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Association between recent cannabis consumption and withdrawal-related symptoms during early abstinence among females with smoked cocaine use disorder

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Abstract

Background: The effects of cannabis on clinical outcomes of treatment services for other drug use disorders remains unclear. The primary aim of the current study was to investigate the effects of recent cannabis consumption on the severity of cocaine withdrawal and depressive symptoms during a 3-week inpatient treatment program for women with cocaine use disorder. The second goal of this study was to test the effect of recent alcohol or tobacco use on the aforementioned outcomes.

Methods: This was a longitudinal study with 2 assessment time points: at enrollment and upon discharge from a medically managed intensive inpatient unit. The sample was composed of 214 early abstinence females with cocaine use disorder. Cocaine withdrawal and depressive symptoms were measured using the Cocaine Selective Severity Assessment (CSSA) and the Beck Depressive Inventory (BDI-II). Recent substance use was evaluated using the Addiction Severity Index (ASI-6).

Results: Patients with cocaine use disorder and with frequent recent cannabis use reported higher severity of cocaine withdrawal and depressive symptoms after 3 weeks of inpatient treatment. Neither recent alcohol nor tobacco use was associated with increased CSSA or BDI outcomes, suggesting these substances play a minor role compared to recent cannabis use in affecting withdrawal-related symptoms.

Conclusions: The assessment of recent cannabis use may help identify patients in need of additional treatment to manage severe cocaine withdrawal symptoms and depressive symptoms during early abstinence.

Keywords

Cannabis; Cocaine; Cocaine Use Disorder; Substance withdrawal syndrome; detoxification

1. Introduction

Cannabis is the most frequently consumed illicit substance worldwide (Legleye et al. 2014), but the impact of its effects on clinical outcomes in patients receiving treatment for other substance use disorder remains unclear (Aharonovich et al. 2005). The prevalence of cannabis use among cocaine dependence is high, particularly among females, and potentially associated with greater impairment and poorer treatment outcome (Pesce et al. 2010). First, adolescent exposure to cannabis predicts early onset of cocaine use disorder later in life (Butelman et al. 2019). Second, cocaine-dependent patients with frequent cannabis use also report more medical, legal, and psychiatric problems (Lindsay et al. 2009). Third, we recently showed that female cocaine-dependent patients reporting lifetime cannabis use had a worse detoxification treatment response during early abstinence, compared to patients without a cannabis use history (Viola et al. 2014b). These studies suggest that patients with cocaine use disorder and with a high pattern of cannabis consumption may have higher rates of relapse and experience more severe withdrawal symptoms, particularly during the initial phase of abstinence (Aharonovich et al. 2005, Aharonovich et al. 2006, Fox et al. 2013, Viola et al. 2014b).

However, studies exploring a “drug substitution hypothesis” have yielded conflicting results (Lau et al. 2015). For instance, in a longitudinal investigation of 122 participants reporting polysubstance use (Socias et al. 2017), a period of intentional use of cannabis was effective in reducing the frequency of smoked cocaine consumption, supporting the potential therapeutic use of cannabinoids for the treatment of cocaine use disorder. In light of these mixed findings, more research to assess the role of cannabis use in the treatment of cocaine use disorder is warranted.

Here, we further investigated the effects of cannabis use phenotypes on important clinical features related to cocaine use disorder in a larger independent sample from our primary investigation (Viola et al. 2014b). Our previous study focused on lifetime cannabis use and here we sought to better understand the acute effects of *current* cannabis use. Thus, our primary aim was to investigate the effects of recent cannabis consumption on the severity of cocaine withdrawal and depressive symptoms during a 3-week inpatient treatment program for women with cocaine use disorder. Our second goal was to investigate the effects of recent alcohol and tobacco use in the aforementioned outcomes. We hypothesized that recent cannabis consumption would increase severity of cocaine withdrawal and depressive symptoms among these patients.

2. Material and Methods

2.1. Study design

We performed an observational study with a longitudinal design in early abstinence female patients with cocaine use disorder. We measured cocaine withdrawal and depressive symptoms at the first (time of enrollment) and third (before discharge) week of a medically managed intensive inpatient treatment program. Hospitalization in inpatient psychiatric units for drug detoxification is one of the treatment options available in the public health-care system in Brazil. Common symptoms for admitting persons who chronically use drugs to inpatient treatment include acute intoxication, withdrawal symptoms, psychiatric comorbidities, suicide ideation, aggressive behavior and psychotic symptoms (Schein and Prati 2013). These admission criteria are consistent with American Society of Addiction Medicine (ASAM) criteria (Stallvik and Nordahl 2014), in which inpatient admission for drug addiction is considered when patients present severe intoxication with imminent risk of danger to self/others. Before hospitalization, patients sign a form that includes their voluntary consent to the treatment and the referral from a health-care professional.

The inpatient treatment program took place on an all-female unit consisting of 3 weeks of drug rehabilitation, including psychoeducation and support groups, moderate physical activity, a balanced diet (2200 Kcal/day), nursing care, and psychological and medical treatment. Patients also had a prescribed symptomatic cocaine detoxification protocol with neuroleptics, antidepressants and mood stabilizers as described previously (Viola et al. 2014a). The medical and nursing staff thoroughly inspected the body and clothes of patients at their enrollment in the treatment program, to ensure patients did not bring substances into the treatment unit. When patients received visits or were allowed to leave the inpatient unit for brief moments, they were accompanied by staff members. In addition, patients were inspected every time before they re-entered the unit to ensure they had no access to alcohol, cigarettes, or drugs. Furthermore, at the end of the 3-week treatment program, patients provided urine samples for drug testing (marijuana, opiate, cocaine, amphetamine, and benzodiazepines) using the Easy@Home 5 Panel Instant Urine Drug Test (EDOAP-754, Easy Healthcare Corporation, USA). Test results confirmed abstinence in all of the study participants.

The Ethical Committee of the enrolled institutions approved the research protocol, and procedures followed were in accordance with the Helsinki Declaration.

2.2. Participants

Participants ($n = 290$) were consecutive admissions to the aforementioned inpatient treatment unit from May, 2015 to December, 2017 and met the following criteria: (1) age of 18 to 45 years old; (2) diagnosis of cocaine use disorder according to Structured Clinical Interview for DSM-5 (SCID-5) (Shankman et al. 2018); (3) self-report of smoked cocaine (crack) as their primary substance problem; and (4) absence of any neurological disorder, severe medical condition, or primary psychotic disorder. Participants were excluded if they failed to provide reliable information regarding their drug use behavior (e.g., inability to recall drug use patterns in the last month; $n = 29$); or if they were discharged before the third

week of treatment resulting in the missing follow-up measurements ($n = 47$). The final sample size was 214.

2.3. Clinical assessment

We used the SCID to assign the diagnosis of cocaine use disorder. The Addiction Severity Index (ASI-6) (McLellan et al. 1980, Kessler et al. 2012) was used to assess the number of days of recent drug use prior to treatment enrollment (last 30 days) and lifetime years of regular (at least 3 days of drug consumption per week) use of cannabis, tobacco, alcohol, and cocaine. Using the ASI-6 we also asked participants about their history of drug-related treatments (number of lifetime inpatient treatments), motivation towards treatment success (scored on a 0–5 scale), and motivation to maintain abstinence from all drugs (scored on a 0–5 scale). We performed the ASI-6 during the second week of treatment.

2.4. Withdrawal-related symptom outcomes

We used the Cocaine Selective Severity Assessment (CSSA) to assess cocaine withdrawal symptoms (Kampman et al. 2004). Moreover, depressive symptoms are common among people with cocaine use disorder and have been associated with greater severity of this disorder, as well as with poor treatment outcomes (McKay et al. 2002, Francke et al. 2013). Thus, we measured depressive symptoms using the Beck Depression Inventory II (BDI-II) (Beck et al. 1996). The CSSA and BDI-II total scores were computed by the sum of each individual item score.

2.5. Statistical analysis

We estimated the sample size based on our previous study where groups of female patients with cocaine use disorder were compared regarding their history of lifetime cannabis consumption (Viola et al. 2014b). We assumed a ratio of 3 patients with no recent cannabis use to 1 patient reporting such history. Using the mean and standard deviation data of the CSSA score from our previous study the sample size for the current investigation was estimated in 212 participants, using a significance level of 5% and a power of 80%.

Concerning our primary goal, we stratified the sample based on the distribution of the ASI-6 variable for recent (last 30 days) use of cannabis. We generated a three-level group variable by categorical binning: (1) no recent cannabis use (0 days); (2) occasional recent cannabis use (≤ 5 days) (Battistella et al. 2013); (3) frequent recent cannabis use (> 5 days). We analyzed sociodemographic and clinical characteristics of these groups by means of analysis of variance (ANOVA), followed by Bonferroni post-hoc test, or chi-square test when appropriate.

The primary analyses consisted of comparisons between groups of recent cannabis use on CSSA and BDI-II outcomes. Thus, we performed linear mixed models since these models took into account of the non-independence of repeated measures within participants by involving each participant's slope and intercept as random effects. A null model and four linear mixed models were performed adding different fixed effects (i.e., predictors). Our first model included the three-level variable "group" only, while the second model included the two-level variable "time" ("T1" and "T2" for the beginning and end of treatment,

respectively). Because groups differed significantly in age and number of past treatments for alcohol/drugs; these two variables were included as covariates in model three and four, respectively. All models tested CSSA and BDI-II scores as the primary outcomes. Additional Bonferroni post-hoc comparisons were performed using univariate ANOVA.

For the second goal of this study, we used the same analytic approach, generating three groups of participants (no recent use; occasional recent use; frequent recent use) based on self-reported days of alcohol or tobacco consumption in the last month. Similar linear mixed models were used to examine the association between groups on CSSA, or BDI-II scores at the first and third week of treatment, controlling for the effects of age and number of past treatments for alcohol/drugs.

We performed ANOVAs and chi-square tests using the Statistical Package for the Social Sciences 25 (SPSS 25, IBM) and effect sizes were calculated by Cohen's *d*. We performed linear mixed models using the package "lmer" and compared them by using the package "MuMIn", both from the open source statistical software R.

3. Results

3.1. Sample description

Table 1 present the sociodemographic and clinical characteristics of the sample according to recent cannabis use. Sixty-four percent ($n = 138$) of the sample reported no recent cannabis use, 14% ($n = 29$) reported occasional cannabis use and 22% ($n = 47$) reported frequent recent cannabis use during the last 30 days. We observed significant group differences in mean age, showing that participants with no recent cannabis use were older than participants who reported frequent recent cannabis consumption (post-hoc: $p = 0.028$; 95 % confidence interval – CI: 0.18 | 6.18).

We found no differences on recent (days in past 30) or lifetime (years of regular use) use of alcohol, tobacco or cocaine. However, as expected, participants with no cannabis use during the last 30 days also reported significantly less years of regular cannabis use in their lifetime, compared to participants with occasional (post-hoc: $p = 0.011$; 95 % CI: -7.70 | -0.77) and frequent (post-hoc: $p < 0.001$; 95% CI: -12.60 | -6.87) recent cannabis use. Moreover, we observed significant group differences in the number of past treatments for alcohol/drugs, but this effect was not observed when Bonferroni post-hoc test were performed (post-hoc: $p = 0.079$; 95 % CI: -3.84 | 0.15; no recent use *versus* frequent use). We found no group differences on motivation toward treatment success, motivation to achieve drug abstinence, or use of medication during treatment.

To be noted, we observed that excluded participants had a similar percentage of cannabis use in the last month prior to treatment enrollment: 67% ($n = 44$) reported no recent cannabis use, 14% ($n = 9$) reported occasional cannabis use and 19% ($n = 12$) reported frequent recent cannabis use, while 11 participants were excluded before the ASI-6 interview and we did not have such information.

3.2. Effects of recent cannabis consumption on CSSA and BDI-II scores

Table 2 shows results from the five linear mixed models (including a null model with no fixed effect) with Model 2 showing the best fit for the set of data. This model revealed a significant effect of time ($\beta = -9.01$, $t = -6.49$, $p < 0.001$), showing that, on average, participants exhibited a reduction of 21.8 % on CSSA scores from enrollment to discharge from the inpatient treatment program. We found a significant group effect (Figure 1A) revealing that participants who reported recent frequent cannabis use had higher CSSA scores than those with no recent cannabis use. Additional post-hoc analysis showed that this effect was specific to the second assessment (frequent vs no use $p = 0.028$; 95% CI: 0.61 | 14.32; $d = 0.431$). The group with occasional recent cannabis use did not differ from the other groups at either time points.

Similarly, we observed a significant effect of time ($\beta = -19.68$, $t = -18.31$, $p < 0.001$) demonstrating that, on average, participants exhibited a reduction of 56.5 % on BDI-II scores from the first to the second assessment. We found a significant group effect ($\beta = 3.63$, $t = 2.34$, $p = 0.020$; Figure 1B) showing that participants who reported recent frequent use of cannabis had higher BDI-II scores than those with no recent cannabis use, as well as compared with those with occasional cannabis recent use. Post-hoc analysis showed that this effect was specific to the second assessment (frequent vs no use $p = 0.030$; 95% CI: 0.31 | 8.62; $d = 0.437$).

3.3. Effects of recent alcohol or tobacco consumption on CSSA and BDI-II scores

We described sample sizes of subgroups based on recent alcohol or tobacco use patterns in Figure 1 legend. For recent alcohol groups, in addition to the effect of time, we found a nonsignificant group effect ($\beta = 3.97$, $t = 1.87$, $p = 0.062$; Figure 1C) on CSSA scores, with higher overall scores found in the frequent recent alcohol use group compared with the group with no alcohol use. We also found a nonsignificant group effect for recent tobacco use on CSSA scores ($\beta = 1.13$, $t = 0.40$, $p = 0.686$; Figure 2E). Similarly, we observed no significant group effects regarding the subgroups of alcohol ($\beta = 1.59$, $t = 1.10$, $p = 0.270$; Figure 1D) or tobacco ($\beta = 0.56$, $t = 0.30$, $p = 0.763$; Figure 2F) on BDI-II scores.

4. Discussion

In this study we investigated the effects of concurrent cannabis use on the outcomes of an inpatient treatment program in female patients with cocaine use disorder. We found that frequent recent cannabis use prior to treatment enrollment was associated with higher cocaine withdrawal and depressive symptoms after 3 weeks of treatment. Neither recent alcohol nor tobacco use predicted cocaine withdrawal or depressive symptoms, suggesting that these substances play a minor role compared to cannabis in affecting treatment outcome.

Cannabis as secondary drug was recently not associated with a greater risk of death in patients with cocaine use disorder (Fuster et al. 2017). However, our findings suggest that taking into account recent patterns of cannabis use prior to admission to an inpatient treatment for cocaine addiction, may help to identify patients for whom cocaine withdrawal-related symptoms may jeopardize treatment success. These findings corroborate our prior

research showing that long-term cannabis use is associated with increased cocaine craving and relapse (Viola et al. 2014b). Moreover, chronic cannabis use may increase the severity of psychotic symptoms during cocaine intoxication (Trape et al. 2014).

Severity of withdrawal symptoms during early abstinence predicts worse pharmacological or psychosocial treatment outcomes among patients with cocaine use disorder, particularly when these symptoms are assessed using the CSSA instrument (Ahmadi et al. 2008). Although the CSSA evaluates depressive symptoms, we included the BDI-II to obtain a more detailed assessment of mood changes during treatment. Previous studies have shown worse clinical outcomes related to cocaine use disorder in patients with major depression than in non-depressed patients (McKay et al. 2002). In this sense, we also observed higher severity of depressive symptoms after 3 weeks of treatment in those participants who reported frequent recent cannabis use.

Neurobiological evidence supports the behavioral cross-sensitization effect of concurrent cannabis and cocaine use (Fox et al. 2013). Emerging evidence from animal studies reveals a higher behavioral sensitivity to cocaine effects due to previous tetrahydrocannabinol (THC) exposure, suggesting that the endocannabinoid system may mediate some neuroadaptations that alter brain reward system functioning to psychostimulants (De Vries et al. 2001, Chadwick et al. 2013). For instance, administration of a cannabinoid agonist during cocaine abstinence alters subsequent cocaine seeking behavior, including enhanced resistance to extinction and reinstatement (González-Cuevas et al. 2007). These pre-clinical findings provide further evidence of the detrimental consequences of cannabis on relevant aspects of cocaine use disorder.

This study should be interpreted in light of its limitations. We used self-reported days of drug use to quantify recent consumption. Whereas actual amount of drug consumed may be more precise, it is complex to measure because of the indiscriminate polysubstance use of our sample. Moreover, the few instruments that assess patterns of cannabis use provide conflicting guidelines for quantity measurement (Robinson et al. 2014). Our sample of female patients younger than 45 years old limits the generalizability of our findings. A replication of this study in older and male patients should be undertaken. Additionally, this study was performed at a single recruitment site with consecutive sampling. Consecutive sampling may be a source of bias regarding temporal or seasonal trends during the inclusion of participants. Despite that we invited all eligible patients during the enrollment period, with a rejection rate of 10% only. Moreover, we cannot rule out potential effects of information bias in our study, since the assessment of patterns of cannabis and cocaine consumption required participants to recall such kind of information during the last 30 days before treatment enrollment. In addition, patients who did not complete the treatment program were excluded from the analyses, which could be considered a source of bias. Despite that, we observed that excluded participants had a similar percentage of cannabis use in the last month prior to treatment enrollment when compared to those included in the study. Moreover, it should be noted that the effects of potential confounding variables were accounted in our main statistical analysis, such as age and number of past treatment for alcohol and drug use. Also, we performed the same analytic approach for other 2 substances, alcohol and tobacco, in addition to cannabis.

5. Conclusions

In female patients with cocaine use disorder who seek inpatient treatment for drug addiction, measurement of recent cannabis use appears to have clinical utility. Specifically we found that recent frequent use of cannabis is associated with more severe cocaine withdrawal and depression symptoms. To the extent that successful drug abstinence predicts better long-term treatment outcome (DiGirolamo et al. 2017), the need to address this cannabis using group of cocaine use disorder patients is critical.

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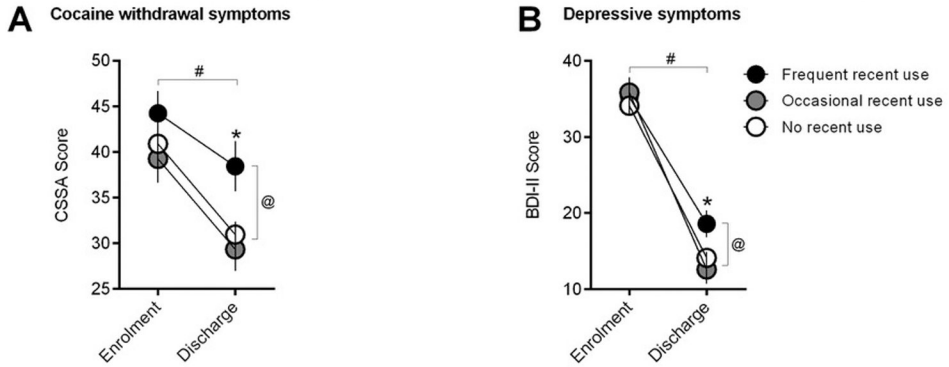
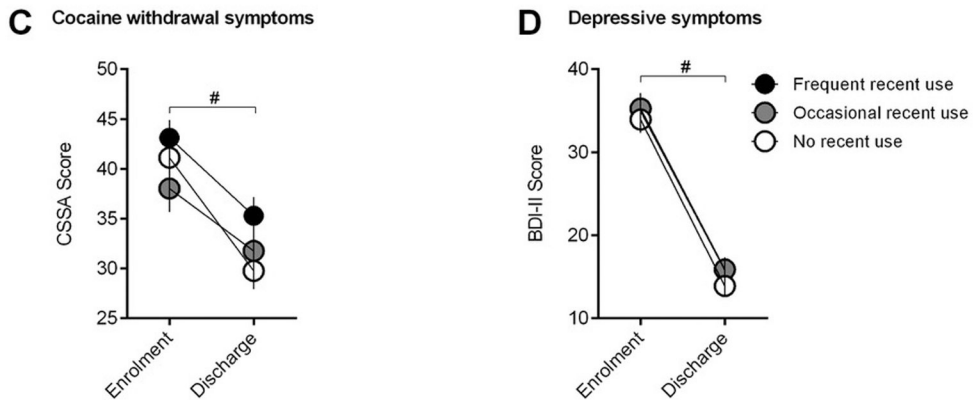
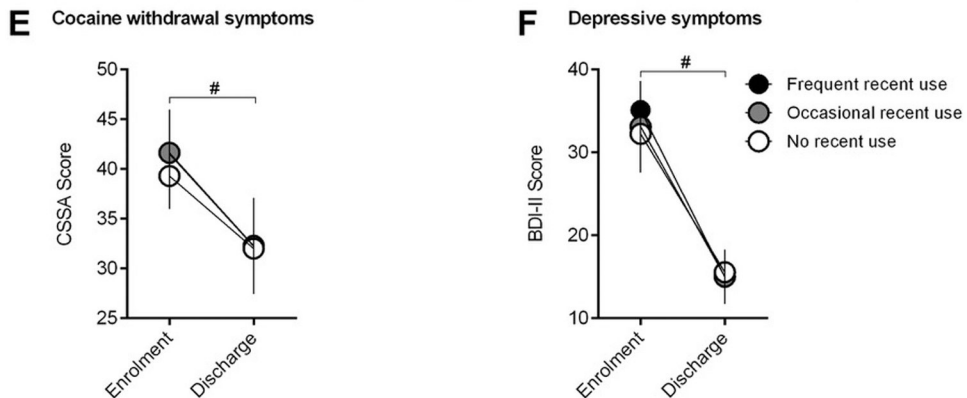
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Cannabis (recent use) subgroups among women with smoked cocaine dependence**Alcohol (recent use) subgroups among women with smoked cocaine dependence****Tobacco (recent use) subgroups among women with smoked cocaine dependence****Figure 1.**

Cocaine withdrawal and depressive symptoms among groups regarding recent substance use. Longitudinal assessment with 2 time points: at the enrollment (first week) and at the discharge (third week) of an inpatient treatment program; CSSA, Cocaine Selective Severity Assessment; BDI-II, Beck Depressive Inventory; Sample size of cannabis groups: No recent use = 138, Occasional recent use = 29, Frequent recent use = 47; Sample size of alcohol groups: No recent use = 85, Occasional recent use = 50, Frequent recent use = 79; Sample size of tobacco groups: No recent use = 28, Occasional recent use = 11, Frequent recent use = 11.

= 175; # = significant time effect in the linear mixed model; @ = significant group effect in the linear mixed model; * = Bonferroni post-hoc test significant effect.

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Sociodemographic and clinical characteristics of the sample

Table 1.

Sociodemographic - mean (SD)	No recent cannabis use (n = 138)	Occasional recent cannabis use (n = 29)	Frequent recent cannabis use (n = 47)	Statistics	p-value	Cohen's d
Age	34.46 (8.20)	33.11 (8.12)	30.58 (7.50)	F = 3.47	.033	.316
Income per month (US\$)	1556.64 (1100)	1870.07 (1332)	1349.01 (842)	F = 2.01	.136	.241
Days of drug consumption last month – mean (SD)						
Tobacco	17.32 (9.85)	19.79 (8.31)	20.25 (8.01)	F = 2.17	.116	.250
Alcohol	6.76 (9.41)	8.21 (8.71)	7.74 (9.25)	F = .407	.666	.108
Cannabis	0 (0)	1.97 (1.21)	21.02 (5.92)	F = 692	>.001	4.46
Cocaine	16.14 (8.52)	17.62 (6.91)	17.34 (8.06)	F = .627	.539	.134
Years of regular drug use – mean (SD)						
Tobacco	17.62 (9.13)	16.97 (10.24)	15.88 (8.01)	F = .495	.610	.119
Alcohol	4.54 (7.13)	5.39 (8.03)	4.89 (5.65)	F = .189	.828	.074
Cannabis	3.62 (5.85)	7.86 (9.43)	13.36 (8.47)	F = 30.89	>.001	.944
Cocaine	8.45 (5.79)	8.23 (6.51)	8.18 (7.20)	F = .037	.964	.033
Motivation for detoxification treatment - mean (SD)						
Motivation towards treatment success	3.80 (0.58)	3.76 (0.62)	3.86 (0.55)	F = .416	.880	.110
Motivation for abstinence of all drugs	3.71 (0.80)	3.76 (0.79)	3.41 (1.20)	F = .860	.425	.157
Medication use during detoxification - % (n)	64.5 (89)	62.1 (18)	46.8 (22)	$\chi^2 = 4.62$.099	-
Past treatments - mean (SD)						
Number of life-time treatments for alcohol/drugs	4.79 (4.33)	4.10 (2.62)	6.64 (7.05)	F = 3.20	.043	.304
Number of life-time inpatient treatments	3.96 (3.56)	3.55 (2.64)	5.32 (5.87)	F = 1.59	.097	.214

Note: Between group comparisons performed by ANOVA or chi-square test. Medication use during inpatient treatment, participants had prescribed symptomatic cocaine detoxification protocol, including neuroleptics, analgesics, antidepressants and mood stabilizers; CSSA, Cocaine Selective Severity Assessment; BDI-II, Beck Depressive Inventory. Cohen's d effect size estimates.

Table 2.

Linear Mixed-Models.

	Group		Time	Age	Treatment Frequency	mR ²	cR ²	Model comparison		p-value
	Occasional	Frequent						AIC	BIC	
<i>CSSA scores</i>										
Null Model	-	-	-	-	-	.000	.813	3682.656	3702.951	
Model 1	-1.64 (-.57)	5.57 (2.37) **				.019	.815	3679.932	3708.346	Null vs 1 0.0347
Model 2	-1.64 (-.57)	5.57 (2.36) **	-9.01 (-6.49) ***			.082	.830	3643.141	3675.614	1 vs 2 <0001
Model 3	-1.61 (-.56)	5.69 (2.38) **	-9.01 (-6.48) ***	.04 (.31)		.082	.831	3645.042	3681.574	2 vs 3 0.7528
Model 4	-1.33 (-.47)	5.10 (2.12) *	-9.01 (-6.47) ***	.06 (.55)	.38 (1.93) †	0.93	.852	3643.272	3683.863	3 vs 4 0.0522
<i>BDI-II scores</i>										
Null Model	-	-	-	-	-	.000	.825	3551.853	3572.149	
Model 1	-.55 (-.30)	3.47 (2.27) *				.008	.830	3550.158	3578.571	Null vs 1 0.058
Model 2	-.55 (-.30)	3.47 (2.27) *	-19.68 (-18.31) ***			.393	.878	3349.139	3381.612	1 vs 2 <0001
Model 3	-.51 (-.28)	3.63 (2.34) *	-19.68 (-18.29) ***	.05 (.62)		.394	.878	3350.749	3387.281	2 vs 3 0.5322
Model 4	-.51 (-.27)	3.63 (2.31) *	-19.68 (-18.27) ***	.05 (.61)	.00 (.00)	.394	.878	3352.749	3393.34	3 vs 4 0.9928

Note. Occasional recent cannabis use group (occasional) and frequent recent cannabis use group (frequent) are compared with the reference group absence of recent cannabis use. Time, “T1” for the beginning of treatment processes and “T2” for the end of treatment processes. Treatment frequency, number of past treatments for alcohol/drugs, β coefficients (t-values) are reported for each fixed effect.

** p < .01

*** p < .001

† p = .054, R² = Marginal R squared for fixed effects (mR²) and conditional R squared (cR²) were reported. AIC, Akaike's An Information Criterion; BIC, Bayesian information criterion. When comparing models fitted by maximum likelihood to the same data, the smaller the AIC or BIC, the better the fit.