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Short communication

Oral cannabidiol does not produce a signal for abuse liability in frequent marijuana smokers

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ABSTRACT

Background: Cannabidiol (CBD) is a naturally occurring constituent of the marijuana plant. In the past few years, there has been great interest in the therapeutic effects of isolated CBD and it is currently being explored for numerous disease conditions (e.g., pain, epilepsy, cancer, various drug dependencies). However, CBD remains a Schedule I drug on the U.S. Controlled Substances Act (CSA). Despite its status, there are no well-controlled data available regarding its abuse liability.
Methods: Healthy, frequent marijuana users ($n = 31$) were enrolled in this within subject, randomized, placebo-controlled, double-blind, multisite study that administered oral cannabidiol (0, 200, 400, 800 mg) alone and in combination with smoked marijuana (0.01%, 5.3–5.8% THC). Participants received one dose combination across 8 once-weekly outpatient sessions (7.5 h). The primary findings on the drug interaction effects were previously reported (Haney et al., 2016). The present study is a secondary analysis of the data to examine the abuse liability profile of oral cannabidiol (200, 400, 800 mg) in comparison to oral placebo and active smoked marijuana (5.3–5.8% THC).
Results: Active marijuana reliably produced abuse-related subjective effects (e.g., high) ($p < 0.05$). However, CBD was placebo-like on all measures collected ($p > 0.05$).
Conclusions: Overall, CBD did not display any signals of abuse liability at the doses tested and these data may help inform U.S. regulatory decisions regarding CBD schedule on the CSA.

1. Introduction

Cannabidiol (CBD) and delta-9-tetrahydracannabinol (THC) are two of the dozens of naturally occurring chemicals present in the marijuana plant (e.g., cannabinoids). The concentration of cannabinoids in marijuana varies considerably depending on the strain and plant breeding techniques. For example, confiscated marijuana in the United States and Australia over the past decade has contained minimal concentrations of CBD (CBD: 0.14–0.17%) (Mehmedic et al., 2010; Swift et al., 2013); however, strains with high concentrations of both THC and CBD (4.5–9.3% CBD) are emerging (Freeman et al., 2014).

Although the mechanism of action of THC has been well documented, the action of CBD on the cannabinoid receptor system is unclear. There is little to no direct activity at CB_1 or CB_2 receptors (Pertwee, 2010); however, there are data suggesting that CBD may increase endocannabinoid tone by inhibiting fatty acid amide hydrolase (FAAH), an enzyme that degrades the endogenous cannabinoid, anandamide (Bisogno et al., 2001; de Petrocellis et al., 2011). Outside of the cannabinoid system, CBD modulates glycine, adenosine, $TRPV_1$, GPR55, and acts as a $5HT_{1A}$ agonist (Pertwee, 2008; Pertwee, 2010). CBD has also been demonstrated to have antioxidant, anti-inflammatory, neuroprotectant and analgesic effects in preclinical models (Hampson et al., 1998; Maione et al., 2011).

Clinically, CBD is available in several countries (e.g., Israel, England) for therapeutic use and is available on the international market (e.g., Canada, Spain) as a combination product of equal concentrations of CBD and THC (Sativex®) for the treatment of multiple sclerosis spasticity. There are also several single entity

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CBD products (e.g., Epidiolex®, Arvisol®) in development and under investigation in clinical trials for several disease conditions (e.g., epilepsy, schizophrenia, diabetes, drug dependence); some of these trials have issued reports on the safety of CBD, but data on the efficacy of these products are not yet available. There are also unregulated, non-pharmaceutical products, such as strains of high-CBD marijuana processed to produce oil, that are being used to treat various illnesses – these preparations have not been studied in clinical trials for safety or efficacy and their chemical constituents are largely unknown (with some unregulated products containing little to no CBD [FDA Warning Letter, 2015]). One U.S. trial is underway to examine the genetic differences between patients with Dravet syndrome (i.e., intractable epilepsy) who are responders and non-responders to non-pharmaceutical CBD oil (NCT02229032).

Despite the significant interest and increasing use of these products, there are no well-controlled published studies that have examined the abuse liability of CBD. Several studies have administered oral doses (≤600 mg) of CBD to healthy participants with little to no marijuana use histories and have reported minimal side effects (Bergamaschi et al., 2011; Bhattacharyya et al., 2010; Cunha et al., 1980; Hollister, 1973; Karniol et al., 1974; Zuardi et al., 1993). Oral CBD has been tested in clinical populations (Huntington's disease, epilepsy patients) at much higher cumulative doses (e.g., 1280 mg/day; 50 mg/kg/day) with reports of somnolence, decreased appetite/weight loss, diarrhea and increased seizure in a small subset of epilepsy patients (Consroe et al., 1991; Devinsky et al., 2016; Tzadok et al., 2016). Despite the frequent statements in the media and the scientific literature that CBD is void of psychoactive effects, this has never been formally assessed – no studies have completed an abuse liability assessment, enrolled the population of interest (marijuana users) or compared CBD effects to a cannabinoid agent with known abuse liability, such as smoked marijuana, as a positive control.

The current study is a secondary analysis of a trial that examined a wide range of oral CBD doses alone and in combination with smoked marijuana and reported that CBD does not alter the subjective, physiological or reinforcing effects of marijuana (see Haney et al., 2016 for detailed methods). The current analyses focus on the abuse liability of a range of oral CBD doses (up to 800 mg) compared to oral placebo (negative control) and smoked marijuana (positive control) in a sample of heavy marijuana smokers.

2. Methods

2.1. Participants

Participants were healthy marijuana smokers who completed in-person screening evaluations that included medical history, physical exam, psychiatric assessments, urinalysis, blood chemistry, and 12-lead ECG. Inclusion criteria included self-report of smoking marijuana at least 4 times per week over the past 4 weeks (half of a joint equivalent on each occasion) and an observed THC-positive urine sample. Exclusion criteria included physiological drug dependence requiring medical care (benzodiazepine, alcohol dependence), pregnancy, and serious medical (e.g., diabetes) or psychiatric (e.g., suicidality) problems (see Haney et al., 2016 for full inclusion/exclusion criteria).

2.2. Drugs

The study was conducted under an Investigational Drug Application from the Food and Drug Administration (113,221). Oral CBD doses (pure synthetic (−)–CBD, STI Pharmaceuticals, Essex, England; packaged by Eminent Services Corp., Frederick, Maryland; size 00 capsules) were prepared in blinded packaging by the investigational pharmacy at each site. Marijuana cigarettes (inactive: 0.01% THC, 0.001% CBD; active: 5.3%–5.8% THC, 0.01% CBD) were provided by Research Triangle Institute (RTI).

2.3. Study design

This was a three-site, 8-week randomized, within-subject, double blind, placebo-controlled outpatient study conducted at Columbia University, the Medical University of South Carolina and the University of Kentucky. Each participant completed a total of 8 sessions (7.5 h) and received one dose combination of oral CBD (0, 200, 400, 800 mg) and smoked marijuana (0.01, 5.3%–5.8% THC) during each session. There was a minimum of 1-week washout between sessions to preclude potential CBD carry-over effects.

This study was approved by the Institutional Review Boards at each university and was conducted in accordance with the Helsinki guidelines for ethical research. All participants provided sober, written informed consent prior to study participation and were paid for their participation.

2.4. Physiological assessments

Heart rate and blood pressure were collected prior to (baseline) and at regular intervals after CBD administration (0.5, 1, 1.4, 1.75, 2, 2.5, 3, 3.5, 4, 4.7, 5.2, 5.7, 6.67 h – designed to capture the time-action effects of both oral CBD and smoked marijuana).

2.5. Performance measures

Two performance measures, a Digit Symbol Substitution Task (DSST) and a Continuous Performance Task (CPT) were assessed. The DSST is a psychomotor task that assesses speed and accuracy of pattern recognition (3 min task) and the CPT measures sustained selective attention (5 min task).

2.6. Participant-rated measures

Visual analog measures were collected before and at regular intervals after drug administration. Participants rated their responses on a 100 mm line, anchored with "not at all" (0 mm) to "extremely" (100 mm). Measures included ratings of marijuana drug effects (e.g., street value, drug liking) and a 44-item mood inventory (e.g., high, good drug effects, sedated, alert, hunger), with selected measures having demonstrated sensitivity to cannabinoid agonists (Haney et al., 2004; Lile et al., 2010).

2.7. Statistical analysis

All measures were initially analyzed as raw time course data using a three-factor repeated measures model (marijuana dose, CBD dose, time). Peak/trough scores were analyzed using a one-factor model (dose). Tukey's post-hoc tests examined the time course of the drug effects, individual doses compared to oral placebo, and differences between the comparator dose conditions (e.g., active marijuana/placebo CBD condition compared to cannabidiol [0, 200, 400, 800 mg]/inactive marijuana conditions). All models were conducted with Proc Mixed in SAS 9.3 (Cary, NC) with significance at $p < 0.05$.

3. Results

A total of 31 participants completed the study across the three study sites: 14 women, 17 men; mean age (±SEM) was 29.1 ± 1.7 years (range: 19–49 years). Participants reported smoking marijuana 6.5 ± 0.2 days per week and lifetime regular use of 9.3 ± 1.2 years (range: 0.5–29 years); 18 participants were cigarette