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The effect of high-dose dronabinol (oral THC) maintenance on cannabis self-administration

Nicolas J. Schlienz, Dustin C. Lee, Maxine L. Stitzer, Ryan Vandrey*

Department of Psychiatry and Behavioral Sciences, Behavioral Pharmacology Research Unit, Johns Hopkins University School of Medicine, Baltimore, MD, 21224, USA

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ABSTRACT

Background: There is a clear need for advancing the treatment of cannabis use disorders. Prior research has demonstrated that dronabinol (oral THC) can dose-dependently suppress cannabis withdrawal and reduce the acute effects of smoked cannabis. The present study was conducted to evaluate whether high-dose dronabinol could reduce cannabis self-administration among daily users.

Methods: Non-treatment seeking daily cannabis users (N = 13) completed a residential within-subjects crossover study and were administered placebo, low-dose dronabinol (120 mg/day; 40 mg tid), or high-dose dronabinol (180–240 mg/day; 60–80 mg tid) for 12 consecutive days (order counterbalanced). During each 12-day dronabinol maintenance phase, participants were allowed to self-administer smoked cannabis containing < 1% THC (placebo) or 5.7% THC (active) under forced-choice (drug vs. money) or progressive ratio conditions.

Results: Participants self-administered significantly more active cannabis compared with placebo in all conditions. When active cannabis was available, self-administration was significantly reduced during periods of dronabinol maintenance compared with placebo maintenance. There was no difference in self-administration between the low- and high-dose dronabinol conditions.

Conclusions: Chronic dronabinol dosing can reduce cannabis self-administration in daily cannabis users and suppress withdrawal symptoms. Cannabinoid agonist medications should continue to be explored for therapeutic utility in the treatment of cannabis use disorders.

1. Introduction

Cannabis (marijuana, hashish) is the most widely used internationally regulated drug, with estimates that 2.7–4.9% of the world population aged 15–64 use cannabis at least once annually (UNODC, 2014). Most cannabis users are able to use the drug in a controlled manner and are able to reduce or quit use with no formal treatment (Hughes et al., 2016). However, a subset of individuals develop a pattern of cannabis use that contributes to significant psychosocial distress and they have great difficulty initiating and sustaining abstinence during attempts to quit (Budney et al., 2007a; Copeland et al., 2001; Davis et al., 2014; Stephens et al., 2012). Evidence-based behavioral treatments for substance use disorders (e.g., motivational interviewing (MI), cognitive behavioral therapy (CBT), contingency management (CM)) are effective in the treatment of cannabis use disorders, but the majority of individuals receiving these interventions fail to achieve sustained abstinence (Benyamina et al., 2008; Budney et al., 2015; Davis et al., 2014; Nordstrom and Levin, 2007). Thus, there is a clear need for advancing the treatment of cannabis use disorder (CUD).

One approach is to identify medications likely to assist in the initiation and/or maintenance of abstinence. Dronabinol (oral delta-9-tetrahydrocannabinol (THC); Marinol®) has been extensively studied as a potential cannabis pharmacotherapy in both laboratory and clinical settings (Budney et al., 2007b; Haney et al., 2004, 2008; Hart et al., 2002; Levin et al., 2011, 2016; Vandrey et al., 2013). Dronabinol is an attractive candidate medication for treating CUD based on the success of comparable agonist or partial agonist medications in the treatment of opioid use disorders (e.g., methadone or buprenorphine; Stotts et al., 2009) and tobacco use disorders (nicotine or varenicline; Raupach and van Schayck, 2011).

In laboratory studies with non-treatment seeking daily cannabis users, dronabinol (30–120 mg/day) reliably and dose-dependently suppressed cannabis withdrawal symptoms (Budney et al., 2007b; Haney et al., 2004, 2008; Vandrey et al., 2013). Dronabinol maintenance (40–120 mg/day) reduced subjective ratings of 'good drug effect' and attenuated increased heart rate following acute administration of smoked cannabis (Hart et al., 2002; Vandrey et al., 2013). Two prior studies evaluated whether dronabinol maintenance alters cannabis self-

* Corresponding author at: Department of Psychiatry and Behavioral Sciences, Behavioral Pharmacology Research Unit, Johns Hopkins University School of Medicine, 5510 Nathan Shock Drive, Baltimore, MD 21224, USA.
E-mail address: rvandrey@jhmi.edu (R. Vandrey).

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administration. One study found no effect of dronabinol maintenance (40–80 mg/day; 10 or 20 mg qid) on rates of cannabis (1.8% THC) self-administration (Hart et al., 2002). In a second study, dronabinol (60 mg/day; 20 mg tid) combined with adrenergic agonist lofexidine (2.4 mg/day), but not dronabinol alone, reduced cannabis self-administration in a laboratory model of relapse (Haney et al., 2008).

Case reports and randomized controlled trials have described the use of dronabinol in clinical settings. Levin and Kleber (2008) detailed two case reports in which treatment-resistant cannabis users achieved sustained cannabis abstinence with the assistance of open-label dronabinol. In one case, dronabinol (40 mg/day) was administered to help initiate abstinence and discontinued following a dose taper. In the second case, dronabinol (initially 40–50 mg/day and tapered to 15–20 mg/day during maintenance) was continued indefinitely due to several instances of cannabis relapse and excessive alcohol consumption upon dronabinol discontinuation. In both cases, concomitant psychiatric medications were administered. To date, two controlled clinical trials of dronabinol-assisted treatment have been completed. In one randomized controlled trial, dronabinol (up to 40 mg/day) reduced subjective ratings of withdrawal and improved treatment retention compared with participants receiving placebo; however, no differences in cannabis use outcomes were observed between study conditions (Levin et al., 2011). In the second study, a combination of dronabinol (20 mg tid) and lofexidine (0.6 mg tid) was compared with placebo. Participants in both medication conditions (active and placebo) decreased cannabis use and approximately 30% achieved at least three weeks of consecutive abstinence, but there was no difference in cannabis use outcomes by medication assignment (Levin et al., 2016).

Despite work evaluating dronabinol as a potential therapeutic in the treatment of CUD relative to other medications, the question remains whether the dronabinol doses previously evaluated have been appropriate for achieving clinical effects given the magnitude of cannabinoid tolerance that can result from daily cannabis use. Prior studies have indicated that daily or near-daily cannabis users can tolerate acute THC doses up to 90 mg (Lile et al., 2013) and daily doses of up to 210 mg (Benowitz and Jones, 1981). Long-term maintenance on high doses of dronabinol is not an attractive clinical approach in the absence of a demonstrated patient or public health gain in switching from inhaled cannabis to oral THC, however, short-term use of dronabinol with concurrent behavioral therapy may be well-tolerated and could help treatment-seeking cannabis users achieve an initial period of abstinence and transition to complete abstinence with a dose taper. Thus, the present study was conducted to evaluate whether, and to what degree, high-dose dronabinol maintenance could reduce cannabis self-administration among daily users. We hypothesized that dose-dependent effects of dronabinol would be observed on rates of cannabis self-administration under progressive ratio and forced-choice experimental conditions. This study also extends previous research by providing additional data regarding the safety and tolerability of acute and repeated dronabinol dose effects in heavy cannabis users.

2. Material and methods

2.1. Participants and recruitment

Cannabis users were recruited through newspaper advertisements and flyers posted on campus and community bulletin boards. Volunteers were eligible for the study if they: 1) were at least 18 years of age; 2) self-reported a minimum of 25 days of cannabis use per month in the previous year and provided a urine specimen with > 50 ng/mL THCCOOH; 3) were not currently taking psychoactive medication; 4) did not meet DSM-IV-TR criteria for an Axis I psychiatric disorder other than nicotine or cannabis dependence; 5) had a negative urine toxicology test for illicit drugs other than cannabis at study admission; 6) were not pregnant, breast feeding, or planning to become pregnant within the next 3 months; 7) were not seeking treatment for cannabis-related problems or using cannabis for a medical disorder; 8) had a normal electrocardiogram (ECG) at intake and no major cardiac events (e.g., heart attack) in the six months prior to study admission.

Written informed consent was obtained prior to clinical evaluation and study participation. The study was approved by the John Hopkins Medicine IRB and conducted in accordance with the ethical standards of the Declaration of Helsinki. Study eligibility was ascertained with a telephone interview followed by a comprehensive in-person clinical evaluation. A physical evaluation, including ECG, was conducted by study medical staff. Routine blood chemistry tests were completed, and participants with clinically significant impairment of kidney/liver function were excluded. The Timeline Follow-Back method (TLFB; Sobell and Sobell, 1992) was used to obtain the amount and frequency of substance use during the prior 3 months. Urine testing for recent drug use and pregnancy was conducted using qualitative rapid tests. The DSM Checklist (Hudziak et al., 1993) modified to include DSM-IV-TR criteria was used to diagnose current Axis I psychiatric disorders. The Marijuana Quit Questionnaire (MQQ; Boyd et al., 2005) was used to obtain a detailed cannabis use history.

Sixteen participants were enrolled in the study, and 13 completed the protocol and were included in the final analysis. Of study non-completers, two were discharged because they indicated a preference for 0.0% THC cannabis (placebo) over 5.7% THC cannabis in the initial exposure period (described in 2.2.1 below), and one participant voluntarily withdrew from the study for personal reasons. Study completers had an average (SD) age of 25 (5) years; 10 were male and 3 were female; 11 were African American, 1 was Caucasian, and 1 was multi-racial. Participants were daily cannabis users, had an average (SD) age of first cannabis use at 15 (2) years of age, had been using cannabis frequently for 9 (6) years, and smoked cannabis 4 (2) times per day at the time of study entry. Ten of the 13 participants met DSM-IV-TR criteria for cannabis dependence. The use of alcohol and other illicit drugs was infrequent (average alcohol consumption was < 1 drink per week). Tobacco use was self-reported by eight participants and was allowed ad-libitum during the study.

2.2. Study procedures

The study used a within-subjects crossover design to compare the effects of low-dose (120 mg/day; 40 mg tid) and high-dose (180–240 mg/day; 60–80 mg tid) dronabinol maintenance relative to placebo on cannabis (placebo and 5.7% THC) self-administration behavior during progressive ratio and forced-choice (cannabis versus money) conditions. The study was conducted on the residential research unit of the Johns Hopkins University Behavioral Pharmacology Research Unit (BPRU) and lasted 39-40 days. The first two study days provided initial exposure and discrimination training to the two cannabis doses (placebo and 5.7% THC). This was followed by a 1-2-day dronabinol dose run-up evaluation to determine individual participant tolerability of acute dronabinol doses up to a target dose of 80 mg. Following the dronabinol dose run-up evaluation, participants completed three counterbalanced dronabinol maintenance phases (placebo, low-dose, high-dose), each lasting 12 consecutive days. Dronabinol dose order was counterbalanced across participants using a balanced Latin Square procedure.

2.2.1. Cannabis exposure and discrimination testing

Participants were told that there were two types of cannabis cigarettes used in the study, labeled “Drug A” and “Drug B.” Participants completed a drug sampling procedure on the first two days of the study. On Day 1, participants self-administered five cannabis cigarettes of “Drug A” and on Day 2 they self-administered five cannabis cigarettes of “Drug B” (1 cigarette each at 11:00, 14:00, 17:00, 20:00, and 23:00). Cannabis self-administration occurred in an ad-libitum manner and subjective drug effect rating assessments were conducted after each exposure. The order of exposure (whether “Drug A” was placebo or