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Motivation deficits and use of alcohol and illicit drugs among individuals with schizophrenia

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Abstract

This study examined the impact of substance use on intrinsic motivation and evaluated the association between intrinsic motivation and substance use recovery among individuals with schizophrenia. Alcohol and illicit drug use and intrinsic motivation were evaluated at baseline and 6-months for 1434 individuals with schizophrenia from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) using self-rated substance use assessments and a derived motivation measure from the Heinrichs-Carpenter Quality of Life Scale. Results revealed patients had moderate motivation deficits overall and a considerable number were using alcohol or illicit drugs at baseline ($n = 576$; 40.2%). Regression models at baseline showed patients with low levels of motivation had higher odds of substance use and those who were using substances had greater motivation deficits. At 6-months, substance using patients continued to demonstrate greater motivation deficits; however, those with high levels of motivation exhibited a greater reduction in their use of substances. Findings remained significant after adjusting for clinical confounds and were consistent across any substance, alcohol, and cannabis use. Our results emphasize concerns

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Conflict of Interest

None.

Role of funding source

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about substance use compounding motivation deficits in schizophrenia, and suggest that disentangling the motivation-substance use relationship in schizophrenia may facilitate efforts aimed at ameliorating these challenges and improving outcomes.

Keywords

substance use; schizophrenia; substance-using schizophrenia; intrinsic motivation; motivation deficits

1. Introduction

Motivation deficits and the use of alcohol or illicit drugs are important factors that can affect recovery from schizophrenia (Fevaha et al., 2014a; Bahorik et al., 2013; Schmidt et al., 2011). Estimates show about half of all adults with schizophrenia use substances (Volkow, 2009); that greater disability is associated with the motivation deficits found in schizophrenia relative to those found in other mental health conditions (Harvey and Strassnig, 2012), and substance use and motivation deficits can negatively affect the course of the disorder (Volkow, 2009; Schmidt et al., 2011). Psychosocial and pharmacological interventions have demonstrated efficacy for improving clinical outcomes in substance-using schizophrenia patients (Kelly et al., 2012), yet numerous other factors can influence recovery (see Horsfall et al., 2009; Wisdom et al., 2011; Drake et al., 2015), including the interest or drive to participate in treatment and reduce substance use. Compared to those who use substances but do not have schizophrenia, studies consistently show patients with schizophrenia who use alcohol or illicit drugs are less motivated to change substance use behaviors, have higher substance use relapse, are more difficult to engage in substance use treatment, and drop out of substance use programs at higher rates (Horsfall et al., 2009). Given the prominence of motivation deficits, its associated disability with schizophrenia (Nakagami et al., 2010; Nakagami et al., 2008; Fevaha et al., 2014a), and the potential link between low motivation and continued substance use (Horsfall et al., 2009), motivation-related disability may be one of the most critical factors influencing poorer recovery in those with the disorder using alcohol and illicit drugs.

The notion of alcohol and illicit drug use influencing motivation has been documented in healthy individuals (Volkow et al., 2016), yet this concept is less well understood in schizophrenia. Studies with healthy individuals report associations between drug use and low motivation (Lane et al., 2005; Volkow et al., 2014) and decreased reactivity to dopamine stimulation contributing to low motivation (Volkow et al., 2014). The dopamine pathway has been implicated in neuroadaptations resulting from repeated drug exposures (Volkow et al., 2007), and as a contributor to negative symptoms in schizophrenia (Talamo et al., 2006), from which the motivation deficits of the disorder emerged (Nakagami et al., 2010). Negative symptoms tend to be lower in substance-using schizophrenia patients (Talamo et al., 2006), and some researchers caution that because substance use is associated with reduced dopamine transmission, continued alcohol or illicit drug use could worsen negative symptoms, and impede recovery (Volkow, 2009). There is potential for motivation to be lower in substance-using schizophrenia patients and for substance use to worsen motivation,

given that negative symptom measures are a valid proxy for motivational capacity. Since researchers have only begun to consider motivation deficits apart from negative symptoms (Fevaha et al., 2014a), whether such findings persist when motivation measures are used is largely unknown and may have implications for treatment and recovery.

Although schizophrenia is associated with profound motivation deficits, such deficits are amenable to change (Nakagami et al., 2010), predict improvement across neurocognitive and psychosocial factors (Nakagami et al., 2010; Fevaha et al., 2014a), and have been suggested to positively impact other factors (Medalia and Brekke, 2010). Thus, it may be the case that even low motivation levels in substance-using schizophrenia patients may contribute to reductions in alcohol or illicit drug use, given these patients have the requisite interest or drive to reduce their use. Indeed, treatment research focused on substance-using schizophrenia patients suggests that they have ability to develop the requisite intrinsic interest or drive to reduce their substance use absent extrinsic reward (e.g., money or rewards) (DiClemente et al., 2008; Nidecker et al., 2008; Graber et al., 2003), and long-term follow-up studies show remission of substance use in this population (Drake et al., 2015), suggesting changes in motivation levels may naturally occur outside of the specialty programs that very few receive. Given the surge of interest in addressing the problem of substance use in schizophrenia, highlighted by the recent emergence of long-term follow-up studies and trials focused on alcohol/illicit-drug use (Horsfall et al., 2009; Wisdom et al., 2011; Kelly et al., 2012; Drake et al., 2015), identifying factors, like motivation, that may impede or improve the trajectory of use is clinically relevant because this comorbidity can lead to worse outcomes, and can contribute to high morbidity and early mortality (Volkow, 2009; Rosen et al., 2008).

This study examined associations between intrinsic motivation and substance use in a large sample of persons with schizophrenia. Specifically, 1434 patients with schizophrenia who participated in the Clinical Antipsychotic Trials of Intervention Effectiveness (Lieberman et al., 2005) were studied to determine the longitudinal impact of substance use on intrinsic motivation and the longitudinal association between intrinsic motivation and substance use recovery.

2. Methods

2.1. Participants

Data were drawn from the CATIE study, which compared the effectiveness of first/second generation antipsychotics through a randomized clinical trial conducted from January 2001 to December 2004 at 57 sites in the United States (Lieberman et al., 2005; Stroup et al., 2003). Details of the CATIE have been reported (Lieberman et al., 2005; Stroup et al., 2003). Briefly, in the first phase, 1493 patients were randomized to receive olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone under double-blind conditions and followed for 18 months or until treatment was discontinued for any reason (Stroup et al., 2003). Participants were eligible if they were aged 18 to 65, had a diagnosis of schizophrenia confirmed using the Structured Clinical Interview for DSM-IV (First, 1997), and could receive oral antipsychotic medications. Participants were excluded if they had schizoaffective disorder,

were in the first episode of schizophrenia, had refractory illness, were pregnant/breast-feeding, or had an unstable medical condition.

2.2. Measures

2.2.1. Alcohol and Illicit Drug Use—Patients were asked whether they used alcohol or illicit drugs (cannabis, cocaine, phencyclidine [PCP], opiates, amphetamines) (yes/no = use/no use) within 90-days prior to interviews during an assessment of their clinical status (Reimherr et al., 2010). An indicator was created for any substance use; 1 (yes/no = any use/otherwise) of all mentioned substances.

2.2.2. Intrinsic Motivation—Using methods established in Nakagami et al. (2008), we evaluated intrinsic motivation using the sum of 3 items derived from the Intrapsychic Foundations subscale of the Heinrichs-Carpenter Quality of Life Scale (Heinrichs et al., 1984): purpose, motivation, and curiosity. Those items measure general trait-like motivation and tap into core constructs within self-determination theory (Nakagami et al., 2008; Fevaha et al., 2014a), which defines intrinsic motivation as the interest in, drive toward, and enjoyment of activities and goals for their own sake, and absent extrinsic reward (Ryan and Deci, 2000). This definition of intrinsic motivation is premised on the assumption that individuals can develop intrinsic drive for engaging in activities and carrying out goals for their own sake. Thus, if substance-using schizophrenia patients have an interest in reducing substance use for their own sake, they can leverage their ability to develop intrinsic drive towards carrying out this goal. While no criterion standard instrument for evaluating intrinsic motivation in schizophrenia currently exists, this derived 3-item measure has been used in numerous studies examining this construct in patients with schizophrenia (Gard et al., 2009; Nakagami et al., 2008; Saperstein et al., 2011; Fevaha et al., 2014a). Lower scores on this derived 3-item measure indicate greater intrinsic motivation deficits; the measure demonstrated good internal consistency in the present sample (Cronbach $\alpha = 0.80$).

2.2.3. Symptomatology and cognitive function—Other measures of interest included the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) to assess psychopathology (30-items rated 1 to 7 across 3 subscales: 7-item positive subscale; 7-item negative sub-scale; 16-item general psychopathology) and a neurocognitive battery to measure global cognitive deficits (Keefe, 2010). Cognitive deficits were assessed across 5 domains, which is consistent with the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (Green et al., 2003), including verbal memory, processing speed, vigilance, working memory, and reasoning. The verbal memory domain score was based on the Hopkins Verbal Learning Test (Brant, 1991). The processing speed domain score was based the Grooved Pegboard (Lafayette Instrument Company, 1989), Wechsler Adult Intelligence Scale Revised Digit Symbol Test (Wechsler, 1981), and verbal fluency measures (Benton, 1978). The vigilance domain score was based on d' averages from the Continuous Performance Test (Cornblatt, 1988). The working memory domain score was based on computerized tests of visuospatial memory and letter number sequencing (Gold et al., 1997). The reasoning domain was based on the Wisconsin Card Sorting Test (Heaton et al., 1993) and the Wechsler Intelligence Scale Mazes (Wechsler, 1991). An overall composite index comprised the standardized average of the 5

composite scores (Keefe, 2010), and was used in this research to measure global cognitive deficits; higher scores indicate better neurocognitive function.

2.3. Procedure

The current study included 1434 patients randomized in phase 1 with complete motivation measure data at baseline. The 1434 participants selected from the CATIE were assessed at baseline by trained raters using substance use measures, the Heinrichs-Carpenter Quality of Life Scale, the neurocognition battery and PANSS. Participants were then randomized to antipsychotic treatment. This study examines substance use and intrinsic motivation data collected at baseline and at 6-months. Of the 1434 assessed at baseline, 621 (43.3%) were available at 6-months. There were no significant differences between those who completed the study and those who withdrew early with regard to gender, race, employment, marital status, neurocognition, negative symptoms, intrinsic motivation or substance use. Patients who withdrew early, however, were younger ($M = 39.82$; $SD = 11.03$) relative to completers ($M = 41.57$; $SD = 11.05$), $t(1430) = -2.98$, $p < 0.001$, and had higher total psychopathology PANSS scores ($M = 76.60$; $SD = 17.47$) relative to completers ($M = 74.07$; $SD = 17.31$), $t(1430) = 2.72$, $p < 0.001$. Pre-randomization (baseline) medication data were available for 995 (69.3%) of the 1432 participants. Of those with baseline medication data, there was no evidence a significant difference found in the dosages of antipsychotics between completers ($M = 349.94$; $SD = 414.89$) relative to those who withdrew early ($M = 377.07$; $SD = 422.93$), $t(993) = 1.01$, $p = 0.309$. All patients provided written informed consent prior to participation. This research was approved by respective institutional review boards.

2.4. Analysis

Analyses were carried out in R version 3.3.1 (R Development Core Team, 2016), and statistical significance was defined at $p < 0.05$. Baseline differences between patients using and not using substances were examined by employing χ^2 (categorical) and independent sample t (continuous) tests. Next, logistic regression analyses were conducted to examine the relationship between intrinsic motivation scores and likelihood of substance use. Baseline analyses concluded with using mixed-effects regression to examine the relationship between substance use and intrinsic motivation. Longitudinal analyses were conducted within a mixed-effects model framework. These analyses began with investigating the longitudinal relationship between substance use and intrinsic motivation. We first fit an unconditional model predicting intrinsic motivation from time (coded: 0=baseline; 1=6-months) to examine change in intrinsic motivation scores from baseline to 6-months. Next, we fit a conditional model predicting intrinsic motivation from time and time-varying substance use variables to examine whether substance use contributed to change in intrinsic motivation. To investigate the longitudinal relationship between intrinsic motivation and substance use, models were fit predicting substance use from time and time-varying intrinsic motivation. All analyses included age, race, gender, negative symptoms, antipsychotic type (e.g., via random assignment) and neurocognition as potentially confounding covariates. Analyses were conducted with an y substance, alcohol, and cannabis, to examine the consistency of the results across the most frequently used substances.

Overall study attrition was 56% at 6-months (Table S1). Rather than discard partial study completers and potentially bias the final sample of individuals analyzed (Schafer & Graham, 2002), the expectation maximization (EM) approach was used to handle missing data during maximum likelihood estimation at the time of analysis for all longitudinal analyses. This approach to missing data imputes missing values through an iterative process of maximum likelihood parameter estimates, which relies on all available data (e.g., existing measurement occasions for each individual participant, overall sample parameter estimates, model covariates, etc.) (Graham, 2009). Although data are assumed to be missing at random, our use of secondary data precludes us from deriving direct empirical evidence about whether this is reasonable; and thus, an alternative strategy is to examine the sensitivity of the results under different conditions (Pigott, 2001). Complete case sensitivity ($N = 621$) analyses were computed, and revealed similar although less powerful results (Table S2 & Table S3).

3. Results

3.1. Overall sample characteristics

Overall, most participants were men (74.0%), white (60.0%), and were 42 years of age ($SD = 11.08$). The mean level of intrinsic motivation ($M = 7.75$; $SD = 4.10$) was comparable with other schizophrenia samples (Fevaha et al., 2014a; Nakagami et al., 2008; Yamada et al., 2010; Nakagami et al., 2010; Davis and Brekke, 2014; Choi et al., 2013), reflecting moderate deficits.

3.2. Sample characteristics and baseline associations between motivation and substance use

As shown in Table 1, a considerable number of schizophrenia patients were using alcohol or illicit drugs at baseline, with 576 (40.2%) of the 1434 reporting any substance use in the prior 90-days. Alcohol (34.5%) and cannabis (17.0%) were the two most common substances used, and use of other substances was minimal. Patients who used substances were more likely to be men, younger, and had more severe positive symptoms and overall psychopathology. Patients who used substances also had fewer neurocognitive deficits and less severe negative symptoms (Table 1).

An examination of the relationship between intrinsic motivation and likelihood of substance use apart from negative symptoms and confounding effects (e.g., age, race, gender, antipsychotic treatment, and neurocognition) revealed a significant negative prediction of substance use by intrinsic motivation scores, suggesting patients with lower baseline motivation levels were more likely to report any baseline substance use ($OR = 1.47$, $p < 0.001$). The same pattern of results was observed in patients using alcohol and cannabis, where those with lower baseline motivation levels were more likely to report baseline alcohol ($OR = 1.37$, $p = 0.011$) and cannabis use ($OR = 1.45$, $p = 0.020$) (Table 2). The effect of these substances on patients' baseline motivation was also considered, with findings showing any substance use ($B = -0.60$, $p < 0.001$), alcohol ($B = -0.47$, $p = 0.025$), and cannabis ($B = -0.58$, -0.05 , $p = 0.031$) each significantly predicted greater intrinsic motivation deficits at baseline (Table 3).

3.3. Longitudinal associations between motivation and substance use

At the 6-month follow-up, substance-using schizophrenia patients continued to exhibit greater intrinsic motivation deficits (Table 4). Specifically, patients' intrinsic motivation levels significantly improved in the overall sample ($B = 0.64, p < 0.001$); however, patients reporting any substance use exhibited significantly less improvement in intrinsic motivation ($B = -0.53, p < 0.001$). This same pattern of results was observed in patients using alcohol ($B = -0.50, p < 0.001$) and cannabis ($B = -0.63, p < 0.001$); where those using alcohol or cannabis showed significantly less improvement in intrinsic motivation (Table 4).

With respect to the 6-month impact of intrinsic motivation on substance use outcomes, high intrinsic motivation levels were associated with significantly greater reductions in substance use ($B = -0.07, p < 0.001$). The consistency of these findings was maintained across patients using alcohol ($B = -0.08, p < 0.001$) and cannabis ($B = -0.14, p < 0.001$), such that high intrinsic motivation levels were associated with a significantly greater reduction in the patients using these substances (Table 5).

4. Discussion

This is the first study, to our knowledge, to examine the impact of substance use on intrinsic motivation and associations between intrinsic motivation and substance use reductions in a large heterogeneous sample of schizophrenia patients. At baseline, all schizophrenia patients had intrinsic motivation deficits, but those with even lower levels of intrinsic motivation were at higher risk of substance use, and substance-using schizophrenia patients had greater deficits. At 6-months, substance-using schizophrenia patients continued to experience greater intrinsic motivation deficits compared to their non-substance using counterparts. Of note, we also found higher intrinsic motivation was associated with greater reductions in substance use over the follow-up. Findings remained significant after adjusting for demographic and clinical confounds and were consistent across patients using any substance, alcohol, and cannabis.

Our results have implications. Motivation is a strong predictor of recovery and functional outcome in schizophrenia (Fevaha et al., 2014a; Medalia and Brekke, 2010), and our results indicate lower motivation levels are more common among substance-using schizophrenia patients, suggesting that this group may be at higher risk of experiencing poor outcomes. Compounding preexisting motivation deficits in schizophrenia via substance use, which is well known to affect motivation and reward processing (Volkow et al., 2016; Volkow et al., 2014; Volkow et al., 2007), would seem to open the possibility for substance-using schizophrenia patients to demonstrate greater difficulty achieving and sustaining treatment goals than those without the disorder. Studies have in part confirmed this assertion, in that substance-using schizophrenia patients have less motivation to change their substance-related behaviors and have higher substance use relapse than their substance-using counterparts without schizophrenia (Horsfall et al., 2009). Clearly, these conditions continue to present unsolved challenges for affected individuals, as well as for their treatment providers (Green, 2005; Mueser et al., 1990). Unfortunately, current treatments for substance-using schizophrenia patients are suboptimal (Hunt et al., 2013), perhaps because the adaptation of existing modalities to their needs is lacking.

At the same time, our results showed higher motivation levels were associated with greater reductions in substance use. While this suggests that substance use should decrease in schizophrenia patients by enhancing the intrinsic value of reducing substance use, low motivation levels coupled with the modest, albeit significant, contribution of motivation to reductions in substance use signal a need for these deficits to be assessed and addressed in the context of formal comorbidity treatment. Given that short-term extrinsic goals (e.g., tangible rewards such as tokens or money) can stimulate initial behavior change when intrinsic motivation levels are low (Nakagami et al., 2010; Silverstein, 2010), brief engagement in programs that seek to build motivation via extrinsic rewards, such as contingency management (Hunt et al., 2013; Drake et al., 2008), followed by long-term participation in programs focused on sustaining the change, like motivational interviewing (Graber et al., 2003; Martino et al., 2006; DiClemente et al., 2008), may be a useful strategy for optimizing outcomes. Finally, evidence suggests that to effectively assist substance-using schizophrenia patients achieve their best quality of life, programs should not be narrowly focused on reducing substance use alone (Drake et al., 2015); thus, motivation deficits should be addressed in the context of other recovery indicators, including substance use, symptoms, functioning, and employment. These findings taken together show an association of level of motivation and substance use, particularly alcohol and cannabis, in schizophrenia, and suggest motivation deficits may be an important treatment target.

Limitations should be noted. The intrinsic motivation measure was derived from the Heinrichs-Carpenter Quality of Life Scale; and is not a stand-alone intrinsic motivation instrument. The Intrinsic Motivation Inventory (IMI; Choi et al., 2010) has been developed and validated in patients with schizophrenia; however, this measure was not available for use in the CATIE. Notably, however, the IMI and the derived intrinsic motivation measure used herein have yielded consistent results in prior studies (Fervaha et al., 2014b), suggesting these measures tap similar constructs. There is a need for replication of our findings using the IMI in substance-using schizophrenia patients, to inform a greater understanding of the intrinsic value associated with substance use in this population. In addition, the derived intrinsic motivation measure used herein limits our examination to general intrinsic motivation deficits, and further work around the specific motivations for why patients continue to use or reduce use will be needed. Given our secondary use of data, we were precluded from examining the potential impact of extrinsic motivators (e.g., money or rewards) on the relationships examined. Our substance use measure was, admittedly limited by self-report (use/no use), and, as substance use was not quantified, we are precluded from drawing conclusions about quantity/frequency. Given the potential for under-reported substance use, our findings may underestimate the actual rates of use (Bahorik et al., 2014). Biomedical measures of drug-use had the largest amount of missing data in the CATIE and recent investigations have cautioned that using multiple measures to confirm substance use may result in overestimates (Johnson et al., 2015). Given these concerns and the study design, we believe our use of self-report substance use is appropriate. Persons with the most severe substance use were likely to meet the CATIE exclusion criteria, potentially limiting generalizability. Dopaminergic transmission via amphetamine may improve motivation (Barch and Carter, 2005; Pietzak et al., 2010); however, we were unable to test these effects due to low base rates of amphetamine; signaling a need for further work in this area. We can

only comment on the observed differences during the 6-month follow-up, largely due to a high rate of attrition, although we would like to emphasize no significant differences were found regarding those who completed the study and those who withdrew early regarding the intrinsic motivation and substance use outcomes. Missing data approaches can yield biased parameter estimates, particularly when attrition is high or the missing data mechanism is unknown (Graham, 2009; Pigott, 2001); and thus, there may be concerns over our use of EM to estimate missing data under suboptimal conditions (e.g., high attrition, lack of direct evidence about whether the missing at random assumption holds, etc.). As our longitudinal analyses with EM showed similar, albeit less powerful results under complete case analysis, and studies have shown this approach can provide unbiased estimates when data are not missing at random (Graham, 2009), we do not believe our missing data approach markedly restricts the applicability of this research. Regardless, the implications derived from our longitudinal findings should be interpreted with caution until future confirmatory studies with a lower level of attrition are conducted. Finally, the influence of motivation on substance use (and vice versa) is not specific to schizophrenia (Harvey and Strassnig, 2015). However, the prevalence of motivational deficits and substance use in this disorder suggests that these relationships are particularly salient and ought to be taken into account.

Although more research is required to replicate these findings with a lower level of attrition and measures specific to the motivational deficit in schizophrenia, our findings most notably emphasize concerns about substance use compounding preexisting motivation deficits in the disorder. Consequently, as part of the ongoing search for interventions to improve substance use outcomes in schizophrenia, a greater focus on motivational deficits and their underlying neurobiology, or the shared mechanisms and causal structure underlying the motivation-substance use relationship, may facilitate efforts aimed at ameliorating these challenges and improve outcomes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Highlights

- Overall, patients with schizophrenia had moderate intrinsic motivation deficits.
- Low motivation in schizophrenia patients was associated with higher odds of substance use.
- Continued substance use was associated with greater motivation deficits over the study.
- Higher motivation levels was associated with faster reductions in substance use over the study.

Table 1

Demographic, clinical, and treatment characteristics of patients with schizophrenia.

	Substance Use <i>n</i> = 576	No Substance Use <i>n</i> = 858	
Variable	<i>M</i> (<i>SD</i>)	<i>M</i> (<i>SD</i>)	<i>p</i> ^a
Demographic Characteristics			
Age, years	38.29 (10.9)	42.1 (10.96)	<0.001
Race/ethnicity— <i>n</i> (% White)	338 (58.6)	526 (61.3)	0.346
Gender— <i>n</i> (% male)	465 (80.7)	597 (69.5)	<0.001
Marital Status— <i>n</i> (% married)	62 (10.7)	104 (12.1)	0.481
Employment— <i>n</i> (% employed)	97 (16.8)	119 (13.8)	0.304
Clinical Characteristics			
PANSS Total ^b , score	76.28 (17.13)	74.93 (17.13)	0.151
General Psych ^c , score	37.53 (9.19)	36.52 (9.26)	0.042
Positive ^d , score	19.28 (5.54)	17.86 (5.6)	<0.001
Negative ^e , score	19.48 (6.41)	20.55 (6.36)	<0.001
Neurocognition ^f , score	0.13 (0.97)	−0.12 (1.12)	<0.001
Alcohol use— <i>n</i> (% use)	495 (34.5)	-	-
Cannabis use— <i>n</i> (% use)	244 (17.0)	-	-
Cocaine use— <i>n</i> (% use)	121 (8.4)	-	-
PCP use— <i>n</i> (% use)	3 (0.2)	-	-
Opiate use— <i>n</i> (% use)	20 (1.3)	-	-
Amphetamine use— <i>n</i> (% use)	29 (2.0)	-	-
Treatment Characteristics ^g			
Antipsychotic— <i>n</i> (% use)	400 (69.4)	636 (74.1)	0.045
Anxiolytic — <i>n</i> (% use)	91 (15.7)	165 (19.2)	0.023
Antidepressant— <i>n</i> (% use)	168 (29.1)	274 (31.9)	0.045
Antiepileptic— <i>n</i> (% use)	87 (15.1)	142 (16.5)	0.047
No Medication— <i>n</i> (% no use)	129 (22.3)	146 (17.0)	0.008
CPZ ^h , daily dose	348.30 (413.97)	375.47 (422.12)	0.315

Note. PCP = phencyclidine; PANSS = positive and negative syndrome scale; CPZ = chlorpromazine equivalent dose. General Psych = General Psychopathology

^aBivariate analyses were computed using χ^2 (categorical) or independent sample *t*-tests (continuous) variables. Between-group comparisons were not computed for substance use variables because drug and alcohol use variables are not mutually exclusive.

^bHigher mean scores indicate greater overall psychopathology.

^cHigher mean scores indicate greater general psychopathology.

^dHigher mean scores indicate greater positive symptoms.

^eHigher mean scores indicate greater negative symptoms.

^fHigher mean neurocognition scores indicate better function (less neurocognitive deficits).

^gAnalyses were conducted on 995 participants.

^hCPZ daily dose equivalents were computed based on pre-randomization antipsychotic dose.

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Table 2

Logistic regression analyses of the relationship between intrinsic motivation scores and likelihood of substance use.

Variable	Substance Use					Alcohol Use					Cannabis Use				
	OR	95% CI	SE	p		OR	95% CI	SE	p		OR	95% CI	SE	p	
<i>n</i> = 576						<i>n</i> = 495					<i>n</i> = 244				
Age	0.72	-0.43, -0.19	0.06	<0.001		0.74	-0.41, -0.17	0.06	<0.001		0.56	-0.73, -0.41	0.08	<0.001	
White	0.86	-0.37, 0.08	0.11	0.203		0.98	-0.25, 0.21	0.12	0.870		0.83	-0.48, 0.11	0.15	0.228	
Male	1.78	0.32, 0.84	0.13	<0.001		1.66	0.24, 0.78	0.13	<0.001		1.96	0.30, 1.07	0.19	<0.001	
No antipsychotic	0.77	-0.66, 0.16	0.21	0.234		0.73	-0.74, -0.10	0.12	0.153		0.70	-0.87, 0.16	0.26	0.181	
Negative Symptoms	0.78	-0.35, -0.11	0.06	<0.001		0.77	-0.37, -0.12	0.06	<0.001		0.85	-0.31, -0.00	0.08	0.046	
Neurocognition	1.18	0.04, 0.29	0.06	0.007		1.15	0.01, 0.27	0.06	0.027		1.23	0.04, 0.38	0.08	0.011	
Low IM	1.47	0.15, 0.63	0.12	<0.001		1.37	0.07, 0.56	0.12	0.011		1.45	0.05, 0.69	0.16	0.020	

Note. Analyses were conducted on the baseline sample; IM = intrinsic motivation

Table 3

Mixed-effects regression analyses predicting intrinsic motivation from substance use, adjusting for demographic and clinical variables.

Intrinsic Motivation				
Variable	B	95%CI	SE	p
Substance Use				
Age	-0.27	-0.48, -0.06	0.10	0.010
White	-0.09	-0.50, 0.30	0.20	0.635
Male	-0.51	-0.96, -0.07	0.22	0.023
No antipsychotic	-0.36	-1.10, 0.36	0.37	0.323
Negative Symptoms	-1.47	-1.67, -1.27	0.10	<0.001
Neurocognition	0.89	0.67, 1.10	0.10	<0.001
Substance use	-0.60	-1.00, -0.20	0.20	<0.001
Alcohol Use				
Age	-0.25	-0.46, -0.04	0.10	0.015
White	-0.07	-0.48, 0.32	0.20	0.699
Male	-0.54	-0.99, -0.09	0.22	0.016
No antipsychotic	-0.36	-1.10, 0.36	0.37	0.325
Negative Symptoms	-1.46	-1.66, -1.26	0.10	<0.001
Neurocognition	0.88	0.66, 1.09	0.10	<0.001
Alcohol use	-0.47	-0.88, -0.05	0.21	0.025
Cannabis Use				
Age	-0.27	-0.48, -0.06	0.10	0.011
White	-0.09	-0.49, 0.31	0.20	0.661
Male	-0.55	-0.99, -0.10	0.22	0.015
No antipsychotic	-0.36	-1.10, 0.36	0.37	0.032
Negative Symptoms	-1.45	-1.65, -1.25	0.10	<0.001
Neurocognition	0.88	-0.67, 1.09	0.10	<0.001
Cannabis use	-0.58	-1.11, -0.05	0.27	0.031

Note. Analyses were conducted on the baseline sample.

Table 4

Longitudinal predictors of motivation deficits among patients with schizophrenia.

Variable	Intrinsic Motivation			
	<i>B</i>	95% <i>CI</i>	<i>SE</i>	<i>p</i>
Time	0.64	0.35, 0.94	0.14	<0.001
Unconditional Model				
Conditional Model with Substance Use ^a				
Age	-0.02	-0.04, -0.00	0.01	<0.001
White	0.08	-0.04, -0.00	0.20	0.678
Male	0.50	-0.31, 0.39	0.23	0.028
Antipsychotics ^b				
Quetiapine	-0.14	-0.82, 0.52	0.34	0.667
Perphenazine	-0.36	-1.08, 0.35	0.36	0.322
Ziprasidone	0.16	-0.51, 0.83	0.34	0.641
Risperidone	0.02	-0.57, 0.62	0.30	0.939
Negative	-0.22	-0.26, -0.19	0.01	<0.001
Neurocognition	0.88	0.66, 1.10	0.11	<0.001
Time	-1.32	-2.99, 0.35	0.85	0.121
Time × Age	0.00	-0.02, 0.03	0.01	0.822
Time × White	-0.16	-0.76, 0.43	0.30	0.590
Time × Male	0.79	0.10, 1.43	0.33	0.023
Time × Antipsychotics ^b				
Time × Quetiapine	0.54	-0.39, 1.48	0.47	0.259
Time × Perphenazine	0.23	-0.67, 1.15	0.46	0.605
Time × Ziprasidone	0.35	-0.63, 1.34	0.50	0.480
Time × Risperidone	0.11	-0.69, 0.92	0.27	0.780
Time × Negative	0.07	0.03, 0.12	0.02	<0.001
Time × Neurocognition	-0.02	-0.33, 0.29	0.21	0.893
Substance Use ^d	-0.53	-0.88, -0.17	0.17	<0.001

Intrinsic Motivation				
Variable	B	95% CI	SE	p
Conditional Model with Alcohol Use ^a				
Age	-0.02	-0.04, -0.00	0.01	<0.001
White	0.07	-0.04, -0.00	0.20	0.729
Male	0.52	-0.32, 0.47	0.22	0.021
Antipsychotics ^b				
Quetiapine	-0.14	-0.80, 0.52	0.34	0.680
Perphenazine	-0.36	-1.08, 0.34	0.36	0.313
Ziprasidone	0.16	-0.49, 0.83	0.34	0.618
Risperidone	0.03	-0.56, 0.62	0.30	0.919
Negative	-0.22	-0.26, -0.19	0.01	<0.001
Neurocognition	0.88	0.66, 1.09	0.10	<0.001
Time	-1.32	-3.02, 0.37	0.86	0.127
Time × Age	0.01	-0.02, 0.03	0.01	0.883
Time × White	-0.15	-0.76, 0.45	0.30	0.616
Time × Male	0.75	0.80, 1.43	0.34	0.027
Time × Antipsychotics ^b				
Time × Quetiapine	0.51	-0.43, 1.47	0.48	0.285
Time × Perphenazine	0.19	-0.72, 1.12	0.47	0.671
Time × Ziprasidone	0.33	-0.66, 1.34	0.51	0.506
Time × Risperidone	0.10	-0.71, 0.92	0.41	0.809
Time × Negative	0.07	0.03, 0.12	0.02	<0.001
Time × Neurocognition	-0.02	-0.34, 0.30	0.16	0.900
Alcohol Use ^d	-0.50	-0.86, -0.14	0.18	<0.001
Conditional Model with Cannabis Use ^a				
Age	-0.02	-0.04, -0.00	0.01	<0.001
White	0.08	-0.32, 0.48	0.20	0.687
Male	0.52	0.07, 0.97	0.23	0.022
Antipsychotics ^b				

Variable	Intrinsic Motivation			
	B	95% CI	SE	p
Quetiapine	-0.17	-0.84, 0.50	0.34	0.620
Perphenazine	-0.38	-1.10, 0.33	0.36	0.296
Ziprasidone	0.13	-0.54, 0.80	0.34	0.701
Risperidone	0.01	-0.59, 0.61	0.30	0.974
Negative	-0.22	-0.25, -0.19	0.01	<0.001
Neurocognition	0.88	0.66, 1.09	0.11	<0.001
Time	-1.32	-3.00, 0.34	0.85	0.120
Time × Age	0.01	-0.02, 0.03	0.01	0.815
Time × White	-0.19	-0.07, 0.40	0.30	0.530
Time × Male	0.76	0.09, 1.42	0.38	0.024
Time × Antipsychotics ^b				
Time × Quetiapine	0.59	-0.34, 1.54	0.47	0.211
Time × Perphenazine	0.27	-0.63, 1.19	0.46	0.553
Time × Ziprasidone	0.36	-0.62, 1.35	0.50	0.471
Time × Risperidone	0.13	-0.67, 0.94	0.41	0.738
Time × Negative	0.07	0.03, 0.12	0.02	<0.001
Time × Neurocognition	-0.03	-0.35, 0.28	0.16	0.829
Cannabis Use ^d	-0.63	-1.10, -0.16	0.23	<0.001

Note. Statistically significant effects are presented in boldface.

^aReference = not using any substances, any alcohol, or any cannabis, respectively.

^bConditional models were fit using penalized quasi likelihood estimation.

^cReference = Olanzapine

^dTime varying covariates estimating the proportion of patients using substances over the follow-up.

Table 5

Longitudinal predictors of substance use among patients with schizophrenia.

Variable	Substance Use				Alcohol Use				Cannabis Use			
	B	95% CI	SE	p	B	95% CI	SE	p	B	95% CI	SE	p
Time	-0.51	-0.72, -0.30	0.10	<0.001	-0.63	-0.84, -0.42	-0.10	<0.001	-0.80	-1.80, -0.58	0.11	<0.001
Age	-0.05	-0.06, -0.03	0.01	<0.001	-0.04	-0.06, -0.02	0.01	<0.001	-0.09	-0.12, -0.07	0.01	<0.001
White	0.28	-0.09, 0.66	0.19	0.146	0.05	-0.33, 0.44	0.20	0.783	0.42	-0.05, 0.90	0.24	0.087
Male	-1.03	-1.46, -0.59	0.22	<0.001	-0.90	-1.35, -0.45	0.23	<0.001	-1.25	-1.83, -0.66	0.30	<0.001
Antipsychotics ^b												
Quetiapine	0.11	-0.53, 0.75	0.33	0.736	0.31	-0.35, 0.99	0.34	0.356	-0.73	-1.57, 0.09	0.42	0.085
Perphenazine	0.67	-0.00, 1.35	0.34	0.054	0.86	0.16, 1.57	0.36	0.016	0.04	-0.79, 0.89	0.43	0.912
Ziprasidone	0.19	-0.44, 0.83	0.32	0.559	0.42	-0.24, 1.09	0.34	0.217	-0.42	-1.25, 0.40	0.42	0.315
Risperidone	0.42	-0.14, 0.99	0.29	0.149	0.65	0.06, 1.25	0.30	0.031	0.13	-0.57, 0.85	0.36	0.708
Negative	-0.06	-0.10, -0.03	0.01	<0.001	-0.07	-0.11, -0.04	0.01	<0.001	-0.07	-0.11, -0.03	0.02	<0.001
Neurocognition	0.27	0.06, 0.47	0.10	0.011	0.31	0.03, 0.46	0.34	0.356	-0.03	0.20, 0.73	0.12	0.803
Time	-2.22	-3.48, -0.96	0.64	<0.001	0.24	-3.91, -1.33	0.11	0.025	-4.73	-5.95, -3.50	0.62	<0.001
Time × Age	0.02	0.01, 0.04	0.01	0.016	0.02	0.01, 0.04	0.01	0.038	0.04	0.02, 0.06	0.01	<0.001
Time × White	0.55	0.10, 1.00	0.22	0.015	0.88	0.43, 1.33	0.23	<0.001	0.23	-0.20, 0.67	0.22	0.294
Time × Male	0.60	0.10, 1.10	0.25	0.019	0.45	-0.06, 0.97	0.26	0.090	0.77	0.16, 1.37	0.30	0.012
Time × Antipsychotics ^b												
Time × Quetiapine	-0.88	-1.62, -0.15	0.37	0.018	-1.39	-0.09, -0.65	0.38	<0.001	2.06	1.31, 2.81	0.38	<0.001
Time × Perphenazine	0.08	-0.56, 0.73	0.33	0.807	-0.78	-1.44, -0.12	0.33	0.021	2.59	1.93, 3.26	0.34	<0.001
Time × Ziprasidone	-0.09	-0.84, 0.66	-0.23	0.812	-0.41	-1.22, 0.39	0.41	0.318	-0.25	-1.05, 0.55	0.41	0.542
Time × Risperidone	-0.34	-0.94, 0.26	0.30	0.268	-0.67	-1.29, -0.05	0.31	0.033	1.25	0.62, 1.89	0.32	<0.001
Time × Negative	0.02	-0.01, 0.06	0.01	0.116	0.06	0.02, 0.09	0.01	0.002	0.04	0.01, 0.07	0.01	0.008
Time × Neurocognition	0.39	0.14, 0.64	0.12	0.002	0.40	0.14, 0.66	0.13	0.002	-0.03	-0.27, 0.21	0.12	0.803
Intrinsic Motivation ^c	-0.07	-0.11, -0.04	0.01	<0.001	-0.08	-0.12, -0.04	0.02	<0.001	-0.14	-0.19, -0.10	0.02	<0.001

Note. Statistically significant effects are presented in boldface. Analyses were conducted on the baseline sample.

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θ Conditional models were fit using penalized quasi likelihood estimation.
 $b_{\text{Reference}}$ = Olanzapine
 $c_{\text{Intrinsic Motivation}}$ = Time varying covariate estimating the average score over the follow-up.