

# Dronabinol and Marijuana in HIV-Positive Marijuana Smokers

## *Caloric Intake, Mood, and Sleep*

Margaret Haney, PhD,\* Erik W. Gunderson, MD,\* Judith Rabkin, PhD,\* Carl L. Hart, PhD,\*<sup>†</sup> Suzanne K. Vosburg, PhD,\* Sandra D. Comer, PhD,\* and Richard W. Foltin, PhD\*

**Objectives:** Individuals with HIV constitute the largest group using cannabinoids for medicinal reasons; yet, no studies have directly compared the tolerability and efficacy of smoked marijuana and oral dronabinol maintenance in HIV-positive marijuana smokers. This placebo-controlled within-subjects study evaluated marijuana and dronabinol across a range of behaviors: eating topography, mood, cognitive performance, physiologic measures, and sleep.

**Methods:** HIV-positive marijuana smokers ( $n = 10$ ) completed 2 16-day inpatient phases. Each dronabinol (5 and 10 mg) and marijuana (2.0% and 3.9%  $\Delta^9$ -tetrahydrocannabinol [THC]) dose was administered 4 times daily for 4 days, but only 1 drug was active per day, thereby maintaining double-blind dosing. Four days of placebo washout separated each active cannabinoid condition.

**Results:** As compared with placebo, marijuana and dronabinol dose dependently increased daily caloric intake and body weight in HIV-positive marijuana smokers. All cannabinoid conditions produced significant intoxication, except for low-dose dronabinol (5 mg); the intoxication was rated positively (eg, "good drug effect") with little evidence of discomfort and no impairment of cognitive performance. Effects of marijuana and dronabinol were comparable, except that only marijuana (3.9% THC) improved ratings of sleep.

**Conclusions:** These data suggest that for HIV-positive marijuana smokers, both dronabinol (at doses 8 times current recommendations) and marijuana were well tolerated and produced substantial and comparable increases in food intake.

**Key Words:** AIDS, appetite, cannabis, medical marijuana, tetrahydrocannabinol

(*J Acquir Immune Defic Syndr* 2007;45:545–554)

Received for publication December 15, 2006; accepted May 16, 2007.

From the \*Division on Substance Abuse, New York State Psychiatric Institute, and Department of Psychiatry, College of Physicians and Surgeons of Columbia University, New York, NY; and <sup>†</sup>Department of Psychology, Columbia University, New York, NY.

Supported by US National Institute on Drug Abuse and the National Center for Complementary and Alternative Medicine (grant DA12698).

Reprints: Margaret Haney, PhD, New York State Psychiatric Institute, College of Physicians and Surgeons of Columbia University, 1051 Riverside Drive, Unit 120, New York, NY 10032 (e-mail: mh235@columbia.edu).

Copyright © 2007 by Lippincott Williams & Wilkins

Objectively defining the effects of cannabinoids, including marijuana, in HIV-positive patients is essential from public health and public policy perspectives. Individuals with HIV constitute the largest group using cannabinoids for medicinal reasons, and a considerable proportion of those with HIV currently smoke marijuana.<sup>1,2</sup> Among HIV patients sampled in American and English medical clinics, 20% to 23% reported current marijuana use,<sup>3,4</sup> whereas the incidence in Canada ranges from 14% to 37%.<sup>5,6</sup> Public support for medical marijuana is strong. Recent polls show that 70% to 80% of the American public supports a policy whereby physicians can prescribe marijuana, and 10 states have passed medical marijuana ballot initiatives in opposition to federal policy prohibiting the use of marijuana.<sup>7,8</sup>

Reasons for smoking marijuana cited by medical marijuana proponents and patients with HIV include counteracting the nausea, anorexia, stomach upset, and anxiety associated with the disease and with antiretroviral therapy. The benefits of smoked marijuana are that its effects peak rapidly (<20 minutes), allowing for dose titration and immediate symptom relief. Although it has been argued that other cannabinoid constituents of marijuana, especially cannabidiol, provide additional benefits, there is little preclinical or clinical evidence to support this hypothesis, particularly at the cannabidiol concentrations typically present in marijuana.<sup>9–13</sup> The primary limitation of marijuana revolves around smoking. Not only are there no accepted standards of marijuana potency and purity, but the respiratory risks of smoking marijuana are similar to those associated with tobacco cigarette use.<sup>1,14,15</sup>

An alternative to smoked marijuana is oral  $\Delta^9$ -tetrahydrocannabinol (THC; dronabinol), the primary psychoactive ingredient in marijuana, which is approved by the US Food and Drug Administration (FDA) to treat nausea and appetite loss associated with cancer and HIV. The benefits of dronabinol are that it is safe, legal standardized doses can be delivered, and it is rarely abused.<sup>16</sup> Absorption of dronabinol is variable, however, and it has a slow rate of onset (peak effects in approximately 120 minutes) and a long duration of action, which make it difficult to titrate dose to achieve the desired effect.<sup>17,18</sup> In addition, nauseated patients can have difficulty taking an oral medication.

Tolerability of dronabinol seems to depend, in part, on marijuana use history. Among HIV-positive nonmarijuana smokers, low-dose dronabinol (2.5 mg 2 times daily) improved mood and decreased nausea but also produced mental

cloudiness and confusion, thereby decreasing patient compliance and resulting in high dropout rates.<sup>2,19–21</sup> Among HIV-infected patients who had smoked marijuana but who were not current smokers, dronabinol (2.5 mg 3 times daily) and marijuana (3.95% THC 3 times daily) administered for 3 weeks were well tolerated and resulted in more weight gain than placebo administration,<sup>22</sup> while having no negative impact on antiretroviral pharmacokinetics or immune function.<sup>21–24</sup> Among current marijuana smokers, much higher acute doses of dronabinol can be safely administered.<sup>25–30</sup> For example, in HIV-positive active marijuana smokers, dronabinol (10 and 20 mg) and smoked marijuana (1.8%, 2.8%, and 3.9% THC) were similarly effective at increasing food intake, with minimal negative drug ratings or decrements in cognitive performance.<sup>28</sup> A limitation of this study is that only acute marijuana and dronabinol doses were tested.

More relevant from a clinical and policy perspective is to characterize the relative tolerability and efficacy of dronabinol and marijuana across a range of repeatedly administered doses. The Institute of Medicine's review of marijuana's clinical utility concluded that too few studies have objectively characterized the potential benefit of marijuana and its constituent cannabinoids.<sup>1</sup> Although smoking was recognized as a poor route for long-term medication administration, the report concluded that further research is essential, because the public policy debates on medical marijuana have been conducted in the absence of empiric data.<sup>31</sup> The present study attempts to address these scientific gaps in the literature. The effects of dronabinol (0, 5, and 10 mg 4 times daily) and marijuana (0.0%, 2.0%, and 3.9% THC 4 times daily) on diet, mood, cognitive performance, and sleep were evaluated under double-blind conditions in the population most likely to be using marijuana medically: HIV-positive marijuana smokers.

## METHODS

### Participants

Table 1 describes the demographic information for the 10 volunteers who participated in the study. Before study onset, participants provided a detailed drug and medical history, received medical and psychiatric evaluations, and signed a consent form detailing all aspects of the research. For inclusion, volunteers had to be 21 to 50 years of age, taking at least 2 antiretroviral medications, currently under the care of a physician for HIV management, smoking marijuana at least twice weekly for the past 4 weeks, and medically and psychiatrically stable. Exclusion criteria were a diagnosis of nutritional malabsorption, major depression, dementia, chronic diarrhea, weakness, fever, significant pulmonary disease, an opportunistic infection within the past 3 months, obesity, use of steroids within the past 3 weeks, or drug dependence (excluding nicotine or marijuana). A urine toxicology assessment was conducted at each screening visit and during study participation. Three of the 10 participants reported occasional intranasal cocaine use, but all were abstinent during study participation, as verified by urine toxicology. All procedures were in accordance with the Helsinki Declaration of 1975, as

**TABLE 1. Demographic Characteristics of Study Participants**

Gender (female/male ratio)	1:9
Age, years	40.1 (±1.9)
Race/ethnicity (black/white/Hispanic ratio)	7:1:2
Education, years	12.4 (±0.9)
CD4 cell count, cells/mm <sup>3</sup>	411.4 (±61.7)
Years since HIV diagnosis	10.0 (±2.1)
BIA	1.0 (±0.1)*
BMI	25.0 (±1.3)
MJ use, days per week	4.6 (±0.6)
MJ cigarettes per day	3.2 (±0.8)
Years of MJ use	18.6 (±3.3)
Cigarette smokers	7
Cigarettes per day	13.4 (±3.3)
Alcohol drinkers	8
Alcohol drinks per week	3.5 (±0.9)

Data are presented as means (±SD) or as frequency or percentage.

\*Two participants had a BIA <0.9, indicating significant muscle mass loss. BIA indicates bioelectric impedance analysis (body cell mass per inches); BMI, body mass index (kg/m<sup>2</sup>); MJ, marijuana.

revised in 2000, and were approved by the New York State Psychiatric Institute's Institutional Review Board.

### Laboratory

Participants, in 3 groups of 3 or 4, lived in a residential laboratory designed for the continuous observation of behavior over extended periods. The residential laboratory consists of 11 rooms in the New York State Psychiatric Institute: 4 private participant rooms, a common recreational area, 2 single-occupancy bathrooms, 2 single-occupancy shower rooms, and 2 vestibules used for exchanging supplies.<sup>25</sup>

Output from a video- and audio-monitoring system terminated in an adjacent room. Participants were observed continuously except while in the bathroom or in private dressing areas, although no recordings were made. Participants and staff communicated using a networked computer system linking each participant's computer with the computer in the control room and allowing for continuous on-line interaction between participants and staff but not between participants.

### Design

A within-subject design was used, in which all volunteers experienced all cannabinoid conditions, thereby increasing statistical power. Table 2, which portrays a representative dosing schedule, shows that the study comprised an initial 16-day inpatient phase, a 5- to 10-day outpatient phase, and another 16-day inpatient phase. During both inpatient phases, participants smoked marijuana and took dronabinol capsules 4 times per day. Each active marijuana and dronabinol dose condition occurred sequentially for 4 days, in randomized order, with a 4-day placebo washout period between each active drug condition. The outpatient phase was included because a consecutive 32-day inpatient study would have been untenable for most participants. During the outpatient phase, participants were instructed to abstain from illicit drugs (excluding marijuana, for which no instructions were given).

**TABLE 2.** Representative Marijuana and Dronabinol Dosing Schedule

Inpatient Phase I			Outpatient 5 to 10 Days	Inpatient Phase II		
Day	MJ	Dronabinol		Day	MJ	Dronabinol
1	0.0	0	17	0.0	0	
2	0.0	0	18	0.0	0	
3	0.0	0	19	0.0	0	
4	0.0	0	20	0.0	0	
5	<b>3.6</b>	0	21	0.0	<b>10</b>	
6	<b>3.6</b>	0	22	0.0	<b>10</b>	
7	<b>3.6</b>	0	23	0.0	<b>10</b>	
8	<b>3.6</b>	0	24	0.0	<b>10</b>	
9	0.0	0	25	0.0	0	
10	0.0	0	26	0.0	0	
11	0.0	0	27	0.0	0	
12	0.0	0	28	0.0	0	
13	0.0	<b>5</b>	29	<b>2.0</b>	0	
14	0.0	<b>5</b>	30	<b>2.0</b>	0	
15	0.0	<b>5</b>	31	<b>2.0</b>	0	
16	0.0	<b>5</b>	32	<b>2.0</b>	0	

Participants took dronabinol capsules 4 times daily (09:00 AM, 1:00 PM, 5:00 PM, and 9:00 PM) and smoked marijuana 4 times daily (10:00 AM, 2:00 PM, 6:00 PM, and 10:00 PM).

Marijuana measured as percentage of THC; dronabinol measured in milligrams.

Outpatient phase lasted 5 to 10 days.

Bold indicates active drug condition; MJ, marijuana.

Marijuana and dronabinol dosing was counterbalanced and double-blind. Drugs were administered using a staggered double-dummy design, such that participants smoked marijuana and received dronabinol capsules 4 times per day but only 1 dose of drug was active at a time. Because the behavioral effects of dronabinol peak in approximately 2 hours, capsule dosing preceded marijuana administration by 1 hour to make it difficult for the participants to determine whether the marijuana or the dronabinol was active.<sup>27,28,32</sup>

**Procedure**

Before study onset, volunteers received several training sessions (3 to 4 hours per session) on the computer tasks; during that time, no drugs were administered. Volunteers also sampled an active dose of dronabinol (10 mg) and smoked placebo marijuana on 1 outpatient day and smoked active marijuana (3.9%) and sampled placebo THC on another day, and their cardiovascular and subjective responses were measured. In addition to providing training, these days in the laboratory helped to give volunteers the experience needed to determine if they wanted to participate in the study.

Participants received additional training on tasks and procedures on the day they moved into the laboratory. As shown in Table 3, the first experimental day began at 8:15 AM the next morning. Each morning, participants completed a 7-item visual analog scale (VAS) sleep questionnaire comprising 100-mm lines marked “not at all” at one end (0 mm) and “extremely” at the other end (100 mm). Participants then completed a 50-item VAS subjective effects battery measuring a range of mood and physical symptoms, were weighed (but

**TABLE 3.** Time Course of Sessions

Time	Event	Time	Event
08:15 AM	Wake, mood scale	2:45 PM	MRF, HSQ
	Sleep questionnaire	3:00 PM	Cognitive task battery
08:30 AM	Weigh-in, food in	3:45 PM	Cognitive task battery
	Heart monitor put on	4:30 PM	End work period
09:00 AM	Capsule 1	5:00 PM	Capsule 3
09:15 AM	Cognitive task battery		Begin evening recreation
09:45 AM	CRF	5:45 PM	CRF
10:00 AM	MJ 1	6:00 PM	MJ 3
10:15 AM	Task battery	6:15 PM	Film 1
10:45 AM	MRF, HSQ	6:45 PM	MRF, HSQ
11:00 AM	Cognitive task battery	9:00 PM	Capsule 4
11:45 AM	Cognitive task battery	9:15 PM	Film 2
12:15 PM	Begin lunch recreation	9:45 PM	CRF
1:00 PM	End lunch recreation	10:00 PM	MJ 4
	Capsule 2	10:45 PM	MRF, HSQ
1:15 PM	Cognitive task battery	11:30 PM	End evening recreation
1:45 PM	CRF		Mood scale
2:00 PM	MJ 2		Heart monitor removed
2:15 PM	Cognitive task battery	12:00 AM	Lights out

DEQ indicates drug effect questionnaire; HSQ, hunger-satiety questionnaire; MJ, marijuana.

not informed of their weight), and were given time to eat breakfast.<sup>33</sup> Participants took the first daily capsule at 9:00 AM. The first of 8 30-minute task batteries, composed of 5 performance measures, and the subjective effects VAS began at 9:15 AM. Participants smoked their first daily marijuana cigarette at 10:00 AM. They completed 3 task batteries from 10:15 AM to 12:15 PM and then had access to the recreation area from 12:15 PM to 1:00 PM. The second capsule administration occurred at 1:00 PM, and the fifth task battery began at 1:15 PM. The second administration of marijuana occurred at 2:00 PM. Three more task batteries were completed from 2:15 PM to 4:30 PM. The third capsule administration occurred at 5:00 PM, and the third marijuana administration occurred at 6:00 PM. From 5:00 PM to 11:30 PM, participants again had access to activities available in the recreation area. Two films were shown each evening. The fourth capsule was administered at 9:00 PM, and the fourth marijuana administration occurred at 10:00 PM. A final subjective effects VAS was completed at 11:30 PM, and lights were turned off by 12:00 AM.

Participants brought an adequate supply of their HIV medications, as prescribed by their primary care physician, and took them daily under staff observation. Tobacco cigarette smokers (n = 7) were permitted to smoke cigarettes ad libitum (except from 11:30 PM to 8:30 AM).

**Marijuana Administration**

Each participant received a marijuana cigarette (provided by the National Institute on Drug Abuse) before each smoking occasion. Marijuana (0.0%, 2.0%, and 3.9% THC) was administered using a standardized cued-smoking procedure, which produces reliable increases in heart rate and plasma Δ<sup>9</sup> THC.<sup>34</sup> Colored lights (mounted on the ceiling of

the recreation area) signaled “light the cigarette” (30 seconds), “get ready” (5 seconds), “inhale” (5 seconds), “hold smoke in lungs” (10 seconds), and “exhale.” Participants smoked 3 puffs in this manner, with a 40-second interval between each puff; an entire cigarette can be pyrolyzed in 3 puffs. Cigarettes were rolled at both ends and were smoked through a hollow plastic cigarette holder, so that the marijuana was not visible. Cigarettes were stored frozen in an airtight container and humidified at room temperature for 24 hours before use.

### Dronabinol Administration

Dronabinol (0, 5, and 10 mg; Unimed Pharmaceuticals, Buffalo Grove, IL) was packaged in size 00 opaque capsules with lactose filler by the New York State Psychiatric Institute Research Pharmacy. Although the recommended dose for appetite stimulation is 2.5 mg administered 2 times daily, larger doses were selected, based on our studies showing that marijuana smokers, including those with HIV, show little effect at smaller dronabinol doses.<sup>2</sup>

### Food

Every morning at 8:30 AM, participants received a box of food containing a variety of meal items, snacks, and beverages that could be consumed at any time within the day. Frozen meals or additional items from the box of food were continuously available by request. Participants scanned custom-designed bar codes whenever they ate or drank, specifying substance and portion. At 11:30 PM, participants returned their food box to a staff member. Food items were not available between 11:30 PM and 8:30 AM the next morning.

### Hunger-Satiety Questionnaire

Forty-five minutes after each marijuana cigarette, participants completed a 6-item VAS (HSQ) rating on how hungry, full, nauseated, and thirsty they felt and how strong the desire to eat was at that moment.<sup>35</sup>

### Marijuana and Capsule Rating Forms

Forty-five minutes after each marijuana cigarette, participants completed a 6-item VAS (MRF) evaluating the strength of the marijuana effect, marijuana liking, desire to smoke marijuana again, whether they felt a good marijuana effect or a bad marijuana effect, and whether the marijuana was active or placebo. Forty-five minutes after each capsule administration, participants completed a 6-item VAS (CRF) evaluating the strength of the capsule; good effects; bad effects; liking; whether the capsule was like a stimulant, sedative, or placebo; and willingness to take the capsule again.

### Cognitive Task Battery

Each task battery consisted of a 3-minute digit-symbol substitution task (DSST), a 3-minute repeated acquisition task, a 10-minute divided attention task (DAT), a 10-minute rapid information task (RIT), immediate and delayed digit-recall tasks, and the 50-item VAS. The battery measures various aspects of learning, memory, vigilance, and psychomotor ability.<sup>36</sup> Participants were instructed to complete each task as quickly and as accurately as possible and to fill in the items on the VAS based on how they were feeling at that moment.

### Tobacco Cigarette Smoking

The number of tobacco cigarettes smoked 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 monitored to prevent these events from occurring.

### Sleep Assessment

#### Objective Measures

Each night, participants wore a Nightcap sleep monitoring system (Respironics, Atlanta, GA), which consists of a portable amplifier attached to 2 leads with adhesive electrodes. A lead attached to the forehead measured body movement, and a lead attached to the eyelid measured eye movement. The Nightcap was turned on at midnight when lights were turned off, and participants were instructed to remain in bed. Measures include sleep latency, total sleep time, and the percentage of time spent in the rapid eye movement (REM) stage of sleep. The Nightcap has been validated using traditional polysomnographic measurement.<sup>37</sup>

#### Subjective Measures

Each morning, participants completed a 6-item VAS (modified from the St. Mary’s Hospital Sleep Questionnaire) rating how well they slept, how early they woke up, how easily they fell asleep, how clear-headed they felt, whether they woke up often, and if they were satisfied with their sleep. A fill-in question estimated how many hours they slept the previous night.<sup>38</sup>

#### Physiologic Measures

Each morning, participants were fitted with a SenseWear Armband (<3 oz; Body Media, Pittsburgh, PA) that recorded heart rate and skin temperature at 10-minute intervals. Participants wore this wireless armband monitor each day from 8:30 AM until 11:30 PM.<sup>39</sup>

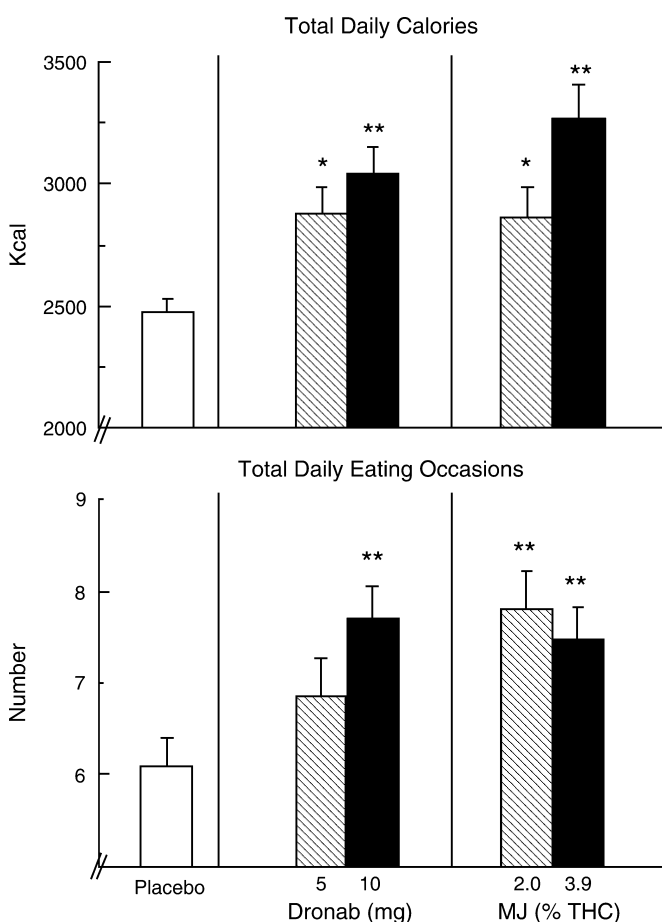
#### Data Analysis

Repeated measures analysis of variance (ANOVA) with planned comparisons was used to determine the effect of marijuana (0.0%, 2.0%, and 3.9% THC administered 4 times daily) and dronabinol (0, 5, and 10 mg administered 4 times daily) on food intake, body weight, subjective effects (peak daily ratings), drug effects (peak daily ratings), task performance (peak scores), heart rate, skin temperature, the number of cigarettes smoked per day, and objective and subjective sleep measures. There were 2 within-group factors (cannabinoid condition and day [1–4] of condition). Percent of energy intake derived from protein, carbohydrates, and fat (estimated as kilocalories from gram intake using Atwater factors) was also assessed.<sup>40</sup> Skin temperature and heart rate were assessed as a function of time of day. Four planned comparisons were done to compare each cannabinoid dose condition with placebo. Because of the large number of comparisons, results were considered statistically significant at *P* values <0.01. Huynh-Feldt corrections were used as a conservative measure to control for potentially uncorrelated within-subjects data.

## RESULTS

### Food Intake

Figure 1, which portrays average caloric intake averaged over the 4 days of each condition as a function of marijuana and dronabinol dose, shows that dronabinol ( $df = 1, 63$  for all planned contrasts; 5 mg,  $F = 9.30$ ; 10 mg,  $F = 18.10$ ;  $P < 0.008$ ) and marijuana (2.0%,  $F = 8.43$ ; 3.9%,  $F = 34.84$ ;  $P < 0.01$ ) dose dependently increased caloric intake compared with placebo. The primary mechanism by which these conditions affected daily food intake was by increasing the number of eating occasions (see Fig. 1), defined as beginning with the first report of an item to be consumed and ending when there was a pause of  $>10$  minutes between food reports.<sup>36</sup> Marijuana and dronabinol increased the number of eating occasions but did not alter the average number of calories consumed during each eating occasion (approximately 404 kcal).



**FIGURE 1.** Mean total daily caloric intake and total number of eating occasions as a function of marijuana (MJ) and dronabinol (Dronab) dose. Each active dose condition reflects the mean across 4 sessions; placebo data represent the mean across 16 sessions. Dronab and MJ were administered 4 times per day. Asterisks denote a significant difference from placebo ( $*P < 0.01$ ;  $**P < 0.005$ ). Error bars represent 1 standard error of the mean (SEM).

Dronabinol and marijuana also produced small but significant shifts in the distribution of macronutrient intake by enhancing the proportion of calories derived from fat. Under placebo conditions, participants derived approximately 51% of their calories from carbohydrates, 36% from fat, and 13% from protein. The low dose of dronabinol (5 mg) significantly increased the proportion of daily calories derived from fat from 36% to 40% ( $F = 11.90$ ;  $P < 0.001$ ) while tending to decrease carbohydrate consumption. The highest strength marijuana cigarettes (3.9%) significantly decreased the percentage of calories derived from protein from 13% to 11% ( $F = 25.23$ ;  $P < 0.0001$ ) while tending to increase fat consumption ( $P < 0.05$ ).

### Body Weight

Maintenance on the higher strength marijuana (3.9%,  $F = 10.00$ ;  $P < 0.01$ ) and higher dose of dronabinol (10 mg,  $F = 10.39$ ;  $P < 0.01$ ) significantly increased body weight. Under placebo conditions, participants' average weight was 77.5 kg. Participants gained 1.2 kg after 4 days of dronabinol (10 mg), and 1.1 kg after 4 days of marijuana (3.9%).

### Hunger and Satiety Questionnaire

Table 4, which shows peak ratings averaged over the 4-day conditions, demonstrates that the highest strength marijuana cigarette (3.9%) significantly increased the desire to eat and ratings of hunger. Dronabinol (10 mg) and the lower strength marijuana cigarettes (2.0%) also increased ratings of dry mouth.

**TABLE 4.** Selected Mean ( $\pm$ SEM) Ratings as a Function of Dronabinol and Marijuana Strength

	Placebo	Dronabinol		Marijuana	
		5 mg	10 mg	2.0%	3.9%
HSQ					
Desire to eat	43 (3)	55 (5)	48 (6)	54 (6)	↑63 (5)**
Hungry	36 (3)	43 (4)	45 (5)	43 (6)	↑61 (5)**
Dry mouth	26 (2)	37 (6)	↑42 (6)**	↑45 (6)**	38 (5)
VAS					
High	27 (2)	28 (5)	↑58 (5)**	↑75 (5)**	↑80 (4)**
Stimulated	22 (2)	21 (4)	41 (5)	↑60 (6)**	↑61 (6)**
Friendly	69 (2)	71 (5)	76 (5)	↑81 (4)**	↑81 (4)**
Self-confident	82 (2)	83 (4)	86 (4)	↑90 (3)**	86 (4)
Can't concentrate	20 (2)	18 (5)	↑38 (6)*	29 (5)	13 (3)
MRF					
Good MJ effect	36 (3)	39 (6)	↑64 (6)**	↑89 (3)**	↑92 (2)**
Liking	33 (3)	34 (5)	↑56 (6)**	↑84 (4)**	↑87 (4)**
Strong	28 (2)	29 (4)	↑51 (5)**	↑83 (4)**	↑86 (4)**
Take again	38 (3)	40 (6)	↑61 (6)**	↑89 (4)**	↑48 (4)**

Peak ratings (0 to 100 mm, VAS) averaged over 4 days of each medication condition. Placebo data represent mean data across 4 4-day conditions interspersed throughout the study. Arrows indicate the direction of the drug effect.

HSQ indicates hunger-satiety questionnaire; MJ, marijuana.

Asterisks represent significant differences between placebo and dose condition:  $*P < 0.01$ ;  $**P < 0.005$ .

### Subjective Effects Ratings

Table 4 and Figure 2 portray peak subjective effects ratings as a function of cannabinoid condition. Ratings of “good drug effect,” “high,” and “mellow” were significantly increased by dronabinol (10 mg) and both active marijuana doses (2.0%, 3.9% THC;  $P < 0.005$ ). Both active marijuana doses also increased ratings of “stimulated,” “friendly,” and “self-confident” ( $P < 0.005$ ). Only dronabinol (10 mg) increased ratings of “can’t concentrate” ( $P < 0.01$ ), whereas only the lower strength marijuana cigarette (2.0%) increased ratings of “anxious.”

### Marijuana Rating Form

Table 4 shows that the higher dronabinol dose (10 mg) and both active marijuana concentrations significantly increased ratings of good drug effect, liking, strength, and desire to smoke again compared with placebo. Note that under active dronabinol conditions, only placebo marijuana was smoked, yet the higher dronabinol dose significantly increased positive ratings for marijuana.

### Drug Effects Questionnaire

The highest strength capsule (10 mg) and marijuana cigarette (3.9%) significantly increased the following capsule ratings: good effect, liking, strength, and willingness to take again. Note that under active marijuana conditions, only placebo capsules were taken, yet the higher marijuana dose significantly increased positive ratings for the capsules.

### Cognitive Performance

Compared with placebo, neither marijuana nor dronabinol significantly altered performance on any of the tasks (eg, measures of learning, memory, vigilance, psychomotor ability).

### Cigarette Smoking

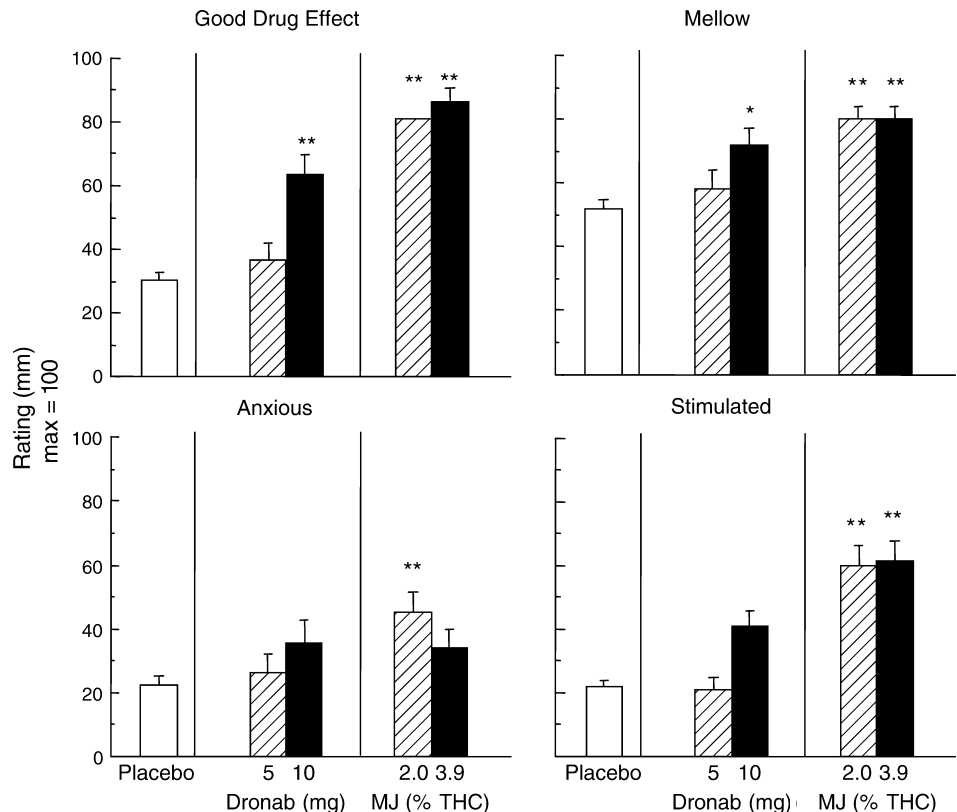
Seven participants smoked tobacco cigarettes. Neither marijuana nor dronabinol significantly influenced the number of cigarettes smoked per day.

### Objective and Subjective Sleep Measures

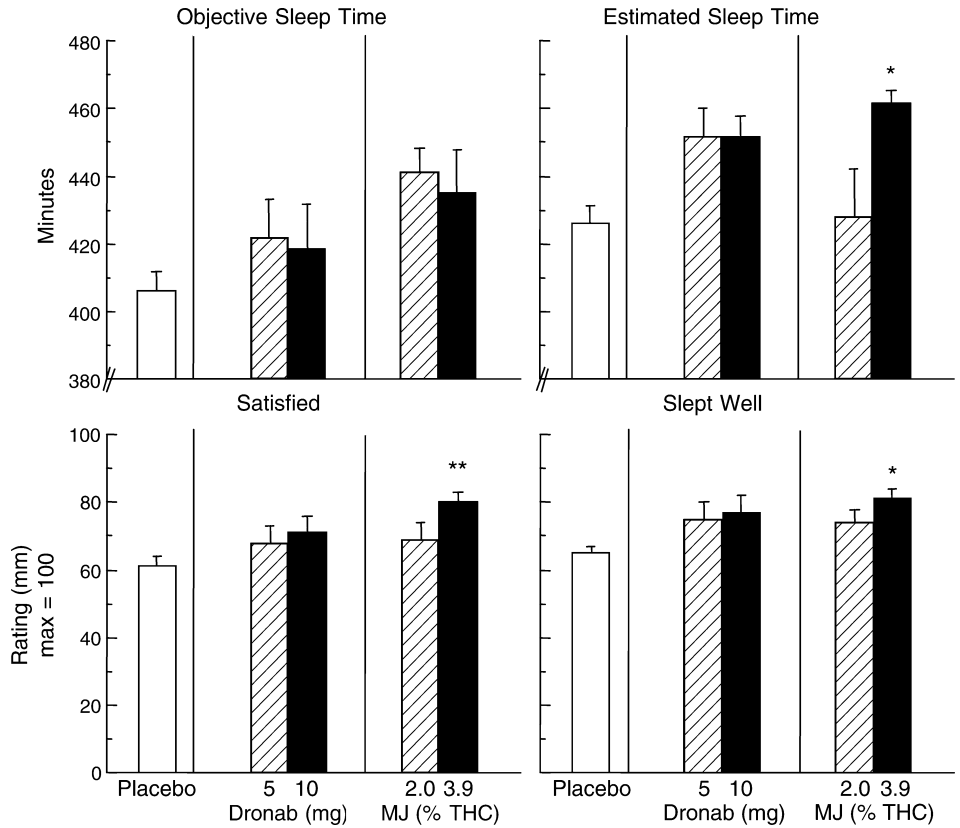
Because of technical problems with the Nightcap, data from only 7 participants could be analyzed. As shown in Figure 3, both marijuana conditions increased an objective determination of the total time spent asleep, although the effect failed to achieve statistical significance. In parallel, the highest strength marijuana cigarettes significantly increased subjective ratings of satisfied and slept well as well as the estimated time spent sleeping.

### Physiologic Measures

Data from 1 participant could not be assessed because of technical problems with the SenseWear armband. Figure 4, which portrays effects as a function of time of day, shows that both dronabinol and marijuana significantly increased mean heart rate throughout the day (except for the morning, when low-dose dronabinol did not have a significant effect). Marijuana but not dronabinol produced small but significant increases in mean skin temperature. In the morning, high-dose marijuana increased skin temperature by 0.4°C (3.9%,  $F = 7.89$ ;



**FIGURE 2.** Selected mean subjective effects ratings as a function of marijuana (MJ) and dronabinol (Dro-nab) dose (see legend for Fig. 1 for details).



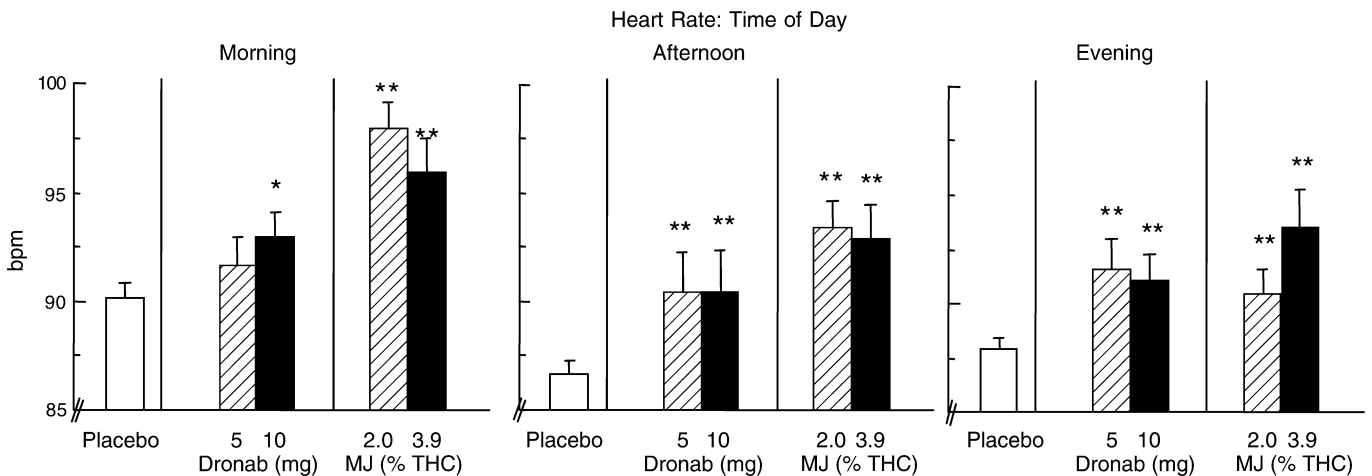
**FIGURE 3.** Mean total time spent asleep using the Nightcap sleep monitoring system (upper left corner, n = 7) and based on subjective estimates of time spent asleep (upper right corner, n = 10). Bottom figures portray selected mean sleep ratings (see legend for Fig. 1 for details). Dronab indicates dronabinol; MJ, marijuana.

$P < 0.01$ ). In the afternoon, both doses of marijuana increased skin temperature by  $0.4^{\circ}\text{C}$  (2.0%,  $F = 10.69$ ; 3.9%,  $F = 8.05$ ;  $P < 0.01$ ).

**Over-the-Counter Medication**

Although not a primary outcome measure, over-the-counter (OTC) medication administration (as needed) was monitored during the study. A disproportionate number of

OTC requests occurred during 16 days of placebo administration (n = 34 requests) compared with 16 days of active cannabinoid administration (n = 11 requests). During placebo administration, 56% (19 of 34) of the OTC requests were for gastrointestinal complaints (nausea, diarrhea, and stomach upset). During dronabinol or marijuana administration, only 9% (1 of 11) of the requests were for gastrointestinal complaints.



**FIGURE 4.** Mean heart rate (n = 9) as a function of time of day and marijuana and dronabinol dose: morning (08:30 AM to 11:59 AM), afternoon (12:00 PM to 4:59 PM), and evening (5:00 PM to 11:30 PM) (see legend for Fig. 1 for details). bpm indicates beats per minute; Dronab, dronabinol; MJ, marijuana.

## DISCUSSION

This study assessed the effects of 2 doses of oral dronabinol and smoked marijuana on food intake within the context of a wide range of behaviors in HIV-positive marijuana smokers. As compared with placebo, both doses of marijuana and dronabinol significantly increased daily caloric intake. For the high-dose dronabinol and marijuana conditions, this resulted in a significant increase in body weight within 4 days (>1 kg). Increased food intake paralleled increased ratings of intoxication for all cannabinoid conditions, except for the low dose of dronabinol (5 mg). Participants reported experiencing a strong drug effect from marijuana and high-dose dronabinol, and the experience was rated positively (eg, increased ratings of good drug effect, friendly, mellow). Although marijuana (2.0%) significantly increased ratings of anxiety (see Fig. 2), there was little evidence otherwise of discomfort or poor tolerability for any cannabinoid condition. Further, the intoxication was not associated with cognitive impairment; neither marijuana nor dronabinol altered performance on any of the psychomotor or memory tasks as compared with placebo. Thus, these data suggest that for HIV-positive marijuana smokers, dronabinol and marijuana produce comparable increases in food intake and improve mood without producing disruptions in psychomotor functioning; marijuana has the added benefit of improving ratings of sleep.

Dronabinol and marijuana increased daily food intake by increasing the number of times participants ate throughout the day, without altering the number of calories consumed during each eating occasion. This pattern is consistent with data from healthy marijuana smokers showing that marijuana selectively increased snack but not meal intake.<sup>41,42</sup> Both dronabinol and marijuana tended to increase the proportion of daily calories derived from fat while decreasing protein intake. Earlier data in HIV-positive participants showed that cannabinoids selectively increased body fat rather than lean muscle mass, perhaps reflecting increased caloric intake and relative fat intake.<sup>22</sup> An ongoing study is evaluating the stability of dronabinol's effect on food intake by administering capsules daily for several weeks.

The failure of cannabinoids to alter performance on cognitive tasks in this population is also consistent with the findings of a range of studies. Under baseline conditions, marijuana smokers often perform worse on cognitive tasks than nonmarijuana smokers.<sup>43</sup> Yet, compared with placebo, acute marijuana or dronabinol administration rarely disrupts cognitive task performance in marijuana smokers, even at doses that produce substantial intoxication.<sup>25,27,28,33,44</sup> Although individuals who do not smoke marijuana may show disrupted cognitive performance after cannabinoid administration,<sup>45</sup> the present data indirectly suggest that tolerance selectively develops to the cognitive effects of marijuana and dronabinol.

Overall, the present findings support the clinical utility of dronabinol in HIV-positive marijuana smokers and contrast with reports suggesting that it is too poorly tolerated or unreliable to be clinically useful.<sup>46,47</sup> The dronabinol data are dose dependent and do not show large inter-individual variability, indicating that the effects are reliable. In addition,

current marijuana smokers are not discomfited by dronabinol effects and have little difficulty in tolerating daily doses up to 8 times larger than those recommended for appetite enhancement, consistent with earlier studies.<sup>25–28,30,39,48</sup> Even though the recommended dose for dronabinol starts at 2.5 mg administered 2 times daily, marijuana smokers are unlikely to experience a clinical effect at a low-dose range.<sup>2,49</sup> Physicians are often unaware of their patients' marijuana use.<sup>50</sup> However, the present data illustrate the importance of discussing marijuana smoking patterns with patients when recommending dronabinol dosing regimens.

Smoked marijuana also has clear medical benefit in HIV-positive marijuana smokers by increasing food intake and improving mood and objective and subjective sleep measures. Although marijuana's effects on food intake and appetite were largely dose related, its intoxicating effects were often not, which may indicate dose titration. Earlier studies showed that experienced marijuana smokers inhale greater volumes of sidestream air with more potent marijuana.<sup>51</sup> The fact that ratings of high and "good marijuana effect" were nearly identical for the 2.0% and 3.9% marijuana cigarettes suggests that the participants adjusted their smoking topography to achieve a desired mood.

It has been reported that among HIV-positive patients who had tried dronabinol and smoked marijuana, 93% reported preferring marijuana.<sup>6</sup> Yet, expectations exert a powerful effect on drug response,<sup>52</sup> and that study was not double-blind. Maintaining double-blind conditions with cannabinoids is difficult,<sup>53</sup> and a considerable strength of the present study is that the blind was maintained: the capsules and marijuana were administered repeatedly throughout the day, but only 1 drug was active at a time. Thus, participants rated placebo marijuana as intoxicating when they had taken active dronabinol (10 mg), and reported "liking" placebo capsules on days when they had smoked active marijuana. Participants were not aware which drug was producing a positive effect. By removing this confound, the pharmacologic effects of dronabinol and marijuana could be dissociated from their expected effects.

One potential confound in data interpretation may be the onset of cannabinoid withdrawal during the placebo phases that followed 4 days of active marijuana or dronabinol. There was little evidence that withdrawal occurred in the present design, however. First, only half of the placebo phases followed an active marijuana or dronabinol condition (see Table 2). Second, cannabinoid withdrawal would be associated with increased ratings of anxiety, sleep disturbance, irritability, and restlessness,<sup>25,33</sup> which did not occur. The participants in the present study were lighter marijuana smokers and received lower daily doses of dronabinol and marijuana than those in withdrawal studies, which likely accounts for the absence of marijuana withdrawal symptoms. Third, sleep ratings were largely comparable in the placebo and active dronabinol conditions and were only improved by high-dose marijuana, suggesting that this effect reflected marijuana's direct effects on sleep rather than a reversal of a withdrawal symptom. Similarly, participants requested 6 times more OTC medication for gastrointestinal issues during the placebo phase than during active dronabinol or marijuana conditions. Symptoms of nausea and diarrhea are not typically associated with marijuana



withdrawal and were likely lower during active cannabinoid conditions because they were relieved by dronabinol and marijuana.

Although it may seem that a study limitation was that plasma THC levels were not obtained, this measure has not been shown to predict food intake or subjective effects poorly.<sup>17,54,55</sup> Dronabinol produces much lower THC titers than smoked marijuana at doses that produce comparable psychoactive effects. In heavy marijuana smokers, dronabinol (20 mg) and marijuana (3.1%) produced identical peak ratings of “high” but marijuana resulted in peak plasma THC levels 400-fold higher than dronabinol (Hart, Haney, and Foltin, 2004, unpublished data).<sup>30</sup> The effects of THC on nausea and emesis are positively associated with intoxication.<sup>56</sup> Thus, it is more clinically relevant to compare the effects of dronabinol and marijuana on food intake and mood than on THC titers.

Along similar lines, a potential criticism may be that the strength of the study marijuana was lower than the average marijuana strength (4.0% to 5.1% THC) sold on New York City streets.<sup>57,58</sup> Although more potent marijuana is available, marijuana cost increases as a function of potency. All the study participants were on a limited income and did not report regular access to high-potency marijuana. More importantly, the study marijuana consistently produced robust increases in marijuana ratings and food intake, demonstrating that the doses of marijuana and the doses of dronabinol were well matched and comparable for this population.

To conclude, this study was designed to provide a comprehensive assessment of smoked marijuana and oral dronabinol effects in HIV-positive marijuana smokers using controlled and relatively naturalistic conditions. The data demonstrate that over 4 days of administration, smoked marijuana and oral dronabinol produced a similar range of positive effects: increasing food intake and body weight and producing a “good effect” without producing uncomfortable levels of intoxication or impairing cognitive function. Although HIV-positive nonmarijuana smokers can experience confusion and anxiety at even low dronabinol doses, marijuana smokers are less likely to find effects such as intoxication and dry mouth untenable than nonsmokers.<sup>19,21</sup> With the understanding that further studies are needed to replicate these findings, this study demonstrates that for HIV-positive individuals who currently smoke marijuana and who can tolerate oral medications, high doses of dronabinol (8 times the standard dose) are as effective and well tolerated as marijuana. Thus, the argument that dronabinol is not clinically useful because of its slow onset and long duration of action is not applicable to marijuana smokers.

#### ACKNOWLEDGMENTS

The authors thank Brooke Roe, Susan Loftus, Diana Paksarian, Lialah Barnett, Jana Colley, Kelly Green, Martin McElhiney, PhD, and Judy Chiu for their excellent assistance in completing this research. They also thank the US National Institute on Drug Abuse and the National Center for Complementary and Alternative Medicine (grant DA 09236) for their support and for providing study marijuana.

#### REFERENCES

1. Institute of Medicine. *Marijuana and Medicine: Assessing the Science Base*. Washington, DC: National Academy Press; 1999.
2. Plasse TF, Gorter RW, Krasnow SH, et al. Recent clinical experience with dronabinol. *Pharmacol Biochem Behav*. 1991;40:695–700.
3. Prentiss D, Power R, Balmas G, et al. Patterns of marijuana use among patients with HIV/AIDS followed in a public health care setting. *J Acquir Immune Defic Syndr*. 2004;35:38–45.
4. Woolridge E, Barton S, Samuel J, et al. Cannabis use in HIV for pain and other medical symptoms. *J Pain Symptom Manage*. 2005;29:358–367.
5. Braitstein P, Kendall T, Chan K, et al. Mary-Jane and her patients: sociodemographic and clinical characteristics of HIV-positive individuals using medical marijuana and antiretroviral agents. *AIDS*. 2001;12:532–533.
6. Ware MA, Rueda S, Singer J, et al. Cannabis use by persons living with HIV/AIDS: patterns and prevalence of use. *J Cannn Therapeut*. 2003;3:3–15.
7. Aggarwal S, Carter G, Steinborn J. Clearing the air: what the latest Supreme Court decision regarding medical marijuana really means. *American Journal of Hospice and Palliative Medicine*. 2005;22:327–329.
8. Okie S. Medical marijuana and the Supreme Court. *N Engl J Med*. 2006;353:648–651.
9. Crippa JA, Zuardi AW, Garrido GEJ, et al. Effects of cannabidiol (CBD) on regional cerebral blood flow. *Neuropsychopharmacology*. 2004;29:417–426.
10. Varvel SA, Wiley JL, Yang R, et al. Interaction between THC and cannabidiol in mouse models of cannabinoid activity. *Psychopharmacology (Berl)*. 2006;186:226–234.
11. Ilan AB, Gevins A, Coleman M, et al. Neurophysiological and subjective profile of marijuana varying concentration of cannabinoids. *Behav Pharmacol*. 2005;16:487–496.
12. Leweke FM, Schneider U, Radwan M, et al. Different effects of nabilone and cannabidiol on binocular depth inversion in man. *Pharmacol Biochem Behav*. 2000;66:175–181.
13. Strasser F, Luftner D, Possinger K, et al. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the Cannabis-in-Cachexia Study Group. *J Clin Oncol*. 2006;24:3394–3400.
14. Taylor DR, Hall W. Respiratory health effects of cannabis: position statement of the Thoracic Society of Australia and New Zealand. *Int Med J*. 2003;33:310–313.
15. Polen MR, Sidney S, Tekawa IS, et al. Health care use by frequent marijuana smokers who do not smoke tobacco. *West J Med*. 1993;158:596–601.
16. Calhoun SR, Galloway GP, Smith DE. Abuse potential of dronabinol (Marinol). *J Psychoactive Drugs*. 1998;30:187–196.
17. Agurell S, Hallidin M, Lindfren J, et al. Pharmacokinetics and metabolism of  $\Delta^1$  tetrahydrocannabinol and other cannabinoids with emphasis on man. *Pharmacol Rev*. 1986;38:21–43.
18. Grinspoon L, Bakalar J. *Marijuana, the Forbidden Medicine*. New Haven, CT: Yale University Press; 1993.
19. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage*. 1995;10:89–97.
20. Beal JE, Olson R, Lefkowitz L, et al. Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. *J Pain Symptom Manage*. 1997;14:7–14.
21. Timpone JG, Wright DJ, Li N, et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. The DATRI 004 Study Group. Division of AIDS Treatment Research Initiative. *AIDS Res Hum Retroviruses*. 1997;13:305–315.
22. Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection. *Ann Intern Med*. 2003;139:258–266.
23. Kosel BW, Aweeka FT, Benowitz NL, et al. The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. *AIDS*. 2002;16:543–550.

24. Bredt BM, Higuera-Alhino D, Shade SB, et al. Short-term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients. *J Clin Pharmacol*. 2002;42:82S–89S.
25. Haney M, Ward AS, Comer SD, et al. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology (Berl)*. 1999a;141:385–394.
26. Haney M, Bisaga A, Foltin RW. Interaction between naltrexone and oral THC in heavy marijuana smokers. *Psychopharmacology (Berl)*. 2003;166:77–85.
27. Haney M, Hart CL, Vosburg SK, et al. Marijuana withdrawal in humans: effects of oral THC or divalproex. *Neuropsychopharmacology*. 2004;29:158–170.
28. Haney M, Rabkin J, Gunderson E, et al. Dronabinol and marijuana in HIV+ marijuana smokers: acute effects on caloric intake and mood. *Psychopharmacology (Berl)*. 2005;181:170–178.
29. Haney M. Opioid antagonism of cannabinoid effects: differences between marijuana smokers and nonmarijuana smokers. *Neuropsychopharmacology*. 2007;32:1391–1403.
30. Hart CL, Ward AS, Haney M, et al. Comparison of smoked marijuana and oral  $\Delta^9$ -THC in humans. *Psychopharmacology (Berl)*. 2002b;164:407–415.
31. Martin BR. Medical marijuana—moving beyond the smoke. *Lancet*. 2002;360:4–5.
32. Mason AP, McBay AJ. Cannabis: pharmacology and interpretation of effects. *J Forensic Sci*. 1985;30:615–631.
33. Haney M, Ward AS, Comer SD, et al. Abstinence symptoms following smoked marijuana in humans. *Psychopharmacology (Berl)*. 1999b;141:395–404.
34. Foltin RW, Brady JV, Fischman MW, et al. Effects of smoked marijuana on social interaction in small groups. *Drug Alcohol Depend*. 1987;20:87–93.
35. Heatherington M, Rolls BJ. Methods of investigating human eating behavior. In: Toates F, Rowland N, eds. *Feeding and Drinking*. Amsterdam: Elsevier; 1987:77–109.
36. Foltin RW, Haney M, Comer SD, et al. Effect of fenfluramine on food intake, mood and performance of humans living in a residential laboratory. *Physiol Behav*. 1996;59:295–305.
37. Ajilore O, Stickgold R, Rittenhouse CD, et al. Nightcap: laboratory and home-based evaluation of a portable sleep monitor. *Psychophysiology*. 1995;32:92–98.
38. Ellis BW, Johns MW, Lancaster R, et al. The St. Mary's hospital sleep questionnaire. *Sleep*. 1981;4:93–97.
39. Hart CL, Haney M, Vosburg SK, et al. Reinforcing effects of oral  $\Delta^9$ -THC in male marijuana smokers in a laboratory choice procedures. *Psychopharmacology (Berl)*. 2005;181:237–243.
40. McLaren DS. *Nutrition and Its Disorders*. 2nd ed. New York: Churchill Livingstone; 1976.
41. Foltin RW, Brady JV, Fischman MW. Behavioral analysis of marijuana effects on food intake in humans. *Pharm Biochem Behav*. 1986;25:577–582.
42. Foltin RW, Fischman MW, Byrne MF. Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. *Appetite*. 1988;11:1–14.
43. Pope HG Jr, Gruber AJ, Hudson JI, et al. Neuropsychological performance in long-term cannabis users. *Arch Gen Psychiatry*. 2001;58:909–915.
44. Hart CL, van Gorp W, Haney M, et al. Effects of acute smoked marijuana on complex cognitive performance. *Neuropsychopharmacology*. 2001;25:757–765.
45. Ramaekers JG, Kauert G, van Ruitenbeek P, et al. High-potency marijuana impairs executive function and inhibitory motor control. *Neuropsychopharmacology*. 2006;31:2296–2303.
46. Hazekamp A, Ruhaak R, Zuurman L, et al. Evaluation of a vaporizing device (volcano) for the pulmonary administration of tetrahydrocannabinol. *J Pharm Sci*. 2006;95:1308–1317.
47. Williamson EM, Evans FJ. Cannabinoids in clinical practice. *Drugs*. 2000;60:1303–1314.
48. Hart CL, Haney M, Ward AS, et al. Effects of oral THC maintenance on smoked marijuana self-administration. *Drug Alcohol Depend*. 2002a;67:301–309.
49. Ben Amar M. Cannabinoids in medicine: a review of their therapeutic potential. *J Ethnopharmacol*. 2006;105:1–25.
50. Furler MD, Einarson TR, Milson M, et al. Medicinal and recreational marijuana use by patients infected with HIV. *AIDS Patient Care STDs*. 2004;18:215–228.
51. Herning RI, Hooker WD, Jones RT. Tetrahydrocannabinol content and differences in marijuana smoking behavior. *Psychopharmacology (Berl)*. 1986;90:160–162.
52. Kirk JM, De Wit H. Responses to oral  $\Delta^9$ -tetrahydrocannabinol in frequent and infrequent marijuana users. *Pharmacol Biochem Behav*. 1999;63:137–142.
53. Wingerchuk D. Cannabis for medical purposes: cultivating science, weeding out the fiction. *Lancet*. 2004;364:315–316.
54. Cocchetto DM, Owens SM, Perez-Reyes M, et al. Relationship between plasma delta-9-tetrahydrocannabinol concentration and pharmacologic effects in man. *Psychopharmacology (Berl)*. 1981;75:158–164.
55. Mattes RD, Engelman K, Shaw LM, et al. Cannabinoids and appetite stimulation. *Pharmacol Biochem Behav*. 1994;49:187–195.
56. Chang AE, Shiling DJ, Stillman RC, et al. Delta-9-tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate. *Ann Intern Med*. 1979;91:819–824.
57. El Sohly MA, Feng S, Murphy TP, et al. Delta 9-tetrahydrocannabivarin (delta 9-THCV) as a marker for the ingestion of cannabis versus Marinol. *J Anal Toxicol*. 1999;23:222–224.
58. Compton WM, Grant BF, Colliver JD, et al. Prevalence of marijuana use disorders in the United States: 1991–1992 and 2001–2002. *JAMA*. 2004;291:2114–2121.