Antidepressant Treatment Of Major Depressive Disorder In Patients With Comorbid Alcohol Use Disorder: Two Meta-Analyses Of Randomized Placebo-Controlled Trials

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Antidepressant Treatment of Major Depressive Disorder in Patients with
Comorbid Alcohol Use Disorder: Two Meta-analyses of Randomized
Placebo-controlled Trials

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Isaac Nathan Smullin Johnson

Yale School of Medicine Class of 2020
# Table of Contents

Dedication and Acknowledgements...........................................................................3  
Abstract.....................................................................................................................4  
Introduction.................................................................................................................7  
Methods for Aim 1.......................................................................................................11  
Results for Aim 1........................................................................................................13  
Methods for Aim 2.......................................................................................................19  
Results for Aim 2........................................................................................................22  
Discussion....................................................................................................................27  
Tables and Figures for Aim 1......................................................................................32  
Tables and Figures for Aim 2......................................................................................44  
References....................................................................................................................56
Dedication and Acknowledgements:

I am thankful for the loving support that I have received from my mother Leslie Bourne, my father Mark Johnson, and my brother Jacob Johnson.
In loving memory of my grandparents Samuel Smullin, Frances Smullin, Paul Johnson, and Ruth Johnson.

I could not have asked for better mentorship than I have received throughout medical school. I am tremendously grateful for the mentorship and guidance I have received in life and in research from my thesis advisor Dr. Michael Bloch and his wife Dr. Angeli Landeros-Weisenberger. They have been an ever-present source of inspiration, support, advice, and humor over the course of my 5 years in medical school.

I am also grateful for the mentorship I have received from Dr. Robert Rohrbaugh, Dr. Andrés Martin, Dr. James Leckman, Dr. Zheala Qayyum, Dr. Brian Fuehrlein, Dr. Linda Mayes, Dr. Kirsten Wilkins, Dr. Karen Jubanyik, Dr. Euripedes Miguel, Dr. Marcelo Hoexter, Dr. Yukiko Kano, Dr. Yu Hamamoto, Dr. Emeric Bojarski, Dr. Eunice Yuen, Dr. João Paulo De Aquino and numerous additional residents, fellows, and faculty who have inspired me with their kindness and generosity.

My work is built upon the sacrifice of my family and my mentors.

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Research reported in this publication was supported by the National Institute on Alcohol Abuse and Alcoholism of the National Institutes of Health under Award Number T35AA023760. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. This publication was also made possible by the Yale School of Medicine Medical Student Research Fellowship.
Abstract

Objective:

Aim 1: To examine the efficacy of antidepressant agents compared with placebo in reducing depressive symptoms in subjects with comorbid Alcohol Use Disorders (AUD).

Aim 2: To examine the efficacy of antidepressant agents compared with placebo on measures of alcohol consumption.

Data Sources:

Aim 1: PubMed was searched for randomized, placebo-controlled trials that examined the efficacy of antidepressant medications for treating depression symptoms with comorbid AUD.

Aim 2: Ovid MEDLINE (1946 to September 23, 2016) and CENTRAL (Issue 8, August 2016) were searched with no language limits for randomized placebo-controlled trials that examined the effects of antidepressant medications on alcohol consumption.

Study Selection:

Aim 1: Trials were included if they: 1) were randomized, placebo-controlled clinical trials, 2) examined the effects of an antidepressant medication for comorbid MDD and AUD, and 3) reported depression outcomes.

Aim 2: Trials were included if they: 1) were randomized, placebo-controlled clinical trials, 2) examined the effects of an antidepressant medication for comorbid MDD and AUD, and 3) reported alcohol consumption outcomes.

Data Extraction:

Aim 1: Random effects meta-analysis was utilized to examine standardized mean difference (SMD) in improvement of depressive symptoms and risk ratio for treatment response.

Stratified subgroup analysis was used to examine the moderating effects of type of antidepressant medication and other trial characteristics.
Aim 2: We examined the effect of antidepressant treatment on four alcohol consumption outcomes: (1) drinking days, (2) drinks per day, (3) hazardous drinking days, and (4) abstinence rates. Our primary outcome was standardized mean difference for continuous measures and risk ratio for dichotomous outcomes using random effects meta-analysis. We also used stratified subgroup analysis to examine the moderating effects of type of antidepressant medication and diagnostic indication.

Results:

Aim 1: Eighteen distinct trial arms involving 1,318 participants were included in this systematic review and meta-analysis. In subjects with AUD, antidepressant medications significantly decreased depression severity compared with placebo (SMD=0.33±0.10 (95% Confidence Interval (CI): 0.14-0.51, k=18, z=3.4, p=0.001). Type of antidepressant medication did not significantly affect the magnitude of depressive symptom improvement compared with placebo (Test for subgroup differences χ²=2.15, df=2, p=0.34). TCAs (SMD=0.51±0.19 (95% CI: 0.15-0.88, k=3, z=2.7, p=0.006) and SSRIs (SMD=0.22±0.12 (95% CI: -0.01-0.46, k=10, z=1.9, p=0.06) suggested similar benefits for depressive symptoms in subjects with comorbid AUD. The use of concomitant psychotherapy (for either depression or alcohol use) (Test for subgroup differences χ²=9.9, df=1, p=0.002) or concomitant pharmacotherapy for AUD (Test for subgroup differences χ²=4.7, df=1, p=0.03) was associated with a significantly smaller measured treatment benefit of antidepressant agents.

Aim 2: Twenty-six trials involving 2,771 participants were included in this systematic review and meta-analysis. Overall, antidepressant use was not associated with significant changes in drinking outcomes (drinking days, drinks per day, abstinence rates, and hazardous drinking days). When antidepressants were utilized to treat comorbid depression symptoms, antidepressant treatment was associated with improved drinking outcomes on some (drinking
days and drinks per day) but not all measures (abstinence rates and hazardous drinking days).

When antidepressants were utilized primarily to treat symptoms of other disorders, antidepressant treatment was associated with worsened drinking outcomes on some (drinking days and drinks per day) but not all measures (abstinence rates and hazardous drinking days). Class of antidepressant treatment did not significantly affect any drinking-related outcomes.

**Conclusion:**

Aim 1: Our meta-analysis suggests that antidepressant medications significantly decrease depressive symptoms in participants with comorbid AUD. The magnitude of depressive symptom improvement in subjects with comorbid AUD appears similar to that achieved in MDD trials without comorbid substance use.

Aim 2: Antidepressant therapy results in improvement in some drinking outcomes when used for comorbid depression, though it may worsen these outcomes in the absence of comorbid depression. More research is needed on the impact of antidepressants on drinking outcomes, including the potential moderating effects of age, genotype, and depression and anxiety symptoms.
Introduction

Major Depressive Disorder (MDD) and Alcohol Use Disorder (AUD) are among the most prevalent mental health conditions in adult populations. AUD is overrepresented in adults with MDD compared with the general population, and depression is overrepresented in patients with AUD.\(^1\) Recent genetic analysis supports a strong genetic overlap between MDD and AUD.\(^2\) Patients with MDD and comorbid AUD tend to experience greater depression severity, depressive symptoms at an earlier age of onset, increased suicidality and functional impairment, higher rates of relapse and decreased likelihood of recovery from depressive symptoms.\(^3\)\(^-\)\(^7\) In patients with AUD, comorbid depressive symptoms are associated with an increased likelihood of treatment dropout and relapse.\(^8\)\(^-\)\(^10\)

Pharmacotherapy with antidepressant medications is a first-line treatment for MDD. In meta-analysis, antidepressant agents demonstrate a significant benefit compared with placebo for the treatment of major depression with effect sizes of 0.30\(^11\) and 0.37\(^12\) reported in the literature and a NNT of 6.\(^13\) Despite the high rate of comorbidity between AUD and MDD, subjects who meet criteria for current or recent alcohol or other substance use disorders are typically excluded from these pivotal randomized, placebo-controlled trials of antidepressant medications. Thus, it is uncertain how well the results of positive antidepressant trials in non-alcohol dependent patients will generalize to clinical MDD populations, where patients often have comorbid AUD.\(^14\)\(^-\)\(^20\)

Previous meta-analyses have found mixed results regarding the efficacy of antidepressants in treating comorbid MDD and AUD. A 2004 meta-analysis found that antidepressants have a “modest beneficial effect” in reducing depressive symptoms in patients with a comorbid substance use disorder (not limited to AUD).\(^21\) A subsequent meta-analysis suggested a similar effect when meta-analysis was confined to just trials involving subjects with comorbid AUD and MDD. This meta-analysis further reported that Selective
Serotonin Reuptake Inhibitors (SSRIs), as a class, were not associated with an increased likelihood of response in terms of depressive symptoms, compared to placebo.\(^{22}\)

A more recent meta-analysis published in 2011 that similarly examined only treatment response, demonstrated that antidepressant agents overall were more effective than placebo at reducing depressive symptoms in patients with comorbid AUD. However, this meta-analysis was not able to demonstrate that SSRIs, as a class, were effective in this population and further suggested that they were less effective than other antidepressants.\(^{13}\)

These previous meta-analyses examined only treatment response and not continuous outcomes. Also, there are additional recent trials with second generation antidepressants that have been published subsequent to these previous reviews.

Alcohol use disorder has a lifetime prevalence of 30.3% in the United States according to results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).\(^{23}\) Comorbid alcohol dependence and depression result in 44% more healthcare costs compared to treating depression alone.\(^{24}\) It has been suggested that alcohol use disorder may be causally linked to increased rates of depression,\(^{25}\) though genetic variations in serotonin transporter (SERT) function have also been implicated in both disorders.\(^{26}\) While second- and third-generation antidepressant medications remain the mainstay for treating depression,\(^{27}\) they can also be used in many other psychiatric conditions that are often comorbid with alcohol use disorder. For example, Americans with alcohol dependence are three times more likely to have an anxiety disorder and more than five times more likely to have nicotine dependence.\(^{23}\) Moreover, antidepressants were at one time the most commonly prescribed medication for alcohol use disorder,\(^{28}\) though several reviews and meta-analyses have questioned their efficacy for this indication.\(^{22, 29, 30}\) Unfortunately, there has been some case report\(^{31}\) and clinical trial\(^{32-35}\) evidence that the SSRI antidepressants may actually increase alcohol consumption in a subset of the population. This would suggest that
providers should consider a different class of antidepressants for patients prone to alcohol use disorder. Of course, this assumes that classes of antidepressants other than SSRIs have superior outcomes.

Two recent meta-analyses demonstrated the efficacy of antidepressants for treating depressive disorders in patients with comorbid alcohol use disorder, but either did not report\textsuperscript{36} or reported only very limited data\textsuperscript{13} on alcohol consumption outcomes. Notably, a 2004 meta-analysis\textsuperscript{21} studied antidepressant effects on both depression and substance use outcomes in the treatment of depressive disorders with comorbid dependence on alcohol or illicit drugs, and demonstrated improvement in substance use outcomes in the subset of studies in which depressive symptoms improved. Similarly, a 2005 meta-analysis\textsuperscript{22} examined alcohol and illicit drug outcomes in both studies of comorbid depression and studies without comorbid depression, but only found a statistically significant effect on substance use outcomes for first-generation antidepressants, in the treatment of comorbid depression and alcohol use disorder.

**Statement of Purpose**

The goals of the current meta-analyses are to update previous meta-analyses, as well as, to examine several unanswered questions regarding the use of antidepressant agents in subjects with MDD and comorbid AUD. In Aim 1, we specifically sought to determine: (1) What is the measured effect size and relative risk of response for subjects with MDD and AUD treated with antidepressant agents compared with placebo?; (2) Do different medication classes (TCA vs. SSRI) have the same measured benefit compared with placebo for subjects with MDD and AUD?; (3) Does the use of concomitant psychotherapy, targeting either depression or alcohol use, or concomitant pharmacotherapy for AUD moderate the benefits of antidepressant agents in the treatment of MDD with comorbid AUD?; and (4) Does the
measured efficacy of antidepressant agents differ in trials where antidepressants are initiated before or after alcohol detoxification is completed?

The systematic review and meta-analysis conducted as part of Aim 2 has the goal of updating and expanding upon previous studies by systematically analyzing trials that study the effects of second- and third-generation antidepressants on alcohol consumption outcomes, regardless of indication for the medication. This aim attempts to better delineate the effects of different antidepressant medication classes, specifically on alcohol consumption.

**Author Contributions**

IJ’s role in Aim 1 was in writing the manuscript, conceptual planning, identifying articles for quantitative synthesis (meta-analysis) through assessment of articles by title, abstract, and full-text based on inclusion and exclusion criteria, extraction and organization of the data from each included article, creation of Table 1 and Figure 1, conducting a review of the literature, and reviewing previous systematic reviews in this area. IJ’s role in Aim 2 was in writing and organizing sections of the manuscript and conducting a review of the literature.

MHB supervised the conceptual planning and execution of both Aim 1 and Aim 2. He also wrote and organized sections of both manuscripts and performed the statistical analyses.

JD’s role in Aim 2 was in writing the manuscript, conceptual planning, identifying articles for quantitative synthesis (meta-analysis) through assessment of articles by title, abstract, and full-text based on inclusion and exclusion criteria, extraction and organization of data, conducting a review of the literature, and reviewing previous systematic reviews in this area.

MN reviewed the manuscript for Aim 1 and BA reviewed the manuscript for Aim 2. FL created all forest and funnel plot figures for both manuscripts. BS, JJ, and MM contributed to writing sections of the manuscript. BS created Table 2 for Aim 1.
Aim 1: Effect of Antidepressants on Depression Outcomes

Methods:

Literature Search

We aimed to identify all randomized, placebo-controlled clinical trials of antidepressants indicated for the treatment of either MDD or chronic dysthymic disorder in participants with comorbid alcohol use disorder, that reported depression outcomes. PubMed MEDLINE (1946 to 12/18/2017) was searched using the search strategy “Alcohol-Related Disorders”[Mesh] AND "Depressive Disorder"[Mesh]) AND ("Antidepressive Agents"[Mesh] OR "Antidepressive Agents"[Pharmacological Action]).” We further limited the search using the clinical trials filter. There were no language limitations on the search. We additionally examined the references of included trials and previous systematic reviews in the area to identify additional citations.13, 21, 22, 37

Study Selection

Following the removal of duplicate citations, abstracts were independently screened by two authors (IJ and BS) for full text review, according to the following inclusion criteria: 1) randomized, placebo-controlled clinical trial, 2) utilization of an antidepressant medication to treat patients with AUD comorbid with either MDD or chronic dysthymic disorder, and 3) trials where depression outcomes were reported. Following this screening, full text articles were then reviewed by the same two authors according to the same inclusion criteria. Disagreements in both screening and full text review phases were resolved by consensus agreement in consultation with a senior reviewer (MHB). We excluded articles conducted in adolescents and articles that included patients who did not meet criteria for a current diagnosis of MDD or dysthymia. We included studies with concomitant use of naltrexone in the treatment and placebo arms despite evidence in previous literature of the confounding effects of this medication on alcohol consumption outcomes.38 This is due to the fact that the
present study focused exclusively on depression-related outcomes, and we conducted a
stratified subgroup analysis to examine the moderating effects of concomitant
pharmacotherapy.

Data Extraction

Custom designed Microsoft Excel spreadsheets were used to extract data. Data
extracted from the identified trials included: bibliographic information; indication for the
trial; antidepressant medication studied; maximum medication dose; duration of study; age
and gender of subjects; number of participants (n) in intention-to-treat sample and number
completing the trial; concomitant psychotherapeutic interventions and whether the
psychotherapy specifically targeted depression or alcohol use; concomitant
psychopharmacological interventions targeting alcohol use; and whether or not participants
were required to stop drinking prior to the start of the study. The primary outcomes extracted
for the meta-analysis included endpoint depressive symptom ratings and response in terms of
depressive symptoms, for both active and placebo arms of each study. If trial outcomes were
only reported in graphical form, a graph digitizer program called GetData\textsuperscript{39} was used to
extract the data. When no aggregate data was available, studies that reported data of multiple
treatment arms or by moderator subtype only were treated as separate studies for each study
moderator.

Statistical Analysis

Statistical analysis was performed using Comprehensive Meta-Analysis (version
3.0).\textsuperscript{40} Given the variation of depression rating scales reported in the included studies,
standardized mean difference was chosen as the summary statistic. For treatment response, a
dichotomous outcome, risk ratio was utilized as the summary statistic. Given the
heterogeneity in medications, trial design, and study outcomes, we chose to use a random-effects model. Heterogeneity was assessed by calculating the Q statistic, and the $I^2$. $I^2$ is a transformation of the Q statistic that indicates the proportion of observed variance that can be attributed to heterogeneity rather than sampling error. Publication bias was assessed by creating funnel plots for the outcome measures by plotting the effect size against standard error for each included trial. In addition, publication bias was statistically tested by the Egger test. We conducted stratified subgroup analyses to examine the effects of type of antidepressant medication (SSRI, TCA, vs. other), whether concomitant psychotherapy was administered and what it was indicated for, whether concomitant medication targeting AUD was administered, and whether detoxification was performed before initiation of antidepressant study medication. We used a mixed-effects meta-regression to examine the effects of participant age and duration of treatment on the measured benefits of antidepressant agents.

**Results**

*Selection of Studies*

Figure 1 depicts our procedure for selection of studies in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Our initial search identified 75 citations, of which 16 clinical trials were eligible for inclusion in this meta-analysis.

Table 1 describes the characteristics of the 18 distinct trial arms from 16 trials included in this systematic review and meta-analysis, involving 1,318 participants. Ten trials examined SSRI medications, 3 trials examined TCA medications, and 5 studies were of other antidepressants including mirtazapine, nefazodone, mianserin, and viloxazine. Either MDD or chronic dysthymic disorder was an indication for antidepressant treatment in each study. In 7 trials, subjects participated in a detoxification period prior to the initiation of
antidepressant therapy. In 12 trials, participants received concomitant psychotherapy, in addition to treatment with the study medication. Concomitant psychotherapy targeted alcohol use in 9 studies and additionally depression in 4 studies. Three trials utilized concomitant pharmacotherapy, such as naltrexone, to target alcohol use. Eighteen trial arms reported depression outcomes as continuous symptom improvement, while 12 trial arms included response data in terms of depressive symptoms. The majority of included studies reported depression outcomes with the Hamilton Rating Scale for Depression (HAM-D). However, the Beck Depression Inventory (BDI), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Lehmann-Rockliff Depression Rating Scale were utilized by one study each. One trial\textsuperscript{59} met our inclusion criteria, but did not contribute usable data to our study. Table 2 examines the risk of bias in each included trial.

**Depression Severity**

In participants with AUD, antidepressant medications significantly decreased depression severity, as compared with placebo (Standardized Mean Difference (SMD)=0.33±0.10 (95% Confidence Interval (CI): 0.14-0.51, k=18, z=3.4, p=0.001). There was significant heterogeneity between studies ($\chi^2$=42.3, df=17, p=0.001, I$^2$=59.8%). Figure 2A depicts the effects of antidepressant use compared with placebo on depression severity overall and stratified by medication type. Compared with placebo, antidepressant types did not demonstrate significant differences in reduction of depression severity, when trials were stratified by medication type (Test for subgroup differences $\chi^2$=2.15, df=2, p=0.34). Selective Serotonin Reuptake Inhibitors (SSRIs) (SMD=0.22±0.12 (95% CI: -0.01-0.46, k=10, z=1.9,
p=0.06), Tricyclic Antidepressants (TCAs) (SMD=0.51±0.19 (95% CI: 0.15-0.88, k=3, 
z=2.7, p=0.006), and other antidepressants (SMD=0.51±0.30 (95% CI: -0.07-1.09, k=5, 
z=1.7, p=0.084) demonstrated similar improvements in depression severity compared with 
placebo. Figure 3A demonstrates funnel plot asymmetry suggestive of publication bias 
(Egger’s test p=0.015).

INSERT FIGURES 2 AND 3 OF AIM 1 HERE

In stratified subgroup analysis, trials in which subjects participated in a detoxification 
period prior to initiating antidepressant treatment (SMD=0.54±0.17 (95% CI: 0.20-0.88, k=7, 
z=3.1, p=0.002) demonstrated a similar measured benefit (Test for subgroup differences 
$\chi^2$=2.7, df=1, p=0.10) of antidepressant treatment compared with trials in which a 
detoxification period did not occur prior to initiation of an antidepressant medication 
(SMD=0.20±0.12 (95% CI: -0.03-0.42, k=11, z=1.7, p=0.09).

Figure 4A depicts the effect of antidepressant treatment relative to placebo, stratified 
by whether or not participants received concomitant psychotherapy during the course of 
antidepressant treatment. In stratified subgroup analysis, trials in which participants did not 
receive concomitant psychotherapy (SMD=0.90±0.25 (95% CI: 0.42-1.39, k=6, z=3.66, 
p<0.001) demonstrated a significantly greater measured benefit of antidepressant treatment, 
compared with placebo, than in trials in which participants received concomitant 
psychotherapy (SMD=0.10±0.07 (95% CI: -0.03-0.23, k=12, z=1.46, p=0.15; Test for 
subgroup differences $\chi^2$=9.9, df=1, p=0.002). The measured benefit of antidepressant 
treatment, compared with placebo, was not significantly different when studies were stratified 
by whether participants did (SMD=0.24±0.13 (95% CI: -0.02-0.49, k=4, z=1.81, p=0.07) or 
did not (SMD=0.38±0.13 (95% CI: 0.12-0.63, k=14, z=2.85, p=0.004) receive psychotherapy
for depression (Test for subgroup differences \( \chi^2=0.58 \), df=1, p=0.45). The measured benefit of antidepressant treatment was significantly different when studies were stratified by whether participants did (SMD=0.12±0.09 (95% CI:-0.05-0.30, k=9, z=1.37, p=0.17) or did not (SMD=0.57±0.18 (95% CI: 0.21-0.93, k=9, z=3.07, p=0.002) receive psychotherapy for alcohol use (Test for subgroup differences \( \chi^2=4.7 \), df=1, p=0.03). There was a significant difference in the measured benefit of antidepressant medications based on whether trials used concomitant pharmacotherapy, such as naltrexone, for alcohol use disorder (Test for subgroup differences \( \chi^2=5.1 \), df=1, p=0.024). Our analysis demonstrated a smaller measured benefit of antidepressant treatment when trials were stratified by whether concomitant pharmacotherapy was initiated to target alcohol use (SMD=-0.00±0.13 (95% CI: -0.26-0.26, k=3, z=-0.0, p=0.99) compared with when it was not initiated (SMD=0.40±0.12 (95% CI: 0.17-0.63, k=15, z=3.4, p=0.001) in the trial.

In meta-regression, participant age (\( \beta=-0.02±0.05 \), 95% CI: -0.11-0.08, k=16, z=-0.32, p=0.75) and duration of antidepressant treatment (\( \beta=0.001±0.02 \), 95% CI: -0.045-0.048, k=16, z=0.06, p=0.96) were not associated with a measured reduction in depression severity following treatment with antidepressants vs. placebo.

**Depression Response Rate**

Participants with AUD demonstrated a significantly greater likelihood of response to antidepressant medications than they did to placebo (Risk ratio (RR)=1.30 (95% Confidence Interval (CI): 1.07-1.58, k=12, z=2.6, p=0.009). There was significant heterogeneity between studies (\( \chi^2=33.3 \), df=11, p<0.001, \( I^2=67\% \)). Figure 2B depicts the response to antidepressant
use compared with placebo overall and stratified by medication type. Compared with placebo, antidepressant types did not demonstrate a significant difference in response, when trials were stratified by medication type. However, there was a trend toward marginally increased response to TCAs (RR=1.97 (95% CI: 1.32-2.96, k=3, z=3.3, p=0.001), as opposed to SSRIs (RR=1.14 (95% CI: 0.91-1.43, k=7, z=1.1, p=0.27) and other antidepressants (RR=1.36 (95% CI: 0.29-6.35, k=2, z=0.39, p=0.7), when compared with placebo (Test for subgroup differences $\chi^2=5.4$, df=2, p=0.07). Figure 3B demonstrates funnel plot asymmetry suggestive of publication bias, despite lack of evidence of publication bias by Egger’s test (Egger’s test p=0.12).

In stratified subgroup analysis, trials in which subjects participated in a detoxification period prior to initiating antidepressant treatment (RR=2.77 (95% CI: 1.12-6.84, k=6, z=2.2, p=0.028) demonstrated a similar likelihood of response to antidepressant treatment compared with trials in which a detoxification period did not occur prior to initiation of an antidepressant medication (RR=1.47 (95% CI: 0.71-3.02, k=6, z=1.0, p=0.30); Test for subgroup differences $\chi^2=1.15$, df=1, p=0.28).

Figure 4B depicts the response to antidepressant treatment compared with placebo, stratified by whether or not participants received concomitant psychotherapy during the course of antidepressant treatment. In stratified subgroup analysis, trials in which participants did not receive concomitant psychotherapy (RR=1.94 (95% CI: 1.17-3.23, k=4, z=2.6, p=0.01) demonstrated a similar likelihood of response to antidepressant treatment vs. placebo, compared with trials in which participants received concomitant psychotherapy (RR=1.13 (95% CI: 0.89-1.43, k=8, z=1.0, p=0.31). There was, however, a trend toward marginally increased response to antidepressants vs. placebo among patients who did not receive concomitant psychotherapy (Test for subgroup differences $\chi^2=3.6$, df=1, p=0.06). The likelihood of response to antidepressant treatment, compared with placebo, was not
significantly different when studies were stratified by whether participants did (RR=1.22 (95% CI: 0.95-1.56, k=4, z=1.54, p=0.12) or did not (RR=1.36 (95% CI: 0.95-1.94, k=8, z=1.68, p=0.09) receive psychotherapy for depression (Test for subgroup differences \( \chi^2 = 0.24, df=1, p=0.62 \)) and also when they were stratified by whether participants did (RR=1.20 (95% CI:0.95-1.51, k=6, z=1.50, p=0.13) or did not (RR=1.47 (95% CI: 0.97-2.23, k=6, z=1.80, p=0.07) receive psychotherapy for alcohol use (Test for subgroup differences \( \chi^2 = 0.71, df=1, p=0.40 \)). Similarly, there was no statistically significant difference in the likelihood of response to antidepressant treatment when studies were stratified by whether concomitant pharmacotherapy was initiated to target alcohol use (RR=1.00 (95% CI: 0.55-1.80, k=2, z=0.0, p=0.99)) or was not (RR=1.37 (95% CI: 1.05-1.79, k=10, z=2.3, p=0.02)) in the trial (Test for subgroup differences \( \chi^2 = 0.93, df=1, p=0.34 \)).

In meta-regression, participant age (\( \beta=-0.039, 95\% \text{ CI: -0.15-0.07, } k=10, z=-0.73, p=0.47 \)) and duration of antidepressant treatment (\( \beta=0.019, 95\% \text{ CI: -0.03-0.07, } k=10, z=0.77, p=0.44 \)) were not associated with differences in the likelihood of depression response following treatment with antidepressants vs. placebo.
Aim 2: Effect of Antidepressants on Alcohol Consumption Outcomes

Methods:

Literature Search

We aimed to identify all randomized placebo-controlled clinical trials of antidepressants that reported alcohol consumption outcomes, regardless of the indication for antidepressant use. Literature search was conducted using Ovid MEDLINE (1946 to September 23, 2016) and the Cochrane Central Register of Controlled Trials (Issue 8, August 2016) with no language restrictions. Search terms used included a combination of alcohol use disorder, alcohol dependence, or alcoholism; and antidepressive agents, serotonin uptake inhibitors, serotonin and noradrenaline reuptake inhibitors, dopamine uptake inhibitors, bupropion, mirtazapine, fluoxetine, fluvoxamine, sertraline, paroxetine, citalopram, escitalopram, venlafaxine, desvenlafaxine, duloxetine, desipramine, imipramine, nefazodone, or viloxazine. Results were then limited to clinical trials. We obtained the primary articles associated with conference abstracts and secondary analyses resulting from our literature search where possible and attempted to identify additional studies via review of references and through consultation with two experts familiar with the published literature in this field.

Study Selection

Following removal of duplicates, abstracts were independently screened by two authors (JD and BA) for full-text review according to the follow inclusion criteria: 1) randomized placebo-controlled clinical trial, 2) of an antidepressant medication for any indication, 3) with alcohol consumption outcomes reported. Following this screening, full text articles were then reviewed by the same two authors, according to the same inclusion criteria. Disagreements in both screening and full text review phases were resolved by consensus agreement. We excluded articles conducted in an inpatient or human lab setting,
and those conducted with adolescents. We also excluded studies with concomitant use of naltrexone in the treatment and placebo arms, due to evidence in previous literature of the confounding effects of this medication on alcohol consumption outcomes.\textsuperscript{38} Prior to data analysis, we also decided to exclude studies of first-generation antidepressants given their limited use in modern clinical practice and that few trials exist, and the fact that we had a sufficient number of articles utilizing second and third-generation antidepressants for statistical analysis.

\textit{Data Extraction}

Data was extracted onto specially designed Microsoft Excel spreadsheets. Background data extracted from the identified trials included: bibliographic information; indication for the trial; antidepressant medication studied; maximum medication dose; duration of study; concomitant psychosocial interventions; age and gender of subjects; moderators of early-onset alcohol use disorder, family history, or genotype; number of participants (n) in intention-to-treat sample and of those completing the trial; and whether or not participants were required to stop drinking prior to the start of the study. Alcohol consumption outcome measures that were extracted included: number of drinks (drinks per drinking day, average drinks per day, or percent change of either of these variables), number or proportion of drinking days, number or proportion of hazardous drinking days, and number of abstinent subjects throughout or at the end of the study. Depression and anxiety outcomes were also extracted, where available. If trial outcomes were only reported in graphical form, a graph digitizer program called GetData\textsuperscript{39} was used to extract the data. Studies that reported data of multiple treatment arms or by moderator subtype only were treated as separate studies for each study moderator, when no aggregate data was available. In long-term studies, where
data was reported at multiple time points, only data closest to a 12-week follow-up period was extracted, in order to maintain consistency with other included studies.

Statistical Analysis

Statistical analysis was performed using Comprehensive Meta-Analysis (version 3.0). Given the variation of alcohol consumption outcomes reported in the included studies for continuous outcomes -- number of drinking days, number of hazardous drinking days and drinks per day, standardized mean difference was chosen as the summary statistic. For abstinence, a dichotomous outcome, risk ratio was utilized as the summary statistic. Given the heterogeneity in medications, trial design and study outcomes, we chose to use a random-effects model. Heterogeneity was assessed by calculating the Q statistic, and the I², a transformation of Q that indicates the proportion of observed variance that can be attributed to heterogeneity, rather than sampling error. Publication bias was assessed by creating funnel plots for the outcome measures by plotting the effect size against standard error for each included trial. In addition, publication bias was statistically tested by the Egger test. We conducted stratified subgroup analyses to examine the effects of type of antidepressant medication (SSRI, SNRI vs other), indication for antidepressant treatment (depression vs. other) and whether detoxification was performed before initiation of the antidepressant study medication.
Results

Selection of Studies

Figure 1 depicts our procedure for selection of studies in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Our initial search identified 354 citations, of which 94 were reviewed in full-text for eligibility. Of the 94 studies eligible for review, 18 were found to be secondary analyses or otherwise duplicate reports of trials already assessed, 39 did not meet the inclusion criteria outlined above, and 11 met the exclusion criteria above. Reasons for not meeting inclusion criteria included the study not being a randomized placebo-controlled clinical trial (21 studies), not being a study of an antidepressant (2 studies), or not reporting results of one of the alcohol consumption outcomes outlined above (16 studies). We excluded studies of adolescents (2 studies) and those that included naltrexone in both the treatment and placebo arms (4 studies). After the literature search, but prior to data analysis we also excluded trials of first-generation antidepressants (5 studies), as discussed above. All categories are exclusive of each other, with excluded studies categorized per the order presented above.

Table 1 describes the characteristics of the 26 studies included in this systematic review, involving 2,771 participants. Seventeen studies were of an SSRI, 1 study was of an SNRI, and 8 studies were of other third-generation antidepressants including bupropion, mirtazapine, and nefazodone. Seven of the 26 included studies had a depressive disorder as a primary indication for the study and were limited to the medications: fluoxetine, sertraline, mirtazapine, and nefazodone. Participants were abstinent from alcohol at the start of the trial (antidepressant initiation) in 15 of the 26 studies, and all but 5 studies...
included some type of concomitant psychotherapy. There was considerable variation in which alcohol consumption outcomes were reported, with the most common outcome being proportion of drinking days per month (DD), followed by drinks per drinking day (DDD) or average drinks per day (ADD) when DDD was not available, abstinence either at the study’s end or throughout the study, and finally proportion of hazardous drinking days per month (HDD). Only 3 studies included all 4 outcome variables of interest, while 35% of the studies included at least 3 of these outcomes.

**Drinking Days**

Overall, the use of antidepressant medications was not associated with any difference in the number of drinking days compared to placebo (standardized mean difference (SMD) \(=0.05 \pm 0.06\) (95% Confidence Interval (CI): 0.06-0.16, k=24, \(z=0.9\), \(p=0.39\)). There was modest but statistically significant heterogeneity between studies (Q-statistic=40.0, df=23, \(p=0.02\), \(I^2=26\%\)). Figure 2A depicts the effects of antidepressant use compared to placebo on number of drinking days stratified by medication type. SSRI, SNRI and other antidepressant medications did not have significantly different effects on number of drinking days compared to placebo (Test for subgroup differences \(\chi^2=2.1\), df=2, \(p=0.34\)). Figure 3A depicts the effects of antidepressant use compared to placebo on number of drinking days stratified by diagnostic indication (depression vs. other). Trials prescribing antidepressants to treat depression (SMD=-0.28 \(\pm\) 0.12 (95% CI:-0.52-0.04, k=5, \(z=-2.3\), \(p=0.02\)) demonstrated a greater reduction in number of drinking days with antidepressant treatment compared to those trials which utilized antidepressants for other indications (SMD=0.14 \(\pm\) 0.07 (95% CI:0.01-0.27, k=19, \(z=2.2\), \(p=0.03\); test for subgroup differences \(\chi^2=9.3\), df=1, \(p=0.002\)).
Antidepressants had no effect on number of drinking days regardless of whether trials started subjects on an antidepressant medication after a detoxication period or not (test for subgroup differences $\chi^2=0.2$, df=1, $p=0.87$). Antidepressant agents, compared to placebo, had no effect on number of drinking days in trials with a detoxification period (SMD=$-0.06 \pm 0.09$ (95% CI:-0.11-0.23, k=15, $z=-0.7$, $p=0.51$) or without a detoxification period prior to initiating antidepressant treatment (SMD=$-0.04 \pm 0.11$ (95% CI:-0.18-0.25, k=9, $z=-0.3$, $p=0.75$). There was no funnel plot asymmetry suggestive of publication bias and the Egger’s test was also not statistically significant ($p=0.11$).

Drinks Per Day

Overall, the use of antidepressant medications was not associated with any difference in the number of drinks per day compared to placebo (SMD=$0.07 \pm 0.06$ (95% CI: -0.04-0.18, k=17, $z=1.27$, $p=0.21$). There was modest but statistically significant heterogeneity between studies (Q-statistic=24.8, df= 16, $I^2=36\%$). Figure 2B depicts the effects of antidepressant use compared to placebo on number of drinks per day stratified by medication type. SSRI, SNRI and other antidepressant medications did not have significantly different effects on number of drinks per day compared to placebo (test for subgroup differences $\chi^2=0.15$, df=1, $p=0.69$). Figure 3B depicts the effects of antidepressant use compared to placebo on number of drinks per day stratified by diagnostic indication (depression vs. other). Trials prescribing antidepressants to treat depression (SMD=$-0.45 \pm 0.15$ (95% CI: -0.74-(-)0.16, k=4, $z=-3.02$, $p=0.003$) demonstrated a greater reduction in number of drinks per day with antidepressant treatment compared to those trials which utilized antidepressants for other
indications (SMD=0.16 ± 0.06 (95% CI: 0.04-0.28, k=13, z=2.61, p=.009; test for subgroup differences χ²=14.3, df=1, p<0.001). Antidepressants had no effect on drinks per day regardless of whether trials started subjects on an antidepressant medication after a detoxification period or not (test for subgroup differences χ²=0.008, df=1, p=0.93). Antidepressants agents, compared to placebo, had no effect on drinks per day in trials with a detoxification period (SMD=0.04 ± 0.11 (95% CI:-0.19-0.26, k=8, z=0.34, p=0.74) or without a detoxification period prior to initiating antidepressant treatment (SMD=0.02 ± 0.10 (95% CI: -0.17-0.22, k=9, z=0.24, p=0.81). There was no funnel plot asymmetry suggestive of publication bias and the Egger’s test was also not statistically significant (p=0.05).

Hazardous Drinking Days

Overall, the use of antidepressant medications was not associated with any difference in number of hazardous drinking days compared to placebo (SMD=0.17± (95% CI: -0.08-0.41, k=14, z=1.35, p=0.18). There was statistically significant heterogeneity between studies (Q-statistic=47.4, df=13, p<0.001, I²=73%). Figure 2C depicts the effects of antidepressant use compared to placebo on hazardous drinking days stratified by medication type. SSRI, SNRI and other antidepressant medications did not have significantly different effects on number of hazardous drinking days compared to placebo (test for subgroup differences χ²=1.0, df=2, p=0.61). Figure 3C depicts the effects of antidepressant use compared to placebo on hazardous drinking days stratified by diagnostic indication (depression vs. other). There was no significant difference in hazardous drinking days when trials were stratified by diagnostic indication (test for subgroup differences I²=3.0, df=1, p=0.08). Trials prescribing antidepressants to treat depression (SMD=-0.52 ± 0.42 (95% CI:-1.34-0.29, k=3, z=-1.26, p=0.21) demonstrated a marginally greater, but not statistically significant, reduction in hazardous drinking days with antidepressant treatment compared to those trials which utilized
Antidepressants for other indications (SMD=0.23 ± 0.13 (95% CI:-0.02-0.29, k=11, z=1.8, p=0.07). Antidepressants had no effect on number of hazardous drinking days regardless of whether trials started subjects on an antidepressant medication after a detoxification period or not (test for subgroup differences I²=0.29, df=1, p=0.59). Antidepressant agents, compared to placebo, had no effect on number of hazardous drinking days in trials with a detoxification period (SMD=0.15 ±0.17 (95% CI:-0.19-0.49, k=10, z=0.85, p=0.40) or without a detoxification period prior to initiation of antidepressant treatment (SMD=-0.07 ± 0.35 (95% CI:-0.77-0.63, k=4, z=-0.19, p=0.85). There was no funnel plot asymmetry suggestive of publication bias and the Egger’s test was also not statistically significant (p=0.94).

Abstinence

Overall, the use of antidepressant medications was not associated with any difference in abstinence rates compared to placebo (risk ratio (RR)=0.99 (95% CI: 0.91-1.08, k=19, z=-0.3, p=0.77). There was no significant heterogeneity between studies (Q-statistic=19.9, df=18, p=0.34, I²=9%). Figure 2D depicts the effects of antidepressant use compared to placebo on abstinence stratified by medication type. SSRI, SNRI and other antidepressant medications did not have significantly different effects on abstinence compared to placebo (test for subgroup differences χ²=0.7, df=2, p=0.69). Figure 3D depicts the effects of antidepressant use compared to placebo on abstinence rates stratified by diagnostic indication (depression vs. other). Both trials prescribing antidepressants to treat depression (RR=1.01 (95% CI: 0.91-1.13, k=19, z=-0.29, p=0.77) and other indications (RR=0.95 (95% CI: 0.91-1.13, k=19, z=-0.29, p=0.77) suggested no effect on abstinence rates (test for subgroup differences χ²=0.5, df=1, p=0.49). Antidepressant agents, compared to placebo, similarly had no effect on abstinence rates in trials with a detoxification period (RR=0.95 (95% CI: 0.84-1.08, k=13, z=-0.8, p=0.42) or without a detoxification period prior to initiation of
antidepressant treatment (RR=1.01 (95% CI: 0.88-1.56, k=6, z=0.17, p=0.87). There was no funnel plot asymmetry suggestive of publication bias and the Egger's test was also not statistically significant (p>0.05).

Discussion

Our systematic review provides evidence in Aim 1 that antidepressant medications significantly decrease depression severity, as compared with placebo, in populations with comorbid MDD and AUD. The magnitude of depressive symptom improvement, using antidepressants, in patients with MDD and comorbid AUD seems fairly comparable to the benefits observed in patients with MDD in general.11,12 Further analysis suggests that the measured benefit of antidepressant agents was greater in trials that did not give concomitant pharmacotherapy for AUD or psychotherapy. Additionally, we did not demonstrate any difference in the measured efficacy of antidepressant agents compared with placebo based on medication class. TCAs and SSRIs showed similar benefits when compared with placebo in subjects with MDD and comorbid AUD.

Our meta-analysis suggests that antidepressant agents can be effective in treating patients with MDD and comorbid AUD. Stratified subgroup analysis suggests that there is no significant difference in the measured efficacy of different classes of antidepressants (e.g. TCAs vs. SSRIs). The clinically significant findings of our study suggest that depressive symptoms warrant similar pharmacological treatment in patients with comorbid AUD. That is, among commonly prescribed antidepressants, there is little evidence for differences in efficacy, and choice of agent should be based on tolerability, side-effect profile, and potential interactions with other medications or addictive substances.
Our systematic review also demonstrated a decrease in the measured benefit of antidepressant agents compared with placebo when other interventions, such as pharmacological treatments for AUD or psychotherapy, were started concomitantly. This result is not surprising, given that concomitant psychotherapy and/or pharmacotherapy for AUD likely produce a greater variation in treatment response (especially in the placebo group) and also may differentially lead to greater improvement in depressive symptoms in the placebo group, since subjects randomized to antidepressants may experience a significant improvement, regardless of whether they receive additional therapy, while subjects randomized to placebo may exhibit greater improvement with additional therapy. Our findings regarding psychotherapy as a moderator are consistent with two previous systematic reviews, but are inconsistent with one meta-analysis that showed no moderating effects of psychotherapy. We suggest that future trials studying this dual diagnosis population might consider minimizing concomitant interventions, such as pharmacotherapy for alcohol use or psychotherapy, in order to more directly study the effect of antidepressants in this population. However, clinically, it seems like providing rigorous pharmacotherapy for AUD and/or psychotherapy might also lead to significant improvements in depressive symptoms. This treatment approach might be particularly useful for patients who have a history of non-responsiveness to antidepressants or are averse to taking them.

We were not able to demonstrate any significant moderating effects when studies were stratified by whether comorbid AUD and MDD subjects participated in a detoxification period prior to the initiation of an antidepressant medication. Nevertheless, the benefit of antidepressant treatment in patients who underwent a detoxification period prior to starting an antidepressant showed a greater benefit compared with patients who did not undergo detoxification. This difference in effect size was, however, not statistically significant. Future
studies may want to examine how the timing of antidepressant initiation in relation to alcohol detoxification alters the efficacy of antidepressants in patients with this comorbidity.

The systematic review conducted in Aim 1 has several limitations that may limit generalizability. There are fairly few studies examining the benefits of antidepressants in subjects with comorbid AUD and MDD. The scarcity of trials limited our power to examine potential moderators. Furthermore, moderators of interest were often correlated across studies, e.g. TCA trials tended to be conducted in earlier years, so they were less likely to involve concomitant psychotherapy or pharmacological treatment for AUD. The included studies also suggest possible publication bias, as there was a large degree of heterogeneity across the included trials. While we were able to identify several sources of heterogeneity within this meta-analysis, there are likely several differences between trials and, thus, multiple potential sources of heterogeneity that were not measured. These include treatment adherence, as well as the length and severity of the current major depressive episode. In addition, this meta-analysis did not include any trials that utilized the commonly prescribed medication classes of Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) or bupropion.

Taken together, our findings in Aim 1 suggest that antidepressant treatment is associated with a decrease in depression severity in patients with comorbid AUD and MDD, regardless of the class of antidepressant studied. This improvement in depressive symptoms seems comparable to the effects observed in MDD patients without comorbid AUD. Trials without concomitant pharmacotherapy targeting AUD or without psychotherapy demonstrated a greater measured benefit of antidepressant treatment. In summary, there appears to be insufficient evidence to suggest that depression should be treated differently pharmacologically in patients with comorbid AUD, and choice of pharmacological agent should be based on tolerability, side-effect profile, and potential interactions with other medications or addictive substances. Given the state of the current evidence base, it would
seem reasonable for clinicians to extrapolate the treatment recommendations for Major Depression in general to subjects who also have comorbid AUD. In addition, effectively treating problematic alcohol use will lead to improvement in overall outcomes.

The systematic review conducted as part of Aim 2 is the first meta-analysis to demonstrate that second and third-generation antidepressants, regardless of class, have neither a positive nor negative effect on alcohol drinking outcomes in a broad selection of trials studying these medications for any indication. In the case of alcohol related outcomes, however, psychiatric diagnosis matters. In an important update to older meta-analyses, our results do show that these newer antidepressants have statistically significant efficacy for decreasing drinking days and drinks per day in the cohort of subjects with alcohol dependence and comorbid depression. These findings, therefore, suggest that any reduction in alcohol intake when an antidepressant is prescribed for depression may be mediated by improvement in depressive symptoms. Alternatively, it is possible that antidepressants do directly reduce alcohol consumption in a subset of patients with comorbid depression and alcohol use disorder. This may be due to the shared etiologies of these two conditions, upon which antidepressants from different classes act. By contrast, our meta-analysis provided some evidence that the use of antidepressants may worsen some drinking related outcomes when these medications are prescribed for indications other than depression. The findings of our meta-analysis do not support the use of any antidepressant medication class over another, as they relate to alcohol consumption outcomes, among a wide cross-section of patients. Nonetheless, there is some evidence that antidepressants are associated with an increase in maladaptive drinking behavior when used for indications other than depression, which could
potentially be explained by a subset of patients who respond differently to antidepressants than the general population.

Strengths of this systematic review and meta-analysis conducted as part of Aim 2 include using broad inclusion criteria for studies that report on alcohol consumption outcomes, regardless of the original indication for these medications. We were further able to maintain a broad optic by examining multiple alcohol consumption outcomes, whereas merely selecting one outcome of interest would have excluded 31-65% of our included articles, depending on the outcome chosen. Moreover, we analyzed these trials by both medication class and diagnostic indication to delineate the extent to which these moderators affect outcomes. Aim 2 does have important limitations that may limit generalizability. Most notably, the wide variety of alcohol consumption outcomes reported throughout the literature affected our ability to synthesize the data. Because most studies did not include all outcomes of interest, each meta-analysis reported herein contains a different combination of studies. Additionally, we included a wide variety of trials studying different medication indications, which necessarily increased heterogeneity.

Given the paucity of data available for antidepressants in the subtypes of subjects discussed above, we believe future research in this field should consider age of onset as a moderator of effect for alcohol consumption outcomes. More research is also needed specifically comparing SSRIs to third-generation antidepressants with other mechanisms of action, such as mirtazapine or bupropion, particularly in a population of subjects with early-onset (before 20 years old) alcohol use disorder.
Tables and Figures for Aim 1
Table 1. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Author</th>
<th>Medication</th>
<th>Medication Class</th>
<th>Dose (mg/day)</th>
<th>Duration (weeks)</th>
<th>n Subjects</th>
<th>Age % Male</th>
<th>Concurrent Therapy</th>
<th>Concurrent Treatment</th>
<th>Detox first?</th>
<th>Psychotherapy Targeting Alcohol Use</th>
<th>Psychotherapy Targeting Depression</th>
<th>Pharmacotherapy for Alcohol Use</th>
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<tr>
<td>Adamson et al., 2015</td>
<td>citalopram</td>
<td>SSRI</td>
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<td>12 step facilitation</td>
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<td>CBT</td>
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Abbreviations: SSRI = Selective Serotonin Reuptake Inhibitor, TCA = Tricyclic Antidepressant, CBT = Cognitive Behavioral Therapy, MET = Motivational Enhancement Therapy, High dep = HAM-D>=17, Low dep = HAM-D <=16
Table 2. Risk of Bias Analysis

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<th>Jadad Score</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias) (clinician-reported outcomes)</th>
<th>Incomplete outcome data addressed (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
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<td>5</td>
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<td>+</td>
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<td>Kranzler et al., 2006</td>
<td>4</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Pettinati et al., 2010</td>
<td>3</td>
<td>+</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
<tr>
<td>Mason et al., 1996</td>
<td>4</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>?</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>Roy-Byrne et al., 2000</td>
<td>3</td>
<td>?</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Hernandez-Avila et al., 2004</td>
<td>3</td>
<td>+</td>
<td>?</td>
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Records identified through database searching (n = 68)

Additional records identified through other sources (n = 7)

Records after duplicates removed (n = 75)

Records excluded by title or abstract (n = 44)

Records screened (n = 75)

Full-text articles assessed for eligibility (n = 31)

Full-text articles excluded (n = 15): Duplicate trial (n = 3)
Participants did not all have depression (n = 4)
Not randomized, placebo-controlled trial (n = 1)
Did not use an antidepressant (n = 1)
Discontinuation study (n = 1)
Examined adolescents (n = 3)
Participants had multiple substance use disorders (n = 2)

Studies included in qualitative synthesis (n = 16)

Studies included in quantitative synthesis (meta-analysis) (n = 16) (n = 18 distinct trial arms)
Figure 2a. Forest Plot-SMD Improvement in Depressive Symptoms
Figure 3a. Funnel Plot-SMD Improvement in Depressive Symptoms
Figure 4a. Forest Plot-SMD Improvement in Depressive Symptoms Stratified by Concomitant Psychotherapy

<table>
<thead>
<tr>
<th>Studies</th>
<th>SMD (LCI, UCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Without Concomitant Psychotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Altamura 1990</td>
<td>1.94 (1.02, 2.85)</td>
</tr>
<tr>
<td>Butterworth 1971</td>
<td>0.62 (-0.02, 1.26)</td>
</tr>
<tr>
<td>Gual 2003</td>
<td>0.40 (-0.04, 0.84)</td>
</tr>
<tr>
<td>Mason 1996</td>
<td>0.79 (-0.08, 1.66)</td>
</tr>
<tr>
<td>Roy 1990</td>
<td>1.70 (0.94, 2.47)</td>
</tr>
<tr>
<td>Krupitsky</td>
<td>0.44 (-0.07, 0.95)</td>
</tr>
<tr>
<td>Random</td>
<td>0.90 (0.42, 1.39)</td>
</tr>
<tr>
<td><strong>With Concomitant Psychotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Adamson 2015</td>
<td>-0.10 (-0.43, 0.24)</td>
</tr>
<tr>
<td>Cornelius 2016</td>
<td>0.17 (-0.08, 1.22)</td>
</tr>
<tr>
<td>Hernandez-Arila 2004</td>
<td>0.07 (-0.54, 0.69)</td>
</tr>
<tr>
<td>Kranzler 2006 - HIGH</td>
<td>0.19 (-0.10, 0.48)</td>
</tr>
<tr>
<td>Kranzler 2006 - LOW</td>
<td>-0.10 (-0.44, 0.23)</td>
</tr>
<tr>
<td>McGrath 1996</td>
<td>0.34 (-0.19, 0.87)</td>
</tr>
<tr>
<td>McLean 1966</td>
<td>0.11 (-0.58, 0.81)</td>
</tr>
<tr>
<td>Moak 2003</td>
<td>0.15 (-0.28, 0.59)</td>
</tr>
<tr>
<td>Pettinati 2001</td>
<td>-0.21 (-0.95, 0.53)</td>
</tr>
<tr>
<td>Pettinati 2010 - Naltrexone</td>
<td>0.17 (-0.36, 0.69)</td>
</tr>
<tr>
<td>Pettinati 2010 - no naltrexone</td>
<td>0.20 (-0.38, 0.77)</td>
</tr>
<tr>
<td>Roy-Byrne 2000</td>
<td>0.46 (-0.07, 1.00)</td>
</tr>
<tr>
<td>Random</td>
<td>0.10 (-0.03, 0.23)</td>
</tr>
<tr>
<td>Overall</td>
<td>0.16 (0.03, 0.28)</td>
</tr>
</tbody>
</table>
Figure 2b. Forest Plot - Risk Ratio of Response

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk Ratio (LCI, UCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRI</strong></td>
<td></td>
</tr>
<tr>
<td>Guel 2003</td>
<td>1.12 (0.67, 1.89)</td>
</tr>
<tr>
<td>Kranzler 2006 - HIGH</td>
<td>1.36 (1.05, 1.77)</td>
</tr>
<tr>
<td>Kranzler 2006 - LOW</td>
<td>0.76 (0.60, 0.97)</td>
</tr>
<tr>
<td>Mosk 2003</td>
<td>1.23 (0.98, 1.55)</td>
</tr>
<tr>
<td>Pettinati 2010 - Naltrexone</td>
<td>1.21 (0.91, 1.61)</td>
</tr>
<tr>
<td>Pettinati 2010 - no naltrexone</td>
<td>0.86 (0.51, 1.45)</td>
</tr>
<tr>
<td>Roy 1993</td>
<td>3.00 (1.29, 7.56)</td>
</tr>
<tr>
<td>Random</td>
<td>1.14 (0.90, 1.43)</td>
</tr>
<tr>
<td><strong>TCA</strong></td>
<td></td>
</tr>
<tr>
<td>Butterworth 1971</td>
<td>1.97 (1.10, 3.54)</td>
</tr>
<tr>
<td>Mason 1996</td>
<td>3.47 (1.24, 9.65)</td>
</tr>
<tr>
<td>McGrath 1996</td>
<td>1.55 (0.79, 3.03)</td>
</tr>
<tr>
<td>Random</td>
<td>1.97 (1.32, 2.96)</td>
</tr>
<tr>
<td><strong>other</strong></td>
<td></td>
</tr>
<tr>
<td>McLean 1986</td>
<td>0.63 (0.26, 1.50)</td>
</tr>
<tr>
<td>Roy-Byrne 2000</td>
<td>3.02 (1.15, 7.97)</td>
</tr>
<tr>
<td>Random</td>
<td>1.36 (0.29, 6.35)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>1.30 (1.07, 1.58)</td>
</tr>
</tbody>
</table>
Figure 3b. Funnel Plot-Risk Ratio of Response
Figure 4b. Forest Plot – Risk Ratio of Response Stratified by Concomitant Psychotherapy

<table>
<thead>
<tr>
<th>Studies</th>
<th>Risk Ratio (LCI, UCI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Without Concomitant Psychotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Butterworth 1971</td>
<td>1.97 (1.10, 3.54)</td>
</tr>
<tr>
<td>Guai 2003</td>
<td>1.12 (0.67, 1.89)</td>
</tr>
<tr>
<td>Mason 1996</td>
<td>3.47 (1.24, 9.65)</td>
</tr>
<tr>
<td>Roy 1996</td>
<td>3.00 (1.19, 7.58)</td>
</tr>
<tr>
<td>Random</td>
<td>1.94 (1.17, 3.23)</td>
</tr>
<tr>
<td><strong>With Concomitant Psychotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Kranzler 2006 – HIGH</td>
<td>1.36 (1.05, 1.77)</td>
</tr>
<tr>
<td>Kranzler 2006 – LOW</td>
<td>0.76 (0.60, 0.97)</td>
</tr>
<tr>
<td>McGrath 1996</td>
<td>1.55 (0.79, 3.03)</td>
</tr>
<tr>
<td>McLean 1966</td>
<td>0.63 (0.26, 1.50)</td>
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<tr>
<td>Moss 2003</td>
<td>1.23 (0.98, 1.55)</td>
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<tr>
<td>Pettinati 2010 – Naltrexone</td>
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</tr>
<tr>
<td>Pettinati 2010 – no naltrexone</td>
<td>0.86 (0.51, 1.45)</td>
</tr>
<tr>
<td>Roy-Byrne 2000</td>
<td>3.02 (1.15, 7.97)</td>
</tr>
<tr>
<td>Random</td>
<td>1.13 (0.89, 1.42)</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td></td>
</tr>
<tr>
<td>Random</td>
<td>1.24 (1.00, 1.53)</td>
</tr>
</tbody>
</table>
Figure Legends for Aim 1:

**Figure 1: Selection of Studies.** Figure 1 is a PRISMA flow diagram depicting selection of studies.

**Figure 2: Effect of antidepressants on depression outcomes-stratified by medication type.** Figure 2A examines the effect of antidepressant agents compared with placebo on depression outcomes, when outcomes were analyzed using standardized mean difference. Figure 2B examines risk ratio of response.

**Figure 3: Funnel Plot.** Figure 3A examines the included clinical trials for publication bias, when outcomes were analyzed using standardized mean difference. Figure 3B examines risk ratio of response.

**Figure 4: Effect of antidepressants on depression outcomes-stratified by concomitant psychotherapy.** Figure 4A examines the effect of antidepressant agents compared with placebo on depression outcomes, when outcomes were analyzed using standardized mean difference. Figure 4B examines risk ratio of response.
Tables and Figures for Aim 2

Table 1. Characteristics of Included Studies, by Antidepressant Medication Class

<table>
<thead>
<tr>
<th>Author</th>
<th>Medication (mg/day)</th>
<th>Indication</th>
<th>Duration in Weeks</th>
<th>n Subjects (% male)</th>
<th>Abstinence at Trial Start</th>
<th>Concurrent Treatment</th>
<th>Outcomes Used in Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SSRI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Charney et al., 2015&lt;sup&gt;60&lt;/sup&gt;</td>
<td>citalopram (40)</td>
<td>Alcohol</td>
<td>12</td>
<td>265 (70)</td>
<td>Yes</td>
<td>MI, Group</td>
<td>DDD, DD, abstinence</td>
</tr>
<tr>
<td>Naranjo et al., 1995&lt;sup&gt;61&lt;/sup&gt;</td>
<td>citalopram (40)</td>
<td>Alcohol</td>
<td>12</td>
<td>99 (57)</td>
<td>No</td>
<td>Psychoeducation</td>
<td>DDD, DD</td>
</tr>
<tr>
<td>Tiilhonen et al., 1996&lt;sup&gt;62&lt;/sup&gt;</td>
<td>citalopram (40)</td>
<td>Alcohol</td>
<td>12</td>
<td>62 (100)</td>
<td>Yes</td>
<td>Supportive</td>
<td>abstinence</td>
</tr>
<tr>
<td>Janiri et al., 1996&lt;sup&gt;63&lt;/sup&gt;</td>
<td>fluoxetine (20)</td>
<td>Alcohol</td>
<td>9</td>
<td>50 (80)</td>
<td>Yes</td>
<td>12-step</td>
<td>abstinence</td>
</tr>
<tr>
<td>Cornelius et al., 1997&lt;sup&gt;64&lt;/sup&gt;</td>
<td>fluoxetine (40)</td>
<td>Depression</td>
<td>12</td>
<td>51 (51)</td>
<td>Yes</td>
<td>Supportive</td>
<td>DDD, DD, HDD, abstinence</td>
</tr>
<tr>
<td>Naranjo et al., 1990&lt;sup&gt;65&lt;/sup&gt;</td>
<td>fluoxetine (40/60)</td>
<td>Alcohol</td>
<td>4</td>
<td>41 (100)</td>
<td>No</td>
<td>None</td>
<td>DDD, DD</td>
</tr>
<tr>
<td>Kabel &amp; Petty, 1996&lt;sup&gt;66&lt;/sup&gt;</td>
<td>fluoxetine (60)</td>
<td>Alcohol</td>
<td>12</td>
<td>28 (100)</td>
<td>Yes</td>
<td>12-step</td>
<td>abstinence</td>
</tr>
<tr>
<td>Kranzler et al., 1995&lt;sup&gt;67&lt;/sup&gt;</td>
<td>fluoxetine (60)</td>
<td>Alcohol</td>
<td>12</td>
<td>101 (80)</td>
<td>No</td>
<td>CBT</td>
<td>DDD, DD</td>
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<tr>
<td>Chick et al., 2004&lt;sup&gt;32&lt;/sup&gt;</td>
<td>fluvoxamine (300)</td>
<td>Alcohol</td>
<td>12</td>
<td>492 (74)</td>
<td>Yes</td>
<td>None</td>
<td>DD, abstinence</td>
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<tr>
<td>Thomas et al., 2008&lt;sup&gt;68&lt;/sup&gt;</td>
<td>paroxetine (60)</td>
<td>Anxiety</td>
<td>16</td>
<td>42 (52)</td>
<td>No</td>
<td>None</td>
<td>DDD, DD, HDD</td>
</tr>
<tr>
<td>Brady et al., 2005&lt;sup&gt;69&lt;/sup&gt;</td>
<td>sertraline (150)</td>
<td>PTSD</td>
<td>12</td>
<td>94 (54)</td>
<td>Yes</td>
<td>CBT</td>
<td>ADD, HDD</td>
</tr>
<tr>
<td>Gual et al., 2003&lt;sup&gt;48&lt;/sup&gt;</td>
<td>sertraline (150)</td>
<td>Depression</td>
<td>24</td>
<td>83 (53)</td>
<td>Yes</td>
<td>None</td>
<td>DD, abstinence</td>
</tr>
<tr>
<td>Hien et al., 2015&lt;sup&gt;70&lt;/sup&gt;</td>
<td>sertraline (200)</td>
<td>PTSD</td>
<td>12</td>
<td>69 (19)</td>
<td>No</td>
<td>Seeking Safety</td>
<td>DDD, HDD, abstinence</td>
</tr>
<tr>
<td>Kranzler et al., 2006&lt;sup&gt;50&lt;/sup&gt;</td>
<td>sertraline (200)</td>
<td>Depression</td>
<td>12</td>
<td>328 (64)</td>
<td>No</td>
<td>Supportive</td>
<td>ADD, DD</td>
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<tr>
<td>Kranzler et al., 2011&lt;sup&gt;33&lt;/sup&gt;</td>
<td>sertraline (200)</td>
<td>Depression</td>
<td>12</td>
<td>134 (81)</td>
<td>Yes</td>
<td>Coping Skills</td>
<td>DD, HDD</td>
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<td>Moak et al., 2003&lt;sup&gt;49&lt;/sup&gt;</td>
<td>sertraline (200)</td>
<td>Depression</td>
<td>12</td>
<td>82 (61)</td>
<td>Yes</td>
<td>CBT</td>
<td>DDD, DD</td>
</tr>
<tr>
<td>Pettinati et al., 2001&lt;sup&gt;29&lt;/sup&gt;</td>
<td>sertraline (200)</td>
<td>Alcohol</td>
<td>14</td>
<td>100 (52)</td>
<td>No</td>
<td>12-step</td>
<td>DD, abstinence</td>
</tr>
<tr>
<td><strong>SNRI</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ciraulo et al., 2013&lt;sup&gt;71&lt;/sup&gt;</td>
<td>venlafaxine (225)</td>
<td>Anxiety</td>
<td>10</td>
<td>81 (78)</td>
<td>Yes</td>
<td>CBT/Relaxation</td>
<td>DD, HDD, abstinence</td>
</tr>
<tr>
<td><strong>Other</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Grant et al., 2007&lt;sup&gt;72&lt;/sup&gt;</td>
<td>bupropion (300)</td>
<td>Smoking</td>
<td>9</td>
<td>58 (84)</td>
<td>Yes</td>
<td>Group</td>
<td>ADD, DD</td>
</tr>
<tr>
<td>Study</td>
<td>Medication</td>
<td>Intervention</td>
<td>Duration</td>
<td>Abstinence Rate</td>
<td>Group Features</td>
<td>Outcomes</td>
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<tr>
<td>-----------------------------------------</td>
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<td>----------------</td>
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<tr>
<td>Karam-Hage et al., 2011&lt;sup&gt;73&lt;/sup&gt;</td>
<td>bupropion</td>
<td>smoking</td>
<td>8</td>
<td>Yes</td>
<td>Group</td>
<td>abstinence</td>
<td></td>
</tr>
<tr>
<td>Bejczy &amp; Soderpalm, 2015&lt;sup&gt;74&lt;/sup&gt;</td>
<td>mirtazapine</td>
<td>Alcohol</td>
<td>8</td>
<td>59 (100)</td>
<td>None</td>
<td>ADD</td>
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</tr>
<tr>
<td>Cornelius et al., 2016&lt;sup&gt;55&lt;/sup&gt;</td>
<td>mirtazapine</td>
<td>Depression</td>
<td>12</td>
<td>14 (71)</td>
<td>MI</td>
<td>DDD, DD, HDD</td>
<td></td>
</tr>
<tr>
<td>Roy-Byrne et al., 2000&lt;sup&gt;75&lt;/sup&gt;</td>
<td>nefazodone</td>
<td>Depression</td>
<td>12</td>
<td>64 (45)</td>
<td>Psychoeducation</td>
<td>ADD, abstinence</td>
<td></td>
</tr>
<tr>
<td>Hernandez-Avila et al., 2004&lt;sup&gt;57&lt;/sup&gt;</td>
<td>nefazodone</td>
<td>Depression</td>
<td>10</td>
<td>41 (49)</td>
<td>Supportive</td>
<td>DDD, DD, HDD, abstinence</td>
<td></td>
</tr>
<tr>
<td>Kranzler et al., 2000&lt;sup&gt;76&lt;/sup&gt;</td>
<td>nefazodone</td>
<td>Alcohol</td>
<td>11</td>
<td>122 (76)</td>
<td>Coping Skills</td>
<td>ADD, DD, HDD, abstinence</td>
<td></td>
</tr>
<tr>
<td>Wetzel et al., 2004&lt;sup&gt;77&lt;/sup&gt;</td>
<td>nefazodone</td>
<td>Alcohol</td>
<td>12</td>
<td>200 (100)</td>
<td>CBT/Supportive</td>
<td>DDD, DD, abstinence</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: SSRI = Selective Serotonin Reuptake Inhibitor, SNRI = Serotonin and Norepinephrine Reuptake Inhibitor, PTSD = Post-traumatic Stress Disorder, MI = Motivational Interviewing, CBT = Cognitive Behavioral Therapy, DDD = Drinks per Drinking Day, ADD = Average Drinks per Day, DD = Drinking Days, HDD = Hazardous Drinking Days
Records identified through
database searching
(n = 446)

Additional records identified
through other sources
(n = 3)

Records after duplicates removed
(n = 354)

Records screened
(n = 354)

Records excluded
(n = 260)

Full-text articles assessed
for eligibility
(n = 94)

Studies included in
qualitative synthesis
(n = 26)

Studies included in
quantitative synthesis
(meta-analysis)
(n = 26)

Full-text articles excluded
(n = 68):
- Duplicate studies (n = 18)
- Not randomized, placebo-controlled trials (n = 21)
- Did not evaluate antidepressants of interest (n = 7)
- Did not report on alcohol consumption outcomes (n = 16)
- Did not examine adult subjects (n = 2)
Figure 2a. Forest Plot-SMD in Drinking Days Stratified by Medication Type
Figure 3a. Forest Plot-SMD in Drinking Days Stratified by Diagnostic Indication

- MDD
  - Cornelius JR 2016
  - Cornelius JR 1997
  - Gual A
  - Hernandez-Avila CA
  - Moak DH
  - Fixed
  - Random

- No MDD
  - Charmey DA
  - Chick J
  - Ciraolo DA-relaxation
  - Ciraolo DA-CBT
  - Grant KM
  - Kranzler HR 2011-LL
  - Kranzler HR 2011-S
  - Kranzler HR 2011
  - Kranzler HR 2011-S
  - Kranzler HR 1995
  - Kranzler HR 2000
  - Narango CA
  - Narango CA-40mg
  - Narango CA-60mg
  - Pettinati HM-Lifetime
  - Pettinati HM-no
  - Thomas SE
  - Wetzel H-CBT
  - Wetzel H-Supportive
  - Fixed
  - Random

Standard Mean Difference in Drinking Days

Decreased Drinking Days with Antidepressants
increased Drinking Days with Antidepressants
Figure 2b. Forest Plot-SMD in Drinks per Day Stratified by Medication Type
Figure 3b. Forest Plot-SMD in Drinks per Day Stratified by Diagnostic Indication

**MDD**
- Cornelius JR 2016: -0.13 [-1.18, 0.91]
- Cornelius JR 1997: -0.68 [-1.24, -0.11]
- Hernandez Avila CA: -0.42 [-1.04, 0.20]
- Moak DH: -0.37 [-0.81, 0.06]
- Fixed: -0.45 [-0.74, 0.28]
- Random: -0.45 [-0.74, 0.28]

**No MDD**
- Bejczy A: 0.00 [-0.51, -0.51]
- Brady KT: 0.24 [-0.16, 0.65]
- Charney DA: 0.24 [-0.00, 0.49]
- Grant KM: 0.02 [-0.50, 0.54]
- Hien DA: 0.38 [-0.20, 0.96]
- Kranzler HR 1995: 0.10 [-0.31, 0.50]
- Kranzler HR 2000: 0.21 [-0.15, 0.57]
- Naranjo CA: 0.32 [-0.18, 0.82]
- Naranjo CA-40mg: 0.00 [-0.93, 0.93]
- Naranjo CA-60mg: -0.48 [-1.35, 0.39]
- Thomas SE: -0.19 [-0.80, 0.42]
- Wetzel H - CBT: -0.10 [-1.50, 0.28]
- Wetzel H - Supportive: 0.43 [0.03, 0.83]
- Fixed: 0.16 [0.04, 0.28]
- Random: 0.16 [0.04, 0.28]
Figure 2c. Forest Plot-SMD in Hazardous Drinking Days Stratified by Medication Type

SSRI
- Brady KT
- Cornelius JR 1997
- Hien DA
- Kranzler HR 2011-LL EO
- Kranzler HR 2011 - S EO
- Kranzler HR 2011 - LL LO
- Kranzler HR 2011 - S LO
- Thomas SE
  - Fixed
  - Random

SNRI
- Ciraulo DA-relaxation
- Ciraulo DA-CBT
  - Fixed
  - Random

Other
- Cornelius JR 2016
- Hernandez-Avila CA
- Kranzler HR 2000
- Wetzel H - Supportive
  - Fixed
  - Random

Standardized Mean Difference in Hazardous Drinking Days

Decreased Hazardous Drinking Days with Antidepressants

Increased Hazardous Drinking Days with Antidepressants

0.63 (0.21, 1.04)
-0.81 (-1.39, -0.24)
0.33 (-1.39, -0.24)
2.38 (0.95, 3.80)
0.13 (-0.56, 0.82)
-0.91 (-1.79, -0.03)
0.41 (-0.08, 0.90)
-0.02 (-0.62, 0.59)
0.18 (-0.03, 0.39)
0.16 (-0.31, 0.64)
0.13 (-0.46, 0.72)
0.38 (-0.29, 1.06)
0.24 (-0.21, 0.68)
0.24 (-0.21, 0.68)
0.65 (-0.42, 1.73)
-1.06 (-1.71, -0.40)
0.17 (-0.19, 0.52)
-0.03 (-0.43, 0.37)
Figure 3c. Forest Plot-SMD in Hazardous Drinking Days Stratified by Diagnostic Indication
Figure 2d. Forest Plot - Risk Ratio of Response - Abstinence Stratified by Medication Type

**SSRI**
- Charney DA
- Chick J
- Cornelius JR 1997
- Guid A
- Hien DA
- Janiri L
- Kabel DI
- Kranzler HR - high
- Kranzler HR - low
- Pettinati HM
- Tilkonen J
- **Fixed**
- **Random**

**SNRI**
- Ciarulo DA relaxation
- Ciarulo DA-CBT
- **Fixed**
- **Random**

**Other**
- Grant KM
- Hernandez-Avilla CA
- Kranzler HR 2000
- Roy-Byrne PP
- Wetzel H - CBT
- Wetzel H - Supportive
- **Fixed**
- **Random**

Decreased Abstinence Rate with Antidepressants | Risk Ratio - Abstinence | Increased Abstinence Rate with Antidepressants
**Figure 3d.** Forest Plot-Risk Ratio of Response-Abstinence Stratified by Diagnostic Indication
Figure Legends for Aim 2:

**Figure 1: Selection of Studies.** Figure 1 is a PRISMA Flow Diagram Depicting Selection of Studies.

**Figure 2: Effect of antidepressants on alcohol use outcomes stratified by medication type.** Figure 2A examines the effects of antidepressant agents compared to placebo on drinking days, Figure 2B examines drinks per day, Figure 2C examines hazardous drinking days and Figure 2D examines abstinence.

**Figure 3: Effect of antidepressants on alcohol use outcomes stratified by diagnostic indication.** Figure 3A examines the effects of antidepressant agents compared to placebo on drinking days, Figure 3B examines drinks per day, Figure 3C examines hazardous drinking days and Figure 3D examines abstinence.
References


