

Treatment of Depression in Patients With Alcohol or Other Drug Dependence

A Meta-analysis

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DEPRESSION AND SUBSTANCE dependencies are among the most prevalent and costly disorders confronting the health care system, and they tend to co-occur,^{1,2} leading to greater overall severity and worse health-related outcomes,³ including increased risk of suicide.⁴⁻⁶ A wide range of initiatives have been developed to improve screening and diagnosis of depressive and drug- or alcohol-use disorders in primary medical care settings where they commonly present, as well as in mental health or addiction treatment programs.⁷ However, controversy about how to treat patients with the concurrent disorders persists. One of the most basic questions is whether to treat depression in the setting of ongoing substance abuse. Recent recommendations suggest concurrent substance abuse should not be a barrier to treating depression.⁸ However, clinicians working with substance-dependent patients are often reluctant, for a variety of reasons, to initiate specific antidepressant treatment, including concerns about confusing substance-induced depressive symptoms with true depressive disorders.⁹ Evidence is needed to help guide treatment.

We therefore undertook a meta-analysis of placebo-controlled trials to

Context Depression and substance abuse are common and costly disorders that frequently co-occur, but controversy about effective treatment for patients with both disorders persists.

Objective To conduct a systematic review and meta-analysis to quantify the efficacy of antidepressant medications for treatment of combined depression and substance use disorders.

Data Sources PubMed, MEDLINE, and Cochrane database search (1970-2003), using the keywords *antidepressant treatment* or *treatment depressed* in conjunction with each of the following *alcohol dependence, benzodiazepine dependence, opiate dependence, cocaine dependence, marijuana dependence, and methadone*; a search of bibliographies; and consultation with experts in the field.

Study Selection Among inclusion criteria used for study selection were prospective, parallel group, double-blind, controlled clinical trials with random assignment to an antidepressant medication or placebo for which trial patients met standard diagnostic criteria for current alcohol or other drug use and a current unipolar depressive disorder. Of the more than 300 citations extracted, 44 were placebo-controlled clinical trials, 14 of which were selected for this analysis and included 848 patients: 5 studies of tricyclic antidepressants, 7 of selective serotonin re-uptake inhibitors, and 2 from other classes

Data Extraction We independently screened the titles and abstracts of each citation, identified placebo-controlled trials of patients with both substance dependence and depression, applied the inclusion criteria, and reached consensus. Data on study methods, sample characteristics, and depression and substance use outcomes were extracted. The principal measure of effect size was the standardized difference between means on the Hamilton Depression Scale (HDS).

Data Synthesis For the HDS score, the pooled effect size from the random-effects model was 0.38 (95% confidence interval, 0.18-0.58). Heterogeneity of effect on HDS across studies was significant ($P < .02$), and studies with low placebo response showed larger effects. Moderator analysis suggested that diagnostic methods and concurrent psychosocial interventions influenced outcome. Studies with larger depression effect sizes (>0.5) demonstrated favorable effects of medication on measures of quantity of substance use, but rates of sustained abstinence were low.

Conclusions Antidepressant medication exerts a modest beneficial effect for patients with combined depressive- and substance-use disorders. It is not a stand-alone treatment, and concurrent therapy directly targeting the addiction is also indicated. More research is needed to understand variations in the strength of the effect, but the data suggest that care be exercised in the diagnosis of depression—either by observing depression to persist during at least a brief period of abstinence or through efforts by clinical history to screen out substance-related depressive symptoms.

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examine whether depression responds to antidepressant medication treatment in substance-dependent patients and the impact of such treatment on concurrent substance abuse. Reviews of a prior generation of studies found little consistent evidence of efficacy but revealed methodological problems, including weak diagnostic methods wherein patients were selected only with scales measuring current depressive symptoms¹⁰⁻¹² Our meta-analysis, therefore, focuses on more recent studies in which depressive disorders were identified by clinical history using established diagnostic criteria. The heterogeneity of study results is critically examined to better understand factors, such as methods of diagnosing depression, that may contribute to medication efficacy in depressed substance abusers.

METHODS

Search Strategy and Study Inclusion Criteria

PubMed, MEDLINE, and Cochrane databases from 1970 through December 2003 were searched using the keywords *antidepressant treatment* or *treatment depressed* in conjunction with each of the following words: *alcohol dependence*, *benzodiazepine dependence*, *opiate dependence*, *cocaine dependence*, *marijuana dependence*, and *methadone*. No language restrictions were applied. In a further effort to locate both published and unpublished studies, the reference lists of key publications and related reviews were examined, and 11 experts in the field were consulted, 9 in the United States and 2 in Europe. The 2 authors (E.V.N. and F.R.L.), both clinical investigators, independently screened the titles and abstracts of each citation, identified placebo-controlled trials involving patients with both substance dependence and depression, applied the inclusion criteria, and reached consensus.

Studies were included if they met the following criteria: (1) Prospective, parallel groups, double-blind, controlled clinical trial with random assignment to an antidepressant medication or placebo; (2) Patients met standard diagnos-

tic criteria set forth in the *Diagnostic and Statistical Manual of Mental Disorders* third, revised third, or fourth edition (DSM-III,¹³ DSM-III-R,¹⁴ DSM-IV¹⁵) for both a current drug (opiate, cocaine, other stimulant, or sedative-hypnotic) or alcohol-use disorder and a current unipolar depressive disorder (major depression, dysthymia, or depression not otherwise specified), diagnoses made by clinical or structured diagnostic interview; (3) Outcome of depressive symptoms is reported; and (4) For trials entering patients both with and without current depressive disorders, the depressed subgroup is an a priori stratification factor in the design. Secondary analyses were excluded because of concern that they may capitalize on chance and bias in favor of medication treatment.¹⁶ Fourteen studies¹⁷⁻³⁰ ultimately met these criteria.

Data Extraction

Data were extracted from reports by 1 of the authors (E.V.N.), checked by the second (F.R.L.), and discrepancies resolved by consensus. The principal outcome measure was the Hamilton Depression Scale (HDS) score.³¹ The measure of effect size was the standardized difference between means (Cohen d), which was calculated from the F test for analysis of covariance on the difference between means for each treatment at study end, covaried for the baseline score or when analysis of covariance was not available from means and SDs or significance level. Data from the sample of all randomly assigned patients, or the most complete sample reported, were used. We also compiled categorical measures of depression response, reflecting the proportion of patients meeting a criterion of clinically significant improvement.

For continuous measures of substance use outcome, consisting of various measures (mainly self-reported) of frequency or quantity of use, standardized differences between means were calculated from raw means and SDs, or estimated from graphs of the data.^{17,23,28} When several such measures were reported within a study, the effect sizes

were averaged to obtain a summary effect. We also compiled categorical measures, representing the proportions of patients meeting various criteria of sustained abstinence or remission.

We compiled a panel of moderator variables, including principal substance-use disorder in each study, placebo response (percentage decrease in the HDS between baseline and at end of study in the placebo group), features of the depression diagnoses and diagnostic methods, sample demographics, class of antidepressant medication, and whether the psychosocial background treatment was manual guided. Compliance with medication was not reported consistently, but the percentage of patients retained in the trial was available for all studies.

Assessment of Study Quality

Each of us independently rated the quality of each study, using a 15-item scale (1 point per item for a maximum score of 15) developed by Detsky and colleagues,³² which addresses fundamental aspects of the methods and reporting of clinical trials, including randomization and blinding procedures, sample selection, therapeutic regimen, outcome measures, and statistical analysis (mean [SD] difference in total scores between raters, 0.57 [51] points; intraclass correlation coefficient, 0.74). In addition, each study was rated according to the guidelines set forth by Schulz and colleagues³³ as adequate, unclear, or inadequate with respect to concealment of treatment allocation from clinical and research staff at the time of randomization in order to avoid selection bias, method of generating the sequence of treatment allocation, and blinding. Supplemental descriptions of these procedures were provided by each of the lead authors. These features have been associated with bias in clinical trials in the medical literature and suggested as important quality indicators.³³

Statistical Analysis

Effect sizes and pooled estimates of effect across studies were calculated with the

Comprehensive Meta-Analysis software package,³⁴ using analysis of variance models for standardized mean differences (Cohen *d*), and the inverse variance model for differences between response rates. Studies were entered as random effects in all models. For the primary outcome measure, the fixed effects model is also reported for comparison. Publication bias was addressed by inspection of the funnel plot on the primary outcome measure and by application of the sensitivity analysis developed by Copas and Shi.³⁵ Heterogeneity was evaluated with the *Q* statistic, and the *I*² statistic, a transformation of *Q* that estimates the percentage of the variation in effect sizes that is due to heterogeneity.³⁶ Categorical moderators (eg, alcohol vs other drug-dependent sample) were entered as grouping variables in the analysis of variance model. Continuous moderators (eg, placebo response) were first regressed against effect size using a weighted regression³⁷ and then dichotomized by median split and analyzed as grouping variables in the analysis of variance; results were similar both ways, and only the dichotomized analyses are reported for ease of presentation and comparison among moderators.

RESULTS

Search Findings

The search strategy yielded more than 300 citations, from which 44 placebo-controlled clinical trials involving drug or alcohol-use disorders and depression were targeted for detailed review. Fourteen trials¹⁷⁻³⁰ met the inclusion criteria for the meta-analysis and included 848 patients randomly assigned to receive medication or placebo (TABLE 1). Sixteen trials³⁹⁻⁵⁴ were excluded because they did not select patients with current syndromal depression—having mainly applied a cutoff score on a cross-sectional scale measuring depressive symptoms. Seven excluded reports were secondary analyses, four⁵⁵⁻⁵⁸ examining redundant subsamples of 1 of the included trials,²² and three⁵⁹⁻⁶¹ reporting positive effects of medication in small depressed sub-

groups from larger trials. Two^{62,63} were preliminary reports of trials later published with complete samples.^{19,22} One trial,⁶⁴ a trend-positive study, was excluded because it was a placebo-controlled discontinuation trial rather than a prospective, parallel groups trial. Four trials could not be included because they are being worked up or submitted for publication—preliminary reports indicating that 1 showed a significant antidepressant effect (David McDowell, MD, written communication, August 29, 2003), 2 showed no difference between medication and placebo (Patrick J. McGrath MD, written communication, August 29, 2003; Susan Tross, PhD, written communication, September 3, 2003), and 1 showed a small nonsignificant trend.⁶⁵

Characteristics of Included Studies and Quality Assessment

Eight of the trials meeting inclusion criteria recruited alcohol-dependent patients,^{17-19,22-25,30} 4 recruited methadone-maintained opiate-dependent patients,^{20,26,27,29} and 2 recruited cocaine-dependent patients.^{21,28} Mean sample ages ranged from 29.0 to 44.5 years (median, 37.9). There was substantial representation of women (median sample, 40% women; range, 8%-55%) and minority patients (median sample, 31% minority; range, 1%-53%). Across samples, large proportions of patients were unmarried (median, 73%; range, 40%-88%), unemployed (median, 47%; range, 30%-49%), or having other indicators of low socioeconomic status such as low educational attainment (median years of education, 13.2; range, 11-15 years). Mean baseline HDS scores ranged from 11.7 to 28.9 (median, 19.5), indicating moderate to severe levels of depressive symptoms. Hamilton Depressive Scale scores that are in the range of 10 to 20 indicate mild to moderate depression and scores higher than 20, severe depression; the higher the score the greater the severity of depression.

Methodological features of the trials are summarized in Table 1. In addition to being randomized, double-blind, and placebo-controlled, the designs of the in-

cluded trials were uniform in using *DSM-III*, *DSM-III-R*, or *DSM-IV* criteria for diagnosing depressive disorders; in providing adequate medication dosages; and in having trial durations of at least 6 weeks and, for most, 12 or more weeks, which is sufficient time for antidepressant effects to occur. Outcomes on the HDS were evaluated either on the sample of all randomized patients or the sample of patients returning for at least 1 visit after randomization so that 827 (97%) of 848 patients were evaluated. For secondary outcomes (categorical response measures and continuous measures of substance use), in several studies data were not available or smaller samples were evaluated, resulting in smaller overall numbers of patients. All studies used independent staff members to carry out the randomization and to prepare blind medication, and all studies were rated as adequate³⁴ with respect to concealment of treatment allocation, method of generating the sequence of treatment allocation, and blinding. The overall study quality ratings on the scale of Detsky et al³² were moderately high, with a mean (SD) of 12.25 (1.00), out of a total possible score of 15 (range, 10-14). Taken together these data suggest the studies contained most essential features of well-designed antidepressant trials.

Depression Outcome and Moderators of Antidepressant Effect

Depression outcome data are summarized in Table 1 and TABLE 2, where studies are listed in order of depression effect size from greatest to least. Eight of the studies¹⁷⁻²⁴ were reported as demonstrating significant or trend significant antidepressant effects, and 6 studies²⁵⁻³⁰ were negative (Table 1). For the principal outcome, the HDS score, the pooled effect size (standardized mean difference between medication and placebo groups) from the random effects model is 0.38 (95% confidence interval [CI], 0.18-0.58). For comparison, the fixed effects model yielded a similar point estimate (0.38) with a narrower CI (95% CI, 0.24-0.51). The raw rates of depression

response were 52.1% for those taking medication and 38.1% for those taking placebo, and the pooled random effects estimate of difference in response rates between treatments was 16.8% (95% CI, 6.9%-26.7%; Table 2).

There is significant heterogeneity of effect on the HDS across studies (Q_{13} , 26.47; $P < .02$; $I^2 = 51\%$ of variability in effect sizes due to heterogeneity). The

analysis of moderators is presented in TABLE 3, and the underlying data can be inspected in Table 1. As can be seen, there is a trend for the medication effect to be larger in the studies of patients dependent on alcohol than in studies of patients dependent on other drugs, but this explains only 7% of the variance and substantial heterogeneity remains within both groupings. Placebo re-

sponse (percentage reduction in the HDS in the placebo group) is a powerful predictor of antidepressant effect, explaining 71% of the variance in effect sizes across studies and eliminating variance due to heterogeneity; placebo response of more than 25% is associated with a pooled estimate of effect size near 0 while low placebo response (<25%) yields a pooled esti-

Table 1. Placebo-Controlled Trials of Antidepressants in Substance-Dependent Patients With Depression: Methodology, Placebo Response, and Effect Size on the Hamilton Depression Scale

Source	Substance Dependence	No. of Patients Randomized	Diagnostic Criteria	Diagnosis	HDS at Baseline, Mean (SD)	Setting and Timing of Diagnosis	Medication, mg	No. of Treatment Weeks	Concurrent Therapy	Placebo Response, %*	HDS Effect Size†	P Value
Altamura et al, ¹⁷ 1990	Alcohol	30	DSM-III-R, HDS >18	DD	25.5 (6.5)	Inpatient, 7 d abstinent	Viloxazine, 400	12	4-wk inpatient, followed by outpatient	16	1.07	<.01
Roy, ¹⁸ 1998	Alcohol	36	DSM-III-R	MDD	22.8 (6.5)	Inpatient, 14 d abstinent	Sertraline, 100	6	Inpatient followed by intensive day hospital	19	1.06	<.01
Mason et al, ¹⁹ 1996	Alcohol	28	DSM-III-R	MDD, secondary‡	19.8 (10.3)	Outpatient, 8 d abstinent	Desipramine, 200	24	Encouraged Alcoholics Anonymous	-5	0.93	<.05
Nunes et al, ²⁰ 1998	Opioid	137	DSM-III-R	MDD, DD, NOS, primary‡	15.9 (3.9)	MMTP, actively using	Imipramine, 300	12	MMTP; counseling as usual	8	0.68	<.001
Nunes et al, ²¹ 1995	Cocaine	69	DSM-III-R	MDD, DD, NOS, primary‡	11.7 (4.7)	Outpatient, actively using	Imipramine, 300	12	Individual counseling	16	0.62	<.05
Cornelius et al, ²² 1997	Alcohol	51	DSM-III-R	MDD	18.5 (8.2)	Inpatient, 9 d abstinent	Fluoxetine, 40	12	Supportive psychotherapy	11	0.57	<.05
Roy-Byrne et al, ²³ 2000	Alcohol	64	DSM-III-R	MDD, primary‡	23.9 (5.2)	Outpatient, actively using	Nefazodone, 500	12	Group CBT skills building, manual§	37	0.47	<.10
McGrath et al, ²⁴ 1996	Alcohol	69	DSM-III-R	MDD, DD, NOS, primary‡	14.9 (5.2)	Outpatient, actively using	Imipramine, 300	12	Individual RP, manual§	11	0.40	<.05
Moak et al, ²⁵ 2003	Alcohol	82	DSM-III-R, HDS \geq 17,	MDD, primary‡	19.1 (2.5)	Outpatient, active or 7 d abstinent	Sertraline, 200	12	Individual CBT for alcohol and depression, manual§	53	0.15	
Carpenter et al, ²⁶ in press	Opioid	95	DSM-III-R	MDD, DD, primary‡	21.1 (4.7)	MMTP, actively using	Sertraline, 200	12	MMTP, counseling as usual	29	0.07	
Kleber et al, ²⁷ 1983	Opioid	46	DSM-III, Raskin >7¶	MDD	19.8	MMTP, actively using	Imipramine, 225	8	MMTP; individual and group counseling	43	0.0	
Schmitz et al, ²⁸ 2001	Cocaine	68	DSM-IV, BDI >10	MDD, primary‡	28.9 (8.1)	Outpatient, actively using	Fluoxetine, 40	12	Individual RP and CBT for depression, manual§	55	0.0	
Petrakis et al, ²⁹ 1998	Opioid	44	DSM-III-R, HDS >13	MDD, DD, NOS‡	14.3 (5.3)	MMTP, actively using	Fluoxetine, 60	12	MMTP; counseling; negative contingencies	52	-0.13	
Pettinati et al, ³⁰ 2001	Alcohol	29	DSM-III-R	MDD, DD	15.2 (8.0)	Outpatient, >3 d abstinent	Sertraline, 200	14	12-step facilitation, manual§	65	-0.21	

Abbreviations: BDI, Beck Depression Inventory; CBT, cognitive behavioral therapy; DD, dysthymia; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; HDS, Hamilton Depression Scale (scores of 10 to 20 indicate mild to moderate depression and scores higher than 20 are considered severe depression); MDD, major depression; MMTP, methadone maintenance treatment program; NOS, depressive disorder not otherwise specified; RP, cognitive behavioral relapse prevention.

*Percentage decrease in the HDS between baseline and end of study in the placebo group.

†Standardized difference between mean scores (Cohen d) of HDS in placebo vs medication groups at end of study with significance levels (as reported in primary source).

‡Primary indicates additional historical criteria imposed in an effort to select depression syndromes that are independent, or not "substance-induced." Secondary indicates that depression began after the onset of alcohol abuse.

§Concurrent psychosocial intervention listed was manual guided.

||One-tailed comparison.

¶Represents the Raskin Depression Scale.³⁸

mate of effect in the range between medium and large. This can be confirmed by inspecting Table 1, wherein the effect sizes and placebo responses are tabulated and by the Forrest plot (FIGURE 1), wherein studies are grouped by placebo response. Similarly, in Table 2, an orderly relationship is observed between placebo response, measured herein by percentage of patients in the placebo group meeting a standard de-

pression response criterion, and difference in response rates between medication and placebo.

Four other significant moderators explained smaller proportions of the variance. Diagnosis of depression after at least a week of abstinence in an inpatient or outpatient setting was associated with greater antidepressant effect while a larger proportion of women in the sample, selective serotonin reup-

take inhibitor (SSRI) medication, and a concurrent psychosocial intervention that was manual guided, such as cognitive behavioral therapy or relapse prevention, were associated with smaller effect sizes. Type of depression diagnosis (major depression vs mixed diagnoses), severity of depression at baseline (HDS score), minority representation in the sample, age, proportion of patients completing the study,

Table 2. Effects of Antidepressant Medication Treatment on Rates of Depression Response, and Abstinence or Sustained Remission From Substance Abuse*

Source	Criterion	Depression Response			Abstinence or Sustained Remission			
		Outcome			Outcome			
		No./Total (%)		Difference, % (95% CI)	Criterion	No./Total (%)		Difference, % (95% CI)
		Medication	Placebo			Medication	Placebo	
Roy, ¹⁸ 1998†	50% reduced HDS	12/18 (67)	4/18 (22)	44 (15 to 74)				
Mason et al, ¹⁹ 1996	50% reduced HDS or final HDS <10	9/11 (82)	2/9 (22)	60 (24 to 95)	No relapse to heavy drinking	11/12 (92)	6/10 (60)	32 (-3 to 66)
Nunes et al, ²⁰ 1998	CGI score of 1 or 2	31/74 (42)	13/63 (21)	21 (6 to 36)	Abstinent throughout last 4 wk of trial	6/42 (14)	1/42 (2)	12 (0 to 23)
Nunes et al, ²¹ 1995	50% reduced HDS	18/38 (47)	8/31 (26)	22 (-1 to 44)	At least 3 consecutive, abstinent weeks	10/38 (26)	4/31 (13)	13 (-5 to 32)
Cornelius et al, ²² 1997†					Abstinent throughout the trial	7/25 (28)	4/26 (15)	13 (10 to 35)
Roy-Byrne et al, ²³ 2000	CGI score of 1 or 2	18/31 (58)	8/25 (32)	26 (1 to 51)	Abstinent at end of study	5/20 (25)	2/11 (18)	7 (-23 to 37)
McGrath et al, ²⁴ 1996	50% reduced HDS	13/27 (48)	9/29 (31)	17 (-8 to 42)	Abstinent in last 4 wk of trial	8/26 (31)	6/29 (21)	10 (-13 to 33)
Moak et al, ²⁵ 2003	50% reduced HDS	33/38 (87)	31/44 (71)	16 (-1 to 34)	No relapse to heavy drinking	14/38 (37)	16/44 (36)	0 (-20 to 21)
Carpenter et al, ²⁶ in press†	50% reduced HDS	15/47 (32)	16/48 (33)	-1 (-20 to 17)				
Schmitz et al, ²⁸ 2001	50% reduced BDI	17/34 (50)	16/34 (47)	3 (-21 to 27)	At least 3 consecutive, abstinent weeks	7/34 (21)	11/34 (32)	-12 (-33 to 9)
Petrakis et al, ²⁹ 1998†	50% reduced HDS	12/23 (52)	11/21 (52)	0 (-30 to 29)				
Pettinati et al, ³⁰ 2001	50% reduced HDS	6/12 (50)	11/17 (65)	-15 (-15 to 51)	Abstinent throughout the trial	3/12 (25)	5/17 (29)	-4 (-37 to 28)
Combined‡		184/353 (52.1)	129/339 (38.1)	16.8 (6.9 to 26.7)		71/247 (28.7)	55/244 (22.5)	8.1 (1.4 to 14.9)

Abbreviations: BDI, Beck Depression Inventory; CGI, Clinical Global Impressions scale; CI, confidence interval; HDS, Hamilton Depression Score.

*The studies by Kleber et al²⁷ and Altamura et al¹⁷ did not have the data necessary for analyses in this table.

†Missing values indicate that such data were not provided in the study.

‡Combined rates shown under medication and placebo are raw rates computed for descriptive purposes. The combined or pooled differences between rates are computed with the inverse variance model with studies as random effects.

and study quality score (Detsky et al³² scale) were not significant moderators.

Substance Use Outcome

The pooled effect size on continuous measures substance use, representing mainly self-reported quantity of use, is 0.25 (95% CI, 0.08-0.42), and the test

for heterogeneity nears significance (Q_{12} , 17.12; $P < .15$; $I^2 = 30\%$). As shown in FIGURE 2, substance use effect sizes were related to depression effect size. Among studies¹⁷⁻²² with depression effect sizes greater than 0.5, the substance use effect size was 0.56 (95% CI, 0.33-0.79) while among studies with

lower depression effect sizes,²³⁻³⁰ the pooled substance use effect size was near 0 (0.07; 95% CI, -0.11 to 0.25; between strata Q_1 , 13.3; $P < .001$). However, as shown in Table 2, rates of sustained abstinence or substance remission were low across studies and treatment groups, with only a small

Table 3. Moderators of Effect of Antidepressant Medication on Outcome of the Hamilton Depression Scale in Substance-Dependent Patients With Depressive Disorders

Moderator	Within Group				Effect of Moderator		
	Effect Size*	Heterogeneity			Q Between	P Value	% Variance Explained‡
		Q_{df} Within	P Value	% Variance Explained†			
Substance type							
Alcohol	0.51 (0.23 to 0.79)	12.4 ₇	.09	44	1.77	.19	7
Other drug	0.24 (-0.06 to 0.54)	12.3 ₅	.04	59			
Placebo response (% decrease HDS)							
<25%	0.68 (0.49 to 0.88)	4.33 ₆	.64	0	18.7	<.001	71
>25%	0.08 (-0.11 to 0.27)	3.45 ₆	.76	0			
Depression diagnosis							
Setting inpatient or >1 week abstinent outpatient							
Yes	0.86 (0.52 to 1.20)	1.76 ₃	.63	0	9.65	.002	36
No	0.25 (0.05 to 0.45)	15.1 ₉	.09	40			
Depression type							
MDD	0.46 (0.11 to 0.81)	10.6 ₅	.06	53	0.13	.72	<.1
MDD and DD	0.34 (0.07 to 0.60)	15.7 ₇	.03	55			
HDS at baseline							
<19.5	0.36 (0.11 to 0.61)	10.7 ₆	.10	44	0.13	.72	<.1
>19.5	0.45 (0.09 to 0.80)	15.6 ₆	.02	62			
Sample features							
Women, %							
<40	0.58 (0.26 to 0.90)	14.0 ₆	.03	57	6.34	.02	24
≥40	0.20 (0.01 to 0.40)	6.15 ₆	.41	2			
Minority, %							
<30	0.34 (0.04 to 0.65)	11.2 ₆	.09	46	0.45	.45	2
>30	0.41 (0.13 to 0.70)	14.8 ₆	.03	59			
Age, y							
<38	0.34 (0.09 to 0.59)	11.3 ₆	.08	47	0.01	.94	<.1
>38	0.46 (0.10 to 0.81)	15.1 ₆	.02	60			
Trial features							
Medication							
SSRI	0.20 (-0.08 to 0.49)	11.9 ₆	.07	50	7.53	.03	28
TCA	0.52 (0.26 to 0.78)	5.38 ₄	.26	26			
Other	0.71 (0.12 to 1.30)	1.65 ₁	.20	39			
Concurrent therapy manual guided							
Yes	0.20 (-0.03 to 0.42)	3.58 ₄	.47	0	3.85	.05	15
No	0.50 (0.22 to 0.78)	19.0 ₆	.02	58			
Completion, %							
<60	0.46 (0.20 to 0.71)	11.4 ₆	.08	47	2.43	.12	9
≥60	0.30 (-0.02 to 0.62)	12.7 ₆	.05	53			
Quality score							
>12	0.34 (0.13 to 0.55)	9.33 ₆	.16	36	0.33	.57	2
≤12	0.46 (0.05 to 0.87)	16.8 ₆	.01	64			

Abbreviations: DD, dysthymia; HDS, Hamilton Depression Scale; MDD, major depression; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

*Standardized difference between means (Cohen d) with 95% confidence intervals from random effects model.

†Percentage of variance within group explained by heterogeneity is given by $I^2 = (H^2 - 1)/H^2$, where $H^2 = Q$ within/ df and $df = k - 1$ (k = the number of studies in the group); or $I^2 = 0$ if Q within $< df$.

‡Percentage of variance explained by the moderator is given by Q between/ Q total, where Q total = 26.47.

pooled difference between medication and placebo.

Assessment of Publication Bias

The funnel plot was inspected and found to be roughly symmetric, suggesting absence of publication bias. The sensitivity analysis³⁵ models the robustness of the pooled effect size with respect to a putative population of all studies (published and unpublished) as a function of parameters reflecting different patterns of selection bias. The model estimates the pooled effect sizes and checks the fit of each to the funnel plot over a range of increasing selection severities (from small to large proportions of missing studies). For our sample, fit to the funnel plot was adequate ($P > .05$) throughout the range of selection biases modeled. However, caution is suggested, since as the number of studies missing increased to 8 or more, the pooled estimate of effect size approached 0.20 and its 95% CI expanded to include 0.

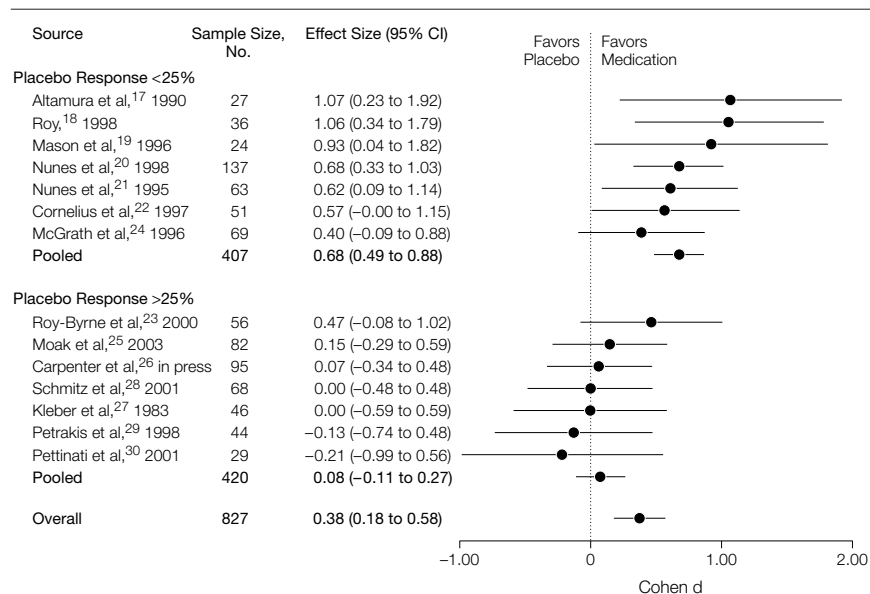
COMMENT

Overall, this meta-analysis finds antidepressant medication effective for treatment of depressive syndromes among patients with alcohol or drug dependence. There was also significant heterogeneity in effect across studies, which was strongly related to placebo response. Six studies, all with high placebo response, yielded effect sizes near 0 while 6 studies, all with low placebo response, yielded effect sizes greater than 0.5. The combined effect size must be interpreted with caution in the setting of heterogeneity, but its magnitude (0.38; 95% CI, 0.18-0.58) represents an effect in the range between small and medium,⁶⁶ similar to the effect size (0.43) found in a recent meta-analysis of antidepressant trials in depressed outpatients.⁶⁷ Reviews of a prior generation of antidepressant trials in alcoholics and opiate-dependent patients found limited evidence of antidepressant efficacy and identified several methodological problems, including short trial lengths, inadequate antidepressant doses, and selection of patients with cross-sectional measures of depressive symp-

toms.¹⁰⁻¹² The findings in our meta-analysis suggest that antidepressant medications can be effective among du-

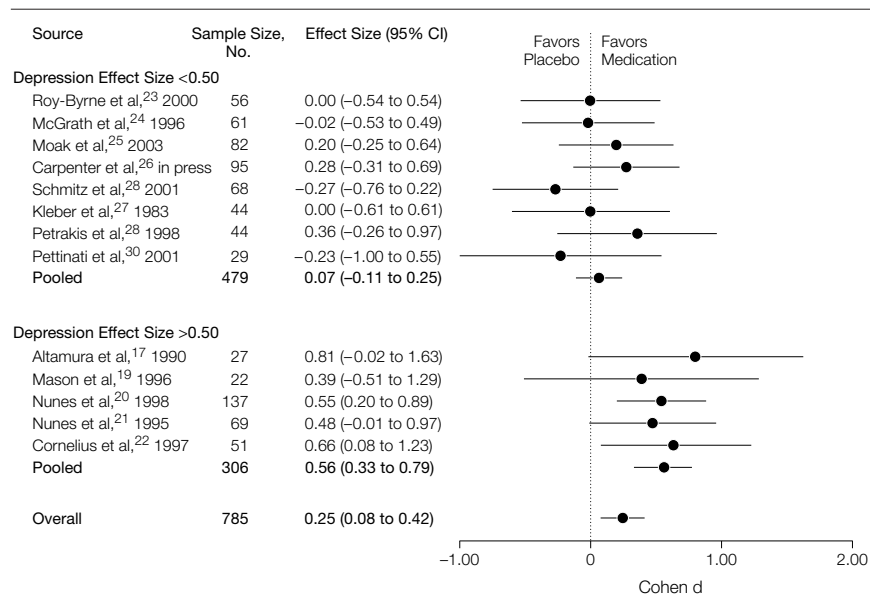
ally diagnosed patients when used at adequate doses, for at least 6 weeks, and for depressive syndromes (ie, major depres-

Figure 1. Effect of Antidepressant Medication on Outcome of Depression (Hamilton Depression Scale)



Effect sizes are Cohen *d*, error bars represent the 95% confidence intervals (CIs). Studies are stratified into groups with low (<25%) vs high (>25%) categories of placebo response, measured as the percentage decrease in the Hamilton Depression Scale between baseline and end-of-study in the placebo group.

Figure 2. Effect of Antidepressant Medication on Outcome of Substance Use*



Effect sizes are Cohen *d* on outcomes reflecting quantity of substance use (mainly by self-report). Error bars represent the 95% confidence intervals (CIs). Studies are stratified into 2 groups based on the size of the effect of medication on depression outcome (Cohen *d* for the Hamilton Depression Scale) effect size lower than 0.50 (low); and effect size greater than 0.50 (high). The study by Roy¹⁸ did not have the data necessary for analysis for this figure.

sion or dysthymia) identified by clinical history and established diagnostic criteria.

The findings also suggest that when medication is effective in treating depression (effect size >0.5), it helps diminish quantity of substance use. However, the proportions of patients achieving sustained abstinence or remission were low, even among studies with robust antidepressant effects. Thus, the effect of treating depression on substance abuse outcome appears limited, and among such dually diagnosed patients, therapies directly targeting the addiction are also needed.

High placebo response likely results either from selection of patients with transient depressions that improve without specific treatment or a concurrent psychosocial intervention that exerts substantial antidepressant effects, obscuring effects of medication. Depressive symptoms among substance-abusing patients are often transient, representing toxic or withdrawal effects that resolve in response to abstinence⁶⁸⁻⁷² or to entry into substance abuse treatment.^{73,74} Studies that diagnosed depression after at least a week of abstinence,^{17-19,22} mainly on inpatient units, yielded larger effect sizes and low placebo response, suggesting the abstinence requirement succeeded in screening out transient symptoms and in selecting primary or independent depressive disorders for treatment.

Thus, our findings are consistent with traditional recommendations that co-occurring depression be diagnosed and treated when it can be observed to persist after at least a brief period of abstinence from substance use.^{68,69,75} Hospitalization is less an option in the era of managed care, nor is it acceptable to many patients. But abstinence can be initiated among outpatients with psychosocial methods, such as brief physician's advice to quit,⁷⁶ motivational interviewing,⁷⁷ or voucher incentives.⁷⁸ Furthermore, some studies^{20,21,23,24} that enrolled patients who were actively using alcohol or other drugs observed medication effects. These studies imposed additional diagnostic

criteria consistent with the *DSM-IV*¹⁵ constructs of *primary* and *substance induced* depression (eg, requiring that depression have antedated the onset of substance abuse, have persisted during past periods of abstinence, or have been of long duration in the current episode). However, several of the negative studies also used such criteria.^{25,26,28,29} Future research should refine such diagnostic methods in order to better distinguish outpatient substance abusers who would benefit from antidepressant treatment.

Inclusion of a manual-guided psychosocial intervention as background treatment was associated with lower effect sizes, and of the 5 studies^{23-25,28,30} in this grouping, 4 of them^{23,25,28,30} had high-placebo response. Such interventions may improve mood by reducing substance use or may have intrinsic antidepressant effects. For example, cognitive behavioral relapse prevention approaches include modules on coping with dysphoric symptoms, and 2 of the studies we reviewed^{25,28} actually augmented this aspect of their interventions. Cognitive behavior therapy also showed promise in a study of depressed alcoholics.⁷⁹ The findings suggest a clinical approach that begins with an evidence-based psychosocial intervention, followed by antidepressant medication if depression does not improve.

The moderating effect of sex should be approached with caution because it was mainly accounted for by predominantly male samples in 3 of the studies that required initial abstinence and had large effects.¹⁷⁻¹⁹ One study²⁵ that examined sex as a moderator within its sample found the opposite pattern—a significant antidepressant effect of sertraline among women but not men.

Selective serotonin reuptake inhibitors performed less well overall than tricyclics or other classes of antidepressants. This finding too must be viewed with caution, since all 5 SSRI studies that were negative^{25,26,28-30} had high-placebo response rates. The 2 SSRI studies with low placebo response^{18,22} yielded substantial medication effects.

Selective serotonin reuptake inhibitors remain an attractive first-line treatment among substance-dependent patients because of their tolerability, low toxic effects, and minimal sedating effects. If an SSRI trial fails, consideration should be given to an agent with noradrenergic or other mechanisms.

Strengths and Limitations

Treatment studies on comorbidity are challenging to carry out because with inclusion criteria requiring 2 current disorders, recruitment is slow. Hence, the single-site studies gathered for this meta-analysis offered, for the most part, small sample sizes and limited statistical power. Combining these studies resulted in a total sample of more than 800 patients and greater power to estimate treatment effects. This meta-analysis was also facilitated by relatively consistent methods and quality indicators across studies although variations in substance use outcome measures may have limited precision to measure treatment effects in that domain. The funnel plot and sensitivity analysis suggest only limited risk of publication bias, consistent with studies in this field being mainly investigator-initiated and thus likely to get published, whether positive or negative.

The variation in sample characteristics across studies, ranging from inpatient or outpatient alcoholics to opiate- or cocaine-dependent patients, can be viewed as a strength with respect to the generalizability of the findings, but it also raises concerns. The neuropharmacology of depression may differ between various substance-dependent populations, suggesting more treatment research is needed particularly among drug-dependent groups. The moderators were identified retrospectively, so that unmeasured confounders could explain the findings, and the moderators often overlapped. Because this is a study-level rather than a patient-level meta-analysis, moderators that reflect patient characteristics, such as sex, must be viewed with particular caution, and the underlying distributions of outcome or moderator vari-

ables cannot be checked. Future studies should isolate and examine factors such as diagnostic methods, medication type, and concurrent psychosocial interventions prospectively, likely requiring larger sample sizes and multisite designs.

The meta-analysis was restricted to studies on treatment of depressive disorders. A number of excluded studies selected substance abusers with depressive symptoms measured by cross-sectional scales, some^{43,44,46,49} with positive results. Screening instruments⁸⁰ have effectively identified treatable depression in primary care settings. Future research should similarly examine brief screens as part of the effort to develop diagnostic approaches that are cost effective and widely disseminable.

Conclusions

Little more than a decade ago, the treatment of depression among substance dependent-patients was discouraged by most clinicians, given evidence on the transient nature of depressive symptoms in the setting of substance abuse,^{68,69,71-74} equivocal findings of earlier treatment studies,¹⁰⁻¹² and concern that focus on depression not distract attention from treatment of the addiction. Recent years have witnessed increased acceptance of such treatment although the likelihood that depression will be recognized among substance-dependent patients continues to vary by treatment setting,⁸¹ and, as in the general population, under-treatment is still probably the rule.^{82,83} The studies reviewed herein lend empirical support to recent recommendations that drug or alcohol abuse not be a barrier to treatment of depression⁸ but suggest that care is needed in diagnosis either to observe patients during at least a brief period of abstinence prior to diagnosis and treatment of depression or to make efforts to distinguish treatable depression by history.

Antidepressant treatment may have a limited impact on alcohol or other drug use, and attention is needed in the treatment plan to specific psychoso-

cial or pharmacologic interventions targeting addiction itself. At the same time, this should not detract from the importance of treating depression, given growing evidence of its adverse prognostic implications in a variety of health domains.^{8,83}

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Study concept and design: Nunes, Levin.

Acquisition of data: Nunes, Levin.

Analysis and interpretation of data: Nunes.

Drafting of the manuscript: Nunes.

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