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ORIGINAL INVESTIGATION

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Bupropion SR worsens mood during marijuana withdrawal in humans

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Abstract *Rationale:* Symptoms of withdrawal after daily marijuana smoking include increased ratings of irritability and depression. Similar mood symptoms are reported by cigarette smokers during nicotine abstinence. *Objective:* Given the successful use of sustained-release bupropion in treating nicotine dependence, this study investigated how maintenance on bupropion influenced symptoms of marijuana withdrawal compared to maintenance on placebo. *Methods:* Marijuana smokers (n=10) were maintained outpatient on active (300 mg/day) or placebo (0 mg/day) bupropion for 11 days, and were then maintained inpatient on the same bupropion dose for 17 days. For the first 4 inpatient days, participants smoked active marijuana [2.8% Δ9-tetrahydrocannabinol (THC)] 5 times/day. For the remaining inpatient days, participants smoked placebo marijuana (0.0% THC) 5 times/day. Participants were then maintained outpatient on the alternate dose of bupropion for 11 days, followed by a second inpatient residential stay, paralleling the first. Medication administration was double-blind. Mood, psychomotor task performance, food intake, and sleep were measured daily during each inpatient phase. The order of active and placebo bupropion maintenance was counterbalanced between groups. *Results:* Bupropion had few behavioral effects when participants smoked active marijuana. During placebo marijuana smoking, i.e., active marijuana withdrawal, ratings of irritability, restlessness, depression, and trouble sleeping were increased by bupropion compared to placebo maintenance. *Conclusions:* These data suggest that bupropion does not show promise as a potential treatment medication for marijuana dependence.

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Introduction

A number of findings support the need for increased treatment options for chronic marijuana smokers. First, daily marijuana use, which is the pattern posing the greatest long-term physical and psychological risks, has been increasing steadily in high school students (Frank and Galea 1995; Johnston et al. 1997, 2000; Martin and Hall 1999). It is estimated that about 10% of those who ever use marijuana become daily users (Johnston et al. 1995). Although these odds are lower than they are for other drugs of abuse such as nicotine, cocaine, or heroin, the large number of individuals who try marijuana guarantees that a substantial number will develop this pattern of use. Second, marijuana users respond in large numbers (for example, 400 clients in 3 months) to advertisements for marijuana-specific treatment programs (Roffman et al. 1988; Stephens et al. 1993, 1994), demonstrating that there is a demand for marijuana treatment. Third, daily marijuana use often results in dependence. In the United States, 7.4% of adults and 14.4% of adolescents who used cannabis in the past year met diagnostic criteria for dependence within the year (Budney et al. 1997).

Controlled laboratory data substantiate the idea that repeated cannabinoid exposure may result in dependence. In rats, administration of the cannabinoid receptor antagonist, SR141716A, following the administration of chronic Δ9-tetrahydrocannabinol (THC), the primary psychoactive component of marijuana, produces dramatic withdrawal symptoms, for example, ptosis, wet-dog shakes, and "anxiety" reactions (Rinaldi-Carmona et al. 1994). In humans, abstinence following maintenance on substantial doses of oral THC (210 mg/day), produced symptoms of withdrawal (Jones et al. 1976, 1981). We have reported that abstinence following maintenance on lower total daily doses of oral THC (80–120 mg) can

also produce withdrawal symptoms, such as increased ratings of anxiety, depression, and irritability, decreased quantity and quality of sleep, and decreased food intake compared to baseline (Haney et al. 1999a; Ward et al. submitted for publication).

A similar constellation of symptoms occurs when individuals are withdrawn from smoked marijuana in a laboratory setting (Haney et al. 1999b); it is important to note that the amounts of marijuana smoked in these laboratory studies were comparable to or less than what the participants reported smoking in the natural ecology. Another study, using a laboratory model of human aggression (Point-Subtraction Aggression Paradigm; Cherek 1981), provides evidence that marijuana withdrawal is associated with increased aggressive behavior. Frequent marijuana smokers abstinent from marijuana for up to 7 days showed greater levels of aggressive responding when provoked, compared to when they were still using marijuana (Kouri et al. 1999). These data suggest that the irritability manifested during marijuana withdrawal may translate into aggressive behavior upon provocation.

Individuals seeking treatment for their marijuana use report a closely similar cluster of withdrawal symptoms as those measured in the laboratory (Budney et al. 1999). Thus, it may be that one factor maintaining daily marijuana smoking is the avoidance of withdrawal symptoms, i.e., people continue to smoke marijuana each day not only to achieve an intoxicated state but also because not smoking is associated with symptoms such as irritability, sleep disturbance, and a loss of appetite. This pattern has been seen with tobacco cigarette smokers, for whom nicotine deprivation leads to smoking in order to reverse symptoms of nicotine withdrawal (USDHHS 1988; Heishman et al. 1994). In fact, pharmacologic aids that reduce nicotine withdrawal and craving are now central to smoking cessation treatment (see Shiffman et al. 2000).

The increases in daily marijuana smoking, the empirical demonstration of marijuana dependence, and the evidence of individuals seeking treatment for marijuana use support the need for medications to treat marijuana abuse. The present study determined if sustained-release bupropion would decrease symptoms of marijuana withdrawal. Bupropion, an indirect noradrenergic and dopaminergic agonist (Ferris and Cooper 1993), has been shown to dose-dependently maintain nicotine abstinence, presumably by reducing the negative mood symptoms associated with nicotine withdrawal (Hurt et al. 1997; Shiffman et al. 2000). Certain mood symptoms of nicotine withdrawal are similar to symptoms of cannabinoid withdrawal, for example, irritability, depression, and anxiety (O'Brien 1996; Haney et al. 1999a, b), suggesting that bupropion may also be useful in the treatment of marijuana dependence.

Bupropion's efficacy as an aid for smoking cessation appears to be independent of its antidepressant effects. First, the effect occurs in individuals who are not depressed (Hurt et al. 1997) and, second, bupropion facilitates nicotine abstinence in approximately 1 week, once steady state is attained, while bupropion's antidepressant effects often take at least 3 weeks to occur. In the present study, regular marijuana smokers were first maintained outpatient on either placebo or active bupropion. Once steady state was attained, participants moved into the laboratory, where they continued to take the same dose of bupropion. For the first 4 inpatient study days, a controlled amount of active marijuana was smoked at regular intervals throughout the day, in order to control for differences in recent marijuana use prior to measuring symptoms of withdrawal. For the remaining 12 inpatient study days, participants smoked placebo rather than active marijuana at regular intervals. Participants then repeated another outpatient and inpatient study phase while receiving the alternate dose of bupropion.

Materials and methods

Participants

Two female and eight male research volunteers (three African-American, two Non-Hispanic Caucasian, four Hispanic) averaging 27±4 years (mean ± SD), participated in a 58-day experiment. Prior to study participation, volunteers provided a detailed drug and medical history, received complete medical and psychiatric evaluations, and signed consent forms detailing all aspects of the research. Participants reported smoking marijuana 6±1 days/week, averaging 6±7 marijuana cigarettes/day. Most participants also reported drinking alcohol weekly (2±1 days/week, 4±1 drinks/occasion). Six reported smoking tobacco cigarettes (14±8 cigarettes/day), and continued to do so during the experiment. Other drug use was infrequent, although one participant reported weekly cocaine use which ceased prior to study onset, as verified by urine drug toxicologies. Participants did not diet, were within accepted weight ranges for their heights [women: 66±14 kg; men: 74±9 (Metropolitan Life Insurance 1983)], and had no self-reported eating abnormalities.

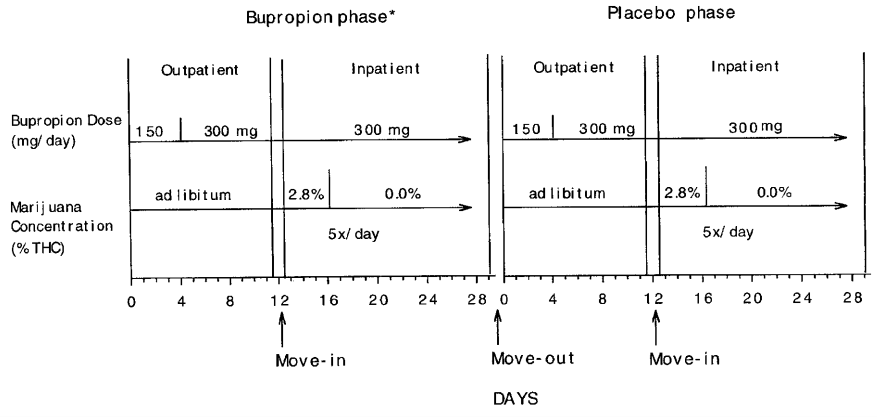
Participants were instructed that the study investigated how medications influence the effects of marijuana. They were told that the strength of both the maintenance medication and marijuana cigarettes might change at any time. Prior to discharge, participants were fully informed about the experimental and drug conditions. All procedures were approved by the New York State Psychiatric Institute's Institutional Review Board.

Laboratory

Participants, in three groups of three to 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: four private participant rooms, a common recreational area, two single-occupancy bathrooms, two single-occupancy shower rooms, and two vestibules used for exchanging supplies (see Haney et al. 1999a for a more detailed laboratory description).

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 staff 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, but not between participants.

Table 1 Study timeline.
THC Δ9-tetrahydrocannabinol



* Order of bupropion and placebo administration was counterbalanced

Procedure

Prior to study onset, participants received two training sessions (3–4 h/session) on the computerized tasks, and two predosing sessions: participants received a dose of bupropion (150 mg) during one predosing session and smoked a marijuana cigarette (2.8% THC) during the other. As shown in Table 1, the study comprised two inpatient and two outpatient phases: an 11-day outpatient phase, an 18-day inpatient phase, a second 11-day outpatient phase, and a final 18-day inpatient phase. Medication administration was double-blind and was counterbalanced (of the participants included in the data analysis, three were maintained on bupropion first, followed by placebo maintenance, while six received the inverse order of bupropion dosing). During the outpatient phases, participants received a 3-day supply of bupropion (0, 300 mg/day) to be taken each morning and each evening at approximately 09:00 and 21:00. This maintenance dose of bupropion was selected because it has been shown to be most effective in treating the mood symptoms of nicotine withdrawal (Hurt et al. 1997; Shiffman et al. 2000). During the bupropion phase, participants started at 150 mg/day, which was increased to 300 mg/day on the 4th day of administration. In order to monitor compliance in taking the medication during the outpatient phase, participants were given an additional capsule of riboflavin (50 mg) under blind conditions to take once daily with their bupropion. Participants, who were instructed not to take vitamins over the course of the study, urinated into a labeled cup each outpatient day, which they refrigerated until they visited the laboratory on the third, sixth, and ninth outpatient morning of each outpatient phase. Compliance was assessed qualitatively by examining urine using ultraviolet light detection. Participants were required to abstain from using all prescription and over-the-counter medications over the course of the study, and to not operate heavy machinery or drink alcohol.

On the day participants moved into the laboratory, they received additional training on tasks and experimental procedures. The first residential experimental day began at 08:30 the following morning. Participants first completed a 7-item visual analog scale (VAS) sleep questionnaire (modified from the St. Mary's Hospital Sleep Questionnaire), which consisted of seven 100-mm lines anchored with "not at all" at the left end and "extremely" at the right end, and labeled with: "I slept well last night," "I woke up early this morning," "I fell asleep easily last night," "I feel clear-headed this morning," "I woke up often last night," "I am satisfied with my sleep last night," and a fill-in question estimating how many hours participants thought they slept the previous night. Participants then completed a 50-item VAS, measuring a range of moods and physical symptoms (described in Haney et al. 1999b). Participants were then weighed and given time to eat breakfast. Eight 30-min task batteries, composed of five performance measures and the VAS, were completed each day. The first task battery began at 09:15, followed at 10:00 by the first marijuana administration of the day. Participants then completed two task batteries from 10:15 to 11:30, each consisted of the same five tasks and the VAS. Participants had access to activities available in the recreation area from 11:30 to 12:50. The second administration of marijuana occurred at 13:00. Five task batteries were completed from 13:15 to 16:30. Marijuana was smoked for the third time each day at 16:00. Beginning at 17:00, participants had access to activities available in the recreation area. Two video-taped films were shown, one beginning at 18:15 and the other at 21:30. The fourth marijuana administration occurred at 19:00, and the fifth marijuana administration occurred at 22:00. The Drug-Effects Questionnaire was completed on the computer 45 min after each administration of marijuana. At 23:30, the recreation area was no longer available. A final VAS and a marijuana withdrawal checklist (modified from a cocaine withdrawal checklist; Brower et al. 1988), in which participants rated the severity in which they experienced 26 symptoms on a four-point scale, were completed at 23:30. Lights were turned off no later than 24:00.

Food

Every morning at 08:30, 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. At 23:30, participants returned their food box to a staff member. Food items were not available between 23:30 and 08:30 the following morning, although water was available at all times.

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 battery measures various aspects of learning, memory, vigilance, and psychomotor ability (see Foltin et al. 1996 for description of the tasks). 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 rooms. Social behaviors occurred in the

recreation area. Social behavior was further categorized as being either verbal or non-verbal.

Marijuana administration

During inpatient phases, marijuana cigarettes were administered 5 times/day at 10:00, 13:00, 16:00, 19:00, and 22:00. Following move-in (day 0), active marijuana was smoked during the first 4 inpatient days of each of the two inpatient phases. On days 5–16, placebo marijuana was administered. Participants moved out on day 17. For marijuana administration, participants received two marijuana cigarettes (0, 2.8% THC weight/weight, provided by the National Institute on Drug Abuse) prior to each scheduled smoking occasion. Marijuana was administered using a cued-smoking procedure, which has been shown to produce reliable increases in heart rate and plasma levels of Δ^9-THC (Foltin et al. 1987). Colored lights (mounted on the ceiling of the social area) signaled 'light the cigarette' (30 s), 'get ready' (5 s), 'inhale' (5 s), 'hold smoke in lungs' (10 s), and 'exhale.' Participants smoked five puffs (three puffs on one cigarette, two on the other) in this manner, with a 40-s interval between each puff; three puffs is often sufficient to pyrolize an entire cigarette. Participants were instructed that they could signal that they wanted to stop smoking by raising their left hand, although no participant did. Since marijuana smokers can discriminate THC content by the color of the plant material (Chait and Pierri 1989), cigarettes were tightly rolled at both ends and were smoked through a hollow plastic cigarette holder so the marijuana was not visible. Cigarettes were stored frozen in an airtight container and humidified at room temperature for 24 h prior to use.

Tobacco cigarette smoking

The number of cigarettes smoked by each participant was recorded each evening by counting the remaining cigarette butts in each participant's ashtray. Participants were instructed not to share cigarettes or to throw out cigarette butts, and were continuously monitored to prevent these events from occurring.

Data analysis

Repeated measures analyses of variance (ANOVA) with planned comparisons were used to determine the effect of bupropion (0, 300 mg/day) during active marijuana administration and during active marijuana withdrawal on subjective effects (peak daily ratings), drug effects (peak daily ratings), task performance, social behavior, food intake [total energy intake, g-intake of carbohydrate, fat, and protein, percent of energy intake derived from each macronutrient estimated as kilocalories from g-intake using Atwater factors (McLaren 1976)], and body weight. In order to determine the effects of bupropion during marijuana administration, the 4 days of active marijuana administration (days 1–4) were compared under both maintenance conditions. Thus, there were two within-group factors [Maintenance (0 mg/day, 300 mg/day bupropion) and Day (1, 2, 3, 4)]. Four planned comparisons to compare placebo and active bupropion across each day of marijuana administration were completed. In order to determine the effects of bupropion during active marijuana withdrawal, the 12 days of placebo marijuana administration were compared under both maintenance conditions in separate analyses. There were two within-group factors [Maintenance (0 mg/day, 300 mg/day bupropion) and Day (1–12)]. Four planned comparisons were completed: placebo and active bupropion were compared across four phases of marijuana withdrawal: days 1–3, days 4–6, days 7–9, and days 10–12. Analysis of certain food data included an additional within-group condition: time of day: 0–12:59 (including breakfast), 13:00–16:59 (including lunch), and 17:00–23:30 (including dinner). Given the number of planned comparisons, only those with P values less than 0.01 were considered statistically significant in an effort to control for type I error. Huynh-Feldt corrections were used, when appropriate.

Results

One participant informed the investigator at debriefing that he had rarely taken the medication during the outpatient phase so his data were not included; the participant would take one pill once over 3 days, then fill all of the urine cups to appear compliant. Thus, the data analyses were limited to nine participants. For measures of food intake, only eight participants' data were analyzed, as one individual stated his intention to begin a diet midway through the study.

Subjective-effects ratings and sleep questionnaire

Each figure and the table portrays the peak rating on the VAS during each day of active and placebo marijuana administration. Figure 1 shows that bupropion did not significantly alter ratings of "I feel irritable," "I feel miserable," or "I feel restless" during active marijuana smoking, but did increase these ratings during the first 6–9 days of placebo marijuana smoking (i.e., marijuana withdrawal). Similarly, Fig. 2 shows that bupropion increased ratings of "I feel unmotivated," and "I feel depressed," during the first 3–6 days of active marijuana withdrawal, but not on days when active marijuana was smoked.

Figure 3 shows that bupropion increased ratings of "I'm having difficulty sleeping" during the first 6 days of marijuana withdrawal; correspondingly, estimates of the number of hours slept on the Sleep Questionnaire were decreased by bupropion over the same timepoints.

As shown in Table 2, bupropion increased ratings of "noises or sounds seem louder than usual" during days 3–6 of marijuana withdrawal, while increasing ratings of "I feel like yawning" and "I feel alert" during days 7–12 of marijuana withdrawal. Bupropion diminished a number of marijuana effects: ratings of "I feel friendly," "I feel social," "I feel high," and "I can't concentrate" were decreased by bupropion during active marijuana availability, yet bupropion had no effect on these rating during marijuana withdrawal. Ratings of "I have an upset stomach" and "I have gooseflesh" were increased by bupropion during both active marijuana availability and active marijuana withdrawal (Table 2).

Drug-effects questionnaire

Ratings of "liking" the marijuana dose were significantly lower during the first 3 days of marijuana withdrawal when participants were maintained on bupropion compared to placebo (F=13.45, P<0.01; data not shown).

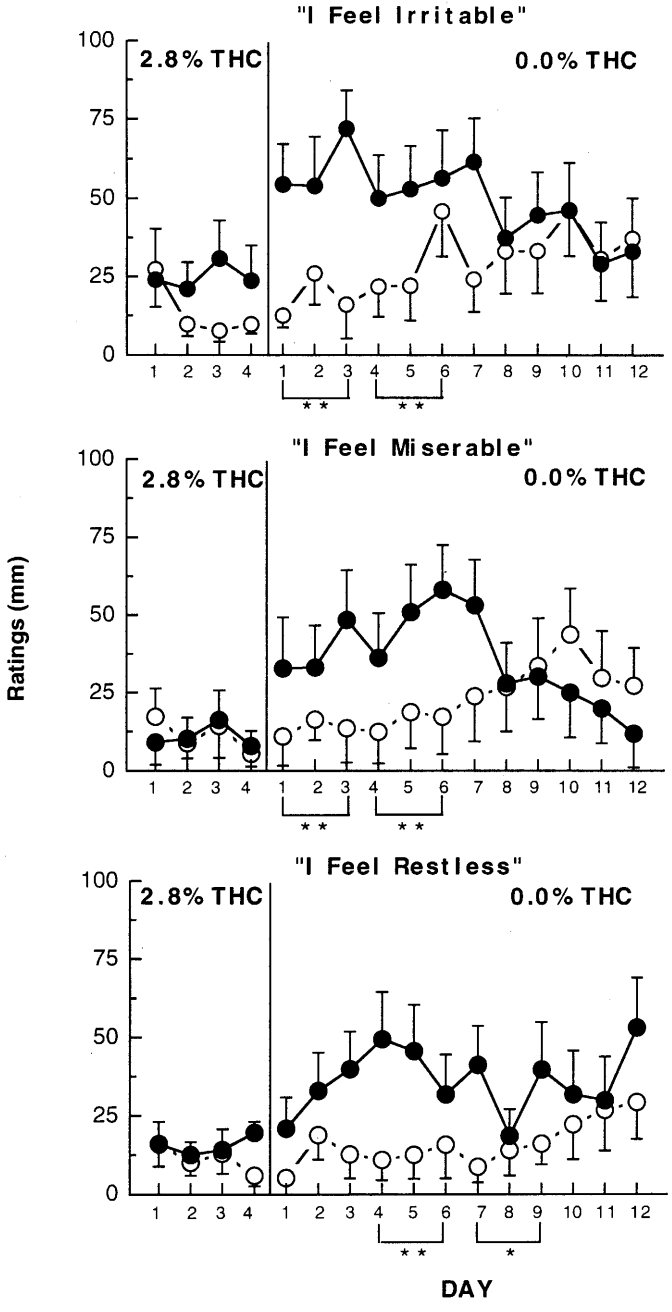


Fig. 1 Selected peak subjective-effects ratings as a function of bupropion dose and day of the marijuana condition. The *open circles* represent placebo bupropion and *filled circles* represent active bupropion. For the active marijuana condition, *asterisks* indicate a significant difference between bupropion and placebo on that day (**P*<0.01; ***P*<0.005). During placebo marijuana smoking, i.e., active marijuana withdrawal, *asterisks* indicate a significant difference between bupropion and placebo for days 1–3, 4–6, 7–9, and 10–12 (**P*<0.01; ***P*<0.005). *Error bars* represent ± SEM

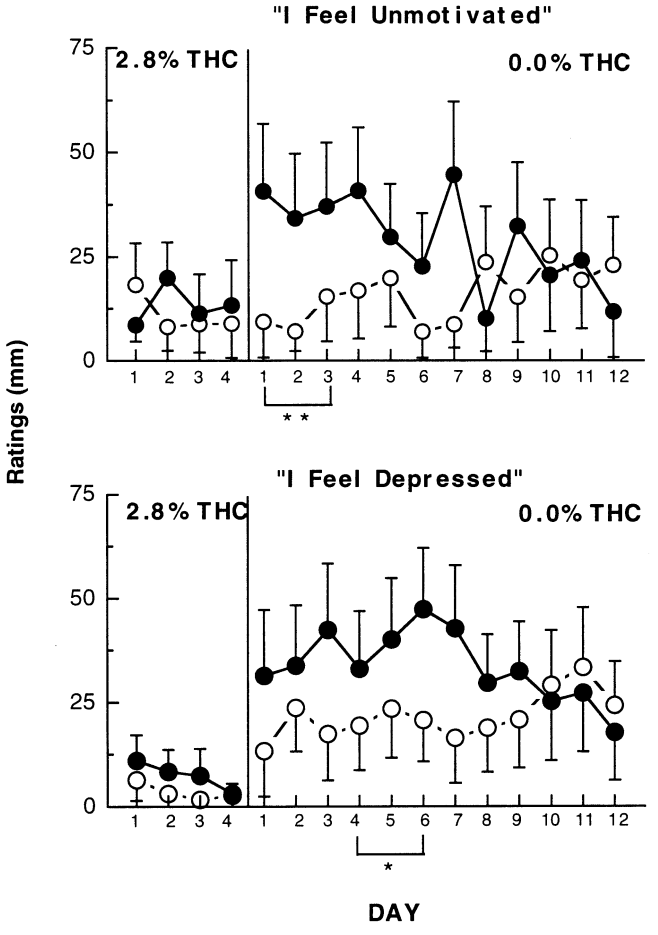


Fig. 2 Selected peak subjective-effects ratings. See Fig. 1 for details

Marijuana withdrawal checklist

Participants reported significantly less marijuana craving on the 2nd day of active marijuana administration during bupropion maintenance compared to placebo maintenance (F=12.61, P<0.004; data not shown).

Food intake

Bupropion had no effect on any of the food intake measures compared to placebo. During active marijuana administration, total daily caloric intake averaged 3483± 119 kcal under placebo maintenance and 3456±119 kcal under bupropion maintenance. During active marijuana withdrawal, total daily caloric intake averaged 2385± 67 kcal under placebo maintenance and 2372±89 kcal under bupropion maintenance. There was no significant change in body weight from the beginning (72±4 kg) to the end (71±3 kg) of study participation.

Social behavior

Bupropion did not alter the amount of time participants spent in their private rooms or in the recreation area during either marijuana condition. Bupropion did, however, decrease the percentage of time participants spent talking during the recreation period on days of active marijuana availability. Specifically, on the 2nd day of active marijuana administration, participants spent 33% of the time in the recreation area talking during placebo administra-

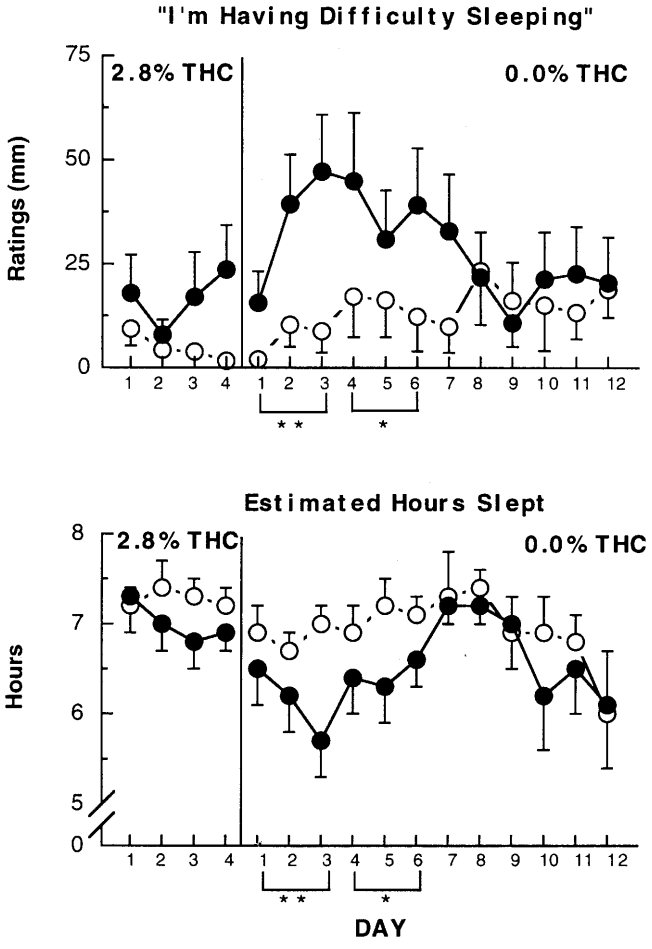


Fig. 3 Selected peak subjective-effects ratings and sleep questionnaire ratings. See Fig. 1 for details

tion compared to 12% of the time spent talking during bupropion administration (F=8.12, P<0.01). On the 4th day of active marijuana smoking, participants spent 42% of the time talking during placebo administration compared to 20% of the time talking during bupropion administration (F=9.04, P<0.01).

Performance effects

As shown in Fig. 4, bupropion generally improved performance on psychomotor tasks during both the active and placebo marijuana conditions. Specifically, participants recognized more odd or even sequences of numbers on the RIT, made fewer errors learning and entering ten-number sequences in the repeated acquisition task, and achieved higher maximum speeds (reflecting greater accuracy tracking the target) on the DAT, during bupropion maintenance compared to placebo. There was one task in which performance was slightly worse under bupropion maintenance: the percentage of correct entries in the DSST task was lower (0.02%) when participants were taking active bupropion compared to placebo (F=7.48, P<0.01; data not shown).

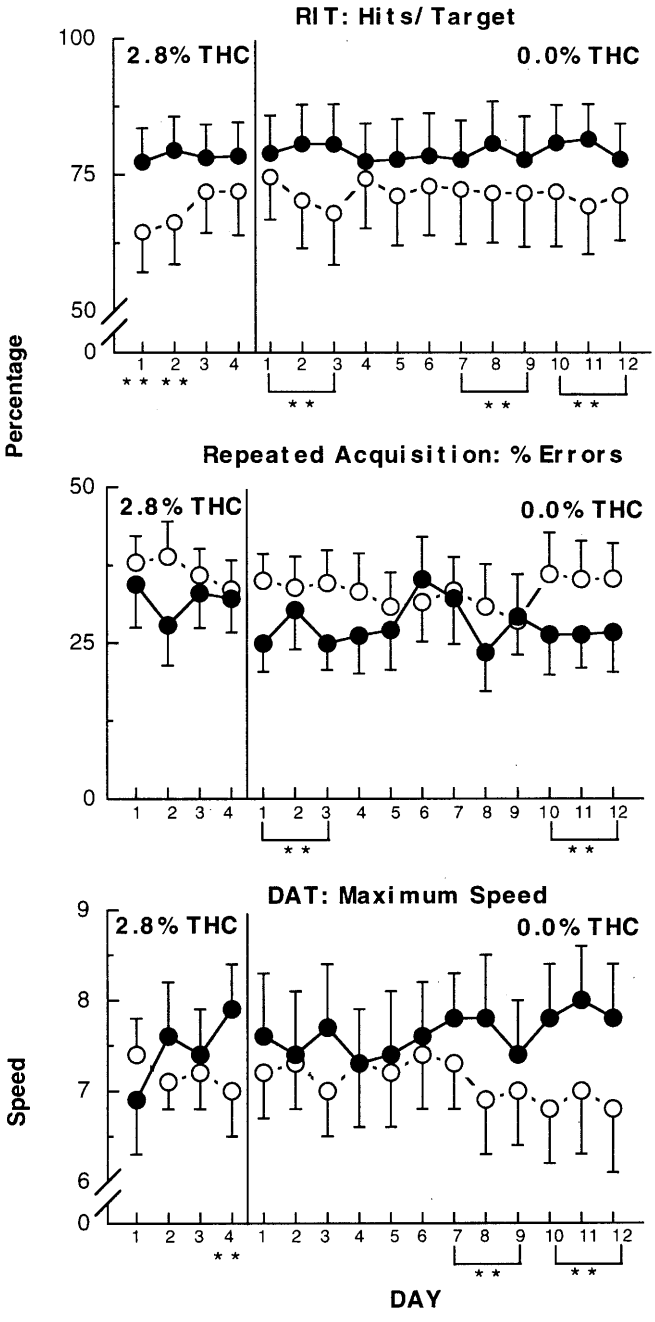


Fig. 4 Selected peak subjective-effects ratings. See Fig. 1 for details. *RIT* Rapid information task, *DAT* divided attention task

Tobacco cigarette smoking

For the seven of the nine participants who smoked tobacco cigarettes, bupropion increased daily cigarette use on days when active marijuana was available, but not when placebo marijuana was available. Specifically, on the 3rd day of active marijuana administration, participants smoked 11±2 cigarettes/day during placebo maintenance, and 17±4 cigarettes/day during bupropion maintenance (F=11.13, P<0.006).

Table 2 Selected mean (± SEM) peak subjective-effects ratings as a function of marijuana condition and bupropion dose. *Note* Visual analog scales (0–100 mm) were completed 10 times/day. *Asterisks* represent significant differences between bupropion maintenance condition

Bupropion	Days of marijuana administration				Days of marijuana withdrawal			
	1	2	3	4	1–3	4–6	7–9	10–12
"Noises or sounds seem louder than usual"								
0 mg	14 (4)	14 (10)	15 (9)	15 (10)	4 (3)	6 (3)	4 (2)	5 (4)
300 mg	6 (2)	13 (6)	9 (4)	5 (3)	9 (4)	19 (9)*	1 (0)	2 (2)
"I feel like yawning"								
0 mg	37 (12)	31 (9)	19 (5)	15 (7)	24 (7)	24 (9)	24 (10)	23 (10)
300 mg	19 (10)	24 (11)	36 (12)	32 (12)	37 (9)	37 (11)	42 (11)**	26 (9)
"I feel alert"								
0 mg	59 (7)	64 (10)	53 (8)	51 (10)	58 (9)	59 (9)	49 (10)	55 (10)
300 mg	59 (8)	56 (7)	61 (9)	55 (10)	57 (8)	62 (10)	65 (9)*	69 (11)*
"I feel friendly"								
0 mg	84 (5)	72 (9)	72 (9)	67 (9)	62 (11)	64 (8)	60 (9)	57 (9)
300 mg	54 (9)**	61 (7)*	54 (8)**	53 (9)**	56 (10)	54 (11)	59 (10)	62 (11)
"I feel social"								
0 mg	82 (6)	76 (9)	76 (8)	76 (10)	64 (9)	67 (8)	59 (9)	56 (10)
300 mg	63 (9)**	57 (9)**	60 (9)**	65 (8)	63 (9)	59 (10)	6 (10)	66 (10)
"I feel high"								
0 mg	58 (10)	48 (12)	46 (12)	37 (12)	3 (2)	4 (3)	9 (8)	13 (11)
300 mg	41 (11)*	45 (11)	38 (10)	27 (9)	3 (2)	4 (2)	1 (0)	1 (1)
"I'm having difficulty concentrating"								
0 mg	46 (13)	35 (13)	45 (12)	42 (12)	34 (13)	40 (12)	39 (11)	39 (11)
300 mg	25 (8)**	24 (8)	28 (12)*	27 (9)	27 (7)	37 (9)	37 (12)	31 (12)
"I have an upset stomach"								
0 mg	12 (5)	16 (9)	5 (3)	4 (2)	5 (3)	10 (6)	8 (5)	10 (4)
300 mg	16 (8)	25 (12)	23 (11)*	10 (5)	20 (8)*	23 (10)	17 (8)	12 (5)
"I have gooseflesh"								
0 mg	4 (3)	2 (1)	3 (2)	2 (1)	2 (1)	2 (1)	2 (2)	3 (2)
300 mg	14 (9)**	10 (8)**	8 (7)	8 (5)	12 (7)*	11 (6)	8 (6)	5 (3)

*$P<0.01$; **$P<0.005$

Discussion

Maintenance on bupropion worsened mood during abstinence from active marijuana. Specifically, regular marijuana smokers, averaging approximately 36 marijuana cigarettes per week prior to study onset, reported being more irritable, miserable, restless, depressed, and unmotivated while receiving bupropion during active marijuana withdrawal compared to placebo. Bupropion also worsened self-reported sleep quality during marijuana withdrawal relative to placebo. None of these effects were present if participants smoked active marijuana, demonstrating that bupropion only worsened most mood symptoms under conditions of marijuana abstinence, following 4 days of controlled, active marijuana smoking.

Similar to the strategy used to treat nicotine dependence, participants took bupropion while they were still smoking active marijuana. Ratings such as "I feel high" and "I'm having difficulty concentrating" were attenuated by bupropion during active marijuana availability compared to placebo bupropion, suggesting that bupropion did not enhance marijuana's effects directly. The most robust influence of bupropion on marijuana's direct effects was a decrease in sociability. Not only did participants report feeling less friendly and social, but they also spent less time talking while in the social area compared to placebo maintenance. The combination of bupropion with active marijuana also resulted in an increase in tobacco cigarette smoking. This effect is counter-intuitive, given that: (1) bupropion is used in the pharmacologic treatment of nicotine dependence and (2) marijuana alone has been shown to decrease tobacco cigarette smoking behavior (Kelly et al. 1990). Overall, these data demonstrate that bupropion slightly altered certain of marijuana's acute behavioral effects, but did not enhance marijuana intoxication overall. Thus, bupropion did not exacerbate marijuana withdrawal symptoms by increasing the development of marijuana dependence.

Bupropion's effects on sleep and on mood tended to abate by approximately the 9th day of active marijuana withdrawal. Given the similar time-course of effects, it is possible that bupropion's effects on sleep mediated the effects on mood, i.e., ratings such as irritability and restlessness were increased by bupropion because partici-

pants were sleep-deprived. However, this appears unlikely, given that bupropion has an opposite pattern of effects when used to treat nicotine dependence. Specifically, approximately 30–50% of patients receiving bupropion for nicotine dependence report insomnia, while also reporting fewer symptoms of depression, irritability, and difficulty concentrating compared to placebo treatment (Ferry 1999; Jorenby et al. 1999; Schiffman et al. 2000). These data demonstrate that bupropion's effect on mood and sleep are dissociable.

Perhaps bupropion's stimulant properties, which made it difficult for participants to sleep, also played a role in improving task performance. Stimulants such as caffeine, nicotine, and amphetamine have been shown to enhance psychomotor task performance (see Foltin and Evans 1993). In the present study, bupropion improved performance on three distinct psychomotor performance tasks regardless of marijuana condition for the duration of the study. Similar improvements in performance have been reported during nicotine withdrawal (Shiffman et al. 2000).

In terms of the duration of marijuana withdrawal symptoms, the current design did not include a baseline phase in which marijuana withdrawal could be compared to a state of non-withdrawal, since our objective was to compare bupropion to placebo rather than to assess marijuana withdrawal per se. Nevertheless, when the placebo bupropion condition is considered, it is clear that certain symptoms, such as depression and irritability were increased and food intake was decreased during marijuana withdrawal compared to active marijuana administration, and that these effects persisted for the 12 days of marijuana withdrawal. These data suggest that symptoms of marijuana withdrawal may last longer than previously suspected. Earlier data with oral THC and smoked marijuana indicated that symptoms abated within 4 days (Jones et al. 1976; Mendelson et al. 1984), while our studies reported that many symptoms were still increasing by the 4th day of active marijuana withdrawal (Haney et al. 1999a, b). Aggressive behavior in abstinent marijuana smokers was also increased for at least 7 days of abstinence (Kouri et al. 1999), further suggesting that marijuana withdrawal symptoms last longer than 4 days.

Alternatively, it may be that these mood changes reflect the participants' baseline mood state, rather than marijuana withdrawal per se. It is also possible that the mood symptoms reflect confinement in the hospital for almost 3 weeks rather than marijuana withdrawal. However, it is worth noting that our earlier studies saw that an identical constellation of symptoms only occurred during periods of marijuana withdrawal, regardless of the time of confinement, and that these mood symptoms differed from baseline (Haney et al. 1999a, b), leading us to conclude that the data most likely reflect marijuana withdrawal. Further, the symptoms are closely similar to those observed in outpatient clinical settings with patients seeking treatment for their marijuana use (Budney et al. 1999).

In conclusion, regular marijuana smokers deprived of active marijuana for 12 days following 4 days of active marijuana smoking had significantly worsened mood while maintained on bupropion as compared to placebo. Our hypothesis that bupropion might be effective for marijuana withdrawal because it shares the same constellation of symptoms as nicotine withdrawal, for example, insomnia, irritability, restlessness, depressed mood, was not supported. Nicotine and cannabinoids have distinct mechanisms of action, and there are distinct neurobiological adaptations associated with repeated administration of each drug (Rodriguez de Fonseca et al. 1997; Ferry 1999), which most likely account for the divergent effects of bupropion in chronic tobacco and marijuana smokers. Although it is possible that lower doses of bupropion might produce less stimulant effects, and improve the mood symptoms of marijuana withdrawal, the present data suggest that bupropion does not show promise as an effective medication to treat individuals seeking treatment for chronic marijuana use.

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References

Brower KJ, Maddahian E, Low FC, Beresford TP (1988) A comparison of self-reported symptoms and DSM-III-R criteria for cocaine withdrawal. Am J Drug Alcohol Abuse 14:347–356

Budney AJ, Kandel DB, Cherek DR, Martin BR, Stephens RS, Roffman R (1997) College on Problems of Drug Dependence Meeting, Puerto Rico: marijuana use and dependence. Drug Alcohol Depend 45:1–24

Budney AJ, Novy PL, Hughes JR (1999) Marijuana withdrawal among adults seeking treatment for marijuana dependence. Addiction 94:1311–1321

Chait LD, Pierri J (1989) Some physical characteristics of NIDA marijuana cigarettes. Addict Behav 14:61–67

Cherek DR (1981) Effects of smoking different doses of nicotine on human aggressive behavior. Psychopharmacology 75:339–345

Ferris RM, Cooper BR (1993) Mechanism of antidepressant activity of bupropion. J Clin Psychiatry Monogr 11:2–14

Ferry LH (1999) Non-nicotine pharmacotherapy for smoking cessation. Prim Care 26:653–669

Foltin RW, Evans SM (1993) Performance effects of drugs of abuse: a methodological survey. Hum Psychopharmacol 8:9–19

Foltin RW, Fischman MW, Pedroso JJ, Pearlson GD (1987) Marijuana and cocaine interactions in humans: cardiovascular consequences. Pharmacol Biochem Behav 28:459–464

Foltin RW, Haney M, Comer SD, Fischman MW (1996) Effect of fluoxetine on food intake of humans living in a residential laboratory. Appetite 27:165–181

Frank B, Galea J (1995) Epidemiologic trends in drug abuse, vol II. NIDA US Department Health and Human Services, NIH

Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW (1999a) Abstinence symptoms following oral THC administration to humans. Psychopharmacology 141:385–394

Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW (1999b) Abstinence symptoms following smoked marijuana in humans. Psychopharmacology 141:395–404

Heishman SJ, Taylor RC, Henningfield JE (1994) Nicotine and smoking: a review of effects on human performance. Exp Clin Psychopharmacol 2:345–395

Hurt RD, Sachs DP, Glover ED, Offord KP, Johnston JA, Dale LC, Khayrallah MA, Schroeder DR, Glover PN, Sullivan CR, Croghan IT, Sullivan PM (1997) A comparison of sustained-release bupropion and placebo for smoking cessation (see comments). N Engl J Med 337:1195–1202

Johnston LD, O'Malley PM, Bachman JG (1995) National survey results on drug use from the monitoring the future study, 1975–1994, vol 1. US Department of Health and Human Services, Washington, DC

Johnston LD, O'Malley PM, Bachman JG (1997) Monitoring the future study: 1975–1995, vol II. US Department Health and Human Services, NIH

Johnston LD, O'Malley PM, Bachman JG (2000) Monitoring the future study: national results on adolescent drug use. US Department Health and Human Services, NIH

Jones RT, Benowitz N, Bachman J (1976) Clinical studies of cannabis tolerance and dependence. Ann NY Acad Sci 282:221–239

Jones RT, Benowitz NL, Herning RI (1981) Clinical relevance of cannabis tolerance and dependence. J Clin Pharmacol 21: 143S–152S

Jorenby DE, Leischow SJ, Nides MA, Rennard SI, Johnston JA, Hughes AR, Smith SS, Muramotor ML, Daughton DM, Doan K, Fiore MC, Baker TB (1999) A controlled trial of sustained-release bupropion, a nicotine patch, or both for smoking cessation. N Eng J Med 340:685–691

Kelly TH, Foltin RW, Rose AJ, Fischman MW, Brady JV (1990) Smoked marijuana effects on tobacco cigarette smoking behavior. J Pharmacol Exp Ther 252:934–944

Kouri EM, Pope HG Jr, Lukas SE (1999) Changes in aggressive behavior during withdrawal from long-term marijuana use. Psychopharmacology 143:302–308

Martin BR, Hall W (1999) The health effects of cannabis: key issues of policy relevance. Bull Narc 49–50:85–116

McLaren DS (1976) Nutrition and its disorders, 2nd edn. Churchill Livingstone, New York

Mendelson JH, Mello NK, Lex BW, Bavli S (1984) Marijuana withdrawal syndrome in a woman. Am J Psychiatry 141: 1289–1290

O'Brien CP (1996) Drug addiction and drug abuse. In: Molinoff PB, Ruddon RW (eds) Goodman's and Gilman's the pharmacological basis of therapeutics, 9th edn. McGraw-Hill, New York

Rinaldi-Carmona M, Barth F, Heaulme M, Shire D et al. (1994) SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett 350:240–244

Rodriguez de Fonseca F, Carrera MRA, Navarro M, Koob GF, Weiss F (1997) Activation of corticotropin-releasing factor in the limbic system during cannabinoid withdrawal. Science 276:2050–2054

Roffman RA, Stephens RS, Simpson EE, Whitaker DL (1988) Treatment of marijuana dependence: preliminary results. J Psychoactive Drugs 20:129–137

Shiffman S, Johnston JA, Khayrallah M, Elash CA, Gwaltney CJ, Paty JA, Gnys M, Evoniuk G, Deveaugh-Geiss J (2000) The effect of bupropion on nicotine craving and withdrawal. Psychopharmacology 148:33–40

Stephens RS, Roffman RA, Simpson EE (1993) Adult marijuana users seeking treatment. J Consult Clin Psychol 61:1100–1104

Stephens RS, Roffman RA, Simpson EE (1994) Treating adult marijuana dependence: a test of the relapse prevention model. J Consult Clin Psychol 62:92–99

US Department of Health and Human Services (1988) The health consequences of smoking: nicotine addiction: a report of the surgeon general (DHHS publication number CDC 88–8406). US Government Printing Office, Washington, DC