ORIGINAL ARTICLE

Imipramine Treatment of Opiate-Dependent Patients With Depressive Disorders

A Placebo-Controlled Trial

Edward V. Nunes, MD; Frederic M. Quitkin, MD; Stephen J. Donovan, MD; Deborah Deliyannides, MD; Katja Ocepek-Welikson, MPhil; Teresa Koenig, RN; Ronald Brady, MD; Patrick J. McGrath, MD; George Woody, MD

Background: The literature is inconclusive on the role of antidepressant medications in treating drug dependence. Studies have either not focused on depressed patients or have selected patients with depressive disorders based on cross-sectional symptoms rather than a syndromal diagnosis. A clinical trial of an antidepressant was, therefore, conducted on drug-dependent patients with syndromal depression.

Methods: Patients receiving methadone hydrochloride maintenance treatment were selected if they met the criteria for a *DSM-III-R* depressive disorder that was chronologically primary, had persisted during a past abstinent period or was long-standing, and persisted during at least 1 month of stable methadone treatment. Subjects were randomized to a 12-week, double-blind, placebo-controlled trial of imipramine hydrochloride. A favorable response was defined as a Clinical Global Impression scale score for depression of 2 ("much improved") or 1 ("very much improved") and at least a 75% reduction in self-reported drug or alcohol use or abstinence.

Results: One hundred thirty-seven patients were randomized, and 84 completed a minimum adequate trial of at least 6 weeks. Among the 84 adequately treated patients, 57% (24/42) receiving imipramine were rated as responders compared with 7% (3/42) receiving placebo ($P<.001$). On measures of mood, there was a robust effect of imipramine. Imipramine was superior to placebo on some self-reported measures of substance use and craving, and mood improvement was associated with improvement in self-reported substance use. However, few patients achieved urine-confirmed abstinence.

Conclusions: Imipramine was an effective antidepressant in patients receiving methadone who were selected via syndromal criteria for depressive illness. Imipramine may reduce substance abuse among patients whose mood improves; however, this effect was less robust.

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From the Depression Evaluation Service, New York State Psychiatric Institute, and the Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York (Drs Nunes, Quitkin, Donovan, Deliyannides, and McGrath and Mss Ocepek-Welikson and Koenig), the Bridge Plaza Treatment and Rehabilitation Services, New York (Dr Brady), and the Department of Psychiatry, the Long Island Jewish/Hillside Hospital, Glen Oaks (Drs Nunes, Quitkin, and Donovan), NY; and the Department of Psychiatry, Philadelphia Veterans Affairs Medical Center and University of Pennsylvania, Philadelphia (Dr Woody).

DRUG DEPENDENCE is a major public health problem and remains difficult to treat, despite effective modalities such as methadone hydrochloride maintenance treatment.[1,2] Antidepressant medications have been extensively studied as adjuncts to the treatment of cocaine dependence, and combined cocaine and opiate dependence, but the results have been mostly negative.[3-12] These efforts sprang from the hypothesis that antidepressants exert a direct effect on the pathophysiological features of addiction, perhaps by normalizing drug-induced dysregulation in the brain reward system.[3,13]

Depression is prevalent in drug-abusing populations,[14,15] where it has often been associated with poor prognosis,[16-23] craving,[24] and relapse.[25] This suggests an alternative hypothesis, ie, that some addicts take drugs in response to depressive syndromes, perhaps in an attempt to "self-medicate."[26,27] The antidepressant trials in cocaine abusers may have fallen short because they did not specifically select depressed patients. In 3 of those studies, subgroup analyses did suggest greater medication effects in depressed subgroups.[7,12,28]

Antidepressant medications have been studied as a treatment for depression in patients receiving methadone maintenance treatment.[29-33] Only 2[31,33] of the 5 studies demonstrated favorable effects of medication on mood. None showed a clear effect on drug abuse. Methodological limitations[34] include small sample sizes, short trial lengths, low doses, and high placebo response rates,[29,30,32] perhaps because depressed subjects were selected with cross-sectional symptom scales rather than clinical history and syndromal diagnosis. Depressive symptoms in substance abusers are often transient,[35-37] attributable to

SUBJECTS AND METHODS

SUBJECTS

Recruitment and treatment took place at 2 community-based, university-affiliated methadone maintenance clinics. Subjects were recruited from among patients newly admitted to methadone treatment or from among established patients referred by their counselors. Patients receiving methadone maintenance treatment, who gave informed consent, were included if they met the criteria for a current *DSM-III-R*[41] depressive disorder (major depression, dysthymia, or depression not otherwise specified) that met at least 1 of the following features: (1) depression was primary, ie, it antedated the onset of regular substance use, defined as use of a substance at least 3 times per week for a month or once a week for a month for cocaine use; (2) depression was secondary and persisted or emerged during a past period of 6 months of complete abstinence; or (3) depression was secondary and of at least 3 months' duration in the current episode. For newly admitted patients, depression had to persist for at least 1 month of stable methadone treatment.

Subjects were excluded if they (1) ever met the criteria for schizophrenia or mania; (2) were judged by one of the evaluating psychiatrists (E.V.N., F.M.Q., S.J.D., D.D., and others) to present a clinically significant suicide risk; (3) had medical contraindications to imipramine treatment, such as pregnancy, cardiac conduction system disease, or unstable medical conditions; (4) had a history of a seizure disorder; (5) had failed to respond to an adequate trial of imipramine in the past; or (6) were in treatment for their depression with another practitioner.

PROCEDURES

At baseline, a psychiatric diagnostic evaluation was conducted by one of the research psychiatrists (E.V.N., F.M.Q., S.J.D., D.D., and others) who administered the Structured Clinical Interview for *DSM-III-R*,[42] modified to relate the course of depressive syndromes to the onset of regular substance use and to abstinent periods during the patient's lifetime.[43] The baseline medical evaluation included a medical history, a physical examination, a complete blood cell count, blood chemistry tests, a urinalysis, and an electrocardiogram.

Eligible patients were given a single-blind placebo for 1 week. Those whose depression was rated as either "much improved" or "very much improved" on the Clinical Global Impression (CGI) scale were removed from the trial. All others were randomly assigned through computer-generated blocks of 4 in a 1:1 imipramine-placebo ratio under double-blind conditions for 12 weeks. In an effort to distribute potential prognostic factors evenly across the treatments, the randomization was stratified by sex and the presence or absence of primary depression, intravenous drug use, panic attacks, and cocaine use. After 84 patients had been randomized, a higher rate of early attrition was noted for those receiving imipramine compared with those receiving placebo. At that point, the randomization was changed to a 2:1 imipramine-placebo ratio through randomized blocks of 3 so that approximately equal numbers of patients achieved an adequate trial of each treatment.

Methadone treatment was administered by the regular clinic staff (R.B. and others) according to state and federal guidelines and was not influenced by the research protocol, which was conducted by a separate team of research clinicians (E.V.N., F.M.Q., S.J.D., D.D., T.K., and others). Two to 3 times per week, patients visited a research nurse (T.K. and others) who asked about medication compliance, answered questions, and dispensed medication. Blood was drawn at weeks 4, 6, and 12 to check the level of imipramine. Patients met weekly with a research psychiatrist (E.V.N., F.M.Q., S.J.D., D.D., and others) who monitored efficacy, compliance, and side effects; performed research ratings; and adjusted the dosage. The medication (unmarked pills containing 50 mg of imipramine hydrochloride or placebo) was titrated, at a rate of 50 mg/wk, toward a maximum dose of 6 pills per day (300 mg of imipramine hydrochloride or placebo). Patients who dropped out of the research protocol continued to receive methadone treatment and psychiatric treatment as clinically appropriate.

OUTCOME ASSESSMENT

Assessments performed at baseline and weekly throughout the trial by the research psychiatrist included the 21-item Hamilton Depression Rating Scale[44]; the CGI scale,[45] modified to rate global improvement for mood and drug use; and a weekly log of quantity and frequency of substance use and craving modeled after the Time-Line Follow-Back.[46] With this scale, the clinician elicits self-reported use and craving of individual substances, including opiates,

a drug's toxic effects, drug withdrawal, or short-term life crises.[38,39]

This study was launched to test the hypothesis that antidepressant medication would result in improved mood and diminished substance abuse in patients with depressive syndromes diagnosed by clinical history who were receiving methadone treatment. Depression was required to be primary (to antedate substance abuse), to have persisted during an abstinent period, or to be relatively chronic in the current episode. An open-label pilot trial of imipramine hydrochloride employing this approach seemed promising.[40] We report the results of the first placebo-controlled trial of an antidepressant that focused on drug-dependent patients with rigorously diagnosed depressive disorders.

RESULTS

SAMPLE CHARACTERISTICS

One hundred sixty-nine patients met the enrollment criteria and began to receive the single-blind placebo. While receiving the single-blind placebo, 26 (15%) of the patients dropped out of the study and 6 (4%) improved and were not randomized, leaving 137 patients who were randomized (74 to imipramine and 63 to placebo). Of these patients, 84 (61%) completed an adequate trial of at least 6 weeks' duration (42 received imipramine and 42 received placebo). Thirty-eight (28%) of the patients completed all 12 weeks of the trial.

cocaine, alcohol, cannabis, sedative-hypnotics, stimulants, phencyclidine hydrochloride, and others, followed by 5 summary items: days per week using substances (any drugs or alcohol), days per week using cocaine or heroin, days per week using drugs intravenously, days per week experiencing a craving for any substance, and average intensity of that craving on a 5-point scale (0=none to 4=severe). Because patients in this trial could be using various drugs or alcohol and no one substance predominated, outcomes in this article are reported for the summary items. Patients responded to 100-mm visual analog scales for drug craving adapted from the Cocaine Craving Scale.[47] Urine samples were collected weekly and analyzed for opiates, cocaine, benzodiazepines, and alcohol by the enzyme-multiplied immunoassay technique.

Specific anchor points for the CGI scale for substance use were established, requiring at least a 75% reduction in self-reported use of a substance vs its level of use at baseline for a score of 2 (much improved) and abstinence for a score of 1 (very much improved). An overall categorical rating of global response to treatment was made by the treating psychiatrist (E.V.N., F.M.Q., S.J.D., D.D., and others) at the study end point. This required substantial improvement in depression, as reflected by a CGI scale score of 2 (much improved) or 1 (very much improved), and either zero use or at least a 75% reduction in use of substances by self-report when the 4 weeks before the end point were compared with the 4 weeks before randomization. The end point was either week 12 or the last week in the study for patients who dropped out or were withdrawn prior to week 12. Among patients who completed at least 6 weeks of treatment, global response was associated with lower Hamilton Depression Rating Scale total scores at the end point (point biserial r=0.69, n=84, P<.001) and lower self-reported days per week using drugs or alcohol (point biserial r=0.37, n=84, P<.001).

Abstinence was evaluated as a composite of the results of urine toxicologic tests and self-reported substance use. A week was scored "urine-confirmed abstinent" if the self-report and the urine sample test results were negative for all substances of abuse. Of 817 urine samples collected, 542 (66%) agreed with the self-report—358 (44%) being positive for 1 or more substances by self-report and the urine sample test results and 184 (23%) being negative for all substances by self-report and the urine sample test results. Among the 275 (34%) of the urine sample test results that did not correspond, 203 (25%) were negative for all substances when the self-report was positive and 72 (9%) were positive for 1 or more substances when the self-report was negative. Thus, agreement between self-reports and urine sample test results was reasonably high, and patients frequently reported use when the urine sample test results were negative. This supports the validity of the self-reports.

DATA ANALYSIS

Categorical measures were compared with χ^2 tests and the Yates correction for continuity. The Fisher exact test was substituted for the χ^2 test for expected cell sizes of less than 5. Continuous baseline measures were compared with t tests. For continuous outcome measures, analyses were conducted on end point scores, either at week 12 or at the last week in the study for early withdrawals. The principal continuous measure of depression severity was the 21-item Hamilton Depression Rating Scale total score. For self-report measures of drug use and craving, the scores during the 4 weeks before the end point were averaged to arrive at single summary scores. An analysis of covariance (ANCOVA) was conducted on end point scores, with baseline scores entered as covariates. For measures of self-reported substance use in the sample completing an adequate trial, tests for heterogeneity of slope were at or close to significance (P<.11), violating the assumption of equal slopes required to test differences between means. Therefore, an analysis of variance (ANOVA) was conducted, entering the following factors: (1) treatment assignment (imipramine or placebo); and (2) substance use at baseline, categorized into low (<1 day per week), medium (1-3 days per week), or high (>3 days per week). The cut points between baseline levels of use were chosen to represent clinically meaningful distinctions that would also produce relatively even group sizes. To evaluate the role of mood improvement or substance use improvement as a mediator of treatment on outcome, regression coefficients and their SEs for treatment and mediator terms in linear models were examined.[48,49] All tests were 2 tailed with the significance level set at α=.05.

Outcome was analyzed in the sample of all randomized patients (N=137) and in the sample of patients who completed a minimum adequate trial (n=84), defined a priori as at least 6 weeks of continuously taking the randomized medication. The results were similar for both samples; to simplify the presentation, results are reported mainly for the adequately treated sample. Unless otherwise specified, all results are given as the mean (±SD).

The demographic and clinical characteristics at baseline of the 84 patients who completed adequate trials, receiving imipramine or placebo, are compared in **Table 1**. Two thirds of the patients in both treatment groups had major depression; in approximately half of the patients in each group, the depression was rated as primary. The Hamilton Depression Rating Scale scores indicate moderate severity of depression. The mean duration (days per month) of substance use was 11.8±11.1 days. The most frequently used substances were opiates and cocaine, followed by alcohol, sedatives, and cannabis. Only a few patients used parenteral drugs or freebase cocaine. The mean methadone dose was 60.3±18.9 mg/d. There were no significant (P>.05)differences between the imipramine- and the placebo-treated groups.

In the imipramine-treated group, the mean of the highest dose achieved was 5.37±1.01 fifty-milligram pills per day (268±50 mg/d); in the placebo-treated group, the mean of the highest dose achieved was 5.81±0.59 identical-appearing placebo pills per day (t=2.44, df=82, P<.02). The mean of the highest blood level (imipramine plus desipramine hydrochloride) achieved by each patient was 424±296 ng/mL.

ATTRITION

The proportion of dropouts prior to a minimum adequate 6-week trial did not differ between those receiving imipramine (32/74 [43%]) and those receiving placebo (21/63 [33%]) (χ^2=1.02, df=1, P<.32). Dropouts

Table 1. Baseline Characteristics of Patients Completing a Minimum Adequate Trial (N=84)*

Characteristics	Patients Receiving Imipramine Hydrochloride (n=42)	Patients Receiving Placebo (n=42)
Demographic		
Age, y	33.4±6.6	35.4±6.4
Female sex	18 (43)	14 (33)
Minority	16 (38)	10 (24)
Unmarried	29 (69)	27 (64)
Unemployed	22 (52)	18 (43)
Education, y	12.0±2.3	12.0±2.3
Methadone dose, mg/d	59.7±19.6	60.9±18.2
Depression		
Major depression	28 (67)	28 (67)
Dysthymia	12 (29)	11 (26)
Depression not otherwise specified	2 (5)	3 (7)
Primary	23 (55)	23 (55)
Secondary or persistent in abstinence	6 (14)	10 (24)
Secondary	13 (31)	9 (21)
Hamilton Depression Rating Scale score	16.2±4.0	15.6±3.8
Substance use†		
Opiates	17 (41)	22 (52)
Cocaine	17 (41)	22 (52)
Freebase cocaine	3 (7)	7 (17)
Alcohol	17 (41)	15 (36)
Sedatives	11 (26)	10 (24)
Cannabis	12 (29)	9 (21)
Parenteral cocaine or heroin	14 (33)	14 (33)
Any substance use	2.52±2.57	3.24±2.50
Cocaine or heroin use	1.73±2.45	2.16±2.26
Light use (≤3 days per month at baseline)	16 (38)	10 (24)

*All data are given as the mean (±SD) or the number (percentage) of patients. None of the differences between groups is significant (P>.05).

†Substance use values are for the 30 days prior to study enrollment. Values for specific substances are given as the number (percentage) of patients using each substance (eg, opiates or cocaine) at least once. Values for "Any substance use" and "Cocaine or heroin use" are given as the mean (±SD) days per week of use.

had significantly higher scores on the visual analog scale rating craving for drugs and alcohol in general (dropouts, 10.2±5.5; completers, 7.7±6.2; t=2.35, df=120, P<.02). No other baseline demographic or clinical characteristics distinguished dropouts and completers.

Most dropouts (33/53 [62%]) were labeled as such because of noncompliance, ie, the patients either did not take the medication regularly or stopped attending treatment sessions. The rate of noncompliance did not differ between the imipramine-treated group (19/74 [26%]) and the placebo-treated group (14/63 [22%]). Side effects accounted for 9 early dropouts receiving imipramine (12%) and 3 receiving placebo (5%). In addition, 3 patients were removed from the trial because of adverse medical events; all were being treated with imipramine. One patient with a history of a convulsion during cocaine use had a witnessed grand mal convulsion from which she recovered uneventfully; results of serum toxicologic tests revealed a substantial amitriptyline hydrochloride level from illicit use. Respiratory distress due to chronic obstructive pulmonary disease developed in 1 patient; this condition might have been worsened by the anticholinergic drying of secretions. One patient got drunk, fell, and fractured his jaw. The rate of removal due to either side effects or adverse medical events was significantly greater for those receiving imipramine (12/74 [16%]) compared with those receiving placebo (3/63 [5%]) (Fisher exact test, P<.04). Two patients receiving placebo were removed from the trial because of worsening suicidal ideation. One patient receiving placebo was removed because of an agitated state probably related to sedative abuse. Two patients (1 receiving imipramine and 1 receiving placebo) were transferred to inpatient treatment because of worsening substance abuse.

GLOBAL RESPONSE, DEPRESSION, AND CRAVING TREATMENT OUTCOME

Treatment outcome for patients who completed an adequate trial is summarized in **Table 2**. The proportion of patients meeting the global response criterion was significantly greater in patients receiving imipramine compared with those receiving placebo. There was also a significant advantage for imipramine compared with placebo in the proportion of patients meeting the depression response criterion. Depression symptoms, as measured by the Hamilton Depression Rating Scale total score, were significantly lower after treatment with imipramine compared with treatment with placebo, as were both measures of craving.

PREDICTORS OF GLOBAL RESPONSE

No baseline demographic or clinical variables significantly (P>.05 for all) predicted global response. There were trends toward more benzodiazepine and alcohol use among nonresponders. The methadone dose was similar in responders (61.8±16.8) and nonresponders (59.6±19.8) (t=0.49, df=81, P=.63). The proportion of responders did not differ significantly among patients with major depression (16/56 [29%]), dysthymia (9/23 [39%]), or depression not otherwise specified (2/5 [40%]) (χ^2=0.98, df=2, P=.61) nor among patients with primary (13/46 [28%]), secondary–persistent-in-abstinence (4/16 [25%]), or secondary (10/22 [46%]) depression (χ^2=2.48, df=2, P=.29). The sample size was not sufficient to evaluate predictors of response by treatment.

TREATMENT OUTCOME FOR SELF-REPORTED SUBSTANCE USE

For self-reported measures of substance use, ANCOVAs yielded trend-significant tests for heterogeneity of slope. Therefore, 2 (treatment) by 3 (levels of baseline drug use) ANOVAs were conducted. For outcome of parenteral use, only 28 patients were using parenterally at baseline, and there was no effect of treatment at the end of the study. **Table 3** provides the outcome for days per week using any substances and days per week using cocaine or heroin. Baseline substance use was a robust predictor of substance use at the end of the study. The treatment effect is significant for days per week using any substances and

Table 2. Summary of Outcome for the Placebo-Controlled Imipramine Trial in Patients Completing an Adequate Trial

Outcome	Patients Receiving*		Difference Between Groups	
	Imipramine Hydrochloride (n=42)	Placebo (n=42)	Test Statistic†	P
Global response‡	24 (57)	3 (7)	21.80	<.001
Depression response‡	28 (67)	11 (26)	12.30	.001
Hamilton Depression Rating Scale total score	8.0±7.4	13.6±6.4	18.00	<.001
Days per week craving any substance	2.7±2.4	4.5±2.5	9.42	.003
Intensity of craving	1.6±1.1	2.3±1.0	7.82	.006
Urine-confirmed abstinence (last 4 weeks of the study)	6 (14)	1 (2)	§	.11

*All data are given as the number (percentage) of patients or the mean (±SD).
†χ^2 Test, df=1, F(1,81) for Hamilton Depression Rating Scale scores and F(1,79) for craving scores (2 patients had missing data).
‡Depression response is defined as a Clinical Global Impression scale depression improvement score of 1 or 2 (at least "much improved"); global response, a depression response and at least a 75% reduction from baseline in self-reported substance use.
§Fisher exact test for the difference between proportions.

Table 3. Outcome for Self-reported Substance Use by Treatment and Baseline Level of Use

Substance Use at Baseline, Days per Week	Substance Use at the End of the Study, Days per Week*		Effect of Baseline		Effect of Treatment		Interaction	
	Patients Receiving Imipramine Hydrochloride	Patients Receiving Placebo	F	P	F	P	F	P
Any substance								
<1 (Low)	0.74±0.94 (16)	0.87±1.21 (10)						
1-3 (Medium)	0.62±0.64 (9)	2.34±1.86 (10)	16.29	<.001	6.01	.02	1.18	.31
>3 (High)	2.71±2.28 (17)	3.87±2.20 (22)						
Cocaine or heroin								
<1 (Low)	0.53±1.17 (23)	0.39±0.95 (16)						
1-3 (Medium)	0.36±0.38 (7)	1.19±1.54 (10)	11.69	<.001	3.20	.08	1.70	.19
>3 (High)	1.61±2.02 (12)	2.77±1.94 (16)						

*All data are given as the mean (±SD). The total number of patients is given in parentheses.

is a trend for days per week using cocaine or heroin. An inspection of the means suggests that the advantage for imipramine occurs among patients with medium or high levels of use at baseline and that there is a floor effect, ie, little change among patients with low use at baseline regardless of treatment.

ABSTINENCE

When the number of urine sample–confirmed abstinent weeks during the 4 weeks before the end of the study is examined, most patients had no substance-free weeks while receiving either imipramine (26/42 [62%]) or placebo (28/42 [67%]), consistent with the floor effect observed in the self-reported data. Continuous abstinence (4 of 4 weeks abstinent at the end of the study) was achieved by 6 (14%) of the 42 patients receiving imipramine and 1 (2%) of the 42 patients receiving placebo (Fisher exact test, P=.11).

OUTCOME IN THE INTENT-TO-TREAT SAMPLE

Outcome was also analyzed in the sample of all randomized patients, using last observations carried forward. The global response criterion was met in 26 (35%) of 74 patients receiving imipramine compared with 4 (6%) of 63 patients receiving placebo (χ^2=14.8, df=1, P<.001). Depression response was achieved by 31 (42%) of 74 patients receiving imipramine compared with 13 (21%) of 63 patients receiving placebo (χ^2=6.11, df=1, P<.02). The Hamilton Depression Rating Scale total score at the end of the study was 10.0±6.9 for those receiving imipramine vs 14.4±7.0 for those receiving placebo (F[1,134]=15.8, P<.001). The days per week using any substance were 1.80±2.03 days for those receiving imipramine vs 2.97±2.28 days for those receiving placebo (F[1,134]=8.69, P<.004).

SUBSTANCE ABUSE OUTCOME IN RELATION TO DEPRESSION RESPONSE

The hypothesis of this study is that improvement in substance use is caused by improvement in mood. As previously described and as noted in Table 3, an ANOVA yielded a significant main effect of treatment on self-reported days per week using any substance. The coefficient (±SE) of the treatment term in that model was as follows: B=0.50±0.20 (F[1,78]=6.01, P<.02). To evaluate the relationship between substance use outcome and mood improvement, the ANOVA model was then ex-

panded by adding depression response (CGI scale score of much or very much improved at the end of the study) as another independent variable. If depression response mediates the effect of treatment on substance use outcome, then the expanded model should yield a main effect of depression response, accompanied by a substantial reduction in the effect of treatment, reflected in the relative sizes of the coefficients from the linear models.[48,49] The results are consistent with mediation. The expanded model yields a significant main effect of depression response ($F[1,72]=6.31$, $P<.02$), in the direction that improvement in depression is associated with lower substance use at the end of the study, and the effect of treatment (coefficient [±SE], B=0.19±0.25; $F[1,72]=0.58$; $P=.45$) is reduced. However, caution is indicated because the effect of depression response describes an association between depression and substance use scores at the end of the study and the direction of causality cannot be inferred.

A stronger case for causality can be made if the mediator precedes the outcome in time.[49] Therefore, for each patient, the week in which depression was first rated as responding (CGI scale depression score ≤2, ie, at least much improved) was compared with the week in which all substances were first rated as responding (CGI scale substance use score ≤2, ie, at least a 75% reduction in self-reported substance use compared with baseline). Among the 27 patients rated as global responders at the end of the study, depression response occurred first in 9 (33%) of the patients, substance use response occurred first in 16 (59%) of the patients, and response occurred during the same week in 2 (7%) of the patients. This is not consistent with a mediated model, where, for most cases, depression response would be expected to occur before substance use response.

In view of the substantial proportion of cases in which substance use improved first, the converse model was evaluated in which mood outcome is the dependent variable and substance use improvement mediates the effect of medication treatment assignment. Regression models were fitted predicting the CGI scale depression improvement score as a function of treatment alone (coefficient [±SE], B=1.12±0.27; $F[1,82]=-17.3$; $P<.001$) and then as a function of change in days per week using any substance (baseline minus end of the study values) (coefficient [±SE], B=0.15±0.06; $F[1,81]=-6.78$; $P<.02$) and medication treatment assignment (coefficient [±SE], B=1.04±0.26; $F[1,81]=-15.7$; $P<.001$). This shows that a reduction in substance use is associated with an improvement in mood, controlling for treatment. However, the size of the treatment term is not substantially reduced by the addition of the substance use improvement term, suggesting that substance use improvement does not mediate the effect of treatment on mood.

COMMENT

A robust antidepressant effect of imipramine was demonstrated in patients receiving methadone maintenance treatment who were selected by clinical history and syndromal criteria for current depression. This clarifies the inconsistent results from prior antidepressant trials in patients receiving methadone,[29-33] in which cross-sectional scales were used to identify depressed patients and in which high placebo response rates were often observed.[29,30,32] The findings suggest that in opiate-dependent patients, stabilized with methadone treatment, a *DSM-III-R* depression syndrome that is primary, persistent during a past abstinent period, or chronic can be treated with an antidepressant medication.

The second goal of this study was to determine whether effective antidepressant treatment reduces illicit drug use. This was viewed as a test of the self-medication hypothesis, which proposes that for some patients substance abuse is an attempt to reduce depressive symptoms. The findings are not consistent with a simple self-medication model. In support of the hypothesis, craving and 1 measure of self-reported substance use were reduced by imipramine treatment and mood improvement was associated with lower self-reported substance use. However, the treatment effect on substance use was not as robust as the antidepressant effect, either statistically or clinically. Few patients became abstinent. Further, substance use improved before depression did in more than half of the responders. These findings resemble those from a similar study of depressed alcoholics[50] and suggest that mood is only 1 of several factors driving substance use and that depression and substance abuse are to a large degree functionally independent disorders.

Methodological limitations include the fact that the findings of treatment effects on illicit drug use rely largely on self-report. The most objective measure, urine sample–confirmed abstinence, did not show a significant ($P=.11$) advantage for imipramine treatment. It has been shown that patients' reports of substance use are accurate when no contingencies are placed on them,[51] and agreement between self-reports and urine toxicologic test results in this study was good. Nevertheless, diminished self-reported substance use, short of abstinence, is not measured by qualitative urine toxicologic tests and could be biased by expectancy effects. The quantitative measurement of urine drug concentrations might provide more objective documentation of reductions in drug use, although this method has limitations.[52,53]

As in most clinical trials with drug-dependent patients, the dropout rate was high, raising concern about bias due to differential attrition. Treatment effects in this trial were equally robust in the all-randomized sample compared with the completer sample, and the imipramine- and placebo-treated groups were well matched on baseline features. Nevertheless, there is no fully adequate way to detect or compensate for differential attrition. Vigorous efforts to reduce attrition and to obtain complete follow-up data should be a priority in future trials.

This study is limited in its ability to identify features of depression that predict antidepressant response in patients with substance dependence. Most of the patients were actively using substances at the outset. This suggests that the emphasis in *DSM-IV* of requiring at least a month of abstinence before diagnosing depression[54] may miss therapeutic opportunities or that the *DSM-IV* category of substance-induced depression may in some cases be an indication for antidepressant treatment. However, the fact remains that most depressive syndromes in al-

cohol- and drug-dependent patients resolve with abstinence or appropriate substance abuse treatment and do not require antidepressants.[35-37,39] Neither the distinction between major and minor depression nor the distinction between primary and secondary depression predicted response. In alcoholics, those with primary[50] and secondary[55] depression have been found to respond to antidepressants. Future research should examine a wider range of clinical features of depression as predictors of antidepressant response,[56] with larger sample sizes to assure that a sufficient number of subjects with each predictor are receiving medication and placebo.

The enrollment criteria selected the small fraction of patients receiving methadone who had persistent depression; it is only to this subgroup that the findings may generalize. A study of 200 consecutive patients who were admitted to our methadone programs showed that 30% met the criteria for depression at admission, but only half of those patients remained depressed after 1 month of stabilization with methadone treatment (E.V.N., F.M.Q., S.J.D., D.D., and T.K., unpublished data, 1993).

Imipramine was associated with more side effects and adverse medical events than placebo. This provides further impetus to refine guidelines for the selection of treatment candidates, as the possible benefits of treatment must be weighed against the risks. It suggests that antidepressants with more favorable side effect and safety profiles, such as serotonin reuptake inhibitors, should be studied in this population. Also, the side effects of tricyclic antidepressants might be reduced by monitoring serum levels and titrating the dose to the low end of the therapeutic range.

Methadone increases the levels of tricyclic antidepressants[57]; conversely, tricyclic antidepressants might increase methadone levels, although pharmacokinetic studies in humans are lacking. Thus, some of the imipramine effect on mood or substance abuse observed in this trial might have been due to increased methadone levels. Serum methadone levels were not measured, and methadone doses were not controlled by the research team. In future trials, serum levels of antidepressant and methadone should be measured, and an upward titration of methadone dose might be conducted prior to initiating antidepressant treatment.

Future studies might also exert more control on the concurrent psychosocial intervention. Various promising psychotherapeutic and behavioral interventions for opiate[58,59] and cocaine[60,61] dependence have emerged. Combining medication with psychosocial interventions in clinical trials has been recommended on methodological grounds,[62] as it might reduce attrition, augment compliance, or augment the effects of medication. Pioneering studies of this type assigned outpatients with cocaine dependence to antidepressant medication or placebo and to 1 of 2 levels of psychosocial intervention.[11,60] The effects of medication were not detected, although the samples were not selected for depression.

This study provides an example of a general strategy of targeting treatments to select subgroups of drug abusers with psychiatric comorbidity. The findings suggest that this approach will not be a panacea, and the field must continue to seek broadly effective treatments, such as methadone. However, the value of treating comorbidity, such as depression, should not be dismissed, even if the immediate effect on substance use is small. Depression is associated with suicide[63,64] and with impaired functioning in work, relationships, and family.[65,66] Whether the treatment of depression might have a long-term effect on the overall well-being of substance abusers and their families remains unknown but provides another incentive and focus for future research.

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Reprints: Edward V. Nunes, MD, New York State Psychiatric Institute (Unit 35), 722 W 168th St, New York, NY 10032.

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