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Tolerability and effects of oral Δ^9-tetrahydrocannabinol in older adolescents with marijuana use disorders☆

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ABSTRACT

Objective: The tolerability and effects of oral Δ^9-tetrahydrocannabinol (THC) have been previously investigated in adult marijuana abusers. However, no studies have included adolescent participants. This double-blind laboratory study investigated the tolerability and effects of oral THC in a group of older adolescents with marijuana use disorders.
Methods: Eight participants (ages 16–21 years), smoking an average of 5.2 days/week and 2.5 "joints"/day, completed this four-session study, during which they received one of four oral THC doses (0, 2.5, 5, 10 mg) each session. Administration of oral THC doses was counterbalanced across participants. During each session, participants completed the Digit-Symbol Substitution Task (DSST) and subjective-effect ratings at baseline and 1, 2, and 3 h after oral THC administration.
Results: Oral THC (5 mg and 10 mg) increased several "positive" subjective-effect ratings (e.g., "Good Drug Effect"), while producing no significant effects on cardiovascular measures, DSST performance, or "negative" subjective-effect ratings.
Conclusions: These results indicate that oral THC was well tolerated and suggest further study of this medication in adolescent marijuana abusers.

1. Introduction

Marijuana is the most commonly used illicit drug in the world, and use usually begins during adolescence (International Narcotics Control Board, 2007; Substance Abuse and Mental Health Services Administration, 2007). In the U.S., for example, 42% of high school seniors have tried marijuana, 19% have used it in the last 30 days, and 5% use it daily (Johnston et al., 2007). Although most adolescents use the drug on an infrequent basis and without apparent negative consequences, an estimated 3.4% meet criteria for a marijuana use disorder (Substance Abuse and Mental Health Services Administration, 2007). Furthermore, adolescent marijuana users are more likely than adults to exhibit dependence symptoms and inability to cut down their use (Chen and Anthony, 2003).

Despite the clear indication that a significant minority of adolescent marijuana users exhibits problems related to use of the drug, adolescents have been the focus of few treatment studies, especially those investigating potential pharmacotherapies. By comparison, a growing number of studies have evaluated the effects of potential marijuana dependence treatment medications in adults. While a wide range of medications has been tested, including bupropion, nefazodone, divalproex sodium, and lofexidine, oral Δ^9-tetrahydrocannabinol (THC) appears to show the most promise (for review, see Hart, 2005). For example, this medication has been demonstrated to attenuate marijuana withdrawal symptoms in inpatient and outpatient laboratory settings among adults over age 21 (Haney et al., 2004; Budney et al., 2007). Given that marijuana-related withdrawal symptoms may be an impediment to cessation of use (Budney et al., 2008; Cornelius et al., 2008), and in light of the dearth of prior research into pharmacotherapy for adolescent marijuana use disorders, these findings indicate that further study of oral THC is warranted in younger marijuana abusers. It is important to note, however, that while single doses of oral THC as high as 30 mg have been studied in adult marijuana abusers (Budney et al., 2007), no prior published studies have explored *any* dose of this medication in adolescents. In the interest of safety, conservative dosing is warranted in initial adolescent pharmacotherapy studies (Roberts et al., 2003). Therefore, we undertook this initial double-blinded, outpatient, within-participant study to determine the tolerability of oral THC (0,

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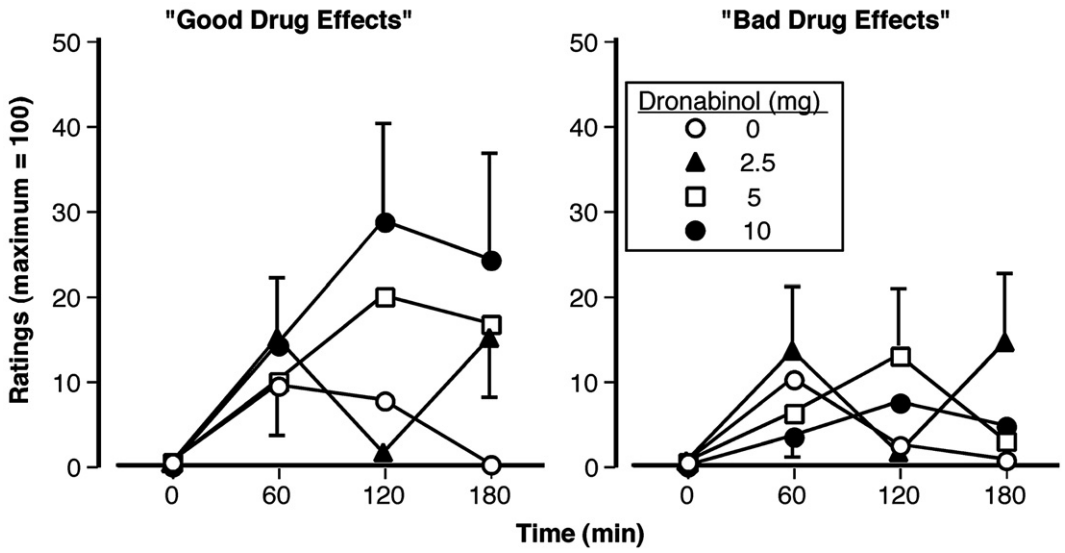

Fig. 1. Selected subjective-effect ratings as a function of oral THC dose and time. Error bars represent one SEM. Overlapping error bars were omitted for clarity. Ratings of "Good Drug Effect" were significantly increased by oral THC (5 and 10 mg: $p<0.05$).

2.5, 5, 10 mg) in a group of older adolescents with marijuana use disorders. The acute effects of oral THC were assessed on several dependent variables, including mood, psychomotor performance, blood pressure, and heart rate.

2. Methods

2.1. Participants

Eight non-treatment seeking participants (mean age [±SD]: 18.8±1.8 years, range 16–21) enrolled and completed this study; three were female (one Black, two White) and five were male (one Hispanic, one Native American, three White). Three met criteria for Marijuana Abuse and five met criteria for Marijuana Dependence. In the 30 days prior to study entry, participants reported smoking marijuana an average of 5.2±2.0 days/week and 2.5±1.5 "joints"/day. Prior to the study, all participants passed comprehensive medical and psychiatric evaluations, and none met criteria for any other Axis I disorder. The Medical University of South Carolina's Institutional Review Board approved this study, and procedures followed were in accordance with the Declaration of Helsinki. All participants 18 to 21 years old provided informed consent. For participants under 18 years old, parents or legal guardians provided informed consent and participants provided assent. All were advised that the study involved administration of oral THC. Potential effects and risks of this medication were discussed extensively. Participants were recruited via word-of-mouth, flyers posted on campus and around town, and local newspaper classified advertisements.

2.2. Design

Participants completed four outpatient laboratory sessions, separated by no less than 1 day and no more than 1 week. They were instructed to abstain from marijuana use 24 h prior to each session. Participants received one of four doses of oral THC (0, 2.5, 5, or 10 mg) during each session and doses were counterbalanced across participants. Physiological (blood pressure, heart rate), psychomotor, and subjective measures were assessed at baseline and repeatedly after drug administration (+60, +120, and +180 min). Adverse events were monitored by the study physician and systematically assessed using the Monitoring of Side Effects Scale (MOSES; Kalachnik, 2001).

2.2.1. Psychomotor performance task

Participants completed a computerized, 3-minute Digit Symbol Substitution Task (DSST; McLeod et al., 1982) designed to assess visual-spatial processing.

2.2.2. Mood

Participants completed a computerized Visual Analog Questionnaire (VAQ) to assess subjective effects of the medication. The VAQ consisted of a series of twenty-five 100-mm lines labeled "not at all" at on end and "extremely" at the other end (Hart et al., 2002a). The lines were labeled with words describing a mood (e.g., "Anxious," "Angry," "Frustrated"), a drug effect (e.g., "High," "Good Drug Effect," "Bad Drug Effect"), or a physical symptom (e.g., "Alert," "Tired," "Sedated"). Participants were also asked to estimate the "street value" of the dose they received each session.

Hourly assessments were sequenced as follows: blood pressure and heart rate (5 min), psychomotor task (5 min), and subjective measures (5 min).

The study physician conducted an assessment at the conclusion of each medication session to assess possible symptoms of THC intoxication. If participants exhibited symptoms of intoxication, they were observed in the laboratory until symptoms resolved. Participants were required to have someone else drive them home at the conclusion of each medication session, and they agreed not to drive or operate machinery for the remainder of the day. At the outset of each subsequent visit, participants were interviewed by the study physician and asked about any residual effects of oral THC from the prior medication session. At the conclusion of the study, participants were fully informed about experimental and drug conditions, and were compensated for their participation. Treatment information was also offered, even though participants did not express interest in treatment.

2.3. Medication

The Investigational Drug Service of the Medical University of South Carolina repackaged tablets of oral THC (2.5, 5, 10 mg; Marinol®, Solvay Pharmaceuticals, Inc.) by placing tablets into a white #00 opaque capsule and adding lactose filler. Placebo consisted of white #00 opaque capsules containing only lactose. All capsules were administered double blind.

Table 1
Peak oral THC effects on the visual analog scale (VAS)

Dronabinol Conditions							
Measure	Placebo	2.5 mg		5 mg		10 mg	
	Mean (SEM)	Mean (SEM)	*F* Value	Mean (SEM)	F Value	Mean (SEM)	*F* Value
Items on which oral THC increased VAS ratings							
Good drug effect	16.75 (8.56)	17.50 (7.47)	0.01	23.12 (8.46)	1.18	34.88 (12.86)	9.55*§
High	13.37 (6.38)	17.00 (11.99)	0.20	19.63 (8.26)	0.60	32.13 (13.07)	4.29*
Liked capsule	9.88 (6.18)	15.75 (7.36)	0.60	19.00 (7.64)	1.44	30.88 (13.03)	7.61*
High quality capsule	6.63 (3.97)	10.63 (6.15)	0.23	17.13 (8.14)	1.56	25.38 (12.99)	4.48*
Potent	5.00 (3.33)	7.75 (5.82)	0.12	15.75 (7.90)	1.98	25.63 (12.73)	6.62*§
Street value ($ U.S.)	1.12 (0.88)	1.75 (1.37)	0.12	2.75 (1.63)	0.86	4.88 (7.50)	2.83*
Items on which oral THC decreased VAS ratings							
Irritable	29.00 (9.46)	27.38 (8.02)	0.06	14.25 (7.09)	5.36*	18.00 (7.16)	2.98
Tired	86.38 (4.59)	67.88 (9.96)	3.23	61.75 (10.80)	5.74*	80.75 (8.11)	0.30

*$p<0.05$, significantly different from placebo.
§$p<0.05$, significantly different from 2.5 mg.

2.4. Data analysis

Repeated measures analyses of variance (ANOVAs) with planned comparisons were used to determine the effects of oral THC on subjective ratings and DSST performance. Dependent measures were analyzed using a two-factor ANOVA: the first factor was oral THC dose (0, 2.5, 5, and 10 mg) and the second factor was time (baseline, +60, +120, and +180 min). For all analyses, ANOVAs provided the error terms needed to calculate planned comparisons that were designed to determine the effects of oral THC dose, i.e., 0 mg vs. three active doses, 2.5 mg vs. two larger doses, and 5 mg vs. 10 mg. Data were considered statistically significant at $p<0.05$.

3. Results

Fig. 1 shows the effects of oral THC on selected subjective-effect ratings over time. The larger oral THC doses (5 and 10 mg) significantly increased ratings of "Good Drug Effect" as compared to placebo ($p<0.05$), while producing no significant effects on ratings of "Bad Drug Effect." A similar pattern of effects was observed when other ratings were examined. That is, oral THC significantly elevated "positive" subjective-effect ratings (e.g., capsule liking and the estimated monetary value of capsule), whereas the drug did not significantly alter "negative" subjective-effect ratings (e.g., confusion and inability to concentrate). Peak significant effects are summarized in Table 1. When peak individual subjective-effect data were examined, it is worth mentioning that two participants rated "good drug effects" and feeling "high" when they received placebo. Ratings were approximately 0 mm out of 1 0 mm. Although not statistically significant, it should be noted that the most common side effects included sedation (4 of 8 participants), increased thirst (3 of 8), dry mouth (3 of 8), and attention/concentration difficulty (2 of 8). These effects were mild and time-limited. Finally, oral THC did not alter DSST performance, heart rate, or blood pressure.

4. Discussion

The results from the present study indicate that acute administration of oral THC (5 and 10 mg) to older adolescent marijuana abusers increased positive subjective effects (e.g., ratings of "Good Drug Effect") without altering negative subjective effects. In addition, the drug produced no significant effects on psychomotor task performance or cardiovascular measures. In general, these findings replicate and extend data obtained under similar conditions in adult marijuana abusers (e.g., Hart et al., 2002b). This is the first report of oral THC-related acute effects in adolescents.

An important finding was that oral THC did not significantly alter cardiovascular measures. This contrasts with adult data indicating ~30% increased heart rate after administration of 10 mg oral THC (Hart et al., 2005). Of note, tolerance to THC cardiovascular effects, including heart rate, may occur after chronic marijuana use (Ponto et al., 2004) or after only a few doses of oral THC (Benowitz and Jones, 1975, 1981). It may be that the 24-hour pre-session marijuana abstinence period, and the minimum of 24 h between oral THC doses, in the present study may have been insufficient to negate cardiovascular tolerance to cannabinoids. Additionally, the participants in the present study may have been more tolerant to cardiovascular effects due to a higher baseline rate of marijuana use, when compared with similar adult studies, including the 2005 study by Hart and colleagues.

Prior literature on the effects of THC on psychomotor performance have been mixed. Upon acute marijuana smoking among adult participants, results have varied between studies, demonstrating no effect on DSST task performance (Hart et al., 2001; Pickworth et al., 1997), mild impairment in task speed only (Heishman et al., 1988), and significant dose-dependent impairment in task performance (Heishman et al., 1989, 1997; Wilson et al., 1994). Upon acute administration of oral THC (5, 10, 15, and 20 mg) to adult marijuana smokers, significant dose-dependent DSST task impairment has been noted (Chesher et al., 1990). However, another study only noted DSST impairment at a 20 mg dose (Hart et al., 2005). As such, the present study may not have explored a sufficiently large dose to elicit task performance impairment.

The largest oral THC dose (10 mg) produced significant elevations of "positive" subjective-effects ratings. This is important for two reasons. First, positive subjective effects support the acceptability of oral THC in this population. Second, these effects may prompt concern about potential reinforcement and risk for abuse and diversion of this medication if used clinically in adolescent marijuana abusers. While data from previous research demonstrate that oral THC may produce relatively modest reinforcing effects (Calhoun et al., 1998, Hart et al., 2005), if prescribed in a clinical setting, careful monitoring of this medication would be warranted.

The present results should be considered in light of methodological limitations. Most importantly, this study involved administration of oral THC in single doses in a laboratory environment. As such, the tolerability and effects observed may not translate to repeated dosing or to less controlled settings. Additionally, the study monitored dose effects only for 3 h after administration. As some measures of drug effects continued to rise at 3 h, it will be important to monitor effects for a longer period in future studies. Another limitation is that the time elapsed between sessions (minimum 24 h) introduced the potential for carry-over effects of prior oral THC dosing during subsequent sessions. However, adult data suggest that psychoactive effects of oral THC do not persist 24 h after administration (Curran et al., 2002).

It is possible, given the known potential adverse effects of adolescent exposure to THC via marijuana use, that the administration

of oral THC to adolescents may be viewed as ethically questionable. However, in the present study, participants had been using marijuana in quantities that, over chronic exposure, far exceeded the amount of THC administered in the laboratory. Additionally, oral THC, due to its route of administration, lacks the respiratory risks of smoked marijuana. It may be argued that short-term exposure to oral THC is not likely to convey significant additional long-term health risk in the context of chronic, heavy marijuana smoking.

In conclusion, the current data show that single doses of oral THC, up to 10 mg, were well tolerated in a sample of older adolescents with marijuana use disorders. Because this was the first study of oral THC in adolescents, relatively low doses were examined. The finding that the drug did not substantially alter cardiovascular measures or psychomotor performance lays the groundwork for further testing of this medication in adolescent marijuana abusers. Given the dearth of research in this area, future studies may take several directions. For example, in the area of medication development, research should investigate the effects of oral THC on marijuana withdrawal (Budney et al., 2007, 2008; Cornelius et al., 2008; Haney et al., 2004).

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