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Does substance use compromise depression treatment in persons with HIV? Findings from a randomized controlled trial

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Abstract

Depression and substance use are significant obstacles to effective HIV care. Using data derived from a randomized controlled trial of persons with HIV who are homeless or marginally housed, this study assesses the utility of antidepressant treatment among persons with HIV, depression, and active substance use. Participants were diagnosed with depressive disorders and randomly assigned to receive directly observed therapy with fluoxetine or a referral to community mental health treatment. Assessments, conducted at baseline and every three months over a nine-month period, included the Hamilton Rating Scale for Depression, the Beck Depression Inventory II, and self-report of alcohol, crack, cocaine, heroin, or methamphetamine use in the past 90 days. To investigate the effect of antidepressant treatment in the setting of active substance use, the authors fit mixed-effects linear regression models to estimate the effect of directly observed fluoxetine on depressive symptom severity after stratifying by any alcohol use or any illicit drug use. To investigate whether alcohol use or illicit drug use moderated the antidepressant treatment response, the authors examined the interaction terms. The effect of directly observed fluoxetine treatment on depression symptom severity was statistically significant irrespective of alcohol use status. When stratified by illicit drug use status, the effect of directly observed fluoxetine treatment on depression symptom severity was statistically significant only among persons who did not use illicit drugs. The interaction terms were not statistically significant. This study found a benefit of antidepressant treatment in persons with HIV, depression, and alcohol use. In addition, this study found no evidence that either alcohol use or illicit drug use moderates the antidepressant treatment response. Altogether, these findings support the use of antidepressant medication in this

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population. The public health impact of research in this area is significant given the known adverse effects of depression on HIV-related health outcomes.

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Keywords

Depression; substance abuse; HIV; syndemics; directly observed therapy

INTRODUCTION

The majority of persons with comorbid depressive and substance use disorders do not get the care that they need (Watkins, Burnam, Kung, & Paddock, 2001). One factor contributing to observed disparities is thought to be clinician concern that active substance use interferes with antidepressant treatment (Davis et al., 2012; Nunes & Levin, 2004). Additionally, some clinicians may attribute mood symptoms to a substance-induced mood disorder and thus defer treatment with an antidepressant (Schuckit et al., 1997). Watkins and colleagues hypothesize that other “attitudinal,” systemic, and economic factors may also explain the lack of care available to persons with “dual diagnoses” (Watkins et al., 2001, p. 1062).

The extent to which substance use moderates (i.e., is an effect modifier for) the antidepressant treatment response is an important clinical issue, especially for persons with HIV. Depressive and substance use disorders are highly prevalent in populations with HIV (Bing et al., 2001) and highly relevant to HIV care (Adams, Zacharia, Masters, Coffey, & Catalan, 2016). They are significantly disabling conditions associated with decreased healthcare utilization including initiation of antiretroviral therapy, poorer adherence to antiretroviral therapy, worse immune status, lower rates of viral suppression, and greater AIDS-related morbidity and mortality (Azar, Springer, Meyer, & Altice, 2010; Carrico et al., 2011; Cook et al., 2008; Durvasula & Miller, 2014; Lucas, Gebo, Chaisson, & Moore, 2002; Tegger et al., 2008; Vos et al., 2012).

In some persons (i.e., men who have sex with men), depression and substance use are considered co-epidemics or “syndemics” because they are associated with HIV-risk behaviour and vulnerability to HIV (Stall, Coulter, Friedman, & Plankey, 2015). Exposure to a greater number of syndemics confers greater risk of HIV infection and poorer HIV-related treatment outcomes such as adherence to antiretroviral therapy and viral suppression (Blashill et al., 2015; Friedman et al., 2015; Mimiaga et al., 2015). Antidepressant treatment has been shown to improve depressive symptomatology among persons with HIV (Rabkin, Wagner, & Rabkin, 1999; Tsai, Karasic, et al., 2013; Zisook et al., 1998), although evidence that antidepressant treatment improves HIV outcomes is mixed (Horberg et al., 2008; Tsai et al., 2010; Tsai, Karasic, et al., 2013; Tsai, Mimiaga, et al., 2013).

Treatment of depression in persons with HIV is often complicated by the patient’s continued substance use (Durvasula & Miller, 2014). To our knowledge, no clinical trial has reported specifically on the antidepressant treatment response among persons with HIV who are actively using alcohol and/or illicit drugs. Many clinical trials of depression treatment

exclude persons with active alcohol or illicit drug use (Pettinati, O'Brien, & Dundon, 2013; Zimmerman, Mattia, & Posternak, 2002). Meta-analyses of the few available trials among general population samples have yielded mixed results (Iovieno, Tedeschini, Bentley, Evins, & Papakostas, 2011; Nunes & Levin, 2004; Torrens, Fonseca, Mateu, & Farré, 2005). The public health impact of research in this area is particularly significant for HIV given that 1) persons with HIV are a vulnerable population, 2) rates of comorbid depression and substance use are high among persons with HIV, and 3) treatment of depression in the context of exposure to multiple syndemics could, in theory, improve HIV-related treatment outcomes. To address this gap in the literature and explore the extent to which active substance use moderates the depression treatment response, we conducted a secondary analysis of data from a randomized controlled trial of antidepressant medication treatment for persons with HIV who are homeless or marginally housed.

METHODS

Subjects

Study methods were reported in detail elsewhere (Tsai, Karasic, et al., 2013) and are briefly summarized here. The study was a randomized controlled trial of directly observed antidepressant medication treatment versus referral for community-based mental health services. Recruitment took place between July 2002 and February 2008 at homeless shelters, free lunch programs, low-income single-room-occupancy hotels, public HIV clinics, and social service agencies. Some participants were recruited from an observational, prospective cohort of homeless and marginally housed persons with HIV (Research in Access to Care for the Homeless) (Robertson et al., 2004; Tsai et al., 2010; Zolopa et al., 1994). At study entry, 67% (90/135) of participants had a history of or current homelessness and all participants were either homeless or marginally housed. The study included English-speaking men and women at least 18 years of age who were infected with HIV, were living in San Francisco, CA, met DSM-IV criteria for Major Depressive Disorder, Minor Depressive Disorder, or Dysthymia using the Structured Clinical Interview for the DSM-IV-TR, and had a score of 13 or greater on the 21-item Beck Depression Inventory-II (BDI). Persons who used alcohol and/or illicit drugs were *not* excluded from the study. Persons were excluded if they were taking psychiatric medication within 3 months prior to entering the study or receiving psychiatric care within 6 months prior to entering the study, had a diagnosis of or symptoms consistent with bipolar disorder, a psychotic disorder, or dementia, or had such severe substance use or suicidal ideation that they required immediate residential or inpatient treatment. Aspects of the study design relevant to the current analysis are summarized below.

Study design

Participants were randomized to one of two groups. Participants were not blind to group assignment. Participants in the treatment group received daily fluoxetine for the first two weeks (directly observed on weekdays and self-administered on weekends) at a dose of 20 mg per day. This was followed by once-weekly directly observed fluoxetine for 22 weeks, followed by self-administered once-weekly fluoxetine for another three months. The starting dose of the once-weekly fluoxetine was 90 mg per week. For participants who only partly or

did not respond to this dose, the dose of once-weekly fluoxetine was increased to 180 mg per week by the study psychiatrist who met with the participants at predetermined intervals to assess medication tolerability and treatment response (Tsai, Karasic, et al., 2013). Control group participants were referred to a nearby community clinic for psychiatric care and interviewed along the same schedule over a 9-month period. Among completers of the study, 36% (23/64) reported having been prescribed antidepressant medication during the 9-month study period. These participants were included in the current analysis. Eighty-three percent (55/66) of treatment group participants and 90% (64/71) of control group participants completed the study.

Assessments

Participants were evaluated for depressive symptom severity with the 17-item Hamilton Rating Scale for Depression (HAMD) and BDI at baseline and monthly over the 9-month period of the study. Self-report of any alcohol, crack, cocaine, heroin, or methamphetamine use in the past 90 days was collected at baseline and every 3 months over the 9-month period. Mental health assessors were blinded to each participant's group assignment.

Statistical analysis

Mixed-effects linear regression was used to assess the effect of alcohol or any illicit drug use within the last 90 days on changes in HAMD scores or BDI scores collected at baseline and the 3-month, 6-month, and 9-month visits. Across the four time points, participants who reported alcohol use in the treatment group were compared with those in the control group, participants who denied alcohol or any illicit drug use in the treatment group were compared with those in the control group, and the interaction between directly observed fluoxetine and alcohol use was analyzed. A similar analysis was conducted for illicit drug use by grouping participants who reported any crack, cocaine, heroin, or methamphetamine use into a single, "any illicit drug use" variable. Mixed-effects Poisson regression was used to assess the influence of directly observed fluoxetine treatment on the number of days of alcohol or any illicit drug use. All analyses were conducted among only those who completed the study. Stata statistical software (version 13, StataCorp LP, College Station, Tex.) was used for all analyses.

Human subjects protection

All participants provided informed consent for the study. Participants received \$25 per week for completing weekly study visits. The study was approved by the University of California San Francisco Committee on Human Research.

RESULTS

Participant characteristics are summarized in Table 1. Participants were generally middle-aged, male, and homeless. Mean scores on the HAMD and BDI suggest that the average participant had moderate to severe depression.

The effect of directly observed fluoxetine treatment on depression symptom severity relative to the effect of community referral was statistically significant irrespective of alcohol use (Table 2). Relative to the baseline standard deviation of the HAMD, the effect size was

1.76/5.4 = 0.33 for participants who used alcohol and 2.34/5.4 = 0.43 for participants who did not use alcohol. For the BDI, the effect sizes were even larger: 3.95/9.7 = 0.41 for participants who did use alcohol and 6.45/9.7 = 0.66 for participants who did not use alcohol.

When stratified by any illicit drug use status, the effect of directly observed fluoxetine treatment on depression symptom severity relative to the effect of community referral was statistically significant only among participants who did not use any illicit drugs. Whereas the observed treatment responses were generally smaller among those who did report alcohol or any illicit drug use than those who did not, the interaction terms were not statistically significant (P-values ranged from 0.59–0.62 for the HAMD and 0.33–0.69 for the BDI).

Directly observed fluoxetine was not associated with a statistically significant reduction in alcohol or illicit drug use days among participants. The incident rate ratio for alcohol use days was 0.56 (95% CI: 0.20 to 1.58; $p = .276$). The incident rate ratio for illicit drug use days was 0.66 (95% CI: 0.17 to 2.60; $p = .548$).

DISCUSSION

In this secondary analysis of data from a randomized controlled trial of directly observed antidepressant medication treatment for persons with comorbid HIV and depression who were homeless and marginally housed, we found that antidepressant treatment significantly reduced depression symptom severity irrespective of comorbid active alcohol use. Effect sizes were small to medium depending on the depression scale used. Although the estimated antidepressant effects were greater among participants who did not use alcohol compared to those who did, the interaction term was not statistically significant. Thus, we found evidence of a benefit to antidepressant treatment and no evidence of a moderating effect of alcohol use on the antidepressant treatment response in persons with HIV, depressive disorders, and active alcohol use.

Among participants with and without illicit drug use, directly observed fluoxetine treatment significantly reduced depression symptom severity only among persons who did not use illicit drugs. The estimated antidepressant effects were greater among participants who did not use illicit drugs compared to those who did, but the interaction term was not statistically significant. Although we found no significant reduction in depressive symptoms with directly observed fluoxetine among persons with HIV, depressive disorders, and active illicit drug use, we also found no evidence that illicit drug use rendered antidepressants less effective in this population. Alongside prior research among persons with HIV, depression, and homelessness (Tsai et al., 2010; Tsai, Karasic, et al., 2013) and research conducted among persons with comorbid depression and substance use in a variety of general population settings (Davis et al., 2012; Iovieno et al., 2011; Nunes & Levin, 2004), our study supports the use of antidepressants in individuals with HIV, depressive disorders, and active alcohol and/or illicit drug use.

The use of antidepressants to reduce substance use has been the subject of recent study, and current evidence is mixed (Hobbs, Kushner, Lee, Reardon, & Maurer, 2011; Nunes & Levin, 2004; Oliveto et al., 2012; Pettinati et al., 2013; Shoptaw et al., 2006). To our knowledge, there has been no prior investigation of this topic in a population with HIV. In this study, antidepressant treatment was not associated with a significant reduction in alcohol or illicit drug use days.

Consistent with broader samples of persons who are homeless and those with HIV (Bing et al., 2001; Fazel et al., 2008; Galvan et al., 2002), it is notable that a substantial portion of the study participants reported alcohol and illicit drug use during the study. In a general household sample from the United States, 68% of persons with substance use disorders and depressive or anxiety disorders did not receive appropriate treatment during the preceding 12-month period (Watkins et al., 2001). Our participants, like other persons with HIV and persons with homelessness (Burnam et al., 2001; Koegel, Sullivan, Burnam, Morton, & Wenzel, 1999), face similar treatment gaps. Our findings support efforts to provide access to antidepressant treatment to persons with comorbid depressive and substance use disorders and are consistent with recommendations that antidepressant treatment should be used in conjunction with evidence-based therapies for substance use (Nunes & Levin, 2004; Watkins et al., 2001).

In addition to general limitations of the study, including the non-blinding of participants (Tsai, Karasic, et al., 2013), this analysis has several other limitations. First, the original study was not powered to detect differences in depression treatment based on alcohol or illicit drug use status. With a larger study, it is possible that we could have generated more definitive conclusions as to the extent to which active substance use may interfere with antidepressant treatment response. Second, creating a composite variable for “any illicit drug use” did not permit us to evaluate the moderating influence of specific drugs on the antidepressant treatment response. Third, because the trial was focused on depression rather than substance use, we know that study participants met DSM-IV criteria for major depressive disorder, minor depressive disorder, or dysthymia; but we did not assess the extent to which substance use was associated with clinically significant impairment and did not assess whether study participants met DSM-IV criteria for substance use disorders. The study also did not track patterns of substance use, such as the phenomenon of “weekending” (or stopping antiretrovirals when planning to use alcohol or bingeing on alcohol), which may uniquely contribute to poorer adherence and be amenable to interventions such as harm reduction strategies (Kenya et al., 2013). Fourth, drug testing was not available to supplement self-report data, and it is possible that our participants underreported their use of alcohol or illicit drug use. Such underreporting, however, would have biased our estimates of the antidepressant treatment response among active users toward the null. Finally, information about cannabis use was not collected.

Despite these limitations, our study supports antidepressant treatment for persons with HIV who have active substance use and comorbid depressive disorders. However, it is likely that both the antidepressant and the method of delivery (i.e., directly observed therapy) contributed to the positive outcomes of the study (Tsai, Karasic, et al., 2013). Research has documented that substance use is a barrier to antidepressant treatment adherence (Akincigil

et al., 2007) and that homelessness, substance use, and depression are barriers to HIV treatment adherence (Moss et al., 2004; Tsai et al., 2010; Tucker, Burnam, Sherbourne, Kung, & Gifford, 2003). In the setting of these barriers, directly observed fluoxetine therapy was an innovative way to deliver depression care to this marginalized population.

Studies with larger sample sizes, in multiple different populations of persons with HIV (e.g., men who have sex with men, persons who inject drugs, adolescents, etc.), and in different settings (including resource-limited settings) are needed to address important questions raised by this work. For example, what is the value (e.g., relief from disability, improved quality of life, cost effectiveness) of directly observed antidepressant treatment in persons with comorbid depression and substance use compared to more traditional health care models? Are other models, for example those using peers or other non-specialized health workers, as effective among persons with comorbid depression and substance use in treating depression, engaging persons in mental health care, and promoting adherence to antidepressant therapy? In light of the growing attention to syndemics, are single component interventions (such as antidepressant treatment alone) or multicomponent treatments required to make a meaningful difference in improving health outcomes when multiple comorbidities are present?

Depression, alcohol, and illicit drug use are associated with other significant medical comorbidities (Prince et al., 2007). Whereas mental health is an important outcome in its own right, a reduction in HIV-related and other medical comorbidities, such as Hepatitis C, as a result of mental health and substance use treatment among persons with HIV would reinforce the need to provide these services alongside traditional medical services. Given prior work in this area and in increasing recognition of the impact of syndemics on treatment outcomes, investment in effective means for depression care delivery among active substance users may alleviate suffering and disability from depression and also improve other health outcomes.

CONCLUSIONS

This is the first study to investigate the effect of antidepressant therapy on depression symptom severity among persons with HIV and active substance use who are homeless. We found no evidence of a significant moderating effect of active substance use on the antidepressant treatment response, supporting the use of antidepressant medication in this population. As research continues to demonstrate the negative impact of depression and substance use on HIV treatment outcomes, our findings suggest that antidepressant treatment among persons with HIV, depression, and active substance use may also have a positive impact on public health.

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Table 1

Participant characteristics at baseline

Characteristic	Treatment arm	Control arm
Age * (Mean (SD))	44.2 (9.09)	42.8 (8.44)
Female * (N (%))	6 (9.1%)	8 (11.3%)
Ever homeless * (N (%))	45 (72.6%)	45 (64.3%)
CD4 count * (Mean (SD))	389 (270)	409 (267)
Receiving antiretroviral therapy * (N (%))	21 (32%)	25 (35%)
Hamilton Rating Scale for Depression score * (Mean (SD))	17.7 (5.38)	17.9 (4.95)
Beck Depression Inventory score * (Mean (SD))	29.2 (8.71)	32.4 (9.97)
Any alcohol use, past 90 days (N (%))	33 (50%)	38 (54%)
Any illicit drug use, past 90 days (N (%))	18 (27%)	22 (31%)

* Previously reported by Tsai and colleagues (Tsai, Karasic, et al., 2013)

Effect of directly observed fluoxetine (treatment arm) versus community referral (control arm) on depressive symptoms

Table 2

Stratification group	Number in treatment arm/Number in control arm	Hamilton Rating Scale for Depression		Beck Depression Inventory	
		Effect of treatment* (95% CI)	p	Effect of treatment* (95% CI)	p
Alcohol users	31/38	-1.76 (-3.42 to -0.10)	.038	-3.95 (-7.36 to -0.54)	.023
Alcohol nonusers	35/33	-2.34 (-4.10 to -0.58)	.009	-6.45 (-10.1 to -2.78)	.001
[Alcohol use x treatment interaction]		-0.62 (-3.03 to 1.80)	.618	-2.49 (-7.49 to 2.52)	.330
Illicit drug users	17/21	-1.51 (-3.47 to 0.46)	.133	-4.32 (-9.48 to 0.81)	.099
Illicit drug nonusers	49/50	-2.22 (-3.72 to -0.73)	.004	-5.47 (-8.31 to -2.62)	<.001
[Illicit drug use x treatment interaction]		-0.74 (-3.41 to 1.94)	.591	-1.15 (-6.72 to 4.41)	.685

* Negative values represent greater reductions in depressive symptom scores in the directly observed fluoxetine group