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Medication-Taking Self-Efficacy and Medication Adherence Among HIV-Infected Cocaine Users

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Abstract

This prospective, observational study tested the ability of self-efficacy for taking antiretroviral medications to predict medication adherence among current and former cocaine and heroin users. Electronic monitors to record bottle openings and self-report measures of medication adherence were used. The sample included 99 men and women who were interviewed at 4-week intervals for 6 months. Mixed effects regression models to test the relationship of substance use and self-efficacy for medication-taking with percent of self-report adherence, dose adherence, number of days adherent, and adherence to medication schedule at each study visit showed that medication-taking self-efficacy was significantly related to all measures of adherence measures declined over the study period whereas self-report adherence did not. Findings suggest that self-efficacy can have a sustained effect on adherence to doses but may not be an influential predictor of adherence to their correct timing.

Keywords

adherence; antiretroviral medication; HIV; self-efficacy; substance use

It is well established that high levels of adherence to antiretroviral therapy (ART) are needed to achieve optimal clinical outcomes. Low adherence can lead to development of viral resistance, particularly for drug classes with low potency and low barriers for genetic resistance (Gardner, Burman, Steiner, Anderson, & Bangsberg, 2009; Gardner et al., 2010). A number of factors have been associated with suboptimal medication adherence in HIV with substance use being a primary target. Substance abuse and HIV have been inextricably linked since the beginning of the epidemic with substance abuse/dependence contributing a

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substantial effect on the spread of the disease (Centers for Disease Control and Prevention [CDC], 2012) and on its treatment (Cofrancesco et al., 2008; Lert & Kazatchkine, 2007). Moreover, current substance use, rather than former use, has been shown to explain the relationship of substance use to adherence (Hicks et al., 2007), suggesting that former users may not have greater adherence challenges associated with drug or alcohol use than those who have never used. It has also been demonstrated that, in addition to indicators of substance use, other psychosocial factors appear to further explain potential causes of suboptimal adherence in HIV-infected substance users. Arnsten and colleagues (2007) reported that greater self-efficacy for taking ART along with other psychosocial characteristics such as positive attitudes toward medications and fewer depressive symptoms was significantly related to a self-reported adherence rate greater than or equal to 90%. They also showed that reduced self-efficacy for ART taking indicated a greater chance of making medication errors defined as dosing discrepant from the prescribed (Arnsten et al., 2007).

Measures of medication taking in the Arnsten et al. study relied on participant self-report, the reliability of which may have been limited by recall memory challenges associated with HIV and/or substance use. Although electronic monitoring of medication adherence also has its limitations (e.g., inability to account for removal of multiple doses at each bottle opening), this method can circumvent the problems posed by self-report. Electronic monitoring can also add to our understanding of adherence by providing measures of schedule adherence. To our knowledge, there has been little focus to understand the association of substance use and self-efficacy for taking ART, especially with respect to the different elements of medication adherence predictors among at-risk substance users across multiple time points is essential. The purpose of our study therefore was to investigate the relationship of current substance use and self-efficacy for taking ART medications in HIV-infected men and women with a history of chemical dependence on heroin or cocaine and to test whether associations differed by type of adherence across time.

Methods

Participants and Measures

Participants in the study were recruited from HIV care clinics in South Florida from 2005 to 2009 as part of a larger study to evaluate neurocognitive sequelae of medication adherence. The target population was men and women with severe heroin or cocaine use histories who had used these drugs at least once in the previous 12 months. Enrollment for this study occurred in two screening phases. The first phase of screening (pre-screening) included a brief questionnaire to assess for the following exclusion/inclusion criteria: (a) use of heroin or cocaine in the previous 12 months, (b) no history of schizophrenia or bipolar disorder, (c) no history of loss of consciousness for longer than 30 minutes, and (d) ability to communicate in English. A total of 365 individuals completed prescreening; 171 of those met pre-screening criteria and were given a follow-up appointment for a formal screening interview. Of those who did not qualify at pre-screening, most did not qualify due to a lack of heroin or cocaine use in the previous 12 months.

An additional inclusion criterion was to meet diagnostic criteria for dependence on heroin or cocaine, either currently or at any point during one's lifetime. This was assessed during the screening interview using the substance use modules of the Structured Clinical Interview for DSM-IV Diagnosis (First, Spitzer, Gibbon, & Williams, 1995). The Addiction Severity Index (McLellan et al., 1992) was also completed during the screening interview to provide self-report data on alcohol and drug use (broken down by each type of drug used) in the previous 30 days as well as complications with employment, relationships, and other issues resulting from drug use. Of the 171 individuals who were given an appointment for the

screening interview, 139 actually completed the screening interview. Thirty-two individuals qualified but did not complete the interview; numerous attempts to contact the 32 individuals were made; however, many were unreachable or indicated they would attend the screening interview but did not. Out of 139 individuals who completed the screening interview, 37 did not meet diagnostic criteria for heroin or cocaine dependence and were ineligible to enroll in the full study. A total of 102 HIV-infected men and women with a diagnosis of heroin or cocaine dependence and who were prescribed ART (verified via medical records) completed baseline study procedures. Data analysis was performed on data from a total of 99 HIV-infected participants who had at least one follow-up assessment over 6 months (3 did not complete any follow-up assessments). The institutional review board of the University of Miami approved the study and all participants gave voluntary informed consent at each phase of the recruitment and enrollment process.

At baseline, in addition to information on demographic characteristics, participants completed the Self-Efficacy for Taking Antiretroviral Medication Scale (Purcell et al., 2004), which measures one's confidence to take medicines under particular circumstances (e.g., *when you are not having any symptoms of illness, when the medicines have been making you feel bad, on weekends and holidays*). The self-efficacy scale has 12 items rated on a 4-point scale from *very unsure* to *very sure* and a possible range of scores from 0 to 36, with higher scores reflecting greater self-efficacy. Reliability analyses showed an alpha of . 92.

Adherence was measured using an electronic monitoring device (Medication Event Monitoring System [MEMS], Aprex, Union City, CA). This medication bottle cap contains microelectronics that record the time and event when the bottle is opened and stores the information. The Track Cap fits on a standard pharmacy bottle with 38 mm, 400 thread closures. The Track Cap was placed on only one of the medication bottles for each participant (a protease inhibitor or on a non-nucleoside reverse transcriptase inhibitor if a protease inhibitor was not part of the regimen). MEMS measures of adherence for one ART medication have been shown to reliably predict adherence with other ART medications (McNabb, Nicolau, Stoner, & Ross, 2003; Wilson, Tchetgen, & Spiegelman, 2001). Participants were trained on appropriate use of the cap and given monetary incentives at the completion of the study for return of the cap. For ethical reasons, participants were not prohibited from using pillboxes, but were strongly encouraged to use such boxes for medicines other than the one using the MEMs cap. Because MEMs-monitored adherence cannot account for "pocket dosing" (placing pills in one's pocket/purse for ingestion at a later time), at each assessment participants were asked if they pocket dosed. If so, that months' adherence measure was recalculated based on the number of reported pocket doses. Cap openings that exceeded the prescribed doses were not included in the total.

Self-report adherence to ART medications was assessed by an interviewer-administered questionnaire for 1 week preceding the study visit (Arnsten et al., 2001). Adherence was defined using percent of doses taken during the previous 7 days.

Participants were followed for a period of 6 months post-baseline. Assessments were conducted every 4 weeks during the 6-month study period during which time medication adherence (MEMs and self-report) and self-reported alcohol and drug use during each prior 4-week period were collected.

Statistical Analysis

Mean and standard deviation (*SD*) were used to report the distribution of age and selfefficacy score; percentage was used to describe the categorical socio-demographic variables, including gender, race/ethnicity (Hispanic, non-Hispanic White, non-Hispanic Black),

sexual orientation (homosexual, heterosexual, bisexual/unknown), education (less than high school, completed high school, more than high school), current residence (own/parent's house, someone else's home, homeless/street/vehicle), personal income in the previous year (< \$3,500, \$3,500–7,000, > \$7,000), disability (*yes, no*), and homeless (*yes, no*).

Although the study targeted individuals who had used either heroin or cocaine in the previous 12 months, no participants reported use of heroin during the study period. Nearly 30% of the sample reported cocaine use during the study, 44% reported using alcohol, and 15% reported use of marijuana. Correlation analyses showed that cocaine and alcohol use were associated with medication adherence measures (p < 0.05) whereas marijuana use was unassociated. Therefore, use of alcohol or cocaine at any point during the study period (*yes, no*) was included as a covariate. Self-report adherence was calculated as the percent correct doses taken for the prior 7 days across all medications; in addition, three measures of medication adherence derived from the electronic monitors were included: (a) percent dose adherence, (b) percent days adherent, and (c) percent schedule adherence (doses taken on time).

Mixed effects regression models were employed to identify significant predictors of adherence to ART based on the longitudinal assessment of adherence at six time points. An autoregressive covariance structure was assumed. All analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Characteristics

Table 1 summarizes the sample characteristics. Of 99 HIV-infected patients, the mean age was 44 years (SD = 7 years), 74% reported being heterosexual, 64% were male, 85% were non-Hispanic Black, 47% did not complete high school, 37% had personal incomes in the previous year less than \$3,500, 55% were on disability, and 56% were homeless. The mean self-efficacy score was 26 (SD = 7).

Adherence Assessments

Table 2 reports the unadjusted mean adherence and the standard error (*SE*) by follow-up time. For self-reported adherence, the means were similar over 6 months, whereas there was a reduction from 76.7 at month 1 to 66.5 at month 6 for percent of MEMs percentage dose adherent, from 66.4 at month 1 to 57.3 at month 6 for percentage days adherent, and from 58.6 at month 1 to 46.1 at month 6 for percentage schedule adherent.

Mixed-Model Regression Analysis

Mixed-model analysis was conducted to identify socio-demographic predictors associated with adherence measures. The results are shown in Tables 3 - 6. Medication-taking self-efficacy was significantly associated with all adherence assessments except percentage schedule adherent (p = .06) with an effect of 1 increase in adherence percent for all four assessments per self-efficacy change (increase). In addition, older age, lower income, and no current alcohol or cocaine use were associated with greater self-reported medication adherence. Alcohol and cocaine use were not associated with the electronically monitored measures of adherence. Also, mixed modeling showed that compared to the first month, there was a significant drop in adherence at months 2, 3, 4, and 6 for percentage dose adherent, percentage days adherent, and percentage schedule adherent, but not for self-reported adherence. A significant effect of race/ethnicity on electronically-measured dose adherence can be seen (Table 4), with both Black and Hispanic participants demonstrating

significantly higher adherence than Whites, but the number of White participants in the study was quite small (n < 10), limiting meaningful interpretation of this finding.

Further analysis was performed to investigate the interaction between self-efficacy and follow-up time for each adherence assessment using mixed modeling. Interaction analysis revealed that there was a significant interactive effect of self-efficacy score and follow-up time on percentage prescribed doses taken (p = .03) and percentage days adherent (p = .03), but not on self-reported adherence (p = .21) or percentage doses taken on time (p = .27).

Discussion

This study adds to existing literature that has investigated the relationship of substance use and medication-taking self-efficacy to everyday adherence behaviors among HIV-infected substance users and extends earlier reports demonstrating the importance of one's beliefs in one's ability to take ART as prescribed for optimal adherence. Unlike previous reports, our study included expanded adherence measures (e.g., dose and schedule) collected over a 6month period to provide further information on the association of substance use and medication-taking self-efficacy on adherence over time. This component of the study was particularly important because individuals must remain adherent to ART over a lifetime and the effects of certain predictive factors may fluctuate with time.

The present findings support those of others and show a significant relationship between greater medication-taking self-efficacy, older age, greater monthly income, and higher levels of self-reported adherence as was found for the relationship of current alcohol or cocaine use on lower self-reported adherence (Arnsten et al., 2007; Golin et al., 2002; Johnson, Heckman, Hansen, Kochman, & Sikkema, 2009). A number of studies with non-substance users have reported older age and higher income to be related to better adherence with findings from the present study, suggesting similar associations with substance users. Older age and income were not associated with alcohol or cocaine use in the present study, suggesting independent relationships with self-reported adherence.

Current alcohol or cocaine use was not related to any of the electronically monitored measures of adherence, a difference that may reflect potential challenges with personal recall of medication-taking behaviors among individuals at risk for impaired recall due to acute effects of intoxication, or the longer term effects of cocaine/alcohol use and/or HIV on cognitive functioning (Waldrop-Valverde et al., 2006). Waldrop-Valverde and colleagues (2006) found that, even among those who used alcohol or cocaine, only a minority had used them frequently during the 6-month study period; so the lack of association of drug use to adherence may have reflected the relatively low incidence of drug use ultimately detected among our sample of HIV-infected individuals in care.

Of note, self-efficacy for taking ART was significantly predictive of dose adherence and number of days adherent over the 6-month follow-up period. No association of self-efficacy and schedule adherence was found, however. This finding may have indicated that an individual's confidence to take ART was related to adherence in broad terms (e.g., feeling confident to be able to take the medicines despite side effects) and was less sensitive to more specific measures of adherence such as schedule adherence. Correct timing of doses may be more susceptible to disruptions in routine or forgetfulness and, therefore, less impacted by self-efficacy for taking medicines. Moreover, an individual can be dose adherent without being schedule adherent as evidenced by lower levels of schedule adherence compared to the other measures of adherence in our sample. It appeared, then, that belief in one's ability to take ART was important for successful adherence among our sample, but that the effect of self-efficacy on actual medication-taking success may have been limited to daily dose

adherence. Identification of predictors of schedule adherence in this group warrant further investigation and are an important next step to understand and improve medication adherence among substance users.

As has been shown in other chronic physical and mental diseases (Berger, Krueger, & Felkey, 2004; Krueger, Berger, & Felkey, 2005), average adherence levels also declined over time in our study sample. An observation effect could have affected adherence levels throughout the course of the study, such that, being enrolled in an adherence study may have had an initial positive influence on medication adherence behaviors that waned over time. Alternatively, medication adherence has been shown to decline in many diseases and conditions including HIV (Bartlett, 2002; Lima et al., 2009; Wu, Aylward, & Steele, 2010), and the findings of our study may also reflect this general tendency.

Several limitations need to be considered in our findings. Participants for our study were recruited from ambulatory HIV care clinics and may, therefore, represent a selection bias. Those persons seeking HIV medical care may be predisposed to higher levels of medicationtaking self-efficacy because they are already motivated to receive care. Evaluation of the role of self-efficacy for determining readiness to initiate ART among substance users not enrolled in HIV care would be an important addition to these findings. Moreover, a sizeable number of participants in our study were lost to follow-up. Those who were retained in the complete study may be better adherers because they were adherent to the study protocol. This type of selection bias may also have affected results. Additionally, although collection of blood specimens to measure HIV viral load were included in the study protocol, only about half of participants completed the separate study visit required for blood collection. Although the HIV viral load would provide a clinical estimate of adherence, we chose not to include this measure due to the amount of missing data. These limitations notwithstanding, the findings of our study add valuable information about the relationship of modifiable selfefficacy beliefs to greater medication adherence in HIV-infected former and current substance users.

Implications of these findings for HIV practitioners who care for patients with substance use issues include the importance of promoting confidence in patients to adhere to their medications. Improved medication-taking self-efficacy can increase medication adherence and, importantly, this study has suggested that this relationship can be sustained over time. Importantly, medication-taking self-efficacy was not an effective predictor of schedule adherence over time indicating that it should be further researched to identify its most salient predictors.

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Clinical Considerations

- Nurses need to continually monitor adherence in their patients, even those who are experienced with antiretroviral therapy treatment.
- Nurses can improve patient self-efficacy for taking their medicines through skill-building exercises, identification, and assistance in resolving adherence barriers.
- Nurses can help to maintain good adherence over time by giving consistent reinforcement (verbally and through sharing evidence of reduced or suppressed viral load).
- Nurses may need to evaluate a patient's knowledge of the accurate timing of doses and his or her understanding of the importance of adhering to the correct schedule.

Socio-Demographic Characteristics of Study Participants

Variable	N	% or Mean (SD)
Age, years	99	43.9 (6.9)
Gender		
Male	63	63.6
Female	36	36.4
Race/ethnicity		
Non-Hispanic-White	5	5.1
Hispanic	10	10.1
Non-Hispanic-Black	84	84.9
Sex orientation		
Homosexual	14	14.1
Heterosexual	73	73.7
Bisexual/Unknown	12	12.1
Education		
Less than high school	46	46.5
High school	31	31.3
More than high school	22	22.2
Current residence		
Own/parent's house	34	34.3
Someone else's home	21	21.2
Homeless/street/vehicle	27	27.3
Treatment facility	17	17.2
Personal annual income last	t year	
<\$3500	36	36.4
\$3500-\$7000	16	16.2
> \$7000	47	47.5
Disability		
No	45	45.5
Yes	54	54.6
Homeless		
No	44	44.4
Yes	55	55.6
Alcohol or Cocaine Use *		
No	49	49.5
Yes	50	50.5
Self-Efficacy Score	99	26.2 (7.2)

* At any time during the study.

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	Self-Re	port Adherence	Do	se Adherent	Day	ys Adherent	Schet	<u>lule Adherent</u>
Month of follow-up	N	Mean ± SE	N	Mean ± SE	N	Mean ± SE	N	Mean ± SE
1	88	83.3 ± 2.8	83	76.7 ± 3.3	83	66.4 ± 3.6	83	58.6 ± 3.8
2	68	87.6 ± 2.7	71	67.8 ± 4.1	71	59.1 ± 4.2	71	49.5 ± 4.2
ŝ	60	83.8 ± 3.4	61	68.0 ± 4.3	61	59.8 ± 4.3	61	50.5 ± 4.6
4	61	84.3 ± 3.6	62	65.5 ± 4.7	62	57.5 ± 4.6	62	47.5 ± 4.6
5	61	85.9 ± 3.6	58	71.3 ± 4.5	58	61.0 ± 4.6	58	51.0 ± 4.7
9	61	84.7 ± 3.5	52	66.5 ± 4.7	52	57.3 ± 4.7	52	46.1 ± 4.8

Model for Self-Report Adherence

Variable	β (95% CI)	SE	t	р
Gender (female vs. male)	-2.4 (-10.7, 5.8)	4.1	-0.59	0.55
Race/Ethnicity				
Hispanic vs. White	3.0 (-16, 21.9)	9.5	0.31	0.75
Black vs. White	-0.2 (-16.5, 16.2)	8.2	-0.02	0.98
Age	0.6 (0.1, 1.2)	0.3	2.45	0.02
Personal income				
< \$3,500 vs. > \$7,000	8.6 (0.2, 17.1)	4.7	1.08	0.28
\$3,500-\$7,000 vs. > \$7,000	5.1 (-4.3, 14.6)	4.2	2.03	0.05
Education				
< high school vs. > high school	2 (-6.5, 10.4)	4.2	0.47	0.64
high school vs. > high school	2.8 (-6.8, 12.4)	4.8	0.58	0.56
Disability (no vs. yes)	-3.6 (-11.6, 4.4)	4.0	-0.90	0.37
Homeless (no vs. yes)	1.4 (-6.0, 8.9)	3.7	0.38	0.70
Alcohol or Cocaine Use (no vs. yes)	7.6 (0.2, 15.0)	3.7	2.04	0.05
Self-Efficacy Score	0.9 (0.4, 1.4)	0.3	3.68	< 0.001
Month of follow-up				
6 vs. 1	-0.2 (-8.6, 8.2)	4.3	-0.04	0.96
5 vs. 1	0.6 (-7.7, 9)	4.2	0.15	0.88
4 vs. 1	1.1 (-7.1, 9.3)	4.2	0.26	0.79
3 vs. 1	-0.7 (-8.7, 7.3)	4.1	-0.18	0.85
2 vs. 1	2.9 (-4.0, 9.7)	3.5	0.82	0.41

Model for Percent Dose Adherent

Variable	β (95% CI)	SE	t	р
Gender (female vs. male)	-9 (-24.1, 6.2)	7.6	-1.2	0.24
Race/Ethnicity				
Hispanic vs. White	36.9 (0.1, 73.6)	18.4	2.0	0.05
Black vs. White	35 (2.4, 67.6)	16.4	2.1	0.04
Age	0.6 (-0.4, 1.5)	0.47	1.2	0.23
Personal Income				
< \$3,500 vs. > \$7,000	4.5 (-10.7, 19.8)	8.5	-0.1	0.98
\$3,500-\$7,000 vs. > \$7,000	-0.3 (-17.2, 16.7)	7.6	0.6	0.56
Education				
< high school vs. > high school	7.6 (-7.7, 22.9)	7.7	0.1	0.33
high school vs. > high school	2 (-15.5, 19.6)	8.8	0.2	0.82
Disability (no vs. yes)	-4 (-18.5, 10.6)	7.3	-0.5	0.59
Homeless (no vs. yes)	2.6 (-11.0, 16.3)	6.8	0.4	0.70
Alcohol or Cocaine Use (no vs. yes)	7.5 (-6.1, 21.0)	6.8	1.1	0.28
Self-Efficacy Score	1.1 (0.2, 2.1)	0.5	2.4	0.02
Month of follow-up				
6 vs. 1	-11 (-20.2, -1.7)	4.7	-2.3	0.02
5 vs. 1	-8.5 (-17, 0.0)	4.3	-1.9	0.05
4 vs. 1	-13.2 (-20.9, -5.5)	3.9	-3.4	0.01
3 vs. 1	-11 (-17.6, -4.3)	3.4	-3.2	< 0.001
2 vs. 1	-10.7 (-15.6, -5.8)	2.5	-4.3	< 0.001

Model for Percent Days Adherent

Variable	β (95% CI)	SE	t	р
Gender (female vs. male)	-11.7 (-27.5, 4.2)	7.9	-1.5	0.15
Race/Ethnicity				
Hispanic vs. White	21.8 (-16.4, 60.0)	19.2	1.1	0.26
Black vs. White	26.8 (-7.0, 60.6)	17.0	1.6	0.12
Age	0.6 (-0.4, 1.6)	0.49	1.2	0.23
Personal Income				
< \$3,500 vs. > \$7,000	3.6 (-12.3, 19.5)	8.9	-0.6	0.55
\$3,500-\$7,000 vs. > \$7,000	-5.3 (-23.0, 12.4)	8.0	0.5	0.66
Education				
< high school vs. > high school	9.9 (-6.2, 25.9)	8.0	1.2	0.22
high school vs. > high school	5.6 (-12.7, 24.0)	9.2	0.6	0.54
Disability (no vs. yes)	-3.7 (-18.9, 11.5)	7.6	-0.5	0.63
Homeless (no vs. yes)	9.3 (-5.0, 23.6)	7.2	1.3	0.20
Alcohol or Cocaine Use (no vs. yes)	10.4 (-3.8, 24.5)	7.1	1.5	0.15
Self-Efficacy Score	1.0 (0.0, 2.0)	0.5	2.0	0.05
Month of follow-up				
6 vs. 1	-9.3 (-18.5, 0.0)	4.7	-2.0	0.05
5 vs. 1	-8.1 (-16.6, 0.3)	4.3	-1.9	0.06
4 vs. 1	-10.8 (-18.3, -3.2)	3.9	-2.8	0.01
3 vs. 1	-8.7 (-15.2, -2.1)	3.3	-2.6	0.01
2 vs. 1	-8.9 (-13.7, -4.0)	2.5	-3.6	< 0.01

Model for Percent Schedule Adherent

Variable	β (95% CI)	SE	t	р
Gender (female vs. male)	-10.3 (-26.7, 6.1)	8.2	-1.3	0.21
Race/Ethnicity				
Hispanic vs. White	12.3 (-27.2, 51.8)	19.8	0.6	0.54
Black vs. White	18.3 (-16.7, 53.3)	17.6	1.0	0.30
Age	0.6 (-0.4, 1.6)	0.51	1.1	0.25
Personal Income				
< \$3,500 vs. > \$7,000	7.1 (-9.4, 23.6)	9.2	-0.2	0.84
\$3,500–\$7,000 vs. > \$7,000	-1.9 (-20.2, 16.5)	8.2	0.9	0.39
Education				
< high school vs. > high school	11.2 (-5.4, 27.8)	8.3	1.3	0.18
high school vs. > high school	6.1 (-12.9, 25.1)	9.5	0.6	0.53
Disability (no vs. yes)	-3.5 (-19.3, 12.3)	7.9	-0.4	0.66
Homeless (no vs. yes)	9.7 (-5.1, 24.5)	7.4	1.3	0.19
Alcohol or Cocaine Use (no vs. yes)	8.8 (-5.9, 23.5)	7.4	1.2	0.24
Self-Efficacy Score	1.0 (-0.1, 2.0)	.051	1.9	0.06
Month of follow-up				
6 vs. 1	-12.7 (-22.2, -3.2)	4.8	-2.6	0.01
5 vs. 1	-9.4 (-18.0, -0.7)	4.4	-2.1	0.03
4 vs. 1	-12.9 (-20.7, -5.2)	3.9	-3.3	0.0012
3 vs. 1	-10.3 (-16.9, -3.6)	3.4	-3.0	0.0027
2 vs. 1	-11 (-15.9, -6.1)	2.5	-4.4	<.0001