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Margaret Haney · Amie S. Ward · Sandra D. Comer
Richard W. Foltin · Marian W. Fischman

Abstinence symptoms following oral THC administration to humans

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Abstract Symptoms of dependence and withdrawal after the frequent administration of high doses (210 mg/day) of oral Δ^9-tetrahydrocannabinol (THC) have been reported, yet little is known about dependence on lower oral THC doses, more relevant to levels attained by smoking marijuana. In a 20-day residential study, male ($n = 6$) and female ($n = 6$) marijuana smokers worked on five psychomotor tasks during the day (0915–1700 hours), and in the evening engaged in private or social recreational activities (1700–2330 hours); subjective-effects measures were completed 10 times/day, and a sleep questionnaire was completed each morning. Food and beverages were available ad libitum from 0830 to 2330 hours. Capsules were administered at 1000, 1400, 1800, and 2200 hours. Placebo THC was administered on days 1–3, 8–11, and 16–19. Active THC was administered on days 4–7 (20 mg qid) and on days 12–15 (30 mg qid). Both active doses of THC increased ratings of "High," "Good Drug Effect," and "Willingness to Take Dose Again" compared to baseline (days 1–3). THC also increased food intake by 35–45%, and decreased verbal interaction among participants compared to placebo baseline. Tolerance developed to the subjective effects of THC but not to its effects on food intake or social behavior. Abstinence from THC increased ratings of "Anxious," "Depressed," and "Irritable," decreased the reported quantity and quality of sleep, and decreased food intake by 20–30% compared to baseline. These behavioral changes indicate that dependence develops following exposure to lower daily doses of THC than have been previously studied, suggesting that the alleviation of abstinence symptoms may contribute to the maintenance of daily marijuana use.

Key words Marijuana · Human · THC · Withdrawal · Dependence · Tolerance · Subjective effect · Performance · Food intake

M. Haney (✉) · A.S. Ward · S.D. Comer · R.W. Foltin
M.W. Fischman
Division on Substance Abuse, New York State Psychiatric Institute and Department of Psychiatry, College of Physicians and Surgeons of Columbia University, 722 West 168th Street, Unit 54, New York, NY 10032, USA
e-mail: mh235@columbia.edu,
Fax: +1-212-543-5991

Introduction

Although the issue of marijuana dependence in humans has received little experimental investigation in the past 20 years, recent epidemiological statistics suggest it may be important to determine the consequences of repeated cannabinoid exposure. Since the early 1990s, marijuana smoking has risen sharply, particularly in young men and women, with approximately 5% of high school seniors in the United States reporting that they smoke marijuana daily (Frank and Galea 1995; Johnston et al. 1995, 1997). In the United States, the estimated lifetime prevalence of a diagnosis of marijuana dependence exceeds 4% (Anthony et al. 1994), while in marijuana users, 7.4% of adults and 14.4% of adolescents meet DSM diagnostic criteria for dependence within the past year (Budney et al. 1997). Further, people are seeking treatment for marijuana abuse, particularly when marijuana-specific programs are advertised (Stephens et al. 1993, 1994; Budney et al. 1998). Approximately 93% of those seeking such treatment report an inability to stop smoking marijuana.

The recent synthesis of the cannabinoid receptor antagonist, SR141716A, has provided the necessary tool to study precipitated withdrawal from Δ-9-tetrahydrocannabinol (THC), the major psychoactive component in marijuana: rats made tolerant to THC following repeated daily injections showed dramatic symptoms of withdrawal, characterized by ptosis, wet-dog shakes, "anxiety" reactions, and disorganized

patterns of motor activity following the administration of SR141716A (Aceto et al. 1995; Tsou et al. 1995; Rodriguez de Fonseca et al. 1997). In human and non-human primates, the discontinuation of a regimen of THC maintenance produced symptoms of withdrawal. Specifically, rhesus monkeys self-administering IV THC demonstrated increased aggressiveness, hyperirritability and anorexia when abstinent from THC (Kaymakcalan 1973). A more recent study in rhesus monkeys demonstrated that withdrawal from IV THC disrupted operant behavior, which was reversed by THC re-administration (Beardsley et al. 1986). In human laboratory studies, physical dependence on THC was suggested in one woman who experienced symptoms of anxiety, dysphoria, anorexia and sweating after cessation from chronic marijuana exposure (ca. nine marijuana cigarettes/day for 21 days; Mendelson and Mello 1984). Similarly, maintenance on high doses of oral THC (210 mg/day) for 10–20 days, produced both tolerance and dependence in human research subjects (Jones et al. 1976, 1981). During THC administration, there was a progressive decline in THC's cardiovascular and subjective effects, e.g. "high." After abrupt cessation of THC administration, the majority of volunteers reported irritability, restlessness, decreased appetite, and sleep disturbances for approximately 4 days after the last dose of THC. Re-administration of THC diminished most symptoms, suggesting that sustained exposure to THC engendered physical dependence.

Although these studies are important in indicating that cannabinoids produce dependence, it may be that THC levels attained by most marijuana smokers are lower so that any withdrawal reactions are muted or non-existent. The purpose of the present study was to determine if abstinence symptoms occur when lower daily oral THC doses (40–60%) are administered for a shorter period of time (4 days) compared to previous studies administering 210 mg THC/day (Jones et al. 1976, 1981). Because abstinence symptoms may be subtle with these lower doses of THC, the study was conducted in a residential laboratory, where a range of behaviors were measured repeatedly throughout the day and over many days, thereby increasing the likelihood of detecting small shifts in behavior.

Materials and methods

Participants

Six male (two African-American, three Non-Hispanic Caucasian, one Hispanic) and six female (two African-American, two Non-Hispanic Caucasian, two Hispanic) healthy research volunteers ranging in age from 21 to 29 years (24.7 ± 3.5: mean ± SD), participated in a 20-day experiment. Prior to study participation, participants provided a detailed drug and medical history, received complete medical and psychiatric evaluations, and signed consent forms detailing all aspects of the research. On average, participants reported smoking marijuana 6.4 days/week (±0.4), ranging from one to eight marijuana cigarettes per occasion. Most participants also reported drinking alcohol weekly (mean: 1 day/week, two drinks/occasion). Nine reported smoking tobacco cigarettes, and continued to do so during the experiment. Other drug use was infrequent. Cannabinoids were the only drug present in the participants' urine, which was tested for the presence of a range of drug metabolites (cocaine, opiates, methadone, benzodiazepines, cannabinoids) during screening and on move-in day. Participants did not diet, were within accepted weight ranges [(women: 61.1 ± 2.4 kg, men: 70.0 ± 2.0 kg (Metropolitan Life Insurance Company 1983)], and had no self-reported eating abnormalities. None of the female participants reported significant changes in mood premenstrually, based on completion of a retrospective 95-item Premenstrual Assessment Form (Halbreich et al. 1982a,b).

Participants were instructed that they were participating in a study on the behavioral effects of THC, the active component of marijuana. They were told that the strength of the THC capsules might change at any time. Prior to discharge, participants were fully informed about the experimental and drug conditions. All procedures were approved by the New York State Psychiatric Institute's Institutional Review Board.

Laboratory

Participants, in three groups of four, lived in a residential laboratory designed for the continuous observation of human behavior over extended periods of time. The residential laboratory consists of 11 rooms in the New York State Psychiatric Institute. There are four private rooms, each equipped with a desk, Macintosh LC computer system, bar-code reader (Worthington Data Solutions, Santa Cruz, Calif., USA), microwave, refrigerator, food preparation space, and bed. The common recreational area has one public room containing couches, video games, and monitors for viewing videotaped movies, two single-occupancy bathrooms and two single-occupancy shower rooms. In addition, two vestibules are used for exchanging supplies, administering drugs, and for meeting with individual participants. A sliding partition, which divides the recreation area in half, was closed from midnight until the next day to ensure the privacy of male and female participants while sleeping.

Output from a video- and audio-monitoring system terminated in an adjacent control room. Participants were observed continuously except while in the bathroom or in private dressing areas. No video- or audio-recordings were made. Communication between participants and experimenters was accomplished using a networked computer system, linking each participant's computer with the computer in the main control room and allowing for a continuous on-line interaction between participants and experimenters; participants did not have access to each other's computers.

Procedure

Prior to residence, participants received two training sessions (3–4 h/session) on the computerized tasks and on a separate day, sampled a single dose of THC. Participants moved into the laboratory on the day before the study, during which they received additional training on tasks and experimental procedures. The first experimental day began at 0830 hours the following morning. The St Mary's Hospital Sleep Questionnaire, consisting of questions and rating scales regarding the previous night's sleep, was completed each morning. Participants then completed a 50-item visual analog scale (VAS), which was a 100-mm line anchored with "not at all" at the left end and "extremely" at the right end. Each line, presented one at a time, was labeled with an adjective describing a mood (e.g., "Content,"), a drug effect (e.g., "High"), or a physical symptom (e.g., "Headache"). Participants were then weighed and given time to eat breakfast. Three work periods occurred each day:

the first work period (0915–0945 hours), consisted of one task battery, composed of five computer tasks and the VAS. At 1000 hours, participants received their first capsules of the day. They then began their second work period (1015–1315 hours), composed of four task batteries; each task battery consisted of the same five tasks and the VAS. The Drug-Effects Questionnaire was completed on the computer 90 min after each capsule administration. The second capsule administration occurred at 1400 hours. The final work period (1415–1615 hours) consisted of three task batteries. Beginning at 1715 hours, participants had access to activities available in the recreation area. The third daily capsule administration occurred at 1800 hours. Two video-taped films were shown, one beginning at 1815 hours and the other at 2115 hours. The final capsule administration occurred at 2200 hours. At 2330 hours, the recreation area was no longer available. A VAS and a marijuana withdrawal checklist (modified from the cocaine withdrawal checklist; Brower et al. 1988), in which participants answered if they did or did not experience a range of symptoms, were completed at 2330 hours. Lights were turned off no later than 2400 hours.

Food

Every morning at 0830 hours, each participant received a box of food containing a variety of meal items, snacks and beverages which could be consumed at any time within the day. Frozen meal items were also continuously available by request. To facilitate choice of frozen meals, participants were provided with a book containing package pictures of each item. Additional units of any item were freely available upon request. Participants were instructed to scan custom-designed bar codes whenever they ate or drank, specifying substance and portion.

Task battery

Each task battery consisted of a 3-min digit-symbol substitution task (DSST), a 3-min repeated acquisition task, a 10-min divided attention task (DAT), a 10-min rapid information task (RIT), an immediate and delayed digit-recall task, and a VAS. The tasks measure various aspects of learning, memory, vigilance and psychomotor ability (see Foltin et al. 1996, for description of each task). Participants were instructed to complete each task as quickly and as accurately as possible.

Social behavior

A computerized observation program was used to categorically record behavior every 2.5 min during each evening recreation period. Behaviors were divided into two categories: private and social. Private behaviors occurred in each participant's private room or in the bathroom/shower room. Social behaviors occurred in the recreation area. Social behavior was rated as being either verbal or non-verbal.

Design

THC (Obergfel Brothers) and placebo (Unimed Pharmaceuticals, Inc.) capsules were administered four times/day at 1000, 1400, 1800 and 2200 hours. During the first 3 inpatient days, participants received placebo THC qid. On days 4–7, the low dose of THC (20 mg qid) was administered, followed by 4 days of placebo (days 8–11). The high dose of THC (30 mg qid) was administered on days 12–15, followed by 4 days of placebo (days 16–19). Participants moved out on day 20.

Following oral THC administration, plasma levels of Δ^9-THC and 11-OH-Δ^9-THC peak at approximately 2 h, while behavioral effects peak at 2–4 h. THC is eliminated in two phases: there is an initial half-life of 4 h and a terminal half-life is 25–36 h; we estimate clearance takes 4–5 days (Hollister et al. 1981; Wall et al. 1983).

For reasons of safety, the order of dosing was not counter-balanced across residential groups. We attempted to counter-balance dosing in an additional set of four participants, but administering the high THC dose before the low dose THC resulted in too strong a reaction in three of the four participants (vomiting, discomfort with the level of intoxication) so the drug was discontinued in this group and the study was canceled.

Data analysis

Repeated measures analyses of variance (ANOVA) with planned comparisons were used to address two issues. The first was to determine the effect of both repeated THC administration and abstinence from repeated THC administration on subjective effects (peak daily ratings), drug effects (peak daily ratings), task performance, social behavior, and food intake [total energy intake, g-intake of carbohydrate, fat, and protein, percent of energy intake derived from each macronutrient estimated as kcal from g-intake using Atwater factors (McLaren 1976)]. The first 3 days of placebo baseline (days 1–3) were compared to the first 3 days of THC administration, and the last 3 days of THC abstinence. These days were chosen because they were predicted to result in the maximal change from baseline: repeated cannabinoid administration has been shown to result in tolerance (Jones et al. 1976; Haney et al. 1997), suggesting the first 3 days of administration would result in the maximal change in behavior. Further, given THC's pharmacokinetics (Wall et al. 1983), we reasoned that abstinence symptoms would be maximal after at least 24 h following the last administration of THC. All 4 days of the THC and abstinence conditions are portrayed in the figures. Thus, there was one between-group factor (Sex) and two within-group factors [Condition (baseline, 20 mg, 30 mg, post-20, post-30) and Day of condition: baseline (days 1, 2, 3), 20 mg THC (days 4, 5, 6), 30 mg THC (days 12, 13, 14), post-20 mg THC (days 9, 10, 11), and post-30 mg THC (days 17, 18, 19)]. Twelve planned comparisons were completed for each measure: baseline was compared to each THC dose (20, 30 mg) and baseline was compared to each abstinence condition (post-20, post-30) for the 3 days of the condition; for one measure, the interaction between sex and condition was significant, so planned comparisons were done separately for men and for women. Analysis of certain food data included an additional within-group condition: time of day: 0–1259 (including breakfast); 1300–1659 (including lunch) and 1700–2330 hours (including dinner). For these data, 12 planned comparisons between baseline and each dose condition were made at the three times of day, rather than for each day of the condition; the days of each condition were collapsed.

A second objective was to determine if tolerance develops to the effects of repeated THC administration. For this comparison, an overall analysis with one between-group factor (Sex) and two within-group factors [Condition (20 mg, 30 mg) and Day of condition (days 1, 4)] was performed. Two planned comparisons were made: peak ratings occurring on the first and last day of each 20 mg condition and the 30 mg condition were compared. Given the large number of planned comparisons overall, only those with P values < 0.01 were considered statistically significant, in an effort to control for type I error. Hunyh-Feldt corrections were used, when appropriate.

Results

During the high dose condition (30 mg qid), two participants were not able to receive the full daily dose

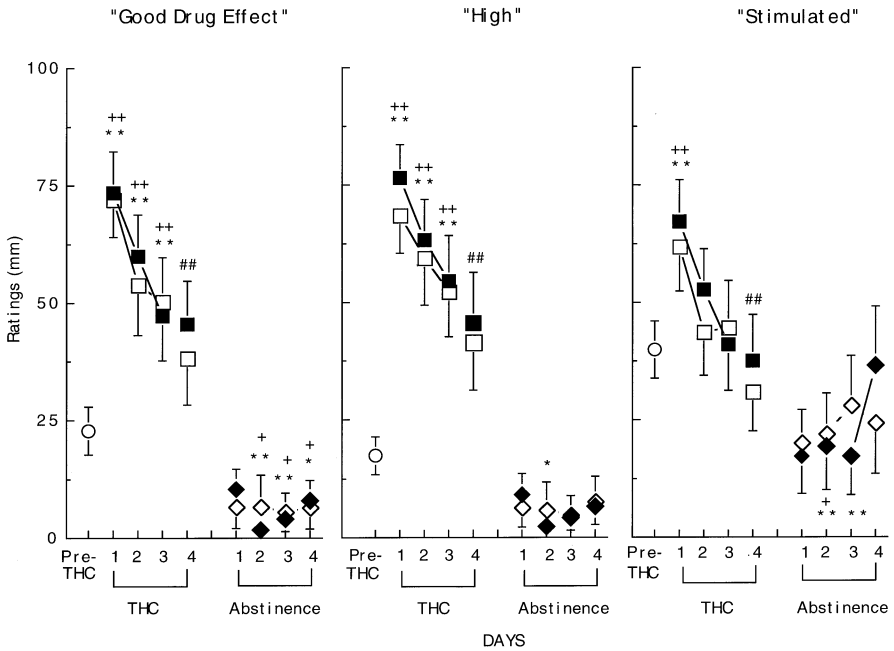

Fig. 1 Selected peak subjective-effects ratings averaged during the initial 3 days of baseline (*circles*) were compared to peak ratings obtained on the first 3 days of THC administration (*squares* □ 20 mg, ■ 30 mg) and on the last 3 days of THC abstinence (*diamonds* ◇ 20 mg, ◆ 30 mg). The last day of THC administration is also portrayed and was compared to the first day of THC administration. The first day of THC abstinence is portrayed, but was not included in the analysis. The interaction between sex and condition was not significant, so data from men and women were pooled. *Plus symbols* denote a significant difference from baseline for the 20 mg THC dose ($+P < 0.01$; $++P < 0.005$). *Asterisks* denote a significant difference from baseline for the 30 mg THC dose ($*P < 0.01$; $**P < 0.005$). Number signs denote a significant difference between day 1 and day 4 ($\#P < 0.01$; $\#\#P < 0.005$). Error bars represent ± standard error of the mean (SEM)

of THC. Specifically, one female participant received 120 mg on the first day, but was uncomfortably intoxicated and was maintained on 80 mg/day for the remaining 3 days. Another female participant received the full dose (120 mg/day) on 2 days of the high-dose condition, but was reduced to 100 mg/day and 80 mg/day on 2 other days of the condition, also due to her discomfort with the duration of intoxication; given the repeated measures design, these data were not excluded from the analysis but were treated as though the full dose had been administered for each of the 4 days.

Subjective-effects ratings

Each figure and table portrays the mean baseline measure averaged across the 3-day initial placebo period, followed by the mean data for each of the 4 days of THC administration, and each of the 4 days of THC abstinence. Figure 1 illustrates that both doses of THC significantly increased ratings of "Good Drug Effect," "High" and "Stimulated" compared to baseline. Tolerance developed to these effects, evidenced by a significant diminution of peak ratings on day 4 of THC administration compared to day 1 of THC administration. During abstinence from either dose of THC, participants rated the placebo capsules as giving them less of a "Good Drug Effect," and making them less "High" and "Stimulated" compared to the placebo capsules at baseline.

As shown in Fig. 2, ratings of "Anxiety" were significantly lower than baseline on the second day of abstinence from the low THC dose. However, by 3 and 4 days of abstinence from the high THC dose, ratings of "Anxiety" were significantly increased. Abstinence also resulted in significant decreases in ratings of "Mellow" (Fig. 2) and increases in ratings of "Depressed" (Fig. 2). These effects peaked earlier during abstinence from the high THC dose compared to the low THC dose.

Additional significant THC effects are reported in Table 1. Both doses of THC increased ratings of "Heaviness in Limbs" and "Noises seem Louder than Usual," (Table 1) and decreased ratings of "Sweating" [20 mg, day 2: $F1,10 = 9.97$; day 3: $F1,10 = 9.97$, $P < 0.01$; 30 mg, day 2: $F1,10 = 9.56$; day 3: $F1,10 = 10.06$, $P < 0.01$ (data not shown)] compared to baseline. Ratings of "Sedated" were increased by the low THC dose, while only the high THC dose increased ratings of "Trouble Sleeping" (Table 1), "Muscle Pain" [day 1: $F1,10 = 6.44$; day 2: $F1,10 = 6.69$; day 3: $F1, 10 = 9.09$, $P < 0.01$ (data not shown)], "Can't Concentrate" [day 1: $F1,10 = 14.05$, $P < 0.001$ (data not shown)] and "Clumsy" [day 1: $F1,10 = 19.00$, $P < 0.002$ (data not shown)]. The high dose also

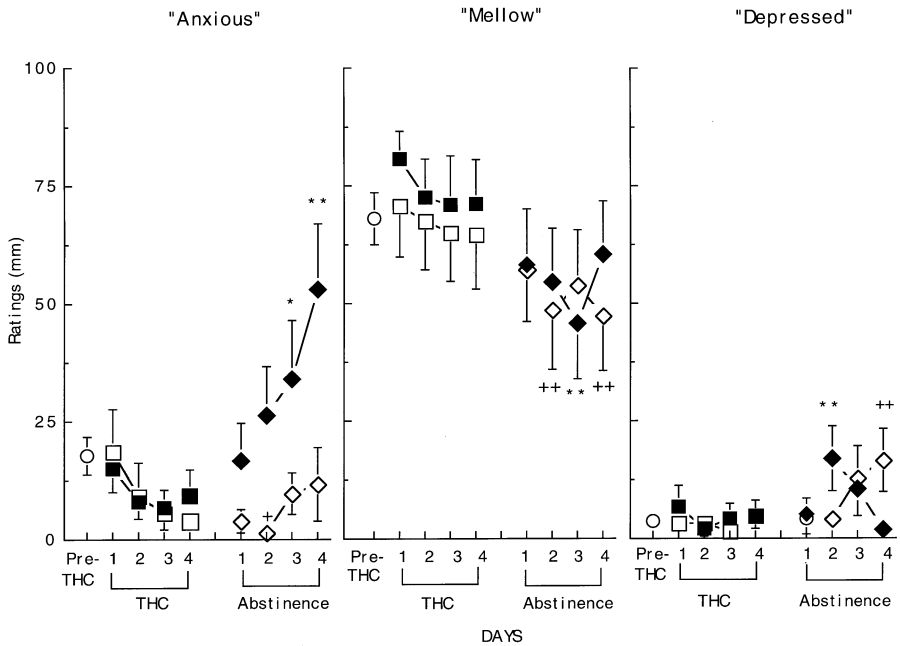

Fig. 2 Selected peak subjective-effects ratings. See Fig. 1 legend for details

Table 1 Means (±SEM) of peak subjective-effects ratings following 4 days of THC administration or abstinence from four days of THC administration

Days	1	2	3	4
"Heaviness in limbs"			Mean initial placebo = 5.2 (1.9)	
20 mg THC	14.5 (8.1)*	17.6 (9.2)**	13.2 (6.2)	11.7 (6.1)
30 mg THC	24.6 (10.4)**	25.0 (9.4)**	22.5 (10.7)**	26.8 (10.7)
Abstinence 20 mg	3.2 (2.3)	8.0 (4.7)	4.8 (4.0)	5.0 (4.2)
Abstinence 30 mg	12.8 (7.9)	7.2 (6.5)	9.8 (7.0)	8.6 (7.7)
"Noises seem louder"			Mean initial placebo = 5.4 (2.0)	
20 mg THC	19.7 (7.1)**	12.8 (7.8)	9.2 (4.3)	5.7 (4.1)#
30 mg THC	20.8 (8.5)**	19.3 (6.6)**	17.4 (8.5)*	13.0 (6.4)
Abstinence 20 mg	3.7 (2.2)	2.1 (1.5)	1.2 (0.9)	1.8 (1.1)
Abstinence 30 mg	6.9 (4.0)	0.7 (0.6)	5.2 (4.5)	2.2 (2.2)
"Sedated"			Mean initial placebo = 30.7 (5.4)	
20 mg THC	50.2 (10.6)*	44.2 (9.3)	31.1 (9.8)	31.5 (8.3)#
30 mg THC	42.8 (11.4)	42.6 (10.6)	43.3 (11.0)	33.9 (9.5)
Abstinence 20 mg	14.3 (6.6)	16.2 (8.1)	17.7 (8.3)	17.2 (6.1)
Abstinence 30 mg	15.5 (7.1)	7.0 (5.0)**	7.6 (5.6)**	17.0 (9.7)
"Irritable"			Mean initial placebo = 23.7 (4.9)	
20 mg THC	41.6 (12.7)	14.3 (5.7)	15.7 (7.4)	6.9 (3.3)#
30 mg THC	37.6 (11.9)	8.6 (4.1)	12.3 (7.8)	15.8 (7.7)
Abstinence 20 mg	10.4 (4.2)	26.5 (8.5)	47.8 (11.7)**	30.6 (8.9)
Abstinence 30 mg	10.0 (3.8)	36.7 (10.7)	44.2 (12.3)	9.7 (3.1)
"Restless"			Mean initial placebo = 26.5 (5.2)	
20 mg THC	19.3 (8.3)	16.8 (8.3)	17.1 (8.6)	17.0 (8.7)
30 mg THC	33.9 (11.5)	17.8 (7.4)	14.2 (6.2)	19.2 (9.2)
Abstinence 20 mg	13.2 (6.1)	32.7 (11.5)	28.2 (11.2)	39.1 (10.4)
Abstinence 30 mg	24.4 (9.5)	38.1 (13.2)	36.1 (13.1)	50.1 (12.6)*
"Trouble Sleeping"			Mean initial placebo = 20.6 (4.9)	
20 mg THC	16.2 (8.9)	19.8 (7.8)	5.5 (3.8)	7.5 (5.0)
30 mg THC	46.5 (13.1)*	19.7 (9.9)	16.9 (8.9)	17.6 (9.3)
Abstinence 20 mg	6.2 (4.5)	19.7 (9.1)	26.0 (9.7)	28.2 (11.4)
Abstinence 30 mg	19.2 (9.3)	36.1 (11.3)	38.8 (12.7)	49.6 (13.0)**

Differences from baseline (averaged across first 3 inpatient days) have been analyzed for days 1–3 of THC administration, and days 2–4 of abstinence from THC ($n = 12$): *$P < 0.01$, **$P < 0.005$. Peak ratings on day 1 and day 4 were also compared (#$P < 0.01$)

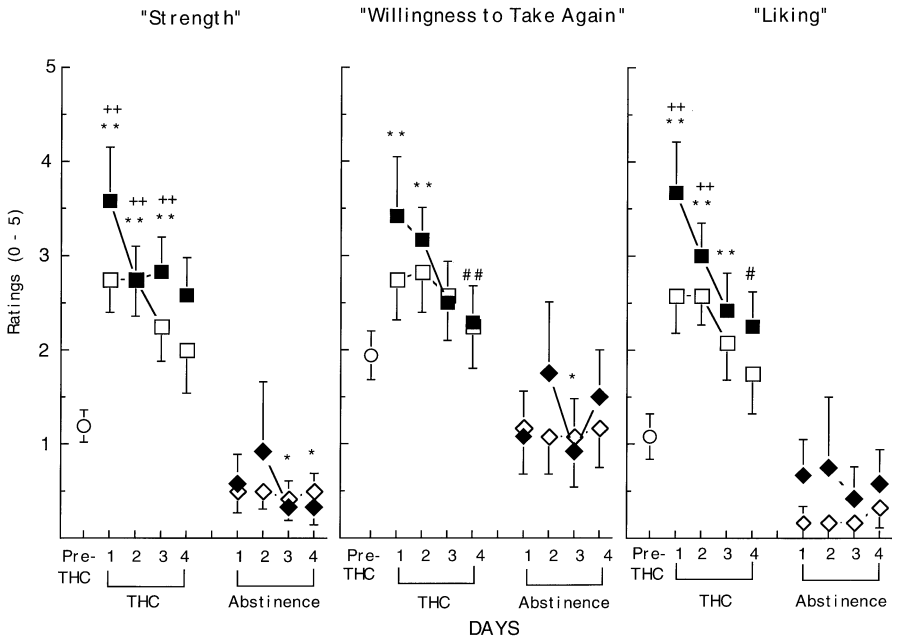

Fig. 3 Peak ratings on the Drug-Effects Questionnaire. See Fig. 1 legend for details

decreased ratings of "Alert [day 3: $F1,10 = 9.34$, $P < 0.009$ (data not shown)]" and "Talkative [day 3: $F1,10 = 13.44$, $P < 0.001$ (data not shown)]. Compared to the first day of administration, the low THC dose had a significantly smaller effect on ratings of "Noises seem louder," and "Sedated" by day 4 of administration, while repeated administration of the higher dose resulted in a significant decrease in ratings of "Can't Concentrate" [$F1,10 = 9.94$, $P < 0.01$ (data not shown)].

As shown in Table 1, ratings of "Irritable" were significantly increased during abstinence from the lower THC dose. During abstinence from the high THC dose, ratings of "Trouble Sleeping" and "Restless" were increased, and ratings of "Sedated" and "Content" [day 3; $F1,10 = 16.63$, $P < 0.006$ (data not shown)] were decreased.

Women had higher ratings of "Chills" (Sex: $F1,10 = 7.52$, $P < 0.05$), "Miserable" (Sex: $F1,10 = 14.08$, $P < 0.004$), "Nauseous" (Sex: $F1,10 = 37.83$, $P < 0.0001$), "Stomach Pain" (Sex: $F1,10 = 9.95$, $P < 0.01$), and "Upset Stomach" (Sex: $F1,10 = 19.06$, $P < 0.001$) than men; these differences were substantial, ranging from 10–40 mm on a 100 mm scale, but did not vary as a function of drug condition.

Drug-effects questionnaire

Figure 3, portraying ratings on the Drug-Effects Questionnaire, shows that THC administration significantly increased ratings of dose strength, willingness to take the capsule again, and dose liking. Participants also reported that the capsules resulted in a "Good Drug Effect" on each day of the 20 mg dose condition (day 1: $F1,10 = 37.85$; day 2: $F1,10 = 25.99$; day 3: $F1,10 = 14.28$, $P < 0.003$) and on each day of the 30 mg dose condition (day 1: $F1,10 = 59.83$; day 2: $F1,10 = 37.85$; day 3: $F1,10 = 23.37$, $P < 0.0003$ (data not shown)]. Repeated administration of the high THC dose significantly decreased ratings of dose strength, willingness to take the dose again, dose liking and "Good Drug Effect" [$F1,10 = 9.38$, $P < 0.01$ (data not shown)]. During abstinence from THC, participants rated the placebo capsules as less strong and were less willing to take the capsules compared to placebo capsules at baseline (Fig. 3).

St. Mary's Hospital Sleep Questionnaire

As shown in Fig. 4, THC administration did not influence how participants rated their previous night's sleep. However, abstinence from both the high and low doses of THC was associated with significant decreases in ratings of "How was your sleep," "How many hours did you sleep" and "How well did you sleep" compared to the initial placebo condition in both men and women.

Marijuana withdrawal checklist

There were no significant changes in the marijuana withdrawal checklist as a function of drug condition.

Food intake

As shown in Fig. 5, both THC doses significantly increased daily caloric intake on each day of THC administration, with no change over the 4 days of each

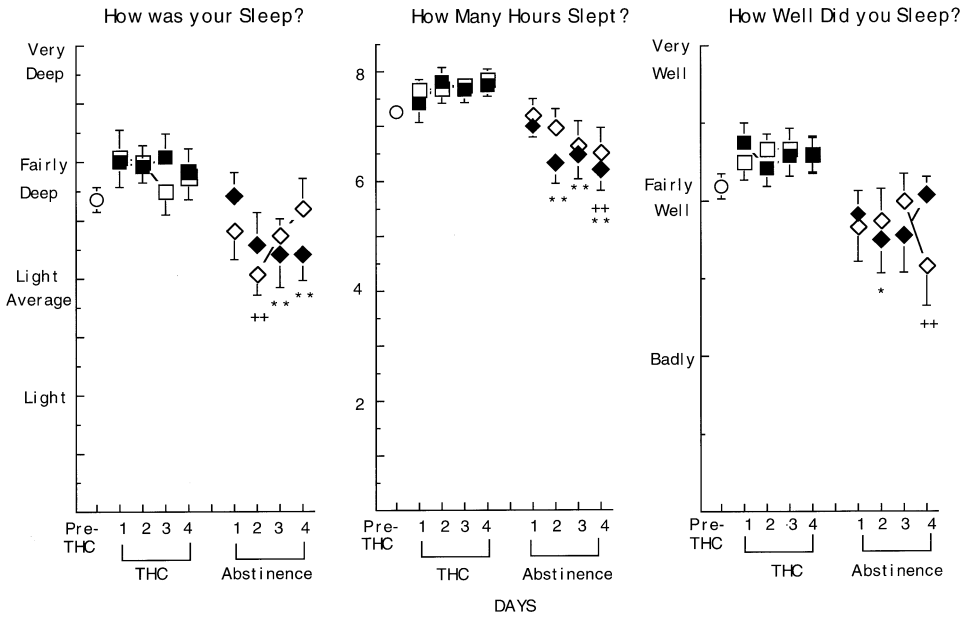

Fig. 4 Mean ratings on the St. Mary's Hospital Sleep Questionnaire. See Fig. 1 legend for details

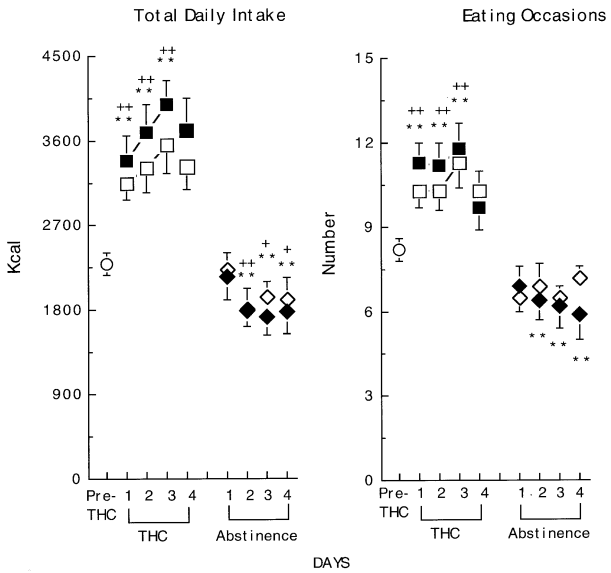

Fig. 5 Mean daily caloric intake and mean number of eatings occasions. See Fig. 1 legend for details

dose condition. THC increased caloric intake in the afternoon (20 mg: $F1,8 = 10.82$; 30 mg: $F1,8 = 21.85$, $P < 0.005$) and evening [20 mg: $F1,8 = 63.56$; 30 mg: $F1,8 = 83.41$, $P < 0.0001$ (data not shown)]. Figure 5 also shows that the mechanism by which THC influenced daily caloric intake was by increasing the number of eating occasions, defined as beginning with the first report of an item to be consumed and ending when there was a pause of greater than 10 min between food reports (Foltin et al. 1996). The average number of calories consumed during each eating occasion was largely unaffected by THC, although on day 3 of the high-THC dose condition, there was a significant increase in the mean eating occasion size compared to baseline [$F1,10 = 8.73$, $P < 0.005$ (data not shown)]. In terms of macronutrient intake, participants derived approximately 56% of their energy intake from carbohydrate, 32% from fat and 12% from protein under baseline conditions. Under the 30 mg THC condition, the percentage of daily calories derived from protein was decreased to 9.7% (data not shown).

Caloric intake was significantly reduced during abstinence from either dose of THC, while the number of eating occasions was only significantly decreased during abstinence from the high THC dose. Abstinence from THC also shifted the balance of macronutrient intake substantially, with participants eating a larger percentage of carbohydrates (61%) and smaller percentage of fat (27%) compared to baseline. The differences were significant for both the low (carbohydrate; day 2: $F1,80 = 17.38$; day 3: $F1,80 = 18.41$; day 4: $F1,80 = 48.00$, $P < 0.0001$; fat; day 2: $F1,80 = 13.72$; day 3: $F1,80 = 13.75$; day 4: $F1,80 = 34.37$, $P < 0.0004$) and the high THC dose [carbohydrate; day 3: $F1,80 = 14.85$, $P < 0.0002$; fat; day 2: $F1,80 = 7.18$; day 3: $F1,80 = 10.90$, $P < 0.009$ (data not shown)].

Women consumed fewer total daily calories than men (Sex: $F1,10 = 17.36$, $P < 0.002$), but the difference did not vary as a function of drug condition. Women averaged a 1.1 kg weight loss over the course of the study, while men averaged a 0.2 kg weight gain.

Social behavior

Neither THC administration nor abstinence from THC significantly affected the amount of time participants spent in private or social areas. There was an overall

significant interaction between sex and condition on the percentage of time participants spent talking in the social area (Sex × Condition: $F4,40 = 3.95$, $P < 0.02$). In men, the low dose of THC decreased time spent talking [day 1: $F1,40 = 18.86$; day 2: $F1,40 = 24.31$; day 3: $F1,40 = 28.84$, $P < 0.006$ (data not shown)], while in women, both the low and the high dose of THC decreased the amount of time spent talking [20 mg, day 2: $F1,40 = 15.33$, $P < 0.01$; 30 mg, day 2: $F1,40 = 19.03$; day 3: $F1,40 = 28.84$, $P < 0.006$ (data not shown)]; there was no significant change in this effect over the 4 days of THC administration for either sex. Further, abstinence from THC did not significantly affect time spent talking in either men or women.

Performance effects

Performance on the DAT was impaired on day 1 of the high THC dose administration: participants were less accurate tracking the moving target compared to baseline [$F1,80 = 31.03$, $P < 0.0002$ (data not shown)]. No other tasks were significantly affected by the THC or the abstinence condition, or differed as a function of sex.

Discussion

These data demonstrate that abstinence from THC maintenance (80–120 mg/day for 4 days) produces subtle but significant disruptions in mood, sleep, and food-intake in men and women. Specific symptoms include substantial increases in ratings of anxiety, depression, irritability, and restlessness and decreases in the amount and frequency of food-intake, and decreases in the self-reported quality and quantity of sleep. These symptoms mimic those reported in an earlier controlled laboratory study administering 210 mg/day of THC for 10–20 days (Jones et al. 1976, 1981), but occurred with smaller doses and a shorter duration of THC administration. This pattern of symptoms also corresponds with interview data obtained in daily marijuana smokers, who report feeling "nervous, tense, and restless" when abstinent from marijuana (Wiesbeck et al. 1996), suggesting that the present results may have relevance to marijuana users, despite the pharmacokinetic differences between oral THC and smoked marijuana.

This pattern of mood changes during abstinence from THC, after 4 days of maintenance, suggests that individuals become dependent on THC and that THC abstinence produced a mild withdrawal syndrome. Clearly, THC withdrawal symptoms are subtle and do not rival symptoms of heroin or alcohol withdrawal. Most likely, the long half-life of cannabinoids attenuates profound physical withdrawal, which has led some to conclude that the issue of dependence has little relevance to marijuana's social use (Hollister 1986). Yet as has been discussed for psychostimulant dependence (Koob et al. 1997), the absence of physical symptoms of withdrawal does not diminish the potential impact of mood or behavioral symptoms of withdrawal on the likelihood of continued drug use. It may be that even subtle symptoms of anxiety, sleep disturbance and a loss of appetite play a role in maintaining heavy marijuana use, i.e. people continue to smoke marijuana each day because not smoking is associated with a range of unpleasant symptoms. Further, it may be that people with a history of using drugs to modulate mood are particularly likely to increase their drug use as a function of minor changes in mood.

An additional consequence of repeated exposure to THC is the development of tolerance to several of its effects. Repeated THC administration resulted in a significant diminution in many of its subjective effects, e.g., ratings of "High," and "Stimulated," as well as ratings of how strong the dose was and how much participants liked and were willing to take the THC capsules again. Earlier studies have shown the development of tolerance to both THC and marijuana's subjective-effects with repeated high-dose administration (Babor et al. 1975; Jones et al. 1976; Nowlan and Cohen 1977; Haney et al. 1997). By contrast, tolerance did not develop to THC's other behavioral effects. For example, THC's substantial effects on food intake did not diminish over the 4 days of THC administration. Selective tolerance to THC's intoxicating effects has important implications for the clinical use of oral THC for appetite enhancement. Tolerance also did not develop to THC's effects on social behavior. Verbal interaction was suppressed during THC administration, replicating earlier data on smoked marijuana (Foltin and Fischman 1988), and this effect did not significantly change with repeated administration. THC had relatively minor effects on task performance in this population of heavy marijuana smokers, although earlier studies in less frequent marijuana smokers showed that marijuana impairs performance on a similar set of tasks (Kelly et al. 1993a,b; Kamien et al. 1994). A direct comparison between different populations of marijuana smokers has shown that heavy marijuana users show fewer performance decrements after smoking marijuana compared to light users (Meyer et al. 1971; Rickles et al. 1973; Cohen and Rickles 1974). Thus, it may be that the present group of heavy marijuana users were already tolerant to THC's disruptive effects on performance despite the 4 days of abstinence preceding THC administration.

The fact that these participants were frequent marijuana smokers until the day they moved into the laboratory not only means that they could be tolerant a priori to certain of THC's effects, but also means that the period considered "baseline" was actually a period of abstinence from smoked marijuana for these individuals. It was difficult to avoid this problem, since we

did not want to expose lighter marijuana users to the dose regimen used in the present study. We reasoned that this design was in fact a conservative approach, since it would minimize rather than amplify the likelihood that we would see an abstinence syndrome. In fact, initial baseline ratings of "Anxiety" and "Irritability" were 2–8 times higher, respectively, in the present study compared to a study in this laboratory in which marijuana users did not undergo a period of abstinence (Haney et al. 1997, unpublished data), suggesting that there may be some indication of abstinence symptoms during the "baseline" period.

An additional design complication was the fact that it was not possible to counter-balance the dose order, thereby limiting any comparisons of the effects of different doses of THC on the development of tolerance and dependence. The fact that the high THC dose was relatively well-tolerated when it was administered 4 days after the low dose suggests that some tolerance may have persisted over the 4-day placebo period separating the active dose days. This fact may also explain why there were few dose-dependent differences in THC's effects. For example, certain abstinence effects were significant following the high THC dose but not the low dose (anxiety, restlessness), but most effects occurred following abstinence from either dose.

The pharmacokinetic differences between oral THC and smoked marijuana may limit the generalizations that can be made from the present study regarding recreational marijuana use. When doses of oral THC used in the present study are compared to concentrations of smoked marijuana that are within the range of those used in the natural ecology (2–4% THC), peak plasma levels of THC are found to be substantially lower following oral THC (Ward et al., in preparation; Hollister et al. 1981). Although it may be that oral THC's prolonged duration of action enhances the development of tolerance and dependence relative to smoked marijuana, we have recent evidence that abstinence following a 4-day exposure to smoked marijuana results in a pattern of abstinence symptoms similar to those observed in the present study (Haney et al., submitted). These data support the idea that the findings of the present study are relevant to daily marijuana users.

To conclude, despite THC's slow elimination, a distinct withdrawal syndrome can be observed following a relatively brief period of chronic administration. Although adolescents are reporting a lower perceived risk of regular marijuana use compared to older adults (Johnston et al. 1997), the present data suggest that tolerance and dependence may in fact be important consequences of daily exposure to cannabinoids.

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