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ORIGINAL INVESTIGATION

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# Comparison of smoked marijuana and oral $\Delta^9$-tetrahydrocannabinol in humans

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**Abstract** *Rationale:* Although smoked marijuana contains at least 60 cannabinoids, $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) is presumed to be the cannabinoid primarily responsible for many marijuana-related effects, including increased food intake and subjective effects. Yet, there has been no systematic comparison of repeated doses of oral $\Delta^9$-THC with repeated doses of smoked marijuana in the same individuals. *Objective:* To compare the effects of oral $\Delta^9$-THC and smoked marijuana in humans under controlled laboratory conditions. *Methods:* Eleven healthy research volunteers, who reported smoking an average of six marijuana cigarettes per day, completed an 18-day residential study. Marijuana cigarettes (3.1% $\Delta^9$-THC, q.i.d.) were smoked or $\Delta^9$-THC (20 mg, q.i.d.) was taken orally using a staggered, double-blind, double-dummy procedure for three consecutive days. Four days of placebo administration separated each active drug condition. Psychomotor task performance, subjective effects, and food intake were measured throughout the day. *Results:* Relative to placebo baseline, oral $\Delta^9$-THC and smoked marijuana produced similar subjective-effect ratings (e.g., "high" and "mellow"), although some effects of smoked marijuana were more pronounced and less prone to the development of tolerance. Additionally, participants reported "negative" subjective effects (e.g., "irritable" and "miserable") during the days after smoking marijuana but not after oral $\Delta^9$-THC. Both drugs increased food intake for 3 days of drug administration, but had little effect on psychomotor performance. *Conclusion:* These results indicate that the behavioral profile of effects of smoked marijuana (3.1% $\Delta^9$-THC) is similar to the effects of oral $\Delta^9$-THC (20 mg), with some subtle differences.

**Keywords** Cannabis · Marinol · Subjective effects · Human · Food intake · Delta-9-tetrahydrocannabinol tolerance · Dependence · Abstinence

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## Introduction

The potential medicinal use of smoked marijuana for symptoms including lack of appetite related to acquired immunodeficiency syndrome (AIDS) wasting disease, chemotherapy-induced nausea, glaucoma-associated intraocular pressure, and various types of pains (Joy et al. 1999) has received increased public attention over the past several years. This interest has occurred despite the availability of a Food and Drug Administration (FDA)-approved oral $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) medication (e.g., Marinol). Proponents of medical marijuana use argue that oral $\Delta^9$-THC has several disadvantages relative to smoked marijuana, including a slower onset of effects (Joy et al. 1999). Additionally, it is possible that marijuana plant constituents other than $\Delta^9$-THC may contribute to marijuana-related therapeutic effects. Indeed, there are over 400 chemicals (approximately 60 are cannabinoids) in marijuana, and the combination and/or balance of these chemicals may mediate therapeutic effects. Few studies have compared the effects of oral $\Delta^9$-THC and smoked marijuana in the same individuals (Tashkin et al. 1973; Ohlsson et al. 1980; Mendelson and Mello 1984). Mendelson and Mello (1984) assessed subjective and reinforcing effects produced by oral $\Delta^9$-THC (17.5 mg) and smoked marijuana (1.83% $\Delta^9$-THC) and reported that smoked marijuana produced larger intoxicating and reinforcing effects than oral $\Delta^9$-THC. Because a broader range of effects produced by oral $\Delta^9$-THC and smoked marijuana was not investigated in

previous studies, relatively little is known about how the drugs compare on other measures.

Several investigators have studied the effects of oral $\Delta^9$-THC and smoked marijuana separately. For example, Wachtel et al. (2002) compared the effects of pure $\Delta^9$-THC to whole-plant marijuana in two groups of participants. One group received the drugs via the oral route and the other group via inhalation. Subjective effects produced by the drugs were similar for both routes of administration. Similarly, Chait and Zacny (1992) reported that acute oral $\Delta^9$-THC and smoked marijuana in separate groups of volunteers produced similar cardiovascular, subjective, and reinforcing effects. Furthermore, in separate studies, Haney and co-workers investigated the effects of repeated doses of oral $\Delta^9$-THC (Haney et al. 1999a) and smoked marijuana (Haney et al. 1999b). They administered oral $\Delta^9$-THC (20 mg and 30 mg, q.i.d.) or smoked marijuana (1.8% or 3.1% $\Delta^9$-THC, q.i.d.) for four consecutive days and found similar effects on most dependent measures. For instance, both drugs increased total daily caloric intake and produced abstinence symptoms upon discontinuation of their use. Despite these indications that smoked marijuana and oral $\Delta^9$-THC produce similar effects, a broader range of such effects of the two drugs following repeated administration in the same individuals have not been compared directly. A direct comparison is needed to evaluate recent claims that smoked marijuana is more effective therapeutically than oral $\Delta^9$-THC, which is currently medically available.

The purpose of this study was to compare directly the effects of repeated oral $\Delta^9$-THC and smoked marijuana administration in human research volunteers using a within-participant design under controlled laboratory conditions. Participants either smoked marijuana cigarettes (3.1% $\Delta^9$-THC, q.i.d.) or ingested $\Delta^9$-THC (20 mg, q.i.d.) using a staggered, double-dummy procedure for three consecutive days, followed by 4 days of placebo administration. The effects of these drugs and drug abstinence were assessed on a range of behaviors, including food intake and psychomotor performance.

## Methods

### Participants

Eleven healthy research volunteers [mean age (±SD) 29.8±4.3 years] completed this 18-day residential study: one participant was female (black) and ten participants were male (seven black, two hispanic, one white). They were solicited via word-of-mouth referral and newspaper advertisement in New York City. Participants were not seeking treatment for their marijuana use and reported smoking an average of 6.3±5.6 marijuana cigarettes per day. Nine participants reported occasional use of alcohol and seven smoked tobacco cigarettes. They used other drugs infrequently, although four participants reported occasional cocaine use. Urine toxicology screens during the screening process confirmed the absence of other illicit drug use. During screening, all volunteers passed comprehensive medical and psychological evaluations, and were within normal weight ranges according to the 1983 Metropolitan Life Insurance Company height/weight table [mean weight (±SD) 74.67±11.29 kg].

Volunteers were informed that they were participating in a study of the behavioral effects of marijuana and oral $\Delta^9$-THC, and that the strength of the marijuana cigarettes and $\Delta^9$-THC tablets might change at any time. Each participant signed a consent form approved by the New York State Psychiatric Institute's Institutional Review Board. At study's completion and prior to discharge, volunteers were fully informed about experimental and drug conditions and were paid for their participation. For completing the entire study, they were compensated at a rate of US $70 per day, which was paid in two weekly installments.

### Laboratory

Three groups of three or four individuals each stayed in a residential laboratory in the New York State Psychiatric Institute (Foltin et al. 1996). There was a common social area, where participants were free to engage in recreation activities. This was a large room that contained two couches, chairs, two video game machines, two television monitors for viewing videotaped films, free-weight exercise equipment, art supplies, reading materials, board games, and two washers/dryers. Each participant had a bedroom with a bed, desk, Macintosh LC computer system, microwave, toaster, refrigerator, food preparation space, and bar-code scanner (Worthington Data Solutions, Santa Cruz, Calif.) for food reporting and requesting. Immediately outside the bedrooms were two single-occupancy bathrooms and two single-occupancy showers. From 0830 hours to 2400 hours, food and tobacco cigarettes were available ad libitum. For the purpose of continuous observation of behavior, cameras and microphones were located throughout the common social area and bedrooms. However, no microphones or cameras were located in bathrooms, showers, or private dressing areas. Communication between the staff and participants was kept to a minimum and was primarily accomplished via a continuous on-line computer network system consisting of the computers in each participant's bedroom and the control room computer.

### Design

Before beginning the study, participants completed two training sessions (3–4 h per session) on the computerized tasks. On two separate additional days, they smoked a marijuana cigarette (3.1% $\Delta^9$-THC) or received an oral $\Delta^9$-THC capsule (20 mg) to provide them experience with the study drugs and to detect adverse reaction. No untoward events were noted.

A representative study design is shown in Table 1. A staggered, double-dummy dosing procedure was employed to administer oral $\Delta^9$-THC and smoked marijuana. Oral $\Delta^9$-THC tablets (placebo or 20 mg) were administered four times per day at 0900, 1300, 1700, and 2100 hours. Because the effects of oral $\Delta^9$-THC peak approximately 1 h post-administration (Haney et al. 1999a), marijuana cigarettes (placebo or 3.1% $\Delta^9$-THC) were smoked 1 h after administration of tablets each day: at 1000, 1400, 1800, and 2200 hours. Thus, the peak effects of both drugs were predicted to occur within a similar time frame. During the first four inpatient days, participants received placebo tablets and placebo marijuana cigarettes. On days 5–7, they received either oral $\Delta^9$-THC or active smoked marijuana. Days 8–11 were an abstinence period during which participants received placebo oral $\Delta^9$-THC and placebo marijuana cigarettes. On days 12–14, the other active drug was administered, followed by another abstinence period (days 15–18). Seven of the participants received active oral $\Delta^9$-THC during days 5–7, and the other four received active marijuana during days 5–7. Participants moved out of the laboratory on day 19.

### Procedure

Participants moved into the laboratory on the day before the study, during which they received additional training. The first experi-

**Table 1** Representative study design. Actual order was varied across participants: oral tetrahydrocannabinol dosing times (0900, 1300, 1700, 2100 hours); marijuana dosing times (1000, 1400, 1800, 2200 hours)

| Day | *1 | 2 | 3 | 4 | 5 | 6 | 7 | *8 | 9 | 10 | 11 | 12 | 13 | 14 | *15 | 16 | 17 | 18 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Oral $\Delta^9$-tetrahydrocannabinol | 0 | 0 | 0 | 0 | 20 | 20 | 20 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Marijuana $\Delta^9$-tetrahydrocannabinol | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 3.1 | 3.1 | 3.1 | 0 | 0 | 0 | 0 |

* Indicates days that were not included in data analyses
Times that subjective-effects ratings and psychomotor tasks performance were assessed: 0830 (before dosing), 1015, 1100, 1145, 1230, 1415, 1500, 1545, 1630 hours

mental day began at 0830 hours the following morning. Participants first completed baseline psychomotor tasks and a 50-item subjective-effects visual analog questionnaire. Participants were then weighed (but were not informed of their weight) and given time to eat breakfast. Following breakfast, eight 30-min computerized task batteries, composed of the subjective-effects questionnaire, a drug-effect questionnaire (DEQ), and psychomotor tasks, were completed each day. Participants were given a 15-min break between each task battery. From 1015 hours to 1345 hours, participants completed four additional task batteries, and from 1415 hours to 1700 hours, they completed four additional task batteries. Beginning at 1715 hours, participants had access to activities available in the social area. Two videotaped films were shown nightly, beginning at 1900 hours and 2130 hours. Lights were turned out at 2400 hours.

### Subjective-effects and psychomotor battery

The visual analog questionnaire consisted of a series of 100-mm lines labeled "not at all" at one end and "extremely" at the other end (Haney et al. 1999b; Hart et al. 2001a). The lines were labeled with adjectives describing a mood (e.g., "I feel... "anxious," "angry," "frustrated"), a drug effect (e.g., "I feel... "high," "good drug effect," "bad drug effect"), or a physical symptom (e.g., "I feel... "headache," "stomach upset," "muscle pain"). Psychomotor tasks (Haney et al. 1999b) consisted of a 3-min digit-symbol substitution task (McLeod et al. 1982), a 3-min repeated-acquisition task (Kelly et al. 1993), a 10-min divided attention task (Miller et al. 1988), a 10-min rapid information task (Wesnes and Warburton 1983), and an immediate and delayed digit-recall task. The DEQ was completed 45-min after each marijuana dosing occasion and participants were instructed to rate their responses based on the marijuana cigarette most recently smoked. On the DEQ, participants were required to rate "good effects" and "bad effects" from the drug on a five-point scale: 0 = "not at all" and 4 = "very much." They were also asked to rate how "strong" the drug effect was as well as their desire "to take the drug again." Lastly, participants were ask to rate how much they liked the drug effect on a 9-point scale: –4 indicated "disliked very much," 0 indicated "feel neutral, or feel no drug effect," and 4 indicated "liked very much."

### Food

Every morning at 0915 hours, each participant 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 meal items, illustrated in a booklet, and additional units of any item were freely available upon request. Participants were instructed to scan custom-designed bar codes whenever they ate or drank, specifying substance and portion. At 2330 hours, participants returned their food box to a staff member. Food items were not available between 2330 hours and 0830 hours the following morning, although water was available at all times.

### Drugs

Participants received two 1-g marijuana cigarettes (0% or 3.1% THC w/w), provided by the National Institute on Drug Abuse, prior to each scheduled smoking occasion. They smoked under a paced-puffing procedure, which produces $\Delta^9$-THC concentration-dependent changes in heart rate and subjective-effects ratings (Foltin et al. 1987; Hart et al. 2001b). Colored lights (mounted on the ceiling of the social area) signaled "light the cigarette" (30 s), "get ready" (5 s), "inhale" (5 s), "hold smoke in lungs" (10 s), and "exhale." Participants smoked five puffs (three puffs on one cigarette, two on the other), with a 40-s interval between each puff. Participants could signal that they wanted to stop smoking by raising their left hand, although no participant did. Cigarettes were tightly rolled at both ends and were smoked through a hollow plastic cigarette holder so that the contents were not visible. At least 12 h prior to administration, cigarettes were removed from a freezer, where they were stored in an airtight container, and humidified at room temperature. Oral $\Delta^9$-THC doses (5-mg tablets and matching placebo provided by Roxane Laboratories, Columbus, Ohio) were packaged into individual plastic bags; each bag contained four tablets. The doses of oral $\Delta^9$-THC and smoked marijuana used were based on our previous studies in which we found that 20 mg oral $\Delta^9$-THC (Haney et al. 1999a) produced similar increases in food intake and subjective effects as 3.1% $\Delta^9$-THC marijuana cigarettes (Haney et al. 1999b) smoked using the procedure described above in different groups of research participants.

### Data analysis

Data from the first habituation day of the study were not included in analyses. Additionally, data from day 8 and day 15 (the days immediately after active oral $\Delta^9$-THC and active smoked marijuana administration) were not included in the analyses because previous studies from this laboratory showed oral $\Delta^9$-THC-related and smoked marijuana-related residual effects are not apparent until at least 24 h following active dosing (Haney et al. 1999a, 1999b). The area under the curve (AUC) for the subjective-effects visual analog questionnaire and psychomotor performance measure was determined using the trapezoidal method (Tallarida and Murray 1981). AUC was used instead of peak effect data to detect effects that occurred throughout the entire day, instead of only one time point. Peak effect data were also analyzed, but only AUC data will be presented, as the results were similar.

Data were analyzed using two-factor, repeated-measures analyses of variance (ANOVAs): the first factor was drug condition (placebo baseline, 20 mg oral $\Delta^9$-THC, placebo after oral $\Delta^9$-THC, 3.1% $\Delta^9$-THC marijuana, and placebo after marijuana) and the second factor was day (1, 2, and 3 under each condition). For all analyses, ANOVAs provided the error terms needed to calculate planned comparisons that were designed to answer three questions: (1) do the effects produced by oral $\Delta^9$-THC differ from the effects produced by smoked marijuana; (2) do the effects produced by oral $\Delta^9$-THC and smoked marijuana change over consecutive days of dosing, relative to placebo baseline; and (3) do residual or abstinence effects occur following oral $\Delta^9$-THC and smoked marijuana administration? To evaluate potential differences between effects produced by oral $\Delta^9$-THC and smoked marijuana,

each day of active oral $\Delta^9$-THC administration was compared to the corresponding active smoked marijuana day (e.g., the first day of 20 mg oral $\Delta^9$-THC versus the first day of 3.1% $\Delta^9$-THC smoked marijuana). To evaluate potential changes in drug effects across days, each day of active oral $\Delta^9$-THC and smoked marijuana was compared to the corresponding placebo baseline day (e.g., the first day of 20 mg oral $\Delta^9$-THC versus the first day of placebo baseline). To evaluate potential abstinence effects, each placebo day following active drug was compared to the corresponding placebo baseline day (e.g., the first day of placebo after 20 mg oral $\Delta^9$-THC versus the first day of placebo baseline). Given the large number of planned comparisons overall, only those $P$ values <0.01 were considered statistically significant, in an effort to control for type-I error. Hunyh-Feldt corrections were used, when appropriate.

The food intake data were based on the participants' reports of food intake and verified by trash examination. Total caloric intake, gram intake of carbohydrate, fat, and protein, proportion of caloric intake from each macronutrient [estimated as kilocalorie from gram-intake using Atwater factors (McLaren 1976)], mean number of eating occasions, and mean eating occasion size were calculated. Mean number of eating occasions and eating occasion size were determined using a minimal inter-occasion interval of 10 min: an eating occasion was defined as beginning with the first report of consuming an item and ending when there was a pause of greater than 10 min between food reports. Eating occasion parameters and the percentage of energy intake derived from each of the three macronutrients were analyzed based on data obtained for the entire day.

## Results

### Subjective effects

Figure 1 displays the AUC for selected subjective-effects measures across the initial three placebo baseline days, the 3 days of oral $\Delta^9$-THC and smoked marijuana administration, and the three placebo days following active drug treatment. Planned comparisons revealed that both oral $\Delta^9$-THC and smoked marijuana increased significantly ratings of "high" ($\Delta^9$-THC $F_{1,80}$=78.3, $P$<0.0001; marijuana $F_{1,80}$=136.8, $P$<0.0001) and "mellow" ($\Delta^9$-THC $F_{1,80}$=9.3, $P$<0.01; marijuana $F_{1,80}$=37.2, $P$<0.0001) on the first day of administration, relative to the first day of placebo baseline. Ratings of "high" remained significantly elevated across all 3 days of both active drug conditions, although a non-significant diminution of this effect was observed for both drugs. While both oral $\Delta^9$-THC and smoked marijuana increased significantly ratings of "mellow" on day 1 of administration, only smoked marijuana produced significant increases over the course of 3 days of drug administration ($P$<0.0001), suggesting the development of tolerance for oral $\Delta^9$-THC. When the effects of the active conditions were compared (Fig. 1), smoked marijuana produced significantly greater ratings of "high" on the first day ($F_{1,80}$=8.1, $P$<0.01) and greater ratings of "mellow" on the first and third days ($F_{1,80}$=9.3, $P$<0.01 and $F_{1,80}$=9.9, $P$<0.01, respectively) than did oral $\Delta^9$-THC. Ratings of "good drug effect," on the third day, was the only other subjective-effect measure on which marijuana produced significantly greater ratings than $\Delta^9$-THC ($F_{1,80}$=12.1, $P$<0.01). Table 2 and Table 3 display other subjective-effects ratings that were significantly altered under each drug condition.

Both active oral $\Delta^9$-THC and smoked marijuana increased significantly DEQ ratings of "good effects," drug strength, drug liking, and desire to take the drug again during all 3 days, relative to the corresponding baseline days (data not shown). Although these ratings were consistently greater during the smoked marijuana condition, there was not a significant difference between active drugs. Ratings of "bad effects," however, were increased significantly on day 1 and day 3 during oral $\Delta^9$-THC administration relative to corresponding days of placebo baseline and marijuana administration.

In contrast to the positive subjective effects described above, during smoked marijuana abstinence (the days following active marijuana administration) several negative subjective effects were increased. Figure 2 shows that ratings of "irritable" (left panel) and "miserable" (right panel) were increased significantly on day 2 and day 3 of smoked marijuana abstinence relative to the corresponding placebo baseline days. Several other subjective effects ("bad drug effect" and "depressed") were altered signif-

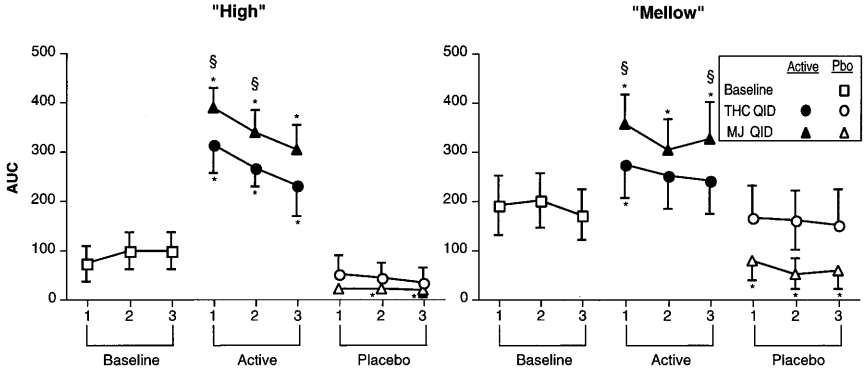


**Fig. 1** Area-under-the-curve (AUC) values for visual analog scale ratings of "high" and "mellow" during the three placebo baseline days, the 3 days of active $\Delta^9$-oral tetrahydrocannabinol (THC; 20 mg) and smoked marijuana (3.1% $\Delta^9$-THC) administration, and the three placebo days following each active condition. *Error bars* represent one SEM. Overlapping error bars were omitted for clarity. *Significant difference between that day and the corresponding placebo baseline day ($P$<0.01). §Significant difference between $\Delta^9$-oral THC and smoked marijuana on that day ($P$<0.01)

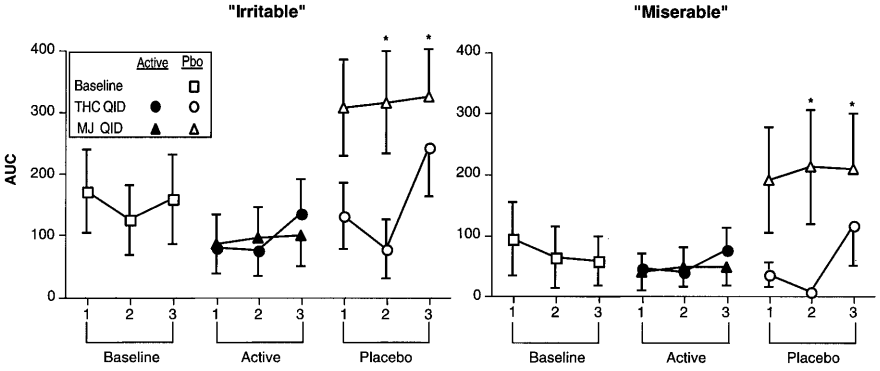


**Fig. 2** Area-under-the-curve (AUC) values for visual analog scale ratings of "irritable" and "miserable" during the three placebo baseline days, the 3 days of active $\Delta^9$-oral tetrahydrocannabinol (THC; 20 mg) and smoked marijuana (3.1% $\Delta^9$-THC) administration, and the three placebo days following each active condition. *Error bars* represent one SEM. Overlapping error bars were omitted for clarity. *Significant difference between that day and the corresponding placebo baseline day ($P<0.01$)

**Table 2** Effects of active oral $\Delta^9$-tetrahydrocannabinol (THC) and smoked marijuana on subjective effects and psychomotor performance. Data are represented as area-under-the-curve values. *DAT* divided attention task, *RA* repeated-acquisition task, *RIT* rapid information task

| Measure | Day 1 | | Day 2 | | Day 3 | |
|---|---|---|---|---|---|---|
| | Mean (SEM) | *F* value | Mean (SEM) | *F* value | Mean (SEM) | *F* value |
| Active oral $\Delta^9$-THC condition | | | | | | |
| Subjective effects | | | | | | |
| Alert | 319.55 (57.20) | 6.65 | 347.27 (62.00) | 14.11* | 316.91 (59.05) | 4.96 |
| Content | 331.82 (47.05) | 4.73 | 299.09 (59.73) | 0.47 | 308.18 (56.74) | 3.66 |
| Good drug effect | 305.82 (56.58) | 61.21* | 279.09 (49.10) | 26.66* | 200.27 (46.95) | 8.87 |
| High | 308.82 (57.34) | 78.33* | 261.55 (37.63) | 37.68* | 228.18 (63.92) | 24.14* |
| Hungry | 171.09 (44.46) | 8.05 | 146.09 (39.31) | 1.54 | 168.09 (50.89 | 4.56 |
| Mellow | 270.82 (68.10) | 9.26* | 248.00 (67.44) | 3.27 | 238.09 (67.37) | 6.50 |
| Sedated | 102.64 (47.16) | 11.61* | 101.73 (47.75) | 11.10* | 117.36 (57.03) | 16.11* |
| Stimulated | 287.91 (60.83) | 45.57* | 295.73 (56.40) | 34.63* | 283.36 (59.96) | 22.95* |
| Performance effects | | | | | | |
| DAT: speed | 36.09 (1.79) | 0.10 | 34.27 (2.86) | 8.61§ | 33.55 (2.82) | 6.56 |
| Digits recalled | 29.55 (4.97) | 1.70 | 31.18 (5.32) | 5.93 | 30.91 (4.94) | 9.40* |
| RIT: false alarm | 377.64 (63.09) | 0.03 | 414.00 (80.20) | 0.01 | 406.27 (77.52) | 0.26 |
| RIT: no. of misses | 571.73 (104.71) | 9.23§ | 590.64 (109.44) | 0.47 | 577.64 (103.14) | 2.24 |
| RA: total trials | 75.90 (16.33) | 10.78* | 85.64 (17.98) | 18.70* | 82.36 (16.65) | 4.22 |
| Active smoked marijuana condition | | | | | | |
| Subjective effects | | | | | | |
| Alert | 358.91 (59.14) | 17.84* | 371.73 (58.17) | 22.84* | 351.73 (64.97) | 13.55* |
| Content | 406.09 (38.40) | 19.70* | 350.73 (49.09) | 5.11 | 325.55 (48.68) | 5.97 |
| Good drug effect | 363.46 (44.39) | 95.62* | 323.27 (45.70) | 44.38* | 303.00 (46.27) | 41.75* |
| High | 385.46 (38.44) | 136.81* | 333.82 (44.45) | 77.85* | 299.82 (50.66) | 57.36* |
| Hungry | 188.36 (52.10) | 12.58* | 206.09 (50.81) | 13.75* | 198.10 (57.36) | 11.34* |
| Mellow | 353.00 (58.61) | 37.21* | 298.64 (62.26) | 13.63* | 322.55 (73.77) | 32.38* |
| Sedated | 129.91 (47.62) | 23.32* | 117.18 (46.44) | 17.11* | 104.46 (48.16) | 11.16* |
| Stimulated | 326.46 (58.44) | 67.80* | 282.36 (52.40) | 28.85* | 266.27 (62.19) | 17.08* |
| Performance effects | | | | | | |
| DAT: speed | 30.73 (2.64 | 15.97§ | 30.91 (3.15) | 27.51§ | 32.46 (2.22) | 10.95§ |
| Digits recalled | 27.64 (4.90) | 0.17 | 27.36 (5.17) | 0.45 | 28.36 (5.47) | 3.57 |
| RIT: false alarm | 513.36 (90.78) | 8.59 | 524.82 (100.35) | 5.18 | 606.46 (137.24) | 12.81* |
| RIT: no. of misses | 650.36 (104.10) | 0.16 | 615.64 (97.67) | 0.02 | 586.46 (91.74) | 0.02 |
| RA: total trials | 64.09 (11.39) | 2.78 | 66.64 (13.56) | 2.36 | 65.82 (12.52) | 0.14 |

* $P<0.01$, measure increased relative to the corresponding placebo baseline day
§ $P<0.01$, measure decreased relative to the corresponding placebo baseline day

**Table 3** Effects of placebo oral $\Delta^9$-tetrahydrocannabinol (THC) and smoked marijuana on subjective effects and psychomotor performance. Data are represented as area-under-the-curve values. *DAT* divided attention task, *RA* repeated-acquisition task, *RIT* rapid information task

| Measure | Day 1 | | Day 2 | | Day 3 | |
|---|---|---|---|---|---|---|
| | Mean (SEM) | *F* value | Mean (SEM) | *F* value | Mean (SEM) | *F* value |
| Placebo oral $\Delta^9$-THC condition (3 days following active oral $\Delta^9$-THC) | | | | | | |
| Subjective effects | | | | | | |
| Bad drug effect | 28.36 (24.29) | 1.12 | 8.64 (6.67) | 0.08 | 15.73 (9.82) | 0.01 |
| Content | 233.55 (62.50) | 0.68 | 217.00 (60.24) | 3.31 | 187.46 (62.26) | 3.13 |
| Depressed | 43.27 (38.68) | 1.11 | 7.00 (6.15) | 2.22 | 66.64 (63.19) | 0.50 |
| Irritable | 131.09 (53.99) | 0.62 | 77.09 (48.20) | 0.86 | 243.64 (80.28) | 2.87 |
| Mellow | 163.27 (64.21) | 0.92 | 158.82 (59.61) | 2.27 | 147.73 (73.49) | 0.66 |
| Miserable | 33.09 (20.40) | 2.81 | 4.55 (3.52) | 2.65 | 112.46 (66.60) | 2.39 |
| Withdrawn | 39.09 (22.49) | 0.09 | 31.91 (31.12) | 0.62 | 35.27 (29.34) | 0.17 |
| Performance effects | | | | | | |
| Digits recalled | 29.82 (4.74) | 2.04 | 31.73 (4.93) | 7.22* | 30.73 (5.47) | 8.89* |
| RIT: no. of misses | 597.91 (113.36) | 4.67 | 552.64 (108.42) | 3.85 | 607.82 (104.50) | 0.23 |
| RA: total errors | 269.09 (25.23) | 9.87* | 270.00 (22.45) | 3.06 | 254.36 (29.72) | 0.10 |
| RA: total trials | 82.09 (16.49) | 18.58* | 82.64 (17.68) | 15.08* | 80.09 (18.34) | 2.96 |
| Placebo smoked marijuana condition (3 days following active smoked marijuana) | | | | | | |
| Subjective effects | | | | | | |
| Bad drug effect | 80.82 (63.38) | 14.11* | 86.27 (63.66) | 13.83* | 84.82 (64.19) | 11.95* |
| Content | 195.46 (60.58) | 3.94 | 135.55 (41.36) | 18.52§ | 132.82 (42.20) | 11.80§ |
| Depressed | 139.73 (77.31) | 19.20* | 160.91 (82.07) | 14.61* | 163.55 (80.94) | 16.42* |
| Irritable | 307.46 (78.36) | 10.81 | 315.82 (83.24) | 14.44* | 324.09 (82.30) | 10.81* |
| Mellow | 76.55 (41.47) | 17.49§ | 49.73 (31.07) | 30.97§ | 56.36 (38.63) | 17.72§ |
| Miserable | 186.36 (85.34) | 6.90 | 207.36 (92.63) | 16.56* | 204.00 (88.74) | 16.94* |
| Withdrawn | 87.09 (52.91) | 4.01 | 125.18 (73.26) | 13.58* | 141.09 (74.30) | 21.82* |
| Performance effects | | | | | | |
| Digits recalled | 30.82 (4.71) | 3.57 | 28.55 (5.29) | 1.48 | 26.64 (4.39) | 1.19 |
| RIT: no. of misses | 534.91 (103.88) | 18.25§ | 533.18 (112.05) | 6.83 | 556.46 (109.28) | 4.86 |
| RA: total errors | 296.73 (30.28) | 22.79* | 302.36 (35.85) | 13.41* | 306.73 (33.37) | 11.66* |
| RA: total trials | 72.82 (14.84) | 8.70 | 72.55 (15.68) | 5.77 | 73.36 (15.00) | 0.54 |

* $P<0.01$, measure increased relative to the corresponding placebo baseline day
§ $P<0.01$, measure decreased relative to the corresponding placebo baseline day

icantly during smoked marijuana abstinence relative to placebo baseline (Table 3). Conversely, there were no significant subjective-effects alterations noted during the oral $\Delta^9$-THC abstinence period.

## Performance effects

Table 2 and Table 3 show that the drugs had little effect on performance. Relative to the corresponding placebo baseline days, smoked marijuana decreased participants' maximal tracking speed on the divided attention task across all 3 days of treatment, and during the 3 days of smoked marijuana abstinence participants made significantly more errors on the repeated-acquisition task. In contrast, during the first 2 days of oral $\Delta^9$-THC administration and the first 2 days of oral $\Delta^9$-THC abstinence, the total number of completed trials on the repeated-acquisition task was increased significantly relative to corresponding placebo baseline days.

## Food intake

Oral $\Delta^9$-THC and smoked marijuana significantly increased mean total caloric intake by approximately 1040 kcal ($P<0.0002$ for all 3 days) and 1080 kcal ($P<0.003$ for all 3 days), respectively, relative to the placebo baseline period (Fig. 3). Both oral $\Delta^9$-THC and smoked marijuana increased the mean number of eating occasions per day by approximately 2.7 meals ($P<0.0004$ for all 3 days) and 3.1 meals ($P<0.004$ for all 3 days), respectively, relative to the placebo baseline period. The drugs also increased protein, carbohydrate, and fat intake, so that the percentage contribution of each macronutrient to total daily energy intake did not change relative to baseline (data not shown). Oral $\Delta^9$-THC and smoked marijuana did not differ on food intake and there were no changes during the placebo period following active drug administration.

## Individual participant data

Figure 4 shows ratings of "hungry" and the number of eating occasions for individual participants as a function of active oral $\Delta^9$-THC and smoked marijuana conditions

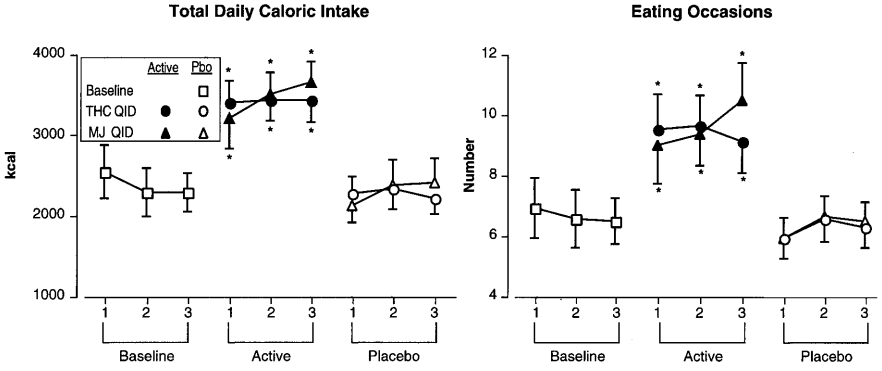


**Fig. 3** Mean total daily caloric intake and number of eating occasions during the three placebo baseline days, the 3 days of active $\Delta^9$-oral tetrahydrocannabinol (THC; 20 mg) and smoked marijuana (3.1% $\Delta^9$-THC) administration, and the three placebo days following each active condition. *Error bars* represent one SEM. Overlapping error bars were omitted for clarity. *Significant difference between that day and the corresponding placebo baseline day ($P$<0.01)

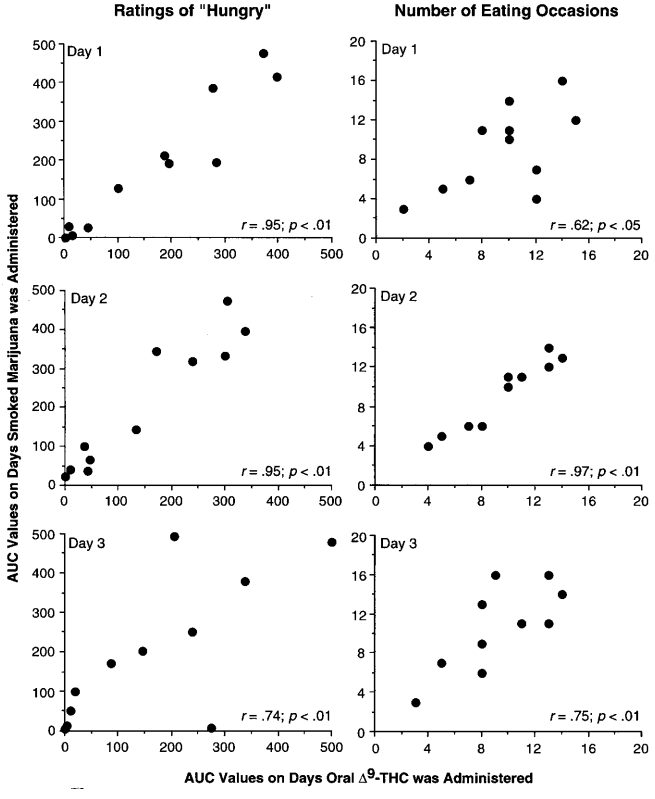


**Fig. 4** Area-under-the-curve (AUC) values for visual analog scale ratings of "hungry" and number of eating occasions for each participant during the 3 days of active $\Delta^9$-oral tetrahydrocannabinol (THC; 20 mg) and smoked marijuana (3.1% $\Delta^9$-THC) administration

over the course of 3 days. Participants responded similarly during both drug conditions. Correlations ranged from 0.62 to 0.95. Data from other measures, including ratings of "good drug effect" and total caloric intake, showed a similar large correlation between the effects of oral $\Delta^9$-THC and smoked marijuana (data not shown).

## Discussion

Oral $\Delta^9$-THC (20 mg) and smoked marijuana (3.1% $\Delta^9$-THC) produced similar effects on subjective-effects ratings, food intake, and psychomotor performance, although a few subjective effects produced by smoked marijuana were more pronounced and less prone to diminution over time. Additionally, there was an abstinence syndrome associated with smoked marijuana, but not with oral $\Delta^9$-THC. The pattern of effects obtained in the present study corresponds well with data from other investigations that assessed the effects of oral $\Delta^9$-THC and smoked marijuana in different groups of participants (Chait and Zacny 1992; Haney et al. 1999a, 1999b; Wachtel et al. 2002). The current data, however, are the first to examine such effects following repeated drug administration in the same individuals under controlled laboratory conditions.

While minimal tolerance developed to oral $\Delta^9$-THC- or smoked marijuana-related subjective effects, other investigators have reported greater tolerance development after repeated drug exposure (Babor et al. 1975; Jones et al. 1976, 1981; Nowlan and Cohen 1977; Haney et al. 1999a, 1999b). At least two considerations are of particular importance in the interpretation of the present results, relative to previous studies: (1) participants received lower daily $\Delta^9$-THC doses and (2) they received only 3 days of repeated active drug administration. For example, in studies by Jones and colleagues, participants received oral $\Delta^9$-THC doses as high as 210 mg per day for 10–20 days (Jones et al. 1976, 1981). In addition, although our previous studies used lower $\Delta^9$-THC doses (Haney et al. 1999a, 1999b) than those used by Jones and colleagues, drugs were administered repeatedly for four consecutive days. Thus, it is likely that a greater diminution of subjective effects was not observed in the present study because of the shorter duration of drug exposure.

Oral $\Delta^9$-THC and smoked marijuana, at doses examined, increased food intake across 3 days of drug

administration by nearly 45% (approximately 1000 Kcal). This finding may have important clinical implications because it suggests that oral $\Delta^9$-THC is as effective as smoked marijuana in increasing food intake, an effect for which smoked marijuana has been proposed medically. The significance of this observation is tempered, however, because oral $\Delta^9$-THC doses tested in the current study were 8–16 times greater than the recommended clinical doses. Additionally, participants in the present study reported smoking marijuana daily, averaging six cigarettes per day. Presumably, this amount is substantially more than the targeted clinical population. Nevertheless, findings from a recent study in which the effects of dronabinol on appetite stimulation in AIDS patients were assessed are in agreement with our results (Beal et al. 1997).

Psychomotor performance was not impaired markedly by either oral $\Delta^9$-THC or smoked marijuana. There is a growing body of data supporting the hypothesis that regular marijuana users show minimal performance impairment after smoking marijuana (Ward et al. 1997; Haney et al. 1999a, 1999b; Hart et al. 2001b), thereby decreasing the likelihood of observing $\Delta^9$-THC-related cognitive and psychomotor performance decrements under experimental conditions. The absence of performance effects may be due to the fact that study participants were probably tolerant to many marijuana-related performance effects.

A salient finding from the present investigation was that participants reported substantially more negative mood states (e.g., "bad drug effect" and "depressed") during the period following the 3 days of smoked marijuana administration. No such alterations were observed during oral $\Delta^9$-THC abstinence. While the finding that an abstinence syndrome can be observed following abrupt cessation of several days of smoked marijuana administration supports data from other clinical studies (Nowlan and Cohen 1977; Georgotas and Zeidenberg 1979; Mendelson et al. 1984; Haney et al. 1999b; Budney et al. 2001), the lack of an observed oral $\Delta^9$-THC abstinence syndrome here appears to be incongruent with previous studies (Jones et al. 1976, 1981; Haney et al. 1999a). Although the reason for this apparent inconsistency is unclear, it is possible that the tested doses of smoked marijuana and oral $\Delta^9$-THC were not well matched. This speculation seems unlikely because both drugs produced comparable effects. Another possibility is that differential formation of metabolites, depending on the route of administration, may decrease withdrawal symptoms. For example, the active metabolite 11-hydroxy-THC is produced in greater amounts following the oral route (Wall and Perez-Reyes 1981). It is possible that increased 11-hydroxy-THC limited the severity of $\Delta^9$-THC-related withdrawal symptoms following oral $\Delta^9$-THC by allowing a more gradual termination of $\Delta^9$-THC-related effects. By contrast, because relatively little 11-hydroxy-THC is present following smoking of marijuana, a more abrupt discontinuation of $\Delta^9$-THC-related effects may occur, causing more withdrawal symptoms. Additionally, because plasma $\Delta^9$-THC and its metabolites were not measured, the possible contribution of other cannabinoids to the current data is unknown.

An important limitation of the current study design is that only one active oral $\Delta^9$-THC dose and one smoked marijuana $\Delta^9$-THC concentration was examined. This point is particularly important given that the drugs produced differential effects on a few subjective-effects ratings (e.g., "high" and "mellow"). Perhaps if a broader range of active doses were studied, a greater range in effects on the dependent variables would have been observed. Despite this limitation, examination of individual participant data showed that there was considerable correspondence between data obtained following oral $\Delta^9$-THC and smoked marijuana. Another possible limitation of the present study is that the participants were already dependent on marijuana when they began the study. Thus, the baseline period was actually a marijuana abstinence period. In fact, several initial baseline negative subjective-effect ratings (e.g., "irritable" and "miserable") were higher in the present study than in other studies from this laboratory in which participants did not undergo an initial marijuana abstinence phase (Haney et al. 1997; Hart et al. 2002), suggesting the presence of abstinence symptoms during the baseline period.

In conclusion, the current results demonstrate that subjective, food intake, and psychomotor performance effects produced by oral $\Delta^9$-THC (20 mg) and smoked marijuana (3.1% $\Delta^9$-THC) are similar, although subjective effects produced by smoked marijuana were slightly more pronounced and less prone to the development of tolerance. Given that smoked marijuana, relative to oral $\Delta^9$-THC, has been shown to have a higher abuse liability (Mendelson and Mello, 1984) and is associated with an increased risk of toxicity (e.g., lung damage; Joy et al. 1999), these data suggest that oral $\Delta^9$-THC is a viable therapeutic option for increasing food intake. Future studies should assess a broader dose range of the two drugs and a wider range of effects produced by the drugs.

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