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Oral Delta-9-tetrahydrocannabinol Suppresses Cannabis Withdrawal Symptoms

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Abstract

Objective: This study assessed whether oral administration of delta-9-tetrahydrocannabinol (THC) effectively suppressed cannabis withdrawal in an outpatient environment. The primary aims were to establish the pharmacological specificity of the withdrawal syndrome and to obtain information relevant to determining the potential use of THC to assist in the treatment of cannabis dependence.

Method: Eight adult, daily cannabis users who were not seeking treatment participated in a 40-day, within-subject ABACAD study. Participants administered daily doses of placebo, 30mg (10mg/tid), or 90mg (30mg/tid) oral THC during three, 5-day periods of abstinence from cannabis use separated by 7-9 periods of smoking cannabis as usual.

Results: Comparison of withdrawal symptoms across conditions indicated that (1) the lower dose of THC reduced withdrawal discomfort, and (2) the higher dose produced additional suppression in withdrawal symptoms such that symptom ratings did not differ from the smoking-as-usual conditions. Minimal adverse effects were associated with either active dose of THC.

Conclusions: This demonstration of dose responsivity replicates and extends prior findings of the pharmacological specificity of the cannabis withdrawal syndrome. The efficacy of these doses for suppressing cannabis withdrawal suggests oral THC might be used as an intervention to aid cannabis cessation attempts.

1. Introduction

Neurobiological and behavioral studies on cannabis withdrawal suggest that it has importance in the development, maintenance, and treatment of cannabis dependence (Budney et al., 2004). Demonstrations of precipitated withdrawal using a cannabinoid receptor antagonist indicate a neurobiological basis for a cannabis withdrawal syndrome (Lichtman and Martin, 2002). Associations between cannabinoid withdrawal and changes in dopamine cell activity in the limbic system and corticotrophin-releasing factor (deFonseca et al., 1997; Diana et al., 1998) suggest that such withdrawal may contribute to cannabis dependence by its influence on emotional, behavioral, and reward processes mediated in the central nervous system (Koob and LeMoal, 2001). Human laboratory studies have characterized a cannabis withdrawal syndrome with common symptoms of anger, anxiety, decreased appetite/weight loss, irritability, restlessness, and sleep difficulty (Budney et al., 2004). Depressed mood, stomach pain/physical discomfort, shakiness, and sweating have been observed less frequently. Most symptoms onset within 24 hours of abstinence, peak within 2-3 days, and last approximately 1-2 weeks. Most adults and many adolescents in treatment for cannabis dependence report a withdrawal symptom profile concordant with that observed in the laboratory, and many report that it contributes to difficulty quitting and that they use cannabis to alleviate withdrawal symptoms (Budney et al., 1999; Stephens et al., 2002; Vandrey et al., 2005; Young et al., 2002).

Establishing the pharmacological specificity of the cannabis withdrawal syndrome is vital to determining whether it is indeed a true withdrawal syndrome (Hughes et al., 1990). That is, is symptom expression due to deprivation of a specific substance [delta-9 tetrahydrocannabinol (THC) in the case of cannabis]? Evidence for such specificity has accrued from the experimental laboratory. Precipitated withdrawal using a CB1 receptor antagonist, and the absence of acute

drug effects and precipitated withdrawal in CB1 receptor knockout mice exposed to THC suggest pharmacological specificity (Ledent et al., 1999; Lichtman and Martin, 2002; Valverde et al., 2000). Smoked cannabis or oral THC appears to relieve withdrawal symptoms when administered after withdrawal is observed during periods of abstinence (Budney et al., 2001; Haney et al., 1999b; Jones and Benowitz, 1976). Smoking placebo cannabis following a period of cannabis smoking does not abate withdrawal, and deprivation of oral THC following administration of oral THC produces abstinence effects similar to those following cessation of smoked cannabis (Haney et al., 1999a; Jones and Benowitz, 1976). In a recent residential laboratory study, Haney et al. demonstrated that oral THC (50mg/day) reduced ratings of anxious, miserable, trouble sleeping, chills, and craving, and suppressed decreases in food intake and weight compared with administration of placebo during a 6-day period of abstinence from daily cannabis smoking (Haney et al., 2004).

Identification of pharmacological specificity has important treatment implications for cannabis dependence. Behavioral therapies for cannabis dependence appear promising, however, as with the behavioral treatments for other drug dependencies, there is much room for improved outcomes (McRae et al., 2003). If THC alleviates cannabis withdrawal, it might be useful as an aid in the treatment of cannabis dependence (Haney et al., 2004; Hart, 2005). Using a cannabinoid agonist such as THC to treat cannabis dependence is comparable to other well-established agonist therapies (e.g., methadone, nicotine replacement).

The present study extends the findings of Haney et al. (2004) by examining pharmacological specificity in a more generalizable environment and by examining dose-responsivity. Specifically, this study examined outpatient administration of a placebo and two active doses of oral THC during periods of cannabis abstinence. Under a low dose (30mg: 10mg/tid),

participants were expected to show some cannabis withdrawal, but less severe symptoms than under the placebo dose. The high dose (90mg: 30 mg/tid) was expected to facilitate additional suppression of withdrawal.

2. Methods

2.1 Participants

Six male and two female volunteers ranging in age from 21 to 54 (mean=32.5) completed a 40-day outpatient study. Participants were recruited via advertisements seeking cannabis users for a non-treatment study on the effects of cannabis use. Participants had to report: using cannabis at least 25 days per month during the previous 6 months, at least a 2-year history of regular cannabis use, and experiencing two or more withdrawal symptoms during previous cessation periods. Individuals were excluded if they: met DSM-IV criteria for a current Axis I disorder including substance use disorders other than cannabis, nicotine, or caffeine dependence; used any illicit substances other than cannabis during the previous 30 days; were taking psychotropic medication; were consuming more than 20 alcoholic drinks per week; were pregnant; were using cannabis under a physician's guidance; were trying to reduce cannabis use, or were seeking treatment for cannabis-related problems. Individuals were also excluded if they reported contraindications for taking oral THC, such as holding a job that involves driving, operating heavy machinery, or had a history of cardiac or allergic disorders. Histories of seizures or head trauma were also exclusion criteria.

A 2-hour screening assessment comprised drug and medical histories and medical and psychiatric evaluation. The University of Vermont Institutional Review Board approved all procedures, and informed consent was obtained. Twenty-two participants initiated the study; 8

completed the study and were included in all analyses. Of the 14 who did not complete, 7 did not show a withdrawal response during the placebo condition, 2 used cocaine, 1 did not smoke cannabis during a study condition that required smoking, 1 required medication for an illness, 1 had a travel conflict, and 1 used insufficient birth control.

Participants reported 15.9 (SD=10.4) mean years of cannabis use, using on 28.5 (SD=1.9) days per month, and using 2.6 (SD=0.5) times per day. Four met DSM-IV criteria for current cannabis dependence and four for cannabis abuse. Four participants were also tobacco smokers. Note that those participants who were excluded from the study because they did not show a withdrawal response (n=7) did not differ significantly ($p > .05$) from the completers regarding gender (71% male), tobacco smokers (42.4%) or mean age 28.0 (SD=6.8), years of marijuana use 11.0 (SD=6.9), days used per month 28.7 (SD=1.9), and number of times used per day 2.9 (SD=1.0). However, they were less likely to meet criteria for cannabis dependence (n=1: 14% vs. 50%); 57% (n=4) met criteria for cannabis abuse and 29% (n=2) did not meet criteria for either abuse or dependence.

2.2 Procedure

An ABACAD within-subjects study design involved three cannabis smoking-as-usual (SAU) conditions (A) and three cannabis abstinence conditions (B, C, D). The three abstinence conditions involved three times per day administration of either: placebo, 10mg oral THC, or 30mg oral THC. To minimize safety concerns associated with use of the high dose of THC, the 30mg/day condition always preceded the 90mg/day condition. Participants were randomized to receive the three doses in one of three orders (placebo-30mg-90mg; 30mg-90mg-placebo; 30mg-placebo-90mg). For ethical reasons, on the last day of each abstinence condition, participants

were asked if they planned to resume cannabis use. If they said yes, they were offered the opportunity to continue in the study. If they said no, they were referred to treatment resources. All participants stated their intent to resume cannabis use.

Participants completed 30-minute laboratory visits each weekday and on the Sunday preceding abstinence conditions. The abstinence conditions were always 5 days (weekdays only) and the SAU conditions varied from 7-9 days (i.e., included one or two weekends). Only data from the five weekdays in each condition were used in the comparative analyses to minimize the effect of specific days (weekday vs. weekend) on symptom ratings.

2.2.1 SAU Conditions

During each SAU condition, participants were requested not to change their usual pattern of marijuana smoking and to abstain from all psychoactive drugs, with the exception of alcohol, nicotine, and caffeine. They were instructed not to make significant changes in their alcohol, caffeine and cigarette use nor their diet or exercise throughout the study. Participants were also instructed not to use cannabis or drink alcohol for at least two hours prior to laboratory visits. At each visit, physiological measures were taken, a urine specimen was collected, breath alcohol level was determined, and a battery of affective and behavioral assessments were completed.

2.2.2 Abstinence Conditions

At each lab visit, participants were administered one dose of oral THC or placebo and were provided with two doses to take home. In addition to the assessments performed in the SAU conditions, two drug effect assessments were administered.

2.2.3 *THC Administration*

Participants were told that each tablet of medication contained either an active dose of THC, placebo, or both. A research nurse dispensed all medication double blind. A 50mg/ml suspension of THC and sesame oil was prepared by extracting the liquid contents of the THC 10mg capsules (dronabinol: Solvay Pharmaceuticals). Capsules containing 10mg and 30mg THC were then prepared by combining the suspension with varying volumes of sesame oil and then filling opaque size #00 gelatin capsules. Matching placebo capsules were prepared using only sesame oil in opaque size #00 gelatin capsules. All capsules were sealed in unidose packaging. Participants were instructed to keep the medication refrigerated and to take the medication at the same times each day, spaced 5 hours apart (e.g. 9am, 2pm and 7pm). To help assure medication compliance, participants were given a beeper and were contacted on 1-3 days of each condition. When paged, participants had to respond within one hour to schedule a time to either come to the lab or allow staff to make a home visit. Medication checks revealed 100% compliance.

2.2.4 *Abstinence Verification*

Quantitative cannabinoid levels were obtained via gas chromatographic-mass spectroscopic of 11-nor-9-carboxy- Δ^9 -tetrahydrocannabinol (THCCOOH), the primary metabolite of THC (Huestis and Cone, 1998). These levels were normalized to urine creatinine concentration to obtain a metabolite-creatinine ratio. Quantitative testing was performed on every other day of the abstinence period. Abstinence during the placebo condition was confirmed if the metabolite-creatinine ratio declined by at least 100% from Sunday to Friday and did not increase by more than 50% from the ratio obtained from the prior specimen. Similar standards have been used

successfully by our lab and others in prior studies (Budney et al., 2003; Huestis and Cone, 1998; Kouri and Pope, 2000). Cannabis abstinence verification during the two active THC conditions could not be verified by this procedure because the primary metabolite of oral THC, like cannabis, is THCCOOH. Hence, quantitative levels of cannabivarin, a compound contained in smoked cannabis that is not in oral THC, were used to determine abstinence during these conditions (ElSohly et al., 2001b; ElSohly et al., 2001a). Cannabivarin can be measured in urine and has similar excretion profile as THCCOOH. The same abstinence criterion used for THCCOOH was used to determine abstinence during the active THC conditions. Quantitative analyses were performed by ElSohly Laboratories (Oxford, Mississippi).

Participants received a total of \$950 if they complied with all aspects of the study. Compensation for participation in the abstinence conditions was provided only after urinalysis results confirmed cannabis abstinence.

2.3 Measures

A drug-history interview assessed use of cannabis and other recreational, prescription, and over-the-counter drugs. The Vermont Structured Diagnostic Interview modified for the DSM-IV was used to diagnose common Axis I psychiatric disorders (Hudziak et al., 1993).

Dependent Measures. Each study day, participants completed the measures below. The primary dependent measure, the *Marijuana Withdrawal Checklist*, comprised 29 items for which participants indicate severity during the prior 24 hours on a 4-pt scale (0=not at all, 1=mild, 2=moderate, 3=severe) (Budney et al., 1999). The items reflect those reported in prior cannabis withdrawal studies and filler items to reduce response bias. A summary Withdrawal Discomfort

Score was computed by summing the 12 items most frequently reported in prior studies (Budney et al., 2001; Budney et al., 2003; Budney et al., 1999).

Secondary dependent measures included the Marijuana Craving Questionnaire (MCQ) which provides a total score and subscale scores of compulsivity, emotionality, expectancy, and purposefulness (Heishman et al., 2001). The Brief Symptom Inventory (BSI) provides scores on nine scales: Somatization, Obsessive-Compulsive, Interpersonal-Sensitivity, Depression, Anxiety, Hostility, Phobic anxiety, Paranoid ideation, and Psychoticism (Derogatis, 1993). The Profile of Mood States (POMS) (McNair et al., 1971) provides six mood scale scores: tension, depression, anger, vigor, fatigue, and confusion (McNair et al., 1971). Last, a 5-item Sleep Inventory assessed sleep-onset latency, total amount of sleep, number of nocturnal awakenings, time of awakening, and subjective sleep quality on a 7-point scale (Carskadon et al., 1976). Heart rate and blood pressure (sitting) were measured via an automated monitor (DINIMAP; Johnson & Johnson, Arlington, TX). Body weight was obtained on a standing mechanical scale (Detecto: Cardinal Scale Manufacturing Co, Webb City, MO).

During the Abstinence conditions participants completed the Addiction Research Center Inventory (ARCI), and the Drug Effects Questionnaire (DEQ). The ARCI characterizes drug effects via 6 subscales: Morphine–Benzedrine Group (MBG), a measure of euphoria; Pentobarbital, Chlorpromazine, Alcohol Group (PCAG), a measure of sedation; Benzedrine Group (BG) and Amphetamine Scale (A), measures of stimulation; Lysergic Acid Diethylamide Scale (LSD) a measure of dysphoria; and Marijuana Scale (M) a measure of marijuana-like effects (Haertzen and Hickey, 1987). The DEQ comprised 8 items (drug effect, bad effect, good effect, liked, sick, sedated, stimulated, and want to take again) measured on a 100mm visual analog scale. At the conclusion of each Abstinence condition, participants also indicated

whether they believed that they received THC or placebo. An Adverse Events Checklist administered during all conditions comprised 21 items rated on a 4-point scale, (0) not present, (1) mild, (2) moderate or (3) severe.

2.4 Data Analysis

The five weekdays within each condition were averaged to obtain a mean for each of the six conditions. We chose to analyze and present mean data across days rather than including day as a separate factor because initial analyses of the Marijuana Withdrawal Checklist items revealed a significant main effect for day for only one item, and showed no significant day x condition interaction effects. Thus, for increased parsimony and clarity, mean data across condition are presented. For each possible withdrawal variable we first report the overall results of a condition effect in a six-cell repeated measures, one-way analyses of variance (ANOVA). Then, using Student-Newman-Kuels multiple comparison tests to examine pairwise differences between conditions, we report whether the variable values with the placebo dose were greater than that of the baseline SAU conditions to verify that an abstinence effect occurred. We restricted further analyses of the ability of THC to suppress withdrawal to those variables with validated abstinence effects ($p < .05$). Among these, we then report whether the 30mg and 90mg dose scores differed from the placebo. If they did, we examined whether the scores with the 30mg or 90mg doses differed from SAU to determine if they fully suppressed withdrawal. We concluded “full suppression” if the active dose condition did not differ from the SAU conditions, recognizing the limitation of basing this conclusion on rejection of the null hypothesis. Analyses were performed using SAS, PROC GLM. For two variables (i.e., irritability and body weight), we observed significant differences among the three SAU conditions. For irritability, analysis of

covariance was performed to compare the abstinence conditions while adjusting for SAU condition. For body weight, initial t-tests were performed to determine if mean weight change (abstinence condition minus preceding baseline condition) was equal to zero. Then, a 3-cell repeated measures ANOVA on these change scores was performed followed by SNK pairwise comparisons.

For the direct effects of THC (ARCI and DEQ), we report whether a condition effect occurred in a one-way, repeated measures ANOVA. We then report tests of dose responsivity, using Student-Newman-Kuels multiple comparison tests to examine pairwise differences among placebo, 30mg, and 90mg conditions.

3. Results

3.1 Manipulation Check

Abstinence Verification. All eight participants met abstinence criteria based on self-report and reduction in cannabinoid and cannabivarin levels, except for two participants whose urine toxicology results failed to meet the abstinence criteria on Day 5 of the Placebo condition. Self-report measures for that day were not included in the analyses for these two participants.

3.2 Withdrawal Measures

Marijuana Withdrawal Checklist. Repeated measures ANOVAs showed significant condition effects ($p < .05$) for the total WDS ($F_{5,35}=11.69$), depressed mood ($F_{5,35}=3.73$), decreased appetite ($F_{5,35}=7.72$), irritability ($F_{5,35}=8.91$), sleep difficulty ($F_{5,35}=4.20$), increased aggression ($F_{5,35}=4.46$), restlessness ($F_{5,35}=2.51$), and craving for marijuana ($F_{5,35}=8.26$) (Tables

1 and 2; Figure 1). Increased anger, nervousness/anxiety and strange dreams showed nonsignificant trends ($p < .10$).

The placebo condition significantly increased the Withdrawal Discomfort Score and 5 Marijuana Withdrawal Checklist items (aggression, craving, depressed mood, irritability, sleep difficulty) compared with the SAU conditions, indicating these were valid withdrawal symptoms. Three additional items (anger, anxiety, strange dreams) showed trends toward a significance increase ($p < .10$). Withdrawal suppression by THC was examined only among the five items whose increase with placebo was significant at $p < .05$. The 30mg dose suppressed the Withdrawal Discomfort Score and 3 individual items (aggression, irritability and sleep difficulty). The 90mg dose also suppressed these symptoms and suppressed two additional symptoms (depressed mood and craving). The 30mg dose fully suppressed aggression, irritability and sleep difficulty, but not the Withdrawal Discomfort Score. The 90mg dose fully suppressed the Withdrawal Discomfort Score and all 5 symptoms. Although not statistically tested, similar trends were seen with the three marginal symptoms (anger, anxiety and strange dreams).

3.3 *Marijuana Craving Questionnaire (MCQ)*

The total craving score on the MCQ showed a significant condition effect ($F_{5,35}=3.77$). The Placebo condition showed a higher mean total craving rating than the SAU conditions indicating an abstinence effect (Table 1). With the 30 and 90mg doses, total craving did not differ from the SAU conditions indicating full suppression of craving. The Expectancy subscale showed an identical pattern of results ($F_{5,35}=3.87$). The Compulsivity subscale showed a significant

difference across conditions ($F_{5,35}=2.70$), but no clear increase with placebo. The two other subscales did not show significant condition effects.

3.4 *Sleep Inventory*

The overall subjective sleep quality rating showed a significant condition effect ($F_{5,35}=4.17$). An abstinence effect was observed during the Placebo condition ($p<.05$), and both the 30mg and 90mg doses fully suppressed this withdrawal effect indicating better sleep ratings with the active THC doses (Table 1). The number of nocturnal awakenings item showed an overall condition effect ($F_{5,35}=2.64$), but only a trend toward an abstinence effect was observed during the placebo condition. No overall condition effects were observed on the other Sleep Inventory items.

3.5 *POMS and BSI*

The POMS Tension scale showed a significant condition effect, $F_{5,35}=3.22$. The Placebo condition showed significantly higher mean scores than 2 of the 3 SAU conditions indicating a withdrawal effect. The 30mg and 90mg doses decreased this scale, but the decrease was not statistically significant (Table 1, 2). The POMS Anger scale also showed a significant condition effect ($F_{5,35}=2.82$), but did not show a significant abstinence effect.

On the BSI, the Hostility and Somatization subscales showed significant effects for condition (Hostility: $F_{5,35}=4.11$; Somatization: $F_{5,35}=2.72$). For Hostility, the placebo condition showed significantly higher mean scores than 2 of the 3 SAU conditions suggesting an abstinence effect, and both THC doses suppressed this increase (Table 2). For Somatization, there was no clear abstinence effect. None of the other BSI scales showed a significant condition effect.

3.6 Weight, Blood Pressure and Heart Rate.

Only the body weight change during the placebo condition differed from zero ($t=-3.44$, $p<.01$) (Figure 1). A significant condition effect was observed for body weight ($F_{2,14}=6.21$) (Table 1). Change in body weight significantly differed between the 90mg condition (mean weight gain) and the placebo condition (mean weight loss) (Table 2; Figure 1). No significant condition effects were observed for blood pressure or heart rate.

3.7 Oral THC Effect Ratings

ARCI and DEQ ratings generally indicated that oral THC produced dose-dependent effects concordant with expectations (Table 3). The Marijuana Scale showed significant dose effects ($F_{2,14}=9.22$), with significant differences observed between the high dose and placebo, the high dose and low dose, but not between the low dose and placebo. Similar findings were observed for the Amphetamine scale ($F_{2,14}=5.87$). On the DEQ, significant dose effects were observed for Drug effect ($F_{2,14}=11.54$), Liked ($F_{2,14}=8.95$), Sick ($F_{2,14}=8.59$), and Good effect ($F_{2,14}=10.34$), and the other four items showed trends towards significance (Bad effect: $F_{2,14}=3.34$, $p=.07$; Sedated: $F_{2,14}=3.39$, $p=.06$; Stimulated: $F_{2,14}=3.32$, $p=.07$; Take Again: $F_{2,14}=3.44$, $p=.06$). For Drug effect, Good effect, and Liked, higher ratings were observed with 90mg than placebo, and with 90mg versus 30mg, but 30mg did not differ from placebo. The only anomalous finding was the Sick rating for 30mg was higher than for the other two conditions. Five of eight participants (62%) correctly identified receiving active drug during the 30mg condition, a percentage not clearly different from chance. All participants identified receiving active drug during the 90mg condition.

3.8 Adverse effects

Only one of the 21 Adverse Event Checklist items (i.e., nervous) showed a significant condition effect ($F_{5,35} = 4.32$). Pairwise comparisons indicated that the nervous rating during one SAU condition was elevated compared to the other 5 conditions. No participant was discontinued or dropped out because of adverse effects, no adverse events required treatment, and no FDA-defined serious adverse events occurred. One participant reported a severe strange dream and feeling “paralyzed” on one day of the 30mg condition; however, he reported a history of similar experiences and this effect did not re-occur with the 90mg condition. Staff noted signs of cannabis-like intoxication in two participants during the 90mg condition.

4. Discussion

This within-subject laboratory study replicates a previous demonstration of the cannabis withdrawal suppressant effect of oral THC (Haney et al., 2004), and extends this finding by demonstrating the effect in the natural environment and by showing dose-responsivity. These findings along with prior observations from the human and animal laboratory clearly indicate the pharmacological specificity of the cannabis withdrawal syndrome. Demonstration of pharmacological specificity is probably the most important criterion for demonstrating that an abstinence syndrome upon cessation of a substance is indeed a *true* drug withdrawal syndrome (Hughes et al., 1990). This finding adds to converging evidence from studies across diverse methodologies that support the validity and clinical importance of the cannabis withdrawal syndrome.

Strong scientific evidence for cannabis withdrawal is important because it is not recognized in the current DSM, yet many individuals seek treatment for cannabis dependence and the

majority report withdrawal symptoms, report they use marijuana to avoid withdrawal, and report that withdrawal undermines their ability to stop cannabis use (Budney et al., 2004). That said, the present findings have potential clinical implications. The efficacy of THC for suppressing cannabis withdrawal clearly suggests that oral THC could be used to abate cannabis withdrawal in dependent individuals who are trying to quit, and this might improve outcomes.

Although no adequate randomized clinical trials of THC or other medications for cannabis dependence have been published, four laboratory studies have evaluated potential medications (Hart, 2005). In single dose studies, bupropion and divalproex worsened some withdrawal symptoms and had no positive effects (Haney et al., 2004; Haney et al., 2001). A small trial investigating divalproex as a treatment for cannabis dependence in adult outpatients also reported that this medication fared no better than placebo (Levin et al., 2004). In another single dose study Nefazodone effectively decreased some cannabis withdrawal symptoms, but did not affect the majority of symptoms (Haney et al., 2003). The most promising demonstration of suppression of cannabis withdrawal was observed in the aforementioned study by Haney et al. (2004). A 50mg dose of THC (10mg/5xday) decreased 4 symptoms and craving. This dose did not produce intoxication, produced few adverse events and was subjectively indistinguishable from placebo.

Our study extended the results of the Haney study in three ways. First, the study found effects in an outpatient setting rather than an inpatient setting. This is important because the outpatient setting is closer to that which would be used in a controlled clinical trial of THC as a treatment option. Second, the study found that a lower daily dose of oral THC (30mg/day rather than 50mg/day) reduced withdrawal discomfort. This is important because some cannabis users may not be able to tolerate higher doses and higher doses may produce adverse effects. Third,

the current study found that a higher dose (90mg/day) showed even greater reduction in withdrawal. This is important because heavier cannabis users would likely show greater tolerance to the effects of THC, and thus may require higher doses of THC to have a good chance of quitting. Importantly, this higher dose did not cause any serious adverse events or cause participants to drop out of the study. However, the high dose did produce some THC intoxication symptoms, and produced some drug effects such as euphoria and liking that suggest abuse potential. Human laboratory studies indicate that oral THC can function as a reinforcer in regular marijuana smokers, but its abuse liability appears modest compared with smoked marijuana (Hart et al., 2005; Chait and Zacny, 1992). Whether the additional suppression gained with the higher dose has importance to the treatment of cannabis dependence could not be addressed in this experimental study of non-treatment seekers. Future studies with clinical samples using various dosing paradigms will need to examine the risks versus benefits of using high versus low doses of oral THC to treat cannabis withdrawal.

Several limitations of the present study warrant comment. First, it is possible that participants used small amounts of cannabis during the abstinence conditions that went undetected. We expect that this would have most likely occurred during the placebo condition where withdrawal symptoms were most severe. If this did occur, the result would have been ratings of less severe withdrawal during placebo, making it more difficult to detect suppressant effects during the THC conditions. Thus, our findings would reflect a conservative demonstration of withdrawal suppression. Second, the sample size was small and included only heavy cannabis users who were not seeking treatment and who experienced withdrawal during the placebo condition. Note that the seven participants who did not show substantial withdrawal during the abstinence period and were discontinued from the study did not differ significantly

from the completers regarding duration, amount, and frequency of cannabis use, but were less likely to meet criteria for a cannabis use disorder. As with other drug withdrawal syndromes there are great individual differences in withdrawal severity, and a significant proportion of users may not experience significant withdrawal during a cessation attempt (Hughes, in press). We also do not know how these findings generalize to treatment seekers, although the rate and duration of cannabis use in this sample was comparable to reports of adults seeking treatment for cannabis dependence, and all participants included in the analyses met criteria for abuse or dependence. Treatment seekers are likely to exhibit greater dependence severity than non-treatment seekers (Budney and Hughes, 2006), which suggests that, if anything, effects would be more robust in treatment seekers.

The demonstration of a dose-dependent suppression of cannabis withdrawal by oral THC provides additional support for validity of the cannabis withdrawal syndrome and its inclusion in the DSM. Although there is now strong evidence for the validity of the syndrome, several questions remain; e.g. does cannabis tolerance and withdrawal covary, is there a prolonged withdrawal syndrome, is its severity related to intensity of use, is it influenced by genotype, expectancy, or conditioning? Perhaps the most important question though is whether the withdrawal syndrome undermines the ability to stop or reduce cannabis use. The present data suggest that a clinical trial of oral THC warrants consideration within the scope of developing pharmacological and behavioral interventions for cannabis dependence.

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Table 1. Adjusted Means During Smoking-as-Usual and Abstinence Conditions

	<u>SAU*</u>	<u>Placebo</u>	<u>30mg</u>	<u>90mg</u>
<i>Withdrawal Checklist</i>				
WDS ^{a,b,c,d,f} (0-36)	1.9	6.2	4.5	2.4
Anxiety (0-3)	.08	.30	.28	.05
Anger ^a (0-3)	.08	.38	.18	.00
Aggression ^{a,b,c,d,e,f} (0-3)	.09	.45	.15	.00
Decreased Appetite ^a (0-3)	.12	.43	.80	.13
Depressed Mood ^{a,b,d,f} (0-3)	.04	.24	.37	.05
#Irritability ^{a,b,c,d,e,f} (0-3)	.26	.93	.35	.15
Marijuana Craving ^{a,b,d,f} (0-3)	.74	1.75	1.53	.88
Restlessness (0-3)	.22	.78	.45	.65
Sleep Difficulty ^{a,b,c,d,e,f} (0-3)	.28	1.13	.45	.53
Stomach Pain (0-3)	.03	.03	.23	.02
Strange Dreams (0-3)	.16	.68	.45	.23
Violent Outbursts (0-3)	.08	.33	.13	.00
<i>Profile of Mood States</i>				
Anger	1.26	3.98	2.00	.33
Confused	3.32	2.61	3.20	4.13
Depressed	.63	1.59	1.33	.73
Fatigue	2.53	2.02	2.93	1.53
Tension ^{a,b}	2.97	5.16	4.33	3.33
Vigor	13.66	13.35	12.75	12.75

Brief Symptom Inventory

Anxiety	.05	.18	.16	.08
Depressed	.03	.06	.10	.05
Hostility ^{a,b,c,d,e,f}	.14	.42	.12	.03
Interpersonal-Sensitivity	.04	.05	.05	.04
Obsessive-Compulsive	.28	.17	.20	.49
Paranoid	.13	.20	.14	.10
Phobic Anxiety	.01	.00	.01	.00
Psychoticism	.02	.02	.01	.00
Somatization	.07	.06	.18	.10

Sleep Scale

Overall Rating ^{a,b,c,d,e,f} (0-7)	2.8	4.2	2.8	2.7
Latency (min)	17.42	33.08	22.05	22.05
Awakenings ^a	0.78	1.37	.75	.95
Time Awake During Night	15.85	30.78	17.25	11.88

Craving Questionnaire

Total ^{a,b,c,d,e,f} (0-84)	38.2	46.2	38.8	37.7
Expectancy ^{a,b,c,d,e,f} (0-21)	11.9	14.2	12.1	12.3
Compulsivity ^a (0-21)	5.5	7.4	6.2	5.6
Purposefulness (0-21)	13.71	15.15	13.03	12.55
Emotionality (0-21)	7.07	9.54	7.43	7.27

Physiological Measures

# Change in Body Weight ^{a,b,d,f}	---	-1.39	-0.71	1.79
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Systolic BP	126.9	129.4	125.5	124.3
Diastolic BP	72.5	75.9	74.3	71.8
Heart Rate	77.4	76.9	76.5	75.8

*SAU = mean score across the 3 smoking-as-usual condition

These measures showed differences across the 3 SAU conditions.

^a indicates a significant condition effect ($p < .05$) observed in the 6-cell (3 smoking as usual and 3 abstinence conditions), oneway analysis of variance comparing mean scores across the five days of each condition; 3- cell analysis of variance for body weight

^b indicates an abstinence effect, i.e., mean score during placebo > SAU; change during placebo > 0 lbs. for body weight.

^c indicates 30mg suppression effect, i.e, mean score during 30mg < placebo;

^d indicates 90mg suppression effect, i.e, mean score during 90mg < placebo;

^e indicates full suppression with 30mg, i.e, mean score during 30mg was not significantly different than SAU; change not different than 0 for body weight.

^f indicates full suppression with 90mg, i.e, mean score during 90mg was not significantly different than SAU; change not different than 0 for body weight.

Table 2. Suppression of Abstinence Effects

	<u>Suppression Effect^a</u>	<u>Full Suppression^b</u>
Marijuana Withdrawal Checklist		
Withdrawal Discomfort Score	30, 90	90
Aggression	30, 90	30, 90
Depressed Mood	90	90
Irritability	30, 90	30, 90
Marijuana Craving	90	90
Sleep Difficulty	30, 90	30, 90
Marijuana Craving Questionnaire		
Total	30, 90	30, 90
Expectancy	30, 90	30, 90
POMS-Tension	30*, 90*	-
BSI Hostility	30, 90	30, 90
Sleep Rating Overall	30, 90	30, 90
Weight Loss	30, 90	90

^a Suppression effect = mean score during 30mg or 90mg less than placebo ($p < .05$)

^b Full Suppression = mean score during 30mg or 90mg was not significantly different than SAU

* $p < .10$

Table 3. Mean ratings of Oral THC Direct Effects

	<u>Placebo</u>	<u>30 mg</u>	<u>90 mg</u>
ARCI			
Marijuana ^{a, d, e} (0-12)	1.3	2.4	3.8
Amphetamine ^{a, d, e} (0-11)	2.2	2.6	3.8
MBG ^b (0-16)	3.3	3.2	4.6
PCAG (0-15)	3.5	4.8	4.2
LSD (0-13)	4.1	4.7	4.5
BG (0-13)	6.0	5.2	5.7
DEQ (0-100)			
Bad ^b	1.8	13.5	8.6
Drug effect ^{a, d, e}	6.9	20.8	50.3
Good ^{a, d, e}	4.9	21.1	50.0
Liked ^b	5.9	22.1	49.2
Sedated ^b	6.0	29.9	26.2
Sick ^{a, c}	1.6	12.3	3.5
Stimulated ^b	7.3	12.9	26.3
Take Again ^b	25.6	31.0	50.0

^a $p < .05$ overall between-condition main effect

^b $p < .10$ overall between-condition main effect; pairwise comparisons not performed.

^c 30 mg/day different from placebo (pairwise comparison: $p < .05$)

^d 90 mg/day different from placebo (pairwise comparison: $p < .05$)

^e 90 mg/day different from 30mg/day (pairwise comparison: $p < .05$)