Gender Differences in Response to Alcohol Use Disorder Treatment

A Systematic Review

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Preface

Over the past two decades, the U.S. Department of Defense (DoD) has invested unparalleled resources into developing effective treatments for military-related psychological health conditions. Systematic reviews are a key component in the knowledge translation process; they function to translate research into evidence-based health-care guidelines that promote optimal clinical care. Although a few government agencies, including the Department of Veterans Affairs and the Agency for Healthcare Research and Quality, have established evidence synthesis centers, there is no similar center within DoD that can synthesize research evidence on psychological health issues of interest. Funded by a three-year contract with the Defense Centers of Excellence for Psychological Health and Traumatic Brain Injury (now part of the Psychological Health Center of Excellence), staff at the Southern California Evidence-based Practice Center, housed at the RAND Corporation, is tasked with conducting research syntheses on psychological health interventions important to military populations.

Among current concerns of military psychological health practitioners are the rates of alcohol use disorder among service personnel, particularly female soldiers, and the most-effective treatments. This systematic review synthesizes the literature on gender differences in response to treatment for alcohol use disorder. The review will be of interest to military and civilian health policymakers and practitioners who oversee or implement—and seek to understand factors that might contribute to differences in the response to—treatment for alcohol use disorder.

None of the authors has any conflict of interest to declare.

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Abstract

Men and women might respond differently to some treatments for alcohol use disorder. If confirmed, such knowledge would be important to consider in selecting the treatment likely to be most efficacious for a patient. The purpose of this systematic review was to synthesize the evidence for gender differences in effects of treatments for the disorder.

We searched both electronic databases (PubMed, PsycINFO, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Clinicaltrials.gov) and bibliographies of existing systematic reviews and included studies. We also contacted trial authors to identify English-language reports of randomized controlled trials (RCTs) involving U.S. patients and systematic reviews published between 1997 and March 2018. Publications had to report on an analysis of gender differences in the effects of pharmacologic and/or psychosocial treatments for adults with alcohol use disorder, report data only for one gender, report treatment effect results by gender, or report gender-coded patient-level outcomes. Two reviewers independently screened literature identified by the searches using predetermined eligibility criteria, abstracted data, and critically appraised publications that met the inclusion criteria. We summarized gender differences in the treatment responses as differences between genders in the difference between the intervention and control group results (difference of differences [DiffSDiff]) together with the 95-percent confidence interval (CI). The quality of evidence was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.

After screening 13,771 citations and reviewing the full text of 1,434 publications, we identified 24 original studies with findings reported in 63 publications and four systematic reviews that met inclusion criteria. Studies assessed gender differences in the efficacy of a treatment modality or the efficacy of an intervention only in male or female study participants. While some individual studies found evidence of gender differences, we did not find evidence of systematic gender differences in treatment effects across studies. The analysis did not detect systematic gender differences in treatment response in studies reporting outcomes for both men and women (DiffSDiff 0.42; CI −0.80, 1.64; 7 RCTs) or in indirect comparisons across studies (DiffSDiff 0.03; CI −0.28, 0.34; p = 0.840). Direct comparisons found conflicting results in individual studies for treatment compliance, but no statistically significant effect was detected in indirect comparisons across 11 RCTs (DiffSDiff 0.31; CI −0.03, 0.65; p = 0.073). Only two studies reported on adverse events, and both evaluated naltrexone: The studies reported more findings of nausea in women taking naltrexone than in men. (Rates of nausea were not related to rates of heavy drinking.) Stratifying interventions by pharmacological, psychological, or combination treatment indicated larger effects for women in combination treatment, but the result was based on only one study and should be interpreted with caution. We found no indication that gender differences in symptom improvement were affected by duration.
(\(p = 0.721\)) or intensity (\(p = 0.270\)) of treatment. Only one of the studies was conducted in primary care, hindering an assessment of whether gender differences vary by treatment setting: In the included studies, we found no significant effect of setting in direct (\(p = 0.224\)) or indirect comparisons (\(p = 0.988\)). Finally, one study conducted at an Army post with an active-duty population found a significant gender difference favoring women in the benefit of a brief telephone-based motivational interviewing intervention, but the sample of women was very small.

In conclusion, although some individual studies demonstrated gender differences in treatment effects, we did not identify systematic differences across studies. Most notably, despite an extensive search and thorough screening procedure, we found very few studies reporting on gender differences, hindering all analyses. For this reason, more studies are needed that assess the presence or absence of gender differences in alcohol use disorder treatment.
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Summary

Misuse of alcohol is a major health concern in the United States, particularly among young adults. Drinking at levels above the amounts defined as safe by well-publicized, evidence-based guidelines places an individual at greater risk for illness, injury, or social or legal problems.

As with the civilian population, where men are more likely than women to be classified as heavy drinkers, men who are full-time (active-duty) military personnel are also more likely than active-duty female military personnel to be classified as heavy drinkers. However, the rates of hazardous or at-risk drinking are similar among active-duty men and women. In addition, active-duty men and women who are at risk for alcohol use disorder (AUD) are equally likely to suffer work, personal, and legal consequences that can be serious.

Numerous government health agencies and professional practice societies have developed evidence-based guidelines for the treatment of AUD, recommending pharmacological treatments, psychosocial treatments, or a combination of both. Although many of these treatments have shown evidence for effectiveness in treating AUD, it is unclear whether women respond differently from men to some treatment modalities. Various studies have addressed gender differences in response to specific treatments, but no efforts have been made to comprehensively address gender differences across common evidence-based treatments, particularly combination therapies. This systematic review assesses gender differences in the reported efficacy and safety of recommended treatments for AUD.

Key Questions

The following questions and subquestions guided the review:

- **Key Question 1**: Do the efficacy and/or safety of first-line treatments for AUD differ according to gender?
  - **Key Question 1a**: Do gender differences vary by pharmacological versus psychosocial treatment?
  - **Key Question 1b**: Do gender differences vary by duration and intensity of treatment?
  - **Key Question 1c**: Do gender differences vary by treatment setting?

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1 The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), provides the diagnostic criteria for alcohol use disorder, which require “yes” responses to two or more of 11 questions that ask about drinking behavior in the prior year. The DSM-5 differs from the 4th edition (DSM-IV) in that DSM-5 combines alcohol abuse and alcohol dependence.
Methods

To answer the key questions, we searched PubMed, PsycINFO, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov from January 1997 to March 2018 and bibliographies of existing systematic reviews to identify reports of English-language randomized controlled trials (RCTs) and other systematic reviews that compared two or more groups and that reported follow-up data by gender on the efficacy of treatment among individuals diagnosed with AUD in the United States or that reported on gender differences in treatment efficacy.

Two independent reviewers screened identified citations using predetermined eligibility criteria. Because outcomes by gender are most often reported as secondary outcomes in studies of treatment for AUD, we retrieved full-text copies of all studies that assessed the efficacy of treatments for AUD recommended in major guidelines and therefore might meet our inclusion criteria. We then scoured the results and discussion sections for outcomes by gender. We contacted trial authors to obtain gender differences data if these were not reported in otherwise eligible RCT evaluations. Reviewers abstracted prespecified study-level information and assessed each included study’s risk of bias; all abstracted data were checked by the project lead for accuracy.

Meta-analyses were conducted to determine the difference of differences (DiffoDiff) for effects in studies that directly compared outcomes for men and women, together with the 95-percent confidence intervals (CIs). Meta-regressions were conducted to assess gender differences indirectly across studies that enrolled only men, only women, or both. Findings are expressed as differences (between intervention and placebo groups) of differences between men and women. The overall quality of evidence was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach, and we differentiated high, moderate, low, and very low confidence in summary results.

Results

After screening 13,771 citations and reviewing 1,434 publications as full text, we identified 24 original studies with findings reported in 63 publications and four systematic reviews that met inclusion criteria. Studies assessed gender differences in the efficacy of a treatment modality or assessed the efficacy of an intervention in only male or female study participants.

Do the Efficacy and/or Safety of First-Line Treatments for AUD Differ According to Gender?

Although some individual studies indicated evidence of gender differences, we did not find evidence of systematic gender differences in the treatment effects across studies. The analysis did not detect systematic gender differences in the treatment response in studies reporting outcomes for men and women (DiffoDiff 0.42; CI –0.80, 1.64; 7 RCTs). Results were similar for the individual outcome, mean percentage of heavy-drinking days as defined by each study (DiffoDiff 0.54; CI –0.88, 1.97; 6 RCTs); and the difference in the percentage of abstinent days
also was not statistically significant (DiffODiff 0.29; CI –1.53, 2.12; 5 RCTs). Indirect comparisons across studies that included only men and only women also found no systematic gender effect in symptom improvement outcomes (DiffODiff 0.03; CI –0.28, 0.34; \( p = 0.840 \)) or specific outcomes, such as percentage of heavy-drinking days (DiffODiff 0.06; CI –0.29, 0.41; \( p = 0.706 \)) or percentage of abstinent days (DiffODiff –0.16; CI –0.55, 0.22; \( p = 0.379 \)).

Direct comparisons (studies directly comparing men and women) found conflicting results in individual studies regarding male-female differences for treatment compliance measures. Indirect comparisons across 11 RCTs found no statistically significant gender effect (DiffODiff 0.31; CI 0.03, 0.65; \( p = 0.073 \)). The difference in the outcome of mean proportion of sessions attended also was not statistically significant across seven RCTs (DiffODiff 0.32; CI –0.23, 0.86; \( p = 0.204 \)).

Only four of the studies reported on adverse events, and only two of these reported on gender differences within the study samples. Both studied naltrexone. The studies found more reports of nausea in women taking naltrexone than in men in some but not all treatment groups.

The quality of evidence was low or very low for all documented estimates. Quality was downgraded by inconsistency across studies (or lack of studies to evaluate consistency), imprecision of the effect estimate, or indirectness in indirect comparisons across studies.

The systematic reviews that met our inclusion criteria addressed specific questions and did not report numerical effect estimates for gender differences.

**Do Gender Differences Vary by Pharmacological Versus Psychological Treatment?**

We identified only one RCT that compared gender differences across a pharmacological and psychological intervention. In the absence of direct comparisons, we stratified the studies by intervention, differentiating pharmacological, psychosocial, and combination treatments.

Although pharmacological interventions (DiffODiff 0.11; CI –0.53, 0.75; 3 RCTs) and psychosocial interventions (DiffODiff 0.78; CI –2.23, 3.79; 4 RCTs) showed no difference across studies, one combination treatment study indicated larger effects for women (DiffODiff 0.34; CI 0.28, 0.40; 1 RCT). However, the result was based on only one study and should be interpreted with caution.

Two pharmacological studies directly comparing men and women within the same trials reported no differences in compliance measures. One study that evaluated a psychosocial intervention found a slight difference in treatment dose (sessions attended) for a couples’ intervention, in favor of male couples (DiffODiff –0.83; CI –0.96, –0.71; 1 RCT); however, the results should be interpreted with caution because it is based on only one RCT.

Two studies reported on gender differences in adverse events and both studies evaluated naltrexone. As already described, the studies reported more incidents of nausea in women in some but not all treatment groups.
Do Gender Differences Vary by Duration and Intensity of Treatment?

We found no interaction effect of the treatment duration in studies reporting on direct comparisons between male and female treatment responses ($p = 0.721$). We also found no effect ($p = 0.175$) in the indirect comparison across all studies (including those of studies focused on only men and on only women).

One study directly compared two doses of intramuscular naltrexone. The study reported a dose-dependent response that exceeded the effect of placebo in men, whereas women’s response to active treatment was not dose dependent and did not exceed that of placebo. Another study assessing different treatment combinations (e.g., naltrexone with or without cognitive behavioral therapy) reported no gender differences.

Across studies directly reporting on gender differences within the study, we found no indication that gender differences were associated with different treatment intensity ($p = 0.270$). An indirect comparison combining all studies, including those in men only and those in women only, also found no interaction effect ($p = 0.994$).

Do Gender Differences Vary by Treatment Setting?

Only one of the studies was conducted in primary care, hindering an effective assessment of whether gender differences vary by treatment setting. In the included studies, we found no significant effect across studies that directly compared treatment response of men and women ($p = 0.224$). We also did not identify an effect by treatment setting in indirect comparisons across studies ($p = 0.988$). The analyses should be interpreted with caution because of the sparsity of primary care data.

One study that was conducted at a U.S. Army post and enrolled an active-duty population found a significant gender difference in the effects of a brief, telephone-based motivational interviewing intervention, favoring women (percentage of heavy-drinking days: Diff = 3.93; CI 3.28, 4.57 and percentage of abstinent days: Diff = 2.96; CI 2.37, 3.55; 1 RCT). The study consisted of only a very small number of women and the findings should be interpreted with caution because of the lack of replication in other research studies in this patient population.

Conclusions

In conclusion, although individual studies demonstrated gender differences in treatment effects, we did not identify systematic differences across studies. Most notably, despite an extensive search and thorough screening procedure, we found very few studies reporting on treatment effects according to gender, hindering all analyses. The review showed a profound lack of information on the presence and absence of gender differences. We scrutinized numerous U.S. RCTs for differential effects for men and women but found very few relevant studies. Those that met inclusion criteria tended to be smaller and/or did not enroll comparable numbers of men and women; tended to assess a wide variety of outcomes, making cross-study comparisons difficult; and tended to have relatively high risk of bias. Thus, more studies are needed that assess the presence or absence of gender differences in alcohol use disorder treatment with appropriate methods.
Acknowledgments

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## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AA</td>
<td>Alcoholics Anonymous</td>
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<tr>
<td>ABCT</td>
<td>alcohol BCT</td>
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<tr>
<td>ABIT</td>
<td>alcohol-based IBT</td>
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<tr>
<td>AUD</td>
<td>alcohol use disorder</td>
</tr>
<tr>
<td>AUDIT</td>
<td>Alcohol Use Disorders Identification Test</td>
</tr>
<tr>
<td>BCT</td>
<td>behavioral couples therapy</td>
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<tr>
<td>BMT</td>
<td>behavioral marriage therapy</td>
</tr>
<tr>
<td>BRENDA</td>
<td>Biopsychosocial, Report, Empathy, Needs, Direct advice, and Assessment</td>
</tr>
<tr>
<td>BRT</td>
<td>brief relationship therapy</td>
</tr>
<tr>
<td>CBI</td>
<td>combined behavioral intervention</td>
</tr>
<tr>
<td>CBT</td>
<td>cognitive behavioral therapy</td>
</tr>
<tr>
<td>CDSR</td>
<td>Cochrane Database of Systematic Reviews</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>DiffoDiff</td>
<td>difference of differences</td>
</tr>
<tr>
<td>DoD</td>
<td>U.S. Department of Defense</td>
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<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 4th edition</td>
</tr>
<tr>
<td>DSM-5</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 5th edition</td>
</tr>
<tr>
<td>EPC</td>
<td>Evidence-based Practice Center</td>
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<tr>
<td>GRADE</td>
<td>Grades of Recommendation, Assessment, Development, and Evaluation</td>
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<tr>
<td>HR</td>
<td>hazard ratio</td>
</tr>
<tr>
<td>HRBS</td>
<td>DoD Survey of Health-Related Behaviors Among Active Duty Military Personnel</td>
</tr>
<tr>
<td>IBT</td>
<td>individual-based therapy</td>
</tr>
<tr>
<td>IPD</td>
<td>individual participant data</td>
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<tr>
<td>MD</td>
<td>medical doctor</td>
</tr>
<tr>
<td>MET</td>
<td>motivational enhancement therapy</td>
</tr>
<tr>
<td>MI</td>
<td>motivational interviewing</td>
</tr>
<tr>
<td>NA</td>
<td>not applicable</td>
</tr>
<tr>
<td>NR</td>
<td>not reported</td>
</tr>
<tr>
<td>OR</td>
<td>odds ratio</td>
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<tr>
<td>PACT</td>
<td>psychoeducational attention control</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized controlled trial</td>
</tr>
<tr>
<td>RHR</td>
<td>relative hazard ratio</td>
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<tr>
<td>ROR</td>
<td>relative odds ratio</td>
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<tr>
<td>RP</td>
<td>relapse prevention</td>
</tr>
<tr>
<td>S-BCT</td>
<td>standard BCT</td>
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<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
<td>SCID</td>
<td>Structured Clinical Interview for the DSM-IV</td>
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<tr>
<td>SMD</td>
<td>standardized mean difference</td>
</tr>
<tr>
<td>TAU</td>
<td>treatment as usual</td>
</tr>
<tr>
<td>TM</td>
<td>telephone-based treatment monitoring and feedback</td>
</tr>
<tr>
<td>TMC</td>
<td>TM plus counseling</td>
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<tr>
<td>VA</td>
<td>Department of Veterans Affairs</td>
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1. Introduction

Misuse of alcohol is a major health concern in the United States, particularly among young adults. As of 2015, 24.7 percent of adults ages 18 and older and 25.1 percent of young adults (ages 18 to 24) in the United States were self-reported binge drinkers (defined as “drinking five or more drinks on the same occasion on at least one day in the past 30 days”) and 6.7 percent were heavy alcohol users (defined as “having this number of drinks on the same occasion on 5 or more days in the past 30 days”) (Center for Behavioral Health Statistics and Quality, 2015). As of 2014, 43 percent of full-time (active-duty) military personnel and 49 percent of all enlisted personnel were 18 to 25 years of age (U.S. Department of Defense [DoD], 2014a).

The 2015 DoD Survey of Health-Related Behaviors Among Active Duty Military Personnel (HRBS) defines three levels of alcohol misuse (Meadows et al., 2018). *Binge drinking* is defined as consuming five or more drinks on one occasion for men (four or more for women) at least once in the previous month; *heavy drinking* is defined as binge drinking on five or more days in the past month. The HRBS defined *hazardous or disordered drinking* (which meets criteria for a possible alcohol use disorder [AUD]) as having a score of four or higher for men and three or higher for women on the World Health Organization’s Alcohol Use Disorders Identification Test [AUDIT]3 (Babor, Higgins-Biddle, et al., 2001). The survey found that across all services, 5.4 percent of personnel were classified as heavy drinkers, and 30.0 percent were classified as binge drinkers. Among military personnel, heavy and binge drinkers were more likely to be serving in the Marine Corps, to have a high school education or less, to have an enlisted grade, and to be younger (17 to 34 years) (Meadows et al., 2018). DoD Instruction [DoDI] 1010.04 mandates yearly screening of all active-duty and Reserve Component personnel for alcohol misuse (using the AUDIT-C screening tool) as part of the annual Periodic Health Assessment (DoD, 2014b). The DoDI defines *at-risk or hazardous alcohol use* as “the consumption of alcohol in daily or weekly amounts greater than those defined as safe by the U.S. Preventive Services Task Force” (Jonas et al., 2012). Across all services, more than one third (35 percent) met criteria for a possible AUD.

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2 Although the Substance Abuse and Mental Health Services Administration (SAMHSA) does not provide separate definitions of heavy drinking for men and women, the National Institute on Alcohol Abuse and Alcoholism (NIAAA) defines *at-risk drinking* as more than 14 drinks per week or four drinks in a given single day for men and more than seven drinks per week or three drinks in a given single day for women (NIAAA, undated).

3 AUDIT is a ten-item questionnaire that assesses risky alcohol use (frequency of drinking, typical quantity, frequency of heavy drinking), dependence (impaired driving, increased salience of heavy drinking, and morning drinking), and harmful use (guilt over drinking, blackouts, drinking-related injuries, and concern of others). The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), provides the diagnostic criteria for alcohol use disorder, which require “yes” responses to two or more of 11 questions that ask about drinking behavior in the prior year. The DSM-5 differs from the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) in that DSM-5 combines alcohol abuse and alcohol dependence.
Drinking at levels above the recommended amounts places an individual at greater risk for illness, injury, and social or legal problems. The 2015 HRBS found that drinking was associated across services with loss of productivity (6.1 percent), engagement in risky behaviors (9.7 percent), and other serious consequences (8.2 percent) (Meadows et al., 2018).

Active-duty men were substantially more likely than their female counterparts to report binge drinking (31.2 percent compared with 23.0 percent) or heavy drinking (6 percent compared with 1.3 percent), but only slightly more likely to report hazardous drinking (36.0 percent compared with 31.3 percent). Men and women were equally likely to report suffering serious and work-related consequences from drinking (Meadows et al., 2018). Concern regarding the rates of alcohol use among service personnel is also increasing because of evidence linking disordered alcohol use with the high rate of sexual assault (Farris and Hepner, 2014). In addition, some evidence suggests that alcohol misuse might have a greater impact on women’s health than on that of men.

Numerous government health agencies and professional practice societies have developed evidence-based guidelines for the treatment of alcohol use disorder, recommending pharmacological treatments, psychosocial treatments, or a combination of both. These organizations (and their guidelines) include the American Psychiatric Association (Kleber et al., 2006); NIAAA/SAMHSA (JBS International, Inc., 2015); the United Kingdom’s National Institute for Health and Care Excellence (2011); and the Department of Veterans Affairs (VA) and DoD (Management of Substance Use Disorders Work Group, 2015). The 2010 American Psychiatric Association guidelines recommend two forms of naltrexone, an oral opioid antagonist (ReVia®) and a longer-acting injectable form (Vivitrol®), both approved by the U.S. Food and Drug Administration for use in treating AUD. Also recommended were acamprosate (Campral®), a γ-aminobutyric acid analog that might decrease alcohol craving in abstinent individuals, and disulfiram (Antabuse™), an inhibitor of one of the enzymes in the alcohol breakdown pathway. Some evidence supports the use of disulfiram for patients whose drinking might be triggered by events that suddenly increase alcohol craving. The American Psychiatric Association also recommends the following psychosocial treatments, based on their evidence of efficacy and effectiveness for treatment of patients with AUD: motivational enhancement therapy; cognitive behavioral therapy (CBT); behavioral therapies (e.g., community reinforcement, contingency management); marital and family therapies; group therapies; psychodynamic therapy or interpersonal therapy; 12-step facilitation; and self-help groups, such as Alcoholics Anonymous. Both acamprosate and disulfiram are suggested to be effective as adjunctive medications in combination with psychosocial treatment in motivated patients.

DoD recommends treatment according to the VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders (Management of Substance Use Disorders Work Group, 2015). For those without documented AUD who screen positive for alcohol misuse, the current guideline recommends a “single brief intervention” regarding alcohol-related risks and advice to abstain or drink within nationally established age and gender-specific limits for daily and weekly consumption (Management of Substance Use Disorders Work Group, 2015). For
those with documented AUD, the guideline recommends (with high strength of evidence) use of one of the following pharmacologic agents: acamprosate, disulfiram, naltrexone oral or extended release (ReVia® or Vivitrol®), or topiramate (Topamax®). For those for whom these agents are contraindicated or ineffective, weak evidence supports the use of gabapentin. The guideline also strongly recommends the use of one of the following psychosocial interventions, based on individual preference: behavioral couples therapy for AUD, CBT for substance use disorders, community reinforcement approach therapy, motivational enhancement therapy, or a 12-step program (Management of Substance Use Disorders Work Group, 2015). The recommendations were based on the conclusions of a systematic review focused on treatment effectiveness, adherence, and adverse events; the quality of the evidence was assessed using a modification of the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) framework. The recommendations also considered the balance of desirable and undesirable medication effects, values and preferences of patients (Andrews et al., 2013), and DoD mission-readiness.

Although a variety of treatments have been found effective for AUD, it is unclear whether women respond differently from men to some treatment modalities (Management of Substance Use Disorders Work Group, 2015). Neuroendocrine differences and differences in rates of alcohol metabolism between men and women suggest the possibility that pharmacologic treatments for AUD might show gender differences in their effectiveness and/or safety (Mason and Lehert, 2012; Greenfield et al., 2010). Extensive research also suggests that men and women might respond differently to psychosocial interventions aimed at treating AUD (Litt, Kadden, and Tennen, 2015).

Various studies have addressed gender differences in response to specific treatments (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Mason, Goodman, et al., 2006), but no efforts have been made to comprehensively address gender differences across common evidence-based treatments, particularly combination therapies. One of the gaps in knowledge identified by the VA/DoD guideline was knowledge regarding gender differences in response to treatment for AUD. If treatment effects differ for men and women, this knowledge would lead to selection of more efficacious treatments. The findings of this review will also help health professionals involved in establishing treatment guidelines. Having a better understanding of potential gender differences in AUD treatment responsiveness could also be used to improve the applicability of the VA/DoD treatment guideline, which is important, because the prevalence of AUD is similar for men and women in the military and untreated AUD can take a heavy toll in terms of readiness and fitness for duty.

**Objective**

This systematic review assesses gender differences in the reported efficacy and safety of the recommended treatments for AUD.
Key Questions

The following key question and subquestions guided the review:

- **Key Question 1**: Do the efficacy and/or safety of first-line treatments for AUD differ according to gender?
  
  - **Key Question 1a**: Do gender differences vary by pharmacological versus psychosocial treatment?
  
  - **Key Question 1b**: Do gender differences vary by duration and intensity of treatment?
  
  - **Key Question 1c**: Do gender differences vary by treatment setting?
2. Methods

Our review synthesized results from randomized controlled trials (RCTs) that (1) evaluated gender differences in the effects of pharmacologic and psychosocial treatments for adults with AUD, (2) reported data for only one gender, (3) reported treatment effect results by gender, or (4) reported gender-coded patient-level outcomes. Our review documents the presence or absence of gender differences in treatment effects in studies that met our inclusion criteria.

The results of literature searches are documented in the next chapter, which focuses on results (Figure 3.1). The systematic review was registered in PROSPERO (CRD42017070895).

Sources

We searched PubMed, PsycINFO, Embase, the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews (CDSR), and Clinicaltrials.gov for English-language RCTs that met eligibility criteria (as will be described later). Reference lists in included studies were searched for both additional original studies and systematic reviews that were not included in the search outputs but referred to gender differences.

Search Strategy

The search strategy was developed by a senior reference librarian for the RAND Corporation’s Knowledge Services and was informed by search results of the prior feasibility scans conducted for this project and by existing systematic reviews on the topic.

The search strings for the identification of RCTs and systematic reviews are described in Appendix A. Because RCTs that reported on gender differences in treatment efficacy or safety might not report these findings in the title or abstract, and because a study might enroll only men or only women, we did not limit the searches by using terms such as “gender difference.” We retrieved and screened full texts of all RCTs and systematic reviews of the interventions of interest to determine whether relevant data were reported in the publications. We limited inclusion to RCTs and systematic reviews to compare effects of interventions with a placebo or control and to ensure random assignment of participants to treatment conditions (particularly by gender), which helps ensure that study groups are comparable at baseline with respect to factors that could affect outcomes of interest.

Contacting Authors

We also contacted 55 authors (using 62 contact addresses) of 83 publications that reported on interventions of interest but did not discuss gender effects and asked for gender effects analysis or data reported by gender. Of these contacted authors, 27 responded. Most respondents
indicated that they were authors of secondary analyses of data already included in our analyses, or they provided further information indicating that their study did not meet our eligibility criteria). Of three authors who agreed to share unique data, one provided a data set; the study participants were all active-duty Army personnel.

Eligibility Criteria

Study inclusion and exclusion criteria are summarized in the following framework of participants, interventions, comparators, outcomes, timing, settings, and study design:

- **Participants:**
  - Studies enrolling participants 18 years of age or older with a diagnosis of AUD confirmed with a clinical diagnosis from a health care professional or validated assessment tool (that used criteria compatible with the DSM-IV criteria for alcohol abuse or alcohol dependence, the DSM-5 criteria for AUD, or the International Classification of Diseases (ICD)-9 or 10 codes for unspecified alcohol-related disorder) were eligible for inclusion. Studies exclusively reporting on patients with a dual clinical diagnosis (e.g., alcohol use disorder and major depressive disorder) were excluded. Although individuals with these comorbidities appear to constitute a sizable proportion of those with AUD, the presence of an additional diagnosis would likely require additional treatments and could potentially confound efforts to see gender differences in response to the primary treatment modality of interest.

- **Interventions:**
  - Studies that evaluated the efficacy of any first-line treatment recommended in the current American Psychiatric Association clinical practice guidelines or included in the VA/DoD clinical practice guideline were eligible for inclusion. These treatments included pharmacologic interventions—disulfiram, naltrexone, and acamprosate—and psychosocial interventions—motivational enhancement therapy, CBT, behavioral therapies (e.g., community reinforcement, contingency management), 12-step facilitation, marital and family therapies, group therapies, psychodynamic therapy or interpersonal therapy, brief therapies, and self-help groups (such as Alcoholics Anonymous). Studies that evaluated the interventions alone or in combination were included.

- **Comparators:**
  - Pharmacological studies were limited to those with controls consisting of a placebo; another drug; or another dose, duration, or route of administration of the same drug. Psychosocial studies were limited to those with wait-list controls; attention-matched controls; or controls consisting of a different type of psychosocial intervention or the same intervention at a different dose, duration, or setting.

- **Outcomes:**
  - Studies had to report alcohol use outcomes (e.g., change in alcohol use, percentage of abstinent days, percentage of days with no heavy drinking or time
to first heavy-drinking day, rate of complete abstinence, rate of no heavy drinking); adverse events associated with the intervention; treatment completion; and/or treatment compliance by intervention arm. Adverse events reported only as the total number of (all or specific) adverse events across treatment arms or reported incompletely (i.e., only specific adverse events for selected patients, such as that group of patients’ reasons for dropping out of the study) were not included.

- Studies had to report an analysis of the effect of gender, enroll only women or only men, report outcomes separately for men and women, or provide individual patient data and specify the gender.

- Timing:
  - Studies had to feature a combined treatment duration and follow-up period of one month or longer.

- Setting:
  - Studies reporting on U.S. populations in any care setting were included.

- Study Design:
  - Studies were limited to RCTs, randomized by either participant or site, and to systematic reviews (including individual participant data [IPD] meta-analyses). RCTs needed to self-identify as such or describe the random allocation of participants to treatment arms. Systematic reviews had to self-identify as such or report on the sources and account for identified studies to be included.

- Other Limiters:
  - English-language reports published since 1997 were included; conference proceedings, letters to journal editors, and commentaries were excluded.

**Inclusion Screening**

Two members of our project team—both experienced literature reviewers with training in epidemiology and statistics, behavioral health, and psychopharmacology—conducted a pilot screening session to screen approximately 25 titles and abstracts (randomly selected to represent the time period covered by the searches) to ensure similar interpretation of the inclusion and exclusion criteria. Following the pilot session, the two reviewers independently screened titles and abstracts of retrieved citations. Citations judged as potentially eligible by one or both reviewers were obtained as full text.

Full text publications were screened against inclusion and exclusion criteria by two independent reviewers. Disagreements were resolved through discussion within the review team, with the project lead making the final decision. Reasons for exclusion at the full-text and subsequent stages were recorded in the electronic database used to manage the articles identified in the literature searches.
Data Extraction

Data collection forms were designed by the project lead with input from the project team. Reviewers pilot tested the data collection forms on a representative selection of studies and on several randomly selected studies, modified the forms, and performed a final pilot on a random selection of ten studies to ensure agreement of interpretation. Data abstraction was conducted using Distiller SR software, designed for systematic reviews. Data at the categorical and free-text study levels were abstracted by one reviewer and checked by a second reviewer. Discrepancies were resolved through discussion in the review team meetings. RAND Evidence-based Practice Center (EPC) biostatisticians abstracted all outcome data to ensure quality; extraction accuracy was checked by the project lead in a random (10-percent) sample of studies.

Each RCT was assigned a study identification number. Information extracted from individual RCTs included the following:

- **basic information**: the year the study was conducted, inclusion and exclusion criteria, sample size (stratified by gender and intervention group), reported power calculation for gender effects (where available), funding source
- **participant characteristics**: gender and the following as stratified by gender—age, marital status, educational attainment, race/ethnicity, current military service status, symptom severity/diagnosis (and instrument used), comorbidities
- **interventions**: pharmacologic agents or descriptions of therapy, duration and frequency, dosage and route of administration for pharmacologic agents, treatment protocol fidelity/flexibility, therapist training, allowance for/use of adjunctive treatments, and treatment intensity (high: treatments that featured both pharmacological and behavioral components; moderate: treatments that were only pharmacological or standard behavioral interventions; low: brief therapies)
- **comparators**: type and description of comparator category (e.g., wait-list, other active treatment or other dosage regimen, placebo) and analysis (e.g., compared with control group or pre-post changes)
- **outcomes**: alcohol use efficacy outcomes and results by gender; adverse events by gender; adherence/compliance; results of gender effect analysis, including size of effect and statistical significance or a statement that no gender differences were observed
- **timing**: follow-up times relative to start and/or end of treatment
- **setting**: type of treatment setting (e.g., community setting, outpatient clinic, residential treatment program), single-site or multisite; outpatient settings were further divided into primary care settings, nonacademic-based AUD treatment programs, and academic-based AUD treatment programs
- **study design**: items relevant to risk of bias assessment, such as methods of randomization, concealment of allocation, and blinding.

If multiple publications appeared to report results of the same study, descriptions of participants were compared. All publications reporting on a study were abstracted and contributed to the study description. For each included study, findings are reported in Appendix B in an evidence table that features details about the intervention, specific comparisons, and outcomes measured (see Table B.1).
Critical Appraisal

Two reviewers independently assessed the risk of bias of the included studies using the Cochrane Risk of Bias tool (Higgins and Green, 2011) for RCTs and the Joanna Briggs Institute tool for systematic reviews (Joanna Briggs Institute, 2017).

Specifically, the following sources of bias were assessed for RCTs: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and providers (performance bias), blinding of outcome assessors (detection bias), completeness of reporting outcome data (attrition bias), and selective outcome reporting (reporting bias). Industry funding, adherence, inclusion of a power analysis to detect gender differences, similarity of groups at baseline, and evidence of gender differences in loss to follow-up were also noted as potential sources of bias. Risk of bias was categorized as good, fair, or poor for each study, based on consideration of the most-relevant items for the specific RCTs and the outcomes of interest and those that actually varied across studies.

We evaluated systematic reviews using the Joanna Briggs Institute Checklist for Systematic Reviews and Research Syntheses (2017). This checklist consists of criteria for the explicit statement of the review question, appropriate inclusion criteria, appropriate search strategies, adequate sources, appropriate critical appraisal criteria, critical appraisal by dual reviewers, methods to minimize abstraction errors, appropriate methods to combine studies, and the assessment of publication bias.

Data Synthesis

The purpose of the systematic review is to synthesize the evidence of gender differences in efficacy and safety of treatments for AUD in RCTs. We report on both the presence and the absence of gender differences in included studies.

We expected to identify five types of studies with regard to gender effects:

1. primary research studies reporting gender effect analysis results
2. primary research studies reporting outcomes separately for subgroups of men and for women
3. primary research studies exclusively in women or exclusively in men (potentially allowing indirect comparisons)
4. primary research studies reporting individual patient data together with the gender of the participant
5. systematic reviews reporting gender effect analysis results.

The data from each type of study were treated as follows.

1. For studies that reported on the results of a gender analysis, we documented the size of the effect and the statistical significance reported in the individual studies. Because of the heterogeneity in interventions and analyses, we summarized these reported gender effects in a narrative synthesis.
2. If studies reported treatment effects separately for male and female participants in subgroup analyses, we documented the treatment effects in these subgroups. We then
compared the treatment effects for both gender groups across studies in a meta-analysis. We compared the difference between the effect of the intervention (relative to the untreated control group) in women to the effect of the intervention (relative to the untreated control group) in men. Hence, throughout Chapter 3, we report the difference of a difference (DiffOfDiff). Positive DiffOfDiffs indicated that the effect was larger (the treatment more beneficial) for women.

3. For studies focused exclusively on women or exclusively on men, we stratified studies by gender and documented treatment effects comparing intervention and control participants. We conducted meta-analyses to compare treatment effects in indirect analyses across studies. To determine the statistical significance of any potentially observed differences across gender groups, we added a gender variable to a meta-analysis model and performed a meta-regression to determine whether the gender of participants was a significant treatment effect modifier. Where possible, these data were combined with studies described in the second study type.

4. One study provided individual patient data. We computed the treatment effect for men and the treatment effect for women and added the findings to pooled analyses.

5. For systematic reviews that addressed gender effects, we documented the results as reported by the review authors in a narrative synthesis.

Meta-Analysis and Subgroup Analyses

For meta-analysis of efficacy outcomes, we used the Hartung-Knapp-Sidik-Jonkman method for random effects meta-analysis (Hartung, 1999; Hartung and Knapp, 2001; Sidik and Jonkman, 2006). This approach might be preferred when the number of studies pooled is small and when there is evidence of heterogeneity (Inthout, Ioannidis, and Borm, 2014). We identified too few (N = 2) studies that reported specific adverse events to justify pooling results. Many specific adverse events are very rare; had we identified a sufficient number of studies to pool, we would have used exact conditional methods to estimate odd ratios (ORs) and 95-percent confidence intervals (CIs). When studies reported the same outcome and were reasonably similar with respect to participants and study conditions, we conducted DiffOfDiff analyses on those outcomes. We also conducted DiffOfDiff analyses on “any” outcome by calculating and pooling standardized mean differences for one continuous outcome per study or pooling risk ratios for dichotomous outcomes. Study heterogeneity was assessed for pooled analyses using the I-squared statistic (Higgins and Green, 2011). When studies were considered to be too dissimilar to conduct meta-analysis, differences among the studies were narratively described.

We planned to carry out subgroup analyses examining gender differences in pharmacological versus psychosocial therapies and in different treatment settings (e.g., inpatient versus outpatient).

We conducted meta-regressions to assess interaction effects of treatment duration, intensity, and setting on overall and gender-specific treatment effects to address the review sub questions.

Quality of Evidence

The quality of the body of evidence was assessed for major outcomes using the GRADE
approach (Balshem et al., 2011). The following domains were considered in assessing the body of evidence: study limitations (risk of bias), indirectness, inconsistency, imprecision, and publication bias. Issues that were not considered include large magnitude of effect, dose-response, and plausible residual confounding.

The quality of evidence is graded on the following scale:

- **High** indicates that the review authors are very confident that the effect estimate lies close to the true effect for a given outcome.
- **Moderate** indicates that the review authors are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low** indicates that the review authors’ confidence in the effect estimate is limited. The true effect might be substantially different from the estimate of the effect.
- **Very low** indicates that the review authors have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

The quality-of-evidence domain rating is summarized in Chapter 4 in a table that details our reasoning for arriving at the overall rating (see Table 4.1).

**Summary of Findings**

Our findings are summarized in Chapter 4 in the aforementioned table, which is organized by key questions and intervention types (Table 4.1). This table lists the intervention and comparators evaluated, the outcomes assessed for each type of comparison, and the type of data—e.g., gender analysis results as reported by study authors; the number of studies and number of participants listed for each outcome assessment, the direction and magnitude of the effect for each outcome, and the quality of the evidence for each outcome (as already described).
3. Results

Results of the Search

We identified 13,166 titles via searches of the databases described in Chapter 2. An additional 605 titles were identified through searches of reference lists of full-text publications. We screened 13,771 citations for potentially relevant publications. Of those, 12,337 were excluded, and full-text publications were sought for the remaining 1,434.

Of the 1,434 publications, 1,335 were excluded. RCT authors were contacted when gender differences were not reported in the original publication but only one dataset meeting inclusion criteria was received. The reasons for exclusion are provided in Figure 3.1 and in Appendix E.

We included 24 original studies, with findings reported in 63 publications (Anton, Moak, Latham, et al., 2005; Anton, Moak, Waid, et al., 1999; Anton, O’Malley, et al., 2006; Babor, 1997; Baros, Latham, and Anton, 2008; Bauer et al., 2007; Brown et al., 2007; Capone et al., 2011; Carroll et al., 1998; Cisler et al., 1998; Crouch, DiClemente, and Pitts, 2015; Cutler and Fishbain, 2005; Davis et al., 2002; DiClemente, 2011; Donovan et al., 2002; Dunson et al., 2008; Fals-Stewart and Birchler, 2002; Fals-Stewart, Birchler, and Kelley, 2006; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, O’Farrell, and Lam, 2009; Friedmann et al., 2013; Friend and Pagano, 2007; Gamble et al., 2010; Garbutt, Kranzler, et al., 2005; Gastfriend and the COMBINE Study Research Group, 2003; Greenfield et al., 2010; Hallgren, McCrady, and Epstein, 2016; Hallgren, Owens, et al., 2015; Holder et al., 2000; Holzhauer et al., 2017; Ilgen and Moos, 2005; Kelly and Hoeppner, 2013; Litt, Kadden, Kabela-Cormier, et al., 2007; Litt, Kadden, and Tennen, 2015; Lynch et al., 2010; Magura, Cleland, and Tonigan, 2013; Manuel, Houck, and Moyers, 2012; Mason, Goodman, et al., 2006; Mason and Lehert, 2012; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; McCrady, Epstein, and Hirsch, 1999; McKay, Van Horn, Oslin, Ivey, et al., 2011; McKay, Van Horn, Oslin, Lynch, et al., 2010; Morgenstern et al., 2007; O’Farrell, Choquette, and Cutter, 1998; Oslin et al., 1997; Pagano et al., 2013; Project MATCH Research Group, 1993; Project MATCH Research Group, 1997a; Project MATCH Research Group, 1997b; Project MATCH Research Group, 1998a; Project MATCH Research Group, 1998b; Schumm et al., 2014; Tonigan et al., 2003; Trevisan et al., 2008; Velasquez, DiClemente, and Addy, 2000; Walker et al., 2017; Wiprovnick, Kuerbis, and Morgenstern, 2015; Witkiewitz, Hartzler, and Donovan, 2010; Witkiewitz, van der Maas, et al., 2007; Worley et al., 2015; Zywiak et al., 2006). One publication (Baros, Latham, and Anton, 2008) used data from two published RCTs (Anton, Moak, Waid, et al., 1999; Anton, Moak, Latham, et al., 2005) to analyze gender differences: The individual trials did not report on gender differences and the authors combined the raw data from their own trials, so we treated the publication as one study in this review.

In addition, four systematic reviews met inclusion criteria (Canidate et al., 2017; Garbutt, Greenblatt, et al., 2014; Kranzler and Van Kirk, 2001; Litten et al., 2013). All included studies in
the reviews were screened for inclusion for this systematic review.

Thirty-two additional publications were classified as pertinent background articles; all were also reference mined.

**Figure 3.1. Preferred Reporting Items for Systematic Review and Meta-Analysis Flow Diagram**

![Preferred Reporting Items for Systematic Review and Meta-Analysis Flow Diagram](image)

**Description of Included Studies**

In this chapter, we describe the 24 individual RCTs using the structure described in Chapter 2 focused on participants, interventions, comparators, outcomes, timing, settings, and study design. More-detailed information about each included study is provided in Appendix B (see Table B.1,
which displays the main publication and related publications, study-specific details, and the
treatment results for men, for women, and any resulting gender differences). One study assessed
the effects of an intervention on military personnel. Although that study did not report findings
by gender, the authors kindly agreed to share their patient-level data.

We also identified four systematic reviews that reported on gender differences in response to
alcohol treatment across studies. (Table B.1 provides a comprehensive overview, describing the
review details and the results reported by the review authors regarding gender differences in
response to AUD treatment).

Participants

Nine studies enrolled only men (Trevisan et al., 2008; Friedmann et al., 2013; Oslin et al.,
1997; Fals-Stewart and Birchler, 2002; Fals-Stewart, Klostermann, et al., 2005; McCrady,
Epstein, and Hirsch, 1999; Morgenstern et al., 2007; Davis et al., 2002; O’Farrell, Choquette,
and Cutter, and 1998); four studies enrolled only women, (Fals-Stewart, Birchler, and Kelley, 2006;
McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; Schumm et al.,
2014); and 11 enrolled both men and women (Litt, Kadden, and Tenn, 2015; McKay, Van
Horn, Oslin, Ivey, et al., 2011; Witkiewitz, Hartzler, and Donovan, 2010; Fals-Stewart,
O’Farrell, and Lam, 2009; Wiprovnick, Kuerbis, and Morgenstern, 2015; Mason, Goodman, et
al., 2006; Garbutt, Kranzler, et al., 2005; Brown et al., 2007; Baros, Latham, and Anton, 2008;
Anton, O’Malley, et al., 2006; Walker et al., 2017). Eight studies enrolled married or cohabiting
couples in which one member of the couple was the identified patient (Fals-Stewart, Birchler,
and Kelley, 2006; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, O’Farrell, and Lam,
2009; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein and Hirsch, 1999; McCrady,
Mean ages ranged from 28 to 58.

Interventions

Six RCTs assessed the effects of pharmacological agents alone (Trevisan et al., 2008;
Friedmann et al., 2013; Oslin et al., 1997; Garbutt, Kranzler, et al., 2005; Mason, Goodman, et
al., 2006; Baros, Latham, and Anton, 2008). One study assessed the effects of gabapentin
(Trevisan et al., 2008); five studies assessed the effects of naltrexone (Friedmann et al., 2013;
Oslin et al., 1997; Garbutt, Kranzler, et al., 2005; Anton, O’Malley, et al., 2006; Baros, Latham,
and Anton, 2008); and two studies assessed the effects of acamprosate (Anton, O’Malley, et al.,
2006; Mason, Goodman, et al., 2006). No studies that met inclusion criteria assessed the effects
of disulfiram.

One study assessed the effects of pharmacological agents with or without a psychosocial
treatment (e.g., CBT) (Anton, O’Malley, et al., 2006).

The remaining RCTs assessed the effects of psychosocial therapies, of which nine assessed
the effects of various forms of couples therapy (Fals-Stewart and Birchler, 2002; Fals-Stewart,
Birchler, and Kelley, 2006; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, O’Farrell, and
Lam, 2009; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Hallgren, et al., 2016; McCrady, Epstein, Cook, et al., 2009; Schumm et al., 2014; O’Farrell, Choquette, and Cutter, 1998); one study assessed the effect of telephone-based mentoring and counseling (McKay, Van Horn, Oslin, Ivey, et al., 2011); two studies assessed individually oriented brief interventions (Brown et al., 2007; Wiprovnick, Kuerbis, and Morgenstern, 2015); one study assessed contingency management around 12-step facilitation (Litt, Kadden, and Tennen, 2015); one study assessed motivational enhancement therapy (Witkiewitz, Hartzler, and Donovan, 2010); one study assessed brief motivational interviewing (Walker et al., 2017); and one study assessed 12-step facilitation (Davis et al., 2002).

Two systematic reviews assessed gender differences in the effects of naltrexone and acamprosate (Garbutt, Greenblatt, et al., 2014; Kranzler and Van Kirk, 2001), and one assessed gender differences in the placebo effect in studies of these agents (Litten et al., 2013).

Treatment duration ranged from four weeks for a study of the effects of gabapentin on relapse (Trevisan et al., 2008) to 72 weeks for a study of extended, telephone-based continuing care (McKay, Van Horn, Oslin, Ivey, et al., 2011) and a study of behavioral relapse prevention following couples therapy (O’Farrell, Choquette, and Cutter, 1998). Several studies assessed the effects of brief behavioral couples therapy but did not directly compare their results to the effects of standard-length behavioral couples therapy (Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, O’Farrell, and Lam, 2009).

Treatment intensity was rated as high for six RCTs, all combining a pharmacologic treatment with counseling (Friedmann et al., 2013; Oslin et al., 1997; Garbutt, Kranzler, et al., 2005; Anton, O’Malley, et al., 2006; Mason, Goodman, et al., 2006; Baros, Latham, and Anton, 2008). Treatment intensity was rated as moderate for 11 RCTs (Trevisan et al., 2008; Witkiewitz, Hartzler, and Donovan, 2010; Fals-Stewart and Birchler, 2002; Fals-Stewart, Birchler, and Kelley, 2006; Fals-Stewart, O’Farrell, and Lam, 2009; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Hallgren, et al., 2016; Schumm et al., 2014; O’Farrell, Choquette, and Cutter, 1998; Litt, Kadden, and Tennen, 2015) and as low for seven RCTs (Brown et al., 2007; Davis et al., 2002; Fals-Stewart, Klostermann, et al., 2005; McKay, Van Horn, Oslin, Ivey, et al., 2011; Morgenstern et al., 2007; Wiprovnick, Kuerbis, and Morgenstern, 2015; Walker et al., 2017). In addition, two RCTs directly compared interventions of different intensities: The COMBINE trial compared the effects of one pharmacological intervention versus two interventions and also compared the effects of a pharmacological intervention with and without a cognitive behavioral intervention (Anton, O’Malley, et al., 2006); Garbutt, Kranzler, and colleagues (2005) compared two different doses of injectable naltrexone with that of placebo.

**Comparators**

All studies of pharmacological agents but one included a placebo group; the exception compared the effectiveness of long-acting injectable naltrexone with that of oral naltrexone (Friedmann et al., 2013).
Studies of psychosocial therapies varied in their choices of comparators. Couples therapies usually included an individually based therapy, and several also included a psychoeducational attention control (PACT).

Outcomes

We categorized outcomes as assessing efficacy, treatment adherence, or adverse events. Efficacy outcomes were always self-reported and varied widely across studies, with only two outcomes being reported by more than one or two studies: percentage of days abstinent (using a 30-day lookback) (Baros, Latham, and Anton, 2008; Anton, O’Malley, et al., 2006; Fals-Stewart, Birchler, and Kelley, 2006; Schumm et al., 2014; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, and Hirsch, 1999; O’Farrell, Choquette, and Cutter, 1998; Fals-Stewart and Birchler, 2002; Mason, Goodman, et al., 2006; Witkiewitz, Hartzler, and Donovan, 2010; Walker et al., 2017) and percentage of heavy-drinking days (Anton, O’Malley, et al., 2006; Trevisan et al., 2008; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, O’Farrell, and Lam, 2009; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Hallgren, et al., 2016; Litt, Kadden, and Tennen, 2015; Mason, Goodman, et al., 2006; Walker et al., 2017).

Most studies reported on some measure of adherence and/or retention by intervention group and gender (if the study enrolled both genders) (Friedmann et al., 2013; Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Oslin et al., 1997; Trevisan et al., 2008; Fals-Stewart and Birchler, 2002; Davis et al., 2002; Fals-Stewart, Birchler, and Kelley, 2006; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, O’Farrell, and Lam, 2009; McCrady, Epstein, Hallgren, et al., 2016; Schumm et al., 2014; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, and Hirsch, 1999). Measures included completion rate (Baros, Latham, and Anton, 2008; Friedmann et al., 2013), dropout rate (Anton, O’Malley, et al., 2006; Friedmann et al., 2013), and attendance rate (Oslin et al., 1997; Schumm et al., 2014; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Hallgren, et al., 2016; Fals-Stewart and Birchler, 2002).

Three studies reported on adverse events of treatment (Baros, Latham, and Anton, 2008; Trevisan et al., 2008; Oslin et al., 1997).

Time to Follow Up

Follow-up times ranged from four weeks from baseline (0 time from the end of treatment) (Trevisan et al., 2008) to 108 weeks from baseline (96 weeks from the end of treatment) (Litt, Kadden, and Tennen, 2015). At least six studies conducted follow-up only at the end of the treatment period.

Setting

All studies were conducted in outpatient treatment settings among community-dwelling individuals in the United States. However, settings were further characterized as either primary
care (Friedmann et al., 2013; Oslin et al., 1997; Garbutt, Kranzler, et al., 2005; Brown et al., 2007); non–university-based AUD treatment programs; (Baros, Latham, and Anton, 2008; McKay, Van Horn, Oslin, Ivey, et al., 2011; Trevisan et al., 2008; Davis et al., 2002; O’Farrell, Choquette, and Cutter, 1998; Fals-Stewart and Birchler, 2002) or university-based (academic medical center) AUD treatment programs (Anton, O’Malley, et al., 2006; Mason, Goodman, et al., 2006; Witkiewitz, Hartzler, and Donovan, 2010; Fals-Stewart, Birchler, and Kelley, 2006; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, O’Farrell, and Lam, 2009; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Hallgren, et al., 2016; Schumm et al., 2014; Litt, Kadden, and Tennen, 2015; Morgenstern et al., 2007). One study in a primary care setting consisted only of non–care-seeking patients (Brown et al., 2007). One telephone-based study was conducted at a military installation (Walker et al., 2017).

Systematic Reviews

Four systematic reviews addressed gender differences in response to treatment across studies (Canidate et al., 2017; Garbutt, Greenblatt, et al., 2014; Kranzler and Van Kirk, 2001; Litten et al., 2013). Reviews were published between 2001 and 2017. All reviews addressed the effects of naltrexone and/or acamprosate.

Critical Appraisal Results

The study quality or risk of bias assessments for each included RCT and systematic review are shown in Appendix C.

Risk of Bias in RCTs

Overall, RCTs were of fair quality. Only four of 24 RCTs had an overall low risk of bias, and five had a high risk of bias.

Twelve RCTs had low risk of bias for random sequence generation, meaning that they described use of adequate methods for randomly allocating participants to intervention groups. The remainder were rated as unclear because they did not describe randomization methods sufficiently to determine the procedure used. Only six RCTs described efforts for allocation concealment. Of those, five had low risk of bias, and one had high risk of bias. The remainder of the studies were unclear.

Six RCTs had low risk of bias for adequacy of the method used to keep participants, providers, and/or outcome assessors blinded to the intervention arm. All outcomes were self-reported, so the risk of detection bias was linked to the blinding of participants to their study condition.

Of the 24 RCTs, 18 were rated as low risk of attrition bias because they either reported no dropouts or reported an intention-to-treat analysis, and only three were high risk.
Nineteen of the 24 RCTs were rated as unclear with regard to selective outcome reporting. Studies rarely described a published protocol or provided some other indication that all preselected outcomes were reported.

Ten of the 24 RCTs were rated as having a high risk of bias for compliance, and ten were rated as having low risk. Compliance did not differ between pharmacological studies and psychosocial studies. Thirteen RCTs were rated as having unclear risk of bias regarding the indication of adequate dosing, primarily because adequate dose has not clearly been established for psychosocial interventions.

Overall, randomization, blinding, compliance, and lack of clarity regarding dosage adequacy were the biggest methodological challenges. For some types of psychosocial studies (e.g., comparisons of couples and individual therapies), blinding to condition would not be possible.

Study Quality for SRs

We identified four systematic reviews that met inclusion criteria. Their quality was judged to be fair. Although all four provided explicit review questions, one or more reviews were inadequate or unclear in terms of inclusion criteria, search strategies, sources, appraisal criteria, the use of dual review for critical appraisal, methods to minimize errors in data extraction, appropriate use of methods to combine studies, and publication bias assessment.

Do the Efficacy and/or Safety of First-Line Treatments for Alcohol Use Disorder Differ According to Gender?

The remainder of the Results section describes the findings for the key questions regarding gender differences in efficacy outcomes, treatment compliance, and adverse events.

In describing the findings, we separate results from direct and indirect comparisons of the differential effects in men and women. Direct comparisons are based on studies that reported on both men and women and allowed estimating gender differences in the treatment response within the study. We compared the difference between the effect of the intervention group and the untreated control group in men with the difference between the effect of the intervention group and the control group in women. Hence, throughout the Results section, we report the DiffODiff. Indirect comparisons assessed the treatment effects across studies in men-only samples and in women-only samples (again, in both cases the individual studies assess the effect of the intervention group relative to an untreated control group) and combined these with subsamples from studies of men and women where possible.

Symptom Improvement

Direct Comparisons Within Studies

Ten studies met inclusion criteria and compared the effects of an intervention or multiple interventions on a measure of AUD treatment in both men and women (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Brown et al., 2007; Fals-Stewart, O’Farrell, and Lam, 2007; ...
2009; Garbutt, Kranzler, et al., 2005; Litt, Kadden, and Tennen, 2015; McKay, Van Horn, Oslin, Ivey, et al., 2011; Wiprovnick, Kuerbis, and Morgenstern, 2015; Witkiewitz, Hartzler, and Donovan, 2010; Mason, Goodman, et al., 2006) or provided data that allowed that comparison (Walker et al., 2017). Four RCTs assessed effects of a pharmacologic agent (naltrexone or acamprosate) with or without a behavioral therapy (Baros, Latham, and Anton, 2008; Garbutt, Kranzler, et al., 2005; Anton, O’Malley, et al., 2006; Mason, Goodman, et al., 2006). The remainder assessed the effects of a behavioral therapy alone. Only one of the RCTs was conducted to assess gender differences as a primary outcome (Litt, Kadden, and Tennen, 2015).

Overall, the RCTs showed no generally consistent findings regarding superior efficacy of treatment for women or men. As Figure 3.2 shows, results varied across studies, with one intervention showing no difference in effect, two showing stronger effects in women, and four showing stronger effects in men (although only one was significant). Incidentally, only a small difference was found favoring men, but the confidence interval included evidence of no effect.

Figure 3.2. Direct Comparisons of Any Intervention for Difference of Differences in Any Outcome

NOTE: The figure shows the effect estimates represented by the difference in the outcome of interest between male participants (compared with the control group) and female participants (compared with the control group). Positive effects indicate that female participants showed larger treatment effects. In this and the following figures, DoD = DiffDoDiff.

Across studies that employed a variety of interventions but assessed treatment effectiveness outcomes between men and women (the difference between men and women in change in percentage of heavy-drinking or risky drinking days) we found no significant difference in the effectiveness of treatment by gender (DiffDoDiff 0.42; CI –0.80, 1.64; 7 RCTs).

Three RCTs that directly compared the effects for men and women in symptom improvement could not be included in pooled analyses. One study evaluated injected long-acting naltrexone and reported the rate of heavy-drinking days expressed as a hazard ratio (HR). The study (Garbutt, Kranzler, et al., 2005) reported a dose-dependent response that exceeded the effect of placebo in men, whereas women’s response to active treatment was not dose-dependent and did not exceed that of placebo (190 mg naltrexone: HR 0.78; CI 0.61, 0.98; 380 mg naltrexone: 0.46;
McKay, Van Horn, Oslin, Ivey, and colleagues (2011) randomized participants to receive continuing care that consisted of phone-based treatment monitoring and feedback only, monitoring and feedback plus counseling, or treatment as usual only. The study reported rates for a composite outcome (“good clinical outcome”); six months after the end of the intervention, differences from treatment as usual were no longer significantly different within or across genders. In a secondary analysis of an RCT that randomized to a brief motivational interviewing intervention or a “spirit only” intervention, Wiprovnick, Kuerbis and Morgenstern (2015) found no significant gender effects and excluded the variable from the final models.

We also investigated the presence of gender differences in specific outcomes of interest. Six studies that reported on the percentage of heavy-drinking days (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Fals-Stewart, O’Farrell, and Lam, 2009; Litt, Kadden, and Tennen, 2015; Mason, Goodman, et al., 2006; Walker et al., 2017) are shown in Figure 3.3.

**Figure 3.3. Direct Comparisons of Any Intervention for Difference of Differences in Percentage of Heavy-Drinking Days**

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>DoD</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anton, 2006</td>
<td>0.34</td>
<td>[0.28; 0.40]</td>
</tr>
<tr>
<td>Baros, 2008</td>
<td>-0.02</td>
<td>[-0.17; 0.13]</td>
</tr>
<tr>
<td>Fals-Stewart, 2009</td>
<td>-0.06</td>
<td>[-0.17; 0.00]</td>
</tr>
<tr>
<td>Litt, 2015</td>
<td>0.28</td>
<td>[0.01; 0.55]</td>
</tr>
<tr>
<td>Mason, 2006</td>
<td>-0.08</td>
<td>[-0.23; 0.11]</td>
</tr>
<tr>
<td>Walker, 2017</td>
<td>3.93</td>
<td>[3.28; 4.57]</td>
</tr>
</tbody>
</table>

**NOTE:** The figure shows the effect estimates represented by the difference in the outcome of interest between male participants (compared with the control group) and female participants (compared with the control group). Positive effects indicate that female participants showed larger treatment effects. DoD = DiffDoDiff.

Interventions were sometimes more favorable for women and sometimes for men. When findings were combined across studies, no statistically significant difference in treatment effectiveness was observed between men and women (DiffDoDiff 0.54; CI –0.88, 1.97; 6 RCTs).

Figure 3.4 shows the results for the five studies that reported on the percentage of abstinent days in a 30-day lookback (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Litt, Kadden, and Tennen, 2015; Mason, Goodman, et al., 2006; Walker et al., 2017).
Figure 3.4. Direct Comparisons of Any Intervention for Difference of Differences in Percentage of Abstinent Days

NOTE: The figure shows the effect estimates represented by the difference in the outcome of interest between male participants (compared with the control group) and female participants (compared with the control group). Positive effects indicate that female participants showed larger treatment effects. DoD = DiffDoDiff.

One study (Litt, Kadden, and Tennen, 2015) found a stronger effect of contingency management for 12-step facilitation among men than among women, and one study (Walker et al., 2017) found a stronger effect of brief motivational interviewing among women than men, but when results were combined across studies, differences were not statistically significant (DiffDoDiff 0.29; CI –1.53, 2.12; 5 RCTs).

Indirect Comparisons Across Studies

In this section, we report the results of indirect analyses across published studies. We assessed the modifying effect of gender on treatment effectiveness across studies using a meta-regression that included both single gender studies and those that reported findings separately for both men and women. This section also summarizes differential male and female treatment effects reported in prior systematic reviews that met our inclusion criteria.

Ten RCTs enrolled men only (Trevisan et al., 2008; Friedmann et al., 2013; Oslin et al., 1997; Fals-Stewart and Birchler, 2002; Fals-Stewart, Klostermann, et al., 2005; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Hallgren, et al., 2016; Morgenstern et al., 2007; Davis et al., 2002; O’Farrell, Choquette, and Cutter, 1998), and three enrolled only women (Fals-Stewart, Birchler, and Kelley, 2006; McCrady, Epstein, Cook, et al., 2009; Schumm et al., 2014). Eighteen RCTs reported at least one effectiveness outcome that was similar enough to allow pooling (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Brown et al., 2007; Davis et al., 2002; Fals-Stewart and Birchler, 2002; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, Birchler, and Kelley, 2006; Fals-Stewart, O’Farrell, and Lam, 2009; Litt, Kadden, and Tennen, 2015; Mason, Goodman, et al., 2006; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; Morgenstern et
al., 2007; Schumm et al., 2014; Trevisan et al., 2008; O’Farrell, Choquette, and Cutter, 1998; Walker et al., 2017). The effect estimate for this pooled analysis indicated no significant gender differences (DiffDiff 0.03; CI –0.28, 0.34; $p = 0.840$), consistent with the direct comparisons.

We also analyzed studies for specific outcomes of interest. Ten RCTs reported on heavy-drinking days (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, O’Farrell, and Lam, 2009; Mason, Goodman, et al., 2006; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; Trevisan et al., 2008; Walker et al., 2017). The analysis did not indicate gender differences (DiffDiff 0.06; CI –0.29, 0.41; $p = 0.706$). Eleven RCTs reported on percentage of abstinent days (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Fals-Stewart and Birchler, 2002; Fals-Stewart, Birchler, and Kelley, 2006; Litt, Kadden, and Tennen, 2015; Mason, Goodman, et al., 2006; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; O’Farrell, Choquette, and Cutter, 1998; Schumm et al., 2014; Walker et al., 2017): The analysis found a DiffDiff that slightly favored men, but the effect was not statistically significant (DiffDiff –0.16; CI –0.55, 0.22; $p = 0.379$).

Published Systematic Reviews

Four prior systematic reviews examined the moderating effects of gender on the effects of naltrexone and/or acamprosate (Canidate et al., 2017; Garbutt, Greenblatt, et al., 2014; Kranzler and Van Kirk, 2001; Litten et al., 2013).

A systematic review of moderators of response to naltrexone by Garbutt, Greenblatt, and colleagues (2014) included five studies in seven publications that assessed the moderating effects of gender. Three of the included studies were also included in our review (the two remaining studies consisted of a non–peer-reviewed letter and a study of a population not diagnosed with AUD). The findings, reported qualitatively, varied across studies, with two studies reporting no significant differences between men and women, one reporting a significant positive effect for women but not for men, and two reporting positive effects in men but not in women.

A 2017 systematic review by Canidate and colleagues included seven trials of naltrexone in men and women or in women alone and focused on symptom improvement in women. Similar to the review by Garbutt, Greenblatt, and colleagues (2014), the findings were reported qualitatively and varied by the outcome measure, supporting modest improvements in drinking quantity and time to relapse but not in drinking frequency.

A 2001 systematic review by Kranzler and Van Kirk included nine trials of naltrexone and 11 of acamprosate. Sex (percentage of men) was not found to be a moderator of the heterogeneity in the percentage of drinking days among studies of naltrexone but was found to be a moderator of cumulative abstinent days across ten studies of acamprosate (the percentage of men in a study was inversely correlated with the efficacy of acamprosate for this outcome, $p < 0.001$).

Litten and colleagues (2013) analyzed the placebo effect across 51 RCTs of naltrexone and acamprosate. They found that the percentage of men in studies was not correlated with the size of the placebo response for any outcome.
Compliance

Direct Comparisons Within Studies

Gender differences in treatment adherence or compliance were reported in three RCTs (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Fals-Stewart, O’Farrell, and Lam, 2009).

The COMBINE Study (Anton, O’Malley, et al., 2006) reported no gender differences in study drop out \((p = 0.73)\), incomplete drinking data \((p = 0.753)\), missing therapy sessions \((p = 0.91)\), stopping or missing medication management sessions \((p > 0.5)\), stopping attending sessions prematurely \((p = 0.126)\), or medication adherence \((p = 0.70)\).

Baros, Latham, and Anton (2008) assessed two outcomes for compliance or adherence. They assessed study completion by determining the proportion who attended all sessions, and they assessed compliance by measuring the change in serum riboflavin in response to naltrexone. Compliance was expressed as the ratio of compliance in the placebo group to that in the intervention group. The study found no significant difference between men and women in study completion rate (relative odds ratio [ROR] 2.18; CI: 0.80, 5.90; 1 RCT). Medication compliance ratio was slightly, albeit significantly, greater for women than for men (ROR 2.89; CI: 1.41, 5.92; 1 RCT).

The third study (Fals-Stewart, O’Farrell, and Lam, 2009), which compared outcomes for gay male and lesbian couples, showed a slight difference in treatment dose (sessions attended) for the couples’ intervention in favor of male couples (Diffodiff –0.83; CI –0.96, –0.71; 1 RCT).

Indirect Comparisons Across Studies

Eleven RCTs reported a measure of compliance that allowed comparison across genders (Davis et al., 2002; Fals-Stewart and Birchler, 2002; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, Birchler, and Kelley, 2006; Fals-Stewart, O’Farrell, and Lam, 2009; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; O’Farrell, Choquette, and Cutter, 1998; Oslin et al., 1997; Schumm et al., 2014). The rate of compliance was estimated to be greater for women across all interventions, but not significantly greater (Diffodiff 0.31; CI –0.03, 0.65; \(p = 0.073\)).

Seven RCTs reported on the difference between men and women in the mean proportion of sessions attended (Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, O’Farrell, and Lam, 2009; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; Oslin et al., 1997; Schumm et al., 2014). For this outcome, the analysis also showed a nonsignificantly greater rate of compliance for women across all interventions (Diffodiff 0.32; CI –0.23, 0.86; \(p = 0.204\)).

Adverse Events

Four included RCTs reported on adverse events. Of these, two reported on a sample in men only (Oslin et al., 1997; Trevisan et al., 2008) and two analyzed gender differences (Baros, Latham, and Anton, 2008; Garbutt, Kranzler, et al., 2005).
In the Baros, Latham, and Anton study of oral naltrexone (2008), men in the naltrexone group had significantly more reports of dizziness (relative to the placebo group) than did women, for whom the rates of dizziness were the same among the active and placebo-treated groups. Women in the naltrexone group had significantly more reports of nausea (relative to placebo) than did men. (Rates of nausea were not related to rates of heavy drinking.) Women in the treated group were significantly less likely to report problems falling asleep and staying asleep than were the women in the placebo group; in contrast, reports of difficulty falling asleep or staying asleep among men did not differ across treatment groups. Garbutt, Kranzler, and colleagues (2005) assessed nine different adverse events across treatment groups in their study of intramuscular naltrexone (two doses of naltrexone and placebo). With two exceptions, they reported similar adverse event rates for men and women. Nausea was significantly higher in women than in men (but only at the lower dose), and only men reported decreased libido. Rates of nausea were not related to rates of heavy drinking.

Indirect comparisons across studies could not be conducted given the large variation in reported outcome and outcome formats.

Do Gender Differences Vary by Pharmacological Versus Psychological Treatment?

To answer this subquestion, we reviewed studies that assessed gender effects for different interventions. In addition, we stratified these studies by treatment type.

Direct Comparison Within Studies

One RCT compared gender differences across intervention types. COMBINE (Anton, O’Malley, et al., 2006) compared the effects of naltrexone and/or acamprosate plus CBT with the effects of placebo plus CBT and naltrexone without CBT for percentage of abstinent days, percentage of heavy-drinking days, time to first heavy-drinking day, and total drinks per day. No differences were reported for acamprosate. Differences across gender were analyzed for naltrexone alone, naltrexone plus CBT, and placebo plus CBT compared with placebo.

The trial reported no gender differences when comparing the effects of naltrexone with those of CBT for the outcome of percentage of heavy-drinking days (DiffDiff 0.00; CI –0.13, 0.13; 1 RCT). However, for the outcome of percentage of abstinent days, larger differences in men than in women between the naltrexone and CBT interventions were observed, significantly favoring men (DiffDiff –0.50; CI –0.64, –0.37; 1 RCT).

In terms of adherence, the trial reported no gender differences in study drop out ($p = 0.73$), incomplete drinking data ($p = 0.753$), missing combined behavioral intervention (CBI) therapy sessions ($p = 0.91$), or stopping or missing medical management sessions ($p > 0.5$). There was a trend for more men than women who received CBT to stop attending sessions prematurely (24.6 percent versus 19.6 percent; $p = 0.126$). Medication adherence, assessed as percentage of pills taken versus returned, did not differ between male and female participants ($p = 0.70$).
The study did not report on adverse events.

**Subgroup Analyses**

We also examined the subgroups of studies that implemented pharmacological, psychosocial (behavioral), and combination treatments and compared outcomes to those of control groups. Figure 3.5 shows gender differences stratified by treatment type for any symptom improvement outcome.

**Figure 3.5. Direct Comparisons of Difference of Differences in Symptom Improvement**

![Figure 3.5](image)

NOTE: The figure shows the effect estimates represented by the difference in the outcome of interest between male participants (compared with the control group) and female participants (compared with the control group). Positive effects indicate that female participants showed larger treatment effects. DoD = DiffoDiff.

Figures 3.6 and 3.7 show effects on specific outcomes of interest, percentage of heavy-drinking days (Figure 3.6) and percentage of abstinent days (Figure 3.7).
Figure 3.6. Direct Comparisons of Difference of Differences in Percentage of Heavy-Drinking Days

NOTE: The figure shows the effect estimates represented by the difference in the outcome of interest between male participants (compared with the control group) and female participants (compared with the control group). Positive effects indicate that female participants showed larger treatment effects. DoD = DiffoDiff.
Figure 3.7. Direct Comparisons of Difference of Differences in Percentage of Abstinent Days

NOTE: The figure shows the effect estimates represented by the difference in the outcome of interest between male participants (compared with the control group) and female participants (compared with the control group). Positive effects indicate that female participants showed larger treatment effects. DoD = DiffDoD.

The outcomes for compliance and adverse events could not be analyzed in a meta-analytic model.

We did not identify intervention types that were consistently associated with gender differences in treatment responses. The following describes the effects within the treatment subgroups in more detail.

Pharmacological Treatments

Symptom Improvement

Four RCTs in total reported on gender differences in symptom improvement associated with a pharmacologic agent for treatment of AUD (Baros, Latham, and Anton, 2008; Anton, O’Malley, et al., 2006; Garbutt, Kranzler, et al., 2005; Mason, Goodman, et al., 2006). Three RCTs reported on gender differences in the effects of naltrexone (Baros, Latham, and Anton, 2008; Anton, O’Malley, et al., 2006; Garbutt, Kranzler, et al., 2005). One of these RCTs reported on gender differences in the effects of naltrexone alone or combined with CBT and acamprosate with or without CBT, but for acamprosate, the authors reported only that no gender differences were observed (Anton, O’Malley, et al., 2006); one reported on the effects of oral naltrexone plus CBT compared with CBT alone (Baros, Latham, and Anton, 2008), and one reported on gender differences in the effects of long-acting injected naltrexone (Garbutt, Kranzler, et al., 2005). One RCT reported on the effects of acamprosate alone (Mason, Goodman, et al., 2006).
A pooled assessment of the three studies of oral agents for percentage of heavy-drinking days showed no gender difference (Diff0Diff 0.11; CI –0.53, 0.75; 3 RCTs) (Figure 3.6). A pooled assessment of the three studies of oral agents for percentage of abstinent days also showed no gender difference (Diff0Diff 0.04; CI –0.04, 0.12; 3 RCTs) (see Figure 3.7).

The fourth study, which reported on gender differences in the efficacy of injected long-acting naltrexone, was not combined with the other studies because it reported the outcome of rate of heavy-drinking days as an HR. The Vivitrex Study (Garbutt, Kranzler, et al., 2005) assessed the effects on heavy-drinking days of monthly injections of 190 mg or 380 mg intramuscular naltrexone or placebo among 627 men and women with AUD. All patients also received 12 sessions of psychosocial intervention. Among participants who received at least one injection, all showed improvement from pretreatment (including those in the placebo group); men showed a dose-dependent response that exceeded the effect of placebo, whereas women’s response to active treatment was not dose dependent and did not exceed that of placebo (190 mg naltrexone: relative HR comparing men and women 0.78; CI 0.61, 0.98; 380 mg: 0.46; CI 0.36, 0.58) (Garbutt, Kranzler, et al., 2005).

Two studies reported qualitative findings for the effects of naltrexone in men only. Oslin and colleagues (1997) found that improvement in abstinence rates, relapse rates, or addiction severity scores did not differ between older men randomized to receive naltrexone and those who received placebo. Friedmann and colleagues (2013) reported that intramuscular long-acting naltrexone was effective compared with oral naltrexone but that poor compliance might affect its effectiveness (all but one participant in the injectable group withdrew).

Indirect Comparisons Across Studies Within the Subgroup

We also assessed gender differences across studies. Studies reporting on both men and women and studies reporting exclusively on men or exclusively on women contributed to this analysis, if available.

Pooling the outcomes for percentage of heavy-drinking days from each of four studies (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Mason, Goodman, et al., 2006; Trevisan et al., 2008) indicated no significantly greater effect of pharmacological treatments on women than on men (Diff0Diff 0.10; CI –0.34, 0.55; p = 0.601).

Pooling the outcomes for percentage of abstinent days from three studies (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Mason, Goodman, et al., 2006) did not indicate significantly greater effects of pharmacological treatments on men or women (Diff0Diff –0.05; CI –0.69, 0.59; p = 0.835).

Compliance

For the group of outcomes that could be categorized as measures of compliance, as outlined in the first key question ("Do the efficacy and/or safety of first-line treatments for alcohol use disorder differ according to gender?")}, the COMBINE study (Anton, O’Malley, et al., 2006) reported no gender differences in study drop out (p = 0.73), incomplete drinking data (p = 0.753), missing therapy sessions (p = 0.91), stopping or missing medication management
sessions ($p > 0.5$), stopping attending sessions prematurely ($p = 0.126$), or medication adherence ($p = 0.70$) across interventions. Baros, Latham, and Anton (2008) found no significant difference between men and women in study completion rate (ROR 2.18; CI: 0.80, 5.90; medication compliance ratio ROR 2.89; CI 1.41, 5.92).

### Adverse Events

For the outcome domain of adverse events, as described in the first key question (“Do the efficacy and/or safety of first-line treatments for alcohol use disorder differ according to gender?”), two studies analyzed gender differences in adverse events associated with naltrexone. In the study by Baros, Latham, and Anton (2008) of oral naltrexone, men in the naltrexone group had significantly more reports of dizziness (relative to the placebo group) than did women, for whom the rates of dizziness were the same for the active and placebo-treated groups. Women in the naltrexone group had significantly more reports of nausea (relative to placebo) than did men. Women in the treated group were significantly less likely to report problems falling asleep and staying asleep than were the women in the placebo group; in contrast, reports of difficulty falling asleep or staying asleep among men did not differ across treatment groups. Garbutt, Kranzler, and colleagues (2005) assessed nine different adverse events across treatment groups in their study of intramuscular naltrexone (two doses of naltrexone and placebo). With two exceptions, they reported similar adverse event rates for men and women. Nausea was significantly higher in women than in men (but only at the lower dose), and only men reported decreased libido. Rates of nausea were not related to rates of heavy drinking.

### Behavioral (Psychosocial) Treatments

#### Symptom Improvement

Seven trials compared the effects of behavioral interventions with a passive control or another treatment and enrolled both men and women. Although each tested a different type of treatment, all implemented some form of CBT: telephone monitoring and counseling (McKay, Van Horn, Oslin, Ivey, et al., 2011), a brief motivational interviewing intervention (Wiprovnick, Kuerbis, and Morgenstern, 2015; Walker et al., 2017), motivational enhancement therapy (Witkiewitz, Hartzler, and Donovan, 2010), a brief telephone counseling intervention (Brown et al., 2007), couples therapy (Fals-Stewart, O’Farrell, and Lam, 2009), and a 12-step facilitation network support/contingency management program (Litt, Kadden, and Tennen, 2015).

Only four of the studies in this subgroup reported data that enabled pooling (Brown et al., 2007; Fals-Stewart, O’Farrell, and Lam, 2009; Litt, Kadden, and Tennen, 2015; Walker et al., 2017). Pooling “any” outcome from the four studies showed no gender differences (DiffoDiff 0.78; −2.23, 3.79; 4 RCTs) as shown in Figure 3.5.

#### Indirect Comparisons Across Studies Within the Subgroup

The findings of 13 RCTs that assessed the effects of any psychosocial intervention, either in men alone, women alone, or men and women separately were pooled using any symptom improvement outcome (Brown et al., 2007; Fals-Stewart, Birchler, and Kelley, 2006; Fals-
Stewart, Klostermann, et al., 2005; Litt, Kadden, and Tennen, 2015; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; Morgenstern et al., 2007; Schumm et al., 2014; McCrady, Epstein, and Hirsch, 1999; Davis et al., 2002; O’Farrell, Choquette, and Cutter, 1998; Fals-Stewart and Birchler, 2002; Walker et al., 2017). The meta-regression reported a non–statistically significant difference between men and women that slightly favored men (DiffDDiff –0.02, CI –0.45, 0.49; p = 0.929).

Eight RCTs assessed the effects on percentage of abstinent days (Fals-Stewart and Birchler, 2002; Fals-Stewart, Birchler, and Kelley, 2006; Litt, Kadden, and Tennen, 2015; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; O’Farrell, Choquette, and Cutter, 1998; Schumm et al., 2014; Walker et al., 2017). The meta-regression reported a non–statistically significant difference between men and women that slightly favored men (DiffDDiff –0.22; CI –0.89, 0.46; p = 0.481).

Compliance

One study (Fals-Stewart, O’Farrell, and Lam, 2009) showed a slight difference in treatment dose (sessions attended) for the couples’ intervention in favor of male couples (DiffDDiff –0.83; CI –0.96, –0.71; 1 RCT).

Indirect Comparisons Across Studies Within the Subgroup

Ten RCTs assessed a measure of adherence, compliance, or retention that allowed the studies to be pooled (Davis et al., 2002; Fals-Stewart and Birchler, 2002; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, Birchler, and Kelley, 2006; Fals-Stewart, O’Farrell, and Lam, 2009; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; O’Farrell, Choquette and Cutter, 1998; Schumm et al., 2014) The analysis found a nonsignificant difference that favored women (DiffDDiff 0.32; CI –0.06, 0.69; p = 0.086).

Six RCTs assessed the outcome mean proportion of sessions attended (Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, Birchler, and Kelley, 2006; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; Schumm et al., 2014). The analysis showed a nonsignificant difference between men and women that favored women (DiffDDiff 0.35; CI –0.31, 1.01; p = 0.235).

Adverse events

No adverse events were reported for studies of psychosocial interventions.

Combination Therapies

Symptom Improvement

Only one trial compared the effects of combination therapies (pharmacological plus psychosocial) across genders (Anton, O’Malley, et al., 2006). As already outlined, COMBINE compared the effects of naltrexone and/or acamprosate plus CBT with the effects of placebo plus CBT and naltrexone without CBT for percentage of abstinent days, percentage of heavy-drinking
days, time to first heavy-drinking day, and total drinks per day. No differences were reported for acamprosate. Differences across gender were analyzed for naltrexone alone, naltrexone plus CBT, and placebo plus CBT compared with placebo.

For the outcome of percentage of heavy-drinking days, the effects of naltrexone plus CBT compared with those of placebo were statistically significantly greater in women than in men (DiffDiff 0.34; CI 0.28, 0.40; 1 RCT). For the outcome of percentage of abstinent days, the effects of naltrexone plus CBT compared with those of placebo were also significantly greater in women than in men (DiffDiff 0.11; CI 0.05, 0.18; 1 RCT).

**Compliance**

The COMBINE study reported no gender differences in study dropout, incomplete drinking data, missing therapy sessions, stopping or missing sessions, or medication adherence.

**Adverse Events**

The COMBINE study did not compare rates or types of adverse events.

**Other Intervention Comparisons**

Several included studies compared the effects of couples therapy with individual therapy. The findings of seven RCTs that compared the effects of couples therapy with those of individual therapy, either in couples in which the male was the identified patient or in couples where either a male or female was the identified patient, were pooled in a meta-regression using any symptom improvement outcome (Brown et al., 2007; Fals-Stewart, Birchler, and Kelley, 2006; Fals-Stewart, Klostermann, et al., 2005; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; Schumm et al., 2014; McCrady, Epstein, and Hirsch, 1999). The analysis showed no statistically significant difference between men and women (DiffDiff −0.10; CI −0.91, 0.70; 7 RCTs). Five RCTs assessed the effects of couples therapy on the outcome heavy drinking days (Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, O’Farrell, and Lam, 2009; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016). The analysis indicated no systematic gender differences (DiffDiff −0.07; CI −1.35, 1.22; 5 RCTs). Seven RCTs assessed the effects of couples therapy on the outcome percent days abstinent (Fals-Stewart and Birchler, 2002; Fals-Stewart, Birchler, and Kelley, 2006; Litt, Kadden, and Tennen, 2015; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; O’Farrell, Choquette, and Cutter, 1998; Schumm et al., 2014). The analysis found a non–statistically significant difference between men and women (DiffDiff −0.17; CI −1.04, 0.70; 7 RCTs).

Combining any adherence outcome for the six studies that compared couples therapy with individual therapy in an indirect comparison across studies (Fals-Stewart, Klostermann, et al, 2005; Fals-Stewart, Birchler, and Kelley, 2006; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; Schumm et al., 2014) found no significant gender difference (DiffDiff 0.18; CI −0.57, 0.92; p = 0.566).
Do Gender Differences Vary by Duration and Intensity of Treatment?

Treatment Duration

One study compared the effectiveness of brief couples counseling with that of standard couples therapy; however, the study did not report on gender differences. The index patients were heterosexual men (Fals-Stewart, Klostermann, et al., 2005).

To assess the effects of intervention duration across genders indirectly across studies, we divided studies into two groups: shorter—those with duration of four months (16 weeks) or less—and longer—those with duration of greater than four months. Among six RCTs that compared men and women within the same trial, four met criteria for shorter duration interventions (Anton, O’Malley, et al., 2006; Greenfield et al., 2010; Baros, Latham, and Anton, 2008; Brown et al., 2007; Litt, Kadden, and Tennen, 2015) and two met the criteria for longer duration interventions (Fals-Stewart, O’Farrell, and Lam, 2009; Mason, Goodman, et al., 2006).

Figure 3.8 shows more variation in the studies with shorter duration but neither subgroup showed a statistically significant difference between men and women (shorter duration: DiffDiff 0.05; CI –0.48, 0.58; p = 0.793; longer duration: DiffDiff –0.05; –0.14, 0.04; p = 0.083).

Figure 3.8. Direct Comparisons for Any Intervention and Any Outcome by Study Duration

Notes: The figure shows the effect estimates represented by the difference in the outcome of interest between male participants, compared with the control group, and female participants, compared with the control group. Positive effects indicate that female participants showed larger treatment effects. DoD = DiffDiff.
We found no interaction effect in the direct comparisons. The gender effect was not significantly different between shorter and longer duration studies (based on an F-test, \( p = 0.721 \)).

Among 17 trials that assessed the effects of an intervention among only men or women or compared interventions across both genders, eight trials met the criterion for longer duration (Fals-Stewart, Birchler, and Kelley, 2006; Fals-Stewart, O’Farrell, and Lam, 2009; McCrady, Epstein, Cook, et al., 2009; Schumm et al., 2014; Mason, Goodman, et al., 2006; Davis et al., 2002; O’Farrell, Choquette, and Cutter, 1998; Fals-Stewart and Birchler, 2002) and nine trials met the criterion for shorter duration (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Brown et al., 2007; Fals-Stewart, Klostermann, et al., 2005; Greenfield et al., 2010; Litt, Kadden, and Tennen, 2015; McCrady, Epstein, Hallgren, et al., 2016; Morgenstern et al., 2007; Trevisan et al., 2008; McCrady, Epstein, and Hirsch, 1999). Based on a meta-regression, no significant difference in treatment effect was seen by gender for either shorter or longer duration interventions (shorter duration intervention: DiffDiff –0.26; CI –0.77, 0.25; \( p = 0.280 \); longer duration interventions: DiffDiff 0.15; CI –0.22, 0.52; \( p = 0.913 \)).

The interaction between gender and duration based on the indirect comparison data was also not statistically significant (F-test, \( p = 0.175 \)).

**Treatment Intensity**

**Direct Comparison Within Studies**

Two studies compared treatments of varying intensity within the same study. Garbutt and colleagues assessed the effects on heavy-drinking days of monthly injections of 190 mg or 380 mg intramuscular naltrexone or placebo (Garbutt, Kranzler, et al., 2005). All patients also received 12 sessions of psychosocial intervention. Among participants who received at least one injection, all showed improvement from pretreatment (including those in the placebo group); men showed a dose-dependent response that exceeded the effect of placebo, whereas women’s response to active treatment was not dose dependent and did not exceed that of placebo. The COMBINE study compared the effectiveness of combinations of naltrexone or placebo with acamprosate or placebo, with or without CBT in both men and women (Anton, O’Malley, et al., 2006). As described earlier, no gender differences were reported for the effects of naltrexone plus acamprosate compared with naltrexone plus placebo or for any other interventions involving acamprosate. Assessment of gender differences focused on the effects of naltrexone with or without CBT. The combinations of naltrexone and CBT did not show greater benefits than either one alone for any of the outcomes for men or women.

**Subgroup Analyses and Meta-Regression**

To assess the differential effects of treatment intensity between men and women in other studies, we estimated the intensity of treatment interventions as described in the Methods section and divided studies into three categories of intensity: high, moderate, and low. Figure 3.9 shows the stratified results.
Notes: The figure shows the effect estimates represented by the difference in the outcome of interest between male participants, compared with the control group, and female participants, compared with the control group. Positive effects indicate that female participants showed larger treatment effects. DoD = DiffDoDiff.

Three RCTs that compared the effects of highly intensive interventions across men and women, including COMBINE (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Mason, Goodman, et al., 2006), did not identify consistent gender differences (DiffDoDiff 0.09; CI –0.46, 0.65; p = 0.550). Two RCTs (Fals-Stewart, O’Farrell, and Lam, 2009; Litt, Kadden, and Tennen, 2015) that compared the effects of moderately intensive interventions across men and women also found no difference (DiffDoDiff 0.09; CI –1.97, 2.16; p = 0.793).

Only two RCTs (Brown et al., 2007; Walker et al., 2017) assessed the effects of a low-intensity intervention across men and women, and the outcome slightly favored men (DiffDoDiff 1.76; CI –25.66, 29.17).

No significant moderating effects of treatment intensity on the treatment response difference between men and women were seen—that is, no differences or interaction in gender differences effects were seen among the three intensity groupings (F-test, p = 0.510).

**Indirect Comparisons Across Studies**

Ten RCTs (Fals-Stewart, Birchler, and Kelley, 2006; Fals-Stewart, O’Farrell, and Lam, 2009; Litt, Kadden, and Tennen, 2015; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; Schumm et al., 2014; Trevisan et al., 2008; McCrady, Epstein, and Hirsch,
1999; O’Farrell, Choquette, and Cutter, 1998; Fals-Stewart and Birchler, 2002) that compared the effects of moderately intensive interventions among only men and women or among both men and women showed no gender differences (Diff\text{Diff} 0.0; CI \text{-}0.68, 0.68; p = 0.988).

Five RCTs (Brown et al., 2007; Davis et al., 2002; Fals-Stewart, Klostermann, et al., 2005; Morgenstern et al., 2007; Walker et al., 2017) assessed the effects of a low-intensity intervention across men and women or among men and women separately, and the outcome slightly and non–significantly favored men (Diff\text{Diff} \text{-}0.12; CI \text{-}0.70, 0.45; p = 0.604).

No significant moderating effects of treatment intensity on the Diff\text{Diff} between men and women were seen (that is, Diff\text{Diff}\text{s} were similar among the three intensity groups). We found no significant effect for the interaction of gender effects and the three intensity groupings (F-test, p = 0.999).

Corresponding analyses for compliance and adverse events were not possible because of the diversity of the data.

**Do Gender Differences Vary by Treatment Setting?**

All included studies were conducted in outpatient treatment settings. One RCT specifically recruited non–treatment-seeking patients from a primary care setting (in contrast with the remainder of studies, which sought patients who desired treatment). Thus, we further subdivided studies into those conducted in primary care settings themselves, specialized AUD treatment within academic medical center primary care facilities, and specialized AUD treatment within nonacademic primary care settings. Figure 3.10 shows effects stratified by setting.

Corresponding analyses for compliance and adverse events were not possible because of the diversity of the data.

Only one RCT that compared effects on men with effects on women was conducted in a primary care setting (Brown et al., 2007); it reported a significant effect of a brief psychosocial intervention, which favored men over women for the outcome of risky drinking days (Diff\text{Diff} \text{-}0.39; CI \text{-}0.43, \text{-}0.35; 1 RCT).

One RCT that compared effects on men with those on women was conducted in a non–university-based AUD treatment setting (Baros, Latham, and Anton, 2008). That study found no gender differences (Diff\text{Diff} \text{-}0.02; CI \text{-}0.17, 0.13; 1 RCT).

Four RCTs (Anton, O’Malley, et al., 2006; Fals-Stewart, O’Farrell, and Lam, 2009; Litt, Kadden, and Tennen, 2015; Mason, Goodman, et al., 2006) compared effects on men with effects on women in a university-based treatment setting. Effects varied, favoring men sometimes and women other times (Diff\text{Diff} 0.12; CI \text{-}0.22, 0.46; 4 RCT).

A meta-regression showed no significant moderating effect of treatment setting in the treatment response between men and women (F-test, p = 0.224).

One RCT (not pictured in Figure 3.10) that assessed the effects of a brief motivational interviewing session with feedback was conducted at a joint Army–Air Force facility among active duty Army personnel, although the intervention was implemented by phone (Walker et al., 2017). That study showed significant differences between men and women, favoring women for
both percentage of abstinent days (DiffDoDiff 3.93; CI 3.28, 4.57) and percentage of heavy-drinking days (DiffDoDiff 2.96; CI 2.37, 3.55; 1 RCT).

**Figure 3.10. Direct Comparisons for Any Outcome by Intervention Setting**

Notes: The figure shows the effect estimates represented by the difference in the outcome of interest between male participants, compared with the control group, and female participants, compared with the control group. Positive effects indicate that female participants showed larger treatment effects. DoD = DiffDoDiff.

**Indirect Comparisons Across Studies**

Only one RCT (Brown et al., 2007) that compared the effects of a brief psychosocial intervention on men with the effects on women was conducted in a primary care setting.

Five RCTs that compared the effects of interventions among only men and women or among both men and women in non–university-based AUD treatment settings nonsignificantly favored women (DiffDoDiff 0.03; CI –0.56, 0.61; \( p = 0.904 \)) (Baros, Latham, and Anton, 2008; Davis et al., 2002; Fals-Stewart and Birchler, 2002; O’Farrell, Choquette, and Cutter, 1998; Trevisan et al., 2008).

Eleven RCTs that compared the effects of interventions among only men and women or among both men and women in university-based AUD treatment settings nonsignificantly favored women (DiffDoDiff 0.03; CI –0.54, 0.59; \( p = 0.919 \)) (Anton, O’Malley, et al., 2006; Fals-Stewart and Birchler, 2002; Fals-Stewart, Birchler, and Kelley, 2006; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, O’Farrell, and Lam, 2009; Litt, Kadden, and Tennen, 2015; Mason,
Goodman, et al., 2006; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; McCrady, Epstein, and Hirsch, 1999; Schumm et al., 2014).

No significant moderating effects of treatment setting grouping were observed in the treatment response between men and women (F-test; $p = 0.988$).
4. Discussion

Despite a thorough search and comprehensive literature screening procedure, we identified a relatively small number of studies that reported on gender differences in the effects of AUD interventions. Twenty-four unique studies met inclusion criteria for individual studies; in addition, four systematic reviews reported gender effects across studies in patients with a diagnosis of AUD.

Summary of Findings

Key results are summarized in Table 4.1. Note that if we combined only studies that included both men and women (i.e., studies that directly compared men with women), a DiffDiff analysis was conducted and we referred to these comparisons as gender differences. If we included studies of only men or only women, we had to assess the differences between men and women indirectly, so we referred to those comparisons as being men vs. women differences.

Do Treatment Effects Differ According to Gender?

Although some individual studies found evidence for gender differences in treatment effectiveness, pooled analysis across studies did not provide evidence for systematic gender differences in AUD treatment effects. The analysis did not detect systematic gender differences in the treatment response in studies reporting outcome for men and women (DiffDiff 0.42; CI –0.80, 1.64; 7 RCTs). Results were similar for the individual outcome mean percentage of heavy-drinking days (DiffDiff 0.54; CI –0.88, 1.97; 6 RCTs) and the difference between the percentage of abstinent days also was not statistically significant (DiffDiff 0.29; CI –1.53, 2.12; 5 RCTs). However, the quality of evidence regarding gender differences—both overall and for specific outcomes—was low because of inconsistency of findings across studies and imprecision in the effect estimates.

Indirect pooled comparisons that included male-only and female-only studies also found no systematic difference between men and women in symptom improvement outcomes (DiffDiff 0.03; CI –0.28, 0.34; \( p = 0.840 \)) or specific outcomes, such as heavy-drinking days (DiffDiff 0.06; CI –0.29, 0.41; \( p = 0.706 \)), or percentage of abstinent days (DiffDiff –0.16; CI –0.55, 0.22; \( p = 0.379 \)). Even after including additional studies, the quality of evidence was very low because of inconsistency of findings across studies, imprecision in the effect estimates (or insufficient numbers of studies), and the indirect nature of the comparisons.

Estimated gender effects on treatment compliance varied widely across studies. Across 11 RCTs, we found no statistically significant gender effect on treatment compliance (DiffDiff 0.31; CI 0.03, 0.65; \( p = 0.073 \)). The difference in the mean proportion of sessions attended was also not statistically significant across seven RCTs (DiffDiff 0.32; CI –0.23, 0.86;
The quality of the evidence regarding compliance was rated as very low because of inconsistency of findings across studies, imprecision in the effect estimates, and indirectness of the comparisons.

Only four of the studies reported on adverse events and only two of these reported on gender differences within the study samples. Both of the latter studies tested naltrexone. The studies reported more cases of nausea in women in some but not all treatment groups.

The quality of evidence regarding gender differences in adverse events was rated very low because of inconsistency of findings across studies, imprecision in the effect estimates, and study limitation given the lack of sufficient number of studies that reported the outcome.

The systematic reviews addressed specific questions and did not report numerical effect estimates for gender differences.

**Do Gender Differences Vary by Treatment?**

We identified only one RCT that compared gender differences in treatment response based on a comparison of a pharmacological and psychological intervention. In the absence of direct comparisons, we compared male and female responses within each of the intervention types, differentiating pharmacological, psychosocial, and combination treatments.

Based on studies that compared responses of men and women to one type of treatment, we found no evidence of gender differences in treatment effectiveness for pharmacological (DiffDoDiff 0.11; CI –0.53, 0.75; 3 RCTs) and psychosocial interventions (DiffDoDiff –0.07; CI 0.89, 0.74; 3 RCTs). However, one combination treatment study indicated larger effects for women than for men (DiffDoDiff 0.34; CI 0.28, 0.40; 1 RCT). The quality of this evidence is rated very low because inconsistency across studies could not be assessed and the result was not replicated; thus, findings should be viewed with caution.

Two pharmacological studies directly comparing men and women within the trial reported no differences in compliance measures. One study that evaluated a psychosocial intervention found a slight difference in treatment dose (session attended) for a couples’ intervention in favor of male couples (DiffDoDiff –0.83; CI –0.96, –0.71; 1 RCT); however, the results should be interpreted with caution because it is based on one RCT only (very low quality of evidence).

Two studies reported on gender differences in adverse events and both studies evaluated naltrexone. As previously stated, the studies reported more incidents of nausea in women in some but not all treatment groups (very low quality of evidence for insufficient numbers of studies).
Table 4.1. Quality of Evidence and Summary of Findings

<table>
<thead>
<tr>
<th>Intervention Type and Outcome Measure</th>
<th>Number of Studies</th>
<th>Study Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Direction and Magnitude of Effect</th>
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<td>Men vs. women difference in symptom improvement (any outcome, 1 per study)</td>
<td>18 RCTs (Anton, O'Malley, et al., 2006; Baros, Latham, and Anton, 2008; Brown et al., 2007; Davis et al., 2002; Fals-Stewart and Birchler, 2002; Fals-Stewart, Klo stermann, et al., 2005; Fals-Stewart, Birchler, and Kelley, 2006; Fals-Stewart, O'Farrell, and Lam, 2009; Litt, Kadden, and Tennen, 2015; Mason, Goodman, et al., 2006; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2009; Morgenstern et al., 2007; O'Farrell, Choquette, and Cutter, 1998; Schumm et al., 2014; Trevisan et al., 2008; Walker et al., 2017)</td>
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<td>Men vs. women difference in percentage of heavy-drinking days</td>
<td>10 RCTs (Anton, O'Malley, et al., 2006; Baros, Latham, and Anton, 2008; Fals-Stewart, Klo stermann, et al., 2005; Fals-Stewart, O'Farrell, and Lam, 2009; Mason, Goodman, et al., 2006; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2009; Trevisan et al., 2008; Walker et al., 2017)</td>
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<tr>
<td>Men vs. women difference in percentage of abstinent days</td>
<td>11 RCTs (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Fals-Stewart and Birchler, 2002; Fals-Stewart, Birchler, and Kelley, 2006; Litt, Kadden, and Tennent, 2015; Mason, Goodman, et al., 2006; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; O’Farrell, Choquette, and Cutter, 1998; Schumm et al., 2014; Walker et al., 2017)</td>
<td>F NA In P NS</td>
<td>No systematic difference (DiffDiff –0.16; CI –0.55, 0.22)</td>
<td>Very low</td>
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</table>

**Compliance**

**Comparisons within studies**

<p>| Gender differences adherence/compliance/retention (1 measure per study) | 3 RCTs (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Fals-Stewart, O’Farrell, and Lam, 2009) | G NA D NA NA | One study reported no gender differences in study dropout ($p = 0.73$), incomplete drinking data ($p = 0.753$), missing therapy sessions ($p = 0.91$), or stopping or missing medication management sessions ($p &gt; 0.5$), stopping attendance of sessions prematurely ($p = 0.126$), or medication adherence ($p = 0.70$); another study showed conflicting results in completion rate ROR 2.18 (0.80, 5.90) and compliance ratio ROR 2.89 (1.41, 5.92); the third study reported a significant difference in sessions attended (DiffDiff –0.83; CI –0.96, –0.71) in favor of men | Very low |</p>
<table>
<thead>
<tr>
<th>Intervention Type and Outcome Measure</th>
<th>Number of Studies</th>
<th>Study Limitations</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Direction and Magnitude of Effect</th>
<th>GRADE</th>
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<tr>
<td>Indirect comparisons across studies</td>
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<tr>
<td>Men vs. women adherence/compliance/retention (any outcome, 1 measure per study)</td>
<td>11 RCTs (Davis et al., 2002; Fals-Stewart and Birchler, 2002; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, Birchler, and Kelley, 2006; Fals-Stewart, O’Farrell, and Lam, 2009; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2009; O’Farrell, Choquette, and Cutter, 1998; Oslin et al., 1997; Schumm et al., 2014)</td>
<td>F NA In Im NS</td>
<td>No systematic difference (DiffDif 0.31; CI –0.03, 0.65)</td>
<td>Very low</td>
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<tr>
<td>Men vs. women mean proportion of sessions attended</td>
<td>7 RCTs (Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, O’Farrell, and Lam, 2009; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2009; Oslin et al., 1997; Schumm et al., 2014)</td>
<td>F NA In Im NS</td>
<td>No systematic difference (DiffDif 0.32; CI –0.23, 0.86)</td>
<td>Very low</td>
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<tr>
<td>Adverse events</td>
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<tr>
<td>Gender difference in adverse events differences (all events)</td>
<td>2 RCTs (Baros, Latham, and Anton, 2008; Garbutt, Kranzler, et al., 2005)</td>
<td>L NA D NA NA</td>
<td>Varied by outcome</td>
<td>Very low</td>
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<tr>
<td>Gender differences in nausea</td>
<td>2 RCTs (Baros, Latham, and Anton, 2008; Garbutt, Kranzler, et al., 2005)</td>
<td>L In D NA NA</td>
<td>Two studies reporting on nausea found more reports of nausea among women in the intervention group relative to placebo than among men, but the effect was shown in only one of two intervention arms in one of the studies with three arms</td>
<td>Very low</td>
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<td>Intervention Type and Outcome Measure</td>
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<td><strong>Pharmacologic interventions vs. psychosocial interventions</strong></td>
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<td>Direct comparison</td>
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<tr>
<td>Gender difference in percentage of heavy-drinking days</td>
<td>1 RCT (Anton, O’Malley, et al., 2006)</td>
<td>G</td>
<td>I</td>
<td>D</td>
<td>P</td>
<td>NS</td>
<td>No systematic difference (Diffodiff 0.00; CI –0.13, 0.13)</td>
<td>Very low</td>
</tr>
<tr>
<td>Gender difference in percentage of abstinent days</td>
<td>1 RCT (Anton, O’Malley, et al., 2006)</td>
<td>G</td>
<td>I</td>
<td>D</td>
<td>I</td>
<td>NS</td>
<td>Larger differences in men comparing naltrexone and CBT (Diffodiff –0.50; CI –0.64, –0.37)</td>
<td>Very low</td>
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<tr>
<td><strong>Pharmacological intervention subgroup</strong></td>
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<tr>
<td>Gender difference in symptom improvement (any outcome, 1 per study)</td>
<td>3 RCTs (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Mason, Goodman, et al., 2006)</td>
<td>G</td>
<td>I</td>
<td>D</td>
<td>P</td>
<td>NS</td>
<td>No systematic difference (Diffodiff 0.11; CI –0.53, 0.75)</td>
<td>Very low</td>
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<tr>
<td>Gender difference in percentage of heavy-drinking days</td>
<td>3 RCTs (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Mason, Goodman, et al., 2006)</td>
<td>G</td>
<td>I</td>
<td>D</td>
<td>P</td>
<td>NS</td>
<td>No systematic difference (Diffodiff 0.11; CI –0.53, 0.75)</td>
<td>Very low</td>
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<tr>
<td>Gender difference in percentage of abstinent days</td>
<td>3 RCTs (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Mason, Goodman, et al., 2006)</td>
<td>G</td>
<td>I</td>
<td>D</td>
<td>I</td>
<td>NS</td>
<td>No systematic difference (Diffodiff 0.04; CI –0.04, 0.12)</td>
<td>Very low</td>
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<tr>
<td>Gender difference in percentage of heavy-drinking days (SMD)</td>
<td>4 RCTs (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Mason, Goodman, et al., 2006; Trevisan et al., 2008)</td>
<td>G</td>
<td>NA</td>
<td>In</td>
<td>NA</td>
<td>NS</td>
<td>No systematic difference (Diffodiff 0.10; CI –0.34, 0.55)</td>
<td>Very low</td>
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<tr>
<td>Gender difference in percentage of abstinent days (SMD)</td>
<td>3 RCTs (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Mason, Goodman, et al., 2006)</td>
<td>G</td>
<td>NA</td>
<td>In</td>
<td>NA</td>
<td>NS</td>
<td>No systematic difference (Diffodiff –0.05 CI –0.69, 0.59)</td>
<td>Very low</td>
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<tr>
<td>Intervention Type and Outcome Measure</td>
<td>Number of Studies</td>
<td>Study Limitations</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Publication Bias</td>
<td>Direction and Magnitude of Effect</td>
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<tr>
<td>Gender differences adherence/compliance/retention (1 measure per study)</td>
<td>2 RCTs (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008)</td>
<td>G NA D NA NA</td>
<td>One study reported no gender differences in study dropout, incomplete drinking data, missing therapy sessions, stopping or missing sessions, stopping attendance of sessions prematurely, or medication adherence; one study showed conflicting results completion rate (ROR 2.18; 0.80, 5.90) and compliance ratio (ROR 2.89; 1.41, 5.92)</td>
<td>Very low</td>
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<tr>
<td>Gender difference in adverse events (all events)</td>
<td>2 RCTs (Baros, Latham, and Anton, 2008; Garbutt, Kranzler, et al., 2005)</td>
<td>G NA D NA NA</td>
<td>Varied by outcome</td>
<td>Very low</td>
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<tr>
<td>Gender differences in nausea</td>
<td>2 RCTs (Baros, Latham, and Anton, 2008; Garbutt, Kranzler, et al., 2005)</td>
<td>G NA D NA NA</td>
<td>More reports of nausea in women in the naltrexone group relative to placebo than in men, but effect was shown in only one of two intervention arms</td>
<td>Very low</td>
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<tr>
<td><strong>Psychosocial intervention subgroup</strong></td>
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<tr>
<td>Gender difference in symptom improvement (any outcome, 1 per study)</td>
<td>4 RCTs (Brown et al., 2007; Fals-Stewart, O’Farrell, and Lam, 2009; Litt, Kadden, and Tennen, 2015; Walker et al., 2017)</td>
<td>F I D P NS</td>
<td>No systematic difference (DiffoDiff 0.78; CI –2.23, 3.79)</td>
<td>Very low</td>
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<tr>
<td>Gender difference in percentage of heavy-drinking days</td>
<td>3 RCTs (Fals-Stewart, O’Farrell, and Lam, 2009; Litt, Kadden, and Tennen, 2015; Walker et al., 2017)</td>
<td>F I D P NS</td>
<td>No systematic difference (DiffoDiff 1.33; CI –4.09, 6.75)</td>
<td>Very low</td>
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<tr>
<td>Gender difference in percentage of abstinent days</td>
<td>2 RCTs (Litt, Kadden, and Tennen, 2015; Walker et al., 2017)</td>
<td>F NA D P NR</td>
<td>No systematic difference (DiffoDiff 0.87; CI –25.58, –27.32)</td>
<td>Very low</td>
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<tr>
<td>Intervention Type and Outcome Measure</td>
<td>Number of Studies</td>
<td>Study Limitations</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Publication Bias</td>
<td>Direction and Magnitude of Effect</td>
<td>GRADE</td>
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<tr>
<td>Gender difference in symptom improvement (any outcome, 1 per study)</td>
<td>13 RCTs (Brown et al., 2007; Davis et al., 2002; Fals-Stewart and Birchler, 2002; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, Birchler, and Kelley, 2006; Litt, Kadden, and Tennen, 2015; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2009; Morgenstern et al., 2007; O’Farrell, Choquette, and Cutter, 1998; Schumm et al., 2014; Walker et al., 2017)</td>
<td>F</td>
<td>NA</td>
<td>In</td>
<td>NA</td>
<td>NS</td>
<td>No systematic difference (DiffDiff –0.02; CI –0.45, 0.49)</td>
<td>Very low</td>
</tr>
<tr>
<td>Men vs. women difference in symptom improvement (any outcome, 1 per study)—subgroup of couples therapy vs. individual therapy</td>
<td>7 RCTs (Brown et al., 2007; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, Birchler, and Kelley, 2006; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2009; Schumm et al., 2014)</td>
<td>F</td>
<td>NA</td>
<td>In</td>
<td>NA</td>
<td>NS</td>
<td>No systematic difference (DiffDiff –0.22; CI –0.68, 0.24)</td>
<td>Very low</td>
</tr>
<tr>
<td>Men vs. women difference in percentage of heavy-drinking days (subgroup of couples therapy vs. individual therapy)</td>
<td>5 RCTs (Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, O’Farrell, and Lam, 2009; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016)</td>
<td>F</td>
<td>NA</td>
<td>In</td>
<td>NA</td>
<td>Begg ( p = 0.015 ); Egger ( p = 0.014 )</td>
<td>No systematic difference (DiffDiff –0.07; CI –1.35, 1.22)</td>
<td>Very low</td>
</tr>
<tr>
<td>Gender differences in compliance, direct comparison</td>
<td>1 RCT (Fals-Stewart, O’Farrell, and Lam, 2009)</td>
<td>F</td>
<td>I</td>
<td>D</td>
<td>Im</td>
<td>NA</td>
<td>Favors men (DiffDiff –0.83; CI –0.96, –0.71)</td>
<td>Very low</td>
</tr>
<tr>
<td>Intervention Type and Outcome Measure</td>
<td>Number of Studies</td>
<td>Study Limitations</td>
<td>Inconsistency</td>
<td>Indirectness</td>
<td>Imprecision</td>
<td>Publication Bias</td>
<td>Direction and Magnitude of Effect</td>
<td>GRADE</td>
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<tr>
<td>Men vs. women adherence/retention, indirect comparison (any outcome, 1 measure per study)</td>
<td>10 RCTs (Davis et al., 2002; Fals-Stewart and Birchler, 2002; Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, Birchler, and Kelley, 2006; Fals-Stewart, O’Farrell, and Lam, 2009; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; O’Farrell, Choquette, and Cutter, 1998; Schumm et al., 2014)</td>
<td>F NA D Im NR</td>
<td>Nonsignificantly favors women (DiffDiff 0.32; CI –0.06, 0.69; p = 0.086)</td>
<td>Very low</td>
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<tr>
<td>Men vs. women mean proportion of sessions attended</td>
<td>6 RCTs (Fals-Stewart, Klostermann, et al., 2005; Fals-Stewart, O’Farrell, and Lam, 2009; McCrady, Epstein, and Hirsch, 1999; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; Schumm et al., 2014)</td>
<td>F NA D Im NR</td>
<td>Nonsignificantly favors women (DiffDiff 0.35; CI –0.31, 1.01; p = 0.235)</td>
<td>Very low</td>
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</table>

**Combination treatment subgroup**

<p>| Gender difference in percentage of heavy-drinking days | 1 RCT (Anton, O’Malley, et al., 2006) | G NA D NA NR | Favors women (DiffDiff 0.34; CI 0.28, 0.40) | Very low |
| Gender difference in percentage of abstinent days    | 1 RCT (Anton, O’Malley, et al., 2006) | G NA D NA NR | Favors women (DiffDiff 0.11; CI 0.05, 0.18) | Very low |
| Gender differences in compliance                      | 1 RCT (Anton, O’Malley, et al., 2006) | G NA D NA NR | No gender differences in study dropout, incomplete drinking data, missing therapy sessions, stopping or missing sessions, or medication adherence. | Very low |</p>
<table>
<thead>
<tr>
<th>Intervention Type and Outcome Measure</th>
<th>Number of Studies</th>
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<th>Inconsistency</th>
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<tr>
<td>Effect of duration</td>
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<tr>
<td>Gender differences and duration</td>
<td>6 RCTs</td>
<td>F–G</td>
<td>NA</td>
<td>In</td>
<td>NA</td>
<td>NA</td>
<td>No systematic effect in direct comparison studies (( p = 0.721 ))</td>
<td>Very low</td>
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<tr>
<td>(any outcome, 1 per study)</td>
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<tr>
<td>Men vs. women and duration</td>
<td>17 RCTs</td>
<td>F–G</td>
<td>NA</td>
<td>In</td>
<td>NA</td>
<td>NA</td>
<td>No systematic effect in indirect comparisons across studies (( p = 0.175 ))</td>
<td>Very low</td>
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<td>(any outcome, 1 per study)</td>
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<td>Intervention Type and Outcome Measure</td>
<td>Number of Studies</td>
<td>Study Limitations</td>
<td>Inconsistency</td>
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<td>Publication Bias</td>
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<td><strong>Effect of intensity</strong></td>
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<td>Comparisons within studies</td>
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<tr>
<td>Gender differences and intensity (any outcome)</td>
<td>2 RCTs (Garbutt, Kranzler, et al., 2005; Anton, O’Malley, et al., 2006)</td>
<td>G</td>
<td>I</td>
<td>D</td>
<td>Im</td>
<td>NA</td>
<td>One study showed a dose-dependent response in men that exceeded the effect of placebo, whereas women’s response to active treatment was not dose-dependent and did not exceed that of placebo; one study found that combinations of naltrexone and CBT did not show greater benefits than either one alone for any of the outcomes for men or women</td>
<td>Very low</td>
</tr>
<tr>
<td>Gender differences and intensity (any outcome)</td>
<td>7 RCTs (Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Brown et al., 2007; Mason, Goodman, et al., 2006; Fals-Stewart, O’Farrell, and Lam, 2009; Litt, Kadden, and Tennen, 2015; Walker et al., 2017)</td>
<td>G</td>
<td>NA</td>
<td>In</td>
<td>NA</td>
<td>NA</td>
<td>No systematic difference in direct comparison studies ($p = 0.510$)</td>
<td>Very low</td>
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<tr>
<td><strong>Indirect comparisons across studies</strong></td>
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<tr>
<td>Gender differences and intensity (any outcome)</td>
<td>11 RCTs (Fals-Stewart, Birchler, and Kelley, 2006; Anton, O’Malley, et al., 2006; Baros, Latham, and Anton, 2008; Mason, Goodman, et al., 2006; Fals-Stewart, O’Farrell, and Lam, 2009; Litt, Kadden, and Tennen, 2015; McCrady, Epstein, Cook, et al., 2009; McCrady, Epstein, Hallgren, et al., 2016; O’Farrell, Choquette, and Cutter, 1998; Fals-Stewart and Birchler, 2002; Walker et al., 2017)</td>
<td>F</td>
<td>NA</td>
<td>In</td>
<td>NA</td>
<td>NA</td>
<td>No systematic difference in indirect comparison studies ($p = 0.990$)</td>
<td>Very low</td>
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</table>

Notes: C = consistent; F = fair; G = good; I = inconsistent; Im = imprecise; In = indirect; L = limitation, all studies reported on naltrexone, no other intervention; NA = not applicable; NR = not reported; NS = not significant; P = poor; SMD = standardized mean difference; wks = weeks.
Do Gender Differences Vary by Duration and Intensity of Treatment?

We found no evidence that gender differences in treatment effectiveness varied by treatment duration, based both on studies reporting on direct comparisons between male and female treatment responses \((p = 0.721)\) and on indirect comparison across all studies (including those of studies focused only on men or only on women) \((p = 0.175)\).

One study directly compared two doses of intramuscular naltrexone. The study reported a dose-dependent response that exceeded the effect of placebo for men, whereas women’s response to active treatment was not dose dependent and did not exceed that of placebo. Another study assessing different treatment combinations (e.g., naltrexone with or without CBT) reported no gender differences.

Across studies directly reporting on gender differences within the study, we found no indication that gender differences were associated with different treatment intensity \((p = 0.270)\). An indirect comparison combining all studies including those of only men and those of only women found no interaction effect \((p = 0.994)\).

The evidence regarding effects of treatment duration and intensity on gender differences in treatment response is rated as very low quality because of inconsistency and indirectness.

Do Gender Differences Vary by Treatment Setting?

Only one of the included studies was conducted in primary care, and only one study was conducted in a military setting, hindering an effective assessment of whether gender differences vary by treatment setting.

We found no significant difference in gender differences within university and nonuniversity treatment settings, either in pooled analyses of studies that made direct comparisons between men and women \((p = 0.224)\) or in analyses that made indirect comparisons using all included studies \((p = 0.988)\). Both direct and indirect analyses should be interpreted with caution because of the sparsity of primary care data. Thus, the evidence regarding effects of treatment setting on gender differences in treatment response is rated as very low quality because of inconsistency, indirectness, and lack of sufficient numbers of studies for the analysis.

Findings Relative to Prior Systematic Reviews

Jarvis (1992) conducted a systematic review and meta-analysis of 20 studies published between 1953 and 1991 that assessed the effects of a variety of interventions, specifically pharmacologic interventions (disulfiram and promethazine), psychosocial and educational interventions, and aversive treatments. Overall, Jarvis reported that women had better short-term benefits than men but poorer long-term benefits. Our review assessed gender differences in studies of both shorter and longer duration but found insufficient evidence on which to base a conclusion. However, it was not clear whether Jarvis distinguished between length of treatment
and length of follow-up in the included studies, and the studies included in that review assessed the effects of several types of treatment not included in ours and no longer in use.

Kazemi and colleagues (2013) conducted a systematic review of interventions designed to address drinking among active duty military personnel. Of the ten studies included in that review, none assessed gender differences. Two studies consisted of only men, but both were conducted in Europe and aimed to decrease drinking in and around a military base, and a diagnosis of AUD was not required for participation in either study. In the first, an RCT of Swiss military personnel who received brief motivational interviewing compared with personnel on a wait-list found that the wait-list group reported significantly more drinks per week at six months than did the intervention group. The second study, conducted in the Swedish military, compared men who attended a two-day course by trained instructors (the Swedish version of PRIME for Life, based on social learning theory) with men who received no intervention: Course participants reported a significant drop in binge drinking at five months, but there were no group differences at 20 months. This review reinforces the need for additional studies, particularly among military personnel.

Three systematic reviews have been published that addressed the use of brief interventions (Kaner et al., 2009; Wilk et al., 1997; Vasilaki, Hosier, and Cox, 2006). None of the studies included in these reviews required a diagnosis of AUD for inclusion, and most were not conducted in the United States; hence the results are difficult to compare with our findings. The 2009 Cochrane review by Kaner et al. reviewed the effects of brief interventions among primary care populations, reported in 22 RCTs, six of which reported outcomes by gender (two of the six were U.S. studies): Among the six studies, men showed significant improvement at one year but women did not. Vasilaki, Hosier, and Cox reviewed the effects of motivational interviewing as a brief intervention: Of 22 included studies, only one assessed gender effects, a U.S. study that assessed the effects of a brief intervention on college students who were assessed as high-risk drinkers in high school, and found no impact of gender on the outcomes. Wilk et al. also reviewed the effects of brief interventions: Of 12 studies, most consisted of men and women but only five RCTs reported data that contributed to quantitative findings (none were conducted in the United States): The review reported that women had a greater likelihood than did men of responding positively to treatment (OR 2.42; CI 1.70, 3.45 vs. OR 1.90; CI 1.57, 2.31). Of the two studies of brief interventions included in our review, one reported no gender differences, and one reported a significant difference in beneficial effect, favoring men. Thus, it is not possible to draw conclusions from either our review or prior ones regarding possible gender differences in the effects of brief interventions for AUD.

Rosenthal and colleagues (2008) published a systematic review on the safety of acamprosate that included 20 RCTs; all but one RCT (Mason, Goodman, et al., 2006) were non-U.S. studies. Although the overall rate of adverse events was significantly higher for acamprosate than for placebo, the rates of discontinuation did not differ between the two. No serious adverse events were reported in any of the studies. Of greatest relevance to our review, Rosenthal et al. found no gender differences in adverse events associated with the use of acamprosate.
Fitzgerald and colleagues (2016) updated a prior qualitative review of reviews on gender differences in effects of population-level alcohol policy interventions. Among 63 reviews of ten categories of policy interventions (e.g., taxation, advertising, school, and workplace), only two reviews reported results by gender because few to no original studies reported baseline participation by gender. Reviews of school-based or higher-education–based alcohol policies found no difference in the effects of these policies across genders. Reviews of studies on the effects of retail price or tax increases found inconsistent effects across studies. Although the Fitzgerald review focused on population-level, primary preventive interventions rather than individual-level treatment interventions, it reinforces the need to assess the effects of all AUD interventions for gender differences. Gender differences in the effects of alcohol policies at the higher education, workplace, and other community levels would be of significant interest to the military.

Strengths and Limitations

This systematic review is the first to assess the presence of gender differences in the efficacy and safety of any evidence-based treatments for AUD that are endorsed by American Psychiatric Association and VA/DoD clinical practice guideline. Thus, a strength of this review is its intent to include all evidence-based treatment modalities.

An additional strength—and limitation—is that we limited inclusion to studies that enrolled only participants with a diagnosis of AUD (as opposed to studies that include those who screen positively for heavy drinking or risky drinking or simply those who want to—or have been mandated to—reduce their alcohol intake). Limiting inclusion to studies of those with an AUD diagnosis tended to exclude studies of brief interventions, particularly those implemented in hospital emergency departments, primary care clinics, and school settings. Thus, we could not assess potential gender differences in treatments focused on those who might be in early stages of AUD or whose alcohol use is beginning to affect their performance.

Our review further limited the studies we included to those of individuals with a diagnosis of AUD with no mental health comorbidities (as opposed to those with dual diagnoses of AUD and another substance use disorder, depressive disorder, anxiety disorder, posttraumatic stress disorder, personality disorder, or psychosis,). This inclusion criterion has several implications with respect to women. First, many excluded studies enrolled participants with both AUD and depression, and because the risk for depressive disorder is higher for women, we might have excluded studies with higher proportions of women compared with the studies that we did include, which tended to include lower percentages of women than men. Second, it is unclear what proportions of women in the included studies had co-occurring depression because it was not consistently reported (and probably not consistently assessed in individual studies). Importantly, co-occurring depression might affect the effectiveness of treatments for AUD.

Another limitation of our review is that we included only studies conducted in the United States because of the possibility of confounding stemming from cultural differences, when our purpose was to assess gender as a potential effect modifier. Several studies, particularly of the
drug acamprosate, were conducted in European countries. A further, related, limitation is that we identified almost no studies of active-duty U.S. military personnel.

The evidence on gender differences in AUD treatment is limited by the small number of studies that address this topic as a primary or a secondary outcome. We identified no studies that assessed gender differences in the effects of the drug disulfiram, even in non-U.S. populations or in those populations with comorbidities, within the time frame of our searches. Few studies that assessed the effects of brief interventions met the criteria for enrolling only participants with a diagnosis of AUD. And among the studies that met inclusion criteria, many had a high risk of bias related to methods for concealing allocation and for blinding, as well as for compliance and dropout. Because no studies had gender differences as their primary outcome, the numbers of male participants always exceeded the numbers of female participants, which could have skewed any findings based on gender comparisons: The one study that enrolled an active-duty military population showed significantly greater beneficial effects for women than for men, but women represented only 8 percent of participants. In addition, estimated treatment efficacy could differ because the criteria for AUD are based on a different average number of drinks per day for men and women. Another effect of the small number of studies and the relatively small numbers of women enrolled in these studies is that these studies, and the overall analyses, lacked power to assess potential impacts of race, ethnicity, and age on gender differences.

An additional limitation of the literature concerns outcome measures. Few studies employed the same or similar measures. Evidence from some of the included studies suggests that some outcome measures might be more sensitive than other outcomes to gender differences in response to treatment (Litt, Kadden, and Tennen, 2015; Mason, Goodman, et al., 2006).

Although we included only RCTs, this decision might have created several limitations. First, as described earlier, not all studies considered gender in randomization, and men and women might have differed at baseline in some important but unidentifiable characteristics that might have skewed the results (known differences, such as baseline alcohol consumption, are taken into account by the comparison of outcomes for men and women with respect to their control groups); the findings of the secondary analysis of data from the COMBINE study support this possibility (Greenfield et al., 2010). Second, blinding was impossible in many psychosocial interventions, particularly those that compared couples therapy with individual therapy.

Implications for Future Research and Practice

Our review does not provide clear evidence that any particular type of AUD treatment is more effective for men or for women. The paucity of literature and the variability of the published findings point to the need for more research that focuses on the differential effectiveness of AUD treatment in men and women.

Studies need to enroll comparable numbers of men and women, randomize on gender, and control for other potential confounding factors, such as co-occurring depression, anxiety, or other substance use disorders; baseline history of—and treatment for—AUD; and possibly age (because some evidence suggests lifetime drinking trajectories differ between men and women).
Active interventions and control conditions need to be designed to evaluate the effects of psychopharmacological interventions separately from the effects of psychosocial interventions and their combination, controlling for such factors as contemporaneous use of other treatments (including attendance at 12-step programs). Given the increased risk for co-occurring depression among women with AUD, a systematic review of the literature on the use of second- and third-generation antidepressants to treat AUD in women, both placebo-controlled and noninferiority studies, is also advisable.

Research on treatment of AUD should strive to assess multiple relevant outcomes and should begin to assess whether particular outcome measures seem to vary based on gender (or on patterns of use that appear to be associated with gender) to arrive at a set of outcome measures that reliably reflects true gender differences in treatment response.

Conclusions

Although some individual studies demonstrated gender differences in treatment effects, we did not identify systematic differences across studies. Although evidence weakly supports a lack of difference between men and women in the efficacy of evidence-based treatments for AUD, the evidence is too low in quality to draw conclusions regarding the potential for gender differences in the efficacy of specific treatment modalities.

Most notably, despite an extensive search and thorough screening procedure, we found very few studies reporting on gender differences, which hindered our analyses. To maximize applicability to the population of interest, only U.S. studies that enrolled adults with a diagnosed AUD and without comorbid conditions were included. The review showed a profound lack of information on the presence and absence of gender differences. We contacted authors and scrutinized numerous U.S. RCTs for differential effects for men and women but found very few relevant studies.

Those studies that met our inclusion criteria tended to be smaller or to not enroll comparable numbers of men and women; to assess a wide variety of outcomes, making cross-study comparisons difficult; and to have relatively high risk of bias. Thus, more studies are needed that assess the presence or absence of gender differences in AUD treatment with appropriate methods.

Future studies should consider diverse treatment outcomes because of the possibility that some treatment modalities could affect various outcomes differentially across genders. Future studies also should consider the potential effect of co-occurring disorders, such as depressive disorder, that differ in prevalence between men and women.
Appendix A. Search Strategies

PubMed Database, from January 1, 1997, to March 20, 2018

Language

English

Search Strategy #1

alcohol drinking[mh] OR alcohol-related disorders[mh] OR “alcohol abuse” OR alcoholism OR alcoholic* OR drinking problem* OR “alcohol use” OR alcohol dependen* OR alcohol intervention*[tiab] OR alcohol intervention*[ot] OR “hazardous drinking” OR (“substance use” OR “substance abuse” OR “substance misuse”) AND (alcohol*[tiab] OR alcohol*[ot])

AND

“Cognitive Therapy”[Mesh] OR “Psychotherapy, Group”[Mesh] OR “Marital Therapy”[Mesh] OR “Family Therapy”[Mesh] OR “Socioenvironmental Therapy”[Mesh] OR therapy OR therapeutic OR behavior therapy[mh] OR treatment OR acamprosate OR disulfiram OR naltrexone OR topiramate OR gabapentin OR behavioral couples therap* OR behavioral therap* OR “community reinforcement” OR “motivational enhancement” OR 12-step OR “network support” OR cognitive behavioral therap* OR group therap* OR twelve-step OR marriage and family therap* OR psychodynamic therap* OR interpersonal therap* OR marital therap* OR family therap* OR motivational interview* OR motivational interviewing[mh]

AND

AND
Filters: Randomized Controlled Trial
NOT
trial protocol[ti] OR study protocol[ti]

**Search Strategy #2**

alcohol drinking[mh] OR alcohol-related disorders[mh] OR “alcohol abuse” OR alcoholism OR alcoholic* OR drinking problem* OR “alcohol use” OR alcohol dependen* OR alcohol intervention*[tiab] OR alcohol intervention*[ot] OR “hazardous drinking” OR (“substance use” OR “substance abuse” OR “substance misuse”) AND (alcohol*[tiab] OR alcohol*[ot]))
AND
“Cognitive Therapy”[Mesh] OR “Psychotherapy, Group”[Mesh] OR “Marital Therapy”[Mesh] OR “Family Therapy”[Mesh] OR “Socioenvironmental Therapy”[Mesh] OR therapy OR therapeutic OR behavior therapy[mh] OR treatment OR acamprosate OR disulfiram OR naltrexone OR topiramate OR gabapentin OR behavioral couples therap* OR behavioral therap* OR “community reinforcement” OR “motivational enhancement” OR 12-step OR “network support” OR cognitive behavioral therap* OR group therap* OR twelve-step OR marriage and family therap* OR psychodynamic therap* OR interpersonal therap* OR marital therap* OR family therap* OR motivational interview*[mh]
AND
AND
gender OR sex OR men OR man OR women OR woman
AND
Filters: Systematic Reviews
NOT
review protocol[ti]
PsycINFO Database, from January 1, 1997, to March 20, 2018

Language
English

Search Strategy
DE “Alcohol Abuse” OR DE “Alcoholism” OR DE “Alcoholic Psychosis” OR DE “Alcohol Intoxication” OR DE “Acute Alcoholic Intoxication” OR DE “Chronic Alcoholic Intoxication” OR DE “Alcohol Withdrawal” OR TI,AB,SU,KW (alcoholism OR alcoholic* OR “alcohol dependent”* OR “alcohol abuse” OR “alcohol use” OR “drinking problem” OR “drinking problems” OR (“substance use” OR “substance abuse” OR “substance misuse”) AND alcohol*) AND DE “Cognitive Behavior Therapy” OR DE “Acceptance and Commitment Therapy” OR DE “Group Psychotherapy” OR DE “Encounter Group Therapy” OR DE “Therapeutic Community” OR DE “Twelve Step Programs” OR DE “Alcoholics Anonymous” OR DE “Marriage Counseling” OR DE “Conjoint Therapy” OR DE “Family Therapy” OR DE “Strategic Family Therapy” OR DE “Structural Family Therapy” OR DE “Psychodynamic Psychotherapy” OR DE “Psychodynamics” OR DE “Interpersonal Psychotherapy” OR TI,AB,SU,KW (“cognitive behavioral therapy” OR “group therapy” OR “group therapies” OR twelve-step OR “marriage therapy” OR “marital therapy” OR “marital therapies” OR “family therapy” OR “psychodynamic therapy” OR “psychodynamic therapies” OR “interpersonal therapy” OR “interpersonal therapies” OR “motivational enhancement” OR treatment* OR therapy OR therapies OR therapeutic OR acamprosate OR disulfiram OR naltrexone OR topiramate OR gabapentin OR “behavioral couples therapy” OR “behavioural couples therapy” OR “behavioral therapy” OR “behavioural therapy” OR “behavioral therapies” OR “behavioural therapies” OR “community reinforcement” OR “motivational enforcement” OR 12-step OR “network support”) AND AF (Author Affiliation) us or usa or united states AND TI,AB,SU,KW (randomi* OR rct*)

Embase Database, from January 1, 1997, to March 20, 2018

Language
English

Search Strategy
‘alcoholism’/exp OR ‘alcoholism’ OR ‘drinking behavior’/exp OR ‘drinking behavior’ OR alcoholi* OR ‘alcohol abuse’/exp OR ‘alcohol abuse’ OR ‘alcohol use’/exp OR ‘alcohol use’ OR ‘alcohol dependence’/exp OR ‘alcohol dependence’ OR ‘alcohol intervention’ OR ‘alcohol interventions’ OR ‘drinking problem’ OR ‘drinking problems’ OR (“substance use”/exp OR “substance use” OR “substance abuse”/exp OR “substance abuse” OR “substance misuse”/exp OR “substance misuse”) AND alcohol*) AND ‘cognitive therapy’/exp OR ‘cognitive therapy’ OR ‘psychotherapy’/exp OR ‘psychotherapy’ OR ‘marital therapy’/exp OR ‘marital therapy’ OR ‘family therapy’/exp OR ‘family therapy’ OR ‘behavior therapy’/exp OR ‘behavior therapy’ OR ‘therapy’/exp OR therapy OR therapies OR therapeutic OR ‘treatment’/exp OR treatment OR ‘acamprosate’/exp OR acamprosate OR ‘disulfiram’/exp OR disulfiram OR ‘naltrexone’/exp OR naltrexone OR ‘topiramate’/exp OR topiramate OR ‘gabapentin’/exp OR
gabapentin OR ‘community reinforcement’ OR ‘motivational enhancement’ OR ‘12 step’ OR ‘network support’ OR ‘twelve step’ OR ‘alcoholics anonymous’/exp OR ‘alcoholics anonymous’
AND
[randomized controlled trial]/lim
AND
[humans]/lim
NOT
‘study protocol’ OR ‘trial protocol’

Cochrane Central Register of Controlled Trials Database, from January 1, 1997, to March 20, 2018

Language
English

Search Strategy
MeSH descriptor: [Alcohol-Related Disorders] explode all trees OR MeSH descriptor: [Alcohol Drinking] explode all trees OR “alcohol abuse” or alcoholi* or “drinking problem” or “drinking problems” or “alcohol use” or “alcohol dependence” or “alcohol dependency” or “alcohol dependent” or “alcohol intervention” or (alcohol* and interven*):ti,ab,kw (Word variations have been searched)
((“substance use” or “substance abuse” or “substance misuse”) and alcohol*):ti,ab,kw (Word variations have been searched)
AND
MeSH descriptor: [Cognitive Therapy] explode all trees OR MeSH descriptor: [Psychotherapy] explode all trees OR MeSH descriptor: [Socioenvironmental Therapy] explode all trees OR MeSH descriptor: [Marital Therapy] explode all trees OR MeSH descriptor: [Family Therapy] explode all trees OR MeSH descriptor: [Behavior Therapy] explode all trees OR (therapy or therapeutic or treatment or acamprosate or disulfiram or naltrexone or topiramate or gabapentin or “behavioral couples therapy” or “behavioral couples therapies” or “behavioral therapy” or “behavioral therapies” or “community reinforcement” or “motivational enhancement” or 12-step or “alcoholics anonymous” or “network support” or “cognitive behavioral therapy” or “cognitive behavioral therapies” or “group therapy” or “group therapies” or twelve-step or “marriage and family therapy” or “marriage and family therapies” or “psychodynamic therapy” or “psychodynamic therapies” or “interpersonal therapy” or “interpersonal therapies” or “marital therapy” or “marital therapies” or “family therapy” or “family therapies”):ti,ab,kw (Word variations have been searched)
NOT
“study protocol” or “trial protocol”:ti,ab,kw (Word variations have been searched)

Cochrane Database of Systematic Reviews, Cochrane “Other Reviews,” from January 1, 1997, to March 20, 2018

Language
English
Search Strategy

MeSH descriptor: [Alcohol-Related Disorders] explode all trees OR MeSH descriptor: [Alcohol Drinking] explode all trees OR “alcohol abuse” or alcoholi* or “drinking problem” or “drinking problems” or “alcohol use” or “alcohol dependence” or “alcohol dependency” or “alcohol dependent” or “alcohol intervention” or (alcohol* and interven*):ti,ab,kw (Word variations have been searched) OR ((“substance use” or “substance abuse” or “substance misuse”) and alcohol*):ti,ab,kw (Word variations have been searched)

AND

MeSH descriptor: [Cognitive Therapy] explode all trees OR MeSH descriptor: [Psychotherapy] explode all trees OR MeSH descriptor: [Socioenvironmental Therapy] explode all trees OR MeSH descriptor: [Marital Therapy] explode all trees OR MeSH descriptor: [Family Therapy] explode all trees OR MeSH descriptor: [Behavior Therapy] explode all trees OR (therapy or therapeutic or treatment or acamprosate or disulfiram or naltrexone or topiramate or gabapentin or “behavioral couples therapy” or “behavioral couples therapies” or “behavioral therapy” or “behavioral therapies” or “community reinforcement” or “motivational enhancement” or 12-step or “alcoholics anonymous” or “network support” or “cognitive behavioral therapy” or “cognitive behavioral therapies” or “group therapy” or “group therapies” or twelve-step or “marriage and family therapy” or “marriage and family therapies” or “psychodynamic therapy” or “psychodynamic therapies” or “interpersonal therapy” or “interpersonal therapies” or “marital therapy” or “marital therapies” or “family therapy” or “family therapies”):ti,ab,kw (Word variations have been searched)

AND

gender or sex or men or man or women or woman:ti,ab,kw (Word variations have been searched)

NOT

“review protocol”:ti,ab,kw (Word variations have been searched)
Appendix B. Evidence Tables and Study Overview

The individual studies are described here in detail, followed by comprehensive evidence tables (Tables B.1 and B.2) of the individual studies and systematic reviews meeting inclusion criteria.

Pharmacological and Combined Intervention Studies

Studies of Men and Women

The COMBINE Study was a 2001 multisite RCT that randomized 1,383 recently abstinent individuals with AUD (428 women and 955 men) to one of eight treatment conditions combining medical management, naltrexone or placebo, acamprosate or placebo, and a CBI or no CBI (a ninth group that received CBI alone but no pills was not included in any gender comparisons) (Anton, O’Malley, et al., 2006). Treatment duration was 16 weeks and assessments were conducted at the end of this period and at up to 68 weeks from baseline (52 weeks from the completion of treatment). The primary efficacy outcome was percentage of days abstinent. Dropout rate and adherence were also measured. The study did not report on adverse events. In the overall analysis, although men experienced a higher percentage of days abstinent than did women ($p = 0.04$), gender did not significantly affect response to treatment (subgroup analyses of gender effects on responses to specific treatments are described later). The authors noted that the study was not powered to detect small gender differences (Anton, O’Malley, et al., 2006).

The Vivitrex Study, a 2002 multisite RCT, randomized 627 actively drinking adults with AUD (423 men and 204 women) to receive one of two monthly doses of long-acting (intramuscular) naltrexone or placebo for six months combined with a psychosocial intervention (Garbutt, Kranzler, et al., 2005). The primary outcome was rate of heavy drinking days. This study did not report on adherence rates or adverse events. In this study, men showed a significantly better response than did women, and the difference was dose-dependent (for 190 mg, a relative hazard ratio [RHR] of 0.78 and a CI of 0.61, 0.98; for 380 mg, an RHR of 0.46 and a CI of 0.36, 0.58) (Garbutt, Kranzler, et al., 2005).

Baros and colleagues assessed gender differences in the responses to combined oral naltrexone and CBT by combining the findings of two clinical trials conducted by the group (Baros, Latham, and Anton, 2008). A total of 211 individuals with AUD who had been abstinent for at least five days (154 men and 57 women) were randomized to receive 12 weeks of oral naltrexone or placebo and weekly CBT. Outcomes assessed at 12 weeks were percentage of days drinking, percentage of heavy-drinking days, and total standard drinks in the prior 90 days using Timeline Followback interviewing. The study also reported on adherence (completion rate and compliance ratio) and on adverse events. In the study of combined oral naltrexone and CBT (Baros, Latham and Anton, 2008), no significant difference was seen between men and women.
in the percentage of heavy-drinking days (DiffDiff = –0.02; CI = –0.17, 0.12); total standard drinks (DiffDiff = 0.07; CI = –0.08, 0.22) or percentage of days abstinent (DiffDiff = –0.02; CI = –0.17, 0.12). However, days to first drink showed a slight but significant difference favoring men (DiffDiff = –0.84; CI = –0.99, –0.69), and drinks per drinking day showed a slight difference favoring women (DiffDiff = 0.34; CI = 0.19, 0.49).

Mason and colleagues randomized 601 men and women in 21 clinics to one of two doses of oral acamprosate (258 on the standard 2g/day dose and 83 on a 3g/day dose) or to placebo for six months; all participants also received eight sessions of brief counseling (Mason, Goodman, et al., 2006). Outcomes reported at six months by gender were percentage of days abstinent, percentage of no heavy-drinking days, rates of continuous abstinence and rates of no heavy drinking (Mason and Lehert, 2012). Mason’s comparison of the effects of standard-dose acamprosate found that although the effects on percentage of days abstinent and percentage of no heavy-drinking days were not significant in either men or women, men had a significantly more beneficial response than did women for those two outcomes. However, women exceeded men in rates of continuous abstinence and rates of no heavy drinking (Mason, Goodman, et al., 2006).

**Men-Only Studies**

Oslin and colleagues randomized 44 older men with AUD to varying doses of naltrexone (three times per week for 12 weeks, with higher doses on Fridays, under the assumption that risk for drinking was higher on the weekend) or to a placebo (Oslin et al., 1997). At the end of the 12 weeks, they assessed abstinence rates (rates of relapse when challenged) and Addiction Severity Index scores. In addition, they assessed group attendance and number of weeks of participation as indexes of adherence, and they assessed adverse events. The study reported no difference in abstinence/relapse rates or Addiction Severity Index scores between the treated group and the placebo group at the end of 12 weeks.

Friedmann and colleagues randomized seven homeless men with AUD to extended-release (intramuscular) naltrexone or to oral naltrexone (Friedmann et al., 2013). Among the intramuscular group, all but one dropped out prior to receiving the second treatment. Thus, the authors reported only the following qualitative finding: “Although XR-NTX [extended-release naltrexone] has demonstrated efficacy in reducing heavy drinking, limited acceptance of the injection might reduce its effectiveness among homeless, alcohol-dependent patients” (Friedmann et al., 2013, p. 94).

Trevisan and colleagues randomized 38 male veterans (mean age 47) with AUD who had just stopped drinking to receive daily gabapentin (1200 mg) or placebo. After four weeks, the authors assessed heavy-drinking days (30-day walkback), number of drinking days, Obsessive Compulsive Drinking Scale score, percentage of heavy-drinking days, and adverse events (Trevisan et al., 2008). The gabapentin group showed no improvement over that of the placebo group in the following outcomes: heavy-drinking days (30-day walkback) (SMD = –0.26; CI = –0.90, 0.38), number of drinking days (SMD = –0.20; CI = –0.84, 0.44), Obsessive Compulsive...
Drinking Scale score (SMD –0.27; CI –0.91, 0.37), and percentage of heavy-drinking days (SMD –0.26; CI –0.90, 0.38).

Psychosocial Interventions

Studies of Men and Women

Project MATCH was a multisite intervention that randomized more than 1,500 adults with AUD to one of three 12-week behavioral interventions—CBT, motivational enhancement therapy (MET), or 12-step facilitation—and assessed the effects on percentage of drinking days at 12 months. The participant population represented two groups: One had recently completed an outpatient treatment program, and the other was in an aftercare program that followed a more intensive inpatient program. The aim of the project was to identify factors that would predict which characteristics, if any, would predict greater effectiveness for one or the other treatments. No differences were reported in the effectiveness of any of the three treatments. A post hoc analysis assessed the role of gender and other factors in predicting the effectiveness of MET compared with the other treatments (Witkiewitz, Hartzler, and Donovan, 2010). They found that among participants who had been treated in an outpatient setting prior to joining the study, MET was more effective than CBT for both men and women who showed lower motivation to stop drinking. However, in a subgroup of participants recruited from an aftercare program following a more intensive therapy program, MET was less effective than CBT for men who drank more heavily or had lower motivation, a difference not seen for women.

Fals-Stewart and colleagues randomized 100 gay and lesbian individuals (52 men, 48 women) with AUD and their non–substance-abusing partner to interventions consisting of behavioral couples therapy (BCT) plus individual-based therapy (IBT) or IBT alone in two separate but parallel trials (Fals-Stewart, O’Farrell and Lam, 2009). Each intervention consisted of 32 sessions over 20 weeks. Percentage of heavy-drinking days was assessed using timeline followback interviews every three months up to one year from baseline. Participants in couples randomized to BCT showed greater improvement than those in the IBT condition. No significant difference in outcomes was seen between gay and lesbian participants (DiffDiff –0.05; CI –0.17, 0.08). No RCTs have compared outcomes between heterosexual couples in which male partners had AUD with those in which the female partners had AUD.

The Network Support Trial (Litt, Kadden, and Tennen, 2015) randomized 210 adults with AUD (122 men, 88 women) to one of three 12-week outpatient treatment interventions: network support, network support plus contingency management, or a control condition referred to as case management. This approach was based on the hypothesis that altering close social support networks to provide greater support of sobriety would improve drinking outcomes and that the effect would be greater in women than in men. Proportion of days abstinent, proportion of heavy-drinking days, drinks per drinking day, and abstinence were assessed over 27 months from baseline using the Form 90 structured interview. A structured interview was also used to assess network support. The study found that men who received the network support intervention, with
or without contingency management, had significantly better outcomes than women (compared with the control condition) for proportion of days abstinent (for men, Diff of Diff was –1.20 and CI was –1.37, –1.03; for women, Diff of Diff was –0.71 and CI was –0.88, –0.54); abstinence (Diff of Diff 0.34; CI 0.06, 0.62); drinks per drinking day (Diff of Diff 0.29; CI 0.02, 0.57); and proportion of heavy-drinking days (this outcome was not significant). Women in the active interventions tended to do worse than men in those interventions and worse than women in the control group throughout the 24 months of follow-up.

McKay and colleagues conducted an 18-month RCT that randomized participants with AUD (162 men, 90 women; 49 percent also reported use of cocaine) in two intensive outpatient programs to receive a continuing care intervention that consisted of telephone-based treatment monitoring and feedback only (TM), TM plus counseling (TMC), or treatment as usual only (TAU) (McKay, Van Horn, Oslin, Ivey, et al., 2011; Lynch et al., 2010). The outcomes for percentage of days drinking, any heavy drinking, and a composite called “good clinical outcome” were assessed every three months through 24 months (six months after the end of the intervention). The percentage of participants for whom follow-up information was obtained was also tracked. Gender showed a significant moderating effect on percentage of days drinking and the composite “good clinical outcome”: Women in both a TM group (percentage of days drinking Diff of Diff was 0.67 and CI was 0.50, 0.85; good clinical outcome ROR was 3.64 and CI was 1.92, 6.90) and TMC group (good clinical outcome ROR was 1.28; CI was 0.65, 2.52) had a significantly lower percentage of drinking days. They also had higher clinical outcome scores than those in the TAU group, whereas neither treatment resulted in a lower percentage of drinking days or improved clinical outcomes among men. TMC also appeared to reduce heavy drinking among women but not men compared with TAU, but the difference was not significant (ROR 1.28; CI 0.65, 2.52). At 24 months, differences from TAU were no longer significantly different within or across genders.

Brown and colleagues randomized 897 non–treatment-seeking individuals with AUD (400 men, 497 women) in 18 primary care clinics to a six-session (three-month) RCT that compared the effects of telephone/mail-based motivational interviewing counseling sessions with those of a passive intervention (a pamphlet on healthy lifestyles) on risky drinking days at the end of the intervention (Brown et al., 2007). At a three-month follow-up, men with alcohol abuse or dependence showed significantly greater benefits from the intervention than did women.

Wiprovnik, Kuerbis, and Morgenstern conducted a secondary analysis of an RCT in which 59 men and women with AUD were randomized to receive a brief (four-week) motivational interviewing intervention or a “spirit only” control intervention. The aim of this analysis was to assess the moderating effect of the patient-therapist bond on treatment efficacy. The primary outcome was mean number of drinks per week. Adherence was not assessed. No significant gender differences were seen in the response to treatment (Wiprovnik, Kuerbis, and Morgenstern, 2015). Witkiewitz, Hartzler, and Donovan conducted a post hoc analysis of data from Project MATCH to assess whether particular factors moderated the effectiveness of MET compared with other treatments (Witkiewitz, Hartzler, and Donovan, 2010). They found that,
among participants who had been treated in an outpatient setting prior to joining the study, MET was more effective than CBT for both men and women who showed lower motivation to stop drinking. However, in a subgroup of participants recruited from an aftercare program following a more intensive therapy program, MET was less effective than CBT for men who drank more heavily or had lower motivation, a difference not seen for women.

Walker and colleagues conducted a study in which 242 U.S. Army personnel (8 percent female) who met criteria for AUD set by the 4th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) but who were not seeking treatment were randomized to a single telephone-based motivational interviewing plus feedback session or to a psychoeducational session (Walker et al., 2017). Efficacy was assessed at six months as the percentage of days of abstinence and percentage of heavy-drinking days. Although they did not assess efficacy by gender, they provided individual participant data by gender. Based on these data, the intervention significantly increased abstinence and decreased heavy-drinking days, and the effect was greater in women than in men.

**Men-Only Studies**

In a study conducted at a VA outpatient clinic in the 1980s, Davis and colleagues randomized 105 male veterans to 26 weeks of “standard” AUD treatment—nonmanualized group therapy and encouragement to participate in a 12-step program—or to minimal treatment that consisted of viewing a series of 13 weekly films on drinking cessation (Davis et al., 2002). To assess efficacy, they measured the percentage of days abstinent, ounces consumed per day, percentage of those who drank, and likelihood of a good clinical response. Adherence was assessed as average length of attendance. Attendance at Alcoholics Anonymous (AA) also was assessed. The authors found that veterans randomized to standard outpatient alcoholism treatment had significantly longer periods of sobriety than did those who received no treatment (SMD –0.48; CI –0.93, –0.02) but that they showed no differences in ounces consumed per drinking day, percentage of days drinking, or likelihood of achieving complete abstinence (Davis et al., 2002). They also found that men in the intervention group were significantly more likely to attend AA meetings (SMD –0.65; CI –1.11, –0.19), an indication of adherence.

O’Farrell and colleagues conducted an RCT to assess the impact of adding relapse prevention (RP) to a six-month behavioral marriage therapy (BMT) program (O’Farrell, Choquette, and Cutter, 1998). They randomized 59 heterosexual couples (male partners diagnosed with AUD and nondrinking partners) who had just completed BMT to 15 sessions of a couples RP program over 12 months or to no further treatment. At 30 months, the authors assessed the percentage of days abstinent and use of an Antabuse® contract. Adherence was not assessed. They found no significant difference between the two treatments in the percentage of days abstinent (SMD –0.08; CI –0.60, 0.43), or in an index of adherence, use of an Antabuse contract with one’s partner. The authors compared the effects of couples RP following BCT for AUD with that of couples therapy alone among couples in which the males had AUD (O’Farrell, Choquette and Cutter, 1998). This was the first U.S. AUD behavioral couples therapy trial to consist of only
male patients (the earlier trials had included both male and female patients but did not assess
gender differences).

McCrady, Epstein, and Hirsch conducted an RCT to assess the impact of adding one of two
maintenance-enhancing therapies to alcohol BCT (ABCT) compared with ABCT alone without
maintenance enhancement. They randomized 90 men and their non-AUD female partners to RP
plus ABCT, to AA facilitation sessions plus ABCT, or to ABCT alone. Treatment consisted of
15 90–minute weekly sessions. The RP group also received four booster sessions over the course
of the year following treatment. Outcomes of the percentage of abstinent days and percentage of
heavy-drinking days were assessed at six months after treatment. In addition, the authors
assessed compliance as the average number of treatment sessions, patient AA attendance
(percentage of any AA attendance or attending more than ten sessions of AA) and spouse Alanon
attendance. No significant differences were seen across treatment groups (McCrady, Epstein, and
Hirsch, 1999).

Fals-Stewart and Birchler randomized 48 heterosexual men with AUD and their non-AUD
partners to 20-week manualized BCT programs (including 12 sessions of BCT combined with
12 sessions of individual cognitive behavioral therapy sessions) led by counselors with a
bachelor’s degree or a master’s degree to assess the role of professional training in treatment
outcomes. They used the Time Line Follow Back method to assess the percentage of days
abstinent between the groups counseled by master’s-level counselors and those counseled by
bachelors’-level counselors (Fals-Stewart and Birchler, 2002). They found no difference in
percentage of days abstinent between the groups.

A subsequent study by Fals-Stewart and another group randomized 100 heterosexual men
with AUD and their non-AUD partners to one of four treatment groups: a brief form of couples
therapy called brief relationship therapy (BRT), standard BCT (S-BCT), IBT, or an educational
control condition. At the end of treatment and at a 12-month follow-up, the authors assessed the
percentage of heavy-drinking days and time to response (Fals-Stewart, Klostermann, et al.,
2005). The percentage of heavy-drinking days in the BRT and S-BCT groups was decreased
compared with that of participants in control groups (SMD –0.73; CI –1.30, –0.16). Participants
in the BRT group responded more quickly to treatment than did those in the S-BCT group, and at
the 12-month follow-up, BRT and S-BCT participants still showed significantly better responses
than did the IBT group (Fals-Stewart, Klostermann, et al., 2005).

Morgenstern and colleagues randomized 89 men who were sleeping with other men to one of
two behavioral interventions for treating AUD: 12 sessions of motivational interviewing (MI)
combined with CBT or four sessions of MI alone (Morgenstern et al., 2007). The outcome was
mean number of drinks per day. They found no difference in the percentage of days abstinent
between a group assigned to MI alone and a group assigned to MI combined with CBT (SMD
0.14; CI –0.31, 0.59) (Morgenstern et al., 2007). Adherence was not assessed.
**Women-Only Studies**

Fals-Stewart, Birchler, and Kelley randomized 159 couples made up of women with AUD and their non-AUD male partners to one of three interventions: 12 sessions of BCT plus 20 sessions of IBT, 32 sessions of IBT alone, or a control educational condition called *PACT*, all manualized (Fals-Stewart, Birchler, and Kelley, 2006). Each intervention was conducted over six months and participants were followed for one year after treatment. Percentage of days abstinent was assessed using the Time Line Follow Back method, and adherence was assessed as number of sessions attended. BCT had a significantly greater effect on the percentage of days abstinent than did individual therapy when compared with the passive treatment condition (BCT had an SMD of $-0.66$ and a CI of $-1.08$, $-0.24$ compared with SMD 0.09; CI $-0.32$, 0.50). The couples therapy participants also had significantly greater participation in treatments and groups than did the individual group, compared with the control.

McCrady and colleagues also compared the efficacy of an ABCT program with that of alcohol-based IBT (ABIT) for women in heterosexual couples (McCrady, Epstein, Cook, et al., 2009). They randomized 102 women to one of the two programs and assessed percentage of days abstinent and percentage of days of heavy drinking at the end of the six-month program and over 12 months of follow-up. They found nonsignificantly greater improvement in the percentage of days abstinent and the percentage of heavy-drinking days in the couples group compared with the individual groups (McCrady, Epstein, Cook, et al., 2009).

In a later study, McCrady and colleagues randomized 59 heterosexual women in couples to the ABCT treatment (12 conjoint sessions) or to a blended intervention consisting of five conjoint sessions and seven individual sessions (blended ABCT) (McCrady, Epstein, Hallgren, et al., 2016). They assessed percentage of days abstinent and percentage of days of heavy drinking at the end of the six-month program and over 12 months of follow-up. They found no significant difference in the percentage of drinking days or heavy-drinking days between groups (McCrady, Epstein, Hallgren, et al., 2016).

Schumm and colleagues also compared couples and individual therapy, randomizing 105 heterosexual women with AUD and their non-AUD male partners to 26 sessions of BCT plus IBT or IBT alone over 20 weeks using the manual developed by Fals-Stewart and O’Farrell (Schumm et al., 2014). Primary outcomes were the percentage of days abstinent over the course of treatment and a one-year follow-up (as well as a series of relationship-related outcomes); adherence was assessed by attendance. The study found no significant difference in the percentage of days abstinent over a one-year follow-up (Schumm et al., 2014).
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Participants</th>
<th>Intervention Treatment</th>
<th>Outcome Results (Men)</th>
<th>Outcome Results (Women)</th>
<th>Outcome Results (Gender Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anton, O’Malley, et al., 2006</td>
<td>N per treatment arm: 1,383</td>
<td>6 active interventions, 16 weeks each:</td>
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<tr>
<td>COMBINE</td>
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<td>Medication management alone:</td>
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<tr>
<td>Main Study</td>
<td></td>
<td>(a) acamprosate (3g/d);</td>
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<td></td>
<td></td>
<td>(b) naltrexone (25mg–100mg/d);</td>
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<td></td>
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<td>(c) acamprosate + naltrexone;</td>
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<td>Combined Behavioral Intervention</td>
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<td>(d) CBI + acamprosate;</td>
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<td>(e) CBI + naltrexone;</td>
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<td>(f) CBI + acamprosate + naltrexone</td>
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<tr>
<td>Study year:</td>
<td>Gender female (% per arm):</td>
<td>Outcome measure: Symptom improvement</td>
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<tr>
<td>2001–2004</td>
<td>32.7% (for placebo group, reported by arm)</td>
<td>Outcome: Response to any treatment</td>
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<tr>
<td>Treatment setting:</td>
<td>Marital status:</td>
<td>Combination of naltrexone, acamprosate, or both; with or without CBI vs. CBI only</td>
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<tr>
<td>Outpatient</td>
<td>44% (placebo group)</td>
<td>(“sex did not significantly affect response to any of the treatments”)</td>
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<td>Number of sites:</td>
<td>Educational attainment:</td>
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<td>11</td>
<td>NR (29% had less than or no more than high school education with no mention of the percentage attaining a college degree or higher)</td>
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<td></td>
<td>% veterans: NR</td>
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<td>Inclusion criteria: Alcohol dependence, determined by DSM-IV criteria, using the Structured Clinical Interview for DSM-IV; 4 to 21 days of abstinence; more than 14 drinks (women) or 21 drinks (men) per week, with at least 2 heavy-drinking days (defined as 4 drinks/day for women and 5 drinks/day for men) during a consecutive 30-day period within the 90 days prior to baseline evaluation</td>
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<td>Therapist training:</td>
<td>Other medical management:</td>
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<tr>
<td></td>
<td>Other pharmacologic intervention:</td>
<td>Licensed health care professional</td>
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<td></td>
<td>Combined behavioral intervention:</td>
<td>Combined behavioral health specialists</td>
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<td></td>
<td>Allowance for/use of adjunctive</td>
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<tr>
<td>treatments:</td>
<td>NR</td>
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<td></td>
<td>Setting: Outpatient treatment</td>
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<td></td>
<td>Duration/frequency: CBI: Up to twenty 50-minute sessions over 16 weeks</td>
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<td></td>
<td>Comparator category:</td>
<td>Other pharmacologic intervention:</td>
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<tr>
<td></td>
<td>Acamprosate, placebo</td>
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<tr>
<td>Study Details</td>
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<td>Exclusion criteria: History of other substance abuse (other than nicotine or cannabis) by DSM-IV criteria in the last 90 days (6 months for opiate abuse) or by urine drug screen, psychiatric disorder requiring medication, unstable medical conditions (e.g., serum liver enzyme levels 3 times the upper limit of normal)</td>
<td>Other behavioral intervention: None</td>
<td>Comparator description: Medical management control: Placebo, CBI + medical management control, CBI alone</td>
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<td>Comparator description: Insufficient power</td>
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<td>Follow-up time: 16 weeks</td>
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<td>Capone et al., 2011 COMBINE Reanalysis</td>
<td>N per treatment arm: 603 (subsample of 1,383)</td>
<td>Naltrexone and/or acamprosate plus medical management</td>
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<td>Parent publications or associations: Anton, O'Malley, et al., 2006</td>
<td>Mean age in years (standard deviation): 44.2 (10.2)</td>
<td>Description of intervention: Pharmacologic and behavioral</td>
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<td>Gender female (% per arm): 31%</td>
<td>Treatment protocol fidelity: Authors cite treatment manual or other source that dictates treatment protocol</td>
<td>Therapist training: Medical doctor (MD)</td>
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<tr>
<td>Marital status: NR</td>
<td>Allowance for/use of adjunctive treatments: Other: Reported in Anton, O'Malley, et al., 2006</td>
<td>Setting: Outpatient treatment</td>
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<tr>
<td>Educational attainment: NR</td>
<td>Duration/frequency: 16 weeks</td>
<td>Comparator category: Other pharmacologic intervention: Placebo Other behavioral intervention: Medical management</td>
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<td>% veterans: NR</td>
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<tr>
<td>Inclusion criteria: NR</td>
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<tr>
<td>Exclusion criteria: NR</td>
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<tr>
<td>Greenfield et al., 2010 COMBINE Reanalysis</td>
<td>Mean age in years (standard deviation), by gender: 44.9 (9.7) (Women) 44.1 (10.4) (Men)</td>
<td>N per treatment arm: Total: 1,226 (an additional 157 received behavioral intervention only and are excluded from this analysis) Gender female (% per arm): 27% Marital status (by gender): 42% (women) 42% (men) Educational attainment, by gender: With college degree or higher 79% (women) 67% (men) % veterans: NR</td>
<td>Comparator description: Placebo plus medical management Description of intervention: Pharmacologic and behavioral Treatment protocol fidelity: Authors say that the treatment is (loosely) based on particular methods Therapist training: MD Allowance for/usage of adjunctive treatments: Participants are required to withdraw/abstain from previous form of therapy Setting: Outpatient treatment Duration/frequency: Medical management: 9 sessions CBI: Up to 20 sessions Medication: daily All: 16 weeks Comparator category: Placebo Other pharmacologic intervention: Compares acamprosate to naltrexone Comparator description: See Anton, O’Malley, et al., 2006</td>
<td>Outcome measure: Symptom improvement Outcome: Craving naltrexone vs. placebo SMD: –0.25 (95% CI: –0.44, –0.06) Outcome: Percentage of abstinent days naltrexone vs. placebo SMD: –0.42 (95% CI: –0.62, –0.23) Outcome: Percentage of heavy-drinking days naltrexone vs. placebo SMD: –0.30 (95% CI: –0.50, –0.11) Outcome: Probability of good clinical response naltrexone vs. placebo SMD: –0.63 (95% CI: –0.82, –0.43) Outcome: Time to first heavy-drinking day naltrexone vs. placebo HR: 0.80 (95% CI: 0.61, 0.99) Outcome: Percentage of abstinent days naltrexone/CBI vs. placebo SMD: –0.07 (95% CI: –0.26, 0.12)</td>
<td>Outcome measure: Symptom improvement Outcome: Craving naltrexone vs. placebo SMD: –0.16 (95% CI: –0.44, 0.13) Outcome: Percentage of abstinent days naltrexone vs. placebo SMD: –0.47 (95% CI: –0.76, –0.18) Outcome: Percentage of heavy-drinking days naltrexone vs. placebo SMD: –0.70 (95% CI: –1.00, –0.41) Outcome: Probability of good clinical response naltrexone vs. placebo SMD: –0.70 (95% CI: –1.00, –0.41) Outcome: Time to first heavy-drinking day naltrexone vs. placebo RHR: 1.19 (95% CI: 0.93, 1.53)</td>
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<tr>
<td>Study Details</td>
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<td>Outcome Results (Men)</td>
<td>Outcome Results (Women)</td>
<td>Outcome Results (Gender Effects)</td>
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<td>Outcome: Percentage of heavy-drinking days naltrexone/CBI vs. placebo SMD: −0.11 (95% CI: −0.30, 0.08)</td>
<td>Outcome: Percentage of heavy-drinking days naltrexone/CBI vs. placebo SMD: −0.44 (95% CI: −0.73, −0.16)</td>
<td>Outcome: Percentage of heavy-drinking days naltrexone/CBI vs. placebo DiffDif: 0.34 (95% CI: 0.28, 0.40)</td>
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<tr>
<td>Exclusion criteria: Meeting DSM-IV criteria for bipolar disorder, schizophrenia, or any other psychiatric disorder for which the individual required current medications; opioid dependence or abuse within six months prior to baseline; current dependence on any drug except marijuana or nicotine; more than seven days of inpatient treatment for a substance use disorder in the 30 days prior to randomization; planned continued participation in any pre-occurring alcohol treatment during the treatment phase of the study; abstinence from alcohol for more than 21 consecutive days prior to randomization</td>
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<td>Outcome: Probability of good clinical response naltrexone/CBI vs. placebo SMD: −0.47 (95% CI: −0.66, −0.28)</td>
<td>Outcome: Probability of good clinical response naltrexone/CBI vs. placebo SMD: −0.73 (95% CI: −1.02, −0.44)</td>
<td>Outcome: Probability of good clinical response naltrexone/CBI vs. placebo DiffDif: 0.26 (95% CI: 0.20, 0.32)</td>
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<td>Outcome: Time to first heavy-drinking day naltrexone/CBI vs. placebo HR: 0.95 (95% CI: 0.70, 1.20)</td>
<td>Outcome: Time to first heavy-drinking day naltrexone/CBI vs. placebo HR: 0.85 (95% CI: 0.58, 1.12)</td>
<td>Outcome: Time to first heavy-drinking day naltrexone/CBI vs. placebo RHR: 1.12 (95% CI: 0.90, 1.39)</td>
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<td>Outcome: Percentage of abstinent days placebo/CBI vs. placebo SMD: −0.13 (95% CI: −0.32, 0.06)</td>
<td>Outcome: Percentage of abstinent days placebo/CBI vs. placebo SMD: −0.54 (95% CI: −0.83, −0.26)</td>
<td>Outcome: Percentage of abstinent days placebo/CBI vs. placebo DiffDif: 0.41 (95% CI: 0.35, 0.47)</td>
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<td>Outcome: Percentage of heavy-drinking days placebo/CBI vs. placebo SMD: −0.21 (95% CI: −0.40, −0.02)</td>
<td>Outcome: Percentage of heavy-drinking days placebo/CBI vs. placebo SMD: −0.70 (95% CI: −1.00, −0.41)</td>
<td>Outcome: Percentage of heavy-drinking days placebo/CBI vs. placebo DiffDif: 0.49 (95% CI: 0.43, 0.56)</td>
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<td>Outcome: Probability of good clinical response placebo/CBI vs. placebo SMD: −0.39 (95% CI: −0.58, −0.20)</td>
<td>Outcome: Probability of good clinical response placebo/CBI vs. placebo SMD: −0.94 (95% CI: −1.24, −0.64)</td>
<td>Outcome: Probability of good clinical response placebo/CBI vs. placebo DiffDif: 0.55 (95% CI: 0.48, 0.61)</td>
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<td>Outcome: Time to first heavy-drinking day placebo/CBI vs. placebo RHR: 1.00 (95% CI: 0.80, 1.25)</td>
<td></td>
<td>Outcome: Time to first heavy-drinking day placebo/CBI vs. placebo RHR: 1.00 (95% CI: 0.80, 1.25)</td>
</tr>
</tbody>
</table>
### Study Details

<table>
<thead>
<tr>
<th>Participants</th>
<th>Intervention Treatment</th>
<th>Outcome Results (Men)</th>
<th>Outcome Results (Women)</th>
<th>Outcome Results (Gender Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N per treatment arm:</td>
<td>Four conditions ($N = 594$) involved a maximum of 9 brief medication management appointments and either active naltrexone and acamprosate, naltrexone and placebo, acamprosate and placebo, or double placebo.</td>
<td>Outcome: Time to first heavy-drinking day placebo/CBI vs. placebo HR: $0.87$ (95% CI: 0.65, 1.09)</td>
<td>Outcome: Time to first heavy-drinking day placebo/CBI vs. placebo HR: $0.87$ (95% CI: 0.58, 1.16)</td>
<td>Adherence/compliance: Treatment adherence Outcome: Dropout rate naltrexone, naltrexone/CBI, placebo/CBI vs. placebo (“There were no gender differences in study dropout [$p = 0.73$], incomplete drinking data [$p = 0.753$], missing CBI therapy sessions [$p = 0.91$], or stopping or missing medication management sessions [$p &gt; 0.5$]. There was a trend for more men than women who received CBI to stop attending CBI sessions prematurely [24.6% vs. 19.6%; $p = 0.126$]. Medication adherence assessed as percentage of pills taken versus returned, did not differ between male and female subjects [$p = 0.70$].”)</td>
</tr>
</tbody>
</table>

*Worley et al., 2015*  
**COMBINE**

<table>
<thead>
<tr>
<th>Parent publications or associations:</th>
<th>Description of intervention: Pharmacologic and behavioral</th>
<th>Outcome measure: Symptom improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medication management alone:</td>
<td>Treatment protocol fidelity: Authors cite a treatment manual or other source that dictates the treatment protocol</td>
<td></td>
</tr>
<tr>
<td>Medication management plus CBI:</td>
<td>Therapist training: MD</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender female (% per arm):</th>
<th>Marital status: 42% married</th>
</tr>
</thead>
<tbody>
<tr>
<td>29%</td>
<td>NR</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Further publications:</th>
<th>Medication management alone:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anton, O’Malley, et al., 2006</td>
<td>Medication management plus CBI:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Mean age in years (standard deviation):</th>
<th>44.2 (9)</th>
</tr>
</thead>
</table>

| Educational attainment: NR |
|---------------------------|---------|

**Outcome measure:** Percentage of heavy-drinking days Combination of medical management and naltrexone, acamprosate, both, with or without CBI vs. CBI only ("The preliminary covariate model indicated that linear time, quadratic time, marital status, and baseline craving were significant predictors of within-treatment percentage of heavy drinking days, while age, gender, and alcohol dependence severity were not.")
### Study Details

<table>
<thead>
<tr>
<th>Participants</th>
<th>Intervention Treatment</th>
<th>Outcome Results (Men)</th>
<th>Outcome Results (Women)</th>
<th>Outcome Results (Gender Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% veterans: NR</td>
<td>Allowance for/use of adjunct treatments: NR</td>
<td>Symptom improvement</td>
<td>Symptom improvement</td>
<td>Symptom improvement</td>
</tr>
<tr>
<td>Inclusion criteria: DSM-IV diagnosis of alcohol dependence, a period of 4 to 21 days of abstinence prior to the baseline assessment, frequent drinking (&gt;14 drinks per week for women, &gt;21 drinks per week for men), and occurrence of at least 2 heavy-drinking days in a 30-day period during the previous 90 days</td>
<td>Setting: Outpatient treatment setting</td>
<td>Days to first drink naltrexone vs. placebo SMD: −1.30 (95% CI: −1.65, −0.95)</td>
<td>Days to first drink naltrexone vs. placebo SMD: −0.46 (95% CI: −0.98, 0.07)</td>
<td>Days to first drink naltrexone vs. placebo SMD: −0.84 (95% CI: −0.99, −0.69)</td>
</tr>
<tr>
<td>Exclusion criteria: current (i.e., past 90 days) abuse or dependence on other drugs, unstable medical problems, current psychiatric disorders requiring medication</td>
<td>Duration/frequency: 16 weeks</td>
<td>Percentage of heavy-drinking days naltrexone vs. placebo SMD: −0.27 (95% CI: −0.59, 0.04)</td>
<td>Percentage of heavy-drinking days naltrexone vs. placebo SMD: −0.25 (95% CI: −0.77, 0.27)</td>
<td>Percentage of heavy-drinking days naltrexone vs. placebo SMD: −0.02 (95% CI: −0.17, 0.13)</td>
</tr>
<tr>
<td>Comparator category: Other behavioral intervention: CBI</td>
<td>Comparator description: Four conditions (N = 603) involved medical management and the same 4 combinations of pharmacotherapy with an adjunct CBI, which involved up to 20 sessions integrating CBT, motivational enhancement, and support system involvement.</td>
<td>Outcome measure: Days to first drink naltrexone vs. placebo SMD: −0.84 (95% CI: −0.99, −0.69)</td>
<td>Outcome: Percentage of heavy-drinking days naltrexone vs. placebo SMD: −0.25 (95% CI: −0.77, 0.27)</td>
<td>Outcome: Percentage of heavy-drinking days naltrexone vs. placebo SMD: −0.02 (95% CI: −0.17, 0.13)</td>
</tr>
<tr>
<td>Power calculation: Other power calculation</td>
<td>Follow-up time: 68 weeks</td>
<td>Outcome measure: Days to first drink naltrexone vs. placebo SMD: −0.46 (95% CI: −0.98, 0.07)</td>
<td>Outcome: Percentage of heavy-drinking days naltrexone vs. placebo SMD: −0.25 (95% CI: −0.77, 0.27)</td>
<td>Outcome: Percentage of heavy-drinking days naltrexone vs. placebo SMD: −0.02 (95% CI: −0.17, 0.13)</td>
</tr>
</tbody>
</table>

### Study Year

<table>
<thead>
<tr>
<th>Study year: NR</th>
<th>N per treatment arm:</th>
<th>Outcome measure:</th>
<th>Outcome measure:</th>
<th>Outcome measure:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baros, Latham, and Anton, 2008; Anton, Moak, Latham, et al., 2005; Anton, Moak, Waid, et al., 1999</td>
<td>Arm 1: 104</td>
<td>Symptom improvement</td>
<td>Symptom improvement</td>
<td>Symptom improvement</td>
</tr>
<tr>
<td>Arm 2: 107</td>
<td>Arm 1: CBT (manualized) + placebo</td>
<td>Days to first drink naltrexone vs. placebo SMD: −1.30 (95% CI: −1.65, −0.95)</td>
<td>Days to first drink naltrexone vs. placebo SMD: −0.46 (95% CI: −0.98, 0.07)</td>
<td>Days to first drink naltrexone vs. placebo SMD: −0.84 (95% CI: −0.99, −0.69)</td>
</tr>
<tr>
<td>Mean age in years (standard deviation), by gender: For placebo groups</td>
<td>Arm 2: CBT + naltrexone (50mg/d)</td>
<td>Percentage of heavy-drinking days naltrexone vs. placebo SMD: −0.27 (95% CI: −0.59, 0.04)</td>
<td>Percentage of heavy-drinking days naltrexone vs. placebo SMD: −0.25 (95% CI: −0.77, 0.27)</td>
<td>Percentage of heavy-drinking days naltrexone vs. placebo SMD: −0.02 (95% CI: −0.17, 0.13)</td>
</tr>
<tr>
<td>Gender female (% per arm): 27%</td>
<td>Description of intervention: Pharmacologic and behavioral</td>
<td>Outcome: Days to first drink naltrexone vs. placebo SMD: −0.46 (95% CI: −0.98, 0.07)</td>
<td>Outcome: Percentage of heavy-drinking days naltrexone vs. placebo SMD: −0.25 (95% CI: −0.77, 0.27)</td>
<td>Outcome: Percentage of heavy-drinking days naltrexone vs. placebo SMD: −0.02 (95% CI: −0.17, 0.13)</td>
</tr>
<tr>
<td>Study year: NR</td>
<td>Treatment protocol fidelity: Authors cite a treatment manual or other source that dictates the treatment protocol</td>
<td>Therapist training: NR</td>
<td>Therapist training: NR</td>
<td>Therapist training: NR</td>
</tr>
<tr>
<td>Marital status (by gender): 42% (women) 47% (men)</td>
<td>Therapist training: NR</td>
<td>Therapist training: NR</td>
<td>Therapist training: NR</td>
<td>Therapist training: NR</td>
</tr>
<tr>
<td>Study Details</td>
<td>Participants</td>
<td>Intervention Treatment</td>
<td>Outcome Results (Men)</td>
<td>Outcome Results (Women)</td>
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<tr>
<td>---------------</td>
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</tr>
<tr>
<td>Treatment setting:</td>
<td>Educational attainment:</td>
<td>Allowance for/use of adjunct treatments:</td>
<td>Outcome: Total standard drinks</td>
<td>Outcome: Total standard drinks</td>
</tr>
<tr>
<td>Outpatient</td>
<td>NR</td>
<td>NR</td>
<td>naltrexone vs. placebo</td>
<td>naltrexone vs. placebo</td>
</tr>
<tr>
<td>Number of sites:</td>
<td>Inclusion criteria:</td>
<td>Setting: Outpatient treatment</td>
<td>SMD: -0.31</td>
<td>SMD: -0.38</td>
</tr>
<tr>
<td>1</td>
<td>Age 21–65, met the DSM-III R criteria for alcohol dependence, drank on average 5 standard drinking units per day in past 30 days, resided within 1 hour of clinic, had stable living situation and collateral, maintained sobriety for 5 days before randomization, no previous inpatient medicated detoxification</td>
<td>Duration/frequency: 12 sessions, 1 per week for 12 weeks Comparator category: Other pharmacologic intervention placebo Comparator description: CBT manualized, based on Project MATCH</td>
<td>Outcome: Drinks per drinking day naltrexone vs. placebo SMD: -0.22</td>
<td>Outcome: Drinks per drinking day naltrexone vs. placebo SMD: -0.56</td>
</tr>
<tr>
<td>Study #1</td>
<td>Power calculation: No</td>
<td>Adherence/compliance: Treatment adherence outcome: Completion rate naltrexone vs. placebo OR: 0.97</td>
<td>Outcome: Percentage of abstinence days naltrexone vs. placebo SMD: -0.37</td>
<td>Outcome: Percentage of abstinence days naltrexone vs. placebo SMD: -0.35</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% CI: -0.54, 0.10)</td>
<td>(95% CI: -0.69, -0.06)</td>
<td>(95% CI: -0.87, 0.17)</td>
</tr>
<tr>
<td>Study #2</td>
<td>Follow-up time: 12 weeks</td>
<td>Adherence/compliance: Treatment adherence outcome: Completion rate naltrexone vs. placebo OR: 0.44</td>
<td>Outcome: Compliance ratio naltrexone vs. placebo OR: 0.38</td>
<td>Outcome: Compliance ratio naltrexone vs. placebo OR: 0.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(95% CI: 0.44, 2.15)</td>
<td>(95% CI: 0.11, 1.29)</td>
<td>(95% CI: 0.11, 1.29)</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria:</td>
<td>Adverse events: Outcome: Decreased appetite naltrexone vs. placebo OR: 1.74</td>
<td>Adverse events: Outcome: Decreased appetite naltrexone vs. placebo OR: 1.74</td>
<td></td>
</tr>
<tr>
<td>Study #1</td>
<td>Other current drug abuse or dependence (including marijuana), ever abused opiates, current major psychiatric disorder, serious/unstable medical condition, current psychotropics or anti-seizure meds or disulfiram, pending legal charges except driving under the influence, liver function test alanine aminotransferase and aspartate aminotransferase &gt; 2.5 times normal</td>
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<tr>
<td>Study Details</td>
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<tr>
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</tr>
<tr>
<td>Study #2</td>
<td>Current abuse of other psychoactive substances except for marijuana and nicotine; ever abused opiates; current major psychiatric disorder; serious/unstable medical condition; current use of disulfiram, anti-seizure meds, or psychoactive medication use; pending legal charges for any violent crime, liver function test alanine aminotransferase and aspartate aminotransferase &gt; 2.5 times normal; use of an opiate antagonist in the month before; pregnant, nursing, or lacking reliable birth control</td>
<td>Description of intervention: Behavioral (individual)</td>
<td>Outcome: Falling asleep naltrexone vs. placebo OR: 0.97 (95% CI: 0.46, 2.04)</td>
<td>Outcome: Falling asleep naltrexone vs. placebo OR: 0.37 (95% CI: 0.12, 1.14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Outcome: Fatigue naltrexone vs. placebo OR: 1.02 (95% CI: 0.52, 2.03)</td>
<td>Outcome: Fatigue naltrexone vs. placebo OR: 1.66 (95% CI: 0.58, 4.74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Outcome: Headache naltrexone vs. placebo OR: 2.34 (95% CI: 1.11, 4.94)</td>
<td>Outcome: Headache naltrexone vs. placebo OR: 1.44 (95% CI: 0.50, 4.13)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Outcome: Nausea naltrexone vs. placebo OR: 1.25 (95% CI: 0.47, 3.36)</td>
<td>Outcome: Nausea naltrexone vs. placebo OR: 7.94 (95% CI: 1.57, 40.23)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Outcome: Sexual dysfunction naltrexone vs. placebo OR: 0.86 (95% CI: 0.44, 1.67)</td>
<td>Outcome: Sexual dysfunction naltrexone vs. placebo OR: 0.47 (95% CI: 0.14, 1.54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Outcome: Staying asleep naltrexone vs. placebo OR: 1.21 (95% CI: 0.62, 2.37)</td>
<td>Outcome: Staying asleep naltrexone vs. placebo OR: 0.18 (95% CI: 0.05, 0.61)</td>
</tr>
<tr>
<td>Brown et al., 2007</td>
<td>N per treatment arm: Arm 1: 452 Arm 2: 445</td>
<td>6 sessions of telephone-based weekly motivational interviewing</td>
<td>Outcome measure: Symptom improvement</td>
<td>Outcome measure: Symptom improvement</td>
</tr>
<tr>
<td>Study year: NR</td>
<td>Age range (years): N(%):</td>
<td>20 to 29 years old: 346 (39%) 30 to 39 years old: 272 (30%) 40 to 49 years old: 207 (23%) 50 to 59 years old: 70 (8%) Missing: 2 (0%—rounded)</td>
<td>Description of intervention: Behavioral (individual)</td>
<td>Treatment protocol fidelity: Authors say that the treatment is (loosely) based on particular methods</td>
</tr>
<tr>
<td>Study Details</td>
<td>Participants</td>
<td>Intervention Treatment</td>
<td>Outcome Results (Men)</td>
<td>Outcome Results (Women)</td>
</tr>
<tr>
<td>---------------</td>
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</tr>
<tr>
<td>Number of sites: 18</td>
<td>Gender female (% per arm): 55%</td>
<td>Therapist training: Addiction counselor</td>
<td>Outcome: Risky drinking days by subjects with alcohol abuse or dependence ASBIR services vs. pamphlet SMD: –0.35 (95% CI: –0.55, –0.15)</td>
<td>Outcome: Risky drinking days by subjects with alcohol abuse or dependence ASBIR services vs. pamphlet SMD: 0.04 (95% CI: –0.14, 0.21)</td>
</tr>
<tr>
<td>Marital status: N(%)</td>
<td>Allowance for/use of adjunctive treatments: NR</td>
<td>Setting: Outpatient treatment</td>
<td>Outcome: Risky drinking days by subjects with alcohol abuse or dependence ASBIR services vs. pamphlet SMD: –0.46 (95% CI: –0.77, –0.16)</td>
<td>Outcome: Risky drinking days by subjects with alcohol abuse or dependence ASBIR services vs. pamphlet SMD: 0.06 (95% CI: –0.19, 0.31)</td>
</tr>
<tr>
<td>Married: 396 (44%)</td>
<td></td>
<td>Duration/frequency: 6 sessions over 12 weeks</td>
<td>Outcome: Risky drinking days by subjects with alcohol abuse or dependence ASBIR services vs. pamphlet SMD: –0.21 (95% CI: –0.48, 0.05)</td>
<td>Outcome: Total consumption by subjects with alcohol abuse ASBIR services vs. pamphlet SMD: –0.07 (95% CI: –0.32, 0.18)</td>
</tr>
<tr>
<td>Single, never married: 377 (42%)</td>
<td>Comparator category: Other behavioral intervention: educational pamphlets</td>
<td>Comparator description: Educational materials sent by mail</td>
<td>Outcome: Total consumption by subjects with alcohol abuse or dependence ASBIR services vs. pamphlet SMD: –0.21 (95% CI: –0.41, –0.02)</td>
<td>Outcome: Total consumption by subjects with alcohol abuse or dependence ASBIR services vs. pamphlet SMD: 0.08 (95% CI: –0.09, 0.26)</td>
</tr>
<tr>
<td>Divorced, separated, widowed: 121 (13%)</td>
<td></td>
<td>Power calculation: Yes</td>
<td>Outcome: Total consumption by subjects with alcohol abuse or dependence ASBIR services vs. pamphlet SMD: 0.11 (95% CI: –0.14, 0.36)</td>
<td>Outcome: Total consumption by subjects with alcohol abuse or dependence ASBIR services vs. pamphlet SMD: 0.11 (95% CI: –0.14, 0.36)</td>
</tr>
<tr>
<td>Missing: 3 (0%—rounded)</td>
<td></td>
<td>Follow-up time: 12 weeks</td>
<td>Outcome: Total consumption by subjects with alcohol abuse or dependence ASBIR services vs. pamphlet SMD: –0.15 (95% CI: –0.44, 0.15)</td>
<td></td>
</tr>
<tr>
<td>Educational attainment: 50% with college degree or higher</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% veterans: NR</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Inclusion criteria: Between the ages of 21 and 59 years, able to speak English, not pregnant, not suicidal, no plans to move out of state, exceeded recommendations on low-risk drinking, met DSM-IV criteria for alcohol abuse or dependence, no alcohol treatment in the past 3 months.</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Exclusion criteria: Men consuming less than 56 standard drinks in 28 days, 4 standard drinks in any one day, or women consuming less than 44 drinks in 28 days or less than 3 drinks on any one day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Details</td>
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<td>Intervention Treatment</td>
<td>Outcome Results (Men)</td>
<td>Outcome Results (Women)</td>
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<tr>
<td>---------------</td>
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</tr>
<tr>
<td>Davis et al.,2002</td>
<td>N per treatment arm:</td>
<td>Arm 1 (minimal treatment): 40</td>
<td>Arm 2 (standard treatment): 49</td>
<td>Outcome measure:</td>
</tr>
<tr>
<td>Study year:</td>
<td></td>
<td>Mean age in years (standard deviation):</td>
<td></td>
<td>Symptom improvement</td>
</tr>
<tr>
<td>Treatment setting:</td>
<td></td>
<td>Gender Female (% per arm): 0</td>
<td></td>
<td>Standard treatment vs. minimum treatment (control)</td>
</tr>
<tr>
<td>Outpatient</td>
<td></td>
<td>Marital status:</td>
<td></td>
<td>Outcome: Complete abstinence</td>
</tr>
<tr>
<td>Number of sites: 1</td>
<td></td>
<td>Arm 1 (minimal treatment): 40.0%</td>
<td>Arm 2 (standard treatment): 43.7%</td>
<td>Standard treatment vs. minimum treatment (control)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Educational attainment:</td>
<td></td>
<td>Treatment protocol fidelity: The authors say that the treatment is (loosely) based on particular methods</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR</td>
<td>Therapist training: PhD psychologist</td>
<td>Outcome: Days drinking</td>
</tr>
<tr>
<td></td>
<td></td>
<td>% veterans: 100%</td>
<td>Allowance for/use of adjunctive treatments: NR</td>
<td>Standard treatment vs. minimum treatment (control)</td>
</tr>
<tr>
<td>Inclusion criteria: Male, alcohol dependent or abuser who had been drinking recently (but not on the days of the initial or group prescreening), had to have a collateral who could be contacted for a follow-up interview after 6 months, available to come for treatment one evening a week</td>
<td>Exclusion criteria: Drinking on the day of the screening, psychotic, used heroin within 1 year, or used cocaine within 6 months</td>
<td>Setting: Outpatient treatment</td>
<td>Duration/frequency: 6 months</td>
<td>Outcome: Length of sobriety</td>
</tr>
<tr>
<td></td>
<td>Comparator category: Other behavioral intervention: minimal treatment—weekly alcohol education movies</td>
<td>Comparator description: Arm 1 (minimal treatment): Weekly group alcoholism education movie, monthly group discussion with therapist</td>
<td>Adherence/compliance: Treatment adherence outcome: AA attendance</td>
<td>Standard treatment vs. minimum treatment (control)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Power calculation: Other power calculation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Details</td>
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<td>Intervention Treatment</td>
<td>Outcome Results (Men)</td>
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</tr>
<tr>
<td>Fals-Stewart and Birchler, 2002</td>
<td>N per treatment arm:</td>
<td>Arm 1 (BCT with master's-level counselor): 24</td>
<td>Arm 1: Individual CBT (20 sessions) plus BCT (12 sessions) with bachelor's level counselor over 12 weeks</td>
<td>Outcome: Average length of attendance</td>
</tr>
<tr>
<td>Study year:</td>
<td>Arm 2 (BCT with bachelor's-level counselor): 24</td>
<td>Arm 2: Individual CBT (20 sessions) plus BCT (12 sessions) with master's level counselor over 12 weeks</td>
<td>Standard treatment vs. minimum treatment (control) SMD: −0.13 (95% CI: −0.53, 0.27)</td>
<td></td>
</tr>
<tr>
<td>Treatment setting:</td>
<td>Study year: NR</td>
<td>Mean age in years (standard deviation):</td>
<td></td>
<td>Outcome: Percentage of abstinent days BCT with a bachelor's-level counselor vs. BCT with a master's-level counselor SMD: 0.08 (95% CI: −0.49, 0.65)</td>
</tr>
<tr>
<td>Outpatient</td>
<td>Treatment setting:</td>
<td>Arm 1 (BCT with master's-level counselor): 37.6 (5.8)</td>
<td>Description of intervention: Behavioral (individual)</td>
<td></td>
</tr>
<tr>
<td>Number of sites: 1</td>
<td>Number of sites: 1</td>
<td>Arm 2 (BCT with bachelor's-level counselor): 36.3 (4.4)</td>
<td>Treatment protocol fidelity: Authors cite a treatment manual or other source that dictates the treatment protocol</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gender Female (% per arm): 0</td>
<td>Gender Female (% per arm): 0</td>
<td>Therapist training: Other bachelor's- and master's-level counselors</td>
<td>Adherence/compliance: Treatment adherence</td>
</tr>
<tr>
<td></td>
<td>Marital status: Married: 100%</td>
<td>Marital status: Married: 100%</td>
<td>Allowance for/use of adjunctive treatments: Participants are required to withdraw/abstain from previous form of therapy</td>
<td>Outcome: BCT attendance</td>
</tr>
<tr>
<td></td>
<td>Educational attainment—years of education (standard deviation):</td>
<td></td>
<td>Setting: Outpatient treatment</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm 1: 12.7 (2.1)</td>
<td></td>
<td>Duration/frequency: 20 60-minute individual CBT sessions, plus 12 BCT sessions, over 20 weeks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm 2: 12.9 (1.9)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Details</td>
<td>Participants</td>
<td>Intervention Treatment</td>
<td>Outcome Results (Men)</td>
<td>Outcome Results (Women)</td>
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<tr>
<td>---------------</td>
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<tr>
<td>Exclusion criteria: Female partner met DSM-IV criteria for a psychoactive substance use disorder in the last 6 months or either partner met DSM-IV criteria for an organic mental disorder, schizophrenia, delusional (paranoid) disorder, or other psychotic disorder</td>
<td>Comparator category: Other behavioral intervention</td>
<td>Compares results from bachelor’s-level vs. master’s-level counselors</td>
<td>Power calculation: Yes</td>
<td>Follow-up time: 52 weeks</td>
</tr>
<tr>
<td>Fals-Stewart, Klostermann, et al., 2005</td>
<td>N per treatment arm:</td>
<td>BRT: 18 total sessions, 6 behaviorally oriented conjoint treatment sessions (active participation by the non–substance-abusing female partners, session content focused on improving communication and problem-solving skills and reinforcing sobriety through the use of abstinence contracting). 12 sessions of 12-step-oriented group counseling for male patients only.</td>
<td>Outcome measure: Symptom improvement</td>
<td>Outcome: Percentage of heavy-drinking days BRT vs. PACT SMD: –0.73 (95% CI: –1.30, –0.16)</td>
</tr>
<tr>
<td>Treatment setting:</td>
<td>Mean age in years (standard deviation), by gender:</td>
<td>Men, PACT: 36.23 (5.61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Outpatient</td>
<td></td>
<td>Women, PACT: 32.96 (5.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of sites: NR</td>
<td></td>
<td>Men, BRT: 34.91 (6.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, BRT: 31.32 (5.32)</td>
<td></td>
<td>S-BCT: 24 total sessions: 12 conjoint treatment sessions and 12 sessions of 12-step group counseling for patients only.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, S-BCT: 32.01 (5.94)</td>
<td></td>
<td>Description of intervention: behavioral (individual)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, IBT: 35.82 (5.00)</td>
<td></td>
<td>Gender female (% per arm): 0%—rounded</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, IBT: 33.82 (6.04)</td>
<td></td>
<td>Marital status: Married: 100%</td>
<td></td>
<td></td>
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<tr>
<td>Educational attainment—years of education (standard deviation), by gender:</td>
<td></td>
<td>Therapist training: addiction counselor</td>
<td></td>
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<tr>
<td>Men, PACT: 13.40 (1.86)</td>
<td></td>
<td>Allowance for/ use of adjunctive treatments: Participants are allowed to continue with other forms(s) of treatment (e.g., antidepressants, group therapy)</td>
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<tr>
<td>Men, BRT: 13.60 (1.52)</td>
<td></td>
<td>Setting: Outpatient treatment</td>
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<tr>
<td>Women, PACT: 13.21 (1.59)</td>
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<tr>
<td>Men, S-BCT: 13.04 (1.69)</td>
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<tr>
<td>Men, IBT: 13.17 (1.91)</td>
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<tr>
<td>Women, S-BCT: 13.96 (1.27)</td>
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<tr>
<td>Women, IBT: 14.07 (1.97)</td>
<td></td>
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<tr>
<td>Power calculation: Yes</td>
<td></td>
<td>Outcome: Percentage of heavy-drinking days IBT vs. PACT SMD: 0.04 (95% CI: –0.52, 0.59)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Outcome: Percentage of heavy-drinking days S-BCT vs. PACT SMD: –0.73 (95% CI: –1.30, –0.16)</td>
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<td></td>
<td></td>
<td>Treatment protocol fidelity: The authors cite a treatment manual or other source that dictates the treatment protocol</td>
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<td></td>
<td></td>
<td>Adherence/compliance: Treatment adherence</td>
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<tr>
<td>Study Details</td>
<td>Participants</td>
<td>Intervention Treatment</td>
<td>Outcome Results (Men)</td>
<td>Outcome Results (Women)</td>
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<tr>
<td>% veterans: NR</td>
<td></td>
<td>Duration/frequency: 60–90 min; 18 sessions; 12 weeks</td>
<td>Outcome: Mean proportion of sessions attended</td>
<td>IBT vs. PACT SMD: −0.36 (95% CI: −0.92, 0.20)</td>
</tr>
<tr>
<td>Inclusion criteria: For men:</td>
<td></td>
<td>Comparator category: Other behavioral intervention—BRT; IBT; PACT</td>
<td></td>
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<tr>
<td>between 20 and 60 years old; married for at least 1 year or living with a significant other in a stable relationship for at least 2 years; meet DSM-IV for Mental Disorders criteria for alcohol dependence and have alcohol as their primary substance of abuse; have medical clearance to engage in abstinence-oriented treatment; agree to refrain from the use of alcohol or illicit drugs for the duration of treatment; refrain from seeking additional substance abuse treatment except for self-help meetings, unless recommended by their primary individual therapist</td>
<td>Comparator description: IBT: 18 sessions, 12 sessions of 12-step group counseling and 6 sessions of individual 12-step oriented counseling PACT: 12 sessions of 12-step group counseling plus 6 educational sessions that included both partners</td>
<td></td>
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<tr>
<td>Exclusion criteria: For female partner:</td>
<td></td>
<td>Power calculation: no</td>
<td></td>
<td></td>
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<tr>
<td>met DSM–IV criteria for a psychoactive substance use disorder in the last 6 months; either partner met DSM–IV criteria for an organic mental disorder, schizophrenia, delusional (paranoid) disorder, or other psychotic disorder</td>
<td>Follow-up time: 52 weeks</td>
<td></td>
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<tr>
<td>Fals-Stewart, Birchler, and Kelley, 2006</td>
<td></td>
<td>Arm 1 (PACT): 32 individual sessions; 12 psycho-educational sessions attended by both partners (no BCT)</td>
<td>Outcome measure: Symptom improvement</td>
<td></td>
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<tr>
<td>N per treatment arm:</td>
<td></td>
<td>Arm 2 (BCT): 12 BCT treatment sessions attended together, with non–substance-abusing partner as active participant. Sessions were used to (a) help female partners remain abstinent from alcohol and other drugs by reviewing and reinforcing commitment to a verbal sobriety contract, negotiated by the</td>
<td>Outcome: Percentage of abstinent days BCT vs. PACT (control) SMD: −0.66 (95% CI: −1.08, −0.24)</td>
<td></td>
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<tr>
<td>Study year: NR</td>
<td>Mean age in years (standard deviation), by gender:</td>
<td></td>
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<tr>
<td>Treatment setting: Women, BCT: 32.41 (6.62) Men, BCT: 35.92 (5.02)</td>
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<tr>
<td>Outpatient</td>
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<tr>
<td>Number of sites: NR</td>
<td>Women, PACT: 34.02 (6.21) Men, PACT: 36.36 (5.46)</td>
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<tr>
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<td></td>
<td>Arm 3 (IBT): 46</td>
<td></td>
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<tr>
<td>Study Details</td>
<td>Participants</td>
<td>Intervention Treatment</td>
<td>Outcome Results (Men)</td>
<td>Outcome Results (Women)</td>
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<tr>
<td>Gender female (% per arm): 100%</td>
<td></td>
<td>partners during the first two BCT sessions; (b) teach more-effective communication skills; and (c) enhance relationship satisfaction and increase positive behavioral exchanges between partners; 20 individual 12-step facilitation sessions;</td>
<td></td>
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<tr>
<td>Marital status: Married: 100%</td>
<td></td>
<td>Arm 3 (IBT): 32-session individual sessions; 12-step facilitation program</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational attainment—years of education (standard deviation), by gender: Women, BCT: 12.91 (9.01)</td>
<td></td>
<td>Description of intervention: Behavioral (individual)</td>
<td></td>
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<tr>
<td>Men, BCT: 13.02 (1.66)</td>
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<tr>
<td>Women, IBT: 12.81 (1.31)</td>
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<tr>
<td>Men, IBT: 12.92 (1.96)</td>
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<td></td>
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</tr>
<tr>
<td>Women, PACT: 12.66 (1.52)</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Men, PACT: 12.87 (1.85)</td>
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<tr>
<td>% veterans: NR</td>
<td></td>
<td>Treatment protocol fidelity: Authors cite a treatment manual or other source that dictates the treatment protocol Therapist training: addiction counselor</td>
<td></td>
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</tr>
<tr>
<td>Inclusion criteria: Women: between 20 and 60 years old; married for at least 1 year or living with a romantic partner in a stable relationship for at least 2 years; meet current alcohol abuse or dependence criteria according to the DSM of Mental Disorders; have alcohol as their primary drug of abuse; agree to refrain from drinking alcohol or using other psychoactive substances during treatment; agree to refrain from seeking additional substance abuse treatment except self-help meetings (e.g., AA) for the duration of treatment, unless otherwise recommended by their primary individual counselor</td>
<td></td>
<td>Allowance for/use of adjunctive treatments: Participants are allowed to continue with other forms(s) of treatment (e.g., antidepressants, group therapy) Setting: Outpatient treatment Duration/frequency: 60 minutes, weekly, 20 weeks Comparator category: Other behavioral intervention IBT; PACT Comparator description: IBT; PACT Power calculation: No Follow-up time: 72 weeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exclusion criteria: Male partner: met DSM–IV criteria for any current psychoactive substance use disorder (except nicotine); either partner displayed evidence of schizophrenia, delusional</td>
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</tbody>
</table>

80
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Participants</th>
<th>Intervention Treatment</th>
<th>Outcome Results (Men)</th>
<th>Outcome Results (Women)</th>
<th>Outcome Results (Gender Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fals-Stewart, O’Farrell, and Lam, 2009</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>N per treatment arm:</td>
<td>Arm 2 (BCT): 32 sessions; both the patient and partner attended 12 BCT treatment sessions together. In these 12 sessions, the partner was an active participant in the intervention. The BCT sessions had two main components: (a) substance-focused interventions to directly build support for abstinence, and (b) relationship-focused interventions to increase positive feelings, shared activities, and constructive communication.</td>
<td>Outcome measure: Symptom improvement</td>
<td>Outcome measure: Symptom improvement</td>
<td>Outcome measure: Symptom improvement</td>
</tr>
<tr>
<td></td>
<td>Study year:</td>
<td>NR</td>
<td></td>
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<tr>
<td></td>
<td>Mean age in years (standard deviation), by gender:</td>
<td>Patient age, men: 31.31 (5.46)</td>
<td>Outcome: Percentage of heavy-drinking days BCT vs. IBT SMD: –0.64 (95% CI: –1.03, –0.24)</td>
<td>Outcome: Percentage of heavy-drinking days BCT vs. IBT SMD: –0.59 (95% CI: –1.00, –0.18)</td>
<td>Outcome: Percentage of heavy-drinking days BCT vs. IBT DiffDif: –0.05 (95% CI: –0.17, 0.08)</td>
</tr>
<tr>
<td></td>
<td>Treatment setting:</td>
<td>Outpatient</td>
<td>Adherence/compliance: Treatment adherence</td>
<td>Adherence/compliance: Treatment adherence</td>
<td>Adherence/compliance: Treatment adherence</td>
</tr>
<tr>
<td></td>
<td>Number of sites:</td>
<td>NR</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Gender female (% per arm): 48%</td>
<td></td>
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<tr>
<td></td>
<td>Marital status:</td>
<td>Married: 100%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Educational attainment—years of education (standard deviation), by gender:</td>
<td>Patient years education, men: 14.94 (1.21)</td>
<td>Treatment protocol fidelity: The therapists cite a treatment manual or other source that dictates the treatment protocol</td>
<td>Treatment adherence</td>
<td>Treatment adherence</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patient years education, women: 13.28 (1.26)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Partner education, men: 14.24 (1.30)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Partner education, women: 14.21 (1.18)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>% veterans: NR</td>
<td></td>
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<tr>
<td></td>
<td>Inclusion criteria:</td>
<td>Met current alcohol abuse or dependence criteria according to the DSM-IV; had alcohol as their primary drug of abuse; living with a same-sex romantic partner in a stable relationship for at least a year; at least 18 years of age; agreed to refrain from drinking alcohol or (paranoid) disorder, or other psychotic disorders (on the basis of the results of a brief initial screening interview)</td>
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<tr>
<td></td>
<td>Setting:</td>
<td>Outpatient treatment</td>
<td>Duration/frequency: 60 minutes; 32 sessions; 20 weeks</td>
<td>Comparator category: Other behavioral intervention—IBT</td>
<td></td>
</tr>
<tr>
<td>Study Details</td>
<td>Participants</td>
<td>Intervention Treatment</td>
<td>Outcome Results (Men)</td>
<td>Outcome Results (Women)</td>
<td>Outcome Results (Gender Effects)</td>
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<td></td>
<td>using other psychoactive substances during treatment; agreed to refrain from seeking additional substance abuse treatment except self-help meetings (e.g., AA) for the duration of treatment, unless otherwise recommended by their primary individual counselor</td>
<td>Comparator description: Arm 1 (IBT): 32 sessions of individual 12-step facilitation</td>
<td></td>
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</tr>
<tr>
<td><strong>Exclusion criteria:</strong> Partner met DSM-IV criteria for any current psychoactive substance use disorder (except nicotine); either partner displayed evidence of schizophrenia, delusional (paranoid) disorder, or other psychotic disorders (based on the results of a brief initial screening interview)</td>
<td><strong>Power calculation:</strong> No</td>
<td>Follow-up time: 72 weeks</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Friedmann et al., 2013</th>
<th><strong>N per treatment arm:</strong></th>
<th><strong>Description of intervention:</strong> Pharmacologic</th>
<th><strong>Treatment protocol fidelity:</strong> Authors cite a treatment manual or other source that dictates the treatment protocol</th>
<th><strong>Outcome measure:</strong> Symptom improvement</th>
<th><strong>Outcome:</strong> Alcohol consumption naltrexone vs. extended-release naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study year:</strong> NR</td>
<td>Arm 1 (oral naltrexone): 4</td>
<td>Arm 2: Depot extended-release naltrexone, 380 mg; intramuscular injection every 4 weeks; 16 weeks</td>
<td><strong>Therapist training:</strong> MD</td>
<td>Outcome: Alcohol consumption naltrexone vs. extended-release naltrexone^*^</td>
<td>(&quot;Although XR-NTX has demonstrated efficacy in reducing heavy drinking, limited acceptance of the injection might reduce its effectiveness among homeless, alcohol-dependent patients.&quot;)</td>
</tr>
<tr>
<td><strong>Treatment setting:</strong> Outpatient</td>
<td>Arm 2 (extended release naltrexone): 3</td>
<td><strong>Allowance for/use of adjunctive treatments:</strong> NR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of sites:</strong> 1</td>
<td>Gender female (% per arm): 0%—rounded</td>
<td><strong>Setting:</strong> Outpatient treatment</td>
<td></td>
<td></td>
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<tr>
<td><strong>Marital status:</strong> NR</td>
<td><strong>Duration/frequency:</strong> 16 weeks</td>
<td></td>
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<tr>
<td><strong>Educational attainment:</strong> NR</td>
<td></td>
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<tr>
<td>% veterans: 100%</td>
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<tr>
<td><strong>Inclusion criteria:</strong> Homelessness, past-year alcohol abuse or dependence by DSM-IV criteria, last reported drink 12 hours to 12 months prior, age 18 to 64 years,</td>
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</tbody>
</table>

^*^Although XR-NTX has demonstrated efficacy in reducing heavy drinking, limited acceptance of the injection might reduce its effectiveness among homeless, alcohol-dependent patients.
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Participants</th>
<th>Intervention Treatment</th>
<th>Outcome Results (Men)</th>
<th>Outcome Results (Women)</th>
<th>Outcome Results (Gender Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>eligible for VA services, no contraindications to naltrexone</td>
<td>Comparator category: Other pharmacologic intervention Oral naltrexone</td>
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<tr>
<td>Exclusion criteria: NR</td>
<td>Comparator description: Arm 1: Oral naltrexone, daily, 50 mg, 16 weeks</td>
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<tr>
<td></td>
<td>Power calculation: No</td>
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<td></td>
<td>Follow-up time: 26 weeks</td>
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<tr>
<td>Garbutt, Kranzler, et al., 2005</td>
<td>N per treatment arm: Arm 1 (placebo): 209 Arm 2 (380mg): 208 Arm 3 (190 mg): 210</td>
<td>Arm 2: 380 mg naltrexone intramuscular injections, every 4 weeks, 24 weeks, adjunctive therapy: BRENDA (Biopsychosocial, Report, Empathy, Needs, Direct advice, and Assessment) supportive therapy</td>
<td>Outcome measure: Symptom improvement</td>
<td>Outcome measure: Symptom improvement</td>
<td>Outcome measure: Symptom improvement</td>
</tr>
<tr>
<td>Study year: 2002–2003</td>
<td>Mean age in years (standard deviation), by gender: Arm 1: 44.7 (11.2) (men) Arm 2: 44.6 (10.0) (women)</td>
<td>Arm 3: 190 mg naltrexone intramuscular injections; every 4 weeks, 24 weeks, adjunctive therapy: BRENDA</td>
<td>Outcome: Heavy drinking naltrexone (190 mg) vs. placebo HR: 0.83 (95% CI: 0.64, 1.07)</td>
<td>Outcome: Heavy drinking naltrexone (380 mg) vs. placebo HR: 1.23 (95% CI: 0.85, 1.78)</td>
<td>Outcome: Heavy drinking naltrexone (190 mg) vs. placebo RHR: 0.78 (95% CI: 0.61, 0.98)</td>
</tr>
<tr>
<td>Treatment setting: Outpatient</td>
<td>Number of sites: 24 Arm 1: 24 Arm 2: 24</td>
<td>Description of intervention: Pharmacologic and behavioral</td>
<td>Outcome measure: Symptom improvement</td>
<td>Outcome measure: Symptom improvement</td>
<td>Outcome measure: Symptom improvement</td>
</tr>
<tr>
<td>Gender female (% per arm): 32%</td>
<td>Marital status: NR</td>
<td>Treatment protocol fidelity: Authors cite a treatment manual or other source that dictates the treatment protocol</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Educational attainment: NR</td>
<td>% veterans: NR</td>
<td>Therapist training: MD</td>
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<tr>
<td>Inclusion criteria: Male or nonpregnant nonlactating female outpatients, ages 18 years or older, a current diagnosis of alcohol dependence defined by the DSM-IV, minimum of 2 episodes of heavy drinking (≥ 5 standard</td>
<td>Allowance for/use of adjunctive treatments: NR</td>
<td>Setting: Outpatient treatment</td>
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<tr>
<td>Duration/frequency: Every 4 weeks; 24 weeks</td>
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<tr>
<td>Study Details</td>
<td>Participants</td>
<td>Intervention Treatment</td>
<td>Outcome Results (Men)</td>
<td>Outcome Results (Women)</td>
<td>Outcome Results (Gender Effects)</td>
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<tr>
<td>Cutter, Kadden, and Tennen, 2015; Litt, Kadden, Kabela-Cormier, et al., 2007</td>
<td>N per treatment arm: Arm 1 (case management): 69 Arm 2 (network support): 71 Arm 3 (network support + contingency management): 70</td>
<td>Comparator category: Placebo Other pharmacologic intervention: long-acting naltrexone 190mg Other behavioral intervention: all groups received BRENDA therapy</td>
<td>Comparator description: Arm 1: placebo, 24 weeks, adjunctive therapy: BRENDA</td>
<td>Power calculation: No</td>
<td>Follow-up time: 25 weeks</td>
</tr>
<tr>
<td>Study year: 2002–2005</td>
<td>Mean age in years (standard deviation), by gender: 45 (11.4) Gender female (% per arm): 42%</td>
<td>Arm 1: Network support (60 minutes weekly for 12 weeks) aimed at helping change social support networks to support abstinence, based on 12-step facilitation treatment</td>
<td>Network support vs. case management SMD: −0.71 (95% CI: −1.15, −0.27)</td>
<td>Network support vs. case management SMD: 0.00 (95% CI: −0.52, 0.52)</td>
<td>Network support vs. case management DiffDiff: −0.71 (95% CI: −0.88, −0.54)</td>
</tr>
<tr>
<td>Treatment setting: Outpatient</td>
<td>Marital status: 50% (men) 46% (women)</td>
<td>Arm 2: network support + contingency management (60 minutes weekly for 12 weeks) included same counseling to change social support networks plus reinforcements contingent on completing assigned recovery tasks</td>
<td>Outcome measure: Symptom improvement</td>
<td>Outcome measure: Symptom improvement</td>
<td>Outcome measure: Symptom improvement</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Outcome: Proportion of abstinent days</td>
<td>Outcome: Proportion of abstinent days</td>
<td>Outcome: Proportion of abstinent days</td>
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<td></td>
<td></td>
<td></td>
<td>Network support vs. case management</td>
<td>Network support vs. case management</td>
<td>Network support vs. case management</td>
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<td></td>
<td></td>
<td></td>
<td>SMD: −0.71 (95% CI: −1.15, −0.27)</td>
<td>SMD: 0.00 (95% CI: −0.52, 0.52)</td>
<td>DiffDiff: −0.71 (95% CI: −0.88, −0.54)</td>
</tr>
</tbody>
</table>

Exclusion criteria: Evidence of liver failure; alanine aminotransferase or aspartate aminotransferase levels greater than 3 times the upper limit of normal; any clinically significant medical condition that in the opinion of the investigator would adversely affect safety or study participation; major depression with suicidal ideation, psychosis, or bipolar disorder (patients with treated depression and stable pharmacotherapy for at least 8 weeks were not excluded); dependence within the past year on benzodiazepines, opiates, or cocaine; more than 7 days of inpatient treatment for substance abuse in the month before screening; use of opiates, oral naltrexone, or disulfiram in the 2 weeks before screening.
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Participants</th>
<th>Intervention Treatment</th>
<th>Outcome Results (Men)</th>
<th>Outcome Results (Women)</th>
<th>Outcome Results (Gender Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of sites: NR</td>
<td>Educational attainment—years of education (standard deviation): 13.7 (2.1)</td>
<td>Description of intervention: Behavioral (individual)</td>
<td>Outcome: Proportion of abstinent days Network support + contingency management vs. case management SMD: -0.11 (95% CI: -0.54, 0.32)</td>
<td>Outcome: Proportion of abstinent days Network support + contingency management vs. case management SMD: 1.09 (95% CI: 0.53, 1.65)</td>
<td>Outcome: Proportion of abstinent days Network support + contingency management vs. case management DiffDiff: -1.20 (95% CI: -1.37, -1.03)</td>
</tr>
<tr>
<td>% veterans: NR</td>
<td>Inclusion criteria: At least 18 years old, meet DSM-IV criteria for alcohol dependence or abuse</td>
<td>Treatment protocol fidelity: Authors cite a treatment manual or other source that dictates the treatment protocol</td>
<td></td>
<td></td>
<td>Outcome: Abstinence network support vs. network support + contingency management vs. case management DiffDiff: 0.34 (95% CI: 0.06, 0.62)</td>
</tr>
<tr>
<td></td>
<td>Exclusion criteria: Acute medical or psychiatric problems requiring inpatient treatment (e.g., acute psychosis); current dependence on drugs (except nicotine and marijuana); intravenous drug use in the previous 3 months; attended more than three AA meetings in the prior month.</td>
<td>Therapist training: Other “Therapist” undefined</td>
<td></td>
<td></td>
<td>Outcome: Drinker Inventory of Consequences total score Network support vs. network support + contingency management vs. case management DiffDiff: 0.14 (95% CI: -0.13, 0.42)</td>
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<tr>
<td></td>
<td></td>
<td>Allowance for/use of adjunctive treatments: Other: Participants neither encouraged or discouraged from attending AA</td>
<td></td>
<td></td>
<td>Outcome: Drinks per drinking day Network support vs. network support + contingency management vs. case management DiffDiff: 0.29 (95% CI: 0.02, 0.57)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Setting: Outpatient treatment</td>
<td></td>
<td></td>
<td>Outcome: Proportion of heavy drinking days Network support vs. network support + contingency management vs. case management DiffDiff: 0.28 (95% CI: 0.00, 0.55)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Duration/frequency: 60 minutes per week, 12 weeks</td>
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<tr>
<td>Study Details</td>
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<tr>
<td>Mason, Goodman, et al., 2006; Mason and Lehert, 2012</td>
<td>N per treatment arm: 601</td>
<td>Arm 1: Placebo</td>
<td>Outcome measure: Symptom improvement</td>
<td>Outcome measure: Symptom improvement</td>
<td>Outcome: Percentage of abstinent days acamprosate vs. placebo SMD: –0.02 (95% CI: –0.30, 0.27)</td>
</tr>
<tr>
<td>Study year: 1997–1999</td>
<td>Arm 1 (placebo): 260</td>
<td>Arm 2: Acamprosate (2g/d)</td>
<td>Outcome: Percentage of abstinent days acamprosate vs. placebo SMD: 0.12 (95% CI: –0.08, 0.32)</td>
<td>Outcome: Percentage of abstinent days men vs. women Diffodiff: 0.07 (95% CI: –0.11, 0.24)</td>
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</tr>
<tr>
<td>Treatment setting: Outpatient</td>
<td>Arm 3 (2g/d acamprosate): 258</td>
<td>Arm 3: Acamprosate (3g/d)</td>
<td>Outcome: Percentage of no heavy-drinking days acamprosate vs. placebo SMD: 0.06 (95% CI: –0.23, 0.34)</td>
<td>Outcome: Percentage of no heavy-drinking days men vs. women Diffodiff: 0.06 (95% CI: –0.11, 0.24)</td>
<td></td>
</tr>
<tr>
<td>Number of sites: 21</td>
<td>Gender female (% per arm): 33%</td>
<td>Description of intervention: Pharmacologic</td>
<td>Outcome: Percentage of heavy-drinking days acamprosate vs. placebo SMD: –0.16 (95% CI: –0.36, 0.04)</td>
<td>Outcome: Percentage of heavy-drinking days men vs. women Diffodiff: –0.06 (95% CI: –0.24, 0.11)</td>
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</tr>
<tr>
<td>Marital status: NR</td>
<td>Overall: study reported percentage of those living alone</td>
<td>Treatment protocol fidelity: Authors cite a treatment manual or other source that dictates the treatment protocol</td>
<td>Therapist training: Other counselors with at least an RN</td>
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<tr>
<td>Placebo: 16%</td>
<td>Placebo: 44.5 (10.0)</td>
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<tr>
<td>Acamprosate 2g 20%</td>
<td>Acamprosate 2g: 44.9 (10.5)</td>
<td>Allowance for/use of adjunctive treatments:</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Acamprosate 3g 18%</td>
<td>Acamprosate 3g: 43.6 (8.9)</td>
<td>Other: All arms: Protocol-specific brief counseling and self-help materials</td>
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<tr>
<td>Educational attainment: NR</td>
<td>Setting: Outpatient treatment</td>
<td>Setting: Outpatient</td>
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<td></td>
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<tr>
<td>Duration/frequency: Daily, 24 weeks</td>
<td>Comparator category: Placebo Other pharmacologic intervention 3g/d acamprosate</td>
<td>Comparator description: Placebo and head-to-head: Placebo vs. acamprosate 2g vs. acamprosate 3g</td>
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<tr>
<td>% veterans: NR</td>
<td>Power calculation: Other power calculation</td>
<td>Follow-up time: Six months</td>
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<tr>
<td>Study Details</td>
<td>Participants</td>
<td>Intervention Treatment</td>
<td>Outcome Results (Men)</td>
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<tr>
<td>need for psychoactive medication; use of any investigational drug, disulfiram, or naltrexone in the month prior to screening; dependence on illicit drugs or unable to provide a pre-randomization urine sample negative for drugs except cannabis (although self-reported drug use history not meeting dependence criteria was allowed); court-mandated treatment; pregnancy, lactation, or refusal to use a reliable method of birth control if a sexually active woman with childbearing potential</td>
<td>Arm 1 ABCT: 30</td>
<td>Arm 1: ABCT (CBT emphasizing cessation and abstinence and techniques to enhance marriage quality: one 90-minute weekly session for 15 weeks)</td>
<td>Outcome measure: Symptom improvement</td>
<td>Outcome: Percentage of abstinent days AA/ABCT vs. ABCT SMD: -0.01 (95% CI: -0.59, 0.58)</td>
<td></td>
</tr>
<tr>
<td>McCrady, Epstein, and Hirsch, 1999; Hallgren, Owens, et al., 2015; Hallgren, McCrady, and Epstein, 2016</td>
<td>Arm 2 RP/ABCT: 31</td>
<td>Arm 2: ABCT plus RP (15 weekly ABCT sessions plus 1 to 3 RP sessions at 1, 3, 6, and 12 months following ABCT treatment)</td>
<td>Outcome: Percentage of abstinent days AA/ABCT vs. ABCT SMD: 0.19 (95% CI: -0.40, 0.79)</td>
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<tr>
<td>Mean age in years (standard deviation): 39.45 (10.27)</td>
<td>Arm 3 AA ABCT: 29</td>
<td>Arm 3: ABCT plus AA (15 weekly ABCT sessions plus encouragement to attend AA and Alanon)</td>
<td>Outcome: Percentage of heavy-drinking days AA/ABCT vs. ABCT SMD: 0.31 (95% CI: -0.27, 0.89)</td>
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<tr>
<td>Gender Female (% per arm): 0</td>
<td>Study year: NR</td>
<td>Marital status: Married: 100%</td>
<td>Treatment protocol fidelity: Authors cite a treatment manual or other source that dictates the treatment protocol</td>
<td>Outcome: Percentage of heavy-drinking days RP/ABCT vs. ABCT SMD: 0.53 (95% CI: -0.06, 1.12)</td>
<td></td>
</tr>
<tr>
<td>Study year: NR</td>
<td>Treatment setting: Outpatient</td>
<td>Educational attainment: NR</td>
<td>Therapist training: PhD psychologist</td>
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</tr>
<tr>
<td>Number of sites: 1</td>
<td>% veterans: NR</td>
<td>Inclusion criteria: Male; current drinking problem (report of four positive responses on the Michigan Alcoholism Screening Test); alcohol consumption in the past 60 days; legally married, or separated but with hopes for reconciliation, or living as married for at least 6 months; spouse or partner willing to participate in study</td>
<td>Allowance for use of adjunctive treatments: Other: Patients could participate in AA or Alanon</td>
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</table>

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<table>
<thead>
<tr>
<th>Study Details</th>
<th>Participants</th>
<th>Intervention Treatment</th>
<th>Outcome Results (Men)</th>
<th>Outcome Results (Women)</th>
<th>Outcome Results (Gender Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion criteria: Psychotic (based on the psychosis and paranoia scales of the Symptom Checklist-90), current cognitive impairment score &gt;25 on the Mini-Mental State Exam, dependence on drug other than alcohol, spouse or partner has drinking problem or is psychotic</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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<tr>
<td>Comparator description: Arm 1: ABCT alone</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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<tr>
<td>Power calculation: Insufficient power</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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<tr>
<td>Follow-up time: 24 weeks</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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<tr>
<td>N per treatment arm:</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
<td></td>
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<tr>
<td>McCrady, Epstein, Cook, et al., 2009</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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<tr>
<td>N per treatment arm:</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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<tr>
<td>Hallgren, Owens, et al., 2015; Hallgren, McCrady, and Epstein, 2016</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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<tr>
<td>Mean age in years (standard deviation), by gender:</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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<td></td>
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<tr>
<td>Arm 1:</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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</tr>
<tr>
<td>45.31 (9.31) (women)</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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<tr>
<td>48.98 (11.08) (men)</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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<tr>
<td>Arm 2:</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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<tr>
<td>44.78 (9.14) (women)</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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<tr>
<td>47.96 (9.56) (men)</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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</tr>
<tr>
<td>Study year: 1997–2000</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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<tr>
<td>Treatment setting: Outpatient</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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<tr>
<td>Marital status: Married: 100%</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
<td></td>
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</tr>
<tr>
<td>Number of sites: NR</td>
<td>Setting: Outpatient treatment</td>
<td>Adherence/compliance: Treatment adherence outcome: Treatment sessions AAV/ABCT vs. ABCT SMD: –0.03 (95% CI: –0.62, 0.55)</td>
<td>Outcome: Treatment sessions RP/ABCT vs. ABCT SMD: –0.12 (95% CI: –0.69, 0.46)</td>
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Description of intervention: The authors cite a treatment manual or other source that dictates the treatment protocol.
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</thead>
<tbody>
<tr>
<td><strong>Educational attainment—years of education (standard deviation), by gender:</strong></td>
<td>Therapist training: PhD psychologist</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Arm 1:</td>
<td>Allowance for/use of adjunctive treatments: NR</td>
<td></td>
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<tr>
<td>15.24 (3.25) (men)</td>
<td></td>
<td></td>
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<tr>
<td>14.54 (2.61) (women)</td>
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<tr>
<td>Arm 2:</td>
<td>Setting: Outpatient treatment</td>
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<tr>
<td>15.30 (2.75) (men)</td>
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<tr>
<td>14.57 (2.56) (women)</td>
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<tr>
<td><strong>% veterans:</strong></td>
<td>NR</td>
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</table>

**Inclusion criteria:** Female; current alcohol abuse or dependence as determined by the Structured Clinical Interview for DSM–IV; consumed alcohol within the past 60 days; married, cohabiting for at least 6 months, or in a committed heterosexual relationship of at least 1 year of duration with intent to continue the relationship; male partner willing to participate in the research and treatment; either no evidence of domestic violence in the past 12 months or, if any physical aggression was reported on the Modified Conflict Tactics Scale, then (a) the victim of the violence reported no fear of retribution from their partner for discussions that might occur in couple therapy, and (b) the violence occurred only in the presence of intoxication, or (c) the violence had resulted in no injury requiring medical attention.

**Exclusion criteria:** Either partner had signs of severe organic brain syndrome as evidenced by a score of <25 on the Mini-Mental State Exam, either partner had signs of a...
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Participants</th>
<th>Intervention Treatment</th>
<th>Outcome Results (Men)</th>
<th>Outcome Results (Women)</th>
<th>Outcome Results (Gender Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McCrady, Epstein, Hallgren, et al., 2016; Holzhauer, et al., 2017</td>
<td>N per treatment arm: Arm 1 (ABCT): 35 Arm 2 (ABBT/Blended): 30</td>
<td>Arm 2: Blended ABCT (B-ABCT): 7 sessions (5 individual and 7 conjoint); male partner assigned to support female during individual CBT sessions, 7 conjoint sessions followed ABCT model to teach partner skills to support sobriety, relationship enhancement interventions, relapse prevention</td>
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<tr>
<td>Mean age in years (standard deviation), by gender: 46.0 (9.1) (women/total)</td>
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<tr>
<td>Study year: 2003–2007</td>
<td>Gender female (% per arm): 100%</td>
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<tr>
<td>Treatment setting: Outpatient</td>
<td>Marital status: Married: 100%</td>
<td>Description of intervention: Behavioral (individual)</td>
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<tr>
<td>Educational attainment—years of education (standard deviation): Arm 1: 14.9 (3.0) Arm 2: 15.7 (2.1) Total: 15.3 (2.7)</td>
<td></td>
<td>Treatment protocol fidelity: Authors cite a treatment manual or other source that dictates the treatment protocol</td>
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<tr>
<td>Number of sites: 1</td>
<td>% veterans: NR</td>
<td>Therapist training: PhD psychologist</td>
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<tr>
<td>Inclusion criteria: Woman; in a committed heterosexual relationship, defined as married, separated with hopes of reconciliation, cohabitating for at least six months, or in a committed dating relationship of at least one year's duration; consumed alcohol in the past 30 days; met criteria for DSM-IV alcohol abuse or dependence.</td>
<td>Allowance for/use of adjunctive treatments: NR</td>
<td>Setting: Outpatient treatment</td>
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<tr>
<td></td>
<td>Duration/frequency: 90 min; 12 weekly sessions; up to 16 weeks to cover 12 sessions</td>
<td>Comparator category: Other behavioral intervention ABIT</td>
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</tr>
</tbody>
</table>

Outcome measure: Symptom improvement
Outcome: Percentage of drinking days
B-ABCT vs. ABCT
SMD: 0.08
(95% CI: –0.48, 0.64)
Outcome: Percentage of heavy-drinking days
B-ABCT vs. ABCT
SMD: 0.69
(95% CI: 0.12, 1.27)
Adherence/compliance: Treatment adherence
Outcome: Treatment attendance
B-ABCT vs. ABCT
SMD: –0.41
(95% CI: –0.98, 0.15)
<table>
<thead>
<tr>
<th>Study Details</th>
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<th>Outcome Results (Women)</th>
<th>Outcome Results (Gender Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exclusion criteria:</strong> Either partner meeting criteria for another current substance use disorder with physiological dependence on drugs other than marijuana or nicotine, or other partner reporting evidence of psychotic symptoms in past six months, either partner showing evidence of significant cognitive impairment, evidence of intimate partner violence in the past 12 months that resulted in injury and/or fear of participating in conjoint therapy.</td>
<td><strong>Comparator description:</strong> Arm 1: ABCT: 12 sessions of couples therapy, focusing on support, shared positive activity, alcohol-related coping skills. Arm 2: TM: Brief weekly (5–10 minute) telephone calls for first 8 weeks, every other week for next 10 months, and once per month for the final 6 months, up to 18 months. Each call consisted of a 10-item &quot;progress assessment&quot; that covered current substance use, other risk factors and protective factors; score given to participant. Arm 3: TMC: same call schedule as for TM; participants also completed the progress assessment and were given their overall risk score at the beginning of each call. Discussion of current goals and the specific objectives to be accomplished to reach each goal and coping responses to existing or anticipated risky situations identified and role-played.</td>
<td><strong>Outcome measure:</strong> Symptom improvement</td>
<td><strong>Outcome measure:</strong> Any heavy drinking</td>
<td><strong>Outcome measure:</strong> Good clinical outcome</td>
<td></td>
</tr>
<tr>
<td><strong>Mean age in years (standard deviation):</strong> McKay, Van Horn, Oslin, Ivey, et al., 2011; Lynch et al., 2010; McKay, Van Horn, Oslin, Lynch, et al., 2010</td>
<td>Gender female (% per arm): 35.7%</td>
<td><strong>Outcome:</strong> Any heavy drinking TM vs. TAU OR: 1.96 (95% CI: Not calculated)</td>
<td><strong>Outcome:</strong> Good clinical outcome TM vs. TAU OR: 0.51 (95% CI: Not calculated)</td>
<td><strong>Outcome:</strong> rates of good clinical outcome Telephone monitoring + TAU (TM) vs. Treatment as usual (TAU) OR: 0.44 (95% CI: Not calculated)</td>
<td><strong>Outcome:</strong> rates of good clinical outcome Telephone monitoring plus counseling + TAU (TMC) vs. Treatment as usual (TAU) ROR: 1.28 (95% CI: 0.65, 2.52)</td>
</tr>
<tr>
<td><strong>N per treatment arm:</strong> McKay, Van Horn, Oslin, Ivey, et al., 2011; Lynch et al., 2010</td>
<td>Marital status: Arm 1: 8%</td>
<td>Arm 2: TM: Brief weekly (5–10 minute) telephone calls for first 8 weeks, every other week for next 10 months, and once per month for the final 6 months, up to 18 months. Each call consisted of a 10-item &quot;progress assessment&quot; that covered current substance use, other risk factors and protective factors; score given to participant.</td>
<td><strong>Outcome:</strong> Any heavy drinking TM vs. TAU OR: 1.96 (95% CI: Not calculated)</td>
<td><strong>Outcome:</strong> Good clinical outcome TM vs. TAU OR: 0.51 (95% CI: Not calculated)</td>
<td><strong>Outcome:</strong> rates of good clinical outcome Telephone monitoring + TAU (TM) vs. Treatment as usual (TAU) OR: 0.44 (95% CI: Not calculated)</td>
</tr>
<tr>
<td><strong>Number of sites:</strong> 2</td>
<td>Educational attainment—years of education (standard deviation), by gender: Arm 1: 11.86 (1.85)</td>
<td>Arm 2: 11.55 (1.95)</td>
<td>Arm 3: 12.01 (1.52)</td>
<td><strong>Outcome measure:</strong> Symptom improvement</td>
<td><strong>Outcome measure:</strong> Any heavy drinking TM vs. TAU OR: 1.96 (95% CI: Not calculated)</td>
</tr>
<tr>
<td>Study Details</td>
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<tr>
<td><strong>Inclusion criteria:</strong> completed 3 weeks of treatment in an intensive outpatient program; have no psychiatric or medical conditions that precluded outpatient treatment; age 18–65 years; no intravenous heroin use within the past 12 months; able to read at the fourth-grade level; have a minimum degree of stability in living situation; DSM-IV AUD diagnosis; willingness to provide names, addresses, and telephone numbers of at least 3 contacts</td>
<td><strong>Treatment protocol fidelity:</strong> The authors cite a treatment manual or other source that dictates the treatment protocol</td>
<td><strong>Outcome:</strong> rates of good clinical outcome</td>
<td><strong>Outcome:</strong> Percentage of days drinking TMC vs. TAU OR: 0.47 (95% CI: Not calculated)</td>
<td></td>
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</tr>
<tr>
<td><strong>Exclusion criteria:</strong> NR</td>
<td><strong>Therapist training:</strong> PhD psychologist</td>
<td><strong>Telephone monitoring</strong> plus counseling + TAU (TMC) vs. treatment as usual (TAU) OR: 0.70 (95% CI: 0.33, 1.48)</td>
<td><strong>Outcome:</strong> rates of good clinical outcome</td>
<td><strong>Comparator category:</strong> Other behavioral intervention monitoring and feedback only (TM) vs. monitoring and feedback plus counseling (TMC) <strong>Comparator description:</strong> Arm 1: Treatment as usual <strong>Setting:</strong> Outpatient treatment</td>
<td></td>
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<tr>
<td><strong>Duration/frequency:</strong> 5–10 min; weekly for 2 months, every other week for next 10 months, one per month for last 6 months; 18 months</td>
<td><strong>Allowance for/use of adjunctive treatments:</strong> Participants required to continue with previous form of therapy</td>
<td><strong>Setting:</strong> Outpatient treatment</td>
<td><strong>Outcome:</strong> rates of good clinical outcome</td>
<td><strong>Follow-up time:</strong> 96 weeks</td>
<td></td>
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<tr>
<td><strong>Power calculation:</strong> Yes</td>
<td><strong>Comparator category:</strong> Other behavioral intervention monitoring and feedback only (TM) vs. monitoring and feedback plus counseling (TMC) <strong>Comparator description:</strong> Arm 1: Treatment as usual</td>
<td></td>
<td><strong>Follow-up time:</strong></td>
<td><strong>Mean age in years (standard deviation):</strong> Mean age in years (standard deviation): <strong>Mean age in years (standard deviation):</strong> <strong>Mean age in years (standard deviation):</strong></td>
<td></td>
</tr>
<tr>
<td>Morgenstern et al., 2007</td>
<td>Arm 1 (MI): 42</td>
<td>Arm 2 (MI + CBT): 47</td>
<td><strong>Outcome:</strong> rates of good clinical outcome</td>
<td><strong>Outcome:</strong> Percentage of days drinking TMC vs. TAU OR: 0.47 (95% CI: Not calculated)</td>
<td></td>
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<tr>
<td><strong>Number of sites:</strong> NR</td>
<td>Arm 2 (MI + CBT): 47</td>
<td><strong>Outcome:</strong> Telephone monitoring + TAU (TM) vs. treatment as usual (TAU) OR: 0.43 (95% CI: 0.16, 1.14)</td>
<td><strong>Outcome:</strong> rates of good clinical outcome</td>
<td><strong>Outcome:</strong> rates of good clinical outcome <strong>Comparator category:</strong> Other behavioral intervention monitoring and feedback only (TM) vs. monitoring and feedback plus counseling (TMC) <strong>Comparator description:</strong> Arm 1: Treatment as usual <strong>Setting:</strong> Outpatient treatment</td>
<td></td>
</tr>
<tr>
<td><strong>Gender female (% per arm):</strong> 0%—rounded</td>
<td><strong>Outcome:</strong> Telephone monitoring plus counseling + TAU (TMC) vs. treatment as usual (TAU) OR: 0.55 (95% CI: 0.18, 1.63)</td>
<td><strong>Outcome:</strong> Telephone monitoring + TAU (TM) vs. treatment as usual (TAU) OR: 0.43 (95% CI: 0.16, 1.14)</td>
<td><strong>Outcome:</strong> rates of good clinical outcome</td>
<td><strong>Outcome:</strong> rates of good clinical outcome <strong>Comparator category:</strong> Other behavioral intervention monitoring and feedback only (TM) vs. monitoring and feedback plus counseling (TMC) <strong>Comparator description:</strong> Arm 1: Treatment as usual <strong>Setting:</strong> Outpatient treatment</td>
<td></td>
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<tr>
<td>Study Details</td>
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<td>Outcome Results (Women)</td>
<td>Outcome Results (Gender Effects)</td>
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<tr>
<td>Marital status:</td>
<td>NR</td>
<td>Description of intervention: behavioral (individual)</td>
<td></td>
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<tr>
<td>Educational attainment:</td>
<td>NR (average education less than college degree)</td>
<td>Treatment protocol fidelity: The authors cite a treatment manual or other source that dictates the treatment protocol</td>
<td></td>
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<tr>
<td>% veterans:</td>
<td>NR</td>
<td>Therapist training: MD</td>
<td></td>
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<tr>
<td>Inclusion criteria:</td>
<td>male, self-reported negative HIV status, sexually active with men during the previous 90 days, positive diagnosis of AUD in the previous 12 months (abuse or dependence), drinking during the previous 30 days, no evidence of thought disorder or severe cognitive impairment, availability to participate in follow-up interviews for a 15-month period</td>
<td>Allowance for use of adjunctive treatments: Participants are required to withdraw/abstain from previous form of therapy</td>
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<tr>
<td>Exclusion criteria:</td>
<td>drug use disorder more severe than AUD (as evidenced by a greater number of DSM-IV dependence symptoms), individuals who reported injection drug use or crack cocaine use in the past 6 months, currently in substance use disorder treatment</td>
<td>Setting: Outpatient treatment</td>
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<tr>
<td>Comparator category:</td>
<td>Other behavioral intervention MI alone vs. MI + CBT</td>
<td>Comparator description: Arm 1 MI: identical to the MI component of MI + CBT</td>
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<tr>
<td>Power calculation:</td>
<td>no</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Follow-up time:</td>
<td>60 weeks</td>
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<tr>
<td>O’Farrell, Choquette, and Cutter, 1998</td>
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<tr>
<td>Study year:</td>
<td>NR</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age:</td>
<td>NR</td>
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</tbody>
</table>

**O’Farrell, Choquette, and Cutter, 1998**

- **N per treatment arm:**
  - Arm 1 (Behavioral Marital Therapy [BMT]): 29
  - Arm 2 (BMT-plus-Relapse Prevention [RP]): 30

- **Description of intervention:**
  - Behavioral (individual)
  - Behavioral (individual)

- **Outcome Measure:**
  - Symptom improvement
  - Percentage of days abstinent

- **Outcome:**
  - BMT + RP vs. BMT-only
  - SMD: –0.08
  - (95% CI: –0.60, 0.43)
<table>
<thead>
<tr>
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<th>Outcome Results (Men)</th>
<th>Outcome Results (Women)</th>
<th>Outcome Results (Gender Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Treatment setting:</strong></td>
<td>Gender Female (% per arm): 0</td>
<td>Treatment protocol fidelity: Authors cite a treatment manual or other source that dictates the treatment protocol</td>
<td>Adherence/compliance: Treatment Adherence</td>
<td>Outcome: Use of BMT-targeted Antabuse contract</td>
<td></td>
</tr>
<tr>
<td><strong>Outpatient</strong></td>
<td>Marital status: Married: 100%</td>
<td>Therapist training: Other therapists</td>
<td></td>
<td>BMT + RP vs. BMT-only</td>
<td>SMD: −0.39 (95% CI: −0.90, 0.13)</td>
</tr>
<tr>
<td><strong>Number of sites:</strong> 1</td>
<td>Educational attainment: NR</td>
<td>Allowance for/use of adjunctive treatments: NR</td>
<td>Setting: Outpatient treatment</td>
<td>Duration/frequency: 78 weeks: 26 weeks BMT couples sessions, 52 weeks additional conjoint couples RP sessions</td>
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<tr>
<td></td>
<td>% veterans: 100%</td>
<td></td>
<td>Comparator category: Other behavioral intervention—BMT without couples relapse prevention</td>
<td>Comparator description: Arm 1: no relapse prevention after 6 months BMT</td>
<td></td>
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<tr>
<td></td>
<td>Inclusion criteria: Male, married or living with partner, diagnosis of alcoholism, who participated in BMT (behavioral marital counseling) study, were randomized to relapse prevention (RP) program or no relapse prevention</td>
<td></td>
<td>Power calculation: No</td>
<td></td>
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<tr>
<td></td>
<td>Exclusion criteria: Abuse of other substances, psychotic</td>
<td></td>
<td>Follow-up time: 120 weeks</td>
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<tr>
<td><strong>Osling et al., 1997; Dundon et al., 2008</strong></td>
<td>N per treatment arm: Arm 1 (placebo): 23 Arm 2 (naltrexone): 21</td>
<td>Arm 2 (naltrexone): 100 mg on Monday and Wednesday; 150 mg on Friday (equal to 50 mg per day) plus weekly group therapy</td>
<td></td>
<td>Outcome measure: Symptom improvement</td>
<td>Outcome: Abstinence rate naltrexone vs. placebo</td>
</tr>
<tr>
<td></td>
<td>Mean age in years (standard deviation): Arm 1 (placebo): 58.9 (6.7) Arm 2 (naltrexone): 56.5 (6.8)</td>
<td>Description of intervention: Pharmacologic and behavioral</td>
<td>Chi-squared value: 0.2 df:1, p-value: 0.659 (&quot;There were no differences in abstinence rates between the naltrexone- and placebo-treated groups.&quot;)</td>
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<tr>
<td></td>
<td>Treatment setting: Outpatient</td>
<td>Treatment protocol fidelity: No manual or reference is cited for the method</td>
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<tr>
<td></td>
<td>Gender Female (% per arm): 0</td>
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<tr>
<td></td>
<td>Marital status: Arm 1 (placebo): 17.4% Arm 2 (naltrexone): 14.3%</td>
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<tr>
<td>Study Details</td>
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<tr>
<td>Educational attainment—years of education (standard deviation):</td>
<td>Arm 1: 12.1(2.7) Arm 2: 12.4(24)</td>
<td>Therapist training: Other case manager, group therapy facilitator, and nurse</td>
<td>Outcome: Addiction Severity Index Alcohol score (ASI) naltrexone vs. placebo Chi-squared value: 0.04 df:1, p-value: 0.833 (“There was no difference between the treatment groups.”)</td>
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<tr>
<td>% veterans: 100%</td>
<td></td>
<td>Allowance for/use of adjunctive treatments: Participants are allowed to continue with other forms(s) of treatment (e.g., antidepressants, group therapy)</td>
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<tr>
<td>Inclusion criteria: Age 50–70 years, DSM-III-R diagnosis of alcohol dependence</td>
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<td>Setting: Outpatient treatment setting</td>
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<tr>
<td>Exclusion criteria: Unstable or serious medical problem; severe dementia; mental retardation; seizure disorder; psychosis; danger to self or others; use of a substance other than caffeine, nicotine, or alcohol in 6 weeks prior; drug screen positive for other illicit substances; hepatitis</td>
<td></td>
<td>Duration/frequency: 12 weeks Comparator category: Placebo Comparator description: Arm 1: Placebo plus weekly group therapy Power calculation: No Follow-up time: 12 weeks</td>
<td>Outcome: Group attendance naltrexone vs. placebo SMD: −0.05 (95% CI: −0.64, 0.54) Outcome: Number of weeks that subjects participated in the study naltrexone vs. placebo SMD: −0.23 (95% CI: −0.82, 0.36) Adverse events: Outcome: Anxiety naltrexone vs. placebo OR: 0.67 (95% CI: 0.19, 2.33) Outcome: Headaches naltrexone vs. placebo OR: 1.13 (95% CI: 0.30, 4.27) Outcome: Joint pain naltrexone vs. placebo OR: 1.13 (95% CI: 0.27, 4.61)</td>
<td></td>
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<tr>
<td>Study Details</td>
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<td>Outcome Results (Men)</td>
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<tr>
<td>Schumm et al., 2014</td>
<td>N per treatment arm:</td>
<td>Arm 1 (IBT): 53 Arm 2 (BCT): 52</td>
<td>Arm 2: (BCT): Conjoint &quot;sessions aimed to build support for abstinence and improve relationship functioning: (a) a Recovery Contract with a calendar to record AA meetings attended, drug urine screen results, and completion of a daily 'trust discussion' in which the patient states an intent to stay abstinent that day and the spouse expresses support for the patient’s efforts; (b) teaching partners to decrease behaviors that might trigger or enable substance use; and (c) helping the couple decrease the patient’s exposure to alcohol and drugs by removing alcohol from the home and avoiding or managing alcohol-related family and social gatherings. BCT relationship-focused interventions were designed to increase positive</td>
<td>Outcome: Low energy naltrexone vs. placebo OR: 1.13 (95% CI: 0.30, 4.27) Outcome: Nausea naltrexone vs. placebo OR: 1.57 (95% CI: 0.31, 8.01) Outcome: Sleep disturbance naltrexone vs. placebo OR: 1.15 (95% CI: 0.34, 3.95) Outcome: Vomiting naltrexone vs. placebo OR: 3.44 (95% CI: 0.13, 89.13)</td>
<td>Outcome measure: Symptom improvement Outcome: Percentage of abstinent days BCT + 12-step-oriented IBT vs. IBT only SMD: –0.26 (95% CI: –0.65, 0.13) Adherence/compliance: Treatment adherence Outcome: Treatment attendance BCT + 12-step-oriented IBT vs. IBT only SMD: –0.10 (95% CI: –0.49, 0.29)</td>
</tr>
<tr>
<td>Study year: 2006–2009</td>
<td>Mean age in years (standard deviation), by gender:</td>
<td></td>
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</tr>
<tr>
<td>Treatment setting:</td>
<td></td>
<td>Arm 1 (IBT): 44.2 (8.6) (women) Arm 2 (BCT): 47.2 (8.8) (men)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of sites: 1</td>
<td>Gender Female (% per arm): 100%</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Marital status—mean years married/cohabitating (standard deviation):</td>
<td></td>
<td>Arm 1 (IBT): 16.6 (9.1) Arm 2 (BCT): 15.3 (10.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study Details</td>
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<tr>
<td><em>Educational attainment—years of education (standard deviation), by gender:</em></td>
<td>Arm 1:</td>
<td>14.4 (2.2) (women)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Arm 2:</td>
<td>14.5 (2.2) (women)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>14.4 (2.2) (men)</td>
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<tr>
<td>% veterans: NR</td>
<td></td>
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<tr>
<td><em>Inclusion criteria:</em></td>
<td></td>
<td>Both partners between 18 and 65 years of age</td>
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<tr>
<td>Women: met alcohol dependence diagnosis according to the SCID in past 12 months; comorbid drug use disorders; consumed alcohol in the 60 days prior to the study; consumed nonbeverage alcohol products (e.g., mouthwash) on no more than 20% of drinking occasions during this time; primary drug of abuse was alcohol according to the authors' treatment algorithm; did not exhibit current alcohol or drug dependence that required inpatient treatment or medical detoxification (however those who were disqualified for one of these two reasons could be considered for inclusion in the study after completion of needed treatment); agreeable to the goal of abstinence during study-based treatment and willing to forgo professional alcoholism counseling other than treatment required for a clinical emergency or to address clinical deterioration or self-help meeting attendance</td>
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<tr>
<td>Men: other than nicotine</td>
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<tr>
<td><em>Description of intervention:</em></td>
<td>Behavioral (individual)</td>
<td></td>
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<tr>
<td><em>Treatment protocol fidelity:</em></td>
<td>Authors cite a treatment manual or other source that dictates the treatment protocol</td>
<td></td>
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<tr>
<td><em>Therapist training:</em></td>
<td>PhD psychologist</td>
<td></td>
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<tr>
<td><em>Allowance for/use of adjunctive treatments:</em></td>
<td>Participants are required to withdraw/abstain from previous form of therapy</td>
<td></td>
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<tr>
<td><em>Setting:</em></td>
<td>Outpatient treatment</td>
<td></td>
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<tr>
<td><em>Duration/frequency:</em></td>
<td>13 or 26 sessions, 60 minutes, over 20 weeks</td>
<td></td>
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<tr>
<td><em>Comparator category:</em></td>
<td>Other behavioral intervention individually based therapy</td>
<td></td>
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<tr>
<td><em>Comparator description:</em></td>
<td>Arm 1: (IBT): male partners did not participate in treatment. Sessions adapted from the individual drug counseling manual. 13 individual-</td>
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</tbody>
</table>

Feasibility & acceptability outcomes: 87% adherence and 85% completion of treatment sessions.
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Participants</th>
<th>Intervention Treatment</th>
<th>Outcome Results (Men)</th>
<th>Outcome Results (Women)</th>
<th>Outcome Results (Gender Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dependence, did not meet diagnosis for a substance use disorder according to the SCID in past 12 months; neither partner met criteria for psychotic disorder according to the SCID; neither partner at imminent risk for homicide or suicide; couple married for at least 1 year or living together in a stable common-law relationship for at least 2 years; couple lived apart for no more than 4 out of the past 12 months; couple had no immediate plans to separate or divorce; on brief IPV questions in the study screening interview, couple denied severe IPV (i.e., that which had resulted in injury) as occurring in the past 3 years on days when both partners were not using substances, and female patient did not report fear that couples therapy might put her at risk for violence.</strong>&lt;br&gt;Exclusion criteria: NA</td>
<td>Based sessions and 13 other sessions with a 12-step oriented focus. Twice weekly week 1–6; alternating once and twice weekly weeks 7–12; biweekly weeks 14–20.</td>
<td><strong>Power calculation:</strong> No</td>
<td><strong>Follow-up time:</strong> 52 weeks</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>N per treatment arm:</strong></th>
<th><strong>Description of intervention:</strong> Pharmacologic</th>
<th><strong>Outcome measure:</strong> Symptom improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm 1 (placebo): 19</td>
<td><strong>Therapist training:</strong> MD</td>
<td><strong>Outcome:</strong> Heavy-drinking days (30 days) gabapentin vs. placebo SMD: −0.26 (95% CI: −0.90, 0.38)</td>
</tr>
<tr>
<td>Arm 2 (gabapentin): 19</td>
<td><strong>Allowance for/use of adjunctive treatments:</strong> NR</td>
<td><strong>Outcome:</strong> Number of drinking days gabapentin vs. placebo SMD: −0.20 (95% CI: −0.84, 0.44)</td>
</tr>
</tbody>
</table>

<p>| Trevisan et al., 2008   | <strong>Mean age in years (standard deviation):</strong> Arm 1 (placebo): 48.2 (9.4) Arm 2 (gabapentin): 46.1 (9.6) | <strong>Gender female (% per arm):</strong> 0%—rounded |
| <strong>Study year:</strong> NR      | <strong>Setting:</strong> Outpatient treatment              | <strong>Setting:</strong> Outpatient treatment |
| <strong>Treatment setting:</strong> Outpatient | <strong>Duration/frequency:</strong> Daily, 4 weeks         | <strong>Duration/frequency:</strong> Daily, 4 weeks |</p>
<table>
<thead>
<tr>
<th>Study Details</th>
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<th>Intervention Treatment</th>
<th>Outcome Results (Men)</th>
<th>Outcome Results (Women)</th>
<th>Outcome Results (Gender Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Educational attainment—years of education (standard deviation): Arm 1: 5% Arm 2: 5% with college degree or higher</td>
<td>Comparator category: Placebo Other pharmacologic intervention Divalproex Comparator description: Arm 1: placebo</td>
<td>Outcome: Obsessive Compulsive Drinking Scale gabapentin vs. placebo SMD: -0.27 (95% CI: -0.91, 0.37)</td>
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<tr>
<td>Inclusion criteria: Met criteria for current DSM-IV criteria for alcohol dependence, determined by structured clinical interview; were abstinent for no more than 1 week; had a breathalyzer reading &lt; 0.02 g/dL at the time of intake</td>
<td>Power calculation: no Follow-up time: 4 weeks</td>
<td>Outcome: Percentage of heavy-drinking days gabapentin vs. placebo SMD: -0.26 (95% CI: -0.90, 0.38)</td>
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<tr>
<td>Exclusion criteria: Current DSM-IV opiate dependence or benzodiazepine abuse or dependence; serious current psychiatric symptoms, such as suicidal or homicidal ideation; already taking anticonvulsant medication including carbamazepine, phenytoin, valproic acid or gabapentin; medical problems that precluded safely entering the study including liver function tests over 3 times the normal level; seizure disorder (epilepsy); pancreatitis; required inpatient detoxification, including a history of delirium tremens, underlying cardiac disease, or unstable psychiatric illness</td>
<td>Adherence/compliance: Treatment adherence</td>
<td>Outcome: Time to relapse gabapentin vs. placebo SMD: 0.23 (95% CI: -0.41, 0.86)</td>
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<td>Outcome: Rates of medication compliance gabapentin vs. placebo F value: 0.8, p-value: 0.45 (Rates of medication compliance in this study were relatively high and were not significantly different among groups.)</td>
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<td>Outcome: Retention rate gabapentin vs. placebo Chi-square value: 19.9, p-value: 0.33 (There were no significant differences in overall retention rates among the groups of subjects assigned to different medication conditions.)</td>
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<tr>
<td>Study Details</td>
<td>Participants</td>
<td>Intervention Treatment</td>
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<td>Outcome Results (Gender Effects)</td>
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<tr>
<td>Walker et al., 2017</td>
<td>N per treatment arm: Arm 1 (Education): 120 Arm 2 (Motivational interviewing plus feedback): 122</td>
<td>Motivational interviewing plus feedback: One 60-minute telephone-delivered session. A personalized feedback report comprising information on behaviors, attitudes, and beliefs as reported in their screening and baseline assessments was created for all participants. Counselor used motivational interviewing skills throughout the session and reviewed the personal feedback report with the participant</td>
<td>NR</td>
<td>NR</td>
<td>Outcome measure: Symptom improvement</td>
</tr>
<tr>
<td>Study year: 2010–2014</td>
<td>Mean age in years (standard deviation): 28.0 (6.3)</td>
<td></td>
<td></td>
<td></td>
<td>Outcome: Percentage of heavy drinking days DiffDiff 3.93 (95% CI 3.28, 4.57)</td>
</tr>
<tr>
<td>Treatment setting:</td>
<td>Gender female (% per arm): 8%</td>
<td></td>
<td></td>
<td></td>
<td>Outcome: Percentage of days abstinent DiffDiff 2.96 (95% CI 2.37, 3.55)</td>
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<tr>
<td>Other:</td>
<td>Marital status: 57%</td>
<td></td>
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<tr>
<td>Number of sites: 1</td>
<td>Educational attainment: NR</td>
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</tbody>
</table>

Adverse events:
Outcome: Safety and side effects
Gabapentin vs. placebo
"[N]o significant differences in side effects reported among subjects in the different medication conditions throughout the study . . . the most frequent side effects, reported by at least 78% of the subjects, were loss of appetite, diarrhea, nervousness, restlessness, difficulty sleeping, feeling drowsy, fatigue, anger or irritability, depressed mood, runny nose, joint or muscle ache, sweating, and night sweats."
<table>
<thead>
<tr>
<th>Study Details</th>
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<th>Intervention Treatment</th>
<th>Outcome Results (Men)</th>
<th>Outcome Results (Women)</th>
<th>Outcome Results (Gender Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent published associations:</td>
<td></td>
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<tr>
<td>Department of Defense CDMRP Grant W81XWH-09-2-0135</td>
<td>0 (all active-duty soldiers)</td>
<td>N per treatment arm:</td>
<td>Arm 1 (MI–motivational interviewing): 29</td>
<td>Arm 2 (MI): Goal of moderation (NOT abstinence), included a detailed, structural, personalized feedback module, flexible schedule with goal of eliciting change talk and strengthening commitment to goals.</td>
<td>Outcome measure: Symptom improvement</td>
</tr>
<tr>
<td>Exclusion criteria: Soldiers otherwise eligible were excluded if they screened positive for a possible psychotic disorder or had a pending deployment that would prevent completion of follow-up assessments.</td>
<td></td>
<td>Arm 2 (spirit-only MI): 30</td>
<td></td>
<td></td>
<td>Outcome: Mean weekly sum of standard drinks</td>
</tr>
<tr>
<td>Study year: NR</td>
<td>Mean age in years (standard deviation): 40.25 (11.79)</td>
<td></td>
<td></td>
<td></td>
<td>Motivational interviewing vs. spirit-only motivational interviewing</td>
</tr>
<tr>
<td>Treatment setting: NR</td>
<td>Gender female (% per arm): 52%</td>
<td></td>
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<td></td>
<td>(&quot;Gender was included in initial models; however, because there were no significant gender effects, it was excluded from the final models.&quot;)</td>
</tr>
<tr>
<td>Number of sites: 1</td>
<td>Marital status: NR</td>
<td></td>
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<tr>
<td>Educational attainment: 72% with college degree or higher</td>
<td>Therapist training: Other master’s and doctoral-level therapists</td>
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<tr>
<td>% veterans: NR</td>
<td>Allowance for/use of adjunctive treatments: NR</td>
<td></td>
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<tr>
<td>Inclusion criteria: Age 18–65 years, drank an average of at least 15 (women) or 24 (men) standard drinks per week, and had a current AUD diagnosis on the basis of</td>
<td>Setting: Other: NR</td>
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<tr>
<td>Study Details</td>
<td>Participants</td>
<td>Intervention Treatment</td>
<td>Outcome Results (Men)</td>
<td>Outcome Results (Women)</td>
<td>Outcome Results (Gender Effects)</td>
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</tr>
<tr>
<td>DSM–IV–TR</td>
<td></td>
<td>Duration/frequency: 4 sessions over 8 weeks</td>
<td>Comparator category: Other behavioral intervention Spirit-only motivational interviewing; Self-change control</td>
<td>Comparator description: Arm 1 (Spirit-only motivational interviewing). Nondirective elements of motivational interviewing, including therapist stance (warmth, genuineness, egalitarianism), emphasis on client responsibility for change, and avoidance of motivational interviewing–inconsistent behaviors such as advising and confronting.</td>
<td>Power calculation: no</td>
</tr>
</tbody>
</table>

Exclusion criteria: Used substances other than alcohol (except nicotine and marijuana) greater than weekly, presented with a psychotic or bipolar disorder, desired to achieve abstinence at baseline, had a history of severe physical withdrawal symptoms from alcohol, or desired to receive substance abuse treatment during the first 8 weeks of the study.

Follow-up time: 8 weeks

Witkiewitz, Hartzler, and Donovan, 2010; Babor, 1997; Bauer et al., 2007; Carroll et al., 1998; Cisler et al., 1998; Crouch, DiClemente, and Pitts, 2015; Cutler and Fishbain, 2005; DiClemente, 2011; N per treatment arm: Arm 1 (CBT): 567 Arm 2 (MET): 577 Age: NR Gender female (% per arm): 23.3% Marital status: NR Educational attainment: NR % veterans: NR Description of intervention: Behavioral (individual) Treatment protocol fidelity: Authors cite a treatment manual or other source that dictates the treatment protocol Therapist training: NR

Outcomes: Percentage of drinking days aftercare vs. outpatient (For percentage of drinking days, "the three-way alcohol dependence by treatment by motivation interaction was significant for males [B (SE) = −0.004 (0.002), P = 0.03, f² = 0.03], but not for females [B (SE) = 0.004 (0.003), P = 0.18, f² = 0.02] in the aftercare sample. The three-way interaction was not significant for the outpatient sample and neither alcohol dependence by treatment by motivation interaction was significant.)

Outcome measure: Symptom improvement
<table>
<thead>
<tr>
<th>Study Details</th>
<th>Participants</th>
<th>Intervention Treatment</th>
<th>Outcome Results (Men)</th>
<th>Outcome Results (Women)</th>
<th>Outcome Results (Gender Effects)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donovan et al., 2002;</td>
<td>Inclusion criteria: Current DSM-III-R diagnosis of alcohol abuse or dependence, alcohol as the principal drug of abuse, active drinking during the three months prior to entrance into the study, minimum age 18, minimum sixth-grade reading level</td>
<td>Allowance for/use of adjunctive treatments: Other: Abstain from other forms of treatment other than AA/self-help groups</td>
<td></td>
<td></td>
<td>dependence nor gender moderated the outcomes found in the outpatient sample.</td>
</tr>
<tr>
<td>Friend and Pagano, 2007;</td>
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<tr>
<td>Gamble et al., 2010;</td>
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<tr>
<td>Holder et al., 2000;</td>
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<tr>
<td>Ilgen and Moos, 2005;</td>
<td>Exclusion criteria: DSM-III-R diagnosis of current dependence on sedative/hypnotic drugs, stimulants, cocaine or opiates; any intravenous drug use in the prior 6 months; currently a danger to self or others; probation/parole requirements that might interfere with protocol participation; lack of clear prospects for residential stability; inability to identify at least one &quot;locator&quot; person to assist in tracking for follow-up assessments; acute psychosis; severe organic impairment; involvement (current or planned) in alternative treatment for alcohol-related problems other than provided by Project MATCH (defined as more than 6 hours of non-study treatment, except for self-help groups such as AA, during the 3 months of study treatment</td>
<td>Duration/frequency: Weekly (CBT, 12-step facilitation) or 4 times (MET); 12 weeks Comparator category: Other behavior intervention Motivational enhancement therapy; 12-step facilitation Comparator description: Head-to-head: CBT vs. MET vs. 12-step facilitation Power calculation: No Follow-up time: 15 months</td>
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<tr>
<td>Kelly and Hoeppner, 2013;</td>
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<tr>
<td>Magura, Cleland, and Tonigan, 2013;</td>
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<tr>
<td>Manuel, Houck, and Moyers, 2012;</td>
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<tr>
<td>Pagano et al., 2013;</td>
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<tr>
<td>Project MATCH Research Group, 1993;</td>
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<tr>
<td>Project MATCH Research Group, 1997a;</td>
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<tr>
<td>Project MATCH Research Group, 1997b;</td>
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<tr>
<td>Project MATCH Research Group,</td>
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<tr>
<td>Study Details</td>
<td>Participants</td>
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<tr>
<td>1998a; Project MATCH Research Group, 1998b; Tonigan, 2003; Velasquez, DiClemente, and Addy, 2000; Witkiewitz, van der Maas, et al., 2007; Zywiak et al., 2006</td>
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<tr>
<td>Study year: 1990–1997</td>
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<tr>
<td>Treatment setting: Outpatient and residential</td>
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<td>Number of sites: 10</td>
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<tr>
<td>ID</td>
<td>Participants</td>
<td>Intervention/Treatment</td>
<td>Analysis</td>
<td>Results</td>
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<tr>
<td><strong>Reference: Canidate et al., 2017</strong></td>
<td><em>Inclusion criteria:</em> RCT; published in English or capable of being translated; published between 1990 and 2016; intervention was oral or injectable naltrexone with or without behavioral intervention; assessed a measurable drinking outcome; presents results for women alone or distinct from men; participants were 18 years of age or older</td>
<td><em>Description of intervention:</em> Naltrexone</td>
<td><em>Analysis:</em> Narrative</td>
<td><em>Symptom improvement:</em> Drinking quantity: no difference</td>
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<tr>
<td></td>
<td></td>
<td><em>Setting:</em> NR</td>
<td><em>Covariates:</em> NR</td>
<td>Frequency of drinking: No difference</td>
<td></td>
</tr>
<tr>
<td><strong>Search date:</strong> January 2016</td>
<td></td>
<td></td>
<td></td>
<td>Time to first drink: favors women; no difference</td>
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</tr>
<tr>
<td><strong>U.S. proportion of studies:</strong> Mainly (&gt;50%)</td>
<td></td>
<td></td>
<td></td>
<td>Adherence/compliance: NR</td>
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<tr>
<td><strong>Number of included studies reporting on gender:</strong> 7</td>
<td></td>
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<td></td>
<td>Adverse events: NR</td>
<td></td>
</tr>
<tr>
<td><strong>Number of RCTs:</strong> 7</td>
<td></td>
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<td></td>
<td>Narrative summary: The results suggest that naltrexone might lead to modest reductions in quantity of drinking and time to relapse, but not on the frequency of drinking in women. However, among 7 studies, only 1 reported a statistically significant improvement in drinking outcomes among women who received naltrexone versus placebo.</td>
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</table>

<table>
<thead>
<tr>
<th>ID</th>
<th>Participants</th>
<th>Intervention/Treatment</th>
<th>Analysis</th>
<th>Results</th>
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</thead>
<tbody>
<tr>
<td><strong>Reference: Garbutt, Greenblatt, et al., 2014</strong></td>
<td><em>Inclusion criteria:</em> studies examining the efficacy or effectiveness of naltrexone treatment for adults with alcohol disorders or alcohol problems treated in inpatient or outpatient settings; at least 90% of the study population meet the DSM (III or IV), ICD-9 CM or ICD-10 criteria for alcohol dependence; study design of naltrexone to placebo and presence of moderator to absence of moderator or naltrexone in the presence of moderator; open-label and blinded RCTs, nonrandomized controlled trials, prospective and retrospective cohort studies and case–control studies with sample size ≥ 30 patients and laboratory studies</td>
<td><em>Description of intervention:</em> naltrexone 50–100mg/day</td>
<td><em>Analysis:</em> narrative</td>
<td><em>Symptom improvement:</em> naltrexone response did not differ between the sexes in 3 studies, was observed only in women in 1 study, and was observed only in men in 2 studies</td>
</tr>
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<td></td>
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<td><em>Setting:</em> residential treatment facility, outpatient treatment setting (e.g., primary care office, clinic)</td>
<td><em>Covariates:</em> NR</td>
<td>Adherence/compliance: NR</td>
</tr>
<tr>
<td><strong>Search date:</strong> April 2012</td>
<td></td>
<td></td>
<td></td>
<td>Adverse events: NR</td>
</tr>
<tr>
<td><strong>U.S. proportion of studies:</strong> NR</td>
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<td></td>
<td>Narrative summary: Other moderators associated with efficacy included male sex (reported in two of five studies).</td>
</tr>
<tr>
<td>ID</td>
<td>Participants</td>
<td>Intervention/Treatment</td>
<td>Analysis</td>
<td>Results</td>
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<tr>
<td></td>
<td>of any sample size</td>
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</table>

*Exclusion criteria:* comorbid condition in participants, such as cocaine dependence or depression; studies evaluating administration schedule, formulation (tablet versus depot), duration of use or adverse events as moderators; studies evaluating adjunctive psychosocial or pharmacological treatments.

**Reference:** Kranzler and Van Kirk, 2001

**Search date:** NR

**U.S. proportion of studies:** slightly (<50%)

**Number of included studies reporting on gender:** NR

**Number of RCTs:** NR

**Inclusion criteria:** placebo-controlled trials of naltrexone or acamprosate for alcohol dependence that used intention to treat analysis

**Exclusion criteria:** NR

**Description of intervention:** naltrexone or acamprosate

**Setting:** NR

**Analysis:** linear regression

**Covariates:** NA

**Symptom improvement:** NA

**Adherence/compliance:** NR

**Adverse events:** NR

**Narrative summary:** naltrexone: because the mean effect size for the percentage of drinking days was highly heterogeneous, a search for potential moderating variables was undertaken. A group of candidate moderators was correlated with a variable constructed from the individual effect sizes for percentage of drinking days drawn from the contributing studies. Hypothesized moderators included sex (% male). Only year of publication was significantly correlated.

Acamprosate (only European studies): sex was correlated significantly with cumulative abstinent days: \(-0.922, \text{number of studies}: 10, p = 0.001\), such that the lower the proportion of males in a study, the more efficacious acamprosate was in increasing cumulative abstinent days.
<table>
<thead>
<tr>
<th>ID</th>
<th>Participants</th>
<th>Intervention/Treatment</th>
<th>Analysis</th>
<th>Results</th>
</tr>
</thead>
</table>
| Reference: Litten et al., 2013  
Search date: December 2011  
U.S. proportion of studies: partially (≥ 50%)  
Number of included studies reporting on gender: 34 (No. of studies with gender data: NR)  
Number of RCTs: 34 (No. of studies with gender data: NR) | Inclusion criteria: randomized, double-blinded, and placebo-controlled trials; primarily included adults (ages ≥ 18 years) who were diagnosed with alcohol dependence according to research diagnostic criteria, such as the DSM and ICD; participants reported being abstinent from alcohol before randomization; participants received a minimum of 4 weeks of naltrexone treatment; studies included one or more of the following endpoints: percentage of abstinent days, total abstinence, percentage of days without heavy drinking or abstinence from heavy drinking; trials of participants with comorbid psychiatric or substance use (other than nicotine) disorders; trials of injectable naltrexone  
Exclusion criteria: NR | Description of intervention: naltrexone (not enough U.S. studies of acamprosate)  
Setting: residential treatment facility, outpatient treatment setting (e.g., primary care office, clinic) | Analysis: Linear regression  
Covariates: NA | Symptom improvement: Endpoint Percent Days Abstinent; r = 0.29 (p = 0.18) between treatment effect and with % male in study (naltrexone only)  
Adherence/compliance: NR  
Adverse events: NR  
Narrative summary: duration of treatment, percentage of male participants, and number of sites were not significantly correlated with placebo response in naltrexone or acamprosate studies |
Appendix C. Critical Appraisal

Table C.1. Table Risk of Bias for Individual Included Studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Random Sequence Generation (Selection Bias)</th>
<th>Allocation Concealment (Selection Bias)</th>
<th>Blinding of Participants and Providers (Performance Bias)</th>
<th>Blinding of Outcome Assessors (Detection Bias)</th>
<th>Completeness of Reporting Outcome Data by Gender (Attrition Bias)</th>
<th>Selective Outcome Reporting (Reporting Bias)</th>
<th>Study Compliance/Completion Rate</th>
<th>Indication of Adequate Dosage</th>
<th>Overall ROB</th>
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<td>Anton, O'Malley, et al., 2006</td>
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<tr>
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<td>Completeness of Reporting Outcome Data by Gender (Attrition Bias)</td>
<td>Selective Outcome Reporting (Reporting Bias)</td>
<td>Study Compliance/Completion Rate</td>
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</table>
Table C.2. Table Critical Appraisal of Systematic Reviews

<table>
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<tr>
<th>Study ID</th>
<th>Explicit Review Question</th>
<th>Appropriate Inclusion Criteria</th>
<th>Appropriate Search Strategy</th>
<th>Adequate Sources</th>
<th>Appropriate Appraisal Criteria</th>
<th>Dual Reviewer Appraisal</th>
<th>Methods to Minimize Errors</th>
<th>Appropriate Methods to Combine Studies</th>
<th>Publication Bias Assessed</th>
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<td>Canidate et al., 2017</td>
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<td>No</td>
</tr>
</tbody>
</table>
Appendix D. Publications Not Meeting Inclusion Criteria with Reasons for Exclusion


Ahmadi, J., K. M. Kampman, D. M. Oslin, H. M. Pettinati, C. Dackis, and T. Sparkman, “Predictors of Treatment Outcome in Outpatient Cocaine and Alcohol Dependence


———, “Alcohol Use Disorder Treatment: The Association of Pretreatment Use and the Role of Drinking Goal,” Journal of the American Board of Family Medicine, No. 1, 2016. Reason for exclusion: Duplicate


———, “Phone-Delivered Brief Motivational Interventions for Mandated College Students Delivered During the Summer Months,” Journal of Substance Abuse Treatment, Vol. 46, No. 5, 2014, pp. 592–596. Reason for exclusion: Duplicate


Brown, T. G., M. Dongier, M. C. Ouitmet, J. Tremblay, F. Chanut, L. Legault, and N. M. Kin, “The Role of Demographic Characteristics and Readiness to Change in 12-Month Outcome


Busch, A. C., S. Hetzel, and R. T. Brown, “Pharmacotherapeutic Intervention to Improve Treatment Engagement Among Alcohol Dependent Veterans After Hospital Discharge,” Alcoholism: Clinical and Experimental Research, 2015. Reason for exclusion: Abstract only


Crist, R. C., G. A. Doyle, K. M. Kampman, and W. H. Berrettini, “A Delta-Opioid Receptor Genetic Variant Is Associated with Abstinence Prior to and During Cocaine Dependence
Reason for exclusion: Participants


Cucciare, M., S. Ghaus, and K. Weingardt, “A Web-Based Intervention for Reducing Alcohol Use in Veterans Presenting to Primary Care: Preliminary Results from an RCT,” *Alcoholism:
Clinical and Experimental Research, Vol. 36, Supplement 1, June 2012, p. 347A. Reason for exclusion: Abstract only


Emmen, M. J., G. M. Schippers, G. Bleijenberg, and H. Wollersheim, “Effectiveness of Opportunistic Brief Interventions for Problem Drinking in a General Hospital Setting:


**Abuse Treatment, Prevention, and Policy**, Vol. 8, September 10, 2013. Reason for exclusion: Background


———, “Treatment Seeking as a Mechanism of Change in a Randomized Controlled Trial of a Mobile Health Intervention to Support Recovery from Alcohol Use Disorders,” *Journal of Substance Abuse Treatment*, Vol. 77, June 2017, pp. 57–66. Reason for exclusion: Duplicate


———, “The Effects of Acamprosate on Alcohol-Cue Reactivity and Alcohol Priming in Dependent Patients: A Randomized Controlled Trial,” *Psychopharmacology*, No. 1, 2009. Reason for exclusion: Duplicate


Hester, R. K., K. L. Lenberg, W. Campbell, and H. D. Delaney, “Overcoming Addictions, a Web-Based Application, and SMART Recovery, an Online and In-Person Mutual Help Group for Problem Drinkers, Part 1: Three-Month Outcomes of a Randomized Controlled


Participants


Lenaerts, Evelien, Catharina Matheï, Frieda Matthys, Dieter Zeeuws, Leo Pas, Peter Anderson, and Bert Aertgeerts, “Continuing Care for Patients with Alcohol Use Disorders: A


Malte, C. A., “Capsule Commentary on Oslin et al., A Randomized Clinical Trial of Alcohol Care Management Delivered in Department of Veterans Affairs Primary Care Clinics Versus Specialty Addiction Treatment,” *Journal of General Internal Medicine*, Vol. 29, No. 1, 2014. Reason for exclusion: Study design


———, “Gabapentin in Alcoholism: From Laboratory Study to Clinical Trial,” *Basic and Clinical Pharmacology and Toxicology*, Vol. 107, Supplement 1, July 2010a, p. 53. Reason for exclusion: Abstract only

———, “Human Laboratory and Clinical Trial Evidence for Gabapentin Treatment of Alcohol Dependence,” *Alcoholism: Clinical and Experimental Research*, Vol. 34, Supplement 3, August 2010b, p. 64A. Reason for exclusion: Abstract only


McKay, J. R., K. G. Lynch, D. S. Shepard, S. Ratichek, R. Morrison, J. Koppenhaver, and H. M. Pettinati, “The Effectiveness of Telephone-Based Continuing Care in the Clinical


McQueen, J., T. E. Howe, L. Allan, and D. Mains, “Brief Interventions for Heavy Alcohol Users Admitted to General Hospital Wards,” *Cochrane Database of Systematic Reviews*, No. 4, 2009. Reason for exclusion: Study design

McQueen, J., T. E. Howe, L. Allan, D. Mains, and V. Hardy, “Brief Interventions for Heavy Alcohol Users Admitted to General Hospital Wards,” *Cochrane Database of Systematic Reviews*, No. 8, 2011. Reason for exclusion: Study design


———, “Primary Care-Based Intervention to Reduce At-Risk Drinking in Older Adults: A Randomized Controlled Trial,” *Addiction*, Vol. 106, No. 1, January 2011, pp. 111–120. Reason for exclusion: Duplicate


Neighbors, C., M. A. Lewis, R. L. Bergstrom, and M. E. Larimer, “Being Controlled by Normative Influences: Self-Determination as a Moderator of a Normative Feedback Alcohol


Neto, D., R. Lambaz, and J. E. Tavares, “Compliance with Aftercare Treatment, Including Disulfiram, and Effect on Outcome in Alcohol-Dependent Patients,” *Alcohol and Alcoholism*, No. 6, 2007. Reason for exclusion: Setting


O’Farrell, T. J., M. Murphy, J. Alter, and W. Fals-Stewart, “Brief Family Treatment Intervention to Promote Continuing Care Among Alcohol-Dependent Patients in Inpatient Detoxification:


O’Malley, S. S., B. J. Rounsaville, C. Farren, K. Namkoong, R. Wu, J. Robinson, and P. G. O’Connor, “Initial and Maintenance Naltrexone Treatment for Alcohol Dependence Using Primary Care vs. Specialty Care: A Nested Sequence of 3 Randomized Trials,” *Archives of*


Ornstein, S. M., P. M. Miller, A. M. Wessell, R. G. Jenkins, L. S. Nemeth, and P. J. Nietert, “Integration and Sustainability of Alcohol Screening, Brief Intervention, and


Prendergast, M. L., K. McCollister, and U. Warda, “A Randomized Study of the Use of Screening, Brief Intervention, and Referral to Treatment (SBIRT) for Drug and Alcohol Use


———, “Reward and Relief Dimensions of Temptation to Drink: Construct Validity and Role in Predicting Differential Benefit from Acamprosate and Naltrexone,” *Addiction Biology*, 2016. Reason for exclusion: Duplicate


Satre, D. D., A. Leibowitz, S. A. Sterling, Y. Lu, A. Travis, and C. Weisner, “A Randomized Clinical Trial of Motivational Interviewing to Reduce Alcohol and Drug Use Among Patients


Schaeffer, C. M., C. C. Swenson, E. H. Tuerk, and S. W. Henggeler, “Comprehensive Treatment for Co-Occurring Child Maltreatment and Parental Substance Abuse: Outcomes from a 24-


Sinadinovic, K., P. Wennberg, and A. H. Berman, “Targeting Problematic Users of Illicit Drugs with Internet-Based Screening and Brief Intervention: A Randomized Controlled Trial,”


Snyder, J. L., and T. G. Bowers, “The Efficacy of Acamprosate and Naltrexone in the Treatment of Alcohol Dependence: A Relative Benefits Analysis of Randomized Controlled Trials,”


Verheul, R., P. Lehert, P. J. Geerlings, M. W. Koeter, and W. van den Brink, “Predictors of Acamprosate Efficacy: Results from a Pooled Analysis of Seven European Trials Including


Westerberg, V. S., W. R. Miller, J. S. Tonigan, “Comparison of Outcomes for Clients in Randomized Versus Open Trials of Treatment for Alcohol Use Disorders,” Journal of
Studies on Alcohol and Drugs, Vol. 61, No. 5, 2000, pp. 720–727. Reason for exclusion: Duplicate data


Zanjani, F., C. Zubritsky, M. Mullahy, and D. Oslin, “Predictors of Adherence Within an Intervention Research Study of the At-Risk Older Drinker: PRISM-E,” Journal of Geriatric...


———, “The Effect of Alcohol Treatment on Social Costs of Alcohol Dependence: Results from the COMBINE Study,” Medical Care, Vol. 48, No. 5, May 2010, pp. 396–401. Reason for exclusion: Duplicate


References


DoD—See U.S. Department of Defense.


NIAAA—See National Institute on Alcohol Abuse and Alcoholism.

O’Farrell, T. J., K. A. Choquette, and H. S. Cutter, “Couples Relapse Prevention Sessions After Behavioral Marital Therapy for Male Alcoholics: Outcomes During the Three Years After


———, *Problematic Substance Use by DoD Personnel*, Department of Defense Instruction 1010.04, February 20, 2014b.


