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Clinical Interventions for Adults with Comorbid Alcohol Use and Depressive Disorders

A Systematic Review and Network Meta-Analysis

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Preface

Over the past two decades, the U.S. Department of Defense (DoD) has invested unparalleled resources in developing effective treatments for military-related psychological health conditions. Systematic reviews are a key component in the knowledge translation process, as they support the development of evidence-based health care guidelines that promote optimal clinical care. Although a few government agencies, including the U.S. 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 focuses exclusively on psychological health issues. Thus, the Southern California Evidence-Based Practice Center, housed at the RAND Corporation, has been awarded a three-year contract to synthesize research on psychological health interventions important to military populations. This document records a systematic review performed during year two of this three-year project. The review will be of interest to military health policymakers and practitioners who oversee or implement clinical interventions for comorbid alcohol use and depressive disorders.

Dr. Grant's spouse is a salaried employee of Eli Lilly and Company and owns stock in the company. He has accompanied his spouse on company-sponsored travel. No other authors have any conflicts of interest to declare.

The research reported here was completed in November 2018 and underwent security review with the sponsor and the Defense Office of Prepublication and Security Review before public release. This research was sponsored by the Psychological Health Center of Excellence (PHCoE) and conducted within the Forces and Resources Policy Center of the RAND National Security Research Division (NSRD), which operates the National Defense Research Institute (NDRI), a federally funded research and development center sponsored by the Office of the Secretary of Defense, the Joint Staff, the Unified Combatant Commands, the Navy, the Marine Corps, the defense agencies, and the defense intelligence enterprise. For more information on the RAND Forces and Resources Policy Center, see www.rand.org/nsrd/ndri/centers/frp or contact the director (contact information is provided on the webpage).

Abstract

Alcohol use disorders (AUDs) and depressive disorders are prevalent, and a significant number of people are diagnosed with both. Identifying effective treatments for patients with co-occurring AUDs and depressive disorders is important, given the potential severity of symptoms, as well as the negative societal consequences of ineffective treatment. The purpose of this systematic review and network meta-analysis (NMA) is to synthesize evidence on the effects of interventions and to compare the relative effectiveness of identified interventions in improving symptoms of adults with co-occurring AUDs and depressive disorders. The review aims to help the Department of Defense with clinical decisionmaking regarding which interventions to use with patients dually diagnosed with co-occurring AUD and depressive disorders.

We searched six databases and three clinical trial registries through May 2018 to identify randomized controlled trials (RCTs) that evaluated the effects and safety of interventions to treat individuals with co-occurring AUD and depressive disorders. Two independent reviewers screened identified citations using predetermined eligibility criteria, assessed relevant citations for eligibility, and extracted study-level information and outcome data. We synthesized data via random effects NMA in a frequentist framework to identify both pairwise effect estimates for each intervention comparison and relative rankings of identified interventions for each outcome. We assessed and reported our confidence in effect estimates and rankings using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

In total, 35 RCTs with 2,634 participants met eligibility criteria. Most studies evaluated clinical interventions for participants with major depressive disorder (51 percent) and alcohol dependence (54 percent) receiving treatment in the United States (60 percent). Overall, the included studies contained 73 intervention arms (all of which were adjunctive to treatment as usual) and two separate networks: one comparing pharmacological interventions (13 classes) and one comparing psychological interventions (six classes). For depressive symptoms, we have moderate confidence in estimates at postintervention of a beneficial effect of cognitive behavioral therapy (CBT) over no treatment additional to treatment as usual (TAU) (standardized mean difference [SMD] -0.84 [-1.05 to -0.63], $k = 2$, $n = 430$), and we have low confidence in an estimate at postintervention of a beneficial effect of tricyclic antidepressants (TCAs) over pharmacological placebo (SMD -0.37 [-0.72 to -0.02], $k = 3$, $n = 137$). For total drinking, we have moderate confidence in an estimate of a beneficial effect at post-intervention of selective serotonin reuptake inhibitors (SSRIs) versus pharmacological placebo (SMD -0.30 [-0.59 to -0.02], $k = 3$, $n = 271$). For functional status, we have moderate confidence in estimates of a beneficial effect at postintervention of SSRIs over pharmacological placebo (SMD -0.92 [-1.36 to -0.47], $k = 3$, $n = 147$). We have moderate confidence that patients receiving SSRIs are more likely on average to experience an adverse event than patients receiving pharmacological placebo.

(odds ratio [OR] 2.20 [0.94 to 5.16], $k = 6$, $n = 722$), and we have low confidence that patients receiving SSRIs are more likely to experience a serious adverse event than patients receiving pharmacological placebo (OR 1.56 [0.81 to 2.94], $k = 3$, $n = 492$). We have very low confidence in all other effect estimates. Subgroup analyses suggest that findings may be more applicable to specific types of alcohol use and depressive disorders, clinical settings, and pharmacological and psychological interventions.

The available evidence suggests potentially actionable benefits at postintervention of CBT for depressive symptoms, TCAs for depressive symptoms, and SSRIs for total drinking and functional status—though SSRIs also have higher risks of adverse events (including serious adverse events), which makes it imperative to formulate recommendations on their net benefit compared with other classes of intervention. We also identified significant effects for several other comparisons that could be prioritized for direct comparisons in future trials but for which we have insufficient confidence to support consideration for policy and practice recommendations on the basis of evidence on effectiveness. Additional studies—in particular, pragmatic, adequately powered, preregistered, and well-reported RCTs—are needed to provide more conclusive evidence about the (comparative) effectiveness of clinical interventions for treating adults with depressive disorders and AUDs. Notably, numerous clinical interventions contained in clinical practice guidelines (CPGs) for these conditions are missing from the current body of evidence. Researchers, policymakers, funders, and practitioners may wish to establish future priorities on researching clinical interventions for this patient population, while committees charged with providing recommendations for health systems and updating CPGs may be interested in using this report as a source of evidence on the comparative effectiveness of these clinical interventions.

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Executive Summary

Introduction

Alcohol use disorders (AUDs) and depressive disorders are prevalent, and a significant number of people are diagnosed with both. Identifying effective treatments for patients with co-occurring AUDs and depressive disorders is important, given the potential severity of symptoms, as well as the negative societal consequences of ineffective treatment. The purpose of this systematic review and network meta-analysis (NMA) is to synthesize evidence on the effects of interventions and to compare the relative effectiveness of identified interventions in improving symptoms of adults with co-occurring AUDs and depressive disorders. The review aims to help the Department of Defense (DoD) with clinical decisionmaking regarding which interventions to use with patients dually diagnosed with co-occurring AUD and depressive disorders.

Key Questions

The following questions and subquestions guided this systematic review:

1. What are the effects of clinical interventions on remission from depression and alcohol use (primary outcomes), depressive symptoms, number of drinks, number of heavy drinking days, withdrawal and craving symptoms, health-related quality of life, functional status, and adverse events in adults with a co-occurring AUD and depressive disorder?
 - a. What are the effects of interventions by type of AUD or depressive disorder?
 - b. What are the effects of interventions by type of clinical setting?
 - c. What are the effects of interventions by type of intervention?
2. What are the relative rankings of identified interventions, in order of effectiveness on outcomes of interest?

Methods

We registered the protocol for this review in PROSPERO (CRD42017078239), the international prospective register of systematic reviews, before completing formal screening of search results against eligibility criteria (Grant et al., 2017). To answer our key questions, we conducted a systematic search through May 2018 of several electronic databases (CINAHL, CDSR, EMBASE, PubMed, PsycINFO, and Web of Science), clinical trial registries (ClinicalTrials.gov, CENTRAL, and ICTRP), and bibliographies of previous systematic reviews. We included randomized controlled trials (RCTs) testing the effects and safety of clinical interventions to treat individuals with co-occurring AUD and depressive disorders. Two independent reviewers screened citations using predetermined eligibility criteria, assessed relevant citations for eligibility, and extracted study-level information and outcome data.

Outcomes of interest included remission from depression and alcohol use (primary outcomes), depressive symptoms, total drinking, heavy drinking, health-related quality of life, functional status, and adverse events.

To synthesize data, we first conducted pairwise meta-analyses of all direct comparisons to assess the statistical heterogeneity within each comparison. Then we qualitatively examined the distribution of characteristics across studies in each network that may modify intervention effects to assess the transitivity assumption of NMA. This transitivity assumption involves assuming that sets of studies comparing different interventions in a network are sufficiently similar to each other with respect to characteristics that moderate their relative effects of interventions, and this assumption leads to assessments of consistency of direct and indirect evidence within each network. Following these assessments, we created network diagrams for each outcome to explore the network geometry and identified two separate networks across outcomes: one for pharmacological and another for psychological interventions. We then synthesized data via random effects NMA in a frequentist framework to identify both pairwise effect estimates for each intervention comparison and the relative rankings of identified interventions' effects on outcomes of interest; NMAs were conducted by intervention class and outcome. We grouped outcome data by follow-up period: immediately postintervention, short-term follow-up (1–5 months postintervention), long-term follow-up (6–11 months postintervention), and very long-term follow-up (12+ months postintervention). For each combination of pairwise comparison, outcome, and time point, we used standardized mean differences (SMDs) for continuous outcomes and odds ratios (OR) for dichotomous outcomes, with a 95 percent confidence interval, to estimate intervention effects.

We assumed a constant heterogeneity variance across all comparisons in each network, assessed between-study clinical and methodological heterogeneity by examining key characteristics of included trials, and assessed between-study statistical heterogeneity for each pairwise comparison using the I^2 statistic. We assessed transitivity by systematically tabulating and examining characteristics across trials, local inconsistency by splitting and comparing direct and indirect evidence, and global inconsistency using design-based decomposition of Cochran's Q as well as a net heat plot. For each outcome and time point, we also ranked interventions in order of effectiveness using p scores. When sufficient data were available, we conducted subgroup analyses to examine the applicability of effects by type of alcohol use and depressive disorder, clinical setting, and intervention. We conducted sensitivity analyses excluding pharmacological interventions that do not have legal approval to be prescribed in the United States, using alternative outcome data reported in included studies, and based on risk of bias assessments. Last, we assessed and reported our confidence in effect estimates and rankings using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. For pairwise estimates in an NMA, the process further involves (1) presenting the direct and indirect effect estimates for the pairwise comparison, (2) rating confidence in both estimates (including an assessment of intransitivity), (3) presenting the network estimate for the

pairwise comparison, and (4) rating the confidence of the network estimate based on the ratings of the direct and indirect estimates, as well as an assessment of coherence.

Results

We included $k = 35$ trials that randomized a total of $n = 2,634$ participants with both a depressive disorder and AUD. Depression involved formal diagnoses of major depressive disorder only (51 percent), a major depressive episode only (9 percent), dysthymic disorder only (6 percent), or more than one of the foregoing disorders (12 percent); use of symptom rating scales to indicate a depressive disorder (17 percent); or simply reporting that participants had “depression” (6 percent). AUD involved formal diagnoses of alcohol dependence (54 percent), formal diagnoses of either alcohol abuse or dependence (23 percent), or simply reporting that participants had some form of “alcoholism,” “alcohol dependence,” or “alcohol addiction” (23 percent). The average participant was middle-aged (median: 42 years; interquartile range [IQR]: 38–45) and male (median: 69 percent; IQR: 52–81 percent). All studies randomized individual participants (rather than clusters of participants) to intervention groups, and most studies (77 percent) involved only one site. Studies took place in 13 countries, with most (60 percent) taking place in the United States. The most common stage in the clinical pathway was outpatient care (40 percent), and the settings primarily focused on alcohol or substance use (49 percent).

Combined, the studies contained 73 intervention arms and two networks: one of pharmacological interventions and one of psychological interventions. The intervention classes in the pharmacological network included atypical antipsychotics (AAPs), glutamatergic antagonists, monoamine reuptake inhibitors (MRIs), N-methyl-D-aspartate (NMDA) antagonists, nonselective and noncompetitive antagonists of the nicotinic acetylcholine receptors (nAChRs), norepinephrine reuptake inhibitors (NRIs), opioid antagonists, sedatives, selective serotonin reuptake inhibitors (SSRIs), serotonin antagonist and reuptake inhibitors (SARIs), tetracyclic antidepressants (TeCAs), tricyclic antidepressants (TCAs), and pharmacological placebo. The intervention classes in the psychological network included cognitive behavioral therapy (CBT), interpersonal therapy (IPT), self-management support (SMS), supportive psychotherapy (SP), psychological placebo, and no additional treatment. Compared with interventions recommended in pertinent clinical practice guidelines (CPGs), included studies evaluated 13 out of 38 pharmacological interventions (34 percent) and 2 out of 11 psychological interventions (18 percent) recommended in the Department of Veterans Affairs/DoD CPGs for alcohol use and major depressive disorders.

All interventions in this body of evidence were adjunctive to a TAU (treatment as usual) cointervention. Components of TAU included standalone interventions (detoxification, psychotherapy, pharmacotherapy, and self-help groups), as well as multicomponent inpatient and outpatient programs in substance use and dual-diagnosis treatment settings. Standalone

detoxification services (4; 11 percent) included the use of agents such as anticonvulsants (dilantin), sedatives (phenobarbital, chloral hydrate, lorazepam), anxiolytics (diazepam), antihistamines (Vistaril), and vitamins (B complex). Standalone psychotherapy (10; 29 percent) included CBT, motivational enhancement therapy, psychoeducation, and SP. Standalone pharmacotherapy (5; 14 percent) included medication specifically for depressive symptoms (e.g., sertraline) and alcohol use (e.g., benzodiazepines, naltrexone), as well as other psychotropic drugs (e.g., anxiolytics, hypnotics). Standalone self-help groups (2; 6 percent) involved Alcoholics Anonymous. Inpatient programs (11; 31 percent) included detoxification, psychotherapy, pharmacotherapy, rehabilitative services, and self-help groups. Outpatient substance use programs (14; 40 percent) included pharmacotherapy, psychotherapy, and self-help groups.

Based on syntheses, the interventions with potentially actionable benefits at postintervention are CBT (versus no additional treatment) for depressive symptoms (SMD -0.84 [-1.05 to -0.63], $k = 2$, $n = 430$, moderate confidence), TCAs (versus pharmacological placebo) for depressive symptoms (SMD -0.37 [-0.72 to -0.02], $k = 3$, $n = 137$, low confidence), SSRIs (versus pharmacological placebo) for total drinking (SMD -0.30 [-0.59 to -0.02], $k = 3$, $n = 271$, moderate confidence), and SSRIs (versus pharmacological placebo) for functional status (SMD -0.92 [-1.36 to -0.47], $k = 3$, $n = 147$, moderate confidence). However, we also have moderate confidence that patients receiving SSRIs are more likely on average to experience an adverse event than patients receiving pharmacological placebo (OR 2.20 [0.94 to 5.16], $k = 6$, $n = 722$), and we have low confidence that patients receiving SSRIs are more likely to experience a serious adverse event than patients receiving pharmacological placebo (OR 1.56 [0.81 to 2.94], $k = 3$, $n = 492$). We have very low confidence in all other effect estimates. Subgroup analyses suggest that findings may be more applicable to specific types of alcohol use and depressive disorders, clinical settings, and pharmacological and psychological interventions. We provide greater detail on results in the next section.

Key Question 1: Intervention Effects on Outcomes of Interest

Remission from Depression

We have very low confidence in all estimates at postintervention; confidence intervals for all comparisons did not exclude a null effect.

Remission from Alcohol Use

We have very low confidence in all estimates at postintervention, including estimates of a beneficial effect of opioid antagonists combined with SSRIs over glutamatergic antagonists (OR 0.16 [0.03 to 0.95], indirect evidence only), opioid antagonists (OR 0.24 [0.10 to 0.61], $k = 1$, $n = 88$), pharmacological placebo (OR 0.34 [0.15 to 0.79], $k = 1$, $n = 80$), and SSRIs (OR 0.32 [0.14 to 0.75], $k = 1$, $n = 81$). Confidence intervals for all other comparisons at postintervention did not exclude a null effect. We also have very low confidence in an estimate at long-term

(6 months postintervention) follow-up of a beneficial effect of opioid antagonists combined with SSRIs compared with SSRIs (OR 0.26 [0.07 to 0.97], $k = 1$, $n = 31$).

Depressive Symptoms

We have moderate confidence in estimates at postintervention of a beneficial effect of CBT over no treatment in addition to TAU (SMD -0.84 [-1.05 to -0.63], $k = 2$, $n = 430$). We have low confidence in an estimate at postintervention of a beneficial effect of TCAs over pharmacological placebo (SMD -0.37 [-0.72 to -0.02], $k = 3$, $n = 137$). We have very low confidence in an estimate of a beneficial effect at postintervention of opioid antagonists in combination with SSRIs over pharmacological placebo (SMD -0.66 [-1.27 to -0.06], $k = 1$, $n = 43$) and SMS over psychological placebo (SMD -0.88 [-1.44 to -0.32], $k = 1$, $n = 54$). We have very low confidence in all other estimates at postintervention; confidence intervals for all other comparisons did not exclude a null effect.

We also have very low confidence at long-term (6 months postintervention) follow-up of a beneficial effect of SSRIs over pharmacological placebo (SMD -0.80 [-1.53 to -0.07], $k = 1$, $n = 31$). We have very low confidence in all other estimates at other follow-up periods; confidence intervals for all other comparisons did not exclude a null effect.

Withdrawal and Craving Symptoms

We have very low confidence in all estimates at postintervention; confidence intervals for all comparisons did not exclude a null effect.

Total Drinking

We have moderate confidence in an estimate of a beneficial effect at postintervention of SSRIs over pharmacological placebo (SMD -0.30 [-0.59 to -0.02], $k = 3$, $n = 271$). We have very low confidence in estimates of a beneficial effect at postintervention of NMDA antagonists over glutamatergic antagonists (SMD -2.23 [-3.30 to -1.16], very indirect evidence only [i.e., no common comparator, with a network distance of at least two edges]), pharmacological placebo (SMD -2.23 [-2.87 to -1.58], indirect evidence only), SARIs (SMD -2.00 [-2.78 to -1.22], indirect evidence only), SSRIs (SMD -1.92 [-2.51 to -1.34], $k = 1$, $n = 80$), TCAs (SMD -2.14 [-3.01 to -1.27], very indirect evidence only), and TeCAs (SMD -1.69 [-2.95 to -0.42], very indirect evidence only). We also have very low confidence in estimates of a beneficial effect of CBT over no additional treatment at postintervention (SMD -0.25 [-0.47 to -0.04], $k = 1$, $n = 350$). We have very low confidence in all other estimates; confidence intervals for all other comparisons did not exclude a null effect.

Heavy Drinking

We have very low confidence in estimates of beneficial effects at postintervention of an opioid antagonist in combination with an SSRI over pharmacological placebo (SMD -0.60 [-1.13 to -0.08], $k = 1$, $n = 43$), and SARIs over opioid antagonists (SMD -0.95 [-1.82 to

−0.08], indirect evidence only), pharmacological placebo (SMD −1.04 [−1.80 to −0.27], $k = 1$, $n = 41$), SSRIs (SMD −0.91 [−1.73 to −0.09], indirect evidence only), TCAs (SMD −1.25 [−2.27 to −0.24] indirect evidence only), and TeCAs (SMD −1.43 [−2.79 to −0.06], indirect evidence only). We have very low confidence in all other estimates at postintervention; confidence intervals for all other comparisons did not exclude a null effect.

Health-Related Quality of Life

We have very low confidence in all estimates at postintervention; confidence intervals for all comparisons did not exclude a null effect.

Functional Status

We have moderate confidence in estimates of a beneficial effect at postintervention of SSRI over pharmacological placebo (SMD −0.92 [−1.36 to −0.47], $k = 3$, $n = 147$). We have very low confidence in estimates of beneficial effects at postintervention of TCAs over pharmacological placebo (SMD −0.83 [−1.36 to −0.28], $k = 2$, $n = 96$), SARIs over pharmacological placebo (SMD −0.63 [−1.24 to −0.03], $k = 1$, $n = 56$), NMDA antagonists over pharmacological placebo (SMD −1.21 [−1.84 to −0.59], indirect evidence only), NMDA antagonists over glutamatergic antagonists (SMD −1.14 [−2.17 to −0.11], indirect evidence only), an AAP in combination with an SSRI over pharmacological placebo (SMD −1.02 [−1.86 to −0.18], indirect evidence only), and SMS compared with psychological placebo (SMD −0.97 [−1.54 to −0.41], $k = 1$, $n = 54$). We have very low confidence in all other estimates; confidence intervals for all other comparisons did not exclude a null effect.

Adverse Events

We have moderate confidence that patients receiving SSRIs are more likely on average to experience an adverse event than patients receiving pharmacological placebo (OR 2.20 [0.94 to 5.16], $k = 6$, $n = 722$), low confidence that patients receiving SSRIs are more likely to experience a serious adverse event than patients receiving pharmacological placebo (OR 1.56 [0.81 to 2.94], $k = 3$, $n = 492$), and very low confidence that patients receiving SSRIs are more likely to experience a serious adverse event than patients receiving an opioid antagonist in combination with an SSRI (OR 4.47 [1.51 to 13.26], $k = 1$, $n = 82$). We have very low confidence in all other estimates; confidence intervals for all other comparisons did not exclude a null effect.

Key Question 1a: Effects by Type of Disorder

We provide estimates for specific types of disorders in this section; as a reminder, our confidence in the body of evidence is primarily low or very low confidence across all outcomes.

Alcohol Use Disorders

Patients with alcohol dependence benefited from

- TCAs over pharmacological placebo on remission from depression at postintervention (OR 0.05 [0.004 to 0.62])
- an opioid antagonist in addition to an SSRI over pharmacological placebo (OR 0.35 [0.15 to 0.79]), SSRIs (OR 0.32 [0.14 to 0.73]), and TCAs (OR 0.08 [0.01 to 0.99]) on remission from alcohol use at postintervention
- SSRIs over pharmacological placebo on remission from alcohol use at long-term follow-up (OR 0.26 [0.07 to 0.97])
- CBT over no additional treatment on depressive symptoms at postintervention (SMD -0.84 [-1.37 to -0.31])
- SSRIs over pharmacological placebo (SMD -0.80 [-1.53 to -0.07]) and CBT over no additional treatment (SMD -1.59 [-1.83 to -1.34]) on depressive symptoms at long-term follow-up
- CBT over no additional treatment (SMD -0.25 [-0.47 to -0.04]), as well as NMDA antagonists over pharmacological placebo (SMD -2.23 [-3.06 to -1.41]), SARIs (SMD -2.00 [-2.97 to -1.03]), and SSRIs (SMD -1.92 [-2.62 to -1.23]), on total drinking at postintervention
- SARIs over opioid antagonists (SMD -0.95 [-1.82 to -0.08]), SARIs over pharmacological placebo (SMD -1.04 [-1.80 to -0.27]), and an opioid antagonist in combination with an SSRI over pharmacological placebo (SMD -0.60 [-1.13 to -0.08]) on heavy drinking at postintervention
- an AAP in combination with an SSRI over pharmacological placebo (SMD -1.02 [-1.86 to -0.18]), NMDA antagonists over pharmacological placebo (SMD -1.21 [-1.84 to -0.59]), SARIs over pharmacological placebo (SMD -0.63 [-1.24 to -0.03]), and SSRIs over pharmacological placebo (SMD -0.92 [-1.36 to -0.47]) on functional status at postintervention.

Patients receiving SSRIs were more likely on average to experience a serious adverse event than patients receiving an opioid antagonist in combination with an SSRI (OR 4.32 [1.45 to 12.87]).

Patients with multiple AUDs benefited from

- SMS over psychological placebo (SMD -0.88 [-1.44 to -0.32]) on depressive symptoms at postintervention
- TCAs over pharmacological placebo (SMD -0.86 [-1.51 to -0.22]) and SMS over psychological placebo (SMD -0.97 [-1.54 to -0.41]) on functional status at postintervention.

Depressive Disorders

Patients with major depressive disorder benefited from

- TCAs over NMDA antagonists (OR 29.41 [1.05 to 824.22]), SSRIs (OR 24.06 [1.49 to 388.60]), and pharmacological placebo (OR 20.00 [1.46 to 273.89]) on remission from depression at postintervention
- an opioid antagonist in combination with an SSRI over an opioid antagonist alone (OR 3.98 [1.71 to 9.26]), an SSRI alone (OR 0.29 [0.14 to 0.64]), and pharmacological placebo (OR 0.37 [0.17 to 0.80]); opioid antagonists over glutamatergic antagonists (OR

5.63 [1.04 to 30.39]); and pharmacological placebo over SSRIs (OR 0.79 [0.71 to 0.88]) on remission from alcohol use at postintervention

- SSRIs over pharmacological placebo (OR 0.26 [0.07 to 0.97]) on remission from alcohol use at long-term follow-up
- SMS over psychological placebo (SMD -0.88 [-1.44 to -0.32]) on depressive symptoms at postintervention
- SSRIs over pharmacological placebo (SMD -0.80 [-1.53 to -0.07]) on depressive symptoms at long-term follow-up
- NMDA antagonists over glutamatergic antagonists (SMD -2.59 [-3.72 to -1.47]), pharmacological placebo (SMD -2.59 [-3.37 to -1.82]), SARIs (SMD -2.37 [-3.24 to -1.50]), SSRIs (SMD -1.92 [-2.45 to -1.39]), and TCAs (SMD -2.05 [-3.37 to -0.73]) on total drinking at postintervention
- SARIs over pharmacological placebo (SMD -1.04 [-2.01 to -0.07]) on heavy drinking at postintervention
- an AAP in combination with an SSRI over pharmacological placebo (SMD -0.91 [-1.82 to -0.003]), NMDA antagonists over pharmacological placebo (SMD -1.11 [-1.83 to -0.39]), SARIs over pharmacological placebo (SMD -0.63 [-1.24 to -0.03]), SSRIs over pharmacological placebo (SMD -0.81 [-1.38 to -0.24]), and SMS over psychological placebo (SMD -0.97 [-1.54 to -0.41]) on functional status at postintervention.

Patients receiving SSRIs were more likely on average to experience a serious adverse event than patients receiving an opioid antagonist in combination with an SSRI (OR 4.32 [1.45 to 12.87]).

Patients with mild depressive disorder benefited from

- CBT over no additional treatment on depressive symptoms at postintervention (SMD -0.86 [-1.08 to -0.63]), short-term follow-up (SMD -0.98 [-1.21 to -0.75]), and long-term follow-up (SMD -1.59 [-1.83 to -1.34])
- CBT over no additional treatment at postintervention (SMD -0.25 [-0.47 to -0.04]) on total drinking at postintervention.

Patients with depressive episodes benefited from SSRIs over pharmacological placebo on remission from alcohol use at postintervention (OR 0.58 [0.37 to 0.90]).

Patients with multiple depressive disorders benefited from

- CBT over no additional treatment on depressive symptoms at postintervention (SMD -0.74 [-1.27 to -0.22]) and short-term follow-up (SMD -0.62 [-1.14 to -0.10])
- TCAs over pharmacological placebo (SMD -0.86 [-1.51 to -0.22]) on functional status at postintervention.

Key Question 1b: Effects by Type of Clinical Setting

We provide estimates for specific types of settings in this section; as a reminder, our confidence in the body of evidence is primarily low or very low confidence across all outcomes.

Stage in Clinical Pathway

Patients receiving inpatient care during the trial benefited from SSRIs over pharmacological placebo (SMD -0.88 [-1.66 to -0.10]) on functional status at postintervention. Patients receiving SSRIs were more likely on average to experience an adverse event than patients receiving pharmacological placebo (OR 3.67 [1.21 to 11.18]).

Patients receiving outpatient care during the trial benefited from

- an opioid antagonist in combination with an SSRI over pharmacological placebo (OR 0.24 [0.06 to 0.86]) and SSRIs (OR 0.20 [0.06 to 0.72]), SARIs over pharmacological placebo (OR 0.21 [0.05 to 0.85]) and SSRIs (OR 0.18 [0.04 to 0.83]), and TCAs over pharmacological placebo (OR 0.28 [0.09 to 0.86]) and SSRIs (OR 0.24 [0.07 to 0.85]) on remission from depression at postintervention
- an opioid antagonist in combination with an SSRI over NMDA antagonists (SMD -0.82 [-1.55 to -0.09]), pharmacological placebo (SMD -0.52 [-1.03 to -0.01]), and SSRIs (SMD -0.65 [-1.15 to -0.15]); TCAs over SSRIs (SMD -0.58 [-1.11 to -0.04]); CBT over no additional treatment (SMD -0.84 [-1.37 to -0.31]); and SMS over psychological placebo (SMD -0.88 [-1.44 to -0.32]) on depressive symptoms at postintervention
- CBT over no additional treatment (SMD -1.59 [-1.83 to -1.34]) on depressive symptoms at long-term follow-up
- NMDAs over pharmacological placebo (SMD -2.02 [-2.65 to -1.39]), SARIs (SMD -1.80 [-2.54 to -1.05]), SSRIs (SMD -1.92 [-2.45 to -1.39]), TCAs (SMD -1.93 [-2.75 to -1.11]), and TeCAs (SMD -1.48 [-2.71 to -0.24]) on total drinking at postintervention
- CBT over no additional treatment (SMD -0.25 [-0.47 to -0.04]) on total drinking at postintervention
- NMDAs over SSRIs (SMD -0.46 [-0.90 to -0.01]); an opioid antagonist in combination with an SSRI over opioid antagonists (SMD -0.46 [-0.88 to -0.03]), pharmacological placebo (SMD -0.57 [-0.98 to -0.16]), SSRIs (SMD -0.57 [-0.98 to -0.16]), and TCAs (SMD -0.79 [-1.45 to -0.12]); and SARIs over opioid antagonists (SMD -0.92 [-1.68 to -0.17]), SSRIs (SMD -1.04 [-1.74 to -0.33]), TCAs (SMD -1.25 [-2.09 to -0.42]), and TeCAs (SMD -1.43 [-2.67 to -0.18]) on heavy drinking at postintervention
- SARIs over pharmacological placebo (SMD -0.63 [-1.24 to -0.03]), TCAs over pharmacological placebo (SMD -0.86 [-1.51 to -0.22]), and SMS over psychological placebo (SMD -0.97 [-1.54 to -0.41]) on functional status at postintervention.

Patients receiving SSRIs were more likely on average to experience a serious adverse event than patients receiving an opioid antagonist in combination with an SSRI (OR 4.44 [1.43 to 13.77]).

Patients receiving both inpatient and outpatient care during the trial benefited from

- SSRIs over pharmacological placebo (OR 0.14 [0.03 to 0.63]) on remission from depression at postintervention
- SSRIs over pharmacological placebo (OR 0.26 [0.07 to 0.97]) on remission from alcohol use at long-term follow-up

- SSRIs over pharmacological placebo (SMD -0.80 [-1.53 to -0.07]) on depressive symptoms at long-term follow-up
- SSRIs over pharmacological placebo (SMD -0.67 [-1.23 to -0.10]) on total drinking at postintervention
- SSRIs over pharmacological placebo (SMD -0.80 [-1.37 to -0.23]) on heavy drinking at postintervention.

Clinical Setting

Patients in substance use treatment settings benefited from

- NMDA antagonists over pharmacological placebo (OR 0.40 [0.16 to 0.99]), and an opioid antagonist in combination with an SSRI over an opioid antagonist alone (OR 0.26 [0.10 to 0.65]), pharmacological placebo (OR 0.27 [0.12 to 0.62]), SSRIs (OR 0.38 [0.17 to 0.85]), and TCAs (OR 0.06 [0.005 to 0.76]) on remission from alcohol use at postintervention
- NMDA antagonists over pharmacological placebo (SMD -2.02 [-2.65 to -1.39]) and SSRIs (SMD -1.92 [-2.45 to -1.39]) on total drinking at postintervention
- NMDA antagonists over SSRIs (SMD -0.46 [-0.90 to -0.01]), and an opioid antagonist in combination with an SSRI over an opioid antagonist alone (SMD -0.46 [-0.88 to -0.03]), an SSRI alone (SMD -0.57 [-0.98 to -0.17]), and pharmacological placebo (SMD -0.57 [-0.97 to -0.16]) on heavy drinking at postintervention
- NMDA antagonists over pharmacological placebo (SMD -1.47 [-2.77 to -0.17]), and SSRIs over pharmacological placebo (SMD -1.17 [-2.12 to -0.23]) on functional status at postintervention.

Patients were more likely on average to experience an adverse event when receiving an opioid antagonist in combination with an SSRI compared with patients receiving pharmacological placebo (OR 4.75 [1.23 to 18.38]) and an SSRI compared with those receiving pharmacological placebo (OR 2.33 [1.12 to 4.83]).

Patients were more likely on average to experience a serious adverse event when receiving SSRIs compared with patients receiving an opioid antagonist in combination with an SSRI (OR 4.44 [1.43 to 13.77]).

Patients in mental health treatment settings benefited from TCAs over pharmacological placebo (SMD -0.86 [-1.51 to -0.22]) on functional status at postintervention.

Patients in dual-diagnosis treatment settings benefited from

- SARIs over pharmacological placebo (OR 0.21 [0.06 to 0.72]) on remission from depression at postintervention
- SSRIs over pharmacological placebo (OR 0.26 [0.07 to 0.97]) on remission from alcohol use at long-term follow-up
- CBT over no additional treatment (SMD -0.84 [-1.37 to -0.31]) and SMS over psychological placebo (SMD -0.88 [-1.44 to -0.32]) on depressive symptoms at postintervention

- SSRIs over pharmacological placebo (SMD -0.80 [-1.53 to -0.0703]) and CBT over no additional treatment (SMD -1.59 [-1.83 to -1.34]) on depressive symptoms at long-term follow-up
- SSRIs over pharmacological placebo (SMD -0.67 [-1.23 to -0.10]) and CBT over no additional treatment (SMD -0.25 [-0.47 to -0.04]) on total drinking at postintervention
- SARIs over pharmacological placebo (SMD -1.04 [-1.69 to -0.38]), and TeCAs (SMD -1.43 [-2.67 to -0.18]), and SSRIs over pharmacological placebo (SMD -0.80 [-1.37 to -0.23]) on heavy drinking at postintervention
- an AAP in combination with an SSRI over pharmacological placebo (SMD -0.91 [-1.82 to -0.003]), SARIs over pharmacological placebo (SMD -0.63 [-1.24 to -0.03]), SSRIs over pharmacological placebo (SMD -0.81 [-1.38 to -0.24]), and SMS over psychological placebo (SMD -0.97 [-1.54 to -0.41]) on functional status at postintervention.

Key Question 1c: Effects by Type of Intervention

We provide estimates for specific types of intervention in this section; as a reminder, our confidence in the body of evidence is primarily low or very low confidence across all outcomes.

Pharmacological Interventions

Patients receiving pharmacological interventions benefited from

- the TCA desipramine over the SSRI citalopram (OR 0.04 [0.002 to 0.73]), the SSRI sertraline (OR 0.07 [0.005 to 0.99]), and pharmacological placebo (OR 0.05 [0.004 to 0.67]) on remission from depression at postintervention
- the NMDA antagonist memantine over the glutamatergic antagonist acamprosate (OR 0.13 [0.02 to 0.90]), TCA desipramine (OR 0.06 [0.004 to 0.89]), the opioid antagonist naltrexone (OR 0.18 [0.05 to 0.73]), the SSRI sertraline (OR 0.21 [0.06 to 0.74]), and the pharmacological placebo (OR 0.27 [0.08 to 0.93]); the SSRI citalopram over the SSRI sertraline (OR 0.50 [0.27 to 0.92]); the SSRI escitalopram over the SSRI sertraline (OR 0.39 [0.15 to 0.99]); the TCA imipramine over the opioid antagonist naltrexone (OR 0.22 [0.06 to 0.83]) and the SSRI sertraline (OR 0.26 [0.08 to 0.84]); naltrexone in combination with sertraline over naltrexone alone (OR 0.25 [0.11 to 0.59]), sertraline alone (OR 0.29 [0.14 to 0.63]), and pharmacological placebo (OR 0.37 [0.17 to 0.81]); and pharmacological placebo over the SSRI sertraline (OR 0.79 [0.71 to 0.88]) on remission from alcohol use at postintervention
- the SSRI fluoxetine over pharmacological placebo (OR 0.26 [0.07 to 0.97]) on remission from alcohol use at long-term follow-up
- the SSRI fluoxetine over pharmacological placebo (SMD -0.80 [-1.53 to -0.07]) on depressive symptoms at long-term follow-up
- the SSRI fluoxetine over pharmacological placebo (SMD -0.67 [-1.23 to -0.10]) and the NMDA antagonist memantine over the SSRI escitalopram (SMD -1.92 [-2.45 to -1.39]) on total drinking at postintervention
- the SSRI fluoxetine over the SSRI citalopram (SMD -0.78 [-1.44 to -0.12]), the SSRI escitalopram (SMD -0.82 [-1.59 to -0.06]), the TCA imipramine (SMD -1.02 [-1.79 to -0.24]), the opioid antagonist naltrexone (SMD -0.77 [-1.43 to -0.11]), the SSRI sertraline (SMD -0.88 [-1.59 to -0.17]), and pharmacological placebo (SMD -0.80

[−1.37 to −0.23]); the NMDA antagonist memantine over the SSRI escitalopram (SMD −0.46 [−0.90 to −0.01]); naltrexone in combination with sertraline over the TCA imipramine (SMD −0.73 [−1.41 to −0.06]), naltrexone alone (SMD −0.49 [−0.89 to −0.08]), sertraline alone (SMD −0.59 [−1.04 to −0.15]), and pharmacological placebo (SMD −0.51 [−0.94 to −0.09]); and the SARI nefazodone over the SSRI citalopram (SMD −1.01 [−1.75 to −0.28]), the SSRI escitalopram (SMD −1.06 [−1.88 to −0.23]), the TCA imipramine (SMD −1.25 [−2.09 to −0.42]), the TeCA mirtazapine (SMD −1.43 [−2.67 to −0.18]), the opioid antagonist naltrexone (SMD −1.01 [−1.74 to −0.28]), the SSRI sertraline (SMD −1.12 [−1.89 to −0.34]), and pharmacological placebo (SMD −1.04 [−1.69 to −0.38]) on heavy drinking at postintervention

- the SSRI escitalopram over pharmacological placebo (SMD −0.88 [−1.66 to −0.10]), the SSRI fluoxetine over pharmacological placebo (SMD −0.81 [−1.38 to −0.24]), the TCA imipramine over pharmacological placebo (SMD −0.83 [−1.36 to −0.29]), the NMDA antagonist memantine over pharmacological placebo (SMD −1.18 [−2.07 to −0.28]), the SARI nefazodone over pharmacological placebo (SMD −0.63 [−1.24 to −0.03]), and the SSRI sertraline over the glutamatergic antagonist acamprosate (SMD −1.89 [−3.71 to −0.06]) and pharmacological placebo (SMD −1.96 [−3.59 to −0.33]) on functional status at postintervention.

Patients were more likely on average to experience a serious adverse event when receiving the SSRI sertraline compared with patients receiving naltrexone in combination with sertraline (OR 4.47 [1.51 to 13.26]).

Psychological Interventions

Patients receiving psychological interventions benefited from

- supportive text messaging over psychological placebo (SMD −0.88 [−1.44 to −0.32]), brief CBT over no additional treatment (SMD −0.74 [−1.27 to −0.22]), and a CBT self-help book over no additional treatment (SMD −0.86 [−1.08 to −0.63]) on depressive symptoms at postintervention
- brief CBT over no additional treatment (SMD −0.62 [−1.14 to −0.10]) and a CBT self-help book over no additional treatment (SMD −0.98 [−1.21 to −0.75]) on depressive symptoms at short-term follow-up
- a CBT self-help book over no additional treatment (SMD −1.59 [−1.83 to −1.34]) on depressive symptoms at long-term follow-up
- a CBT self-help book over no additional treatment (SMD −0.25 [−0.47 to −0.04]) on total drinking at postintervention
- supportive text messaging over psychological placebo (SMD −0.97 [−1.54 to −0.41]) on functional status at postintervention.

Key Question 2: Relative Rankings of Identified Interventions' Effects on Outcomes of Interest

Pharmacological Interventions at Postintervention

Remission from depression: An opioid antagonist in combination with an SSRI, SARIs, and TCAs are possibly superior intervention classes, while glutamatergic antagonists, MRIs, and NMDA antagonists are possibly inferior intervention classes.

Remission from alcohol use: An opioid antagonist in combination with an SSRI, TCAs, NMDA antagonists, and an AAP in combination with an SSRI are possibly superior intervention classes, while opioid antagonists and glutamatergic antagonists are possibly inferior intervention classes.

Depressive symptoms: TCAs are probably a superior intervention classes, and an opioid antagonist in combination with an SSRI and opioid antagonists are possibly superior intervention classes. NMDA antagonists and nAChRs are possibly inferior intervention classes.

Withdrawal and craving symptoms: An AAP in combination with an SSRI, SARIs, and NMDA antagonists are possibly superior intervention classes, while TeCAs and TCAs are possibly inferior intervention classes.

Total drinking: SSRIs are probably superior intervention classes, and NMDA antagonists and TeCAs are possibly superior intervention classes. TCAs and glutamatergic antagonists are possibly inferior intervention classes.

Heavy drinking: SARIs, an opioid antagonist in combination with an SSRI, and NMDA antagonists are possibly superior intervention classes, while TCAs and TeCAs are possibly inferior intervention classes.

Health-related quality of life: Glutamatergic antagonists are possibly superior to pharmacological placebo.

Functional status: SSRIs are very likely a superior intervention class, while NMDA antagonists, an AAP in combination with an SSRI, and TCAs are possibly superior intervention classes. Glutamatergic antagonists are possibly an inferior intervention class.

Adverse events: MRIs, NMDA antagonists, and nAChRs are possibly superior intervention classes. Glutamatergic antagonists, TCAs, TeCAs, an opioid antagonist in combination with an SSRI, and an AAP in combination with an SSRI are possibly inferior intervention classes. SSRIs are very likely an inferior intervention class.

Serious adverse events: An opioid antagonist in combination with an SSRI is possibly a superior intervention class. NMDA antagonists are possibly an inferior intervention class. SSRIs are probably an inferior intervention class.

Pharmacological Interventions at Follow-Up

Remission from alcohol use: SSRIs are possibly a superior intervention class to pharmacological placebo at long-term follow-up.

Depressive symptoms: SSRIs are possibly a superior intervention class to pharmacological placebo at long-term follow-up.

Functional status: SSRIs are possibly a superior intervention class to pharmacological placebo at long-term follow-up.

Psychological Interventions

Remission from alcohol use: SMS is possibly superior to psychological placebo at postintervention.

Depressive symptoms: At postintervention, CBT is very likely superior to no additional treatment, while SMS is possibly superior to CBT.

Total drinking: At postintervention, SMS is possibly superior to psychological placebo and CBT is possibly superior to no additional treatment.

Functional status: SMS is possibly superior to psychological placebo at postintervention and short-term follow-up.

Discussion

The available evidence suggests potentially actionable benefits at postintervention of CBT for depressive symptoms, TCAs for depressive symptoms, and SSRIs for total drinking and functional status—though SSRIs also have higher risks of adverse events (including serious adverse events), which makes it imperative to formulate recommendations on their net benefit compared with other classes of intervention. We also identified significant effects for several other comparisons that could be prioritized for direct comparisons in future trials but for which we have insufficient confidence to support consideration for policy and practice recommendations on the basis of evidence on effectiveness. Additional studies—in particular, pragmatic, adequately powered, preregistered, and well-reported RCTs—are needed to provide more conclusive evidence about the (comparative) effectiveness of clinical interventions for treating adults with depressive disorders and AUDs. Notably, numerous clinical interventions contained in CPGs for these conditions are missing from the current body of evidence. Researchers, policymakers, funders, and practitioners may wish to establish future priorities on researching clinical interventions for this patient population, while committees charged with providing recommendations for health systems and updating CPGs may be interested in using this report as a source of evidence on the comparative effectiveness of these clinical interventions.

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Abbreviations

9Q	Nine-question
AAP	atypical antipsychotic
AUD	alcohol use disorder
AUDIT	Alcohol Use Disorder Identification Test
BDI	Beck Depression Intervention
CBT	cognitive behavioral therapy
CDSR	Cochrane Database of Systematic Reviews
CENTRAL	Cochrane Central Register of Controlled Trials
CGI	Clinical Global Impressions
CI	confidence interval
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CPG	Clinical Practice Guideline
DoD	Department of Defense
DSM	Diagnostic and Statistical Manual of Mental Disorders
GAF	Global Assessment of Functioning
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
HDRS	Hamilton Depression Rating Scale
ICD	International Classification of Diseases
ICTRP	International Clinical Trials Registry Platform
IPT	interpersonal therapy
IQR	interquartile range
MADRS	Montgomery-Åsberg Depression Rating Scale
MAST	Michigan Alcoholism Screening Test
MECIR	Methodological Expectations of Cochrane Intervention Reviews
MEMS	Medication Event Monitoring System
MMPI	Minnesota Multiphasic Personality Inventory
MRI	monoamine reuptake inhibitor

nAChR	nicotinic acetylcholine receptor
NAT	negative automatic thought
NIMH	National Institute of Mental Health
NMA	network meta-analysis
NMDA	N-methyl-D-aspartate
NRI	norepinephrine reuptake inhibitor
OCDS	Obsessive Compulsive Drinking Scale
OR	odds ratio
PHCoE	Psychological Health Center of Excellence
PHQ	Patient Health Questionnaire
PICOTSS	populations, interventions, comparators, outcomes, timing, setting, and study design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	randomized controlled trial
SAFTEE	Systematic Assessment for Treatment of Emergent Events
SARI	serotonin antagonist and reuptake inhibitor
SCID	Structured Clinical Interview for <i>DSM-IV</i> Axis I Disorders
SF-36	36-Item Short-Form Health Survey
SMD	standardized mean difference
SMS	self-management support
SOFAS	Social and Occupational Functioning Assessment Scale
SP	supportive psychotherapy
SSRI	selective serotonin reuptake inhibitor
SUD	substance use disorder
TAU	treatment as usual
TCA	tricyclic antidepressant
TeCA	tetracyclic antidepressant
TIDieR	template for intervention description and replication
VA	Department of Veterans Affairs
ZDS	Zung's Self-Rating Depression Scale

1. Introduction

Alcohol use disorders (AUDs) and depressive disorders are prevalent behavioral health conditions among adult populations with significant personal, societal, and economic consequences. Best estimates of current (past 12-month) rates for noninstitutionalized, civilian populations indicate that 13.9 percent of adults meet criteria for an AUD and 6.7 percent of adults meet criteria for a major depressive episode, based on symptoms in the past 12 months (B. F. Grant et al., 2015; Center for Behavioral Health Statistics and Quality, 2016). In addition, approximately 2 percent of active-duty service members in the Military Health System are diagnosed with alcohol abuse or alcohol dependence (Deployment Health Clinical Center, 2017). Adults with an AUD are more likely than those without an AUD to have worse physical, mental health, and social functioning (B. F. Grant et al., 2015). Depression is one of the leading causes of disease burden worldwide (World Health Organization, 2001) and is associated with significantly increased risks of morbidity and mortality (Mykletun et al., 2009; National Institute for Health and Clinical Excellence, 2009). Approximately 4–5 percent of active-duty service members in the Military Health System are diagnosed with a depressive disorder (Deployment Health Clinical Center, 2017).

These two conditions often co-occur: civilian adults with any AUD (mild, moderate, or severe) in the past 12 months have 1.2 (95-percent confidence interval [CI] 1.08–1.35) times the odds of having a major depressive disorder compared with adults without an AUD (B. F. Grant et al., 2015). Co-occurring AUD and depression results in worse treatment outcomes on average than for patients diagnosed with only one of these disorders (DeVido and Weiss, 2012). Consequently, identifying effective clinical interventions for adult patients with both an AUD and depressive disorder is a health policy priority.

Numerous psychological and pharmacological interventions are recommended for patients with an AUD or depressive disorder, though current clinical practice guidelines (CPGs) often focus on one or the other type of disorder, despite the prevalence and significance of their co-occurrence (Management of Substance Use Disorders Working Group, 2015; Management of Major Depressive Disorder Working Group, 2016). Cognitive behavioral therapy (CBT) is the most prominent clinical psychological intervention for the treatment of both AUDs and depressive disorders. Rather than a distinct intervention technique, CBT represents a “family” of related psychotherapies drawing on a shared foundation of maladaptive cognitive and behavioral habits as mechanisms of behavioral health issues (Mansell, 2008). Given the increasing prominence of combining psychotherapeutic and pharmacologic approaches, CBT is often likely to be offered alongside pharmacotherapies approved for treating depression or alcohol use among patients with co-occurring AUD and depressive disorders (Arias and Kranzler, 2008; National Institute for Health and Clinical Excellence, 2009). Previous systematic reviews

provide empirical support for psychotherapies and pharmacotherapies for the treatment of patients with an AUD (Jonas et al., 2014; Klimas et al., 2014) or a depressive disorder (Cuijpers et al., 2008; Arroll et al., 2009; Churchill et al., 2013), as well as the use of certain antidepressants to treat depression in patients with comorbid AUDs (Iovieno et al., 2011). However, rigorous evidence is needed regarding the use of these interventions to treat patients with *both* an AUD and a depressive disorder (DeVido and Weiss, 2012).

The objective of this review is to examine the current state of evidence regarding the comparative effectiveness of clinical interventions for adult patients with co-occurring AUD and depressive disorders, in order to inform clinical decisionmaking within the Military Health System. To achieve this objective, we performed a network meta-analysis (NMA), which combines both direct and indirect comparisons of intervention effects. An NMA obtains an effect estimate for each possible pair of interventions, including those that have not been directly compared. The absence, before NMA, of mixed-treatment comparisons that include both direct and indirect evidence has hindered a comprehensive understanding of the comparative effectiveness of interventions for patients with an AUD and depressive disorder (Nunes and Levin, 2004; Hobbs et al., 2011; Iovieno et al., 2011; Baker et al., 2012; DeVido and Weiss, 2012; Riper et al., 2014; Foulds et al., 2015). NMA enables assessment of the relative effectiveness of interventions and calculation of a ranking of identified interventions in order of effectiveness on outcomes of interest (Pompoli et al., 2014). As such, it is a powerful research tool to assist patients, providers, and policymakers to make informed decisions about which intervention is most likely to improve health care at the individual and population levels (Lumley, 2002; Sox and Greenfield, 2009). A ranking of the effectiveness of clinical interventions on key outcomes for these patients—namely, their depressive symptoms and amount of drinking (Baker et al., 2012; DeVido and Weiss, 2012; Riper et al., 2014)—could provide valuable information for treatment recommendations.

Key Questions

The following questions and subquestions guided this systematic review:

1. What are the effects of clinical interventions on remission from depression and alcohol use (primary outcomes), depressive symptoms, total drinking, heavy drinking, withdrawal and craving symptoms, health-related quality of life, functional status, and adverse events in adults with a co-occurring AUD and depressive disorder?
 - a. What are the effects of interventions by type of AUD or depressive disorder?
 - b. What are the effects of interventions by type of clinical setting?
 - c. What are the effects of interventions by type of intervention?
2. What are the relative rankings of identified interventions, in order of effectiveness on outcomes of interest?

2. Methods

We performed a systematic review to identify randomized controlled trials (RCTs) testing the effects of clinical interventions for treating individuals with co-occurring AUDs and depressive disorders, in order to conduct an NMA to determine the comparative effectiveness of interventions. We registered the protocol for this review in PROSPERO (CRD42017078239), the international prospective register of systematic reviews, before completing formal screening of search results against eligibility criteria (Grant et al., 2017). We prepared the protocol and this report using the relevant Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statements (Hutton et al., 2015; Moher et al., 2015; Shamseer et al., 2015), as well as the Methodological Expectations of Cochrane Intervention Reviews (MECIR) (Higgins, Lasserson, et al., 2016).

Search Strategy

We searched for RCTs in the following electronic databases through May 2018: the Cumulative Index to Nursing and Allied Health Literature, the Cochrane Database of Systematic Reviews, the Excerpta Medica Database, PubMed, PsycINFO, and Web of Science. In addition, we searched the clinical trial registries ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials, and the World Health Organization's International Clinical Trials Registry Platform through May 2018. A reference librarian for RAND's Knowledge Services (J. L.) developed the search strings in consultation with the lead and senior authors (S. G. and S. H.) using terms identified in previous reviews on interventions for AUDs and depressive disorders (Nunes and Levin, 2004; Hobbs et al., 2011; Iovieno et al., 2011; Baker et al., 2012; DeVido and Weiss, 2012; Riper et al., 2014; Foulds et al., 2015). We used searched terms related to alcohol use, depression, and randomized trials (see Appendix A for the full search strings for each database). We also reference-mined the bibliographies of previous systematic reviews.

Eligibility Criteria

Studies

We applied the following inclusion and exclusion criteria related to the types of populations, interventions, comparators, outcomes, timing, setting, and study design (PICOTSS)

- **Populations:** We included studies with adult participants (i.e., at least 50 percent of the sample was 18 years of age or older) who had a clinical diagnosis of both an AUD and depressive disorder according to *Diagnostic and Statistical Manual of Mental Disorders (DSM)* or International Classification of Diseases (ICD) diagnostic criteria (see Appendix B for the list of eligible diagnoses). We included studies with participants who have

additional comorbidities (e.g., other mental health or substance use disorders [SUDs]) so long as the patients had a clinical diagnosis of both an AUD and depressive disorder. In addition to formal diagnostic procedures, we also included studies that used nonoperationalized diagnostic criteria, validated clinician-reported symptom questionnaires, or self-reported symptom questionnaires with established thresholds to identify patients with eligible diagnoses.

- Interventions: We included studies evaluating a clinical intervention to treat patients with AUD and depressive disorder. We did not exclude studies based on the specific therapeutic approach (e.g., psychotherapies, pharmacotherapies, complementary and alternative medicine, self-management) so long as the evaluated intervention was intended to improve depressive symptoms or reduce alcohol use.
- Comparators: We included studies with any comparator (active comparator, “treatment as usual” [TAU] or “standard care,” placebo, wait-list control, no treatment).
- Outcomes: We included studies that reported one or more of the following outcomes: remission from depression and alcohol use (primary outcomes), depressive symptoms, total drinking, heavy drinking, withdrawal and craving symptoms, health-related quality of life, functional status, and adverse events.
- Timing: We included studies with any follow-up period for outcome assessment and any intervention dosage (intensity, frequency, duration).
- Setting: We did not excluded studies by setting.
- Study Design: We included parallel-group, individually, or cluster-randomized controlled trials only. We did not exclude studies based on publication status (e.g., gray literature, conference abstracts). While we did not exclude studies based on language, we used search limits in our electronic search strategies to English-language reports.

Classes of Intervention Nodes

The term NMA comes from visualizing the interventions that have been evaluated for a population of interest as forming a network in which the interventions are represented by dots (or “nodes”) and comparisons between interventions are represented by lines (or “edges”) in a diagram (E. S. Grant and Calderbank-Batista, 2013). We a priori registered the following classes of intervention as the nodes of interest for our network:

- antidepressant pharmacotherapies
 - Examples include sertraline, fluoxetine, and nefazodone.
- alcohol-deterrent pharmacotherapies
 - Examples include acamprosate, naltrexone, and disulfiram.
- combined pharmacotherapy for both depressive disorder and AUD
 - Examples would include a combination of the pharmacotherapies for depression and alcohol just listed.
- CBT without pharmacotherapy
 - CBT would include any intervention that explicitly attempts to change patterns of thinking and behavior that are thought to influence patients’ alcohol- and depressive-related problems and behaviors (Klimas et al., 2014).

- CBT with pharmacotherapy
 - Examples would include a combination of CBT as just described and any listed pharmacotherapy.
- self-management support (SMS) interventions
 - An example is supportive text messaging (Agyapong et al., 2012).
- facilitated 12-step interventions
 - Facilitated 12-step interventions differ from the Alcoholics Anonymous program, which is peer based and not facilitated (Ferri, Amato, and Davoli, 2006).
- pharmacologic placebo
 - An example is a sugar pill with a look, feel, weight, color, and taste identical to those of the active pharmacotherapy.
- psychological placebo
 - An example is an attention-matched control group.
- waiting list
 - A waiting list involves a group of participants assigned to receive an intervention after the active intervention group.
- no treatment
 - We assigned interventions to this node when participants did not receive any treatment additional to TAU.
- other approaches
 - We included interventions from eligible studies when they did not fit into one of the aforementioned a priori nodes.

After we completed the intervention search but before extracting and analyzing outcome data, we used the nodes listed here as a guide in deciding on the final treatment nodes based on consensus among the review team leads (S. G. and S. H.), external advisers, and client representatives about the class of each included intervention (James et al., 2018).

Eligibility Screening and Assessment

Two reviewers (the lead author [S. G.], a doctoral-level experienced systematic reviewer, and one of two doctoral students [G. A., E. H.] with experience in systematic reviews) independently screened the titles and abstracts of retrieved citations. We obtained citations judged as potentially eligible by at least one reviewer for independent, full-text screening by the two reviewers. Following a pilot session to ensure similar interpretation of each inclusion and exclusion criterion, the two reviewers independently applied the eligibility criteria to the full texts of citations passing the title and abstract screening stage; we resolved any disagreements between the two reviewers through discussion within the review team. We documented the flow of citations throughout this process in an electronic database (DistillerSR), with the reasons for excluding citations recorded in the electronic database.

Data Extraction

The lead author (S. G.) designed the data-collection form with input from the project team. We collected study-level data for each PICOTSS criterion using the PRISMA-Equity Extension for participant data (Welch et al., 2012; Welch et al., 2015), the template for intervention description and replication (TIDieR) checklist for intervention and comparator data (Hoffmann et al., 2014), ClinicalTrials.gov criteria for outcomes and timing data (Zarin et al., 2011), the Consolidated Framework for Implementation Research for study setting data (Damschroder et al., 2009), and information related to the risk of bias for study design (Higgins, Sterne, et al., 2016)

- Populations: gender, age, race/ethnicity, socioeconomic status, baseline depression symptoms, baseline alcohol consumption, and other comorbid psychological/behavioral health conditions
- Interventions and comparators: name, hypothesized mechanism of action, materials, procedures, providers, format/modality, location/timing, amount, preplanned tailoring or adaptation, post hoc modifications, fidelity measurement, fidelity data, and cointerventions
- Outcomes (remission from depression and alcohol use, depressive symptoms, total drinking, heavy drinking, withdrawal and craving symptoms, health-related quality of life, functional status, and adverse events in adults with a co-occurring AUD and depressive disorder) for each follow-up point of measurement: domain, measure (including psychometric properties), metric (e.g., change from baseline), and method of aggregation (e.g., means, proportions)
- Timing: time points of outcome assessment
- Setting: month and year, geographic region, number of sites, inner setting (immediate health care setting where intervention is implemented), and outer setting (external context or environment that might influence intervention implementation)
- Study design: purpose, recruitment method, inclusion and exclusion criteria, starting and ending sample size, items relevant to risk of bias (see “Risk of Bias Within Individual Studies” section), and whether a power calculation was reported by study authors.

Two reviewers (S. G. and either G. A. or E. H.) independently extracted study-level descriptive data in an electronic database. In addition, two reviewers (the lead author, S. G., and a biostatistician M. B.) independently extracted all outcome data for meta-analyses. If different reports appeared to be from the same study, we compared descriptions of participants to ensure that data from the same study populations entered each analysis only once.

Risk of Bias Within Individual Studies

Two reviewers (S. G. and either G. A. or E. H.) independently assessed the risk of bias of included studies using the Cochrane Risk of Bias tool (Higgins et al., 2011). Specifically, reviewers assessed the risk of bias related to the following: 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), selective outcome reporting (reporting bias), and other biases (e.g., implementation fidelity).

Data Synthesis

We conducted pairwise meta-analyses of all direct comparisons to assess the statistical heterogeneity within each comparison. Then, we qualitatively examined the distribution of characteristics across studies in each network that may modify intervention effects to assess the transitivity assumption of NMA—that is, that participants hypothetically could be randomized to any interventions included in a network (Salanti, 2012). This transitivity assumption involves assuming that sets of studies comparing different interventions in a network are sufficiently similar to each other with respect to characteristics that moderate their relative effects of interventions, and this assumption leads to assessments of consistency of direct and indirect evidence within each network (E. S. Grant and Calderbank-Batista, 2013). Following these assessments, we conducted NMA using random effects models in a frequentist framework with the *netmeta* package (version 0.9-8) in the R statistical environment (Rücker et al., 2019). We first grouped outcome data into different follow-up periods: immediately postintervention, short-term follow-up (1–5 months postintervention), long-term follow-up (6–11 months postintervention), and very long-term follow-up (12+ months postintervention). When individual studies provided multiple eligible outcomes for the same domain and time period, we included the outcomes most similar to outcomes for other studies in the primary analysis in order to reduce statistical heterogeneity. For adverse events, we prioritized outcome conditions in the following order: proportion who experienced an adverse event, mean number of adverse events, and proportion who dropped out as a result of adverse events. We conducted analyses using alternative outcome data reported in included studies to assess the robustness of findings from the primary analysis. All codes and analyses can be found in our online supplemental RMarkdown file.

To explore the geometry of networks in each analysis, we created network diagrams in which each node represents one of the intervention classes, each line connecting two nodes represents that an RCT directly compared the two intervention classes represented by the nodes, and the size of each line represents the number of RCTs directly comparing the two intervention classes represented by the nodes (note that the distance between nodes does not represent any parameter from the data). For each combination of pairwise comparison, outcome, and time point, we used standardized mean differences (SMDs) for continuous outcomes and odds ratios (OR) for dichotomous outcomes, with a 95 percent CI, to estimate intervention effects. We used SMDs rather than mean differences because we expected studies to use various measures and we wanted to increase the number of studies that could be combined in a meta-analysis. We coded outcomes so that SMDs less than 0 and ORs less than 1 corresponded to beneficial effects of the first intervention compared with the second. For each outcome and time point, we ranked

interventions in order of effectiveness using p scores—a frequentist measure comparable to the surface under the cumulative ranking curve value (Salanti, Ades, and Ioannidis, 2011). P scores measure the extent of certainty that an intervention is better than another intervention averaged over all competing interventions (Rücker and Schwarzer, 2015). They are based on the point estimates and standard errors of network estimates, and their values represent the rank of a treatment within the given range of competing treatment; these values vary from 0 to 1, with 1 meaning an intervention is theoretically the best and 0 meaning an intervention is theoretically the worst.

We addressed within-study correlation of effects from multiarm trials through the netmeta procedures for reweighting all comparisons of each multiarm trial (Rücker, 2012; Rücker and Schwarzer, 2014). We assumed a constant heterogeneity variance across all comparisons in each network, defined via a generalized methods-of-moments estimate of the between-studies variance (Jackson, White, and Riley, 2012). We assessed between-study clinical and methodological heterogeneity by examining characteristics of the participants, interventions, outcomes, settings, and study designs of included trials, and we explored important sources in prespecified subgroup analyses (see below). We assessed between-study statistical heterogeneity for each pairwise comparison using the I^2 statistic. We assessed transitivity (similar distribution of potential effect modifiers across studies) by systematically tabulating and examining characteristics across trials (Salanti, 2012). We assessed local inconsistency (agreement of direct and indirect evidence in each network) by splitting and comparing direct and indirect evidence (Dias et al., 2010); and we assessed global inconsistency using design-based decomposition of Cochran’s Q , as well as a net heat plot (Krahn, Binder, and König, 2013). The net heat plot uses color-coding to highlight hot spots of inconsistency between specific direct evidence in the whole network: the stronger the intensity of the color, the greater the evidence of inconsistency (Krahn, Binder, and König, 2013). All techniques for assessing local and global inconsistency require a closed loop, as they require direct and indirect evidence to exist in order for these types of evidence to be compared. When sufficient data were available, we conducted subgroup analyses to examine the applicability of effects by type of alcohol use and depressive disorder, clinical setting, and intervention. We also conducted sensitivity analyses excluding pharmacological interventions that do not have legal approval to be prescribed in the United States, using alternative outcome data reported in included studies, and based on risk of bias assessments.

Confidence in Estimates of Intervention Effects

We assessed and reported our confidence in each pairwise effect estimate and relative rankings of identified interventions using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach (Guyatt et al., 2008; Puhan et al., 2014; Salanti et al., 2014; Brignardello-Petersen et al., 2018). The traditional approach involves

initially assigning a body of direct evidence of RCTs a rating of “high” confidence and then assessing five domains for possible downgrading of confidence by one or two levels (Guyatt et al., 2008)

- Limitations of included studies (none, serious, or very serious): We considered downgrading one level (“serious”) when most information is from studies at moderate risk of bias and two levels (“very serious”) from studies at high risk of bias (Guyatt, Oxman, Vist, Kunz, Brozek, et al., 2011)
- Indirectness (none, serious, or very serious): We considered downgrading one level (“serious”) when some differences exist between the population, the intervention, or the outcomes measured in relevant research studies and those under consideration in our review, and two levels (“very serious”) when substantial differences exist (Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Falck-Ytter, et al., 2011)
- Inconsistency (none, serious, or very serious): We considered downgrading one level (“serious”) when substantial heterogeneity existed or when only two studies provided information to a meta-analytic estimate, and two levels (“very serious”) when considerable heterogeneity existed or when only one study provided information to a meta-analytic estimate (Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Glasziou, et al., 2011)
- Imprecision (none, serious, or very serious): We considered downgrading one level (“serious”) when the 95 percent CI included the null effect and two levels (“very serious”) when the 95 percent CI included appreciable benefit or harm (Guyatt, Oxman, Kunz, Brozek, et al., 2011)
- Publication bias (suspected or undetected): We considered downgrading one level (“suspected”) when evidence suggested a selective publication of study findings that likely substantially alters estimates of a nonnull effect (Guyatt, Oxman, Montori, et al., 2011).

For pairwise estimates in an NMA, rating confidence in indirect evidence for an effect estimate involved taking the lowest confidence rating from effect estimates with a common comparator and assessing whether to downgrade for potential intransitivity. The process further involves (1) presenting the direct and indirect effect estimates for the pairwise comparison, (2) rating confidence in both estimates, (3) presenting the network estimate for the pairwise comparison, and (4) rating the confidence of the network estimate based on the ratings of the direct and indirect estimates, as well as an assessment of coherence (Puhan et al., 2014; Brignardello-Petersen et al., 2018). Based on these assessments, we reported our confidence in each pairwise effect estimate and overall ranking using one of four categories (Hultcrantz et al., 2017)

- **High** indicates that we are very confident that there is a nonnull effect—that a pairwise effect estimate indicates that one intervention is beneficial over (superior to) another—or that the intervention ranking is accurate
- **Moderate** indicates that the review authors are moderately confident that there is a nonnull effect or that the intervention ranking is accurate

- **Low** indicates that the review authors have limited confidence that there is a nonnull effect or that the intervention ranking is accurate
- **Very low** indicates that the review authors have very little confidence that there is a nonnull effect or that the intervention ranking is accurate.

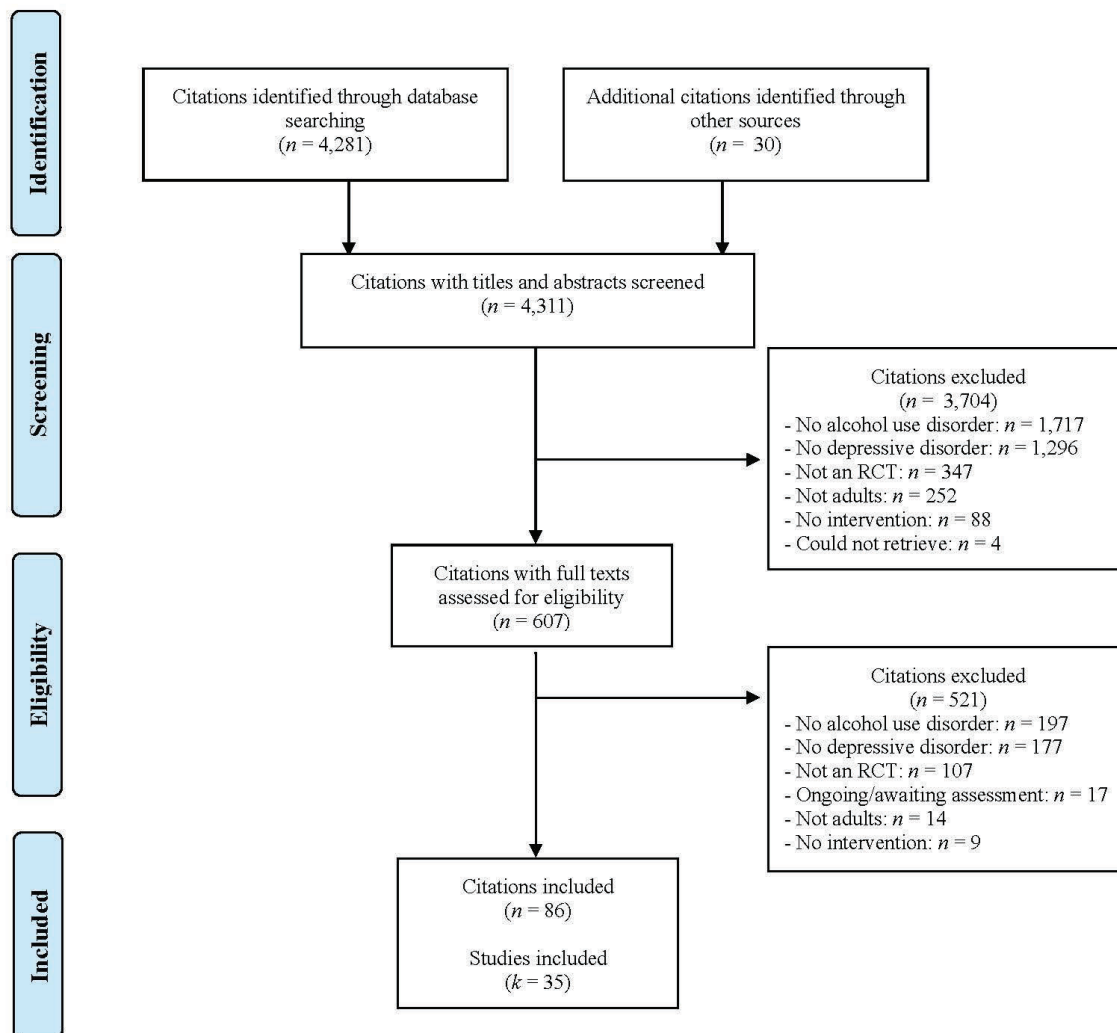
A proposed (but unofficial) process for applying GRADE to intervention rankings in an NMA involves identifying the ranking of each intervention according to p scores, as well as the confidence in the effect estimate of each intervention class versus a referent intervention class.

3. Results

Study Selection

We identified a total of 4,311 citations for review through electronic literature searches and reference mining of relevant systematic reviews (Figure 3.1). We excluded 3,704 citations during title and abstract screening, yielding 607 citations for full-text eligibility assessment. We excluded 521 citations at this stage; 17 citations were related to ongoing studies or those awaiting a final assessment (see Appendix C). We ultimately included 86 citations reporting 35 studies that randomized a total of 2,512 participants.

Figure 3.1. Flow of Citations in Our Literature Review



Study Characteristics

A concise summary of details can be found in Table 3.1 (pharmacological intervention network) and Table 3.2 (psychological intervention network). Detailed information about each included study can be found in Appendix D.

Study Designs

This body of evidence primarily involved small, single-site, and individually randomized trials. All studies randomized individual participants (rather than clusters of participants) to intervention groups. Aside from one three-arm trial (Zielinski, 1979) and one four-arm trial (Pettinati et al., 2010), all other studies (33; 94 percent) randomized participants to either of two intervention groups. Studies were published from 1971 to 2017: 4 (11 percent) in the 1970s, 2 (6 percent) in the 1980s, 6 (17 percent) in the 1990s, 12 (34 percent) in the 2000s, and 11 (31 percent) in the 2010s. Studies recruited participants through dual-diagnosis treatment programs, SUD treatment programs, mental health treatment programs, hospitals, halfway houses, clinician referrals, family and friend referrals, and community advertising. Only 7 studies reported a power analysis—4 of which met the minimum sample requirements of their reported power analysis (Muhonen et al., 2008; Pettinati et al., 2010; Thapinta, Skulphan, and Kittrattanapaiboon, 2014; Thapinta et al., 2017). Most studies (27; 77 percent) involved only one site, while 2 studies involved two sites (Mason et al., 1996; Han et al., 2013); 1 study involved three sites (Muhonen et al., 2008); 2 studies involved five sites (Thapinta, Skulphan, and Kittrattanapaiboon, 2014; Thapinta et al., 2017); and 1 study each involved 7 (Loo et al., 1988), 8 (Adamson et al., 2015), and 13 sites (Kranzler et al., 2006). Study sample size ranged from 14 to 350 (median of 48 participants per study).

Settings

This body of evidence primarily involved U.S.-based studies in outpatient, SUD treatment settings, though a dozen other countries, two other stages in the clinical pathway (inpatient only and inpatient followed by outpatient care), and two other clinical settings (mental health and dual diagnosis) are represented. Studies took place in 13 countries, with 21 studies taking place in the United States; 2 in Italy and in Thailand; and 1 each in Croatia, Finland, France, Ireland, New Zealand, Russia, South Korea, Spain, and Turkey. Of the 35 studies, 25 (71 percent) reported the stage in the clinical pathway and the type of clinical setting. Regarding the stage in the clinical pathway, 14 studies (40 percent) involved outpatient care, 9 (26 percent) involved inpatient care, and 4 (11 percent) involved inpatient followed by outpatient care. Regarding the clinical setting, 17 (49 percent) took place in a treatment setting primarily focused on alcohol or substance use, 1 (3 percent) took place in a treatment setting primarily focused on depressive or mental health disorders, and 9 (26 percent) took place in a treatment setting that focused on both types of psychiatric conditions (substance use and mental health).

Table 3.1. Summary of Studies Included in the Pharmacological Intervention Network

Study	Country	N	Age	Female (Percent)	Depression	Alcohol	Stage	Setting	Sites	Intervention 1	Intervention 2	Weeks	Cointervention
SSRI vs. placebo													
Adamson, 2015	New Zealand	138	44	59	Major depressive episode (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	Outpatient	SUD	8	Citalopram	Pharmacologic placebo	12	Pharmacotherapy, outpatient program
Cornelius et al., 1997	United States	51	35	49	Major depressive disorder (<i>DSM-III</i>)	Alcohol dependence (<i>DSM-III</i>)	Inpatient + outpatient	Both	1	Fluoxetine	Pharmacologic placebo	12	Inpatient + outpatient program
Gual et al. 2003	Spain	83	47	53	Major depressive disorder and/or dysthymic disorder (<i>DSM-IV/ICD-10</i>)	Alcohol dependence (<i>DSM-IV/ICD-10</i>)	Outpatient	SUD	1	Sertraline	Pharmacologic placebo	24	Outpatient program
Kranzler et al., 2006	United States	345	43	36	Major depressive disorder (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	NR	NR	13	Sertraline	Pharmacologic placebo	10	Outpatient program
Krupitsky et al., 2013	Russia	60	42	22	Depressive episode (<i>ICD-10</i>)	Alcohol dependence (<i>ICD-10</i>)	Inpatient	SUD	1	Escitalopram	Pharmacologic placebo	13	Outpatient program
Moak et al., 2003	United States	82	42	39	Major depressive episode or dysthymic disorder (<i>DSM-III</i>)	Alcohol abuse or dependence (<i>DSM-III</i>)	NR	NR	1	Sertraline	Pharmacologic placebo	12	Psychotherapy
Pettinati et al., 2010	United States	170	43	38	Major depressive disorder (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	Outpatient	SUD	1	Sertraline	Pharmacologic placebo	14	Psychotherapy
Roy, 1998	United States	36	41	8	Major depressive episode (<i>DSM-III</i>)	Alcohol dependence (<i>DSM-III</i>)	Inpatient + outpatient	SUD	1	Sertraline	Pharmacologic placebo	6	Inpatient + outpatient program
SSRI vs. opioid antagonist + SSRI													
Pettinati et al., 2010	United States	170	43	38	Major depressive disorder (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	Outpatient	SUD	1	Sertraline	Naltrexone + sertraline	14	Psychotherapy
Salloum, 2007	United States	106	NR	46	Major depressive disorder (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	NR	NR	1	Fluoxetine	Naltrexone + fluoxetine	26	Psychotherapy
SSRI vs. AAP + SSRI													
Han et al., 2013	South Korea	35	40	34	Major depressive disorder (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	Inpatient	Both	2	Escitalopram	Aripiprazole + escitalopram	6	Detoxification, inpatient program
SSRI vs. NMDA antagonist													
Muhonen et al., 2008	Finland	80	48	45	Major depressive disorder (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	Outpatient	SUD	3	Escitalopram	Memantine	26	Outpatient program
SSRI vs. opioid antagonist													
Pettinati et al., 2010	United States	170	43	38	Major depressive disorder (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	Outpatient	SUD	1	Sertraline	Naltrexone	14	Psychotherapy
SSRI vs. TCA													
Cocchi, 1997	Italy	122	42	22	"Depression"	"Alcoholic"	Inpatient	SUD	1	Paroxetine	Amitriptyline	3-4	Detoxification

Study	Country	N	Age	Female (Percent)	Depression	Alcohol	Stage	Setting	Sites	Intervention 1	Intervention 2	Weeks	Cointervention
TCA vs. placebo													
Butterworth, 1971	United States	40	23-60	0	Depression (LRDR of 10+ or clinical impression)	"Alcoholic"	Inpatient	SUD	1	Imipramine	Pharmacologic placebo	3	Detoxification, inpatient program
Mason et al., 1996	United States	28	39	14	Major depressive disorder (<i>DSM-III</i>)	Alcohol dependence (<i>DSM-III</i>)	Outpatient	SUD	2	Desipramine	Pharmacologic placebo	26	Psychotherapy, self-help group
McGrath et al., 1996	United States	69	37	51	Major depressive disorder, dysthymic disorder, or depressive disorder not otherwise specified (<i>DSM-III</i>)	Alcohol abuse or dependence (<i>DSM-III</i>)	Outpatient	Depression	1	Imipramine	Pharmacologic placebo	12	Outpatient program
TCA vs. MRI													
Mielke and Gallant, 1978	United States	20	37	NR	Major depressive disorder (<i>DSM-II</i>)	"Alcoholism"	Inpatient	SUD	1	Imipramine	AHR-1118	4	Inpatient program
TCA vs. TCA													
Loo et al., 1988	France	129	38	14	Major depressive episode or dysthymic disorder (<i>DSM-III</i>)	Alcohol abuse or dependence (<i>DSM-III</i>)	NR	NR	7	Tianeptine	Amitriptyline	4-8	Pharmacotherapy
TCA vs. TeCA													
Altintoprak et al., 2008	Turkey	44	4	8	Major depressive disorder (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	Inpatient	SUD	1	Amitriptyline	Mirtazapine	8	Detoxification
TeCA vs. placebo													
Cornelius et al., 2016	United States	14	41	29	Major depressive disorder (<i>DSM-IV</i>)	Alcohol abuse or dependence (<i>DSM-IV</i>)	Outpatient	Both	1	Mirtazapine	Pharmacologic placebo	12	Psychotherapy
McLean et al., 1986	United Kingdom	35	37	31	Depression (HDRS of 17+)	"Alcohol dependence"	Inpatient	SUD	1	Mianserin	Pharmacologic placebo	4	Inpatient program
Opioid antagonist vs. placebo													
Oslin, 2005	United States	74	63	20	Major depressive disorder (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	NR	NR	1	Naltrexone	Pharmacologic placebo	12	Psychotherapy, pharmacotherapy
Pettinati et al., 2010	United States	170	43	38	Major depressive disorder (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	Outpatient	SUD	1	Naltrexone	Pharmacologic placebo	14	Psychotherapy
Opioid antagonist vs. opioid antagonist + SSRI													
Pettinati et al., 2010	United States	170	43	38	Major depressive disorder (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	Outpatient	SUD	1	Naltrexone + sertraline	Naltrexone	14	Psychotherapy
SARI vs. placebo													
Hernandez-Avila et al., 2004	United States	41	43	51	Major depressive disorder (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	Outpatient	Both	1	Nefazodone	Pharmacologic placebo	10	Psychotherapy

Study	Country	N	Age	Female (Percent)	Depression	Alcohol	Stage	Setting	Sites	Intervention 1	Intervention 2	Weeks	Cointervention
Roy-Byrne et al., 2000	United States	64	40	55	Major depressive disorder (<i>DSM-III</i>)	Alcohol dependence (<i>DSM-III</i>)	Outpatient	Both	1	Nefazodone	Pharmacologic placebo	12	Psychotherapy
Opioid antagonist + SSRI vs. placebo													
Pettinati et al., 2010	United States	170	43	38	Major depressive disorder (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	Outpatient	SUD	1	Naltrexone + sertraline	Pharmacologic placebo	14	Psychotherapy
AAP vs. placebo													
Golik-Gruber et al., 2003	Croatia	40	NR	0	"Depression"	"Alcohol addiction"	Inpatient	SUD	1	Sulpride	Pharmacologic placebo	3	Outpatient program
Glutamatergic antagonist vs. placebo													
Witte et al., 2012	United States	23	46	43	Major depressive disorder (<i>DSM-IV</i>)	Alcohol abuse or dependence (<i>DSM-IV</i>)	NR	NR	1	Acamprosate	Pharmacologic placebo	12	Outpatient program
nAChRs vs. placebo													
Ralevski et al., 2013	United States	21	50	29	Major depressive disorder (<i>DSM-IV</i>)	Alcohol dependence (<i>DSM-IV</i>)	NR	NR	1	Mecamylamine	Pharmacologic placebo	12	Outpatient program
NRI vs. placebo													
Altamura et al., 1990	NR	30	45	20	Dysthymic disorder (<i>DSM-III</i>)	Alcohol dependence (<i>DSM-III</i>)	NR	NR	1	Viloxazine	Pharmacologic placebo	12	Inpatient + outpatient program
TCA + sedative vs. placebo													
Shaw et al., 1975	United States	30	32	0	Depression (BDI, MMPI, ZDS)	Alcoholism (National Council on Alcoholism)	Inpatient + outpatient	SUD	1	Chlordiazepoxide + imipramine	Pharmacologic placebo	4	Inpatient + outpatient program

NOTES: AAP = atypical antipsychotic, BDI = Beck Depression Intervention, HDRS = Hamilton Depression Rating Scale, LRDR = Lehmann-Rockliff Depression Rating, MMPI = Minnesota Multiphasic Personality Inventory, MRI = monoamine reuptake inhibitor, nAChRs = nonselective noncompetitive antagonists of the nicotinic acetylcholine receptors, NMDA = N-methyl-D-aspartate, NR = not reported, NRI = norepinephrine reuptake inhibitor, SARI = serotonin antagonist and reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor, TCA = tricyclic antidepressant, TeCA = tetracyclic antidepressant, ZDS = Zung's Self-Rating Depression Scale.

Table 3.2. Summary of Studies Included in the Psychological Intervention Network

Study	Country	N	Age	Female (Percent)	Depression	Alcohol	Stage	Setting	Sites	Intervention 1	Intervention 2	Weeks	Cointervention
CBT vs. no additional treatment													
Thapinta, Skulphan, and Kittrattanapaiboon, 2014	Thailand	80	45	18	Mild depression or moderate depression (9Q of 7–18)	“Alcohol dependence”	Outpatient	Both	5	Brief CBT	No additional treatment	3	Psychotherapy, pharmacotherapy
Thapinta et al., 2017	Thailand	350	39	12	Mild depression (PHQ-9 of 5–8)	Alcohol dependence (DSM-IV)	Outpatient	Both	5	CBT self-help book	No additional treatment	1	Psychotherapy
CBT vs. placebo													
Petersen and Zettle, 2009	United States	30	38	50	Major depressive disorder (DSM-IV)	Alcohol abuse or dependence (DSM-IV)	Inpatient	SUD	1	Acceptance and commitment therapy	Psychological placebo	3-4	Inpatient program
SMS vs. placebo													
Agyapong et al., 2012	Ireland	54	49	54	Major depressive disorder (DSM-IV)	Alcohol abuse or dependence (DSM-IV)	Outpatient	Both	1	Supportive text messaging	Psychological placebo	13	Inpatient + outpatient program
Zielinski, 1979	United States	36	40	25	Depression (BDI, MMPI, ZDS)	“Alcoholic”	Inpatient + outpatient	SUD	1	Activity level monitoring + social skills training	Psychological placebo	13	Inpatient + outpatient program
Zielinski, 1979	United States	36	40	25	Depression (BDI, MMPI, ZDS)	“Alcoholic”	Inpatient + outpatient	SUD	1	Activity level monitoring	Psychological placebo	13	Inpatient + outpatient program
IPT vs. no additional treatment													
Holzhauer et al., 2017	United States	48	37	100	Major depressive disorder (DSM-IV)	Alcohol dependence (DSM-IV)	Outpatient	SUD	1	IPT	No additional treatment	16	Outpatient program
IPT vs. SP													
Markowitz et al., 2008	United States	26	38	31	Dysthymic disorder (DSM-IV)	Alcohol abuse or dependence (DSM-IV)	Outpatient	Both	1	IPT for dysthymic disorder	Brief SP	16	Pharmacotherapy, self-help group

NOTES: IPT = interpersonal therapy, PHQ = Patient Health Questionnaire, SP = supportive psychotherapy.

Participants

This body of evidence primarily involved middle-aged Caucasian or white men with major depressive disorder and alcohol dependence, though approximately half of the body of evidence involved patients with other alcohol use and depressive disorders. All participants experienced both depression and an AUD. Depression involved formal diagnoses of major depressive disorder only (18; 51 percent), a major depressive episode only (3; 9 percent), dysthymic disorder only (2; 6 percent), or one or more of the foregoing disorders (4; 12 percent); use of symptom rating scales (6; 17 percent); or simply reporting that participants had “depression” (2; 6%). AUD involved formal diagnoses of alcohol dependence (19; 54 percent), formal diagnoses of either alcohol abuse or dependence (8; 23 percent), or simply reporting that participants had some form of “alcoholism,” “alcohol dependence,” or “alcohol addiction” (8; 23 percent). The median average age for participants in a trial was 42 years (interquartile range [IQR]: 38–45; full range: 32–63). The median percentage of female participants in a trial was 31 percent (IQR: 19–48 percent; full range: 0–100 percent). Only 20 studies (57 percent) provided data on the race/ethnicity of participants; in these studies, the median percentage of Caucasian/white participants in a trial was 76 percent (IQR: 18–49 percent; full range: 47–100 percent).

Interventions

This body of evidence included 14 classes of pharmacological interventions, 3 classes of psychological interventions, and 3 control interventions. Using the Department of Veterans Affairs (VA)/Department of Defense (DoD) CPGs for alcohol use and major depressive disorders as a point of reference (Management of Substance Use Disorders Working Group, 2015; Management of Major Depressive Disorder Working Group, 2016), included studies evaluated 15 out of 49 interventions (31 percent) recommended in the guidelines. All interventions were provided as adjunctive to TAU, which included standalone detoxification, standalone psychotherapy, standalone pharmacotherapy, standalone self-help groups, and multicomponent inpatient and outpatient programs in substance use and dual-diagnosis treatment settings.

Pharmacological Interventions

This body of evidence included 14 (combinations of) classes of pharmacological intervention as adjunctive to TAU: AAPs, AAPs and SSRIs, glutamatergic antagonists, MRIs, nonselective noncompetitive antagonists of the nAChRs, NMDA antagonists, NRIs, opioid antagonists, opioid antagonists and SSRIs, SSRIs, SARIs, TCAs, TCAs and sedatives, and TeCAs. Included studies evaluated 13 out of 38 pharmacological interventions (34 percent) recommended in the VA/DoD CPGs for alcohol use and major depressive disorders.

AAPs: One study delivered three 50-mg capsules of sulpiride daily for 6 weeks.

AAPs and SSRIs: One study delivered the AAP aripiprazole and the SSRI escitalopram to

inpatients following a detoxification period. Patients received a flexible dose of aripiprazole (5–15 mg daily) and escitalopram (10–20 mg daily) for 6 weeks. Aripiprazole was started at 5 mg per day during the first week and then increased to 15 mg per day, while escitalopram was started at 10 mg per day during the first week and then increased to 20 mg per day. Throughout the 6 weeks, patients received an average of 7.0 (3.5) mg of aripiprazole and 13.2 (6.1) mg of escitalopram per day.

Glutamatergic antagonists: One study had physicians deliver the glutamatergic antagonist acamprosate to outpatients at 2,000 mg (two 333-mg capsules three times) per day for 12 weeks.

MRIs: One study delivered the MRI compound AHR-1118 to inpatients at a hospital-based addiction clinic for 4 weeks. Patients initially received one 25 mg tablet twice per day, scaled up to one tablet in the morning and two at 4:00 p.m. if there were no side effects and there was insufficient therapeutic response by the fourth day. The maximum dose of two tablets at 8:00 a.m. and two at 4:00 p.m. was initiated on the seventh day if the patient still showed no significant or incapacitating side effects and there was room for therapeutic improvement.

nAChRs: One study delivered the nAChR mecamylamine for 12 weeks. Patients started at 2.5 mg once per day, which was increased to 5 mg twice per day over 3 weeks.

NMDA antagonists: One study had physicians deliver the NMDA antagonist memantine to outpatients for 26 weeks. Patients started at 5 mg per day, which was increased at weekly intervals by 5 mg per day to 20 mg per day; the physician instructed patients to take memantine in the morning. After 4 weeks, the physician could decrease the dose if a patient could not tolerate the medication. Patients' average daily consumption of medication was 17.4 (2.8) mg during the first 12 weeks and 17.4 (3.2) mg during the remaining study weeks.

NRIs: One study delivered the NRI viloxazine after a 1-week washout period. Patients received 400 mg per day in four administrations over 12 weeks (4 weeks of hospitalization followed by 8 weeks of outpatient care).

Opioid antagonists: Two studies delivered the opioid antagonist naltrexone to outpatients. One study delivered 50 mg per day over 12 weeks total. The other study delivered naltrexone over 14 weeks: 50 mg per day for the first 4 days, then 100 mg per day through the twelfth week, and 50 mg per day for the final 2 weeks.

Opioid antagonists and SSRIs: Two studies delivered both an opioid antagonist and an SSRI to outpatients. The opioid antagonist was naltrexone in both studies, while the SSRI was either sertraline or fluoxetine. One study delivered 50 mg of naltrexone and 20 to 60 mg of fluoxetine per day for 6 months. The other study delivered naltrexone and sertraline over 14 weeks; naltrexone was delivered at 50 mg per day for the first 4 days, then 100 mg per day through the twelfth week, and 50 mg per day for the final 2 weeks, while sertraline was delivered at 50 mg per day during the second week, titrated up by 50 mg per day every third day until the maximum dose of 200 mg per day was reached, and reduced to 100 mg per day in the final week.

SSRIs: Twelve studies delivered an SSRI. Five studies delivered sertraline: four to patients receiving outpatient care only and one to patients who started in inpatient care and eventually

moved to outpatient care. Across all five studies, patients received sertraline for 6 to 24 weeks at doses ranging from 50 to 200 mg per day. Three studies delivered escitalopram: one to inpatients following a detoxification period (10 to 20 mg per day for 6 weeks), one during the initial stage of alcohol remission (10 mg per day in the morning for 13 weeks), and one to outpatients (5 to 20 mg per day in the morning for 26 weeks). Two studies delivered fluoxetine: one study to patients receiving inpatient care for the first 2 weeks followed by 10 weeks of outpatient care (20 to 40 mg per day), and another study to patients receiving 6 months of outpatient care only (20 to 60 mg per day). One study delivered citalopram for 12 weeks: 20 mg per day in the first week and two 20-mg capsules per day for the remaining weeks (the dose could be increased to three 20-mg capsules per day if patients remained depressed after 6 weeks). One study delivered 20 mg of paroxetine per day for 3 to 4 weeks.

SARIs: Two studies delivered the SARI nefazodone to outpatients: one study at 200 to 600 mg per day for 10 weeks, and the other at 200 to 500 mg per day for 12 weeks.

TCAs and sedatives: One study had a psychiatric nurse deliver the 150 mg of the TCA imipramine and 40 mg of the sedative chlordiazepoxide daily for an average of 31 days.

TeCAs: Two studies delivered the TeCA mirtazapine and one study the TeCA mianserin. Mirtazapine doses ranged from 15 to 60 mg per day for 8 to 12 weeks, while the mianserin dose involved 30 to 60 mg per day for 4 weeks.

TCAs: Eight studies delivered a TCA. Three studies delivered imipramine at doses of 50 to 300 mg for 3 to 12 weeks. Three studies delivered amitriptyline at doses from 25 to 150 mg per day and from 3 to 8 weeks. One study had physicians deliver desipramine (median of 200 mg per day) for 6 months. One study delivered tianeptine at doses of 37.5 mg per day for 4 to 8 weeks.

Psychological Interventions

This body of evidence included four psychological interventions as adjunctive to TAU: CBT, IPT, SMS, and SP. Included studies evaluated 2 out of 11 psychological interventions (18 percent) recommended in the VA/DoD CPGs for alcohol use and major depressive disorders. In addition, no included studies evaluated group mutual help programs such as 12-Step Facilitation, Alcoholics Anonymous, or Narcotics Anonymous.

CBT: Three studies delivered CBT. One study involved brief CBT, which helped patients to alter or create new ways to view the world and change their negative automatic thoughts (NATs), learn how to change behaviors, and acquire ways of dealing with everyday problems in ways that lead to less negative affect and physical discomfort. Ten trained registered nurses (with master's degrees in mental health and psychiatric nursing) delivered six sessions over 3 weeks (two 40- to 60-minute sessions a week). The second study involved a CBT self-help book that provided psychoeducational material that explained how cognition and depression are related, as well as providing explanations, examples, and exercises for handling NATS. The third study involved acceptance and commitment therapy to help patients accept negative thoughts and emotions, choose a valued direction of action, and take action in this valued direction. A graduate student in clinical psychology delivered six 30- to 60-minute sessions every two weeks to each

individual inpatient. While it is often labeled as a “third-wave” therapy, we included acceptance and commitment therapy in the class of cognitive behavioral interventions for two reasons. First, acceptance and commitment therapy originates from the cognitive behavioral approach and thus has a cognitive behavioral mechanism of action. Second, we wanted to be consistent with our method of classifying interventions in the pharmacological network, which were based not on the “generation” (the pharmacological equivalent of “waves”) of antidepressants but rather on their mechanisms of action.

IPT: Two studies delivered IPT. The first study only reported that community therapists delivered eight sessions of IPT as part of their usual caseload to individual outpatients for 16 weeks (one session every other week). The second study delivered IPT specifically for dysthymic disorder. This version of IPT employed the “common factors” of psychotherapy, a medical model of illness that excuses the patient from blame, and a focus on emotional responses and coping strategies to resolve life crises. Underlying this version of IPT was the hypothesis that dysthymic patients are likely to use alcohol as self-medication for dysphoria, eventually leading to a comorbid AUD. Eight therapists with master’s and doctoral degrees in social work with experience in treating depression were trained in and followed a manual to deliver 16 to 18 sessions (50 minutes each over 16 weeks) on helping patients to change their life situations so as to improve their mood disorders.

SMS: Two studies delivered SMS. One study had two intervention arms delivering SMS: one in which patients received activity level monitoring, and another in which patients received both activity level monitoring and social skills training. Activity level monitoring involved a therapist (doctoral candidate in clinical psychology) engaging patients in five sessions (one during inpatient care and four booster sessions during outpatient care) of discussing immediate plans, generating a list of short-term goals, and making efforts to include recreational or avocational pursuits, as well as work projects. For social skills training, patients completed an individualized assessment to identify specific areas of social difficulty, and the therapist then used this information to engage the patient in repeated role playing (behavior rehearsal) and, in turn, modeling responses to a problematic social situation. The second study delivered supportive text messaging—that is, computer-delivered text messages (twice per day for 3 months) about dealing with stress, maintaining good mental well-being, promoting abstinence from alcohol, dealing with cravings, promoting adherence with medication, and providing general support.

SP: One study had seven therapists who were trained in and followed an intervention manual to deliver 50-minute sessions of brief SP (16 to 18 sessions over 16 weeks).

Control Interventions

This body of evidence included three control interventions as adjunctive to TAU: pharmacological placebo, psychological placebo, and no additional treatment.

Pharmacological placebo: Twenty-one studies in the pharmacological intervention network used a comparison arm in which the participants received a pharmacological placebo (i.e., a pill or tablet similar to and delivered similarly to the active pharmacological intervention).

Psychological placebo: Three studies in the psychological intervention network used a comparison arm in which the participants received a psychological placebo (i.e., attention-matched procedures that did not contain a specified, systematic therapeutic intervention for this patient population).

No additional treatment: Three studies in the psychological intervention network used a comparison arm in which the participants received no other treatments in addition to the TAU also received by participants receiving the active psychological intervention.

Treatment-as-Usual Cointerventions

All interventions in this body of evidence were adjunctive to a TAU cointervention. Components of TAU included standalone interventions (detoxification, psychotherapy, pharmacotherapy, and self-help groups) and multicomponent inpatient and outpatient programs in substance use and dual-diagnosis treatment settings. Standalone detoxification services (4; 11 percent) included the use of agents such as anticonvulsants (dilantin), sedatives (phenobarbital, chloral hydrate, lorazepam), anxiolytics (diazepam), antihistamines (Vistaril), and vitamins (B complex). Standalone psychotherapy (10; 29 percent) included CBT, motivational enhancement therapy, psychoeducation, and SP. Standalone pharmacotherapy (5; 14 percent) included medication specifically for depressive symptoms (e.g., sertraline) and alcohol use (e.g., benzodiazepines, naltrexone), as well as other psychotropic drugs (e.g., anxiolytics, hypnotics). Standalone self-help groups (2; 6 percent) involved Alcoholics Anonymous. Inpatient programs (11; 31 percent) included detoxification, psychotherapy, pharmacotherapy, rehabilitative services, and self-help groups. Outpatient substance use programs (14; 40 percent) included pharmacotherapy, psychotherapy, and self-help groups.

Outcomes

This body of evidence predominantly consists of psychometrically validated questionnaires measuring constructs immediately at postintervention. A summary of outcome data across studies can be found in Table 3.3.

Remission from depression: Nineteen studies (54 percent) reported measuring remission from depression using the BDI (Beck, Steer, and Carbin, 1988), Clinical Global Impressions (CGI) scale (Busner and Targum, 2007), Global Assessment of Functioning (GAF; Hall, 1995), HDRS (Hamilton, 1960), Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979), and Zung's Self-Rating Depression Scale (Zung, 1965). No studies reported remission from depression at time points beyond postintervention.

Table 3.3. Summary of Outcome Data Across Studies

Study	Remission from Depression	Remission from Alcohol Use	Depressive Symptoms	Total Drinking	Heavy Drinking	Withdrawal and Craving Symptoms	Health-Related Quality of Life	Functional Status	Adverse Events
Adamson et al., 2015	Proportion with MADRS < 10 at postintervention	Mean percentage days abstinent at postintervention	Mean MADRS at postintervention	Mean drinks per drinking day at postintervention	Mean percentage of days heavy drinking at postintervention	Mean Leeds Dependence Questionnaire at postintervention	—	—	Proportion self-reporting at least one adverse event at postintervention
Agyapong et al., 2012	—	Proportion abstinent at immediately and 3 months postintervention	Mean BDI at immediately and 3 months postintervention	Mean units of alcohol per drinking day at immediately and 3 months postintervention	—	Mean OCDS at immediately and 3 months postintervention	—	Mean GAF at immediately and 3 months postintervention	—
Altamura et al., 1990	—	—	—	—	—	—	—	—	—
Altintoprak et al., 2008	—	—	—	—	—	Mean Alcohol Craving Scale at postintervention	—	—	—
Butterworth, 1971	—	—	Mean LRDR at postintervention	—	—	—	—	Proportion with “improvement in global response” at postintervention	Proportion with at least one physician-recorded adverse event at postintervention
Cocchi, 1997	Proportion “not depressed” using ZDS at postintervention	—	Mean ZDS at postintervention	—	—	—	—	—	—
Cornelius et al., 1997	—	Proportion abstinent at postintervention Mean number of days abstinent at 9 months postintervention	Mean HDRS at immediately and 9 months postintervention	Mean drinks per drinking day at postintervention Number of drinks in the past week at 9 months postintervention	Cumulative number of days heavy drinking at postintervention	—	—	Mean Global Assessment Scale at immediately and 9 months postintervention	Proportion with at least one side effect at immediately and 9 months postintervention
Cornelius et al., 2016	—	—	Mean BDI at postintervention	Mean drinks per drinking day at postintervention	Mean number of days heavy drinking per week at postintervention	Mean OCDS at postintervention	—	—	—

Study	Remission from Depression	Remission from Alcohol Use	Depressive Symptoms	Total Drinking	Heavy Drinking	Withdrawal and Craving Symptoms	Health-Related Quality of Life	Functional Status	Adverse Events
Golik-Gruber et al., 2003	Proportion with depression (BDI) at postintervention	—	—	—	—	—	—	—	—
Gual et al., 2003	Proportion with ≥ 50% reduction on MADRS at postintervention	Proportion who did not relapse at postintervention	—	—	—	—	—	—	—
Han et al., 2013	Proportion with ≥ 50% reduction on BDI at postintervention	Proportion who did not relapse at postintervention	Mean BDI at postintervention	—	—	Mean Korean Alcohol Urge Questionnaire at postintervention	—	Mean CGI severity at postintervention	Proportion who dropped out because of adverse events at postintervention
Hernandez-Avila et al., 2004	—	Proportion abstinent at postintervention	Mean HDRS at postintervention	Mean drinks per drinking day at postintervention	Mean number of days heavy drinking per week at postintervention	—	—	—	Mean SAFTEE score at postintervention
Holzhauser and Gamble, 2017	—	—	—	—	—	—	—	—	—
Kranzler et al., 2006	Proportion with ≥ 50% reduction on HDRS at postintervention	Mean percentage days abstinent at postintervention	Mean HDRS at postintervention	—	—	—	—	—	Proportion with a treatment-emergent adverse event at postintervention
Krupitsky et al., 2013	—	Mean number of days remission at postintervention	Mean HDRS at postintervention	—	Mean gamma-glutamyltransferase activity at postintervention	Mean OCDS at postintervention	—	Proportion with considerable or very considerable improvement on CGI at postintervention	Proportion with at least one adverse event at postintervention
Loo et al., 1988	Proportion with ≥ 50% reduction on MADRS at postintervention	—	—	—	—	—	—	—	Proportion who discontinued treatment at postintervention
Markowitz et al., 2008	Proportion with “remission” at postintervention	Mean percentage days abstinent at postintervention	Mean HDRS at postintervention	—	—	—	—	—	—
Mason et al., 1996	Proportion with “depression response” at postintervention	Proportion who did not relapse at postintervention	Mean HDRS at postintervention	—	—	—	—	—	Proportion who dropped out because of adverse events at postintervention

Study	Remission from Depression	Remission from Alcohol Use	Depressive Symptoms	Total Drinking	Heavy Drinking	Withdrawal and Craving Symptoms	Health-Related Quality of Life	Functional Status	Adverse Events
McGrath et al., 1996	Proportion with $\geq$ 50% reduction on HDRS at postintervention	Proportion with past-week abstinence at postintervention	Mean HDRS at postintervention	Mean drinks per drinking day at postintervention	Mean percentage of days heavy drinking in the past week at postintervention	—	—	Proportion much improved or better on CGI at postintervention	Proportion who dropped out because of adverse events at postintervention
McLean, Ancill, and Szulecka, 1986	Proportion with HDRS <17 at postintervention	—	Mean HDRS at postintervention	—	—	—	—	—	Proportion who experienced transient drowsiness at postintervention
Mielke and Gallant, 1978	Proportion with moderate/marked improvement on the CGI at postintervention	—	—	—	—	—	—	—	Proportion with at least one side effect at postintervention
Moak et al., 2003	Proportion with $\geq$ 50% reduction on BDI at postintervention	Mean percentage days abstinent at postintervention	Mean HDRS at postintervention	Mean drinks per drinking day at postintervention	—	—	—	—	Proportion with at least one adverse event at postintervention
Muhonen et al., 2008	Proportion with MADRS < 12 at postintervention	Mean AUDIT at postintervention	Mean MADRS at postintervention	Mean daily grams alcohol at postintervention	Mean number of days heavy drinking at postintervention	Mean OCDS at postintervention	Mean VAS at postintervention	Mean SOFAS at postintervention	Proportion with at least one adverse event at postintervention
Oslin, 2005	Proportion with HDRS < 10 at postintervention	Proportion abstinent at postintervention	—	—	Proportion relapsed to heavy drinking at postintervention	—	—	—	—
Petersen and Zettle, 2009	Proportion with HDRS < 14 at postintervention	—	Mean HDRS at postintervention	—	—	—	—	—	—
Pettinati et al., 2010	Proportion “not depressed” at postintervention	Proportion abstinent at postintervention	Mean HDRS at postintervention	—	Mean days to relapse to heavy drinking at postintervention	—	—	—	Proportion who discontinued treatment because of adverse events at postintervention
Ralevski et al., 2013	—	—	Mean HDRS at postintervention	—	—	—	—	—	Proportion who experienced at least one medical or psychiatric adverse event at postintervention

Study	Remission from Depression	Remission from Alcohol Use	Depressive Symptoms	Total Drinking	Heavy Drinking	Withdrawal and Craving Symptoms	Health-Related Quality of Life	Functional Status	Adverse Events
Roy, 1998	Proportion with $\geq$ 50% reduction on HDRS at postintervention	Proportion who did not relapse at postintervention	Mean HDRS at postintervention	—	—	—	—	Proportion very much improved on CGI at postintervention	—
Roy-Byrne, 2000	Proportion with HDRS < 8 at postintervention	Proportion abstinent at postintervention	Mean HDRS at postintervention	Mean drinks per drinking day at postintervention	—	Mean VAS at postintervention	—	Proportion very much improved or much better on CGI at postintervention	Mean number of adverse events per participant at postintervention
Salloum, 2007	—	—	—	—	—	—	—	—	—
Shaw et al., 1975	—	—	—	—	—	—	—	—	—
Thapinta, Skulphan, and Kittrattanapaboon, 2014	—	—	Mean 9Q at immediately and 1 month postintervention	—	—	—	—	—	—
Thapinta et al., 2017	—	—	Mean PHQ-9 at immediately, 1 month, and 6 months postintervention	Mean cubic cm of alcohol per day at immediately, 3 months, and 6 months postintervention	—	—	—	—	—
Witte, 2012	Proportion with “remission” at postintervention	Mean percentage days abstinent at postintervention	Mean HDRS at postintervention	Mean drinks per drinking day at postintervention	—	Mean OCDS at postintervention	Mean Quality of Life Enjoyment and Satisfaction Questionnaire at postintervention	Mean CGI improvement at postintervention	Proportion who experienced at least one adverse event at postintervention
Zielinski, 1979	—	Proportion who did not relapse at 6 and 12 months postintervention	—	—	—	—	—	—	—

NOTES: AUDIT = Alcohol Use Disorder Identification Test, OCDS = Obsessive Compulsive Drinking Scale, SAFTEE = Systematic Assessment for Treatment of Emergent Events, SOFAS = Social and Occupational Functioning Assessment Scale, VAS = Visual Analog Scale.

Remission from alcohol use: Twenty-three studies (68 percent) reported measuring remission from alcohol use using the Addiction Severity Index (McLellan et al., 1992), Alcohol Dependence Scale (Skinner and Horn, 1984), AUDIT (Allen et al., 1997), Drinking Behavior Interview (Shelton, Hollister, and Gocka, 1969), and Michigan Alcoholism Screening Test (MAST; Selzer, 1971), as well as measures of abstinence, relapse to (heavy) drinking, and time to first drink. Three studies reported remission from alcohol use at time points beyond postintervention: one at short-term follow-up (3 months postintervention), one at long-term follow-up (9 months postintervention), and another at long-term (6 months postintervention) and very long-term follow-up (12 months postintervention).

Depressive symptoms: Thirty-two studies (91 percent) measured depressive symptoms using the 9Q (Department of Mental Health, Thailand Ministry of Public Health, 2009), BDI (Beck, Steer, and Carbin, 1988), CGI scale (Busner and Targum, 2007), Cornell Dysthymia Rating Scale (Hellerstein et al., 2002), HDRS (Hamilton, 1960), Hopkins Symptom Checklist (Derogatis et al., 1974), LRDR, MMPI (Butcher, 2005), MADRS (Montgomery and Åsberg, 1979), PHQ-9 (Kroenke, Spitzer, and Williams, 2001), Quick Inventory of Depressive Symptomatology Self-Report (Trivedi et al., 2004), and Zung's Self-Rating Depression Scale (Zung, 1965). Four studies reported depressive symptoms at time points beyond postintervention: two at short-term follow-up (1 and 3 months postintervention), one at long-term follow-up (9 months postintervention), and one at short-term (1 month postintervention) and long-term follow-up (6 months postintervention).

Total drinking: Eighteen studies (53 percent) measured total drinking using number of drinks per (drinking) day, week, or month; cumulative number of drinks; and number of drinking days. Three studies reported total drinking at time points beyond postintervention: one at short-term follow-up (3 months postintervention), one at long-term follow-up (9 months postintervention), and one each at short-term (1 and 3 months postintervention) and long-term follow-up (6 months postintervention).

Heavy drinking: Twelve studies (35 percent) measured heavy drinking using heavy drinking days and time to heavy drinking. No studies reported heavy drinking at time points beyond postintervention.

Withdrawal and craving symptoms: Ten studies (29 percent) measured withdrawal and craving symptoms using the Alcohol Self-Efficacy Scale (DiClemente et al., 1994), Korean Alcohol Urge Questionnaire, Leeds Dependence Questionnaire (Raistrick et al., 1994), OCDS (Anton, Moak, and Latham, 1995), Pennsylvania Alcohol Craving Scale (Flannery, Volpicelli, and Pettinati, 1999), and Visual Analog Scale of Craving. Only one study reported withdrawal and craving symptoms at short-term follow-up (3 months postintervention).

Health-related quality of life: Four studies (12 percent) measured health-related quality of life using the Quality of Life Enjoyment and Satisfaction Questionnaire (Endicott et al., 1993), the 36-Item Short-Form Health Survey (SF-36; Ware and Sherbourne, 1992), and the Visual Analog Scale for quality of life (Scott and Huskisson, 1976). No studies reported on health-related quality of life at time points beyond postintervention.

Functional status: Ten studies (29 percent) measured functional status using the CGI scale (Busner and Targum, 2007), GAF (Hall, 1995), Global Assessment Scale (Endicott et al., 1976), SF-36 (Ware and Sherbourne, 1992), and SOFAS (Morosini et al., 2000). Two studies reported functional status at time points beyond postintervention: one at short-term follow-up (3 months postintervention) and one at long-term follow-up (9 months postintervention).

Adverse events: Twenty-two studies (65 percent) measured adverse events using the Dosage Record and Treatment Emergent Symptoms Scale (Guy, 1976), SAFTEE (Levine and Schooler, 1984), Treatment Emergent Symptom Side Effects Scale (National Institute of Mental Health, 1985), and Udvalg for Kliniske Undersogelser Side Effect Rating Scale (Lingjaerde et al., 1987), as well as physician documentation of adverse events, number of patients dropping out because of adverse events, and generic measures of (serious) adverse events. Only one study reported adverse events at long-term follow-up (9 months postintervention). We conducted an additional analysis on data identified as “serious” adverse events from six studies (17 percent).

Risks of Bias

A summary of risk of bias across studies can be found in Table 3.4.

Random sequence generation: Eight studies (23 percent) had low risk, and the remaining 27 studies (77 percent) had unclear risk of selection bias related to adequate generation of the random sequence of numbers for allocation.

Allocation concealment: Seven studies (20 percent) had low risk, and the remaining 28 studies (80 percent) had unclear risk of selection bias related to adequate concealment of the allocation sequence.

Blinding of participants and providers: Of the seven studies in the psychological intervention network, all of them had high risk of performance bias because of the inability to blind participants and providers, except for one study (Agyapong et al., 2012) that was able to blind “providers” because interventions were delivered through an automated computer program. Of the 28 studies in the pharmacological intervention network, 2 (7 percent) had high risk of bias, 2 (7 percent) had unclear risk of bias, and 24 (86 percent) had low risk of performance bias related to blinding participants and providers.

Blinding of participants and providers: Of the seven studies in the psychological intervention network, one (14 percent) had high risk, three (43 percent) had unclear risk, and three (43 percent) had low risk of detection bias related to blinding outcome assessors. Of the 28 studies in the pharmacological intervention network, 1 (4 percent) had high risk of bias, 9 (32 percent) had low risk of bias, and 18 (64 percent) had unclear risk of detection bias related to blinding outcome assessors.

Table 3.4. Summary of Risks of Bias Across Studies

Study	Random Sequence Generation	Allocation Concealment	Blinding Participants	Blinding Providers	Blinding Assessors	Completeness of Outcome Data	Selective Outcome Reporting	Funder
Adamson et al., 2015	Low	Low	Low	Low	Low	Low	Low	Public
Agyapong et al., 2012	Low	Unclear	High	Low	High	Low	Low	Public
Altamura et al., 1990	Unclear	Unclear	Low	Low	Unclear	Low	High ^a	Unclear
Altintoprak et al., 2008	Unclear	Unclear	Low	Low	Unclear	Unclear	High ^a	Unclear
Butterworth, 1971	Unclear	Unclear	Low	Low	Unclear	Low	Unclear	Unclear
Cocchi, 1997	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Cornelius et al., 1997	Unclear	Low	Low	Low	Low	Low	Unclear	Public
Cornelius et al., 2016	Unclear	Low	Low	Low	Unclear	Low	Low	Public
Golik-Gruber et al., 2003	Unclear	Unclear	High	High	High	Low	Unclear	Unclear
Gual et al., 2003	Unclear	Unclear	Low	Low	Unclear	High	High ^a	Unclear
Han et al., 2013	Unclear	Unclear	Low	Low	Unclear	High ^a	Unclear	Some private
Hernandez-Avila et al., 2004	Low	Unclear	High	Low	Low	Low	Unclear	Some private
Holzhauser and Gamble, 2017	Unclear	Unclear	High	High	Unclear	Low	High ^a	Public
Kranzler et al., 2006	Low	Unclear	Low	Low	Unclear	High	High ^a	Some private
Krupitsky et al., 2013	Low	Low	Low	Low	Low	Low	High ^a	Unclear
Loo et al., 1988	Unclear	Unclear	Low	Low	Unclear	Low	Unclear	Unclear
Markowitz et al., 2008	Low	Unclear	High	High	Low	High	Unclear	Public
Mason et al., 1996	Unclear	Unclear	Low	Low	Unclear	High	High ^a	Public
McGrath et al., 1996	Unclear	Unclear	Low	Low	Low	High	Unclear	Some private
McLean, Ancill, and Szulecka, 1986	Unclear	Unclear	Low	Low	Low	Low	Unclear	Unclear
Mielke and Gallant, 1978	Unclear	Unclear	Low	Low	Unclear	Low	High ^a	Public
Moak et al., 2003	Unclear	Unclear	Low	Low	Unclear	Unclear	High ^a	Some private
Muhonen et al., 2008	Low	Low	Low	Low	Unclear	High	Low	Some private
Oslin, 2005	Unclear	Unclear	Unclear	Unclear	Unclear	High	High ^a	Some private
Petersen and Zettle, 2009	Low	Low	High	High	Low	High	High ^a	Unclear
Pettinati et al., 2010	Unclear	Unclear	Low	Low	Unclear	High ^a	High ^a	Some private
Ralevski et al., 2013	Unclear	Unclear	Low	Low	Low	Low	High ^a	Public
Roy, 1998	Unclear	Unclear	Low	Low	Low	High ^a	High ^a	Unclear
Roy-Byrne et al., 2000	Unclear	Unclear	Low	Low	Low	High	High ^a	Some private

Study	Random Sequence Generation	Allocation Concealment	Blinding Participants	Blinding Providers	Blinding Assessors	Completeness of Outcome Data	Selective Outcome Reporting	Funder
Salloum, 2007	Unclear	Unclear	Low	Low	Unclear	Unclear	High ^a	Public
Shaw et al., 1975	Unclear	Unclear	Low	Low	Unclear	Low	High ^a	Unclear
Thapinta, Skulphan, and Kittrattanapaiboon, 2014	Unclear	Unclear	High	High	Unclear	High	Unclear	Public
Thapinta et al., 2017	Unclear	Unclear	High	High	Low	Low	Unclear	Public
Witte et al., 2012	Unclear	Unclear	Low	Low	Unclear	High	Low	Some private
Zielinski, 1979	Unclear	Unclear	High	High	Unclear	Low	Unclear	Unclear

^a High risk of bias for some but not all outcomes.

Completeness of outcome data: Three studies (9 percent) had unclear risk of bias, as the attrition and exclusions were insufficiently reported. We judged 14 studies (40 percent) to be at high risk of bias because of substantial overall or differential attrition such that we believed the amount of and reasons for missing data to induce clinically relevant bias in the observed effect size. We judged that 18 studies (51 percent) had low risk of attrition bias related to completeness of outcome data at postintervention, as the amount of missing outcome data was minimal and unlikely to induce clinically relevant bias in the observed effect size. Of the two studies with short-term follow-up data, one had low and the other unclear risk of attrition bias. The one study with longer-term follow-up data had high risk of attrition bias.

Selective outcome reporting: Five studies (14 percent) had low risk of bias, 13 (37 percent) had unclear risk of bias, and 17 (49 percent) had high risk of reporting bias for at least one outcome related to selective reporting of outcome data.

Sources of funding: Thirteen studies (37 percent) did not report funding sources, 12 studies (35 percent) reported only public sources of funding, and 10 studies (29 percent) reported at least one private source of funding with a potential conflict of interest.

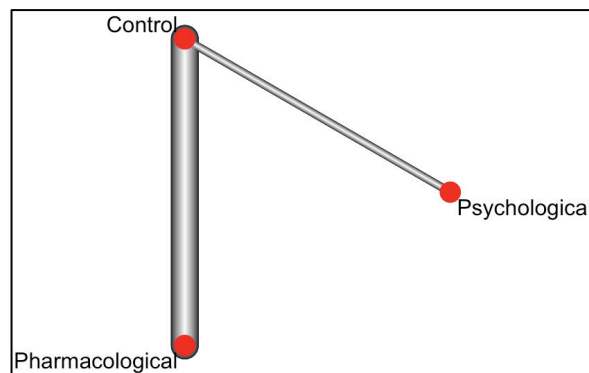
Network Geometry

Overall, we considered identified interventions to be comparable, as they could be used in theory and are used in practice as clinical interventions for patients with comorbid alcohol use and depressive disorders. That is, using the VA/DoD CPGs for alcohol use and major depressive disorders as a point of reference (Management of Substance Use Disorders Working Group, 2015; Management of Major Depressive Disorder Working Group, 2016), included studies all evaluated classes of interventions that could be recommended as acute treatment, following indications for treatment of and then confirmation of diagnoses of both an alcohol use and depressive disorder. Studies all took place in specialty care clinical settings, with treatments delivered by specialty health care providers and outcomes assessed using accepted measures. The only major difference across trials that concerned us regarding the transitivity assumption of NMA involved the length of treatment, which ranged from 3 to 26 weeks. We consequently

tabulated and compared length of treatment across intervention arms in each network, and we downgraded confidence in network estimates in which we judged the risk of intransitivity to be high as a result of considerable differences in treatment lengths.

The included studies contained 73 intervention arms, which we classified into three overarching categories: pharmacological interventions ($n = 37$), psychological interventions ($n = 9$), and control interventions ($n = 27$). We identified 42 direct comparisons: 22 direct comparisons of a pharmacological intervention and a control intervention, 8 of a psychological intervention and a control intervention, 10 of pharmacological interventions, and 2 of psychological interventions. We did not identify any studies directly comparing a pharmacological intervention with a psychological intervention (Figure 3.2).

Figure 3.2. Network Structure by Intervention Category



We then split these categories further by intervention class, which we used for the final nodes in our NMAs. Given that participants in all studies received TAU in addition to the interventions listed here, our network involves and analyzes the following intervention classes as adjunctive to TAU:

- pharmacological intervention classes
 - AAPs: aripiprazole (Han et al., 2013) and sulpiride (Golik-Gruber et al., 2003)
 - glutamatergic antagonists: acamprosate (Witte et al., 2012)
 - MRIs: AHR-1118 (Mielke and Gallant, 1978)
 - NMDA antagonists: memantine (Muhonen et al., 2008)
 - nonselective, noncompetitive antagonists of nAChRs: mecamylamine (Ralevski et al., 2013)
 - NRIs: viloxazine (Altamura et al., 1990)
 - opioid antagonists: naltrexone (Oslin, 2005; Salloum, 2007; Pettinati et al., 2010)
 - sedatives: chlordiazepoxide (Shaw et al., 1975)
 - SSRIs: citalopram (Adamson et al., 2015), escitalopram (Muhonen et al., 2008; Han et al., 2013; Krupitsky et al., 2013), fluoxetine (Salloum, 2007; Cornelius et al., 1997), paroxetine (Cocchi, 1997), and sertraline (Roy, 1998; Gual et al., 2003; Moak et al., 2003; Kranzler et al., 2006; Pettinati et al., 2010)

- SARIs: nefazodone (Roy-Byrne et al., 2000; Hernandez-Avila et al., 2004)
- TeCAs: mianserin (McLean, Ancill, and Szulecka, 1986) and mirtazapine (Altintoprak et al., 2008; Cornelius et al., 2016)
- TCAs: amitriptyline (Loo et al., 1988; Cocchi, 1997; Altintoprak et al., 2008), desipramine (Mason et al., 1996), imipramine (Butterworth, 1971; Shaw et al., 1975; Mielke and Gallant, 1978; McGrath et al., 1996), and tianeptine (Loo et al., 1988)
- psychological intervention classes
 - CBT: acceptance and commitment therapy (Petersen and Zettle, 2009), brief CBT (Thapinta, Skulphan, and Kittrattanapaiboon, 2014), and CBT self-help book (Thapinta et al., 2017)
 - IPT: IPT for Dysthymic Disorder (Markowitz et al., 2008)
 - SMS: activity level monitoring (Zielinski, 1979), social skills training (Zielinski, 1979), and supportive text messaging (Agyapong et al., 2012)
 - SP: brief SP (Markowitz et al., 2008)
- control intervention classes
 - pharmacological placebo (Butterworth, 1971; Shaw et al., 1975; McLean, Ancill, and Szulecka, 1986; Altamura et al., 1990; McGrath et al., 1996; Cornelius et al., 1997; Roy, 1998; Roy-Byrne et al., 2000; Golik-Gruber et al., 2003; Gual et al., 2003; Moak et al., 2003; Hernandez-Avila et al., 2004; Oslin, 2005; Kranzler et al., 2006; Pettinati et al., 2010; Witte et al., 2012; Krupitsky et al., 2013; Ralevski et al., 2013; Adamson et al., 2015; Cornelius et al., 2016)
 - psychological placebo (Zielinski, 1979; Petersen and Zettle, 2009; Agyapong et al., 2012)
 - no additional treatment (Thapinta, Skulphan, and Kittrattanapaiboon, 2014; Holzhauer and Gamble, 2017; Thapinta et al., 2017).

Examining the network structure at the level of intervention class (rather than category) revealed two separate networks in our body of evidence: one of pharmacological interventions and pharmacological placebos (Figure 3.3); and another of psychological interventions, psychological placebos, and no additional treatment (Figure 3.4).

In the pharmacological network, the most common nodes were pharmacological placebo (21 trial groups; 685 participants), SSRI (12 trial groups; 611 participants), and TCA (8 trial groups; 291 participants), with SSRI versus pharmacological placebo as the most frequent direct comparison (eight comparisons). The nine studies with head-to-head comparisons involved MRIs versus TCAs (Mielke and Gallant, 1978), NMDA antagonists versus SSRIs (Muhonen et al., 2008), opioid antagonists versus SSRIs (Pettinati et al., 2010), SSRIs versus an SSRI combined with an AAP (Han et al., 2013), SSRIs versus an SSRI combined with an opioid antagonist (Salloum, 2007; Pettinati et al., 2010), SSRIs versus TCAs (Cocchi, 1997), TCAs versus TCAs (Loo et al., 1988), and TeCAs versus TCAs (Altintoprak et al., 2008).

In the psychological network, the most common nodes were CBT (three trial groups; 230 participants), psychological placebo (three trial groups; 55 participants), and no additional treatment (three trial groups; 238 participants), with SMS versus psychological placebo as the most frequent direct comparison (three comparisons). The only two head-to-head comparisons of

Figure 3.3. Pharmacological Network Structure by Intervention Class

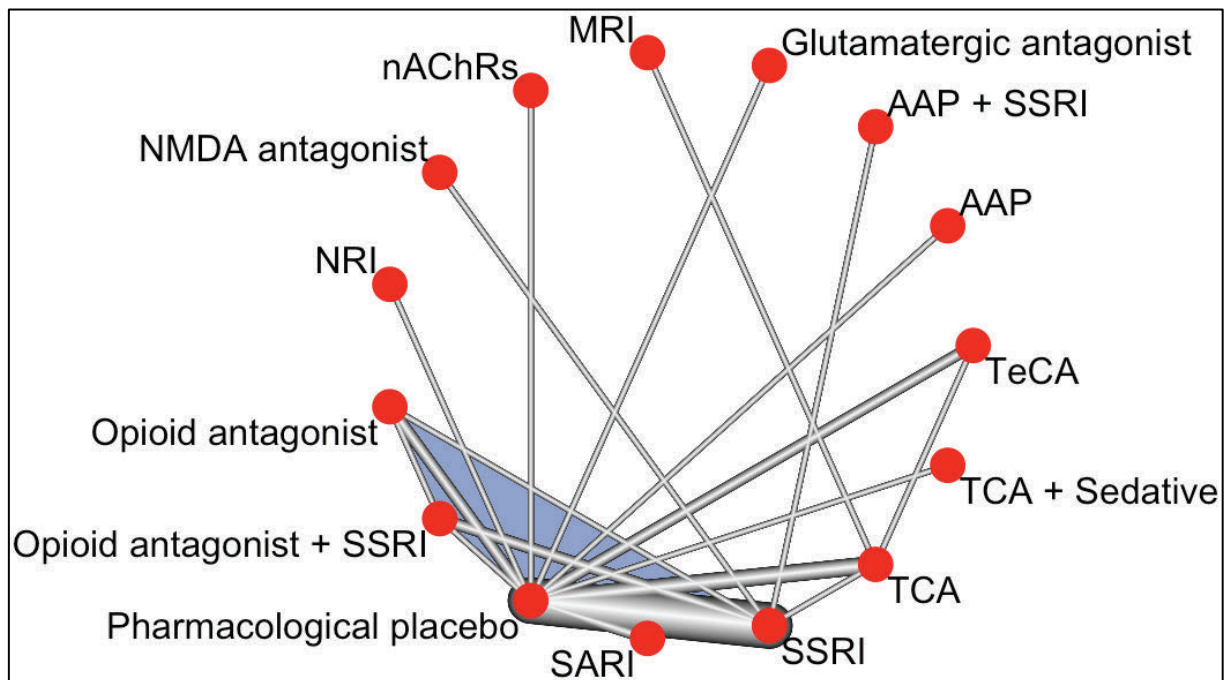
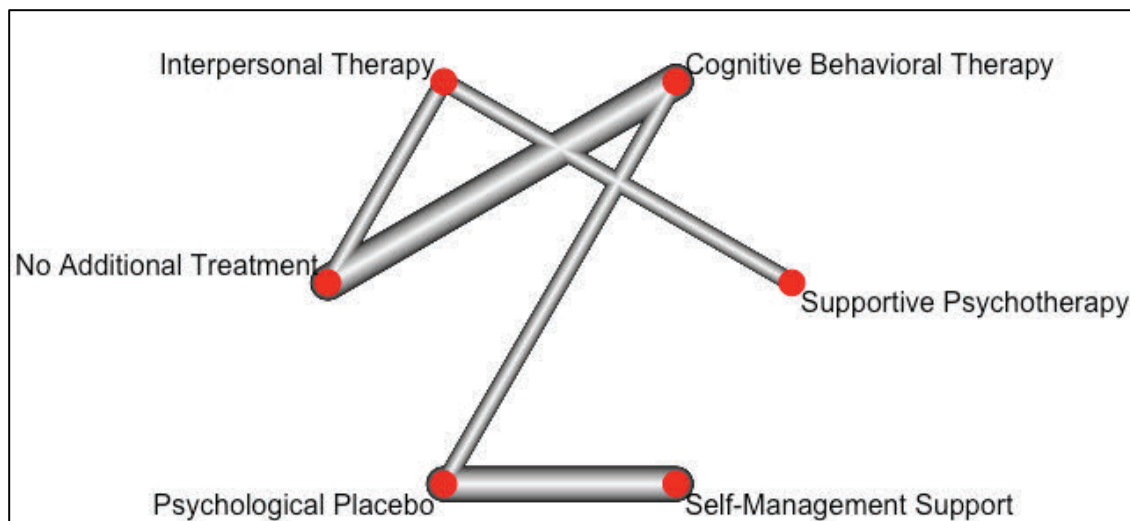


Figure 3.4. Psychological Network Structure by Intervention Class



active psychological interventions involved a direct comparison of two SMS interventions (Zielinski, 1979) and another of IPT versus SP (Markowitz et al., 2008).

Key Question 1: Pairwise Effect Estimates from Network Meta-Analyses

Unless otherwise stated, all effect estimates are measured at postintervention. The network geometry for each analysis is presented in Appendix E, as are differences in the sensitivity

analyses from the default analyses, and the GRADE ratings and extracted outcome data can be found in the online supplemental data file. The effect estimates in the narrative are phrased so that SMDs less than 0 and ORs less than 1 favor the relatively effective intervention. In contrast, the effect estimates in the tables must be formatted such that SMDs less than 0 and ORs less than 1 favor the intervention in the column, and SMDs greater than 0 and ORs greater than 1 favor the intervention in the row.

Remission from Depression

Pharmacological interventions: Eighteen pharmacological intervention studies (64 percent) reported data on 12 intervention classes (23 direct comparisons). We did not detect significant heterogeneity in the network globally ($Q(3) = 4.89, p = 0.18$), and hotspots of inconsistency were absent from the net heat plot. Based on confidence ratings using the GRADE approach, we have very low confidence in all estimates at postintervention (Table 3.5), and confidence intervals for all comparisons did not exclude a null effect—including between active interventions and pharmacological placebo (Figure 3.5).

Table 3.5. Pharmacological Intervention Effect Estimates at Postintervention for Remission from Depression and Alcohol Use

AAP	0.95 [0.0518; 17.3812]	1.37 [0.0730; 25.7568]	1.58 [0.0630; 39.4245]	1.58 [0.1050; 23.7934]	1.13 [0.1162; 11.0487]	0.37 [0.0293; 4.7676]	1.71 [0.2352; 12.4941]	0.36 [0.0239; 5.3310]	1.29 [0.1629; 10.2722]	0.68 [0.0695; 6.5611]	1.32 [0.0814; 21.4972]
—	AAP + SSRI	1.45 [0.0700; 29.8662]	1.66 [0.0638; 43.2700]	1.67 [0.1134; 24.4897]	1.19 [0.1130; 12.6279]	0.39 [0.0293; 5.2945]	1.81 [0.2160; 15.1217]	0.38 [0.0228; 6.2299]	1.36 [0.1772; 10.4937]	0.71 [0.0693; 7.3201]	1.39 [0.0776; 25.0460]
—	0.27 [0.0233; 3.2247]	Glutamatergic antagonist	1.15 [0.0412; 32.0451]	1.15 [0.0674; 19.7206]	0.83 [0.0729; 9.3706]	0.27 [0.0186; 3.9827]	1.25 [0.1445; 10.8158]	0.26 [0.0153; 4.4201]	0.94 [0.1007; 8.8340]	0.49 [0.0436; 5.5659]	0.96 [0.0524; 17.7572]
—	—	—	MRI	1.00 [0.0459; 21.9430]	0.72 [0.0459; 11.2739]	0.24 [0.0121; 4.6248]	1.09 [0.0863; 13.7055]	0.23 [0.0099; 5.1707]	0.82 [0.0646; 10.4263]	0.43 [0.0439; 4.1878]	0.84 [0.0342; 20.6169]
—	0.98 [0.1194; 7.9900]	3.56 [0.5921; 21.4583]	—	NMDA antagonist	0.72 [0.0869; 5.9154]	0.24 [0.0219; 2.5435]	1.08 [0.1712; 6.8669]	0.23 [0.0168; 3.0466]	0.82 [0.1424; 4.7024]	0.43 [0.0534; 3.4177]	0.84 [0.0568; 12.3250]
—	0.41 [0.0537; 3.1103]	1.49 [0.2758; 8.0635]	—	0.42 ^b [0.1359; 1.2876]	Opioid antagonist	0.33 [0.0605; 1.7961]	1.51 [0.4967; 4.6073]	0.32 [0.0369; 2.6927]	1.14 [0.3502; 3.7198]	0.60 [0.1275; 2.7870]	1.17 [0.1228; 11.0914]
—	1.67 [0.2082; 13.4557]	6.11^a [1.0532; 35.4318]	—	1.71 [0.5060; 5.8048]	4.10^a [1.6431; 10.2123]	Opioid antagonist + SSRI	4.59 ^b [0.9324; 22.5961]	0.96 [0.0842; 10.8561]	3.46 ^b [0.6929; 17.3095]	1.81 [0.2689; 12.1625]	3.54 [0.2838; 44.1849]
—	0.57 [0.0842; 3.9245]	2.10 [0.4473; 9.8391]	—	0.59 ^b [0.2361; 1.4669]	1.41 [0.7139; 2.7719]	0.34^a [0.1486; 0.7937]	Pharmacological placebo	0.21 [0.0333; 1.3033]	0.75 [0.4181; 1.3616]	0.39 ^b [0.1303; 1.1911]	0.77 [0.1090; 5.4606]
—	0.76 [0.0862; 6.6570]	2.76 [0.4348; 17.5799]	—	0.78 [0.1978; 3.0418]	1.85 [0.5463; 6.2925]	0.45 [0.1212; 1.6895]	1.32 [0.4769; 3.6421]	SARI	3.62 [0.5277; 24.8570]	1.89 [0.2222; 16.0969]	3.70 [0.2534; 54.1027]
—	0.54 [0.0804; 3.6471]	1.98 [0.4143; 9.4316]	—	0.55 [0.2292; 1.3420]	1.33 [0.6616; 2.6561]	0.32^a [0.1395; 0.7504]	0.94^b [0.7482; 1.1868]	0.71 [0.2521; 2.0275]	SSRI	0.52 [0.1695; 1.6084]	1.02 [0.1324; 7.8959]
—	1.02 [0.1121; 9.3726]	3.74 [0.5613; 24.9210]	—	1.05 [0.2513; 4.3813]	2.51 [0.6892; 9.1274]	0.61 [0.1537; 2.4390]	1.78 [0.5938; 5.3527]	1.35 [0.3026; 6.0461]	1.89 [0.6152; 5.8179]	TCA	1.96 [0.2068; 18.5403]
—	—	—	—	—	—	—	—	—	—	—	TeCA

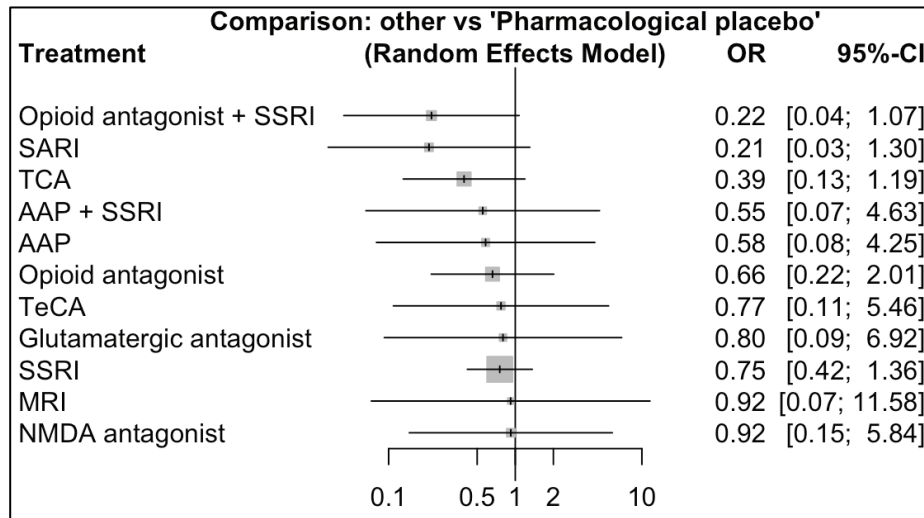
NOTES: The upper right triangle provides estimates for remission from depression, and the bottom left triangle provides estimates for remission from alcohol use.

OR < 1 favors the intervention in the column, and OR > 1 favors the intervention in the row.

^a The confidence interval does not include an estimate of no effect.

^b At least one sensitivity analysis had a substantively different estimate (see Appendix F).

Figure 3.5. Forest Plot of Effect Estimates (Active Pharmacological Interventions Versus Pharmacological Placebo) on Remission from Depression at Postintervention

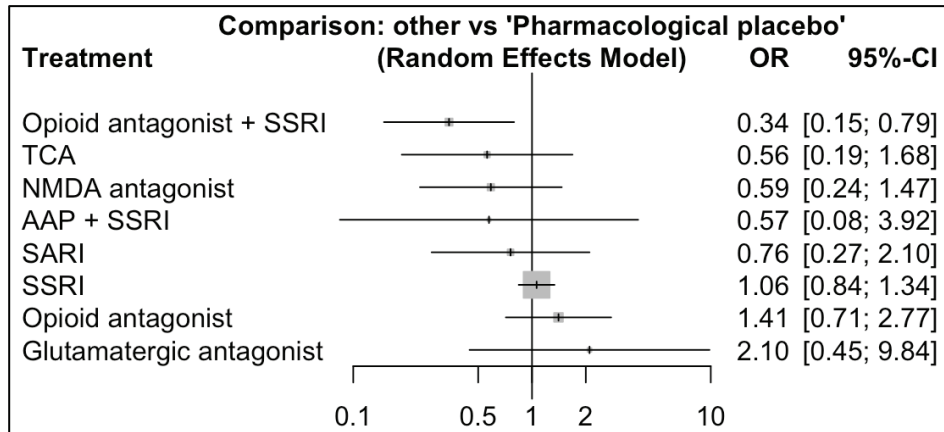


Psychological interventions: Two psychological intervention studies (29 percent) reported data on four intervention classes (two direct comparisons). We have very low confidence in estimates at postintervention of SP compared with IPT (OR 0.23 [0.02 to 2.59], $k = 1$, $n = 26$) and CBT compared with psychological placebo (OR 0.47 [0.08 to 2.66], $k = 1$, $n = 30$).

Remission from Alcohol Use

Pharmacological interventions: Seventeen pharmacological intervention studies (61 percent) reported data on nine intervention classes (22 direct comparisons). We did not detect significant heterogeneity in the network globally ($Q(2) = 0.73$, $p = 0.69$), and hotspots of inconsistency were absent from the net heat plot. We have very low confidence in all estimates at postintervention (see Table 3.5), including estimates at postintervention of a beneficial effect of opioid antagonists combined with SSRIs over glutamatergic antagonists (OR 0.16 [0.03 to 0.95], indirect evidence only), opioid antagonists (OR 0.24 [0.10 to 0.61], $k = 1$, $n = 88$), pharmacological placebo (OR 0.34 [0.15 to 0.79], $k = 1$, $n = 80$), and SSRIs (OR 0.32 [0.14 to 0.75], $k = 1$, $n = 81$). Confidence intervals for all other comparisons at postintervention did not exclude a null effect—including between each active intervention and pharmacological placebo (Figure 3.6). However, after excluding studies with high risk of bias from the network, we identified an estimate (excluding a null effect) of a beneficial effect of SSRIs over pharmacological placebo (OR 0.69 [0.47 to 0.9998], $k = 5$, $n = 410$) in which we would have low (as opposed to very low) confidence had this been the default analysis. We also have very low confidence in an estimate at long-term (6 months postintervention) follow-up of a beneficial effect of opioid antagonists combined with SSRIs over SSRIs (OR 0.26 [0.07 to 0.97], $k = 1$, $n = 31$).

Figure 3.6. Forest Plot of Effect Estimates (Active Pharmacological Interventions Versus Pharmacological Placebo) on Remission from Alcohol Use at Postintervention



Psychological interventions: Two psychological intervention studies (29 percent) reported data on four intervention classes (two direct comparisons). We have very low confidence in estimates at postintervention of SMS compared with psychological placebo (OR 0.40 [0.12 to 1.30], $k = 1$, $n = 54$) and SP compared with IPT (OR 0.86 [0.21 to 3.50], $k = 1$, $n = 26$). We also have very low confidence in estimates of SMS compared with psychological placebo at short-term (OR 0.61 [0.20 to 1.83], $k = 1$, $n = 54$), long-term (OR 0.47 [0.10 to 2.17], $k = 1$, $n = 36$), and very long-term follow-up (OR 0.28 [0.06 to 1.31], $k = 1$, $n = 36$).

Depressive Symptoms

Pharmacological interventions: Twenty pharmacological intervention studies (71 percent) reported data on 11 intervention classes (25 direct comparisons). We detected significant heterogeneity in the network globally ($Q(12) = 20.82$, $p = 0.05$), which was due to significant within-design heterogeneity in comparisons of pharmacological placebo versus SSRI ($Q(6) = 15.38$, $p = 0.02$) rather than inconsistency between designs ($Q(2) = 3.53$, $p = 0.17$). Hotspots of inconsistency were absent from the net heat plot. We have low confidence in an estimate at postintervention of a beneficial effect of TCAs over pharmacological placebo (SMD -0.37 [-0.72 to -0.02], $k = 3$, $n = 137$); we downgraded confidence from “high” to “low” because of a risk of attrition bias in the body of evidence, as well as concerns about intransitivity in this body of evidence (specifically differences in length of treatment among studies in the network). We have very low confidence in an estimate of a beneficial effect at postintervention of opioid antagonists in combination with SSRIs over pharmacological placebo (SMD -0.66 [-1.27 to -0.06], $k = 1$, $n = 43$) and at long-term (6 months postintervention) follow-up of a beneficial effect of SSRIs over pharmacological placebo (SMD -0.80 [-1.53 to -0.07], $k = 1$, $n = 31$). We have very low confidence in all other estimates at postintervention (Table 3.6); confidence intervals for all other comparisons did not exclude a null effect—including between each active intervention and pharmacological placebo (Figure 3.7).

Psychological interventions: Five psychological intervention studies (71 percent) reported data on six intervention classes (four direct comparisons). We have moderate confidence in estimates at postintervention of a beneficial effect of CBT over no treatment additional to TAU (SMD -0.84 [-1.05 to -0.63], $k = 2$, $n = 430$, $I^2 = 0$ percent); we downgraded confidence from “high” to “moderate” because the body of evidence only had two studies providing direct evidence for assessing consistency. We have very low confidence in estimates at postintervention of a beneficial effect of SMS over psychological placebo (SMD -0.88 [-1.44 to -0.32], $k = 1$, $n = 54$), as well as estimates at postintervention of CBT compared with psychological placebo (SMD -0.19 [-0.99 to 0.61], $k = 1$, $n = 30$), IPT compared with SP (SMD -0.35 [-1.13 to 0.42], $k = 1$, $n = 26$), psychological placebo compared with no treatment additional to TAU (SMD -0.65 [-1.48 to 0.18], indirect evidence only [mean path length = 2]), SMS compared with CBT (SMD -0.69 [-1.67 to 0.29], indirect evidence only [mean path length = 2]), and SMS compared with no treatment additional to TAU (SMD -1.53 [-2.53 to 0.53], indirect evidence only [mean path length = 3]). We also have very low confidence in estimates of SMS compared with psychological placebo at short-term follow-up (SMD -0.17 [-0.74 to 0.39], $k = 1$, $n = 54$), as well as CBT compared with no treatment additional to TAU at short-term (SMD -0.88 [-2.93 to 1.18], $k = 2$, $n = 430$, $I^2 = 35$ percent) and at long-term follow-up (SMD -0.17 [-0.74 to 0.39], $k = 1$, $n = 350$).

Withdrawal and Craving Symptoms

Pharmacological interventions: Eight pharmacological intervention studies (29 percent) reported data on eight intervention classes (eight direct comparisons). We did not detect significant heterogeneity in the network globally ($Q(1) = 0.01$, $p = 0.91$), though we were not able to assess hotspots of inconsistency in a net heat plot because of a lack of closed loops in the network geometry. We have very low confidence in all estimates at postintervention (Table 3.6), and confidence intervals for all comparisons did not exclude a null effect—including between each active intervention and pharmacological placebo (Figure 3.8).

Psychological interventions: One psychological intervention study (14 percent) reported data on two intervention classes (one direct comparison). We have very low confidence in estimates of psychological placebo compared with SMS at postintervention (SMD -0.29 [-0.83 to 0.25], $k = 1$, $n = 54$) and SMS compared with psychological placebo at short-term follow-up (SMD -0.46 [-1.03 to 0.12], $k = 1$, $n = 54$).

Table 3.6. Pharmacological Intervention Effect Estimates at Postintervention for Depressive and Withdrawal and Craving Symptoms

AAP + SSRI	-0.11 [-1.36; 1.13]	0.41 [-0.86; 1.68]	0.25 [-0.81; 1.31]	-0.28 [-1.29; 0.74]	-0.45 [-1.47; 0.57]	0.21 [-0.63; 1.06]	-0.10 [-1.07; 0.88]	0.07 [-0.74; 0.89]	-0.16 [-1.05; 0.74]	0.09 [-0.98; 1.16]
-0.55 [-1.67; 0.57]	Glutamatergic antagonist	0.53 [-0.79; 1.85]	0.36 [-0.80; 1.52]	-0.16 [-1.27; 0.94]	-0.34 [-1.44; 0.77]	0.33 [-0.59; 1.25]	0.02 [-1.03; 1.06]	0.19 [-0.76; 1.13]	-0.04 [-1.03; 0.94]	0.21 [-0.92; 1.33]
—	—	nAChRs	-0.17 [-1.35; 1.02]	-0.69 [-1.82; 0.44]	-0.86 [-2.00; 0.26]	-0.20 [-1.15; 0.75]	-0.51 [-1.58; 0.56]	-0.34 [-1.31; 0.63]	-0.57 [-1.58; 0.44]	-0.32 [-1.48; 0.83]
-0.22 [-1.06; 0.62]	0.33 [-0.64; 1.30]	—	NMDA antagonist	-0.52 [-1.43; 0.38]	-0.70 [-1.60; 0.21]	-0.03 [-0.74; 0.67]	-0.34 [-1.20; 0.52]	-0.17 [-0.85; 0.50]	-0.40 [-1.17; 0.36]	-0.16 [-1.12; 0.81]
—	—	—	—	Opioid antagonist	-0.17 [-0.85; 0.50]	0.49 [-0.12; 1.10]	0.18 [-0.60; 0.97]	0.35 [-0.25; 0.96]	0.12 [-0.57; 0.81]	0.37 [-0.52; 1.26]
—	—	—	—	—	Opioid antagonist + SSRI	0.66^a [0.06; 1.27]	0.36 ^b [-0.43; 1.14]	0.52 [-0.08; 1.13]	0.30 [-0.39; 0.99]	0.54 [-0.35; 1.44]
-0.57 [-1.34; 0.20]	-0.02 [-0.84; 0.80]	—	-0.35 [-0.88; 0.17]	—	—	Pharmacological placebo	-0.31 [-0.80; 0.19]	-0.14 [-0.35; 0.07]	-0.37^b [-0.72; -0.02]	-0.12 [-0.78; 0.53]
-0.20 [-1.14; 0.73]	0.35 [-0.63; 1.32]	—	0.01 [-0.73; 0.76]	—	—	0.37 [-0.16; 0.90]	SARI	0.17 [-0.37; 0.71]	-0.06 [-0.67; 0.55]	0.19 [-0.64; 1.01]
-0.49 [-1.21; 0.23]	0.06 [-0.81; 0.92]	—	-0.27 [-0.72; 0.17]	—	—	0.08 [-0.20; 0.36]	-0.29 [-0.89; 0.31]	SSRI	-0.23 [-0.59; 0.14]	0.02 [-0.67; 0.70]
-1.05 [-2.51; 0.42]	-0.50 [-1.99; 0.99]	—	-0.83 [-2.18; 0.52]	—	—	-0.48 [-1.72; 0.77]	-0.84 [-2.20; 0.51]	-0.55 [-1.83; 0.72]	TCA	0.25 [-0.50; 0.99]
-0.98 [-2.29; 0.33]	-0.43 [-1.77; 0.90]	—	-0.77 [-1.95; 0.41]	—	—	-0.41 [-1.47; 0.65]	-0.78 [-1.97; 0.40]	-0.49 [-1.59; 0.60]	0.06 [-0.59; 0.72]	TeCA

NOTES: The upper right triangle provides estimates for depressive symptoms, and the bottom left triangle provides estimates for withdrawal and craving symptoms. SMD < 0 favors the intervention in the column, and SMD > 0 favors the intervention in the row.

^a The confidence interval does not include an estimate of no effect.

^b At least one sensitivity analysis had a substantively different estimate (see Appendix F).

Figure 3.7. Forest Plot of Effect Estimates (Active Pharmacological Interventions Versus Pharmacological Placebo) on Depressive Symptoms at Postintervention

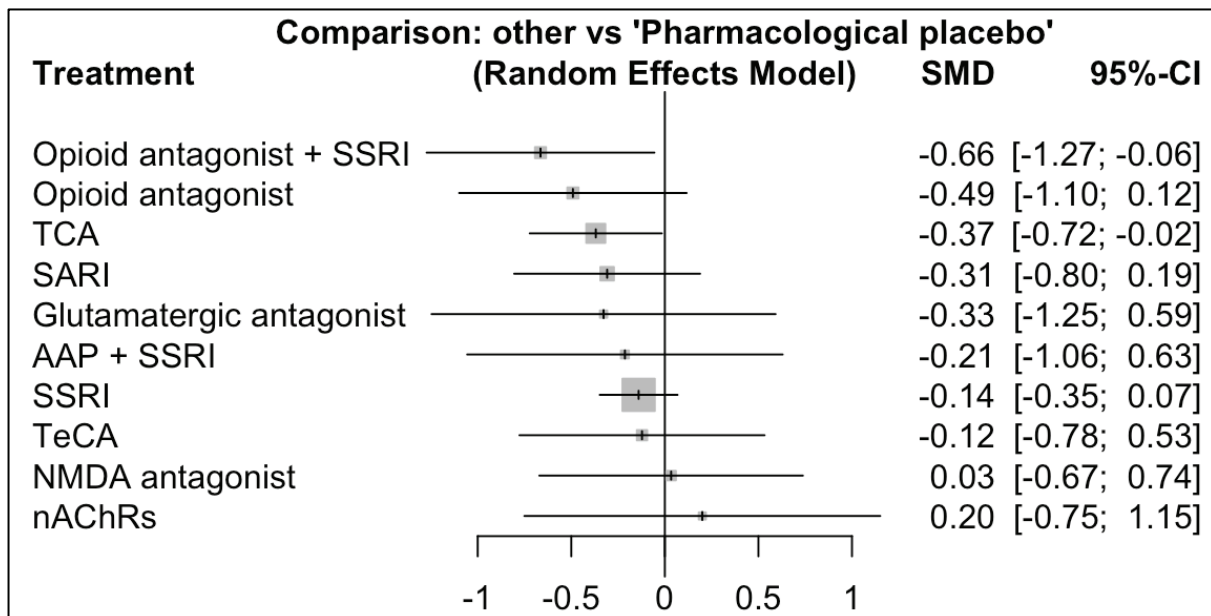
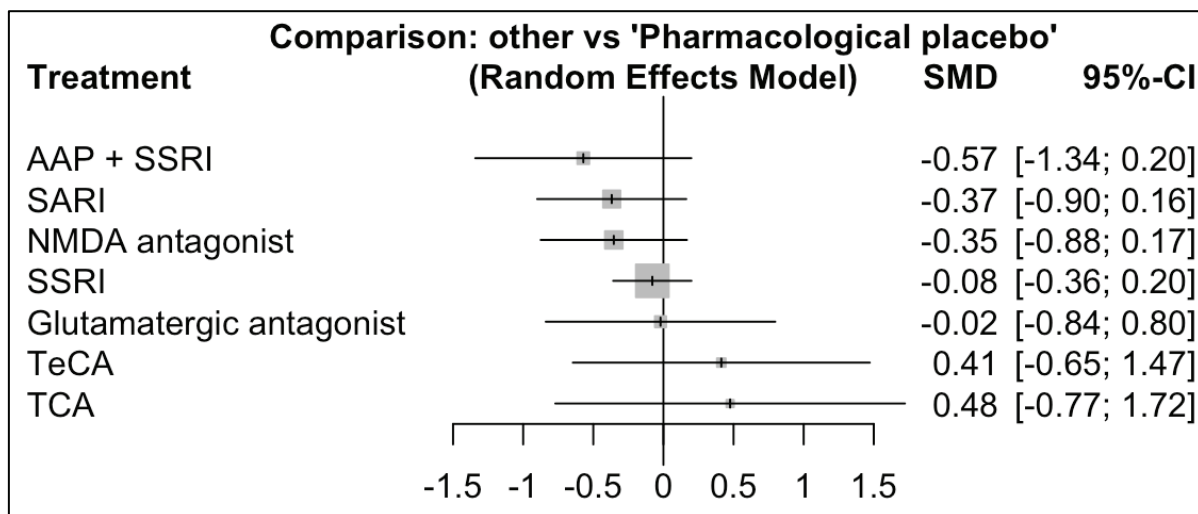


Figure 3.8. Forest Plot of Effect Estimates (Active Pharmacological Interventions Versus Pharmacological Placebo) on Withdrawal and Craving Symptoms at Postintervention

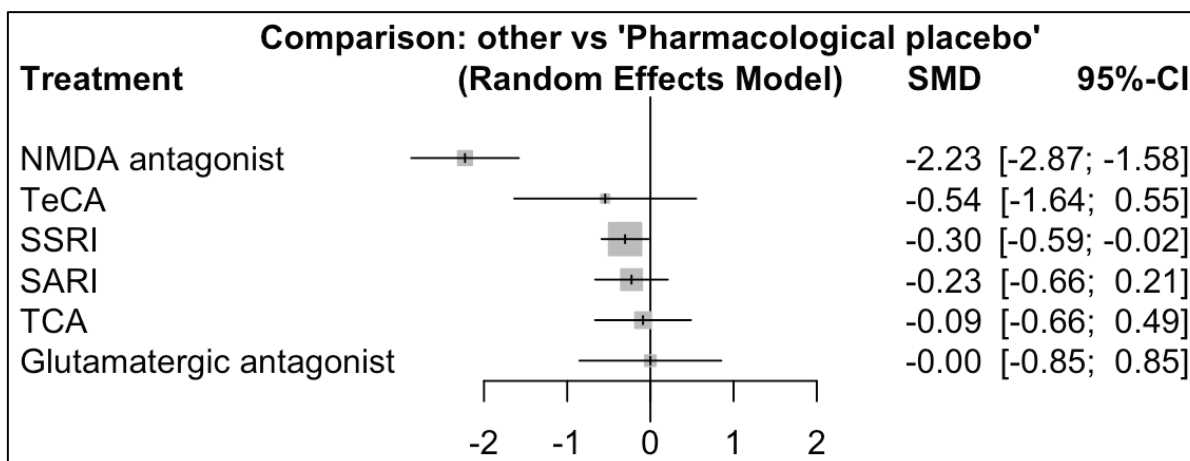


Total Drinking

Pharmacological interventions: Nine studies (32 percent) reported data on seven intervention classes (nine direct comparisons). We did not detect significant heterogeneity in the network globally ($Q(3) = 3.78, p = 0.29$), though we were not able to assess hotspots of inconsistency in a net heat plot because of a lack of closed loops in the network geometry. We have moderate

confidence in an estimate of a beneficial effect at postintervention of SSRIs over pharmacological placebo (SMD -0.30 [-0.59 to -0.02], $k = 3$, $n = 271$); we downgraded confidence from “high” to “moderate” because of a risk of selective outcome reporting. We have very low confidence in estimates of a beneficial effect at postintervention of NMDA antagonists over glutamatergic antagonists (SMD -2.23 [-3.30 to -1.16], very indirect evidence only [i.e., no common comparator, with a network distance of at least two edges]), pharmacological placebo (SMD -2.23 [-2.87 to -1.58], indirect evidence only), SARIs (SMD -2.00 [-2.78 to -1.22], indirect evidence only), SSRIs (SMD -1.92 [-2.51 to -1.34], $k = 1$, $n = 80$), TCAs (SMD -2.14 [-3.01 to -1.27], very indirect evidence only), and TeCAs (SMD -1.69 [-2.95 to -0.42], very indirect evidence only). We have very low confidence in all other estimates at postintervention (Table 3.7); confidence intervals for all other comparisons did not exclude a null effect—including between each active intervention and pharmacological placebo (Figure 3.9).

Figure 3.9. Forest Plot of Effect Estimates (Active Pharmacological Interventions Versus Pharmacological Placebo) on Total Drinking at Postintervention



Psychological interventions: Two studies (29 percent) reported data on four intervention classes (two direct comparisons). We have very low confidence in estimates of SMS compared with psychological placebo at postintervention (SMD -0.47 [-1.01 to 0.07], $k = 1$, $n = 54$) and short-term follow-up (SMD -0.14 [-0.70 to 0.43], $k = 1$, $n = 54$). We also have very low confidence in estimates of a beneficial effect of CBT over no treatment additional to TAU at postintervention (SMD -0.25 [-0.47 to -0.04], $k = 1$, $n = 350$), as well as estimates with confidence intervals that did not exclude a null effect at short-term (SMD -0.10 [-0.31 to 0.12], $k = 1$, $n = 350$) and long-term follow-up (SMD -0.14 [-0.70 to 0.43], $k = 1$, $n = 350$).

Table 3.7. Pharmacological Intervention Effect Estimates at Postintervention for Total and Heavy Drinking

Glutamatergic antagonist	—	—	—	—	—	—	—	—
2.23^a [1.16; 3.30]	NMDA antagonist	0.49 [−0.26; 1.25]	−0.02 [−0.83; 0.79]	0.58 [−0.09; 1.25]	−0.45 [−1.47; 0.57]	0.46 [−0.14; 1.06]	0.80 [−0.14; 1.74]	0.97 [−0.35; 2.29]
—	—	Opioid antagonist	−0.51 ^b [−1.07; 0.04]	0.09 [−0.33; 0.50]	−0.95^a [−1.82; −0.08]	−0.04 [−0.49; 0.41]	0.31 [−0.48; 1.09]	0.48 [−0.73; 1.68]
—	—	—	Opioid antagonist + SSRI	0.60^a [0.08; 1.13]	−0.43 [−1.37; 0.50]	0.48 [−0.06; 1.02]	0.82 ^b [−0.03; 1.67]	0.99 [−0.26; 2.24]
−0.00 [−0.85; 0.85]	−2.23^b [−2.87; −1.58]	—	—	Pharmacological placebo	−1.04^a [−1.80; −0.27]	−0.13 [−0.43; 0.17]	0.22 [−0.45; 0.88]	0.39 [−0.74; 1.52]
0.23 [−0.73; 1.18]	−2.00^b [−2.78; −1.22]	—	—	0.23 [−0.21; 0.66]	SARI	0.91^a [0.09; 1.73]	1.25^a [0.24; 2.27]	1.43^a [0.06; 2.79]
0.30 [−0.59; 1.20]	−1.92^b [−2.51; −1.34]	—	—	0.30^a [0.02; 0.59]	0.08 [−0.44; 0.60]	SSRI	0.34 [−0.39; 1.07]	0.51 [−0.66; 1.69]
0.09 [−0.94; 1.12]	−2.14^b [−3.01; −1.27]	—	—	0.09 [−0.49; 0.66]	−0.14 [−0.86; 0.58]	−0.22 [−0.86; 0.43]	TCA	0.17 [−1.14; 1.48]
0.54 [−0.84; 1.93]	−1.69^b [−2.95; −0.42]	—	—	0.54 [−0.55; 1.64]	0.32 [−0.86; 1.49]	0.24 [−0.89; 1.37]	0.45 [−0.78; 1.69]	TeCA

NOTES: The upper right triangle provides estimates for heavy drinking, and the bottom left triangle provides estimates for total drinking. SMD < 0 favors the intervention in the column, and SMD > 0 favors the intervention in the row.

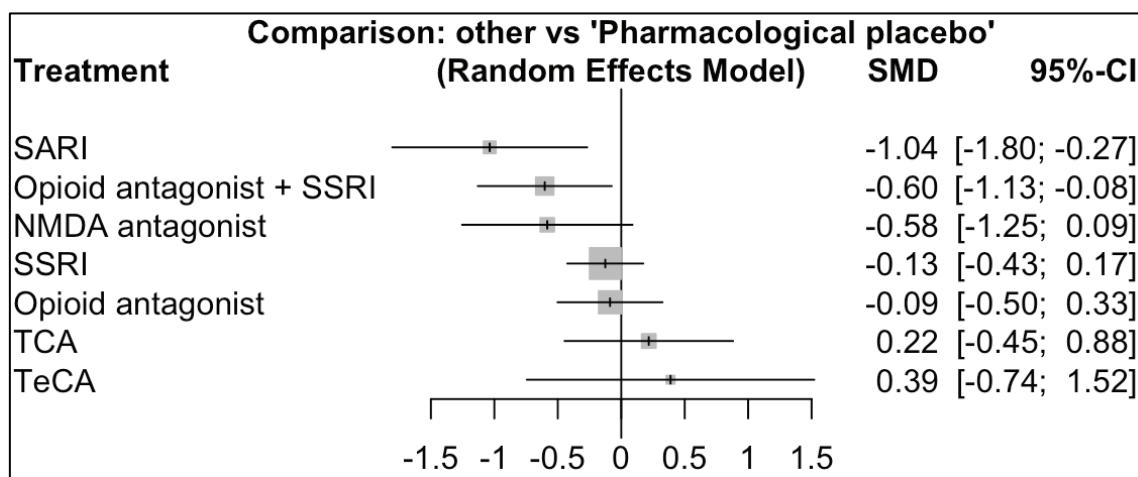
^a The confidence interval does not include an estimate of no effect.

^b At least one sensitivity analysis had a substantively different estimate (see Appendix F).

Heavy Drinking

Pharmacological interventions: Nine studies (32 percent) reported data on seven intervention classes (14 direct comparisons). We did not detect significant heterogeneity in the network globally ($Q(4) = 7.15, p = 0.13$); there was significant within-design heterogeneity in comparisons of pharmacological placebo versus SSRI ($Q(2) = 6.00, p = 0.05$), but we did not detect inconsistency between designs ($Q(2) = 1.15, p = 0.56$). Hotspots of inconsistency were absent from the net heat plot. We have very low confidence in estimates of beneficial effects at postintervention of an opioid antagonist in combination with an SSRI over pharmacological placebo (SMD -0.60 [-1.13 to -0.08], $k = 1, n = 43$), and SARIs over opioid antagonists (SMD -0.95 [-1.82 to -0.08], indirect evidence only), pharmacological placebo (SMD -1.04 [-1.80 to -0.27], $k = 1, n = 41$), SSRIs (SMD -0.91 [-1.73 to -0.09], indirect evidence only), TCAs (SMD -1.25 [-2.27 to -0.24] indirect evidence only), and TeCAs (SMD -1.43 [-2.79 to -0.06], indirect evidence only). We have very low confidence in all other estimates at postintervention (see Table 3.7); confidence intervals for all other comparisons did not exclude a null effect—including between each active intervention and pharmacological placebo (Figure 3.10).

Figure 3.10. Forest Plot of Effect Estimates (Active Pharmacological Interventions Versus Pharmacological Placebo) on Heavy Drinking at Postintervention



Psychological interventions: No studies reported data on heavy drinking.

Health-Related Quality of Life

Pharmacological interventions: Two pharmacological intervention studies (7 percent) reported data on four intervention classes (two direct comparisons). We have very low confidence in estimates of SSRIs compared with NMDA antagonists at postintervention (SMD -0.09 [-0.53 to 0.35], $k = 1, n = 80$) and glutamatergic antagonists compared with pharmacological placebo (SMD -0.33 [-1.15 to 0.50], $k = 1, n = 23$; Table 3.8).

Table 3.8. Pharmacological Intervention Effect Estimates at Postintervention for Health-Related Quality of Life and Functional Status

AAP + SSRI	—	—	—	—	—	—
−0.95 [−2.12; 0.22]	Glutamatergic antagonist	—	0.33 [−0.50; 1.1504]	—	—	—
0.20 [−0.64; 1.03]	1.14^b [0.11; 2.17]	NMDA antagonist	—	—	−0.09 [−0.53; 0.35]	—
−1.02^b [−1.86; −0.18]	−0.07 [−0.89; 0.75]	−1.21^a [−1.84; −0.59]	Pharmacological placebo	—	—	—
−0.39 [−1.42; 0.64]	0.56 [−0.46; 1.58]	−0.58 [−1.45; 0.29]	0.63^b [0.03; 1.24]	SARI	—	—
−0.10 [−0.81; 0.60]	0.85 [−0.09; 1.78]	−0.30 [−0.74; 0.14]	0.92^a [0.47; 1.36]	0.28 [−0.47; 1.04]	SSRI	—
−0.19 [−1.19; 0.80]	0.76 [−0.22; 1.73]	−0.39 [−1.21; 0.44]	0.83^b [0.29; 1.36]	0.19 [−0.62; 1.00]	−0.09 [−0.79; 0.61]	TCA

NOTES: The upper right triangle provides estimates for health-related quality of life, and the bottom left triangle provides estimates for functional status. SMD < 0 favors the intervention in the column, and SMD > 0 favors the intervention in the row.

^a The confidence interval does not include an estimate of no effect.

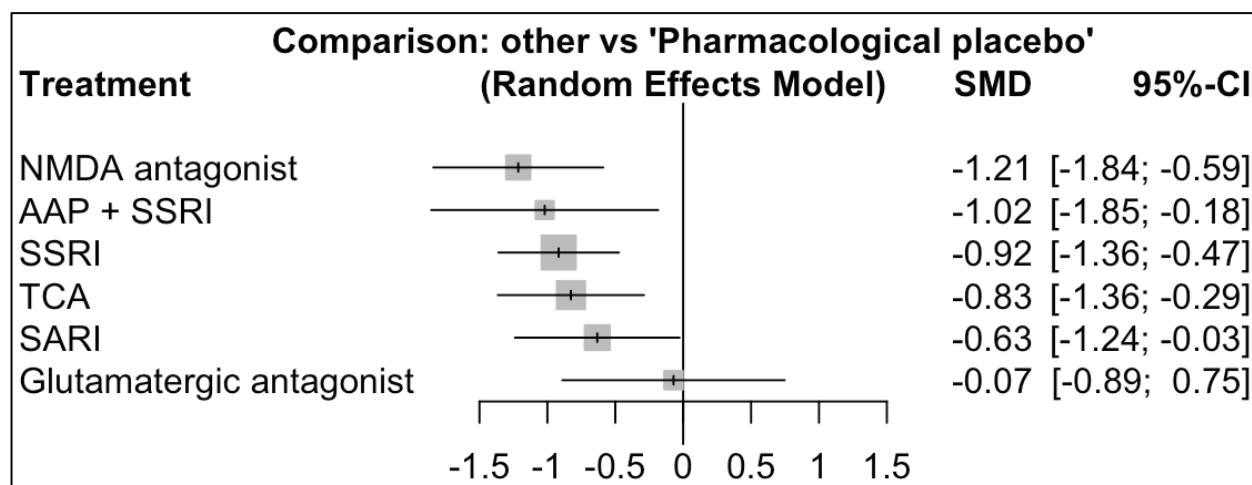
^b At least one sensitivity analysis had a substantively different estimate (see Appendix F).

Psychological interventions: No psychological intervention studies reported data on health-related quality of life.

Functional Status

Pharmacological interventions: Nine pharmacological intervention studies (32 percent) reported data on seven intervention classes (nine direct comparisons). We did not detect significant heterogeneity in the network globally ($Q(3) = 1.76, p = 0.62$), though we were not able to assess hotspots of inconsistency in a net heat plot because of a lack of closed loops in the network geometry. We have moderate confidence in estimates of a beneficial effect at postintervention of SSRI over pharmacological placebo (SMD −0.92 [−1.36 to −0.47], $k = 3$, $n = 147$); we downgraded confidence from “high” to “moderate” because of a risk of selective outcome reporting. We have very low confidence in estimates of beneficial effects at postintervention of TCAs over pharmacological placebo (SMD −0.83 [−1.36 to −0.28], $k = 2$, $n = 96$), SARIs over pharmacological placebo (SMD −0.63 [−1.24 to −0.03], $k = 1$, $n = 56$), NMDA antagonists over pharmacological placebo (SMD −1.21 [−1.84 to −0.59], indirect evidence only), NMDA antagonists over glutamatergic antagonists (SMD −1.14 [−2.17 to −0.11], indirect evidence only), and an AAP in combination with an SSRI over pharmacological placebo (SMD −1.02 [−1.86 to −0.18], indirect evidence only). We also have very low confidence in an estimate of SSRIs compared with pharmacological placebo at long-term (six months postintervention) follow-up (SMD −0.70 [−1.42 to 0.03], $k = 1$, $n = 31$). We have very low confidence in all other estimates at postintervention (see Table 3.8); confidence intervals for all other comparisons did not exclude a null effect—including between each active intervention and pharmacological placebo (Figure 3.11).

Figure 3.11. Forest Plot of Effect Estimates (Active Pharmacological Interventions Versus Pharmacological Placebo) on Functional Status at Postintervention



Psychological interventions: One psychological intervention study (14 percent) reported data on two interventions (one direct comparison). We have very low confidence in estimates of a beneficial effect of SMS over psychological placebo at postintervention (SMD -0.97 [-1.54 to -0.41], $k = 1$, $n = 54$) and an estimate with confidence intervals that did not exclude a null effect at short-term follow-up (SMD -0.54 [-1.12 to 0.04], $k = 1$, $n = 54$).

Adverse Events

Pharmacological interventions: Seventeen pharmacological intervention studies (61 percent) reported adverse event data on 12 intervention classes (22 direct comparisons), with six studies (21 percent) reporting serious adverse event data on 7 intervention classes (11 direct comparisons; Table 3.9). We detected significant heterogeneity in the adverse event network globally ($Q(8) = 17.41$, $p = 0.03$), which was due to significant within-design heterogeneity in comparisons of pharmacological placebo versus SARIs ($Q(1) = 11.55$, $p < 0.001$) rather than inconsistency between designs ($Q(1) = 0.66$, $p = 0.42$). We did not detect significant heterogeneity in the serious adverse event network globally ($Q(2) = 0.62$, $p = 0.74$). We were not able to assess hotspots of inconsistency in a net heat plot for both adverse events and serious adverse events. We have moderate confidence that patients receiving SSRIs are more likely on average to experience an adverse event than patients receiving pharmacological placebo (OR 2.20 [0.94 to 5.16], $k = 6$, $n = 722$); we downgraded confidence from “high” to “moderate” because of a wide confidence interval, as the 95 percent CI does not exclude a null effect. We also have low confidence that patients receiving SSRIs are more likely to experience a serious adverse event than patients receiving pharmacological placebo (OR 1.56 [0.81 to 2.94], $k = 3$,

$n = 492$); we downgraded confidence from “high” to “low” because of a risk of attrition bias, as well as a wide confidence interval. We have very low confidence that patients receiving SSRIs are more likely to experience a serious adverse event than patients receiving an opioid antagonist in combination with an SSRI (OR 4.47 [1.51 to 13.26], $k = 1$, $n = 82$). We have very low confidence in all other estimates at postintervention; confidence intervals for all other comparisons did not exclude a null effect—including between each active intervention and pharmacological placebo (Figures 3.12 and 3.13). However, after excluding studies with high risk of bias from the network, we identified an estimate (excluding a null effect) that patients receiving SSRIs are more likely on average to experience an adverse event than patients receiving pharmacological placebo (OR 2.57 [1.30 to 5.08]), in which we would have had high (as opposed to moderate) confidence had this been the default analysis.

Table 3.9. Pharmacological Intervention Effect Estimates at Postintervention for Adverse Events

AAP + SSRI	0.30 [0.01; 11.50]	0.05 [0.001; 2.86]	0.07 [0.001; 2.89]	0.06 [0.001; 2.94]	0.13 [0.004; 4.22]	0.60 [0.02; 16.26]	0.12 [0.01; 2.27]	0.16** [0.01; 3.74]	0.27 [0.02; 4.38]	0.29 [0.01; 7.01]	0.43 [0.01; 23.97]
—	Glutamatergic antagonist	0.18 [0.01; 5.98]	0.23 [0.01; 5.81]	0.21 [0.01; 7.44]	0.43 [0.02; 9.68]	2.00 [0.11; 36.39]	0.42 [0.05; 3.81]	0.53 [0.04; 6.77]	0.92 [0.09; 9.82]	0.98 [0.07; 12.72]	1.44 [0.04; 50.36]
—	—	MRI	1.31 [0.04; 46.89]	1.18 [0.02; 58.07]	2.37 [0.07; 78.77]	11.16 [0.41; 303.87]	2.32 [0.15; 35.31]	2.95 [0.15; 59.27]	5.11 [0.30; 88.43]	5.44 [0.50; 59.38]	8.05 [0.16; 393.28]
—	—	—	nAChRs	0.90 [0.02; 34.10]	1.82 [0.07; 44.77]	8.53 [0.43; 169.34]	1.78 [0.17; 18.21]	2.26 [0.16; 31.86]	3.91 [0.33; 46.55]	4.16 [0.29; 59.86]	6.15 [0.16; 230.77]
—	—	—	—	NMDA antagonist	2.01 [0.07; 60.89]	9.46 [0.38; 233.56]	1.97 [0.12; 32.10]	2.50 [0.12; 53.54]	4.33 [0.30; 61.74]	4.62 [0.21; 100.33]	6.82 [0.13; 350.23]
—	—	—	—	3.43 [0.26; 45.48]	Opioid antagonist	4.70 [0.54; 41.12]	0.98 [0.11; 8.88]	1.24 [0.10; 15.77]	2.15 [0.25; 18.22]	2.29 [0.18; 29.66]	3.39 [0.10; 117.67]
—	—	—	—	9.18 [0.63; 132.90]	2.67 [0.86; 8.26]	Opioid antagonist + SSRI	0.21 ^b [0.03; 1.36]	0.26 ^b [0.03; 2.54]	0.46 [0.08; 2.75]	0.49 [0.05; 4.78]	0.72 [0.03; 20.61]
—	—	—	—	3.18 [0.25; 39.80]	0.93 [0.39; 2.20]	0.35 [0.12; 1.05]	Pharmacological placebo	1.27 [0.36; 4.49]	2.20 ^b [0.94; 5.16]	2.34 [0.64; 8.61]	3.46 [0.21; 55.75]
—	—	—	—	—	—	—	—	SARI	1.73 ^b [0.38; 7.93]	1.84 ^b [0.30; 11.30]	2.72 [0.13; 57.67]
—	—	—	—	2.05 [0.18; 23.59]	0.60 [0.26; 1.39]	0.22^a [0.08; 0.66]	0.64 [0.34; 1.23]	—	SSRI	1.07 [0.22; 5.05]	1.57 [0.09; 28.82]
—	—	—	—	3.18 [0.03; 351.16]	0.93 [0.02; 53.77]	0.35 [0.01; 21.31]	1.00 [0.02; 52.85]	—	1.55 [0.03; 86.37]	TCA	1.48 [0.07; 31.80]
—	—	—	—	3.18 [0.03; 376.08]	0.93 [0.01; 58.20]	0.35 [0.01; 23.04]	1.00 [0.02; 57.31]	—	1.55 [0.03; 93.57]	1.00 [0.004; 289.57]	TeCA

NOTES: The upper right triangle provides estimates for adverse events, and the bottom left triangle provides estimates for serious adverse events. OR < 1 favors the intervention in the column, and OR > 1 favors the intervention in the row.

^a The confidence interval does not include an estimate of no effect.

^b At least one sensitivity analysis had a substantively different estimate (see Appendix F).

Psychological interventions: No studies reported data on adverse events.

Figure 3.12. Forest Plot of Effect Estimates (Active Pharmacological Interventions Versus Pharmacological Placebo) on Adverse Events at Postintervention

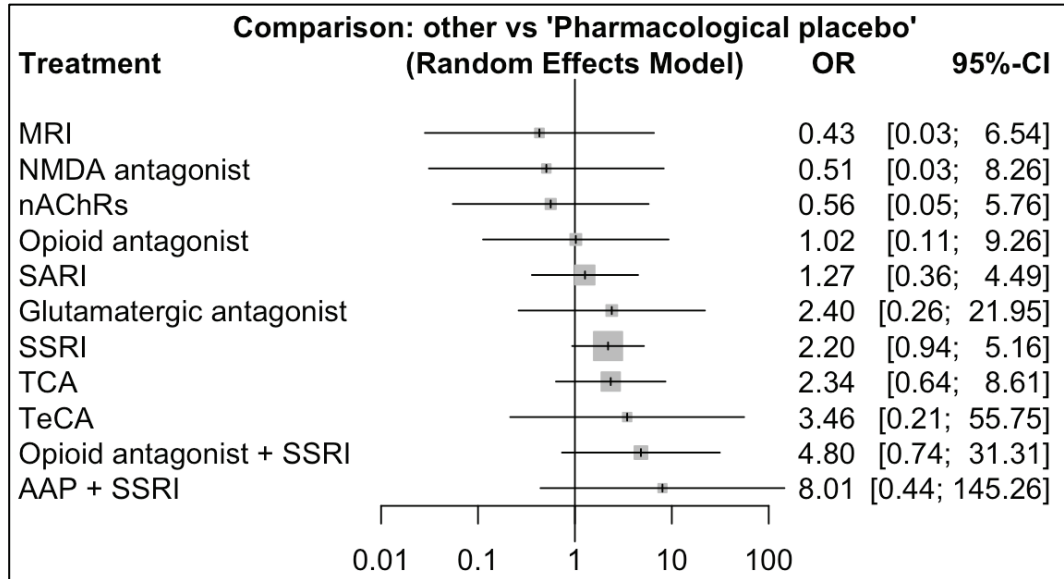
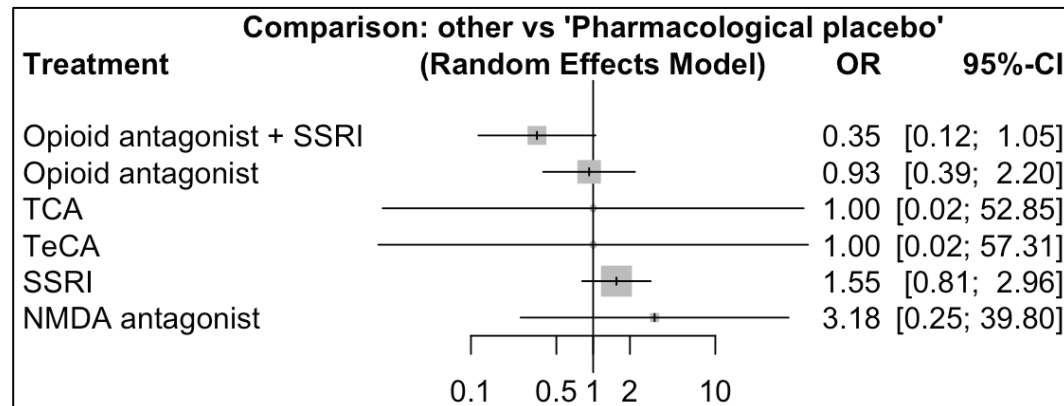


Figure 3.13. Forest Plot of Effect Estimates (Active Pharmacological Interventions Versus Pharmacological Placebo) on Serious Adverse Events at Postintervention



Key Question 1a: Effects by Type of Disorder

Alcohol Use Disorders

Of the 29 studies that provided data on the type of AUD, 16 (55 percent) included participants with alcohol dependence, 7 (24 percent) with multiple AUDs, and 6 (21 percent) with “alcoholism.”

Alcohol Dependence

Remission from depression. Patients benefited from TCA over pharmacological placebo (OR 0.05 [0.004 to 0.62]) at postintervention. Confidence intervals for all other comparisons did not exclude a null effect.

Remission from alcohol use. Patients benefited from an opioid antagonist in addition to an SSRI over pharmacological placebo (OR 0.35 [0.15 to 0.79]), SSRIs (OR 0.32 [0.14 to 0.73]), and TCAs (OR 0.08 [0.01 to 0.99]) at postintervention, as well as SSRIs over pharmacological placebo at long-term follow-up (OR 0.26 [0.07 to 0.97]). Confidence intervals for all other comparisons did not exclude a null effect.

Depressive symptoms. Patients benefited from CBT over no additional treatment at postintervention (SMD -0.84 [-1.37 to -0.31]), SSRIs over pharmacological placebo at long-term follow-up (SMD -0.80 [-1.53 to -0.07]), and CBT over no additional treatment at long-term follow-up (SMD -1.59 [-1.83 to -1.34]). Confidence intervals for all other comparisons did not exclude a null effect.

Total drinking. Patients benefited from CBT over no additional treatment (SMD -0.25 [-0.47 to -0.04]), as well as NMDA antagonists over pharmacological placebo (SMD -2.23 [-3.06 to -1.41]), SARIs (SMD -2.00 [-2.97 to -1.03]), and SSRIs (SMD -1.92 [-2.62 to -1.23]) at postintervention. Confidence intervals for all other comparisons did not exclude a null effect.

Heavy drinking. Patients benefited from SARIs over opioid antagonists (SMD -0.95 [-1.82 to -0.08]), SARIs over pharmacological placebo (SMD -1.04 [-1.80 to -0.27]), and an opioid antagonist in combination with an SSRI over pharmacological placebo (SMD -0.60 [-1.13 to -0.08]) at postintervention.

Withdrawal and craving symptoms. Confidence intervals for all comparisons at postintervention did not exclude a null effect.

Health-related quality of life. Confidence intervals for all comparisons at postintervention did not exclude a null effect.

Functional status. Patients benefited at postintervention from an AAP in combination with an SSRI over pharmacological placebo (SMD -1.02 [-1.86 to -0.18]), NMDA antagonists over pharmacological placebo (SMD -1.21 [-1.84 to -0.59]), SARIs over pharmacological placebo (SMD -0.63 [-1.24 to -0.03]), and SSRIs over pharmacological placebo (SMD -0.92 [-1.36 to -0.47]). Confidence intervals for all other comparisons did not exclude a null effect.

Adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Serious adverse events. Patients receiving SSRIs were more likely on average to experience a serious adverse event than patients receiving an opioid antagonist in combination with an SSRI (OR 4.32 [1.45 to 12.87]). Confidence intervals for all comparisons did not exclude a null effect.

Multiple

Remission from depression. Confidence intervals for all comparisons did not exclude a null effect.

Remission from alcohol use. Confidence intervals for all comparisons did not exclude a null effect.

Depressive symptoms. Patients benefited at postintervention from SMS over psychological placebo (SMD -0.88 [-1.44 to -0.32]). Confidence intervals for all other comparisons did not exclude a null effect.

Total drinking. Confidence intervals for all comparisons did not exclude a null effect.

Heavy drinking. Confidence intervals for all comparisons did not exclude a null effect.

Withdrawal and craving symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Health-related quality of life. Confidence intervals for all comparisons did not exclude a null effect.

Functional status. Patients benefited at postintervention from TCAs over pharmacological placebo (SMD -0.86 [-1.51 to -0.22]) and SMS over psychological placebo (SMD -0.97 [-1.54 to -0.41]). Confidence intervals for all other comparisons did not exclude a null effect.

Adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Serious adverse events. Confidence intervals for all comparisons did not exclude a null effect.

“Alcoholism”

Remission from depression. Confidence intervals for all comparisons did not exclude a null effect.

Depressive symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Functional status. Confidence intervals for all comparisons did not exclude a null effect.

Adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Serious adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Depressive Disorders

Of the 29 studies that provided data on the type of depressive disorder, 15 (52 percent) included participants with major depressive disorder, 1 (3 percent) with mild depressive disorder, one (3 percent) with dysthymic disorder, 4 (14 percent) with multiple depressive disorders, and 5 (17 percent) with “depression.”

Major Depressive Disorder

Remission from depression. Patients benefited at postintervention from TCAs over NMDA antagonists (OR 29.41 [1.05 to 824.22]), SSRIs (OR 24.06 [1.49 to 388.60]), and pharmacological placebo (OR 20.00 [1.46 to 273.89]). Confidence intervals for all other comparisons did not exclude a null effect.

Remission from alcohol use. Patients benefited at postintervention from an opioid antagonist in combination with an SSRI over an opioid antagonist alone (OR 3.98 [1.71 to 9.26]), an SSRI

alone (OR 0.29 [0.14 to 0.64]), and pharmacological placebo (OR 0.37 [0.17 to 0.80]); opioid antagonists over glutamatergic antagonists (OR 5.63 [1.04 to 30.39]); and pharmacological placebo over SSRI (OR 0.79 [0.71 to 0.88]). Patients benefited at long-term follow-up from SSRIs over pharmacological placebo (OR 0.26 [0.07 to 0.97]). Confidence intervals for all other comparisons did not exclude a null effect.

Depressive symptoms. Patients benefited from SMS over psychological placebo at postintervention (SMD -0.88 [-1.44 to -0.32]) and from SSRIs over pharmacological placebo at long-term follow-up (SMD -0.80 [-1.53 to -0.07]).

Total drinking. Patients benefited from NMDA antagonists over glutamatergic antagonists (SMD -2.59 [-3.72 to -1.47]), pharmacological placebo (SMD -2.59 [-3.37 to -1.82]), SARIs (SMD -2.37 [-3.24 to -1.50]), SSRIs (SMD -1.92 [-2.45 to -1.39]), and TCAs (SMD -2.05 [-3.37 to -0.73]) at postintervention. Confidence intervals for all other comparisons did not exclude a null effect.

Heavy drinking. Patients benefited from SARIs over pharmacological placebo at postintervention (SMD -1.04 [-2.01 to -0.07]). Confidence intervals for all other comparisons did not exclude a null effect.

Withdrawal and craving symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Health-related quality of life. Confidence intervals for all comparisons did not exclude a null effect.

Functional status. Patients benefited at postintervention from an AAP in combination with an SSRI over pharmacological placebo (SMD -0.91 [-1.82 to -0.003]), NMDA antagonists over pharmacological placebo (SMD -1.11 [-1.83 to -0.39]), SARIs over pharmacological placebo (SMD -0.63 [-1.24 to -0.03]), SSRIs over pharmacological placebo (SMD -0.81 [-1.38 to -0.24]), and SMS over psychological placebo (SMD -0.97 [-1.54 to -0.41]). Confidence intervals for all other comparisons did not exclude a null effect.

Adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Serious adverse events. Patients receiving SSRIs were more likely on average to experience a serious adverse event than patients receiving an opioid antagonist in combination with an SSRI (OR 4.32 [1.45 to 12.87]). Confidence intervals for all comparisons did not exclude a null effect.

Mild Depressive Disorder

Depressive symptoms. Patients benefited from CBT over no additional treatment at postintervention (SMD -0.86 [-1.08 to -0.63]), short-term follow-up (SMD -0.98 [-1.21 to -0.75]), and long-term follow-up (SMD -1.59 [-1.83 to -1.34]).

Total drinking. Patients benefited at postintervention from CBT over no additional treatment at postintervention (SMD -0.25 [-0.47 to -0.04]). Confidence intervals at short-term and long-term follow-up did not exclude a null effect.

Dysthymic Disorder

Remission from depression. Confidence intervals for all comparisons did not exclude a null effect.

Remission from alcohol use. Confidence intervals for all comparisons did not exclude a null effect.

Depressive symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Depressive Episode

Remission from depression. Confidence intervals for all comparisons did not exclude a null effect.

Remission from alcohol use. Patients benefited at postintervention from SSRIs over pharmacological placebo (OR 0.58 [0.37 to 0.90]).

Depressive symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Total drinking. Confidence intervals for all comparisons did not exclude a null effect.

Heavy drinking. Confidence intervals for all comparisons did not exclude a null effect.

Withdrawal and craving symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Functional status. Confidence intervals for all comparisons did not exclude a null effect.

Adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Multiple

Remission from depression. Confidence intervals for all comparisons did not exclude a null effect.

Remission from alcohol use. Confidence intervals for all comparisons did not exclude a null effect.

Depressive symptoms. Patients benefited from CBT over no additional treatment at postintervention (SMD -0.74 [-1.27 to -0.22]) and short-term follow-up (SMD -0.62 [-1.14 to -0.10]). Confidence intervals for all other comparisons did not exclude a null effect.

Total drinking. Confidence intervals for all comparisons did not exclude a null effect.

Heavy drinking. Confidence intervals for all comparisons did not exclude a null effect.

Functional status. Patients benefited at postintervention from TCAs over pharmacological placebo (SMD -0.86 [-1.51 to -0.22]).

Adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Serious adverse events. Confidence intervals for all comparisons did not exclude a null effect.

“Depression”

Remission from depression. Confidence intervals for all comparisons did not exclude a null effect.

Remission from alcohol use. Confidence intervals for all comparisons did not exclude a null effect.

Depressive symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Functional status. Confidence intervals for all comparisons did not exclude a null effect.

Adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Serious adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Key Question 1b: Effects by Type of Setting

Stage in Clinical Pathway

Of the 25 studies that provided data on the stage in the clinical pathway, 9 (36 percent) included participants in inpatient care, 13 (52 percent) in outpatient care, and 3 (12 percent) in both.

Inpatient

Remission from depression. Confidence intervals for all comparisons did not exclude a null effect.

Remission from alcohol use. Confidence intervals for all comparisons did not exclude a null effect.

Depressive symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Heavy drinking. Confidence intervals for all comparisons did not exclude a null effect.

Withdrawal and craving symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Functional status. Patients benefited at postintervention from SSRIs over pharmacological placebo (SMD -0.88 [-1.66 to -0.10]). Confidence intervals for all other comparisons did not exclude a null effect.

Adverse events. Patients receiving SSRIs were more likely on average to experience an adverse event than patients receiving pharmacological placebo (OR 3.67 [1.21 to 11.18]). Confidence intervals for all comparisons did not exclude a null effect.

Serious adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Outpatient

Remission from depression. Patients benefited at postintervention from an opioid antagonist in combination with an SSRI over pharmacological placebo (OR 0.24 [0.06 to 0.86]) and SSRIs (OR 0.20 [0.06 to 0.72]), SARIs over pharmacological placebo (OR 0.21 [0.05 to 0.85]) and SSRIs (OR 0.18 [0.04 to 0.83]), and TCAs over pharmacological placebo (OR 0.28 [0.09 to 0.86]) and SSRIs (OR 0.24 [0.07 to 0.85]). Confidence intervals for all other comparisons did not exclude a null effect.

Remission from alcohol use. Confidence intervals for all comparisons did not exclude a null effect.

Depressive symptoms. Patients benefited at postintervention from an opioid antagonist in combination with an SSRI over NMDA antagonists (SMD -0.82 [-1.55 to -0.09]), pharmacological placebo (SMD -0.52 [-1.03 to -0.01]), and SSRIs (SMD -0.65 [-1.15 to -0.15]); TCAs over SSRIs (SMD -0.58 [-1.11 to -0.04]); CBT over no additional treatment (SMD -0.84 [-1.37 to -0.31]); and SMS over psychological placebo (SMD -0.88 [-1.44 to -0.32]). Patients also benefited at long-term follow-up from CBT over no additional treatment (SMD -1.59 [-1.83 to -1.34]). Confidence intervals for all other comparisons did not exclude a null effect.

Total drinking. Patients benefited at postintervention from NMDAs over pharmacological placebo (SMD -2.02 [-2.65 to -1.39]), SARIs (SMD -1.80 [-2.54 to -1.05]), SSRIs (SMD -1.92 [-2.45 to -1.39]), TCAs (SMD -1.93 [-2.75 to -1.11]), and TeCAs (SMD -1.48 [-2.71 to -0.24]). Patients also benefited at postintervention from CBT over no additional treatment (SMD -0.25 [-0.47 to -0.04]). Confidence intervals for all other comparisons did not exclude a null effect.

Heavy drinking. Patients benefited at postintervention from NMDAs over SSRIs (SMD -0.46 [-0.90 to -0.01]); an opioid antagonist in combination with an SSRI over opioid antagonists (SMD -0.46 [-0.88 to -0.03]), pharmacological placebo (SMD -0.57 [-0.98 to -0.16]), SSRIs (SMD -0.57 [-0.98 to -0.16]), and TCAs (SMD -0.79 [-1.45 to -0.12]); SARIs over opioid antagonists (SMD -0.92 [-1.68 to -0.17]), SSRIs (SMD -1.04 [-1.74 to -0.33]), and TCAs (SMD -1.25 [-2.09 to -0.42]), and TeCAs (SMD -1.43 [-2.67 to -0.18]). Confidence intervals for all other comparisons did not exclude a null effect.

Withdrawal and craving symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Health-related quality of life. Confidence intervals for all comparisons did not exclude a null effect.

Functional status. Patients benefited at postintervention from SARIs over pharmacological placebo (SMD -0.63 [-1.24 to -0.03]), TCAs over pharmacological placebo (SMD -0.86 [-1.51 to -0.22]), and SMS over psychological placebo (SMD -0.97 [-1.54 to -0.41]). Confidence intervals for all other comparisons did not exclude a null effect.

Adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Serious adverse events. Patients receiving SSRIs were more likely on average to experience a serious adverse event than patients receiving an opioid antagonist in combination with an SSRI (OR 4.44 [1.43 to 13.77]). Confidence intervals for all other comparisons did not exclude a null effect.

Both

Remission from depression. Patients benefited at postintervention from SSRIs over pharmacological placebo (OR 0.14 [0.03 to 0.63]).

Remission from alcohol use. Patients benefited at long-term follow-up from SSRIs over pharmacological placebo (OR 0.26 [0.07 to 0.97]). Confidence intervals for all other comparisons did not exclude a null effect.

Depressive symptoms. Patients benefited at long-term follow-up from SSRIs over pharmacological placebo (SMD -0.80 [-1.53 to -0.07]). Confidence intervals for all other comparisons did not exclude a null effect.

Total drinking. Patients benefited at postintervention from SSRIs over pharmacological placebo (SMD -0.67 [-1.23 to -0.10]). Confidence intervals for all other comparisons did not exclude a null effect.

Heavy drinking. Patients benefited at postintervention from SSRIs over pharmacological placebo (SMD -0.80 [-1.37 to -0.23]).

Functional status. Confidence intervals for all comparisons did not exclude a null effect.

Adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Clinical Setting

Of the 25 studies that provided data on the clinical setting, 15 (60 percent) included participants in a substance use care setting, 1 (4 percent) in a mental health care setting, and 9 (36 percent) in both.

Substance Use

Remission from depression. Confidence intervals for all comparisons did not exclude a null effect.

Remission from alcohol use. Patients benefited at postintervention from NMDA antagonists over pharmacological placebo (OR 0.40 [0.16 to 0.99]), and from an opioid antagonist in combination with an SSRI over an opioid antagonist alone (OR 0.26 [0.10 to 0.65]), pharmacological placebo (OR 0.27 [0.12 to 0.62]), SSRIs (OR 0.38 [0.17 to 0.85]), and TCAs (OR 0.06 [0.005 to 0.76]). Confidence intervals for all other comparisons did not exclude a null effect.

Depressive symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Total drinking. Patients benefited at postintervention from NMDA antagonists over pharmacological placebo (SMD -2.02 [-2.65 to -1.39]) and SSRIs (SMD -1.92 [-2.45 to -1.39]). Confidence intervals for all other comparisons did not exclude a null effect.

Heavy drinking. Patients benefited at postintervention from NMDA antagonists over SSRIs (SMD -0.46 [-0.90 to -0.01]) and an opioid antagonist in combination with an SSRI over an opioid antagonist alone (SMD -0.46 [-0.88 to -0.03]), an SSRI alone (SMD -0.57 [-0.98 to -0.17]), and pharmacological placebo (SMD -0.57 [-0.97 to -0.16]). Confidence intervals for all other comparisons did not exclude a null effect.

Withdrawal and craving symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Health-related quality of life. Confidence intervals for all comparisons did not exclude a null effect.

Functional status. Patients benefited at postintervention from NMDA antagonists over pharmacological placebo (SMD -1.47 [-2.77 to -0.17]) and SSRIs over pharmacological placebo (SMD -1.17 [-2.12 to -0.23]). Confidence intervals for all other comparisons did not exclude a null effect.

Adverse events. Patients were more likely on average to experience an adverse event when receiving an opioid antagonist in combination with an SSRI compared with patients receiving pharmacological placebo (OR 4.75 [1.23 to 18.38]), as well as an SSRI compared with pharmacological placebo (OR 2.33 [1.12 to 4.83]). Confidence intervals for all other comparisons did not exclude a null effect.

Serious adverse events. Patients were more likely on average to experience a serious adverse event when receiving SSRIs compared with patients receiving an opioid antagonist in combination with an SSRI (OR 4.44 [1.43 to 13.77]). Confidence intervals for all other comparisons did not exclude a null effect.

Mental Health

Remission from depression. Confidence intervals for all comparisons did not exclude a null effect.

Remission from alcohol use. Confidence intervals for all comparisons did not exclude a null effect.

Depressive symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Total drinking. Confidence intervals for all comparisons did not exclude a null effect.

Heavy drinking. Confidence intervals for all comparisons did not exclude a null effect.

Functional status. Patients benefited at postintervention from TCAs over pharmacological placebo (SMD -0.86 [-1.51 to -0.22]).

Adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Both

Remission from depression. Patients benefited at postintervention from SARIs over pharmacological placebo (OR 0.21 [0.06 to 0.72]). Confidence intervals for all other comparisons did not exclude a null effect.

Remission from alcohol use. Patients benefited at long-term follow-up from SSRIs over pharmacological placebo (OR 0.26 [0.07 to 0.97]). Confidence intervals for all other comparisons did not exclude a null effect.

Depressive symptoms. Patients benefited at postintervention from CBT over no additional treatment (SMD -0.84 [-1.37 to -0.31]) and SMS over psychological placebo (SMD -0.88 [-1.44 to -0.32]). Patients also benefited at long-term follow-up from SSRIs over pharmacological placebo (SMD -0.80 [-1.53 to -0.0703]) and CBT over no additional treatment

(SMD -1.59 [-1.83 to -1.34]). Confidence intervals for all other comparisons did not exclude a null effect.

Total drinking. Patients benefited at postintervention from SSRIs over pharmacological placebo (SMD -0.67 [-1.23 to -0.10]) and CBT over no additional treatment (SMD -0.25 [-0.47 to -0.04]). Confidence intervals for all other comparisons did not exclude a null effect.

Heavy drinking. Patients benefited at postintervention from SARIs over pharmacological placebo (SMD -1.04 [-1.69 to -0.38]) and TeCAs (SMD -1.43 [-2.67 to -0.18]), and SSRIs over pharmacological placebo (SMD -0.80 [-1.37 to -0.23]). Confidence intervals for all other comparisons did not exclude a null effect.

Withdrawal and craving symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Functional status. Patients benefited at postintervention from an AAP in combination with an SSRI over pharmacological placebo (SMD -0.91 [-1.82 to -0.003]), SARIs over pharmacological placebo (SMD -0.63 [-1.24 to -0.03]), SSRIs over pharmacological placebo (SMD -0.81 [-1.38 to -0.24]), and SMS over psychological placebo (SMD -0.97 [-1.54 to -0.41]). Confidence intervals for all other comparisons did not exclude a null effect.

Adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Serious adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Key Question 1c: Effects by Type of Intervention

Pharmacological Interventions

Remission from depression. Patients benefited at postintervention from the TCA desipramine over the SSRI citalopram (OR 0.04 [0.002 to 0.73]), the SSRI sertraline (OR 0.07 [0.005 to 0.99]), and pharmacological placebo (OR 0.05 [0.004 to 0.67]). Confidence intervals for all other comparisons did not exclude a null effect.

Remission from alcohol use. Patients benefited at postintervention from the NMDA antagonist memantine over the glutamatergic antagonist acamprosate (OR 0.13 [0.02 to 0.90]), the TCA desipramine (OR 0.06 [0.004 to 0.89]), the opioid antagonist naltrexone (OR 0.18 [0.05 to 0.73]), the SSRI sertraline (OR 0.21 [0.06 to 0.74]), and pharmacological placebo (OR 0.27 [0.08 to 0.93]); the SSRI citalopram over the SSRI sertraline (OR 0.50 [0.27 to 0.92]); the SSRI escitalopram over the SSRI sertraline (OR 0.39 [0.15 to 0.99]); the TCA imipramine over the opioid antagonist naltrexone (OR 0.22 [0.06 to 0.83]) and the SSRI sertraline (OR 0.26 [0.08 to 0.84]); naltrexone in combination with sertraline over naltrexone alone (OR 0.25 [0.11 to 0.59]), sertraline alone (OR 0.29 [0.14 to 0.63]), and pharmacological placebo (OR 0.37 [0.17 to 0.81]); and pharmacological placebo over the SSRI sertraline (OR 0.79 [0.71 to 0.88]). Patients also benefited at long-term follow-up from the SSRI fluoxetine over pharmacological placebo (OR 0.26 [0.07 to 0.97]). Confidence intervals for all other comparisons did not exclude a null effect.

Depressive symptoms. Patients benefited at long-term follow-up from the SSRI fluoxetine over pharmacological placebo (SMD -0.80 [-1.53 to -0.07]). Confidence intervals for all other comparisons did not exclude a null effect.

Total drinking. Patients benefited at postintervention from the SSRI fluoxetine over pharmacological placebo (SMD -0.67 [-1.23 to -0.10]) and the NMDA antagonist memantine over the SSRI escitalopram (SMD -1.92 [-2.45 to -1.39]). Confidence intervals for all other comparisons did not exclude a null effect.

Heavy drinking. Patients benefited at postintervention from the SSRI fluoxetine over the SSRI citalopram (SMD -0.78 [-1.44 to -0.12]), the SSRI escitalopram (SMD -0.82 [-1.59 to -0.06]), the TCA imipramine (SMD -1.02 [-1.79 to -0.24]), the opioid antagonist naltrexone (SMD -0.77 [-1.43 to -0.11]), the SSRI sertraline (SMD -0.88 [-1.59 to -0.17]), and pharmacological placebo (SMD -0.80 [-1.37 to -0.23]); the NMDA antagonist memantine over the SSRI escitalopram (SMD -0.46 [-0.90 to -0.01]); naltrexone in combination with sertraline over the TCA imipramine (SMD -0.73 [-1.41 to -0.06]), naltrexone alone (SMD -0.49 [-0.89 to -0.08]), sertraline alone (SMD -0.59 [-1.04 to -0.15]), and pharmacological placebo (SMD -0.51 [-0.94 to -0.09]); and the SARI nefazodone over the SSRI citalopram (SMD -1.01 [-1.75 to -0.28]), the SSRI escitalopram (SMD -1.06 [-1.88 to -0.23]), the TCA imipramine (SMD -1.25 [-2.09 to -0.42]), the TeCA mirtazapine (SMD -1.43 [-2.67 to -0.18]), the opioid antagonist naltrexone (SMD -1.01 [-1.74 to -0.28]), the SSRI sertraline (SMD -1.12 [-1.89 to -0.34]), and pharmacological placebo (SMD -1.04 [-1.69 to -0.38]). Confidence intervals for all other comparisons did not exclude a null effect.

Withdrawal and craving symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Health-related quality of life. Confidence intervals for all comparisons did not exclude a null effect.

Functional status. Patients benefited at postintervention from the SSRI escitalopram over pharmacological placebo (SMD -0.88 [-1.66 to -0.10]), the SSRI fluoxetine over pharmacological placebo (SMD -0.81 [-1.38 to -0.24]), the TCA imipramine over pharmacological placebo (SMD -0.83 [-1.36 to -0.29]), the NMDA antagonist memantine over pharmacological placebo (SMD -1.18 [-2.07 to -0.28]), the SARI nefazodone over pharmacological placebo (SMD -0.63 [-1.24 to -0.03]), and the SSRI sertraline over the glutamatergic antagonist acamprosate (SMD -1.89 [-3.71 to -0.06]) and pharmacological placebo (SMD -1.96 [-3.59 to -0.33]). Confidence intervals for all other comparisons did not exclude a null effect.

Adverse events. Confidence intervals for all comparisons did not exclude a null effect.

Serious adverse events. Patients were more likely on average to experience a serious adverse event when receiving the SSRI sertraline compared with patients receiving naltrexone in combination with sertraline (OR 4.47 [1.51 to 13.26]). Confidence intervals for all other comparisons did not exclude a null effect.

Psychological Interventions

Remission from depression. Confidence intervals for all comparisons did not exclude a null effect.

Remission from alcohol use. Confidence intervals for all comparisons did not exclude a null effect.

Depressive symptoms. Patients benefited at postintervention from supportive text messaging over psychological placebo (SMD -0.88 [-1.44 to -0.32]), brief CBT over no additional treatment (SMD -0.74 [-1.27 to -0.22]), and a CBT self-help book over no additional treatment (SMD -0.86 [-1.08 to -0.63]). Patients also benefited from brief CBT over no additional treatment (SMD -0.62 [-1.14 to -0.10]) and a CBT self-help book over no additional treatment (SMD -0.98 [-1.21 to -0.75]) at short-term follow-up, as well as a CBT self-help book over no additional treatment at long-term follow-up (SMD -1.59 [-1.83 to -1.34]). Confidence intervals for all other comparisons did not exclude a null effect.

Total drinking. Patients benefited at postintervention from a CBT self-help book over no additional treatment (SMD -0.25 [-0.47 to -0.04]). Confidence intervals for all other comparisons did not exclude a null effect.

Withdrawal and craving symptoms. Confidence intervals for all comparisons did not exclude a null effect.

Functional status. Patients benefited at postintervention from supportive text messaging over psychological placebo (SMD -0.97 [-1.54 to -0.41]). Confidence intervals for this comparison at short-term follow-up did not exclude a null effect.

Key Question 2: Rankings of Overall Intervention Effectiveness

A summary of findings can be found in Tables 3.10 and 3.11.

Table 3.10. Summary of Findings for Pharmacological Interventions

Remission from depression at postintervention				
Intervention class	OR (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
Opioid antagonist + SSRI	0.22 (0.04 to 1.07)	Very low	1 (0.81)	Possibly superior
SARI	0.21 (0.03 to 1.30)	Very low	2 (0.80)	Possibly superior
TCA	0.39 (0.13 to 1.19)	Very low	3 (0.67)	Possibly superior
AAP + SSRI	0.55 (0.07 to 4.63)	Very low	4 (0.52)	Unsure of superiority/inferiority
AAP	0.58 (0.08 to 4.25)	Very low	5 (0.50)	Unsure of superiority/inferiority
Opioid antagonist	0.66 (0.22 to 2.01)	Very low	6 (0.46)	Unsure of superiority/inferiority
TeCA	0.77 (0.11 to 5.46)	Very low	7 (0.42)	Unsure of superiority/inferiority
SSRI	0.75 (0.42 to 1.36)	Very low	8 (0.41)	Unsure of superiority/inferiority
Glutamatergic antagonist	0.80 (0.09 to 6.92)	Very low	9 (0.41)	Unsure of superiority/inferiority
MRI	0.92 (0.07 to 11.58)	Very low	10 (0.38)	Possibly inferior
NMDA antagonist	0.92 (0.15 to 5.84)	Very low	11 (0.36)	Possibly inferior
Pharmacological placebo	—	—	12 (0.26)	Reference comparator
Remission from alcohol use at postintervention				
Intervention class	OR (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
Opioid antagonist + SSRI	0.34 (0.15 to 0.79)	Very low	1 (0.89)	Possibly superior
TCA	0.56 (0.19 to 1.68)	Very low	2 (0.69)	Possibly superior
NMDA antagonist	0.59 (0.24 to 1.47)	Very low	3 (0.68)	Possibly superior
AAP + SSRI	0.57 (0.08 to 3.92)	Very low	4 (0.63)	Possibly superior
SARI	0.76 (0.27 to 2.10)	Very low	5 (0.55)	Unsure of superiority/inferiority
Pharmacological placebo	—	—	6 (0.40)	Reference comparator
SSRI	1.06 (0.84 to 1.34)	Very low	7 (0.33)	Unsure of superiority/inferiority ^a
Opioid antagonist	1.41 (0.71 to 2.77)	Very low	8 (0.19)	Possibly inferior
Glutamatergic antagonist	2.10 (0.45 to 9.84)	Very low	9 (0.15)	Possibly inferior
Remission from alcohol use at long-term follow-up				
Intervention class	OR (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SSRI	0.26 (0.07 to 0.97)	Very low	1 (N/A)	Possibly superior
Pharmacological placebo	—	—	2 (N/A)	Reference comparator

<i>Depressive symptoms at postintervention</i>				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
Opioid antagonist + SSRI	−0.66 (−1.27 to −0.06)	Very low	1 (0.85)	Possibly superior
Opioid antagonist	−0.49 (−1.10 to 0.12)	Very low	2 (0.73)	Possibly superior
TCA	−0.37 (−0.72 to −0.02)	Low	3 (0.66)	Probably superior
SARI	−0.31 (−0.80 to 0.19)	Very low	4 (0.59)	Unsure of superiority/inferiority ^a
Glutamatergic antagonist	−0.33 (−1.25 to 0.59)	Very low	5 (0.58)	Unsure of superiority/inferiority ^a
AAP + SSRI	−0.21 (−1.06 to 0.63)	Very low	6 (0.49)	Unsure of superiority/inferiority
SSRI	−0.14 (−0.35 to 0.07)	Very low	7 (0.42)	Unsure of superiority/inferiority
TeCA	−0.12 (−0.78 to 0.53)	Very low	8 (0.42)	Unsure of superiority/inferiority
NMDA antagonist	0.03 (−0.67 to 0.74)	Very low	9 (0.29)	Possibly inferior
Pharmacological placebo	—	—	10 (0.24)	Reference comparator
nAChRs	0.20 (−0.75 to 1.15)	Very low	11 (0.22)	Possibly inferior
<i>Depressive symptoms at long-term follow-up</i>				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SSRI	−0.80 (−1.53 to −0.07)	Very low	1 (N/A)	Possibly superior
Pharmacological placebo	—	—	2 (N/A)	Reference comparator
<i>Withdrawal/craving symptoms at postintervention</i>				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
AAP + SSRI	−0.57 (−1.34 to 0.20)	Very low	1 (0.84)	Possibly superior
SARI	−0.37 (−0.90 to 0.16)	Very low	2 (0.73)	Possibly superior
NMDA antagonist	−0.35 (−0.88 to 0.17)	Very low	3 (0.73)	Possibly superior
SSRI	−0.08 (−0.36 to 0.20)	Very low	4 (0.46)	Unsure of superiority/inferiority
Glutamatergic antagonist	0.02 (−0.84 to 0.80)	Very low	5 (0.44)	Unsure of superiority/inferiority
Pharmacological placebo	—	—	6 (0.37)	Reference comparator
TeCA	0.41 (−0.65 to 1.47)	Very low	7 (0.22)	Possibly inferior
TCA	0.48 (−0.78 to 1.72)	Very low	8 (0.20)	Possibly inferior
<i>Total drinking at postintervention</i>				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
NMDA antagonist	−2.23 (−2.87 to −1.58)	Very low	1 (0.999)	Possibly superior
TeCA	−0.54 (−1.64 to 0.55)	Very low	2 (0.62)	Possibly superior
SSRI	−0.30 (−0.59 to −0.02)	Low	3 (0.57)	Probably superior
SARI	−0.23 (−0.66 to 0.21)	Very low	4 (0.48)	Unsure of superiority/inferiority

TCA	-0.09 (-0.66 to 0.49)	Very low	5 (0.34)	Possibly inferior
Glutamatergic antagonist	-0.00 (-0.85 to 0.85)	Very low	6 (0.29)	Possibly inferior
Pharmacological placebo	—	—	7 (0.20)	Reference comparator
Total drinking at long-term follow-up				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SSRI	-0.43 (-1.14 to 0.29)	Very low	1 (N/A)	Unsure of superiority/inferiority
Pharmacological placebo	—	—	2 (N/A)	Reference comparator
Heavy drinking at postintervention				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SARI	-1.04 (-1.80 to -0.27)	Very low	1 (0.94)	Possibly superior
Opioid antagonist + SSRI	-0.60 (-1.13 to -0.08)	Very low	2 (0.79)	Possibly superior
NMDA antagonist	-0.58 (-1.25 to 0.09)	Very low	3 (0.76)	Possibly superior
SSRI	-0.13 (-0.43 to 0.17)	Very low	4 (0.44)	Unsure of superiority/inferiority
Opioid antagonist	-0.09 (-0.50 to 0.33)	Very low	5 (0.40)	Unsure of superiority/inferiority
Pharmacological placebo	—	—	6 (0.30)	Reference comparator
TCA	0.22 (-0.45 to 0.88)	Very low	7 (0.19)	Possibly inferior
TeCA	0.39 (-0.74 to 1.52)	Very low	8 (0.17)	Possibly inferior
Health-related quality of life at postintervention				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SSRI vs NMDA antagonist	-0.09 (-0.53 to 0.35)	Very low	N/A	Unsure of superiority/inferiority
Glutamatergic antagonist vs placebo	-0.33 (-1.15 to 0.50)	Very low	N/A	Glutamatergic antagonist possibly superior to pharmacological placebo
Functional status at postintervention				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
NMDA antagonist	-1.21 (-1.84 to -0.59)	Very low	1 (0.88)	Possibly superior
AAP + SSRI	-1.02 (-1.86 to -0.18)	Very low	2 (0.71)	Possibly superior
SSRI	-0.92 (-1.36 to -0.47)	Moderate	3 (0.64)	Very likely superior
TCA	-0.83 (-1.36 to -0.29)	Very low	4 (0.59)	Possibly superior
SARI	-0.63 (-1.24 to -0.03)	Very low	5 (0.45)	Unsure of superiority/inferiority
Glutamatergic antagonist	-0.07 (-0.89 to 0.75)	Very low	6 (0.15)	Possibly inferior
Pharmacological placebo	—	—	7 (0.08)	Reference comparator

Functional status at long-term follow-up				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SSRI	-0.70 (-1.42 to 0.03)	Very low	1 (N/A)	Possibly superior
Pharmacological placebo	—	—	2 (N/A)	Reference comparator
Adverse events at postintervention				
Intervention class	OR (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
MRI	0.43 (0.03 to 6.54)	Very low	1 (0.78)	Possibly superior
NMDA antagonist	0.51 (0.03 to 8.26)	Very low	2 (0.75)	Possibly superior
nAChRs	0.56 (0.05 to 5.76)	Very low	3 (0.74)	Possibly superior
Pharmacological placebo	—	—	4 (0.67)	Reference comparator
Opioid antagonist	1.02 (0.11 to 9.26)	Very low	5 (0.62)	Unsure of superiority/inferiority
SARI	1.27 (0.36 to 4.49)	Very low	6 (0.57)	Unsure of superiority/inferiority ^a
Glutamatergic antagonist	2.40 (0.26 to 21.96)	Very low	7 (0.40)	Possibly inferior
SSRI	2.20 (0.94 to 5.16)	Moderate	8 (0.38)	Very likely inferior
TCA	2.34 (0.64 to 8.61)	Very low	9 (0.37)	Possibly inferior
TeCA	3.46 (0.21 to 55.75)	Very low	10 (0.33)	Possibly inferior
Opioid antagonist + SSRI	4.80 (0.74 to 31.31)	Very low	11 (0.21)	Possibly inferior
AAP + SSRI	8.01 (0.44 to 145.26)	Very low	12 (0.18)	Possibly inferior
Adverse events at long-term follow-up				
Intervention class	OR (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
Pharmacological placebo	—	—	1 (N/A)	Reference comparator
SSRI	1.06 (0.02 to 57.01)	Very low	2 (N/A)	Unsure of superiority/inferiority
Serious adverse events at postintervention				
Intervention class	OR (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
Opioid antagonist + SSRI	0.35 (0.12 to 1.05)	Very low	1 (0.88)	Possibly superior
Opioid antagonist	0.93 (0.39 to 2.20)	Very low	2 (0.56)	Unsure of superiority/inferiority
Pharmacological placebo	—	—	3 (0.53)	Reference comparator
TCA	1.00 [0.02 to 52.85]	Very low	4 (0.51)	Unsure of superiority/inferiority
TeCA	1.00 [0.02 to 57.31]	Very low	5 (0.51)	Unsure of superiority/inferiority
SSRI	1.55 (0.81 to 2.96)	Low	6 (0.29)	Probably inferior
NMDA antagonist	3.18 (0.25 to 39.80)	Very low	7 (0.22)	Possibly inferior

^a Sensitivity analysis excluding studies at high risk of bias yielded a substantively different result.

Table 3.11. Summary of Findings for Psychological Interventions

<i>Remission from depression at postintervention</i>				
Intervention class	OR (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
IPT vs. SP	4.33 (0.39 to 48.61)	Very low	N/A	Unsure of superiority/inferiority
CBT vs. placebo	0.47 (0.08 to 2.66)	Very low	N/A	Unsure of superiority/inferiority
<i>Remission from alcohol use at postintervention</i>				
Intervention class	OR (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SMS vs. placebo	0.40 (0.12 to 1.30)	Very low	N/A	SMS possibly superior to placebo
IPT vs. SP	1.16 (0.29 to 4.69)	Very low	N/A	Unsure of superiority/inferiority
<i>Remission from alcohol use at short-term follow-up</i>				
Intervention class	OR (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SMS vs. placebo	1.64 (0.55 to 4.91)	Very low	N/A	Unsure of superiority/inferiority
<i>Remission from alcohol use at long-term follow-up</i>				
Intervention class	OR (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SMS vs. placebo	2.14 (0.46 to 9.98)	Very low	N/A	Unsure of superiority/inferiority
<i>Remission from alcohol use at very long-term follow-up</i>				
Intervention class	OR (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SMS vs. placebo	3.55 (0.76 to 16.43)	Very low	N/A	Unsure of superiority/inferiority
<i>Depressive symptoms at postintervention</i>				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SMS	-1.53 (-2.53 to -0.53)	Very low	1 (0.97)	Possibly superior
CBT	-0.84 (-1.05 to -0.63)	Moderate	2 (0.59)	Very likely superior
Placebo	-0.65 (-1.48 to 0.18)	Very low	3 (0.42)	Unsure of superiority/inferiority
No additional treatment	—	—	4 (0.02)	Reference comparator
IPT vs. SP	-0.35 (-1.13 to 0.42)	Very low	N/A	Unsure of superiority/inferiority
<i>Depressive symptoms at short-term follow-up</i>				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SMS vs. placebo	-0.17 (-0.74 to 0.39)	Very low	N/A	Unsure of superiority/inferiority
CBT vs. no additional treatment	-0.88 (-2.93 to 1.18)	Very low	N/A	Unsure of superiority/inferiority ^a

<i>Depressive symptoms at long-term follow-up</i>				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
CBT vs. no additional treatment	-0.17 (-0.74 to 0.39)	Very low	N/A	Unsure of superiority/inferiority
<i>Total drinking at postintervention</i>				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SMS vs. placebo	-0.47 (-1.01 to 0.07)	Very low	N/A	SMS possibly superior to placebo
CBT vs. no additional treatment	-0.25 (-0.47 to -0.04)	Very low	N/A	CBT possibly superior to no additional treatment
<i>Total drinking at short-term follow-up</i>				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SMS vs. placebo	-0.14 (-0.70 to 0.43)	Very low	N/A	Unsure of superiority/inferiority
CBT vs. no additional treatment	-0.10 (-0.31 to 0.12)	Very low	N/A	Unsure of superiority/inferiority
<i>Total drinking at long-term follow-up</i>				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
CBT vs. no additional treatment	-0.14 (-0.70 to 0.43)	Very low	N/A	Unsure of superiority/inferiority
<i>Withdrawal and craving symptoms at postintervention</i>				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SMS vs. placebo	0.29 (-0.25 to 0.83)	Very low	N/A	Unsure of superiority/inferiority
<i>Withdrawal and craving symptoms at short-term follow-up</i>				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SMS vs. placebo	-0.46 (-1.03 to 0.12)	Very low	N/A	Unsure of superiority/inferiority
<i>Functional status at postintervention</i>				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SMS vs. placebo	-0.97 (-1.54 to -0.41)	Very low	N/A	SMS possibly superior to placebo
<i>Functional status at short-term follow-up</i>				
Intervention class	SMD (95% CI)	Confidence in nonnull effect	Ranking (p score)	Interpretation of findings
SMS vs. placebo	-0.54 (-1.12 to 0.04)	Very low	N/A	SMS possibly superior to placebo

^a Sensitivity analysis excluding studies at high risk of bias yielded a substantively different result.

Pharmacological Interventions at Postintervention

Remission from depression. An opioid antagonist in combination with an SSRI, SARIs, and TCAs are possibly superior intervention classes, while glutamatergic antagonists, MRIs, and NMDA antagonists are possibly inferior intervention classes. We are unsure of the superiority/inferiority of an AAP in combination with an SSRI, AAPs, opioid antagonists, TeCAs, and SSRIs.

Remission from alcohol use. An opioid antagonist in combination with an SSRI, TCAs, NMDA antagonists, and an AAP in combination with an SSRI are possibly superior intervention classes, while opioid antagonists and glutamatergic antagonists are possibly inferior intervention classes. We are unsure of the superiority/inferiority of SARIs and SSRIs.

Depressive symptoms. TCAs are probably a superior intervention classes, and an opioid antagonist in combination with an SSRI and opioid antagonists are possibly superior intervention classes. NMDA antagonists and nAChRs are possibly inferior intervention classes. We are unsure of the superiority/inferiority of SARIs, glutamatergic antagonists, an AAP in combination with an SSRI, SSRIs, and TeCAs.

Withdrawal and craving symptoms. An AAP in combination with an SSRI, SARIs, and NMDA antagonists are possibly superior intervention classes, while TeCAs and TCAs are possibly inferior intervention classes; we are unsure of the superiority/inferiority of SSRIs and glutamatergic antagonists.

Total drinking. SSRIs are probably superior intervention classes, and NMDA antagonists and TeCAs are possibly superior intervention classes. TCA and glutamatergic antagonists are possibly inferior intervention classes. We are unsure of the superiority/inferiority of SARIs.

Heavy drinking. SARIs, an opioid antagonist in combination with an SSRI, and NMDA antagonists are possibly superior intervention classes, while TCAs and TeCAs are possibly inferior intervention classes; we are unsure of the superiority/inferiority of SSRIs and opioid antagonists.

Health-related quality of life. Glutamatergic antagonists are possibly superior to pharmacological placebo; we are unsure of the superiority/inferiority of SSRIs versus NMDA antagonists.

Functional status. SSRIs are very likely a superior intervention class, while NMDA antagonists, an AAP in combination with an SSRI, and TCAs are possibly superior intervention classes. Glutamatergic antagonists are possibly an inferior intervention class.

Adverse events. MRIs, NMDA antagonists, and nAChRs are possibly superior intervention classes. Glutamatergic antagonists, TCAs, TeCAs, an opioid antagonist in combination with an SSRI, and an AAP in combination with an SSRI are possibly inferior intervention classes. SSRIs are very likely an inferior intervention class. We are unsure of the superiority/inferiority of opioid antagonists and SARIs.

Serious adverse events. An opioid antagonist in combination with an SSRI is possibly a superior intervention class. NMDA antagonists are possibly an inferior intervention class. SSRIs

are probably an inferior intervention class. We are unsure of the superiority/inferiority of opioid antagonists, TCAs, and TeCAs.

Pharmacological Interventions at Follow-Up

Remission from alcohol use. SSRIs are possibly a superior intervention class to pharmacological placebo at long-term follow-up.

Depressive symptoms. SSRIs are possibly a superior intervention class to pharmacological placebo at long-term follow-up.

Total drinking. We are unsure of the superiority/inferiority of SSRIs versus pharmacological placebo.

Functional status. SSRIs are possibly a superior intervention class to pharmacological placebo at long-term follow-up.

Adverse events. We are unsure of the superiority/inferiority of SSRIs versus pharmacological placebo.

Psychological Interventions

Remission from depression. We are unsure of the superiority/inferiority of IPT versus SP and CBT versus psychological placebo at postintervention.

Remission from alcohol use. SMS is possibly superior to psychological placebo at postintervention, though we are unsure of the superiority/inferiority of SMS versus psychological placebo at short-, long-, and very long-term follow-up. We are also unsure of the superiority/inferiority of IPT versus SP at postintervention.

Depressive symptoms. At postintervention, CBT is very likely superior to no additional treatment, while SMS is possibly superior to psychological placebo at postintervention; we are unsure of the superiority/inferiority of psychological placebo versus no additional treatment, as well as IPT versus SP. We are also unsure of the superiority/inferiority of SMS versus psychological placebo, as well as CBT versus no additional treatment at short-term follow-up, and of CBT versus no additional treatment at long-term follow-up.

Total drinking. At postintervention, SMS is possibly superior to psychological placebo, and CBT is possibly superior to no additional treatment. We are unsure of their superiority/inferiority at short-term follow-up, and of CBT versus no additional treatment at long-term follow-up.

Withdrawal and craving symptoms. We are unsure of the superiority/inferiority of SMS versus psychological placebo at postintervention and short-term follow-up.

Functional status. SMS is possibly superior to psychological placebo at postintervention and short-term follow-up.

4. Discussion

Summary of Findings

AUDs and depressive disorders are prevalent behavioral health conditions among military and civilian adult populations with significant personal, societal, and economic consequences (World Health Organization, 2001; Mykletun et al., 2009; National Institute for Health and Clinical Excellence, 2009; DeVido and Weiss, 2012; Grant et al., 2015; Center for Behavioral Health Statistics and Quality, 2016; Deployment Health Clinical Center, 2017). While numerous psychological and pharmacological interventions are recommended for patients with an AUD or depressive disorder, current CPGs often focus on one or the other type of disorder despite the prevalence and significance of their co-occurrence (Management of Substance Use Disorders Working Group, 2015; Management of Major Depressive Disorder Working Group, 2016). Therefore, the aim of this systematic review and NMA was to synthesize findings from RCTs on and identify the comparative effectiveness of the clinical interventions included in these RCTs for patients with co-occurring AUDs and depressive disorders. A total of 35 studies that randomized a total of 2,512 participants met inclusion criteria and provided data on the comparative effectiveness of two networks of interventions (adjunctive to treatment as usual) on which to draw conclusions: pharmacological interventions and psychological interventions.

Using a systematic review and NMA, we estimated the pairwise comparative effectiveness of 14 classes of pharmacological interventions and 4 classes of psychological interventions used as clinical interventions to treat patients with both an alcohol use and a depressive disorder. Less than half of the classes of intervention were significantly more effective than control interventions on at least one outcome of interest at postintervention: an AAP in combination with an SSRI (functional status), CBT (depressive symptoms and total drinking), NMDA antagonists (total drinking and functional status), an opioid antagonist in combination with an SSRI (remission from alcohol use, depressive symptoms, and heavy drinking), SARIs (heavy drinking and functional status), SMS (depressive symptoms and functional), SSRIs (total drinking and functional status), and TCAs (depressive symptoms and functional status). Only SSRIs were significantly more effective (on remission from alcohol use and depressive symptoms) than control interventions at longer-term follow-up. Moreover, included studies evaluated only 13 out of 38 pharmacological interventions (34 percent) and 2 out of 11 psychological interventions (18 percent) recommended in the VA/DoD CPGs for alcohol use and major depressive disorders; and no included studies evaluated group mutual help programs such as 12-Step Facilitation, Alcoholics Anonymous, or Narcotics Anonymous.

We are sufficiently confident only in estimates at postintervention about the benefits of CBT (on depressive symptoms), SSRIs (on total drinking and functional status), and TCAs (on depressive symptoms) to warrant their consideration for policy and practice recommendations

based on the balance of desirable and undesirable effects. Based on subgroup analyses, this confidence is most applicable to CBT for depressive symptoms of patients with alcohol dependence and mild depression receiving inpatient care in a dual-diagnosis setting, TCAs for the depressive symptoms of outpatients, the SSRI fluoxetine for total drinking of patients in either inpatient or outpatient dual-diagnosis settings, and the SSRIs fluoxetine or escitalopram for the functional status of patients with alcohol dependence and major depression receiving inpatient care in dual-diagnosis or SUD-specific settings. We do not have sufficient confidence in any beneficial estimates of intervention classes on either of our two primary outcomes (remission from depression and remission from alcohol use), or at any time point later than postintervention. Furthermore, we found SSRIs to have significantly higher risks of adverse events (including serious adverse events), most applicably to the SSRI sertraline for patients with alcohol dependence and major depression receiving either inpatient or outpatient care in an SUD-specific clinical setting.

Our very low confidence in most effect estimates is primarily driven by sparse networks with limited data. Most bodies of evidence included only indirect evidence or direct evidence from only one or two studies. This absence of evidence on interventions with very low confidence does *not* indicate evidence of absence of effects but rather that future studies are needed. Specifically, more pragmatic, adequately powered, preregistered, and well-reported RCTs are needed to provide more-conclusive evidence about the (comparative) effectiveness of clinical interventions for treating adults with depressive disorders and AUDs. We provide more detailed summaries of findings in the sections that follow.

Pharmacological Intervention Classes

We identified information on the comparative effectiveness of pharmacological intervention classes for all outcomes of interest, though our confidence in the body of evidence was very low for the vast majority of effect estimates—in particular because most networks were sparse and had limited data, with most bodies of evidence including only indirect evidence or direct evidence from only one or two studies. For remission from depression, all effect estimates did not exclude the null effect. For remission from alcohol use, an opioid antagonist in combination with an SSRI may be beneficial over pharmacological placebo at postintervention, and SSRIs may be beneficial over pharmacological placebo at long-term follow-up, though we have very low confidence in these estimates. For depressive symptoms, we have low confidence that TCAs are beneficial over pharmacological placebo at postintervention, very low confidence that an opioid antagonist in combination with an SSRI are beneficial over pharmacological placebo at postintervention, and very low confidence that SSRIs are beneficial over pharmacological placebo at postintervention and long-term follow-up. For remission from withdrawal and craving symptoms, all effect estimates did not exclude the null effect. For total drinking, we have moderate confidence that SSRIs are beneficial over pharmacological placebo at postintervention, and very low confidence that NMDA antagonists are beneficial over pharmacological placebo at

postintervention. For heavy drinking, we have low confidence that SARIs, as well as an opioid antagonist in combination with an SSRI, are beneficial over pharmacological placebo at postintervention. For functional status, we have moderate confidence that SSRIs are beneficial over pharmacological placebo at postintervention, and we have very low confidence that NMDA antagonists, an AAP in combination with an SSRI, TCAs, and SARIs are beneficial over pharmacological placebo at postintervention. However, we have moderate confidence that patients receiving SSRIs are more likely to experience adverse events and low confidence and that they are more likely to experience serious adverse events than patients receiving pharmacological placebo at postintervention.

Psychological Intervention Classes

We identified information on the comparative effectiveness of psychological intervention classes for most outcomes of interest, though our confidence in the body of evidence was very low for the vast majority of effect estimates—again in particular because most bodies of evidence included only indirect evidence or direct evidence from only a single trial. All effect estimates did not exclude the null effect for remission from depression, remission from alcohol use, and withdrawal and craving symptoms. For depressive symptoms, we have moderate confidence that CBT is beneficial over no additional treatment at postintervention, though very low confidence that SMS is beneficial over psychological placebo at postintervention. For total drinking, we have very low confidence that CBT is beneficial over no additional treatment at postintervention. For functional status, we have very low confidence that SMS is beneficial over psychological placebo at postintervention.

Applicability to Types of Disorders, Settings, and Interventions

Subgroup analyses indicated several types of disorders, settings, and interventions to which findings may be more applicable. The potential benefit of an opioid antagonist in combination with an SSRI over pharmacological placebo on remission for alcohol use at postintervention may be most applicable to patients with alcohol dependence and major depressive disorder, as well as patients in SUD-specific clinical settings. The potential benefit of SSRIs over pharmacological placebo on remission for alcohol use at postintervention may be most applicable to the SSRI fluoxetine for patients with alcohol dependence and major depressive disorder, as well as patients starting SSRIs in an inpatient dual-diagnosis setting and continuing them through their transition to outpatient care. The potential benefit of an opioid antagonist in combination with an SSRI over pharmacological placebo on depressive symptoms at postintervention may be most applicable to outpatients. The potential benefit of CBT over no additional treatment on depressive symptoms at postintervention may be most applicable to brief CBT and CBT self-help books for outpatient dual-diagnosis clinical settings serving patient populations with alcohol dependence, as well as mild or multiple types of depressive disorder. The potential benefit of SMS over psychological placebo on depressive symptoms at postintervention may be most

applicable to supportive text messaging for outpatient dual-diagnosis clinical settings serving patient populations with major depressive disorder, as well as multiple types of AUDs. The potential benefit of SSRIs over pharmacological placebo on total drinking at postintervention may be most applicable to patients starting the SSRI fluoxetine in an inpatient dual-diagnosis setting and continuing them through their transition to outpatient care. The potential benefit of NMDA antagonists over pharmacological placebo on total drinking at postintervention may be most applicable to the NMDA antagonist memantine for patients with alcohol dependence and major depressive disorder receiving outpatient care in an SUD-specific clinical setting. The potential benefit of CBT over no additional treatment on total drinking at postintervention may be most applicable to a CBT self-help book for patients with alcohol dependence and mild depressive disorder receiving outpatient care in a dual-diagnosis clinical setting. The potential benefit of SARIs over pharmacological placebo on heavy drinking at postintervention may be most applicable to the SARI nefazodone for patients with alcohol dependence and major depressive disorder in a dual-diagnosis clinical setting. The potential benefit of an opioid antagonist in combination with an SSRI over pharmacological placebo on heavy drinking at postintervention may be most applicable to naltrexone in combination with sertraline for patients with alcohol dependence receiving outpatient care in an SUD-specific clinical setting. The potential benefit of SSRIs over pharmacological placebo on functional status at postintervention may be most applicable to the SSRIs escitalopram, fluoxetine, and sertraline for patients with alcohol dependence and major depressive disorder receiving inpatient care in SUD-specific and dual-diagnosis clinical settings. The potential benefit of NMDA antagonists over pharmacological placebo on functional status at postintervention may be most applicable to the NMDA antagonist memantine for patients with alcohol dependence and major depressive disorder in SUD-specific clinical settings. The potential benefit of an AAP in combination with an SSRI over pharmacological placebo on functional status at postintervention may be most applicable to patients with alcohol dependence and major depressive disorder in dual-diagnosis clinical settings. The potential benefit of TCAs over pharmacological placebo on functional status at postintervention may be most applicable to the TCA imipramine for patients with multiple types of AUDs and depressive disorders receiving outpatient care in mental health clinical settings. The potential benefit of SARIs over pharmacological placebo on functional status at postintervention may be most applicable to the SARI nefazodone for patients with alcohol dependence and major depressive disorder receiving outpatient care in dual-diagnosis clinical settings. The potential benefit of SMS over psychological placebo on functional status at postintervention may be most applicable to supportive text messaging for patients with major depressive disorder and multiple types of AUDs receiving outpatient care in dual-diagnosis clinical settings. The potential risk that patients receiving SSRIs may experience adverse events (compared with pharmacological placebo) may be most applicable to patients receiving inpatient care in an SUD-specific clinical setting.

Other Reviews in This Area

The results of this review are comparable to the conclusions of previous reviews in this area. Previous reviews have found antidepressants to be more effective than placebo in treating depression among patients with comorbid AUDs (Nunes and Levin, 2004; Iovieno et al., 2011), as well as finding clinical intervention in general (any form of medication or psychosocial treatment) for depression co-occurring with an AUD to be associated with an early improvement in depressive symptoms (Foulds et al., 2015). The most recent Cochrane review of antidepressants in the treatment of people with co-occurring depression and alcohol dependence found that antidepressants had positive effects on certain relevant outcomes related to depression and alcohol use (e.g., remission from alcohol use and total drinking) but not on other relevant outcomes (e.g., remission from depression, depressive symptoms), and the risk of developing adverse effects appeared to be minimal (Agabio, Trogu, and Pani, 2018). Moreover, a review on combined cognitive-behavioral therapy and motivational interviewing for patients with depressive disorders and AUDs found small but clinically significant effects compared with treatment as usual on depressive symptoms and alcohol consumption (Riper et al., 2014). Our review builds on these previous studies through the use of NMA to provide estimates of the comparative effectiveness of different classes of intervention across a range of outcomes.

Strengths and Limitations

This review has several strengths: an a priori research design, duplicate study selection and data extraction of study information, a comprehensive search of electronic databases, and comprehensive assessments of confidence in the body of evidence used to formulate review conclusions. However, some limitations are worth noting. Specifically, we did not contact trial authors for missing data or to find other potential studies not identified by the search strategy; additional outcome data (if existent), information about potential risks of bias, and other potential studies identified by trial authors have the potential to influence the effect estimates and confidence in the body of evidence. In addition, we used SMDs for estimating effects of continuous outcomes; while most data come from established measures for depressive symptoms (e.g., HDRS), drinking (Timeline Follow-Back), withdrawal and craving symptoms (e.g., OCDS), quality of life (SF-36), and functional status (e.g., CGI scale), development and use of core outcome measurement sets for this clinical area would help allay concerns about the sensitivity of the direction and magnitude-of-effect estimates arising from application of suboptimal instruments (Boers et al., 2014). Moreover, this review was restricted to RCTs, which restricts the classes of potentially eligible interventions to those amenable to randomization only. While we identified almost three dozen trials, most trials were underpowered, almost all of the evidence on effects is at postintervention without longer-term follow-ups, and the networks of evidence for outcomes were sparse. Numerous clinical interventions recommended in the DoD/VA CPGs for major depressive disorder and SUDs are missing from the body of evidence,

and numerous other (nonclinical) interventions important to patients and their families are possibly missing because of the RCT-only eligibility criterion. Relatedly, it is worth noting that, per the nature of subgroup analyses, findings by type of disorder and setting could be merely the result of which interventions were studied in which populations and settings, rather than a context-specific (i.e., population- or setting-specific) effect of (classes of) interventions.

Clinical Implications

Committees charged with providing recommendations for health systems and updating CPGs may be interested in using this report as a source of evidence on the comparative effectiveness of these interventions. Of the numerous psychological and pharmacological interventions recommended in CPGs for patients with an AUD or depressive disorder (Management of Substance Use Disorders Working Group, 2015; Management of Major Depressive Disorder Working Group, 2016), the available evidence suggests potentially actionable benefits for patients with both an AUD and a depressive disorder at postintervention of CBT for depressive symptoms, TCAs for depressive symptoms, and SSRIs for total drinking and functional status—though SSRIs also have higher risks of adverse events (including serious adverse events), which makes it imperative to formulate recommendations on their net benefit compared with other classes of intervention. These findings can inform the next update to CPGs for AUDs and depressive disorders.

Several findings are relevant to the current DoD/VA CPG for SUDs (Management of Substance Use Disorders Working Group, 2015). For example, CBT is strongly recommended for patients with AUD, either as a first-line treatment or as an adjunctive intervention in combination with pharmacotherapy. In future updates, this recommendation could specifically highlight that CBT may also help patients with AUD who have a co-occurring depressive disorder in reducing their depressive symptoms. Moreover, the current SUD guideline does not make any recommendations for or against the use of SSRIs or TCAs. However, the guideline does note that weight change (gain or loss) is more common when antidepressants are used in combination with acamprosate than either medication alone, that the TCAs desipramine and imipramine (both included in our review) may have interactions with disulfiram, and that they found evidence suggesting no benefit of the SSRIs citalopram and fluoxetine (both included in our review) for patients with AUD alone. In future updates, CPG groups may wish to make recommendations related to SSRIs and TCAs for patients with AUD and a co-occurring depressive disorder—though they should specifically highlight the potential interactions with acamprosate related to weight gain, the interactions of specific TCAs (versus others) with disulfiram, and the potential applicability of certain SSRIs (versus others) for patients with an AUD.

Several findings also are relevant to the current DoD/VA CPG for major depressive disorders (Management of Major Depressive Disorder Working Group, 2016). For example, CBT is

strongly recommended as a first-line treatment for uncomplicated mild-to-moderate major depressive disorder, and computer-based CBT is strongly recommended for patients with mild-to-moderate major depressive disorder (either as an adjunctive intervention or as a first-line treatment). Moreover, CBT is strongly recommended for patients (with all severities and complexities of major depressive disorder) at high risk for relapse during the continuation phase of treatment in order to reduce the risk of subsequent relapse or recurrence, access to evidence-based psychosocial services (including brief CBT) is considered optimal for collaborative care for major depressive disorder in primary-care settings, and patient education about the benefits of bibliotherapy using cognitive-behavioral principles is recommended for patients with mild major depressive disorder (as adjunctive treatment, or an alternative to pharmacotherapy or psychotherapy). Future updates to the major depressive disorder CPG could specifically highlight the evidence on the benefit of CBT for patients with major depressive disorder and a co-occurring AUD—particularly when current guidance does not recommend a specific evidence-based psychotherapy over another.

SSRIs and TCAs feature prevalently in the current guidance for major depressive disorder, so future guideline groups interested in recommendations for patients with a co-occurring AUD should thoroughly examine the potential implications throughout the guideline. For example, all of the SSRIs included in our review (citalopram, escitalopram, fluoxetine, paroxetine, and sertraline) are strongly recommended for consideration as a first-line treatment for uncomplicated mild-to-moderate major depressive disorder. While the CPG recommends starting with SSRIs (but not TCAs) if the clinician and patient make a shared decision to initiate antidepressant monotherapy (rather than psychotherapy), the CPG also recommends basing the selection on safety and side-effect profiles—meaning recommendations for patients with major depressive disorder and an AUD should consider highlighting our findings on the risk of (serious) side effects for SSRIs. As another example, three of the TCAs identified in our review (amitriptyline, desipramine, and imipramine but not tianeptine) are strongly recommended (along with patient education about their safety and side-effect profiles) for patients with treatment-resistant major depressive disorder who have had at least two adequate pharmacotherapy trials. In addition, the CPG currently recommends that patients who have demonstrated partial or no response to initial pharmacotherapy monotherapy switch to another monotherapy (medication or psychotherapy) or augment with a second medication or psychotherapy. Taken together, recommendations for these complex patients who also have a co-occurring AUD may wish to highlight the TCAs identified in our review—or CBT as the potential psychotherapy augmenting the initial pharmacotherapy monotherapy.

Research Implications

Researchers, policymakers, funders, and practitioners may wish to establish future priorities on researching clinical interventions for this patient population. Future studies—in particular,

pragmatic, adequately powered, preregistered, and well-reported RCTs—are needed to provide more-conclusive evidence about the (comparative) effectiveness of clinical interventions for treating adults with depressive disorders and AUDs. We identified significant effects for several comparisons that could be prioritized for direct comparisons in future trials but for which we have insufficient confidence to support consideration for policy and practice recommendations on the basis of evidence on effectiveness. These interventions include AAPs in combination with SSRIs on functional status at postintervention; CBT on total drinking at postintervention; NMDA antagonists on total drinking and functional status at postintervention; opioid antagonists in combination with SSRIs on remission for alcohol use, depressive symptoms, and heavy drinking at postintervention; SARIs on heavy drinking and functional status at postintervention; SMS on depressive symptoms and functional status at postintervention; SSRIs on remission for alcohol use and depressive symptoms at long-term follow-up; and TCAs on functional status at postintervention. In addition to more studies on interventions included in this review, studies are needed on other interventions used to treat AUDs and depressive disorders. Numerous clinical interventions contained in the VA/DoD CPGs for these conditions (e.g., 12-Step Facilitation, behavioral couples therapy, the community reinforcement approach, disulfiram, gabapentin, motivational enhancement therapy, and topiramate for AUDs; 5-HT₂ and 5-HT₃ receptor antagonists, behavioral activation, monoamine oxidase inhibitors, mindfulness-based therapies, norepinephrine and dopamine reuptake inhibitors, problem-solving therapy, and serotonin and norepinephrine reuptake inhibitors for depressive disorders) are missing from the current body of evidence (Department of Veterans Affairs and Department of Defense, 2015; Department of Veterans Affairs and Department of Defense, 2016). To clarify, the absence of evidence on interventions with very low confidence and for which we did not identify any trials does *not* indicate evidence of absence of effects—thus the importance of future trials on these interventions. To contribute rigorous evidence on the effects of clinical interventions for activated patients, as well as evidence on subpopulations of patients with strong treatment preferences, future researchers should consider the use of patient preference trials and trials using Zelen’s design (Torgerson and Roland, 1998; Torgerson and Sibbald, 1998).

Appendix A. Electronic Search Strategies

This appendix provides the electronic search strategies used to identify citations for the systematic review.

ClinicalTrials.gov

Search Run: May 23, 2018

Search 1

((alcohol OR “binge drinking” OR alcoholic OR “drinking problem”) AND (depression OR depressive OR dysthymia OR melancholy OR dysthymic OR melancholia OR “seasonal affective disorder” OR “premenstrual dysphoric disorder” OR “mood dysregulation”))

Search 2

(alcoholism AND (depression OR depressive OR dysthymia OR melancholy OR dysthymic OR melancholia OR “seasonal affective disorder” OR “premenstrual dysphoric disorder” OR “mood dysregulation”))

CENTRAL

Search Run: May 22, 2018

Alcohol* OR “binge drinking” OR alcoholic OR “drinking problem”

AND

depression OR depressive* OR dysthymia OR melancholy OR dysthymic OR melancholia OR “seasonal affective disorder*” OR “premenstrual dysphoric disorder*” OR “mood dysregulation”

CDSR

Search Run: May 22, 2018

“alcohol use disorder*” OR alcoholic OR alcoholics OR alcoholism OR “alcohol related disorder*” OR “binge drink*” OR “alcohol withdrawal*” OR “drinking problem*” OR “alcohol abuse*” OR “alcohol use*” OR “alcohol dependent” OR “alcohol dependence” OR “alcohol disorder” OR “alcohol disorder”

AND

depressive* OR depression OR depressed OR melancholia OR melancholy OR melancholic OR “premenstrual dysphoric disorder*” OR “seasonal affective disorder*” OR dysthymi* OR “mood dysregulation”

CINAHL

Search Run: May 22, 2018

Limits: English Language

(MH "Alcohol-Related Disorders+") OR TI "alcohol use disorder*" OR AB "alcohol use disorder*" OR TI alcoholic OR AB alcoholic OR TI alcoholics OR AB alcoholics OR TI alcoholism OR AB alcoholism OR TI "alcohol related disorder*" OR AB "alcohol related disorder*" OR TI "binge drink*" OR AB "binge drink*" OR TI "alcohol withdrawal*" OR AB "alcohol withdrawal*" OR TI "drinking problem*" OR AB "drinking problem*" OR TI "alcohol abuse*" OR AB "alcohol abuse*" OR TI "alcohol use*" OR AB "alcohol use*" OR TI "alcohol dependent" OR AB "alcohol dependent" OR TI "alcohol dependence" OR AB "alcohol dependence" OR TI "alcohol disorder" OR AB "alcohol disorder"

AND

(MH "Depression+") OR TI depressive* OR AB depressive* OR TI depression OR AB depression OR TI depressed OR AB depressed OR TI melancholia OR AB melancholia OR TI melancholy OR AB melancholy OR TI melancholic OR AB melancholic OR TI "premenstrual dysphoric disorder*" OR AB "premenstrual dysphoric disorder*" OR TI "seasonal affective disorder*" OR AB "seasonal affective disorder*" OR TI dysthymi* OR AB dysthymi* OR TI "mood dysregulation" OR AB "mood dysregulation"

AND

(MH "Clinical Trials") OR (MH "Randomized Controlled Trials") OR TI randomized OR AB randomized OR TI placebo OR AB placebo OR TI randomly OR AB randomly OR TI trial

NOT

(MH "Animals, Laboratory")

NOT

TI "study protocol*" OR AB "study protocol*" OR TI "trial protocol*" OR AB "trial protocol*"

EMBASE

Search Run: May 22, 2018

Limits: English Language

'alcoholism'/exp OR 'Alcohol Use Disorders Identification Test'/exp OR 'alcohol use disorder*':ab,ti OR alcoholic:ab,ti OR alcoholics:ab,ti OR alcoholism:ab,ti OR 'alcohol related disorder*':ab,ti OR 'binge drink*':ab,ti OR 'alcohol withdrawal*':ab,ti OR 'drinking problem*':ab,ti OR 'alcohol abuse*':ab,ti OR 'alcohol use*':ab,ti OR 'alcohol dependent':ab,ti OR 'alcohol dependence':ab,ti OR 'alcohol disorder*':ab,ti

AND

'depression'/exp OR depressive*:ab,ti OR depression:ab,ti OR depressed:ab,ti OR melancholia:ab,ti OR melancholy:ab,ti OR melancholic*:ab,ti OR 'premenstrual dysphoric disorder*':ab,ti OR 'seasonal affective disorder*':ab,ti OR dysthymi*:ab,ti OR 'mood dysregulation':ab,ti

AND

'controlled clinical trial'/exp OR randomized:ab,ti OR placebo:ab,ti OR randomly:ab,ti OR trial:ti

NOT
(‘animal’/exp NOT ‘human’/exp)
NOT
‘study protocol*’:ab,ti OR ‘Trial protocol*’:ab,ti

PsycInfo

Search Run: May 22, 2018

Limits: English Language

DE “Alcoholism” OR DE “Alcoholic Psychosis” OR TI “alcohol use disorder*” OR AB “alcohol use disorder*” OR TI alcoholic OR AB alcoholic OR TI alcoholics OR AB alcoholics OR TI alcoholism OR AB alcoholism OR TI “alcohol related disorder*” OR AB “alcohol related disorder*” OR TI “binge drink*” OR AB “binge drink*” OR TI “alcohol withdrawal*” OR AB “alcohol withdrawal*” OR TI “drinking problem*” OR AB “drinking problem*” OR TI “alcohol abuse*” OR AB “alcohol abuse*” OR TI “alcohol use*” OR AB “alcohol use*” OR TI “alcohol dependent” OR AB “alcohol dependent” OR TI “alcohol dependence” OR AB “alcohol dependence” OR TI “alcohol disorder” OR AB “alcohol disorder”

AND

(DE “Major Depression” OR DE “Anaclitic Depression” OR DE “Dysthymic Disorder” OR DE “Endogenous Depression” OR DE “Late Life Depression” OR DE “Postpartum Depression” OR DE “Reactive Depression” OR DE “Recurrent Depression” OR DE “Treatment Resistant Depression”) OR (DE “Atypical Depression”) OR TI depressive* OR AB depressive* OR TI depression OR AB depression OR TI depressed OR AB depressed OR TI melancholia OR AB melancholia OR TI melancholy OR AB melancholy OR TI melancholic OR AB melancholic OR TI “premenstrual dysphoric disorder*” OR AB “premenstrual dysphoric disorder*” OR TI “seasonal affective disorder*” OR AB “seasonal affective disorder*” OR TI dysthymi* OR AB dysthymi* OR TI “mood dysregulation” OR AB “mood dysregulation”

AND

DE “Clinical Trials” OR TI randomized OR AB randomized OR TI placebo OR AB placebo OR TI randomly OR AB randomly OR TI trial OR MR “Clinical Trial”

NOT

DE “Animal Models”

NOT

TI “study protocol*” OR AB “study protocol*” OR TI “trial protocol*” OR AB “trial protocol*”

PubMed

Search for Clinical Trials

Search Run: May 22, 2018

Limits: English Language

“Alcohol related disorders”[MeSH] OR alcohol use disorder*[tiab] OR alcoholic[tiab] OR alcoholics[tiab] OR alcoholism[tiab] OR alcohol related disorder*[tiab] OR binge drink*[tiab] OR alcohol withdrawal*[tiab] OR drinking problem*[tiab] OR alcohol abuse*[tiab] OR alcohol use*[tiab] OR alcohol dependent[tiab] OR alcohol dependence[tiab] OR alcohol disorder*[tiab]

AND

Depressive Disorder"[MeSH] OR "Depression"[MeSH] OR depressive*[tiab] OR depression[tiab] OR depressed[tiab] OR melancholia[tiab] OR melancholy[tiab] OR melancholic*[tiab] OR premenstrual dysphoric disorder*[tiab] OR seasonal affective disorder*[tiab] OR dysthymi*[tiab] OR mood dysregulation[tiab] OR depression[ot] OR depressive[ot]

AND

randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[mesh:noexp] OR randomly[tiab] OR trial[ti]

NOT

("animals"[MeSH] NOT "humans" [MeSH])

NOT

(study protocol*[tiab] OR Trial protocol*[tiab])

Systematic Reviews Search

Search Run: May 22, 2018

"Alcohol related disorders"[MeSH] OR alcohol use disorder*[tiab] OR alcoholic[tiab] OR alcoholics[tiab] OR alcoholism[tiab] OR alcohol related disorder*[tiab] OR binge drink*[tiab] OR alcohol withdrawal*[tiab] OR drinking problem*[tiab] OR alcohol abuse*[tiab] OR alcohol use*[tiab] OR alcohol dependent[tiab] OR alcohol dependence[tiab] OR alcohol disorder*[tiab]

AND

"Depressive Disorder"[MeSH] OR "Depression"[MeSH] OR depressive*[tiab] OR depression[tiab] OR depressed[tiab] OR melancholia[tiab] OR melancholy[tiab] OR melancholic*[tiab] OR premenstrual dysphoric disorder*[tiab] OR seasonal affective disorder*[tiab] OR dysthymi*[tiab] OR mood dysregulation[tiab] OR depression[ot] OR depressive[ot]

AND

systematic [sb]

NOT

("animals"[MeSH] NOT "humans" [MeSH])

Web of Science

Search Run: May 22, 2018

Limits: English Language

TS=("alcohol use disorder*") OR TS=(alcoholic) OR TS=(alcoholics) OR TS=(alcoholism) OR TS=("alcohol related disorder*") OR TS=("binge drink*") OR TS=("alcohol withdrawal*") OR TS=("drinking problem*") OR TS=("alcohol abuse*") OR TS=("alcohol use*") OR TI=("alcohol dependent") OR TS=("alcohol dependence") OR TS=("alcohol disorder")

AND

TS=(depressive*) OR TS=(depression) OR TS=(depressed) OR TS=(melancholia) OR TS=(melancholy) OR TS=(melancholic*) OR TS=("premenstrual dysphoric disorder*") OR TS=("seasonal affective disorder*") OR TS=(dysthymi*) OR TS=("mood dysregulation")

AND

TS=(randomized) OR TS=(placebo) OR TS=(randomly) OR TI=(trial)

NOT

TS=(rat OR rats OR mice OR mouse OR monkey OR monkeys))

World Health Organization ICTRP

Run: May 23, 2018

Search 1

Depress* AND alcohol*

Search 2

Binge drink* AND depress*

Search 3

Drinking problem AND depress*

Search 4

alcohol* AND melanchol*

Search 5

alcohol* AND seasonal affective disorder

Search 6

alcohol* AND dysthym*

Search 7

alcohol* AND premenstrual dysphoric disorder

Search 8

alcohol* AND mood dysregulation

Search 9

Binge drink* AND melanchol*

Search 10

Binge drink* AND seasonal affective disorder

Search 11

Binge drink* AND dysthym*

Search 12

Binge drink* AND premenstrual dysphoric disorder

Search 13

Binge drink* AND mood dysregulation

Search 14

Drinking problem AND melanchol*

Search 15

Drinking problem AND seasonal affective disorder

Search 16

Drinking problem AND dysthym*

Search 17

Drinking problem AND premenstrual dysphoric disorder

Appendix B. Eligible Diagnoses

This appendix provides the diagnoses of AUDs and depressive disorders that we used for studies to be eligible. We used the *DSM*, fifth edition (*DSM-V*), to generate the following list of diagnoses (American Psychiatric Association, 2013), with the ICD codes also provided (World Health Organization, 1992). We included corresponding diagnoses from previous versions of the *DSM* as well (American Psychiatric Association, 2000).

Alcohol Use Disorder Diagnoses

Included Diagnoses

- Mild AUD
 - ICD-9: 30.500
 - ICD-10: F10.10
- Moderate AUD
 - ICD-9: 303.90
 - ICD-10: F10.20
- Severe AUD
 - ICD-9: 303.90
 - ICD-10: F10.20
- Alcohol withdrawal
 - ICD-9: 291.81
 - ICD-10: F10.239, F10.232
- Unspecified alcohol-related disorder
 - ICD-9: 291.9
 - ICD-10: F10.99

Excluded Diagnoses

- Alcohol intoxication
 - ICD-9: 303.00
 - ICD-10: F10.929

Depressive Disorder Diagnoses

Included Diagnoses

- Alcohol-induced depressive disorder
 - ICD-9: 291.89
 - ICD-10: F10.14, F10.24, F10.94

- Major depressive disorder in full remission (single episode)
 - ICD-9: 296.26
 - ICD-10: F32.5
- Major depressive disorder in full remission (recurrent episodes)
 - ICD-9: 296.36
 - ICD-10: F33.52
- Major depressive disorder in partial remission (single episode)
 - ICD-9: 296.25
 - ICD-10: F32.4
- Major depressive disorder in partial remission (recurrent episodes)
 - ICD-9: 296.35
 - ICD-10: F33.41
- Major depressive disorder with psychotic features (single episode)
 - ICD-9: 296.24
 - ICD-10: F32.3
- Major depressive disorder with psychotic features (recurrent episodes)
 - ICD-9: 296.34
 - ICD-10: F33.3
- Mild major depressive disorder (single episode)
 - ICD-9: 296.21
 - ICD-10: F32.0
- Mild major depressive disorder (recurrent episodes)
 - ICD-9: 296.31
 - ICD-10: F33.0
- Moderate major depressive disorder (single episode)
 - ICD-9: 296.22
 - ICD-10: F32.1
- Moderate major depressive disorder (recurrent episodes)
 - ICD-9: 296.32
 - ICD-10: F33.1
- Other specified depressive disorder
 - ICD-9: 311
 - ICD-10: F32.8
- Persistent depressive disorder (dysthymia)
 - ICD-9: 300.4
 - ICD-10: F34.1
- Severe major depressive disorder (single episode)
 - ICD-9: 296.23
 - ICD-10: F32.2
- Severe major depressive disorder (recurrent episodes)
 - ICD-9: 296.33
 - ICD-10: F33.2

- Unspecified depressive disorder
 - ICD-9: 311
 - ICD-10: F32.9
- Unspecified major depressive disorder (single episode)
 - ICD-9: 296.20
 - ICD-10: F32.9
- Unspecified major depressive disorder (recurrent episodes)
 - ICD-9: 296.30
 - ICD-10: F33.9

Excluded Diagnoses

- Bipolar I disorder: current or most recent episode depressed
 - ICD-9: 296.51, 296.52, 296.53, 296.43, 296.55, 296.56, 296.50
 - ICD-10: F31.31, F31.32, F31.4, F31.5, F31.75, F31.76, F31.9
- Bipolar II disorder
 - ICD-9: 296.89
 - ICD-10: F31.81
- Cyclothymic disorder
 - ICD-9: 301.13
 - ICD-10: F34.0
- Depressive disorder due to another medical condition
 - ICD-9: 293.83
 - ICD-10: F06.31, F06.32, F06.34
- Depressive episodes with short-duration hypomania
- Disruptive mood dysregulation disorder
 - ICD-9: 296.99
 - ICD-10: F34.8
- Other specified bipolar and related disorder
 - ICD-9: 296.89
 - ICD-10: F31.89
- Premenstrual dysphoric disorder
 - ICD-9: 625.4
 - ICD-10: N94.3
- Substance/medication-induced depressive disorder (other than alcohol)
 - ICD-9: 292.84
 - ICD-10: F11.14, F11.24, F11.94, F13.14, F13.24, F13.94, F14.14, F14.24, F14.94, F15.14, F15.24, F15.94, F16.14, F16.24, F16.94, F18.14, F18.24, F18.94, F19.14, F19.24, F19.94
- Unspecified bipolar and related disorder
 - ICD-9: 296.80
 - ICD-10: F31.9

Appendix C. Studies Ongoing or Waiting Assessment

This appendix provides details about studies that could be eligible once completed but are still ongoing or have not provided sufficient information for us to determine eligibility.

Becker 2017

References	Becker, A., A. M. Ehret, and P. Kirsch, "From the Neurobiological Basis of Comorbid Alcohol Dependence and Depression to Psychological Treatment Strategies: Study Protocol of a Randomized Controlled Trial," <i>BMC Psychiatry</i> , Vol. 17, April 2017, p. 10. DRKS00010249, "From the Neurobiological Basis of Comorbid Alcohol Dependence and Depression to Psychological Treatment Strategies: Bridging the Knowledge Gap," 2017. As of March 15, 2019: http://www.drks.de/DRKS00010249
Participants	Adults with AUD and depression according to <i>DSM-V</i> criteria
Setting	Central Institute of Mental Health, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany
Intervention 1	Behavioral therapy: A two-hour, group-based behavioral activation therapy session, delivered by a psychotherapist once a week for 6 weeks
Intervention 2	Complementary and alternative medicine: A two-hour, group-based, mindfulness-based training session, delivered by a psychotherapist once a week for 6 weeks
Outcomes	Remission from alcohol use: Alcohol Dependence Scale Depression symptoms: BDI, MADRS Total drinking: Form 90 Interview Withdrawal and craving symptoms: Alcohol Urge Questionnaire, OCDS Health-related quality of life: Münchner Lebensqualitäts-Dimensionen Liste Adverse events: "All adverse events are documented"
Notes	Ongoing trial

Butler Hospital 2016

References	NCT02705898, "Lifestyle Physical Activity Intervention for Depressed Alcohol Dependent Women," 2016. As of March 15, 2019: https://clinicaltrials.gov/show/NCT02705898
Participants	<i>DSM-V</i> AUD and score of 1 on either of the first two items of the PHQ
Setting	Not reported
Intervention 1	Lifestyle intervention: A 12-week lifestyle physical activity plus Fitbit intervention. This will include (1) a single in-person physical activity counseling orientation session; (2) six brief, phone-based physical activity counseling sessions focused on increasing physical activity and strategically using bouts of physical activity to cope with affect and alcohol cravings; (3) use of the Fitbit fitness tracker for physical activity goal-setting and daily self-monitoring; and (4) weekly supportive messages delivered by email.

Intervention 2	Psychological placebo: A Health Education Contact Control. The Health Education Contact Control condition will include (1) an in-person orientation session, (2) six telephone-delivered health education sessions, and (3) weekly health-related emails.
Outcomes	Remission from alcohol use: Percentage of days abstinent Depressive symptoms: Quick Inventory of Depressive Symptomatology
Notes	Ongoing trial

Cape 2010

References	ACTRN12610000390088, "Pilot Study for the Rapid Alleviation of Depression in Depressed Alcohol Dependent Persons Using Ketamine," 2010. As of March 15, 2019: http://www.anzctr.org.au/ACTRN12610000390088.aspx
Participants	Adults aged 18–65 with major depression (MADRS scores >20) and diagnosed with <i>DSM-IV-TR</i> alcohol dependence
Setting	Local alcohol and drug service in Otago, New Zealand
Intervention 1	Ketamine: Four separate infusions of ketamine (seven days apart)
Intervention 2	Pharmacological placebo: Four separate infusions of saline (seven days apart)
Outcomes	Remission from depression: Proportion of subjects showing remission indicated by a MADRS < 7 Number of drinks: Reduction in alcohol consumption assessed via Timeline Follow-Back recording Adverse events: Safety and tolerability based on self-report by interview and on Medication Side-Effects Questionnaire by interview
Notes	Unclear whether study data have been analyzed and reported

Gamble 2009

References	NCT00851669, "The MEADOW PROJECT (Mending the Effects of Alcohol and Depression on Women) and the Bridge Program (Connecting Recovery Treatment and Behavioral Health)," 2009. As of March 15, 2019: http://clinicaltrials.gov/show/NCT00851669
Participants	Adults aged 18–65 with current alcohol dependence and major depression
Setting	Not reported
Intervention 1	IPT: IPT for co-occurring alcohol dependence and major depression
Intervention 2	No additional treatment: Individual psychotherapy following usual care practice in a chemical dependency treatment program
Outcomes	Remission from alcohol use: Percentage days abstinent using Timeline Follow-Back Depressive symptoms: BDI, HDRS Number of drinks: Average drinks per drinking day using the Timeline Follow-Back
Notes	Unclear whether study data have been analyzed and reported

Hare 2017

References	NCT03265808, “Allogeneic Human Mesenchymal Stem Cell Infusion Versus Placebo in Subjects with Alcohol Use Disorder and Major Depression,” 2017. As of March 15, 2019: https://clinicaltrials.gov/show/NCT03265808
Participants	Adults with AUD and depression according to <i>DSM-V</i> criteria
Setting	University of Miami
Intervention 1	Allogeneic human mesenchymal stem cells
Intervention 2	Placebo
Outcomes	Depression symptoms: MADRS Total drinking: Alcohol use Heavy drinking: Heavy drinking days Withdrawal and craving symptoms: Alcohol Urge Questionnaire, OCDS Functional status: GAF, global clinical functioning
Notes	Ongoing trial

Hunt 2005

References	Hunt, S, A. Baker, D. J. Kavanagh, F. J. Kay-Lambkin, T. J. Lewin, B. Kelly, and V. J. Carr, “Combined Versus Single Focused Interventions for Comorbid Depression and Alcohol Problems: Introduction to the DAISI Project,” <i>Australian and New Zealand Journal of Psychiatry</i> , Vol. 39, Supp. 2, 2005, pp. A27–A28.
Participants	People with alcohol and depressive disorders
Setting	Not reported
Intervention 1	CBT: Ten sessions of depression-focused CBT and motivational interviewing strategies
Intervention 2	CBT: Ten sessions of alcohol-focused CBT and motivational interviewing strategies
Intervention 3	CBT: Ten sessions of CBT and motivational interviewing strategies with an integrated depression and alcohol focus
Intervention 4	Psychological placebo: A single case formulation and assessment feedback session
Outcomes	Depressive symptoms: “Symptoms of depression” Number of drinks: “Alcohol use”
Notes	Conference abstract with insufficient details to confirm eligibility for our review

Ionescu 2011

References	Ionescu, D., C. Dehelean, S. Timofei Funar, and R. Dumache, "A Comparative Evaluation of Therapy Escitalopram Versus Memantine in the Case of Patients with Alcohol Dependence and Co-Morbid Major Depressive Disorder," <i>Toxicology Letters</i> , Vol. 205, 2011, p. S89.
Participants	Alcohol-dependent patients with comorbid major depressive disorder
Setting	Municipal psychiatric department
Intervention 1	SSRI: 20 mg of escitalopram for 26 weeks
Intervention 2	NMDA antagonist: 20 mg of memantine for 26 weeks
Outcomes	Total drinking: AUDIT (quantity-frequency) Withdrawal and craving symptoms: OCDS
Notes	Conference abstract with insufficient details to confirm eligibility for our review

Kavanagh 2005

References	ACTRN12605000647639, "Collaborative Management of Depression and Alcohol Misuse by General Practitioners and Correspondence-Based Programs," 2005. As of March 15, 2019: http://www.anzctr.org.au/ACTRN12605000647639.aspx
Participants	Adult patients meeting <i>DSM-IV</i> criteria for an AUD and depression or dysthymia
Setting	Primary care in Australia
Intervention 1	CBT: Correspondence-based treatments (four weekly and four fortnightly letters) for alcohol only that are based on empirically supported CBT
Intervention 2	CBT: Correspondence-based treatments (four weekly and four fortnightly letters) for alcohol and depression that are based on empirically supported CBT
Outcomes	Depressive symptoms: Degree of depression Number of drinks: Alcohol intake
Notes	Unclear whether study data have been analyzed and reported

Krupitsky 2013

References	Krupitsky, E. M., S. M. Yerish, K. V. Rybakova, and A. S. Kiselev, "Single Blind Placebo Controlled Randomized Clinical Trial of Trazodon for Alcoholism Comorbid with Affective Disorders," <i>Alcoholism: Clinical and Experimental Research</i> , Vol. 37, 2013, p. 18A.
Participants	Alcoholism comorbid with mild to moderate depression
Setting	Outpatient clinic
Intervention 1	SARI: Trazodone (150 mg/day) for 3 months
Intervention 2	Pharmacological placebo: Identical-looking placebo daily for 3 months
Outcomes	Depressive symptoms: HDRS, MADRS Total drinking: Timeline Follow-Back

	Withdrawal and craving: OCDS, Penn Alcohol Craving Scale, and Visual Analog Scale of Craving for alcohol Adverse events: Side effects
Notes	Conference abstract with insufficient details to confirm eligibility for our review

Mason 1998

References	Mason, B. J., F. R. Salvato, L. D. Williams, and R. B. Cutler, "Naltrexone and/or Sertraline in Outpatients with Alcoholism and Depression: Conference Abstract," 11th European College of Neuropsychopharmacology Congress, Paris, France, October 31–November 4, 1998.
Participants	Patients aged 18–65 years who met <i>DSM-IV</i> criteria for (1) alcohol dependence and (2) major depression or dysthymia
Setting	Not reported
Intervention 1	SSRI: Up to 200 mg/day of sertraline Opioid antagonist: 50 mg/day of naltrexone
Intervention 2	SSRI: Up to 200 mg/day of sertraline Pharmacological placebo: Matched placebo for naltrexone
Outcomes	Depressive symptoms: HDRS Number of drinks: Weekly alcohol consumption Heavy drinking days: Greater than or equal to five drinks a day for males; greater than or equal to four drinks a day for females
Notes	Conference abstract with insufficient details to confirm eligibility for our review

McAndrew 2017

References	McAndrew, A., W. Lawn, T. Stevens, L. Porffy, B. Brandner, and C. J. A. Morgan, "A Proof-of-Concept Investigation into Ketamine as a Pharmacological Treatment for Alcohol Dependence: Study Protocol for a Randomised Controlled Trial," <i>Trials</i> , Vol. 18, No. 1, 2017, p. 159.
Participants	Adults with (1) <i>DSM-V</i> severe AUD or <i>DSM-IV</i> alcohol dependence and (2) mild depression (> 14 on BDI-II)
Setting	Patients will be primarily recruited from substance misuse and addiction psychiatry services in Central, North West, and South London, as well as Devon, Dorset, Wiltshire, Somerset, and Bristol
Intervention 1	Ketamine: Three weekly infusions (40 minutes each) of intravenous infusions of Ketalar (0.8 mg/kg made up to 50 ml with saline) over 40 minutes Psychological therapy: Seven sessions (one hour each) of a manualized, relapse-prevention-based therapy
Intervention 2	Pharmacological placebo: Three weekly infusions (40 minutes each) of intravenous infusions of saline 0.9 percent IV over 40 minutes Psychological therapy: Seven sessions (one hour each) of a manualized, relapse-prevention-based therapy

Intervention 3	Ketamine: Three weekly infusions (40 minutes each) of intravenous infusions of Ketalar (0.8 mg/kg made up to 50 ml with saline) over 40 minutes Psychological placebo: Seven sessions (one hour each) educating patients about the risks of alcohol use and the effects of alcohol on the body
Intervention 4	Pharmacological placebo: Three weekly infusions (40 minutes each) of intravenous infusions of saline 0.9 percent IV over 40 minutes Psychological placebo: Seven sessions (one hour each) educating patients about the risks of alcohol use and the effects of alcohol on the body
Outcomes	Remission from alcohol use: Relapse rates, number/percentage days abstinent Depression outcomes (unclear domains): BDI, HDRS Drinking outcomes (unclear domains): Alcohol and drug use history, Alcohol Timeline Follow-Back, drink diary Withdrawal and craving symptoms: Alcohol Craving Questionnaire, Craving Visual Analogue Scale Health-related quality of life: Short-Form 12-Item Health Survey Adverse events: “All adverse events will be recorded until 6 months post-treatment”
Notes	Ongoing trial

Oquendo 2007

References	NCT00449007, “Fluoxetine and Bupropion to Treat Patients with Depression and Alcoholism,” 2007. As of March 15, 2019: http://clinicaltrials.gov/show/NCT00449007
Participants	Patients aged 18–65 years suffering from a major depressive episode (unipolar only) and alcohol dependence or abuse
Setting	Not reported
Intervention 1	SSRI: 6 months of fluoxetine
Intervention 2	Norepinephrine-dopamine reuptake inhibitor: 6 months of bupropion
Outcomes	No eligible outcomes reported
Notes	The recruitment status of this study is unknown. The completion date has passed, and the status has not been verified in more than two years.

Penberthy 2012

References	NCT01528748, “Clinical Trial of CBASP for Individuals with Co-Occurring Chronic Depression and Alcohol Dependence,” 2012. As of March 15, 2019: https://clinicaltrials.gov/show/NCT01528748
Participants	Adults aged 21–65 with a clinical diagnosis of a current major depressive disorder and alcohol dependence
Setting	Not reported
Intervention 1	CBT: Individual Cognitive Behavioral Analysis System of Psychotherapy on a weekly basis (20 sessions total over a period of 21 weeks)

Intervention 2	Not reported (likely a single-arm trial)
Outcomes	Depressive symptoms: HDRS Number of drinks: Drinks consumed per drinking day
Notes	Ongoing trial

Petrakis 2012

References	NCT01551329, “Ketamine for Depression and Alcohol Dependence,” 2012. As of March 15, 2019: https://clinicaltrials.gov/show/NCT01551329
Participants	Male or female veterans with (1) <i>DSM-IV-TR</i> major depressive episode and (2) <i>DSM-IV-TR</i> alcohol dependence
Setting	Patient recruited through the West Haven VA clinics
Intervention 1	Ketamine: Intravenous ketamine (0.5 mg/kg)
Intervention 2	Pharmacological placebo: Saline solution
Outcomes	Depressive symptoms: HDRS
Notes	Unclear whether study data have been analyzed and reported

Winkel 2000

References	Winkel, R., H. D. Koritsch, H. Piayda, and U. Trenckmann, “Efficacy of St. John’s Wort Extract LI 160 in Depressive, Alcohol Addicted Patients,” <i>International Journal of Neuropsychopharmacology</i> , Vol. 3, Supp. 1, 2000, p. S314.
Participants	Patients aged 18–65 years who met the ICD-10/ <i>DSM-III-R</i> criteria for current depressive disorders and alcoholism
Setting	One center
Intervention 1	St. John’s wort: 900 mg of hypericum extract LI 160 daily
Intervention 2	Pharmacological placebo: Daily placebo
Outcomes	Depressive symptoms: HDRS, BDI, Depression Scale According to von Zerssen, test for assessing the severity of depression according to Obermair, Symptom Checklist according to Derogatis Health-related quality of life: Global assessment of patient’s state
Notes	Conference abstract with insufficient details to confirm eligibility for our review

Yoon 2015

References	NCT02461927, “Ketamine for the Rapid Treatment of Major Depressive Disorder and Alcohol Use Disorder,” 2015. As of March 15, 2019: https://clinicaltrials.gov/show/NCT02461927
Participants	Male or female veterans aged 21–65 years old with (1) current major depressive disorder without psychotic features by <i>DSM-V</i> and (2) a minimum of 4 of 11 current AUD symptoms by <i>DSM-V</i>
Setting	Not reported
Intervention 1	Ketamine: Intravenous ketamine (0.5 mg/kg) once a week for 4 weeks (a total of four infusions) Opioid antagonist: Intramuscular naltrexone (380 mg) once a month (a total of two injections)
Intervention 2	Ketamine: Intravenous ketamine (0.5 mg/kg) once a week for 4 weeks (a total of four infusions) Pharmacological placebo: Intramuscular placebo once a month (a total of two injections)
Intervention 3	Sedative: Intravenous midazolam (0.045 mg/kg) once a week for 4 weeks (a total of four infusions) Pharmacological placebo: Intramuscular placebo once a month (a total of two injections)
Outcomes	Remission from alcohol use: Rate of complete abstinence from alcohol using the Timeline Follow-Back Depressive symptoms: MADRS
Notes	Ongoing trial

Appendix D. Included Studies

This appendix provides information on the studies that we have included as part of our review.

Adamson 2015

References	Parent study Adamson, S. J., J. D. Sellman, J. A. Foulds, C. M. Frampton, D. Deering, A. Dunn, J. Berks, L. Nixon, and G. Cape, “A Randomized Trial of Combined Citalopram and Naltrexone for Nonabstinent Outpatients with Co-Occurring Alcohol Dependence and Major Depression,” <i>Journal of Clinical Psychopharmacology</i>, Vol. 35, No. 2, April 2015, pp. 143–149. Additional ACTRN12606000413527, “Treatment Evaluation of Alcohol and Mood,” 2006. As of March 15, 2019: http://www.anzctr.org.au/ACTRN12606000413527.aspx Foulds, J. A., J. Douglas Sellman, S. J. Adamson, J. M. Boden, R. T. Mulder, and P. R. Joyce, “Depression Outcome in Alcohol Dependent Patients: An Evaluation of the Role of Independent and Substance-Induced Depression and Other Predictors,” <i>Journal of Affective Disorders</i>, Vol. 174, March 15, 2015, pp. 503–510. Foulds, J. A., R. T. Mulder, G. Newton-Howes, S. J. Adamson, J. M. Boden, and J. D. Sellman, “Personality Predictors of Drinking Outcomes in Depressed Alcohol-Dependent Patients,” <i>Alcohol and Alcoholism</i>, Vol. 51, No. 3, May 2016, pp. 296–301. Foulds, J. A., K. Ton, M. A. Kennedy, S. J. Adamson, R. T. Mulder, and J. D. Sellman, “OPRM1 Genotype and Naltrexone Response in Depressed Alcohol-Dependent Patients,” <i>Pharmacogenetic and Genomics</i>, Vol. 25, No. 5, May 2015, pp. 270–273.
Study design	Study dates: 2007 to 2011 Objective: To determine whether combining naltrexone with citalopram produced better treatment outcomes than naltrexone alone in patients with co-occurring alcohol dependence and depression. Randomization: Individually randomized, 1:1 ratio, stratified by gender and depression type (independent or substance induced) Recruitment method: Participants were recruited by advertising, as well as from addiction treatment centers and psychiatric clinics (compensation of vouchers worth NZ \$40 for participation). Inclusion criteria: Aged 17 to 65 years; <i>DSM-IV</i> criteria for alcohol dependence and major depressive episode in the past 4 weeks according to responses to the Structured Clinical Interview for <i>DSM-IV</i>; greater than 20 on the MADRS for past week symptoms of depression. Alcohol dependence was the primary substance disorder, and participants were not required to be abstinent from alcohol when entering the study. Three clinical investigators categorized participants as having substance-induced depression unless there was a history of the following (according to the Structured Clinical Interview for <i>DSM-IV</i>): an episode of major depression occurring before first onset of heavy drinking; a previous episode of major depression that continued for more than 1 month into a

	period of abstinence or started during a period of abstinence; and a previous episode of major depression associated with mood symptoms substantially in excess of what would be expected given the duration or amount of alcohol use at the time. Exclusion criteria: Past regular intravenous drug use for more than 2 weeks; recreational use of any opioid drugs in the previous 4 weeks or a current requirement for ongoing opioid use; psychosis, including psychotic delirium complicating alcohol or other drug withdrawal; mania or hypomania; significant current suicidality or homicidality; current severe psychiatric symptoms requiring hospitalization; unstable physical disease; use of disulfiram, naltrexone, antidepressant, or mood-stabilizing medication in the past 4 weeks; serum aspartate aminotransferase, alanine transaminase, or gamma glutamyl transpeptidase greater than 3, the upper limit of the laboratory reference range, or a bilirubin level above the upper limit of the reference range; pregnancy, breastfeeding, or unwillingness to use a reliable method of contraception in female participants of childbearing age; and current or pending imprisonment. Power calculation: Target sample size of 220 (minimum required to provide an 80-percent probability of detecting an effect size of 0.38 for the primary outcomes) Sample size: 138 total (73/65)
Setting	Geographic location: Urban, provincial, and rural catchments in New Zealand Intervention sites: Eight outpatient addiction clinics
Participants	Age: 43.6 (9.1) Gender: 59 percent female Race/ethnicity: 17 percent New Zealand Maori Other socioeconomics/demographics: 14 years of education; 46 percent married; 55 percent employed; 24 percent living alone Baseline depression: 76 percent independent depression; 24 percent substance-induced depression; major depression disorder onset age of 24.3 (11.4); MADRS of 31.0 (5.8), Symptom Checklist 90 of 2.0 (0.7); 76 percent previous antidepressant use, 30 percent previous depression treatment Baseline alcohol use: Percentage of days abstinent of 25.8 (27.4), percentage of days heavy drinking of 58.9 (33.6), mean drinks per drinking day of 14.3 (8.0); alcohol dependence onset age of 29.8 (10.4); Leeds Dependence Questionnaire of 19.5 (6.5); 54 percent previous alcohol or other drug treatment Other baseline health: 47 percent current anxiety disorder, 13 percent current cannabis user disorder, 4 percent stimulant use disorder
Intervention 1	Category: Pharmacological intervention Class: SSRI Name: Citalopram Materials: Opaque capsule of citalopram Providers: There were 19 research clinicians involved in the overall study—aged 34 to 61 (mean 48), 56 percent female, 78 percent New Zealand European ethnicity, 9 to 30 years of experience working in the addiction field, and training in various disciplines (psychiatry, psychiatric nursing, social work, clinical psychology, or counseling) Format/modality: Individually Location/timing: Outpatient addiction clinics

	Amount: 12 weeks total. One 20-mg capsule daily in week 1; if tolerated, the dose was then increased to two 20-mg capsules for weeks 2–12. After 6 weeks, the dose could be further increased to three 20-mg capsules if patients remained depressed. Modifications: Unblinding during the first 12 weeks was permitted for severe adverse reactions or other emergencies Fidelity measurement: Adherence was monitored via self-report and counting pills at clinic visits Fidelity data: Percentage of days medication taken of 83.8 (22.0), maximum dose of 38.3 (9.4) mg, 68 percent consumed on $\geq$ 80 percent of days, and 5.2 (1.2) sessions attended
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Opaque capsule of vitamin C Providers: There were 19 research clinicians involved in the overall study—aged 34 to 61 (mean 48), 56 percent female, 78 percent New Zealand European ethnicity, 9 to 30 years of experience working in the addiction field, and training in various disciplines (psychiatry, psychiatric nursing, social work, clinical psychology, or counseling) Format/modality: Individually Location/timing: Outpatient addiction clinics Amount: 12 weeks total. One 100-mg capsule daily in week 1. If tolerated, the dose was then increased to two capsules. After 6 weeks, the dose could be further increased to three capsules if patients remained depressed. Modifications: Unblinding during the first 12 weeks was permitted for severe adverse reactions or other emergencies Fidelity measurement: Adherence was monitored via self-report and counting pills at clinic visits Fidelity data: Percentage of days medication taken of 87.9 (15.7), maximum dose of 40.0 (8.1) mg, 76 percent consumed on $\geq$80 percent of days, and 5.1 (1.4) sessions attended
Cointervention	Open-label naltrexone: 25 mg daily for week 1, increased to 50 mg for weeks 2–12 in patients without significant adverse effects. The dose could be further increased to 75 or 100 mg after 6 weeks. Actual percentage of days medication taken was 85.3 (20.7) for citalopram participants and 87.6 (16.4) for placebo participants; maximum dose was 55.5 (19.2) mg for citalopram participants and 61.3 (22.5) mg for placebo participants; 72 percent of citalopram participants and 78 percent of placebo participants consumed on $\geq$ 80 percent of days. Maximum dose was 50 mg for 79 percent of the sample, with 3 percent on a lower dose and 18 percent on a higher dose (16 percent on 100 mg). Clinical case management: All participants received manualized clinical case management delivered by experienced addiction clinicians (predominantly nursing or social work trained with postgraduate qualifications) who took a four-day training course specific to the study. Clinical case management comprised motivational enhancement, education, support for improved social functioning, encouraging significant other involvement, problem solving, medication adherence, and mood management strategies. Participants were supported to work toward abstinence or to reduce their consumption, although abstinence was promoted as the most clinically appropriate goal. Participants' progress was discussed at fortnightly telephone

	supervision. Research clinicians also maintained contact with participants' nominated significant others to corroborate history obtained from the participants. Treatment was overseen by an addiction medicine specialist or psychiatrist at each site. Participants could be prescribed benzodiazepines to treat alcohol withdrawal. Benzodiazepines were prescribed to six patients: four were low-dose, short-term use to aid detoxification in the first 3 weeks of treatment; one was for detoxification later in treatment, and one was a preexisting prescription for occasional anxiety management as required. Disulfiram, acamprosate, and antidepressants other than citalopram were not permitted during the trial.
Outcomes	Remission from depression: MADRS of less than 10 at postintervention (12 weeks postbaseline) Remission from alcohol use: Percentage of days abstinent from alcohol (Timeline Follow-Back) at postintervention (12 weeks postbaseline) Depressive symptoms: (1) MADRS and (2) Symptom Checklist 90 at postintervention (12 weeks postbaseline) Total drinking: Mean drinks per drinking day (Timeline Follow-Back) at postintervention (12 weeks postbaseline) Heavy drinking: Percentage of days heavy drinking (> 80 g of pure alcohol for men and > 60 g for women) at postintervention (12 weeks postbaseline) Withdrawal and craving symptoms: Leeds Dependence Questionnaire at postintervention (12 weeks postbaseline) Health-related quality of life: Not reported Functional status: Not reported Adverse events: Self-report adverse effect profile form at postintervention (12 weeks postbaseline)
Risks of bias	Random sequence generation: Low (computer-generated random number table) Allocation concealment: Low (administrative staff member independent of study investigators or research clinicians; allocation sequence record stored securely) Blinding of participants: Low (identical-looking opaque capsules prepaced by staff independent of investigators and treatment teams) Blinding of providers: Low (identical-looking opaque capsules prepaced by staff independent of investigators and treatment teams) Blinding of outcome assessors: Low (identical-looking opaque capsules prepaced by staff independent of investigators and treatment teams) Completeness of outcome data: Low (only ~3 percent attrition) Selective outcome reporting: Low (registration number: ACTRN12606000413527) Funder: Health Research Council of New Zealand (grant HRC 07/138)

Agyapong 2012

References	Parent study Agyapong, V. I., S. Ahern, D. M. McLoughlin, and C. K. Farren, “Supportive Text Messaging for Depression and Comorbid Alcohol Use Disorder: Single-Blind Randomised Trial,” <i>Journal of Affective Disorders</i>, Vol. 141, No. 2–3, December 10, 2012, pp. 168–176. Additional Agyapong, V., S. Ahern, and C. Farren, “Supportive Text Messaging for Depression and Comorbid Alcohol Use Disorder: Single-Blind Randomised Trial,” <i>Alcohol and Alcoholism</i>, Vol. 48, September 2013, p. i24. Agyapong, V., D. McLoughlin, and C. K. Farren, “Usefulness of Supportive Text Messages to Patients with Alcohol Use Disorder and Comorbid Depression—A Single-Blind Randomised Trial,” <i>European Psychiatry</i>, Vol. 27, 2012, p. 1. Agyapong, V., D. M. McLoughlin, and C. K. Farren, “6-month Outcomes of a Single Blind Randomised Trial of Supportive Text Messaging for Depression and Comorbid Alcohol Use Disorder,” <i>European Psychiatry</i>, Vol. 28, 2013. Agyapong, V. I., D. M. McLoughlin, and C. K. Farren, “Six-Months Outcomes of a Randomised Trial of Supportive Text Messaging for Depression and Comorbid Alcohol Use Disorder,” <i>Journal of Affective Disorders</i>, Vol. 151, No. 1, October 2013, pp. 100–104. Agyapong, V. I., J. Milnes, D. M. McLoughlin, and C. K. Farren, “Perception of Patients with Alcohol Use Disorder and Comorbid Depression About the Usefulness of Supportive Text Messages,” <i>Technology and Health Care</i>, Vol. 21, No. 1, 2013, pp. 31–39. NCT01037868, “Usefulness of Supportive Text Messages in the Treatment of Depressed Alcoholics,” 2009. As of March 18, 2019: http://clinicaltrials.gov/show/NCT01037868
Study design	Study dates: February 2010 to January 2012 Objective: To explore the effects of supportive text messages on mood and abstinence outcomes for patients with depression and comorbid AUD Randomization: Individually randomized Recruitment method: Participants were recruited during the last week of the 4-week inpatient dual-diagnosis treatment program in Saint Patrick’s University Hospital Inclusion criteria: Age over 18 years; able to provide informed consent; Mini Mental State Examination score ≥ 25; major depressive disorder according to the Structured Clinical Interview for <i>DSM-IV</i> Axis I Disorders (SCID); alcohol dependency or alcohol abuse according to the SCID; enrolled in the inpatient dual-diagnosis treatment program in Saint Patrick’s University Hospital; had a mobile phone; familiar with text messaging technology; able to read; and available for follow-up during the study period Exclusion criteria: Bipolar affective disorder, psychotic disorder, or current poly-substances dependence or abuse according to the SCID Power calculation: No power calculation—sample size based on study resources Sample size: 54 total (26/28)
Setting	Geographic location: Dublin, Ireland Intervention sites: One site—Saint Patrick’s University Hospital, a large 250-bed university teaching psychiatric hospital and the largest tertiary referral center for psychiatric inpatients in the Republic of Ireland

Participants	Age: 48.6 (10.2) Gender: 54 percent female Race/ethnicity: Not reported Other socioeconomics/demographics: 67 percent in a relationship (married or cohabiting); 15.3 (2.2) years of education (56 percent with a secondary- and 44 percent with a tertiary-level education); 63 percent employed Baseline depression: 100 percent major depressive disorder; BDI-II of 31.8 (8.6) Baseline alcohol use: 93 percent alcohol dependency, 7 percent alcohol abuse; 66.6 (25.1) drinking days in past three months, 22.8 (11.6) units of alcohol per drinking day; OCDS of 24.8 (6.2); Alcohol Abstinence Self-Efficacy Scale of 41.5 (11.7) Other baseline health: 140.6 (222.7) gamma-glutamyltransferase; 45.1 (44.0) aspartate transaminase; 94.9 (5.8) mean corpuscular volume; Mini Mental State Examination of 29.4 (0.9); GAF score of 48.4 (6.6)
Intervention 1	Category: Psychological intervention Class: SMS Name: Supportive text messaging Materials: Computer program for sending and phones for receiving text messages Procedures: Computer-delivered text messages specifically designed around multiple themes aimed at dealing with stress, maintaining good mental well-being, promoting abstinence from alcohol, dealing with cravings, promoting adherence with medication, and providing general support Providers: The messages were written by the research team and two addiction counselors, sent by a computer program, and set up and monitored by the research worker who undertook the randomization. Format/modality: Individually delivered through mobile phone technology Location/timing: Outpatient (community-based) following inpatient program Amount: Twice-daily (10:00 a.m. and 7:00 p.m.) messages for three months (180 unique messages total). Roughly 50 percent targeted improvement in mood and compliance with medication, and the other ~50 percent targeted abstinence from alcohol. Roughly 80 percent reflected lessons participants had learned on the dual-diagnosis treatment program. Tailoring/adaptation: None—on any given day, the same text messages were sent to all participants who were in receipt of the intervention. Fidelity measurement: Self-report questionnaire Fidelity data: 67 percent reported that they always read the supportive text messages, 17 percent that they often read them, 12 percent that they sometimes read them, and 4 percent that they rarely read the text messages.
Intervention 2	Category: Control intervention Class: Psychological placebo Name: Psychological placebo Materials: Computer program for sending and phones for receiving text messages Procedures: Computer-delivered text messages thanking them for participating in the study

	Providers: The messages were written by the research team, sent by a computer program, and set up and monitored by the research worker who undertook the randomization. Format/modality: Individually delivered through mobile phone technology Location/timing: Outpatient (community-based) delivery following 4-week inpatient program Amount: Once every 2 weeks for 3 months.
Cointervention	Inpatient program: Before receiving the interventions of interest, participants completed a 4-week inpatient program consisting of lectures on the definition, epidemiology, medical complications of alcohol dependence and affective disorders, interaction between mood and substances, psychotherapy, and pharmacotherapy; twice-weekly individual SP sessions; and group video sessions on managing anxiety and stress, stigma, relaxation techniques, and assertiveness. The program focused on relapse prevention and recovery planning; as part of a group discussion, each participant produced and discussed a practical plan to avoid relapse of mood and substance use. Follow-up care: Participants could attend the hospital aftercare program (35 percent), self-help groups (43 percent), or alcohol counseling (44 percent), as well as be reviewed by a general practitioner (48 percent) or psychiatrist (28 percent).
Outcomes	Remission from depression: Not reported Remission from alcohol use: (1) Total number of days abstinent (Timeline Follow-Back), (2) proportion of patients continuously abstinent from alcohol, and (3) time to first alcoholic drink at postintervention (3 months postbaseline) and 3-month follow-up (short-term) Depressive symptoms: BDI-II at postintervention (3 months postbaseline) and 3-month follow-up (short-term) Total drinking: Units of alcohol per drinking day (Timeline Follow-Back) at postintervention (3 months postbaseline) and 3-month follow-up (short-term) Heavy drinking: Not reported Withdrawal and craving symptoms: (1) OCDS and (2) Alcohol Self-Efficacy Scale at postintervention (3 months postbaseline) and 3-month follow-up (short-term) Health-related quality of life: Not reported Functional status: GAF at postintervention (3 months postbaseline) and 3-month follow-up (short-term) Adverse events: Not reported
Risks of bias	Random sequence generation: Low (random numbers generated using Excel) Allocation concealment: Unclear (participants were assigned the next available number from the randomization sequence and, depending on whether the number was even or odd, they were placed, respectively, in the intervention group or control group) Blinding of participants: High (not possible to blind because of nature of the interventions) Blinding of providers: Low (intervention delivered by computer program) Blinding of outcome assessors: High (despite being asked not to discuss their treatment with the rater, many participants inadvertently did so at the follow-up assessment; the rater correctly guessed the treatment allocation for 78 percent of participants)

	Completeness of outcome data (postintervention): Low (~7 percent overall attrition and no differential attrition) Completeness of outcome data (3-month follow-up): Low (~11 percent overall attrition and ~7 percent differential attrition) Selective outcome reporting: Low (registration number: NCT01037868) Funders: Saint Patrick’s Hospital Foundation and the Department of Psychiatry, Trinity College, Dublin
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Altamura 1990

References	Parent study Altamura, A. C., M. C. Mauri, T. Girardi, and B. Panetta, “Alcoholism and Depression: A Placebo Controlled Study with Viloxazine,” <i>International Journal of Clinical Pharmacology Research</i>, Vol. 10, No. 5, 1990, pp. 293–298.
Study design	Study dates: Not reported Objective: To assess the efficacy of viloxazine versus a placebo as an antidepressant in reducing alcohol abuse and its tolerability in chronic alcoholic patients Randomization: Individually randomized Recruitment method: Not reported Inclusion criteria: Aged 21–60 years; <i>DSM-III-R</i> diagnosis of alcohol dependence; <i>DSM-III-R</i> diagnosis of dysthymia; and 18+ on the HDRS Exclusion criteria: “Cirrhotic patients, drug addicts, and those with relevant internal and neurological conditions” Power calculation: Not reported Sample size: 30 total (15/15)
Setting	Geographic location: Italy Intervention sites: Not reported External context: Not reported
Participants	Age: 44.5 (14.4) Gender: 20 percent female Race/ethnicity: Not reported Other socioeconomics/demographics: Not reported Baseline depression: Not reported Baseline alcohol use: 10.2 (7.1) years of alcohol consumption Other baseline health: Not reported
Intervention 1	Category: Pharmacological intervention Class: NRI Name: Viloxazine Procedures: 1-week washout period before intervention delivery Format/modality: Individually delivered Location/timing: 4 weeks of hospitalization followed by 8 weeks of outpatient care

	Amount: 400 mg daily in four administrations, for 12 weeks Fidelity data: One patient (7 percent) dropped out on day 5 because of refusal of treatment
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Procedures: 1-week washout period before intervention delivery Format/modality: Individually delivered Location/timing: 4 weeks of hospitalization followed by 8 weeks of outpatient care Amount: 400 mg daily in four administrations, for 12 weeks Fidelity data: Two patients (13 percent) dropped out on days 5 and 18 because of refusal of treatment
Cointervention	Inpatient care: Patients received inpatient care during the first 4 weeks of treatment Outpatient care: Patients received outpatient care during the final 8 weeks of treatment
Outcomes	Remission from depression: Not reported Remission from alcohol use: Drinking Behavior Interview at postintervention (12 weeks post-baseline) Depressive symptoms: HDRS at postintervention (12 weeks postbaseline) Total drinking: Not reported Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Dosage Record and Treatment Emergent Symptoms Scale at postintervention (12 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double-blind randomized conditions) Blinding of providers: Low (double-blind randomized conditions) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): Low (10 percent overall attrition and ~6 percent differential attrition) Selective outcome reporting: High (outcomes reported insufficiently for use in meta-analysis) Funder: Unclear (not reported)

Altintoprak 2008

References	Parent study Altintoprak, A. E., N. Zorlu, H. Coskunol, F. Akdeniz, and G. Kitapcioglu, “Effectiveness and Tolerability of Mirtazapine and Amitriptyline in Alcoholic Patients with Co-Morbid Depressive Disorder: A Randomized, Double-Blind Study,” <i>Human Psychopharmacology: Clinical and Experimental</i>, Vol. 23, No. 4, 2008, pp. 313–319.
Study design	Study dates: Not reported Objective: To evaluate and compare the effectiveness and tolerability of mirtazapine and amitriptyline for the treatment of patients with alcohol dependence comorbid with depressive disorder Randomization: Individually randomized Recruitment method: Recruited from Ege University School of Medicine Hospital specialized addiction unit and assessed via the SCID by a trained psychiatrist Inclusion criteria: Aged 18 to 65 years; <i>DSM-IV</i> diagnostic criteria for current diagnosis of both alcohol dependence and major depressive disorder; experiencing a current depressive episode with a score 14+ on the 17-item HDRS after detoxification; absence of serious physical illness (as assessed through physical examination and routine laboratory screening); and (for female patients) protected against pregnancy Exclusion criteria: Presence of another major psychiatric disorder on the <i>DSM-IV</i> Axis I other than depressive disorder; history of a psychiatric problem other than depressive disorder; presence of organic brain diseases; past history of hypersensitivity to mirtazapine or amitriptyline; pregnant or breastfeeding; another drug dependence and abuse (excluding nicotine and caffeine); and consuming alcohol during the study Power calculation: Not reported Sample size: 44 total (24/20)
Setting	Geographic location: Izmir, Turkey Intervention sites: Ege University School of Medicine Hospital External context: Not reported
Participants	Age: 44.0 (7.9) Gender: 8 percent female Race/ethnicity: Not reported Other socioeconomics/demographics: 64 percent married, 14 percent single, 22 percent divorced; 11 percent completed primary school, 17 percent secondary school, 36 percent high school, 33 percent college Baseline depression: 42 percent prior depression episodes Baseline alcohol use: MAST of 38.9 (6.1); 12.1 (3.9) years of alcohol misuse; alcohol craving score of 164.9 (27.5) Other baseline health: Spielberger State-Trait Anxiety Inventory trait anxiety score of 45.8 (4.6) and state anxiety score of 52.5 (4.2)
Intervention 1	Category: Pharmacological intervention Class: TeCA Name: Mirtazapine Materials: Opaque capsules Procedures: Completion of alcohol detoxification treatment with diazepam

	(approximately 10–14 days) before intervention delivery Format/modality: Individually delivered Location/timing: Inpatient care Amount: Mean dose of 45.0 (17.55) mg/day over 8 weeks (started with 15 mg/day, increased to 30 mg/day at the third day, and increased to 45–60 mg/day if the severity of symptoms persisted at the end of the first week)
Intervention 2	Category: Pharmacological intervention Class: TCA Name: Amitriptyline Materials: Opaque capsules Procedures: Completion of alcohol detoxification treatment with diazepam (approximately 10–14 days) before intervention delivery Format/modality: Individually delivered Location/timing: Inpatient care Amount: Mean dose of 125.0 (20.4) mg/day over 8 weeks (started with 50 mg/day, increased to 100 mg/day at the third day, and increased to 125–150 mg/day if the severity of symptoms persisted at the end of the first week)
Cointervention	Inpatient care: Patients were made to abstain from alcohol. A standard detoxification protocol was applied: oral diazepam (20–60 mg/day), vitamins of the B complex, and diazepam (gradually tapered off, stopped after 10–14 days). Administration of other psychotropics and anticraving agents, as well as consumption of alcohol, was not permitted during the study.
Outcomes	Remission from depression: Not reported Remission from alcohol use: MAST at postintervention (8 weeks postbaseline) Depressive symptoms: Not reported Total drinking: Not reported Heavy drinking: Not reported Withdrawal and craving symptoms: Alcohol craving questionnaire at postintervention (8 weeks postbaseline) Health-related quality of life: Not reported Functional status: Not reported Adverse events: Udvalg for Kliniske Undersogelser Side Effect Rating Scale at postintervention (8 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double-blind randomized conditions) Blinding of providers: Low (double-blind randomized conditions) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): Unclear (20 percent overall attrition and insufficient information to determine reasons for differential attrition) Selective outcome reporting: High (depressive symptoms and adverse events reported insufficiently for use in meta-analysis)

	Funder: Unclear (not reported)
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Butterworth 1971

References	Parent study Butterworth, A. T., "Depression Associated with Alcohol Withdrawal: Imipramine Therapy Compared with Placebo," <i>Quarterly Journal of Studies on Alcohol</i> , Vol. 32, No. 2, June 1971, pp. 343–348.
Study design	Study dates: Not reported Objective: To evaluate the effect of imipramine on depression Randomization: Individually randomized Recruitment method: Recruited alcoholic patients undergoing detoxification in the acute treatment ward of the East Louisiana State Hospital Inclusion criteria: Male; alcoholic patient undergoing detoxification; depression according to either investigators' clinical impression or the LRDR as modified by Rockliff (score of 10+) Exclusion criteria: Hepatic disease; organic brain damage; psychosis Power calculation: Not reported Sample size: 40 total (20/20)
Setting	Geographic location: Louisiana, United States Intervention sites: East Louisiana State Hospital External context: Not reported
Participants	Age: 23 to 60 Gender: 0 percent female Race/ethnicity: 83 percent white Other socioeconomics/demographics: "All were from a low socioeconomic group bordering on the Skid Row level" Baseline depression: "Moderately to severely depressed according to our clinical impression, and with Lehmann-Rockliff scores of 12 or higher" Baseline alcohol use: 60 percent had been alcoholics for 1–5 years, 40 percent for 10+ years; "all had been admitted voluntarily. Many had been hospitalized repeatedly for detoxification, in some instances as many as 30 times." Other baseline health: "One patient was diagnosed as a passive-aggressive personality, passive-dependent type, and another as an inadequate personality. Of the nonpsychiatric disorders, four patients had essential hypertension, and one of these also had mild diabetes."

Intervention 1	Category: Pharmacological intervention Class: TCA Name: Imipramine Materials: Liquid form of imipramine pamoate oral concentrate. Medications (dispensed by dropper) were mixed with a small amount of orange juice. Procedures: Completion of inpatient detoxification before intervention delivery Format/modality: Individually delivered orally Location/timing: Inpatient care (hospitalized patients) once transferred to the Alcoholic Treatment Service following detoxification Amount: Provided for 3 weeks. Each cubic centimeter contained 25 mg of imipramine hydrochloride activity. Dosage began with 1 cc three times a day (75 mg/day), increased to a maximum of 8 cc daily according to individual requirements, but reduced if indicated by side effects. Fidelity data: The two most frequently administered maintenance doses were 3 cc (75 mg) and 6 cc (150 mg) daily
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Identical-appearing liquid placebo. Medications (dispensed by dropper) were mixed with a small amount of orange juice. Procedures: Completion of inpatient detoxification before intervention delivery Format/modality: Individually delivered orally Location/timing: Inpatient care (hospitalized patients) once transferred to the Alcoholic Treatment Service following detoxification Amount: Provided for 3 weeks. Dosage began with 1 cc three times a day (75 mg/day), increased to a maximum of 8 cc daily according to individual requirements, but reduced if indicated by side effects Fidelity data: The most common maintenance dosage of placebo was 3 cc daily
Cointervention	Inpatient detoxification: Anticonvulsant, sedative, and a tranquilizing agent (if required) for detoxification. Ninety-five percent received the following medications for 3–4 days following their admission to the acute treatment ward: 1.5 g of diphenylhydantoin (Dilantin) three times a day; 0.5 g of phenobarbital three times a day; 100 mg of hydroxyzine hydrochloride (Vistaril) daily. Forty percent also received 500 mg of chloral hydrate daily. Twenty percent received antihistamines and decongestants for upper respiratory infections. Ten percent received analgesics for headaches. Three percent received antispasmodic for gastric upset. Three percent received an antihypertensive drug for moderate hypertension. Inpatient care: Patients were transferred to the Alcoholic Treatment Service for additional care after their acute symptoms had subsided and their general physical state had improved. Care included educational and rehabilitative measures; no psychotherapy was given.
Outcomes	Remission from depression: Not reported Remission from alcohol use: Not reported Depressive symptoms: LRDR at postintervention (3 weeks postbaseline)

	Total drinking: Not reported Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Global response at postintervention (3 weeks postbaseline) Adverse events: Recorded daily by the reviewing physician at postintervention (3 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double-blind randomized conditions) Blinding of providers: Low (double-blind randomized conditions) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): Low (~3 percent overall attrition and 5 percent differential attrition) Selective outcome reporting: Unclear (no trial registration) Funder: Unclear (not reported)

Cocchi 1997

References	Parent study Cocchi, R., "Paroxetine vs Amitriptyline in Depressed Alcoholics," <i>European Neuropsychopharmacology</i> , Vol. 7, Supp. 2, 1997, p. S254.
Study design	Study dates: Not reported Objective: To evaluate the antidepressant activity of paroxetine in treating depressed alcoholics under detoxification/rehabilitation, as compared with amitriptyline Randomization: Individually randomized Recruitment method: Not reported Inclusion criteria: <i>DSM-IV</i> diagnosis 10.24 Exclusion criteria: Not reported Power calculation: Not reported Sample size: 122 total (61/61)
Setting	Geographic location: Senigallia, Italy Intervention sites: Alcohol Unit, casa di Cura Villa Silvia per malattie nervose e mentali External context: Not reported
Participants	Age: 42.2 (11.0) Gender: 22 percent female Race/ethnicity: Not reported Other socioeconomics/demographics: Not reported Baseline depression: "Depressed"; Zung's Self-Rating Depression Scale of 66.1 (8.09)

	Baseline alcohol use: “Alcoholic” Other baseline health: Not reported
Intervention 1	Category: Pharmacological intervention Class: SSRI Name: Paroxetine Format/modality: Individually delivered orally Location/timing: Inpatient care Amount: 20 mg per day for 3–4 weeks Fidelity data: Treatment lasted an average of 23 days
Intervention 2	Category: Pharmacological intervention Class: TCA Name: Amitriptyline Format/modality: Individually delivered orally Location/timing: Inpatient care Amount: 25 mg per day for 3–4 weeks Fidelity data: Treatment lasted an average of 23 days
Cointervention	Inpatient detoxification: Detoxifying therapy
Outcomes	Remission from depression: No longer depressed (according to Zung’s Self-Rating Depression Scale) at postintervention (3–4 weeks postbaseline) Remission from alcohol use: Not reported Depressive symptoms: Zung’s Self-Rating Depression Scale at postintervention (3–4 weeks postbaseline) Total drinking: Not reported Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Not reported
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Unclear (not reported) Blinding of providers: Unclear (not reported) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): Low (no attrition) Selective outcome reporting: Unclear (no trial registration) Funder: Not reported

Cornelius 1997

References	Parent study Cornelius, J. R., I. M. Salloum, J. G. Ehler, P. J. Jarrett, M. D. Cornelius, J. M. Perel, M. E. Thase, and A. Black, "Fluoxetine in Depressed Alcoholics: A Double-Blind, Placebo-Controlled Trial," <i>Archives of General Psychiatry</i>, Vol. 54, No. 8, August 1997, pp. 700–705. Additional Cornelius, J. R., K. A. Perkins, I. M. Salloum, M. E. Thase, and H. B. Moss, "Fluoxetine Versus Placebo to Decrease the Smoking of Depressed Alcoholic Patients," <i>Journal of Clinical Psychopharmacology</i>, Vol. 19, No. 2, April 1999, pp. 183–184. Cornelius, J. R., I. M. Salloum, M. D. Cornelius, J. M. Perel, J. G. Ehler, P. J. Jarrett, R. L. Levin, A. Black, and J. J. Mann, "Preliminary Report: Double-Blind, Placebo-Controlled Study of Fluoxetine in Depressed Alcoholics," <i>Psychopharmacology Bulletin</i>, Vol. 31, No. 2, 1995, pp. 297–303. Cornelius, J. R., I. M. Salloum, J. G. Ehler, P. J. Jarrett, M. D. Cornelius, A. Black, J. M. Perel, and M. E. Thase, "Double-Blind Fluoxetine in Depressed Alcoholic Smokers," <i>Psychopharmacology Bulletin</i>, Vol. 33, No. 1, 1997, pp. 165–170. Cornelius, J. R., I. M. Salloum, J. G. Ehler, P. J. Jarrett, J. M. Perel, and M. E. Thase, "Fluoxetine vs Placebo in Depressed Alcoholic Smokers," <i>Psychopharmacology Bulletin</i>, Vol. 32, No. 3, 1996. Cornelius, J. R., I. M. Salloum, R. F. Haskett, D. C. Daley, M. D. Cornelius, M. E. Thase, and J. M. Perel, "Fluoxetine Versus Placebo in Depressed Alcoholics: A 1-Year Follow-Up Study," <i>Addictive Behaviors</i>, Vol. 25, No. 2, March–April 2000, pp. 307–310. Cornelius, J. R., I. M. Salloum, R. F. Haskett, J. G. Ehler, P. J. Jarrett, M. E. Thase, and J. M. Perel, "Fluoxetine Versus Placebo for the Marijuana Use of Depressed Alcoholics," <i>Addictive Behaviors</i>, Vol. 24, No. 1, January–February 1999, pp. 111–114. Cornelius, J. R., I. M. Salloum, M. E. Thase, R. F. Haskett, D. C. Daley, A. Jones-Barlock, C. Upsher, and J. M. Perel, "Fluoxetine Versus Placebo in Depressed Alcoholic Cocaine Abusers," <i>Psychopharmacology Bulletin</i>, Vol. 34, No. 1, 1998, pp. 117–121.
Study design	Study dates: Started in May 1992 Objective: To evaluate the efficacy of a selective serotonergic medication (fluoxetine) for the treatment of depressed alcoholics Randomization: Individually randomized, stratified for sex and race Recruitment method: All patients were recruited from consecutive admissions on the inpatient services of this hospital Inclusion criteria: Aged 18 to 65 years; following a 2–3 day detoxification with minor tranquilizers and a subsequent 1-week washout period: (1) <i>DSM-III-R</i> diagnosis of major depressive disorder (primary diagnosis) and (2) <i>DSM-III-R</i> diagnosis of alcohol dependence Exclusion criteria: Diagnosis of bipolar disorder, schizoaffective disorder, schizophrenia, or nonalcohol substance dependence; hyperthyroidism or hypothyroidism; clinically significant liver disease (liver function tests 3x normal or higher); notable cardiac or renal impairment; pregnancy; mental retardation; clinically evident cognitive impairment; received antipsychotic or antidepressant medication in the month before admission to the hospital

	Power calculation: None reported Sample size: 51 total (25/26)
Setting	Geographic location: Pittsburgh, Pennsylvania, United States Intervention sites: Western Psychiatric Institute and Clinic of the University of Pittsburgh (a large, comprehensive, urban university psychiatric hospital) External context: Not reported
Participants	Age: 34.8 (10.2) Gender: 49 percent female Race/ethnicity: 47 percent white; 53 percent black Other socioeconomics/demographics: 12 percent married; 31 percent employed Baseline depression: 6.8 (1.1) of the nine <i>DSM-III-R</i> diagnostic criteria for major depression; 24-item HDRS of 33.1 at presentation and 18.5 (8.1) after detoxification and washout; BDI of 27.2 (12.4) at presentation and 16.0 (10.4) after detoxification and washout Baseline alcohol use: 5.7 (1.7) of the nine <i>DSM-III-R</i> diagnostic criteria for alcohol dependence; 49.8 (29.0) days drinking in the past 90 days; 36.0 (27.0) days drinking to drunkenness in past 90 days Other baseline health: 39 percent suicide attempt in current episode, 35 percent suicide attempt in the week before admission to hospital, 61 percent lifetime suicide attempt, 9 percent suicidal ideations in the week before hospitalization; 51.4 (7.6) Global Assessment Scale after detoxification and washout
Intervention 1	Category: Pharmacological intervention Class: SSRI Name: Fluoxetine Procedures: Delivered after detoxification and a subsequent 1-week medication-free washout period Format/modality: Individually delivered Location/timing: Inpatient for first 2 weeks and outpatient for the remaining 10 weeks Amount: 12 weeks. Participants were initially given one capsule (20 mg), which could be increased to two capsules after 2 weeks. Fidelity measurement: Verification of compliance with medication was assessed by weekly pill counts and by plasma levels of fluoxetine and norfluoxetine at weeks 2, 4, and 12 Fidelity data: Maximum daily dose of 1.25 (0.45) capsules per day. Substantial blood levels of fluoxetine were observed in more than 99 percent of blood specimens of patients.
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Procedures: Delivered after detoxification and a subsequent 1-week medication-free washout period Format/modality: Individually delivered

	Location/timing: Inpatient for first 2 weeks and outpatient for the remaining 10 weeks Amount: 12 weeks. Participants were initially given one capsule, which could be increased to two capsules after 2 weeks. Fidelity measurement: Verification of compliance with medication was assessed by weekly pill counts Fidelity data: Maximum daily dose of 1.25 (0.45) capsules per day
Cointervention	Dual-diagnosis facility (acute treatment phase): Weekly SP sessions and weekly meetings with an attending psychiatrist with expertise in evaluating and treating dual-disorder patients. Attendance at Alcoholics Anonymous also was encouraged. Attended 15.0 (18.4) Alcoholics Anonymous sessions and 9.4 (3.0) psychotherapy sessions on average. Long-term community care: Following completion of the acute phase of the study, patients were referred back to their respective catchment areas for long-term naturalistic treatment by physicians unrelated to this study. The patients did not receive protocol medication during this time but rather received open-label medication from their local psychiatrists. Eleven of the 15 patients (73 percent) of those randomized to fluoxetine during the acute phase of the study continued on fluoxetine in the subsequent 9 months, while 12 of the 16 patients (75 percent) of those randomized to placebo during the acute phase of the study continued off antidepressant medication in the subsequent 9 months (though 4 patients had been started on SSRI antidepressants).
Outcomes	Remission from depression: Not reported Remission from alcohol use: (1) Number of weeks until first drink and (2) number of patients abstinent throughout entire trial at postintervention (12 weeks postbaseline); (3) number of days any alcohol and (4) number of days intoxicated at long-term follow-up (9 months postbaseline) Depressive symptoms: (1) HDRS-24 and (2) BDI at postintervention (12 weeks postbaseline) and long-term follow-up (9 months postbaseline) Total drinking: (1) Cumulative number of drinks, (2) cumulative number of drinking days, and (3) drinks per drinking day at postintervention (12 weeks postbaseline); (4) number of drinks in the last week at long-term follow-up (9 months postbaseline) Heavy drinking: (1) Cumulative number of days of heavy drinking and (2) number of weeks until first heavy drinking at postintervention (12 weeks postbaseline) Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Global Assessment Scale at postintervention (12 weeks postbaseline) and long-term follow-up (9 months postbaseline) Adverse events: Side effects at postintervention (12 weeks postbaseline) and long-term follow-up (9 months postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Low (identical-looking opaque capsules) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Low (blind to assignment) Completeness of outcome data (postintervention): Low (0 percent attrition)

	Completeness of outcome data (long-term follow-up): High (40 percent overall attrition) Selective outcome reporting: Unclear (no trial registration) Funders: Grants AA09127 and AA10523 from the National Institute on Alcohol Abuse and Alcoholism and grant MH30915 from the Mental Health Clinical Research Center, Rockville, Maryland
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Cornelius 2016

References	Parent study Cornelius, J. R., T. Chung, A. B. Douaihy, L. Kirisci, J. Glance, J. Kmiec, D. Fitzgerald, M. A. Wesesky, and I. Salloum, "Mirtazapine in Comorbid Major Depression and an Alcohol Use Disorder: A Double-Blind Placebo-Controlled Pilot Trial," <i>Psychiatry Research</i>, Vol. 242, August 30, 2016, pp. 326–330. Additional Cornelius, J., "Two Mirtazapine Pilot Trials in Young and in Older Depressed Alcoholics," <i>American Journal on Addictions</i>, Vol. 25, No. 4, June 2016, pp. 313–314. Cornelius, J., T. Chung, A. Douaihy, and J. Glance, "Mirtazapine Pilot Trial in Youthful MDD/AUD Subjects," <i>American Journal on Addictions</i>, Vol. 26, No. 3, 2017, pp. 250–251. Cornelius, J. R., T. A. Chung, A. Douaihy, J. Glance, J. Kmiec, M. A. Wesesky, D. Fitzgerald, and I. Salloum, "Double-Blind Mirtazapine Pilot Trial in AUD/MDD," <i>Alcoholism: Clinical and Experimental Research</i>, Vol. 40, 2016, p. 233A. Cornelius, J., A. Douaihy, and D. Daley, "Two Mirtazapine Pilot Trials in Depressed Alcoholics," <i>American Journal on Addictions</i>, Vol. 24, No. 1, January 2015, pp. 56–57. NCT02185131, "Double-Blind Pilot Trial of Mirtazapine for the Treatment of Co-Occurring AD/MDD," 2014. As of March 18, 2019: https://clinicaltrials.gov/show/NCT02185131 NCT02646449, "Treatment of Young Adults with Comorbid AUD/MDD: A Pilot Medication Trial," 2016. As of March 18, 2019: https://clinicaltrials.gov/show/NCT02646449
Study design	Study dates: June 2014 to July 2016 Objective: To evaluate the efficacy of mirtazapine for treating both the depressive symptoms and the level of alcohol consumption of subjects with comorbid major depressive disorder and an AUD Randomization: Individually randomized Recruitment method: Not reported Inclusion criteria: Aged 18 to 65 years; meet criteria for both current <i>DSM-IV</i> major depressive disorder and an AUD; be eligible for outpatient treatment Exclusion criteria: Age less than 18 or over 65; presence of psychotic symptoms or a diagnosis involving psychosis; receiving psychotropic medication in the prior month; current <i>DSM</i> diagnosis of dependence or abuse on substances other than alcohol, cannabis, nicotine, or caffeine; current significant medical or neurological condition; suicidal ideation in the last 3 months, or lifetime suicidal attempt; positive pregnancy test or breastfeeding; inability or unwillingness to use contraceptive methods; inability to

	read or understand study forms; pending incarceration; current participation in another research study Power calculation: “Recruitment for this pilot study was discontinued when time and money for the study were exhausted” Sample size: 14 total (7/7)
Setting	Geographic location: Pittsburgh, Pennsylvania, United States Intervention sites: Western Psychiatric Institute and Clinic of the University of Pittsburgh (a large, comprehensive, urban university psychiatric hospital) External context: Not reported
Participants	Age: 41.3 (8.8) Gender: 29 percent female Race/ethnicity: 50 percent white Other socioeconomic/demographics: Not reported Baseline depression: BDI of 26.9 (9.6) Baseline alcohol use: 6.6 (2.0) drinks per drinking day; 33.6 (13.6) drinks per week; 5.2 (1.9) days of alcohol use per week; 3.5 (1.6) heavy drinking days per week; OCDS of 24.2 (7.4) Other baseline health: Not reported
Intervention 1	Category: Pharmacological intervention Class: TeCA Name: Mirtazapine Materials: Identical-looking opaque capsules Format/modality: Individually delivered Location/timing: Outpatient Amount: Capsules taken once per day at bedtime for 12 weeks—15 mg of mirtazapine for the first 2 weeks of the trial and 30 mg for the remaining 10 weeks
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Identical-looking opaque capsules Format/modality: Individually delivered Location/timing: Outpatient Amount: Capsules taken once per day at bedtime for 12 weeks
Cointervention	Motivational enhancement therapy
Outcomes	Remission from depression: Not reported Remission from alcohol use: Not reported Depressive symptoms: BDI at postintervention (12 weeks postbaseline) Total drinking: (1) Drinks per week, (2) drinks per drinking day, and (3) days of alcohol use per week at postintervention (12 weeks postbaseline)

	Heavy drinking: Heavy drinking days per week at postintervention (12 weeks postbaseline) Withdrawal and craving symptoms: OCDS at postintervention (12 weeks postbaseline) Health-related quality of life: Not reported Functional status: Not reported Adverse events: SAFTEE-Systematic Inquiry at postintervention (12 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Low (identical-looking opaque capsules) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): Low (0 percent attrition) Selective outcome reporting: Low (NCT02185131) Funders: National Institute on Alcohol Abuse and Alcoholism (R21 AA022123, R21 AA022863, R01 AA013370, R01 AA015173, K24 AA15320) and the National Institute on Drug Abuse (R01 DA019142, P50 DA05605, K02 DA017822)

Golik-Gruber 2003

References	Parent study Golik-Gruber, V., D. Breitenfeld, E. N. Gruber, and D. Karlović, “Sulpiride Psychopharmacotherapy in Patients with Alcohol Addiction and Depression Comorbidity,” <i>Acta Clinica Croatica</i>, Vol. 42, No. 1, 2003, pp. 29–33.
Study design	Study dates: Not reported Objective: To confirm the efficacy of sulpiride in the early treatment of patients with comorbidity of alcohol addiction and major depressive disorders Randomization: Individually randomized Recruitment method: Recruited from the daily treatment program for alcohol addiction at the University Department of Psychiatry, Sestre milosrdnice University Hospital, Zagreb Inclusion criteria: None reported Exclusion criteria: Suicidal risk; serious hepatic, renal, or cardiac disease; mental retardation; not taking any psychoactive drugs before the study Power calculation: Not reported Sample size: 40 total (20/20)
Setting	Geographic location: Zagreb, Croatia Intervention sites: Daily treatment program for alcohol addiction at the University Department of Psychiatry, Sestre milosrdnice University Hospital, Zagreb External context: Not reported
Participants	Age: Not reported Gender: 0 percent female

	Race/ethnicity: Not reported Other socioeconomics/demographics: Not reported Baseline depression: “Mild to moderate depression symptoms” Baseline alcohol use: <i>DSM-IV</i> criteria for alcohol addiction Other baseline health: Not reported
Intervention 1	Category: Pharmacological intervention Class: AAP Name: Sulpiride Format/modality: Individually delivered Location/timing: Inpatient hospital addiction program Amount: Three 50-mg capsules daily for 6 weeks
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Vitamins Format/modality: Individually delivered Location/timing: Inpatient hospital addiction program Amount: Three vitamins daily for 6 weeks
Cointervention	Daily addiction program: All patients received psychotherapy in both individual and group sessions.
Outcomes	Remission from depression: Presence of depressive disorder according to the BDI at postintervention (3 weeks postbaseline) Remission from alcohol use: Not reported Depressive symptoms: Not reported Total drinking: Not reported Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Not reported
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: High (open study) Blinding of providers: High (open study) Blinding of outcome assessors: High (open study) Completeness of outcome data (postintervention): Low (no attrition) Selective outcome reporting: Unclear (no trial registration) Funder: Unclear (not reported)

Gual 2003

References	Parent study Gual, A., M. Balcells, M. Torres, M. Madrigal, T. Diez, and L. Serrano, "Sertraline for the Prevention of Relapse in Detoxicated Alcohol Dependent Patients with a Comorbid Depressive Disorder: A Randomized Controlled Trial," <i>Alcohol and Alcoholism</i>, Vol. 38, No. 6, November–December 2003, pp. 619–625.
Study design	Study dates: February 1998 to June 2001 Objective: To evaluate (1) the efficacy of sertraline at achieving stable abstinence in recently detoxified alcohol-dependent patients with major depression or dysthymia, (2) the efficacy of this drug at ameliorating depressive symptoms and quality of life in these patients, and (3) the tolerability and safety of sertraline in such patients Randomization: Individually randomized Recruitment method: Recruited from outpatients attending the Alcohol Unit therapeutic program who recently underwent an acute alcohol detoxification Inclusion criteria: At least 18 years old; <i>DSM-IV</i> and ICD-10 criteria for alcohol dependence; <i>DSM-IV</i> and ICD-10 criteria for major depression, dysthymia, or both; remained abstinent for at least 2 weeks following detoxification; negative drug and alcohol urine screen at inclusion; for female patients of child-bearing age, a negative pregnancy test at inclusion, and use of an effective and safe contraceptive method from 3 months preceding and throughout the study Exclusion criteria: Women who were pregnant, breastfeeding, or of childbearing potential and were not using reliable contraceptive methods or who wished to become pregnant during the study or within a month after the study; patients with a primary psychiatric disorder apart from alcohol dependence and depressive symptoms; patients with moderate or severe liver disease including active cirrhosis or acute hepatitis; patients showing a high suicide risk; patients whom the investigator believed would require therapy with additional psychotropic drugs, electroconvulsive therapy, or intensive psychotherapy during the study; patients with a history of convulsive disorders, cerebral organic disease, or laxative misuse within the 6 months before receiving the test drug; patients who had received therapy with depot neuroleptics during the 6 months before their inclusion in the study; patients requiring therapy with reserpine, methyl dopa, guanetidine, or clonidine, or who might require general anaesthesia or drugs that interact with sertraline or any serotonergic drug during the study; patients with a history of failure on sertraline or any other SSRI, either alone or combined with another therapy, for treating the current depressive episode; patients in whom sertraline therapy was contraindicated; patients with the following conditions: severe allergies or multiple adverse reactions to drugs, unstable thyroid disease, or severe organic diseases; patients who had suffered severe infections or major surgery 1 month before their inclusion in the study; patients considered insufficiently motivated for the therapy or with other emotional or intellectual problems that might limit the patient's ability to comply with the protocol requirements; patients who had been involved in other clinical studies within the 6 months before the onset of this study or who were involved in such studies simultaneously with this study; patients who had not undergone a sufficient washout period since the administration of previous psychotropic medications; patients who insisted on giving blood while participating in the study and/or 1 month after the end of the study; patients with a prothrombin time out of normal range Power calculation: Determined a priori based in previous clinical trials of acamprosate in alcohol dependence with a similar design, assuming an α risk of 0.05, a β risk of 0.20, and an anticipated intergroup difference of at least 20 percent in cumulative abstinence duration proportion. These provided an anticipated sample size of 50 patients per group. Sample size: 83 total (44/39)

Setting	Geographic location: Barcelona, Spain Intervention sites: Alcohol Unit of the Hospital Clínico y Provincial External context: Not reported
Participants	Age: 46.7 (9.5) Gender: 53 percent female Race/ethnicity: Not reported Other socioeconomics/demographics: Not reported Baseline depression: 3.3 (4.8) years of depression; 22.6 (7.4) MADRS score; 13.4 (4.8) HDRS score Baseline alcohol use: 16.0 (8.8) years of alcoholism Other baseline health: 47.8 (10.3) SF-36 Physical Component Score; 39.2 (11.7) SF-36 Mental Component Score
Intervention 1	Category: Pharmacological intervention Class: SSRI Name: Sertraline Format/modality: Individually delivered Location/timing: Outpatient care Amount: 50–150 mg/day for 24 weeks. The sertraline dose was initially 50 mg/day and could be titrated up to 150 mg/day over the first 8 weeks at the investigator's discretion. Average of 141.0 (9.7) days on treatment. Fidelity data: 55 percent completed treatment
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Matching packets Format/modality: Individually delivered Location/timing: Outpatient care Amount: Delivered for 24 weeks; average of 143.8 (10.3) days on treatment Fidelity data: 55 percent completed treatment
Cointervention	An outpatient alcohol unit therapeutic program
Outcomes	Remission from depression: Responder rate (reduction of at least 50 percent with respect to baseline in scores on the MADRS) at postintervention (24 weeks postbaseline) Remission from alcohol use: (1) Rate of relapse (intake of an average of 50 g alcohol per day for at least 3 days per week or the intake of 100 g alcohol in a single dose), (2) rate of treatment failure (occurrence of at least three relapses as just defined during the course of the study), (3) cumulative abstinence duration (number of days of abstinence recorded during the study), and (4) time to first relapse at postintervention (24 weeks postbaseline) Depressive symptoms: (1) MADRS and (2) HDRS at postintervention (24 weeks postbaseline) Total drinking: Not reported

	Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: SF-36 (1) Physical Component Score and (2) Mental Component Score at postintervention (24 weeks postbaseline) Functional status: SF-36 (1) physical functioning and (2) social functioning at postintervention (24 weeks postbaseline) Adverse events: Spontaneously reported by the patient or observed by the investigator during study visits and classified according to the World Health Organization Adverse Reactions Terminology system at postintervention (24 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): High (45 percent attrition) Selective outcome reporting: High (depressive symptoms, health-related quality of life, and functional status reported insufficiently for meta-analysis) Funder: Unclear (not reported)

Han 2013

References	Parent study Han, D. H., S. M. Kim, J. E. Choi, K. J. Min, and P. F. Renshaw, "Adjunctive Aripiprazole Therapy with Escitalopram in Patients with Co-Morbid Major Depressive Disorder and Alcohol Dependence: Clinical and Neuroimaging Evidence," <i>Journal of Psychopharmacology</i>, Vol. 27, No. 3, 2013, pp. 282–291.
Study design	Study dates: Not reported Objective: To evaluate the augmentation of escitalopram with aripiprazole on depressive symptoms as well as craving for alcohol in patients with alcohol dependence and major depressive disorder Randomization: Individually randomized using a 1:1 ratio. Recruitment method: Recruited patients who were evaluated by the Department of Psychiatry of Chung Ang University Medical Center and Eunpyeong Hospital for comorbid alcohol problems and major depressive disorder Inclusion criteria: Psychiatrist diagnosis of patients as having comorbid <i>DSM-IV</i> major depressive disorder and alcohol dependence, based on the Structured Clinical Interview before and after detoxification; first onset comorbid major depression and alcohol dependence or recurrent psychotropic medication naive patients with major depressive disorder and alcohol dependence; MAST score >19 for alcohol problems; BDI >19; impaired behaviors or distress due to maladaptive patterns that are consistent with <i>DSM-IV</i> criteria for major depressive disorder. Exclusion criteria: History or current episode of other Axis I psychiatric diseases; other substance abuse history (except for tobacco); medical illness; claustrophobia Power calculation: None reported Sample size: 35 total (17/18)

Setting	Geographic location: Seoul, Republic of Korea Intervention sites: Department of Psychiatry of (1) Chung Ang University Medical Center and (2) Eunpyeong Hospital External context: Not reported
Participants	Age: 39.6 (7.6) Gender: 34 percent female Race/ethnicity: Not reported Other socioeconomics/demographics: 11.6 (2.4) years of education Baseline depression: BDI of 30.7 (11.5) Baseline alcohol use: MAST of 26.4 (12.8); Korean Alcohol Urge Questionnaire of 22.4 (7.6) Other baseline health: 46 percent smokers
Intervention 1	Category: Pharmacological intervention Class: AAP and SSRI Name: Aripiprazole and escitalopram Format/modality: Individually delivered Location/timing: Inpatient delivery following a detoxification period Amount: Flexible daily dose of aripiprazole (5–15 mg Abilify, Otsuka, Korea) and escitalopram (10–20 mg Lexapro, Lundbeck, Korea) for 6 weeks. Aripiprazole was started at 5 mg/day during the first week and then increased to 15 mg/day thereafter. Escitalopram was started at 10 mg/day during the first week and then increased to 20 mg/day thereafter. Fidelity data: Average of 7.0 (3.5) mg aripiprazole and 13.2 (6.1) mg escitalopram per day
Intervention 2	Category: Pharmacological intervention Class: SSRI Name: Escitalopram Format/modality: Individually delivered Location/timing: Inpatient delivery following a detoxification period. Amount: Flexible daily dose of escitalopram (10–20 mg Lexapro, Lundbeck, Korea) for 6 weeks. Escitalopram was started at 10 mg/day during the first week and then increased to 20 mg/day thereafter. Fidelity data: 14.0 (7.2) mg escitalopram per day
Cointervention	Detoxification: Over a period of 5–10 days, patients were detoxified with lorazepam (1–4 mg/day), thiamine (100 mg/day orally) and multiple vitamin (containing folate) injection according to validated protocols. After this detoxification period, patients started treatment with either aripiprazole and escitalopram or escitalopram only. Inpatient: Three-session education regarding the nature and health consequences of alcohol dependence (conducted by a doctor and social worker) and three-session individual SP was provided to all patients during the study period. Lorazepam (average 1.5 mg per day), zolpidem, and propranolol as necessary were used for managing tremor, anxiety, and insomnia. Anticraving medications for alcohol, such as acamprosate and naltrexone, were not used.

Outcomes	Remission from depression: Reduction in follow-up BDI scores to less than 50 percent of initial BDI scores at postintervention (6 weeks postbaseline) Remission from alcohol use: Relapse into alcohol dependence (either five or more standard drinks [50 mg/day] on a drinking occasion or drinking on more than 5 days per week) at postintervention (6 weeks postbaseline) Depressive symptoms: BDI at postintervention (6 weeks postbaseline) Total drinking: Not reported Heavy drinking: Not reported Withdrawal and craving symptoms: Korean Alcohol Urge Questionnaire at postintervention (6 weeks postbaseline) Health-related quality of life: Not reported Functional status: CGI-severity at postintervention (6 weeks postbaseline) Adverse events: Dropping out because of adverse events at postintervention (6 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): • Adverse events: Low (0 percent attrition) • Remission from depression, remission from alcohol use, depressive symptoms, and withdrawal and craving symptoms: High (14 percent overall attrition and 18 percent differential attrition) Selective outcome reporting: Unclear (no trial registration) Funder: Korea Otsuka Pharmaceuticals (K-O-2010-3)

Hernandez-Avila 2004

References	Parent study Hernandez-Avila, C. A., V. Modesto-Lowe, R. Feinn, and H. R. Kranzler, "Nefazodone Treatment of Comorbid Alcohol Dependence and Major Depression," <i>Alcoholism: Clinical and Experimental Research</i>, Vol. 28, No. 3, March 2004, pp. 433–440.
Study design	Study dates: Not reported Objective: To compare nefazodone, in conjunction with SP, with placebo in reducing mood, anxiety, and insomnia symptoms and alcohol consumption among alcohol-dependent subjects with comorbid major depression Randomization: Individually randomized Recruitment method: Recruited by newspaper advertisement and referrals from area clinicians Inclusion criteria: 21 to 65 years of age; able to speak and read English; <i>DSM-IV</i> criteria for major depression for at least 1 week after discontinuation of heavy drinking and before randomization; scored 17+ on the 17-item HDRS with a score of 1+ on item

	1: criteria for a current <i>DSM-IV</i> diagnosis of alcohol dependence; drank an average of 18+ drinks per week for men or 14+ drinks per week for women; heavy drinking (5+ drinks for men and 4+ drinks for women) on at least 1 day per week during the month preceding screening Exclusion criteria: History of major medical or psychiatric problems other than major depression or an anxiety disorder; had clinically significant baseline laboratory abnormalities or a positive pregnancy test; met current <i>DSM-IV</i> criteria for drug dependence other than for alcohol or nicotine; had a positive urine drug screen; were being treated with disulfiram or naltrexone; were deemed to be a serious suicide risk; were being treated with any psychotropic drug Power calculation: None reported Sample size: 41 total (21/20)
Setting	Geographic location: Hartford, Connecticut, United States Intervention sites: University of Connecticut Health Center External context: Not reported
Participants	Age: 42.9 (8.6) Gender: 51 percent female Race/ethnicity: Not reported Other socioeconomic/demographics: 34 percent married; 71 percent employed; 20 percent income of <\$30,000, 37 percent of \$30,000–\$60,000, 43 percent of \$60,000+; 46 percent completed high school or less, 34 percent college, 20 percent graduate school Baseline depression: HDRS of 16.8 (2.1) Baseline alcohol use: 2.6 (1.8) weekly drinking days; 7.4 (5.8) drinks per drinking day; 8.0 (6.8) weekly drinks; 0.1 (0.6) weekly heavy drinking days (for women, 4+ drinks in a day; for men, 5+ drinks in a day) Other baseline health: 32 percent antisocial personality disorder; 29 percent any anxiety disorder (12 percent social phobia, 12 percent panic disorder, 10 percent generalized anxiety disorder, 5 percent obsessive-compulsive disorder, 2 percent simple phobia); 24 percent dysthymic disorder; Spielberger State Anxiety Inventory of 49.5 (9.7)
Intervention 1	Category: Pharmacological intervention Class: SARI Name: Nefazodone Procedures: Delivered after a 1-week placebo lead-in period. Medication was dispensed at each visit (weekly for the first 5 weeks and then every other week). Format/modality: Individually delivered Location/timing: Outpatient delivery Amount: 200–600 mg/day for 10 weeks. Initiated at a dose of 100 mg twice daily and was then titrated up to a maximum dose of 300 mg twice daily. Fidelity measurement: Compliance was monitored via tablet counts Fidelity data: 62 percent completed treatment. Patients took an average of 4.6 (1.6) tablets a day for 8.3 (4.0) weeks.

Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Procedures: Delivered after a 1-week placebo lead-in period. Medication was dispensed at each visit (weekly for the first 5 weeks and then every other week). Format/modality: Individually delivered Location/timing: Outpatient delivery Amount: 10 weeks Fidelity measurement: Compliance was monitored via tablet counts Fidelity data: 75 percent completed treatment. Patients took an average of 4.1 (1.3) tablets a day for 8.9 (3.8) weeks.
Cointervention	SP: Manual-guided SP at each study visit (total of eight sessions: weekly for the first 5 weeks and then every other week)
Outcomes	Remission from depression: Not reported Remission from alcohol use: Total abstinence from alcohol at postintervention (10 weeks postbaseline) Depressive symptoms: HDRS at postintervention (10 weeks postbaseline) Total drinking: Using the Timeline Follow-Back, (1) weekly drinks, (2) weekly drinking days, and (3) drinks per drinking day at postintervention (10 weeks postbaseline) Heavy drinking: Using the Timeline Follow-Back, weekly heavy drinking days (for women, 4+ drinks in a day; for men, 5+ drinks in a day) at postintervention (10 weeks postbaseline) Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Self-reported treatment-emergent adverse effects using a symptom checklist derived from the SAFTEE at postintervention (10 weeks postbaseline)
Risks of bias	Random sequence generation: Low (urn randomization procedure, which balanced group assignment on sex, age, educational level, percentage of heavy drinking days, and severity of depressive symptoms at the time of the initial assessment) Allocation concealment: Unclear (not reported) Blinding of participants: High (double blind, though all of the nefazodone-treated subjects correctly guessed their treatment assignment) Blinding of providers: Low (double blind) Blinding of outcome assessors: Low (a research nurse, a clinical research evaluator, and a physician, all of whom were blinded to the patients' treatment statuses, conducted the assessments) Completeness of outcome data (postintervention): Low (0 percent attrition) Selective outcome reporting: Unclear (no trial registration) Funders: Supported by NIH Grants P50-AA03510, K24-AA13736, and M01-RR06192 and the Bristol-Myers Squibb Co.

Holzhauer 2017

References	Parent study Holzhauer, C. G., and S. A. Gamble, "Depressive Symptoms Mediate the Relationship Between Changes in Emotion Regulation During Treatment and Abstinence Among Women with Alcohol Use Disorders," <i>Psychology of Addictive Behaviors</i>, Vol. 31, No. 3, May 2017, pp. 284–294.
Study design	Study dates: Not reported Objective: To examine the extent to which changes in emotion regulation during treatment predicted women's depression and PTSD symptom severity at treatment completion and subsequent alcohol use following treatment Randomization: Individually randomized Recruitment method: Recruited from a multidisciplinary substance use treatment program for individuals with co-occurring disorders in an outpatient chemical dependency clinic. Female patients who reported symptoms of depression (defined as total scores of 5+ on the PHQ-9) during their initial intake appointments were referred to the study by staff clinicians. Study staff contacted potential participants and invited them to complete a baseline evaluation to determine their eligibility for the study. Inclusion criteria: Female; 18 to 65 years old; met past year criteria for <i>DSM-IV</i> alcohol dependence; met past year criteria for <i>DSM-IV</i> major depression Exclusion criteria: Current or past psychosis; current or past bipolar disorder; moderate or severe mental retardation; acute suicidal intent requiring emergency intervention; intravenous drug use in the past year Power calculation: None reported Sample size: 48 total (25/23)
Setting	Geographic location: United States Intervention sites: Outpatient chemical dependency clinic External context: Not reported
Participants	Age: 37.4 (11.5) Gender: 100 percent female Race/ethnicity: 63 percent white/Caucasian, 31 percent black/African American, 6 percent multiple racial identities Other socioeconomics/demographics: 13.4 (2.3) years of education; 58 percent never married, 15 percent married or living with someone, 27 percent separated or divorced; 77 percent unemployed; median household income of \$11,840.00 Baseline depression: 63 percent primary major depression, 26 percent substance-induced depression; BDI-II of 32.6 (10.7) Baseline alcohol use: Not reported Other baseline health: 69 percent posttraumatic stress disorder; 70 percent borderline personality disorder; 22 percent current cannabis, cocaine, or opioid dependence; 50 percent current nicotine dependence
Intervention 1	Category: Psychological intervention Class: IPT Name: IPT Providers: Community therapists who delivered IPT as part of their usual caseload

	Format/modality: Individually delivered Location/timing: Outpatient delivery Amount: Eight biweekly sessions (16 weeks)
Intervention 2	Category: Control intervention Class: No additional treatment Name: No additional treatment Location/timing: Outpatient delivery Amount: 16 weeks
Cointervention	Outpatient care: All women in the study received standard, group-based chemical dependency treatment that was abstinence oriented. The groups were held 3 days per week for 90 minutes in each session. Psychiatric evaluation and medication management were provided on an as-needed basis. Group sessions focused on teaching patients symptom management of co-occurring conditions and alcohol-related coping skills.
Outcomes	Remission from depression: Not reported Remission from alcohol use: Percentage days abstinent (Timeline Follow-Back) at postintervention (16 weeks postbaseline) and short-term follow-up (24 weeks postbaseline) Depressive symptoms: BDI-II at postintervention (16 weeks postbaseline) and short-term follow-up (24 weeks postbaseline) Total drinking: Not reported Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Not reported
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: High (not possible given nature of interventions) Blinding of providers: High (not possible given nature of interventions) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): Low (~2 percent attrition) Completeness of outcome data (short-term follow-up): Unclear (~15 percent overall attrition but differential attrition unclear) Selective outcome reporting: High (remission from alcohol use and depressive symptoms reported insufficiently for meta-analysis) Funder: Grant K23AA017246 from the National Institute on Alcohol Abuse and Alcoholism

Kranzler 2006

References	Parent study Kranzler, H. R., T. Mueller, J. Cornelius, H. M. Pettinati, D. Moak, P. R. Martin, R. Anthenelli, K. J. Brower, S. O'Malley, B. J. Mason, D. Hasin, and M. Keller, "Sertraline Treatment of Co-Occurring Alcohol Dependence and Major Depression," <i>Journal of Clinical Psychopharmacology</i>, Vol. 26, No. 1, February 2006, pp. 13–20.
Study design	Study dates: Not reported Objective: To evaluate the safety and efficacy of sertraline in patients with co-occurring major depressive disorder and alcohol dependence Randomization: Individually randomized. Two groups of patients were randomized separately to receive either sertraline or placebo: group A had HDRS scores of 17+ after the placebo lead-in, and group B had scores 16 or less after the placebo lead-in. The medication groups within each stratum were balanced for recent outpatient/inpatient status. Recruitment method: Recruited from outpatient and inpatient sources in the community using announcements and advertisements and from the pool of patients seeking alcohol treatment at the participating sites Inclusion criteria: Outpatients at time of screening; 21 to 65 years old; modified <i>DSM-IV</i> diagnosis of major depressive disorder (all met <i>DSM-IV</i> criteria for major depressive disorder, except that symptoms could have occurred during a period of heavy alcohol use); a current <i>DSM-IV</i> diagnosis of alcohol dependence; 17+ on the 17-item HDRS; average of 18+ drinks weekly for men and 14+ drinks weekly for women during the month before screening; at least one heavy drinking day per week (5+ drinks on one occasion for men and 4+ drinks for women) during the month before screening; at least four days with no heavy drinking during placebo lead-in period to allow alcohol-induced depressive symptoms to diminish Exclusion criteria: Pregnant or nursing; women of childbearing potential not using an effective method of contraception; clinically significant co-occurring psychiatric or medical diagnoses (including dependence on any psychoactive substance other than alcohol or nicotine during the preceding year); current treatment with disulfiram, naltrexone, or psychotropic medication; serum aminotransferase levels or other measures of hepatic function that were greater than 250 percent of normal; significant suicidal risk Power calculation: None reported Sample size: 345 total (unknown)
Setting	Geographic location: United States Intervention sites: 13 sites External context: Not reported
Participants	Age: 42.7 (range: 21–64) Gender: 36 percent female Race/ethnicity: 93 percent European American Other socioeconomics/demographics: 39 percent married; 97 percent high school graduates Baseline depression: 6.2 (1.1) <i>DSM-IV</i> symptoms of major depressive disorder; HDRS score of 17.2 (5.1); CGI score for major depressive disorder of 4.1 (0.7)

	Baseline alcohol use: 5.1 (1.0) <i>DSM-IV</i> symptoms of alcohol dependence; 11.5 (9.0) years since onset of alcohol dependence; 86 percent with a first-degree relative with a history of alcoholism; 53.1 (36.8) standard drinks per week; CGI score for alcohol dependence of 4.1 (0.8) Other baseline health: Not reported
Intervention 1	Category: Pharmacological intervention Class: SSRI Name: Sertraline Materials: Medication was dispensed in bottles with Medication Event Monitoring System (MEMS) caps, which contain an electronic monitoring device that records the date and time of bottle-cap openings. Procedures: Delivered after a 1–2 week placebo lead-in period. The duration of the lead-in period varied with the individual’s capacity to sustain nonhazardous drinking and to schedule a visit to initiate randomized treatment. Providers actively promoted adherence to medication. Format/modality: Individually delivered Location/timing: Outpatient delivery Amount: 10 weeks. The starting dose was 50 mg daily until the end of week 1. In the absence of dose-limiting side effects, the dose was subsequently increased at weekly intervals by 50 mg to a maximum allowable dose of 200 mg daily. The dose was maintained at that level during weeks 6–10, although if the maximum dose was not achieved by week 4, it could be increased during the final 6 weeks of the study to a maximum of 200 mg/day sertraline. Decreases in the dose because of adverse effects were possible throughout the study period. Although the protocol provided guidelines for dose adjustments, these determinations were made individually by site. Tailoring/adaptation: Patients who achieved a satisfactory therapeutic response and who wished to continue treatment beyond the end of week 10 were continued double-blind on the same medication they were taking at the end of week 10 for an additional 14-week period. For the purpose of the follow-up study, a satisfactory response was defined by a final HDRS score of less than 8 and CGI-improvement score of 1 or 2 (very much improved or much improved) for at least the last 2 weeks of the study and at least a 50-percent reduction in drinking from baseline. Patients who did not continue in the extension study were tapered off medication by reducing the daily dose by one capsule every 2 to 3 days until the medication was completely discontinued. Fidelity measurement: Computerized medication containers to monitor adherence Fidelity data: 74 percent of group A and 76 percent of group B were adherent (80+ percent of doses taken). The number of days of treatment was 62.4 (27.5) for group A and 64.2 (25.8) for group B. The median daily dose across the 10 weeks of study ranged from 50 to 150 mg for group A and 50 to 100 mg for group B.
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Medication was dispensed in bottles with MEMS caps, which contain an electronic monitoring device that records the date and time of bottle-cap openings Procedures: Delivered after a 1–2 week placebo lead-in period. The duration of the lead-in period varied with the individual’s capacity to sustain nonhazardous drinking

	and to schedule a visit to initiate randomized treatment. Providers actively promoted adherence to medication. Format/modality: Individually delivered Location/timing: Outpatient delivery Amount: 10 weeks. The starting dose was one tablet daily until the end of week 1. In the absence of dose-limiting side effects, the dose was subsequently increased at weekly intervals by one tablet to a maximum allowable dose of four tablets daily. The dose was maintained at that level during weeks 6–10, although if the maximum dose was not achieved by week 4, it could be increased during the final 6 weeks of the study to a maximum of four tablets daily. Decreases in the dose because of adverse effects were possible throughout the study period. Although the protocol provided guidelines for dose adjustments, these determinations were made individually by site. Tailoring/adaptation: Patients who achieved a satisfactory therapeutic response and who wished to continue treatment beyond the end of week 10 were continued double-blind on the same medication they were taking at the end of week 10 for an additional 14-week period. For the purpose of the follow-up study, a satisfactory response was defined by a final HDRS score of less than 8 and CGI-improvement score of 1 or 2 (very much improved or much improved) for at least the last 2 weeks of the study and at least a 50 percent reduction in drinking from baseline. Patients who did not continue in the extension study were tapered off medication by reducing the daily dose by one capsule every 2 to 3 days until the medication was completely discontinued. Fidelity measurement: Computerized medication containers to monitor adherence Fidelity data: 74 percent of group A and 77 percent of group B were adherent (80+ percent of doses taken). The number of days of treatment was 66.6 (22.9) for group A and 69.9 (22.8) for group B. The median daily dose across the 10 weeks of study ranged from a sertraline equivalent of 50–182 mg for group A and 50–150 mg for group B.
Cointervention	Outpatient care: Supportive therapy consisting of general support for abstinence, promotion of compliance, and monitoring of medication side effects at each study visit (weeks 1, 2, 3, 4, 6, 8, and 10). Therapy was delivered according to a manual developed specifically for this study. Patients were instructed to abstain from alcohol and psychoactive substances (except nicotine) during the study, and a urine drug screen was performed at the week 2 visit to assess compliance with this requirement. Those who tested positive on this screen were counseled about the importance of abstinence, and urine drug screens were repeated at each subsequent visit.
Outcomes	Remission from depression: 50-percent reduction in HDRS scores at postintervention (10 weeks postbaseline) Remission from alcohol use: Percent days abstinent at postintervention (10 weeks postbaseline) Depressive symptoms: (1) HDRS and (2) BDI at postintervention (10 weeks postbaseline) Total drinking: Standard drinks per week (Timeline Follow-Back) at postintervention (10 weeks postbaseline) Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Treatment emergent adverse events at postintervention (10 weeks postbaseline)

Risks of bias	Random sequence generation: Low (computer-generated randomization schedule) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): High (~42 percent overall attrition, with last observation carried forward used for missing data) Selective outcome reporting: High (total drinking reported insufficiently for meta-analysis) Funders: Pfizer Pharmaceuticals supported the conduct of this study. Manuscript preparation was supported by NIH grant K24 AA13736.
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Krupitsky 2013

References	Parent study Krupitsky, E. M., S. M. Yerish, A. S. Kiselev, V. A. Berntsev, N. A. Alexandrovsky, M. N. Torban, S. P. Eroshin, and O. F. Eryshev, "A Double-Blind, Placebo-Controlled, Randomized Clinical Trial of Escitalopram for the Treatment of Affective Disorders in Alcohol Dependent Patients in Early Remission," in Nash Boutros, ed., <i>The International Psychiatry and Behavioral Neurosciences Yearbook—2012</i>, Vol. 2, Hauppauge, N.Y.: Nova Biomedical Books, 2013, pp. 239–256. Additional Krupitsky, E. M., S. M. Yerish, V. A. Berntsev, A. S. Kiselev, N. A. Alexandrovsky, M. N. Torban, S. P. Eroshin, and O. F. Eryshev, "Double Blind Placebo Controlled Randomized Clinical Trial of Escitalopram for Alcoholism Comorbid with Affective Disorders (Depression and Anxiety)," <i>Alcoholism: Clinical and Experimental Research</i>, Vol. 34, 2010, p. 167A. Krupitsky, E., S. Yerish, and A. Kiselev, "Clinical Trial of Escitalopram for Alcoholism Comorbid with Affective Disorders," <i>European Neuropsychopharmacology</i>, Vol. 20, 2010, p. S571. Krupitsky, E., S. Yerish, and A. Kiselev, "Clinical Trial of Escitalopram for Alcoholism Comorbid with Affective Disorders," <i>Alcoholism: Clinical and Experimental Research</i>, Vol. 36, 2012, p. 297A.
Study design	Study dates: Not reported Objective: To study the efficacy of one of the most selective SSRIs, escitalopram, for the treatment of alcoholics with comorbid affective disorders (mild to moderate depression) Randomization: Individually randomized Recruitment method: The investigators studied medical records of patients admitted to the Narcology Department for inpatient treatment to select those meeting the enrollment criteria Inclusion criteria: Aged 18 to 50 years; diagnosed with alcohol dependence according to the criteria of ICD-10, associated with a depression episode, a moderate depression episode, or a recurrent depression disorder; if their test of the expired air proved alcohol to be negative; abstained from taking alcohol for at least 7 days (no alcohol withdrawal symptoms); mild or moderate cases of depression (scored 7–23 by the HDRS); for females, not pregnant and agreed to use adequate contraception for the trial period; provided phone number for follow-up purposes

	Exclusion criteria: Taking another psychotropic drug; marked organic brain lesion; marked somatic pathology (such as a severe disease of the liver, kidneys, or cardiovascular or nervous systems); a psychotic state or a severe psychiatric disease in their history (schizophrenia, epilepsy, manic-depressive psychosis); any other chemical dependence except alcohol and tobacco; receiving another pharmacological treatment or psychotherapy for their alcohol dependence Power calculation: None reported Sample size: 60 total (29/31)
Setting	Geographic location: Saint Petersburg, Russia Intervention sites: Department of Narcology (Addiction Psychiatry) of the Saint Petersburg Bekhterev Psycho-Neurological Research Institute External context: Not reported
Participants	Age: 42.4 (4.6) Gender: 22 percent female Race/ethnicity: Not reported Other socioeconomics/demographics: 64 percent employed Baseline depression: Not reported Baseline alcohol use: 10.7 (1.3) years of alcohol withdrawal symptoms; 10.5 (1.4) years with loss of control to stop drinking once started to drink; 10.2 (1.5) years with loss of control over behavior under the influence of alcohol Other baseline health: GAF 61.3 (18.6)
Intervention 1	Category: Pharmacological intervention Class: SSRI Name: Escitalopram Materials: Escitalopram tablets or capsules containing 50 mg of riboflavin Procedures: Tablets or capsules were given at each weekly visit; patients received a 3-week supply of the drug each time in case they missed 1–2 visits Providers: Pharmacists of the Bekhterev Institute and the Scientific Production Enterprise Bios (Saints Petersburg) Format/modality: Individually delivered Location/timing: Delivered during the initial stage of alcohol remission (abstinence) Amount: 10 mg daily in the morning for 13 weeks Fidelity measurement: Compliance was estimated in two ways: by counting the capsules not taken by the patient at each of his or her visits and by determining the riboflavin in the patient's urine by fluorescence under ultraviolet light with the wavelength 444 nm Fidelity data: Compliance measured by the presence of riboflavin in their urine, which ranged from 65 to 100 percent
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Placebo (starch) tablets and capsules containing 50 mg of riboflavin Procedures: Tablets and capsules were given at each weekly visit; patients received a 3-week supply of the drug each time in case they missed 1–2

	Providers: Pharmacists of the Bekhterev Institute and the Scientific Production Enterprise Bios (Saint Petersburg) Format/modality: Individually delivered Location/timing: Delivered during the initial stage of alcohol remission (abstinence) Amount: Once daily in the morning for 13 weeks Fidelity measurement: Compliance was estimated in two ways: by counting the capsules not taken by the patient at each of his or her visits and by determining the riboflavin in the patient's urine by fluorescence under ultraviolet light with the wavelength 444 nm Fidelity data: Compliance measured by the presence of riboflavin in their urine, which ranged from 65 to 100 percent
Cointervention	Medical management: All the patients involved were given a standardized course of medical management, which included elements of cognitive behavioral psychotherapy, according to the guidelines for the addiction patients' counseling, at every weekly visit.
Outcomes	Remission from depression: Not reported Remission from alcohol use: (1) Dropping out of treatment because of relapse (renewal of heavy drinking for 3 or more days in a row without a break [5+ drinks for men and 4+ drinks for women], or missing three or more visits in a row), (2) average days of remission, and (3) time to first drink at postintervention (13 weeks postbaseline) Depressive symptoms: (1) MADRS, (2) HDRS, and (3) Zung's Self-Rating Depression Scale at postintervention (13 weeks postbaseline) Total drinking: Quantity of alcohol consumed at postintervention (13 weeks postbaseline) Heavy drinking: Gamma-glutamyltransferase at postintervention (13 weeks postbaseline) Withdrawal and craving symptoms: (1) Pennsylvania Alcohol Craving Scale, (2) OCDS, and (3) Visual Analog Scale of Craving for alcohol (VASC) at postintervention (13 weeks postbaseline) Health-related quality of life: Not reported Functional status: (1) GAF and (2) CGI scale at postintervention (13 weeks postbaseline) Adverse events: Incidence tables (presence of any side effects and their number, the number of days with the side effects present, and the number of subjects having the side effects) at postintervention (13 weeks postbaseline)
Risks of bias	Random sequence generation: Low (generating random numbers in Excel) Allocation concealment: Low (drugs were placed into numbered containers; the randomization code was kept at the Bekhterev Institute and could be unsealed at any moment in an emergency) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Low (investigators, doctors, patients, and any other staff members taking part in the experiment were unaware which group any particular patient belonged to) Completeness of outcome data (postintervention): Low (0 percent attrition) Selective outcome reporting: High (total drinking reported insufficiently for meta-analysis) Funder: Not reported

Loo 1988

References	Parent study Loo, H., R. Malka, R. Defiance, D. Barrucand, J. Y. Benard, H. Niox-Riviere, A. Raab, A. Sarda, G. Vachonfrance, and A. Kamoun, "Tianeptine and Amitriptyline: Controlled Double-Blind Trial in Depressed Alcoholic Patients," <i>Neuropsychobiology</i>, Vol. 19, No. 2, 1988, pp. 79–85.
Study design	Study dates: Not reported Objective: To evaluate the therapeutic activity and acceptability of tianeptine in alcoholic subjects and to compare them with those of a reference antidepressant, amitriptyline Randomization: Individually randomized Recruitment method: Not reported Inclusion criteria: <i>DSM-III</i> chronic alcoholism (alcohol abuse or alcohol dependence); withdrawn from alcohol 2–5 weeks before inclusion in the trial; <i>DSM-III</i> depressive syndrome (major depressive episode or dysthymic disorder); 20+ on the MADRS Exclusion criteria: Persistent alcohol intoxication at the time of the trial; presence of psychotic traits; recent antidepressant or neuroleptic treatment; serious somatic illness; pregnancy or the absence of contraception in a woman of childbearing potential Power calculation: Not reported Sample size: 129 total (64/65)
Setting	Geographic location: France Intervention sites: Seven sites External context: Not reported
Participants	Age: 38.2 (1.0) Gender: 14 percent female Race/ethnicity: Not reported Other socioeconomics/demographics: Not reported Baseline depression: 50 percent major depressive episode, 50 percent dysthymic disorder Baseline alcohol use: 96 percent alcohol dependence, 4 percent alcohol abuse Other baseline health: 75 percent hospitalized, 25 percent ambulatory
Intervention 1	Category: Pharmacological intervention Class: TCA Name: Tianeptine Materials: Identical-looking tablets Procedures: Delivered following 3–10 days (mean 5.7; SD 0.2) of placebo Format/modality: Individually delivered Amount: Three tablets (12.5 mg/tablet; 37.5 mg total) daily for 4–8 weeks
Intervention 2	Category: Pharmacological intervention Class: TCA Name: Amitriptyline

	Materials: Identical-looking tablets Procedures: Delivered following 3–10 days (mean 5.7; SD 0.2) of placebo Format/modality: Individually delivered Amount: Three tablets (25 mg/tablet; 75 mg total) daily for 4–8 weeks
Cointervention	Center care: Psychotropic drugs such as anxiolytics and/or hypnotics as needed
Outcomes	Remission from depression: Improvement of at least 50 percent in the overall MADRS score at postintervention (4–8 weeks postbaseline) Remission from alcohol use: Not reported Depressive symptoms: (1) MADRS and (2) Hopkins Symptom Checklist at postintervention (4–8 weeks postbaseline) Total drinking: Not reported Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Discontinued treatment at postintervention (4–8 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): Low (17 percent overall attrition and 2 percent differential attrition) Selective outcome reporting: Unclear (no trial registration) Funder: Not reported

Markowitz 2008

References	Parent study Markowitz, J. C., J. H. Kocsis, P. Christos, K. Bleiberg, and A. Carlin, “Pilot Study of Interpersonal Psychotherapy Versus Supportive Psychotherapy for Dysthymic Patients with Secondary Alcohol Abuse or Dependence,” <i>Journal of Nervous and Mental Disease</i>, Vol. 196, No. 6, 2008, pp. 468–474.
Study design	Study dates: Not reported Objective: To compare IPT with brief SP for dysthymic disorder and alcohol abuse Randomization: Individually randomized (1:1 allocation ratio) Recruitment method: Recruited through flyers, word of mouth, and screening for other depression studies at Cornell University Medical College. Prospective subjects were screened by telephone with oral consent and invited to an interview if apparently protocol eligible.

	Inclusion criteria: Anglophone; age range 18–60 years; primary <i>DSM-IV</i> dysthymic disorder with early onset (before age 21); <i>DSM-IV</i> alcohol abuse defined by SCID interview and clinically secondary (later in onset than dysthymic disorder); score >13 on the HDRS-24; GAF score <61. In practice, subjects with alcohol dependence were also included if they were judged not to require pharmacological detoxification. Exclusion criteria: Other current substance abuse or dependence (except cannabis abuse and nicotine dependence); history of schizophrenia, psychosis, mania or hypomania, organic mental syndrome; cluster A, antisocial, or borderline personality disorder; mental retardation; significant acute suicide risk; concurrent psychotherapy or pharmacotherapy; or unstable medical condition Power calculation: Not reported Sample size: 26 total (14/12)
Setting	Geographic location: Ithaca, New York, United States Intervention sites: Cornell University Medical College External context: Not reported
Participants	Age: 38.4 (10.5) Gender: 31 percent female Race/ethnicity: 69 percent white, 31 percent black/Hispanic Other socioeconomics/demographics: 23 percent married or living with someone, 58 percent never married, 19 percent widowed/divorced/separated; 23 percent high school or GED, 77 percent some college or greater; 77 percent full-time/part-time employment, 23 percent unemployed Baseline depression: 54 percent current major depression; 77 percent early onset dysthymic disorder Baseline alcohol use: 77 percent alcohol dependence, 23 percent alcohol abuse Other baseline health: 54 percent other Axis I disorders, 77 percent Axis II disorder, 12 percent Axis III disorder; 77 percent trauma history
Intervention 1	Category: Psychological intervention Class: IPT Name: IPT for dysthymic disorder Theory of change: Employs the “common factors” of psychotherapy, a medical model of illness that excuses the patient from blame, and a focus on emotional responses to and coping strategies to resolve life crises such as complicated bereavement, a role dispute (struggle with a significant other), or role transition (major life change, here including sobriety). The therapeutic assumption was that dysthymic patients were likely to use alcohol as self-medication for dysphoria, eventually leading to comorbid alcohol abuse (or dependence). Both chronic depression and alcohol abuse were defined as treatable medical illnesses that impaired patients’ lives but were not their fault. Procedures: Patients were encouraged patients to change their life situations so as to improve their mood disorder Providers: Therapists ($n = 8$), had master’s of social work and PhD degrees, were trained, and followed a manual. They were experienced in treating depression but had not participated in previous alcoholism studies. Therapists completed at least two pilot cases before certification, save one late substitute therapist who completed only one case. Study therapists belonged to separate, amicably competitive teams and received weekly supervision from team leaders.

	Format/modality: Individually delivered Amount: Up to 18 50-minute sessions over 16 weeks Fidelity measurement: All sessions were audiotaped. Independent, blinded raters reviewed random early and late session tapes for each therapist-patient dyad using the National Institute of Mental Health (NIMH) Collaborative Study Psychotherapy Rating Scale and deemed them treatment adherent. Fidelity data: 57 percent completed treatment
Intervention 2	Category: Psychological intervention Class: SP Name: Brief SP Theory of change: Employs common factors such as elicitation of affect and reflective listening but provides no explicit theoretical formulation to the patient and does not focus as directly on exploring pragmatic options for changing the environment Materials: Intervention manual Providers: Therapists ($n = 7$) had master's of social work and PhDs, completed a minimum of two pilot cases following an unpublished manual, and were certified by a supervisor, an experienced psychoanalytic clinician. Study therapists belonged to separate, amicably competitive teams and received weekly supervision from team leaders. Format/modality: Individually delivered Amount: Up to 18 50-minute sessions over 16 weeks Fidelity measurement: All sessions were audiotaped. Independent, blinded raters reviewed random early and late session tapes for each therapist-patient dyad using the NIMH Collaborative Study Psychotherapy Rating Scale and deemed them treatment adherent. Fidelity data: 58 percent completed treatment
Cointervention	Alcoholics Anonymous: Subjects in both treatments were encouraged to attend Alcoholics Anonymous sessions. However, subjects in both treatment groups almost unanimously refused to attend Alcoholics Anonymous meetings. Many argued that they had an alcohol problem, "but it's not that bad," and stated that they would prove they did not need Alcoholics Anonymous by achieving abstinence without Alcoholics Anonymous meetings. Medical referrals: Subjects were questioned about medical history and referred for medical evaluation when indicated. Medications with psychoactive effects were proscribed (e.g., chronic beta blockers, sedative hypnotics, and more than transient antihistamine use).
Outcomes	Remission from depression: (1) Remission (at least 50 percent improvement on HDRS, final HDRS <7, and final GAF >70); and (2) response (improvement of at least 50 percent in HDRS score) at postintervention (16 weeks postbaseline) Remission from alcohol use: Percentage of days abstinent in the prior month at postintervention (16 weeks postbaseline) Depressive symptoms: (1) HDRS, (2) BDI, and (3) Cornell Dysthymia Rating Scale at postintervention (16 weeks postbaseline) Total drinking: Not reported Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported

	Health-related quality of life: Not reported Functional status: Not reported Adverse events: Not reported
Risks of bias	Random sequence generation: Low (computer-generated random number program) Allocation concealment: Unclear (not reported) Blinding of participants: High (not possible because of nature of intervention) Blinding of providers: High (not possible because of nature of intervention) Blinding of outcome assessors: Low (independent evaluators blinded to clinical assignment–rated subjects) Completeness of outcome data (postintervention): High (there were considerable missing data in this small cohort; analyses based on the comparison of treatment groups using small subject samples, of differing baselines, and with considerable imputed data in some analyses must be considered preliminary and interpreted with caution) Selective outcome reporting: Unclear (no trial registration) Funders: Supported by grants from the NIMH (MH-49635), the Weill Cornell Department of Psychiatry, and MINT: Mental Health Initiative

Mason 1996

References	Parent study Mason, B. J., J. H. Kocsis, E. C. Ritvo, and R. B. Cutler, “A Double-Blind, Placebo-Controlled Trial of Desipramine for Primary Alcohol Dependence Stratified on the Presence or Absence of Major Depression,” <i>JAMA</i>, Vol. 275, No. 10, March 13, 1996, pp. 761–767. Additional Mason, B. J., and J. H. Kocsis, “Desipramine Treatment of Alcoholism,” <i>Psychopharmacology Bulletin</i>, Vol. 27, No. 2, 1991, pp. 155–161. Mason, B. J., and J. H. Kocsis, “Desipramine in the Treatment of Depressed Alcoholics,” <i>American Journal of Psychiatry</i>, Vol. 151, No. 8, August 1994, p. 1248.
Study design	Study dates: Not reported Objective: To assess the use of desipramine for secondary depression in primary alcohol dependence and its effect on abstinence Randomization: Individually randomized, with stratification on the presence of secondary depression (our analysis includes only those with secondary depression) Recruitment method: Recruited through public service announcements, referral from psychiatry inpatient service toward the end of their stay, and referral from psychiatric outpatient departments of the New York Hospital Cornell Medical Center, and the University of Miami School of Medicine Inclusion criteria: Aged 18 to 65 years; <i>DSM-III-R</i> criteria for alcohol dependence; <i>DSM-III-R</i> criteria for major depression of at least 3 weeks’ duration; maximum of 3 months of current abstinence from alcohol; medically stable; not pregnant, psychotic, actively suicidal, cognitively impaired, or dependent on any substance except alcohol or nicotine Exclusion criteria: Not reported Power calculation: None reported Sample size: 28 total (15/13)

Setting	Geographic location: Miami, Florida; and New York, New York, United States Intervention sites: Outpatient psychiatry departments of two urban medical centers External context: Not reported
Participants	Age: Median (IQR)—36 (22) in Arm 1 and 41 (15.5) in Arm 2 Gender: 14 percent female Race/ethnicity: 75 percent white Other socioeconomic/demographics: Median (IQR) years of education—15 (4) in Arm 1 and 15 (15.8) in Arm 2 Baseline depression: HDRS—20.5 (9.8) in Arm 1 and 19 (11) in Arm 2; 61 percent with family history of depression Baseline alcohol use: Median (IQR) Alcohol Dependence Scale—23.5 (10.5) in Arm 1 and 23 (13) in Arm 2; median (IQR) drinks per day—15 (15) in Arm 1 and 13 (6.8) in Arm 2; 66 percent with family history of alcoholism Other baseline health: Median (IQR) <i>DSM-III-R</i> Axis IV psychosocial stress—4 (2) in Arm 1 and 4 (1) in Arm 2; median (IQR) Mini Mental State Examination—30 (1) in Arm 1 and 30 (1) in Arm 2
Intervention 1	Category: Pharmacological intervention Class: TCA Name: Desipramine Procedures: Patients were seen weekly for the first 4 weeks to monitor adverse reactions and to establish a steady-state dose, and every other week thereafter for the duration of the study Providers: Physicians Format/modality: Individually delivered Location/timing: Outpatient care (investigators' offices in the alcohol disorder clinics of the psychiatry outpatient departments of the two urban medical centers) Amount: Six months. Desipramine was titrated to a clinically indicated constant dose (median, 200 mg per day for all patients). Medication was prescribed in divided doses for the first week of the study and then changed to bedtime dosing for the remainder of the study. In the case of worsening depression, patients had their dose adjusted to therapeutic response up to 300 mg a day. Fidelity measurement: Plasma desipramine concentration was assayed the day following an evening dose on a monthly basis using a modification of the liquid chromatographic method. Results were reviewed by a physician not involved in patient ratings to verify compliance and make dose recommendations to ensure adequacy of desipramine treatment. Patients were required to return empty medication bottles or unused medication at every study visit, to be counted as an additional estimate of compliance with the prescribed dose. Fidelity data: Median (IQR) final dose of 200 (150) mg per day
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Procedures: Patients were seen weekly for the first 4 weeks to monitor adverse reactions and to establish a steady-state dose, and every other week thereafter for the duration of the study

	Providers: Physicians Format/modality: Individually delivered Location/timing: Outpatient care (investigators' offices in the alcohol disorder clinics of the psychiatry outpatient departments of the two urban medical centers) Amount: Six months. Medication was prescribed in divided doses for the first week of the study and then changed to bedtime dosing for the remainder of the study. In the case of worsening depression, patients had their dose adjusted to therapeutic response up to 300 mg a day. Fidelity measurement: Dosing instructions equivalent to those in the desipramine arm were given by the nonblinded physician to blinded therapists for placebo-treated patients to preserve the double-blind study design. Patients were required to return empty medication bottles or unused medication at every study visit, to be counted as an additional estimate of compliance with the prescribed dose.
Cointervention	Outpatient care: Patients were precluded from taking disulfiram (Antabuse) or psychotropic medications, but they were encouraged to participate in Alcoholics Anonymous (average of two meetings per week) and any other psychosocial treatments they found beneficial Referrals: Patients meeting criteria for relapse were referred to more intensive or alternative treatment
Outcomes	Remission from depression: Depression response (reduction in the baseline HDRS total score of at least 50 percent or a final HDRS total score less than 10) at postintervention (6 months postbaseline) Remission from alcohol use: (1) Drinking relapse (more than 2 heavy-drinking days per week for 2 consecutive weeks or if collateral report of heavy drinking coincided with patient refusal to continue in the trial) and (2) the 29-item self-report Alcohol Dependence Scale at postintervention (6 months postbaseline) Depressive symptoms: HDRS-24 at postintervention (6 months postbaseline) Total drinking: Number of light-drinking days (>6 drinks per occasion) at postintervention (6 months postbaseline) Heavy drinking: Number of heavy-drinking days (up to 6 drinks per occasion) at postintervention (6 months postbaseline) Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Treatment Emergent Symptom Side Effects Scale at postintervention (6 months postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): High (~21 percent overall attrition) Selective outcome reporting: High (total drinking and heavy drinking not reported) Funder: National Institute on Alcohol Abuse and Alcoholism, grants AA06866 and AA08111

McGrath 1996

References	Parent study McGrath, P. J., E. V. Nunes, J. W. Stewart, D. Goldman, V. Agosti, K. Ocepek-Welikson, and F. M. Quitkin, "Imipramine Treatment of Alcoholics with Primary Depression: A Placebo-Controlled Clinical Trial," <i>Archives of General Psychiatry</i>, Vol. 53, No. 3, March 1996, pp. 232–240. Additional McGrath, P. J., E. V. Nunes, J. W. Stewart, K. Ocepek-Welikson, and F. M. Quitkin, "Antidepressant Treatment of Primary Depression in Alcoholics: A Placebo-Controlled Randomized Clinical Trial," <i>Psychopharmacology Bulletin</i>, 1995, p. 598.
Study design	Study dates: Not reported Objective: To evaluate whether primary depression identified in actively drinking alcoholics responds to TCAs, whether a TCA is safe to administer to actively drinking alcoholic outpatients without physical dependency on alcohol, and whether patients whose depression responds to an antidepressant and concurrent alcohol counseling decrease their drinking Randomization: Individually randomized Recruitment method: Recruited through advertisements and referrals. <i>DSM-III-R</i> diagnoses were made by a research psychiatrist using the structured clinical interview for <i>DSM-III-R</i>, patient version. The temporal sequence of addictive and nonaddictive disorders was determined by dating the age of onset of each structured clinical interview depressive and addictive disorder and by dating any periods of abstinence of 6 months or longer. Each diagnosis was reviewed for presence before a depressive disorder or during an abstinent period. Inclusion criteria: Aged 18 to 65 years; met <i>DSM-III-R</i> criteria for either current alcohol dependence or abuse; met <i>DSM-III-R</i> criteria for current major depression, dysthymia, or depressive disorder not otherwise specified (depressive disorder was required to be primary, defined as either having had its onset before the onset of alcohol abuse or having continued during at least 6 months of sobriety) Exclusion criteria: A history of mania; psychosis; seizure disorder; severe current physical dependence on alcohol requiring inpatient detoxification; abstinence of 2 weeks' duration at baseline; current serious and unstable physical illnesses; dependence on (though not abuse of) another substance (apart from nicotine) within the last 6 months; women not using adequate contraception; patients who rated their depression as "much improved" or "very much improved" on the CGI scale after 1 week of single-blind placebo Power calculation: None reported Sample size: 69 total (36/33)
Setting	Geographic location: New York, New York, United States Intervention sites: Research clinic External context: Not reported
Participants	Age: 37.4 (6.7) in Arm 1 Gender: 51 percent female Race/ethnicity: 81 percent white Other socioeconomics/demographics: 20 percent married; 14.5 (2.7) years of education; 51 percent employed

	Baseline depression: 72 percent with major depression; 71 percent with atypical depression; 47 percent past dysthymia; HDRS of 14.9 (5.2); Hopkins Symptom Checklist, 90-item self-rated version, score of 20.8 (5.2); 86 percent depressive disorder among first-degree relatives Baseline alcohol use: 96 percent with alcohol dependence; MAST of 13.8 (6.5); 3.8 (7.8) days of Alcohol Anonymous attendance in the past 30 days; 27.2 (12.3) average age of onset of alcohol disorder; 66 percent of days spent drinking and 44 percent spent drinking heavily (6+ ounces per day); 10.2 (9.9) drinks per drinking day; 86 percent AUD among first-degree relatives Other baseline health: 16 percent with positive urine screen for other substances of abuse (tetrahydrocannabinol, benzodiazepine, cocaine); 12 percent with bipolar depression (not otherwise specified)
Intervention 1	Category: Pharmacological intervention Class: TCA Name: Imipramine Materials: Identical tablets Providers: Physicians Format/modality: Individually delivered Location/timing: Outpatient care (university-based depression research clinic) Amount: Single daily dose given at bedtime for 12 weeks. Patients began at 50 mg and increased by 50 mg every 3–5 days until a maximum dose of 300 mg was reached, there was significant improvement, or side effects became dose limiting. Fidelity measurement: An adequate trial of imipramine was prospectively defined as 4 weeks of double-blind medication with a minimum dose of at least 150 mg of imipramine hydrochloride for 2 consecutive weeks. Plasma levels of imipramine and desipramine were measured at weeks 6 and 12. Fidelity data: Average dose of 262 (43) mg daily
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Identical tablets Providers: Physicians Format/modality: Individually delivered Location/timing: Outpatient care (university-based depression research clinic) Amount: Single daily dose given at bedtime for 12 weeks Fidelity measurement: An adequate trial of placebo was prospectively defined as 4 weeks of double-blind medication equivalent to the imipramine minimum dose (at least 150 mg of imipramine hydrochloride for 2 consecutive weeks) Fidelity data: Patients received on average the number of pills required for the average dose of 262 (43) mg imipramine daily
Cointervention	Outpatient care: Patients received care toward abstinence in counseling and Alcoholics Anonymous. Patients were seen for weekly individual relapse prevention counseling sessions by a trained therapist and received weekly individual supervision by a psychologist experienced in the treatment of substance abuse. The focus of the counseling was identifying individual high-risk situations for drinking and developing

	cognitive and behavioral coping strategies to avoid alcohol use in those situations. Attendance at Alcoholics Anonymous was strongly encouraged. Patients attended an average of 7.4 (4.0) counseling sessions.
Outcomes	Remission from depression: (1) Rating depression as “much improved” or “very much improved” on the CGI scale, (2) HDRS decrease at least 50 percent, and (3) HDRS decrease at least 50 percent and final score is 6 or less at postintervention (12 weeks postbaseline) Remission from alcohol use: Abstinent in the (1) last week and (2) last 4 weeks at postintervention (12 weeks postbaseline) Depressive symptoms: HDRS at postintervention (12 weeks postbaseline) Total drinking: (1) Percentage of days drinking in the last week and (2) drinks per drinking day at postintervention (12 weeks postbaseline) Heavy drinking: Percentage of days drinking heavily in the last week at postintervention (12 weeks postbaseline) Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Dropped out because of adverse events at postintervention (12 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Low (outcome assessments done by blinded provider) Completeness of outcome data (postintervention): High (completer analyses with 19 percent overall attrition and 13 percent differential attrition) Selective outcome reporting: Unclear (no trial registration) Funders: Grant AA9539 from the National Institute on Alcohol Abuse and Alcoholism and grant NIMH 30906 from the Mental Health Clinical Research Center, New York, New York. Medication and matching placebo were supplied by the Ciba-Geigy Corporation, Summit, New Jersey.

McLean 1986

References	Parent study McLean, P. C., R. J. Ancill, and T. K. Szulecka, “Mianserin in the Treatment of Depressive Symptoms in Alcoholics: A Double-Blind Placebo Controlled Study Using a Computer Delivered Self-Rating Scale,” <i>Psychiatria Polska</i>, Vol. 20, No. 6, November–December 1986, pp. 417–427.
Study design	Study dates: Not reported Objective: To evaluate the effectiveness of mianserin in treating depressive symptoms that occur in a population of alcoholics requiring inpatient treatment for detoxification Randomization: Individually randomized Recruitment method: Recruited patients admitted to an alcoholism treatment unit for detoxification and treatment of alcoholism

	Inclusion criteria: Alcohol dependence; depression (17+ on the HDRS). Exclusion criteria: Psychosis; organic brain disease; mental subnormality; pregnant or lactating females; those who at the time of admission or within the preceding 2 weeks had been receiving antidepressant or other psychotropic medication Power calculation: None reported Sample size: 35 total (17/18)
Setting	Geographic location: Nottingham, United Kingdom Intervention sites: Alcoholism Treatment Unit at Mapperley Hospital External context: Not reported
Participants	Age: Median of 36.5 (ranged from 22 to 61) Gender: 31 percent female Race/ethnicity: Not reported Other socioeconomics/demographics: Not reported Baseline depression: HDRS of 27.0 (6.1) Baseline alcohol use: Not reported Other baseline health: 19 percent sociopathic personality disorder; 9 percent significant anxiety or phobic symptoms
Intervention 1	Category: Pharmacological intervention Class: TeCA Name: Mianserin Materials: Tablets Format/modality: Individually delivered Location/timing: Inpatient care (hospital-based addiction clinic) Amount: 4 weeks total. One tablet of 30 mg mianserin (as Norval [Bencard]) at night was dispensed for the first week. The dose was then increased to two tablets of 60 mg mianserin at night for the next 3 weeks.
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Tablets Format/modality: Individually delivered Location/timing: Inpatient care (hospital-based addiction clinic) Amount: 4 weeks total. One tablet at night was dispensed for the first week. The dose was then increased to two tablets at night for the next 3 weeks.
Cointervention	Inpatient care: All patients were prescribed a conventional detoxification regime, usually using chlordiazepoxide in reducing doses, and a standard course of multivitamin injections. Night sedation by benzodiazepine drugs was prescribed as necessary and appropriate therapy was instituted for physical conditions. No antidepressant medication other than that prescribed in the course of the study was administered. All patients took part in the therapeutic program of the unit (e.g., group meetings, individual counseling, relaxation, and occupational therapy). The goal of the treatment in all cases was total abstinence from alcohol.

Outcomes	Remission from depression: HDRS less than 17 at postintervention (4 weeks postbaseline) Remission from alcohol use: Not reported Depressive symptoms: HDRS at postintervention (4 weeks postbaseline) Total drinking: Not reported Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: “Unwanted effects” at postintervention (4 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Low (computer-administrated outcome assessments) Completeness of outcome data (postintervention): Low (~9 percent overall attrition and 5 percent differential attrition) Selective outcome reporting: Unclear (no trial registration) Funder: Not reported

Mielke 1978

References	Parent study Mielke, D. H., and D. M. Gallant, “Controlled Evaluation of a Pyrrolidine Derivative (AHR-1118) Versus Imipramine,” <i>Current Therapeutic Research—Clinical and Experimental</i>, Vol. 24, No. 6, 1978, pp. 734–737.
Study design	Study dates: Not reported Objective: To evaluate an antidepressant agent in a controlled study of patients with unipolar depression who were admitted for treatment of their alcoholism Randomization: Individually randomized Recruitment method: Recruited patients admitted to an inpatient alcoholism treatment unit Inclusion criteria: Research Diagnostic Criteria for Major Depressive Disorder; baseline clinical laboratory and EKG results within normal limits Exclusion criteria: Other psychotic disorders; predrug score of less than 50 on Zung’s Self-Rating Depression Scale; previous history of drug abuse; history of chronic antisocial behavior; received either antidepressant or neuroleptic medication within 2 weeks of admission to the study Power calculation: None reported Sample size: 20 total (10/10)

Setting	Geographic location: Mandeville, Louisiana, United States Intervention sites: Inpatient Alcoholism Treatment Service of Southeast Louisiana Hospital External context: Not reported
Participants	Age: 36.9 (ranged from 22 to 53) Gender: Not reported Race/ethnicity: “The majority of the patients were Caucasian” Other socioeconomics/demographics: “Approximately half having at least a high school education” Baseline depression: Not reported Baseline alcohol use: Not reported Other baseline health: Not reported
Intervention 1	Category: Pharmacological intervention Class: TCA Name: Imipramine Materials: Tablets Format/modality: Individually delivered Location/timing: Inpatient care (hospital-based addiction clinic) Amount: 4 weeks total. Initially one 50 mg tablet twice daily, scaled up to one tablet in the morning at two at 4:00 p.m. if no side effects and there was insufficient therapeutic response by the fourth day. The maximum dose of two tablets at 8:00 a.m. and two at 4:00 p.m. was initiated on the seventh day if the patient still showed no significant or incapacitating side effects and if there was room for therapeutic improvement.
Intervention 2	Category: Pharmacological intervention Class: Monoamine reuptake inhibitors Name: AHR-1118 Materials: Tablets Format/modality: Individually delivered Location/timing: Inpatient care (hospital-based addiction clinic) Amount: 4 weeks total. Initially one 25 mg tablet twice daily, scaled up to one tablet in the morning at two at 4:00 p.m. if no side effects and there was insufficient therapeutic response by the fourth day. The maximum dose of two tablets at 8:00 a.m. and two at 4:00 p.m. was initiated on the seventh day if the patient still showed no significant or incapacitating side effects and if there was room for therapeutic improvement.
Cointervention	Inpatient care: Hospital-based addiction treatment unit. Patients who coincidentally developed infections also received antibiotics.
Outcomes	Remission from depression: Not reported Remission from alcohol use: Not reported Depressive symptoms: (1) Kellner Rating Scale for Depression, (2) CGI scale, and (3) Zung’s Self-Rating Depression Scale at postintervention (4 weeks postbaseline) Total drinking: Not reported

	Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Side effects at postintervention (4 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): Low (no attrition) Selective outcome reporting: High (depressive symptoms measured with three different scales, and none are reported sufficiently for meta-analysis) Funder: Alcohol, Drug Abuse, and Mental Health Administration grant MH 03701 from NIMH

Moak 2003

References	Parent study Moak, D. H., R. F. Anton, P. K. Latham, K. E. Voronin, R. L. Waid, and R. Durazo-Arvizu, "Sertraline and Cognitive Behavioral Therapy for Depressed Alcoholics: Results of a Placebo-Controlled Trial," <i>Journal of Clinical Psychopharmacology</i>, Vol. 23, No. 6, December 2003, pp. 553–562. Additional National Institute on Alcohol Abuse and Alcoholism, "Sertraline and Cognitive Therapy in Depressed Alcoholics," 2005. As of March 19, 2019: https://clinicaltrials.gov/show/NCT00000458
Study design	Study dates: Not reported Objective: To determine the efficacy of sertraline when added to CBT in the treatment of individuals with depression and alcoholism Randomization: Individually randomized. Urn randomization was used to balance subject variables that were likely to affect subject outcome: gender, outpatient versus inpatient recruitment, major depression versus dysthymia, alcohol abuse versus dependence, and primary (independent) depression versus family history of affective disorder. Recruitment method: Recruited treatment-seeking individuals who responded to newspaper advertisements or who were referred from clinical sources. Potential subjects were seen for an intake assessment by either a psychiatrist or a nurse. Inclusion criteria: Current <i>DSM-III-R</i> criteria for primary (independent) major depressive episode, dysthymic disorder, or a clear family history of affective disorder without comorbid substance abuse in a first-degree relative (parent, sibling, or child); at least 17 on the HDRS both at screening and at the end of 1 week of single-blind placebo; current <i>DSM-III-R</i> criteria for alcohol dependence or abuse; drank a minimum of 40 standard drinks during the month before study entry; not having more than one past inpatient alcohol detoxification. Women of childbearing potential were required to use a reliable form of birth control.

	Exclusion criteria: Any current psychoactive substance dependence other than nicotine; psychoactive substance abuse in the month before study entry other than marijuana; current panic disorder or posttraumatic stress disorder; lifetime history of bipolar affective or psychotic disorder; treatment-resistant depression; any significant current suicidal ideation or plan; homicidal ideation; unstable medical illness; history of a seizure disorder. If a subject required outpatient detoxification, they had to have been off the detoxification medication for at least 48 hours before being started on single-blind placebo. Subjects who were receiving serotonergic medications, including SSRIs, had to be completely off these medications for at least 4 weeks before study entry. Other psychoactive medications, including TCAs, had to be discontinued for at least 2 weeks. Power calculation: None reported Sample size: 82 total (38/44)
Setting	Geographic location: United States Intervention sites: Not reported External context: Not reported
Participants	Age: 42 (10) Gender: 39 percent female Race/ethnicity: 1 percent Native American, 99 percent Caucasian Other socioeconomics/demographics: 15 (2) years of education Baseline depression: 100 percent major depressive episode criteria, “some” met dysthymic disorder criteria, and 15 percent did not have independent depression but did have a clear family history of an affective disorder without comorbid substance abuse in a first-degree relative; HDRS of 19.1 (2.5); BDI of 23.0 (9.1) Baseline alcohol use: 1 percent AUD, 99 percent alcohol dependence; OCDS of 18.8 (6.1); Alcohol Dependence Scale 17.7 (7.6); 11.5 (8.3) years of problem drinking; 10.9 (4.8) drinks per drinking day; 4.9 (1.9) days of heavy drinking (5+ drinks) per week; 22 percent days abstinent in past 90 days Other baseline health: Not reported
Intervention 1	Category: Pharmacological intervention Class: SSRI Name: Sertraline Materials: Matched tablets Providers: Physician Format/modality: Individually delivered Location/timing: Outpatient care Amount: 12 weeks total. Four tablets daily with a 100-mg riboflavin tablet. Participants started on 50 mg daily and titrated up to 200 mg daily over a 2-week period. At the end of the study, the dosage was titrated back down to 50 mg over a 7-day period and then stopped before the week-12 visit. A study physician saw all subjects weekly for the first 6 weeks of the study and then every other week for the remaining 6 weeks. Study physicians could prescribe a reduced dosage if they felt that side effects warranted a reduction. In these cases, the dosage was reduced one tablet at a time (50-mg increments) until the side effect either was relieved or could be tolerated by the subject. Fidelity measurement: Participants were asked each week for a urine sample for riboflavin to monitor compliance with taking medication. Because participants were

	instructed to take their study medication in the morning before their visit, riboflavin samples were obtained less than 8 hours after study medication was taken. Medication compliance was defined as having a urine riboflavin level of at least 1,500 ng/mL in at least 75 percent of urine samples. Fidelity data: 79 percent medication compliance
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Matched tablets Format/modality: Individually delivered Location/timing: Outpatient care Amount: 12 weeks total. Four tablets daily with a 100-mg riboflavin tablet. A study physician saw all subjects weekly for the first 6 weeks of the study and then every other week for the remaining 6 weeks. Study physicians could prescribe a reduced dosage if they felt that side effects warranted a reduction. In these cases, the dosage was reduced one tablet at a time until the side effect either was relieved or could be tolerated by the subject. Fidelity measurement: Participants were asked each week for a urine sample for riboflavin to monitor compliance with taking medication. Because participants were instructed to take their study medication in the morning before their visit, riboflavin samples were obtained less than 8 hours after study medication was taken. Medication compliance was defined as having a urine riboflavin level of at least 1,500 ng/mL in at least 75 percent of urine samples. Fidelity data: 77 percent medication compliance. The mean daily dosage was 186 mg.
Cointervention	CBT: Individual, manual-driven CBT developed during Project MATCH specifically for the treatment of alcohol dependence. Participants in Project MATCH received eight core sessions that helped them acquire the skills necessary to become abstinent from alcohol. In addition, participants were able to use four elective sessions from a menu of elective sessions. The elective sessions that were most relevant to depression (awareness of negative thinking, managing negative thinking, managing depression, and increasing pleasant activities) were included as core sessions in this study. To accommodate this, one core session (seemingly irrelevant decisions) was eliminated (although it could still be included as an elective session) and two core sessions (awareness of negative thinking and management of negative thinking) were combined into one session. The first session was delivered during the single-blind week to provide the subject with some initial tools to maintain abstinence and to establish contact with the therapist; participants received an average of ten sessions. A psychologist experienced in the delivery of Project MATCH CBT met with the therapists for weekly supervision and also periodically monitored audiotapes of therapy sessions to ensure that CBT was delivered uniformly to all subjects in the study.
Outcomes	Remission from depression: Significant depression (HDRS score of at least 50 percent of baseline score) at postintervention (12 weeks postbaseline) Remission from alcohol use: (1) Percentage of days abstinent and (2) time to first drink at postintervention (12 weeks postbaseline) Depressive symptoms: (1) HDRS and (2) BDI at postintervention (12 weeks postbaseline) Total drinking: Drinks per drinking day at postintervention (12 weeks postbaseline)

	Heavy drinking: Time to first heavy drinking day at postintervention (12 weeks postbaseline) Withdrawal and craving symptoms: OCDS at postintervention (12 weeks postbaseline) Health-related quality of life: Not reported Functional status: Not reported Adverse events: (1) Adverse effects and (1) serious adverse events at postintervention (12 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): Unclear (not clear whether those who did not complete medication also did not complete outcome assessment) Selective outcome reporting: High (time to first drink, time to first heavy drinking day, and OCDS were not statistically significant but were reported insufficiently for meta-analysis) Funder: Grant AA10476 from the National Institute on Alcohol Abuse and Alcoholism. Pfizer supplied the study drug and matched placebo for this research.

Muhonen 2008

References	Parent study Muhonen, L. H., J. Lonnqvist, K. Juva, and H. Alho, "Double-Blind, Randomized Comparison of Memantine and Escitalopram for the Treatment of Major Depressive Disorder Comorbid with Alcohol Dependence," <i>Journal of Clinical Psychiatry</i>, Vol. 69, No. 3, 2008, pp. 392–399. Additional Muhonen, L. H., J. Lahti, H. Alho, J. Lonnqvist, J. Haukka, and S. T. Saarikoski, "Serotonin Transporter Polymorphism as a Predictor for Escitalopram Treatment of Major Depressive Disorder Comorbid with Alcohol Dependence," <i>Psychiatry Research</i>, Vol. 186, No. 1, March 30, 2011, pp. 53–57. Muhonen, L. H., J. Lahti, D. Sinclair, J. Lonnqvist, and H. Alho, "Treatment of Alcohol Dependence in Patients with Co-Morbid Major Depressive Disorder—Predictors for the Outcomes with Memantine and Escitalopram Medication," <i>Substance Abuse Treatment, Prevention, and Policy</i>, Vol. 3, October 3, 2008, p. 20. Muhonen, L. H., J. Lonnqvist, J. Lahti, and H. Alho, "Age at Onset of First Depressive Episode as a Predictor for Escitalopram Treatment of Major Depression Comorbid with Alcohol Dependence," <i>Psychiatry Research</i>, Vol. 167, No. 1–2, May 15, 2009, pp. 115–122. NCT00368862, "Efficacy Study of Memantine Hydrochloride and Escitalopram for the Treatment of Co-Morbid Depression and Alcoholism," 2006. As of March 19, 2019: http://clinicaltrials.gov/show/NCT00368862
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Study design	Study dates: December 20, 2004, to May 25, 2006 Objective: To evaluate possible new treatments for major depressive disorder in patients with comorbid alcohol dependence in a municipal alcohol treatment unit Randomization: Individually randomized (1:1 allocation ratio and random permuted blocks) Recruitment method: Screened adults voluntarily seeking outpatient treatment for alcohol problems at three municipal alcohol treatment units. Patients who had a history of heavy drinking (5 or more daily drinks for men and 4 or more daily drinks for women) for at least 10 years, had significant depression (BDI-II score >17), and were interested in voluntarily taking part in the study were recommended by their doctor or social worker therapist to the study physician's interview and screening. Patients were interviewed by a psychiatrist using the SCID. Inclusion criteria: Aged 26 to 65 years; <i>DSM-IV</i> criteria for major depressive disorder; <i>DSM-IV</i> criteria for alcohol dependence Exclusion criteria: Prior inpatient detoxification within the previous 4 weeks; other substance use dependence screened by urine test (amphetamine, benzodiazepines, cocaine, tetrahydrocannabinol, and opiates); schizophrenia or other psychotic disorder and bipolar I and II disorder; acute risk of suicide; pregnant or breastfeeding; severe untreated somatic problem; a serious liver dysfunction (aspartate aminotransferase and alanine aminotransferase >200 U/L); mental disability. Other medications prescribed by the patient's physician were allowed, with the exception of other antidepressants. Power calculation: The sample size was defined by dichotomous power analysis in which $\alpha = .05$, $\beta = 0.10$, $f(\alpha\beta) = 10.5$, $p_1 = 10$, $p_2 = 40$, and $N = p_1 \times (100 - p_1) + p_2 \times (100 - p_2)/(p_2 - p_1) \times 10.5 = 38$. Sample size: 80 total (40/40)
Setting	Geographic location: Helsinki, Finland Intervention sites: Three municipal alcohol treatment clinics (Annankatu, Malmi, and Töölö clinics) External context: Helsinki, Finland, is a city of a half million inhabitants, and municipal alcohol treatment clinics provide various nonprofit medical and psychosocial options yearly for 6,000 people with alcohol problems.
Participants	Age: 47.7 (8.3) Gender: 45 percent female Race/ethnicity: 100 percent white Other socioeconomics/demographics: Not reported Baseline depression: First depressive episode at 26 (12.7); duration of current depression of 34.9 (49) months; 9.8 (8.1) total depressive episodes Baseline alcohol use: 44 percent abstinent the past 1–3 months; 13 percent abstinent in the past year; first alcohol intoxication at 15.4 (3.1) years; onset of regular use of alcohol at 20.6 (6.5) years; onset of alcohol abuse at 28.9 (8.2) years; onset of alcohol dependence at 29.9 (8.4) years; 43 percent alcohol abuse at time of randomization; 77 percent alcohol problems among relatives; AUDIT score of 27.9 (6.8) Other baseline health: Not reported
Intervention 1	Category: Pharmacological intervention Class: SSRI Name: Escitalopram

	Materials: The study medication was double-dummy packed: The medication was labeled and controlled by an independent supplier Providers: Physician Format/modality: Individually delivered Location/timing: Outpatient care Amount: 26 weeks total. The starting dose was 5 mg and was increased at weekly intervals by 5 mg/day to 20 mg/day. After 4 weeks, the study physician was allowed to decrease the dose if a patient could not tolerate the medication. Patients were instructed to take the study medication in the morning. Fidelity measurement: Patients returned to the alcohol treatment clinic at weeks 1, 2, 4, 12, and 26 for medication checking and dispensing. The study medication intake since the previous visit was recorded using the medication diary. The study medication intake was measured with the pill count from the returned blister packs. Fidelity data: The average daily consumption of medication was 16.9 (3.6) mg for weeks 1–12 and 15.9 (4.4) mg for weeks 13–26
Intervention 2	Category: Pharmacological intervention Class: NMDA antagonist Name: Memantine Materials: The study medication was double-dummy packed: The medication was labeled and controlled by an independent supplier Providers: Physician Format/modality: Individually delivered Location/timing: Outpatient care Amount: 26 weeks total. The starting dose was 5 mg and was increased at weekly intervals by 5 mg/day to 20 mg/day. After 4 weeks, the study physician was allowed to decrease the dose if a patient could not tolerate the medication. Patients were instructed to take the study medication in the morning. Fidelity measurement: Patients returned to the alcohol treatment clinic at weeks 1, 2, 4, 12, and 26 for medication checking and dispensing. The study medication intake since the previous visit was recorded using the medication diary. The study medication intake was measured with the pill count from the returned blister packs. Fidelity data: The average daily consumption of medication was 17.4 (2.8) for weeks 1–12 and 17.4 (3.2) mg for weeks 13–26
Cointervention	Outpatient care: 7.4 (9.3) visits to the outpatient clinics during the study period
Outcomes	Remission from depression: MADRS scores of 12 or less at postintervention (26 weeks postbaseline) Remission from alcohol use: AUDIT at postintervention (26 weeks postbaseline) Depressive symptoms: (1) MADRS and (2) BDI at postintervention (26 weeks postbaseline) Total drinking: (1) Alcohol consumption (AUDIT Q-F) and (2) alcohol intake (grams) per day at postintervention (26 weeks postbaseline) Heavy drinking: Heavy drinking days (AUDIT-3) at postintervention (26 weeks postbaseline) Withdrawal/craving symptoms: OCDS at postintervention (26 weeks postbaseline)

	Health-related quality of life: Visual Analog Scale at postintervention (26 weeks postbaseline) Functional status: SOFAS at postintervention (26 weeks postbaseline) Adverse events: Adverse events at postintervention (26 weeks postbaseline)
Risks of bias	Random sequence generation: Low (Vassar Statistic randomizing algorithm; the randomization was concealed until the study database was locked on June 6, 2006, by an independent clinical study monitor) Allocation concealment: Low (randomly assigned by a person independent of screening) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): High (27 percent overall attrition) Selective outcome reporting: Low (all outcomes in trial registration are reported sufficiently for meta-analysis: NCT00368862) Funders: National Public Health Institute, the Finnish Foundation for Alcohol Research, and the Helsinki Health Center Research Fund. Study medication was provided by Lundbeck Oy Ab, Turku, Finland.

Oslin 2005

References	Parent study Oslin, D. W., "Treatment of Late-Life Depression Complicated by Alcohol Dependence," <i>American Journal of Geriatric Psychiatry</i>, Vol. 13, No. 6, June 2005, pp. 491–500. Additional "Curbing Drinking Alleviates Depression in Dually Diagnosed Seniors: Study Examines Effectiveness of Naltrexone Plus SSRI," <i>Brown University Geriatric Psychopharmacology Update</i>, Vol. 9, No. 8, 2005, pp. 1–5. Gopalakrishnan, R., J. Ross, C. O'Brien, and D. Oslin, "Course of Late-Life Depression with Alcoholism Following Combination Therapy," <i>Journal of Studies on Alcohol and Drugs</i>, Vol. 70, No. 2, March 2009, pp. 237–241. NCT00018824, "Treating Alcohol Use in Older Adults with Depression," 2001. As of March 19, 2019: http://clinicaltrials.gov/show/NCT00018824
Study design	Study dates: 1999 to 2001 Objective: To test the efficacy of naltrexone combined with sertraline for the treatment of older adults with major depression and alcohol dependence Randomization: Individually randomized (stratified by gender and recruitment site in a block design) Recruitment method: Recruited through advertisements in the local media and from clinical referrals Inclusion criteria: At least 55 years old; <i>DSM-IV</i> criteria for alcohol dependence; <i>DSM-IV</i> criteria for a depressive disorder (substance-induced or primary major depression); successfully complete detoxification from alcohol (at least 3 consecutive

	days of abstinence before the start of the study medication). Primary major depression required the diagnosis of depression starting before the alcohol dependence or persisting during a 3-month period of alcohol abstinence. Exclusion criteria: Current <i>DSM-IV</i> diagnosis of any psychoactive substance dependence other than alcohol or nicotine; evidence of opioid use in the past 30 days (self-report or urine drug screen); severe medical or physical illnesses (e.g., AIDS or active hepatitis); significant hepatocellular injury (elevated total bilirubin levels) Power calculation: Not reported Sample size: 74 total (37/37)
Setting	Geographic location: United States Intervention sites: Not reported External context: Not reported
Participants	Age: 63.4 (6.3) Gender: 20 percent female Race/ethnicity: 66 percent white Other socioeconomics/demographics: 45 percent married Baseline depression: 68 percent with primary depression; 31 percent independent major depression, 64 percent alcohol-induced depression, 5 percent indeterminate; 27 percent had ever participated in outpatient mental health treatment; 26 percent receiving an antidepressant at the time of screening; HDRS of 21.8 (5.4) Baseline alcohol use: 39.6 (10.8) years of alcohol use; 17.3 (9.9) years of drinking to intoxication; drank alcohol heavily in 68 percent, drank at all in 79 percent, and had 8.4 (5.4) drinks per drinking day in the 90 days preceding the detoxification period; 51 percent no previous formal treatment for alcohol dependence, 18 percent had participated in one treatment episode, 30 percent had been in more than one previous treatment; Addiction Severity Index of 0.66 (0.18) Other baseline health: 8 percent had a lifetime suicide attempt; Physical Component Score from the Medical Outcomes Scale (SF-36) of 45.0 (9.4); Mental Component Score from the SF-36 of 35.7 (10.6)
Intervention 1	Category: Pharmacological intervention Class: Opioid antagonist Name: Naltrexone Materials: Study medication (ReVia) was provided in blister cards to assist in measuring adherence and as an aid for patients. Providers: Nurses and physician Format/modality: Individually delivered Location/timing: Outpatient care Amount: 12 weeks total (50 mg per day) Fidelity measurement: Adherence to study medication regimen was monitored by self-report of medication use and by pill counts
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo

	Materials: Provided in blister cards to assist in measuring adherence and as an aid for patients Providers: Nurses and physician Format/modality: Individually delivered Location/timing: Outpatient care Amount: 12 weeks total (daily) Fidelity measurement: Adherence to study medication regimen was monitored by self-report of medication use and by pill counts
Cointervention	Outpatient care: After 1 week of naltrexone or placebo, participants were started on sertraline 50 mg/day for 1 week, increasing to 100 mg/day as tolerated. In addition to receiving medication, participants were seen regularly by a nurse to support abstinence and assist in treatment. The supportive therapy (BRENDA) was conducted by a nurse (RN or master's level), with sessions lasting 20–30 minutes. BRENDA is a manualized compliance-enhancement therapy based on a six-stage acronym framework: biopsychosocial evaluation, report to patient on assessment, empathetic understanding of the patient's situation, needs that must be addressed, direct advice to patient on how to meet those needs, and assessment of reaction or behaviors of the patient to advice and adjustment as necessary for best care. Each session focused on progress made toward the goal of reducing alcohol consumption and improving depression. Although abstinence is the stated goal for each patient, reductions in drinking are encouraged while working toward this goal. Sessions were initially weekly for 8 weeks, then biweekly. Participants took sertraline on 79 percent of study days, and 84 percent completed 3 months of psychosocial treatment (attended at least 80 percent of the weekly therapy visits).
Outcomes	Remission from depression: HDRS of 10 or less at postintervention (12 weeks postbaseline) Remission from alcohol use: (1) Abstinence and (2) Addiction Severity Index at postintervention (12 weeks postbaseline) Depressive symptoms: HDRS at postintervention (12 weeks postbaseline) Total drinking: Alcohol consumption at postintervention (12 weeks postbaseline) Heavy drinking: Relapse to heavy drinking at postintervention (12 weeks postbaseline) Withdrawal/craving symptoms: Not reported Health-related quality of life: Medical Outcomes Study Short Form (SF-36) at postintervention (12 weeks postbaseline) Functional status: Not reported Adverse events: SAFTEE at postintervention (12 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Unclear (not reported) Blinding of providers: Unclear (not reported) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): High (27 percent overall attrition) Selective outcome reporting: High (Addiction Severity Index, depressive symptoms, total drinking, and health-related quality of life are not reported, and adverse events are reported insufficiently for meta-analysis: NCT00018824)

	Funders: NIMH grants K08 MH01599-01 and 5P30MH52129 and a VA Medication Errors Reporting Program award. Study medication for the acute-phase trial was supplied by Pfizer Pharmaceuticals and DuPont Pharmaceuticals as part of an investigator-initiated proposal. Support for the preparation and submission of the article was provided by the Philadelphia VA Medical Center and the Veterans Integrated Service Network 4 Mental Illness Research, Education and Clinical Center.
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Petersen 2009

References	Parent study Petersen, C. L., and R. D. Zettle, "Treating Inpatients with Comorbid Depression and Alcohol Use Disorders: A Comparison of Acceptance and Commitment Therapy Versus Treatment as Usual," <i>The Psychological Record</i>, Vol. 59, No. 4, Fall 2009, pp. 521–536. Additional Petersen, C. L., <i>Treatment of Comorbid Depression and Alcohol Use Disorders in an Inpatient Setting: Comparison of Acceptance and Commitment Therapy Versus Treatment as Usual</i>, dissertation, Wichita State University, 2007, Ann Arbor, Mich.: University Microfilms International, 3311798, 2008.
Study design	Study dates: November 16, 2006, to March 1, 2006 Objective: To evaluate whether inpatients would experience greater therapeutic benefits from supplementing a 12-step program for chemical dependency with individual sessions of acceptance and commitment therapy Randomization: Individually randomized Recruitment method: Recruited sequentially over a 5-month period from individuals involuntarily committed (by a court because of a psychiatric or substance-use issue) to a chemical dependency unit within a southern state hospital. Individuals admitted for treatment of an AUD who were also diagnosed by medical staff upon admission as exhibiting a depressive disorder were referred and evaluated as possible participants. Inclusion criteria: Presence of a unipolar depressive disorder according to <i>DSM-IV</i> criteria; presence of alcohol abuse, alcohol dependence, or polysubstance dependence with alcohol being a substance of issue according to <i>DSM-IV</i> criteria; capacity to provide informed consent and complete a questionnaire battery Exclusion criteria: Diagnosable with substance-induced depression; exhibit signs of intoxication at any time during the project's assessment or treatment phases; under the age of 18; civil-court committed individuals to forensic services Power calculation: Not reported Sample size: 30 total (15/15)
Setting	Geographic location: Whitfield, Mississippi, United States Intervention sites: Involuntary inpatient chemical dependency unit in a southern state hospital (Mississippi State Hospital) External context: Not reported
Participants	Age: 37.8 (9.7) Gender: 50 percent female Race/ethnicity: 63 percent Caucasian, 33 percent African American, 4 percent Native American

	Other socioeconomics/demographics: 17 percent married, 83 percent single; 11.9 (2.4) years of education Baseline depression: 83 percent depressive disorder not otherwise specified, 13 percent major depressive disorder, 4 percent dysthymic disorder; 54 percent with no history of psychiatric treatment, 38 percent with history of inpatient psychiatric treatment (1.3 treatment episodes on average), 8 percent with history of outpatient psychiatric treatment (1.0 treatment episode on average); 17 percent with previous antidepressant therapy; HDRS of 24.9 (7.4), BDI of 26.3 (10.8) Baseline alcohol use: 62 percent alcohol dependence, 38 percent alcohol abuse; 75 percent with history of inpatient psychiatric treatment (3.0 treatment episodes on average), 25 percent with no history of psychiatric treatment; drank on 56 percent of days in past 3 months, had 12.0 (10.5) drinks per day Other baseline health: 29 percent previous suicide attempt
Intervention 1	Category: Psychological intervention Class: CBT Name: Acceptance and commitment therapy Theory of change: Help patients to accept negative thoughts and emotions, then choose a valued direction of action, and finally take action in this valued direction Materials: Handbook (S. C. Hayes, K. D. Strosahl, and K. G. Wilson, <i>Acceptance and Commitment Therapy: An Experiential Approach to Behavior Change</i>, New York: Guilford) Procedures: Simultaneously addressed both depressive and alcohol-related issues on a biweekly basis for the duration of the treatment phase. Incorporated metaphors and exercises designed to promote defusion and acceptance of troubling private events, mindfulness, and value-directed overt behavioral change. Providers: Graduate student in clinical psychology Format/modality: Individually delivered Location/timing: Inpatient care Amount: Six 30- to 60-minute sessions every 2 weeks Fidelity measurement: Duration of the treatment phase, number of individual therapy sessions, and hours of individual therapy received during treatment. To monitor treatment integrity, a random sample of the total number of acceptance and commitment therapy sessions conducted (24 of 62) was audiotaped. Half of these sessions were subsequently reviewed and judged by a staff psychologist knowledgeable in acceptance and commitment therapy to correspond adequately with the treatment manual (10-point Likert scale). Fidelity data: 22.7 (6.0) days in treatment, 5.2 (0.6) therapy sessions, 3.1 (0.3) hours of therapy, and average treatment integrity of 8.2 (0.8)
Intervention 2	Category: Control intervention Class: Psychological placebo Name: Psychological placebo Procedures: Therapists were instructed to provide the type of approach they deemed appropriate for participants based on their presenting issues, with the primary therapeutic goal of TAU sessions (presumably) being abstinence from alcohol (rather than alleviation of comorbid depression).

	Providers: Staff drug and alcohol counselors Format/modality: Individually delivered Location/timing: Inpatient care Amount: One-hour sessions; the frequency of therapy sessions was determined by availability in the therapist's schedule. Fidelity measurement: Duration of the treatment phase, number of individual therapy sessions, and hours of individual therapy received during treatment Fidelity data: 33.3 (12.3) days in treatment, 4.3 (1.6) therapy sessions, and 4.3 (1.6) hours of therapy
Cointervention	Inpatient care: Services and interventions common to all inpatients in a chemical dependency unit, based on an ongoing 12-step program (Minnesota model). All participants were involved in at least five hours of alcohol and drug group therapy per week, focused primarily on the 12 steps of recovery. For at least 10 hours per week, all participants were involved in educational services dealing with chemical dependence, relapse prevention, medical issues, personal growth, social skills, anger management, coping skills, and information concerning the process of recovery. All participants attended nightly 12-step-based meetings (Alcoholics Anonymous and Narcotics Anonymous). All participants also attended medically related groups and lectures intended to aid in each individual's health promotion. Weekly spirituality-based meetings, daily meditations, and daily therapeutic recreational and leisure activities, including art and music therapy, were provided to all individuals. All participants were involved in four seminars/study groups per week that focused on recovery and relapse prevention. Any decisions about the administration of prescription medications were made by the medical or psychiatric provider involved in the participant's treatment. Finally, as noted previously, all participants, regardless of treatment approach, were prescribed at least one antidepressant medication during their hospitalization, antidepressant medication that was administered individually at a nurse's station in order to monitor compliance.
Outcomes	Remission from depression: (1) Asymptomatic (HDRS score of less than 14), (2) asymptomatic (BDI of less than 14), (3) improved, (4) recovered, and (5) improved and/or recovered at postintervention (3–4 weeks postbaseline) Remission from alcohol use: Not reported Depressive symptoms: (1) HDRS and (2) BDI–II at postintervention (3–4 weeks postbaseline) Total drinking: Alcohol consumption (Timeline Follow-Back) at postintervention (3–4 weeks postbaseline) Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Not reported
Risks of bias	Random sequence generation: Low (random draw) Allocation concealment: Low (participants and investigators enrolling participants could not foresee assignment) Blinding of participants: High (not possible given nature of intervention) Blinding of providers: High (not possible given nature of intervention)

	Blinding of outcome assessors: Low (blind outcome assessors) Completeness of outcome data (postintervention): High (~14 percent overall and ~12 percent differential attrition, with reasons for attrition differing between groups) Selective outcome reporting: High (alcohol consumption was collected but not reported) Funder: Not reported
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Pettinati 2010

References	Parent study Pettinati, H. M., D. W. Oslin, K. M. Kampman, W. D. Dundon, H. Xie, T. L. Gallis, C. A. Dackis, and C. P. O'Brien, "A Double-Blind, Placebo-Controlled Trial Combining Sertraline and Naltrexone for Treating Co-Occurring Depression and Alcohol Dependence," <i>American Journal of Psychiatry</i>, Vol. 167, No. 6, June 2010, pp. 668–675. Additional Dundon, W. D., H. M. Pettinati, and J. K. Garson, "An Examination of Potential Trends of Racial Response to Pharmacological Treatment for Depressed Alcoholics," <i>Alcoholism: Clinical and Experimental Research</i>, Vol. 34, No. 6, 2010, p. 176A. Plebani, J. G., H. M. Pettinati, K. M. Kampman, W. D. Dundon, and K. G. Lynch, "Relationship Between Gender, Relapse to Drinking and Subsequent Depression in a Pharmacotherapy Trial for Comorbid Depression and Alcohol Dependence," <i>Alcoholism: Clinical and Experimental Research</i>, Vol. 32, No. 6, June 2008, pp. 193A. Roth, T. L., E. M. Mahoney, W. D. Dundon, and H. M. Pettinati, "Combination Pharmacotherapy Sertraline and Naltrexone Decreases Suicidal Ideation Scores in Co-Morbid Depressed Alcoholics," <i>Alcoholism: Clinical and Experimental Research</i>, Vol. 36, 2012, p. 245A. "Sertraline Plus Naltrexone Superior for Depressed Alcohol-Dependent Patients," <i>Brown University Psychopharmacology Update</i>, Vol. 21, No. 9, 2010, pp. 1–7. University of Pennsylvania, "Sertraline for Alcohol Dependence and Depression," January 2000. As of March 19, 2019: https://clinicaltrials.gov/show/NCT00004554
Study design	Study dates: January 2000 to August 2005 Objective: To evaluate the efficacy of combining approved medications for depression (sertraline) and alcohol dependence (naltrexone) for treating patients with both an AUD and depressive disorder Randomization: Individually randomized; urn randomization was used to evenly distribute patients across groups using four pretreatment variables: gender, regular smoker (>5 cigarettes/week), randomization HDRS score (10–20 vs. ≥21), and drinking frequency (fewer vs. ≥68 percent days drinking in past 90 days). Recruitment method: Patients learned of the study from newspaper advertisements, local professionals, or friends and family. After an initial telephone screening, patients were invited for evaluation. Inclusion criteria: Aged 21 to 75 years; current <i>DSM-IV</i> major depression and alcohol dependence diagnoses; on average 12 or more alcoholic drinks per week; had a drink on 40 percent or more days in the 90 days before treatment; 3 consecutive abstinent days just before starting medication; score 10 or higher on the HDRS

	Exclusion criteria: Substance dependence besides alcohol or nicotine; had bipolar-affective, schizophrenic, other psychotic, or organic mental disorders; were regularly taking an antidepressant; needed psychiatric medications other than an antidepressant; had a significant medical disease; were pregnant or breastfeeding Power calculation: The a priori study plan had determined that $n = 40$ in the medication combination group and $n = 120$ in the other three treatment groups combined; the study could detect moderate effect sizes between the two groups with 80 percent power while controlling for $\alpha = 0.01$. Sample size: 170 total (42/40/49/39)
Setting	Geographic location: Philadelphia, Pennsylvania, United States Intervention sites: Treatment Research Center, a research-sponsored outpatient substance abuse treatment facility External context: Not reported
Participants	Age: 43.4 (8.6) Gender: 38 percent female Race/ethnicity: 65 percent Caucasian Other socioeconomics/demographics: 14.2 (2.6) years of education; 21 percent currently married; 72 percent mid- to upper socioeconomic status Baseline depression: 49 percent reported a family history of depression; mean HDRS of 23.1 (6.3) Baseline alcohol use: 75 percent reported a family history of alcohol or drug problems; reported having alcohol problems for 21.1 (9.8) years; received prior alcohol treatment 2.4 (6.7) times; drank on 75 percent of days and drank heavily on 68 percent of days in the last month; averaged 12.4 drinks per drinking day Other baseline health: 32 percent smokers
Intervention 1	Category: Pharmacological intervention Class: Opioid antagonist and SSRI Name: Naltrexone and sertraline Materials: Dispensed weekly in blister cards Format/modality: Individually delivered Location/timing: Outpatient care Amount: 14 weeks. Patients took 50 mg/day of naltrexone for 4 days and then added 50 mg/day for 3 days to the maximum naltrexone dose of 100 mg/day. In the next week, patients added 50 mg/day of sertraline and were titrated up, adding 50 mg/day every third day, to the maximum sertraline dose of 200 mg/day. Medical clinicians could exercise flexibility in dosing patients who could not tolerate maximum daily doses. Patients continued with treatment until the thirteenth week, when naltrexone was reduced to 50 mg/day while maintaining sertraline at 200 mg/day. In the fourteenth week, naltrexone was continued at 50 mg/day and sertraline was reduced to 100 mg/day. Medications were completed by the last treatment day. Fidelity measurement: Percentage of prescribed pills taken while in treatment Fidelity data: Medication adherence rate of 91 percent

Intervention 2	Category: Pharmacological intervention Class: SSRI Name: Sertraline Materials: Dispensed weekly in blister cards Format/modality: Individually delivered Location/timing: Outpatient care Amount: 14 weeks. Patients took 50 mg/day of placebo for 4 days and then added 50 mg/day for 3 days to the maximum dose of 100 mg/day. In the next week, patients added 50 mg/day of sertraline and were titrated up, adding 50 mg/day every third day, to the maximum sertraline dose of 200 mg/day. Medical clinicians could exercise flexibility in dosing patients who could not tolerate maximum daily doses. Patients continued with treatment until the thirteenth week, maintaining sertraline at 200 mg/day. In the fourteenth week, sertraline was reduced to 100 mg/day. Medications were completed by the last treatment day. Fidelity measurement: Percentage of prescribed pills taken while in treatment Fidelity data: Medication adherence rate of 82 percent
Intervention 3	Category: Pharmacological intervention Class: Opioid antagonist Name: Naltrexone Materials: Dispensed weekly in blister cards Format/modality: Individually delivered Location/timing: Outpatient care Amount: 14 weeks. Patients took 50 mg/day of naltrexone for 4 days and then added 50 mg/day for 3 days to the maximum naltrexone dose of 100 mg/day. In the next week, patients added 50 mg/day placebo and were titrated up, adding 50 mg/day every third day, to the maximum placebo dose of 200 mg/day. Medical clinicians could exercise flexibility in dosing patients who could not tolerate maximum daily doses. Patients continued with treatment until the thirteenth week, when naltrexone was reduced to 50 mg/day. In the fourteenth week, naltrexone was continued at 50 mg/day. Medications were completed by the last treatment day. Fidelity measurement: Percentage of prescribed pills taken while in treatment Fidelity data: Medication adherence rate of 85 percent
Intervention 4	Category: Pharmacological intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Dispensed weekly in blister cards Format/modality: Individually delivered Location/timing: Outpatient care Amount: 14 weeks. Patients took 50 mg/day of “sertraline placebo” for 4 days and then added 50 mg/day for 3 days to the maximum “sertraline placebo” dose of 100 mg/day. In the next week, patients added 50 mg/day of placebo and were titrated up, adding 50 mg/day every third day, to the maximum “naltrexone placebo” dose of 200 mg/day. Medical clinicians could exercise flexibility in dosing patients who could not tolerate maximum daily doses. Patients continued with treatment until the thirteenth week, when

	“naltrexone placebo” was reduced to 50 mg/day while maintaining “sertraline placebo” at 200 mg/day. In the fourteenth week, “naltrexone placebo” was continued at 50 mg/day and “sertraline placebo” was reduced to 100 mg/day. Medications were completed by the last treatment day. Fidelity measurement: Percentage of prescribed pills taken while in treatment Fidelity data: Medication adherence rate of 91 percent
Cointervention	Outpatient care: Weekly, individual CBT using the National Institute on Alcohol Abuse and Alcoholism Project MATCH manual, adapted to also treat depression. Over the 14-week trial, patients attended 8.2 CBT sessions (59 percent of 14 possible sessions) and 3.4 support group meetings.
Outcomes	Remission from depression: No depression (9 or lower score on the last HDRS score in the final 3 treatment weeks) at postintervention (14 weeks postbaseline) Remission from alcohol use: (1) Total abstinence (percentage of patients who were abstinent on all days) and (2) time to return to any drinking at postintervention (14 weeks postbaseline) Depressive symptoms: HDRS at postintervention (14 weeks postbaseline) Total drinking: Not reported Heavy drinking: (1) Time to relapse (median number of days in treatment before a heavy drinking day; a heavy drinking day was defined as consuming in a day 5 or more drinks for men, or 4 or more drinks for women) and (2) percentage of patients not drinking heavily (in a day, 5 or more drinks for men, or 4 or more drinks for women) at postintervention (14 weeks postbaseline) Withdrawal/craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: SAFTEE at postintervention (14 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): High for remission from depression and depressive symptoms (>25 percent attrition for any given comparison) Selective outcome reporting: High (time to return to any drinking and percentage of patients not drinking heavily were not reported sufficiently for inclusion in meta-analyses) Funder: This study was funded by the National Institute on Alcohol Abuse and Alcoholism, grant R01-AA09544-10. Pfizer Pharmaceuticals donated sertraline and matching placebo.

Ralevski 2013

References	Parent study Ralevski, E., J. S. Jane, E. O'Brien, E. Edens, B. Arnaout, K. Kerfoot, K. Keegan, J. Weiner, M. Russo, and I. Petrakis, "Mecamylamine for Treatment of People with Dual Diagnoses of Depression and Alcohol Dependence," <i>Journal of Dual Diagnosis</i>, Vol. 9, No. 4, 2013, pp. 301–310. Additional Ralevski, E., J. S. Jane, A. O'Brien, J. Weiner, E. Edens, B. Arnaout, K. Kerfoot, R. Dwan, and I. Petrakis, "Mec1005mylamine for the treatment of patients with depression and alcohol dependence," <i>Alcoholism: Clinical and Experimental Research</i>, Vol. 36, 2012, p. 296A. Yale University and National Alliance for Research on Schizophrenia and Depression, "Mecamylamine for the Treatment of Patients with Depression and Alcohol Dependence," August 2007. As of March 19, 2019: https://clinicaltrials.gov/show/NCT00563797
Study design	Study dates: August 2007 to July 2014 Objective: To assess the efficacy of mecamylamine augmentation of an antidepressant in reducing drinking, smoking, and depressive symptoms Randomization: Individually randomized; randomization was stratified by smoking status. Recruitment method: Not reported Inclusion criteria: Met current <i>DSM-IV</i> criteria for major depression; met current <i>DSM-IV</i> criteria for alcohol dependence; had been on a stable antidepressant dose for two weeks Exclusion criteria: Taking medications thought to influence drinking behavior (e.g., acamprosate, disulfiram, naltrexone, topiramate, or ondansetron); had a significant underlying medical condition; met current <i>DSM-IV</i> criteria for bipolar disorder, posttraumatic stress disorder, schizophrenia, or schizophrenia-type disorders Power calculation: Not reported Sample size: 21 total (11/10)
Setting	Geographic location: Connecticut, United States Intervention sites: Not reported External context: Not reported
Participants	Age: 49.6 (9.0) Gender: 29 percent female Race/ethnicity: 76 percent Caucasian, 24 percent African American Other socioeconomics/demographics: 24 percent single, 19 percent married/cohabitating, 52 percent separated/divorced, 5 percent widowed Baseline depression: HDRS of 13.3 (4.3) Baseline alcohol use: 11.5 (8.7) drinks per drinking day, 22.3 (7.8) drinking days in the past month, 20.0 (9.6) heavy drinking days in the past month; Alcohol Dependence Scale score of 19.7 (10.0) Other baseline health: 33 percent taking concomitant medications; 14.9 (6.6) cigarettes per day among smokers

Intervention 1	Category: Pharmacological intervention Class: nAChRs Name: Mecamylamine Format/modality: Individually delivered Location/timing: Outpatient care Amount: 12 weeks (5 to 10 mg daily in divided doses). Participants started at 2.5 mg once daily (the second dose was placebo), and the dose was increased to 5.0 mg twice daily over 3 weeks.
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Placebo capsules were prepared by the pharmacy and were identical in size and color to the medication capsules. Format/modality: Individually delivered Location/timing: Outpatient care Amount: 12 weeks (equally divided doses to mecamylamine)
Cointervention	Outpatient care: Participants were started on 20 mg of paroxetine or an equivalent medication (if paroxetine was contraindicated) before starting treatment with mecamylamine. Twelve individuals received paroxetine (20 mg) for 2 weeks before being randomly assigned to either mecamylamine or placebo. Nine individuals were taking other antidepressants before beginning the study medication: five were receiving citalopram, one duloxetine, one escitalopram, one fluoxetine, and one sertraline. All participants received medical management, a behavioral intervention designed for individuals with alcohol dependence. The objective of medical management is to approximate a primary care environment for delivering care for alcohol-dependent individuals with a focus on negative consequences of drinking and education regarding medication regimen and compliance. Seven participants were taking concomitant medications, four were taking sleep medications, and three were prescribed benzodiazepines as needed for anxiety ($n = 5$ in the placebo group and $n = 2$ in the mecamylamine group).
Outcomes	Remission from depression: Not reported Remission from alcohol use: Abstinence rates at postintervention (12 weeks postbaseline) Depressive symptoms: HDRS at postintervention (12 weeks postbaseline) Total drinking: (1) Number and (2) percentage of drinking days at postintervention (12 weeks postbaseline) Heavy drinking: (1) Number and (2) percentage of heavy drinking days (5 or more standard drinks for men and 4 or more standard drinks for women on a single occasion) at postintervention (12 weeks postbaseline) Withdrawal and craving symptoms: OCDS at postintervention (12 weeks postbaseline) Health-related quality of life: Not reported Functional status: Not reported Adverse events: SAFTEE at postintervention (12 weeks postbaseline)

Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Low (blind to medication assignment) Completeness of outcome data (postintervention): Low (analyses included all participants) Selective outcome reporting: High (remission from alcohol use, total drinking, heavy drinking, and withdrawal and craving symptoms had “no significant main effects” but were not reported sufficiently for inclusion in meta-analyses) Funders: Support for this study was provided by National Alliance for Research on Schizophrenia and Depression and the VA Veterans Integrated Service Network 1 Mental Illness Research, Education and Clinical Center.
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Roy 1998

References	Parent study Roy, A., “Placebo-Controlled Study of Sertraline in Depressed Recently Abstinent Alcoholics,” <i>Biological Psychiatry</i>, Vol. 44, No. 7, October 1, 1998, pp. 633–637.
Study design	Study dates: Took place over a 3-year period Objective: To assess the efficacy of sertraline for depressed, recently abstinent alcoholics Randomization: Individually randomized Recruitment method: Recruited inpatients who were abstinent for at least 2 weeks (in the locked Alcoholic Rehabilitation Unit) Inclusion criteria: Met current <i>DSM-III-R</i> criteria for current major depressive episode; met current <i>DSM-III-R</i> criteria for alcohol dependence Exclusion criteria: Schizophrenia, bipolar disorder, obsessive-compulsive disorder, dementia, other <i>DSM-III-R</i> major Axis I disorder, nonalcohol substance dependence, epilepsy, organic mental disorder, significant medical disorder; abuse of another substance where alcohol was not the main substance of abuse; received antidepressant medication in the previous month Power calculation: Not reported Sample size: 36 total (18/18)
Setting	Geographic location: East Orange, New Jersey, United States Intervention sites: Alcoholic Rehabilitation Unit of the VA Medical Center External context: The veterans hospital served an impoverished inner-city population, with 50 percent of the patients admitted to the substance abuse program being homeless.
Participants	Age: 40.9 (6.7) Gender: 8 percent female Race/ethnicity: 47 percent Caucasian, 47 percent African American, 6 percent Hispanic

	Other socioeconomics/demographics: 56 percent separated/divorced/widowed, 25 percent single, 19 percent married; 83 percent working class, 17 percent middle class Baseline depression: 47 percent with primary depression; 7.0 (7.2) months of depression; HDRS of 22.3 (6.5); BDI of 31.6 (8.6) Baseline alcohol use: Age at onset of alcoholism of 23.0 (6.8), 17.9 (8.0) years of alcoholism; 4.8 (6.2) weeks of abstinence at study entry Other baseline health: 8 percent with lifetime history of illicit drugs
Intervention 1	Category: Pharmacological intervention Class: SSRI Name: Sertraline Materials: Identical-appearing opaque capsules Format/modality: Individually delivered Location/timing: Started as inpatient care and eventually moved to outpatient care Amount: 6 weeks (100 mg once daily). Fidelity measurement: Compliance as outpatients was monitored by weekly pill count.
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Identical-appearing opaque capsules Format/modality: Individually delivered Location/timing: Started as inpatient care and eventually moved to outpatient care Amount: 6 weeks (once daily) Fidelity measurement: Compliance as outpatients was monitored by weekly pill count.
Co-intervention	Inpatient and outpatient care: Details not reported
Outcomes	Remission from depression: (1) Treatment response using the HDRS, (2) treatment response using the BDI, and (3) number removed from the study because of depression worsening or lack of improvement at postintervention (6 weeks postbaseline) Remission from alcohol use: Relapse to drinking at postintervention (6 weeks postbaseline) Depressive symptoms: (1) HDRS and (2) BDI at postintervention (6 weeks postbaseline) Total drinking: Not reported Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: CGI scale (“very much improved”) at postintervention (6 weeks postbaseline) Adverse events: Not reported

Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Low (blind to medication status) Completeness of outcome data (postintervention): High for depressive symptoms (61 percent attrition and reasons for attrition differing vastly between groups) Selective outcome reporting: High (BDI was not significant but reported insufficiently for inclusion in meta-analyses) Funder: Not reported
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Roy-Byrne 2000

References	Parent study Roy-Byrne, P. P., K. P. Pages, J. E. Russo, C. Jaffe, A. W. Blume, E. Kingsley, D. S. Cowley, and R. K. Ries, "Nefazodone Treatment of Major Depression in Alcohol-Dependent Patients: A Double-Blind, Placebo-Controlled Trial," <i>Journal of Clinical Psychopharmacology</i>, Vol. 20, No. 2, April 2000, pp. 129–136.
Study design	Study dates: Not reported Objective: To test the efficacy of nefazodone versus placebo for the treatment of depression in actively drinking alcohol-dependent patients who were also participating in weekly group treatment for alcoholism Randomization: Individually randomized Recruitment method: Recruited through local newspaper and radio advertisements and hospital flyers Inclusion criteria: Aged 18 to 55 years; met current <i>DSM-III-R</i> criteria for major depression; met current <i>DSM-III-R</i> criteria for alcohol dependence; reported a major depressive episode during a period of at least 1 month of sobriety Exclusion criteria: Intravenous drug use; other drug use more than once per week; schizophrenia; bipolar disorder; active suicidal ideation with a plan; recent history of delirium tremens or alcohol-withdrawal seizures; current treatment for depression or alcoholism; serious medical problems; treatment with medications that are contraindicated in combination with nefazodone (Seldane, Hismanal, or Propulsid); pregnancy; untreated hypothyroidism or hyperthyroidism; clinically significant liver dysfunction; active cardiac or renal impairment (defined as hospitalization or change in treatment plan in last 6 months); homelessness Power calculation: Not reported Sample size: 64 total (32/32)
Setting	Geographic location: Seattle, Washington, United States Intervention sites: Harborview Medical Center Outpatient Psychiatry Clinic, University of Washington, Seattle External context: Not reported
Participants	Age: 40.2 (8.2) Gender: 55 percent female

	Race/ethnicity: 92 percent white Other socioeconomics/demographics: 27 percent married; 14.2 (2.3) years of education; 70 percent employed Baseline depression: 100 percent major depression, 45 percent dysthymia; HDRS of 23.9 (5.2) Baseline alcohol use: 100 percent alcohol dependence, 39 percent alcohol abuse; craving for alcohol visual analog scale of 5.6 (2.0); AUDIT of 26.4 (6.1); 9.8 (10.3) drinks per day in the week before intake Other baseline health: 77 percent with one or more (1.7 on average) comorbid Axis I diagnoses: 31 percent social phobia, 28 percent generalized anxiety disorder, 22 percent specific phobias, 13 percent panic disorder, 11 percent posttraumatic stress disorder, 8 percent obsessive-compulsive disorder, 5 percent agoraphobia without panic disorder, 3 percent antisocial personality, 2 percent anorexia, 2 percent adjustment disorder; Hamilton Anxiety Rating Scale of 23.5 (8.3); CGI severity of illness of 4.9 (0.8); Drug Abuse Screening Test of 7.5 (6.6)
Intervention 1	Category: Pharmacological intervention Class: SARI Name: Nefazodone Format/modality: Individually delivered Location/timing: Outpatient care Amount: 12 weeks. Dosing was started at one capsule (100 mg) twice daily and was titrated at a rate of one additional capsule (100 mg) per week until the patients were taking two capsules in the morning and three capsules at night (500 mg total). Tailoring/adaptation: Patients who experienced side effects were given routine instructions for alleviating those reactions. For example, if patients complained of being sedated, they were instructed to take a higher dose in the evening than in the morning. Fidelity measurement: Although patients were instructed to return unused medication, the majority failed to do this reliably, so the pill count could not be used to measure compliance. Because of finding limitations, nefazodone levels were not measured. Fidelity data: For patients who received nefazodone for at least the 4 weeks required for full titration ($N = 27$), the mean (SD) dose was 460 (75) mg. Twenty patients were given 500 mg, three were given 400 mg, and four were given 300 mg.
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Theory of change: Not reported Format/modality: Individually delivered Location/timing: Outpatient care Amount: 12 weeks. Dosing was started at one capsule (100 mg) twice daily and was titrated at a rate of one additional capsule (100 mg) per week until the patients were taking two capsules in the morning and three capsules at night (500 mg total). Tailoring/adaptation: Patients who experienced side effects were given routine instructions for alleviating those reactions. For example, if patients complained of being sedated, they were instructed to take a higher dose in the evening than in the morning.

	Fidelity measurement: Although patients were instructed to return unused medication, the majority failed to do this reliably, so the pill count could not be used to measure compliance. Because of finding limitations, nefazodone levels were not measured.
Cointervention	Outpatient care: Patients engaged in a cognitive-behavioral skills training and psychoeducational group for alcohol dependence and depression led by an experienced therapist. The format was an open-ended 12-session cycle. Themes addressed included cognitive function, alcohol, and depression; the decisional balance; assertion training and drink-refusal skills; insomnia; tolerating distress; lifestyle moderation strategies; cognitive self-therapy skills; rumination; behavioral management skills; support group options; tolerance and the biphasic response to alcohol; and stress management. Group sessions lasted one hour once per week. These topics recycled every 12 weeks so that all patients received essentially the same information within the group context.
Outcomes	Remission from depression: (1) Full response (HDRS score of less than 8) and (2) partial response (50 percent decrease in HDRS scores from baseline) at postintervention (12 weeks postbaseline) Remission from alcohol use: (1) Met criteria for alcohol dependence using the AUDIT and (2) abstinent at postintervention (12 weeks postbaseline) Depressive symptoms: HDRS at postintervention (12 weeks postbaseline) Total drinking: Drinks consumed per day at postintervention (12 weeks postbaseline) Heavy drinking: Not reported Withdrawal and craving symptoms: Visual analog scale at postintervention (12 weeks postbaseline) Health-related quality of life: Not reported Functional status: CGI scale (1) “very much improved” or “much better” and (2) discrete score at postintervention (12 weeks postbaseline) Adverse events: Side effects (single open-ended question) at postintervention (12 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Low (blind to treatment condition) Completeness of outcome data (postintervention): High (52 percent overall attrition and 28 percent differential attrition) Selective outcome reporting: High (partial response [50 percent decrease in HDRS scores from baseline] was not significant but reported insufficiently for inclusion in meta-analyses) Funder: This study was supported in part by an investigator-initiated grant from Bristol-Meyers Squibb.

Salloum 2007

References	Parent study Salloum, I. M., “Drug Treatment for Depressed Alcoholics (Naltrexone/Fluoxetine),” ClinicalTrials.gov identifier NCT00006204,” 2007. As of March 19, 2019: https://clinicaltrials.gov/ct2/show/NCT00006204 Additional Salloum, I. M., J. R. Cornelius, A. Douaihy, R. Caceda, F. Miao, and L. Kirisci, “Differential Impact of Cannabis Abuse on Depression Remission in Comorbid Depression and Alcoholism,” <i>Alcoholism: Clinical and Experimental Research</i>, Vol. 36, 2012, p. 299A. Salloum, I. M., J. R. Cornelius, A. Douaihy, and D. C. Daley, “Predicting Medication Adherence and Treatment Completion Among Depressed Alcoholics,” <i>Alcoholism: Clinical and Experimental Research</i>, Vol. 37, 2013, p. 198A. Salloum, I. M., J. R. Cornelius, A. Douaihy, and L. Kirisci, “Gender Difference in Alcohol Treatment Response in Patients with Comorbid Alcoholism and Depression,” <i>Alcoholism: Clinical and Experimental Research</i>, Vol. 35, 2011, p. 19A. Salloum, I. M., J. Perel, J. R. Cornelius, A. Douaihy, D. C. Daley, T. M. Kelly, and L. Kirisci, “Naltrexone Decreases Plasma Concentration of Fluoxetine/Norfluoxetine in Depressed Alcoholics: Results from a Double-Blind, Placebo-Controlled Study,” <i>Alcoholism: Clinical and Experimental Research</i>, Vol. 30, No. 9, September 2006, pp. 165A. Salloum, I. M., J. M. Perel, J. R. Cornelius, A. Douaihy, L. Kirisci, J. C. Helsel, and M. E. Thase, “Therapeutic Drug Monitoring (TDM) and Treatment Response in Major Depression with Comorbid Alcoholism,” <i>Neuropsychopharmacology</i>, Vol. 35, 2010, pp. S314–S315.
Study design	Study dates: March 2000 to January 2006 Objective: To test the efficacy of the combination of naltrexone and fluoxetine versus fluoxetine alone in the treatment of patients with alcoholism and comorbid major depression Randomization: Individually randomized (1:1 allocation ratio) Recruitment method: Not reported Inclusion criteria: Aged 18 to 65 years; met <i>DSM-IV</i> criteria for alcohol dependence; met <i>DSM-IV</i> criteria for major depressive disorder; absence of any hazardous drinking within 48 to 120 hours (defined as more than or equal to 3 drinks/day for females and more than or equal to 4 drinks/day for males); no more than 15 days of complete abstinence before study. Exclusion criteria: Psychiatric conditions including schizophrenia, schizoaffective disorder, any nonbipolar psychiatric disorder, bipolar disorders, primary anxiety disorder, mental retardation, and signs of impaired cognitive functioning; any nonalcohol substance dependence except for nicotine; opioid abuse, opioid dependence, or on opioid maintenance treatment; neurological conditions including epilepsy, history of brain injury, encephalitis, or any organic brain syndrome or focally abnormal electroencephalograph examination; medical conditions including severe cardiac, liver, kidney, endocrine, hematologic, and other impairing or unstable medical conditions or impending surgery; persistent elevation of liver enzymes indicating active liver disease; females who are pregnant or unable or unwilling to use reliable birth control methods; unable to read or understand study forms and agree to informed consent Power calculation: Not reported Sample size: 106 total (not reported)

Setting	Geographic location: Pittsburgh, Pennsylvania, United States Intervention sites: Not reported External context: Not reported
Participants	Age: Not reported Gender: 46 percent female Race/ethnicity: Not reported Other socioeconomics/demographics: Not reported Baseline depression: Not reported Baseline alcohol use: Not reported Other baseline health: Not reported
Intervention 1	Category: Pharmacological intervention Class: Opioid antagonist and SSRI Name: Naltrexone and fluoxetine Format/modality: Individually delivered Location/timing: Outpatient care Amount: 6 months (fluoxetine dose range of 20–60 mg/day and naltrexone dose of 50 mg/day) Fidelity measurement: MEMS-caps method was used to monitor adherence to study medication. Fidelity data: Average fluoxetine dose of 31.8 (14.9) mg
Intervention 2	Category: Pharmacological intervention Class: SSRI Name: Fluoxetine Materials: Also received placebo to match the two pills received in the other intervention arm Format/modality: Individually delivered Location/timing: Outpatient care Amount: 6 months (fluoxetine dose range of 20–60 mg/day) Fidelity measurement: MEMS-caps method was used to monitor adherence to study medication. Fidelity data: Average fluoxetine dose of 33.4 (14.8) mg
Cointervention	Outpatient care: Weekly individual Dual Disorders Recovery Counseling during the first month and every 2 weeks during the second through sixth months
Outcomes	Remission from depression: Not reported Remission from alcohol use: Not reported Depressive symptoms: HDRS at 3 and 6 months postintervention (9 and 12 months postbaseline) Total drinking: Alcohol use (Timeline Follow-Back) at 3 and 6 months postintervention (9 and 12 months postbaseline)

	Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Not reported
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): Unclear (not reported) Selective outcome reporting: High (outcomes were reported insufficiently for inclusion in meta-analyses) Funder: National Institute on Alcohol Abuse and Alcoholism

Shaw 1975

References	Parent study Shaw, J. A., P. Donley, D. W. Morgan, and J. A. Robinson, "Treatment of depression in alcoholics," <i>American Journal of Psychiatry</i> , Vol. 132, No. 6, June 1975, pp. 641–644.
Study design	Study dates: Not reported Objective: To compare two groups of depressed alcoholics given either placebo or chlordiazepoxide and imipramine Randomization: Individually randomized Recruitment method: Recruited treatment-seeking patients in a multifaceted halfway house Inclusion criteria: Diagnosis of alcoholism according to the recommendations of the National Council on Alcoholism (reported at least one of the major obligatory criteria: physiological dependence, tolerance, or a major alcohol-associated illness); depression according to the depression scale of the MMPI, Zung's Self-Rating Depression Scale, and BDI; geographic proximity for the follow-up evaluation (within 50 miles of halfway house) Exclusion criteria: Medical contraindications to disulfiram, chlordiazepoxide, or imipramine Power calculation: Not reported Sample size: 30 total (15/15)
Setting	Geographic location: United States Intervention sites: Multifaceted halfway house External context: Not reported
Participants	Age: 31.6 (ranged from 18 to 50) Gender: 0 percent female

	Race/ethnicity: Not reported Other socioeconomics/demographics: 47 percent married, 36 percent single, 16 percent divorced, 3 percent separated; 52 percent active duty in the U.S. Army; 6 percent employed civilians; 52 percent graduated from high school, 41 percent had attended college Baseline depression: 88 percent scored two standard deviations above the mean on the MMPI depression scale, 40 percent scored three standard deviations above the mean on the MMPI depression scale; 76 percent were mildly depressed according to the BDI, 15 percent were severely depressed according to the BDI; 84 percent were clinically depressed according to Zung's Self-Rating Depression Scale Baseline alcohol use: 57 percent reported a drinking problem in excess of 2 years; 10 percent reported a drinking problem in excess of 10 years; 64 percent reported their drinking had increased in the 6 months before treatment; 66 percent were daily drinkers; 41 percent preferred beer, 31 percent preferred liquor, 28 percent preferred liquor and beer, 0 percent preferred wine; 72 percent had experienced blackouts, 22 percent reported more than 10 previous blackout episodes; 21 percent reported at least one episode of delirium tremens, 3 percent had repeated episodes of delirium tremens; 71 percent described shakes following drinking, 50 percent noted gastrointestinal distress associated with drinking, 9 percent reported either seizures or liver trouble Other baseline health: Not reported
Intervention 1	Category: Pharmacological intervention Class: TCA and sedative Name: Chlordiazepoxide and imipramine Providers: Psychiatric nurse Format/modality: Individually delivered Location/timing: Inpatient and outpatient care Amount: 40 mg of chlordiazepoxide and 150 mg of imipramine daily for an average of 31 days
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Identical to other intervention arm Providers: Psychiatric nurse Format/modality: Individually delivered Location/timing: Inpatient and outpatient care Amount: Daily for an average of 31 days
Cointervention	Inpatient and outpatient care: All of the patients had been detoxified before entering the study. The multifaceted halfway house included inpatient care for a period of no longer than 2 weeks and an outpatient program providing individual counseling, group counseling, chemotherapy, and strongly emphasizing Alcoholics Anonymous. Halfway house policy was to administer disulfiram (250 mg per day) to every patient unless there were medical contraindications (informed consent for disulfiram was a condition for acceptance into the facility).
Outcomes	Remission from depression: Not reported Remission from alcohol use: Not reported

	Depressive symptoms: (1) BDI, (2) depression scale of the MMPI, and (3) Zung's Self-Rating Depression Scale at postintervention (4 weeks postbaseline) Total drinking: Not reported Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Not reported
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): Low (3 percent overall attrition) Selective outcome reporting: High (outcomes were statistically not significant but reported insufficiently for inclusion in meta-analyses) Funder: Not reported

Thapinta 2014

References	Parent study Thapinta, D., S. Skulphan, and P. Kittrattanapaiboon, "Brief Cognitive Behavioral Therapy for Depression Among Patients with Alcohol Dependence in Thailand," <i>Issues in Mental Health Nursing</i>, Vol. 35, No. 9, September 2014, pp. 689–693.
Study design	Study dates: October 2011 to December 2012 Objective: To evaluate the short-term efficacy of brief CBT for reducing depression among Thai general hospital patients with alcohol dependence Randomization: Individually randomized Recruitment method: Recruited by staff nurses at district and provincial hospitals in northern Thailand Inclusion criteria: Aged 18 to 60 years; having the ability to communicate in Thai; having a diagnosis of alcohol dependence; having a score of 7 to 18 (mild to moderate depression) on the 9Q; receiving fluoxetine as an antidepressant; having no evidence of moderate or severe suicide risk; having a willingness to participate in the research project Exclusion criteria: None reported Power calculation: Sample size calculations for each group were based on a previous study and indicated that 25 patients were required per group for an effect size = 0.8, alpha = 0.05, and power = 0.80. Sample size: 80 total (40/40)
Setting	Geographic location: Thailand Intervention sites: Five district and provincial hospitals in outpatient departments External context: District and provincial hospitals provide much of the primary care for the Thai public and the majority of people with depressive and SUDs initially present in primary care settings rather than in psychiatric specialty settings.

Participants	Age: 44.9 (8.2) Gender: 18 percent female Race/ethnicity: Not reported Other socioeconomics/demographics: 5 percent no education, 65 percent primary school education, 20 percent secondary school education, 7 percent bachelor's degree or higher Baseline depression: 9Q of 12.0 (3.5), indicating mild depression on average Baseline alcohol use: Most participants had started drinking alcohol between 16 and 20 years of age. Other baseline health: Not reported
Intervention 1	Category: Psychological intervention Class: CBT Name: Brief CBT Theory of change: Based on Beck's Cognitive Theory of Depression. It focused on processes such as participants' perceptions and behaviors, helping them to alter or create new ways to view the world and change their NATs, learn how to change behaviors, and acquire ways of dealing with everyday problems in ways that lead to less negative affect and physical discomfort. Procedures: The first session contained a psychoeducational overview of the cognitive model to enhance the participants' understanding of depression and of brief six-session CBT; this first session also helped participants identify their NATs. During the second to sixth sessions, the participants received training to identify and manage their automatic thoughts. Within the sessions, the therapist rated automatic thoughts in comparison with the severity of depressed emotion and worked with the participants to modify their NATs. Every session included homework assignments (which included behavior activation); these assignments were reviewed in the next session. In the final session, therapists provided a summary of the treatment and conducted a posttest evaluation with the 9Q. Providers: Ten trained registered nurses with master's degrees in mental health and psychiatric nursing, working in the study hospitals, served as the therapists for this study. The nurse-therapists attended 24 hours of brief six-session CBT intervention training. They also received approximately six hours of supervision by two instructors of the Faculty of Nursing, Chiang Mai University, who are experts in CBT. The supervision included observation and feedback for each session, as well as case conferences. The research team randomly visited and observed the interventionists for one or more sessions. Location/timing: Outpatient Amount: Six sessions (two 40- to 60-minute sessions a week) over 3 weeks
Intervention 2	Category: Control intervention Class: No additional treatment Name: No additional treatment
Cointervention	Outpatient care: General counseling and, if needed, antidepressant medication
Outcomes	Remission from depression: Not reported Remission from alcohol use: Not reported Depressive symptoms: Nine-question (9Q) assessment tool for depression severity at postintervention (3 weeks postbaseline) and 4 weeks postintervention (7 weeks postbaseline)

	Total drinking: Not reported Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Not reported
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: High (not possible because of nature of intervention) Blinding of providers: High (not possible because of nature of intervention) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): High (25 percent overall and 15 percent differential attrition) Selective outcome reporting: Unclear (no protocol reported) Funder: The Integrated Management for Alcohol Intervention Program, Mental Health Department, Ministry of Public Health Thailand provided funding for this research.

Thapinta 2017

References	Parent study Thapinta, D., S. Skulphan, V. Kitsumban, and C. Longchoopol, "Cognitive Behavior Therapy Self-Help Booklet to Decrease Depression and Alcohol Use Among People with Alcohol Dependence in Thailand," <i>Issues in Mental Health Nursing</i>, June 14, 2017, pp. 1–7.
Study design	Study dates: Not reported Objective: To evaluate the effectiveness of a CBT self-help booklet with usual care in decreasing depression and alcohol use among people with co-occurring alcohol dependence and mild depression Randomization: Individually randomized Recruitment method: Recruited patients from primary care services in community hospitals Inclusion criteria: Aged 18 to 60 years; alcohol dependence based on <i>DSM-IV</i> criteria; a score in the mild depression (5–8) range on the PHQ-9 Thai version; demonstrate normal communication and intelligence on the Mini-Mental State Examination, Thai version; were not currently receiving antidepressant medication, alcohol-related medication, or CBT; able to read and write in Thai Exclusion criteria: Having a current diagnosis of psychosis by a psychiatrist; any physical illness that required inpatient care Power calculation: The sample size calculation was based on a previous study with $p = .05$, power = 0.8, and effect size = 0.3, which indicated that 175 participants would be needed in each study group. Sample size: 350 total (175/175)

Setting	Geographic location: Thailand Intervention sites: Primary care services in community hospitals. Study sites were chosen randomly from within each of Thailand's major regions: central, north, northeast, eastern, and south. Community hospitals in the study were located in Nonthaburi (Central), Tak (North), Ubon Ratchathani (Northeast), Rayong (East), and Surat Thani (South). The sample size for each condition in the study in each province was n = 35, except Rayong (a relatively small province in a relatively small region, n = 30 in each condition) and Nonthaburi (a relatively populous province in a very populous region, n = 40 in each condition). External context: Not reported
Participants	Age: 39.1 (10.9) Gender: 12 percent female Race/ethnicity: Not reported Other socioeconomics/demographics: 2 percent no education, 42 percent primary school, 40 percent secondary school, 8 percent diploma, 6 percent bachelor's degree, 1 percent higher than bachelor's degree Baseline depression: PHQ-9 of 7.0 (1.1) Baseline alcohol use: 553.6 (372.7) cubic centimeters of alcohol per day Other baseline health: Not reported
Intervention 1	Category: Psychological intervention Class: CBT Name: CBT self-help book Materials: The booklet was a color book with 44 pages, size 21 cm × 14.5 cm (8.26 in × 5.71 in) Procedures: The booklet included five components: (1) an introduction that provided instruction on how to use the book; (2) explanations and examples of NATs (the focus of CBT intervention) that had been generated from a focus group of people with alcohol dependence and mild depression; (3) psychoeducational material that explained how cognition and depression were related and how CBT could decrease depression; (4) examples of situations presented to NATs were provided and were explained by the CBT model; and (5) exercises to help users practice identifying NATs, evaluate NATs, respond to them, and engage in problem-solving to ensure that NATs were not distortions of observable reality. On the first day of use, the booklet asked participants to read instructions and to identify at least three NATs, which was followed by discussion of the illustrative examples that demonstrated how to prove or disprove these thoughts, how to restructure their NATs, and how to use problem-solving skills. Participants were then asked by the booklet to identify NATs every three days, and to repeat the process of proving or disproving, restructuring, and problem-solving. On the nonpractice days, participants were asked to review their most recent NAT practice and what they had done in that session. Providers: Nurses explained how to use the booklet and encouraged participants to read the instructions and the psychoeducational material. Participants were able to contact the nurses by phone if they had any questions. Location/timing: Outpatient Amount: One week

Intervention 2	Category: Control intervention Class: No additional treatment Name: No additional treatment
Cointervention	Outpatient primary care: Usual care services provided by the community hospital included self-care for depression and brief explanation about depression (causes, signs, symptoms, treatment, and counseling) and medical treatment for any physical symptoms as needed.
Outcomes	Remission from depression: Not reported Remission from alcohol use: Not reported Depressive symptoms: PHQ-9 at postintervention (1 week postbaseline), 1 month postintervention (5 weeks postbaseline), 3 months postintervention (14 weeks postbaseline), and 6 months postintervention (27 weeks postbaseline) Total drinking: Cubic centimeters of alcohol consumed per day at postintervention (1 week postbaseline), 1 month postintervention (5 weeks postbaseline), 3 months postintervention (14 weeks postbaseline), and 6 months postintervention (27 weeks postbaseline) Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Not reported
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: High (not possible because of nature of intervention) Blinding of providers: High (not possible because of nature of intervention) Blinding of outcome assessors: Low (blind to the assignment of participants to the study groups) Completeness of outcome data (postintervention): Low (5 percent overall and 2 percent differential attrition) Selective outcome reporting: Unclear (no protocol reported) Funders: The Thai Health Promotion Foundation and Integrated Management for Alcohol Intervention Program provided grant support.

Witte 2012

References	Parent study Witte, J., K. Bentley, A. E. Evins, A. J. Clain, L. Baer, P. Pedrelli, M. Fava, and D. Mischoulon, "A Randomized, Controlled, Pilot Study of Acamprosate Added to Escitalopram in Adults with Major Depressive Disorder and Alcohol Use Disorder," <i>Journal of Clinical Psychopharmacology</i> , Vol. 32, No. 6, December 2012, pp. 787–796. Additional Massachusetts General Hospital and National Alliance for Research on Schizophrenia and Depression, "Acamprosate Added to Escitalopram and Behavioral Treatment for Comorbid Depression and Alcoholism," March 2007. As of March 19, 2019: https://clinicaltrials.gov/show/NCT00452543
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Study design	Study dates: March 2007 to May 2010 Objective: To examine the efficacy and safety of acamprosate augmentation of escitalopram in patients with concurrent major depressive disorder and AUDs Randomization: Individually randomized Recruitment method: Recruited through advertisements and referrals from within the study authors' institution and the Boston area Inclusion criteria: Aged 18 to 65 years; met <i>DSM-IV</i> criteria for major depressive disorder; met <i>DSM-IV</i> criteria for alcohol abuse or dependence; be off any previous antidepressants for at least 2 weeks by the time of the baseline visit (4 weeks in the case of fluoxetine); be off benzodiazepines and other psychotropic medications for at least 1 week by the time of the baseline visit Exclusion criteria: Suicidal ideation where study participation was deemed unsafe by the study clinician; women who were pregnant or breastfeeding, or women of childbearing potential not using a medically accepted means of contraception; serious or unstable medical illness; clinical or laboratory evidence of untreated hypothyroidism; lifetime history of organic mental disorder, schizophrenia spectrum illness, bipolar disorder, major depressive disorder with psychotic features, SUD other than alcohol or nicotine active in the prior 12 months; current use of other psychotropic drugs other than antihistamines; failure to respond during the course of the current depressive episode to two or more adequate antidepressant trials (defined as ≥ 6 weeks of escitalopram ≥ 20 mg/d or its equivalent); participation in depression-focused or addiction-focused psychotherapy (participation in Alcoholics Anonymous was allowed); investigational psychotropic drug use in the prior year; need for medical alcohol detoxification in the opinion of the screening physician in accordance with methods used in the multicenter Sequenced Treatment Alternatives to Relieve Depression study Power calculation: Power analysis was originally based on intent-to-treat analysis with 40 subjects and assumed a 30-percent difference in alcohol consumption (50 percent reduction vs. 20 percent reduction in the acamprosate and placebo groups, respectively). With $\alpha = 0.05$, 74 percent power was estimated to detect a difference between the two groups. Sample size: 23 total (12/11)
Setting	Geographic location: Boston, Massachusetts, United States Intervention sites: Not reported External context: Not reported
Participants	Age: 46 (14) Gender: 43 percent female Race/ethnicity: 91 percent white Other socioeconomics/demographics: Not reported Baseline depression: 43 percent recurrent major depressive disorder; HDRS-17 of 18.0 (5.5); Quick Inventory of Depressive Symptomatology Self-Report of 11.9 (3.6) Baseline alcohol use: 96 percent current alcohol dependence, 4 percent current alcohol abuse; 5.5 (3.0) drinks per drinking day, 22.4 (18.7) drinks per week, 91.3 (73.8) drinks per month; 40 percent days abstinent; OCDS of 29.5 (6.8) Other baseline health: 22 percent lifetime drug abuse; CGI-severity of illness of 3.8 (0.8); Quality of Life Enjoyment and Satisfaction Questionnaire of 61.4 (18.8); SF-36 General Health of 66.9 (13.8)

Intervention 1	Category: Pharmacological intervention Class: Glutamatergic antagonist Name: Acamprosate Providers: Study physician Location/timing: Outpatient Amount: 12 weeks (2,000 mg/day). Initial dosing for acamprosate was two 333 mg capsules three times a day, plus 10 mg/d escitalopram. The escitalopram was dosed flexibly per the discretion of the study physician, starting at 10 mg/d and modified based on apparent efficacy and tolerability. Increases were allowed to 20 mg/d at week 2 or later, and to 30 mg/d at week 4 or later. A maximum dose of 30 mg escitalopram was allowed in cases in which patients may have had limited improvement on the lower doses. Fidelity measurement: Medication adherence was assessed with the medication adherence question of the Quick Inventory of Depressive Symptomatology Self-Report at each study visit. Patients were asked how often they missed their medication, with answers ranging from 0 to 9: 0 (not applicable), 1 (never), 2 (rarely), 3 (sometimes), 4 (less than half of the time), 5 (approximately half of the time), 6 (more than half of the time), 7 (very often), 8 (nearly all the time), and 9 (all the time). Fidelity data: 33 (34) days spent in treatment
Intervention 2	Category: Control intervention Class: Pharmacological placebo Name: Pharmacological placebo Materials: Identical to acamprosate Providers: Study physician Location/timing: Outpatient Amount: 12 weeks. Initial dosing was two capsules three times a day. Fidelity measurement: Medication adherence was assessed by the number of returned pills and with the medication adherence question of the Quick Inventory of Depressive Symptomatology Self-Report at each study visit. Patients were asked how often they missed their medication, with answers ranging from 0 to 9: 0 (not applicable), 1 (never), 2 (rarely), 3 (sometimes), 4 (less than half of the time), 5 (approximately half of the time), 6 (more than half of the time), 7 (very often), 8 (nearly all the time), and 9 (all the time). Fidelity data: 21 (17) days spent in treatment
Cointervention	Outpatient care: One week after enrollment, all patients began receiving escitalopram (10 to 30 mg/day) and a behavioral intervention for AUD as described in the Medical Management Treatment Manual from the National Institute of Alcohol Abuse and Alcoholism's Combining Medications and Behavioral Interventions Monograph Series. The escitalopram was dosed flexibly per the discretion of the study physician, starting at 10 mg/d and modified based on apparent efficacy and tolerability. Increases were allowed to 20 mg/d at week 2 or later, and to 30 mg/d at week 4 or later. A maximum dose of 30 mg escitalopram was allowed in cases in which patients may have had limited improvement on the lower doses.

	All entering patients received a list of withdrawal symptoms to watch for and the pager number of the principal investigator, who was available 24/7 to answer questions and triage patients to the appropriate level of care. An alcohol withdrawal management protocol was put in place, with primary emphasis on ensuring the subject's medical safety. For mild symptoms (loss of appetite, irritability, and tremulousness), a chlordiazepoxide taper for up to 4 days would be provided. A study physician would contact the patient daily during the taper to determine whether the patient required a more intensive level of care. In case of more serious withdrawal symptoms (including tremulousness, heart rate persistently more than 100 beats per minute, severe insomnia, hypervigilance, hallucinations, mental status changes, seizures, or delirium), the patient would be immediately transferred to the nearest emergency department. The initial medical management treatment session at the baseline visit (40–60 minutes) involved discussion of the alcohol abuse or dependence diagnosis and negative consequences from drinking, a recommendation to abstain from consuming alcohol, medication information, strategies to enhance medication adherence, and referral to support groups such as Alcoholics Anonymous. A phone call was made by the doctor 3 days after the baseline visit to check on progress and adverse events. The six subsequent study visits included medical management sessions (15- to 25-minute visits) in which the physician assessed the participant's drinking, overall functioning, medication adherence, and any adverse events.
Outcomes	Remission from depression: (1) Remission (final HDRS-17 score of less than 8) and response (a 50-percent or greater improvement in the HDRS-17 score from baseline to end point) at postintervention (12 weeks postbaseline) Remission from alcohol use: Percentage of days abstinent at postintervention (12 weeks postbaseline) Depressive symptoms: (1) HDRS-17 and (2) Quick Inventory of Depressive Symptomatology Self-Report at postintervention (12 weeks postbaseline) Total drinking: (1) Drinks per month, (2) drinks per week, and (3) drinks per drinking day at postintervention (12 weeks postbaseline) Heavy drinking: Not reported Withdrawal and craving symptoms: OCDS at postintervention (12 weeks postbaseline) Health-related quality of life: (1) SF-36 General Health and (2) Quality of Life Enjoyment and Satisfaction Questionnaire at postintervention (12 weeks postbaseline) Functional status: (1) CGI-severity, (2) CGI-improvement, (3) SF-36 Mental Health, (4) SF-36 Emotional Functioning, and (5) SF-36 Social Functioning at postintervention (12 weeks postbaseline) Adverse events: Physician documentation of adverse events at postintervention (12 weeks postbaseline)
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: Low (double blind) Blinding of providers: Low (double blind) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data (postintervention): High (48 percent overall attrition)

	Selective outcome reporting: Low (all outcomes from study protocol reported sufficiently for inclusion in meta-analysis) Funders: The investigators reported support and honoraria from the National Association for Research on Schizophrenia and Depression, Forest Laboratories, Bristol-Meyers Squibb, Eli Lilly, and National Institutes of Health Grants K23DA00510 and K24DA030443.
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Zielinski 1977

References	Parent study Zielinski, J. J., “Behavioral Treatments of Depression with Alcoholics Receiving Pharmacological Aversion,” Behavior Therapist, Vol. 2, No. 5, 1979, pp. 25–27.
Study design	Study dates: Not reported Objective: To examine behavioral treatments of depression with alcoholics receiving pharmacological aversion Randomization: Individually randomized Recruitment method: Recruited through a private alcohol treatment center, with patients undergoing testing on the first rest day after their first aversion treatment, which allowed for a zero blood alcohol level and familiarity with the treatment setting and procedures Inclusion criteria: Scoring in the clinically depressed direction on two of the three depression scales (T-score of 70 or above on Scale D of the MMPI, 18 or above on the BDI, and 50 or above on Zung’s Self-Rating Depression Scale) Exclusion criteria: Not reported Power calculation: Not reported Sample size: 36 total (12/12/12)
Setting	Geographic location: Portland, Oregon, United States Intervention sites: Raleigh Hills Treatment Center External context: Not reported
Participants	Age: 40 Gender: 25 percent female Race/ethnicity: 100 percent Caucasian Other socioeconomics/demographics: Average of 13 years of education Baseline depression: Not reported Baseline alcohol use: Began drinking “out of control” at an average age of 33.7 years; each patient exhibited most of the classical symptoms of addiction (e.g., blackouts). Other baseline health: Not reported
Intervention 1	Category: Psychological intervention Class: SMS Name: Activity level monitoring and social skills training Procedures: In addition to activity level monitoring (see Intervention 2), patients received social skills training. To facilitate an individualized assessment, the completed Rathus Assertiveness Schedule was used to identify specific areas of social difficulty

	for each patient. Through directed questioning, the therapist attempted to define the characteristics of a particular situation that the patient described as problematic. Using this information, the therapist engaged the patient in repeatedly role-playing (behavior rehearsal) and, in turn, modeling responses to the social situation. The therapist coached each patient on both verbal content and style (e.g., tone of voice) and nonverbal concomitants of an appropriate response (e.g., eye contact). The emphasis was on helping the patient to feel comfortable with a response that both the patient and the therapist thought was appropriate. Role-played situations were not limited to negative assertion but also included those requiring a commendatory response, if these were problematic for the patient. Each patient also received role-playing practice with selected situations from the social skills assessment to assess the effect of practice on the ability to respond to these specific situations. The format of rehearsal, modeling, and coaching was retained. Providers: Therapist (doctoral candidate in clinical psychology) Format/modality: Individually delivered Location/timing: Inpatient and outpatient Amount: Five booster sessions during outpatient care follow-up to 2-week inpatient program
Intervention 2	Category: Psychological intervention Class: SMS Name: Activity level monitoring Procedures: Patients met with the therapist on a rest day (i.e., no aversion treatment) during their initial admission. Each patient was engaged in a discussion of immediate plans, and a list of short-term goals was generated. Efforts were made to include recreational or avocational pursuits, as well as work projects. This first session stressed the selection of goals that could easily be completed by the next meeting in 3 weeks. Patients were told to do at least one very enjoyable activity each day. Each goal was written down for the patient, with the therapist retaining a copy. Patients were told to complete the “assignments” before the next session. However, no contingency was in effect except therapist praise and encouragement—or the withholding of the same—for the completion or noncompletion of these assignments. Constraints of the setting precluded the use of a contingency strategy. Patients were given aid in generating a list of goals if they had difficulty in doing so themselves. The list was revised and enlarged at sessions two through five. Patients who had difficulty completing their assignments were encouraged to do better and given the option of changing the list. The emphasis was on accomplishing what had been planned. Providers: Therapist (doctoral candidate in clinical psychology) Format/modality: Individually delivered Location/timing: Inpatient and outpatient Amount: 12 weeks; one session during inpatient care and four booster sessions during outpatient care follow-up to 2-week inpatient program
Intervention 3	Category: Control intervention Class: Psychological placebo Name: Psychological placebo Procedures: Patients in this group were engaged in informal discussions regarding their general well-being. Efforts were made to give no specific instructions or advice but to hold therapist time constant. Providers: Therapist (doctoral candidate in clinical psychology)

	Location/timing: Inpatient and outpatient Amount: Five booster sessions during outpatient care follow-up to 2-week inpatient program
Co-intervention	Inpatient and outpatient care: The Raleigh Hills Treatment Center focuses its treatment of alcoholism on pharmacological aversive counterconditioning, though it also offers a program with a number of components: detoxification, counseling and “roundtable” discussions, milieu treatment, and a program of reinforcement conditioning (booster) sessions during the year following treatment.
Outcomes	Remission from depression: Not reported Remission from alcohol use: Relapsed at 3 and 9 months postintervention (6 months and 1 year postbaseline) Depressive symptoms: Not reported Total drinking: Not reported Heavy drinking: Not reported Withdrawal and craving symptoms: Not reported Health-related quality of life: Not reported Functional status: Not reported Adverse events: Not reported
Risks of bias	Random sequence generation: Unclear (not reported) Allocation concealment: Unclear (not reported) Blinding of participants: High (not possible because of nature of intervention) Blinding of providers: High (not possible because of nature of intervention)) Blinding of outcome assessors: Unclear (not reported) Completeness of outcome data: Low (5 percent overall attrition) Selective outcome reporting: Unclear (no protocol reported) Funder: Not reported

Appendix E. Network Geometry

This appendix provides the network diagram for each outcome in the review. Each node represents one of the intervention classes, each line connecting two nodes represents that an RCT directly compared the two intervention classes represented by the nodes, and the size of each line represents the number of RCTs directly comparing the two intervention classes represented by the nodes (note that the distance between nodes does not represent any parameters from the data).

**Figure G.1. Remission from Depression at Postintervention—
Pharmacological Interventions**

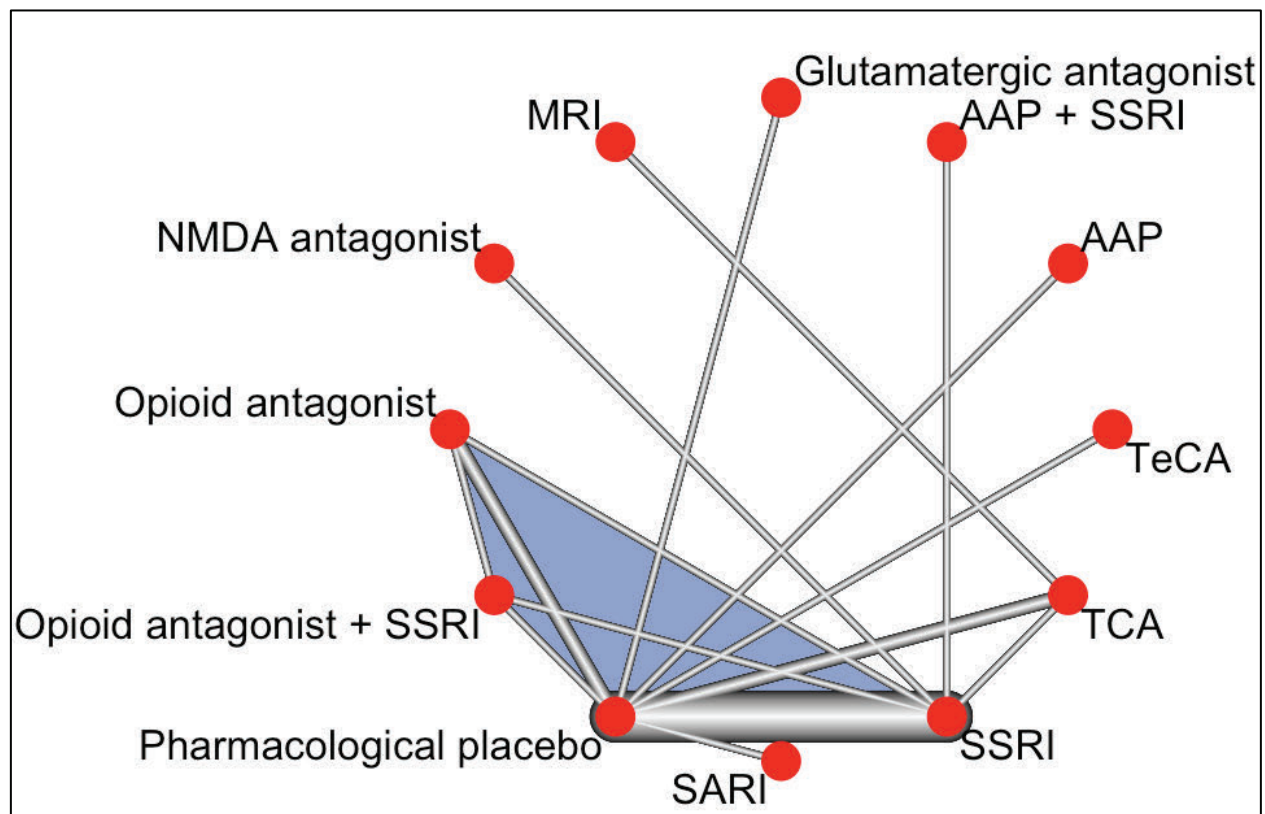


Figure G.2. Remission from Alcohol at Postintervention—Pharmacological Interventions

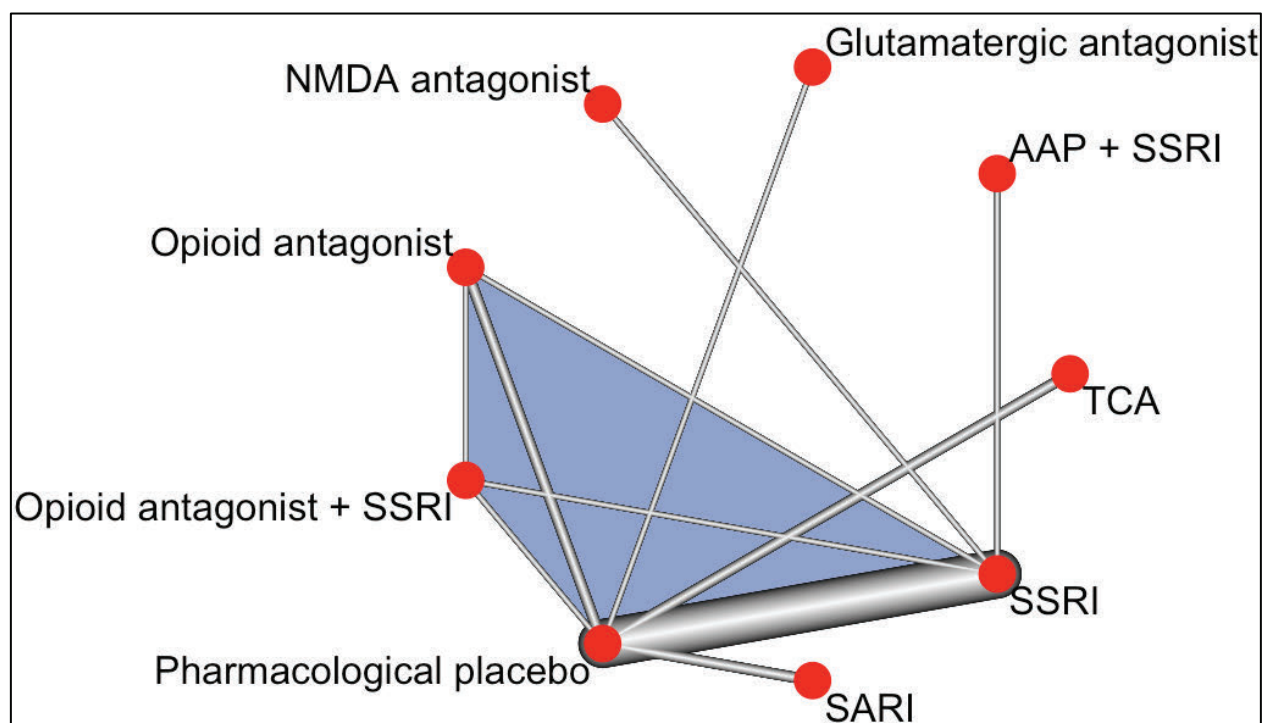


Figure G.3. Depressive Symptoms at Postintervention—Pharmacological Interventions

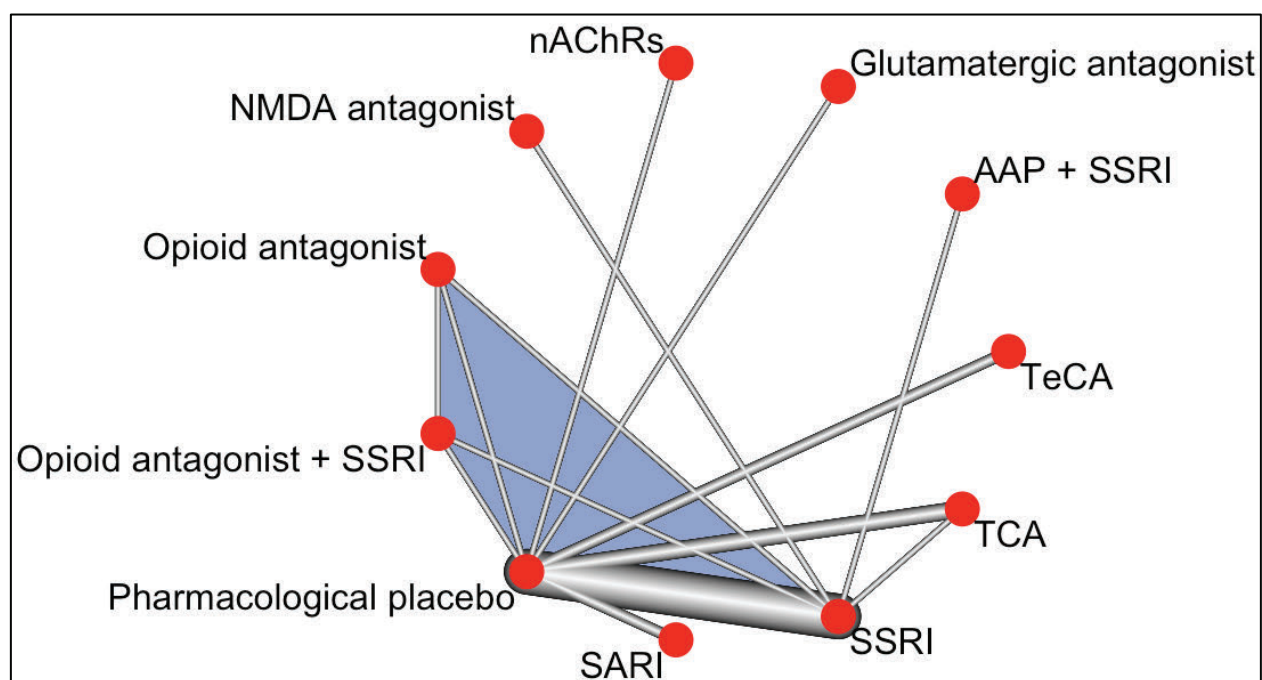


Figure G.4. Depressive Symptoms at Postintervention—Psychological Interventions

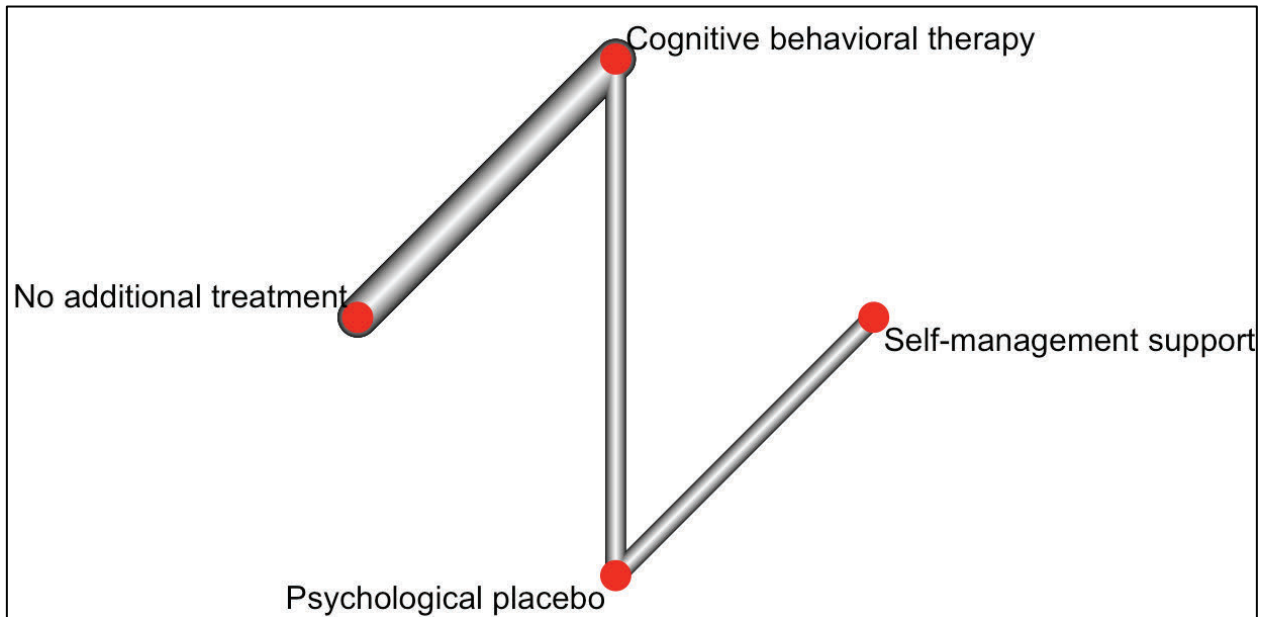


Figure G.5. Total Drinking at Postintervention—Pharmacological Interventions

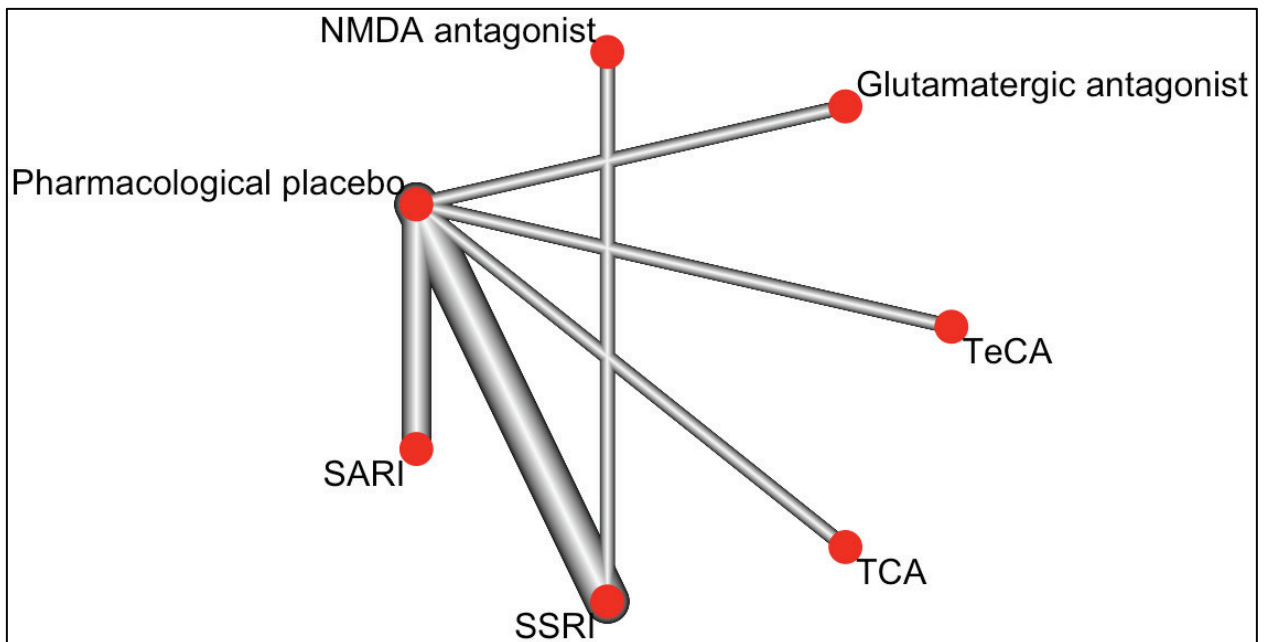


Figure G.6. Heavy Drinking at Postintervention—Pharmacological Interventions

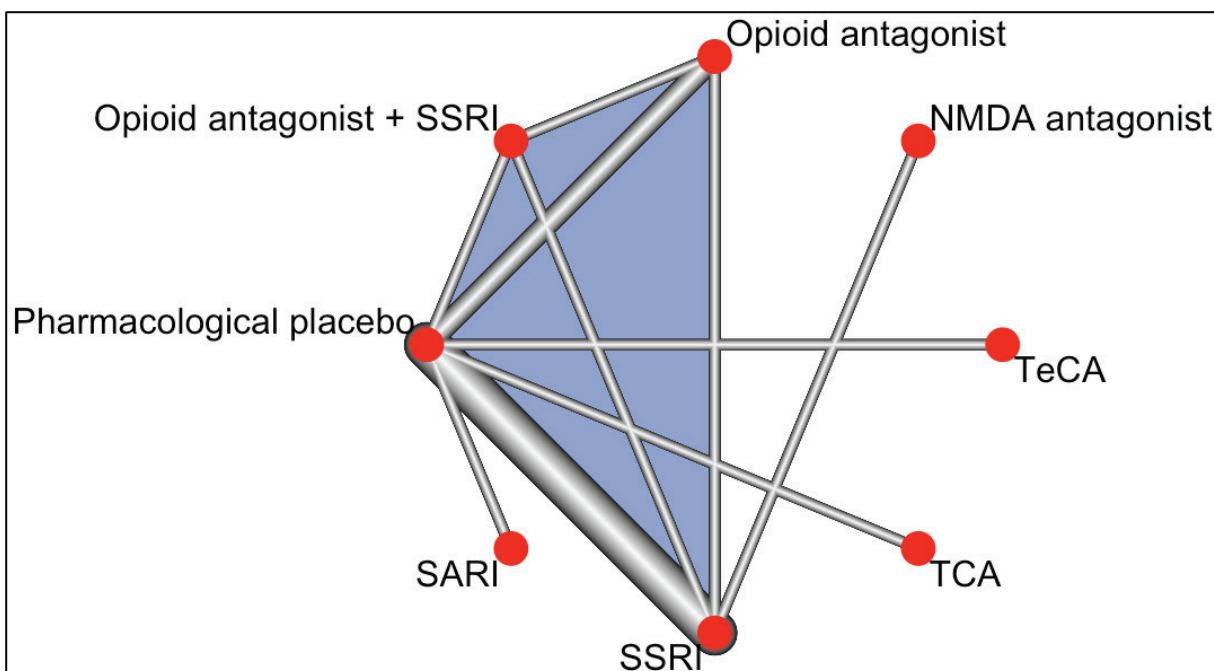


Figure G.7. Withdrawal and Craving Symptoms at Postintervention—Pharmacological Interventions

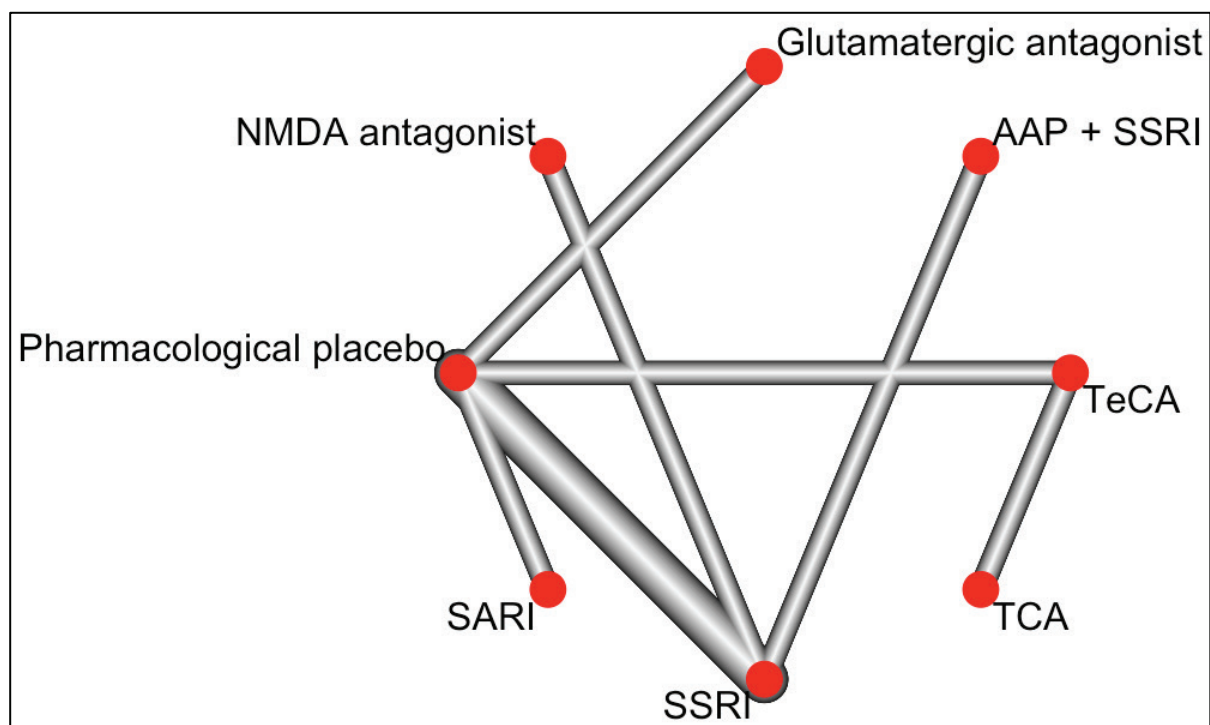


Figure G.8. Functional Status at Postintervention—Pharmacological Interventions

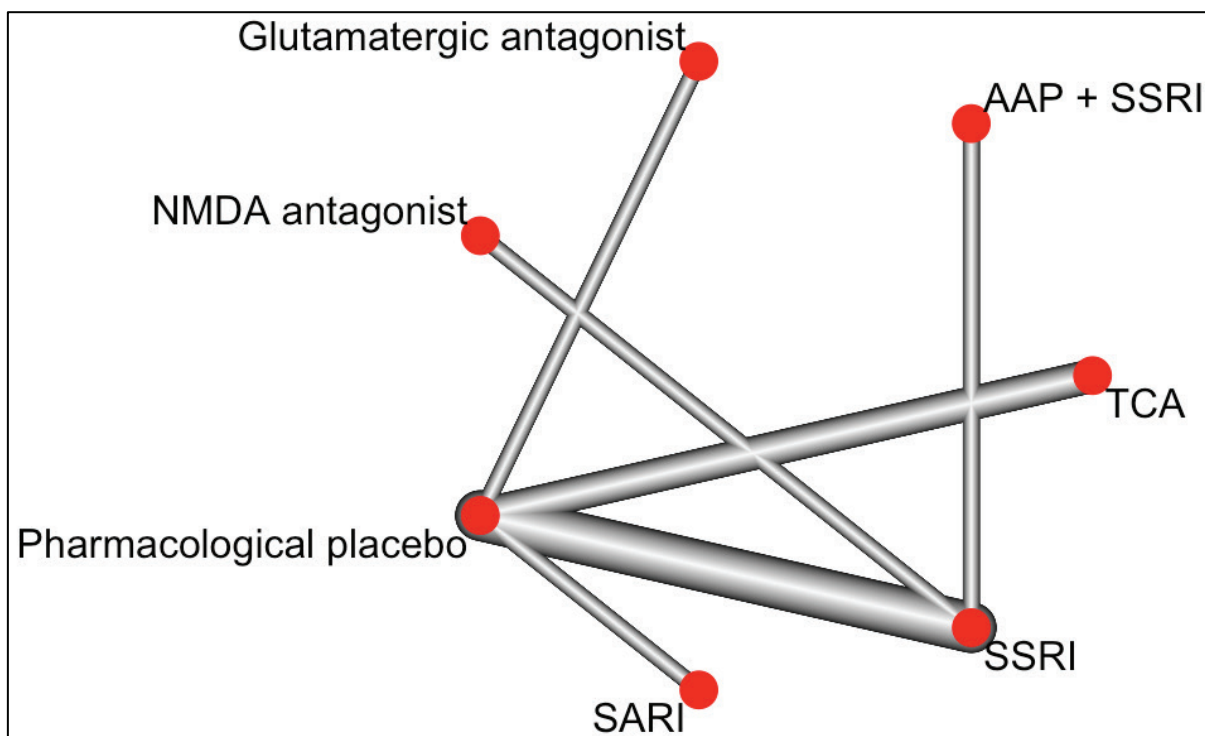


Figure G.9. Adverse Events at Postintervention—Pharmacological Interventions

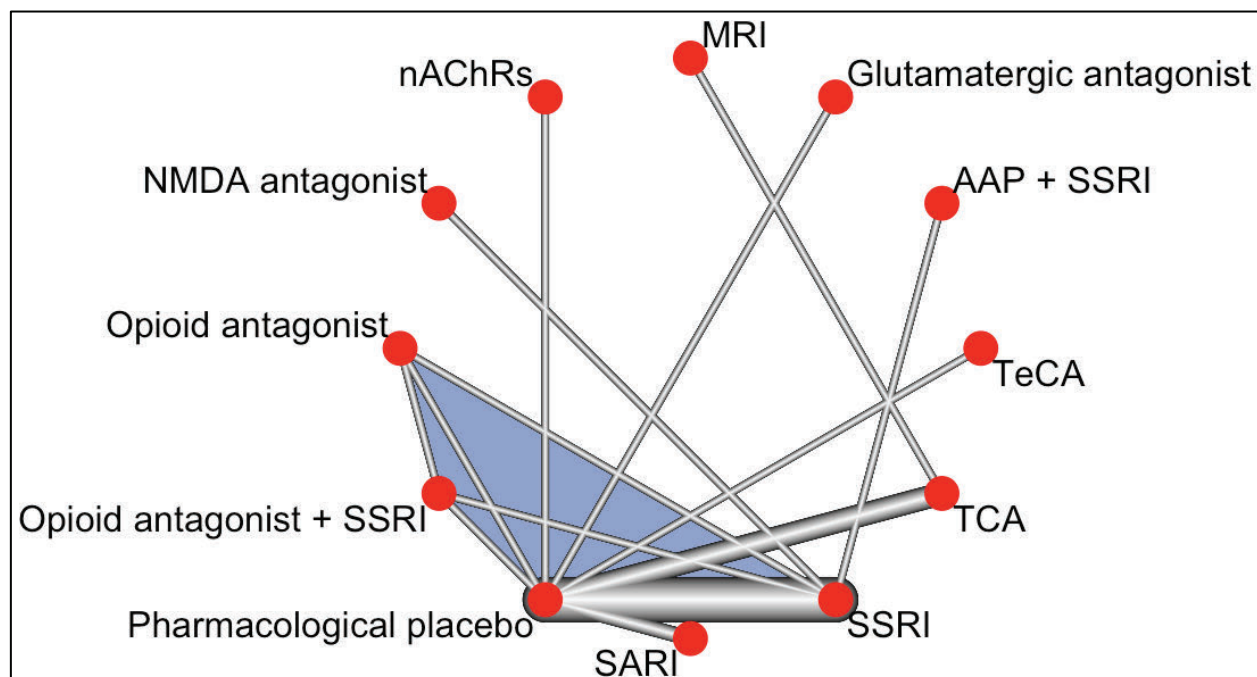
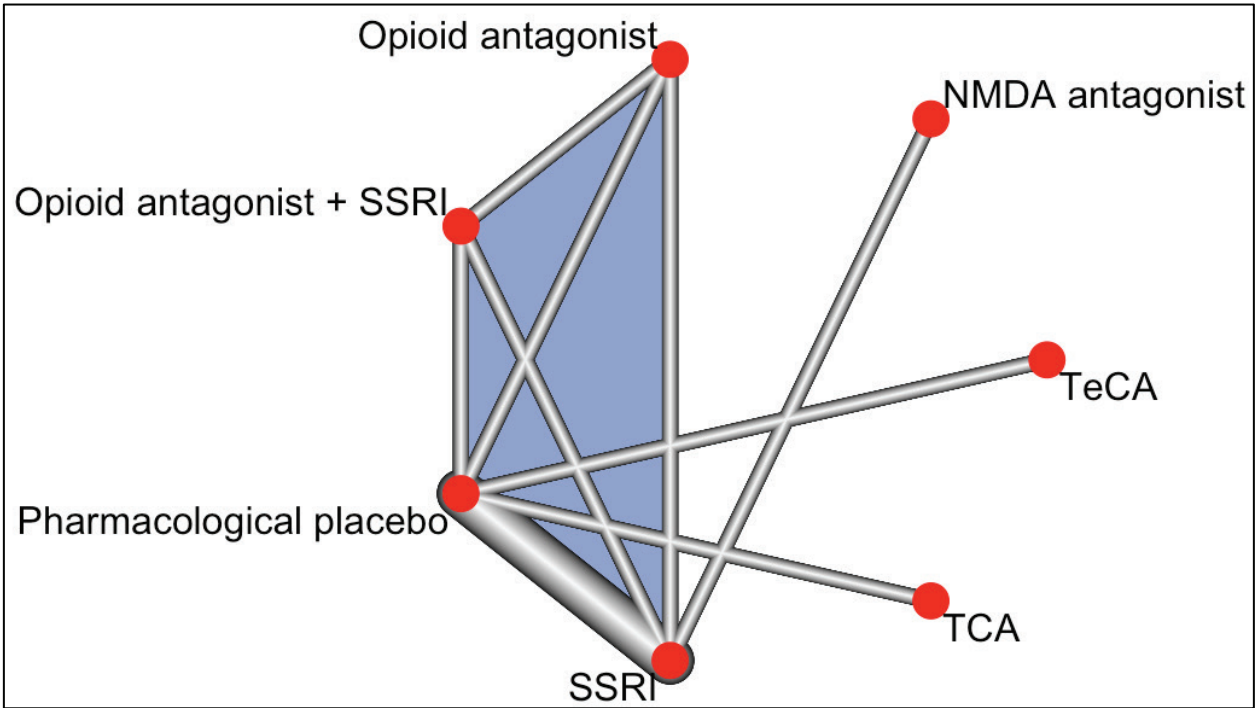


Figure G.10. Serious Adverse Events at Postintervention—Pharmacological Interventions



Appendix F. Sensitivity Analyses

This appendix provides the results of sensitivity analyses for each outcome in the review when sufficient data were available. As findings did not substantially differ for the vast majority of sensitivity analyses, only substantive differences from the default analyses are reported. All sensitivity analyses can be found in our online supplemental RMarkdown file.

Decision Space

The following analyses (which removed studies evaluating MRIs, SARIs, TCAs, and TeCAs) yielded substantively different results from the default analysis.

Adverse Events

We identified estimates (excluding a null effect) of patients receiving SSRIs (OR 1.70 [1.08 to 2.67]) and an SSRI in combination with an opioid antagonist (OR 3.71 [1.04 to 13.29]) to be more likely on average to experience an adverse event than patients receiving pharmacological placebo.

Alternative Outcome Data

The following analyses (which used alternative outcome data reported in included studies) yielded substantively different results from the default analysis.

Remission from Depression

Only one of five sensitivity analyses for remission from depression yielded an estimate at postintervention of a beneficial effect (excluding a null effect) of TCAs compared with pharmacological placebo (OR 0.30 [0.09 to 0.93]).

Remission from Alcohol Use

One of two psychological intervention sensitivity analyses for remission from alcohol use at short-term follow-up yielded an estimate of a beneficial effect of SMS versus psychological placebo (SMD -2.26 [-3.31 to -1.20]).

Depressive Symptoms

In contrast to the default analysis, one of seven sensitivity analyses for depressive symptoms yielded an estimate at postintervention of TCAs compared with pharmacological placebo that did not exclude a null effect (SMD -0.33 [-0.68 to 0.02]), one of the two psychological intervention sensitivity analyses yielded an estimate of a beneficial effect of IPT over SP (SMD -1.27 [-2.12 to -0.43]), and the sensitivity analysis of SSRIs versus pharmacological placebo at long-term follow-up did not exclude a null effect (SMD -0.52 [-1.24 to 0.20]).

Total Drinking

In contrast to the default analysis, one of ten sensitivity analyses for total drinking yielded estimates at postintervention of NMDA antagonists that did not exclude null effects, and the psychological intervention sensitivity analysis for total drinking at short-term follow-up yielded an estimate of a beneficial effect of CBT versus not additional treatment (SMD -0.36 [-0.58 to -0.15]).

Heavy Drinking

In the one sensitivity analysis for heavy drinking, we identified additional estimates of beneficial effects at postintervention of an opioid antagonist in combination with SSRI over opioid antagonists (SMD -0.51 [-1.01 to -0.01]), as well as an opioid antagonist in combination with SSRI over TCAs (SMD -0.81 [-1.59 to -0.03]).

Functional Status

In contrast to the default analysis, the effect estimates in one of the two sensitivity analyses for functional status did not exclude the null effect for an AAP in combination with an SSRI versus pharmacological placebo (SMD -0.71 [-2.04 to 0.62]) and pharmacological placebo versus SARIs (SMD 0.63 [-0.12 to 1.38]); estimates from both sensitivity analyses of glutamatergic antagonists versus NMDA antagonists did not exclude a null effect.

Adverse Events

In two of the five sensitivity analyses for adverse events, we identified an estimate (excluding a null effect) of patients receiving SSRIs to be more likely on average to experience an adverse event than patients receiving pharmacological placebo; in one of the five sensitivity analyses, we identified estimates (excluding a null effect) indicating high risks of adverse events for an AAP in combination with an SSRI over SARIs (OR 15.92 [1.14 to 221.81]), an opioid antagonist in combination with an SSRI over pharmacological placebo (OR 3.71 [1.04 to 13.29]), an opioid antagonist in combination with an SSRI over SARIs (OR 9.55 [1.82 to 49.95]), SSRIs over SARIs (OR 4.37 [1.39 to 13.77]), and TCAs over SARIs (OR 5.98 [1.47 to 24.24]).

Risks of Bias

The following analyses (which excluded studies with critical risks of bias) yielded substantively different results from the default analysis.

Remission from Depression

We identified estimates (excluding a null effect) of a beneficial effect at postintervention of an opioid antagonist in combination with SSRI over pharmacological placebo (OR 0.25 [0.06 to 0.99]) and SSRIs (OR 0.24 [0.06 to 0.97]).

Remission from Alcohol Use

We identified estimates (excluding a null effect) of a beneficial effect at postintervention of NMDA antagonists over opioid antagonists (OR 0.31 [0.11 to 0.88]), NMDA antagonists over pharmacological placebo (OR 0.38 [0.16 to 0.92]), and SSRIs over pharmacological placebo (OR 0.69 [0.47 to 0.9998]).

Depressive Symptoms

We identified estimates (excluding a null effect) of a beneficial effect at postintervention of an opioid antagonist in combination with an SSRI over SARIs (SMD -0.54 [-1.06 to -0.02]), while the estimate of TCAs versus pharmacological placebo did not exclude a null effect (SMD -0.26 [-0.64 to 0.12]).

Functional Status

In contrast to the default analysis, the analysis for functional status yielded an estimate at postintervention of TCAs compared with pharmacological placebo that did not exclude a null effect (SMD -0.74 [-1.71 to 0.22]).

Adverse Events

We identified an estimate (excluding a null effect) indicating higher risks of adverse events for an AAP in combination with an SSRI over SARIs (OR 29.06 [1.92 to 439.76]), an opioid antagonist in combination with an SSRI over pharmacological placebo (OR 5.14 [1.35 to 19.56]), an opioid antagonist in combination with an SSRI over SARIs (OR 15.96 [2.76 to 92.33]), SSRIs over pharmacological placebo (OR 2.57 [1.30 to 5.08]), SSRIs over SARIs (OR 7.98 [2.12 to 30.05]), and TCAs over SARIs (OR 6.69 [1.08 to 41.59]).

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