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Abstinence phenomena of chronic cannabis-addicts prospectively monitored during controlled inpatient detoxification: Cannabis withdrawal syndrome and its correlation with delta-9-tetrahydrocannabinol and -metabolites in serum

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ABSTRACT

Objective: To investigate the course of cannabis withdrawal syndrome (CWS) within a controlled inpatient detoxification setting and to correlate severity of CWS with the serum-levels of delta-9-tetrahydrocannabinol (THC) and its main metabolites 11-hydroxy-delta-9-tetrahydrocannabinol (THC-OH) and 11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH).
Methods: Thirty-nine treatment-seeking chronic cannabis dependents (ICD-10) were studied on admission and on abstinent days 2, 4, 8 and 16, using a CWS-checklist (MWC) and the Clinical Global Impression-Severity scale (CGI-S). Simultaneously obtained serum was analysed to its concentration of THC, THC-OH and THC-COOH.
Results: MWC peaked on day 4 (10.4 ± 4.6 from 39 points) and declined to 2.9 ± 2.4 points on day 16. Women had a significantly stronger CWS than men. The CWS was dominated by craving > restlessness > nervousness > sleeplessness. CGI-S peaked with 5 out of 7 points. On admission, THC and its metabolites did negatively correlate with the severity of CWS. There was no significant correlation afterwards, no matter if CWS was medicated or not. THC-OH in serum declined most rapidly below detection limit, on median at day 4. At abstinence day 16, the THC-levels of 28.2% of the patients were still above 1 g/ml (range: 1.3 to 6.4 ng/ml).
Conclusions: CWS increased and then decreased without any correlation between its severity and the serum-levels of THC or its main metabolites after admission. According to the CGI-S, most patients achieved the condition of 'markedly ill'. Serum THC-OH was most clearly associated with recent cannabis use. Residual THC was found in the serum of almost one-third of the patients at abstinence day 16.

1. Introduction

Cannabis is a psychotropic substance with widespread use worldwide, surpassed only by nicotine and alcohol (UNDOC, 2013). In Germany, for example, the12-month prevalence for cannabis use amounts to 4.5% for adults in general, with highest rates in the age groups of 18–20 years (16.2%) and 21–24 years (13.7%; Pabst et al., 2013). 12-month prevalence for cannabis dependence (DSM-IV) was recently estimated as 0.5% in all German adults (Pabst et al., 2013).

Retrospective studies on larger clinical (Wiesbeck et al., 1996; Levin et al., 2010) and epidemiological (Agrawal et al., 2008; Hasin et al., 2008) populations have shown that discontinuation of regular cannabis use is frequently followed by one or more symptoms like anxiety, irritability, craving for cannabis, or sleeping problems, which are associated with distress and impairment of daily activities and with relapse to cannabis use (Budney et al., 2004; Allsop et al., 2011). Starting from various definitions the existence of a clinical cannabis withdrawal syndrome (CWS) was validated in prospective studies with outpatients or untreated subjects supervised after cessation of cannabis use (Budney et al., 1999; Kouri

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and Pope, 2000; Budney et al., 2004; Arendt et al., 2007; Allsop et al., 2011) and by inpatient laboratory studies (Haney et al., 2008, 2010). On this basis diagnostic criteria for CWS have been recently operationalized and newly included in DSM-5 (American Psychiatric Association, 2013). In ICD-10, the CWS is still vaguely defined (Dilling et al., 2004). The CWS emerges most pronounced after stopping a lengthy and heavy cannabis intake and in treated samples its intensity is associated with a patient's motivation for detoxification and with characteristics of the treatment setting (Budney et al., 2004). In most cases, the syndrome reaches its peak between the 2nd and 6nd day after cessation of cannabis inhalation and usually lasts for about 14 days (Kielholz and Ladewig, 1970; Wiesbeck et al., 1996; Budney et al., 2004). Some symptoms such as 'sleeplessness', 'irritability', or 'strange dreams', however, may last for longer (Budney et al., 2004; Vandrey et al., 2011; Lee et al., 2014). It is interesting to note in this context that down-regulated cannabinoid CB1 receptors return to normal functioning after about 4 weeks of abstinence (Hirvonen et al., 2012), which would constitute a physiological time frame for the occurrence of abstinence symptoms.

Studies on the CWS carried out within clinical inpatient settings provide further evidence for the validity of this syndrome, but are still rare (Preuss et al., 2010; Lee et al., 2014). In a controlled inpatient environment, the CWS is expected to be less influenced by relapse-associated cues than in an everyday environment (Budney et al., 2004). Moreover, inpatient conditions provide improved relapse prevention and easier detection of relapses (Dasgupta, 2007). In the inpatient study of Preuss et al. (2010) with treatment-seeking white adolescents and young adults ($n = 73$) who were observed for 10 days, the intensity of most self-reported symptoms peaked on the first day in treatment and then decreased nearly linearly. Intensity of most symptoms ranged between low and moderate (Preuss et al., 2010). The symptom rated as 'strong' or 'very strong' most frequently (37.9%) was craving (Preuss et al., 2010).

Since the CWS in animal experiments and human studies can be alleviated by the administration of Δ-9-tetrahydrocannabinol (THC; Budney et al., 2007; Haney et al., 2008; Vandrey et al., 2013), which is mainly responsible for the euphoric and reinforcing effects of cannabis (Cone and Huestis, 1993; Mechoulam, 1999), it is likely that a decrease in THC levels in the extracellular brain fluid is crucially involved in the formation of the syndrome. In 2006, to the time when our study started, there was only one small study available, which had investigated the course of plasma cannabinoids after initiation of abstinence in chronic cannabis users (8 men were followed for 10–15 days; Johansson et al., 1989). Because that study revealed high inter-individual variability in the elimination half-lives of THC (Johansson et al., 1989), the question arises whether THC-levels in the peripheral blood-compartment are associated with severity of cannabis withdrawal symptoms. The first study that addressed this question was published most recently; in non-treatment seeking, African–American chronic cannabis dependent patients, an overarching correlation between CWS and serum THC had not been found (Lee et al., 2014). In addition to THC, which is highly lipophilic with a long terminal elimination half-life of up to 12.6 days in blood from chronic cannabis users (Johansson et al., 1989), two major metabolites are of interest in the present context: the hydrophilic and also psychoactive metabolite 11-hydroxy-Δ-9-tetrahydrocannabinol (THC-OH) and the lipophilic, but no longer psychoactive metabolite 11-nor-Δ-9-tetrahydrocannabinol-9-carboxylic acid (THC-COOH) (Mechoulam, 1999; Grotenhermen, 2003; Musshoff and Madea, 2006).

The present study had therefore two objectives. First, to describe – under controlled inpatient conditions – the course of the CWS from shortly after cessation of chronic cannabis inhalation to up to 16 days, and second, to relate the CWS-severity to serum levels of THC and its metabolites.

2. Methods

2.1. Sample

The study was conducted in 2006–2011 in an inpatient ward for detoxification from alcohol, medical drugs, and cannabis at the Psychiatric University-Hospital in Essen, Germany. Patients could be included into the study if they (a) were diagnosed as cannabis dependent according to ICD-10 (Dilling et al., 2004), (b) had consumed cannabis by inhalation daily or almost daily during the 6 months before admission, (c) had consumed cannabis within 24 h before admission, (d) had used no other psychotropic substances (except tobacco) or medication during 4 weeks before admission, and (e) had no active comorbid psychiatric or somatic disorder which could noticeably affect the course of cannabis detoxification treatment. Furthermore, patients had to be able to understand the explanation of the study and to voluntarily give their informed consent. Patients were excluded who during detoxification treatment exhibited a comorbidity requiring additional treatment, or showed positive results in their alcohol or drug screenings (see below) during treatment, or discontinued treatment within the first 48 h. Also those patients were excluded from the study who used cannabis during their inpatient treatment, as evidenced by self-report or by clinical observation or by indisputable urine screening results. In addition, patients were to be excluded who reduced their tobacco use for more than one quarter, in order to prevent interference of tobacco withdrawal symptoms with the study results.

2.2. Inpatient detoxification treatment

Treatment usually was scheduled for up to 16 days, but could be extended if necessary. The multimodal treatment program consisted of medical visits; single and group therapeutic sessions which contained motivational enhancement, cognitive-behavioral treatment elements (Benyamina et al., 2008) and psycho-education; movement therapy and occupational therapy; and social counseling. Also, referral to subsequent long-term rehabilitation programs was offered.

Parts of the routine treatment were randomized breath alcohol analyses and semi-quantitative drug screenings for cannabis, barbiturates, benzodiazepines, opiates, cocaine, amphetamines, methadone, and ethyl-glucuronide in urine. The patients agreed not to leave the ward without being accompanied by staff members and not to receive unchecked visitors. On ethical grounds, CWS could be medicated if needed in this prospective cohort-study. When patients showed distressing withdrawal symptoms such as anxiety, dysphoria, restlessness or sleep disturbance, nursing staff could administer escalating doses of gabapentin (up to 600 mg q.i.d.), or if this was not sufficiently effective, chlorprothixene (up to 50 mg q.i.d.; Bonnet and Scherbaum, 2010; Mason et al., 2012).

The treatment was considered as completed when the psychiatric and somatic condition of patients had improved so far that rehabilitation treatment became possible.

2.3. Assessments

After admission to treatment an interview based on the European Addiction Severity Index (Gsellhofer et al., 1997) was performed in order to obtain socio-demographic, addiction-specific, psychiatric and other relevant medical information. Substance use during the previous 6 months was assessed using a timeline follow-back interview (TLFB; Fals-Stewart et al., 2000). Furthermore, the body mass index (BMI) was determined on day 1. Additional information about previous psychiatric diagnoses was obtained by review of discharge letters and/or by contacting the referring physicians.

During detoxification treatment the severity of the CWS was measured by a modified version of the Marijuana Withdrawal Checklist (MWC; Budney et al., 1999). In its original version the MWC consists of 10 symptoms (craving for cannabis, irritability, nervousness/anxiety, restlessness/tension, depression, anger/aggression, sleeplessness, strange dreams, loss of appetite, headache), which are rated on a 4-point scale (0 = not at all, 1 = mild, 2 = moderate, 3 = heavy; Budney et al., 1999). We added two symptoms ('sweating' and 'nausea'; Allsop et al., 2011; Vandrey et al., 2008) to the original MWC (Budney et al., 1999). In contrast to other studies, the MWC was not handed out to be filled in by the patients, but was used as an interview.

Simultaneously with the MWC, the Clinical Global Impression-Severity scale (CGI-S; Busner and Targum, 2007) was carried out in order to classify the general severity of the CWS. Ratings of the CGI-S range from 1 = normal to 7 = extremely ill (Busner and Targum, 2007). In addition, at day 1 and at the end of the scheduled study observation period (day 16) or before premature discharge the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962) was used to assess the psychiatric burden of our study population. All instruments were performed in the late morning by the principal investigator (U.B.). At day 16 or before discharge the screening questionnaire from the Structured Clinical Interview for DSM-IV Axis II (SCID-II) (Wittchen et al., 1997) was completed by the patients.

Blood and urine samples were scheduled for 9 a.m. on days 1, 2, 4, 8, 12 and 16. Blood was centrifuged, plasma separated and the samples were frozen at −20 °C. On the same day, the material was sent to commercial clinical chemistry laboratories, which performed quantitative measures in serum by