



Long-term cannabis abuse and early-onset cannabis use increase the severity of cocaine withdrawal during detoxification and rehospitization rates due to cocaine dependence



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ABSTRACT

Background: Long-term and early-onset cannabis consumption are implicated in subsequent substance-related problems. The aim of this follow-up study was to investigate whether these patterns of cannabis use could impact cocaine withdrawal severity and cocaine craving intensity during detoxification. In addition, we investigated their impact in the rehospitization rates due to cocaine dependence 2.5 years after detoxification assessment.

Methods: The sample was composed of 93 female cocaine-dependent inpatients who were enrolled in an inpatient detoxification unit. Cocaine withdrawal symptoms were measured at the 4th, 9th and 14th days of detoxification using the cocaine selective severity assessment (CSSA). Data on the age of first years of drug use – alcohol, cannabis and cocaine – and the years of substance abuse were obtained using the Addiction Severity Index (ASI-6). Other relevant clinical variables were also investigated, including a 2.5 years follow-up assessment of number of rehospitization due to cocaine dependence.

Results: Early-onset cannabis use and long-term cannabis abuse were associated with an increase instead of a reduction in the severity of cocaine withdrawal symptoms and craving intensity during detoxification. In addition, long-term cannabis abuse predicted higher number of rehospitization due to cocaine dependence after 2.5 years of the first detoxification assessment.

Conclusions: Early-onset cannabis use and long-term cannabis abuse are associated with a worse detoxification treatment response. Our findings may help to identify patients who will struggle more severely to control cocaine withdrawal syndrome during early drug abstinence, and indicate that cannabis use prior to cocaine withdrawal should be considered an adverse factor.

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1. Introduction

Early-onset drug use is considered a significant predictor of the subsequent development of drug abuse and dependence (Sintov et al., 2009; Trenez et al., 2012). Around 34% of adolescents in the U.S. reported early-onset use of tobacco, alcohol and illicit substances (Moss et al., 2014), but during this period cannabis is the most popular illicit drug (Chadwick et al., 2013). Therefore, previous studies have shown that a significant percentage of teens (5.6%) who initiate cannabis use before the age of 15 report daily substance use and further drug abuse (Johnston et al., 2004), suggesting that

early-onset cannabis use is a risk factor for further drug-related problems (Lynskey et al., 2003). However, the debate regarding the harmful consequences of cannabis consumption is still ongoing and the main reasons for this include the poor quality of current evidence and the small number of studies on this topic (Calabria et al., 2010).

Early-onset cannabis use and abuse are also associated with potential progression to the use of other illicit substances such as cocaine. Estimations regarding the prevalence of cannabis use among primary cocaine users range between 50 and 70% (Hall and Lynskey, 2005; Lynskey et al., 2003; Wagner and Anthony, 2002). Moreover, the treatment of cocaine dependence conventionally involves detoxification programs for the management and reduction of drug craving and abstinence symptoms. However, the severity of withdrawal symptoms can vary among drug users

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(Francke et al., 2013), and multiple factors, including the history of other substance consumption, could impact treatment response (Ahmadi et al., 2008). In this sense, recent evidence indicated that concomitant cocaine and long-term cannabis use might increase craving for cocaine during drug abstinence (Fox et al., 2013). Therefore, a potential role of patterns of cannabis consumption in cocaine dependence-related problems is suggested.

Despite that, research has yet to address the consequences of cannabis use on specific clinical manifestations during the initial period of cocaine detoxification. This topic is of particular interest given that the severity of cocaine withdrawal symptoms at the first two weeks of treatment is a robust predictor of the ensuing treatment response (Kampman et al., 2001, 2004). Therefore, the aim of this follow-up study was to investigate whether long-term cannabis abuse and early-onset cannabis use could impact cocaine withdrawal severity and cocaine craving intensity during the first two weeks of detoxification treatment. In addition, we investigated the impact of cannabis consumption patterns in the rehospitalization rates due to cocaine dependence after 2.5 years of assessment.

2. Methods

2.1. Participants

One hundred and twenty-two female cocaine-dependent inpatients of a detoxification treatment public hospital unit in Southern Brazil took part in this study. Inclusion criteria were as follows: (1) age 18 to 45; (2) diagnosis of physiological dependence on cocaine (smoked or snorted) according to the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV). Participants were excluded from this study if (1) for any reason they did not report or did not provide reliable information regarding the age at the first year of drug use and patterns of drug use behavior ($n = 14$); (2) for any reason they were discharged early, before the third week of treatment, resulting in absence from follow-up measurements ($n = 12$); (3) they presented any severe cognitive impairment that resulted in an altered state of consciousness or agitation ($n = 3$). Thus, the final sample was composed of 93 participants.

2.2. Measures and procedures

Participants were invited to take part in the study during the first three days of treatment and provided written informed consent to participate. The detoxification treatment program consisted of three weeks of drug rehabilitation, including psychoeducation and support groups, nursing care, moderate physical activity, a balanced diet, and medical treatment. The clinical assessment protocol was composed of self-administered questionnaires and semi-structured interviews, applied within the first two weeks of treatment, and comprised of the assessment of relevant variables such as comorbid psychiatric diagnosis, history of drug use and drug-related problems, patterns of multiple drug use, and socio-demographic information. A trained team of psychologists conducted all interviews and instrument application.

Data on the age at the first year of drug use – alcohol, cannabis and cocaine – and the number of years of substance abuse were obtained using the Addiction Severity Index (ASI-6; Kessler et al., 2012; McLellan et al., 1980). To characterize early- or late-onset cannabis use, we considered the mean age at the first use of cannabis (15.32 years old) to classify those participants below or above such a mean. Participants were also divided into two groups according to the presence or absence of long-term cannabis abuse—defined as more than 5 years of substance abuse using at least three days per week. Additional data regarding the consequences of substance use were investigated by the ASI-6 subscales of family support problems, legal problems, employment problems and drug-related problems.

Cocaine withdrawal symptoms were measured at the 4th, 9th, and 14th days of detoxification using the cocaine selective severity assessment (CSSA; Kampman et al., 1998). The CSSA is an 18-item clinic-based measure of the severity of cocaine abstinence symptoms and each of the 18 individual items is scored on a 0–7 scale, in which 0 represents no symptoms and 7 represents maximum severity. The signs and symptoms included on the CSSA assessment were cocaine craving, depressed mood, appetite changes, sleep disturbances, lethargy, and bradycardia, which are manifestations that commonly occur after abrupt cessation of cocaine use. In addition, items 4 and 5 of the instrument are aimed at investigating the cocaine craving symptoms. Therefore, specific craving symptoms were defined as the sum value of these two items. In order to verify the percentage of variation regarding the severity of the withdrawal symptoms, we calculated the fractional change $\{[(14\text{th day CSSA score} - 4\text{th day CSSA score})/4\text{th day CSSA score}] \times 100\}$. Moreover, if a negative value was derived from the fractional change equation, a reduction in withdrawal symptoms was assumed (Wilson and Hernández-Hall, 2009). Otherwise, in the case

of a positive value an increase of withdrawal symptoms was assumed. Thus, the withdrawal symptoms variation was also categorized into a dichotomous variable.

Additional clinical and socio-demographic data were considered. Nicotine dependence severity was assessed by the Fagerstrom test (Heatherton et al., 1991). The effects of the presence of comorbid diagnosis, including mood disorders, anxiety disorders and posttraumatic stress disorder (PTSD) were investigated. Therefore, the Structured Clinical Interview for DSM Disorders (SCID I; Del-Ben et al., 2001) was conducted by a psychiatrist and two psychologists with clinical experience. In addition, analyses of pharmacotherapy effects, such as the use of mood stabilizers, antipsychotics or antidepressants, were performed (benzodiazepines were not prescribed in this treatment protocol). Participants also answered questions about socio-demographic characteristics, including information about years of formal education, estimated income per month, and days of abstinence prior to treatment admission.

This study was conducted from December, 2010 to December, 2011. Since all participants belong to the same treatment catchment area, we monitored how many rehospitalizations due to cocaine dependence occurred from the first assessment until June, 2014 (2.5 years). The research protocol was approved by the Ethical Committee of the enrolled institutions.

2.3. Statistical analysis

The Shapiro–Wilk test was used for the analysis of normality of data distributions for each variable. Descriptive statistics for psychosocial variables were conducted using chi-square tests or *t*-tests for independent samples, as well as group comparisons regarding CSSA total scores, cocaine craving intensity, number of rehospitalizations due to cocaine dependence, patterns of drug use behavior, onset of drug use, pharmacotherapy, and the presence of comorbid diagnosis. Fractional change between group effects (long-term versus non-long-term-cannabis abuse and early- versus late-onset cannabis use) was assessed by analysis of covariance (ANCOVA), controlling for mean age. In addition, two multiple logistic regression models were used to analyze the (a) influence of early-onset cannabis use and, (b) the duration of cannabis abuse predicting withdrawal outcomes. In these models the dependent variable was the dichotomous fractional change of CSSA scores during detoxification. We included age as a predicting factor in these models since we found a slight difference between the early- and late-onset cannabis use groups. In the first equation, in order to exclude confusion factors regarding the early use of other drugs, we included in the model whether participants did or did not have early use of alcohol, tobacco and cocaine (also considering the mean age of first use of these drugs in the whole sample). In the second equation, in order to exclude confusion factors regarding the duration of other drug abuse we included the number of years of alcohol, tobacco and cocaine abuse. Finally, we performed a linear multiple regression with one block including whether or not participants had early-onset cannabis use, whether or not they reported long-term cannabis abuse, and number of years of cocaine consumption as predictors of the number of rehospitalizations due to cocaine dependence after 2.5 years since first assessment. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 20.0 (SPSS Inc., Chicago, IL, USA), using two-sided tests and a significance level set at 0.05.

3. Results

3.1. Descriptive statistics

All participants reported having smoked cocaine and 89% reported having snorted cocaine as well. Overall, 66% of the sample reported early-onset cannabis use and 52% reported long-term cannabis abuse.

Participants with early-onset cannabis use presented a higher severity of cocaine withdrawal symptoms and specific cocaine craving symptoms at the 14th day of detoxification compared with those with late-onset cannabis use (see Table 1). In addition, a trend association was found between early-onset cannabis use and more craving symptoms at the 4th day of treatment. Similarly, those with long-term cannabis abuse presented higher cocaine withdrawal symptoms at the 9th and 14th days of assessment compared with those that did not report such a pattern of drug use, but no interaction was found regarding craving symptoms (see Table 2).

Additional analysis demonstrated that the early-onset cannabis use group also presented early-onset alcohol use and that the long-term cannabis abuse group presented more employment problems related to addiction. In addition, participants with early-onset cannabis use and long-term cannabis abuse presented significantly more total hospitalizations due to cocaine dependence, as well as more rehospitalizations after treatment discharge in a 2.5

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