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Substance type moderates the longitudinal association between depression and substance use from pre-treatment through a 1-year follow-up

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ABSTRACT

Background: Research examining directionality of the relationship between depressive symptoms and substance use following treatment entry is limited. Furthermore, substances differ in their neurobiological effects on mood. The relationship between depression and substance use following treatment entry may be moderated by dependence on specific substances. The study tested (a) lagged effects between depressive symptoms and substance use frequency following substance use treatment entry through a 1-year post-treatment follow-up and (b) if substance dependence type moderates these effects.

Methods: Participants ($N = 263$) entering residential treatment were assessed for DSM-IV substance dependence, depressive symptoms (Beck Depression Inventory), and percentage of substance use days at post-treatment, 1-, 3-, 6- and 12-month follow-up assessments (time t_0 to t_4). Linear mixed effects models tested lagged effects between depressive symptoms and substance use frequency and the impact of substance type (i.e., dependence on alcohol, cannabis, opioid, cocaine, hallucinogen/PCP) on this relationship.

Results: After controlling for concurrent effects, substance type moderated each longitudinal relationship. Depressive symptoms significantly predicted substance use frequency at the subsequent follow-up assessment, only among individuals with pre-treatment opioid dependence ($B = 5.55$, $SE = 0.89$, $z = 6.21$, $p < 0.01$). Substance use frequency significantly predicted depressive symptoms at the subsequent follow-up assessment, but not among individuals with cannabis dependence at pre-treatment ($B = 1.01$, $SE = 0.22$, $t(524) = 4.49$, $p < 0.01$).

Conclusions: The directionality of depression-substance use comorbidity may differ based on the substance of dependence at pre-treatment. Opioid users may especially benefit from treating both depression and substance use.

1. Introduction

There is a high incidence of depression among individuals receiving substance use treatment (Chen et al., 2011; Daughters et al., 2008; Goldner et al., 2014) and over half report clinically significant depressive symptom levels at treatment entry (Suter et al., 2011). Both individuals with independent major depressive disorder and those with substance-induced major depressive disorder present to substance use treatment with greater psychosocial stressors related to employment, legal and family/social sources than individuals without depression (Leventhal et al., 2006). Additionally, comorbid major depressive disorder is associated with more severe substance use (Burns et al., 2005; Dierker et al., 2018). Furthermore, depression can affect substance use treatment outcomes. Higher levels of depressive symptoms at treatment entry are associated with a decreased likelihood of abstinence after treatment (Dodge et al., 2005) and a greater risk for relapse (Suter et al., 2011). Given the impact of pre-treatment depression on substance use treatment response, it follows that understanding the relationship between substance use and depression following treatment entry is also critical to improving post-treatment substance use outcomes.

The mechanism by which substance use is related to depression following treatment entry remains unclear. In line with negative reinforcement models of substance use, depressive symptoms may increase risk for subsequent substance use via the motivation to alleviate negative affective states (Baker et al., 2004; Koob, 2013). For example, 86.8% of individuals report using substances to feel better (Boys et al., 2001), and greater depression severity at pre-treatment predicts

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decreased likelihood of abstinence at discharge (Dodge et al., 2005). On the other hand, substance use following treatment may trigger subsequent depressive symptoms. Frequent substance use is expected to limit an individuals' behavioral repertoire so that substance administration is pursued to the exclusion of other potentially rewarding behaviors (Bickel et al., 2014; Markou et al., 1998). Following substance use treatment, individuals who lapse into frequent substance use may experience significant social, occupational, and interpersonal impairment and have difficulty restoring use of rewarding non-substance related behaviors which were previously lost. The resulting restricted access to a variety of environmental reinforcers following treatment may, in turn, make such individuals vulnerable to depressive symptoms (Carvalho et al., 2011). Additionally, the physical effects of substance use may trigger depressive symptoms. For example, researchers propose that fatigue resulting from the sleep-disturbing effects of alcohol may trigger low mood the next day (Howland et al., 2010; Roehrs et al.,1991). In line with both viewpoints, the only known study to examine this relationship post-treatment found a bidirectional relationship between substance use and depression (Worley et al., 2012), yet this study did not account for concurrent effects between substance use and depression, which could spuriously inflate the strength of lagged relationships observed between these two conditions.

In addition to considering the directionality of the relationship between substance use and depression, an individuals' substance of dependence, or substance type, may impact this effect. Substances vary in their neurobiological effects. For example, neuroadaptations resulting from frequent use of stimulants are known to result in depressive symptoms when use is interrupted (e.g., Zorick et al., 2010). This is less so the case with the frequent use of hallucinogens or dissociatives (e.g., Schenk et al., 2007). Additionally, different substances are characterized by differing self-administration patterns. For example, psychostimulant use is characterized by greater impulsivity than opiate use (Badiani et al., 2011) and may be more likely used to gain immediate relief from negative mood associated with depression. Furthermore, frequent use of illegal substances may result in a higher level of stigma, both social and structural, compared to legal substances (Room, 2005), which in turn is associated with greater impairment and internalized shame (Luoma et al., 2007). Perceived discrimination has been linked to a range of mental health problems, including increased depressive symptoms (Pascoe and Richman, 2009).

In sum, different substances are associated with different mechanisms and consequences of use and may, therefore, moderate the relationship between substance use and depression. Indeed, the prevalence of co-occurring depression and substance use disorder varies across substance types (Dakwar et al., 2011; Grant et al., 2004). For example, rates of substance-induced depression have been found to be significantly greater among cocaine dependent individuals when compared to individuals with opioid or cannabis dependence (Dakwar et al., 2011). However, to our knowledge, no study has examined substance type as a moderator of the longitudinal relationship between substance use and depression.

Finally, most previous research examining the relationship between depression and substance use has involved a primarily White participant sample (e.g., Worley et al., 2012), which limits the generalizability to minority groups. Indeed, African Americans who use substances are an understudied group, despite being at a higher risk for illicit substance use disorders (Center for Behavioral Health Statistics and Quality, 2017) and having a lower likelihood of abstinence at treatment discharge (Dodge et al., 2005). Furthermore, among African American men, low income is associated with depressive symptoms, which in turn is associated with substance use (Kim et al., 2003). Accordingly, high rates of comorbidity are observed in low-income African American individuals in treatment for substance use (e.g., Chen et al., 2011). As such, a test of the factors impacting the relationship between substance use and depression among low-income African American individuals will aide in a better understanding of this phenomenon among a vulnerable and under-studied population.

The current study advances previous research of co-occurring depression and substance use after treatment entry by testing (1) if level of depressive symptoms predicts substance use frequency and if substance use frequency predicts depressive symptoms while accounting for the concurrent relationship between these two variables, and (2) if these lagged relationships are moderated by the pretreatment substance of dependence. Given evidence for both directions of causality in past research examining the onset of depression and substance use (Boschloo et al., 2013; Brook et al., 2002; Crum et al., 2008; Fergusson et al., 2009; Lo et al., 2015), it was hypothesized that lagged effects would be positive and significant in both directions following treatment entry. Further, as an exploratory hypothesis, substance type was predicted to moderate the longitudinal relationships between depression and frequency of use among this polysubstance using population. Finally, by studying a predominantly low-income, African American sample, this study seeks to further existing knowledge about moderators of comorbid depression and substance use in this under-studied population.

2. Method

2.1. Participants

Participants were recruited upon treatment entry to a 136-bed residential substance use treatment center in Northeast Washington, DC as part of a larger randomized control trial (Daughters et al., 2018). Participants were excluded (n = 17 of 280) if they were at < 5th grade English reading level, reported current psychotic symptoms, or had initiated psychotropic medication use within the past three months, resulting in a final sample of n = 263. Participants were predominantly African American, low-income, male and a majority had been court-mandated to treatment (Table 1).

Table 1
Pre-treatment participant characteristics.

	Total (n = 263)
Age, mean (SD)	42.7 (11.8)
Male, No. (%)	186 (70.7)
African American, No. (%)	249 (94.7)
Education, No. (%)	
< HS	71 (27)
HS graduate or GED	120 (45.6)
Post HS/GED vocational or some college	72 (27.4)
Unemployed, No. (%)	213 (81)
Income Level, No. (%)	144 (54.8)
$0-$9,999	56 (21.3)
$10,000-$29,999	63 (24.0)
$30,000-$100,000	191 (72.6)
Court mandated to treatment	1.5 (1.1)
No. substances used weekly in the past year, mean (SD)	
BDI-II, mean total score (SD)	10.5 (9.9)
DSM-IV Substance Dependence Diagnoses, No. (%)	
Cocaine	86 (32.7)
Opiates	31 (11.8)
Cannabis	28 (10.6)
Alcohol	81 (30.8)
Hallucinogen/ PCP	37 (14.1)
Did not meet criteria for DSM-IV Substance Dependence	66 (25.1)
DSM-IV Mood and Anxiety Disorder Diagnoses, No. (%)	
Major Depressive Disorder	48 (18.3)
Bipolar Disorder	10 (3.8)
Panic Disorder	4 (1.5)
Generalized Anxiety Disorder	22 (8.4)
Social Phobia	11 (4.2)
Post-Traumatic Stress Disorder	19 (7.2)

Note: SD = Standard Deviation, HS = High School, GED = General Equivalency Diploma, DSM-IV – Diagnostic and Statistical Manual – IV, BDI = Beck Depression Inventory.

2.2. Procedure

Patients at the substance use treatment center participated in an intake interview to assess eligibility and provide informed consent. All participants received treatment as usual (TAU) and were randomized to one of two additional treatment conditions including an experimental behavioral treatment or a contact time matched control condition. Data from both treatment conditions were combined for the current analyses as treatment was not a focus of the current aims, and did not significantly affect depression or substance use frequency at each follow-up wave (detailed information regarding the parent trial and effect of treatment condition in Daughters et al., 2018). Assessments occurred at pre-treatment, post-treatment (3–4 weeks following pre-treatment), and at 1-, 3-, 6- and 12-month post-treatment follow-ups. Participation was compensated for each attended assessment. All study procedures were approved by the Institutional Review Board.

2.3. Measures

2.3.1. Potential covariates

Demographic information including Age, Sex, Income and Mandatory status (i.e., whether participant was court-mandated to treatment) were collected at the pre-treatment assessment. Lifetime Major Depressive Disorder diagnoses were determined using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; First and Gibbon, 2004).

2.3.2. Depressive symptoms

Depressive symptoms were represented by the total score on the Beck Depression Inventory (BDI-II; Beck et al., 1996). Participants responded to 21 items that reflect DSM-IV diagnostic criteria for depression, using a scale of 0 (not present) to 3 (severe). This measure has demonstrated reliability in previous research (0.92 with an outpatient sample and 0.93 for a nonclinical sample (Beck et al., 1996)), and in the current sample (alpha reliability across assessments ranged from 0.81 to 0.94).

2.3.3. DSM-IV substance dependence

DSM-IV substance dependence in the past year was assessed by trained interviewers at the pre-treatment assessment using the Substance Dependence section of Module E in the SCID-I (First and Gibbon, 2004). Opioid dependence was diagnosed if an individual met dependence criteria for heroin or non-prescribed use of a prescription medication. The majority (83.9%) of participants with baseline opioid dependence reported weekly use of heroin.

2.3.4. Post-treatment substance use frequency

The Timeline Followback (TLFB; Sobell and Sobell, 1992) is an interview measure in which participants are asked to recall daily substance use starting with the assessment date and ending on the date of the last assessment. This measure was used to assess any alcohol use, illicit use of a substance or prescription medication following treatment entry. This measure has demonstrated high test-retest reliability, convergent and discriminant validity, and agreement with collateral reports of substance use and urinalyses (Hjorthøj et al., 2012). Percentage of days used between two consecutive assessments were computed by counting the number of days with any reported use and dividing this by the total number of days between assessments.

2.4. Data analyses

The data used for the current analyses consisted of a hierarchical structure, i.e., assessments nested within time points, which in turn are nested within individuals. This study used multilevel modeling (MLM, Raudenbush and Bryk, 2002), which allows (a) modeling of the relationship between depressive symptoms and substance use frequency while accounting for the hierarchical structure of the data, (b) cross-level interactions, wherein regression parameters (e.g., slopes) at lower levels are modeled as dependent variables in regression equations at higher levels, (c) modeling of lagged effects between depressive symptoms and substance use frequency to build evidence for the directionality of this relationship, and (d) flexible handling of missing data using Full Information Maximum Likelihood estimation.

Analyses were conducted using R (R Development Core Team, 2017). Two multilevel base models were examined in these analyses: (a) *substance use frequency→ depression*: a lagged model with substance use frequency at Time t-1 as the within-subjects fixed effect predicting depressive symptoms reported at Time t and (b) *depression → substance use frequency*: a lagged model with depression levels at Time t-1 predicting substance use frequency at Time t (see Fig. 1). In order to test whether the observed lagged effects held even when accounting for the concurrent relationship between depression and substance use, first, coefficients representing this concurrent relationship for each individual were estimated by including a random slope in a concurrent base model where substance use at Time t predicted depression at Time t. Next, these coefficients were included as covariates in the lagged models. Depressive symptoms and substance use frequency were positively skewed at all assessment points (all skewness and kurtosis estimates > 1; all Kolmogorov-Smirnov and Shapiro-Wilk tests showing deviation from normality at $p < 0.01$). Therefore, these variables were log transformed to fit them to a normal probability distribution. For the model in which substance use frequency was the dependent variable, a zero-inflated negative binomial model was used to account for the large number of zeros in this variable.[1]

To determine the best random effect structure, a backwards model selection approach was used for the two models, comparing a maximally specified random effects structure with nested models of reduced complexity via likelihood ratio tests (Baayen et al., 2008). Comparisons showed that the maximal random-effects structure justified by the data was by-subject random intercepts. Thus, these terms were included in all models.

To examine whether potential covariates [i.e., age, sex, income, presence of lifetime DSM-IV major depressive disorder (MDD) diagnosis, pretreatment substance dependence (No = 0, Yes = 1), court mandated status (No = 2, Yes = 1), and treatment condition[2]] influenced the lagged relationships between depressive symptoms and substance use frequency, main effects of these variables and their interactions with the primary predictor (i.e., depressive symptoms or substance use frequency) were included as fixed effects in the lagged models described above. Variables with significant associations were included as covariates in the subsequent analyses. Finally, five dichotomous variables representing past year diagnoses of substance dependence in each substance category (i.e., opioid, cocaine, alcohol, cannabis, and hallucinogen/PCP) were added as predictors to the lagged models to test whether substance type moderates the lagged relationships between depression and substance use frequency. In these models, main effects of all substance dependence variables, as well as the interaction between each substance dependence variable with the main predictor (i.e., depression or substance use frequency) were added as within-person fixed effects. We interpret only the interaction between each substance dependence variable and the main predictor variable, as the hypotheses relate to the moderation of the slope between depressive symptoms and substance use frequency by substance type, and not the main effect of substance type on the dependent variable.

[1] Zero days of use were reported by 250 participants at post-treatment, 170 at 1-month FU, 126 at 3-month FU, 95 at 6-month FU, and 94 at 12-month FU.

[2] Participants from both treatment conditions were combined for the current analyses, as treatment condition was not a variable of interest in this study, and not significantly related to substance use frequency or depressive symptoms at each follow-up wave (Daughters, Magidson et al., 2017).

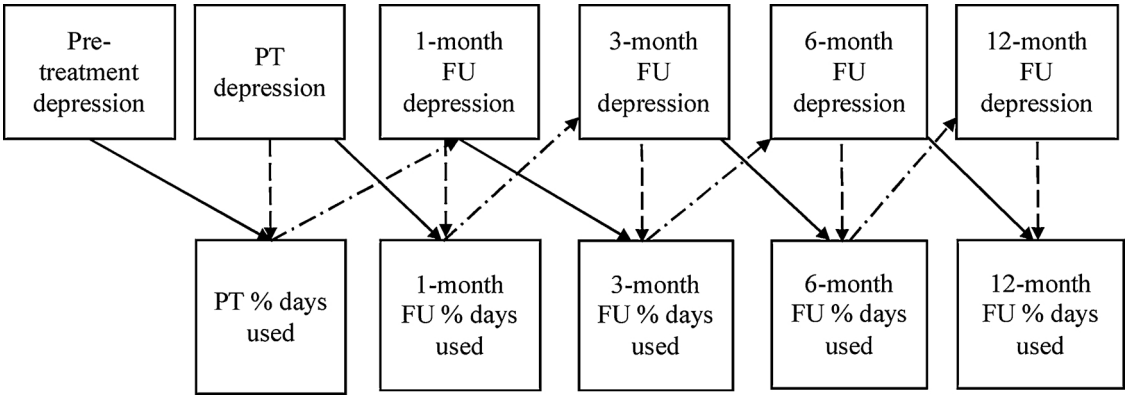

Fig. 1. Timeline of assessments with concurrent and lagged effects between depression symptoms and frequency of use. *Note:* PT = post-treatment, FU = follow-up.

3. Results

3.1. Participant characteristics

Pre-treatment demographic and pre-treatment characteristics are reported in Table 1. Sample means for the total BDI score, and percent days used substances at post-treatment and follow-up assessments are presented in Table 2.

3.2. Test for systematic attrition

Participant retention rates were 95.4% at post-treatment, 84.4% at 1-month FU, 81.7% at 3-month FU, 82.9% at 6-month FU, and 84% at 12-month FU. To test for systematic attrition, logistic regression analyses were conducted by including pre-treatment levels of relevant study variables, i.e., age, sex, income, mandatory status, treatment condition, past year substance use dependence (cocaine, opiates, alcohol, cannabis, hallucinogen/PCP), lifetime diagnosis of MDD, in a single block, predicting attrition at each follow-up assessment. Individuals who attrited did not differ from those who attended the assessment based on these variables at post-treatment (χ^2 (20) = 16.92, p = 0.67), 1-month FU (χ^2 (20) = 25.80, p = 0.17), 3-month FU (χ^2 (20) = 23.47, p = 0.26), 6-month FU (χ^2 (20) = 15.97, p = 0.72) or 12-month FU (χ^2 (20) = 21.06, p = 0.39).

3.3. Test of covariates

Potential covariates (i.e., sex, age, income, lifetime MDD diagnosis, mandatory status, pretreatment substance dependence, treatment condition) were examined using MLM to determine if they were related to the lagged effects between depressive symptoms and substance use frequency. Results of these covariate analyses are presented in Supplementary Table 1.

3.4. Lagged effects between substance use frequency and depressive symptoms

First, a significant concurrent effect was observed between substance use frequency and depressive symptoms for the sample overall (B = 0.59, SE = 0.18, t (844) = 3.26, p < 0.01). A positive coefficient indicates that a higher substance use frequency was associated with greater depressive symptoms. This effect was allowed to vary across participants by including a random slope in the MLM, and the coefficient representing the strength of the concurrent effect was included as a Level 2 predictor in the lagged models described below. This enabled testing of lagged effects while accounting for the concurrent effect between substance use frequency and depression.

Separate models were used to evaluate each lagged relationship between depressive symptoms and substance use frequency. Results are presented in Table 3. Substance use frequency at Time t-1 significantly predicted greater depressive symptoms at Time t. This effect continued to be significant when accounting for concurrent effects between substance use and depression. Depressive symptoms at Time t-1 did not significantly predict substance use frequency at Time t with or without concurrent effects included as a covariate. However, the confidence intervals around the coefficients representing the two lagged effects (CI $_{\text{substance use frequency} \rightarrow \text{depression}}$ = 1.21 — 0.39; CI $_{\text{depression} \rightarrow \text{substance use frequency}}$ = 2.40 — -0.62) when accounting for concurrent effects are overlapping, suggesting that these effects do not differ significantly from each other.

3.5. Substance type (past year substance dependence diagnosis) as a moderator of lagged effects

Next, a set of dichotomous variables representing the presence of a past year DSM-IV diagnosis of dependence in each substance category (i.e., opiates, cocaine, alcohol, cannabis, hallucinogen/PCP) was added to the lagged models as predictors. This was done to examine whether the *type* of substance for which a person meets criteria for substance dependence at pre-treatment moderates the predictive relationship between substance use frequency and depressive symptoms. The effect of substance use frequency at Time t-1 predicting depressive symptoms at Time t was moderated by past year cannabis dependence (Table 4). Follow up analyses showed that this lagged effect was significant for individuals who were not diagnosed with past year cannabis dependence at pre-treatment (B = 1.01, SE = 0.22, t (524) = 4.49, p < 0.01) but not for those who were (B = -0.64, SE = 0.76, t (64) = -0.85, p = 0.40). Therefore, substance use frequency predicted higher depressive symptoms at a subsequent assessment for individuals not diagnosed with cannabis dependence.

Table 2
Depressive symptoms and substance use at each time point.

	PT	1-month FU	3-month FU	6-month FU	12-month FU
BDI-II, mean (SD)	9.1 (9.6)	7.1 (9.2)	8.3 (10.3)	8.6 (10.6)	8.8 (10.4)
Percent days used since last assessment, mean (SD)	0.5 (4.1)	7.2 (18.1)	14.8 (27.6)	15.4 (27.7)	15.2 (27.4)

Note: PT = post treatment, FU = Follow-up.

Table 3
Lagged effects between substance use frequency and depressive symptoms.

a. Effect of substance use frequency at time t-1 on depressive symptoms at time t

	B	SE	t	p
Without accounting for concurrent effect				
Intercept	1.55	0.06	23.27	< 0.001
Substance use frequency	0.79	0.21	3.75	< 0.001
While accounting for concurrent effect				
Intercept	2.24	0.13	17.47	< 0.001
Concurrent effect	−1.18	0.19	−6.16	< 0.01
Substance use frequency	0.80	0.21	3.86	< 0.001

b. Effect of depressive symptoms at time t-1 on substance use frequency at time t

	B	SE	z	p
Without accounting for concurrent effect				
Intercept	−28.40	1.50	−18.99	< 0.001
Depressive symptoms	0.47	0.72	1.15	0.25
While accounting for concurrent effect				
Intercept	−31.58	2.43	−13.01	< 0.001
Concurrent effect	4.07	2.55	1.59	0.11
Depressive symptoms	0.89	0.77	1.15	0.25

Table 4
Moderation by substance of dependence on the lagged effect of substance use frequency predicting depressive symptoms.

	B	SE	t	p
Intercept	2.38	11.96	2.00	< 0.001
Concurrent effect	−1.15	0.20	−5.67	< 0.001
Percent days used	0.27	0.55	0.48	0.63
Hallucinogen/PCP dependence	0.04	0.18	0.21	0.84
Opioid dependence	0.06	0.20	0.32	0.75
Alcohol dependence	0.22	0.14	1.55	0.12
Cocaine dependence	−0.01	0.14	−0.08	0.93
Cannabis dependence	0.24	0.21	1.16	0.25
Percent days used X Hall/PCP dependence	0.88	0.61	1.45	0.15
Percent days used X Opioid dependence	−0.59	0.74	−0.80	0.42
Percent days used X Alcohol dependence	0.08	0.48	0.17	0.87
Percent days used X Cocaine dependence	−0.35	0.47	−0.75	0.45
Percent days used X Cannabis dependence	−1.58	0.71	−2.23	0.03

Note: Substance dependence variables represent past year DSM-IV diagnosis of substance dependence.

Table 5
Moderation by substance of dependence on the lagged effect of depressive symptoms predicting substance use frequency.

Covariate	B	SE	z	P
Intercept	−29.41	4.43	−6.64	< 0.001
Concurrent effect	5.03	2.51	2.00	0.05
Percent days used	3.45	1.46	2.37	0.02
Hallucinogen/PCP dependence	7.54	3.70	2.04	0.04
Opioid dependence	−3.13	2.48	−1.26	0.21
Alcohol dependence	3.16	2.14	1.48	0.14
Cocaine dependence	−5.93	2.21	−2.68	0.01
Cannabis dependence	5.50	2.84	1.93	0.05
Percent days used X Hall/PCP dependence	−2.49	1.63	−1.53	0.13
Percent days used X Opioid dependence	5.18	1.32	3.92	< 0.001
Percent days used X Alcohol dependence	−1.43	1.29	−1.11	0.27
Percent days used X Cocaine dependence	6.15	1.16	5.29	< 0.001
Percent days used X Cannabis dependence	−2.07	1.34	−1.54	0.13

Note: Substance dependence variables represent past year DSM-IV diagnosis of substance dependence.

The effect of depressive symptoms at Time t-1 predicting substance use frequency at Time t was moderated by past year opioid and cocaine dependence (Table 5). Follow up analyses showed that depressive symptoms significantly predicted greater substance use frequency for individuals with past year opioid dependence (see Fig. 2) (B = 5.55, SE = 0.89, z = 6.21, p < 0.01) but not for those without (B = 0.37, SE = 0.78, z = 0.48, p = 0.63). The simple slope analysis for cocaine dependence did not yield significant main effects of depressive symptoms predicting frequency of use for those with (B = 3.83, SE = 3.71, z = 1.03, p = 0.30) or without (B = -0.13, SE = 0.85, z = -0.16, p = 0.88) cocaine dependence at pre-treatment.

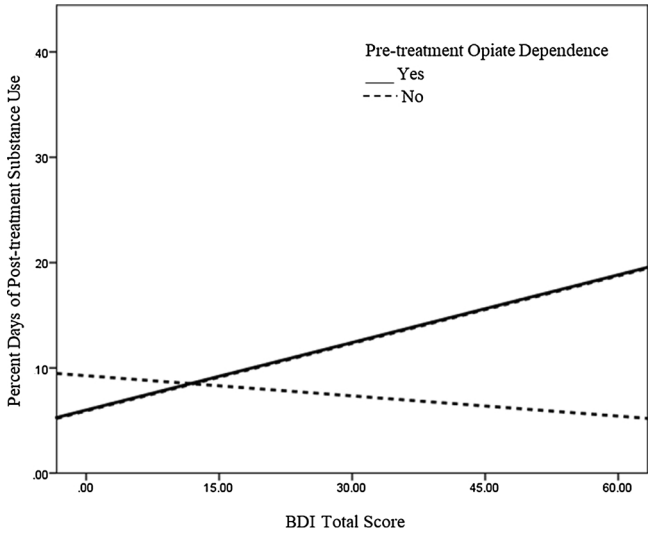

Fig. 2. Effect of depression on frequency of use for individuals with and without Opioid Dependence at Pretreatment.
Note: BDI = Beck Depression Inventory - II

4. Discussion

The current study examined the longitudinal relationship between substance use frequency and depressive symptoms among predominantly African American, low-income, substance users from pre-treatment until 12 months following residential substance use treatment. The results suggest that substance use significantly predicts subsequent depressive symptoms, even when accounting for the concurrent association between the two, although this association is not significant for those with pre-treatment past year cannabis dependence. A significant predictive relationship between depressive symptoms and

later substance use was not observed for the entire sample. However, depression did predict subsequent substance use frequency for individuals with pre-treatment past year opioid dependence. To our knowledge, this study is the first to examine substance of dependence (i.e., substance type) as a moderator of this longitudinal relationship. Additionally, by studying predominantly low-income, African American participants, this study furthers understanding about the relationship between depression and substance use among a vulnerable and relatively under-studied population.

Previous research on the substance use-depression relationship has suggested a bi-directional relationship (e.g., Gilman and Abraham, 2001). However, studies have focused heavily on alcohol rather than illicit substance use, and researchers have not examined the possibility that directionality may differ based on substance dependence type. Initial findings from the current study differed from previous research by providing support only for the direction of substance use leading to depression. However, including substance type as a moderator in the model revealed that substance use frequency predicts depressive symptoms for some individuals, while depressive symptoms predict substance use frequency for others, depending on the substance of dependence at pre-treatment. This highlights the importance of considering what substance an individual is dependent on when predicting the relationship between depression and substance use, and suggests that combining individuals with varied substance dependence in similar analyses may produce misleading results.

In the current analysis, depressive symptoms predicted substance use frequency among individuals with – but not those without – past year opioid dependence. One potential explanation for this finding is the neurobiological effect of opioid use on mood. Some evidence suggests that opioids such as heroin, which act primarily on mu opioid receptors, may have antidepressant effects in the short term - though they can actually contribute to depression in the long term (Lutz and Kieffer, 2013; White, 2004). It may be that opioid users who experience depressive symptoms use illicit opioids to relieve negative affect, despite the potential long-term consequences. Given high rates of depression among individuals with opioid dependence (Strain, 2002), future studies are needed that examine possible mediators of the relationship between depression and substance use following treatment, as well as interventions that target depression during substance use treatment. There is some evidence that the opioid agonist treatments buprenorphine and methadone may be particularly effective for opioid dependence due to their antidepressant effects (Schäfer et al., 2011; Tenore, 2008), and that the addition of antidepressants during treatment for opioid dependence can improve substance use outcomes even among individuals *without* current depression (Gonzalez et al., 2003; Torrens et al., 2005). The current findings highlight the importance of such tailored treatment approaches for individuals with opioid use disorders in order to proactively address depression risk and its implications for relapse.

An unexpected finding from the current study was the apparent "protective" effect of past-year cannabis dependence on the association between substance use and depression (i.e., post-treatment substance use frequency predicted depression for individuals without – but not with – cannabis dependence). This finding suggests a weaker relationship between substance use and depression among individuals who meet criteria for cannabis dependence compared to other substances of dependence. It is notable that previous longitudinal research has found a positive predictive relationship between heavy cannabis use and depression (Lev-Ran et al., 2014); however, we are not aware of any studies that have compared this relationship between cannabis users and other substance users. Previous studies have indicated that cannabis users in treatment may be more ambivalent about stopping substance use (Budney et al., 1998) and more likely to engage in treatment due to criminal justice involvement (Campbell et al., 2013) compared to cocaine users and opiate users, respectively. Substance use after treatment may thus be viewed less negatively among cannabis users, which could be one explanation for the current finding. Furthermore, some research has suggested that cannabinoids may have antidepressant effects, though these appear to reverse at high doses (e.g., Bambico et al., 2007; El-Alfy et al., 2010). Additional research is needed to better understand the neurobiological effects of cannabis on mood, and future studies may also consider potential differences between individuals with and without cannabis dependence in residential treatment settings to clarify the mechanism behind the effect found in the current study.

The findings of this study must be interpreted in light of its limitations. The dependent variable reflects the frequency of *any* alcohol or illicit substance use, not just the substance they reported dependence for at pre-treatment. As such, more research is needed to determine whether the relationship between substance use and depression varies as a function of the type of substance that the participant used post-treatment. However, it is important to study factors leading to *any* substance use following treatment because polysubstance use is common during this stage. Furthermore, use of a different substance may increase risk for using the primary substance of dependence (Hyman and Sinha, 2009). Additionally, individuals who remit from their primary substance of use may go on to develop a new substance use disorder during a three-year follow-up (Blanco et al., 2014). As such, the current results are still valuable as they may enable researchers and clinicians to predict the relationship between depression and substance use using the type of substance on which a participant initially reports dependence.

Participants were recruited from a residential substance use treatment center in an urban setting where 73 percent of patients were referred from the criminal justice system, and a majority of them were African American, unemployed, and reported an income in the poverty range. Therefore, although the study relates to a vulnerable and relatively unrepresented sample, more research is needed to determine whether the current findings generalize to rural, outpatient treatment settings, individuals who enter treatment voluntarily, and those of a higher SES.

Self-report measures were used to quantify depressive symptoms and substance use frequency, which may be affected by response bias. Additionally, the current study focused on the frequency of substance use but did not include a measure of the quantity of a substance consumed in each instance. While frequency has been demonstrated to be an important substance use outcome, predicting the incidence of psychiatric disorders including mood and substance use (e.g., Kandel et al., 1997), future research is needed to determine whether the results concerning frequency of substance use generalize to substance use severity. This study draws on data from a clinical trial that commenced prior to the release of the DSM-5. As such, it is unclear if individuals who did not meet criteria for substance dependence would have met criteria for mild substance use disorder, highlighting the need for future replication using severity specifiers. Strengths of the current study include recruitment of an understudied sample and the use of robust statistical methods, including controlling for the concurrent substance use-depression relationship in the lagged effects models, which lends confidence to the findings.

The current study is among the first to examine the longitudinal relationship between substance use and depression after treatment in a sample of low-income, predominantly African American polysubstance users. The findings indicate that the type of substance on which individuals are dependent moderates the relationship between substance use and depression after residential treatment. Understanding and predicting post-treatment substance use and comorbid mental health diagnoses is vital for improving the effectiveness of treatment, and this study has important implications for tailoring treatment to improve long-term outcomes. For example, the current findings emphasize the need to proactively address depression in the treatment of opioid dependence, which may, in turn, result in less frequent post-treatment substance use. Additional research is needed to better understand the

pathways by which substance use can lead to depression and vice-versa; this study highlights the importance of considering substance type in future research on this relationship.

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Contributors

Deepika Anand co-originated the study concept, conducted the statistical analyses, drafted the methods and results and guided the drafting of the introduction and discussion. Anna Bartuska drafted the introduction and Catherine Paquette prepared the discussion. Stacey Daughters co-originated the study concept, advised on all aspects of the study, and provided critical revision of the manuscript. All authors approved the final version for publication.

Conflict of interest

No conflict declared.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.01.002.

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