



Cannabis withdrawal severity and short-term course among cannabis-dependent adolescent and young adult inpatients

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ABSTRACT

Objective: While previous studies questioned the existence of a cannabis withdrawal syndrome (CWS), recent research provided increasing evidence of a number of clinical symptoms after cessation of frequent cannabis consumption. The aim of this study is to prospectively assess the course of CWS in a sample of cannabis-dependent inpatients and to provide an estimate of the proportion of subjects experiencing CWS.

Methods: 118 subjects, aged 16–36 years, diagnosed with a cannabis dependence (DSM-IV, assessed by SCID I) were enrolled in the study. CWS was assessed prospectively over 10 days using a modified version of the Marijuana Withdrawal Checklist. Personality dimensions were assessed with the NEO-FFI.

Results: 73 subjects (61.3%) completed all assessments over the observation period. Most symptoms peaked on day 1. Model-based analyses revealed a high and low intensity CWS group. Less than half of the patients belonged to the high intensity craving, psychological, or physical withdrawal symptoms group. Symptom intensity decreased almost linearly over time. Indicators of cannabis consumption intensity as well as personality dimensions, but not recalled withdrawal were related to membership in the high intensity CWS group.

Discussion: A clinically relevant CWS may only be expected in a subgroup of cannabis-dependent patients. Most subjects with an elevated CWS experience physical and psychological symptoms. The small to negligible associations between recalled and prospectively assessed symptoms raise questions about the validity of the former approach.

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1. Introduction

Cannabis products are the most frequently consumed illicit substances in Western countries. It is estimated that about 65 million European adults have tried this substance at least once (EMCDDA, 2006). Around 5–15% of all lifetime consumers subsequently develop a substance use disorder (Perkonig et al., 1999; Wittchen et al., 2007), 1–7% suffer from cannabis dependence (Chen et al., 2005; Perkonig et al., 2008).

One important criterion for substance dependence according to ICD10 and DSM-IV is a withdrawal state when substance use is reduced or ceased. This is evidenced by the characteristic withdrawal syndrome for the substance, or by use of the same (or closely

related) substance with the intention of relieving or avoiding withdrawal symptoms. While the withdrawal syndromes of other legal and illegal substances, including cocaine, opiates, alcohol, or even nicotine are well documented, a cannabis withdrawal syndrome (CWS) is mentioned but poorly defined. Correspondingly, diagnostic criteria are not well established (Budney et al., 2004). However, findings from experimental and observational research with animals and human subjects support a CWS comprising psychological and physiological symptoms (Budney et al., 2004; Budney and Hughes, 2006). Discovery of the cannabinoid CB1 receptor and the development of a cannabinoid antagonist (SR141617A, rimonabant) resulted in studies which precipitated CWS in mice, rats, and dogs (Justinova et al., 2005).

Commonly observed symptoms in humans include anger, aggression, anxiety, decreased appetite, weight loss, irritability, restlessness, and sleep difficulty (e.g. Budney et al., 2004). Depressed mood, stomach pain, physical discomfort, tremor, and sweating have also been reported, but occur less frequently. Most symptoms begin within 24 h of abstinence, peak before day 3 after cessation of cannabis consumption, and last approximately 1–2

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weeks (Budney et al., 2003, 2004; Kouri and Pope, 2000). Regarding the frequency of symptoms, an early inpatient study of habitual cannabis users reported that 55–89% experienced irritability, restlessness, insomnia, or anorexia after discontinuation of oral THC (Tetrahydrocannabinol, Jones et al., 1976). Based on the Marijuana Withdrawal Checklist, MWC (Budney et al., 1999), a more recent study of adolescent frequent consumers reported a clinically relevant CWS with four or more severe symptoms in only 10% of the subjects whereas 58% reported at least four symptoms with mild intensity (Vandrey et al., 2005). In an adult outpatient sample comprising cannabis-dependent subjects, 85% reported four or more symptoms of any intensity and 33% reported four or more severe symptoms (Budney et al., 1999). Based on other assessment instruments lower proportions were reported from epidemiologic studies (Agrawal et al., 2008; Hasin et al., 2008). Comparing subjects within and across these studies suggests that withdrawal severity is greater among more frequent cannabis users. Consumption frequency as well as CWS intensity are positively associated with comorbid psychiatric symptoms and personality traits in adults as well as in adolescents (Budney et al., 1999; Barnes et al., 2005; Chabrol et al., 2004; Cornelius et al., 2008; Hasin et al., 2008).

While the existence of a CWS is supported in the literature, several shortcomings need to be addressed: Observational research is mostly based on retrospective assessments of CWS which is subject to recall bias and fails to provide valid information on the symptom course (for example Budney et al., 1999; Cornelius et al., 2008; Hasin et al., 2008; Vandrey et al., 2005; Wiesbeck et al., 1996). Data on the latter is provided from experimental research but these samples rarely comprised dependent consumers according to DSM-IV criteria (Budney et al., 2004). Comparatively little observational research is based on samples with a diagnosed cannabis dependence in all study participants (for example Budney et al., 1999; Arendt et al., 2007). Less evidence is available from adolescents or young adult samples. However, these results are essentially similar (Cornelius et al., 2008; Nocon et al., 2006; Vandrey et al., 2005). Results from a prospective CWS assessment in a small sample of cannabis-dependent adolescent outpatients have recently been made available (Milin et al., 2008). In their study, a 1-week interval between each of their four assessments may be too long to appropriately assess symptom course after cessation of consumption.

Retrospective assessments of withdrawal symptoms suggest the importance of subgrouping subjects with a high and low or no CWS. However, there is currently no evidence available which is based on a prospective assessment of physical and psychological symptoms during cannabis withdrawal. Therefore, this study prospectively assesses the course of CWS among cannabis-dependent subjects seeking detoxification, and aims to classify subjects according to their reported symptoms. It aims to provide an estimate of the proportion of dependent subjects experiencing a CWS without the threat of bias typically associated with long-term recall periods. Specifically, this paper has four aims: First, to assess the characteristics, severity and course of CWS over a period of 10 days among in cannabis-dependent inpatients. We hypothesized an initial increase of symptom intensity during the first days of the stay followed by a subsequent decrease. Second, we analysed the necessity to distinguish between subgroups with a characteristically different CWS course. We expected at least two subgroups, the first of which should comprise subjects with moderate-to-strong symptoms and the second subjects with no or only mild symptoms. Third, we assessed potential predictors of CWS. As such, we focused on variables related to drug consumption and personality. We assumed that subjects with more intense cannabis consumption and more severe cannabis dependence should experience a stronger CWS. Concerning the hypothesis on symptom course, we assumed that subjects who had their last dose almost immediately prior to admission are in an earlier stage of CWS and should experi-

ence milder symptoms at the beginning of their stay. However, this is not expected to influence the overall intensity of CWS. Fourth, we studied the association between retrospective reports of a CWS and the prospectively assessed CWS. We hypothesized a positive association between these assessments.

2. Methods

2.1. Sample, in- and exclusion criteria

Inpatients meeting the inclusion criteria as described below were consecutively enrolled into the study at the beginning of their detoxification in a closed addiction treatment ward at the Johanna-Odebrecht-Foundation psychiatric hospital, Greifswald, Germany. All patients were seeking planned detoxification and were admitted voluntarily to the ward for detoxification treatment for a time period of 5–10 days. None of the participants was volunteering for an inpatient stay as part of a non-routine hospitalization or was admitted for an emergency or unplanned hospitalization. Inpatient treatment for the purpose of drug detoxification is commonly offered by German psychiatric hospitals; but cannabis dependence alone is not an indication for admission to a detoxification treatment in all regions and institutions. Greifswald is a small town in the least populated state of Germany with comparatively few individuals addicted to illicit drugs such as opioids. For this reason adolescents or young adults with a shorter history of abuse without concomitant DSM-IV Axis I disorder were admitted.

Inclusion criteria were a diagnosed cannabis dependence according to DSM-IV, without concomitant alcohol- or other (multiple) substance dependence. Subjects were excluded from the study if they tested positive for any other drug other than cannabis on the day of admission to avoid confounding by multiple substance abuse. Furthermore, subjects with other current DSM-IV Axis I diagnosis, or severe somatic or neurological disorders were transferred to another psychiatric ward and excluded from the study. Patients agreed to non-psychopharmacological treatment during the study period. They had free and unlimited access to coffee and cigarettes during the hospitalization.

In total 118 adolescents and young adults met the inclusion criteria. The sample comprised 101 males and 17 females with an average age of 19.6 ± 2.9 years (range 16–36 years, two subjects being older than 25 years). During the 10-day observation period drop-out occurred (Table 1). All drop-outs (except for one case) were attributed to discharge when no more cannabinoids were detectable in the urine drug screening from day 4 onwards. Patients were discharged because health-care providers will cover detoxification treatment only as long as the substance is detectable. One person did not provide information on symptom intensity and was excluded from the analyses. To assess the sensitivity of our results to attrition we computed the models as described in Section 2.5 on the first 6 days with more than 80% complete cases. These results revealed no relevant differences compared to an analysis based on all measurement points. Sensitivity analysis with the number of valid measurement points per person as predictor was not associated with inclusion in the high versus low withdrawal symptoms group as described in results (physical: odds ratio 1.0 (95% CI 0.8–1.3); psychological: odds ratio 0.9 (95% CI 0.7–1.2); craving: odds ratio 1.1 (95% CI 0.9–1.5)).

2.2. Instruments

A modified German version of the Marijuana Withdrawal Checklist (MWC, Budney et al., 1999) was used to measure withdrawal symptoms, and is further described in the following section. History of cannabis consumption, criteria for cannabis dependence and patient's psychosocial characteristics were assessed using the German Version of the SCID I (Wittchen et al., 1997). As part of the SCID I interview, cannabis withdrawal was assessed retrospectively. This comprised the general previous experience of a CWS, and a subsequent open-ended question asking for the recall of specific single withdrawal symptoms. Psychosocial characteristics concerning legal history, family background, and treatment history were assessed with a semi-structured interview as recommended by the German Society for Addiction Research and Addiction Treatment (DGS, 2001).

Study participants were interviewed on their history of cannabis use. This encompassed an open-ended question concerning the last amount of cannabis consumed, and a second open-ended question concerning the time of last consumption before admission. On the day of admission, inpatient's urine samples were taken to assess the baseline THC level and to exclude other recent or current substance use, including opioids, cocaine, benzodiazepines, ecstasy, and amphetamines. Moreover, breath alcohol level was measured. Based on the THC urine sample at admission, subjects were subgrouped into "low" and "high" THC level group, using the median as cut-off point. All subjects in the study consumed cannabis daily or almost daily.

To control for concomitant nicotine consumption, cigarette smoking was assessed over the course of the study. A validated German translation of the Neo-Five Factor Inventory (Costa and McCrae, 1992) was used to assess personality dimensions (neuroticism, extraversion, openness, agreeableness and conscientiousness). All instruments that were employed repeatedly are presented in Table 1. The remaining instruments were administered during the first 2 days of the stay.

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