Title
Directly observed antidepressant medication treatment and HIV outcomes among homeless and marginally housed HIV-positive adults: A randomized controlled trial

Permalink
https://escholarship.org/uc/item/5mc4709m

Journal
American Journal of Public Health, 103(2)

ISSN
0090-0036

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Publication Date
2013-02-01

DOI
10.2105/AJPH.2011.300422

Peer reviewed
Depressive, pain, and substance use disorders are highly prevalent among persons living with HIV/AIDS and among the homeless and marginally housed. The triple diagnosis of depression, HIV, and substance use poses unique treatment challenges for clinicians: successful management of one condition is often dependent on successful management of the others, and the optimal sequencing of depression treatment, substance use treatment, and stabilization of psychosocial comorbidities remains unclear. Adherence to the entire continuum of HIV care is often hampered by depression, HIV, and substance use treatment strategy for HIV-positive homeless and marginally housed adults, a vulnerable population with multiple barriers to adherence. (Am J Public Health. 2013;103:308–315. doi:10.2105/AJPH.2011.300422)

Objectives. We assessed whether directly observed fluoxetine treatment reduced depression symptom severity and improved HIV outcomes among homeless and marginally housed HIV-positive adults in San Francisco, California, from 2002 to 2008.

Methods. We conducted a nonblinded, randomized controlled trial of once-weekly fluoxetine, directly observed for 24 weeks, then self-administered for 12 weeks (n = 137 persons with major or minor depressive disorder or dysthymia). Hamilton Depression Rating Scale score was the primary outcome. Response was a 50% reduction from baseline and remission a score below 8. Secondary measures were Beck Depression Inventory-II (BDI-II) score, antiretroviral uptake, antiretroviral adherence (measured by unannounced pill count), and HIV-1 RNA viral suppression (< 50 copies/mL).

Results. The intervention reduced depression symptom severity (b = −1.97; 95% confidence interval [CI] = −0.85, −3.08; P < .001) and increased response (adjusted odds ratio [AOR] = 2.40; 95% CI = 1.86, 3.10; P < .001) and remission (AOR = 2.97; 95% CI = 1.29, 3.87; P < .001). BDI-II results were similar. We observed no statistically significant differences in secondary HIV outcomes.

Conclusions. Directly observed fluoxetine may be an effective depression treatment strategy for HIV-positive homeless and marginally housed adults, a vulnerable population with multiple barriers to adherence.
We excluded potential participants if they did not live in San Francisco; were unwilling to take fluoxetine; had a CD4+ T-lymphocyte cell count nadir of 350 cells per milliliter or lower and were not currently taking ART; were unable to commit to the required study visits; reported taking antidepressant medications, mood stabilizers, or other neuroleptics within 3 months prior to study entry; reported being under psychiatric care within 6 months prior to study entry; reported a previous diagnosis of bipolar disorder or schizophrenia; exhibited signs and symptoms consistent with a DSM-IV diagnosis of dementia, any psychotic disorder, or bipolar disorder; were deemed to have a current substance use disorder of a severity requiring immediate residential or inpatient treatment; were at imminent risk of completed suicide; were pregnant; were prescribed a medication or had a history of a medical condition that could harmfully interact with fluoxetine; or were already participating in an ongoing adherence study.

**Study Design**

Participants who remained eligible at the end of the screening process were randomly assigned to receive fluoxetine treatment or referral to the community for psychiatric care (Figure 1). We employed blocked randomization within categories of DSM-IV diagnosis, substance use, ART use, and CD4 count, with a random choice of 8, 10, or 12 participants in each block. We generated the randomized treatment assignment list prior to study enrollment. Participants were enrolled and assigned to a treatment arm by research staff who obtained the assignment from a password-protected database maintained by the study programmer. Only the study programmer and senior epidemiologist had access to the randomization list (K. R. and E. D. C.).

Participants assigned to the intervention arm received an explanation of their psychiatric diagnosis and were told that they would be treated with fluoxetine. Treatment was directly observed for 24 weeks, introduced in 3 phases of gradually increasing independence from the study provider: (1) 20 milligrams fluoxetine directly observed each weekday and self-administered on weekends, for 2 weeks; (2) 90 milligrams fluoxetine directly observed weekly, for 22 weeks; and (3) 90 milligrams fluoxetine self-administered weekly, for 12 weeks. In 2005, midway through the study, the manufacturer (Eli Lilly & Co, Indianapolis, IN) ceased donating samples of Prozac Weekly. Therefore, we switched participants from that medication to 90 milligrams generic fluoxetine, also taken weekly. All directly observed doses were delivered in the Tenderloin District at the study research site, a system previously shown to be effective for isoniazid distribution in a similar population.

A study psychiatrist met with intervention arm participants weekly for the first month, every 2 weeks for the second month, and monthly thereafter. At each visit, the psychiatrist conducted a thorough psychiatric interview and mental status exam and inquired about treatment response and possible adverse side effects. Study psychiatrists also used the 17-item Hamilton Rating Scale for Depression (Ham-D) and the Clinical Global Impression Severity and Improvement scales to guide assessment of treatment response. These instruments were administered without blinding, because the clinical assessments were separate from the blinded study assessments. The dose of fluoxetine was increased to 180 milligrams once weekly for partial responders and non-responders. If deemed necessary by study psychiatrists, augmenting medications were added to treat symptoms to remission. We reimbursed intervention arm participants $25 per week for completion of all scheduled directly observed doses and $25 per week for the final 12 weeks of self-administered treatment.

Participants randomized to the referral arm received an explanation of their diagnosis and were advised to seek treatment at a public mental health clinic that specialized in the care of HIV-positive persons, located 0.5 mile away along a major public transportation corridor. Referral arm participants received a $25 weekly incentive to come to the research study site to update contact information and undergo data collection procedures.

**Outcome Measures and Covariates**

Research visits occurred monthly and coincided with psychiatric treatment visits when possible. Structured interviews were used to collect information about participants’ sociodemographic characteristics, health behaviors, and HIV care at baseline, as well as their experience of gastrointestinal, neuropsychiatric, constitutional, and sexual symptoms every 3 months. We determined CD4+ T-lymphocyte cell count through standard techniques (Unilab, San Jose, CA).

The primary outcome of interest was depression symptom severity, assessed with the Ham-D and administered by experienced clinical raters who were blinded to treatment assignment. We defined remission as a virtual absence of depressive symptoms (Ham-D ≤ 7) and response as a clinically meaningful degree of symptom reduction (≥ 50% reduction in symptom severity from baseline). Our secondary depression outcome measure was the 21-item Beck Depression Inventory-II (BDI-II) with remission (BDI-II ≤ 8) and response defined similarly.

Among study participants who were eligible for ART at baseline (i.e., CD4+ T-lymphocyte cell count nadir < 350 cells/mL), we defined uptake of ART as the patient being on ART as of a given visit. Among study participants on ART at baseline, we measured ART adherence with unannounced pill counts conducted at the participant’s usual place of residence. We defined viral suppression as HIV-1 RNA less than 50 copies per milliliter. Plasma was processed and stored at −40°C within 6 hours of collection. We determined HIV-1 viral load with the HIV-1 Amplicor Monitor version 1.5 ultrasensitive assay (Roche Molecular Systems, Alameda, CA), with a lower detection limit of 20 copies per milliliter. We assessed all outcomes monthly.

**Statistical Analysis**

We used the t test for continuous variables and the χ² test for categorical variables to compare the 2 study arms on baseline sociodemographic and clinical characteristics. To estimate the average effect of treatment on outcomes over the entire study, we fit generalized linear mixed models to the data with the SAS procedure GLIMMIX (SAS Institute Inc, Cary, NC). For all analyses, we used an unstructured working covariance matrix. For the continuous dependent variables (Ham-D, BDI-II, ART adherence), we assumed a model relating treatment and time effects linearly to the dependent variable, whereas for the binary dependent variables (response, remission, ART uptake, viral suppression), we assumed a model.
154 Excluded
73 No-show
58 Not interested
100 Under psychiatric care or currently taking antidepressant medications
251 Self-reported diagnosis of bipolar disorder
158 Self-reported diagnosis of schizophrenia
37 Self-reported diagnosis of both bipolar disorder and schizophrenia
25 Self-reported HIV-negative
70 Lives out of area
40 Answered "no" to pre-screen
6 Not taking ART and CD4 nadir ≥ 350
61 Currently taking mood stabilizer or other neuroleptic
31 Participating in adherence study
145 Other

218 Excluded
137 No-show
17 Refused
22 BDH-II ≤ 13
35 Other mental disorder
7 Other

198 Excluded
42 No-show
8 Refused
41 Met DSM-IV criteria for current mania
40 Did not meet DSM-IV criteria for major/minor depression or dysthymia
20 Currently taking antidepressant
37 Other mental disorder
2 Inaccurate information provided
1 Not taking ART and CD4 nadir ≥ 350
7 Other

19 Excluded
6 No-show
2 Refused
5 BDH-II ≤ 13
6 Inaccurate information provided

35 Excluded
2 No-show
1 Refused
6 Met DSM-IV criteria for current mania
1 Met DSM-IV criteria for major/minor depression or dysthymia
3 Currently taking antidepressant
16 Other mental disorder
1 Other

35 Excluded
5 No-show
5 Refused
4 Met DSM-IV criteria for bipolar disorder
1 Currently taking mood stabilizer or other neuroleptic
1 Participating in adherence study
8 SCID Positive
11 Other

137 Randomized
119 From the community
18 From REACH

66 Assigned to intervention arm
64 Received intervention as assigned
2 Dropped out immediately
4 Dropped out
3 Lost to follow-up
2 Died

71 Assigned to referral arm
71 Received referral as assigned
3 Dropped out
3 Lost to follow-up
1 Died

55 Included in analysis
64 Included in analysis

Note. ART = antiretroviral therapy; BDH-II = Beck Depression Inventory-II; DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; REACH = Research in Access to Care for the Homeless; SCID = Structured Clinical Interview for DSM-IV. Prescreening with self-report of depression; administration of 21-item BDH-II; structured clinical assessment of candidates with a BDH-II score > 13 to confirm diagnosis of major depressive disorder, minor depressive disorder, or dystymia; and interview with study psychiatrist to confirm interest and psychiatric diagnosis, assess appropriateness of antidepressant medication treatment, and review coordination of care with potential participant’s primary care provider.

FIGURE 1—Stages of screening process for homeless and marginally housed participants with HIV and depression for controlled trial of directly observed fluoxetine treatment.
relating treatment and time effects linearly to the logit of the probabilities. We used the RANDOM statement and specified that the linear predictor contained an intercept term (τ0) and a normally distributed deviation (ɛij) from the mean. We also explored adding treatment-by-time interactions to the models for primary outcomes, because of the smaller sample size and lack of sufficient degrees of freedom.

We used the F test to assess whether the interaction terms were jointly statistically significant. For example, the models with binary dependent variables were represented mathematically as follows:

\[
\text{logit}(\pi_{ij}) = \alpha_i + X_{ij} \beta = \alpha + \varepsilon_{ij} + X_{ij} \beta,
\]

where \( \pi_{ij} \) denotes the outcome for participant \( i \) in month \( j \), \( X_{ij} \) denotes the design matrix for the explanatory variables for treatment assignment and time, \( \beta \) denotes the vector of regression coefficients for the explanatory variables, and the random intercepts \( \alpha_i \) are a linear combination of a grand mean (α) and a normally distributed deviation (ɛij) from the mean. We conducted all analyses in SAS version 9.2.

### RESULTS

We screened 1744 potential participants, 1555 from the community and 189 from the Research in Access to Care for the Homeless cohort (Figure 1). Nearly two thirds were found to be ineligible during the prescreening process; the most common reason was self-report of alternative diagnoses such as bipolar disorder (25.3%) and schizophrenia (16.5%). Of the 647 potential participants who underwent screening with the BDI-II, 471 (73%) had a BDI-II score higher than 13. These potential participants were eligible to undergo structured diagnostic assessment, and nearly two thirds did not meet DSM-IV criteria for inclusion. A study psychiatrist reviewed the remaining 190 potential participants: 137 were confirmed to be eligible and appropriate for the study and consented to participate in the randomized trial. Thus, the trial did not meet its enrollment goal.

Sixty-six participants were randomly assigned to the intervention arm and 71 to the referral arm. Participants recruited from the Research in Access to Care for the Homeless cohort differed from those recruited from the community on history of homelessness (94% vs 64%; \( P = .012 \)) and recent alcohol use (22% vs 51%; \( P = .024 \)) but were otherwise comparable. A slightly higher proportion of participants in the intervention arm than in the referral arm reported a history of ever using heroin (36.5% vs 24.3%; \( P = .125 \)), and a slightly smaller proportion were on ART at baseline (61.8% vs 69.4%; \( P = .07 \)), but their

### TABLE 1—Baseline Characteristics of Homeless and Marginally Housed Participants with HIV and Depression in Controlled Trial of Directly Observed Fluoxetine Treatment

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Weekly Fluoxetine Arm (n = 64)</th>
<th>Community Referral Arm (n = 71)</th>
<th>Test Statistic, P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recruited from REACH</td>
<td>10 (15.2)</td>
<td>8 (11.3)</td>
<td>0.45, .615</td>
</tr>
<tr>
<td>Age, y</td>
<td>44.2 ± 9.09</td>
<td>42.8 ± 8.44</td>
<td>-0.94, .348</td>
</tr>
<tr>
<td>Female</td>
<td>6 (9.1)</td>
<td>8 (11.3)</td>
<td>0.18, .781</td>
</tr>
<tr>
<td>White</td>
<td>32 (48.5)</td>
<td>36 (50.7)</td>
<td>0.07, .795</td>
</tr>
<tr>
<td>Ever homeless</td>
<td>45 (72.6)</td>
<td>45 (64.3)</td>
<td>1.04, .307</td>
</tr>
<tr>
<td>Illegal drug useb</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>52 (82.5)</td>
<td>60 (85.7)</td>
<td>0.25, .642</td>
</tr>
<tr>
<td>Past 30 d</td>
<td>10 (16.1)</td>
<td>13 (18.6)</td>
<td>0.14, .82</td>
</tr>
<tr>
<td>Crack cocaine use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>42 (66.7)</td>
<td>46 (65.7)</td>
<td>0.01, .908</td>
</tr>
<tr>
<td>Past 30 d</td>
<td>11 (18.0)</td>
<td>9 (12.9)</td>
<td>0.68, .47</td>
</tr>
<tr>
<td>Heroin use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>23 (36.5)</td>
<td>17 (24.3)</td>
<td>2.36, .125</td>
</tr>
<tr>
<td>Past 30 d</td>
<td>2 (3.3)</td>
<td>3 (4.3)</td>
<td>0.09, &gt; .999</td>
</tr>
<tr>
<td>Methamphetamine use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever</td>
<td>44 (69.8)</td>
<td>48 (66.6)</td>
<td>0.03, .874</td>
</tr>
<tr>
<td>Past 30 d</td>
<td>8 (12.9)</td>
<td>11 (15.7)</td>
<td>0.21, .805</td>
</tr>
<tr>
<td>Alcohol use: past 30 d</td>
<td>29 (46.0)</td>
<td>34 (48.6)</td>
<td>0.09, .77</td>
</tr>
<tr>
<td>DSM-IV diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major depression</td>
<td>50 (75.8)</td>
<td>51 (71.8)</td>
<td>0.33, .849</td>
</tr>
<tr>
<td>Minor depression</td>
<td>5 (7.6)</td>
<td>7 (9.9)</td>
<td></td>
</tr>
<tr>
<td>Dysthymia</td>
<td>11 (16.7)</td>
<td>13 (18.3)</td>
<td></td>
</tr>
<tr>
<td>CD4+ T-lymphocyte count, cells/mL</td>
<td>388.8 ± 269.86</td>
<td>408.9 ± 266.73</td>
<td>0.44, .663</td>
</tr>
<tr>
<td>CD4+ count nadir &lt; 350 cells/mL</td>
<td>34 (51.5)</td>
<td>36 (50.7)</td>
<td>0.01, .924</td>
</tr>
<tr>
<td>Receiving antiretroviral therapy</td>
<td>21 (61.8)</td>
<td>25 (69.4)</td>
<td>0.07, &gt; .999</td>
</tr>
</tbody>
</table>

Note. DSM-IV = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; REACH = Research in Access to Care for the Homeless.

*For continuous variables, comparisons used t tests; for categorical variables, \( \chi^2 \) tests.

bCrack cocaine, heroin, or methamphetamine use.
were otherwise statistically comparable (Table 1). Mean Ham-D scores at baseline (intervention participants = 17.7; referral participants = 17.9;  P=.787) indicated moderate levels of depression severity.

Medication Delivery
Participants randomized to the intervention arm were observed receiving 2233 (92.9%) of 2403 scheduled observed doses of daily fluoxetine and 3374 (90.9%) of 3713 scheduled observed doses of weekly fluoxetine, on weekdays. They also reported having taken 1215 (99.5%) of 1221 scheduled self-administered doses of daily fluoxetine on weekends. Among the 55 participants retained at 36 weeks in the intervention arm, 27 (49.1%) reported taking fluoxetine alone, 20 (36.4%) reported taking fluoxetine in combination with another type of psychotropic medication (most commonly mirtazapine [n = 9]), and 5 (9.1%) reported not taking any fluoxetine but reported taking other psychotropic medications (most commonly bupropion [n = 3]).

The mean dose of fluoxetine achieved was 18 milligrams (±4.4 mg) per day among participants still taking daily fluoxetine by the end of the study and 137 milligrams (±73.5 mg) per week among those taking weekly fluoxetine. Among the 64 participants retained at 36 weeks in the referral arm, 7 (10.9%) reported taking fluoxetine and 16 (25.0%) reported taking another type of psychotropic medication (most commonly bupropion [n = 5]).

Treatment Efficacy and Continuation
Participants in both study arms experienced improved mood, but mean depression severity was lower in the intervention arm at each assessment (Figure 2). We observed similar trends on the BDI-II and on response and remission (Table 2). The mixed-model analysis confirmed a statistically significant main effect of treatment on the Ham-D (b = −1.97; 95% confidence interval [CI] = −0.85, −3.08;  P<.001) and a treatment-by-time interaction (F = 6.25;  P=.014). We obtained similar results when we used the Ham-D to categorize participants as responders (adjusted odds ratio [AOR] = 2.40; 95% CI = 1.86, 3.10;  P<.001) and remitters (AOR = 2.97; 95% CI = 2.29, 3.87;  P<.001). In the mixed-model analysis for BDI-II score, we found a statistically significant main effect of treatment (b = −4.00; 95% CI = −1.65, −6.35;  P=.001) but not a treatment-by-time interaction (F = 1.74;  P= .19).

Use of the BDI-II to categorize participants also yielded similar results (responders, AOR = 2.01; 95% CI = 1.56, 2.59;  P<.001; remitters, AOR = 3.11; 95% CI = 2.36, 4.11;  P<.001).

By the end of the study, similar proportions of ART-eligible participants in each study arm were receiving ART (intervention, 73.1%; referral, 75.0%;  P=.999). The mixed-model analysis revealed no statistically significant effects of the intervention on ART uptake (AOR = 1.18; 95% CI = 0.83, 1.68;  P= .34). Participants in the intervention and referral arms had a similar average percentage of ART adherence (b = 0.05; 95% CI = −0.02, 0.12;  P=.2). We found no statistically significant difference in viral suppression (AOR = 1.04; 95% CI = 0.97, 1.12;  P=.23).

Fifty-five (83.3%) of 66 participants assigned to intervention completed the study: 2 died, 6 dropped out (including 2 who dropped out prior to baseline assessment and therefore did not contribute data to Table 1), and 3 were lost to follow-up. Sixty-four (90.1%) of 71 participants assigned to the referral arm completed the study: 1 died, 3 dropped out, and 3 were lost to follow-up. There were no suicides. Eight of 9 dropouts and all deaths occurred in the first 2 months.

DISCUSSION

We showed that directly observed treatment with fluoxetine improved depression symptom severity but not average ART adherence or probability of viral suppression in a group of homeless and marginally housed persons with comorbid HIV and depression. The observed benefit was substantial: at the 36-week follow-up, the average 3.5-point Ham-D treatment difference was equivalent to a Cohen’s d effect size greater than the mean effect size observed in short-term trials of serotonin-specific reuptake inhibitors (d = 0.40).39 Our estimated effect of fluoxetine treatment also compared favorably to the mean estimated effect observed in other classic long-term trials of serotonin-specific reuptake inhibitors (AOR = 1.66; 95% CI 1.12, 2.48).40

Our study added to the literature with 2 notable features. Our intervention specifically targeted homeless and marginally housed HIV-positive persons, a vulnerable population with a tremendous burden of unmet mental health
Persons with substance use disorders may have needs\(^{16-18}\) and for whom novel evidence to inform practice and policy is urgently needed.\(^{41}\) Persons with substance use disorders may have difficulty adhering to clinical trial protocols and are frequently excluded from antidepressant medication treatment trials conducted in outpatient settings.\(^{42}\) Homeless and marginally housed persons have high rates of substance use disorders\(^{3-5}\) and are therefore de facto excluded. Yet we obtained adherence rates comparable to those achieved in other studies,\(^{43}\) and our retention rate (85\%) over 9 months compared favorably with those observed in both long-term\(^{40}\) and short-term\(^{44}\) studies conducted among outpatients with fewer psychosocial comorbidities. Directly observed ART has been shown to improve ART adherence in marginalized populations with multiple psychosocial adherence barriers.\(^{45}\) Fluoxetine is uniquely suited for directly observed treatment and can easily be incorporated into substance use treatment or other structured counseling programs.

A second notable feature of our study is that it adds to the scant evidence\(^{40}\) on the long-term (≥ 6 months’ duration) treatment of depressed mood. Most of the data supporting this practice come from randomized withdrawal studies, which generalize poorly and can be problematic to interpret.\(^{46}\) The 2-arm parallel (classic) randomized controlled trial has been described as more closely approximating real-world effectiveness,\(^{40}\) but few such trials of antidepressant medications exist. One research team screened 2693 abstracts for a meta-analysis on serotonin-specific reuptake inhibitor treatment of major depression but discovered only 6 long-term, 2-arm parallel randomized controlled studies.\(^{40}\)

We observed no statistically significant improvement in secondary HIV outcomes among participants randomized to the intervention arm. Lack of statistical power likely contributed to our lack of a statistically significant estimated effect, because we were unable to recruit the planned number of participants. However, other studies have also had mixed findings. Similar to our analysis, a study of collaborative care for depression implemented in 3 Veterans Affairs HIV clinics showed improvements in depression and HIV symptom severity but not ART adherence.\(^{23}\) A marginal structural model analysis demonstrated an effect of depression treatment on virological outcomes,\(^{22}\) but the authors explicitly noted that the data did not permit them to determine what additional counseling and social support services may have been delivered along with antidepressant medication treatment. An intervention among HIV-positive persons that combined cognitive behavioral therapy and adherence counseling yielded improvements in both depression and ART adherence but not virological outcomes.\(^{21}\) In other fields of medicine, randomized trials of depression interventions have also failed to improve clinical outcomes such as glycemic control,\(^{47}\) suggesting that barriers other than depressed mood are interfering with adherence.\(^{46}\) Taken together, these studies suggest that improving ART adherence may require more than improvements in mood alone and that adherence counseling\(^{19}\) and mobilizing other forms of social support may be necessary to improve adherence.

### TABLE 2—Depression Outcomes at Baseline and Follow-Up Among Homeless and Marginally Housed Participants With HIV and Depression in Controlled Trial of Directly Observed Fluoxetine Treatment

<table>
<thead>
<tr>
<th>Measure</th>
<th>Weekly Fluoxetine Arm, Mean ± SD or No. (%)</th>
<th>Community Referral Arm, Mean ± SD or No. (%)</th>
<th>Test Statistic (b)</th>
<th>Mixed-Effects Estimate, (b) or AOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ham-D</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>17.7 ± 5.38</td>
<td>17.9 ± 4.95</td>
<td>0.27</td>
<td>-1.97 (-0.85, -3.08)</td>
</tr>
<tr>
<td>12 wk</td>
<td>7.9 ± 6.33</td>
<td>10.1 ± 4.55</td>
<td>2.16</td>
<td>0.33</td>
</tr>
<tr>
<td>24 wk</td>
<td>6.3 ± 5.10</td>
<td>9.0 ± 4.58</td>
<td>3.00</td>
<td>0.003</td>
</tr>
<tr>
<td>36 wk</td>
<td>4.3 ± 3.86</td>
<td>7.8 ± 5.68</td>
<td>4.02</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.40 (1.86, 3.10)</td>
</tr>
<tr>
<td>12 wk</td>
<td>37 (62.7)</td>
<td>25 (36.8)</td>
<td>8.51</td>
<td>0.004</td>
</tr>
<tr>
<td>24 wk</td>
<td>35 (64.8)</td>
<td>30 (44.8)</td>
<td>4.83</td>
<td>0.028</td>
</tr>
<tr>
<td>36 wk</td>
<td>46 (82.1)</td>
<td>37 (56.9)</td>
<td>8.88</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Remission (Ham-D ≤ 7)</strong></td>
<td></td>
<td></td>
<td></td>
<td>2.97 (2.29, 3.87)</td>
</tr>
<tr>
<td>Baseline</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>12 wk</td>
<td>29 (50.9)</td>
<td>21 (30.9)</td>
<td>5.17</td>
<td>0.023</td>
</tr>
<tr>
<td>24 wk</td>
<td>34 (65.4)</td>
<td>27 (40.3)</td>
<td>7.37</td>
<td>0.007</td>
</tr>
<tr>
<td>36 wk</td>
<td>48 (88.9)</td>
<td>35 (53.9)</td>
<td>17.17</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>BDI-II</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29.2 ± 8.71</td>
<td>32.4 ± 9.97</td>
<td>2.12</td>
<td>-4.00 (-1.65, -6.35)</td>
</tr>
<tr>
<td>12 wk</td>
<td>14.4 ± 10.78</td>
<td>20.0 ± 10.66</td>
<td>2.91</td>
<td>0.004</td>
</tr>
<tr>
<td>24 wk</td>
<td>11.3 ± 10.28</td>
<td>17.3 ± 10.98</td>
<td>2.98</td>
<td>0.004</td>
</tr>
<tr>
<td>36 wk</td>
<td>8.2 ± 8.76</td>
<td>15.0 ± 9.85</td>
<td>3.94</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
<td></td>
<td>2.01 (1.56, 2.59)</td>
</tr>
<tr>
<td>Baseline</td>
<td>30 (52.6)</td>
<td>27 (39.7)</td>
<td>2.09</td>
<td>0.148</td>
</tr>
<tr>
<td>12 wk</td>
<td>37 (72.6)</td>
<td>32 (50.0)</td>
<td>6.01</td>
<td>0.014</td>
</tr>
<tr>
<td>24 wk</td>
<td>43 (78.2)</td>
<td>33 (51.6)</td>
<td>9.08</td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Remission (BDI-II ≤ 8)</strong></td>
<td></td>
<td></td>
<td></td>
<td>3.12 (2.36, 4.11)</td>
</tr>
<tr>
<td>Baseline</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>12 wk</td>
<td>20 (35.1)</td>
<td>12 (17.7)</td>
<td>4.95</td>
<td>0.03</td>
</tr>
<tr>
<td>24 wk</td>
<td>26 (51.0)</td>
<td>18 (28.1)</td>
<td>6.28</td>
<td>0.01</td>
</tr>
<tr>
<td>36 wk</td>
<td>40 (72.7)</td>
<td>21 (32.8)</td>
<td>18.86</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Note. AOR = adjusted odds ratio; BDI-II = Beck Depression Inventory-II; CI = confidence interval; HAM-D = Hamilton Rating Scale for Depression; NA = not applicable.

\(^b\)For continuous variables, comparisons used \(t\) tests; for categorical variables, \(\chi^2\) tests.

\(^b\)Derived from generalized linear mixed models relating treatment and time effects either linearly to the dependent variable (for depression scores) or linearly to the logit of the probabilities (for response and remission).
Limitations

Our study lacked a placebo control group. Even though use of placebos is common in psychopharmacological research, depression is known to adversely affect HIV outcomes and is treatable with medication.\textsuperscript{13,15} Therefore, we considered offering a 9-month placebo to be unethical. Intervention arm participants had intensive clinical contact with study staff, which itself may be therapeutic.\textsuperscript{52} However, participants in the referral arm also had significant contact with study staff, which would tend to mitigate this effect. Our positive finding on the primary outcome is all the more notable in light of the documented crossover contamination by referral arm participants who obtained mental health treatment outside the study.

The recruitment phase lasted more than 5 years because of the large screening sample needed to identify eligible participants. Although the refusal rate was low (5.6%), the large proportion of potential participants found to be ineligible may have compromised our ability to generalize the findings to all HIV-positive homeless and marginally housed adults with symptoms of depression. We were unable to formally compare the characteristics of potential participants who were screened for eligibility but declined to participate with those of study participants. However, our study sample was broadly similar to those obtained by systematic sampling.\textsuperscript{4,16,28,53}

Notably, up to 12% of potential participants with symptoms of depression who underwent structured diagnostic assessment may have instead met diagnostic criteria for bipolar disorder, a proportion similar to the findings of a previous study.\textsuperscript{54} Our results highlight the importance of carefully assessing persons presenting with depressive symptoms, so as to avoid exposing patients with unrecognized bipolarity to antidepressant medications that may be ineffective or destabilizing.\textsuperscript{55}

Conclusions

Our randomized controlled trial demonstrated that directly observed treatment with weekly fluoxetine resulted in improved mood among a cohort of homeless and marginally housed persons living with HIV. The statistically and clinically significant effects on mood that we observed are especially notable because they occurred in a population with ongoing substance abuse problems, homelessness, and other psychosocial comorbidities. Directly observed weekly fluoxetine may be an effective strategy to treat depression and potentially improve HIV treatment outcomes in individuals who might otherwise be considered poor candidates for treatment because of multiple barriers to treatment adherence.

About the Authors

At the time of the study, Alexander C. Tsai was with the Langley Porter Psychiatric Institute, University of California, San Francisco. Dan H. Karasic, James L. Sorensen, and James W. Dilley were with the Department of Psychiatry, and Guendolyn P. Hammer, Edwin D. Charlebois, Kathy Ragland, Andrew R. Moss, and David R. Bangsberg were with the Epidemiology and Prevention Interventions Center, Division of Infectious Diseases, San Francisco General Hospital, University of California, San Francisco.

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This article was accepted August 16, 2011.

Contributors


Acknowledgments

This study was funded by the National Institute of Mental Health (NIMH; grants R01 MH 63011-01A1 and K24 MH-087227 to D. R. Bangsberg). The Research in Access to Care for the Homeless cohort, from whom some of the study participants were drawn, was funded by NIMH (grant R01 MH-054907 to D. R. Bangsberg). A. C. Tsai received support from the Robert Wood Johnson Foundation Health and Society Scholars Program. Roche donated HIV RNA kits. Study doses of Prozac Weekly were donated by Eli Lilly from 2002 through 2005.

Early screening data from this research were presented in part at the 15th International AIDS Conference, Bangkok, Thailand, July 11–16, 2004, and at the American Psychiatric Association Annual Meeting, San Diego, CA, May 23, 2007. Outcomes data were presented at the International Association of Physicians in AIDS Care International HIV Treatment Adherence Conference, Miami, FL, April 6, 2009.

We thank Judith Rabkin for critical input on the design of the study and the interpretation of the findings, Steve Safran for helpful comments, the participants who made this study possible by sharing their experiences, and the staff who conducted the interviews.

Note. The sponsors had no role in study design, data collection, or interpretation of the findings. The findings and conclusions are solely the responsibility of the authors and do not necessarily represent the official views of the sponsors.

Human Participant Protection

The University of California, San Francisco committee on human research approved all study procedures. Study participants provided informed consent separately for screening and the subsequent randomized controlled trial. Potential participants identified with a BDI-II higher than 13 who declined to participate were offered referral to an outside agency for further evaluation.

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