ORIGINAL ARTICLE

Pharmacotherapy Plus Psychotherapy for Treatment of Depression in Active Injection Drug Users

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Context: Depressive disorders are common among opiate abusers and are associated with detrimental behavioral effects. However, there is little precedent for offering active drug users complex treatments for depression.

Objective: To determine whether combined psychotherapy and pharmacotherapy treatment reduces reported depressive symptoms compared with an assessment-only condition among out-of-treatment drug injectors.

Design: Randomized controlled trial.

Setting: Research office located at an academic medical center.

Patients: Active injection drug users with a *DSM-IV* diagnosis of major depression, dysthymia, substance-induced mood disorder with symptoms persisting for at least 3 months, or major depression plus dysthymia, and a Modified Hamilton Rating Scale for Depression (HAM-D) score greater than 13.

Intervention: Combined psychotherapy (8 sessions of cognitive behavior therapy) plus pharmacotherapy (citalopram).

Main Outcome Measures: Modified HAM-D scale scores at the end of 3 months of combined treatment.

Results: The 109 study subjects were 64% male and had a mean age of 36.7 years and a mean baseline HAM-D score of 20.7. Depression subtypes included major depression only (63%), substance-induced depression (17%), and major depression plus dysthymia (17%). In the intent-to-treat analysis, participants in treatment averaged 2.11 HAM-D points greater improvement than control subjects ($P=.08$), and 26.1% of combined treatment patients (n=53) compared with 12.5% of control patients (n=56) were in remission ($P=.047$). Nearly 40% of fully adherent subjects (receiving >75% of either psychotherapy or pharmacotherapy) were in remission at follow-up (odds ratio, 3.6; $P=.04$).

Conclusions: Combined treatment for depression is significantly superior to a control condition (assessment only) in proportion of patients in remission, but not in HAM-D improvement among drug injectors. Full adherence to treatment is associated with the largest treatment effects. Our findings demonstrate that active drug users with dual diagnoses are able to participate in conventional treatment.

Arch Gen Psychiatry. 2004;61:152-159

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DEPRESSIVE DISORDERS ARE common among opiate abusers, with rates ranging from 14% to 55%.[1-3] A significant challenge in the study of depression in opiate users is that opiates may induce symptoms that are difficult to distinguish from symptoms of primary mood disorders. Depressive symptoms may be attributable to an opiate's toxic effects, drug withdrawal, or short-term life crises. Although there have been recent attempts to develop diagnostic criteria and interview instruments that differentiate opiate-related symptoms from independent mood disorders including major depression, there is general agreement that the task of establishing a primary-secondary distinction is especially difficult among patients with unrelenting, chronic, and severe substance abuse disorders.[4-7]

The impact of depression on opiate users is extensive. Comorbid depression may be associated with premature dropout from treatment, and it has been associated with poorer prognosis after drug treatment.[2,8-11] Comorbid depression also may serve as an important trigger for high-risk injection practices, continued drug use, or drug relapse.[12-15] Situations involving negative mood states are among the most frequently cited precipitants of relapse across several types of addictive sub-

stances.[13] Substance abuse by psychiatric patients may be motivated by efforts to alleviate symptoms of the primary psychiatric disorder; conversely, mood disorders may be induced by substance use.

Despite these psychiatric treatment needs, treatment of depression among active drug users who are not enrolled in drug treatment has never been clinically tested. This may be in part because active drug users do not seek treatment for depression, and because of the belief that a diagnosis of major depression cannot be reliably made in the context of daily drug use. It may also be due to practical considerations. Drug injectors often lead significantly disrupted lives, making adherence to treatment difficult, which in turn may limit the effectiveness of depression treatment.

Among opiate abusers receiving methadone maintenance treatment, however, 4 of 5 pharmacologic trials have demonstrated favorable effects on mood.[16-20] Nonetheless, there is little precedent for offering active drug users treatment for depression with pharmacotherapy. Drug injectors enrolled in methadone maintenance treatment have received psychotherapy for depression, such as cognitive behavior therapy (CBT), to prevent relapse to opiate use.[21] Some research suggests that CBT may be a viable option for out-of-treatment drug users, despite the difficulty with adherence to treatment.[22] Callahan et al[23] found improved retention and treatment outcome in those who participated in a combination psychological and pharmacologic intervention, as compared with heroin users receiving pharmacotherapy alone.

In the Multidisciplinary Intervention for Needle Users to Reduce Viral Acquisition (MINERVA) study presented herein, we recruited active injection drug users for a randomized study testing the efficacy of combined CBT and pharmacotherapy for the treatment of depression. In MINERVA, we took the position that requiring abstinence before diagnosing depression limits therapeutic options, that primary-secondary depression distinctions are often difficult to discern, and that the cause of depressive symptoms (drug-induced or endogenous) may not be critical given that comorbid depression confers a poor long-term prognosis in substance abusers, regardless of the primary-secondary distinction. When antidepressant treatment is considered, combining pharmacotherapy and psychotherapy may be the most powerful intervention, particularly for those with more severe and/or chronic depression.[24] Our goal was to determine whether combined treatment would reduce reported depressive symptom scores compared with an assessment-only condition among out-of-treatment drug injectors.

METHODS

DESCRIPTION OF THE STUDY SITE AND PARTICIPANT POPULATION

Between March 1, 2000, and June 30, 2003, we recruited participants in Rhode Island for a randomized study of combined psychotherapy and pharmacotherapy for the treatment of depression in out-of-treatment drug injectors. We advertised the study as a "quality-of-life" research project with a financial incentive at various community agencies, through newspaper advertisements and on the street with flyers. Those interested were directed to call the study telephone number to be screened by study research assistants, who inquired about most of the inclusion criteria. During the recruitment period, the study telephone received 1518 calls. If eligible after a telephone screening that included demographics, recent drug use and needle-sharing behavior, and use of prescribed psychoropic medications questions, individuals were asked to come to the research site at Rhode Island Hospital, Providence, for a more detailed assessment.

Inclusion criteria included the following: (1) age between 18 and 70 years; (2) injection of opiate or cocaine during the preceding 30 days; (3) injection-related risk behavior (ie, needle sharing) during the preceding 30 days; (4) meeting criteria for a *DSM-IV* diagnosis (Structured Clinical Interview for *DSM-IV*–Patient Version [SCID-P])[25] of either (*a*) major depression, (*b*) dysthymia, (*c*) substance-induced mood disorder with symptoms persisting at least 3 months, or (*d*) major depression plus dysthymia; (5) having a score on the Modified Hamilton Rating Scale for Depression (HAM-D)[26] greater than or equal to 14; (6) not currently enrolled in drug treatment (methadone, residential, outpatient); (7) absence of current or past diagnosis of bipolar disorder, schizophrenia, schizoaffective disorder, schizophreniform disorder, or delusional disorder; (8) able to speak and read English sufficiently to complete the procedures of the study; (9) having a verifiable mailing address; (10) providing contact names for follow-up assessments; and (11) providing written informed consent for this study, which was approved by the Rhode Island Hospital/Lifespan Institutional Review Board.

At the baseline visit, participants underwent urine toxicologic testing for cocaine metabolites and heroin to confirm active drug use status, and women received urine pregnancy testing. Participants were then administered a 90-minute structured interview, which included sections on demographics; SCID-P mood, drug, and alcohol modules; and human immunodeficiency virus (HIV) risk behaviors. At the conclusion of the interview, participants were escorted to the blood laboratory for HIV antibody testing. Refusal to undergo HIV testing did not exclude eligible persons from participation in the study.

On the basis of the telephone screen, 161 individuals were invited and came to the study office for a full screening interview; 52 did not meet full eligibility criteria. One hundred nine persons were eligible for the study and enrolled, with 53 assigned to the combined therapy group and 56 to the assessment-only control group. Participants assigned to the control group were given a 2-week follow-up appointment to receive the results of their HIV tests (including posttest counseling) and 3-, 6-, and 9-month follow-up appointments for face-to-face research assessments. At each assessment visit, subjects also received any medical or mental health referrals requested.

Participants assigned to the intervention group were scheduled to receive a total of 8 individual psychotherapy (CBT) visits (during the course of 3 months) and 3 pharmacotherapy visits (monthly for 3 months). After this acute, combined 3-month phase, subjects were offered continuation pharmacotherapy alone for study months 3 to 6. Treatment group participants were scheduled for their first psychotherapy appointment and medication appointment within a week of the baseline assessment. Participants in the treatment group also returned to Rhode Island Hospital for follow-up assessment interviews at 3, 6, and 9 months after baseline.

To maximize study retention, the protocol strongly emphasized the importance of follow-up, and, at each interview, research assistants obtained contact information for at least 2 other people who could be contacted to help locate the participant. At each psychotherapy visit, participants in the treat-

ment group had brief contact with research assistants to receive their financial compensation of $15. Pharmacotherapy visits were not financially compensated, as they typically cooccurred with a psychotherapy or assessment visit, which was financially compensated. Participants in the intervention group could receive up to $240 ($120 for assessment and $120 for attending all psychotherapy appointments). Remuneration at assessments was not dependent on attendance at therapy sessions.

Although we scheduled all therapy appointments at the time of a visit, we maintained a flexible schedule for persons missing visits. Study staff were available by mobile telephone and toll-free numbers, which allowed participants to call and to change appointments. Research assistants called study participants on the day before and the morning of all scheduled therapy appointments. When a participant failed to attend a session, a call to reschedule the appointment was made. Treating clinicians were accommodating in attempts to arrange the full complement of CBT and medication visits within the first 3 study months. In addition, we provided transportation via cabs or bus tokens for all study visits.

TREATMENT

Cognitive Behavior Therapy

This treatment was aimed at reducing the participant's level of depression and increasing his or her coping skills regarding depression. This 8-session therapy was a modified version of a "Coping With Depression" protocol treatment intervention used by Brown et al[27] for treatment of depression in alcoholic patients. The first sessions were devoted to presenting a social learning view of depression and guiding the participant in learning how to identify and differentiate mood states. The next sessions addressed acquiring skills in 3 specific areas: increasing pleasant activities, changing negative cognitions, and improving social skills and increasing positive social interactions.[28] Each participant was encouraged to develop a personalized plan to work on problem areas by means of a participant workbook. Each session consisted of a review of material from the previous session, presentation of new material, discussion and exercises related to the new material, and a homework assignment. The treatment was administered in 60-minute individual sessions by PhD-level clinical psychologists trained and supervised in the protocol by 2 of us (D.S.H. and S.E.R.) at weekly trainings.

Pharmacotherapy

Participants were scheduled to meet with a psychiatrist monthly for 3 months. Whenever possible, psychiatric visits took place immediately after CBT sessions. Psychiatrists followed the clinical management guidelines developed by Fawcett and colleagues.[29] Participants were first prescribed citalopram, 20 mg. The dose and dosage schedule were determined by the clinical judgment of the treating psychiatrist (up to 60 mg). If citalopram was not effective or produced adverse effects, the psychiatrist could prescribe venlafaxine hydrochloride, 37.5 mg (up to 375 mg), or bupropion hydrochloride, 150 mg (up to 300 mg). Once a satisfactory response was achieved with any of the aforementioned medications, participants continued to receive that dose for the remainder of the acute combined treatment period, that is, up to 3 months. At each medication visit, subjects received 1 month's worth of study medication. Medication study visits were limited to 15 minutes to ensure that the study psychiatrist was not providing other active psychotherapy ingredients to the treatment group. Eleven participants were switched from citalopram to venlafaxine and 2 were switched from citalopram to bupropion during the study.

Study medication use was confirmed by pill counts, self-report, and, at the 3-month visit, serum levels (citalopram only) for those who reported continued use of study medication. All participants who reported citalopram use at the 3-month assessment had serum levels verifying self-report.

CBT MONITORING

The training for the 2 PhD-level clinical psychologists began with a study of the project CBT manual. They also received 2 hours of didactic training in HIV risk reduction, injection behaviors, and local substance abuse treatment programs. Therapist manuals developed for the project were used in both initial training and continuing supervision. Each therapist then performed the intervention with 3 pilot training cases before study initiation. Adherence to the intervention protocol was monitored by having the therapist complete a checklist after each intervention session.[30] All intervention sessions were audiotaped, and 10% were randomly reviewed by the therapy supervisor (S.E.R.) for internal quality control to prevent deviation from the protocol.

MEASURES

Adherence to the treatment protocol was assessed as the number of CBT appointments the participant attended and the percentage of days on which prescribed medications were taken during the first 3 study months (acute phase). We also constructed a dichotomous indicator, "fully adherent dose," defined a priori by consensus of the study investigators as attendance at 6 or more of the 8 scheduled CBT sessions or adherence to the pharmacotherapy regimen on 75% or more of the days on which medications were prescribed.

We used the SCID-P to diagnose depression type (major depression, dysthymia, "substance-induced mood disorder" with symptoms persisting for at least the past 3 months, or major depression plus dysthymia).[26] Frequency of heroin use was assessed as the reported number of days on which heroin was used in the past 30 days according to the Addiction Severity Index.[31]

The modified HAM-D scale was used to assess depression severity at both baseline and follow-up.[26] Treatment remission was defined as a 3-month HAM-D score of 8 or less.[32] As a secondary outcome, we defined treatment responders as those with a 50% or greater improvement relative to baseline HAM-D scores.[33] We tested as outcome measures both the continuous 3-month HAM-D score and the dichotomous indicators assessing remission and relative reductions of 50% or greater.

ANALYTIC METHODS

We present an "intent-to-treat" analysis based on 3-month assessment data from the end of combined treatment. There were 94 subjects for whom 3-month follow-up data were available, and our primary analyses used multiple imputation of missing data.[34,35] We used Proc MI as implemented in SAS release 8.2 to generate 20 imputed data sets under the multivariate normal model.[36] Variables included in the imputation process were sex, age, race, educational attainment, baseline HAM-D score, "full" treatment adherence, and 3-month HAM-D score. We used the companion procedure Proc MIAnalyze to generate parameter estimates and corrected SEs.[36] The imputation procedures assumed that data were missing at random, implying that the probability of being missing at follow-up was unrelated to depression severity at follow-up. Since it was possible that participants whose depression severity increased might be more likely to be missing at follow-up, we conducted a sensitivity analysis in which imputed values were increased (or de-

Table 1. Intake Characteristics by Treatment Condition

	Total (n = 109)	Treatment (n = 53)	Control (n = 56)	*t* or χ^2	*P* Value
Age, y*	36.7 (8.7)	37.2 (8.5)	36.2 (9.0)	−0.60†	.55
Education, y*	11.5 (2.2)	11.5 (2.2)	11.5 (2.2)	0.04†	.97
HAM-D score*	20.7 (3.9)	20.9 (4.0)	20.4 (3.8)	−0.76†	.45
Heroin use days*	21.8 (9.8)	23.1 (9.2)	20.6 (10.2)	−1.38†	.17
Sex, No. (%) male	70 (64.2)	31 (58.5)	39 (69.6)	1.48‡	.22
Race, No. (%) white	89 (81.7)	44 (83.0)	45 (80.4)	0.129‡	.72
Depression type, No. (%)					
Major depression only	69 (63.3)	33 (62.3)	36 (64.3)	2.57‡	.46
Dysthymia only	2 (1.8)	0.(0.0)	2 (3.6)		
Substance-induced depression	19 (17.4)	9 (17.0)	10 (17.9)		
Major depression plus dysthymia	19 (17.4)	11 (20.8)	8 (14.3)		
Missing follow-up	15 (13.8)	7 (13.2)	8 (14.9)	0.027‡	.87

Abbreviation: HAM-D, Hamilton Rating Scale for Depression.
*Mean (SD).
†Unpaired, 2-tailed *t* test.
‡χ^2 Test.

creased, depending on the substantive problem) by some constant.[35] Thus, we also report on analyses using "worst-case scenario" substitution in which the missing observations were assigned the highest observed 3-month HAM-D score (score, 34).

We used analysis of covariance to estimate treatment differences on 3-month HAM-D scores adjusting for baseline depression severity. For convenience in obtaining parameter estimates and adjusted SEs by means of Proc MIAnalyze, we used regression with treatment coded as a dummy variable (1, treatment; 0, control) to conduct the analyses of covariance.

We present contingency tables to describe treatment differences on depression remission. In each imputed data set, the cell frequencies are integers, but the average of imputed cell frequencies are not so constrained. We used logistic regression in conjunction with Proc MIAnalyze to estimate logit coefficients and corrected SEs. It should also be noted that the test statistic for parameters estimated by means of multiple imputation is reported as a *t* statistic in which the parameter estimate is divided by the corrected estimate of SE. To facilitate description, we report effects on odds rather than the raw logit coefficients.

RESULTS

Participants averaged 36.7 years of age and 11.5 years of education (**Table 1**). A majority (64.2%) were male, and 82% were white. Fifty-one percent had been unemployed for the 3 months before study enrollment, 8% were married, and 8% were HIV positive. Injectors were primarily heroin users, with only 10% using cocaine more frequently than heroin and 2 persons not using any heroin in the past 30 days. The mean (SD) number of heroin use days in the preceding month was 21.8 (9.8), and 91% met criteria for current opioid dependence. Depression types included major depression only (63%), major depression and dysthymia (17%), substance-induced depression (17%), and dysthymia only (2%). The average baseline score on the HAM-D was 20.7 (3.9). Fifteen participants (13.8%) were lost to follow-up at 3 months. The treatment groups did not significantly differ with respect to intake characteristics, heroin or cocaine use or dependence, baseline levels of depression, or depression type. In addition, the proportion of subjects lost to follow-up was highly consistent across treatment conditions (Table 1). Two participants in the treatment group had emergency department visits for suicidal ideation within the first study months; both halted the intervention. There were no adverse medication effects that led to treatment cessation.

To determine whether participants with more severe depression at baseline were more likely to be lost to follow-up, we compared baseline HAM-D scores for subjects observed at 3 months with those of subjects lost to follow-up. The mean±SD baseline HAM-D score for subjects observed at 3 months (20.71±3.77) was trivially higher ($t=.41$, $P=.68$) than the mean for the 15 subjects lost to follow-up (20.26±3.95).

We assessed both the number of CBT appointments that participants attended and their daily use of prescribed depression medications. Only 26 (49%) of the 53 participants assigned to treatment attended 50% or more of their CBT appointments and only 20 (38%) attended 75% or more. Participants were even less likely to adhere to their daily pharmacotherapy regimens. Only 18 (34%) took antidepressant medications on 50% or more of the days on which they were prescribed, and 16 (30%) had pharmacotherapy adherence rates of 75% or greater. Participants who adhered to CBT tended to adhere to their prescribed pharmacotherapy regimens and vice versa. Of the 20 participants who attended 75% or more of their CBT appointments, 13 (65%) used antidepressant medications on 75% or more of the days on which it was prescribed. Twenty-three (43%) of the 53 subjects assigned to the combined treatment group were fully adherent to treatment.

As measured by mean HAM-D scores, significant improvements in depression at 3 months were observed in both arms of the study. Among controls, mean 3-month HAM-D scores were 3.48 points lower than at baseline ($t=3.48$, $P=.001$). For participants assigned to combined treatment, HAM-D scores at 3 months averaged 6.04 points ($t=5.24$, $P<.001$) lower than at baseline. Eighteen (19%) of the 94 subjects with valid 3-month data

Table 2. Depression Remission at 3-Month Follow-up by Treatment Condition

	Complete Data (n = 94)		Multiple Imputation* (n = 109)		Worst-Case Substitution† (n = 109)	
Remission: HAM-D ≤8	Treatment	Control	Treatment	Control	Treatment	Control
Yes, No. (%)	12 (26.1)	6 (12.5)	13.7 (25.8)	7.0 (12.4)	12 (22.6)	6 (10.7)
No, No. (%)	34 (73.9)	42 (87.5)	39.4 (74.3)	49.1 (87.6)	41 (77.4)	50 (89.3)
No. of subjects	46	48	53	56	53	56
Odds ratio	2.57 (P = .047‡)		2.47 (P = .049‡)		2.44 (P = .047‡)	

Abbreviation: HAM-D, Hamilton Rating Scale for Depression.
*Cell frequencies and percentages are the average values across the 20 imputed data sets. The estimated odds ratio and associated P value were obtained with SAS 8.2 Proc Logistic in combination with Proc MIAnalyze (SAS Institute Inc, Cary, NC).
†All observations with missing 3-month follow-up data were defined as not improving on the HAM-D.
‡One-tailed P values.

Table 3. Depression Remission at Follow-up by Treatment Adherence

	Treatment Group, No. (%)		
	Treatment Adherence		
Remission: HAM-D ≤8	Full	Low	Controls
Yes	9.00* (39.1)	4.65 (15.5)	6.95 (12.4)
No	14.00 (60.9)	25.35 (84.5)	49.05 (87.6)
	Full vs low: OR† = 5.00, t = 1.79, $P_{\alpha/2}$ = .04		
	Full vs controls: OR‡ = 6.41, t = 2.44, $P_{\alpha/2}$ = .008		

Abbreviations: HAM-D, Hamilton Rating Scale for Depression; OR, odds ratio.
*Cell frequencies are not integers because they are the average cell frequency for the 20 imputed data sets.
†The estimated odds ratios and associated P values were obtained with SAS 8.2 Proc Logistic in combination with Proc MIAnalyze (SAS Institute Inc, Cary, NC). Proc MIAnalyze gives multiple imputation parameter estimates and an adjusted t test for the null hypothesis that the population parameter is 0. A dummy variable was constructed to contrast participants with full and low adherence to treatment.
‡A dummy variable was constructed to contrast participants with full adherence with controls.

were in remission (HAM-D score ≤8) at follow-up and 21 (22%) reported relative reductions of 50% or greater in their HAM-D scores.

When outcomes were compared between the treatment and control groups on 3-month HAM-D means adjusted for baseline HAM-D scores, the observed mean differences were directionally consistent with the hypothesized treatment effects, but were not statistically significant at conventionally accepted levels. When we used the subjects for whom complete data were observed, participants in treatment averaged about 2.11 points lower than controls on 3-month HAM-D scores ($\beta = -2.11$, $t_{91} = -1.42$, $P_{\alpha/2} = .08$). The standardized effect size for the completely observed data was 0.29, which could be described as a small but meaningful effect.[37] The estimated mean difference using multiple imputation ($\beta = -2.17$, $t = -1.46$, $P_{\alpha/2} = .07$) was similar in both magnitude and statistical reliability. Not surprisingly, using worst-case substitution attenuated the estimated differences in treatment means ($\beta = -1.90$, $t_{106} = -1.07$, $P_{\alpha/2} = .14$).

A more robust pattern of treatment effects was observed when rates of remission were compared (**Table 2**). Subjects randomized to combined treatment were roughly 2.5 times more likely than controls to be in remission at the 3-month follow-up. The odds ratio (OR) obtained by means of complete data (OR, 2.57; $P_{\alpha/2} = .047$) was of similar magnitude to those obtained by multiple imputation (OR, 2.47; $P_{\alpha/2} = .049$) and worst-case substitution (OR, 2.44; $P_{\alpha/2} = .047$) (Table 2). We replicated this analysis by using the indicator of treatment response (not presented in Table 2). The results were completely consistent statistically, and the magnitude of observed effects was very similar to those reported for remission. The treatment response rate was 30.4% in the combined treatment group and 14.6% in the control group.

We used logistic regression models to estimate treatment effects, controlling first for basic background characteristics (age, race, sex, and educational attainment) and second for an indicator of treatment adherence. Herein, we report only the effects estimated by means of multiple imputation of missing values; however, results using only complete data and worst-case substitution were substantively and statistically consistent. Adjusting for background characteristics, participants assigned to the treatment condition were estimated to be about 2.67 ($t = 1.71$, $P_{\alpha/2} = .04$) times more likely than controls to be in remission; none of the background characteristics was a significant predictor. When treatment adherence was added to the model, the magnitude of the estimated treatment effect was sharply attenuated and not statistically significant (OR, 1.39; $t = 0.46$, $P_{\alpha/2} = .32$). However, participants who fully adhered to the treatment protocol were more than 3 times (OR, 3.64; $t = 1.80$, $P_{\alpha/2} = .04$) more likely to be in remission at follow-up. Thus, differences between subjects assigned to different treatment conditions were mediated by adherence to the prescribed treatment protocols.

To examine this further, we constructed a 3-category indicator contrasting (1) participants randomized to the combined treatment arm who fully adhered to the treatment protocol with (2) subjects randomized to combined treatment but who had lower adherence and with (3) controls. **Table 3** gives average cell frequencies and column percentages averaged across the 20 imputed data sets. Almost 40% of participants who fully adhered to treatment were in remission at 3-month follow-up. By comparison, only 15.5% of participants randomized to treatment with low adherence, and only 12.4% of controls,

reported such responses. We constructed dummy variables to compare participants with high treatment adherence with those with low treatment adherence and with controls. We used SAS Proc Logistic in conjunction with Proc MIAnalyze to obtain estimated ORs and tests of significance. Participants who fully adhered to treatment were significantly more likely to be in remission than controls (OR, 6.41; $t=2.44$, $P_{\alpha/2}=.008$) or subjects randomized to treatment with low adherence (OR, 5.00; $t=1.79$, $P_{\alpha/2}=.04$). Results observed when response to treatment (50% reduction in HAM-D scores) was analyzed were completely consistent with these findings.

In addition, we used dummy variable regression to perform analysis of covariance comparing adjusted 3-month mean HAM-D scores across the 3-category treatment adherence indicator. After adjustment for baseline differences on the HAM-D, participants with full treatment adherence had significantly lower 3-month HAM-D scores than either low-adherence participants assigned to treatment ($\beta=-4.77$, $t=-2.29$, $P_{\alpha/2}=.01$) or controls ($\beta=-4.88$, $t=-2.63$, $P_{\alpha/2}=.004$).

We examined drug use reported for the 30 days before the 3-month assessment. Overall, participants reported using heroin 12.31 (SD, 12.33) days, representing 8.72 fewer heroin use days than at baseline. Treatment groups did not differ significantly with respect to the frequency of heroin use ($P=.69$) or cocaine use ($P=.29$) at follow-up.

To determine whether institutionalization was related to treatment adherence, we examined drug treatment and incarceration during follow-up. Within the treatment group, all 5 participants who entered residential treatment had low adherence, while none of the highly adherent participants entered residential treatment ($P=.06$). Similarly, participants with low treatment adherence reported an average of 13 days of incarceration during follow-up compared with 1.9 days among persons with high adherence ($P=.04$).

Regardless of treatment assignment, depression status was associated with frequency of heroin use. Participants in remission at 3 months, on average, reported 7.38 days of heroin use compared with 13.49 days of heroin use among those not in remission ($t=1.91$, $P=.06$); they also reported fewer cocaine use days (2.17 vs 5.56; $P=.14$).

Twenty-four participants entered detoxification programs between baseline and the 3-month assessment (control, 18.8%, vs treatment, 32.6%; $P=.16$), and 10 participants entered residential treatment (5 each in the control and treatment groups; $P>.99$).

COMMENT

Depression, a highly prevalent and debilitating disorder among substance abusers with significant behavioral and quality-of-life implications, frequently remains untreated in this population. The targets of this combined pharmacotherapy-psychotherapy randomized clinical trial were depressed, active injection drug users who continued high-risk injection practices. Our results demonstrate that combined treatment for depression is superior to a control condition of assessment only; however, only a minority of this population experienced depression remission during a 3-month follow-up. Not surprisingly, effective response to treatment is driven by adherence to treatment.

The remission rate in the combined treatment group was 26% (the >50% response rate for this group was 30.4%), lower than the intent-to-treat response rates of 47% to 51% in meta-analyses of pharmacologic monotherapy trials that exclude substance abusers.[38] The control group remission and response rates were also lower than those typically reported in the control arms of medication trials.[39] These findings speak to the severe, chronic nature of depression in this population, and the limited generalizability of findings from many of the randomized controlled trials of antidepressant medications.

Treatment resistance may have many causes, such as the presence of comorbid psychiatric disorders. Of course, continuing drug abuse itself is associated with treatment resistance, and the outcome of treatment may depend on the efficacy of therapy for the comorbid disorder as well as for the depression. In addition to the severity of depression, this population is likely to have other factors associated with poor response, including a family history of affective disorders, previous episodes of depression, negative life events, and poor social support.[33]

While 15% of participants assigned to the combined treatment neither used the prescribed medication nor attended any CBT session, nearly 40% met our definition of being fully adherent to treatment by attending at least 75% of CBT sessions or using 75% of pharmacotherapy. Those who were fully adherent had superior results, with 40% reporting a treatment remission, near the response rate reported in meta-analyses of non–substance abusers.

The low adherence to treatment may have been due in part to drug users' erratic lifestyles, one of the ongoing challenges of caring for this population. Our findings also suggest that entry into residential drug treatment and incarceration may lower adherence to treatment, although this remains speculative. Adherence may also have been low, of course, because study participants did not perceive benefits from treatment or did not engage well with therapists, or because appointments interfered with drug-seeking activities. Nonetheless, one of the important findings here is a demonstration that it is possible to engage a substantial proportion of depressed active injection drug users in a multisession, combination antidepressant therapy. Methods for engaging this population included collecting locator information at the start of the study and at visits, informing participants about follow-up assessment and therapy schedules, being flexible and supportive about appointment scheduling, providing resources for travel, and hiring experienced staff. These methods are known to be useful in following up substance users in research settings.[40] In addition, our protocol offered a small financial compensation for attendance at CBT sessions, which may have increased treatment adherence.

Our finding that persons who adhered to CBT tended to follow the prescribed pharmacologic regimen and vice versa may also offer insight into the possible advantage of combined treatment for depressed, active opiate users. Each treatment modality may offset perceived draw-

backs of the other, and each works differently, addressing different symptoms and problem areas.[24,41,42] Provision of psychotherapy may enhance adherence to medication or foster retention when medication effects are delayed. Conversely, medications may encourage patients to persist in therapy until a therapeutic alliance is formed and coping skills are learned. Nonetheless, persons who adhere to treatment may differ from nonadherers and may respond differently to treatments other than those tested in this study.

Baker et al[21] demonstrated that a 6-session intervention for injection drug users in methadone maintenance was successful in attracting and retaining clients. Previous or ongoing treatment for substance abuse may be necessary to evaluate psychotherapeutic treatments, and there is strong evidence in favor of using psychosocial interventions to augment the effectiveness of methadone maintenance.[11,43] But what is the best approach for the majority of injection drug users who remain without substance abuse treatment? Are there criteria that can be used to screen out drug users who are unlikely to adhere to or benefit from antidepressant therapy? The MINERVA study was a first attempt at developing antidepressant treatment for this population. Perhaps a lower-intensity approach such as motivational interviewing, with fewer sessions, would benefit out-of-treatment injection drug users and might serve as a prelude to combined depression treatment.[44] Indeed, the cause of depressive symptoms (primary or secondary) may have a bearing on optimal treatment duration. For patients with concurrent depression and opiate abuse, more intensive treatment may be needed.

The issue of adherence in trials of pharmacologic agents is important because failure of adherence may lead investigators to invalid conclusions about the effectiveness of a medication, or could undermine a study's internal validity. We used self-report and pill counts to rate medication use, and drug serum levels to confirm recent use, but other methods such as Medication Events Monitoring System caps may be more accurate in describing the pattern of medication use. Eighty-five percent of participants used at least some of the offered treatment, either medication or psychotherapy. We defined 75% completion of either modality as a "full dose" on the basis of other clinical trials literature. Although this is not the subject of this article, we do not know the threshold for a treatment effect for either modality in our combined therapy regimen.

The MINERVA study had several additional limitations. First, all data are self-reported. Second, we did not examine the therapeutic alliance between patients and therapists, which may impact adherence to treatment and outcome. Third, the follow-up occurred at 3 months; the duration of recurrent mood episodes for patients with major depression averages 20 weeks.[45] The effects of combined treatment on depressive symptoms may be attenuated or enhanced after longer periods of follow-up. Because depression represents, for most patients, a chronic or recurring condition, longer outcome studies are required to assess the need for ongoing interventions. Fourth, this study tested only a limited number of antidepressant medications and a single form of psychotherapy; other studies might consider different treatment options, for instance, testing combinations of antidepressant agents or augmentation by using a nonantidepressant, or examining the comparative effectiveness of group and individual interventions. Fifth, our study design was unable to determine the active component of combined treatment. Disentangling the relative contribution of pharmacotherapy and psychotherapy is not possible here, although, as previously noted, most persons receiving a full dose of treatment used both modalities. Finally, we did not design this study with a specific adherence enhancement component, as we might in future studies.

Clearly, there is a need for strategies to improve drug abusers' adherence with the range of outpatient treatment, including substance abuse treatment, mental health treatment, or a combination of both. Currently, there is a poor fit between dually diagnosed substance-abusing patients and the available drug and mental health treatment systems. Most mental health and drug treatment programs do not provide integrated treatment for their dually diagnosed clients.[46] Developing and improving programs for patients with dual diagnoses who do not seek drug treatment may be important both in terms of HIV risk reduction and as a potential prelude to drug treatment entry.

Submitted for publication April 16, 2003; final revision received July 3, 2003; accepted July 14, 2003.

This research was supported by grants R01-MH61141 and R01-MH62719 from the National Institute of Mental Health, Bethesda, Md. Dr Stein is a recipient of Mid-Career Investigator Award K24 DA 00512 from the National Institute on Drug Abuse, Bethesda.

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Correction

Errors in Byline and Affiliations. In the Original Article titled "Pharmacotherapy Plus Psychotherapy for Treatment of Depression in Active Injection Drug Users," published in the February issue of the ARCHIVES (2004;61:152-159), an author's name was inadvertently omitted from the byline on page 152. The byline should have appeared as follows: "Michael D. Stein, MD; David A. Solomon, MD; Debra S. Herman, PhD; Jennifer L. Anthony, PhD; Susan E. Ramsey, PhD; Bradley J. Anderson, PhD; Richard Brown, PhD; Ivan W. Miller, PhD." Also on that page, the affiliations paragraph should have appeared as follows: "From the Departments of Medicine (Drs Stein, Herman, Ramsey, and Anderson) and Psychiatry (Drs Solomon, Anthony, Brown, and Miller), Brown University School of Medicine, Providence, RI."