Drug and Alcohol Dependence 136 (2014) 85–91

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Investigation of sex-dependent effects of cannabis in daily cannabis smokers

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ARTICLE INFO

Article history:
Received 30 July 2013
Received in revised form
15 November 2013
Accepted 16 December 2013
Available online 3 January 2014

Keywords:
Cannabinoids
Abuse liability
Sex-differences
Subjective effects

ABSTRACT

Background: Women exhibit an accelerated progression from first cannabis use to cannabis use disorder (CUD) and show pronounced negative clinical issues related to CUD relative to men. Whether sex-dependent differences in cannabis' direct effects contribute to the heightened risk in women is unknown. This analysis directly compared cannabis' abuse-related subjective effects in men and women matched for current cannabis use.

Methods: Data from four double-blind, within-subject studies measuring the effects of active cannabis (3.27–5.50% THC, depending on study) relative to inactive cannabis (0.00% THC) were combined for this analysis. Data from equal numbers of men and women from each study matched for current cannabis use were pooled (total $n = 35$ men; 35 women); cannabis' effects were analyzed according to cannabis condition (active versus inactive) and sex.

Results: Active cannabis produced more robust subjective effects associated with abuse liability ('Good,' 'Liking,' 'Take Again') and intoxication ('High,' 'Stimulated') relative to inactive cannabis ($p \leq 0.0001$). Women reported higher ratings of abuse-related effects ['Take Again' and 'Good' ($p \leq 0.05$)] relative to men under active cannabis conditions but did not differ in ratings of intoxication. Active cannabis increased heart rate ($p \leq 0.0001$) equally for both sexes.

Conclusions: The results from this study suggest that when matched for cannabis use, women are more sensitive to the subjective effects related to cannabis' abuse liability relative to men, which may contribute to the enhanced vulnerability to developing CUD. Thus, sex is an important variable to consider when assessing the development of CUD.

1. Introduction

Cannabis is the most widely used illicit drug worldwide (United Nations Office on Drugs and Crime, 2013), and has the highest rates of abuse in the United States relative to other illicit drugs, with 18.1 million people reporting use in the previous month, a number that has increased by over 20% since 2007 (Substance Abuse and Mental Health Services Administration, 2012a). In the United States, the number of people seeking treatment for cannabis use increased by 21% between 2000 and 2010 (Substance Abuse and Mental Health Services Administration, 2012b). With a growing number of states legalizing cannabis for medical and non-medical purposes (Hoffmann and Weber, 2010; National Conference of State Legislature, 2013), it is conceivable that increased access and legalization may lead to higher rates of use and increased risk of dependence. Elucidating the variables that contribute to the development of abuse and dependence can improve prevention and treatment for such disorders.

The estimated probability of initiating cannabis use and subsequently developing a cannabis use disorder (CUD) is higher in men (Wagner and Anthony, 2007). However, women show an accelerated progression from first use to CUD relative to men providing evidence for a 'telescoping effect' (Hernandez-Avila et al., 2004; Ehlers et al., 2010; Khan et al., 2013). Sex-differences have also been reported in the overall effects that daily cannabis use can have on physical and mental well-being; the quantity of cannabis smoked per day was shown to be negatively associated with self-reported measures of Quality of Life, an effect that was more pronounced in women than men (Lev-Ran et al., 2012). Additionally, men and women differ in the magnitude of withdrawal symptoms, with women exhibiting greater physiological symptoms associated with withdrawal relative to men (Copersino et al., 2010); this is a variable that is hypothesized to contribute to relapse in cannabis-dependent treatment seekers (Haney et al., 2013).

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http://dx.doi.org/10.1016/j.drugalcdep.2013.12.013

Assessing cannabis' acute effects is an important determinant when investigating variables that contribute to continued cannabis use and the development of abuse and dependence. Preclinical studies with laboratory animals demonstrate that females are more sensitive to the behavioral and physiological effects of cannabinoids compared to males (for review, see Craft et al., 2013). Of note, female rats are more sensitive to the reinforcing effects of cannabinoids with faster acquisition of cannabinoid self-administration, higher rates of responding for cannabinoids (Fattore et al., 2007), and increased rates of cue and drug-induced reinstatement (Fattore et al., 2010).

Very little has been reported on sex-dependent differences in smoked cannabis' effects in humans; our laboratory reported subtle differences in cannabis' acute effects between men and women in a pattern that reflects preclinical studies, with women reporting higher ratings of cannabis' positive subjective effects relative to men (Cooper and Haney, 2009). Females have also been reported to rate feeling 'more dizzy' after smoking cannabis or receiving intravenous THC; no sex-dependent differences were observed in cardiovascular endpoints or subjective ratings of intoxication (Mathew et al., 2003). However, sex-dependent effects of cannabinoids were not the primary focus of these studies, therefore, they were not designed with adequate power to assess these effects. In addition to the small sample size, the men and women in these studies were not matched according to pattern of cannabis use, an important consideration when comparing the acute effects of cannabis between groups since tolerance to cannabis' effects occurs with repeated use (Haney et al., 1997; Hart et al., 2002).

The objective of the current study was to directly compare cannabis' subjective and cardiovascular effects in men and women matched for frequency and magnitude of current cannabis use. Data obtained from the above-mentioned cannabis-administration study and three subsequent controlled laboratory studies with similar designs yielded a sample with adequate power to assess differences in cannabis' effects between men and women while matching for cannabis use. Because three of the four studies were designed to assess medication effects, only data obtained under placebo medication conditions were used for this analysis.

2. Methods

Data from four outpatient studies carried out at New York State Psychiatric Institute were used for this analysis (total $N = 146$). These double-blind, within-subject studies were designed to assess cannabis' effects in non-treatment seeking recreational (non-medicinal) cannabis smokers who were not interested in treatment, and measured the subjective ratings of drug quality, drug effect, mood, and physiological effects of a single strength of active cannabis (3.27–5.50% THC, strengths varied according to study) relative to inactive cannabis (0.00% THC). From each study, data from equal numbers of men and women matched for frequency of cannabis use (days/week) and amount smoked per day (joints/day) were pooled. Subjective and cardiovascular effects of cannabis smoked according to a controlled smoking procedure were analyzed according to cannabis condition (active and inactive) and sex.

2.1. Participants

Volunteers ages 21–50 were recruited through newspaper advertisements requesting volunteers to participate in research studying the effects of cannabis, and those who met inclusion/exclusion criteria after an initial telephone screen were invited to the laboratory for further screening. Prior to enrollment, participants gave written informed consent, received a psychiatric and medical evaluation, and provided a detailed drug use and medical history. Participants were accepted into the study if they were healthy, as determined by a physical examination, electrocardiogram, and urine and blood chemistries. All eligible participants currently smoked ≥ 3 cannabis cigarettes at least four times a week for the previous four weeks before screening, based on self-report and clinical interviews, and tested positive on a cannabis urine toxicology screen. Participants were excluded if they repeatedly used other illicit drugs, as determined by urine toxicology and self-report, or met criteria for alcohol dependence. Urine toxicology screens were performed during every screening visit and before each session. Exclusion criteria included Axis I psychopathology (DSM-IV edition) as assessed by clinical interview, current use of over-the-counter or prescription medications, with the exception of oral contraceptives, pregnancy or nursing. Volunteers were told that the study objective was to determine cannabis' effects on mood and physiology and that during each session they would smoke a portion of a cannabis cigarette, but that the strength of the cannabis would vary. Participants were admitted into the studies only after written informed consent to participate was given and eligibility criteria were verified. All study procedures were approved by the Institutional Review Board of the New York State Psychiatric Institute and were in accord with the Declaration of Helsinki.

2.2. Design and procedures

The studies included 5–10 outpatient sessions over the course of 2–8 weeks at the New York State Psychiatric Institute. Sessions began around 9 AM, and were 6–7 h in duration. Before study onset, participants were familiarized with computerized tasks and study procedures with 1–2 training sessions, during which time cannabis was not administered. Some of these studies included medication administration before cannabis smoking; only data from placebo medication conditions were utilized for this analysis. A within-subject design was used in which all participants received active and inactive cannabis and medication strengths. For studies testing medication effects, one capsule containing placebo or the test medication (naltrexone or dronabinol) was administered 45 min before cannabis was smoked. The order of cannabis and medication dosing was randomized across sessions. All studies included a minimum of 48 h between test sessions, enough time to allow for drug clearance in medication administration studies to ensure no carryover effects of naltrexone or dronabinol from a previous session.

2.2.1. Experimental session. For all studies, participants were instructed not to smoke cannabis or cigarettes after midnight the night before each session and not to eat breakfast. Before the session, carbon monoxide levels were measured to confirm no recent smoking, breath alcohol levels were assessed, and use of illicit drugs other than cannabis was determined by a urine toxicology screen. If carbon monoxide levels indicated that the participant had smoked cannabis or a cigarette prior to arrival (>8 ppm) the session was rescheduled. A standardized breakfast was provided to all participants prior to session onset.

Before capsule administration and cannabis smoking, baseline subjective-effects questionnaires were completed and heart rate and blood pressure were measured using a Sentry II vital signs monitor (Model 6100: NBS Medical Services, Costa Mesa CA). Participants smoked a cannabis cigarette according to a cued-smoking procedure shown to produce reliable increases in heart rate and plasma THC levels (Foltin et al., 1987): Investigators instructed participants to 'inhale' (5 s), 'hold smoke in lungs' (10 s) and 'exhale'. Participants smoked according to this procedure with a 40-s interval between puffs until 50 or 75% of the cigarette was pyrolyzed depending on the study (3–7 puffs). Subjective ratings of drug effect