD, -3.1 (-5.8 to -0.3)	Low
Drinks per drinking day	1; 240	Medium; RCTs	Unknown	Direct	Imprecise	WMD, 1.9 (-1.5 to 5.2)	Insufficient

CI = confidence interval; mg = milligram; RCT = randomized controlled trial; RR = risk ratio; WMD = weighted mean difference.

Table D-6. Injectable naltrexone compared with placebo for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Return to any drinking	2; 939	Medium; RCTs	Consistent	Direct	Imprecise	RR, 0.96 (0.90 to 1.03)	Low (no benefit)
Return to heavy drinking	2; 615	Medium; RCTs	Inconsistent	Direct	Imprecise	RR 1.00 (0.82 to 1.21)	Low (no benefit)
Drinking days	2; 467	Medium; RCTs	Consistent	Direct	Imprecise	WMD, -4.99 (-9.49 to -0.49)	Low
Heavy drinking days	3[a]; 956	Medium to high; RCTs	Consistent	Direct	Imprecise	WMD, -4.68 (-8.63 to -0.73)	Low
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient

[a] Contains data from personal communication (B. Silverman, November 14, 2013).[63]

CI = confidence interval; NA = not applicable; RCT = randomized controlled trial; RR = risk ratio; WMD = weighted mean difference.

Table D-7. Baclofen compared with placebo for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Return to any drinking	8; 995	Low to medium; RCTs	Inconsistent	Direct	Imprecise	Pooled RR, 0.83 (0.70 to 0.98), 6 RCTs, n=883 participants[a]	Low (for benefit)
Return to heavy drinking	4; 483	Low to medium; RCTs	Inconsistent	Direct	Imprecise	Pooled RR, 0.92 (0.80 to 1.06), 2 RCTs, n=319 participants[b]	Low (for no benefit)
Drinking days, %	5; 714	Low to medium; RCT	Inconsistent	Direct	Imprecise	Pooled WMD -5.55 (-18.79 to 7.69), 5 RCTs, n=714 participants	Low (for no benefit)
Heavy drinking days, %	9; 1,112	Low to medium; RCT	Inconsistent	Direct	Imprecise	Pooled WMD, -2.16 (-7.34to 3.02), 7 RCTs, n=760 participants	Low (for no benefit)
Drinks per drinking day	2; 146	Low to medium; RCT	Inconsistent	Direct	Imprecise	Pooled WMD, 0.85 (-2.23 to 3.93)	Low (for no benefit)
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	2; 384	Low to medium	Consistent result, but different measures	Direct	Imprecise	No significant difference at 52 weeks on Q-LES-Q (3.4 [0.8] vs. 3.6 [0.7], p>0.1, SF-36 physical functioning score (absolute difference: 0.2 [-5.3 to 5.6]), or SF-36 mental functioning score (absolute difference 1.0 [-5.7 to 7.7])	Low (for no difference)
Mortality	4; 660	Low to medium	Inconsistent	Direct	Imprecise	Very few total events: total of 8 vs. 3 for baclofen vs. placebo; all but one of the deaths were from a 52-week trial of high-dose baclofen (up to 300 mg)[118]	Insufficient

[a] Two of the studies did not report sufficient data to include in the meta-analysis (combined n=112).

[b] Two of the studies did not report sufficient data to include in the meta-analysis (combined n=164); one of those reported a significant reduction with BAC.

BAC = baclofen; CI = confidence interval; mg = milligram; NA = not applicable; Q-LES-Q = Quality of Life Enjoyment and Satisfaction Questionnaire; RCT = randomized controlled trial; RR = risk ratio; SF-36 = 36-Item Short Form Survey; vs. = versus; WMD = weighted mean difference.

Table D-8. Gabapentin compared with placebo for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Return to any drinking	3; 522	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 0.92 (0.83 to 1.02)	Low (for benefit)
Return to heavy drinking	3; 522	Low to medium; RCTs	Consistent	Direct	Imprecise	RR, 0.90 (0.82 to 0.98)	Low
Drinking days	1; 112	High; RCT	NA	Direct	Imprecise	No statistically significant difference p=0.2	Insufficient
Heavy drinking days	3; 600	Low to high; RCTs	Consistent	Direct	Imprecise	Nonsignificant group differences in all 3 studies	Low
Drinks per drinking day	2; 428	Medium; RCT	Consistent	Direct	Imprecise	No difference between groups	Low
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

CI = confidence interval; NA = not applicable; RR = risk ratio.

Table D-9. Ondansetron compared with placebo for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Return to any drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	2; 172	Medium to high RCTs	Consistent	Direct	Imprecise	No group differences in either study	Low
Heavy drinking days	2; 172	Medium to high RCTs	Inconsistent	Direct	Imprecise	Group differences significant in only 1 study	Insufficient
Drinks per drinking day	1; 70	Medium; RCT	NA	Direct	Imprecise	No difference between groups	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

CI = confidence interval; NA = not applicable; RCT = randomized controlled trial.

Table D-10. Prazosin compared with placebo for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Return to any drinking	1; 96	Medium	NA	Direct	Imprecise	No group difference (p=0.26)	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	2; 188	Medium to high RCTs	Consistent	Direct	Imprecise	No group differences in either study	Insufficient
Heavy drinking days	2; 188	Medium to high RCTs	Consistent	Direct	Imprecise	No group differences in either study	Insufficient
Drinks per drinking day	2; 188	Medium to high RCTs	Consistent	Direct	Imprecise	No group differences in either study	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

CI = confidence interval; NA = not applicable; RCT = randomized controlled trial.

Table D-11. Topiramate compared with placebo for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Return to any drinking	1; 106	High; RCT	NA	Direct	Imprecise	TOP: 53.8% PLA: 72.2%	Insufficient
Return to heavy drinking	1; 170	High; RCT	NA	Direct	Imprecise	TOP: 10% PLA: 14% (study limited to persons with comorbid cocaine use disorder)	Insufficient
Drinking days	8; 1,080	Low-high; RCTs	Consistent	Direct	Imprecise	Pooled WMD for % drinking days, -7.2; 95% CI, -14.3 to -0.1; 4 RCTs; N=570; I^2=46% Mixed findings in remaining 4 trials, 2 U.S.-based trials in general AUD populations showed benefit with topiramate	Moderate
Heavy drinking days	9; 1,210	Low-high; RCTs	Consistent	Direct	Imprecise	WMD, -6.2; 95% CI, -10.9 to -1.4; 5 RCTs, N=720; I^2=16% Mixed findings in remaining 4 trials, 2 U.S.-based trials in general AUD populations showed benefit with topiramate	Moderate[b]
Drinks per drinking day	7; 922	Low-high; RCT	Consistent	Direct	Precise	WMD, -2.0; 95% CI, -3.1 to -1.0; RCTs, N=752; I^2=33%	Moderate[b]
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	2; 541	Low-high; RCT	Inconsistent	Direct	Imprecise	Reduced risk in larger study with low risk of bias (N=371, data shown in next 2 cells, p=0.01[34]	Low
Quality of life or function	2; 118	High; RCT	Consistent	Direct	Imprecise	No difference between topiramate and placebo. Results from larger study (N=106) all p>0.80)[139]	Low
Mortality	3; 507	Low-high; RCT	Consistent	Direct	Imprecise	NR	Insufficient

12w = 12 weeks; AUD = alcohol use disorder; CI = confidence interval; N = sample size; NA = not applicable; NR = not reported; PLA = placebo; RCT = randomized controlled trial; TOP = topiramate; WMD = weighted mean difference.

Table D-12. Varenicline compared with placebo for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Return to any drinking	2; 240	Low to medium; RCT	Consistent	Direct	Imprecise	No differences in either study; e.g., in larger study (N=200): VAR: 97.9% PLA: 98.0%	Low for no benefit
Return to heavy drinking	2; 240	Low to medium; RCT	Consistent	Direct	Imprecise	No differences in either study; e.g., in larger study (N=200): VAR: 92.7% PLA: 95.0%	Low for no benefit
Drinking days	5; 472	Low to high; RCTs	Consistent	Direct	Imprecise	Significant reduction in only 1 study with high RoB	Low for no benefit
Heavy drinking days	6; 603	Low to high; RCTs	Inconsistent	Direct	Imprecise	Significant reduction in only 1 study with low RoB	Low for no benefit
Drinks per drinking day	4; 432	Low to high; RCTs	Inconsistent	Direct	Imprecise	-1.4 (-2.94 to 0.13)	Low for no benefit
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	1; 200	Low	Unknown	Direct	Imprecise	One study found no difference in SF-12 mental (mean difference 0.7; p=0.55) or physical (mean difference 0.4; p=0.38) scores between varenicline-treated and placebo-treated patients.	Insufficient
Mortality	1;200	Low	Unknown	Direct	Imprecise	During the 13-week treatment period, there was 1 shooting death in the varenicline arm and no deaths in the placebo arm.	Insufficient

12w = 12 weeks; CI = confidence interval; N = sample size; NA = not applicable; PLA = placebo; RCT = randomized controlled trial; RoB =risk of bias; SF-12 = 12-Item Short Form Survey ; VAR = varenicline; WMD = weighted mean difference.

Table D-13. Acamprosate compared with disulfiram for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Return to any drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Heavy drinking days	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	0[a]; 0	NA	NA	NA	NA	NA	Insufficient
Mortality	0[a]; 0	NA	NA	NA	NA	NA	Insufficient

[a] The one study reporting this outcome was rated high risk of bias.[155] It reported one traffic accident in the disulfiram group and none in the acamprosate group over 52 weeks. No details of the event were described; it was noted that the study coordinator determined that the event was not related to the study treatment. One person committed suicide and two persons drowned in the acamprosate group, but there were no events in the disulfiram group. Quality of life improved for both groups over the 52-week followup compared with baseline with no difference between the acamprosate and disulfiram groups.

CI = confidence interval; NA = not applicable.

Table D-14. Acamprosate compared with naltrexone for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Return to any drinking	3; 800	Low; RCTs	Consistent	Direct	Imprecise	RR, 1.03; 95% CI, 0.96 to 1.10[a]	Moderate
Return to heavy drinking	4; 1,141	Low; RCTs	Consistent	Direct	Imprecise	RR, 1.02; 95% CI, 0.93 to 1.11[a]	Moderate
Drinking days	2; 720	Low; RCTs	Inconsistent	Direct	Imprecise	WMD, -2.98 (-13.42 to 7.45)[a]	Low
Heavy drinking days	1; 612	Low; RCT	Unknown	Direct	Unknown	Significant NTX by CBI interaction, p=0.006	Insufficient
Drinks per drinking day	2; 720	Low; RCTs	Inconsistent	Direct	Unknown	Unable to pool data[b]	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	2; 774	Low to high; RCT	Unknown	Direct	Imprecise	NSD for all measures except SF-12v2 physical health, which favored NTX+CBI	Insufficient
Mortality	1[c]; 162	High; RCT	Unknown	Direct	Imprecise	1 death in the study	Insufficient

[a] Positive value indicates that naltrexone is favored.

[b] Two trials reported some information about drinks per drinking day, but not enough data for us to conduct quantitative synthesis. One trial conducted in Australia reported no statistically significant difference between acamprosate and naltrexone (mean, SD: 7.5, 6.1 vs. 5.9, 6.1; P not reported).[24, 25 3748] The COMBINE study reported that analyses of alternative summary measures of drinking, including drinks per drinking day (p=0.03), were consistent with those for the co-primary end points (percent days abstinent from alcohol and time to first heavy drinking day), all showing a significant naltrexone by CBI interaction.[8]

[c] One study reported one death but did not specify in which treatment group it occurred.[8, 152]

CBI = combined behavioral intervention; CI = confidence interval; COMBINE = Combined Pharmacotherapies and Behavioral Intervention; NA = not applicable; NSD = no significant difference; NTX = naltrexone; RCT = randomized controlled trial; RR = risk ratio; SD = standard deviation; vs. = versus; WMD = weighted mean difference.

Table D-15. Disulfiram compared with naltrexone for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size	Strength-of-Evidence Grade
Return to any drinking	1[a]; 254	High; RCT	Unknown	Direct	Imprecise	No statistically significant difference	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	1[a]; 254	High; RCT	Unknown	Direct	Imprecise	No statistically significant difference	Insufficient
Heavy drinking days	1[a]; 254	High; RCT	Unknown	Direct	Imprecise	No statistically significant difference	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	1[b]; 162	High; OLRCT	Unknown	Direct	Imprecise	Total of 1 event	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	1[b]; 162	High; OLRCT	Unknown	Direct	Imprecise	No difference between groups	Insufficient
Mortality	1[c]; 162	High; OLRCT	Unknown	Direct	Imprecise	Total of 1 death	Insufficient

[a] The single study that reported this outcome was rated high risk of bias.[40 3728] The trial reported no statistically significant difference between disulfiram and naltrexone for number of subjects achieving total abstinence (51 vs. 38, p=0.11), the percentage of days abstinent (96.6 vs. 95.4, p=0.55), or the percentage of heavy drinking days (3.2 vs. 4, p=0.65).

[b] The only study that reported this outcome was rated high risk of bias.[155] It reported one traffic accident in the disulfiram group and no accident or injuries in the naltrexone group. No details of the event were described; it was noted that the study coordinator determined that the event was not related to the study treatment. Quality of life improved for both groups over the 52-week followup compared with baseline with no difference between the disulfiram and naltrexone groups.

[c] The only study that reported this outcome was rated high risk of bias.[40] One person died in the naltrexone group, and no deaths were reported in the disulfiram group.

NA = not applicable; OLRCT = open label randomized controlled trial; RCT = randomized controlled trial; vs. = versus.

Table D-16. Topiramate compared with naltrexone for Key Questions 1 and 2

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size	Strength-of-Evidence Grade
Return to any drinking	1[a]; 52	High; DBRCT	Unknown	Direct	Imprecise	No statistically significant difference	Insufficient
Return to heavy drinking	0; 0	NA	NA	NA	NA	NA	Insufficient
Drinking days	1[a]; 52	High; DBRCT	Unknown	Direct	Imprecise	No statistically significant difference	Insufficient
Heavy drinking days	1[a]; 52	High; DBRCT	Unknown	Direct	Imprecise	No statistically significant difference	Insufficient
Drinks per drinking day	0; 0	NA	NA	NA	NA	NA	Insufficient
Accidents	0; 0	NA	NA	NA	NA	NA	Insufficient
Injuries	0; 0	NA	NA	NA	NA	NA	Insufficient
Quality of life or function	2[b]; 284	High; OLRCT	Inconsistent	Direct	Imprecise	NA	Insufficient
Mortality	0; 0	NA	NA	NA	NA	NA	Insufficient

[a] The only included trial that was eligible for KQ 1 was rated as high risk of bias and reported no significant differences between topiramate and naltrexone for proportion of abstinent subjects, cumulative abstinence duration, time to first relapse, or heavy drinking weeks.[52] Significantly more subjects in the topiramate group participated in AA than in the naltrexone group (19.2 percent versus 4.1 percent, p=0.04).

[b] The two studies that reported this outcome were rated as high risk of bias.

AA = Alcoholics Anonymous ; DBRCT = double blind randomized controlled trial; KQ = Key Question; NA = not applicable; OLRCT = open label randomized controlled trial.

KQ 3

Table D-17. Acamprosate compared with placebo for Key Question 3

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Withdrawals due to AEs	16; 5,480	Medium to high; RCTs	Inconsistent	Direct	Imprecise	RR, 1.16 (0.86 to 1.56)	Low
Anorexia	0; 0	NA	NA	NA	NA	NA	Insufficient
Anxiety	2; 624	Medium to high; RCT	Consistent	Direct	Imprecise	RR, 1.90 (1.42 to 2.54)	Low
Cognitive dysfunction	0; 0	NA	NA	NA	NA	NA	Insufficient
Diarrhea	14; 4,188	Medium to high; RCTs	Consistent	Direct	Precise	RR, 1.58(1.27 to 1.97	Moderate
Dizziness	2; 151	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 1.66 (0.37 to 7.44)	Low
Headache	7; 1,643	Medium; RCTs	Inconsistent	Direct	Imprecise	RR, 1.02 (0.63 to 1.66)	Low
Insomnia	4; 820	Medium; RCT	Inconsistent	Direct	Imprecise	RR, 1.32 (0.85 to 2.05)	Low
Nausea	8; 1,828	Low to high ; RCTs	Consistent	Direct	Imprecise	RR, 1.08 (0.84 to 1.37)	Moderate
Numbness/tingling/paresthesias	2; 831	Medium to high; RCT	Consistent	Direct	Imprecise	RR, 1.23 (0.79 to 1.92)	Low
Rash	2; 105	Low to high; RCT	Consistent	Direct	Imprecise	RR, 5.14 (0.62 to 42.39)	Low
Suicide attempts or suicidal ideation	3; 1,173	Medium to high; RCT	Inconsistent	Direct	Imprecise	RR, 0.86 (0.17 to 4.27)	Insufficient
Taste abnormalities	0; 0	NA	NA	NA	NA	NA	Insufficient
Vision changes	0; 0	NA	NA	NA	NA	NA	Insufficient
Vomiting	5; 1,840	Medium to high; RCTs	Inconsistent	Direct	Imprecise	RR, 1.33 (0.74 to 2.38)	Low

AE = adverse event; CI = confidence interval; NA = not applicable; RCT = randomized controlled trial; RR = risk ratio.

Table D-18. Disulfiram compared with placebo or control for Key Question 3

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size	Strength-of-Evidence Grade
Withdrawals due to AEs	1; 605	Medium; DBRCT	Unknown	Direct	Imprecise	DIS 250: 1.0% DIS 1: 0.0% RIB: 0.5%	Insufficient
Anorexia	0; 0	NA	NA	NA	NA	NA	Insufficient
Anxiety	0; 0	NA	NA	NA	NA	NA	Insufficient
Cognitive dysfunction	1; 130	Medium; DBRCT	Unknown	Direct	Imprecise	DIS: 82.5% PLA: 64.5%[a]	Insufficient
Diarrhea	0; 0	NA	NA	NA	NA	NA	Insufficient
Dizziness	0; 0	NA	NA	NA	NA	NA	Insufficient
Drowsiness	2; 735	Medium; DBRCT	Unknown	Indirect	Imprecise	One study found no significant difference the other found DIS: 90.5% PLA: 80.6%[a]	Insufficient
Headache	0; 0	NA	NA	NA	NA	NA	Insufficient
Insomnia	0; 0	NA	NA	NA	NA	NA	Insufficient
Nausea	1; 130	Medium; DBRCT	Unknown	Direct	Imprecise	DIS: 58.7% PLA: 41.9%[a]	Insufficient
Numbness/tingling/ paresthesias	1; 130	Medium; DBRCT	Unknown	Direct	Imprecise	DIS: 39.7% PLA: 45.2%[a]	Insufficient
Rash	0; 0	NA	NA	NA	NA	NA	Insufficient
Suicide attempts or suicidal ideation	0; 0	NA	NA	NA	NA	NA	Insufficient
Taste abnormalities	1; 130	Medium; DBRCT	Unknown	Direct	Imprecise	DIS: 47.6% PLA: 52.6%[a]	Insufficient
Vision changes	1; 130	Medium; DBRCT	Unknown	Direct	Imprecise	DIS: 47.6% PLA: 41.9%[a]	Insufficient
Vomiting	1; 130	Medium; DBRCT	Unknown	Direct	Imprecise	DIS: 31.7% PLA: 24.2%[a]	Insufficient

[a] Statistical significance not assessed.[40 3728]

AE = adverse event; DBRCT = double blind randomized controlled trial; DIS = disulfiram; NA = not applicable; PLA = placebo; RIB = riboflavin.

Table D-19. Naltrexone compared with placebo for Key Question 3

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Withdrawals due to AEs	21; 3,256	Medium; RCTs	Consistent	Direct	Imprecise	RR, 1.38 (0.99 to 1.93)	Moderate
Anorexia	1; 175	Medium; RCT	Unknown	Direct	Imprecise	RR, 7.56 (0.97 to 59.14)	Insufficient
Anxiety	10; 1,870	Medium; RCTs	Consistent	Direct	Imprecise	RR, 1.02 (0.87 to 1.20)	Low
Cognitive dysfunction	1; 123	Medium; RCT	Unknown	Direct	Precise	RR, 1.30 (1.04 to 1.61)	Insufficient
Diarrhea	13; 2,755	Medium; RCTs	Inconsistent	Direct	Imprecise	RR, 1.10 (0.83 to 1.46)	Low
Dizziness	19; 3,271	Medium; RCTs	Consistent	Direct	Precise	RR, 1.99 (1.47 to 2.69)	Moderate
Headache	24; 4,093	Medium; RCTs	Inconsistent	Direct	Imprecise	RR, 0.98 (0.86 to 1.12)	Low
Insomnia	13; 2,224	Medium; RCTs	Consistent	Direct	Imprecise	RR, 1.28 (1.01 to 1.64)	Low
Nausea	33; 5,557	Medium; RCTs	Consistent	Direct	Precise	RR, 1.73 (1.51 to 1.98)	Moderate
Numbness/tingling/ paresthesias	2; 226	Medium; RCT	Unknown	Direct	Imprecise	RR, 0.97 (0.68 to 1.38)	Insufficient
Rash	5; 522	Medium; RCTs	Inconsistent	Direct	Imprecise	RR, 0.69 (0.15 to 3.23)	Low
Suicide	0; 0	NA	NA	NA	NA	NA	Insufficient
Taste abnormalities	1; 123	Medium; RCT	Unknown	Direct	Imprecise	RR, 0.99 (0.71 to 1.38)	Insufficient
Vision changes (blurred vision)	2; 154	Medium; RCTs	Inconsistent	Direct	Imprecise	RR, 1.16 (0.71 to 1.90)	Low
Vomiting	13; 2,861	Medium; RCTs	Consistent	Direct	Precise	RR, 1.53 (1.23 to 1.91)	Moderate

AE = adverse event; CI = confidence interval; NA = not applicable; RCT = randomized controlled trial; RR = risk ratio.

Table D-20. Baclofen compared with placebo for Key Question 3

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Withdrawals due to AEs	6; 931	Low to medium; RCTs	Consistent	Direct	Imprecise	RR, 1.40 (0.83 to 2.38)	Low
Anxiety	3; 388	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 1.33 (0.81 to 2.17)	Low
Cognitive dysfunction	2; 495	Low to medium; RCTs	Consistent	Direct	Imprecise	RR, 1.58 (0.93 to 2.70)	Low
Diarrhea	4; 581	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 0.76 (0.47 to 1.22)	Low
Dizziness	13; 1,231	Low to medium; RCTs	Consistent	Direct	Imprecise	RR, 1.89 (1.40 to 2.55)	Moderate
Drowsiness	7; 937	Low to medium; RCTs	Inconsistent	Direct	Precise	RR, 1.46 (1.15 to 1.86)	Moderate
Fatigue	6; 632	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 1.40 (0.99 to 1.98)	Low
Headache	8; 941	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 1.29 (0.96 to 1.73)	Low
Insomnia	3; 537	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 0.76 (0.35 to 1.66)	Low
Nausea	4; 643	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 1.11 (0.72 to 1.72)	Low
Numbness	2; 207	Low to medium; RCTs	Consistent	Direct	Imprecise	RR, 7.78 (1.42 to 42.56)	Low
Rash	5; 475	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 0.88 (0.3 to 1.80)	Low
Sleepiness	2; 235	Low to medium; RCTs	Consistent	Direct	Imprecise	RR, 1.81 (1.11 to 2.97)	Moderate
Suicide attempts or suicidal ideation	1; 104	Low to medium; RCTs	Consistent	Direct	Imprecise	RR, 3.66 (0.41 to 32.31)	Low
Taste abnormalities	2; 495	Low to medium; RCTs	Consistent	Direct	Imprecise	RR, 2.28 (0.45 to 11.59)	Low
Vision changes	2; 235	Low to medium; RCTs	Consistent	Direct	Imprecise	RR, 1.30 (0.61 to 2.79)	Low
Vomiting	2; 495	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 0.97 (0.50, 1.88)	Low

AE = adverse event; CI = confidence interval; RCT = randomized controlled trial; RR = risk ratio.

Table D-21. Gabapentin compared with placebo for Key Question 3

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Withdrawals due to AEs	2; 488	Low to medium; RCT	Inconsistent	Direct	Imprecise	RR, 1.28 (0.42 to 3.82)	Low
Anorexia	0; 0	NA	NA	NA	NA	NA	Insufficient
Anxiety	1; 228	Medium; RCT	Unknown	Direct	Imprecise	RR, 1.98 (0.82 to 4.77)	Low
Cognitive dysfunction	1; 104	High; RCT	Unknown	Direct	Imprecise	RR, 2.76 (1.51 to 5.06)	Low
Diarrhea	2; 442	Medium to high; RCTs	Consistent	Direct	Imprecise	RR, 1.78 (0.59 to 5.36)	Low
Dizziness	3; 532	Medium to high; RCTs	Consistent	Direct	Precise	RR, 1.70 (1.24 to 2.32)	Moderate
Headache	2; 488	Low to medium; RCTs	Consistent	Direct	Precise	RR, 0.80 (0.58 to 1.11)	Low
Insomnia	2; 488	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 0.84 (0.55 to 1.30)	Low
Nausea	2; 422	Medium to high; RCTs	Inconsistent	Direct	Imprecise	RR, 0.83 (0.47 to 1.45)	Low
Numbness/tingling/paresthesias	1; 338	Medium; RCT	Unknown	Direct	Imprecise	RR, 0.54 (0.2 to 1.42)	Low
Rash	1; 338	Medium; RCT	Unknown	Direct	Imprecise	RR, 1.98 (0.82 to 4.77)	Low
Suicide attempts or suicidal ideation	1; 338	Medium; RCT	Unknown	Direct	Imprecise	RR, 0.33 (0.01 to 8.03)	Insufficient
Taste abnormalities	0; 0	NA	NA	NA	NA	NA	Insufficient
Vision changes	1; 104	High; RCT	Unknown	Direct	Imprecise	RR, 5.44 (1.51 to 19.63)	Insufficient
Vomiting	2; 442	Medium to high; RCT	Consistent	Direct	Imprecise	RR, 1.64 (0.77 to 3.47)	Low

AE = adverse event; CI = confidence interval; NA = not applicable; RCT = randomized controlled trial; RR = risk ratio.

Table D-22. Ondansetron compared with placebo for Key Question 3

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size	Strength-of-Evidence Grade
Withdrawals due to AEs	0; 0	NA	NA	NA	NA	NA	Insufficient
Anorexia	0; 0	NA	NA	NA	NA	NA	Insufficient
Anxiety	0; 0	NA	NA	NA	NA	NA	Insufficient
Cognitive dysfunction	0; 0	NA	NA	NA	NA	NA	Insufficient
Diarrhea	1; 26	High	NA	Direct	Imprecise	ODN: 2.0% PLA: 5.8% (p<0.05)	Insufficient
Dizziness	0; 0	NA	NA	NA	NA	NA	Insufficient
Headache	1; 26	High	NA	Direct	Imprecise	ODN: 14.0% PLA: 17.3% (p<0.05)	Insufficient
Insomnia		NA	NA	NA	NA	NA	Insufficient
Nausea	1; 26	High	NA	Direct	Imprecise	ODN: 18.0% PLA: 13.5% (p<0.05)	Insufficient
Numbness/tingling/paresthesias	0; 0	NA	NA	NA	NA	NA	Insufficient
Rash	0; 0	NA	NA	NA	NA	NA	Insufficient
Suicide attempts or suicidal ideation	0; 0	NA	NA	NA	NA	NA	Insufficient
Taste abnormalities	0; 0	NA	NA	NA	NA	NA	Insufficient
Vision changes	0; 0	NA	NA	NA	NA	NA	Insufficient
Vomiting	0; 0	NA	NA	NA	NA	NA	Insufficient

AE = adverse event; NA = not applicable; OND = ondansetron; PLA = placebo.

Table D-23. Prazosin compared with placebo for Key Question 3

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Withdrawals due to AEs	0; 0	NA	NA	NA	NA	NA	Insufficient
Anorexia	0; 0	NA	NA	NA	NA	NA	Insufficient
Anxiety	0; 0	NA	NA	NA	NA	NA	Insufficient
Cognitive dysfunction	0; 0	NA	NA	NA	NA	NA	Insufficient
Diarrhea	0; 0	NA	NA	NA	NA	NA	Insufficient
Dizziness	2;188	Medium to high; RCT	Inconsistent	Direct	Imprecise	Med RoB study reported NSD; High RoB study reported higher rates in prazosin group, p=0.02	Insufficient
Headache	1; 92	Medium; RCT	Unknown	Direct	Imprecise	NSD	Insufficient
Insomnia	0; 0	NA	NA	NA	NA	NA	Insufficient
Nausea	1; 92	Medium; RCT	Unknown	Direct	Imprecise	NSD	Insufficient
Numbness/tingling/paresthesias	0; 0	NA	NA	NA	NA	NA	Insufficient
Rash	0; 0	NA	NA	NA	NA	NA	Insufficient
Suicide attempts or suicidal ideation	0; 0	NA	NA	NA	NA	NA	Insufficient
Taste abnormalities	0; 0	NA	NA	NA	NA	NA	Insufficient
Vision changes	0; 0	NA	NA	NA	NA	NA	Insufficient
Vomiting	0; 0	NA	NA	NA	NA	NA	Insufficient

AE = adverse event; CI = confidence interval; Med = medium; NA = not applicable; NSD = no significant difference; RCT = randomized controlled trial; RoB = risk of bias.

Table D-24. Topiramate compared with placebo for Key Question 3

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Withdrawals due to AEs	7; 1042	Low to high; RCTs	Inconsistent	Direct	Imprecise	RR, 2.45 (1.09 to 5.53)	Low
Anxiety	0; 0	NA	NA	NA	NA	NA	Insufficient
Cognitive dysfunction	4; 765	Low to high; RCTS	Consistent	Direct	Precise	RR, 2.37 (1.58 to 3.55)	Moderate
Diarrhea	5; 864	Low to high; RCT	Inconsistent	Direct	Imprecise	RR, 1.27 (0.86 to 1.87)	Low
Dizziness	4; 782	Low to high; RCTs	Consistent	Direct	Precise	RR, 2.29 (1.39 to 3.78)	Moderate
Headache	5; 955	Low to high; RCT	Inconsistent	Direct	Imprecise	RR, 1.02 (0.71 to 1.45)	Low
Insomnia	3; 696	Low to high; RCT	Consistent	Direct	Imprecise	RR, 1.28 (0.88 to 1.88)	Low
Nausea	3; 696	Low to high; RCT	Inconsistent	Direct	Imprecise	0.73 (0.46 to 1.14)	Low
Numbness/tingling/paresthesias	8; 1292	Low to high; RCTs	Consistent	Direct	Precise	3.08 (2.11 to 4.49)	Moderate
Rash	0; 0	NA	NA	NA	NA	NA	Insufficient
Suicide attempts or suicidal ideation	1; 30	Low; RCT	NA	Direct	Imprecise	RR, 0.38 (0.02 to 8.59)	Insufficient
Taste abnormalities	6; 847	Low to High; RCT	Consistent	Direct	Imprecise	RR, 3.01 (1.70 to 5.34)	Moderate
Vision changes	2; 200	Low	Consistent	Direct	Imprecise	RR, 2.01 (0.98 to 4.11)	Low
Vomiting	0; 0	NA	NA	NA	NA	NA	Insufficient

AE = adverse event; CI = confidence interval; NA = not applicable; RCT = randomized controlled trial; RR = risk ratio.

Table D-25. Varenicline compared with placebo for Key Question 3

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)	Strength-of-Evidence Grade
Withdrawals due to AEs	4;519	Low to high: RCTs	Inconsistent	Direct	Imprecise	RR, 2.39 (0.69 to 8.23)	Low
Anxiety	2;329	Low to medium; RCTs	Consistent	Direct	Imprecise	RR, 1.27 (0.65 to 2.49)	Low
Cognitive dysfunction	0; 0	NA	NA	NA	NA	NA	Insufficient
Diarrhea	3;502	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 0.69 (0.35 to 1.37)	Low
Dizziness	2;329	Low to medium; RCTs	Consistent	Direct	Imprecise	RR, 1.98 (0.95 to 4.13)	Low
Headache	3;502	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 1.12 (0.78 to 1.47)	Low
Insomnia	3;502	Low to medium; RCTs	Consistent	Direct	Imprecise	RR, 1.26 (0.76 to 2.09)	Low
Nausea	4;522	Low to medium; RCTs	Consistent	Direct	Precise	RR, 2.34 (1.38 to 3.97)	Moderate
Rash	1;198	Low; RCT	NA	Direct	Imprecise	RR, 0.52 (0.13 to 2.02)	Insufficient
Suicide attempts or suicidal ideation	0; 0	NA	NA	NA	NA	NA	Insufficient
Taste abnormalities	1;131	Medium; RCT	NA	Direct	Imprecise	RR, 0.63 (0.16 to 2.52)	Insufficient
Vision changes	1;131	Medium: RCT	NA	Direct	Imprecise	RR, 2.09 (0.40 to 11.04)	Insufficient
Vomiting	2;329	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 0.99 (0.51 to 1.94)	Low

CI = confidence interval; NA = not applicable; RCT = randomized controlled trial; RR = risk ratio.

Table D-26. Acamprosate compared with disulfiram for Key Question 3

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size N (%)	Strength-of-Evidence Grade
Withdrawals due to AEs	2; 262	High; OLRCT	Consistent	Direct	Imprecise	Change to text summary ACA: 0 (0) DIS: 6 (5)[a]	Insufficient
Anorexia	0; 0	NA	NA	NA	NA	NA	Insufficient
Anxiety	0; 0	NA	NA	NA	NA	NA	Insufficient
Cognitive dysfunction	0; 0	NA	NA	NA	NA	NA	Insufficient
Diarrhea	0; 0	NA	NA	NA	NA	NA	Insufficient
Dizziness	0; 0	NA	NA	NA	NA	NA	Insufficient
Headache	1; 162	High; OLRCT	Unknown	Direct	Precise	No difference between groups	Insufficient
Insomnia	0; 0	NA	NA	NA	NA	NA	Insufficient
Nausea	0; 0	NA	NA	NA	NA	NA	Insufficient
Numbness/tingling/paresthesias	0; 0	NA	NA	NA	NA	NA	Insufficient
Rash	1; 162	High; OLRCT	Unknown	Direct	Precise	No difference between groups	Insufficient
Suicide attempts or suicidal ideation	0; 0	NA	NA	NA	NA	NA	Insufficient
Taste abnormalities	0; 0	NA	NA	NA	NA	NA	Insufficient
Vision changes	0; 0	NA	NA	NA	NA	NA	Insufficient
Vomiting	0; 0	NA	NA	NA	NA	NA	Insufficient

[a] Three patients withdrawn due to side effects in disulfiram group but statistical significance not assessed.[159]

ACA = acamprosate; AE = adverse event; DIS = disulfiram; N = sample size; NA = not applicable; OLRCT = open label randomized controlled trial.

Table D-27. Acamprosate compared with naltrexone for Key Question 3

Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size (95% CI)[a]	Strength-of-Evidence Grade
Withdrawals due to AEs	3; 1110	Medium to high; RCT	Consistent	Direct	Imprecise	RR, 1.07 (0.38 to 3.05)	Low
Anorexia	0; 0	NA	NA	NA	NA	NA	Insufficient
Anxiety	0; 0	NA	NA	NA	NA	NA	Insufficient
Cognitive dysfunction	0; 0	NA	NA	NA	NA	NA	Insufficient
Diarrhea	5; 993	Low to high; RCTs	Consistent	Direct	Imprecise	RR, 1.90 (1.35 to 2.68)	Moderate
Dizziness	4; 306	Low to high; RCT	Inconsistent	Direct	Imprecise	RR, 0.67 (0.11 to 4.04)	Low
Headache	4; 463	Medium; RCT	Inconsistent	Direct	Imprecise	RR, 0.52 (0.22 to 1.22)	Low
Insomnia	2; 144	Low to medium; RCTs	Inconsistent	Direct	Imprecise	RR, 1.36 (0.73 to 2.53)	Low
Nausea	6; 1,155	Low to high; RCTs	Consistent	Direct	Imprecise	RR, 0.56 (0.35 to 0.88)	Low
Numbness/tingling/ paresthesias	0; 0	NA	NA	NA	NA	NA	Insufficient
Rash	0; 0	NA	NA	NA	NA	NA	Insufficient
Suicide	0; 0	NA	NA	NA	NA	NA	Insufficient
Taste abnormalities	0; 0	NA	NA	NA	NA	NA	Insufficient
Vision changes	0; 0	NA	NA	NA	NA	NA	Insufficient
Vomiting	2; 648	Low; RCTs	Consistent	Direct	Precise	RR, 0.60 (0.39 to 0.93)	Moderate

[a] In this column, a positive value favors naltrexone.

AE = adverse event; CI = confidence interval; NA = not applicable; RCT = randomized controlled trial; RR = risk ratio.

Table D-28. Disulfiram compared with naltrexone for Key Question 3

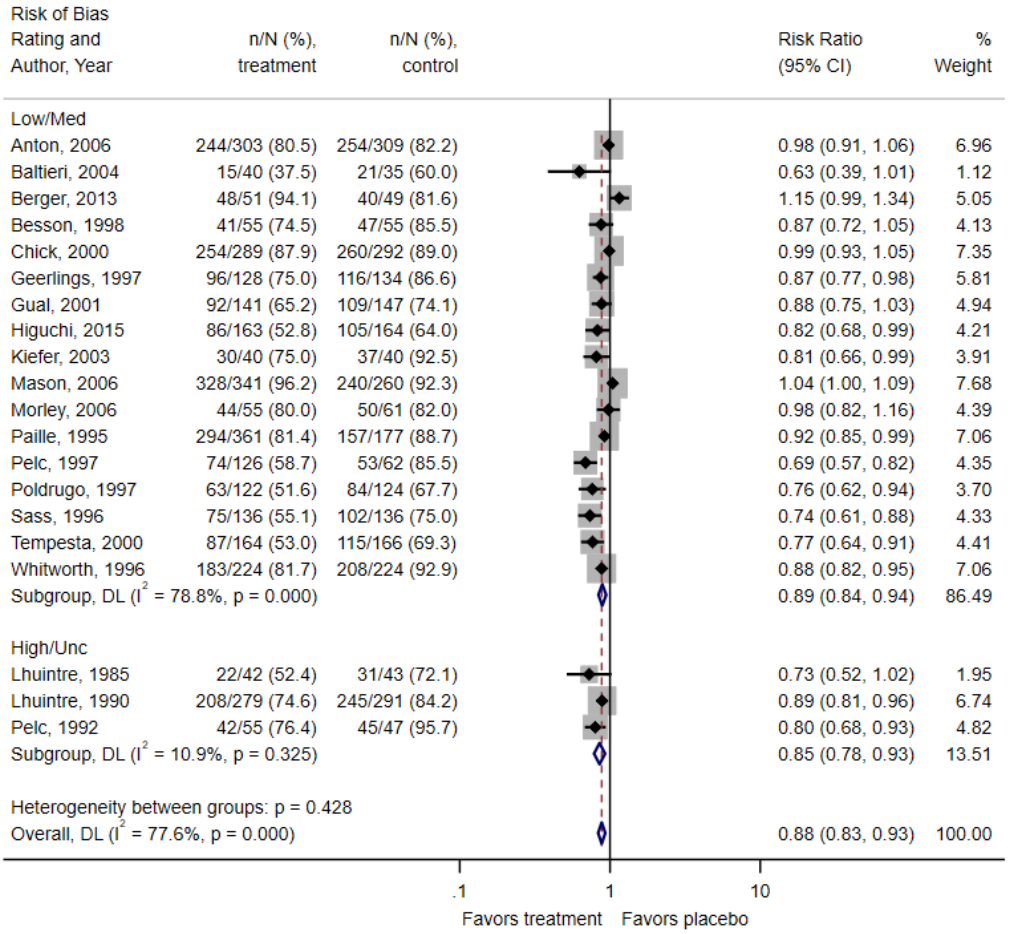
Outcome	Number of Studies; Number of Subjects	Risk of Bias; Design	Consistency	Directness	Precision	Summary Effect Size	Strength-of-Evidence Grade
Withdrawals due to AEs	4; 445	High; 3 OLRCTs and 1 DBRCT	Consistent	Direct	Imprecise	In the only DBRCT there was no difference between groups	Insufficient
Anorexia	0; 0	NA	NA	NA	NA	NA	Insufficient
Anxiety	0; 0	NA	NA	NA	NA	NA	Insufficient
Cognitive dysfunction	1; 445	High; DBRCT	Unknown	Direct	Imprecise	DIS: 83% NTX: 83% p=0.00	Insufficient
Diarrhea	1; 100	High; OLRCT	Unknown	Direct	Imprecise	DIS: 1% NTX: 8%	
Dizziness	0; 0	NA	NA	NA	NA	NA	Insufficient
Headache	1; 162	High; OLRCT	Unknown	Direct	Imprecise	No statistical difference	
Insomnia	0; 0	NA	NA	NA	NA	NA	Insufficient
Nausea	2; 225	High; 1 OLRCT and 1 DBRCT	Inconsistent	Direct	Imprecise	Replace with text summary	Insufficient
Numbness/tingling/ paresthesias	0; 0	NA	NA	NA	NA	NA	Insufficient
Rash	1; 162	High; OLRCT	Unknown	Direct	Imprecise	No statistical difference	Insufficient
Suicide attempts or suicidal ideation	0; 0	NA	NA	NA	NA	NA	Insufficient
Taste abnormalities	1; 445	High; DBRCT	Unknown	Direct	Imprecise	DIS:48% NTX: 53% p=0.58	Insufficient
Vision changes	1; 445	High; DBRCT	Unknown	Direct	Imprecise	DIS = 48% NTX = 60% p=0.19	Insufficient
Vomiting	1; 445	High; DBRCT	Unknown	Direct	Imprecise	DIS = 32% NTX = 25% p=0.39	Insufficient

AE = adverse event; DBRCT = double blind randomized controlled trial; DIS = disulfiram; NA = not applicable; NTX = naltrexone; OLRCT = open label randomized controlled trial.

Appendix E. Meta-Analyses

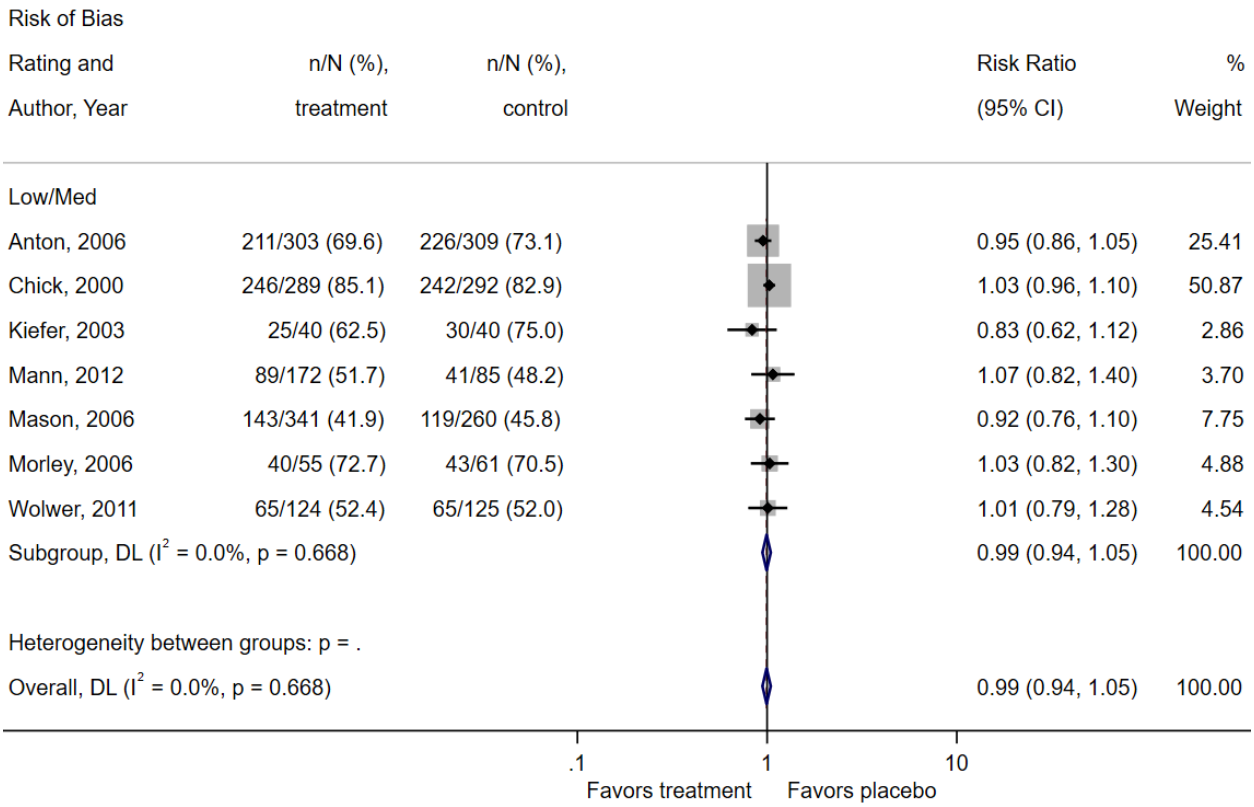
Key Question 1. Meta-Analysis Results

Figure E-1. Acamprosate versus placebo: Return to any drinking by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear .

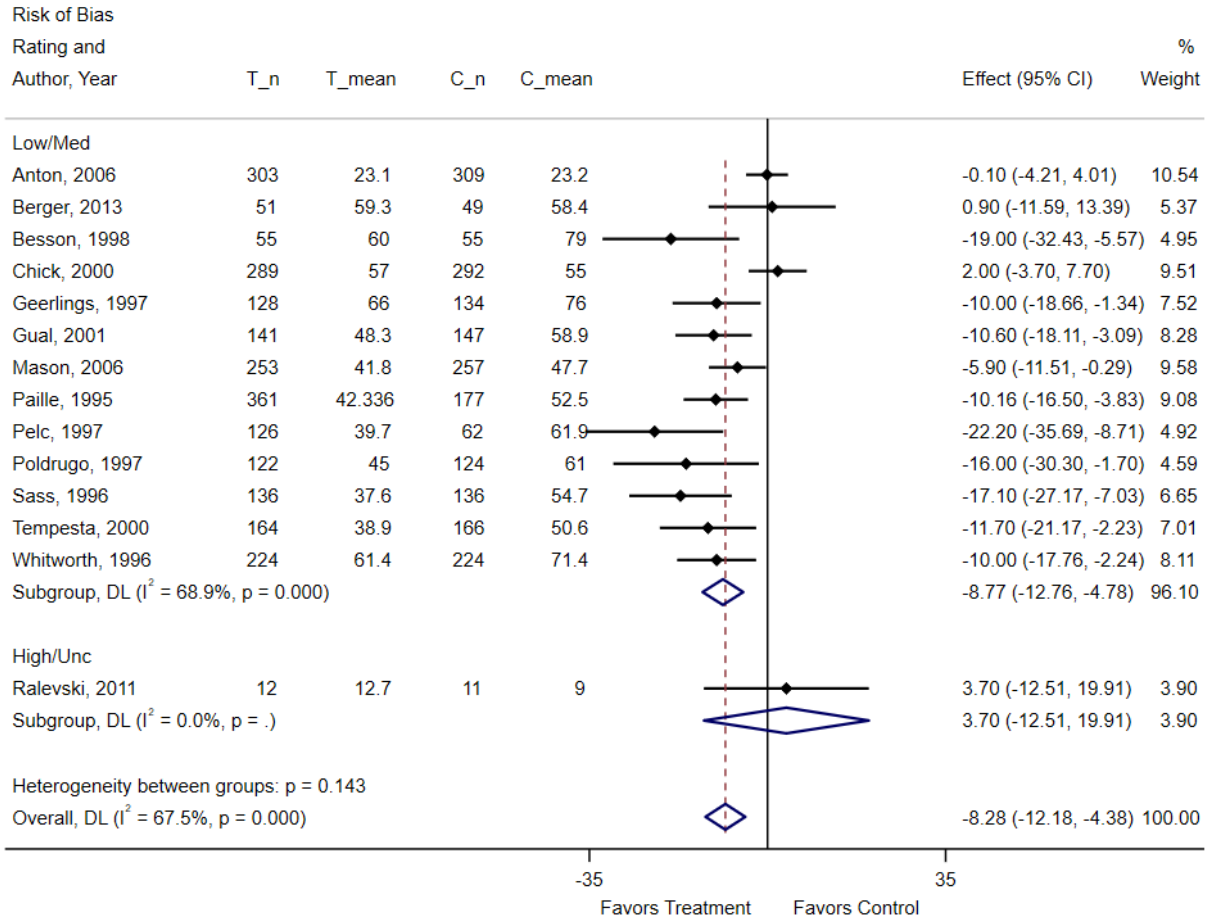
Figure E-2. Acamprosate versus placebo: Return to heavy drinking overall (all risk-of-bias ratings)



NOTE: Weights are from random-effects model

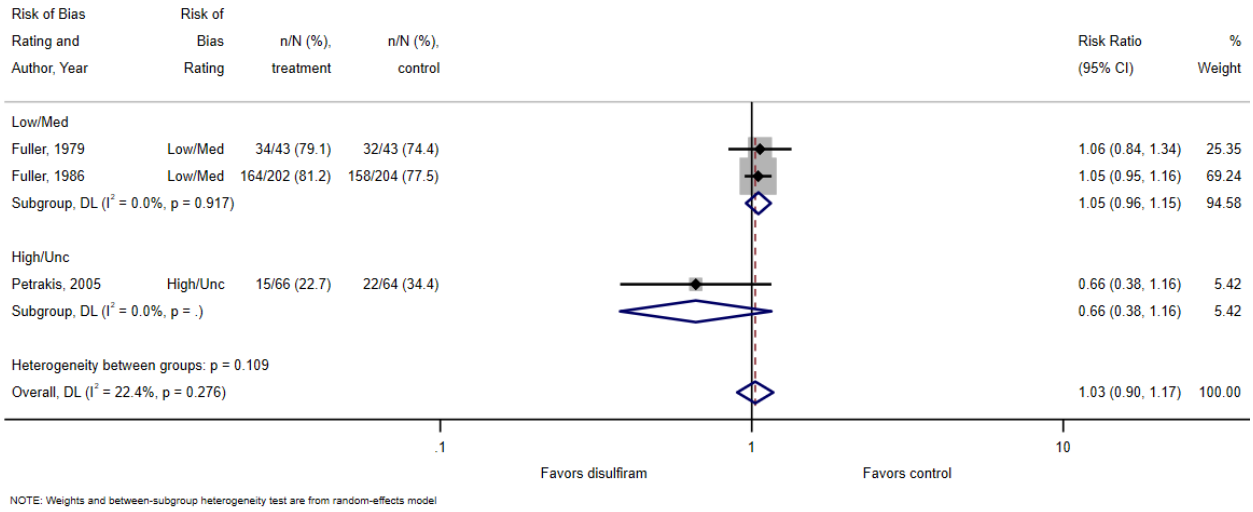
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-3. Acamprosate versus placebo: Percent drinking days by risk-of-bias rating



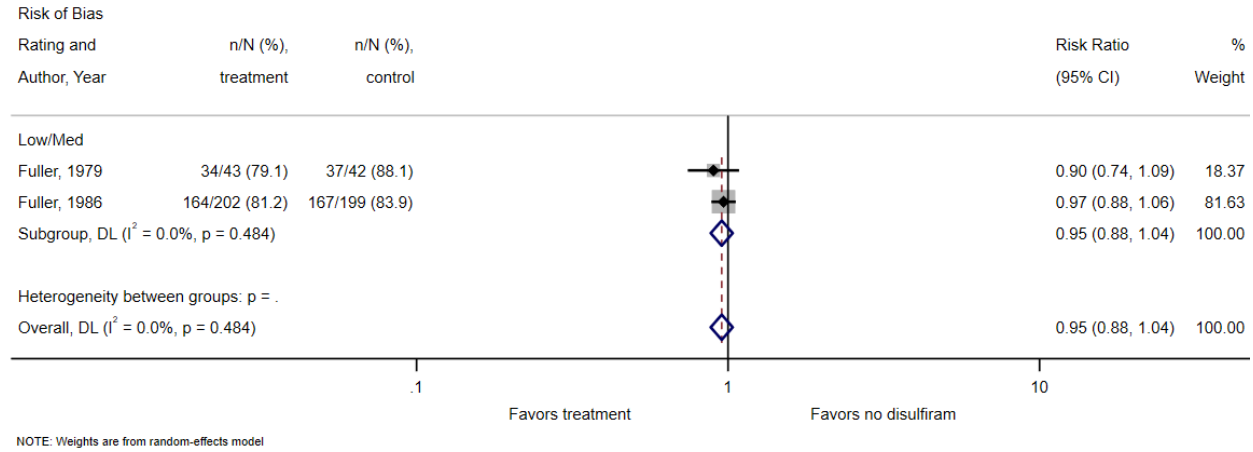
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-4. Disulfiram versus control: Return to any drinking by risk-of-bias



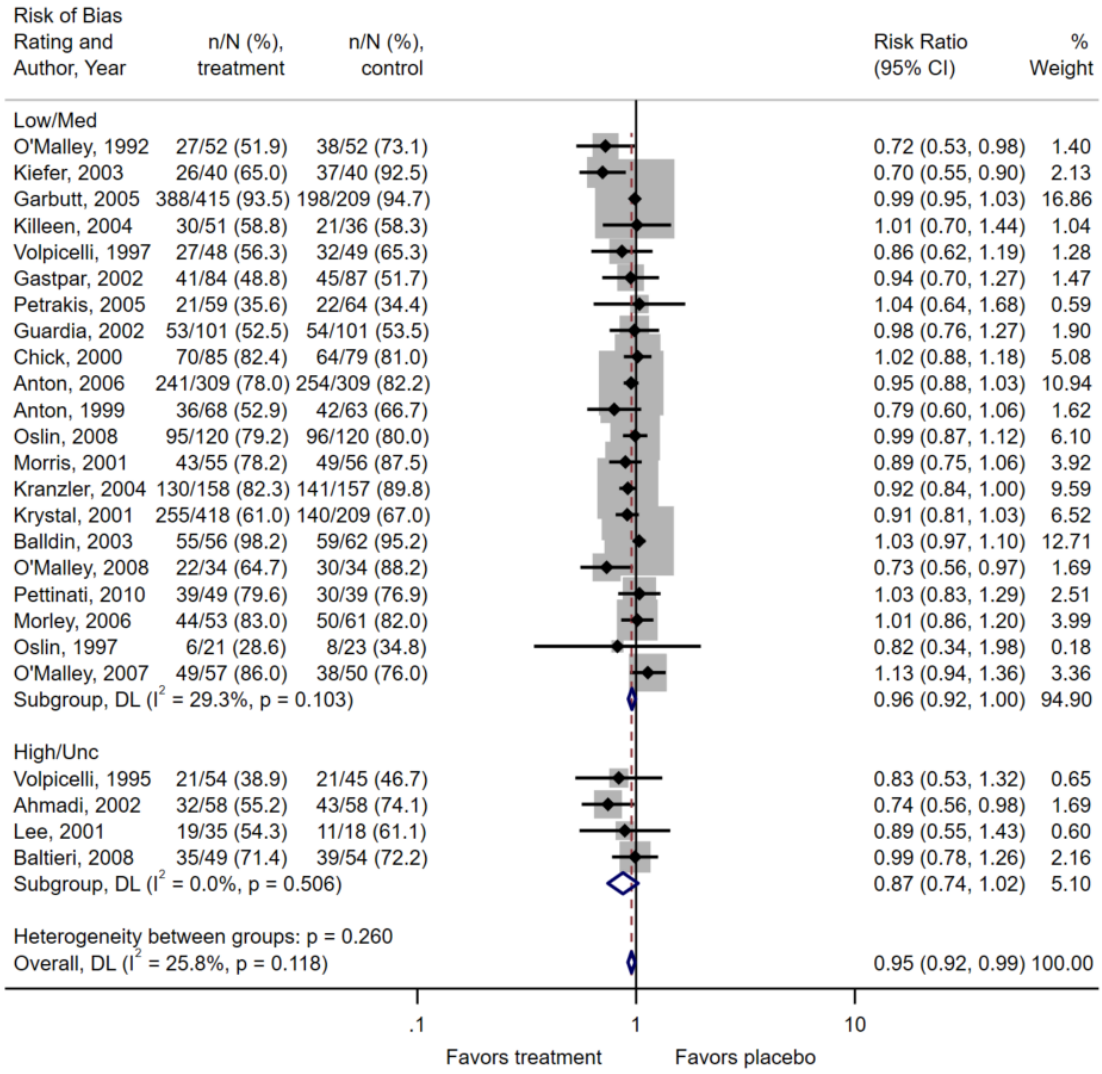
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-5. Disulfiram versus no disulfiram: Return to any drinking by risk-of-bias



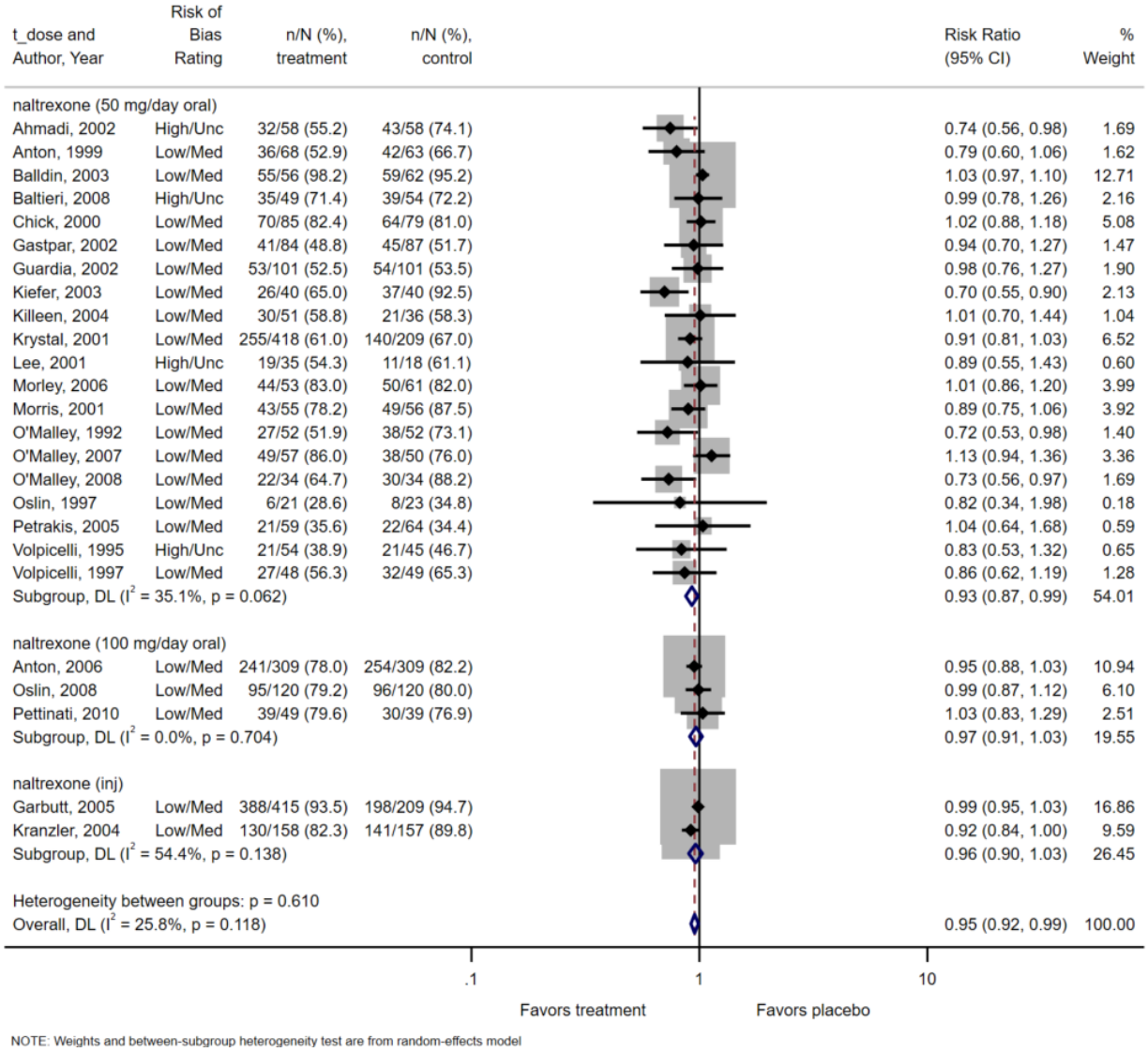
CI = confidence interval; Med = medium; n/N = sample size.

Figure E-6. Naltrexone versus placebo: Return to any drinking by risk-of-bias rating



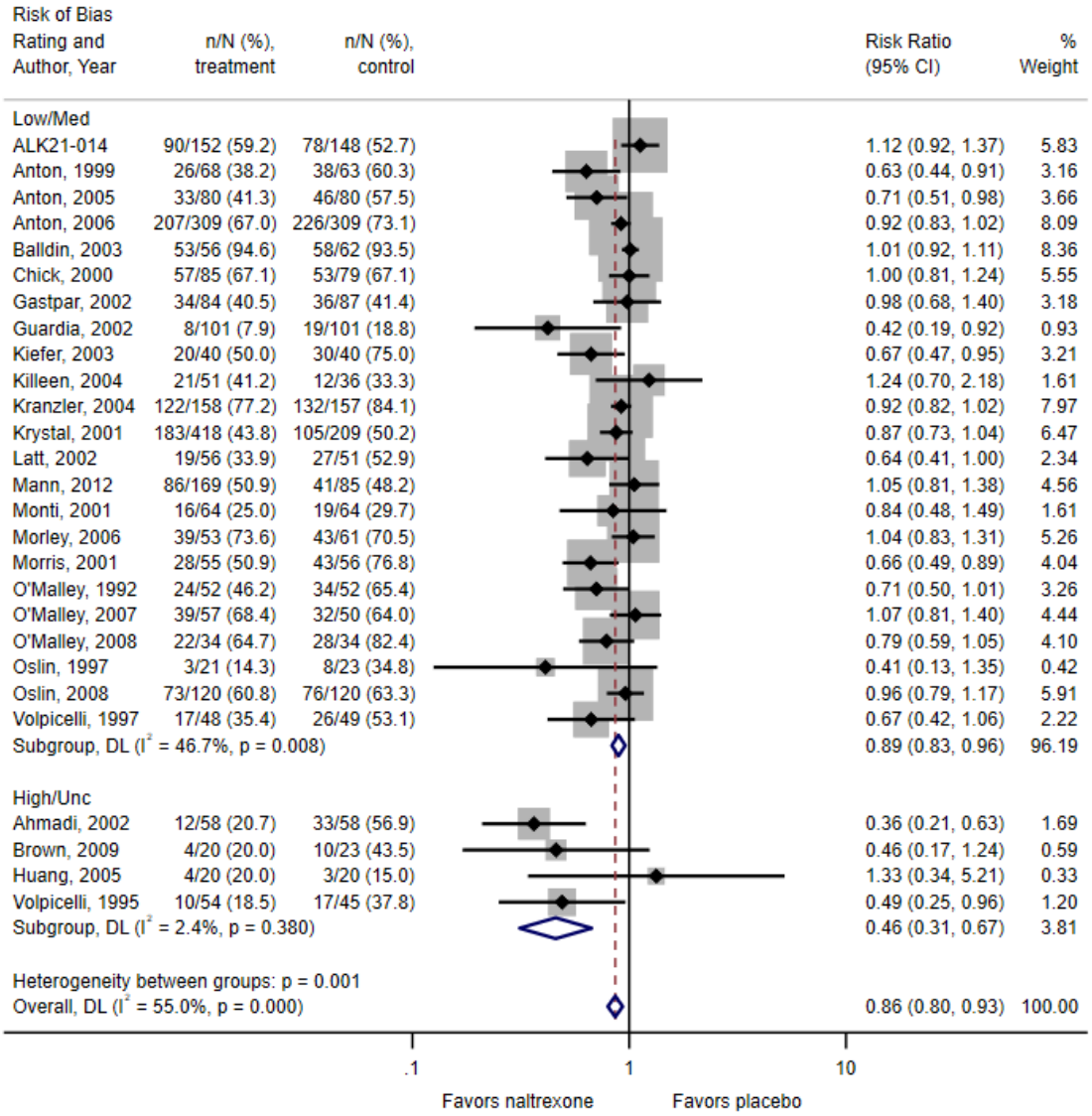
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-7. Naltrexone versus placebo: Return to any drinking by naltrexone dose



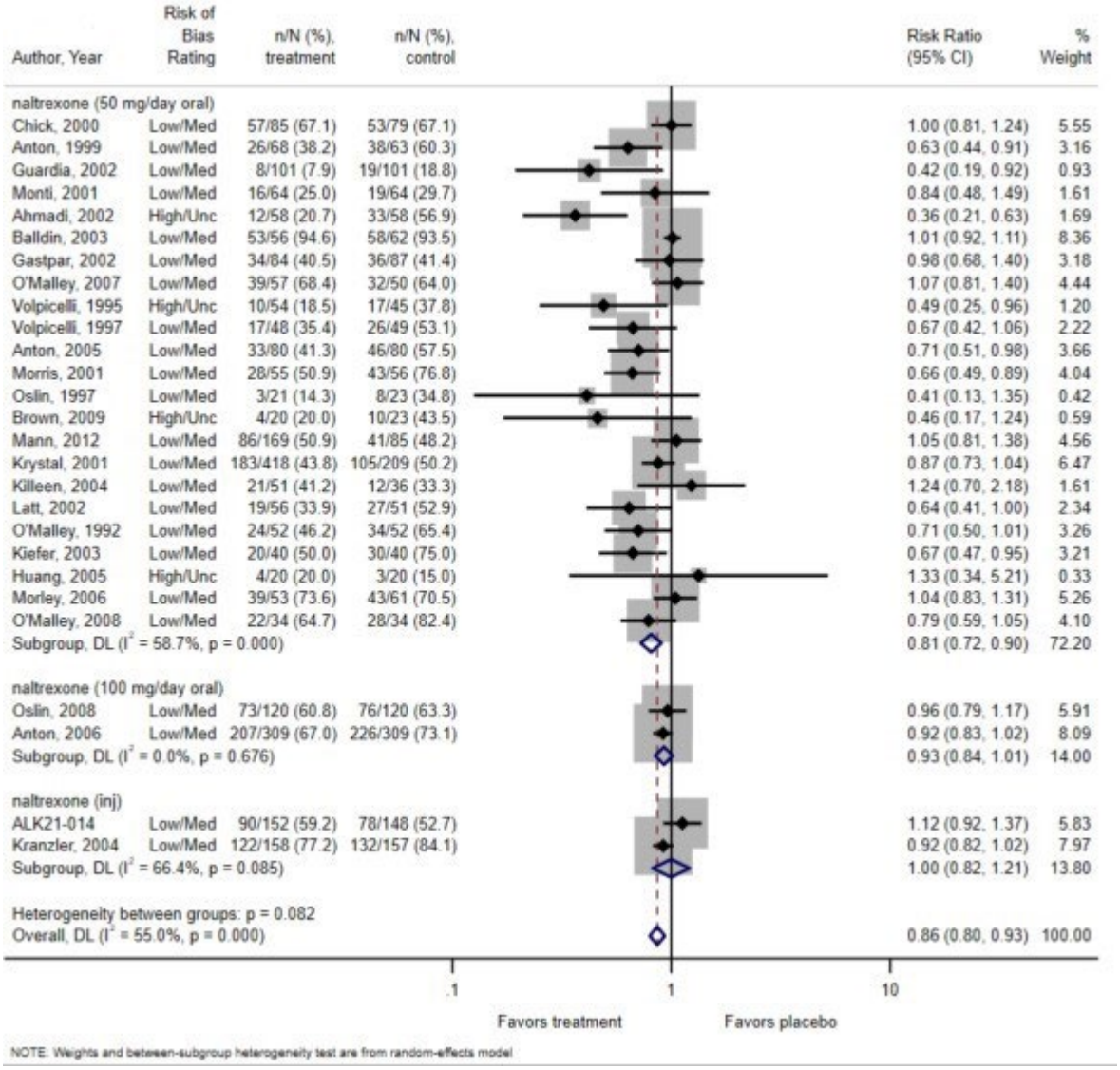
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-8. Naltrexone versus placebo: Return to heavy drinking by risk-of-bias rating



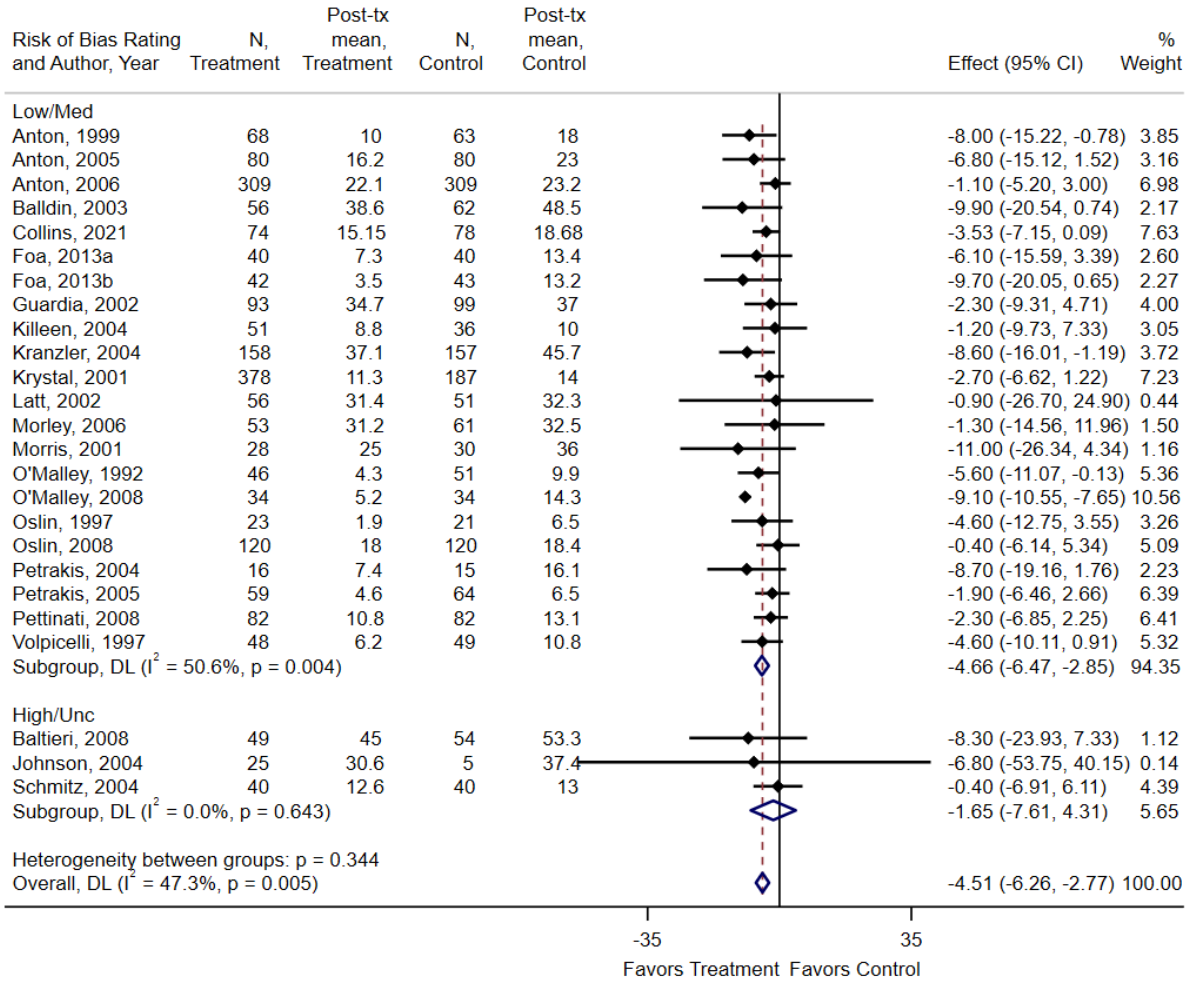
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-9. Naltrexone versus placebo: Return to heavy drinking by naltrexone dose



CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

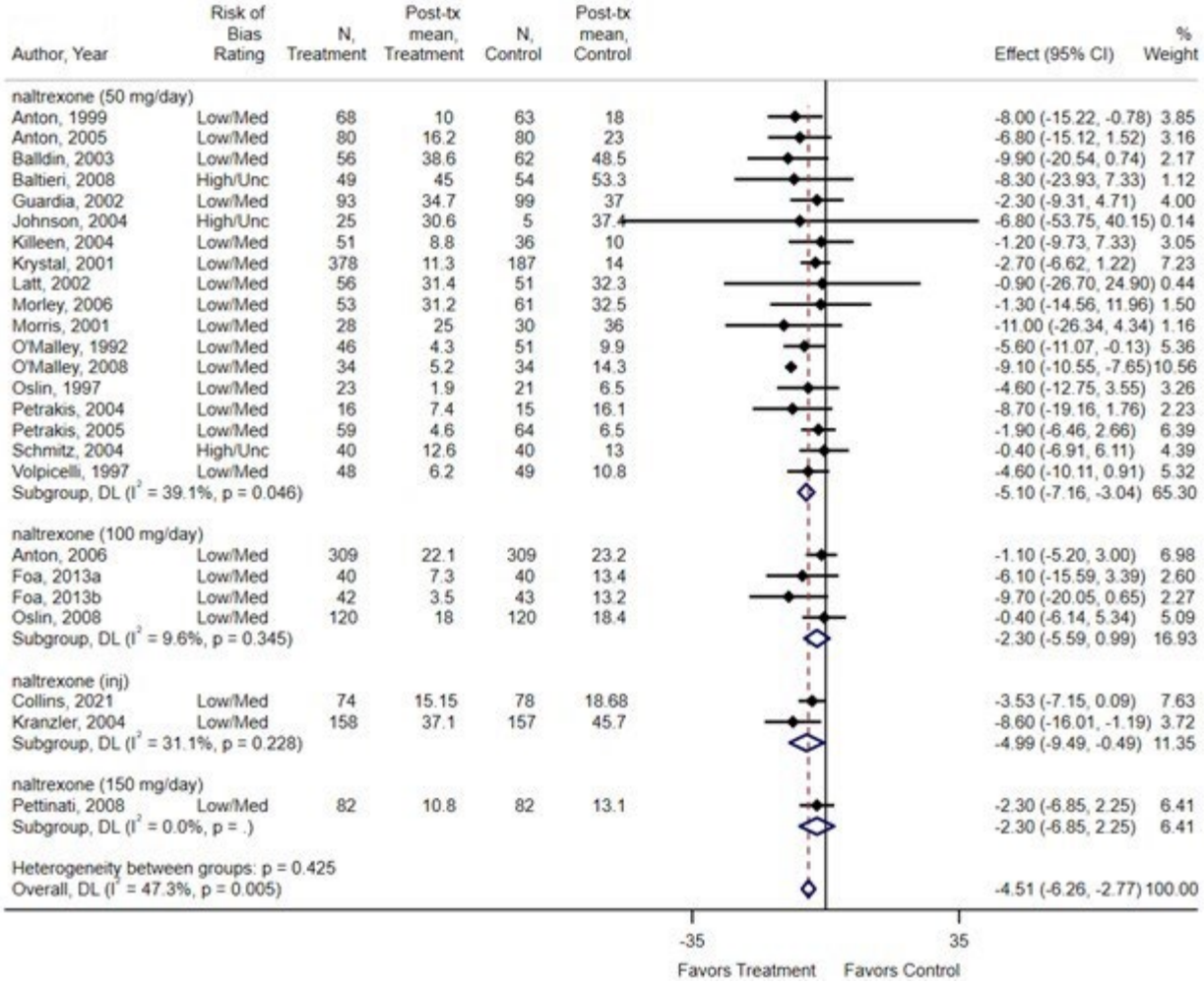
Figure E-10. Naltrexone versus placebo: Percent drinking days by risk-of-bias rating



Notes: Foa, 2013 a PTSD exposure therapy + NTX vs. PTSD exposure therapy + placebo; Foa 2013 b Supportive counseling + NTX vs. supportive counseling + placebo

CI = confidence interval; Med = medium; n/N = sample size; tx = treatment; Unc = unclear; vs. = versus.

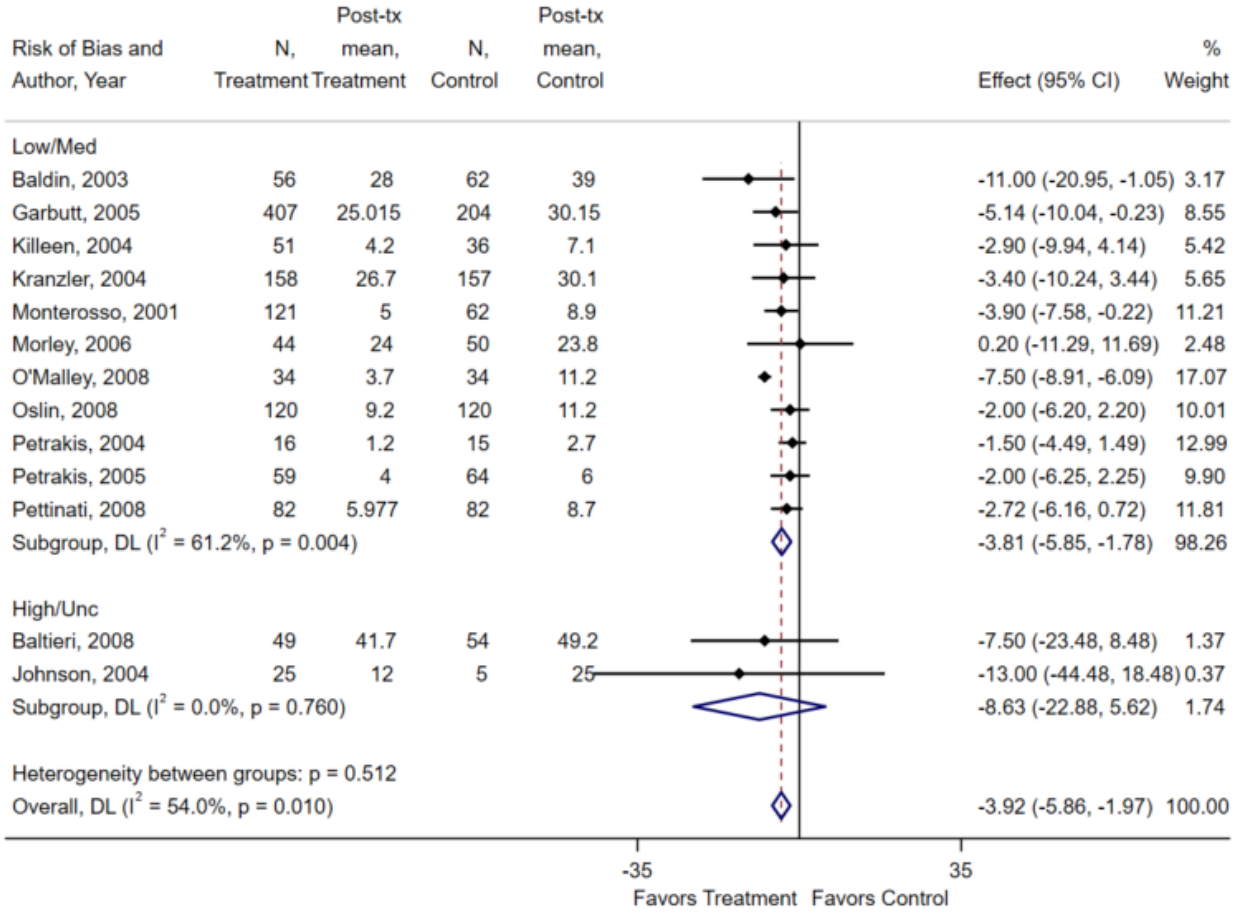
Figure E-11. Naltrexone versus placebo: Percent drinking by naltrexone dose



Notes: Foa, 2013a PTSD exposure therapy + NTX vs. PTSD exposure therapy + placebo; Foa, 2013b Supportive counseling + NTX vs. supportive counseling + placebo

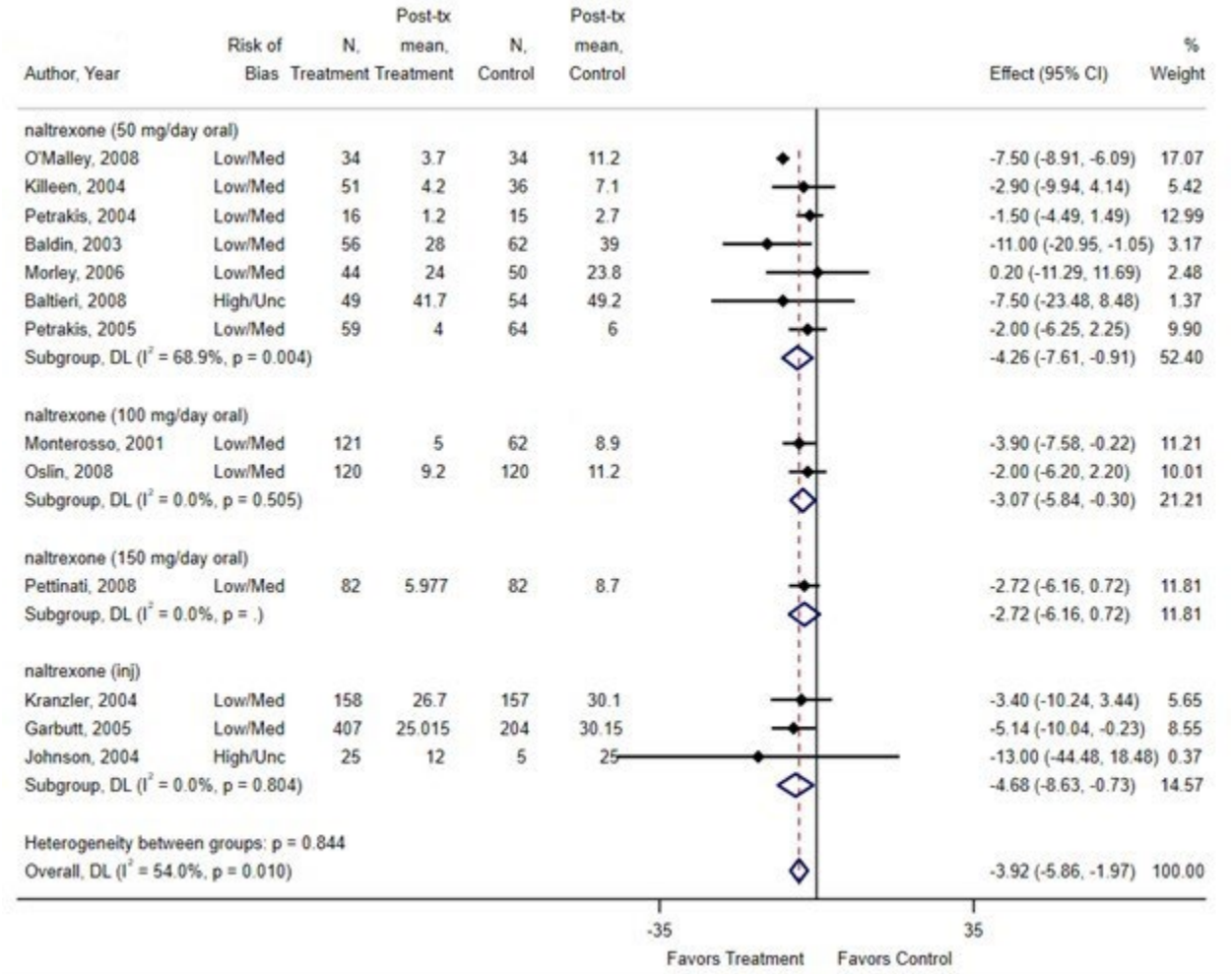
CI = confidence interval; Med = medium; N = sample size; NTX = naltrexone; PTSD = posttraumatic stress disorder; tx = treatment; vs. = versus.

Figure E-12. Naltrexone versus placebo: Percent heavy drinking days by risk-of-bias rating



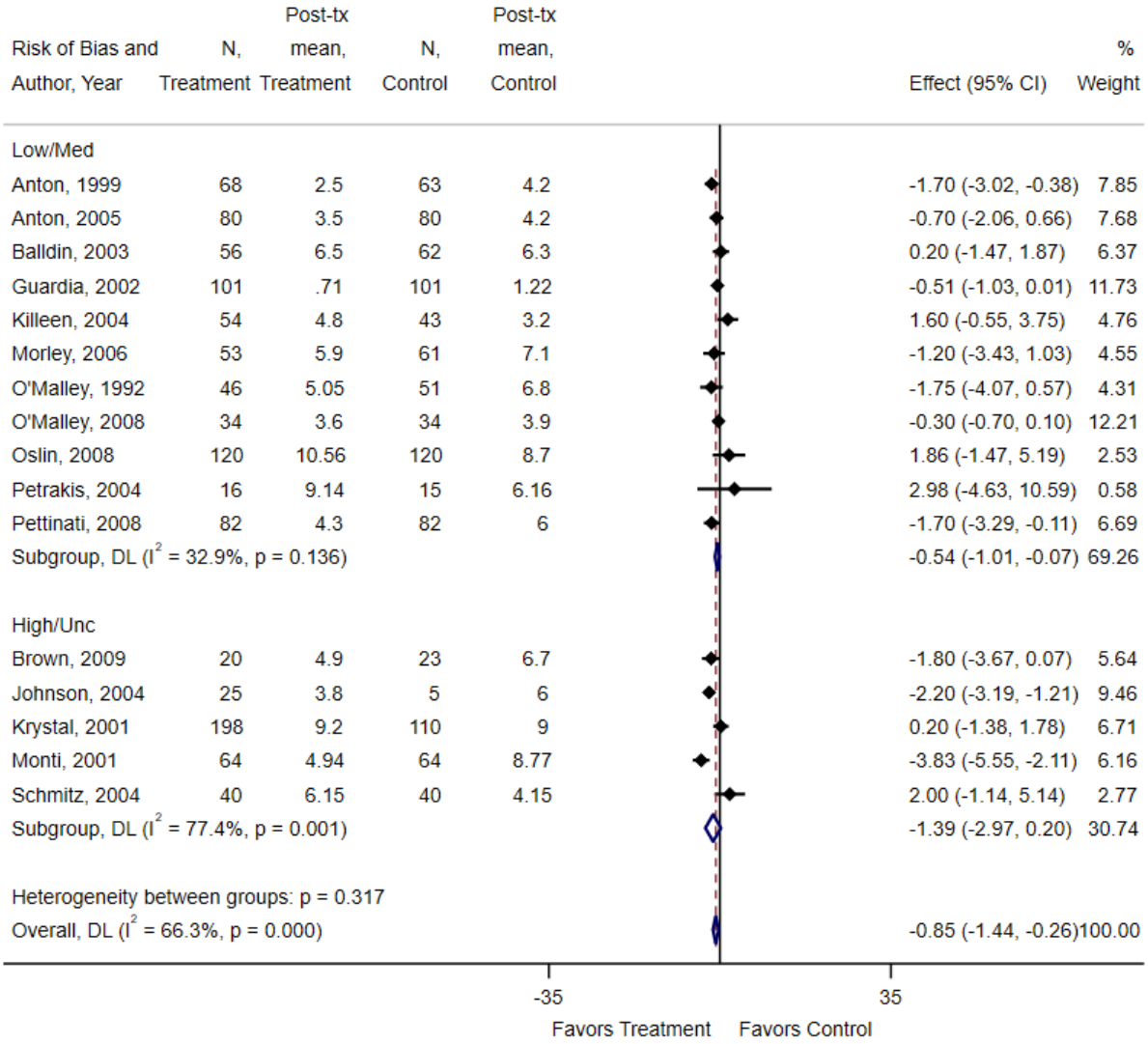
CI = confidence interval; Med = medium; n/N = sample size; tx = treatment; Unc = unclear.

Figure E-13. Naltrexone versus placebo: Percent heavy drinking days by naltrexone dose



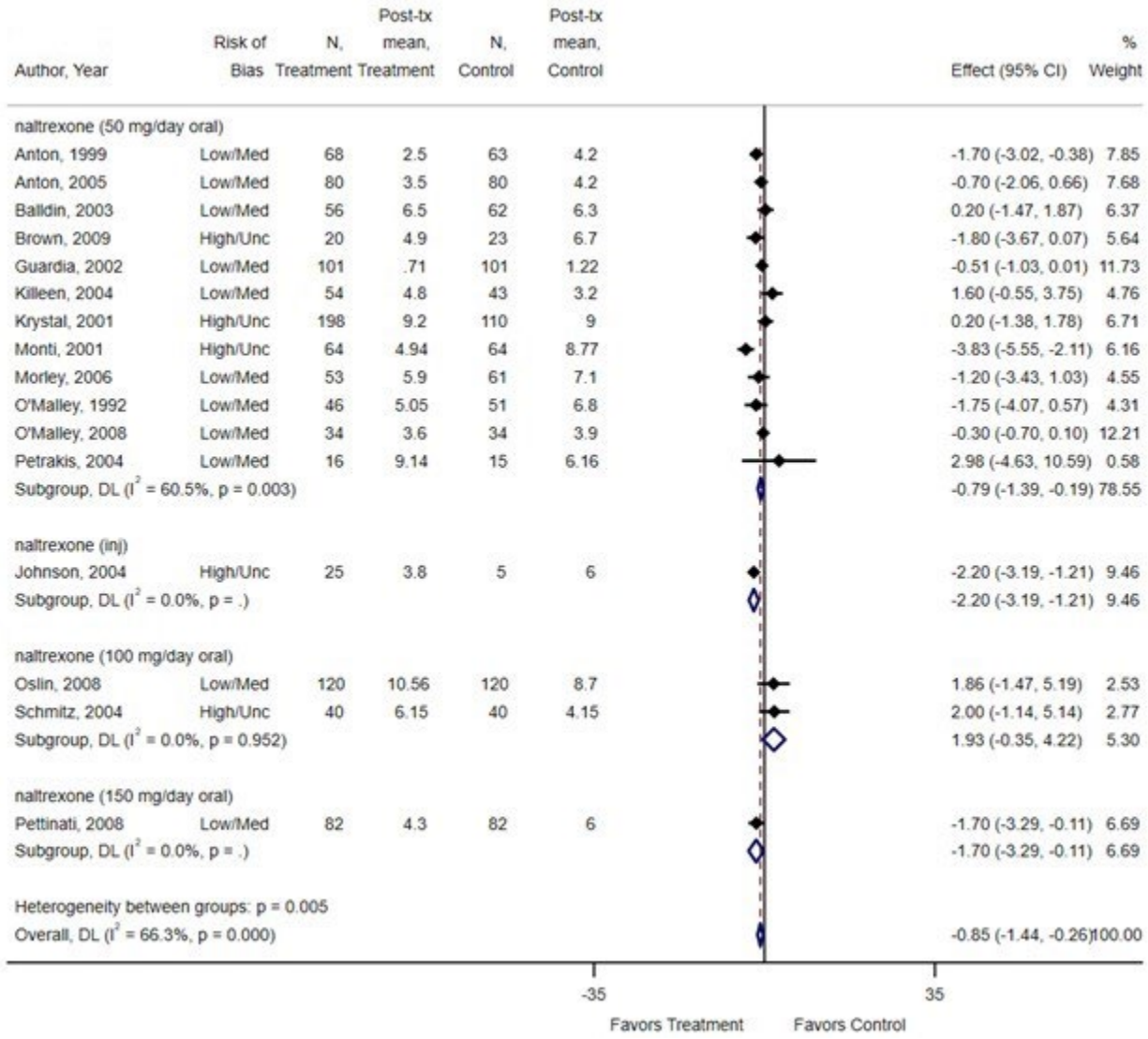
CI = confidence interval; Med = medium; n/N = sample size; tx = treatment; Unc = unclear.

Figure E-14. Naltrexone versus placebo: Drinks per drinking day by risk-of-bias



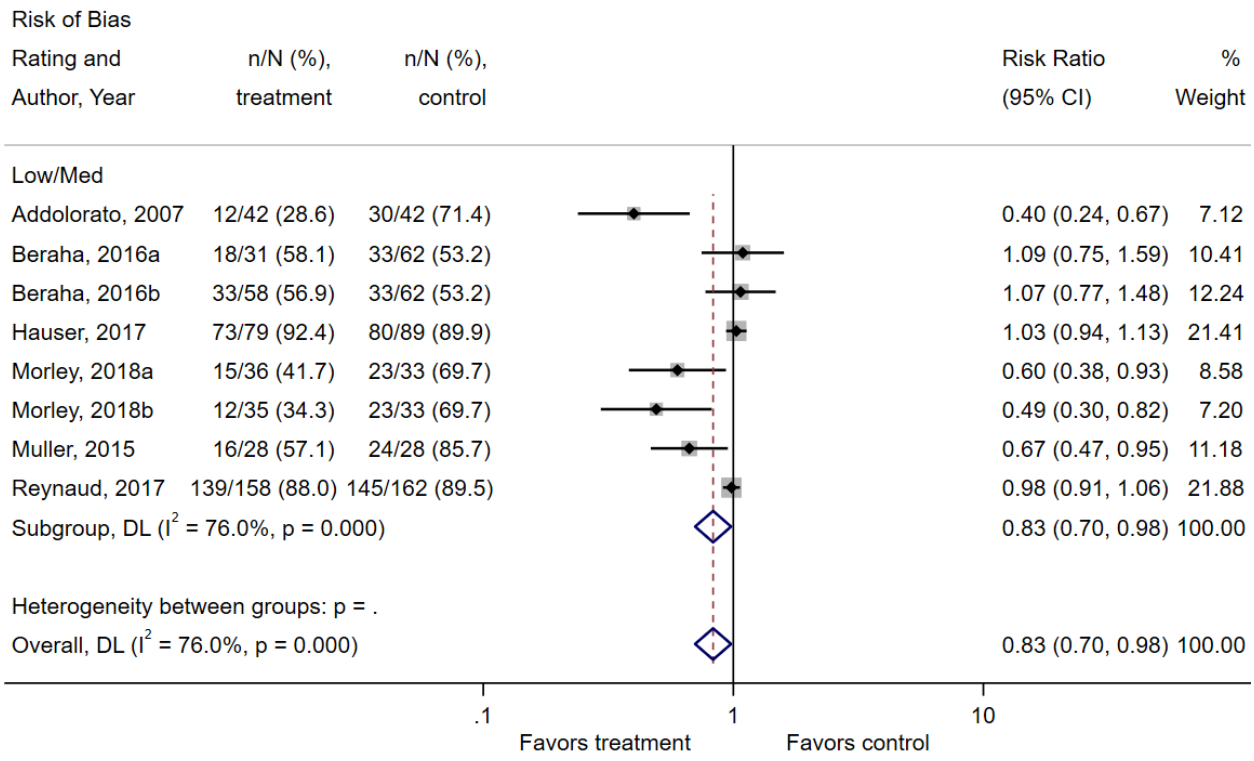
CI = confidence interval; Med = medium; n/N = sample size; tx = treatment; Unc = unclear.

Figure E-15. Naltrexone versus placebo: Drinks per drinking day by naltrexone dose



CI = confidence interval; Med = medium; n/N = sample size; tx = treatment Unc = unclear.

Figure E-16. Baclofen versus placebo: Return to any drinking

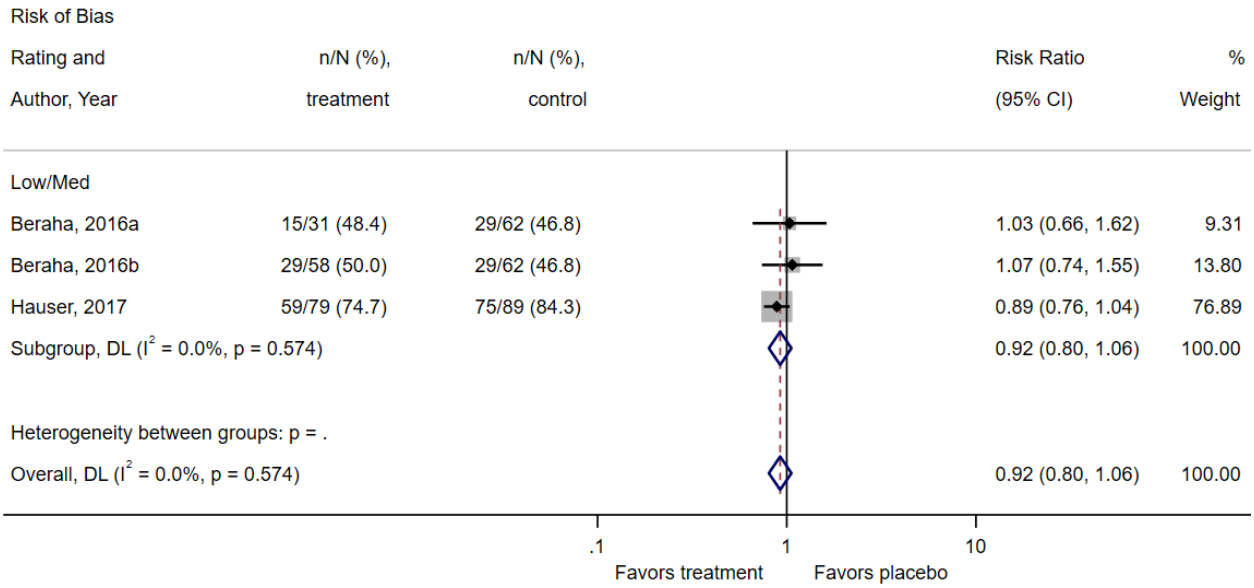


NOTE: Weights are from random-effects model

Notes: Beraha, 2016a dose is 30 mg; Beraha, 2016b dose is up to 150 mg; Morley, 2018a dose is 30 mg; Morley, 2018b dose is 75 mg

CI = confidence interval; Med = medium; mg = milligram; n/N = sample size.

Figure E-17. Baclofen versus placebo: Return to heavy drinking

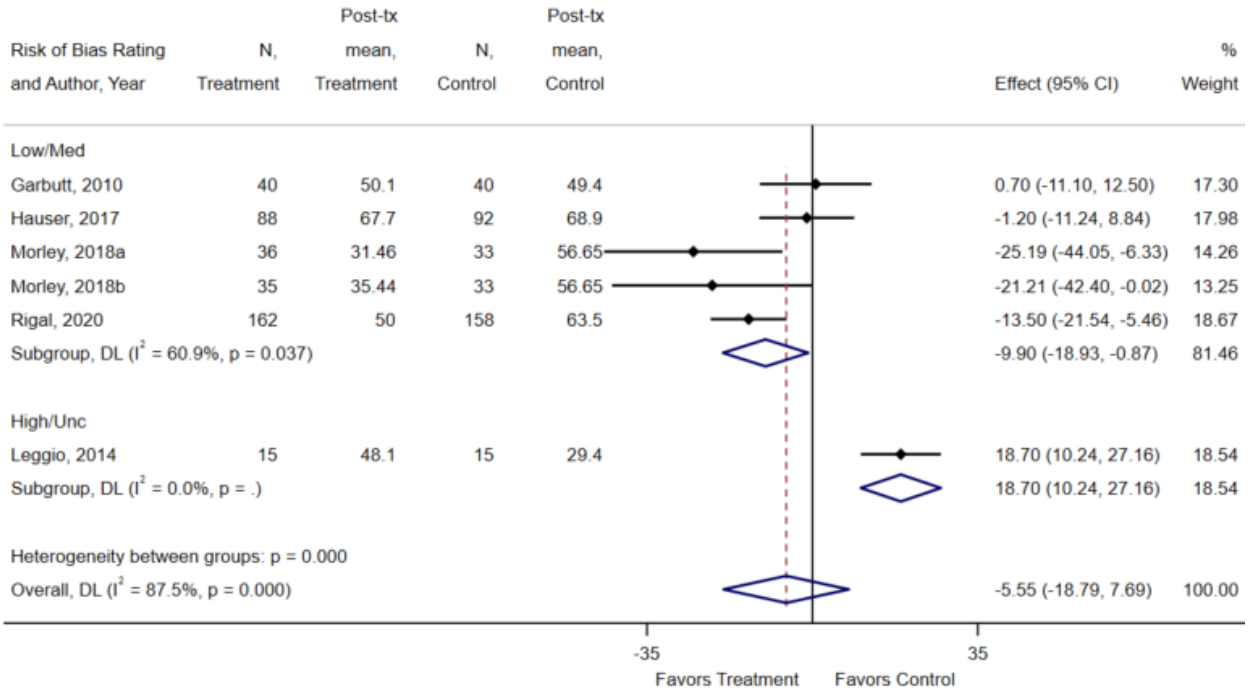


NOTE: Weights are from random-effects model

Notes: Beraha, 2016a dose is 30 mg; Beraha, 2016b dose is up to 150 mg

CI = confidence interval; Med = medium; mg = milligram; n/N = sample size.

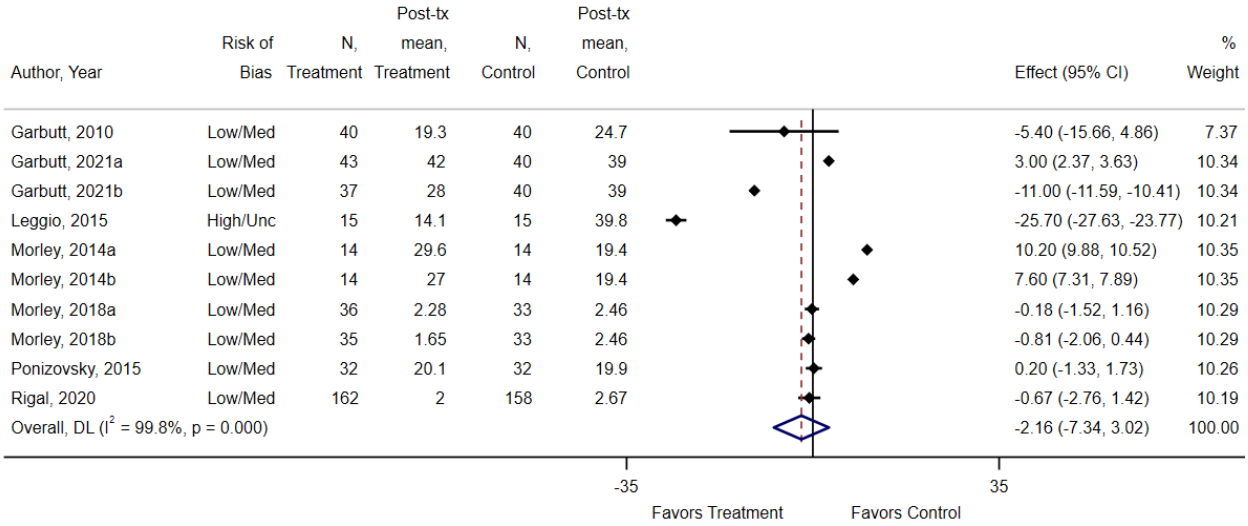
Figure E-18. Baclofen versus placebo: Percent drinking days



Notes: Morley, 2018a dose is 30 mg; Morley, 2018b dose is 75 mg

CI = confidence interval; Med = medium; mg = milligram; n/N = sample size; tx = treatment; Unc = unclear.

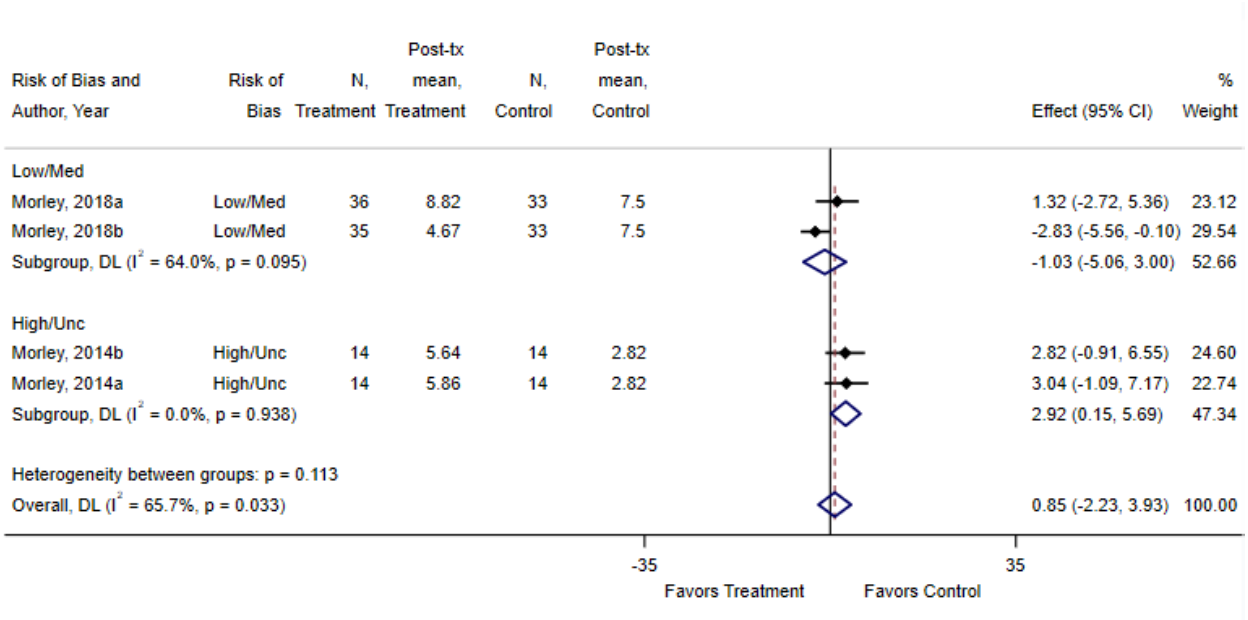
Figure E-19. Baclofen versus placebo: Percent heavy drinking days



Notes: Garbutt 2021a dose is 30 mg; Garbutt 2021b dose is 90 mg; Morley, 2018a dose is 30 mg; Morley, 2018b dose is 75 mg; Krupitskii, 2017[110] reported 0 events and is not shown in the figure.

CI = confidence interval; Med = medium; mg = milligram; n/N = sample size; tx = treatment; Unc = unclear.

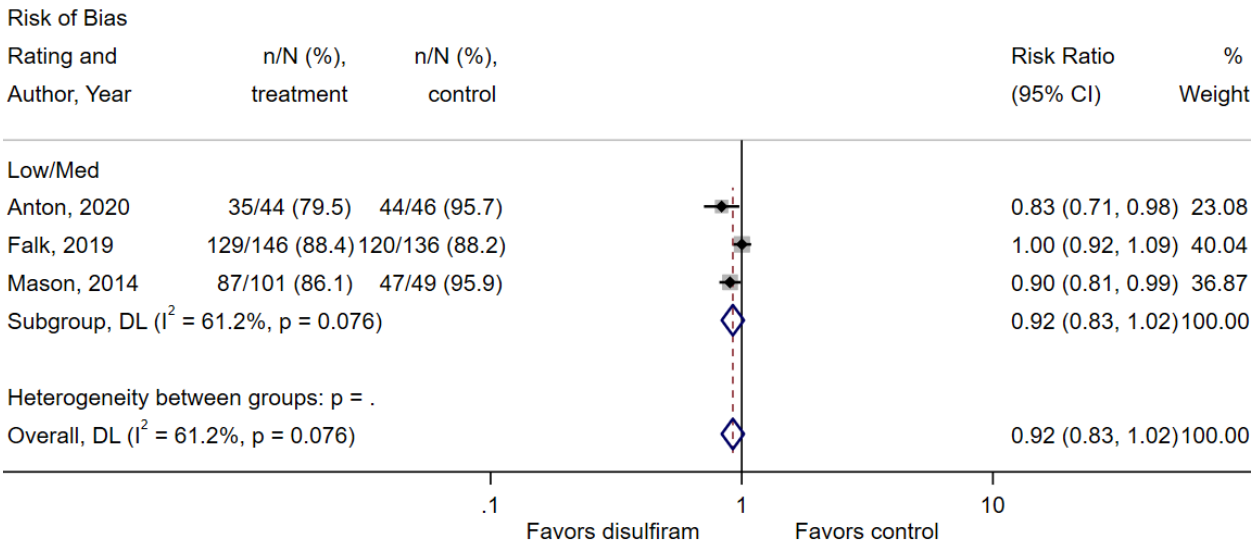
Figure E-20. Baclofen versus placebo: Drinks per drinking day



Notes: Morley,2014a dose is 30 mg; Morley, 2014b dose is 60 mg; Morley, 2018a dose is 30 mg; Morley, 2018b dose is 75 mg

CI = confidence interval; Med = medium; mg = milligram; n/N = sample size; tx = treatment ; Unc = unclear.

Figure E-21. Gabapentin versus placebo: Return to any drinking

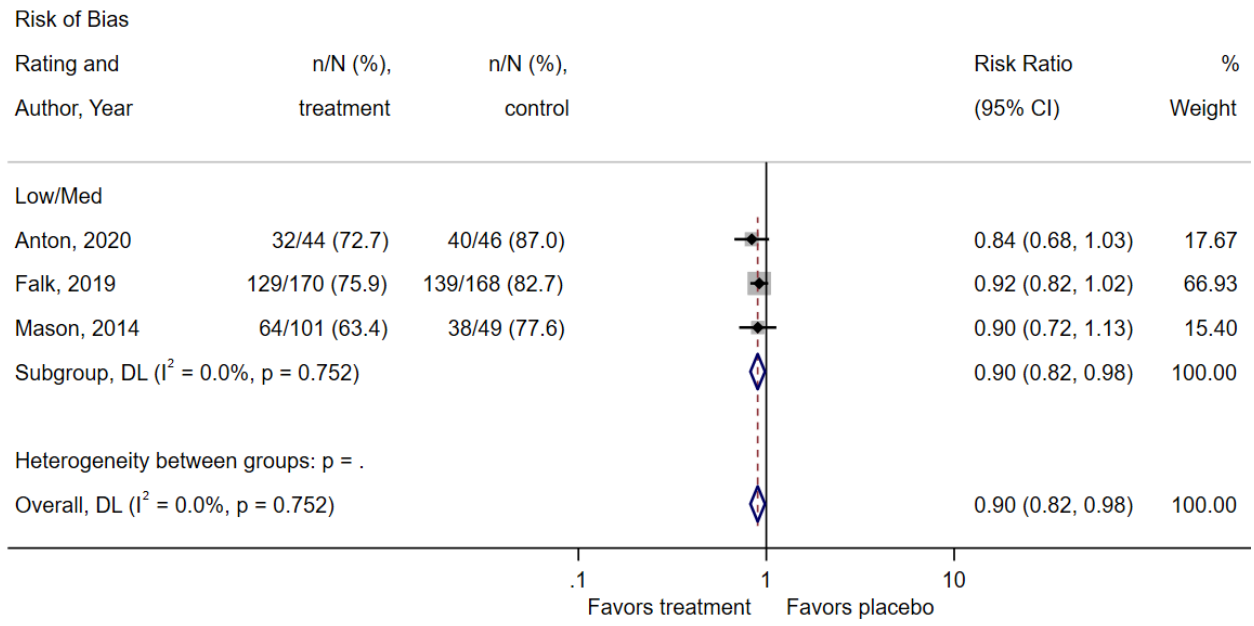


NOTE: Weights are from random-effects model

Note: Mason, 2014 reflects combination of two gabapentin doses.

CI = confidence interval; Med = medium; n/N = sample size.

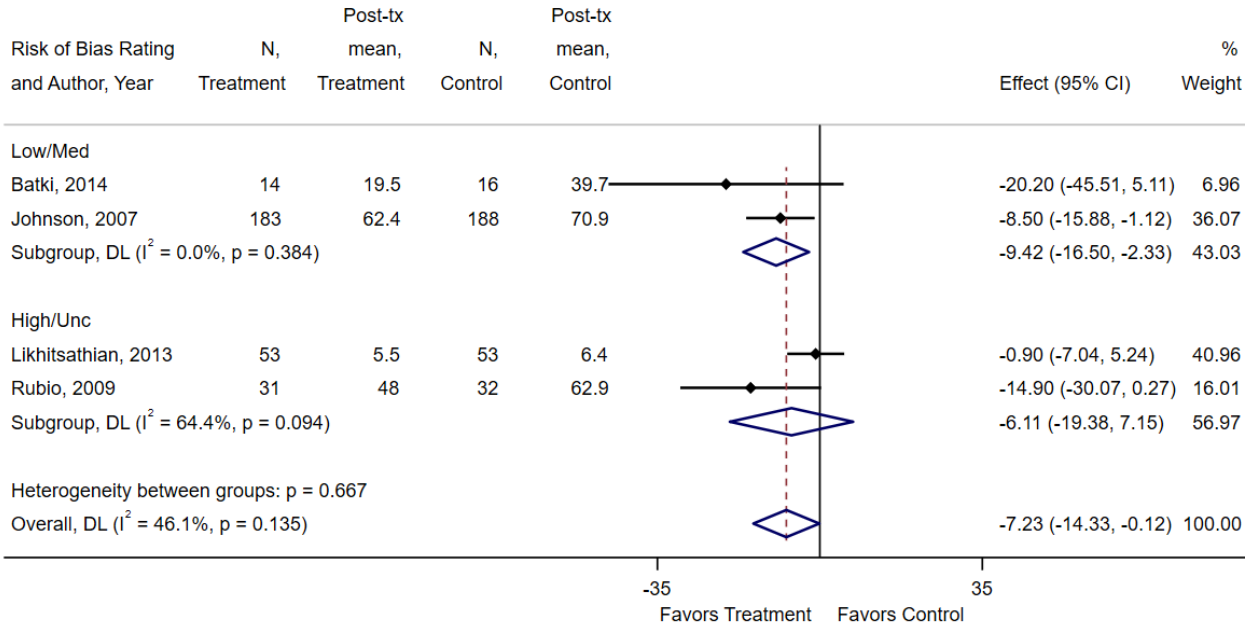
Figure E-22. Gabapentin versus placebo: Return to heavy drinking



NOTE: Weights are from random-effects model

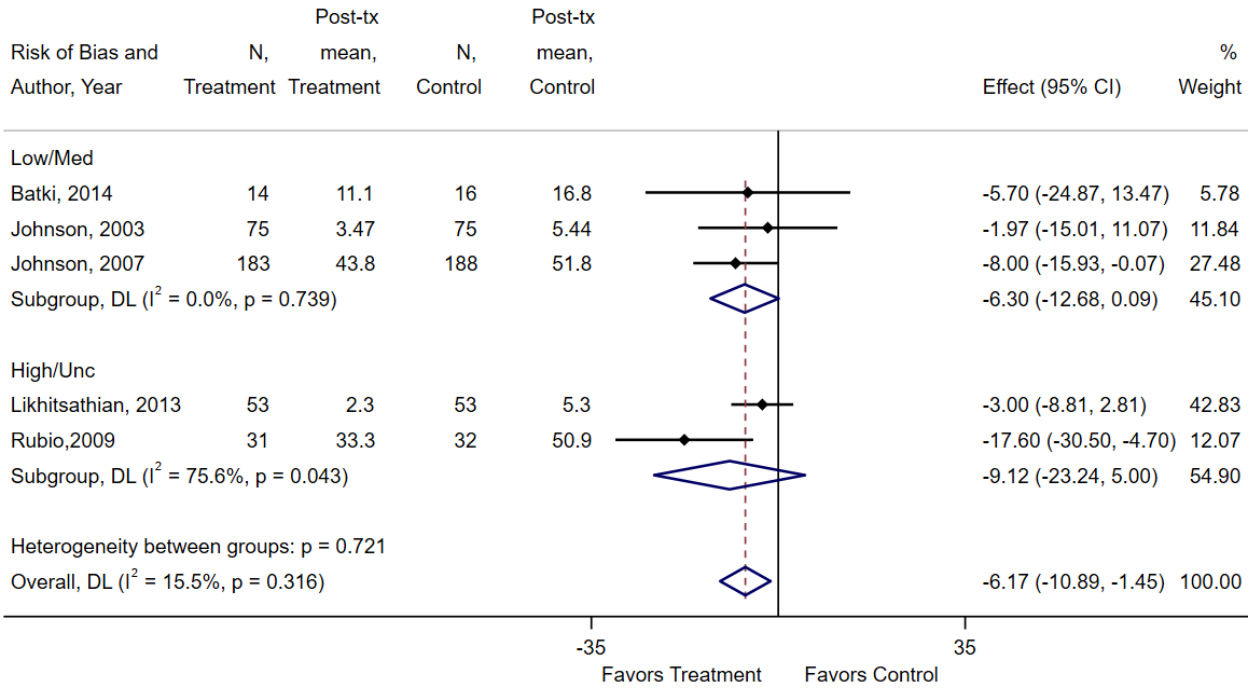
CI = confidence interval; Med = medium; n/N = sample size.

Figure E-23. Topiramate versus placebo: Percent drinking days by risk-of-bias



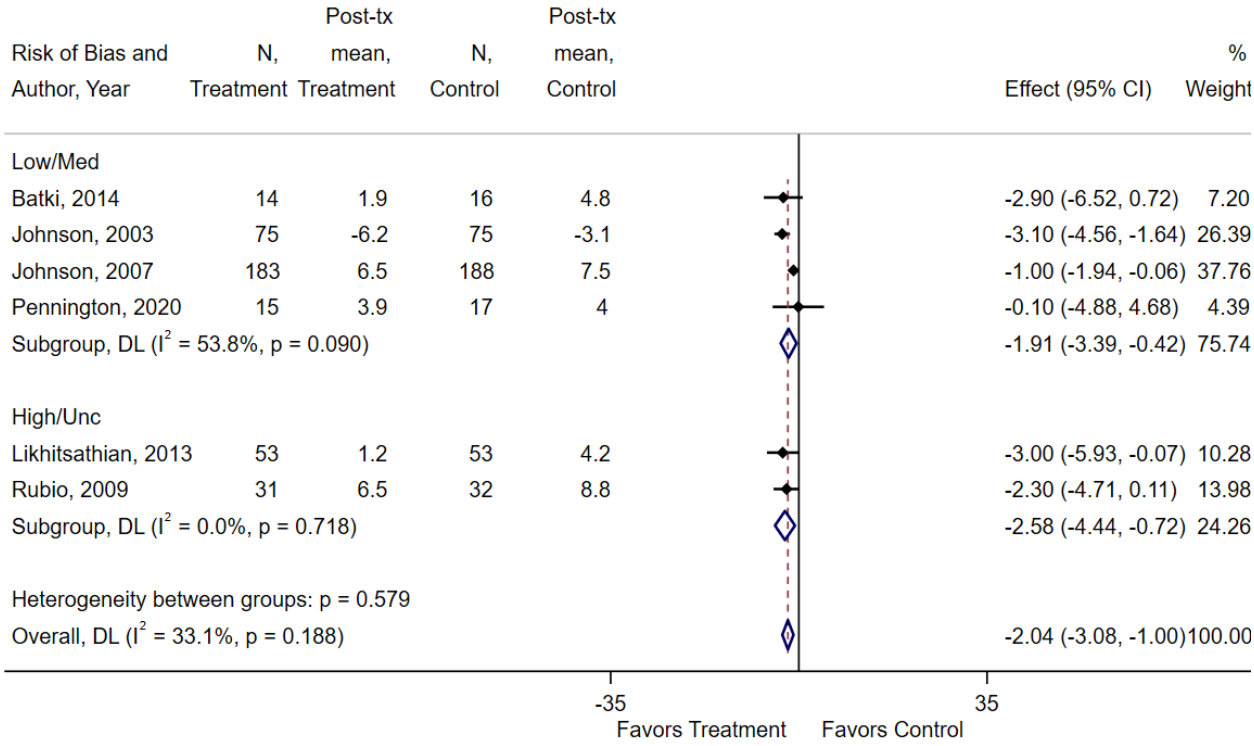
CI = confidence interval; Med = medium; n/N = sample size; tx = treatment; Unc = unclear.

Figure E-24. Topiramate versus placebo: Percent heavy drinking days by risk-of-bias



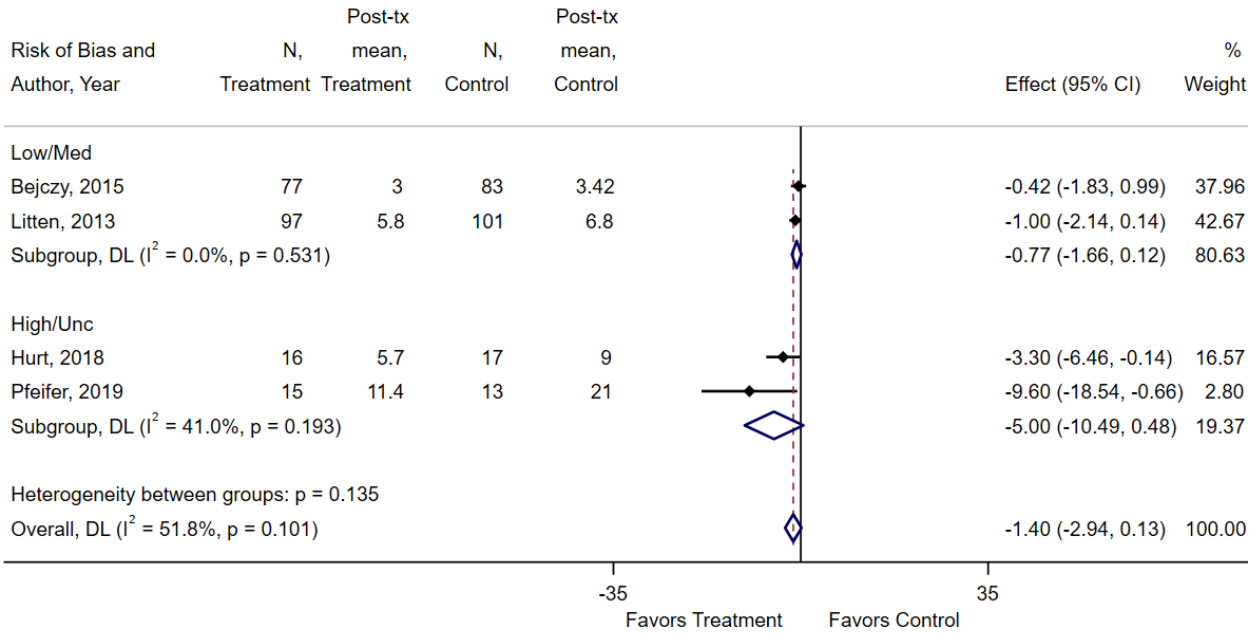
CI = confidence interval; Med = medium; n/N = sample size; tx = treatment; Unc = unclear.

Figure E-25. Topiramate versus placebo: Drinks per drinking day by risk-of-bias



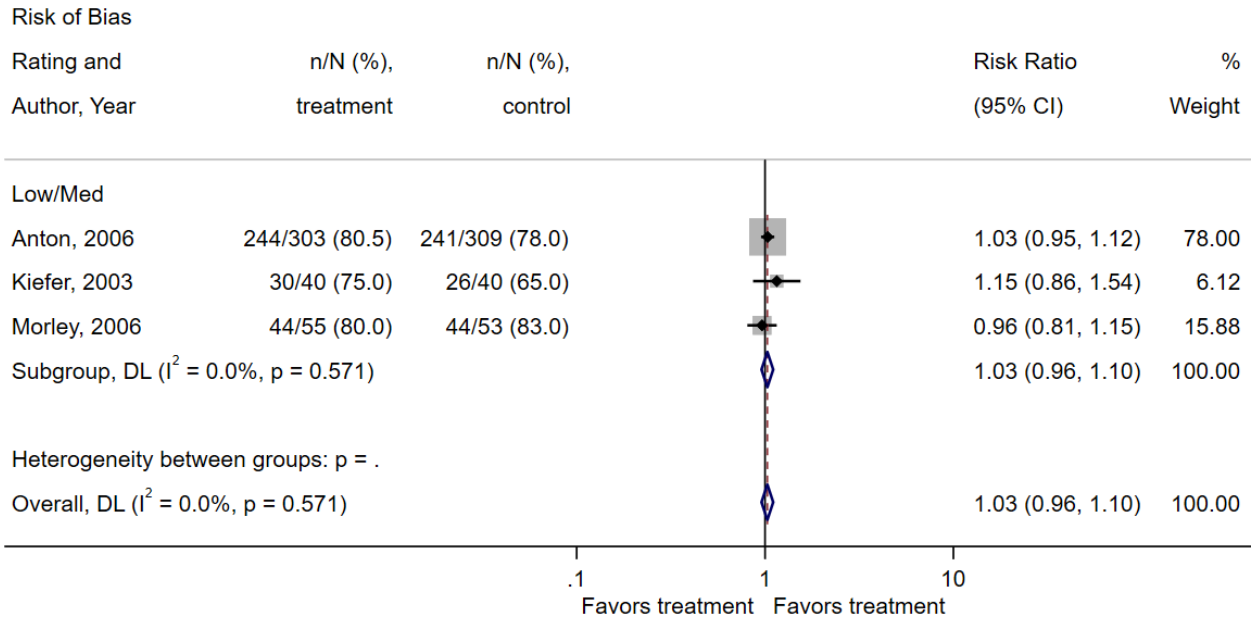
CI = confidence interval; Med = medium; n/N = sample size; tx = treatment; Unc = unclear.

Figure E-26. Varenicline versus placebo: Drinks per drinking day



CI = confidence interval; Med = medium; n/N = sample size; tx = treatment; Unc = unclear.

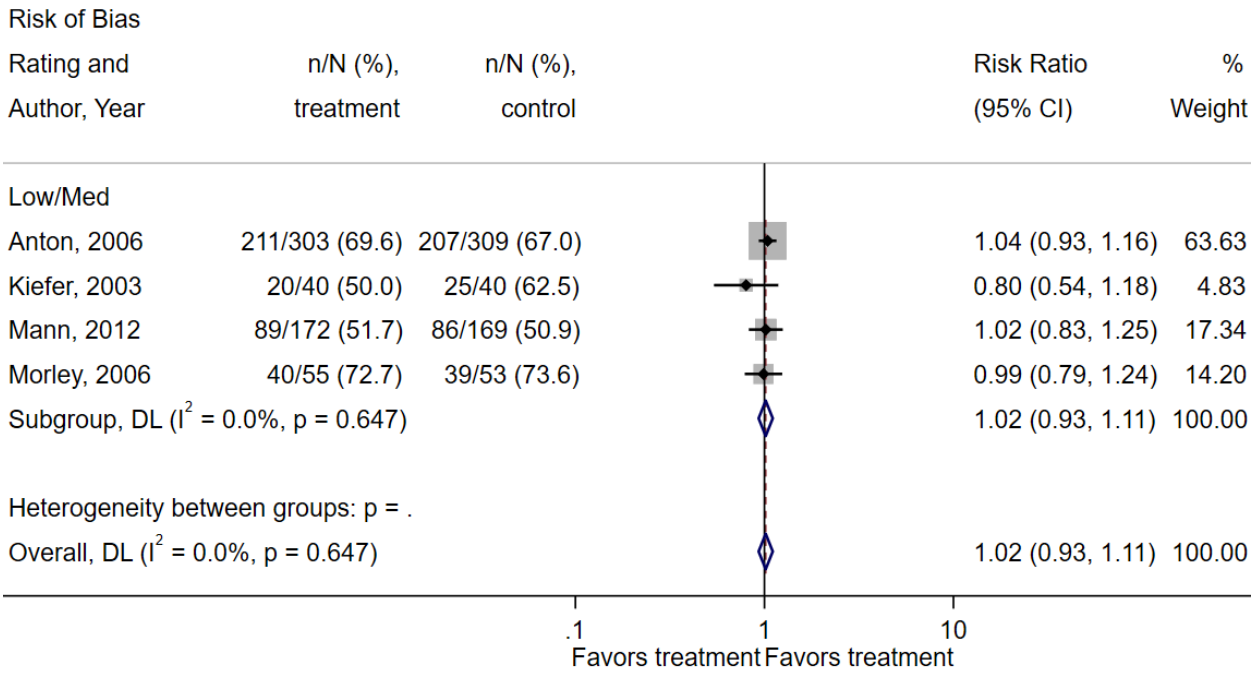
Figure E-27. Acamprosate versus naltrexone: Return to any drinking by risk-of-bias



NOTE: Weights are from random-effects model

CI = confidence interval; Med = medium; n/N = sample size.

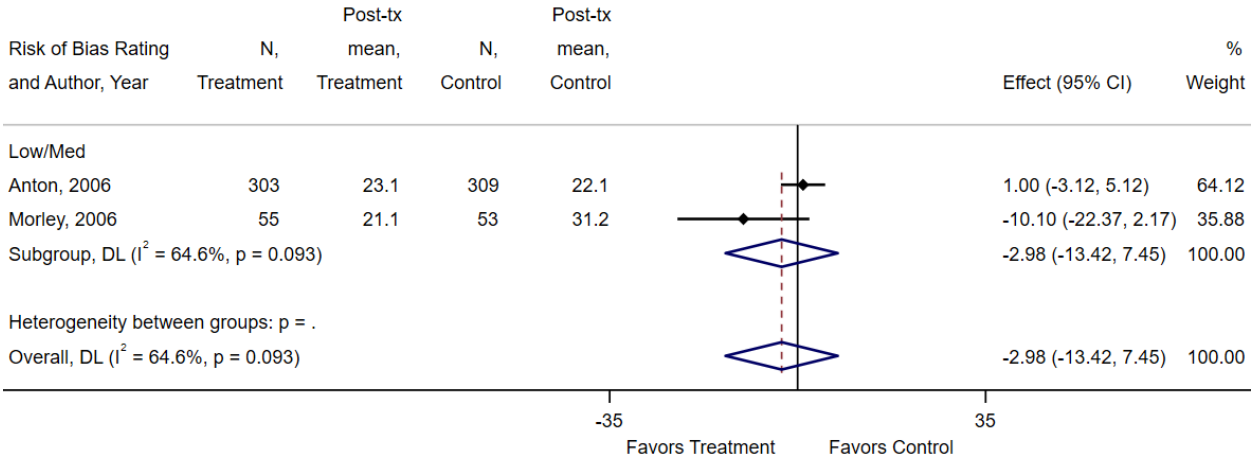
Figure E-28. Acamprosate versus naltrexone: Return to heavy drinking by risk-of-bias



NOTE: Weights are from random-effects model

CI = confidence interval; Med = medium; n/N = sample size.

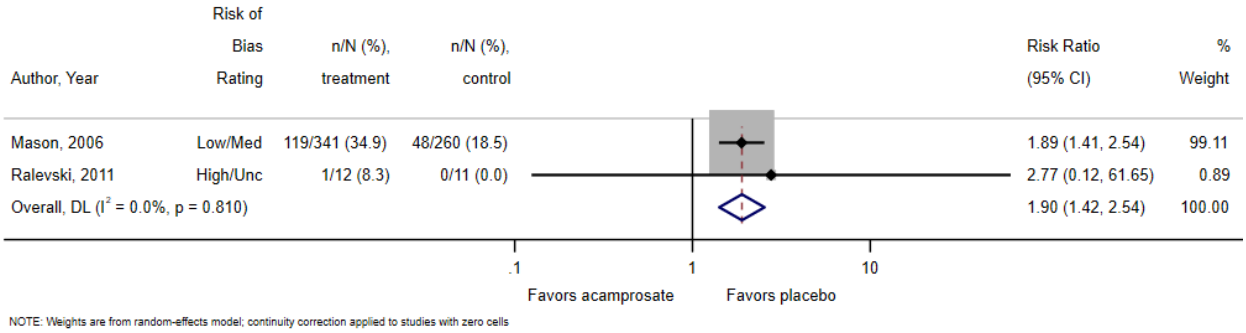
Figure E-29. Acamprosate versus naltrexone: Percent drinking days by risk-of-bias



CI = confidence interval; Med = medium; n/N = sample size.

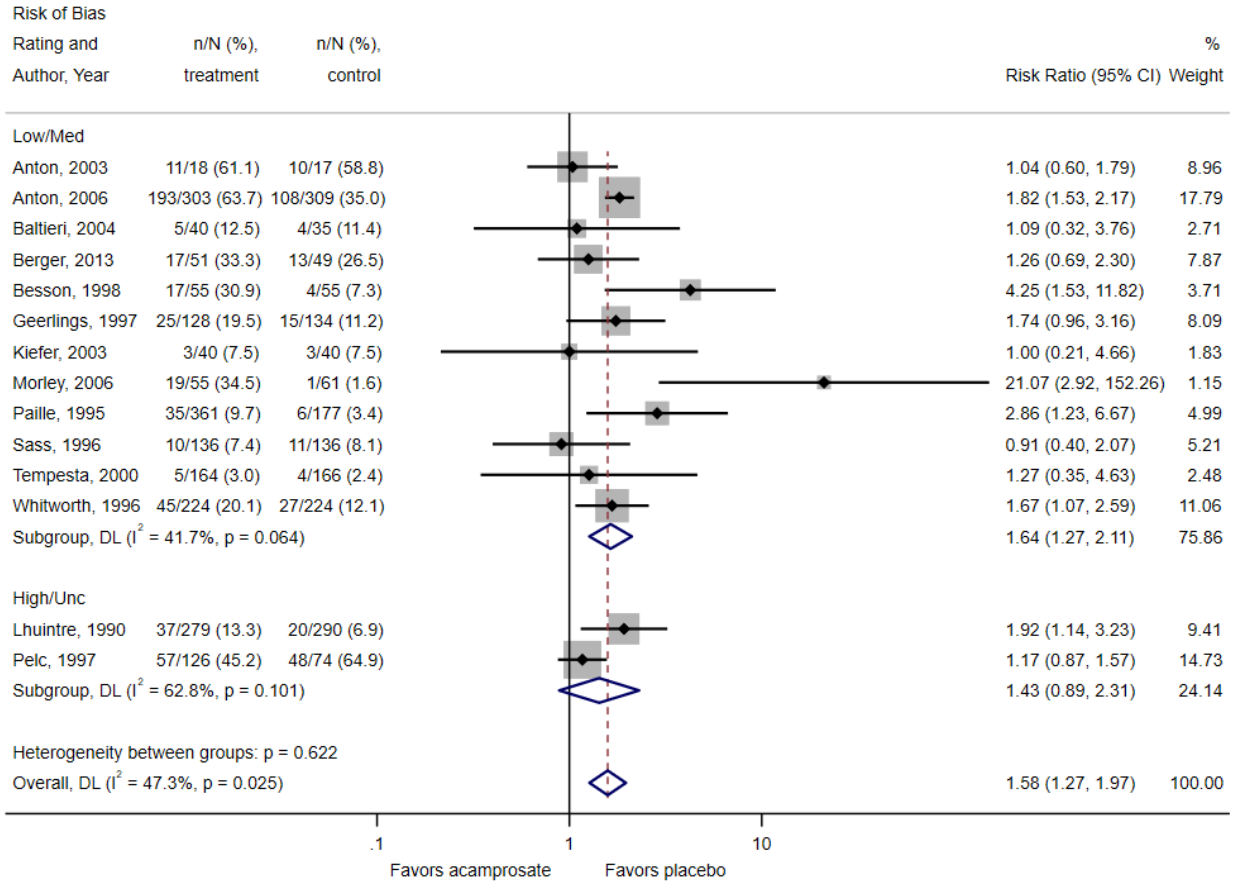
Key Question 3. Meta-Analysis Results

Figure E-30. Acamprosate versus placebo: Anxiety by risk-of-bias rating



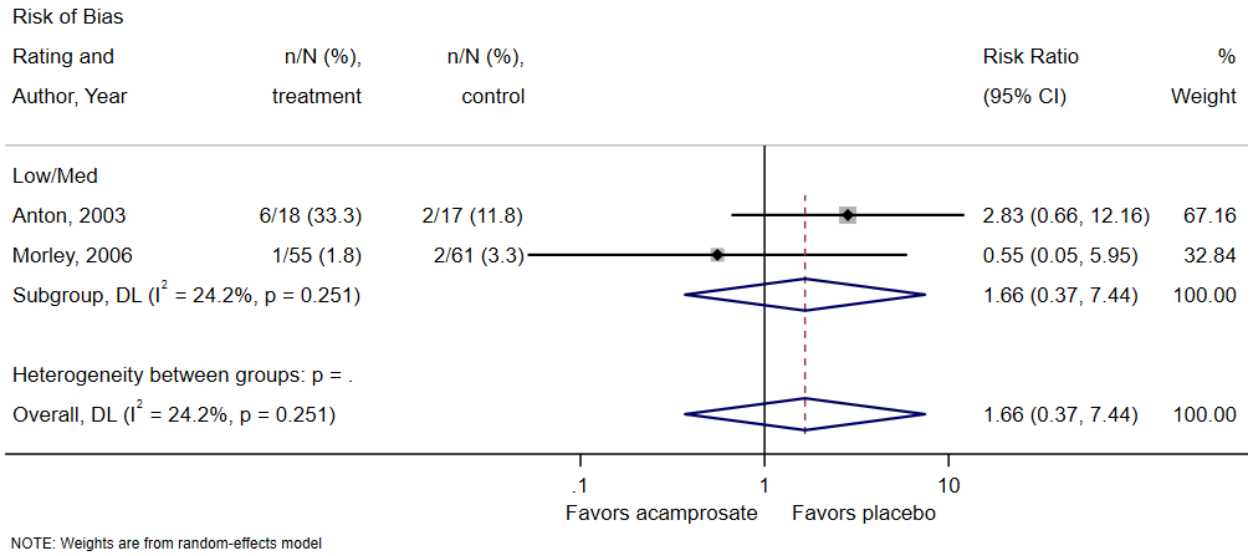
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-31. Acamprosate versus placebo: Diarrhea by risk-of-bias rating



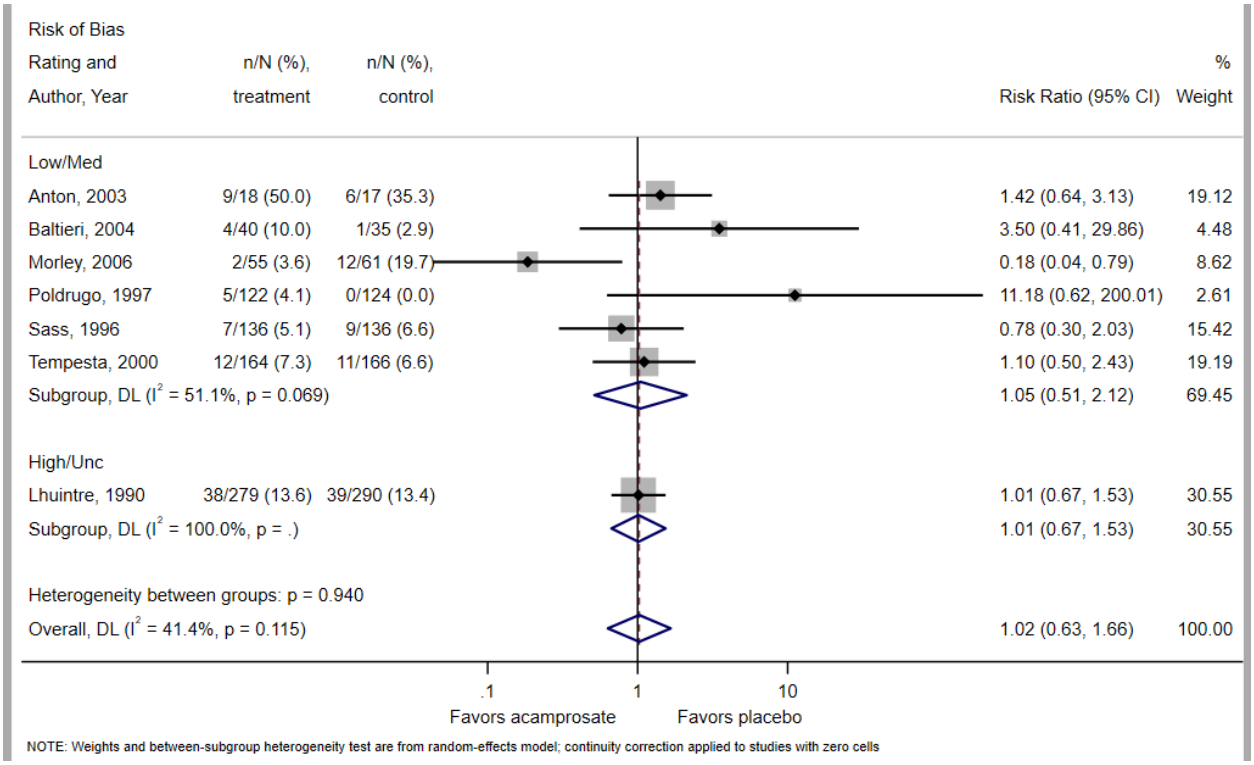
CI = confidence interval; Med = medium; n/N = sample size.

Figure E-32. Acamprosate versus placebo: Dizziness by risk-of-bias rating



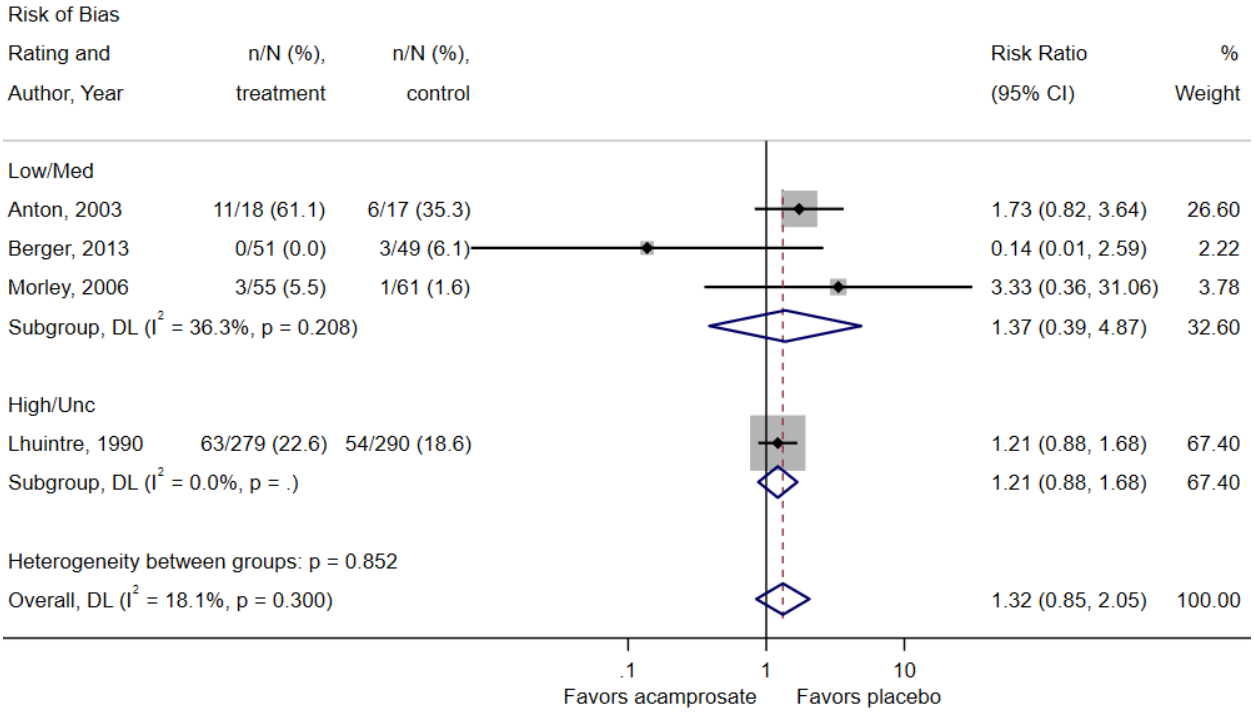
CI = confidence interval; Med = medium; n/N = sample size.

Figure E-33. Acamprosate versus placebo: Headache by risk-of-bias rating



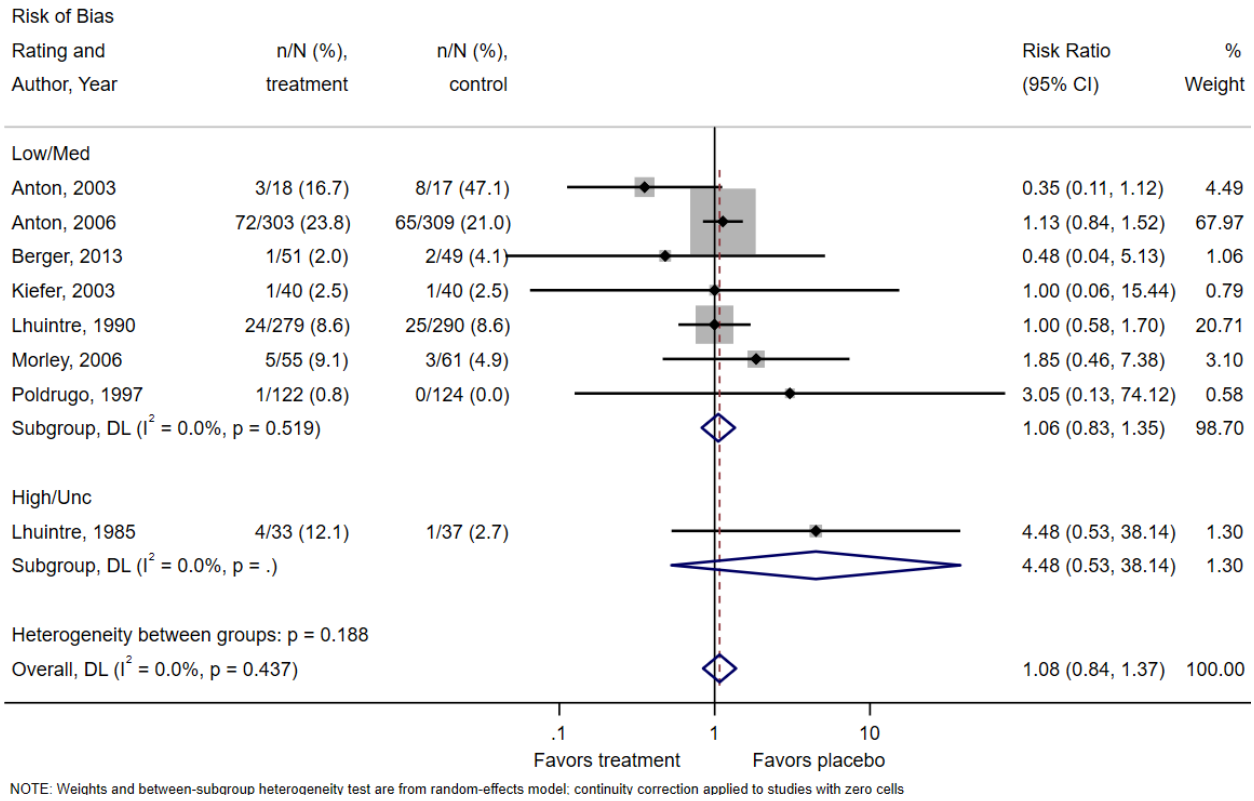
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-34. Acamprosate versus placebo: Insomnia by risk-of-bias rating



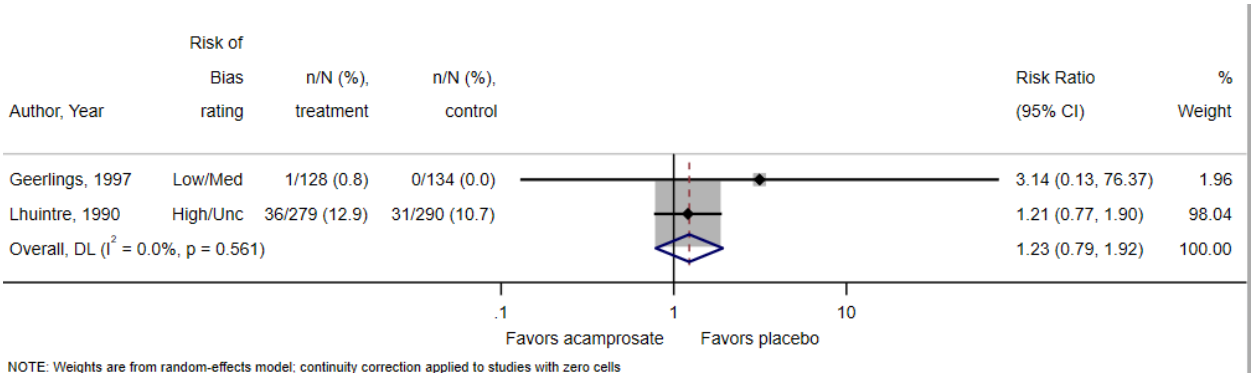
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-35. Acamprosate versus placebo: Nausea by risk-of-bias rating



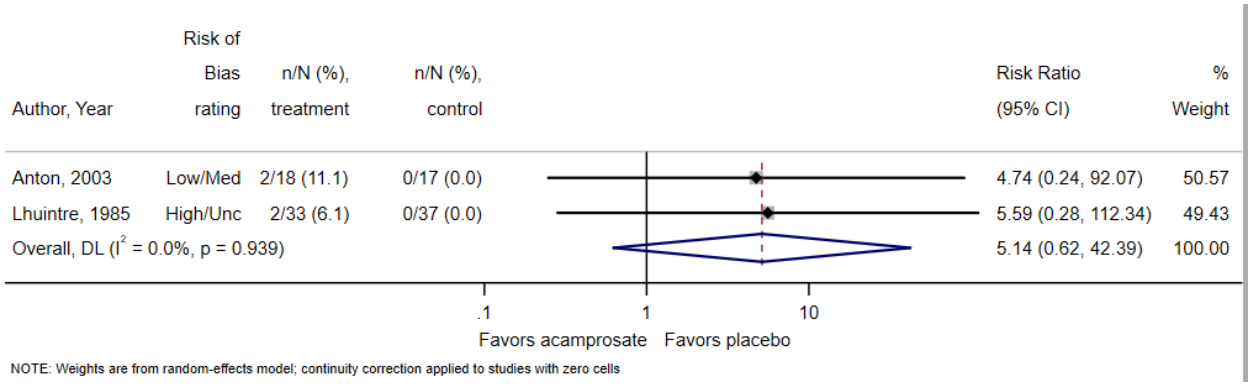
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-36. Acamprosate versus placebo: Numbness by risk-of-bias rating



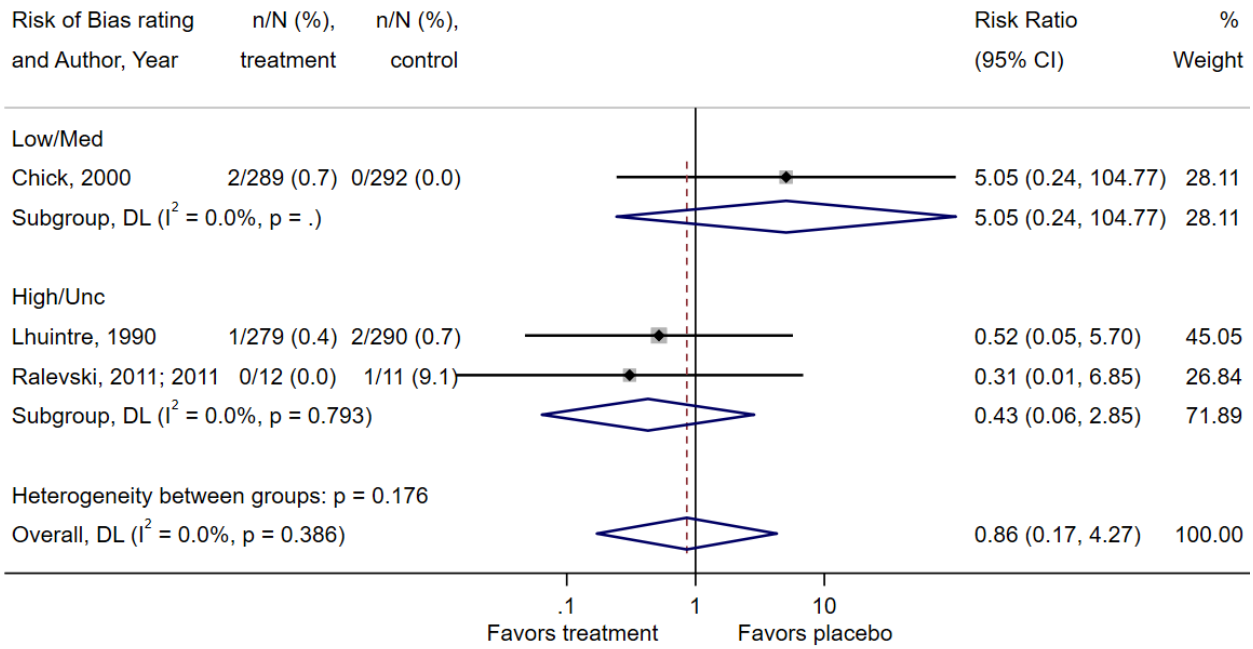
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-37. Acamprosate versus placebo: Rash by risk-of-bias rating



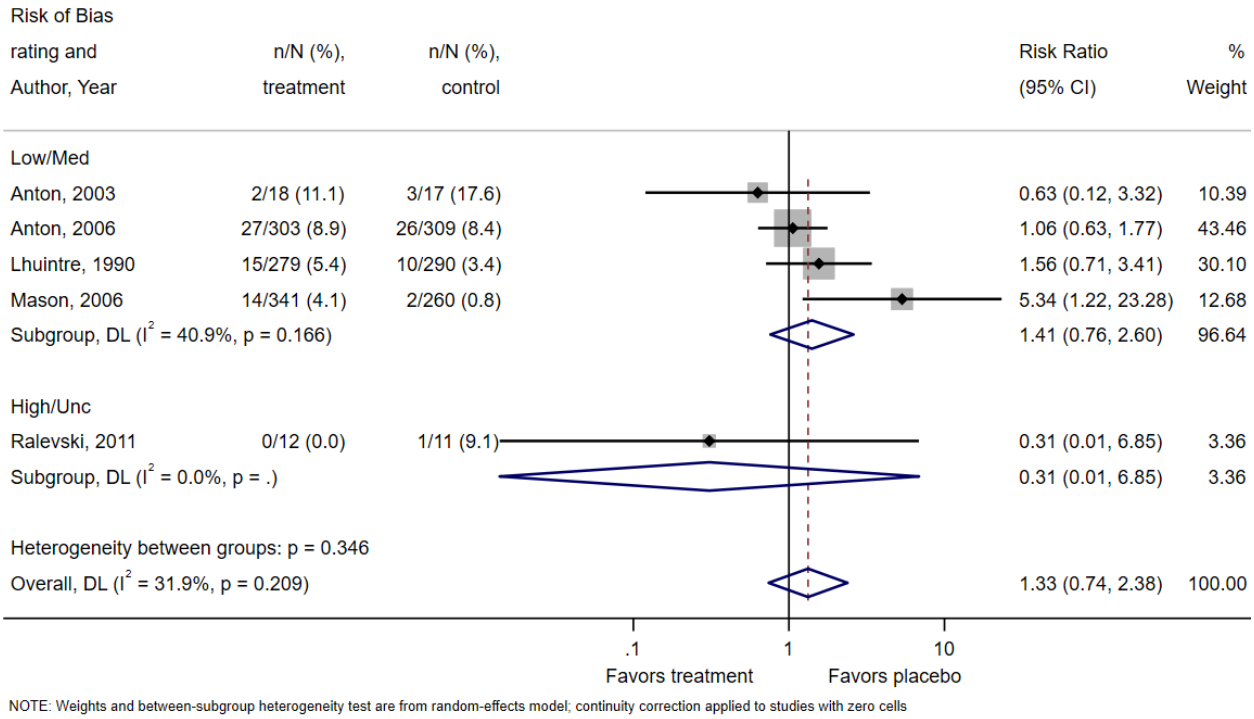
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-38. Acamprosate versus placebo: Suicide attempts/suicide ideation by risk-of-bias rating



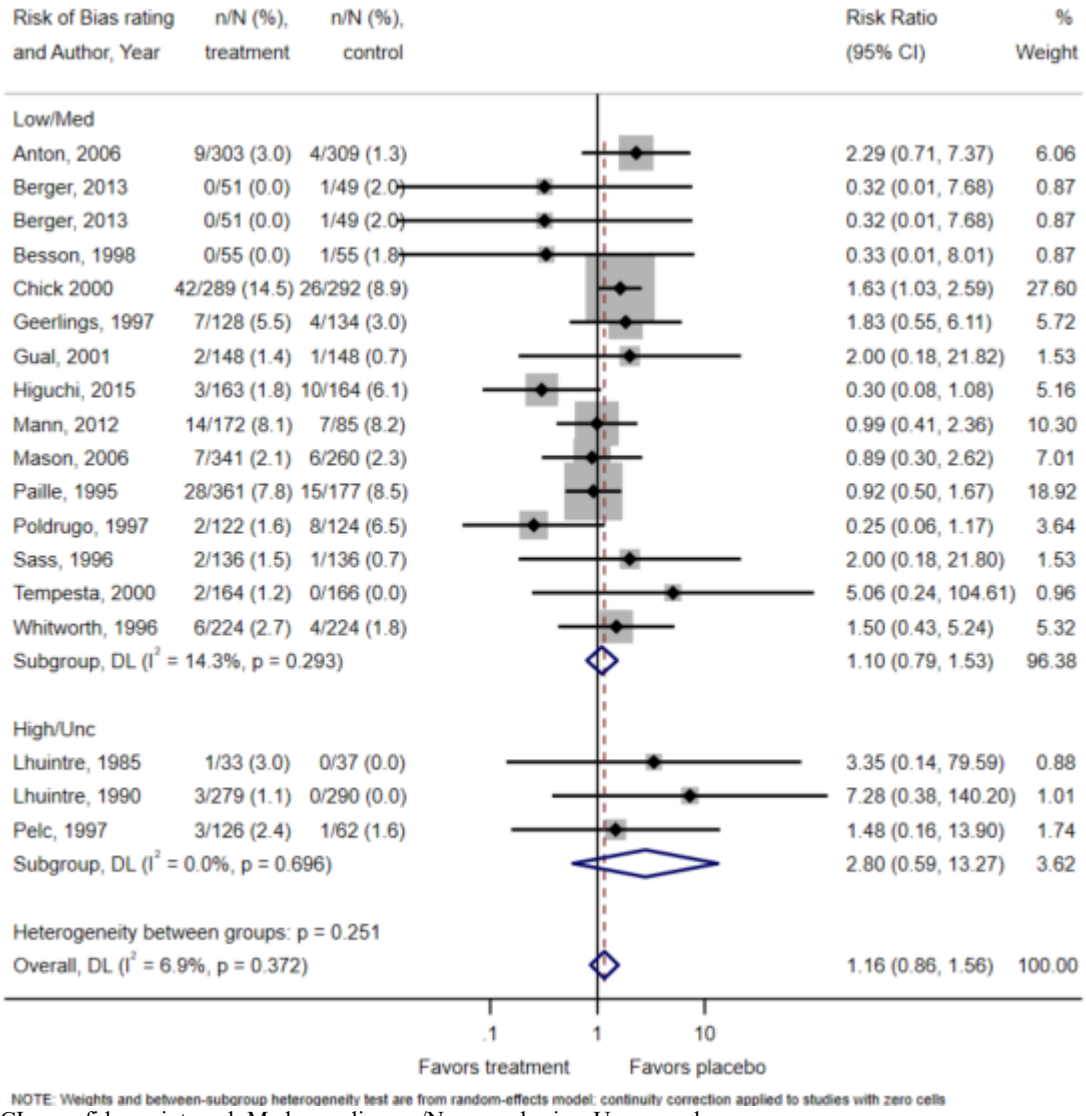
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-39. Acamprosate versus placebo: Vomiting by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

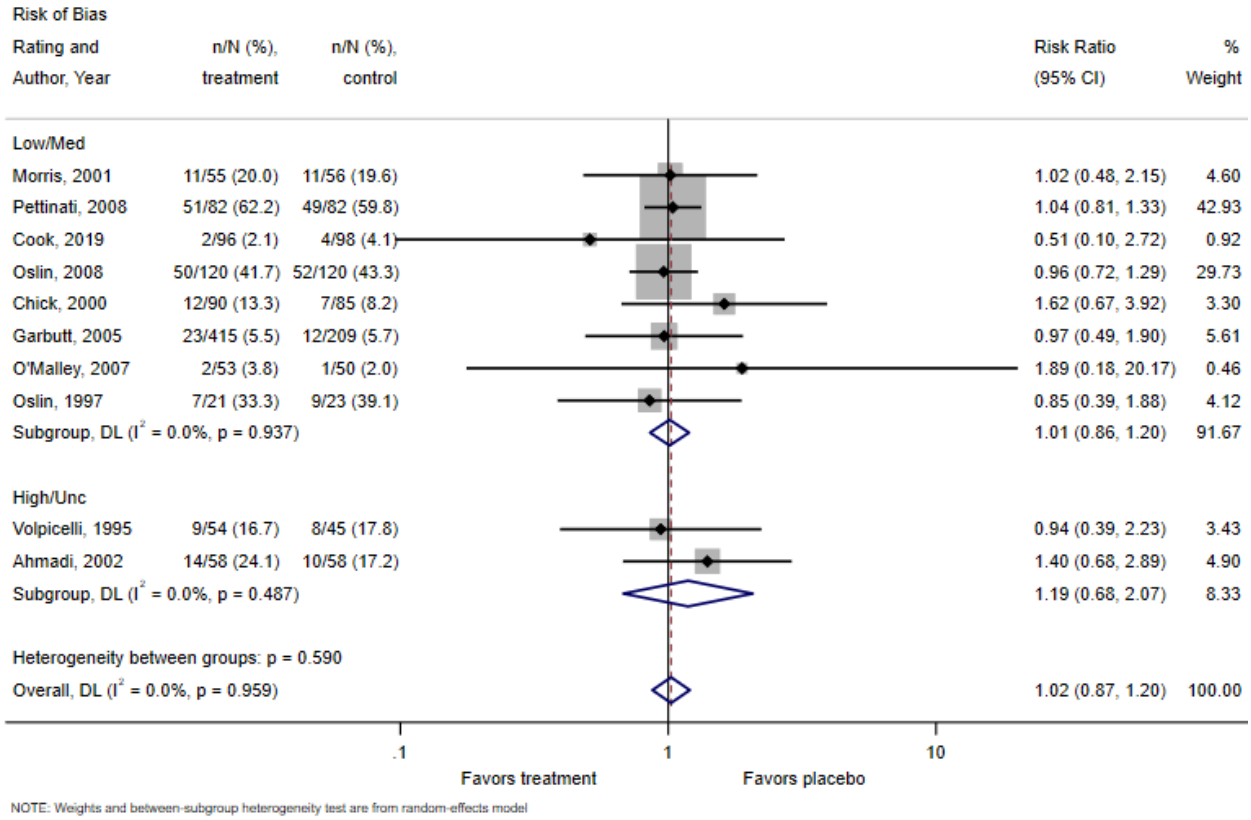
Figure E-40. Acamprosate versus placebo: Withdrawals due to adverse events by risk-of-bias rating



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model; continuity correction applied to studies with zero cells

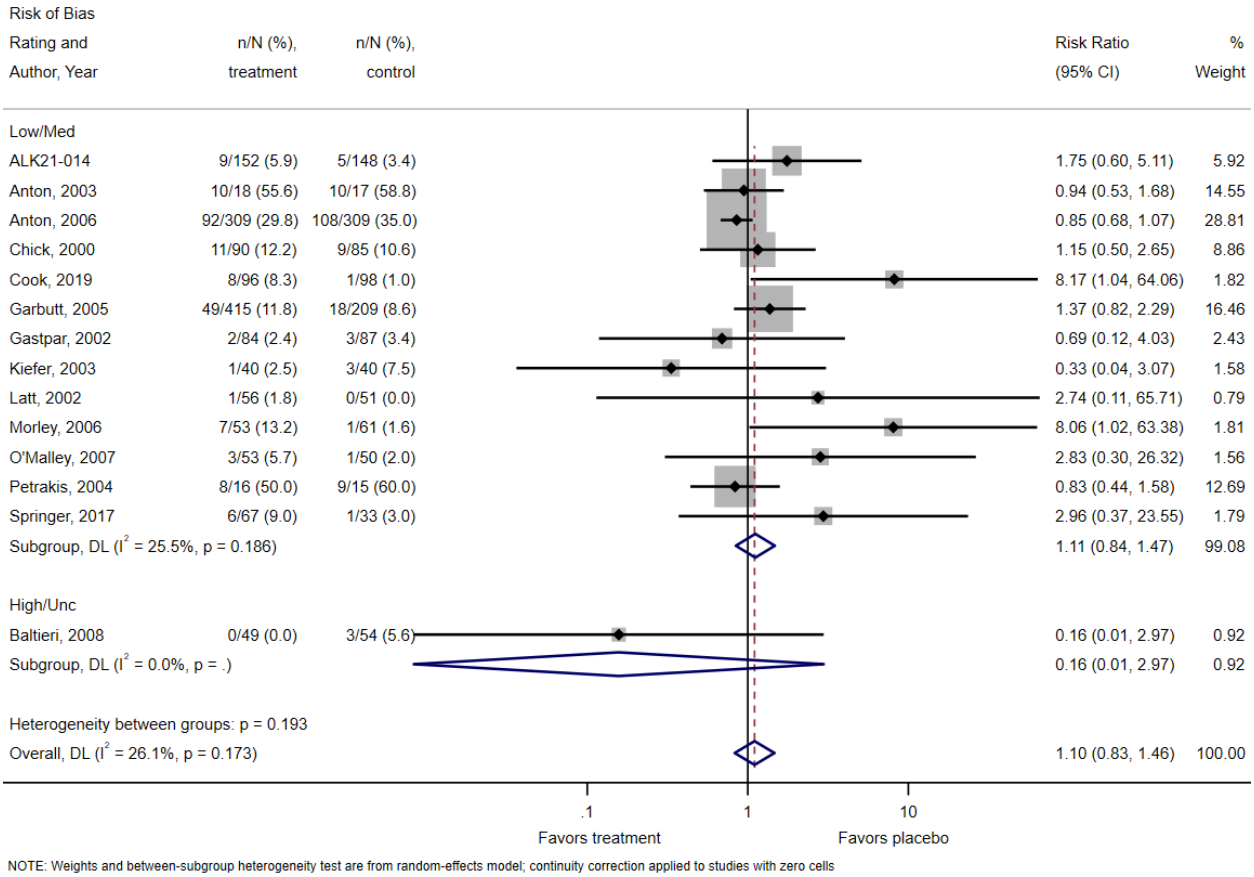
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-41. Naltrexone versus placebo: Anxiety by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

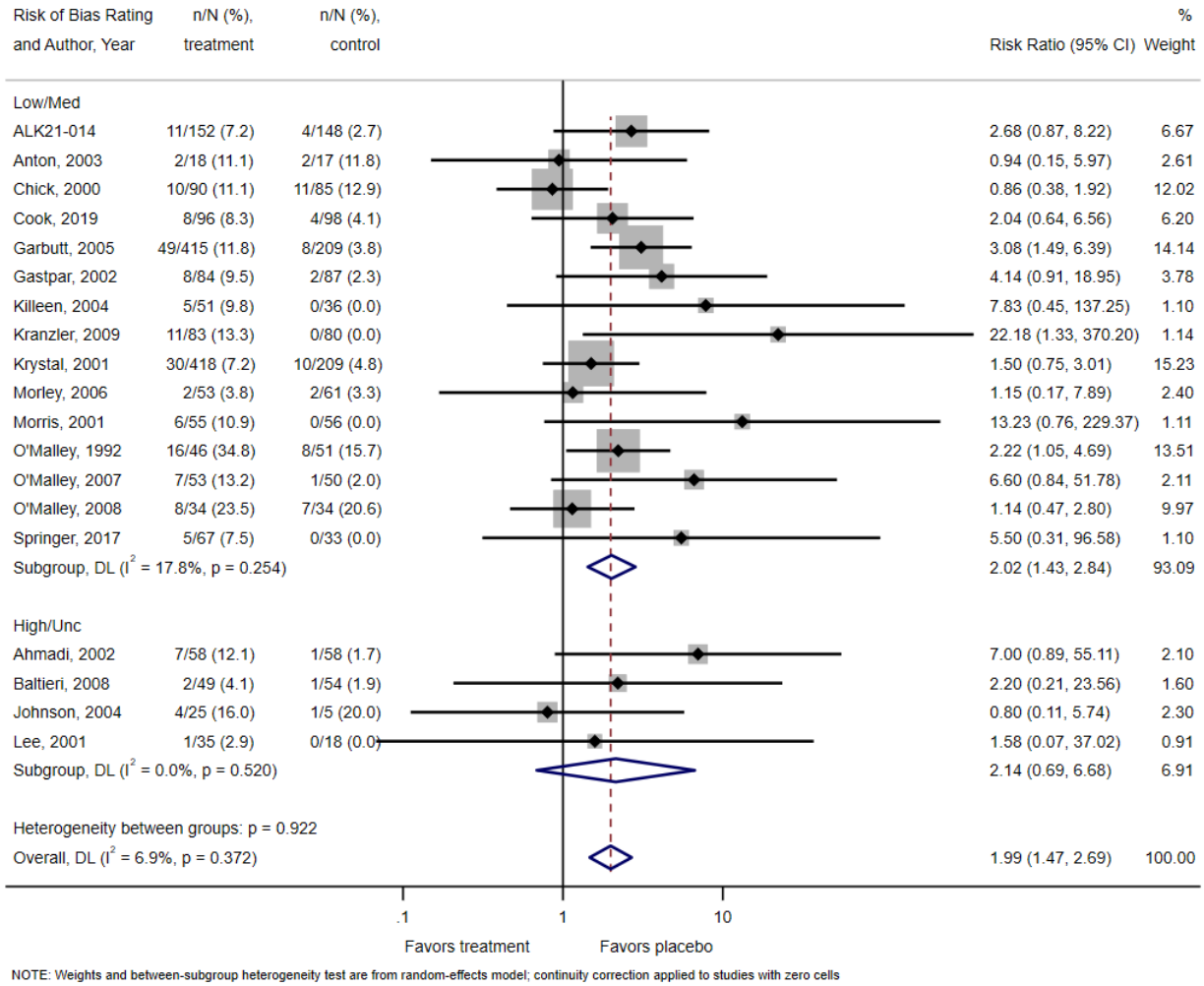
Figure E-42. Naltrexone versus placebo: Diarrhea by risk-of-bias rating



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model; continuity correction applied to studies with zero cells

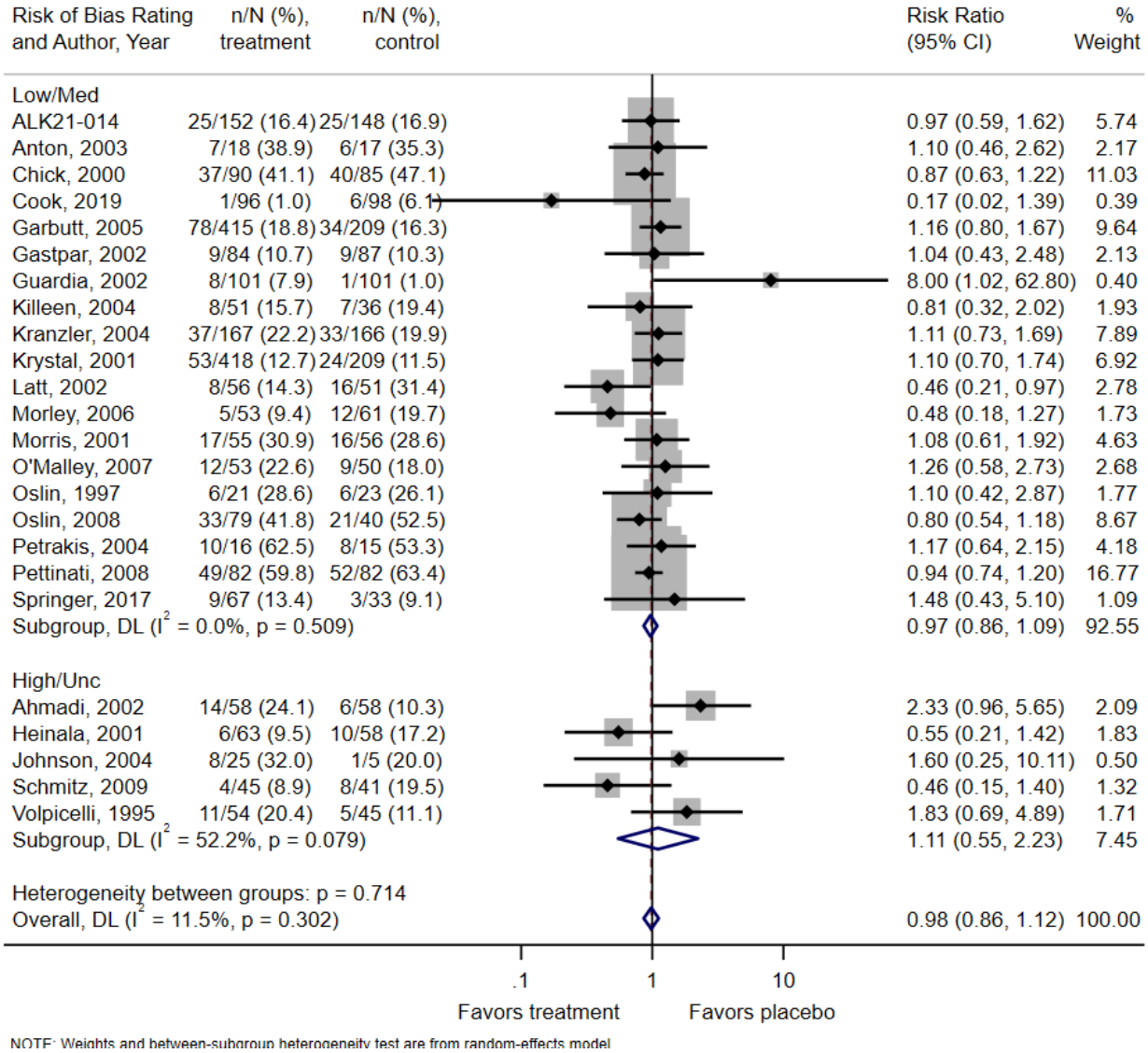
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-43. Naltrexone versus placebo: Dizziness by risk-of-bias rating



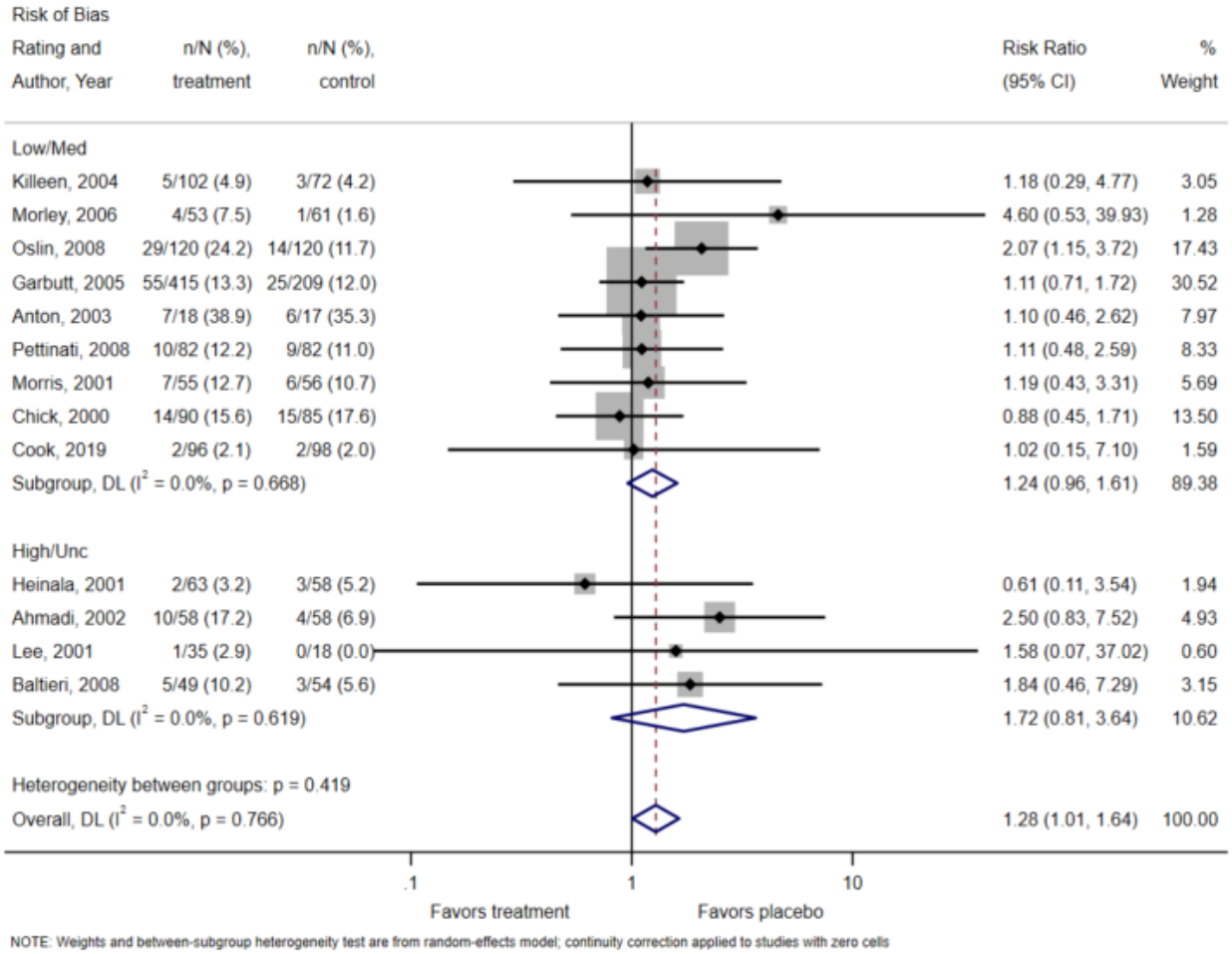
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-44. Naltrexone versus placebo: Headache by risk-of-bias rating



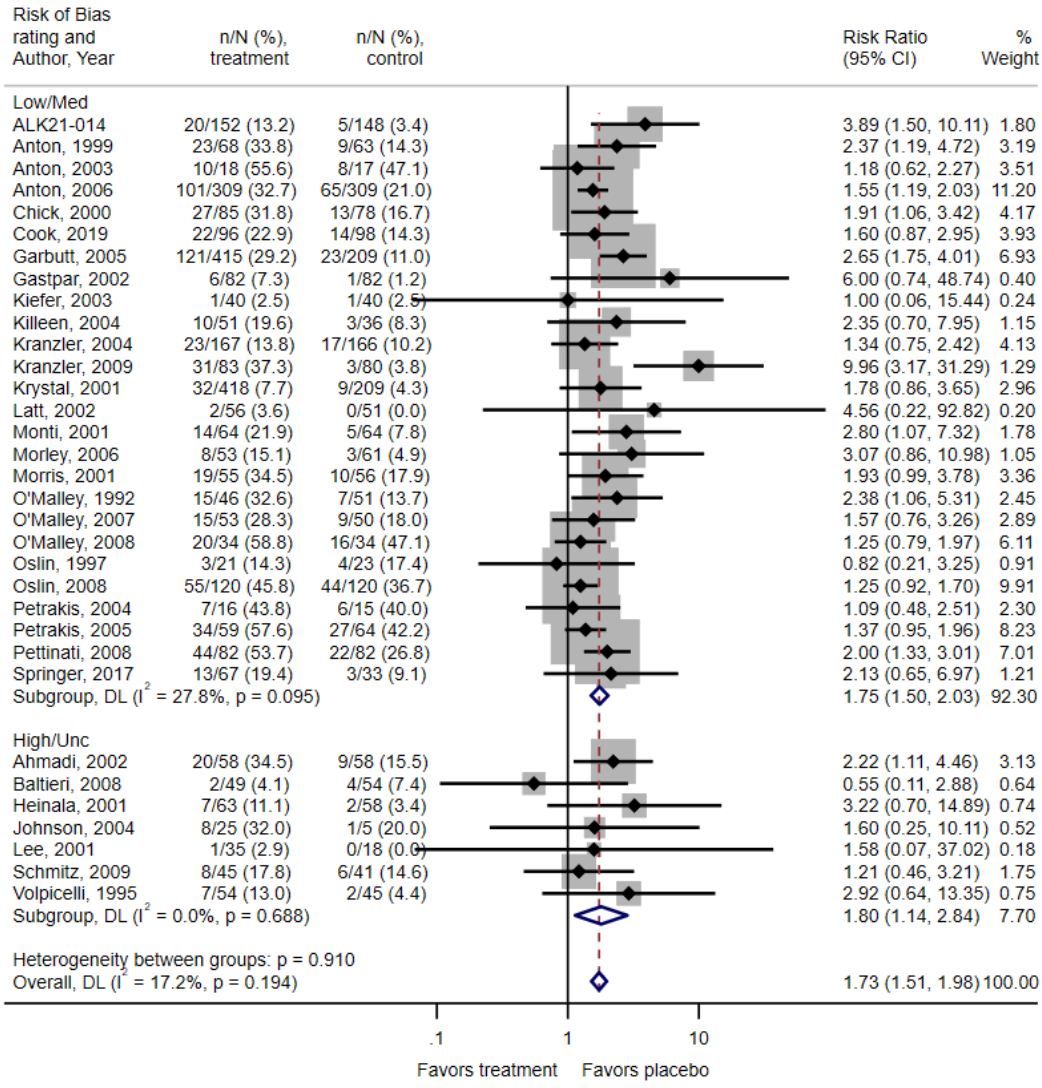
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-45. Naltrexone versus placebo: Insomnia by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

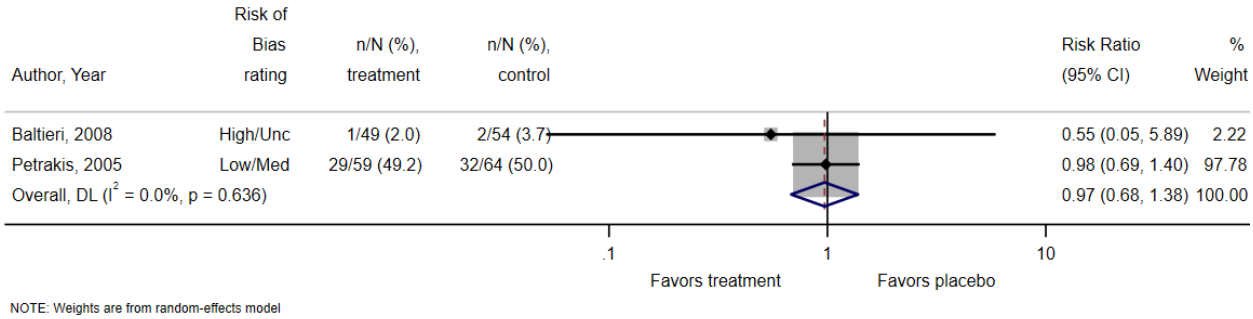
Figure E-46. Naltrexone versus placebo: Nausea by risk-of-bias rating



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model; continuity correction applied to studies with zero cells

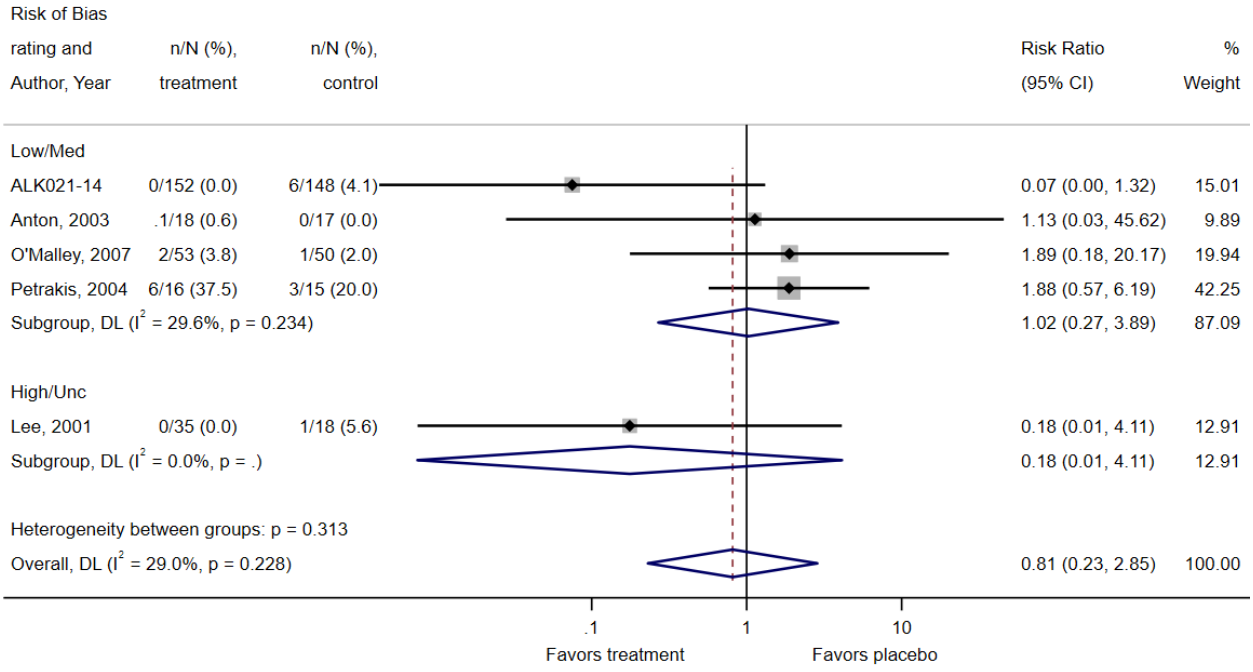
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-47. Naltrexone versus placebo: Numbness by risk-of-bias rating



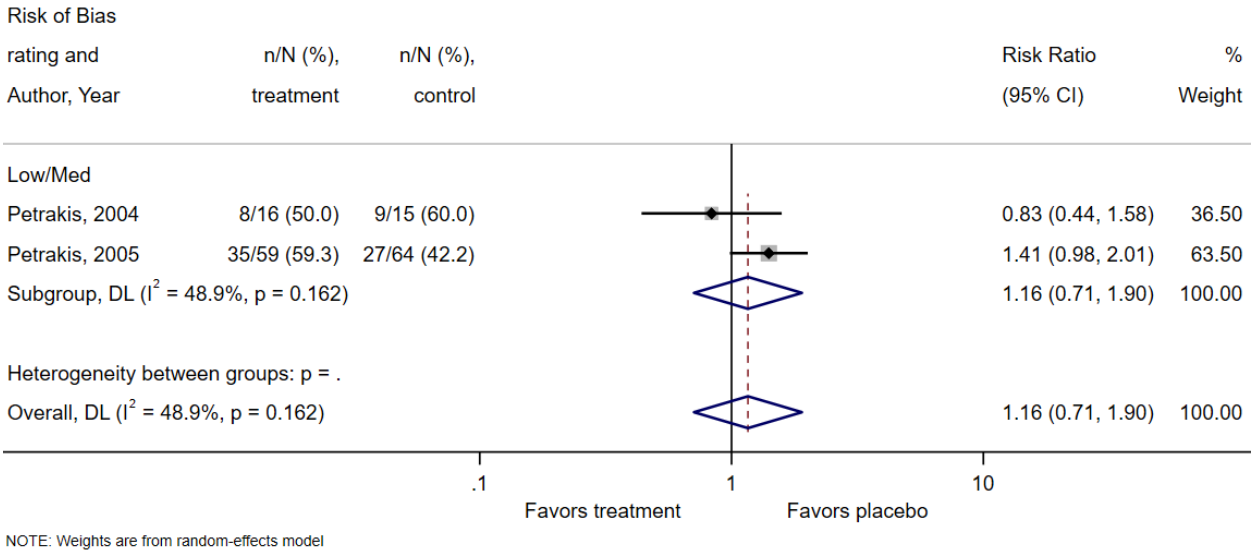
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-48. Naltrexone versus placebo: Rash by risk-of-bias rating



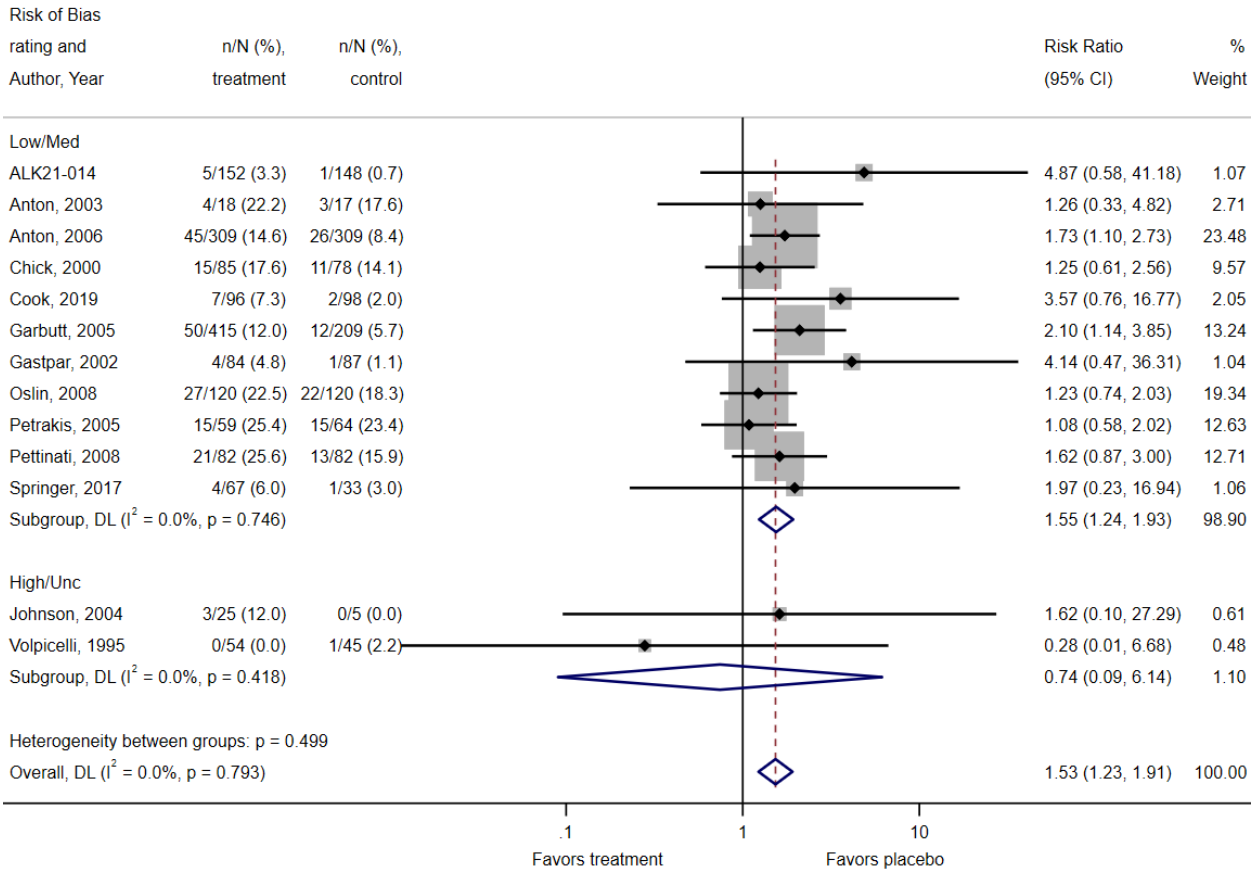
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-49. Naltrexone versus placebo: Vision changes (blurred vision) by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size.

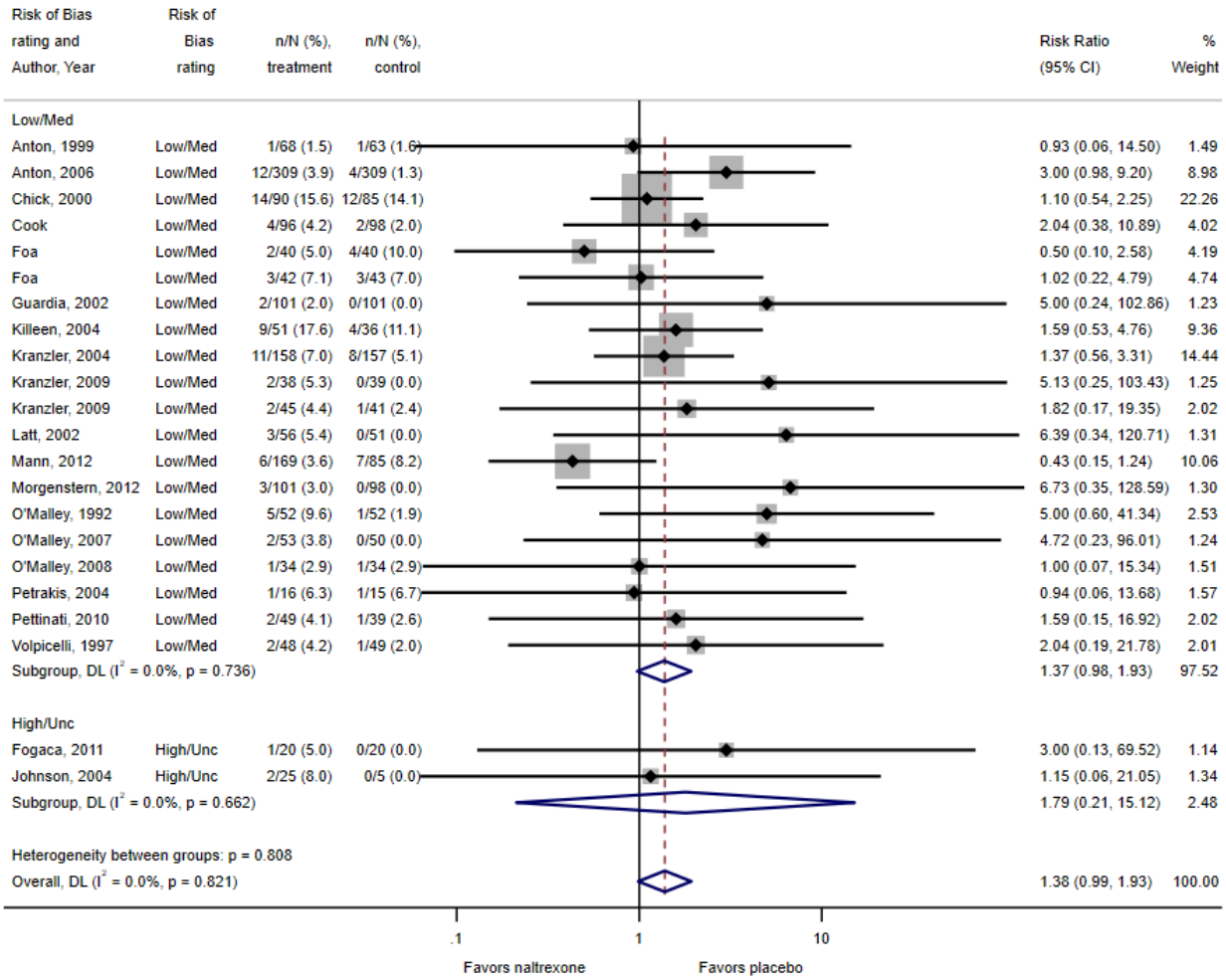
Figure E-50. Naltrexone versus placebo: Vomiting by risk-of-bias rating



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model; continuity correction applied to studies with zero cells

CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

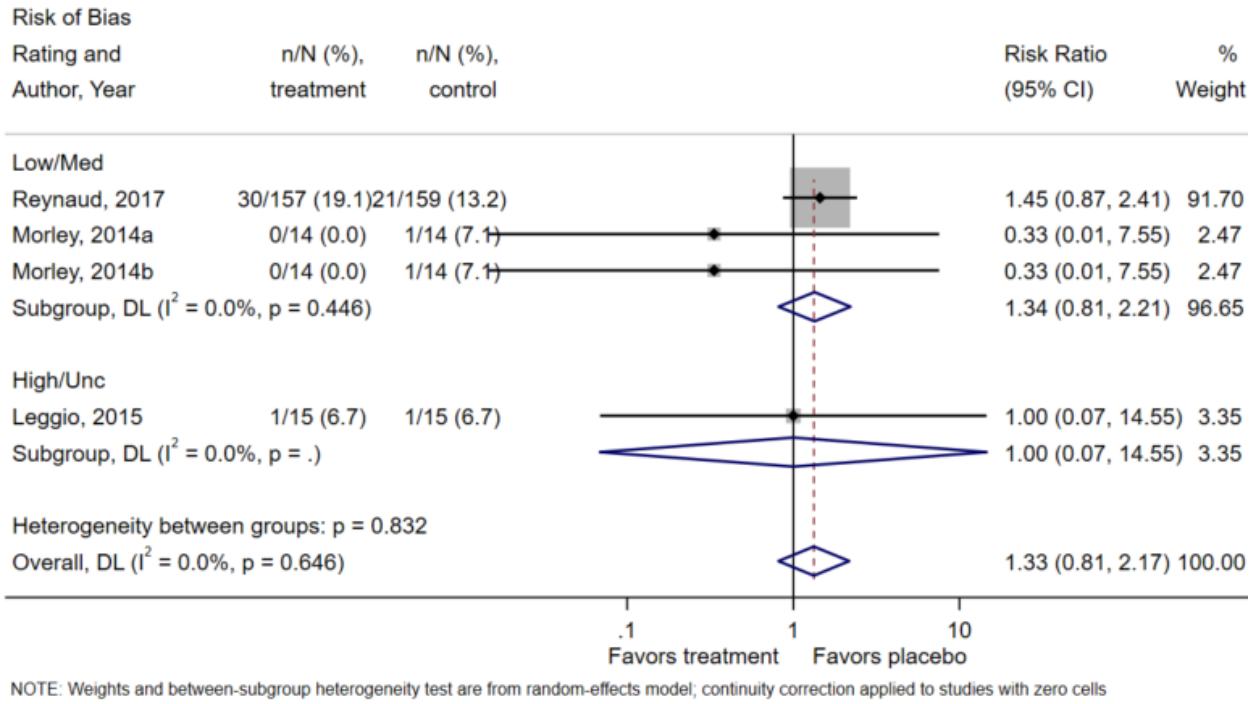
Figure E-51. Naltrexone versus placebo: Withdrawals due to adverse events by risk-of-bias rating



Notes: Foa, 2013a PTSD exposure therapy + NTX vs. PTSD exposure therapy + placebo; Foa, 2013b Supportive counseling + NTX vs. supportive counseling + placebo

CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear; vs. = versus.

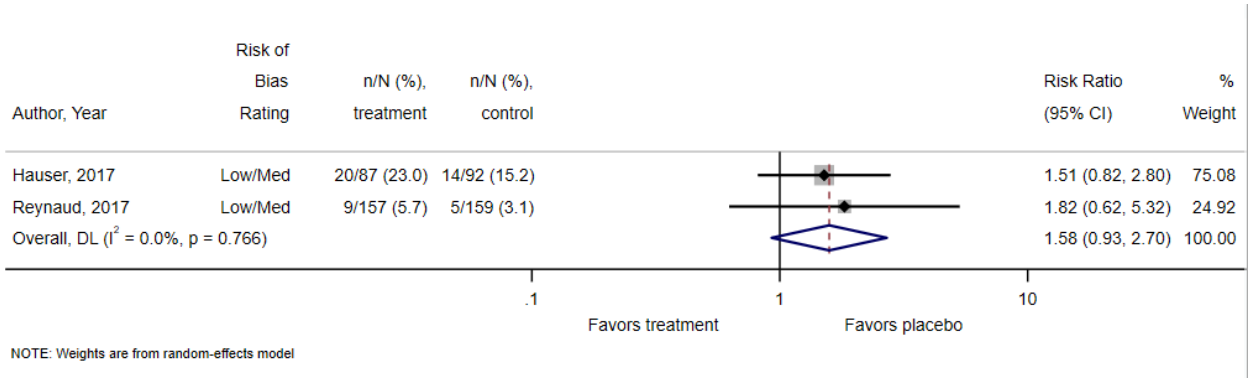
Figure E-52. Baclofen versus placebo: Anxiety by risk-of-bias rating



Notes: Morley,2014a dose is 30 mg; Morley, 2014b dose is 60 mg; Müller et al. reported depressed mood/anxiety and was not included here.

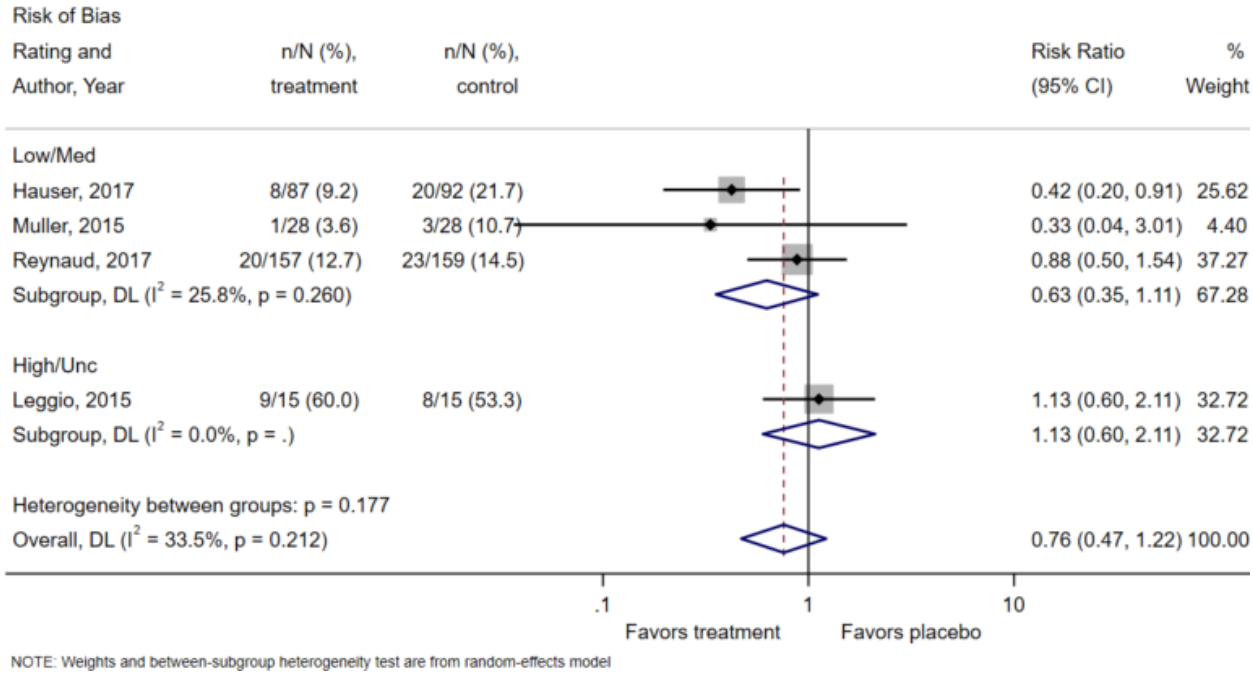
CI = confidence interval; Med = medium; mg = milligram; n/N = sample size; Unc = unclear.

Figure E-53. Baclofen versus placebo: Cognitive dysfunction or confusion by risk-of-bias rating



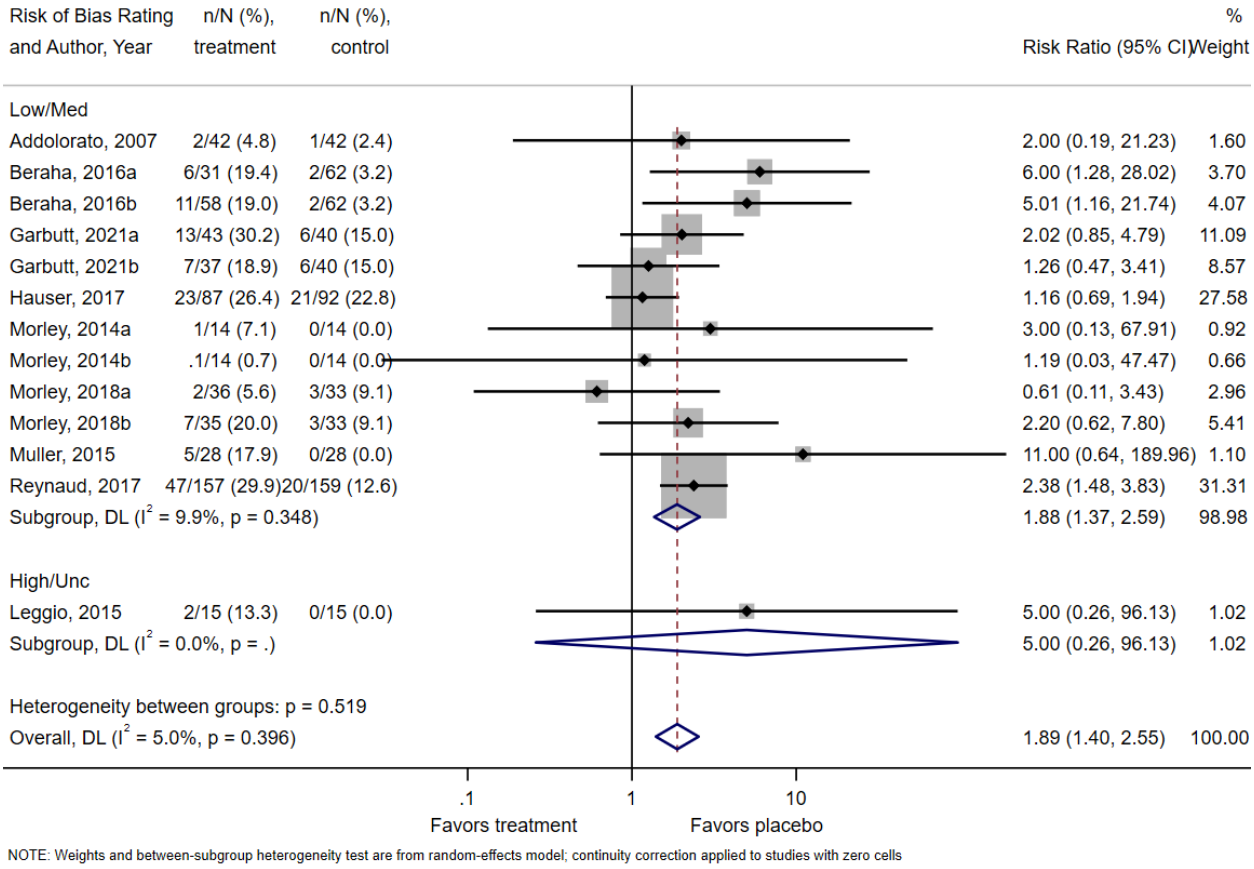
CI = confidence interval; Med = medium; n/N = sample size.

Figure E-54. Baclofen versus placebo: Diarrhea by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size.

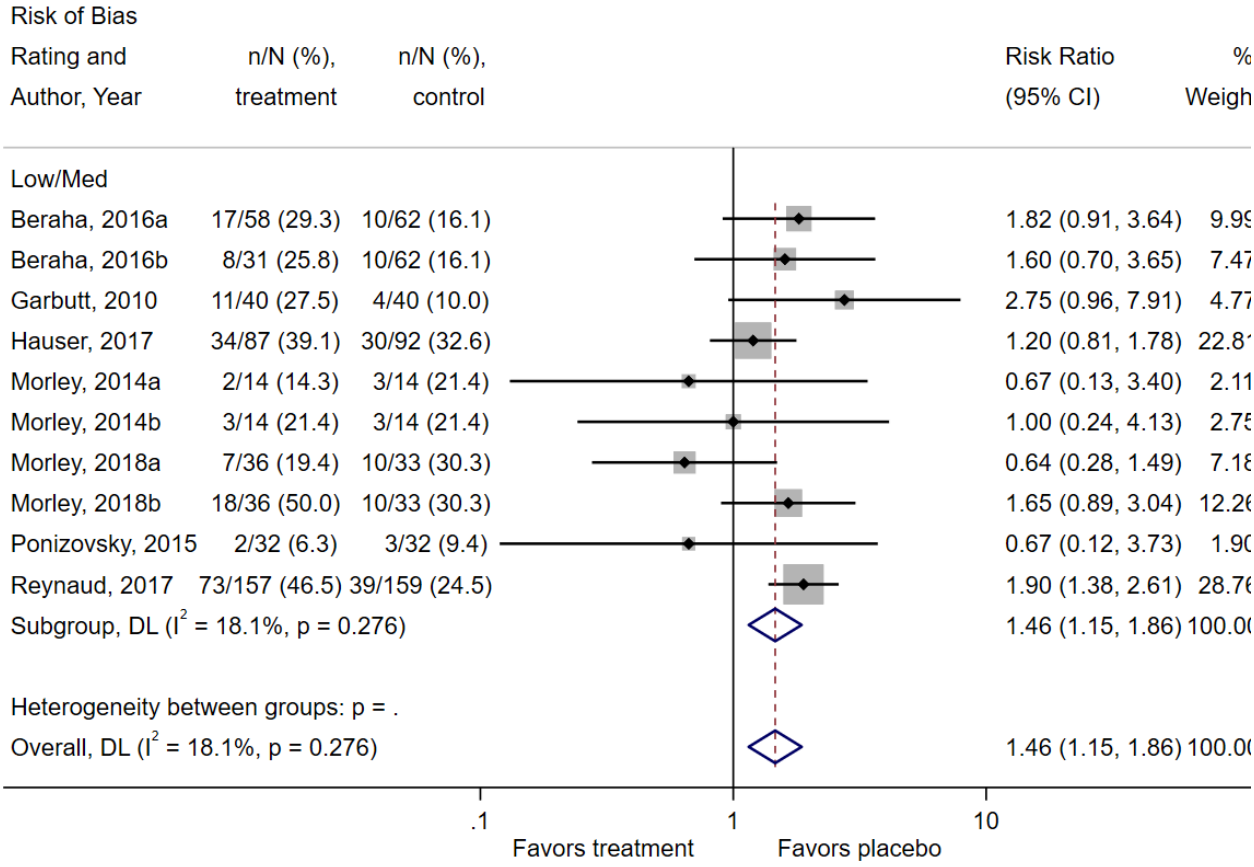
Figure E-55. Baclofen versus placebo: Dizziness by risk-of-bias rating



Notes: Beraha, 2016a dose is 30 mg; Beraha, 2016b dose is up to 150 mg; Garbutt 2021a dose is 30 mg; Garbutt 2021b dose is 90 mg; Morley,2014a dose is 30 mg; Morley, 2014b dose is 60 mg; Morley, 2018a dose is 30 mg; Morley, 2018b dose is 75 mg

CI = confidence interval; Med = medium; mg = milligram; n/N = sample size; Unc = unclear.

Figure E-56. Baclofen versus placebo: Drowsiness by risk of bias

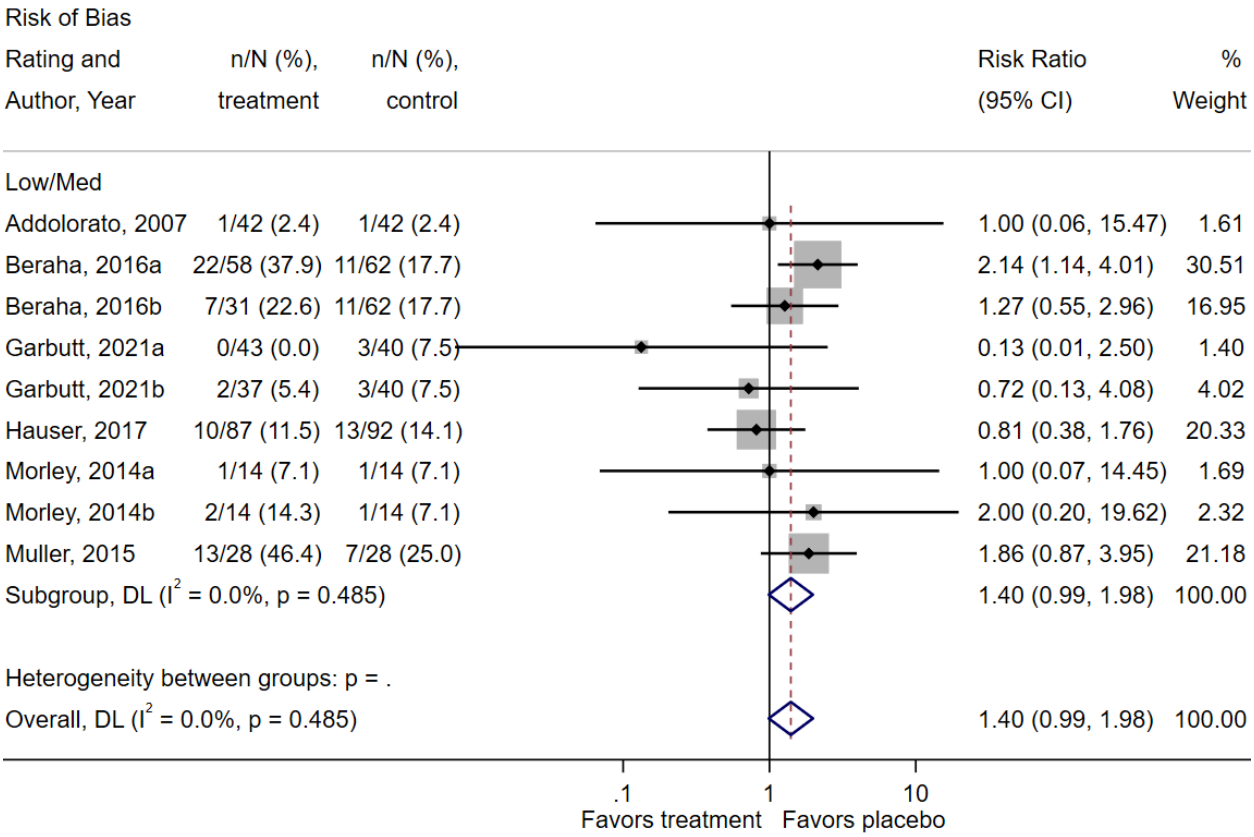


NOTE: Weights are from random-effects model

Notes: Beraha, 2016a dose is 30 mg; Beraha, 2016b dose is up to 150 mg; Morley,2014a dose is 30 mg; Morley, 2014b dose is 60 mg; Morley, 2018a dose is 30 mg; Morley, 2018b dose is 75 mg

CI = confidence interval; Med = medium; mg = milligram; n/N = sample size.

Figure E-57. Baclofen versus placebo: Fatigue by risk-of-bias

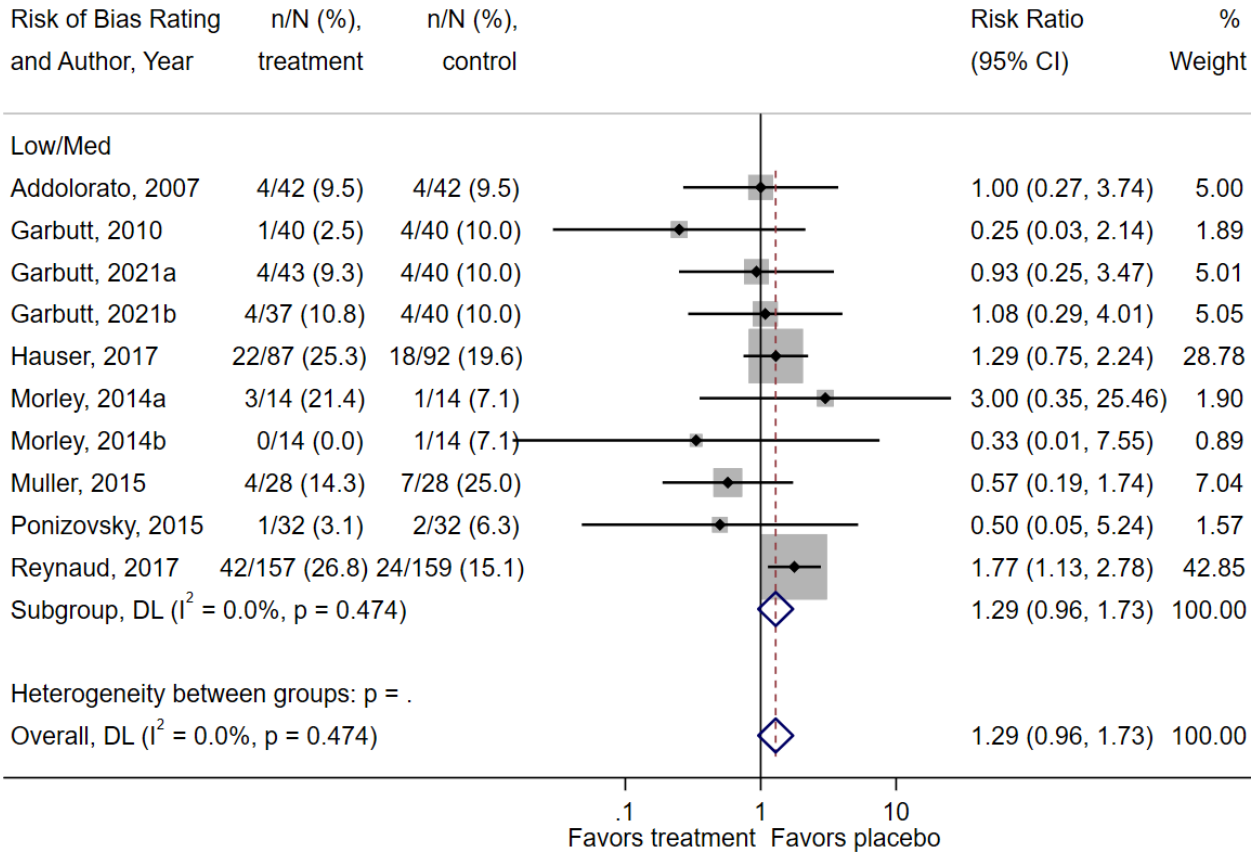


NOTE: Weights are from random-effects model; continuity correction applied to studies with zero cells

Notes: Beraha, 2016a dose is 30 mg; Beraha, 2016b dose is up to 150 mg; Garbutt 2021a dose is 30 mg; Garbutt 2021b dose is 90 mg; Morley,2014a dose is 30 mg; Morley, 2014b dose is 60 mg

CI = confidence interval; Med = medium; mg = milligram; n/N = sample size.

Figure E-58. Baclofen versus placebo: Headache by risk-of-bias rating

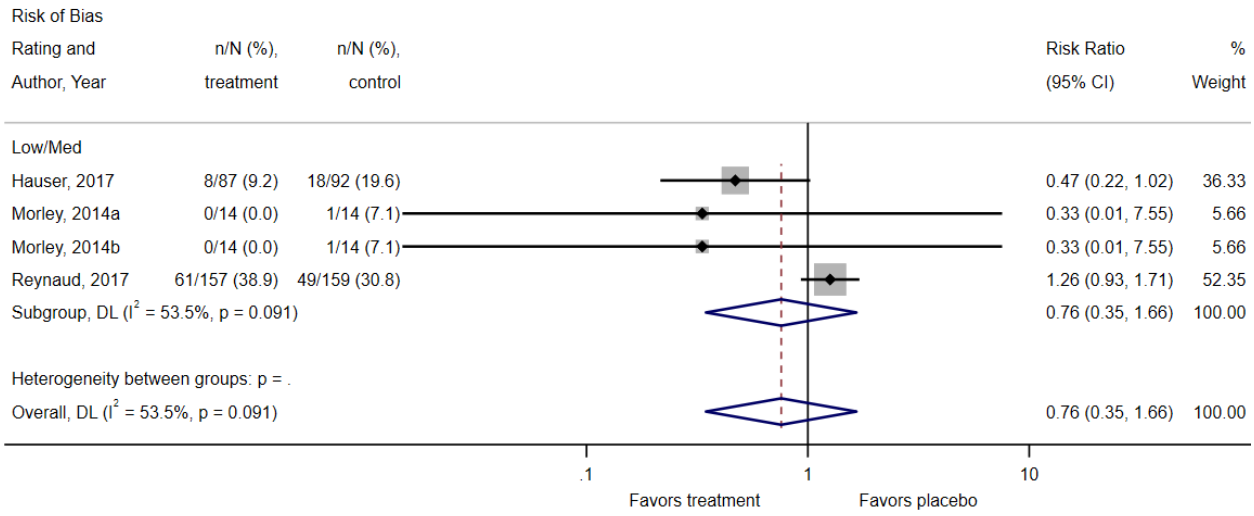


NOTE: Weights are from random-effects model; continuity correction applied to studies with zero cells

Notes: Garbutt 2021a dose is 30 mg; Garbutt 2021b dose is 90 mg; Morley,2014a dose is 30 mg; Morley, 2014b dose is 60 mg

CI = confidence interval; Med = medium; mg = milligram; n/N = sample size.

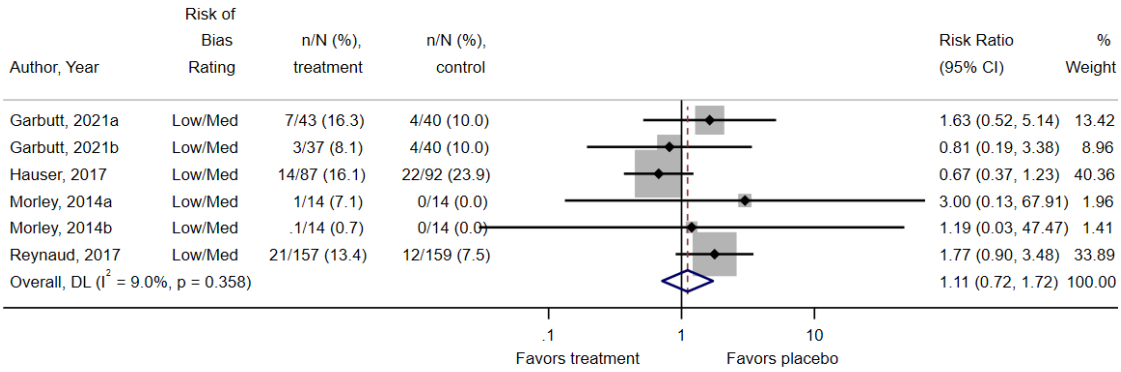
Figure E-59. Baclofen versus placebo: Insomnia by risk-of-bias rating



Notes: Morley, 2014a dose is 30 mg; Morley, 2014b dose is 60 mg

CI = confidence interval; Med = medium; mg = milligram; n/N = sample size.

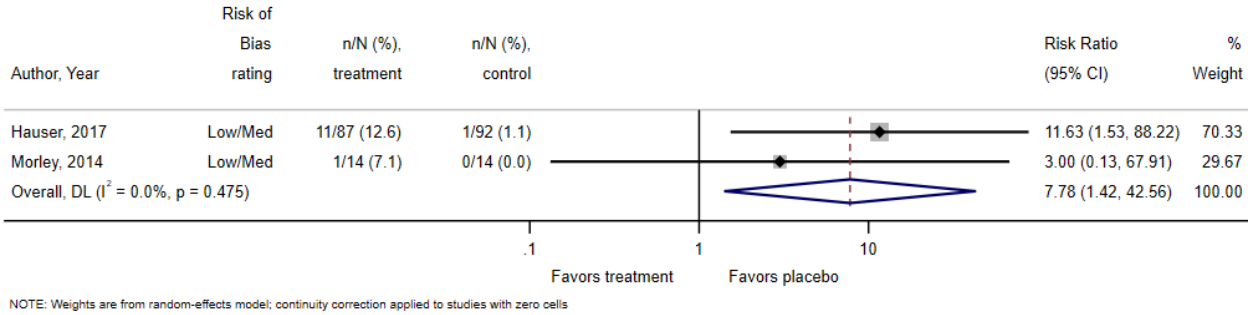
Figure E-60. Baclofen versus placebo: Nausea by risk-of-bias rating



Notes: Garbutt 2021a dose is 30 mg; Garbutt 2021b dose is 90 mg; Morley, 2014a dose is 30 mg; Morley, 2014b dose is 60 mg; Müller, 2015[115] reported GI symptoms as 1 of 28 in the baclofen arms versus 3 of 28 in the placebo arm.

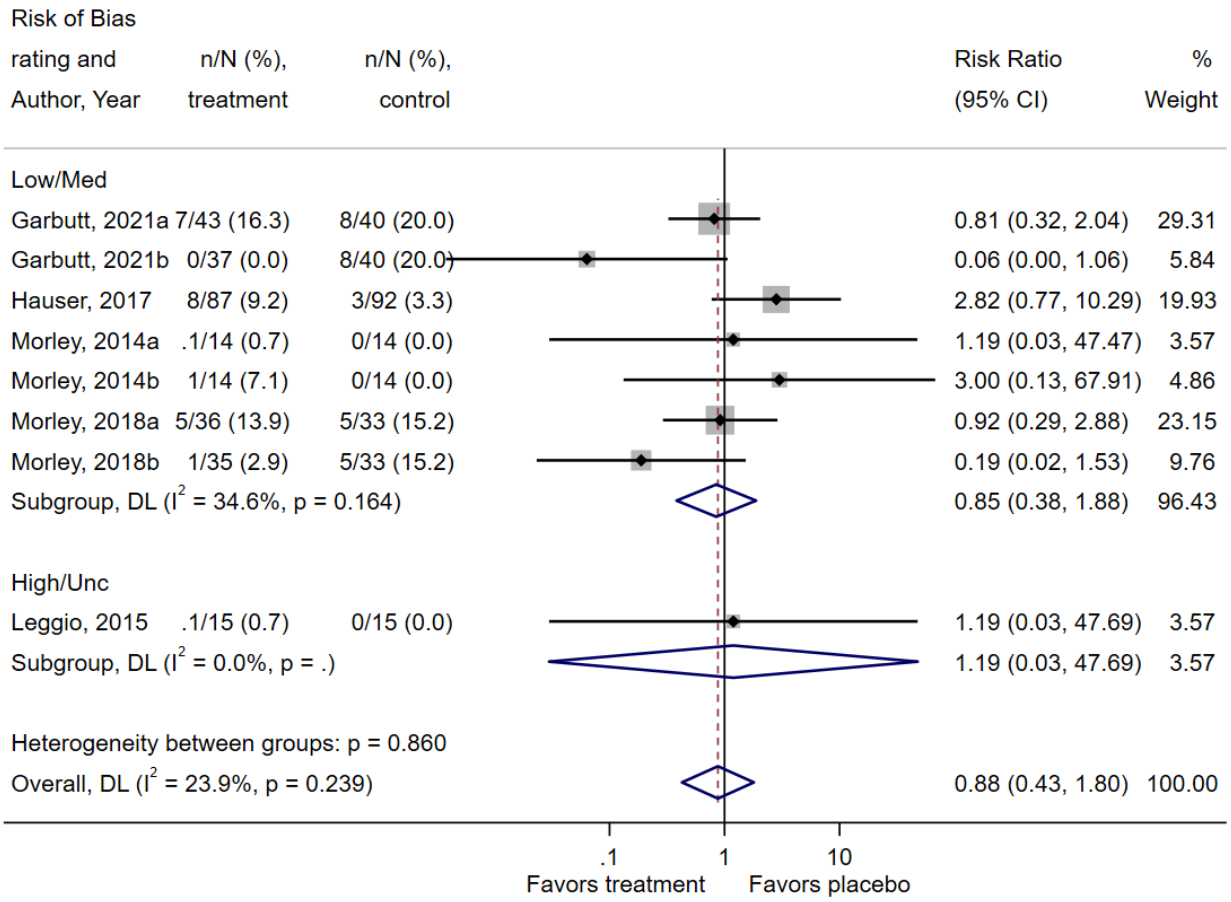
CI = confidence interval; Med = medium; mg = milligram; n/N = sample size.

Figure E-61. Baclofen versus placebo: Numbness by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size.

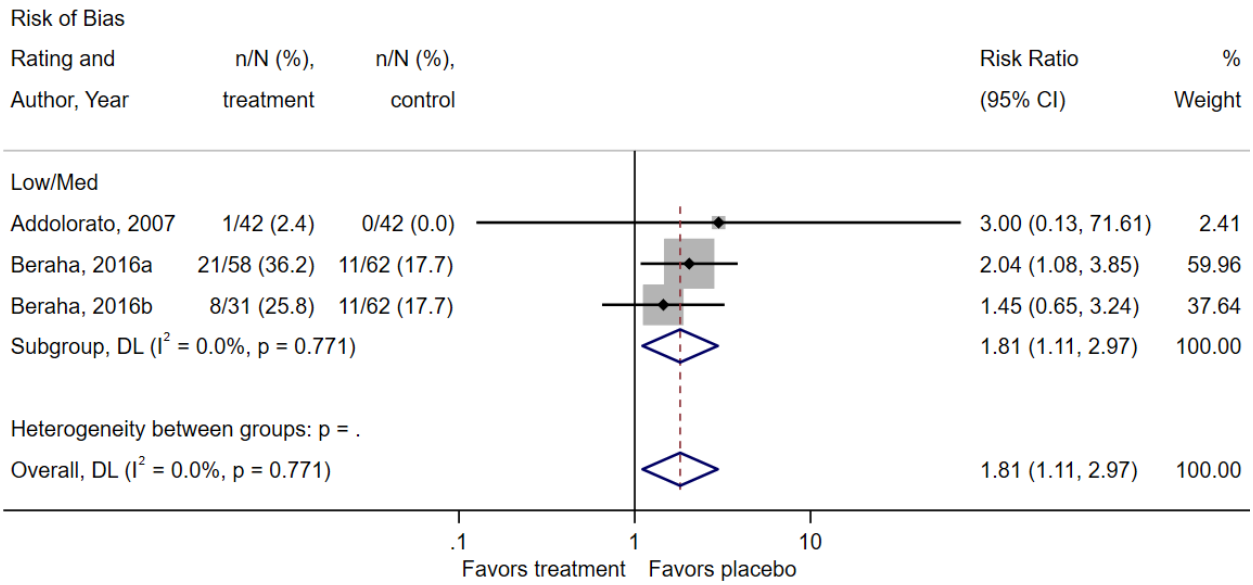
Figure E-62. Baclofen versus placebo: Rash by risk-of-bias rating



Notes: Garbutt 2021a dose is 30 mg; Garbutt 2021b dose is 90 mg; Morley,2014a dose is 30 mg; Morley, 2014b dose is 60 mg; Morley, 2018a dose is 30 mg; Morley, 2018b dose is 75 mg

CI = confidence interval; Med = medium; mg = milligram; n/N = sample size; Unc = unclear.

Figure E-63. Baclofen versus placebo: Sleepiness by risk-of-bias rating

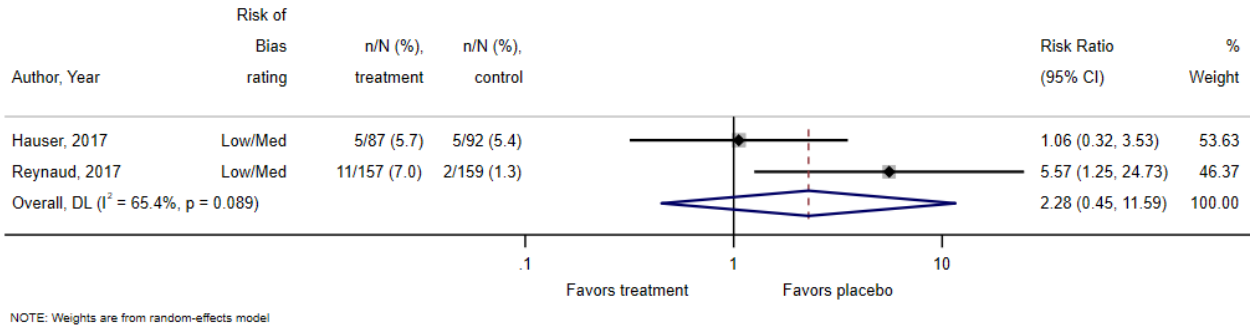


NOTE: Weights are from random-effects model; continuity correction applied to studies with zero cells

Notes: Beraha, 2016a dose is 30 mg; Beraha, 2016b dose is up to 150 mg

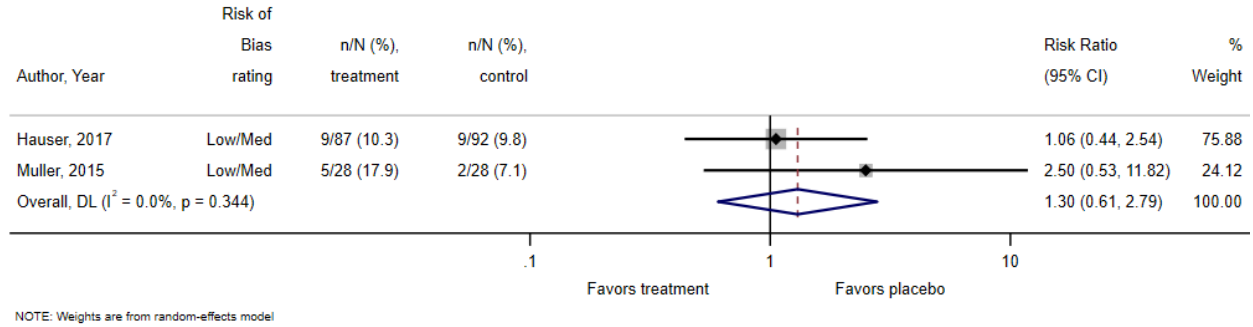
CI = confidence interval; Med = medium; mg = milligram; n/N = sample size.

Figure E-64. Baclofen versus placebo: Taste abnormalities by risk-of-bias rating



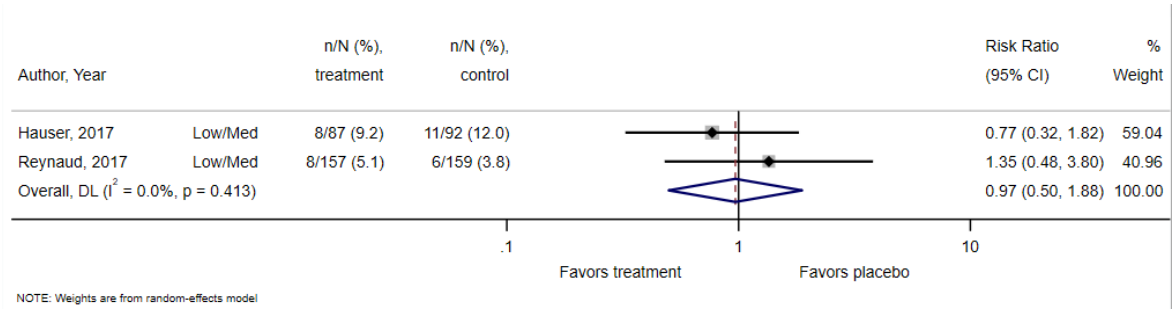
CI = confidence interval; Med = medium; n/N = sample size.

Figure E-65. Baclofen versus placebo: Vision changes (blurred vision) by risk-of-bias rating



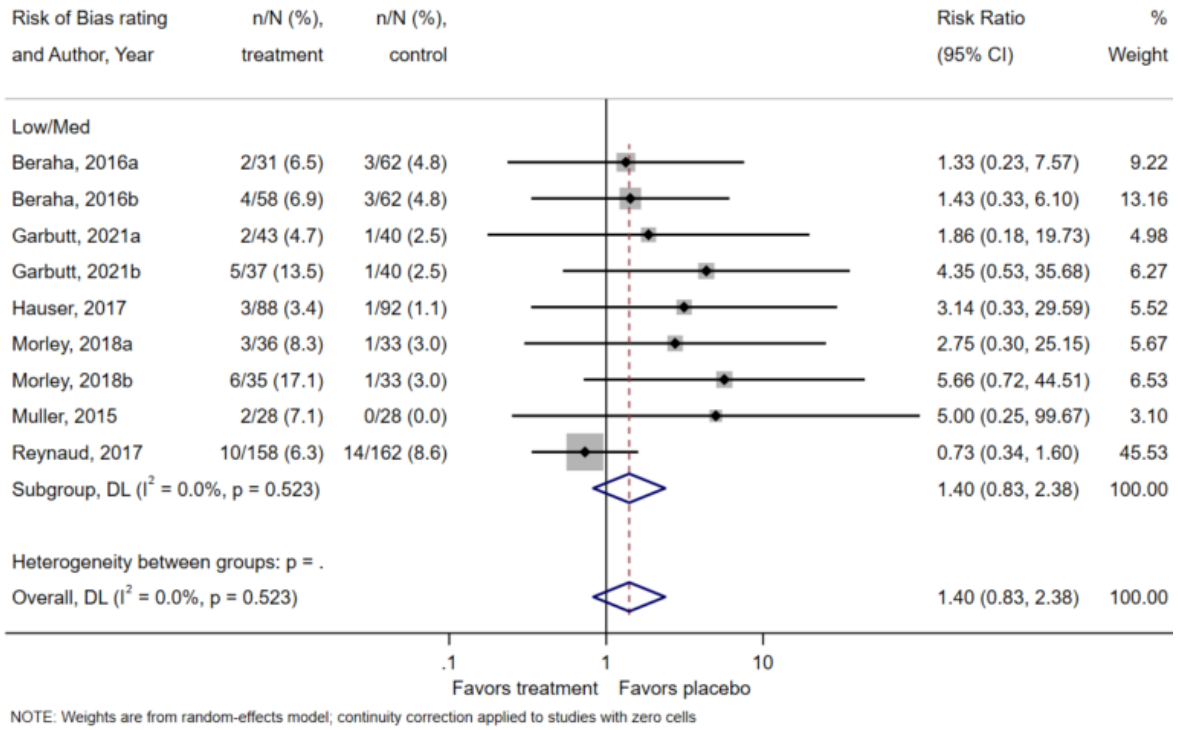
CI = confidence interval; Med = medium; n/N = sample size.

Figure E-66. Baclofen versus placebo: Vomiting by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size.

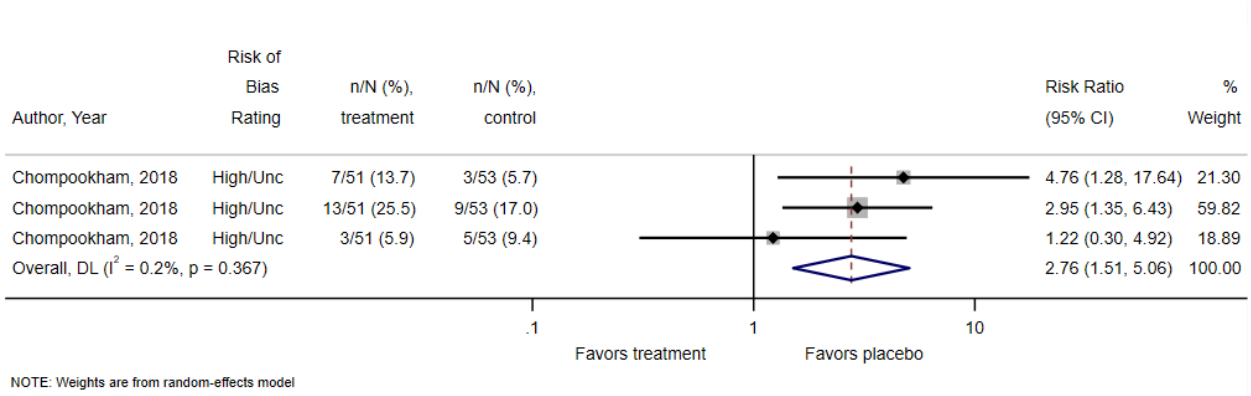
Figure E-67. Baclofen versus placebo: Withdrawals due to adverse events by risk-of-bias rating



Notes: Beraha, 2016a dose is 30 mg; Beraha, 2016b dose is up to 150 mg; Garbutt 2021a dose is 30 mg; Garbutt 2021b dose is 90 mg; Morley, 2018a dose is 30 mg; Morley, 2018b dose is 75 mg; Morley 2014[112] reported 0 events.

CI = confidence interval; Med = medium; mg = milligram; n/N = sample size.

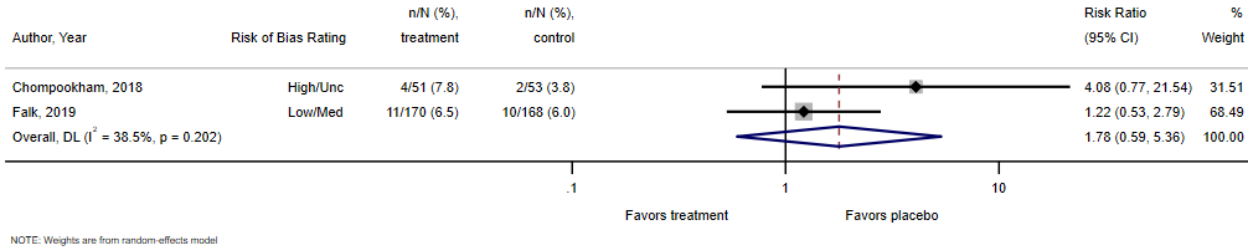
Figure E-68. Gabapentin versus placebo: Cognitive dysfunction by risk-of-bias rating



Note: Three different measures of cognitive dysfunction (confusion, amnesia, and thought distortion) from Chompookham, 2018[120]

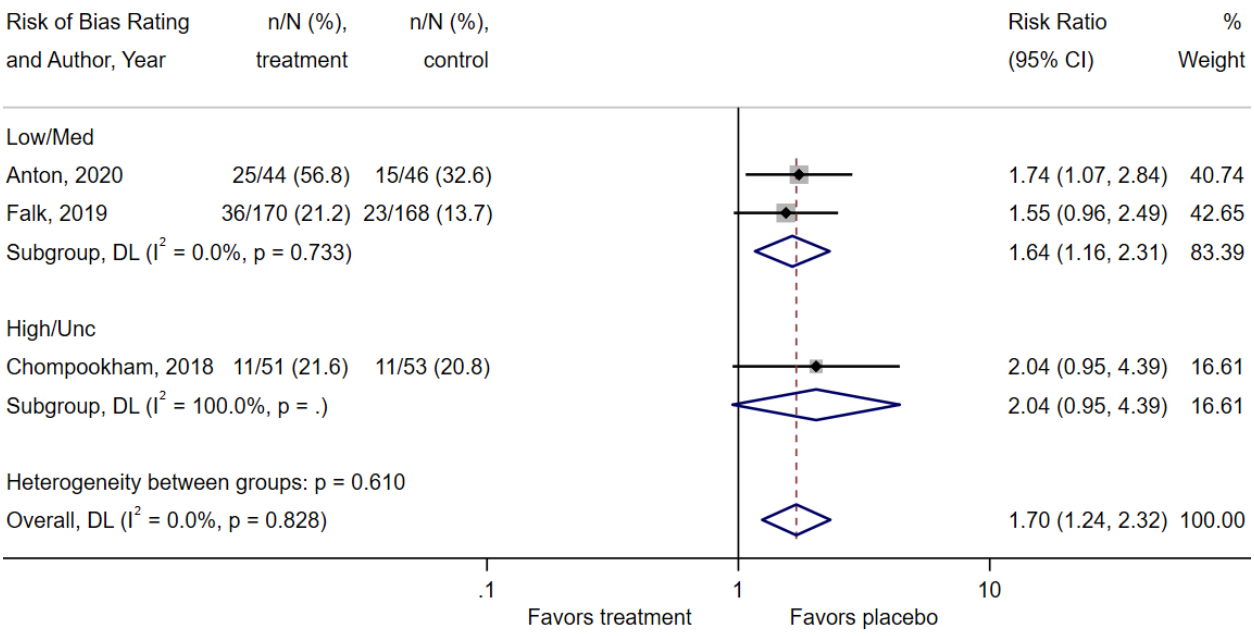
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-69. Gabapentin versus placebo: Diarrhea by risk-of-bias rating



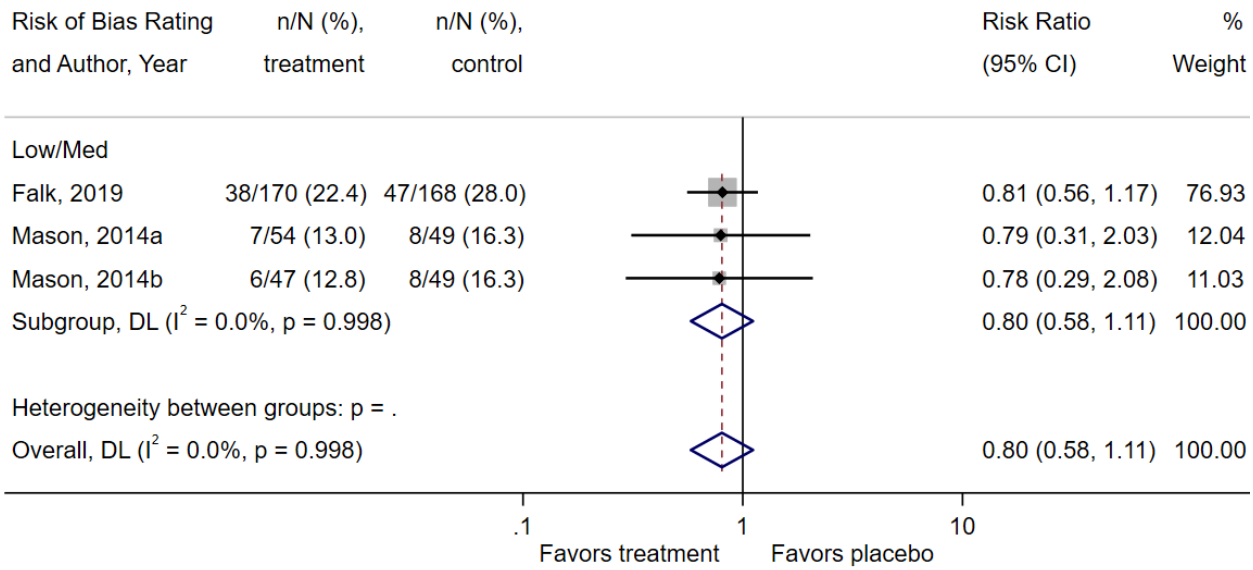
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-70. Gabapentin versus placebo: Dizziness by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-71. Gabapentin versus placebo: Headache by risk-of-bias rating

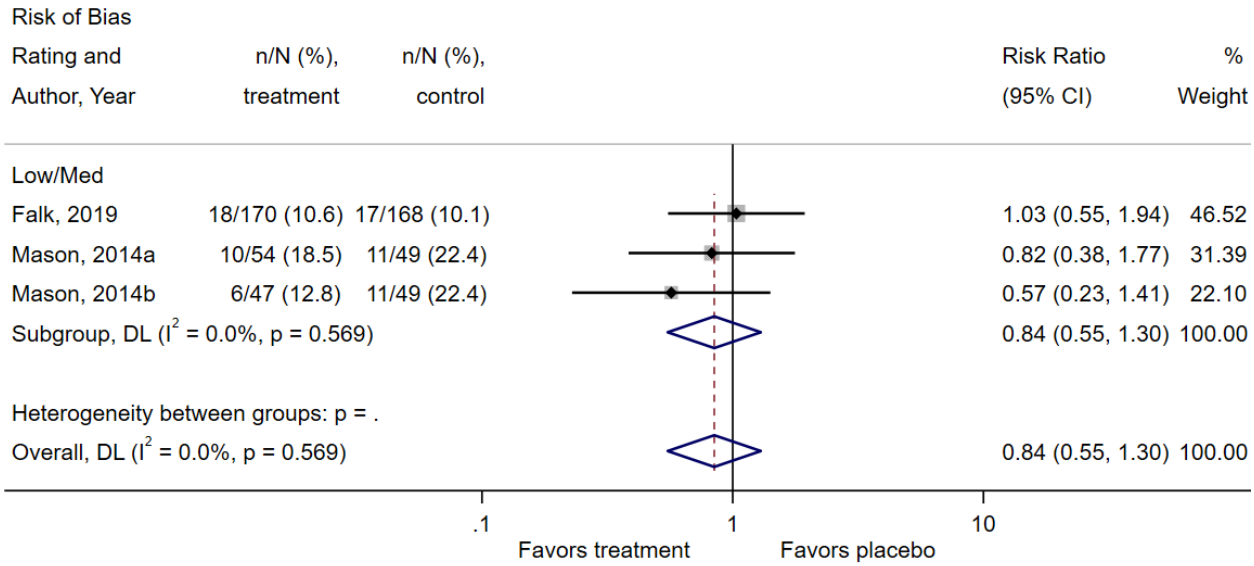


NOTE: Weights are from random-effects model

Notes: Mason, 2014a dose is 900 mg; Mason, 2014b dose is 1,800 mg

CI = confidence interval; Med = medium; mg = milligram; n/N = sample size.

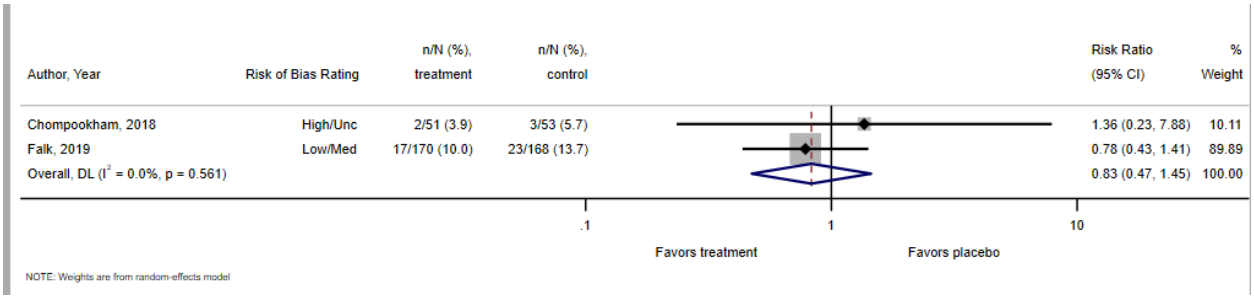
Figure E-72. Gabapentin versus placebo: Insomnia by risk-of-bias rating



Notes: Mason, 2014a dose is 900 mg; Mason, 2014b dose is 1,800 mg

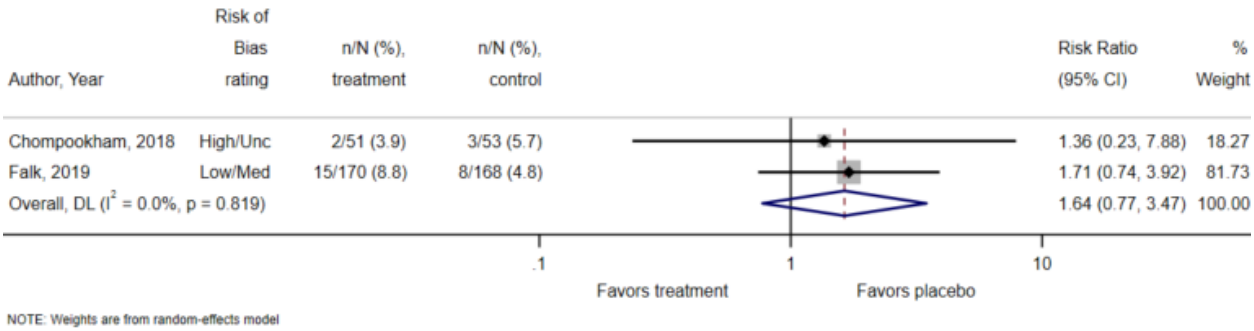
CI = confidence interval; Med = medium; mg = milligram; n/N = sample size.

Figure E-73. Gabapentin versus placebo: Nausea by risk-of-bias rating



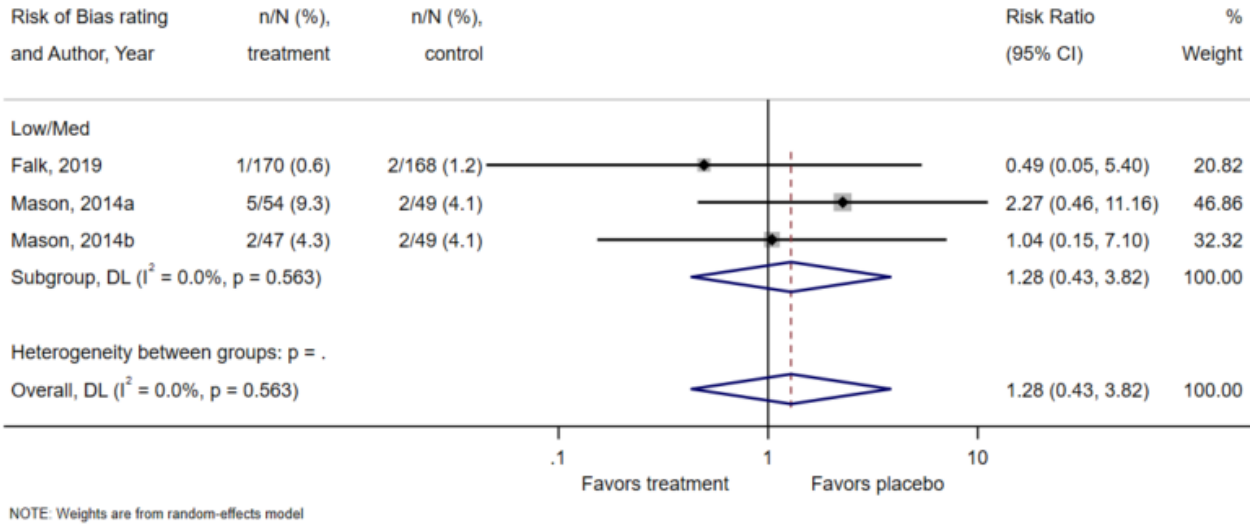
CI = confidence interval; Med = medium; mg = milligram; n/N = sample size; Unc = unclear.

Figure E-74. Gabapentin versus placebo: Vomiting by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

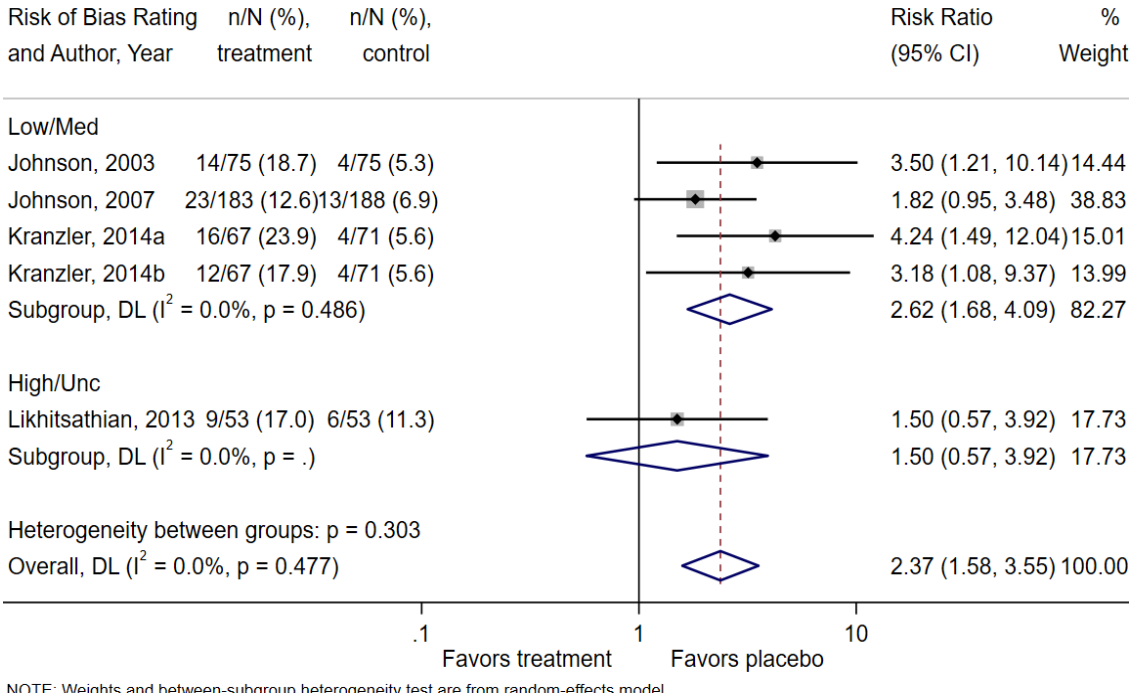
Figure E-75. Gabapentin versus placebo: Withdrawals due to adverse events by risk-of-bias rating



Notes: Mason, 2014a dose is 900 mg; Mason, 2014b dose is 1,800 mg

CI = confidence interval; Med = medium; mg = milligram; n/N = sample size.

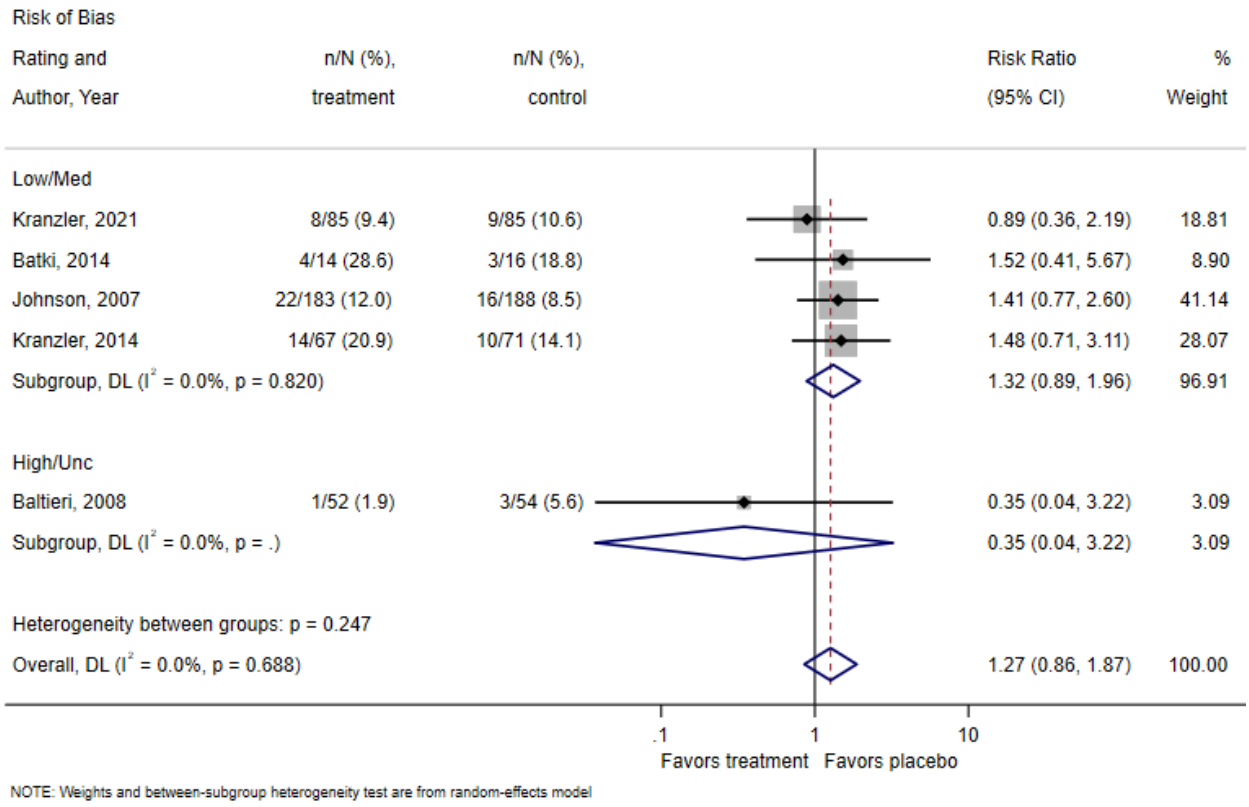
Figure E-76. Topiramate versus placebo: Cognitive dysfunction by risk-of-



Notes: Kranzler, 2014a is difficulty with memory; Kranzler, 2014b is difficulty concentrating

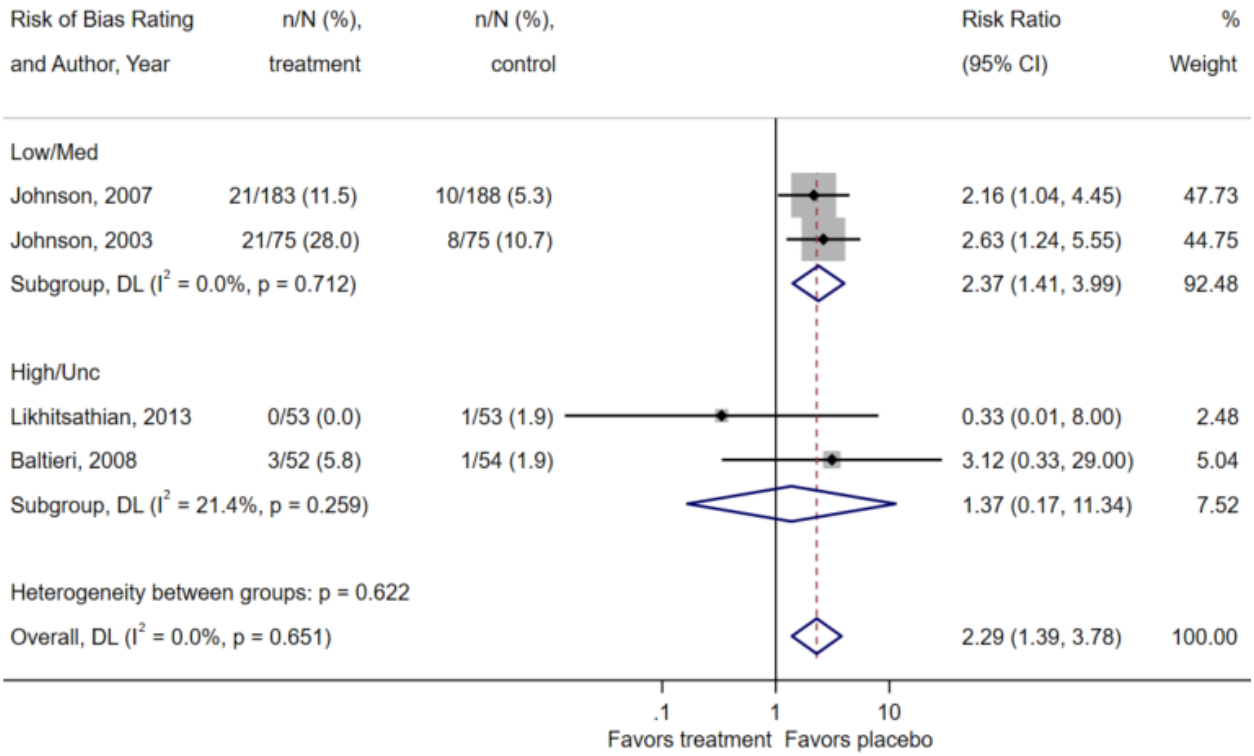
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-77. Topiramate compared with placebo: Diarrhea by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

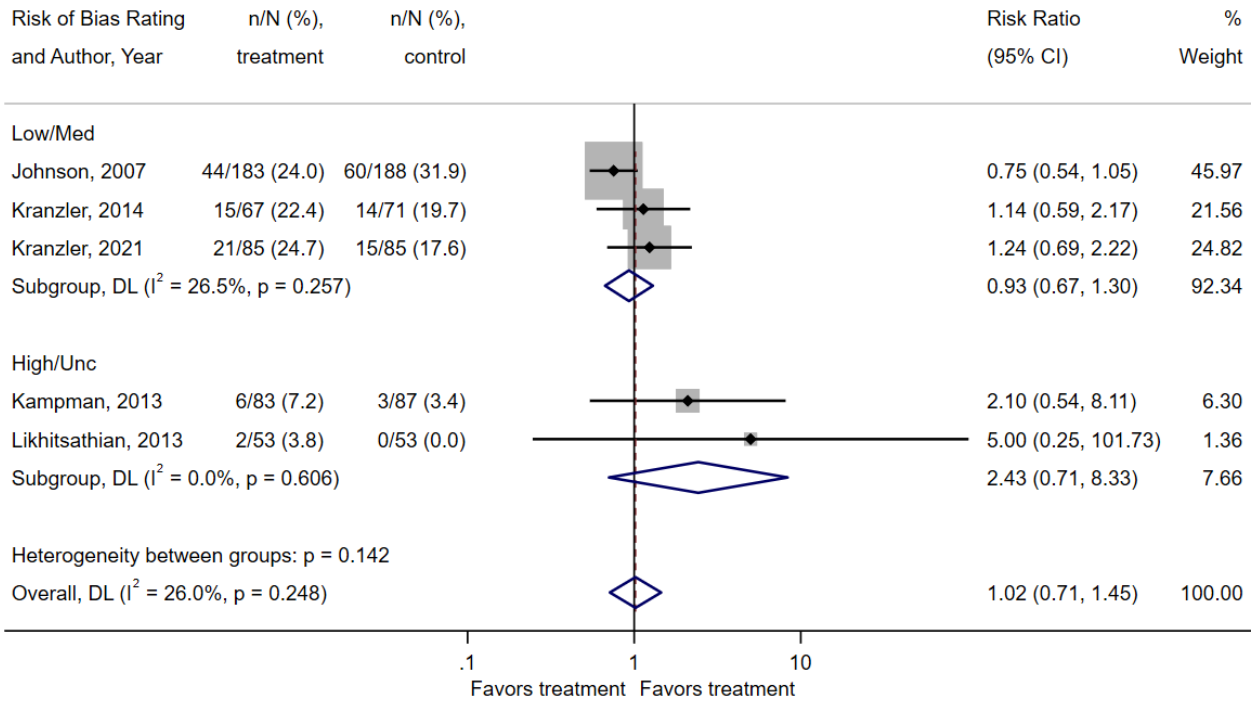
Figure E-78. Topiramate versus placebo: Dizziness by risk-of-bias rating



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model; continuity correction applied to studies with zero cells

CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

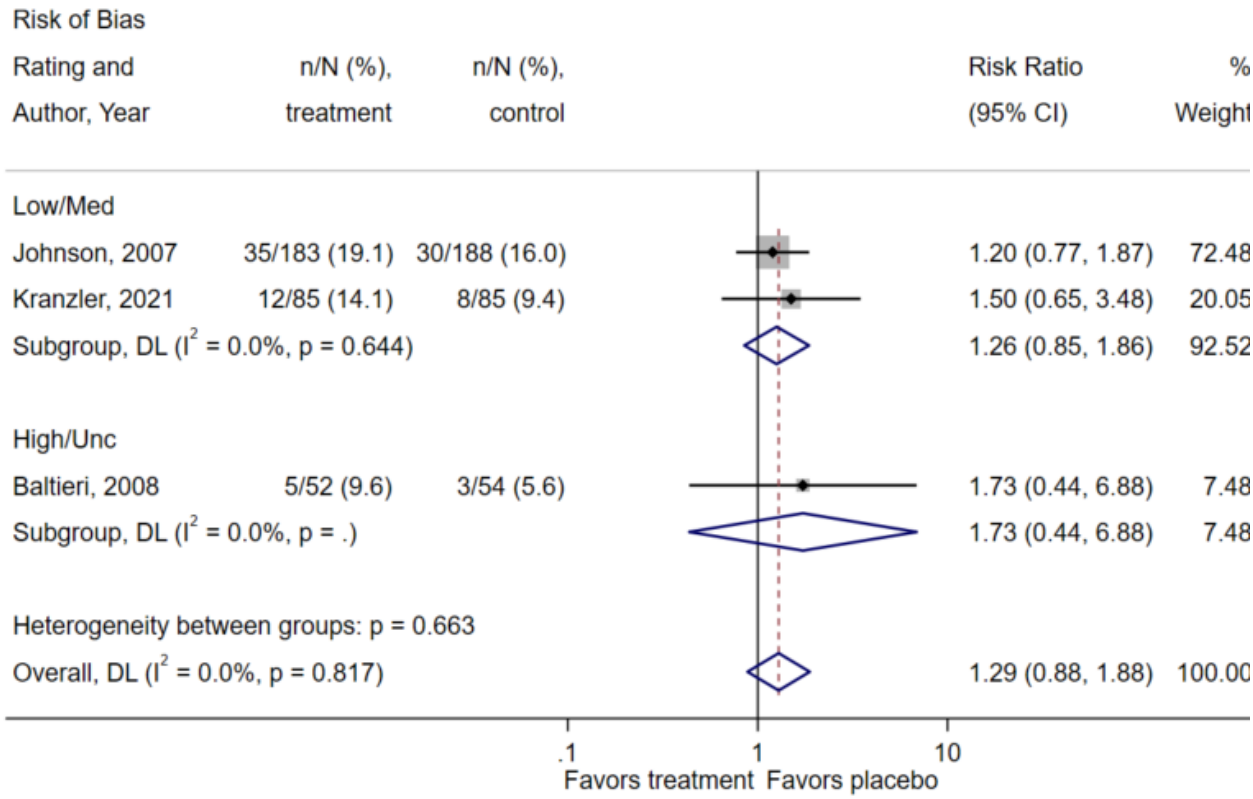
Figure E-79. Topiramate versus naltrexone: Headache by risk-of-bias rating



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model; continuity correction applied to studies with zero cells

CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

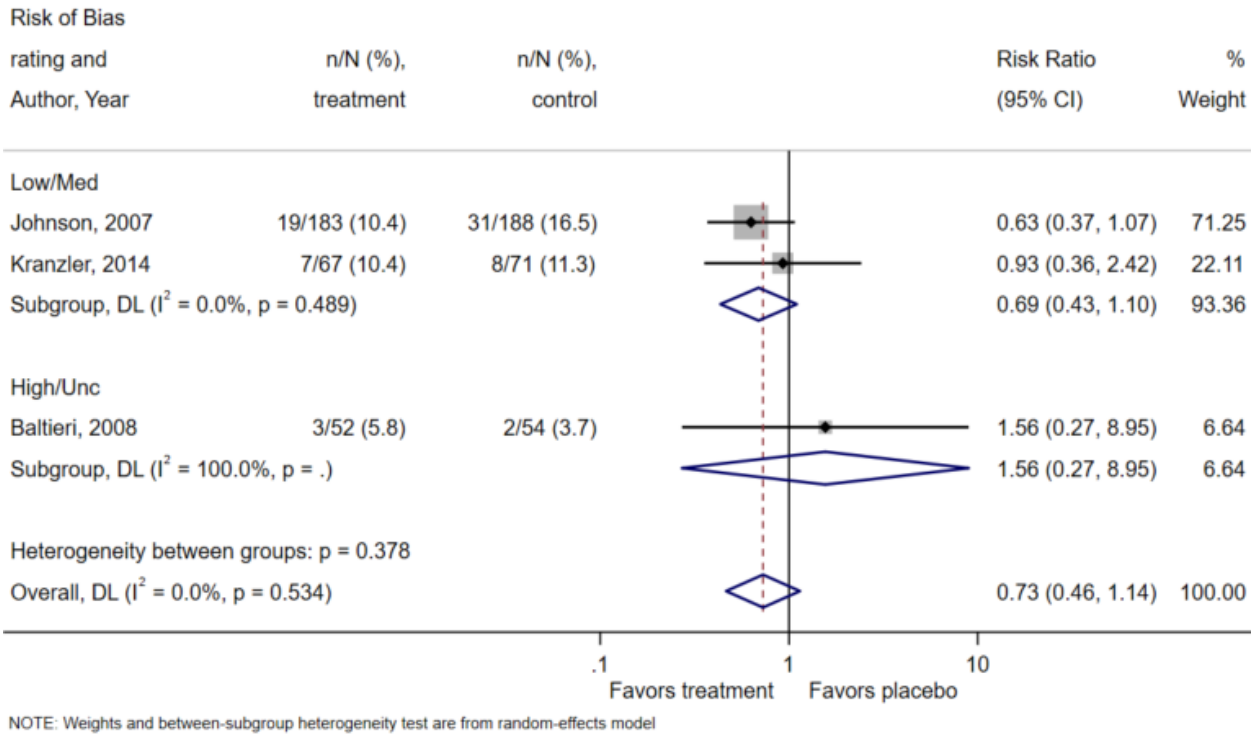
Figure E-80. Topiramate versus placebo: Insomnia by risk-of-bias rating



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

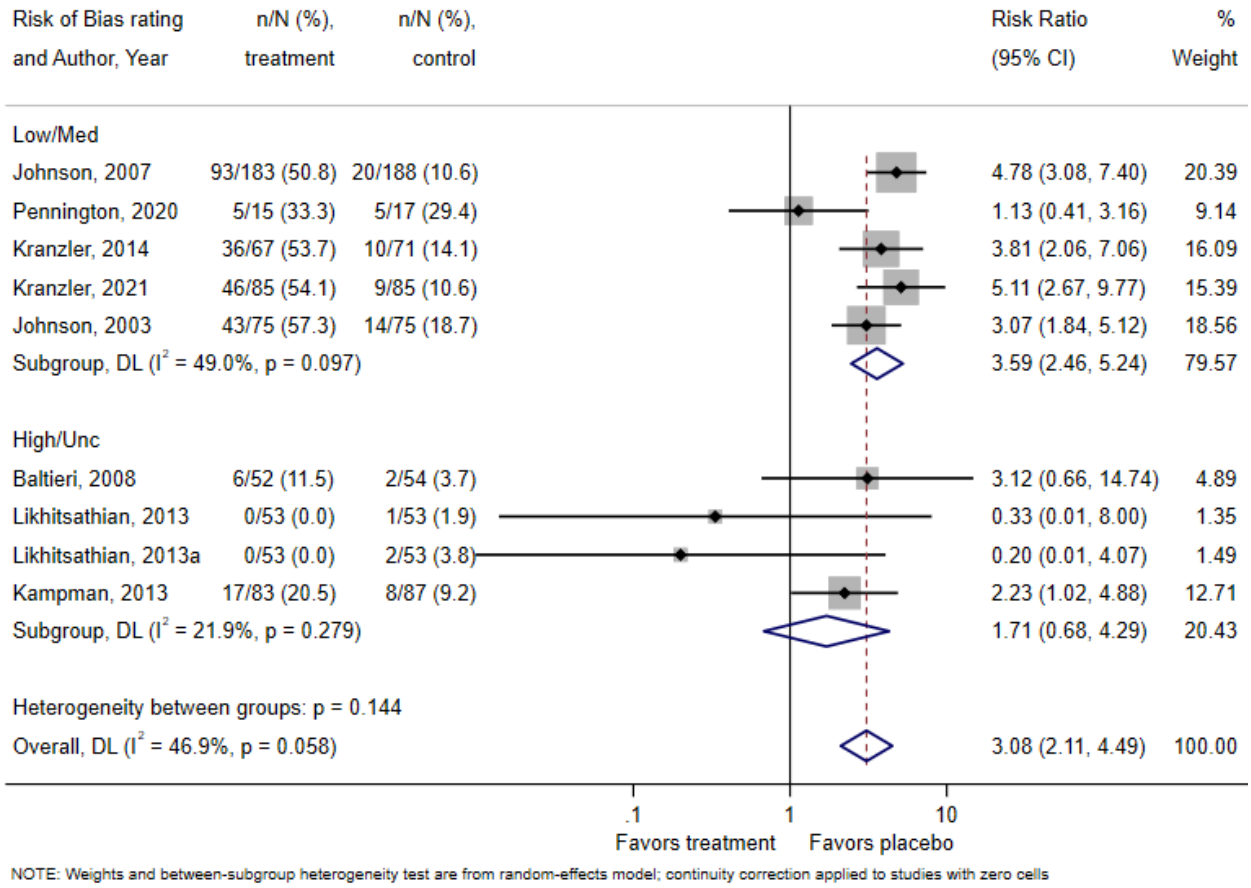
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-81. Topiramate versus placebo: Nausea by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

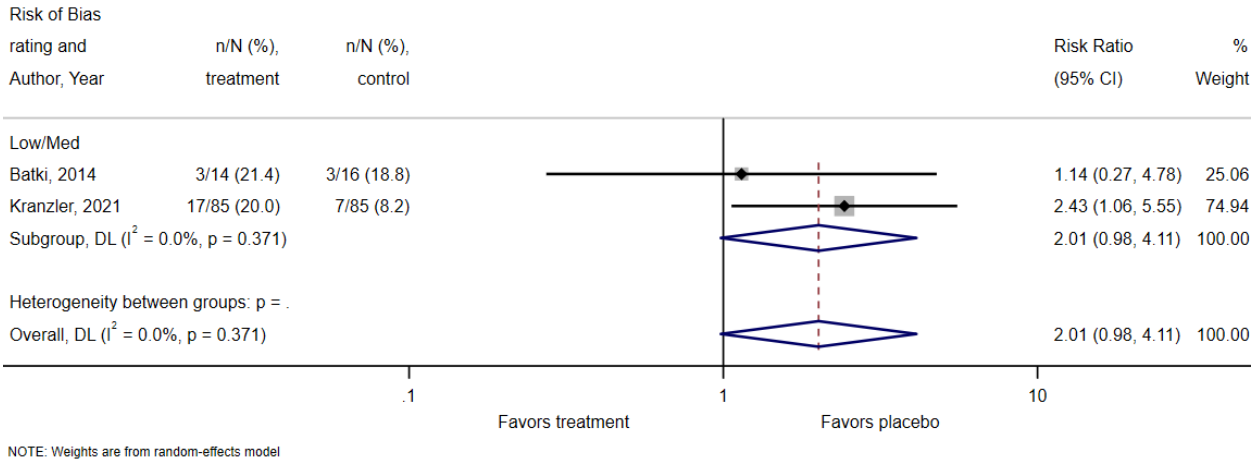
Figure E-82. Topiramate versus placebo: Numbness by risk-of-bias rating



Notes: Likhitsathia, 2013a is tongue numbness; Likhitsathia, 2013b is numbness

CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

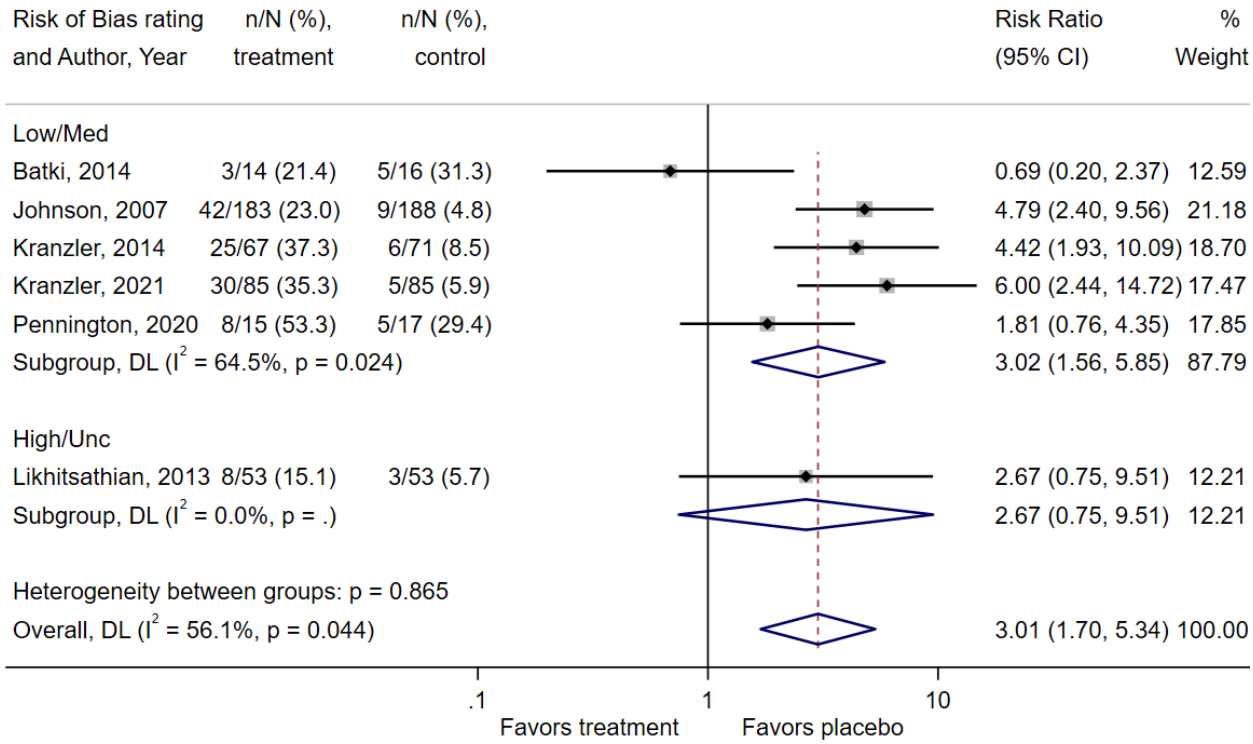
Figure E-83. Topiramate versus placebo: Vision changes (blurred vision) by risk-of-bias rating



NOTE: Weights are from random-effects model

CI = confidence interval; Med = medium; n/N = sample size.

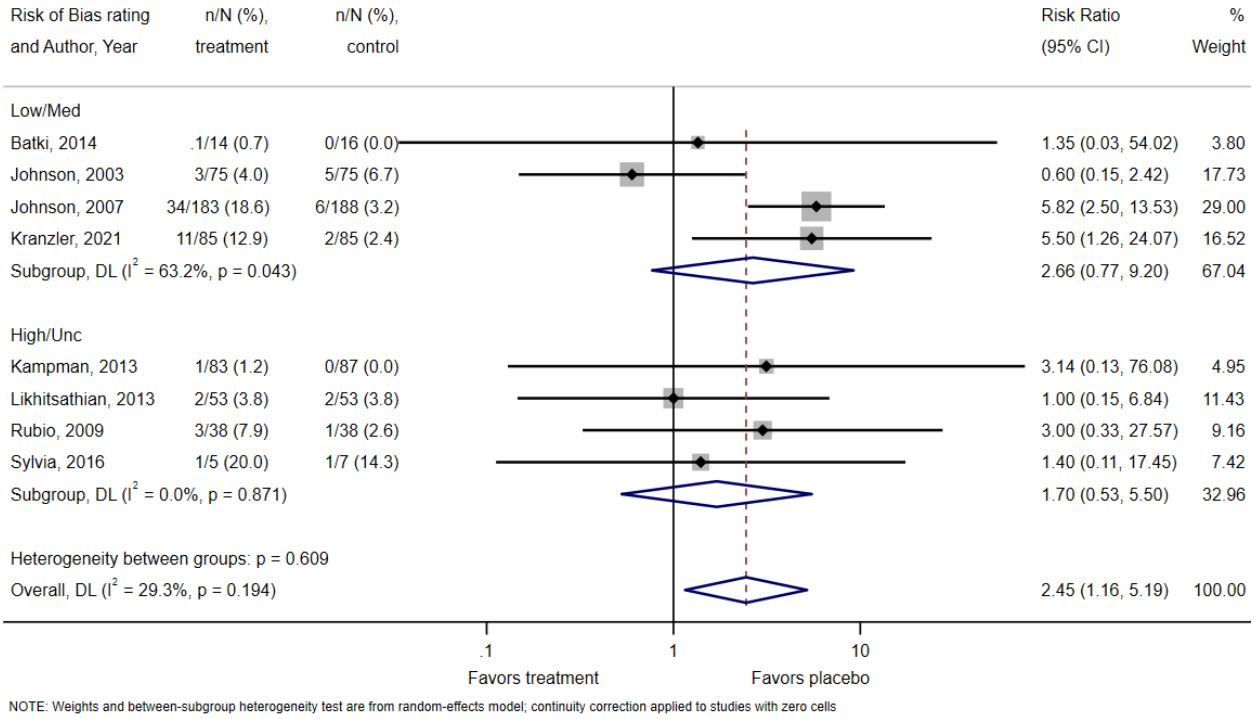
Figure E-84. Topiramate versus placebo: Taste abnormalities by risk-of-bias rating



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model

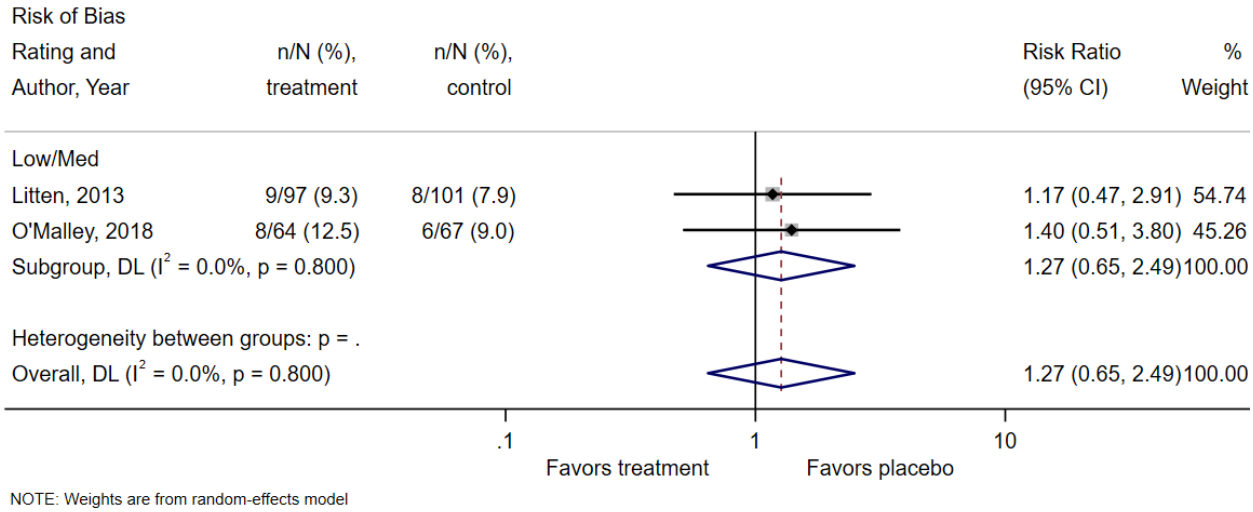
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-85. Topiramate versus placebo: Withdrawals due to adverse events by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

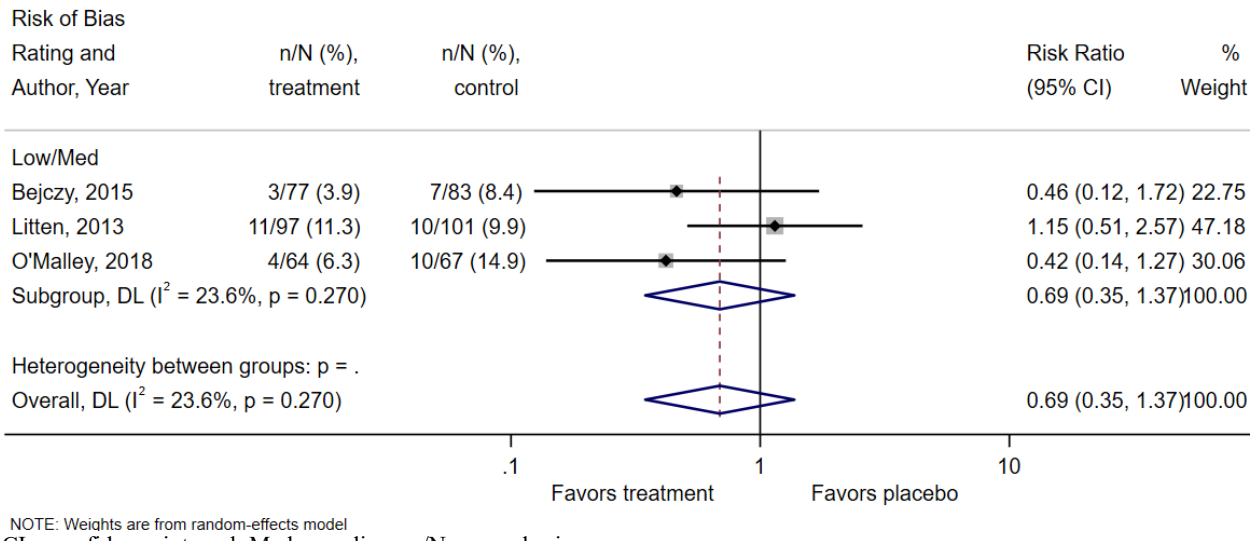
Figure E-86. Varenicline versus placebo: Anxiety by risk-of-bias rating



NOTE: Weights are from random-effects model

CI = confidence interval; Med = medium; n/N = sample size.

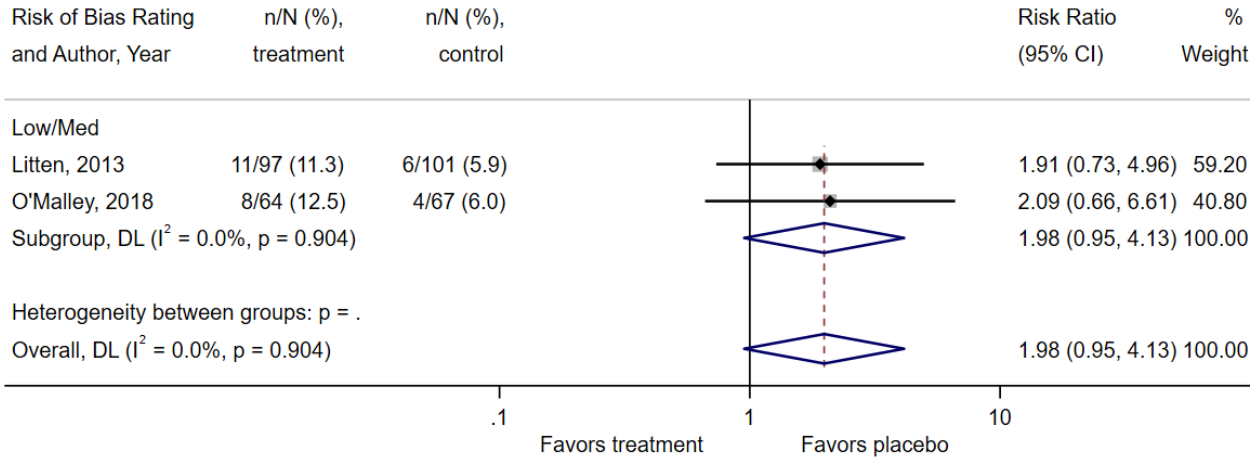
Figure E-87. Varenicline versus placebo: Diarrhea by risk-of-bias rating



NOTE: Weights are from random-effects model

CI = confidence interval; Med = medium; n/N = sample size.

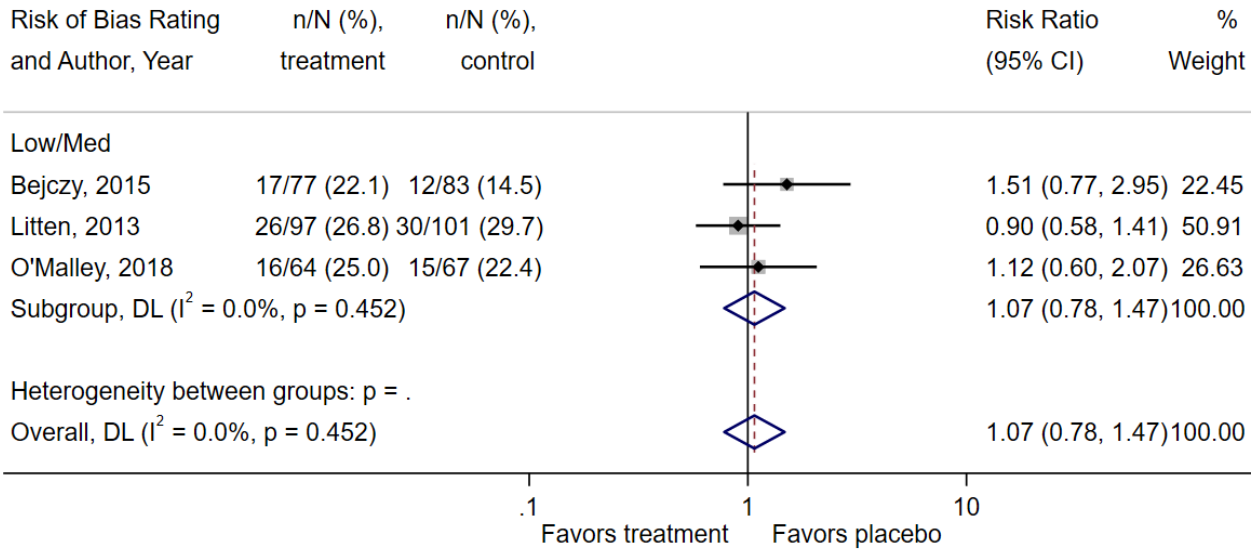
Figure E-88. Varenicline versus placebo: Dizziness by risk-of-bias rating



NOTE: Weights are from random-effects model

CI = confidence interval; Med = medium; n/N = sample size.

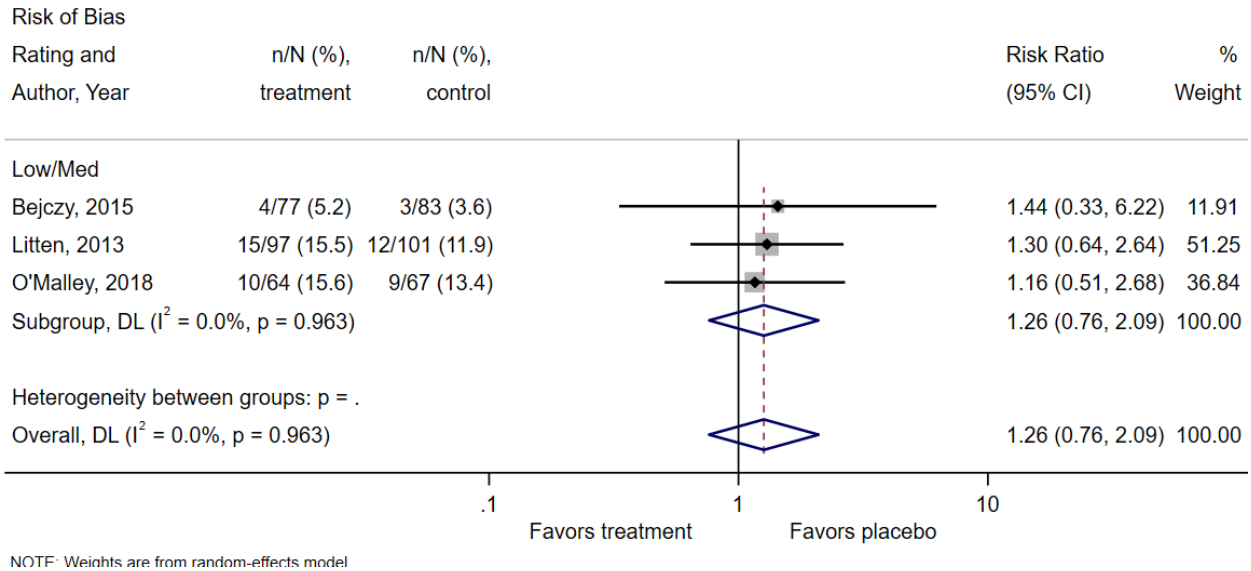
Figure E-89. Varenicline versus placebo: Headache by risk-of-bias rating



NOTE: Weights are from random-effects model

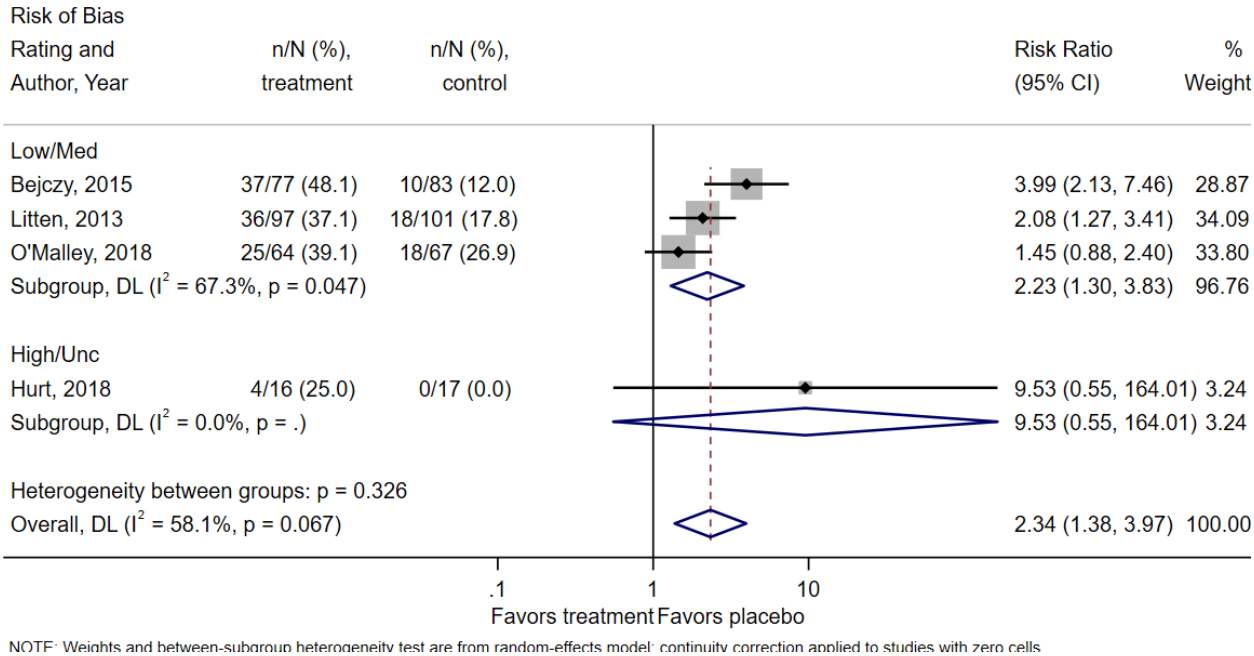
CI = confidence interval; Med = medium; n/N = sample size.

Figure E-90. Varenicline versus placebo: Insomnia by risk-of-bias rating



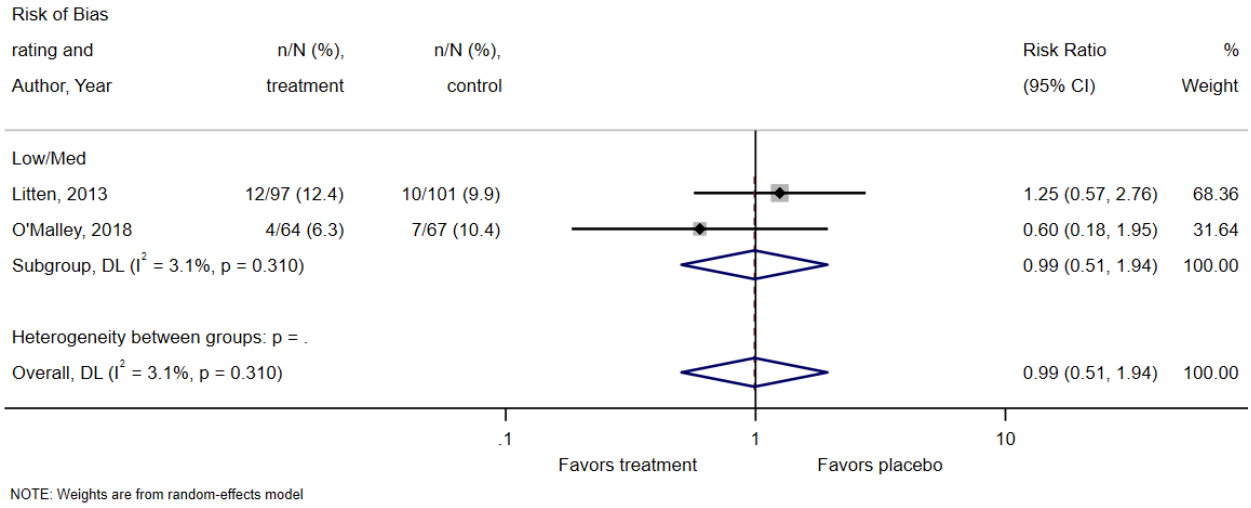
CI = confidence interval; Med = medium; n/N = sample size.

Figure E-91. Varenicline versus placebo: Nausea by risk-of-bias rating



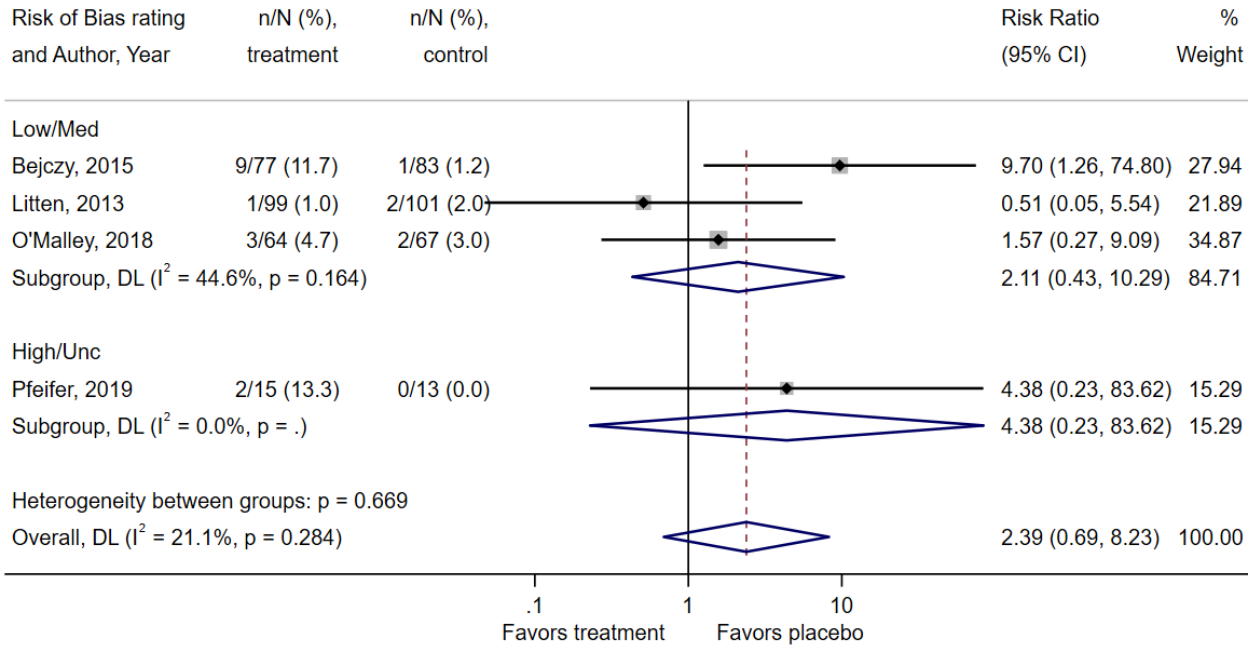
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-92. Varenicline versus placebo: Vomiting by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size.

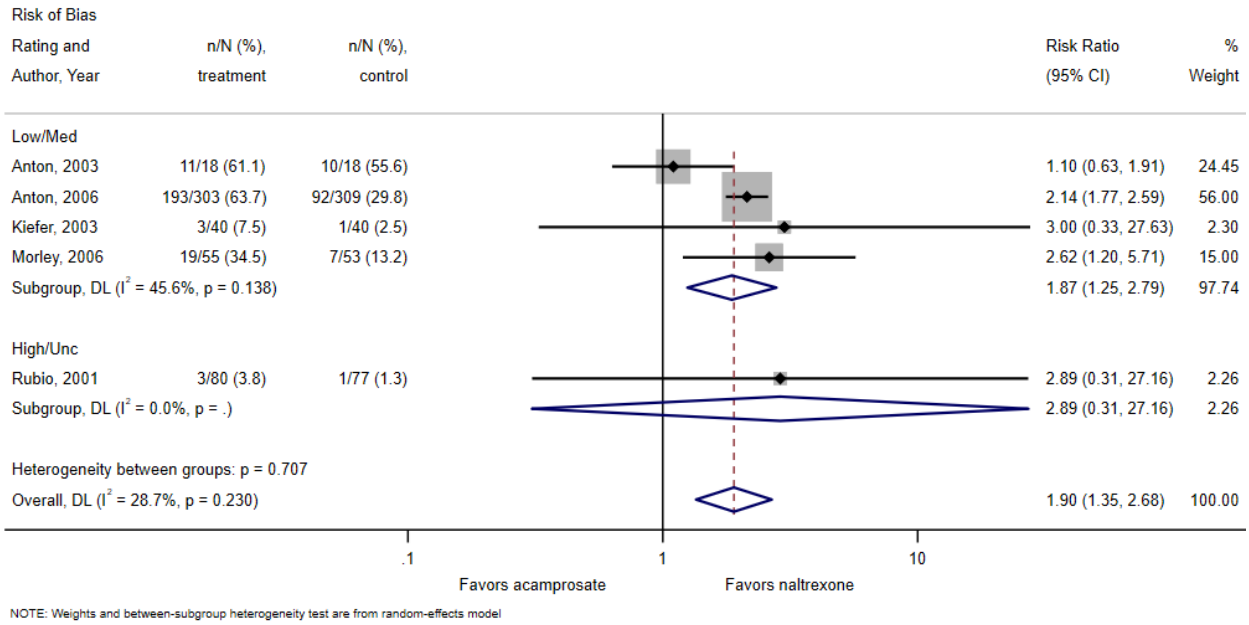
Figure E-93. Varenicline versus placebo: Withdrawals due to adverse events by risk-of-bias rating



NOTE: Weights and between-subgroup heterogeneity test are from random-effects model; continuity correction applied to studies with zero cells

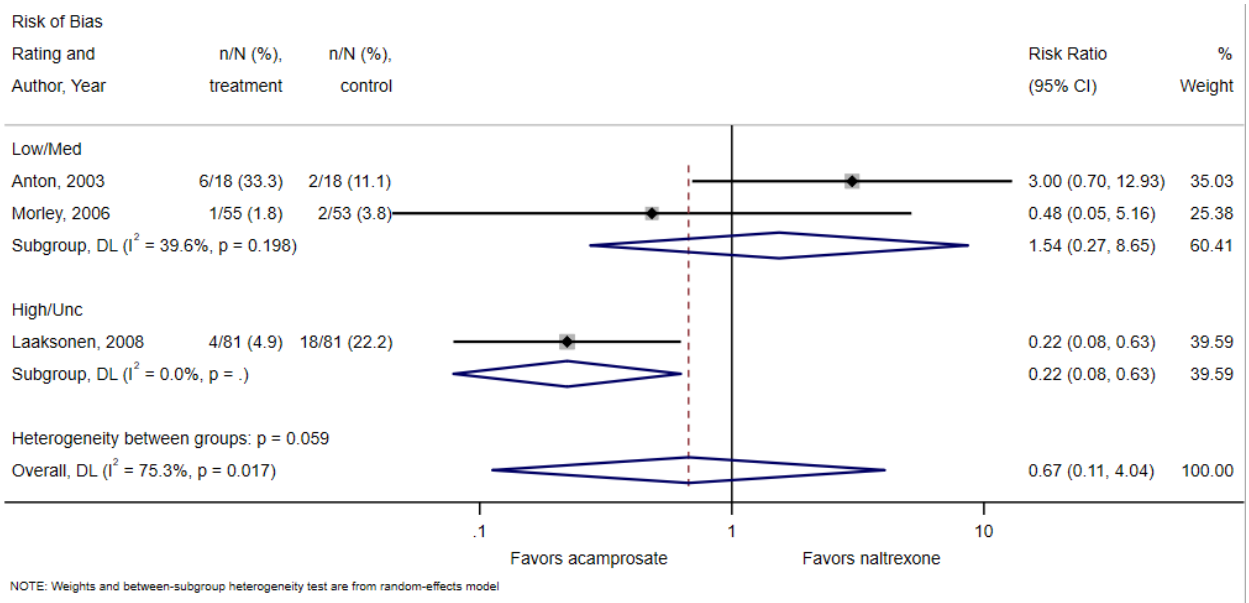
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-94. Acamprosate versus naltrexone: Diarrhea by risk-of-bias rating



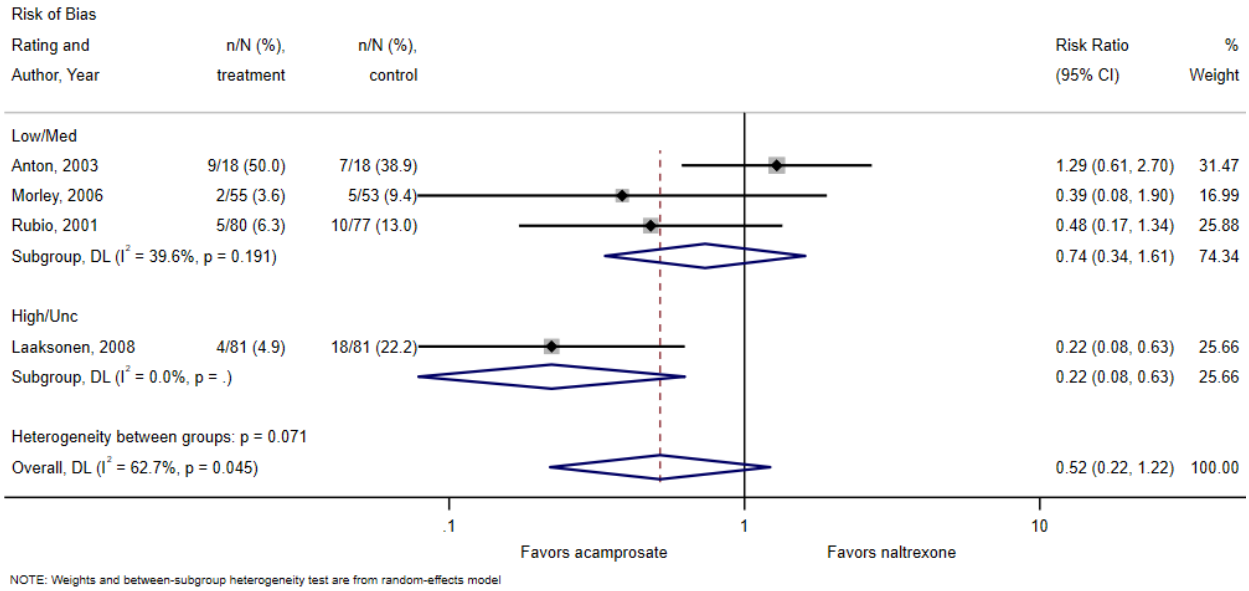
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-95. Acamprosate versus naltrexone: Dizziness by risk-of-bias rating



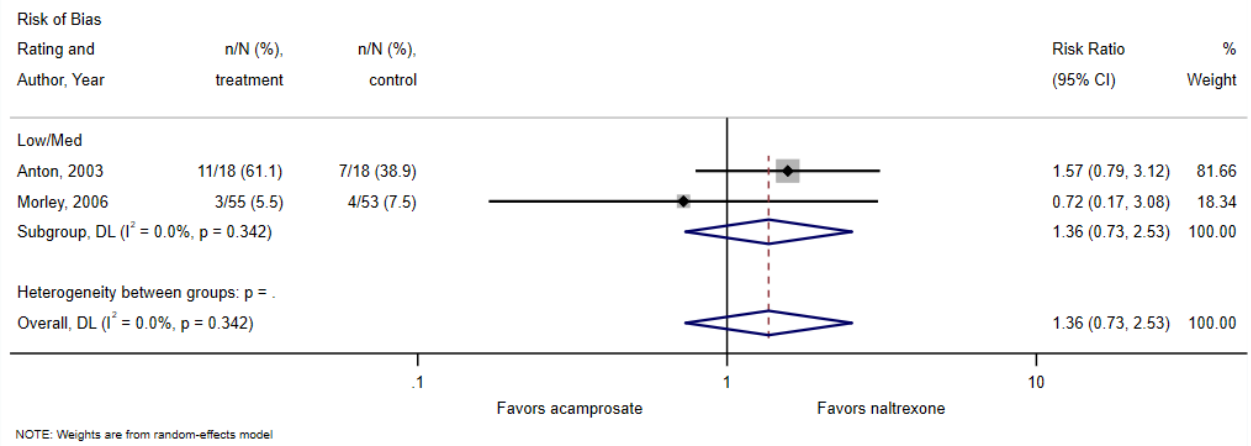
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-96. Acamprosate versus naltrexone: Headache by risk-of-bias rating



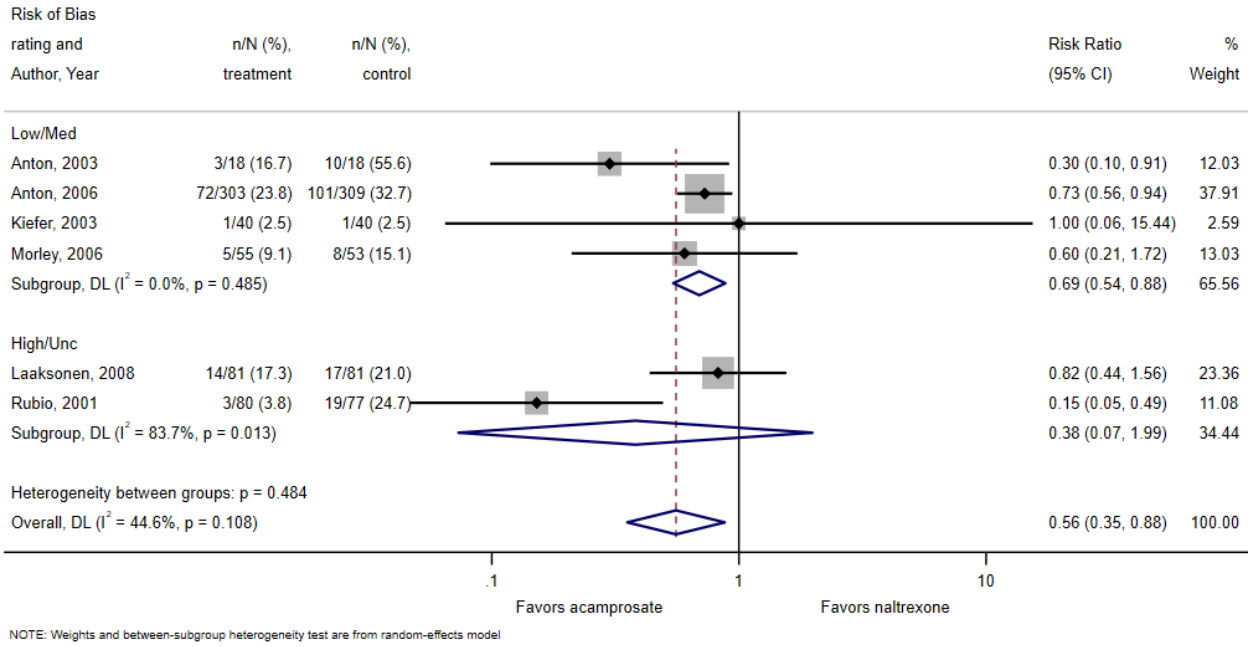
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-97. Acamprosate versus naltrexone: Insomnia by risk-of-bias rating



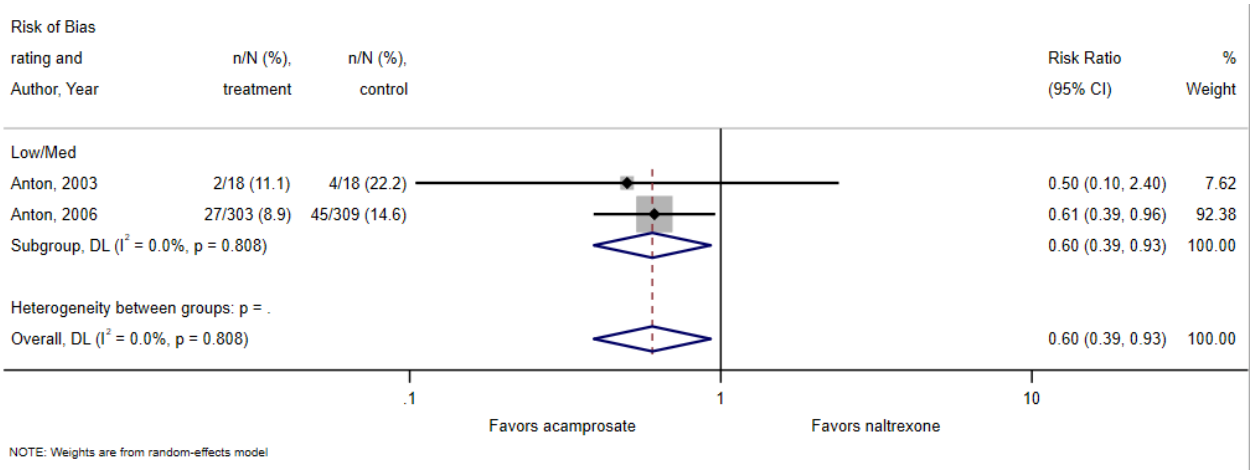
CI = confidence interval; Med = medium; n/N = sample size.

Figure E-98. Acamprosate versus naltrexone: Nausea by risk-of-bias rating



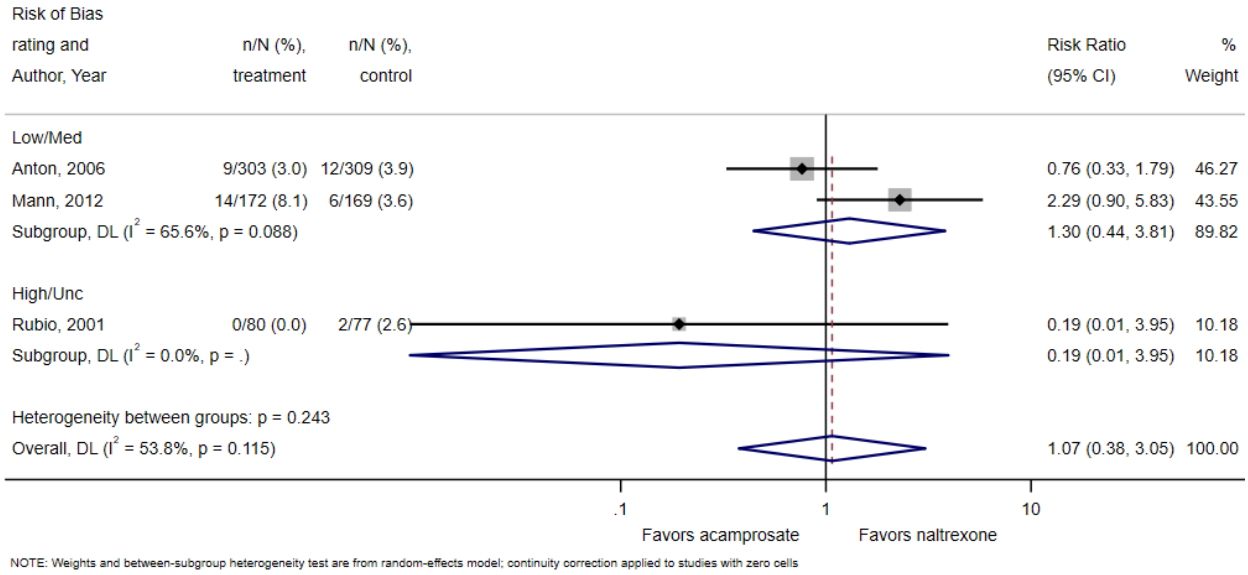
CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

Figure E-99. Acamprosate versus naltrexone: Vomiting by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size.

Figure E-100. Acamprosate versus naltrexone: Withdrawals due to adverse events by risk-of-bias rating



CI = confidence interval; Med = medium; n/N = sample size; Unc = unclear.

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