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ORIGINAL INVESTIGATION

**Margaret Haney · Judith Rabkin · Erik Gunderson · Richard W. Foltin**

# Dronabinol and marijuana in HIV+ marijuana smokers: acute effects on caloric intake and mood

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**Abstract** *Rationale:* No studies to date have directly compared the tolerability and efficacy of smoked marijuana and oral dronabinol in HIV+ marijuana smokers. *Objectives:* The aim of this study was to compare dronabinol (0, 10, 20, 30 mg p.o.) and marijuana [0.0, 1.8, 2.8, 3.9% $\Delta^9$-tetrahydrocannabinol (THC)] in two samples of HIV+ marijuana smokers: those with ($n$=15) and those without ($n$=15) a clinically significant loss of muscle mass (<90% body cell mass/height), which is one component of AIDS wasting. *Methods:* Mood, physical symptoms, self-selected food intake, cardiovascular data, and cognitive task performance were measured before and repeatedly after dronabinol and marijuana administration in eight 7-h sessions. Marijuana and dronabinol were administered in randomized order using a within-subject, staggered, double-dummy design. *Results:* As compared to placebo, (1) marijuana (1.8, 2.8, 3.9% THC) and the lower dronabinol doses (10, 20 mg) were well tolerated (e.g., few physical symptoms, significant increases in ratings of "good drug effect") in both groups of participants; the highest dose of dronabinol (30 mg) was poorly tolerated in a subset of participants; (2) marijuana and dronabinol significantly increased caloric intake in the low bioelectrical impedance analysis (BIA) group but not in the normal BIA group; and (3) drug effects on cognitive performance were minor. *Conclusions:* These data suggest that for experienced marijuana smokers with clinically significant muscle mass loss, both dronabinol (at acute doses at least four to eight times the current recommendation) and marijuana produce substantial and comparable increases in food intake without producing adverse effects.

**Keywords** Cannabinoids · AIDS · THC · Appetite

All authors are associated with the Department of Psychiatry at the College of Physicians and Surgeons of Columbia University.

M. Haney (✉) · J. Rabkin · E. Gunderson · R. W. Foltin
New York State Psychiatric Institute,
College of Physicians and
Surgeons of Columbia University,
1051 Riverside Dr., Unit 120,
New York, NY, 10032, USA
e-mail: mh235@columbia.edu
Tel.: +1-212-5436539
Fax: +1-212-5435991

## Introduction

Although antiretroviral therapy has been associated with a dramatic decline in AIDS-related morbidity and wasting (Palella et al. 1998; Abrams 2000), a substantial proportion of people with HIV remain unable to maintain normal body weight (Dworkin and Williamson 2003). Some individuals report using cannabinoids, i.e., synthetic or plant-derived substances acting at the cannabinoid receptor, to enhance appetite and to counter the nausea, anorexia, and stomach upset associated with the disease and with antiretroviral therapy, yet little has been published about the clinical effectiveness of these drugs in an HIV+ population (Institute of Medicine 1999). In fact, the public policy debate regarding the medical use of marijuana has been conducted largely in the absence of data typically used to evaluate pharmacotherapies (Martin 2002).

Currently, there are two cannabinoids of primary interest for clinical use: smoked marijuana and oral $\Delta^9$-tetrahydrocannabinol (THC, dronabinol, Marinol), which is the primary psychoactive component of marijuana. The benefits of dronabinol are that it is safe, standardized doses can be delivered, it is FDA-approved for the treatment of nausea and appetite loss, and it is rarely abused (Calhoun et al. 1998). However, dronabinol has a slow onset (peak effects in approximately 120 min) and long duration of action (Agurell et al. 1986), which may make it difficult to titrate dose to achieve the desired effect (Grinspoon and Bakalar 1993). In addition, nauseated patients may have difficulty tolerating an oral medication. Smoked marijuana has a rapid onset of effect (peak effects in 20 min), which allows for dose titration and immediate symptom relief. Yet, smoking is a crude cannabinoid delivery system, with

respiratory risks similar to those associated with tobacco cigarette use (Institute of Medicine 1999; Wu et al. 1988; Polen et al. 1993).

Studies on the effects of cannabinoids in patients with HIV are particularly important given that they constitute the largest group using dronabinol and marijuana for medicinal reasons (Institute of Medicine 1999; Plasse et al. 1991), and a considerable proportion of those with HIV smoke marijuana, e.g., 23% of patients with HIV in public health clinics in California reported smoking marijuana within the past month (Prentiss et al. 2004). Yet there are a large number of unanswered questions about the effect of marijuana and dronabinol in this population. First, given that dronabinol may be poorly tolerated, it is important to compare the effect of marijuana and dronabinol on food intake within the context of other behavioral effects. A recent between-groups study in patients with HIV (who were not current marijuana smokers) demonstrated that both dronabinol (2.5 mg TID) and marijuana (3.95% THC TID) resulted in more weight gain than placebo (Abrams et al. 2003). Yet the effect of a range of dronabinol and marijuana doses across multiple dimensions of behavior (eating topography, mood, physical symptoms, and cognitive performance) within the same individual has not been evaluated.

Second, none of the studies conducted in patients with HIV to date have specifically included current marijuana smokers, although this is precisely the population most relevant to the issue of medical marijuana. In non-marijuana smokers, dronabinol (2.5 mg b.i.d.) administered for over 6 weeks improved mood and decreased nausea, but also produced mental cloudiness and confusion, which decreased patient compliance and resulted in high drop-out rates (Plasse et al. 1991; Beal et al. 1995, 1997). However, healthy marijuana smokers tolerate large acute doses of dronabinol (20, 30 mg) without difficulty (Foltin et al. 1986, 1988; Haney et al. 1999a,b, 2003; Hart et al. 2002b). At these doses, body weight increased by 2–3 kg in just 4 days. Thus, the question of relative tolerability and efficacy needs to be determined in the population most likely to be using cannabinoids medically: HIV+ marijuana smokers.

The third question to be addressed in the present study is whether the effects of dronabinol and marijuana vary as a function of lean muscle mass. HIV+ marijuana smokers with a clinically significant muscle mass loss (<90% body cell mass/height), as assessed by bioelectrical impedance analysis (BIA), were compared to those with normal muscle mass. Loss of muscle mass is one component of AIDS wasting. Although neither marijuana nor dronabinol is predicted to restore lean muscle mass, the Institute of Medicine considers it a priority to increase body weight in individuals who have symptoms of wasting (Institute of Medicine 1999). Thus, both populations of HIV+ marijuana smokers were recruited in order to evaluate the effects of dronabinol and marijuana in both of these clinically relevant populations.

## Materials and methods

### Participants

Table 1 describes the demographic information for the 30 research volunteers who participated in the study. Five additional volunteers (two low BIA, three normal BIA) started the protocol but discontinued for personal reasons or due to noncompliance with the protocol. One volunteer completed the study but then revealed that he had stopped taking his HIV medications, so his data were not included. Before study onset, participants provided a detailed drug and medical history, received medical and psychiatric evaluations, and signed consent forms detailing all aspects of the research. All volunteers viewed a list of the foods that were to be available during study sessions, and those enrolled reported that most of the items were acceptable to them. Body mass index (kilograms per square meter) and body composition, measured by BIA (Model BIA 101Q, RJL Systems, Clinton Township, MI), were calculated during screening and on the eighth session day. BIA measures the body's electrical conductivity to determine the type, volume, and distribution of fluid and tissue. BIA values are a ratio of body cell mass divided by height (inches) and adjusted for age, sex, and ethnicity. Those less than 90% of ideal body cell mass based on HIV-validated norms were placed in the low BIA group (Kotler et al. 1996). Fifteen participants had a BIA greater than 90% (normal BIA) and 15 had a BIA less than 90% (low BIA).

The inclusion criteria were as follows: 21–50 years of age, prescribed at least two antiretroviral medications (verified by examination of medications in their original containers), 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.

**Table 1** Demographic characteristics of study participants

| | Low BIA | Normal BIA |
|---|---|---|
| Sex (female/male) | 3/12 | 0/15 |
| Age (years) | 36±7 | 36±5 |
| Race/ethnicity (black/white/Hispanic) | 6/6/3 | 9/3/3 |
| Education (years) | 13±2 | 13±3 |
| Viral suppression (%) | 53 | 47 |
| CD4 cell count (cells/mm$^3$) | 428±321 | 449±301 |
| Years since HIV diagnosis | 7.0±5.0 | 7.3±5.3 |
| BIA | 0.81±0.04 | 1.03±0.1 |
| BMI | 21.5±1.8 | 25.2±2.1 |
| Marijuana use (no. days per week) | 6±2 | 5±2 |
| Marijuana cigarettes per day | 3±2 | 3±1 |
| Years of marijuana use | 12.2±8.3 | 10.8±2.6 |
| Cigarette smokers (*n*) | 12 | 7 |
| Cigarettes per day | 12±3 | 5±2 |
| Alcohol, drinks/week | 4±2 | 6±4 |

Data are presented as means±SD or as frequency or percentage
*BIA* bioelectric impedance analysis (body cell mass/inches), *BMI* body mass index (kilograms per square meter)

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, measuring cocaine, opiates, methamphetamine, benzodiazepines, and cannabinoid metabolites, was conducted at each screening visit and on each day of study participation. Ten of the 30 participants (six low BIA, four normal BIA) reported occasional intranasal cocaine use, but all were able to maintain abstinence during study participation, as verified by urine toxicology. Note that one of the 30 participants reported purchasing marijuana through buyers clubs in New York City; the remaining 29 participants purchased their marijuana on the street which, based on material confiscated within the past 5 years, has a typical strength of 4.0–5.1% THC (ElSohly et al. 1999; Compton et al. 2004). Although marijuana potency can be much higher, cost increases as a function of potency, and none of the participants studied in this sample reported using high-potency marijuana on a regular basis.

Participants were instructed that the study objective was to compare the effects of marijuana and dronabinol in individuals with HIV. They were told that at each session they would take two capsules containing placebo or various strength dronabinol pills and that they would take three puffs from a single marijuana cigarette containing varying concentrations of THC. The New York State Psychiatric Institute's Institutional Review Board approved all procedures.

## Design

Before study onset, participants received one or two training sessions on the computerized tasks, during which no drugs were administered. Participants then completed eight experimental sessions over the course of 3–4 weeks. Sessions were limited to at most three times per week, with a minimum of 1 day between sessions to prevent carryover effects. The schedule for each session is illustrated in Table 2. Experimental sessions began at 0900 hours and lasted until 1600 hours. Participants were instructed not to eat breakfast before the session and to refrain from using illicit drugs (other than possibly marijuana) for the duration of the study. Alcohol use was to be excluded 24 h before or following a laboratory session, and marijuana use the morning of the session was prohibited. A urine specimen was collected and a breath alcohol test was conducted before each session to confirm compliance. Sessions were cancelled if there was evidence of illicit drug use or alcohol or marijuana use that morning.

Participants were served a standardized breakfast (e.g., bagel or cereal, juice, coffee/tea) and then, baseline cardiovascular measures, a balance task (the total number of seconds participants could balance for a maximum of 30 s on each foot) (Evans et al. 1994), questionnaires measuring mood and physical symptoms, and performance tasks were completed. Participants were administered dronabinol, and then smoked three timed puffs of a marijuana cigarette 1 h later (see below); participants and research assistants were blind to capsule and marijuana strength. Cardiovascular, subjective effects, and performance measures were completed at baseline and at 30- to 60-min intervals after capsule and marijuana administration (see Table 2). Detailed measures of food intake were recorded for 4 h, beginning 1 h after the marijuana administration (2 h after capsule administration). Specifically, participants received a box of food containing a variety of meal items (e.g., tuna, cheese, turkey, soup), snacks (e.g., cookies, fruit, ice cream, chips, candy bars) and beverages (e.g., soda, juice, water, ice tea) that could be consumed ad libitum. Frozen meal items (e.g., meat loaf, pasta, chicken, pizza) also became available by request at this time. To facilitate choice of frozen meals, a book containing package pictures of each item was provided. Additional units of any item

**Table 2** Time course of sessions

| Time | Event | Time | Event |
|---|---|---|---|
| -45 | Begin session | 120 | BP, MRF, VAS |
| | Weigh-in | | Food Available |
| | Breathalyzer, Urine Toxicology | 180 | BP, CRF, MRF, VAS |
| | Light Breakfast | | Performance Battery |
| | Balance, BP, VAS | 240 | BP |
| | Performance Battery | 270 | BP, VAS, Performance Battery |
| 0 | **Capsule** | 300 | BP |
| 30 | BP, CRF, VAS | 330 | CRF, MRF |
| 60 | **Marijuana** | | Delayed recall and recognition |
| 75 | CRF, MRF, HSQ | 360 | BP, HSQ, VAS |
| 90 | BP, VAS | | Performance Battery |
| | Performance Battery | | Field Sobriety |
| | Immediate Word Recall | | End session |

*BP* Blood pressure/heart rate, *VAS* Visual analog scale of subjective effects, *CRF* Capsule Rating Form, *HSQ* Hunger-Satiety Questionnaire

were available. Participants recorded the time and the portion size of any item they consumed under the observation of a research assistant.

Tobacco cigarette smokers were permitted to smoke at the same time points across sessions to minimize nicotine-withdrawal symptoms. At the end of each session, participants were required to pass a field sobriety task and the balance task. If behavior was impaired, participants remained at the laboratory until the drug effects subsided, or were sent home in a taxi. Participants were provided payment for subway fare at the end of each session and were instructed not to drive a car that day. Those who completed the study were paid $560 after their final session.

## Study medications

Marijuana and dronabinol dose order was randomized and counterbalanced across participants. Marijuana and dronabinol were administered using a staggered, double-dummy design in which no more than one dose of drug was active in a given session. Since the behavioral effects of dronabinol peak in 2–4 h (Mason and McBay 1985), capsule dosing preceded marijuana administration by 1 h to make it difficult for the participants to distinguish whether the marijuana or the dronabinol was active (Haney et al. 2004).

Dronabinol (0, 10, 20, 30 mg; Marinol, Unimed Pharmaceuticals, Inc, Buffalo Grove, IL) was packaged into size 00 opaque capsules with lactose filler by the Presbyterian Hospital Research Pharmacy. Although the recommended dronabinol dose for appetite stimulation is 2.5 mg b.i.d. (Plasse et al. 1991), higher doses were selected, based on our earlier studies showing that healthy marijuana smokers tolerate much higher doses of dronabinol (Haney et al. 1999a, 2004; Hart et al. 2002a); in this population, 3.1% THC marijuana cigarettes produce closely similar subjective effects as 20-mg dronabinol capsules (Hart et al. 2002b), justifying the range of marijuana and dronabinol doses currently tested.

Marijuana (0, 1.8, 2.8, 3.9% THC), provided by the National Institute of Drug Abuse was administered using a cued-smoking procedure, which produces reliable increases in heart rate and plasma $\Delta^9$-THC (Foltin et al. 1987). Participants were instructed through an intercom to "light the cigarette" (30 s), "prepare" (5 s), "inhale" (5 s), "hold smoke in lungs" (10 s), and "exhale." Participants smoked three puffs in this manner, with a 40-s interval between each puff. Since the color of marijuana leaves varies as a function of its THC content (Chait and Pierri 1989), cigarettes were rolled at both ends and were smoked through a hollow plastic cigarette holder so that the marijuana was not visible. Marijuana cigarettes were stored frozen in an airtight container and humidified at room temperature for 24 h before use.

## Subjective-effects questionnaires and performance tasks

### *Visual analog scales*

Participants completed a 50-item visual analog scale (VAS) at baseline and at 30- to 60-min intervals. The VAS consisted of a 100-mm line anchored with "not at all" at the left end and "extremely" at the right end, labeled with a range of moods and physical symptoms (Haney et al. 1999b).

### *Capsule rating form*

Participants completed a 5-item VAS, rating the strength of the drug effect, good effect, bad effect, willingness to take drug again, and drug liking from 45 to 150 min after the first capsule administration. In addition, participants were asked to indicate whether they thought the drug was most like a placebo, sedative, or stimulant.

### *Marijuana rating form*

Participants completed a 5-item VAS from 15 to 150 min after marijuana administration, rating the strength of the drug effect, good effect, bad effect, willingness to take drug again, and drug liking.

### *Hunger-satiety questionnaire*

Participants completed a 6-item VAS at baseline and 15 min after marijuana, rating how hungry, full, nauseated, thirsty they felt, as well as how strong the desire to eat was at that moment (Heatherington and Rolls 1987).

### *Performance battery*

Participants completed a four-item task battery, consisting of a 3-min digit–symbol substitution task (DSST), a 3-min repeated acquisition task, a 10-min divided attention task (DAT), and an immediate and a delayed digit-recall task. The battery measures various aspects of learning, memory, vigilance, and psychomotor performance (Foltin et al. 1996). Participants were instructed to complete each task as quickly and as accurately as possible.

### *Word recall/recognition task*

To assess immediate free recall, participants studied a list of 12 common nouns for 90 s and then wrote as many words as they could remember at 0.5 h after smoking marijuana. To assess delayed free recall, this task was re-

peated 4.5 h after marijuana, followed by a recognition test, in which participants were asked to identify the 12 words shown earlier from a list containing 48 words (Evans et al. 1998).

### *Physiological measures*

Heart rate and blood pressure were measured using a Sentry II vital signs monitor (Model 6100, NBS Medical Services, Costa Mesa, CA) at baseline and at 30 to 60 min intervals.

### Data analysis

Repeated measures analyses of variance (ANOVAs) were used to compare subjective-effects ratings, task performance, drug-effects ratings, caloric intake, and cardiovascular measures. There were two within-group factors (drug: 0, 10, 20, 30 mg dronabinol, 0.0, 1.8, 2.8, 3.8% THC marijuana, and time within session: baseline through 360 min post-capsule). Six planned comparisons were completed for each measure, comparing each dronabinol and marijuana dose condition with placebo (data from the two placebo sessions were averaged). Due to the number of subjective-effects measures, $p$ values less than 0.01 were considered statistically significant. Huynh–Feldt corrections were used, when appropriate.

## Results

### Food intake

Figure 1, which portrays average caloric intake as a function of marijuana and dronabinol condition in the low and normal muscle mass groups, shows that the low BIA group consumed significantly more calories in each dronabinol condition ($df$=1,98 for all planned contrasts: 10 mg: $F$=14.32; 20 mg: $F$=15.47; 30 mg: $F$=7.21, $p$<0.01) and in two marijuana conditions (1.8%: $F$=9.70; 3.9%: $F$=7.56, $p$<0.01) compared with the placebo condition. For the normal BIA group, who consumed approximately 200 calories more under baseline conditions, neither marijuana nor dronabinol significantly affected caloric intake. The proportion of macronutrients consumed was not altered by drug condition for either group: participants derived approximately 52% of their calories from carbohydrates, 36% from fat and 12% from protein, regardless of marijuana or dronabinol dose.

### Subjective-effects ratings

Figure 2 portrays the time course of ratings of "high" for each drug dose for the low and normal muscle mass groups. Each drug condition, except for the lowest dose of dronabinol (10 mg) increased ratings of "high" for the low BIA group (1.8%: $F$=9.54; 2.8%: $F$=8.17; 3.9%: $F$=24.24; 20 mg: $F$=18.88; 30 mg: $F$=14.82, $p$<0.01) and the normal BIA group (1.8%: $F$=17.92; 2.8%: $F$=23.29; 3.9%: $F$=21.99; 20 mg: $F$=14.50; 30 mg: $F$=23.91, $p$<0.001). Ratings of "good drug effect" showed an identical pattern of effects. Peak subjective effects for marijuana occurred within 30 min of smoking, whereas peak effects of dronabinol occurred approximately 180 min following ingestion.

Table 3 portrays selected subjective effects averaged over the course of the session as a function of drug dose and participant group. Both groups reported feeling slightly sedated by dronabinol (low BIA, 10 mg: $F$=8.69; normal BIA, 30 mg: $F$=11.31, $p$<0.01), whereas the normal BIA group also felt sedated after smoking a 2.8% marijuana cigarette ($F$=10.76, $p$<0.005). The normal BIA

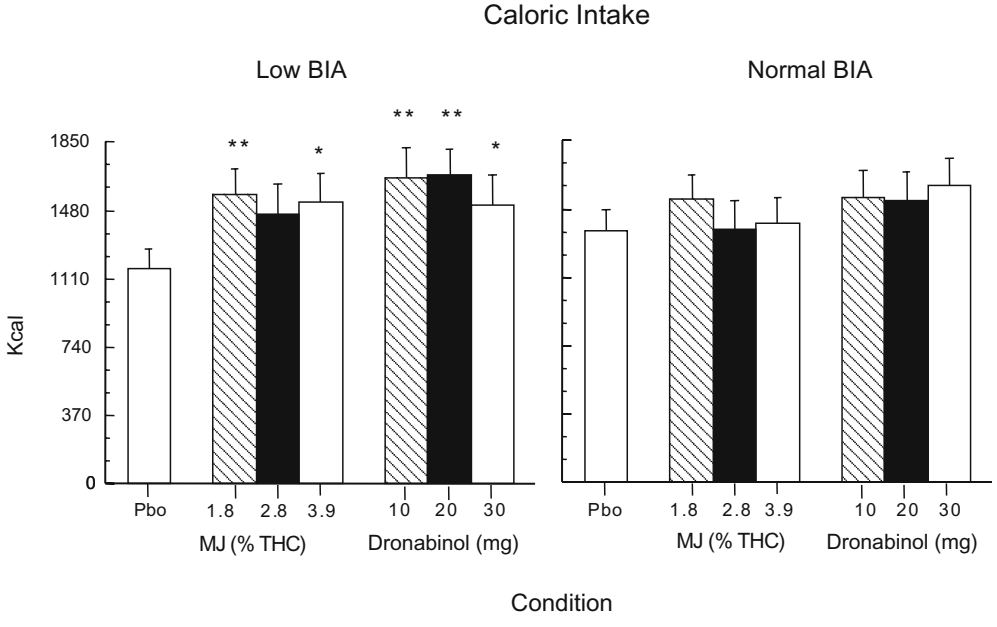


**Fig. 1** Mean caloric intake as a function of marijuana and dronabinol dose and muscle mass condition (low BIA, <90% body cell mass/height; normal BIA, >90% body cell mass/height). Placebo data represent the mean across two sessions. *Asterisks* denote a significant difference from placebo marijuana and dronabinol (*$p$<0.01; **$p$<0.005). *Error bars* represent one standard error of the mean (SEM)

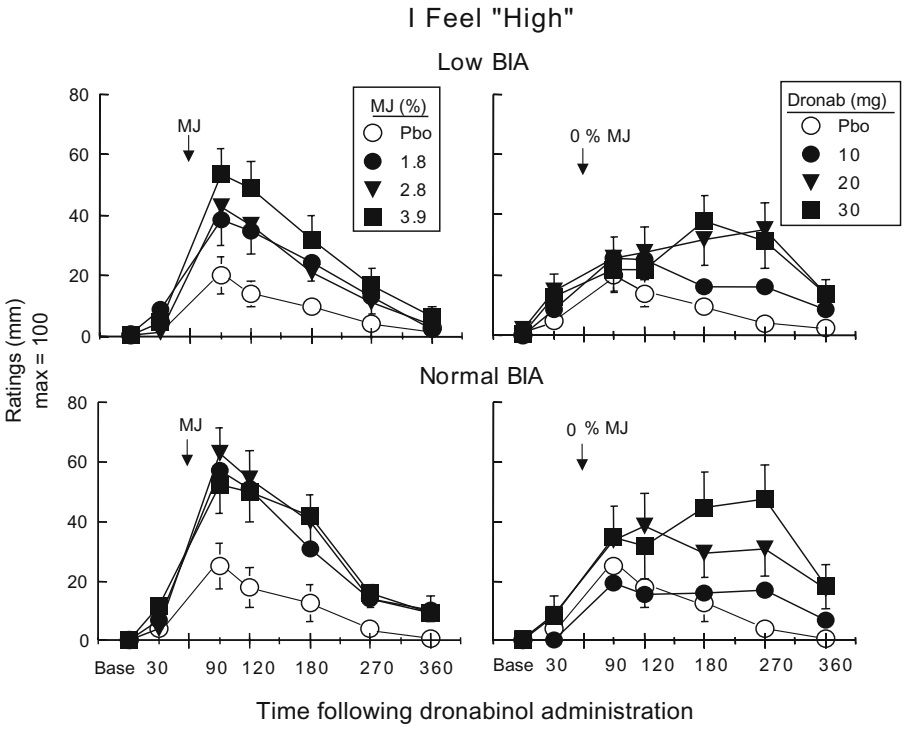


**Fig. 2** Ratings of "high" as a function of time, marijuana, and dronabinol dose and muscle mass condition. *Dronab* dronabinol. See Fig. 1 legend for details

group reported feeling stimulated by marijuana (2.8%: $F$=26.57; 3.9%: $F$=19.20, $p$<0.01) and dronabinol (20 mg: $F$=9.52, $p$<0.01). At the 30-mg dronabinol dose, the normal BIA group reported being more forgetful ($F$=10.17, $p$<0.01), withdrawn ($F$=11.73, $p$<0.001), and to be dreaming more ($F$=10.53, $p$<0.01). The highest dronabinol dose also produced small but significant increases in ratings of clumsy, heavy limbs, heart pounding, jittery, and decreases in ratings of energetic, social, and talkative in the normal BIA group ($p$<0.01; data not shown).

## Marijuana rating form and capsule rating form

On the Marijuana Rating Form, active marijuana increased ratings of good drug effect (2.8, 3.9% THC), strength (2.8,

**Table 3** Selected mean (± SEM) subjective-effects ratings as a function of dose and study group

| BIA | Placebo | Marijuana | | | THC | | |
|---|---|---|---|---|---|---|---|
| | | 1.8% | 2.8% | 3.9% | 10 mg | 20 mg | 30 mg |
| "Sedated" | | | | | | | |
| Low | 3.1 (0.6) | 8.5 (1.5) | 7.8 (1.7) | 10.6 (2.0) | ⇑11.9 (1.9)* | 7.9 (1.5) | 8.0 (1.6) |
| Normal | 3.3 (0.9) | 6.2 (1.4) | ⇑11.0 (2.2)** | 8.6 (1.9) | 4.9 (1.2) | 9.6 (1.8) | ⇑11.2 (2.3)** |
| "Stimulated" | | | | | | | |
| Low | 16.3 (1.1) | 20.0 (2.4) | 15.5 (2.3) | 23.0 (2.8) | 18.0 (2.4) | 20.3 (2.5) | 20.8 (2.5) |
| Normal | 5.5 (1.1) | 12.2 (2.2) | ⇑21.5 (2.9)** | ⇑19.1 (2.7)** | 9.6 (1.7) | ⇑15.1 (2.4)* | 14.0 (2.6) |
| "Forgetful" | | | | | | | |
| Low | 4.8 (0.6) | 6.2 (1.2) | 9.6 (1.7) | 7.6 (1.6) | 8.2 (1.4) | 9.8 (1.5) | 7.2 (1.2) |
| Normal | 11.0 (0.6) | 12.3 (2.7) | 13.6 (2.7) | 13.3 (2.4) | 8.9 (2.2) | 12.4 (2.6) | ⇑18.7 (3.0)* |
| "Withdrawn" | | | | | | | |
| Low | 3.7 (2.0) | 4.4 (0.9) | 5.8 (1.5) | 4.8 (1.0) | 4.7 (0.9) | 4.9 (1.1) | 6.0 (1.3) |
| Normal | 2.2 (1.2) | 3.5 (1.3) | 8.1 (1.8) | 5.4 (1.6) | 5.4 (1.7) | 6.3 (1.6) | ⇑11.1 (2.4)** |
| "Dreaming more" | | | | | | | |
| Low | 6.1 (3.3) | 8.8 (1.8) | 9.0 (2.1) | 5.7 (1.2) | 10.2 (1.9) | 6.6 (1.3) | 7.4 (1.6) |
| Normal | 7.7 (6.8) | 8.5 (2.5) | 7.4 (2.2) | 15.0 (2.9) | 7.8 (2.4) | 12.8 (2.8) | ⇑19.1 (3.3)* |

Ratings (0–100 mm, visual analog scale) averaged over the course of the 6.5-hour session. Placebo data represent the mean across two sessions. Arrows indicate the direction of the drug effect. Asterisks represent significant differences between placebo and dose condition *$p$<0.01; **$p$<0.005

3.9% THC), liking (3.9% THC), and desire to smoke again (3.9% THC) compared with placebo in the low BIA group ($p<0.01$; data not shown). These same ratings were increased by each active marijuana cigarette condition in the normal BIA group ($p<0.001$; data not shown). On the Capsule Rating Form, ratings of capsule strength were significantly increased by the highest dose of dronabinol in the low ($p<0.01$; data not shown) but not in the normal BIA group.

### Hunger and satiety questionnaire

The highest strength marijuana cigarette (3.95%) significantly increased ratings of dry mouth in both participant groups ($p<0.01$); ratings averaged 8–10 mm under placebo conditions and increased to 21–23 mm after the marijuana was smoked. The 3.95% marijuana condition also increased ratings of thirsty compared to placebo, from 15.9 to 24.4 mm, in the low BIA group ($p<0.004$).

### Performance effects

Marijuana did not significantly alter performance on any of the tasks compared to placebo for either group of participants. In the low BIA group, dronabinol (20 mg) produced small but significant decreases in the number of Digit Symbol Substitutions entered correctly (from 70.8 to 66.3; $p<0.01$), the number of 7-digit numbers entered in the Digit Recall Task (from 7.1 to 6.8; $p<0.01$), and in the maximum speed attained in the Divided Attention Task (from 4.7 to 4.0; $p<0.01$). For the normal BIA group, dronabinol (30 mg) significantly decreased the number of 7-digit numbers entered in the Digit Recall Task (from 5.4 to 4.7; $p<0.01$).

### Word recall/recognition task

Neither marijuana nor dronabinol significantly altered word recall or recognition in either BIA group.

### Cardiovascular effects

Blood pressure was not significantly affected by marijuana or dronabinol in either group. Baseline heart rate was comparable (72–74 bpm) in the low and normal BIA groups, but dronabinol increased heart rate for the normal BIA participants: heart rate was increased by approximately 5 bpm by 20 mg dronabinol ($p<0.01$) and by approximately 8 bpm by 30 mg dronabinol ($p<0.0001$).

### Side effects

In the low BIA group, three participants reported adverse effects: one was dizzy following placebo, one was nauseated following the 10-mg dronabinol dose and too intoxicated following the 30-mg dose, whereas in the third participant, the 20-mg dronabinol dose produced nausea and headache and the 30-mg dose produced an uncomfortable level of intoxication and vomiting. In the normal BIA group, five participants experienced adverse effects: one reported diarrhea following 3.9% marijuana, one reported nausea following placebo and headache following the 30-mg dronabinol dose, and three reported that the 30-mg dronainol dose produced an uncomfortable level of intoxication.

## Discussion

The present study assessed the acute effects of oral dronabinol and smoked marijuana on food intake, cognitive task performance, and mood in HIV+ marijuana smokers. As compared to placebo, both marijuana and dronabinol significantly increased caloric intake in volunteers with low muscle mass, but not in those with normal muscle mass. Both groups consumed a comparable number of calories following active marijuana or dronabinol (1400–1657 kcal in 4 h), but the low BIA group consumed approximately 200 fewer calories under placebo conditions than the normal BIA group. Thus, the appetite-enhancing effects of cannabinoids were significant for the volunteers with low muscle mass, who consumed less food under placebo conditions.

The intoxicating effects of dronabinol and marijuana did not vary as a function of muscle mass group, as both drugs produced comparable increases in ratings of "high" and "good drug effect." These effects were more rapid in onset and shorter in duration for marijuana compared to dronabinol, as predicted based on their rates of absorption (Agurell et al. 1986). Although dronabinol's long duration of action is argued to be a negative feature in the medical marijuana debates, current marijuana smokers had few difficulties with acute dronabinol doses (10, 20 mg) that were four to eight times larger than doses recommended for appetite enhancement. That is, both marijuana and dronabinol produced positive subjective-effects ratings, without increasing ratings of negative mood, (e.g., "bad drug effect," "miserable") as compared to placebo. By contrast, the highest dose of dronabinol (30 mg) produced at least one adverse effect (e.g., headache, nausea, over-intoxication) in 20% of the participants, suggesting that this dose may be poorly tolerated, even among marijuana smokers.

One concern with the therapeutic use of cannabinoids has been that they impair cognitive performance (Hall and Degenhardt 2003). For example, healthy, daily marijuana smokers score significantly worse on neuropsychological tests when compared to controls, or when compared to the same individuals after they were abstinent from marijuana for several weeks (Pope et al. 2001). Yet, acute dronabinol or marijuana did not have substantial effects on cognitive task performance in the present study as compared to placebo. Similar findings have been reported in healthy

marijuana smokers and indirectly suggest tolerance develops to the cognitive-impairing effects of cannabinoids (Haney et al. 1999a,b, 2004; Hart et al. 2001). Thus, chronic cannabinoid use may worsen overall performance compared to non-use, but acute marijuana or dronabinol administration does not worsen performance in those who currently smoke marijuana.

One strength of the current design was that the dosing procedures masked which drug was active. Expectations exert a powerful effect on drug response (Kirk and De Wit 1999), and by removing this confound, the pharmacological effects of dronabinol and marijuana could be dissociated from their expected effects. One limitation to the study design was that food intake was limited to a 4-h period, during which a variety of food was available. This may have contributed to large caloric intake under placebo conditions, potentially minimizing the appetite-enhancing effects of marijuana and dronabinol; many of the participants were on a limited income, and some reported using this opportunity to eat for free. A second limitation is that the study was designed to capture marijuana's peak mood and performance effects but may have missed marijuana's peak effects on food intake. Food became available when the effects of dronabinol were peaking (2 h post-capsule), whereas marijuana's peak effects occurred approximately 30 min earlier. Yet, Fig. 2 demonstrates that although marijuana's effects had peaked at 30 min, participants were almost equally "high" at the 1-h time point, when food became available. Thus, although both oral dronabinol and smoked marijuana significantly increased food intake relative to placebo, marijuana may have produced larger effects if food had become available immediately after the marijuana was smoked. An ongoing study will address these two limitations by comparing dronabinol and marijuana over several weeks in an inpatient setting.

Note that although it would seem like a logical study weakness to not compare plasma THC levels following dronabinol and marijuana, this measure has been shown to poorly predict either food intake or subjective effects (e.g., Cocchetto et al., 1981; Mattes et al. 1994). For example, in heavy marijuana smokers, 20 mg dronabinol and 3.1% marijuana produced identical peak ratings of "high" but the marijuana resulted in peak plasma THC levels 400-fold higher than dronabinol (Hart et al. 2002b and unpublished data). Thus, plasma THC levels would not have provided more information about the utility of dronabinol as compared to marijuana.

To conclude, the present study attempts to address scientific gaps in issues relevant to the medical use of marijuana. We report that both acute marijuana and dronabinol increased food intake in HIV+ marijuana smokers with clinically low muscle mass while producing positive effects on mood and few disruptions in cognitive performance in either muscle mass group. Improving options for increasing food intake remains of critical importance for the treatment of HIV (Palenicek et al. 1995). Cannabinoids tend to increase fat rather than lean muscle mass (Abrams et al. 2003), yet patients who are able to maintain stable weight often report improved quality of life (Beal et al. 1995; Struwe et al. 1993). Cannabinoids per se appear to be relatively safe: controlled laboratory studies show that neither dronabinol nor marijuana given over several weeks negatively affects antiretroviral pharmacokinetics, viral load, CD4 T-lymphocyte counts, or other health indications (Abrams et al. 2003; Timpone et al. 1997; Kosel et al. 2002). In the long term, however, smoking marijuana produces respiratory risks, so a current research goal is to develop alternative routes of cannabinoid administration with faster rates of onset than dronabinol (Martin 2002; Tashkin 1999; Robson 2001).

Neither marijuana nor dronabinol will be appropriate for everyone with HIV-related weight loss. For example, in non-marijuana smokers, much lower doses of dronabinol (e.g., 2.5 mg) produced confusion and anxiety (Beal et al. 1995; Timpone et al. 1997). Yet these symptoms were not evident in marijuana smokers. Thus, the argument that dronabinol is not clinically useful because of its slow onset and long duration of action appears less relevant to individuals who currently smoke marijuana. Therefore, for HIV+ populations who currently smoke marijuana and who can tolerate oral medications, an acute dose of dronabinol four to eight times the standard dose is as effective and well tolerated as marijuana.

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## References

Abrams DI (2000) Potential interventions for HIV/AIDS wasting: an overview. J Acquir Immune Defic Syndr 25:S74–S80

Abrams DI, Hilton JF, Leiser RJ, Shade SB, Elbeik TA, Aweeka FT, Benowitz NL, Bredt BM, Kosel B, Aberg JA, Deeks SG, Mitchell TF, Mulligan K, Bacchetti P, McCune JM, Schambelan M (2003) Short-term effects of cannabinoids in patients with HIV-1 infection. Ann Intern Med 139:258–266

Agurell S, Halldin M, Lindfren J, Ohlsson A, Widman M, Gillespie H, Hollister L (1986) Pharmacokinetics and metabolism of $\Delta^1$ tetrahydrocannabinol and other cannabinoids with emphasis on man. Pharmacol Rev 38:21–43

Beal JE, Olson R, Laubenstein L, Morales JO, Bellman P, Yangco B, Lefkowitz L, Plasse TF, Shepard KV (1995) Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage 10:89–97

Beal JE, Olson R, Lefkowitz L, Laubenstein L, Bellman P, Yangco B, Morales JO, Murphy R, Powderly W, Plasse TF, Mosdell KW, Shepard KV (1997) Long-term efficacy and safety of dronabinol for acquired immunodeficiency syndrome-associated anorexia. J Pain Symptom Manage 14:7–14

Calhoun SR, Galloway GP, Smith DE (1998) Abuse potential of dronabinal (Marinol). J Psychoactive Drugs 30:187–196

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

Cocchetto DM, Owens SM, Perez-Reyes M, DiGuiseppi S, Miller LL (1981) Relationship between plasma delta-9-tetrahydrocannabinol concentration and pharmacologic effects in man. Psychopharmacology 75:158–164

Compton WM, Grant BF, Colliver JD, Glantz MD, Stinson FS (2004) Prevalence of marijuana use disorders in the United States: 1991–1992 and 2001–2002. JAMA 291:2114–2121

Dworkin MS, Williamson JM (2003) AIDS wasting syndrome: trends, influence on opportunistic infections, and survival. J Acquir Immune Defic Syndr 33:267–273

ElSohly MA, Feng S, Murphy TP, Ross SA, Nimrod A, Mehmedic Z, Fortner N (1999) Delta 9-tetrahydrocannabivarin (delta 9-THCV) as a marker for the ingestion of cannabis versus Marinol. J Anal Toxicol 23:222–224

Evans SM, Troisi JR II, Griffiths RR (1994) Tandospirone and alprazolam: comparison of behavioral effects and abuse liability in humans. J Pharmacol Exp Ther 271:683–694

Evans SM, Haney M, Levin FR, Foltin RW, Fischman MW (1998) Mood and performance changes in women with premenstrual dysphoric disorder: acute effects of alprazolam. Neuropsychopharmacology 19:499–516

Foltin RW, Brady JV, Fischman MW (1986) Behavioral analysis of marijuana effects on food intake in humans. Pharmacol Biochem Behav 25:577–582

Foltin RW, Brady JV, Fischman MW, Emurian CS, Dominitz J (1987) Effects of smoked marijuana on social interaction in small groups. Drug Alcohol Depend 20:87–93

Foltin RW, Fischman MW, Byrne MF (1988) Effects of smoked marijuana on food intake and body weight of humans living in a residential laboratory. Appetite 11:1–14

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

Grinspoon L, Bakalar J (1993) Marihuana, the forbidden medicine. Yale University Press, New Haven

Hall W, Degenhardt L (2003) Medical marijuana initiatives: are they justified? How successful are they likely to be? CNS Drugs 17:689–697

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

Haney M, Bisaga A, Foltin RW (2003) Interaction between naltrexone and oral THC in heavy marijuana smokers. Psychopharmacology 166:77–85

Haney M, Hart CL, Vosburg SK, Nasser J, Bennett A, Zubaran C, Foltin RW (2004) Marijuana withdrawal in humans: effects of oral THC or divalproex. Neuropsychopharmacology 29:158–170

Hart CL, van Gorp W, Haney M, Foltin RW, Fischman MW (2001) Effects of acute smoked marijuana on complex cognitive performance. Neuropsychopharmacology 25:757–765

Hart CL, Haney M, Ward AS, Fischman MW, Foltin RW (2002a) Effects of oral THC maintenance on smoked marijuana self-administration. Drug Alcohol Depend 67:301–309

Hart CL, Ward AS, Haney M, Comer SD, Foltin RW, Fischman MW (2002b) Comparison of smoked marijuana and oral $\Delta^9$-THC in humans. Psychopharmacology 164:407–415

Heatherington M, Rolls BJ (1987) Methods of investigating human eating behavior. In: Toates F, Rowland N (eds) Feeding and drinking. Elsevier, Amsterdam, pp 77–109

Institute of Medicine (1999) Marijuana and medicine: assessing the science base. National Academy Press, Washington, DC

Kirk JM, De Wit H (1999) Responses to oral $\Delta^9$-tetrahydrocannabinol in frequent and infrequent marijuana users. Pharmacol Biochem Behav 63:137–142

Kosel BW, Aweeka FT, Benowitz NL, Shade SB, Hilton JF, Lizak PS, Abrams DI (2002) The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. AIDS 16:543–550

Kotler DP, Burastero S, Wang J, Pierson RN (1996) Prediction of body cell mass, fat-free mass, and total body water with bioelectrical impedance analysis: effects of race, sex, and disease. Am J Clin Nutr 64:489S–497S

Martin BR (2002) Medical marijuana—moving beyond the smoke. Lancet 360:4–5

Mason AP, McBay AJ (1985) Cannabis: pharmacology and interpretation of effects. J Forensic Sci 30:615–631

Mattes RD, Engelman K, Shaw LM, Elsohly MA (1994) Cannabinoids and appetite stimulation. Pharmacol Biochem Behav 49:187–195

Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD (1998) Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. New Engl J Med 338:853–860

Palenicek JP, Graham NMH, He YD, Hoover DA, Oishi JS, Kingsley L, Saah AJ (1995) Weight loss prior to clinical AIDS as a predictor of survival. Multicenter AIDS Cohort Study Investigators. J Acquir Immune Defic Syndr 10:366–373

Plasse TF, Gorter RW, Krasnow SH, Lane M, Shepard KV, Wadleigh RG (1991) Recent clinical experience with dronabinol. Pharmacol Biochem Behav 40:695–700

Polen MR, Sidney S, Tekawa IS, Sadler M, Friedman GD (1993) Health care use by frequent marijuana smokers who do not smoke tobacco. Western J Med 158:596–601

Pope HG, Gruber AJ, Hudson JI, Huestis MA, Yurgelun-Todd D (2001) Neuropsychological performance in long-term cannabis users. Arch Gen Psychiatry 58:909–915

Prentiss D, Power R, Balmas G, Tzuang G, Israelski DM (2004) Patterns of marijuana use among patients with HIV/AIDS followed in a public health care setting. J Acquir Immune Defic Syndr 35:38–45

Robson P (2001) Therapeutic aspects of cannabis and cannabinoids. Br J Psychol 178:107–115

Struwe M, Kaempfer SH, Geiger CJ, Pavia AT, Plasse TF, Shepard KV, Ries K, Evans TG (1993) Effect of dronabinol on nutritional status in HIV infection. Ann Pharmacother 27:827–831

Tashkin DP (1999) Marihuana and the lung. In: Nahas GG, Pace N, Cancro R (eds) Marihuana and medicine. Humana Press, Totowa, NJ, pp 279–287

Timpone JG, Wright DJ, Li N, Egorin MJ, Enama ME, Mayers J, Galetto G (1997) The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronobinol for the treatment of HIV wasting syndrome. The DATRI 004 Study Group. Division of AIDS Treatment Research Initiative. AIDS Res Hum Retroviruses 13:305–315

Wu T, Tashkin DP, Djahed B, Rose JE (1988) Pulmonary hazards of smoking marijuana as compared with tobacco. New Engl J Med 318:347–351