Antidepressants for Major Depressive Disorder and Dysthymic Disorder in Patients With Comorbid Alcohol Use Disorders: A Meta-Analysis of Placebo-Controlled Randomized Trials

Nadia Iovieno, MD; Enrico Tedeschini, MD; Kate H. Bentley, BA; A. Eden Evins, MD, MPH; and George I. Papakostas, MD

Objective: Mood and alcohol use disorders are often co-occurring, each condition complicating the course and outcome of the other. The aim of this study was to examine the efficacy of antidepressants in patients with unipolar major depressive disorder (MDD) and/or dysthymic disorder with comorbid alcohol use disorders and to compare antidepressant and placebo response rates between depressed patients with or without comorbid alcohol use disorders.

Data Sources: MEDLINE/PubMed publication databases were searched for randomized, double-blind, placebo-controlled trials of antidepressants used as monotherapy for the acute-phase treatment of MDD and/or dysthymic disorder in patients with or without alcohol use disorders. The search term *placebo* was cross-referenced with each of the antidepressants approved by the US, Canadian, or European Union drug regulatory agencies for the treatment of MDD and/or dysthymic disorder.

Study Selection: 195 articles were found eligible for inclusion in our analysis, 11 of which focused on the treatment of MDD/dysthymic disorder in patients with comorbid alcohol use disorders. The search was limited to articles published between January 1, 1980, and March 15, 2009 (inclusive).

Results: We found that antidepressant therapy was more effective than placebo in patients with comorbid alcohol use disorders (risk ratio of response = 1.336; $P = .021$). However, this was not the case when selective serotonin reuptake inhibitor (SSRI) antidepressants were examined alone ($P > .05$). There was no significant difference in the relative efficacy of antidepressants (versus placebo) when comparing studies in MDD/dysthymic disorder patients with or without alcohol use disorders ($P = .973$). Meta-regression analyses yielded no significant differences in the risk ratio of responding to antidepressants versus placebo in trials with comorbid alcohol use disorders, whether antidepressants were used alone or adjunctively to psychotherapy, whether they were used in patients actively drinking or recently sober, or whether they were used in pure MDD or in combined MDD and dysthymic disorder populations.

Conclusions: These results support the utility of certain antidepressants (tricyclics, nefazodone) in treating depression in patients with comorbid alcohol use disorders. More data on the use of newer antidepressants, including the SSRIs, for this select patient population are needed.

J Clin Psychiatry 2011;72(8):1144–1151

Submitted: *May 4, 2010; accepted September 15, 2010.*
Online ahead of print: *April 19, 2011 (doi:10.4088/JCP.10m06217).*
Corresponding author: *Nadia Iovieno, MD, Department of Psychiatry, Massachusetts General Hospital, Harvard Medical School, 50 Staniford Street–Suite 401, Boston, MA 02114 (niovieno@partners.org).*

Major depressive disorder (MDD) and dysthymic disorder are highly prevalent and are frequently associated with significant disability, morbidity, and mortality. According to the World Health Organization, MDD has a 12-month prevalence in developed countries between 3.1% and 9.6%,[1] and it contributes to a significant financial, logistical, and psychosocial burden on developed as well as developing nations.[2] Major depressive disorder and dysthymic disorder are often complicated by the co-occurrence of substance use disorders, especially alcohol abuse or dependence. For example, a recent systematic review of studies examining the association between alcohol use disorders and MDD found a median prevalence of current alcohol use disorders of 16% in patients with MDD and a lifetime median prevalence of alcohol use disorders of 30%.[3] More recently, the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial found that 24% of patients with MDD also met criteria for a concurrent alcohol use disorder at baseline.[4] The co-occurrence of MDD and alcohol use disorder may present diagnostic and management challenges, as many symptoms of depression may also arise as the direct physiologic effects of the substance, and differentiating between primary and secondary (ie, substance induced) MDD can be complicated in clinical practice. However, several cross-sectional and longitudinal epidemiologic studies have provided support for the strong and specific association between alcohol use disorder and primary MDD, indicating that this association is not entirely an artifact of misdiagnosed intoxication and withdrawal effects.[5–7] When depression co-occurs with alcohol use disorders, the course and the outcomes of each disorder seem to be complicated by the other. Patients with concurrent MDD and alcohol use disorder tend to have an earlier age at onset of depression, greater depressive symptomatology, more functional impairment, increased risk of relapse, decreased likelihood of recovery, and increased suicidality.[8–12] On the other hand, in alcohol-dependent patients, a concurrent MDD strongly predicts higher rates of both treatment drop out and relapse to drinking.[13–15] Moreover, the presence of a dual diagnosis is associated with high rates of medical and psychiatric comorbidity and increased

use of general medical health services as well as psychiatric hospitalizations.[15–17] It has been recommended that patients with alcohol use disorder and comorbid MDD not be treated for their depression until they are abstinent from alcohol for at least 4 weeks.[18] Indeed, there is evidence that, for some with alcohol-induced mood disorder, the mood disorder will resolve with abstinence. Unfortunately, depressive symptoms may complicate or delay the ability to attain abstinence. Recently, there has been some evidence that antidepressants may improve depressive symptoms in patients with concurrent alcohol use disorders, even if they have only a limited effect in decreasing alcohol use in these subjects.[3,4,19–21]

The vast majority of our knowledge regarding the efficacy of antidepressants for the treatment of MDD or dysthymic disorder derives from randomized, double-blind, placebo-controlled trials that employ standard criteria, which typically aim to exclude certain groups of patients,[22–28] including pregnant or breastfeeding women, children, adolescents and the elderly, patients with psychotic symptoms, patients at imminent risk of suicide, patients with active or recent alcohol use disorders or drug use disorders, as well as patients with serious and unstable medical illness (Axis III comorbidity). Therefore, there is an important gap in clinical knowledge regarding whether antidepressants are also effective in relieving depression in these special populations. In fact, it has even been suggested that treatment outcomes may differ between patients who are and are not typically included in antidepressant treatment trials,[22] although not all studies support this finding.[27] As a result, separate clinical trials are often required in order to establish whether antidepressant agents are effective and safe in treating depression in patients typically excluded from MDD/dysthymic disorder efficacy trials.

To date, there continues to be a paucity of randomized, double-blind, placebo-controlled trials that have been conducted to evaluate the efficacy, safety, and tolerability of antidepressants as monotherapy for patients with unipolar depressive disorders (MDD, dysthymic disorder) and co-occurring alcohol use disorders. Although previous meta-analyses have found antidepressants to be more effective than placebo in the treatment of MDD/dysthymic disorder in patients with alcohol use disorders,[19,20] efficacy for newer agents (ie, the selective serotonin reuptake inhibitors [SSRIs]) was questionable. However, 2 additional studies focusing on the use of the SSRIs in patients with MDD/ dysthymic disorder and alcohol use disorders have since been published[29,30] which, again, bring into question the utility of the SSRIs for the treatment of this specific patient population. In addition, a systematic effort to compare the characteristics of randomized, double-blind, placebo-controlled clinical trials of antidepressants focusing on MDD/dysthymic disorder patients with or without alcohol use disorder, including elements of study design, patient characteristics, and drug and placebo outcomes has yet to be conducted. Examining whether there are differences in clinical characteristics or treatment outcomes between depressed patients with or without alcohol use disorders could provide insights that would help in the design of future antidepressant treatment studies in these comorbid MDD patients. Therefore, the purpose of the present work is to conduct an updated meta-analysis of randomized, double-blind, placebo-controlled antidepressant monotherapy studies for patients with unipolar depression (MDD and dysthymic disorder) with comorbid alcohol use disorders and to compare study design characteristics, patient characteristics, and drug/placebo outcomes between MDD/dysthymic disorder studies that do or do not focus on patients with comorbid alcohol use disorders.

Clinical Points

- Depression and alcohol use disorders often co-occur and may present diagnostic and management challenges.
- Current evidence supports the efficacy of antidepressants in treating depression in patients with comorbid alcohol abuse and/or dependence.
- Clinicians should consider the use of antidepressants as first-line therapy for targeting depressive symptoms in patients with unipolar depression and concurrent alcohol use.

METHOD

Data Sources and Search Strategy

We sought to identify double-blind, randomized, placebo-controlled trials of antidepressants used as monotherapy for the treatment of MDD/dysthymic disorder in patient populations that were or were not specifically selected for the presence of a comorbid alcohol use disorders for possible inclusion in the meta-analysis. As antidepressants, we defined pharmacologic agents that have or had received a letter of approval by the US, Canadian, or European Union drug regulatory agencies for the treatment of MDD and/or dysthymic disorder. According to this definition, the following pharmacologic agents met criteria to be considered as antidepressants: amitriptyline, nortriptyline, imipramine, desipramine, clomipramine, trimipramine, protriptyline, dothiepin, doxepin, lofepramine, amoxapine, maprotiline, amineptine, nomifensine, bupropion, phenelzine, tranylcypromine, isocarboxazid, moclobemide, brofaromine, fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine, zimelidine, tianeptine, ritanserin, trazodone, nefazodone, agomelatine, venlafaxine, desvenlafaxine, duloxetine, viloxazine, milnacipran, reboxetine, mirtazapine, and mianserin.

Eligible studies were first identified using searches of PubMed/MEDLINE by cross-referencing the search term *placebo* with each of the above-mentioned agents. The

© Copyright 2011 Physicians Postgraduate Press, Inc.

PubMed/MEDLINE search was limited to articles that were published between January 1, 1980, and March 15, 2010 (inclusive). The year 1980 was used as a cutoff in our search in order to decrease diagnostic variability, since the *DSM-III* was introduced in 1980. In order to expand our database, we then reviewed the reference list of all studies identified with PubMed/MEDLINE. Final inclusion of articles was determined by consensus between the authors.

Study Selection

We searched for randomized, double-blind, placebo-controlled trials of antidepressants used as monotherapy for the acute-phase treatment of MDD or dysthymic disorder with or without comorbid alcohol use disorders. We then searched for studies that also met all of the following criteria:

1. Defined either MDD or dysthymic disorder according to the *Diagnostic and Statistical Manual of Mental Disorder*, Third Edition[31]; *Diagnostic and Statistical Manual of Mental Disorders*, Third Edition, Revised[32]; *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition[33]; Research Diagnostic Criteria[34]; or Feighner's Diagnostic Criteria.[35]
2. Were of at least 4 weeks in duration.
3. Focused on the use of antidepressants in their oral formulation.
4. Presented entirely original (not previously published) data.
5. Focused on the treatment of adult patients.
6. Did not exclusively focus on the treatment of patients with treatment-resistant depression, bipolar depressive disorder, depression with psychotic features, minor depression, or perinatal depression.
7. Did not exclusively focus on the treatment of MDD in patients with comorbid substance use disorders other that alcohol or patients with a specific comorbid medical illness.
8. Involved the use of the Hamilton Depression Rating Scale (HDRS),[36] the Montgomery-Asberg Depression Rating Scale (MADRS),[37] or the Clinical Global Impressions-Improvement of Illness Scale (CGI-I)[38] as one of their outcome measures.

Definitions

Clinical response was defined as a 50% or greater reduction in HDRS or MADRS scores, baseline to endpoint, or a CGI-I score < 3 at the final visit. For consistency, the HDRS was chosen over the MADRS or CGI-I when response rates from multiple scales were reported. For studies that reported only CGI-I–based response rates, the HDRS-based response rates were either obtained from the sponsor or imputed using the method described by Walsh et al.[39] In cases in which continuous (change in depression severity scores) but not dichotomous (response rates) outcomes were presented and dichotomous outcomes could not be obtained from the study authors, we converted continuous outcomes to dichotomous outcomes using the following method: a multiple regression was conducted, with response rate as the dependent variable and percent score reduction as the independent variable, using data from as many studies that reported both outcomes. Unobtainable response rates were then calculated with the use of the regression coefficients derived, applied to the given percent score reduction for that study. Some studies depicted changes in HDRS scores only graphically. In these instances, changes in HDRS scores were obtained by measuring each data point with rounding to the nearest 0.5. Discontinuation rate was defined as per each protocol. For consistency, we used intent-to-treat (ITT)–based response rates in the present analysis. Whenever ITT-based response rates were not available in the publication, the sponsor was contacted to obtain ITT-based response rates. In cases in which the sponsor could not retrieve ITT-based response rates, we utilized response rates based on completers. The probability of receiving placebo was computed from the number of treatment arms and the randomization schedule (ie, 1:1:1) of each trial. For example, a 2-arm trial with a 2:1 randomization favoring antidepressant treatment yields a 1 in 3 chance of receiving placebo.

Quantitative Data Synthesis

Response rates between groups were compared with the use of analysis of variance. In addition to sample size, when antidepressant response rates were compared between trials involving patients with versus those without comorbid alcohol use disorders, the probability of being randomized to placebo as well as dosing (fixed versus flexible) were also entered as covariates because they were found to predict antidepressant response rates in a previous meta-analysis.[40] Similarly, in addition to sample size, when placebo response rates were compared between these 2 clinical trial groups (ie, those that did versus those that did not select for the presence of comorbid alcohol use disorders), severity at baseline, year of publication, and the probability of being randomized to placebo were also entered as covariates for the same reason. Random-effects meta-analysis was utilized to estimate the pooled risk ratio of responding to antidepressants versus placebo in MDD/dysthymic disorder trials that specifically selected for the presence of comorbid alcohol use disorders. A meta-regression analysis was used in order to compare risk ratio of responding to antidepressants versus placebo between these 2 clinical trial groups (ie, those that did versus those that did not select for the presence of comorbid alcohol use disorders). For this meta-regression analysis, year of publication, severity at baseline, and the probability of being randomized to placebo were also entered as covariates since they had also previously been found to influence the risk ratio of clinical response following antidepressant versus placebo therapy. Finally, a meta-regression analysis was conducted in order to compare the risk ratio of discontinuing antidepressants versus placebo between these 2 clinical trial groups (trials involving patients with versus those without

Table 1. Trials in Major Depressive Disorder (MDD)/Dysthymic Disorder Patients With Comorbid Alcohol Use Disorders

Author	Duration, Wk	Antidepressant Arm (dose)	Antidepressant, n	Placebo, n	Abstinence Required to Enter the Trial (duration)	Concurrent Therapy	Mood Disorder Diagnosis	Alcohol Use Disorder
Altamura et al,[42] 1990	12	Viloxazine (400 mg/d)	15	15	No	No	Dysthymic disorder	Dependence
Mason et al,[43] 1996	24	Desipramine (50–300 mg/d)	15	13	7 d	No	MDD	Dependence
McGrath et al,[44] 1996	12	Imipramine (50–300 mg/d)	36	33	No	Individual CBT	MDD-dysthymic disorder	Dependence or abuse
Cornelius et al,[45] 1997	12	Fluoxetine (20–40 mg/d)	25	26	7 d	Supportive psychotherapy	MDD	Dependence
Roy et al,[46] 1998	6	Sertraline (100 mg/d)	18	18	14 d	No	MDD	Dependence
Roy-Byrne et al,[47] 2000	12	Nefazodone (200–600 mg/d)	32	32	No	Group CBT	MDD	Dependence
Gual et al,[48] 2003	24	Sertraline (50–150 mg/d)	44	39	14 d	No	MDD-dysthymic disorder	Dependence
Moak et al,[49] 2003	12	Sertraline (50–200 mg/d)	38	44	No	Individual CBT	MDD-dysthymic disorder	Dependence or abuse
Hernandez-Avila et al,[50] 2004	10	Nefazodone (200–600 mg/d)	21	20	7 d	Supportive psychotherapy	MDD	Dependence
Kranzler et al,[29] 2006	10	Sertraline (50–200 mg/d)	159	169	4 d	Supportive psychotherapy	MDD	Dependence
Pettinati et al,[30] 2010	14	Sertraline (50–200 mg/d)	40	39	No	Individual CBT	MDD	Dependence

Abbreviation: CBT = cognitive-behavioral therapy.

comorbid alcohol use disorders). For this meta-regression analysis, only study duration was entered as covariate since no other variable had previously been found to influence the risk ratio of discontinuing antidepressants versus placebo.[41]

Finally, as a post hoc analysis, we sought to examine the impact of antidepressant medications on drinking. Articles were reviewed, and all authors were contacted in order to obtain the number of heavy drinking days (as per protocol) during the last week of the trial. Such data were available for 2 trials only. Thus, a random-effects meta-analysis was used to compare the percentage of heavy drinking days between antidepressant- and placebo-treated patients for these 2 studies.

All tests conducted were 2-tailed, with α set at the .05 level.

RESULTS

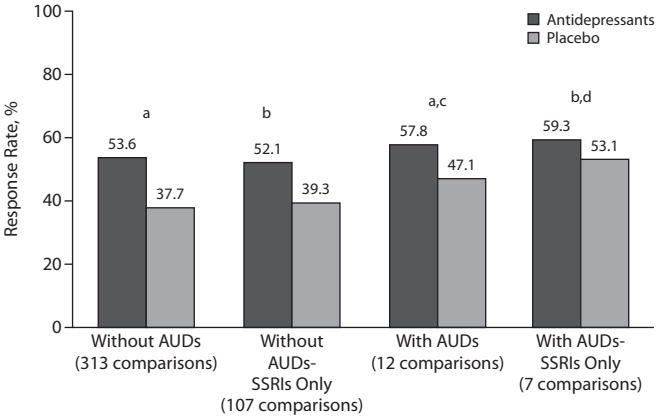
Initially, 7,349 abstracts were identified in PubMed/Medline. Of these, 6,926 were excluded for a number of reasons (other topics, reviews). The remaining 423 abstracts described clinical trials of antidepressants for MDD/dysthymic disorder. These 423 articles were obtained and reviewed thoroughly. Fifteen additional articles were identified after reviewing the reference lists of these 423 articles as well as 2 large meta-analyses. One hundred articles were excluded because they presented data published elsewhere, 25 articles were excluded because they focused on children and/or adolescents with depression, and 34 were excluded because they focused on the treatment of depressive disorders other than MDD or dysthymic disorder (bipolar disorder, MDD with psychotic features, minor depression, "neurotic depression"), because they focused on perinatal MDD, because the diagnosis of MDD/dysthymic disorder was based on the *DSM-II*, or because they did not state which, if any, diagnostic criteria were used to define MDD/dysthymic disorder. One study was excluded because it focused on patients with treatment-resistant depression, 14 were excluded because they focused on the treatment of patients with depression and comorbid drug use disorders, and 61 were excluded because they focused on the treatment of patients with depression and comorbid Axis III disorders. Three were excluded because they did not involve the use of an oral form of an antidepressant (selegiline), 3 because they were less than 4 weeks in duration, and 2 studies because they did not involve the use of the HDRS, MADRS, or CGI-I.

Thus, a total of 195 articles were found eligible for inclusion in our pooled analysis (list available upon request). Eleven of the 195 trials focused on MDD/dysthymic disorder patients specifically selected for the presence of comorbid alcohol use disorders. While 189 articles reported the results of a single trial, 6 reported results of several (a total of 14) trials. Thus, a total of 325 antidepressant versus placebo comparisons from 203 clinical trials were pooled (46,820 patients randomized to treatment with an antidepressant [n = 29,664] versus placebo [n = 17,156]), 12 of which were derived from clinical trials on the treatment of MDD or dysthymic disorder with comorbid alcohol use disorders (891 patients randomized to treatment with an antidepressant [n = 443] versus placebo [n = 448]). A specific description of characteristics of trials involving MDD/dysthymic disorder patients with comorbid alcohol use disorders is reported in Table 1. A statistically significant difference was found between trials that were not versus those that were specifically focusing on treating MDD/ dysthymic disorder in patients with

© Copyright 2011 Physicians Postgraduate Press, Inc.

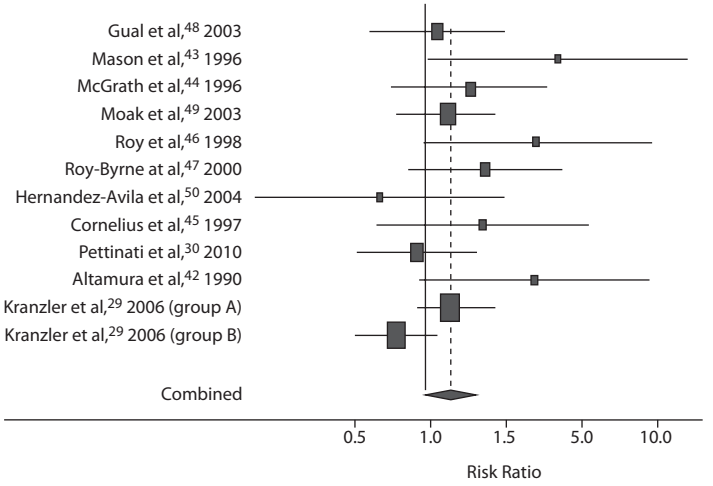
comorbid alcohol use disorders for the following variables: mean ± SD study duration in weeks (7.1 ± 2.9 versus 13.2 ± 5.4, respectively, $P < .001$), baseline severity in terms of mean ± SD 17-item HDRS scores at baseline (21.6 ± 4.0 versus 17.0 ± 3.8, respectively, $P < .001$), mean ± SD probability of receiving placebo (35.5% ± 9.1% versus 47.9% ± 7.2%, respectively, $P < .001$), mean proportion of women (61.6% versus 37.0%, respectively, $P < .001$), and mean ± SD sample size per treatment arm (94.4 ± 58.8, versus 37.1 ± 23.3, respectively, $P < .001$). There was no statistically significant difference between the 2 trial groups in mean ± SD age in years (44.0 ± 8.9 versus 41.5 ± 3.2, respectively, $P = .167$) as well as in mean year of publication (± number of years) (1996 ± 7.9 versus 2000 ± 5.6, respectively, $P = .062$).

Figure 1. Efficacy of Antidepressants Versus Placebo in Major Depressive Disorder (MDD)/Dysthymic Disorder With or Without Comorbid Alcohol Use Disorders (AUDs)



[a]$P = .973$ comparing the risk ratio of response of antidepressants versus placebo in MDD/dysthymic disorder with AUDs (n = 891) and without AUDs (n = 46,820).
[b]$P = .224$ comparing the risk ratio of response of antidepressants versus placebo in MDD/dysthymic disorder with AUDs (n = 659) and without AUDs (n = 19,780), specifically in trials with SSRIs.
[c]$P = .021$ for antidepressants versus placebo in MDD/dysthymic disorder with AUDs.
[d]$P = .263$ for antidepressants versus placebo in MDD/dysthymic disorder with AUDs in trials with SSRIs.
Abbreviations: SSRI=selective serotonin reuptake inhibitor.

Figure 2. Effect of Antidepressants in Trials of Major Depressive Disorder/Dysthymic Disorder With Comorbid Alcohol Use Disorders[a]



[a]Solid line represents risk ratio = 1; dotted line represents the pooled risk ratio. Boxes represent risk ratios, and box sizes are proportional to study sample size. Horizontal lines represent the 95% confidence interval of the risk ratio.

Meta-Analysis Results

Response rates for antidepressants versus placebo in clinical trials of MDD/dysthymic disorder patients with comorbid alcohol use disorders were 57.8% (256/443) versus 47.1% (211/448), respectively (number needed to treat [NNT], approximately 9). Response rates for antidepressants versus placebo in clinical trials of MDD/dysthymic disorder patients without comorbid alcohol use disorders were 53.6% (15,907/29,664) versus 37.7% (6,469/17,156), respectively (NNT, approximately 6) (Figure 1). There was no statistically significant difference in antidepressant response rates ($P = .097$) and placebo response rates ($P = .342$) between the 2 clinical trial groups (ie, those that did versus those that did not select for the presence of comorbid alcohol use disorders).

The result of the random-effects meta-analysis indicated that antidepressant therapy resulted in statistically significant higher response rates than placebo in MDD/dysthymic disorder patients with comorbid alcohol use disorders (risk ratio = 1.336; 95% CI, 1.045–1.708; $P = .021$) (Figure 2). There was no statistical evidence for heterogeneity in the risk ratio of response to antidepressants versus placebo in these trials ($Q_{11} = 17.110$, $P = .105$). However, when only studies that involved the use of SSRIs were analyzed, the result of the random-effects meta-analysis indicated no statistically significant difference in the response rates of antidepressants versus placebo in this selected patient population (risk ratio = 1.160; 95% CI, 0.895–1.503; $P = .263$), while a statistically significant difference in the response rates of SSRIs versus placebo was observed in clinical trials of MDD/ dysthymic disorder patients without comorbid alcohol use disorders (risk ratio = 1.346; 95% CI, 1.293–1.400; $P < .001$). There was no statistical evidence for heterogeneity in the risk ratio of response to antidepressants versus placebo in trials involving the use of SSRIs in MDD/dysthymic disorder patients with and without comorbid alcohol use disorders ($Q_6 = 8.783$, $P = .186$, and $Q_{106} = 109.371$, $P = .392$, respectively). Response rates for SSRI- and placebo-treated patients from studies of MDD/dysthymic disorder with comorbid alcohol use disorders were 59.3% (192/324) versus 53.1% (178/335), respectively (NNT, approximately 16). Response rates for SSRI- and placebo-treated patients from studies of MDD/dysthymic disorder without comorbid alcohol use disorders were 52.1% (6,140/11,781) versus 39.3% (3,143/7,999), respectively (NNT, approximately 7) (Figure 1).

Meta-regression analysis suggested no statistically significant difference in the risk ratio of responding to antidepressant versus placebo (coefficient = −0.0019, $P = .973$) and in the risk ratio of prematurely discontinuing antidepressant versus placebo due to any reason (coefficient = −0.0470, $P = .550$) or due to adverse events (coefficient = −0.0804, $P = .743$) when comparing studies involving MDD/dysthymic disorder patients with or without comorbid alcohol use disorders. Meta-regression analyses also suggested no statistically significant difference in the risk ratio of responding to antidepressants versus placebo among trials of MDD/dysthymic disorder patients with comorbid alcohol use disorders when comparing trials that involved antidepressant therapy alone versus those that included a concurrent psychotherapy (coefficient = −0.0949, $P = .531$), as well as when comparing trials that included only patients with alcohol dependence versus those that included both alcohol dependence and abuse (coefficient = −0.1147, $P = .381$), when comparing trials that required a minimum period of abstinence from alcohol versus those that included patients who were actively drinking (coefficient = −0.0138, $P = .915$), and when comparing trials that included only patients with MDD versus those that included patients with both MDD and dysthymic disorder (coefficient = −0.0360, $P = .774$). Moreover, the baseline severity of drinking (assessed as the number of heavy drinking days in the week before randomization) did not predict a significant difference in the response rate to antidepressants (coefficient = −0.644, $P = .467$).

Finally, we conducted a post hoc meta-analysis specifically focusing on the impact of antidepressant medications on drinking, using as outcome measure the number of heavy drinking days (as per protocol) during the last week of the trial. For the 2 studies for which these data were available, the result of the random-effects meta-analysis indicated that there was no statistically significant difference in the percentage of heavy drinking days between antidepressant- and placebo-treated patients (risk ratio = 0.691; 95% CI, 0.355–1.342; $P = .275$) and there was no evidence for statistically significant heterogeneity ($Q_1 = 0.341$, $P = .559$).

DISCUSSION

This analysis is the most comprehensive to date examining the efficacy of antidepressants for the treatment of unipolar depression in patients with comorbid alcohol use disorders, and it is the first to compare the effect size of antidepressants versus placebo in this select patient population and in the general MDD/dysthymic disorder population. Our work suggests that antidepressants are more effective than placebo in treating depression in patients with comorbid alcohol use disorders (with an NNT for response of, approximately, 1 in 9), without any evidence of across-study heterogeneity. This finding is consistent with results from previous meta-analyses,[19,20] which reported that antidepressants are effective in treating depression in patients with co-occurring depression and alcohol use disorder, and lends further support to the argument that antidepressants should represent first-line therapy for targeting depressive symptoms in patients with MDD or dysthymic disorder and concurrent alcohol use disorders. However, similar to the 2 previous meta-analyses conducted on this topic, our meta-analysis also failed to detect a significant treatment effect for the SSRIs in this population, despite the addition of 2 studies not previously pooled. This is principally due to a high placebo response rate in these studies. Thus, the majority of evidence supporting the use of antidepressants in our meta-analysis derives from studies that involved nefazodone and the tricyclic antidepressants imipramine and desipramine, while the use of SSRIs for treating depression in this selected patient population is not convincingly supported by the evidence. Finally, we did not find antidepressant treatment to result in greater sobriety than placebo administration in this population, although it should be pointed out that this outcome may have been due to the relative paucity of data (data could only be obtained from 2 of the studies) and the short follow-up duration (ie, perhaps significant effects may have been detected if the duration of follow-up was longer).

However, it should also be pointed out that our present results differ in some ways from those cited in the 2 prior meta-analyses on the subject.[19,20] For example, while the meta-analysis of Nunes and Levin[20] found that the concurrent use of a psychosocial treatment reduced the absolute numerical difference between antidepressant and placebo response rates, whereas the presence of at least 1 week of abstinence increased the efficacy of antidepressant therapy versus placebo, our analysis could not replicate these 2 findings. Our work indeed showed that the efficacy of antidepressants was not influenced whether antidepressants were used alone or adjunctively to psychotherapy (either cognitive behavioral therapy or supportive psychotherapy), whether used in patients actively drinking or recently sober (ie, a few days), or whether used in pure MDD or in combined MDD and dysthymic disorder populations. In fact, in regression analyses, we did not find any relationship between the severity of baseline drinking and treatment outcome. That the presence/absence or severity of recent sobriety does not predict outcome suggests that the decision whether to recommend antidepressants in this patient population should not be determined by these variables, at least as far as the potential efficacy of treatment is concerned.

There are several factors that may explain the discrepancy between our findings and those of Torrens et al[19] or Nunes and Levin.[20] For example, our meta analysis focused on patients with depression and alcohol use disorders, while Nunes and Levin[20] also included studies examining depression with comorbid cocaine or opiate use disorders, which may account for the difference in meta-analysis findings. In fact, Nunes and Levin[20] did report a small difference in effect size between alcohol use disorder and opiate/cocaine use disorder studies (smaller effect size in the latter group). Finally, an additional finding of our study was that the effect size (ie, the difference in response rates between antidepressant- and

© Copyright 2011 Physicians Postgraduate Press, Inc.

placebo-treated patients) was not statistically different when comparing general MDD/dysthymic disorder trials that typically exclude patients with active alcohol use disorder versus those MDD/dysthymic disorder trials that specifically focus on the treatment of depression with comorbid alcohol use disorders, which suggest that power calculations for the design of future studies in this patient population should be in line with those for the general MDD/dysthymic disorder population.

Several limitations should be taken into account when interpreting our findings. Specifically, one limitation pertains to the identification of studies to be included in pooled analyses or meta-analyses. For example, it is quite possible that either publication bias or the file drawer phenomenon, whereby unpublished studies are more likely to be equivocal than published trials, may have distorted our findings or inflated our results (since our study only focused on published clinical trials). It would be interesting to examine whether the inclusion of unpublished studies strengthens or weakens our findings. Moreover, the present work involves pooling clinical trials for the treatment of adults with MDD and comorbid alcohol use disorders, which involve a number of inclusion and exclusion criteria. Therefore, the findings of this study may not be generalized to populations of depressed patients who are typically excluded from these types of clinical trials (ie, adolescents, patients with bipolar depression, psychotic MDD, patients actively abusing other illicit drugs, or women with perinatal depression). Perhaps this phenomenon may explain why, in contrast to reports from nonclinical trial populations,[8–11] we found lower depression severity in patients participating in MDD/alcohol use disorder clinical trials than MDD/non–alcohol use disorder trials. A final limitation is the relatively small number of clinical trials focusing in comorbid MDD and alcohol use disorder and, in particular, the complete lack of data on a number of newer antidepressants (such as venlafaxine, duloxetine, desvenlafaxine, bupropion, or agomelatine).

In conclusion, the results of the present analysis suggest that antidepressants are effective in the treatment of depression in patients who also present with comorbid alcohol use disorders. These findings have important practical consequences for both patients and clinicians because they support the utilization of antidepressants for the treatment of unipolar depression in patients with alcohol use disorders, a condition associated with disability, high rates of medical and psychiatric comorbidity, and increased use of general medical health services as well as psychiatric hospitalizations.

Drug names: bupropion (Wellbutrin, Aplenzin, and others), citalopram (Celexa and others), clomipramine (Anafranil and others), desipramine (Norpramin and others), desvenlafaxine (Pristiq), doxepin (Zonalon, Silenor, and others), duloxetine (Cymbalta), escitalopram (Lexapro and others), fluoxetine (Prozac and others), fluvoxamine (Luvox and others), imipramine (Tofranil and others), isocarboxazid (Marplan), milnacipran (Silvella and others), mirtazapine (Remeron and others), nortriptyline (Pamelor, Aventyl, and others), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil and others), protriptyline (Vivactil and others), selegiline (Emsam, Eldepryl, and others), sertraline (Zoloft and others), tranylcypromine (Parnate and others), trazodone (Oleptro and others), trimipramine (Surmontil and others), venlafaxine (Effexor and others).

Author affiliations: Department of Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston (all authors); Department of Psychiatry, University of Pisa, Italy (Dr Iovieno); and Department of Psychiatry, University of Modena and Reggio Emilia, Modena, Italy (Dr Tedeschini).

Potential conflicts of interest: **Dr Evins** has served as a consultant for Pfizer and Boehringer-Ingelheim and has received research grant support from Pfizer and GlaxoSmithKline. **Dr Papakostas** has served as a consultant for Abbott, AstraZeneca, Brainsway, Bristol-Myers Squibb, Cephalon, Eli Lilly, GlaxoSmithKline, Evotec, Inflabloc, Jazz, Otsuka, PAMLAB, Pfizer, Pierre Fabre, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Shire, and Wyeth; has received honoraria from Abbott, Astra Zeneca, Bristol-Myers Squibb, Brainsway, Cephalon, Eli Lilly, Evotec, GlaxoSmithKline, Inflabloc, Jazz, Lundbeck, Otsuka, PAMLAB, Pfizer, Pierre Fabre, Ridge Diagnostics, Shire, Titan, and Wyeth; has received research support from Bristol-Myers Squibb, Forest, National Institute of Mental Health, PAMLAB, Pfizer, and Ridge Diagnostics (formerly known as Precision Human Biolaboratories); and has served (in the past, but not currently) on the speaker's bureau for Bristol-Myers Squibb and Pfizer. **Drs Iovieno** and **Tedeschini** and **Ms Bentley** report no competing interests.

Funding/support: None reported.

REFERENCES

1. Nandi A, Beard JR, Galea S. Epidemiologic heterogeneity of common mood and anxiety disorders over the lifecourse in the general population: a systematic review. *BMC Psychiatry*. 2009;9(1):31.
2. Fava M, Evins AE, Dorer DJ, et al. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. *Psychother Psychosom*. 2003;72(3):115–127.
3. Sullivan LE, Fiellin DA, O'Connor PG. The prevalence and impact of alcohol problems in major depression: a systematic review. *Am J Med*. 2005;118(4):330–341.
4. Davis LL, Wisniewski SR, Howland RH, et al. Does comorbid substance use disorder impair recovery from major depression with SSRI treatment? an analysis of the STAR*D level one treatment outcomes. *Drug Alcohol Depend*. 2010;107(2-3):161–170.
5. Hasin DS, Grant BF. Major depression in 6050 former drinkers: association with past alcohol dependence. *Arch Gen Psychiatry*. 2002;59(9):794–800.
6. Samet S, Hasin D. Clinical implications of epidemiologic data for diagnosis and treatment of psychiatric comorbidity. *Psychiatr Ann*. 2008;38(11):709–715.
7. Schuckit MA, Smith TL, Danko GP, et al. A comparison of factors associated with substance-induced versus independent depressions. *J Stud Alcohol Drugs*. 2007;68(6):805–812.
8. Sher L, Stanley BH, Harkavy-Friedman JM, et al. Depressed patients with co-occurring alcohol use disorders: a unique patient population. *J Clin Psychiatry*. 2008;69(6):907–915.
9. Davis LL, Frazier E, Husain MM, et al. Substance use disorder comorbidity in major depressive disorder: a confirmatory analysis of the STAR*D cohort. *Am J Addict*. 2006;15(4):278–285.
10. Cornelius JR, Salloum IM, Day NL, et al. Patterns of suicidality and alcohol use in alcoholics with major depression. *Alcohol Clin Exp Res*. 1996;20(8):1451–1455.
11. Davis LL, Rush JA, Wisniewski SR, et al. Substance use disorder comorbidity in major depressive disorder: an exploratory analysis of the Sequenced Treatment Alternatives to Relieve Depression cohort. *Compr Psychiatry*. 2005;46(2):81–89.
12. Conner KR, McCloskey MS, Duberstein PR. Psychiatric risk factors for suicide in the alcohol-dependent patient. *Psychiatr Ann*. 2008;38(11):742–748.
13. Gamble SA, Conner KR, Talbot NL, et al. Effects of pretreatment and posttreatment depressive symptoms on alcohol consumption following treatment in Project MATCH. *J Stud Alcohol Drugs*. 2010;71(1):71–77.
14. Greenfield SF, Weiss RD, Muenz LR, et al. The effect of depression on return to drinking: a prospective study. *Arch Gen Psychiatry*. 1998;55(3):259–265.
15. Fortney JC, Booth BM, Curran GM. Do patients with alcohol dependence use more services? a comparative analysis with other chronic

disorders. *Alcohol Clin Exp Res*. 1999;23(1):127–133.
16. Holder HD, Hallan JB. Impact of alcoholism treatment on total health care costs: a six-year study. *Adv Alcohol Subst Abuse*. 1986;6(1):1–15.
17. Oslin DW, O'Brien CP, Katz IR. The disabling nature of comorbid depression among older DUI recipients. *Am J Addict*. 1999;8(2):128–135.
18. Brown SA, Schuckit MA. Changes in depression among abstinent alcoholics. *J Stud Alcohol*. 1988;49(5):412–417.
19. Torrens M, Fonseca F, Mateu G, et al. Efficacy of antidepressants in substance use disorders with and without comorbid depression: a systematic review and meta-analysis. *Drug Alcohol Depend*. 2005;78(1):1–22.
20. Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence: a meta-analysis. *JAMA*. 2004;291(15):1887–1896.
21. Pettinati HM. Antidepressant treatment of co-occurring depression and alcohol dependence. *Biol Psychiatry*. 2004;56(10):785–792.
22. Wisniewski SR, Rush AJ, Nierenberg AA, et al. Can phase III trial results of antidepressant medications be generalized to clinical practice? a STAR*D report. *Am J Psychiatry*. 2009;166(5):599–607.
23. Zetin M, Hoepner CT. Relevance of exclusion criteria in antidepressant clinical trials: a replication study. *J Clin Psychopharmacol*. 2007;27(3):295–301.
24. Posternak MA, Zimmerman M, Keitner GI, et al. A reevaluation of the exclusion criteria used in antidepressant efficacy trials. *Am J Psychiatry*. 2002;159(2):191–200.
25. Zimmerman M, Mattia JI, Posternak MA. Are subjects in pharmacological treatment trials of depression representative of patients in routine clinical practice? *Am J Psychiatry*. 2002;159(3):469–473.
26. Zimmerman M, Chelminski I, Posternak MA. Exclusion criteria used in antidepressant efficacy trials: consistency across studies and representativeness of samples included. *J Nerv Ment Dis*. 2004;192(2):87–94.
27. Sullivan PF, Joyce PR. Effects of exclusion criteria in depression treatment studies. *J Affect Disord*. 1994;32(1):21–26.
28. Partonen T, Sihvo S, Lönnqvist JK. Patients excluded from an antidepressant efficacy trial. *J Clin Psychiatry*. 1996;57(12):572–575.
29. Kranzler HR, Mueller T, Cornelius J, et al. Sertraline treatment of co-occurring alcohol dependence and major depression. *J Clin Psychopharmacol*. 2006;26(1):13–20.
30. Pettinati HM, Oslin DW, Kampman KM, et al. A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. *Am J Psychiatry*. 2010;167(6):668–675.
31. American Psychiatric Association. *Task Force on Nomenclature and Statistics, American Psychiatric Association Committee on Nomenclature and Statistics: Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: American Psychiatric Assn.; 1980.
32. American Psychiatric Association. *Work Group to Revise DSM-III: Diagnostic and Statistical Manual of Mental Disorder: DSM-III-R*. Washington, DC: American Psychiatric Association; 1987.
33. American Psychiatric Association. *American Psychiatric Association. Task Force on DSM-I: Diagnostic and Statistical Manual of Mental Disorders: DSM-IV*. Washington, DC: American Psychiatric Association; 1994.
34. Spitzer RL, Endicott J, Robins E. Research diagnostic criteria: rationale and reliability. *Arch Gen Psychiatry*. 1978;35(6):773–782.
35. Feighner JP, Robins E, Guze SB, et al. Diagnostic criteria for use in psychiatric research. *Arch Gen Psychiatry*. 1972;26(1):57–63.
36. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56–62.
37. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
38. Guy W. *ECDEU Assessment Manual for Psychopharmacology.* US Dept Health, Education, and Welfare publication (AD) 76-338. Rockville, MD: National Institute of Mental Health; 1976:218–222.
39. Walsh BT, Seidman SN, Sysko R, et al. Placebo response in studies of major depression: variable, substantial, and growing. *JAMA*. 2002;287(14):1840–1847.
40. Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? a meta-regression of double-blind, randomized clinical trials in MDD. *Eur Neuropsychopharmacol*. 2009;19(1):34–40.
41. Tedeschini E, Fava M, Goodness TM, et al. Relationship between probability of receiving placebo and probability of prematurely discontinuing treatment in double-blind, randomized clinical trials for MDD: a meta-analysis. *Eur Neuropsychopharmacol*. 2010;20(8):562–567.
42. Altamura AC, Mauri MC, Girardi T, et al. Alcoholism and depression: a placebo controlled study with viloxazine. *Int J Clin Pharmacol Res*. 1990;10(5):293–298.
43. Mason BJ, Kocsis JH, Ritvo EC, et al. A double-blind, placebo-controlled trial of desipramine for primary alcohol dependence stratified on the presence or absence of major depression. *JAMA*. 1996;275(10):761–767.
44. McGrath PJ, Nunes EV, Stewart JW, et al. Imipramine treatment of alcoholics with primary depression: A placebo-controlled clinical trial. *Arch Gen Psychiatry*. 1996;53(3):232–240.
45. Cornelius JR, Salloum IM, Ehler JG, et al. Fluoxetine in depressed alcoholics. A double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 1997;54(8):700–705.
46. Roy A. Placebo-controlled study of sertraline in depressed recently abstinent alcoholics. *Biol Psychiatry*. 1998;44(7):633–637.
47. Roy-Byrne PP, Pages KP, Russo JE, et al. Nefazodone treatment of major depression in alcohol-dependent patients: a double-blind, placebo-controlled trial. *J Clin Psychopharmacol*. 2000;20(2):129–136.
48. Gual A, Balcells M, Torres M, et al. Sertraline for the prevention of relapse in detoxicated alcohol dependent patients with a comorbid depressive disorder: a randomized controlled trial. *Alcohol Alcohol*. 2003;38(6):619–625.
49. Moak DH, Anton RF, Latham PK, et al. Sertraline and cognitive behavioral therapy for depressed alcoholics: results of a placebo-controlled trial. *J Clin Psychopharmacol*. 2003;23(6):553–562.
50. Hernandez-Avila CA, Modesto-Lowe V, Feinn R, et al. Nefazodone treatment of comorbid alcohol dependence and major depression. *Alcohol Clin Exp Res*. 2004;28(3):433–440.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Early Career Psychiatrists section. Please contact Marlene P. Freeman, MD, at mfreeman@psychiatrist.com.

 © COPYRIGHT 2011 PHYSICIANS POSTGRADUATE PRESS, INC.