Delta-9-Tetrahydrocannabinol Effects in Schizophrenia: Implications for Cognition, Psychosis, and Addiction

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Background: *Recent advances in the neurobiology of cannabinoids have renewed interest in the association between cannabis and psychotic disorders.*

Methods: *In a 3-day, double-blind, randomized, placebo-controlled study, the behavioral, cognitive, motor, and endocrine effects of 0 mg, 2.5 mg, and 5 mg intravenous Δ-9-tetrahydrocannabinol (Δ-9-THC) were characterized in 13 stable, antipsychotic-treated schizophrenia patients. These data were compared with effects in healthy subjects reported elsewhere.*

Results: *Delta-9-tetrahydrocannabinol transiently increased 1) learning and recall deficits; 2) positive, negative, and general schizophrenia symptoms; 3) perceptual alterations; 4) akathisia, rigidity, and dyskinesia; 5) deficits in vigilance; and 6) plasma prolactin and cortisol. Schizophrenia patients were more vulnerable to Δ-9-THC effects on recall relative to control subjects. There were no serious short- or long-term adverse events associated with study participation.*

Conclusions: *Delta-9-tetrahydrocannabinol is associated with transient exacerbation in core psychotic and cognitive deficits in schizophrenia. These data do not provide a reason to explain why schizophrenia patients use or misuse cannabis. Furthermore, Δ-9-THC might differentially affect schizophrenia patients relative to control subjects. Finally, the enhanced sensitivity to the cognitive effects of Δ-9-THC warrants further study into whether brain cannabinoid receptor dysfunction contributes to the pathophysiology of the cognitive deficits associated with schizophrenia.*

Key Words: Delta-9-tetrahydrocannabinol, cannabinoids, cannabis, self-medication, cognition, schizophrenia

The relationship between cannabis and schizophrenia is of interest from two perspectives. First, recent studies suggest a possible causal relationship between cannabis and schizophrenia (Arseneault et al 2002; van Os et al 2002; Zammit et al 2002), and recent advances in the neurobiology of cannabinoids have renewed interest in this association. Second, cannabis is one of the illicit substances most commonly used/misused by schizophrenia patients (McCreadie 2002).

Cannabis use has been reported to have a negative impact on the expression and course of schizophrenia (Linszen et al 1994; Negrete and Knapp 1986; Negrete et al 1986). In contrast, studies based on self-report of subjective effects suggest that schizophrenia patients use substances such as cannabis to "self-medicate" negative symptoms, depression, and side effects of antipsychotics, to relieve boredom, to provide stimulation, to "feel good," to "get high," or to "relax" and to socialize with peers (Addington and Addington 1997; Addington and Duchak 1997; Brunette et al 1997; Dixon et al 1991; Fowler et al 1998; Goswami et al 2004; Peralta and Cuesta 1992; Schneier and Siris 1987). These studies, however, rely on retrospective self-report and therefore are subject to denial and rationalization, both of which play a role in substance misuse disorders. Cannabis alters perception and has amnestic effects, both of which influence the recall of events. Furthermore, because cannabis is often used in combination with other substances, sometimes without knowledge of the user, attributing certain effects solely to cannabis is difficult. Finally, it is possible that the positive and negative effects of cannabis might be dose related, and this could be only crudely assessed in existing studies. The contrasting conclusions of self-report and epidemiologic studies raise the possibility that schizophrenia patients might derive some immediate "benefits" from cannabis at the expense of later, negative consequences.

The present study was undertaken to characterize the dose-related effects of the principal active ingredient of cannabis, Δ-9-tetrahydrocannabinol (Δ-9-THC), in schizophrenia patients under controlled laboratory conditions according to standardized assessments. Delta-9-tetrahydrocannabinol was hypothesized to reduce certain symptoms and medication side effects in schizophrenia patients at the expense of worsening others. Another goal was to compare the effects of Δ-9-THC in schizophrenia patients with those in healthy subjects ($n = 22$) who participated in a parallel study (D'Souza et al 2004). We hypothesized group differences in the effects of Δ-9-THC on measures of memory, attention, positive symptoms, perceptual alterations, and hormones.

Methods and Materials

The study was conducted at the Neurobiological Studies Unit, VA Connecticut Healthcare System (VACT), West Haven, Connecticut and the Abraham Ribicoff Research Facilities, Connecticut Mental Health Center, New Haven, Connecticut. Subjects were recruited by advertisements and by word of mouth and were paid for their participation. The methods of the parallel study involving healthy subjects were identical to those of the

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current study (D'Souza et al 2004). This study was approved by the Protocol Review Committee of the Department of Psychiatry, Yale University School of Medicine (YUSM), New Haven, Connecticut and the institutional review boards of both VACT and YUSM. The study was carried out in accordance with the Helsinki Declaration of 1975.

Consent Process

During the consent process, which lasted a minimum of three sessions, subjects were informed that the study 1) was not a treatment for schizophrenia; 2) carried the risk of symptom worsening, relapse, and hospitalization; and 3) was not a sanction to use cannabis. Subjects were also aware that they could drop out at any time. Subjects were required to correctly answer at least 80% of a questionnaire about the study risks and benefits. They were also required to correctly answer two critical questions about the anticipated negative effects of Δ-9-THCs on their symptoms and whether the study was designed as a treatment. The subject's clinician, significant other(s), or the family were involved in the consent process. An independent clinician who was not a member of the research team was involved in the consent process to monitor the integrity of the consent process and to establish ties with the subject to serve as an ombudsperson over the course of the study. The subject's clinician and ombudsperson held the authority both to deny subjects entry into and to withdraw subjects from the study.

Screening

Diagnosis of schizophrenia or schizoaffective disorder was confirmed by interview with a research psychiatrist, a structured psychiatric interview for DSM-IV (Spitzer et al 1990), and chart review. Subjects who were deemed clinically unstable as evidenced by recent or current hospitalization, homicidality, suicidality, and/or grave disability were excluded. Cannabis-naïve individuals were excluded to minimize any risk of promoting future cannabis use/abuse. Only those subjects with at least one exposure to cannabis but without a lifetime cannabis use disorder were included. Subjects were excluded for recent (3 months) abuse of or dependence (1 year) on substances, excluding nicotine. A general physical and neurologic examination, electrocardiogram, and laboratory tests (serum electrolytes, liver function tests, complete blood count with differential, and urine toxicology) were also conducted. Healthy subjects (n = 22) were recruited and screened in parallel, as described elsewhere (D'Souza et al 2004).

Test Days

Subjects completed 3 test days, during which they received 5 or 2.5 mg of Δ-9-THC or vehicle (ethanol) by intravenous (IV) route in a randomized, counterbalanced order under double-blind conditions. The IV route of administration was chosen to reduce inter- and intra-individual variability in plasma Δ-9-THC levels with smoking (Azorlosa et al 1992). The latter is influenced by the rate, depth, and duration of puffs, the volume inhaled, the duration of breath-holding, pulmonary dead space and vital capacity, the amount lost by smoke escaping into the air, and a subject's adeptness at smoking. The doses chosen were based on previous studies demonstrating the feasibility and safety of IV Δ-9-THC administration (Agurell et al 1986; Lindgren et al 1981; Ohlsson et al 1980; Volkow et al 1991, 1996). Because there are no data regarding the amount of Δ-9-THC schizophrenia patients receive or extract from a typical cannabis cigarette, the doses chosen were extrapolated from known data in the general population. There is great variability in the weight (.2–1 g) of a typical cannabis cigarette (Adams and Martin 1996), the Δ-9-THC content (19–43 mg) of cannabis (Adams and Martin 1996; ElSohly et al 2000), and the levels of other cannabinoids in cannabis that contribute to the net effect of cannabis and modulate Δ-9-THC effects (Karniol and Carlini 1973; Karniol et al 1974, 1975; Turner et al 1980). Because only 10%–25% of the Δ-9-THC content of a cannabis cigarette enters the circulation when smoked (Adams and Martin 1996), the available Δ-9-THC dose range is 2–11 mg. The doses used in this study (2.5 and 5 mg) are within the dose range of recreational cannabis use and mimic the time course of plasma Δ-9-THC levels associated with the clinical "high" (Agurell et al 1986; Lindgren et al 1981; Ohlsson et al 1980) associated with .5–1.5 of a standard National Institute on Drug Abuse cannabis cigarette.

Test days were separated by at least 1 week (more than 3 times the elimination half-life of Δ-9-THC) to minimize carryover effects. Subjects were instructed to refrain from consuming caffeinated beverages, alcohol, and illicit drugs from 2 weeks before testing until study completion; self-reported abstinence was confirmed on each test day. Subjects fasted overnight, reported to the test facility at approximately 8 AM, and were provided a standard breakfast. They were permitted to take only their morning dose of antipsychotic medication and side-effect medication. No other medications were permitted until the completion of each test day. Smoking was not permitted beyond 1 hour before the beginning of testing. Illicit drug use and pregnancy were ruled out by urine tests on the morning of each test day. Subjects were attended to by a research psychiatrist, a research nurse, and a research coordinator. Clear "stopping rules" were determined a priori, and rescue medications (lorazepam and haloperidol) were available if necessary.

Outcome Measures

Cognitive. A cognitive test battery in a fixed sequence was initiated 30 min after Δ-9-THC administration. It was decided a priori that if subjects took extra time to complete the behavioral ratings, specific tests in the fixed sequence of the cognitive battery would be dropped. The hippocampus has a high density of cannabinoid receptors (Herkenham et al 1991), cannabinoids impair learning and recall (reviewed in Lichtman et al 2002), and the hippocampus plays a critical role in learning and recall. Therefore, learning and immediate and delayed recall were measured with the Hopkins Verbal Learning Test (Brandt 1991; Bylsma et al 1991). The Hopkins Verbal Learning Test consists of three consecutive trials of immediate free recall of a 12-item semantically categorized list, followed 30 min later by testing of delayed free, cued, and recognition recall. One of six equivalent versions of the test was administered on each test day. Cannabinoids have been shown to impair performance on several attentional tasks in animals and humans (Abood and Martin 1992; Hooker and Jones 1987; Johns 2001; Marks and MacAvoy 1989; Pope et al 2001; Verrico et al 2004). Moreover, some of these cognitive deficits might persist in long-term users of marijuana even after cessation of use (Solowij 1998; Solowij et al 1991). Therefore, vigilance and distractibility to visual stimuli were measured with a continuous performance task (Gordon 1986) in which subjects attended to numbers presented sequentially on a screen. Subjects were instructed to push a button to signal when a "1" was preceded by a "9." The distractibility task was identical to the vigilance task, with the exception that numbers were presented sequentially in three contiguous columns. Subjects were instructed to attend to the middle column and ignore the

outer two columns. Finally, the verbal fluency test was included because it has been shown to be sensitive to frontal cortical function, and cannabinoids have been shown to impair many aspects of frontal cortical function (Cabeza et al 2000; Indefrey and Levelt 2004; Lundqvist et al 2001; McGraw et al 2001; Solowij 1998; Solowij et al 1991). The verbal fluency task requires subjects to generate as many words as possible beginning with a specified letter during a 1-min interval (Corkin et al 1964). Equivalent versions of this task were administered on the 3 test days with letters equated for frequency in English (Borkowski et al 1967).

Behavioral. Behavioral ratings were conducted periodically as in Table 1 and are described in further detail elsewhere (D'Souza et al 2004). Ratings were also readministered 140 min after Δ-9-THC administration to capture Δ-9-THC effects retrospectively, because the intensity of peak THC effects at the +10 and +80 time points were predicted to interfere with self-report. By this time (+140 min) the intoxicating effects of cannabis have worn off, and subjects are able to reflect back about the peak effects earlier in the study. This allowed us to tease out any potential overlap in behavioral effects. Clinically significant increases in positive symptoms were defined as a 3-point or greater increase in the PANSS positive symptom subscale. Positive, negative, and general symptoms were assessed with relevant subscales of the Positive and Negative Syndrome Scale (PANSS) (Kay et al 1989), perceptual alterations were measured with the Clinician-Administered Dissociative Symptoms Scale (CADSS) (Bremner et al 1998), and feeling states associated with cannabis intoxication were measured with a self-reported visual analogue scale of four items ("high," "calm and relaxed," "tired," and "panic") (Haertzen 1965, 1966). The same research coordinators rated all 3 days of a subject, and the same staff rated both schizophrenia patients and healthy control subjects. Interrater reliability sessions were conducted every 1 to 2 months. The intraclass coefficient for positive and negative symptom subscales of the PANSS were consistently greater than .85.

Motor. A motor evaluation battery that included scales for drug-induced parkinsonism (Simpson and Angus 1970), akathisia (Barnes 1989), and dyskinesia (Abnormal Involuntary Movements Scale; Guy et al 1978) were administered with the subject sitting in bed. Because subjects were not allowed to ambulate during testing for safety reasons, the Simpson Angus Scale for parkinsonism was modified to include only the items for tremor and a composite rigidity score (shoulders, elbows, wrist, head rotation).

Neurochemical. Blood was sampled from the IV line opposite to the one used for administering the study drug, for Δ-9-THC and its primary inactive metabolite (11-nor-9-carboxy-Δ-9-tetrahydrocannabinol [11-nor-Δ-9-THC-9-COOH]), and also to provide a behaviorally independent measure of cannabinoid effects by assaying prolactin and cortisol (D'Souza et al 2004). For Δ-9-THC and its main metabolite, only blood samples from the two active THC conditions were assayed. Immediately after collection, blood samples were put on ice and centrifuged, and the extracted plasma was alliquoted into vials for storage at −70°C until time of assay. Prolactin and cortisol were assayed in duplicate with radioimmunoassay, whereas Δ-9-THC and 11-nor-Δ-9-THC-9-COOH were assayed by gas chromatography mass spectroscopy, as described elsewhere (D'Souza et al 2004).

Safety. Vital signs were recorded periodically. A field sobriety test was conducted at the end of each test day. On completing the last test day, an exit interview was conducted to determine whether subjects had been adequately informed be-

Table 1. Schedule of Procedures

Time (min)	Procedure
−90	Confirmation of abstinence from caffeine, alcohol, drugs, medications
	Vital signs
	Urine drug screen, urine pregnancy test
	Placement of intravenous lines
−60	Behavioral assessments
	PANSS
	CADSS
	VAS for "high," "calm and relaxed," "tired," and "panic"
	Motor assessments: parkinsonism (Simpson Angus), akathisia (Barnes), dyskinesia (AIMS)
	Blood sampling: Δ-9-THC, cortisol, prolactin
	Vital signs
0	IV Δ-9-THC (0, 2.5, or 5 mg) over 2 min
+10	Vital signs: every 2 min (10 min) followed by every 5 min (20 min) and then every 10 min
	Behavioral Assessments
	PANSS
	CADSS
	VAS for "high," "calm and relaxed," "tired," and "panic"
	Blood sampling: Δ-9-THC, cortisol, prolactin
	Motor assessments: parkinsonism (Simpson Angus), akathisia (Barnes), dyskinesia (AIMS)
+30	Learning (immediate recall): HVLT
	Verbal fluency
	Free, cued, and recognition delayed recall: HVLT
	Distractibility and vigilance: Gordon Box
+50	Vital signs
+80	Behavioral Assessments
	PANSS
	CADSS
	VAS for "high," "calm and relaxed," "tired," and "panic"
	Blood sampling: Δ-9-THC, cortisol, prolactin
	Vital signs
+140	Retrospective behavioral assessments to capture peak effects that occurred between 0 and +140 minutes
	PANSS
	CADSS
	VAS for "high," "calm and relaxed," "tired," and "panic"
	Blood sampling: Δ-9-THC, cortisol, prolactin
	Vital signs
+200	Behavioral assessments
	PANSS
	CADSS
	VAS for "high," "calm and relaxed," "tired," and "panic"
	Blood sampling: Δ-9-THC, cortisol, prolactin
	Vital signs
End of each day	Field sobriety test, Mini-Mental State Examination, vital signs, physician evaluation
Last day	Exit interview
Months 1, 3, 6	Assessment of cannabis use, desire, craving
	Assessment for emergence of new psychiatric or medical problems

PANSS, Positive and Negative Syndrome Scale; CADSS, Clinician-Administered Dissociative Symptoms Scale; VAS, visual analog scale; AIMS, Abnormal Involuntary Movements Scale; Δ-9-THC, Δ-9-tetrahydrocannibinol; HVLT, Hopkins Verbal Learning Test.

fore study participation and to obtain feedback regarding study procedures. The study was amended to include prospective assessments of safety. One, 3, and 6 months after the last test session cannabis use, the emergence of any new medical or psychiatric symptoms and the course of schizophrenia (number of emergency room visits, and hospitalizations) were assessed. For those subjects who were not evaluated prospectively, a retrospective assessment was conducted.

Statistical Analyses

All analyses were performed in SAS version 8.2 (SAS Institute, Cary, North Carolina). The change from baseline data was assessed for normality before analysis according to normal probability plots and Kolmogorov-Smirnov test statistics. Positive and Negative Syndrome Scale subscale scores, VAS scores, and CADSS clinician and subject ratings were analyzed in SAS PROC MIXED according to mixed-effects models with dose (placebo, 2.5 mg, and 5 mg), time (P10 − baseline, P80 − baseline, P200 − baseline), and dose × time interaction as fixed effects and structured variance–covariance pattern matrix (Brown and Prescott 1999). The best-fitting variance–covariance matrix according to the Akaike Information Criterion was selected. Order effect was considered in all models but was never significant at the .05 level and hence was dropped from all models except for the continuous performance task and extrapyramidal symptoms data, where it was significant. When a significant dose × time interaction was observed, follow-up pairwise comparisons between the least squares means at the three doses at P10 and at P80 were performed. Recall (Hopkins Verbal Learning Test), measures of vigilance and distractibility, verbal fluency, and retrospective behavioral data were analyzed according to mixed models with dose as a fixed effect and a structured variance–covariance matrix. The overall α level for each hypothesis was fixed at the .05 level. When the dose effect was significant, follow-up pairwise comparisons between doses were performed. Bonferroni correction was applied within but not across hypotheses.

All the behavioral assessments and cognitive tests showed the absence of variance during the placebo Δ-9-THC (vehicle) administration in healthy subjects. For example, as expected, healthy control subjects had no PANSS positive symptom scores at baseline, and this did not change after administration of placebo Δ-9-THC. Furthermore, behavioral responses during the Δ-9-THC conditions were highly skewed in healthy subjects. These two factors precluded the application of typical analyses of variance or mixed models to the comparison between the behavioral responses of healthy control subjects and of schizophrenia patients. Hence, we used a nonparametric approach (Brunner 2002) with group as a between-subjects factor. For all repeatedly measured outcomes within a test day (PANSS, CADSS, VAS) the %F1_LD_F2 SAS macro was used, and dose and time were included as within-subject factors. For all outcomes measured only once per test day (recall, distractibility, vigilance) the %F1_LD_F1 macro was used, and dose was included as a within-subject factor. Relative effects plots were used to interpret significant interactions and main effects.

Results

Of 20 subjects screened, 4 were found ineligible, and 3 did not initiate the study. Thirteen subjects completed at least 1 test day, 12 subjects at least 2 test days, and 9 subjects completed all 3 test days. Test days for some subjects had to be rescheduled because of scheduling conflicts (n = 2) and discovery that subjects had taken a prohibited substance (caffeine, unapproved medication, or alcohol) within 2 weeks of testing (n = 1). Subjects had mild to moderate baseline symptoms, were all receiving stable doses of antipsychotic medications (Table 2), and had all been exposed to cannabis (Table 3). Because analyses of the principal outcome measures in a proportion (n = 13) of the intended sample (n = 20) were compelling, the study was terminated to avoid exposing any more subjects to potential risk. For parsimony, only those retrospective data that conflict with data collected at other time points are reported. Schizophrenia subjects and healthy subjects were significantly different for age, education, socioeconomic status, smoking status, and treatment with antipsychotic drugs but not for lifetime cannabis exposure (Table 3).

Table 2. Demographics

	Schizophrenia Patients (n = 13)	Healthy Subjects (n = 22)
Gender	10 men, 3 women	14 men, 8 women
Age (y)		
All	44.46 ± 10.4	29 ± 11.6
Men	45.6 ± 10.8	30.4 ± 11.8
Women	40.67 ± 14	26.8 ± 11.6
Education (y)		
All	14 ± 1.96	16.3 ± 1.9
Men (n = 10)	13.4 ± 1.28	16.4 ± 2
Women (n = 3)	16 ± 4.38	16.1 ± 1.9
Handedness		
Right	10	18
Left	3	4
Race		
Caucasian	6	15
African American	5	6
Native American	1	0
Hispanic	1	0
Indian	0	1
Smoking status	11	5
Weight (lb)		
All	165.33 ± 27.23	174.7 ± 46.4
Men (n = 11)	172.43 ± 24.9	184.1 ± 40.2
Women (n = 3)	140.5 ± 54.85	158.1 ± 54.3
Diagnosis		
Paranoid	9	
Undifferentiated	2	
Catatonic	0	
Disorganized	0	
Schizoaffective	2	
Symptomatology (PANSS Total Score)	34.1 (9.4)	
Medications		
Haloperidol	2	
Haloperidol Decanoate	1	
Fluphenazine	1	
Fluphenazine Decanoate	3	
Thiothixene	3	
Risperidone	1	
Olanzapine	2	
Lithium carbonate	2	
Benztropine	5	

Data are presented as n or mean ± SD.

Table 3. Cannabis Use History

	Schizophrenia Patients	Healthy Subjects
Estimated Lifetime Cannabis Exposure (No. of Exposures)		
<5	5	7
5–10	1	0
11–20	1	3
21–50	3	2
51–100	0	4
>100	3	6
Last Exposure to Cannabis		
Past wk	1	0
1 wk–1 mo	0	4
1–6 mo	0	6
6 mo–1 y	2	1
1–5 y	3	4
5–10 y	0	3
>10 y	7	4

Learning and Recall (Hopkins Verbal Learning Test)

Learning and recall results are illustrated in Figure 1. Delta-9-tetrahydrocannabinol impaired immediate recall [dose $F(2,14.9) = 19.64$, $p < .0001$; trial $F(2,26) = 12.08$, $p = .0002$] and learning across trials [dose × trial $F(4,30.4) = 3.59$, $p = .0165$]. With successive trials the dose-related effects of Δ-9-THC became more evident. For the second immediate recall trial, there were significant differences between placebo and both active doses [0 vs. 2.5 mg: $F(1,18.1) = 8.91$, $p = .0079$; 0 vs. 5 mg: $F(1,18.2) = 13.04$, $p = .002$], and for the third trial the pairwise comparisons among all three dose groups were significant [0 vs. 2.5 mg: $F(1,13.3) = 29.8$, $p < .0001$; 0 vs. 5 mg: $F(1,13.4) = 58$, $p < .0001$; 5 vs. 2.5 mg: $F(1,13.2) = 8.15$, $p = .0134$].

Delta-9-tetrahydrocannabinol significantly impaired delayed free recall [dose $F(2,16.5) = 6.7$, $p = .0074$] and delayed cued recall [dose $F(2,17.8) = 6.15$, $p = .0093$], with significant differences between placebo and both active doses. Although Δ-9-THC impaired delayed recognition recall [dose $F(2,27) = 3.5$, $p = .0445$], only the difference between placebo and 5 mg was significant. Delta-9-tetrahydrocannabinol also increased the number of intrusions [dose $F(2,18.4) = 4.12$, $p = .0332$], with significant differences between placebo and 5 mg. Finally, Δ-9-THC increased the number of false positives generated during recall [dose $F(2,17.8) = 4.88$, $p = .0205$], with significant differences between placebo and 5 mg.

Relative to healthy control subjects, schizophrenia patients performed worse on the immediate recall tasks at baseline [group $\chi^2(1) = 23.248$, $p = .00$]. Furthermore, schizophrenia patients were more sensitive to the dose-related learning impairments produced by Δ-9-THC [group × trial $\chi^2(1.67) = 4.66$, $p = .014$; group × trial × dose: $\chi^2(2.30) = 3.83$, $p = .017$]. Relative to control subjects, schizophrenia patients performed worse on delayed free recall [group $\chi^2(1) = 22.048$, $p = .00$], delayed cued recall [$\chi^2(1) = 13.36$, $p = .00026$], and delayed recognition recall [$\chi^2(1) = 7.12$, $p = .00763$], but there were no significant dose × groups interactions for any of these tasks.

Distractibility and Vigilance. Because of time limitations, only 7 subjects were able to complete the distractibility and vigilance tasks for all test days. Delta-9-tetrahydrocannabinol increased omission errors in the vigilance task, with a trend toward significance [dose $F(2,12.3) = 2.88$, $p = .09$] but had no significant effect on commission errors. Delta-9-tetrahydrocannabinol did not have significant effects on omission and commission errors in the distractibility task.

Although there were significant group differences in hit rates for the distractibility [$\chi^2(1) = 31.159$, $p = .00$] and vigilance [$\chi^2(1) = 17.295$, $p = .00003$] tasks between schizophrenia patients and control subjects, there were no significant group × dose interactive effects (Table 4).

Verbal Fluency. Delta-9-tetrahydrocannabinol did not have significant effects on the number of words generated in 1 min or the number of perseverations.

Symptoms of Psychosis (Positive and Negative Syndrome Scale)

Positive Symptoms (PANSS). Delta-9-tetrahydrocannabinol transiently increased scores of the PANSS positive symptoms subscale [dose $F(2,68) = 5.26$, $p = .0075$; time $F(2,68) = 19.77$, $p < .0001$; dose × time $F(4,68) = 4.90$, $p = .0016$], with significant differences at the 10-min (P10) and 80-min (P80) time points between placebo and both 2.5 mg and 5 mg

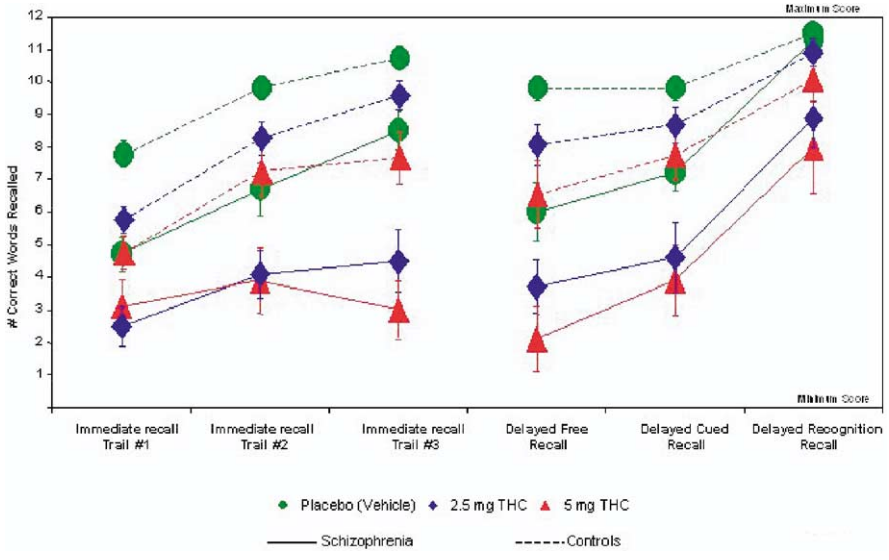

Figure 1. Learning and recall (means ± SEM) according to the Hopkins Verbal Learning Test. THC, Δ-9-tetrahydrocannabinol.

Table 4. Delta-9-Tetrahydrocannibinol (Δ-9-THC) Effects on Neuropsychological Test Performance

Outcome Measure	Placebo	2.5 mg Δ-9-THC	5 mg Δ-9-THC	Dose Effect
Hopkins Verbal Learning Test				
n	12	12	9	
Immediate recall total	19.8 ± 6	10.3 ± 8	7.8 ± 7.4	Dose: $F(2,14.9) = 19.64$, $p < .0001$ Trial: $F(2,26) = 12.08$, $p = .0002$
Immediate recall 1	4.7 ± 1.8	2.5 ± 2.2	3.1 ± 2.5	Dose × trial: $F(4,30.4) = 3.59$, $p = .0165$
Immediate recall 2	6.7 ± 2.8	4.1 ± 2.6	3.9 ± 3	Immediate recall 2: 0 vs. 2.5 mg: $F(1,18.1) = 8.91$, $p = .0079$ 0 vs. 5 mg: $F(1,18.2) = 13.04$, $p = .002$
Immediate recall 3	8.5 ± 2.1	4.5 ± 3.3	3 ± 2.7	Immediate recall 3: 0 vs. 2.5 mg: $F(1,13.3) = 29.8$, $p < .0001$ 0 vs. 5 mg: $F(1,13.4) = 58$, $p < .0001$ 5 vs. 2.5 mg: $F(1, 13.2) = 8.15$, $p = .0134$
Delayed free recall	6 ± 3.1	3.7 ± 2.8	2.1 ± 3	$F(2,16.5) = 6.7$, $p = .0074$
Delayed recognition recall	11.3 ± .5	8.9 ± 3.2	8 ± 4.2	$F(2,27) = 3.5$, $p = .0445$
Intrusions	.9 ± 1.4	2.5 ± 2.5	3.6 ± 2.5	$F(2,18.4) = 4.12$, $p = .0332$
False positives	1.2 ± 2.2	3 ± 2.1	4 ± 4	$F(2,17.8) = 4.88$, $p = .0205$
Perseverations	.6 ± .7	1.2 ± 1.6	.6 ± 1	$F(2,18.5) = 1.41$, $p = .2704$
Vigilance				
n	12	11	7	
Omission errors	4.4 ± 5.3	7.5 ± 8.3	9 ± 6.6	$F(2,12.3) = 2.88$, $p = .09$
Commission errors	3.6 ± 5.6	6.5 ± 8.6	11.3 ± 20.3	$F(2,16.9) = 1.52$, $p = .246$
Distractibility				
n	12	11	7	
Omission errors	14.4 ± 10.3	18.7 ± 7.5	18.5 ± 8.4	$F(2,15.7) = 2.26$, $p = .137$
Commission errors	14.6 ± 27.1	19.7 ± 19	16.3 ± 9.1	$F(2,15.4) = 2.31$, $p = .133$
Verbal Fluency				
n	12	12	9	
No. words generated	11.1 ± 2.6	10 ± 4.5	7.6 ± 4.7	$F(2,16.4) = 2.47$, $p = .1153$
Perseverations	0.5 ± .9	0.5 ± .5	0.4 ± .5	$F(2,17.8) = .32$, $p = .73$

Δ-9-THC, but not between the two active doses. By the last time point, positive symptoms returned to baseline levels (Figure 2).

With a threshold score of clinically significant positive symptoms (PANSS positive symptom subscale score ≥3 points) defined a priori, schizophrenia patients seemed to be more sensitive to the effects of Δ-9-THC. Eighty percent of the schizophrenia group but only 35% of control subjects had a suprathreshold response to 2.5 mg Δ-9-THC, and 75% of schizophrenic patients but only 50% of control subjects had a suprathreshold response to 5 mg Δ-9-THC (Figure 3); however, the interactions between group, dose, and time were not significant [$\chi^2(2.87) = .42$, $p = .73$].

Negative Symptoms (PANSS). Delta-9-tetrahydrocannabi-

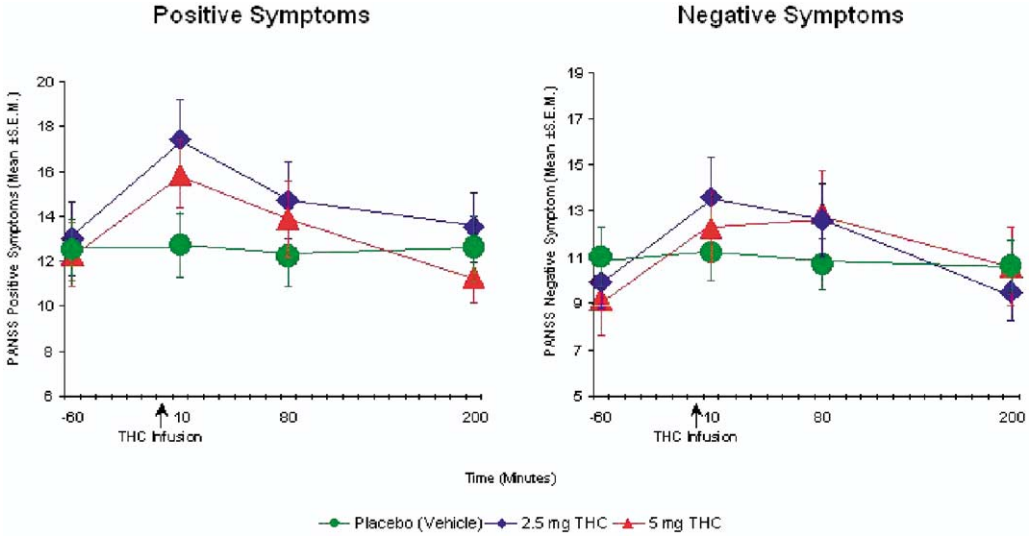

Figure 2. Positive and negative symptoms (means ± SEM) according to the Positive and Negative Symptoms Scale (PANNS). THC, Δ-9-tetrahydrocannabinol.

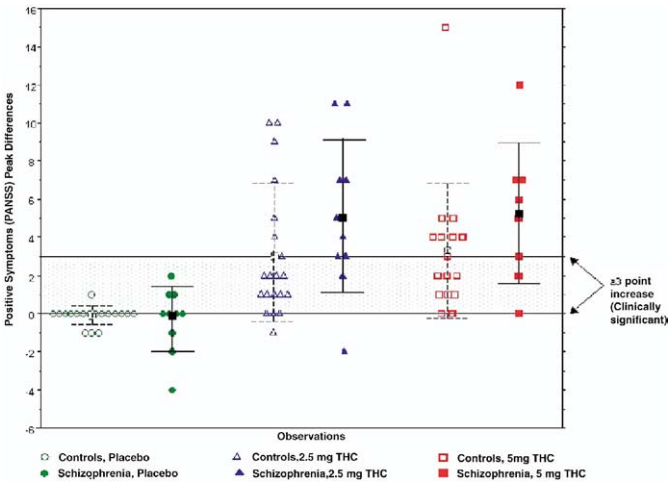

Figure 3. Peak increase in Positive and Negative Symptoms Scale (PANNS) positive symptoms (group means ± 1 SD).

nol transiently increased scores of the PANSS negative symptoms subscale (Figure 2); although the dose effect was significant, the dose × time interaction was not [time $F(2,26.7) = 7.24$, $p = .0031$; dose $F(2,16.7) = 3.61$, $p = .0499$; dose × time $F(4,31.3) = 1.96$, $p = .125$]. Subjects were reported to seem more blunted, less talkative, less spontaneous, and more internally preoccupied.

General Symptoms (PANSS). Delta-9-tetrahydrocannabinol transiently increased scores of the PANSS general symptoms subscale [time $F(2,52.7) = 8.14$, $p = .0008$; dose $F(2,16.7) = 1.91$, $p = .17$; dose × time $F(4,52.9) = 4.31$, $p = .0043$], including somatic concern, guilt feelings, tension, uncooperativeness, unusual thought content, poor attention, and preoccupation. The increases in general symptoms between placebo and 5 mg were significantly different both 10 min and 80 min after Δ-9-THC administration.

Perceptual Alterations (Clinician-Administered Dissociative Symptoms Scale)

Delta-9-tetrahydrocannabinol transiently increased scores of the CADSS clinician-rated perceptual alterations subscale [dose $F(2,23) = 7.35$, $p = .0034$; time $F(2,27.4) = 17.97$, $p < .0001$; dose × time $F(4,32.1) = 2.88$, $p = .038$] (Figure 4). Subjects were rated as being "spaced out," seeming separated or detached from the test environment, having said or done something bizarre, or needing redirection. At both 10 min and 80 min after Δ-9-THC administration, the increases in clinician-rated perceptual alterations were significantly different between placebo and both active doses but not between the two active doses. Similarly, Δ-9-THC transiently increased self-reported perceptual alterations, with a trend toward significance [time $F(2,55.4) = 8.01$, $p = .0009$; dose $F(2,25.9) = 3.07$, $p = .063$; dose × time $F(4,55.2) = 2.1$, $p = .09$].

Delta-9-tetrahydrocannabinol increased perceptual alterations in both groups, but there were no significant group × dose × time differences for either clinician-rated [$\chi^2(3.09) = .81$, $p = .48$] or subject-rated [$\chi^2(1.87) = .13$, $p = .86$] CADSS scores.

Feeling States

The effects of Δ-9-THC on VAS "high" scores were not statistically significant [dose × time $F(4,52.5) = 1.65$, $p = .176$]. There were baseline group differences in VAS "high" between schizophrenia patients and control subjects [$\chi^2(1) = 7.45$, $p = .0063$], but the interactions between group, dose, and time were not significant [$\chi^2(2.79) = .58$, $p = .61$].

Delta-9-tetrahydrocannabinol had no statistically significant effects on VAS scores of "calm and relaxed" [dose × time $F(4,29.3) = .45$, $p = .77$], "panic" [dose × time $F(4,52.2) = .65$, $p = .626$], or "tired" [dose × time $F(4,29.3) = .92$, $p = .485$]; however, analysis of the retrospective time-point data suggested that Δ-9-THC increased VAS scores of "panic" [dose $F(2,15) = 3.2$, $p = .069$] and "tired" [dose $F(2,15) = 3.38$, $p = .061$], with a trend toward significance (Figure 5).

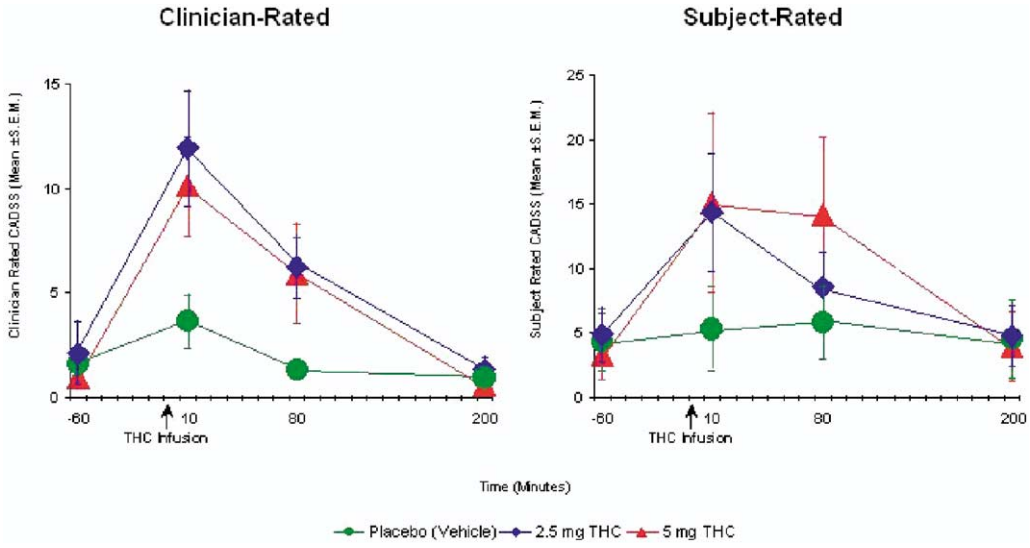

Figure 4. Perceptual alterations (means ± SEM) according to the Clinician-Administered Dissociative Symptoms Scale (CADSS). THC, Δ-9-tetrahydrocannabinol.

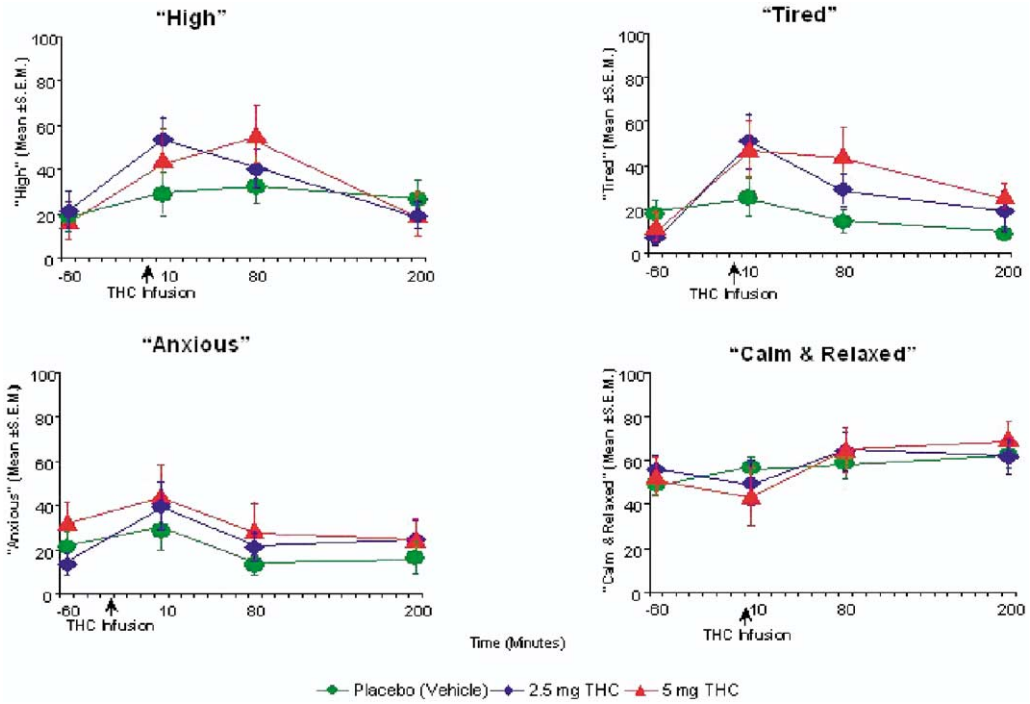

Figure 5. Feeling states (means ± SEM) according to visual analogue scales. THC, Δ-9-tetrahydrocannabinol.

Extrapyramidal Symptoms (Dyskinesia, Akathisia, and Parkinsonism)

After controlling for significant order effects of test day, Δ-9-THC increased total Abnormal Involuntary Movement Scale score, with a trend toward significance [dose $F(2,15) = 3.38$, $p = .06$]. After controlling for significant order effects of test day, Δ-9-THC increased Barnes Akathisia Scale total scores [dose $F(2,14.2) = 5.91$, $p = .0135$]. There were significant differences between the 5-mg dose and the two other doses. Delta-9-tetrahydrocannabinol also increased a composite score of rigidity (Simpson Angus Scale), with a trend toward significance [dose $F(2,23) = 2.61$, $p = .09$] without significant effects on tremor scores [dose $F(2,18.2) = .19$, $p = .831$] (Table 5).

Neurochemical Effects

Prolactin. Delta-9-tetrahydrocannabinol increased serum prolactin levels significantly [dose $F(2,16.9) = 1.42$, $p = .2695$; time $F(2,23.5) = 1.64$, $p = .2151$; dose × time $F(4,27.4) = 3.16$, $p = .0296$]. Although there were significant baseline group differences between schizophrenia patients and control subjects [group $\chi^2(1) = 16.58$, $p = .00005$] and group × time interactions [$\chi^2(1.62) = 12.147$, $p = .00003$], the group × dose × time interactions were not significant (Figure 6).

Cortisol. Delta-9-tetrahydrocannabinol also increased serum cortisol levels significantly [dose $F(2,19.4) = 6.15$, $p = .0085$; time $F(2,23.1) = 13.97$, $p = .0001$; dose × time $F(4,26.9) = 6.41$, $p = .0009$], with significant differences

Table 5. Delta-9-Tetrahydrocannibinol (Δ-9-THC) Effects on Dyskinesia, Parkinsonism, and Akathisia

Outcome Measure	*n*	Dose (mg)	Time Points −60	Time Points +10	Dose Effect
Barnes Akathisia Scale					
Total	12	0	1.5 ± 2.75	1.83 ± 2.76	$F(2,14.2) = 5.91$, $p = .0135$
	12	2.5	2.25 ± 2.34	3.58 ± 2.97	Placebo vs. 5 mg $F(1,14.6) = 11.83$, $= .0039$
					2.5 vs. 5 mg $F(1, 14.6) = 5.45$, $p = .0343$
	9	5	.89 ± 1.54	3.29 ± 2.69	
Simpson Angus Scale					
Total Rigidity	12	0	.55 ± 1.21	.30 ± .95	$F(2,23) = 2.61$, $p = .0954$
	12	2.5	1 ± 1.86	1.50 ± 2.32	
	9	5	0 ± 0	.86 ± 1.46	
Tremor	12	0	.42 ± .67	.55 ± .69	$F(2,18.2) = .19$, $p = .8312$
	12	2.5	.75 ± .62	1 ± .77	
	9	5	.11 ± .33	.29 ± .49	
Abnormal Involuntary Movements Scale					
Total	12	0	3.17 ± 2.69	3.5 ± 3.92	$F(2,15) = 3.38$, $p = .0615$
	12	2.5	2.33 ± 3.26	4.42 ± 3.73	
	9	5	1.78 ± 1.3	4.14 ± 2.73	

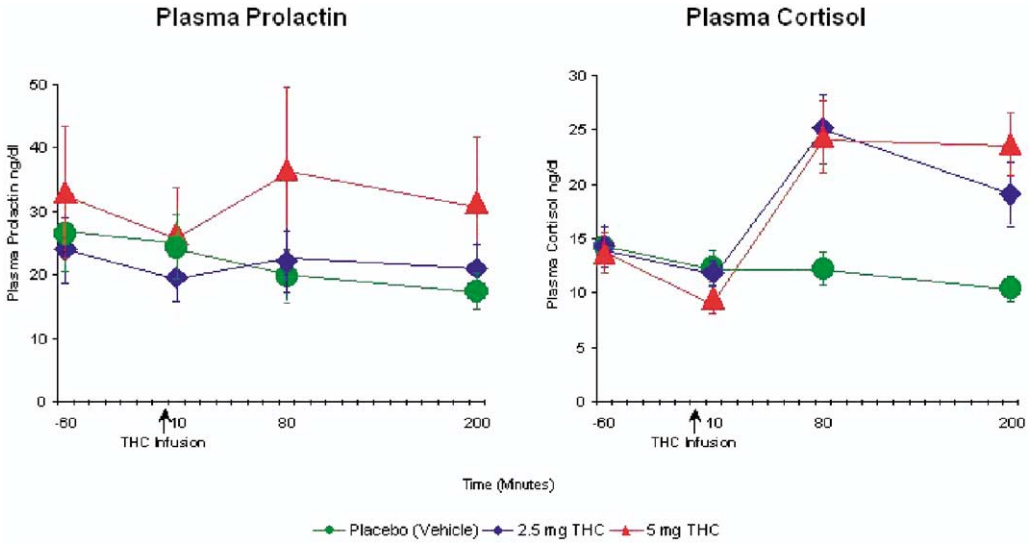

Figure 6. Endocrine effects (means ± SEM). THC, Δ-9-tetrahydrocannabinol.

between placebo and both active conditions at the +80 and +140 time points. There were significant group × time interactions [$\chi^2(1.56) = 3.76$, $p = .03337$] but no significant group × dose × time interactions (Figure 6).

Δ-9-THC and 11-nor-Δ-9-THC-9-COOH. The increases in plasma Δ-9-THC and 11-nor-Δ-9-THC-9-COOH levels were not significantly different from those in healthy individuals (group × dose × time+, ns), with peak levels occurring at the +10 time point and subsiding thereafter.

Safety

Delta-9-tetrahydrocannabinol transiently increased scores of the PANSS anxiety item [dose × time $F(4,51.6) = 3.57$, $p = .01$]; however, by the end of the test day, PANSS anxiety item scores returned to baseline levels. Delta-9-tetrahydrocannabinol had no significant effects on the depression item of the PANSS. One subject who failed to disclose a remote history of untreated hypertension at screening experienced hypertension, anxiety, and paranoia after receiving 5 mg Δ-9-THC. Her symptoms were relieved with haloperidol 5 mg and lorazepam 2 mg. She was voluntarily admitted to the research unit for monitoring and treatment of blood pressure and was discharged 48 hours later without any sequelae. One subject experienced severe anxiety on the placebo test day and withdrew consent; testing was terminated immediately. One subject diagnosed with paranoid schizophrenia who did not like the effects of Δ-9-THC withdrew consent after completing 2 test days and became paranoid about research staff and his clinicians. Evaluation by chart review 1, 3, and 6 months after study completion (including dropouts) compared with an equivalent prestudy time period did not reveal any data suggesting a negative impact of study participation on the course of illness or on cannabis use.

Discussion

To our knowledge, this study represents the first attempt to 1) characterize the effects of uniform doses of Δ-9-THC on the symptoms and medication side effects associated with schizophrenia, using standardized assessments; and 2) to compare these effects with those in healthy control subjects. The principal findings of this study are that Δ-9-THC transiently exacerbated a range of positive and negative symptoms, perceptual alterations, cognitive deficits, and medication side effects associated with schizophrenia without producing any obvious "beneficial" effects. Furthermore, schizophrenia patients were more vulnerable to Δ-9-THC effects on learning and memory.

Cognition

Consistent with the literature (Heishman et al 1990; Hooker and Jones 1987; Miller and Cornett 1978), Δ-9-THC disrupted learning, immediate recall, and delayed free recall in a dose-related fashion. Better delayed recognition recall relative to free recall suggests that Δ-9-THC might preferentially disrupt retrieval over encoding. Floor effects on learning evident with the 5-mg condition might have prevented the detection of larger group differences. Delta-9-tetrahydrocannabinol also increased the number of intrusions, an effect which is hypothesized to contribute to the mechanism of "thought disorder" associated with cannabis intoxication (Pfefferbaum et al 1977). Finally, schizophrenia patients were specifically more vulnerable to the effects of Δ-9-THC on learning and recall. Although admittedly speculative, this finding raises the possibility that cannabinoid receptor dysfunction might contribute to the neurobiology of the learning and memory impairments associated with schizophrenia.

Positive and Negative Symptoms

The increases in negative symptoms were modest; however, the PANSS negative symptoms subscale might not adequately discriminate between primary negative symptoms and those that are secondary to positive symptoms. Thus, there remains the possibility that the increases in PANSS negative symptoms scores might have been secondary to increases in positive symptoms. Two recent studies have shown that cannabis is associated with both positive and negative dimensions of psychosis, which are independent of each other (Stefanis et al 2004; Verdoux et al 2003a, 2003b). The PANSS is unable to distinguish between negative symptoms that might be uniquely or distinctively associated with schizophrenia and very similar symptoms that might be associated with other disorders or drug-induced states. Therefore, there remains the possibility that the increases in PANSS negative symptoms scores were not true negative symptoms of

schizophrenia. Similarly, even though the PANSS had fairly specific anchor points, it is possible that there might have been some overlap in rating some of the effects of Δ-9-THC across some of the measures.

The increases in psychosis were brief, modest, and occurred even though subjects were clinically stable, medication-responsive, and were receiving therapeutic doses of antipsychotics. Whether antipsychotics might have blunted Δ-9-THC effects in schizophrenia patients is impossible to know because this study did not compare medicated and unmedicated subjects. The absence of other statistically significant differences in Δ-9-THC effects other than cognitive effects was surprising; however, in interpreting these group comparisons it should be noted that the groups were not matched for antipsychotic treatment, the sample was small, and nonparametric analysis might be associated with lower power to detect group differences. The observation that Δ-9-THC increased positive symptoms without altering gross orientation does not support the notion that cannabis produces a "toxic psychosis" (Hall and Degenhardt 2000; Hollister 1998). There was no evidence of any serious negative impact of study participation on the short- or long-term expression or course of schizophrenia, or future cannabis use. These data are consistent with the safety of studies with ketamine (reviewed in Carpenter 1999) and amphetamine (Abi-Dargham et al 1998; Laruelle et al 1995) in schizophrenia and suggest that, with careful subject selection and adequate safeguards, such studies can be conducted safely (Carpenter 1999; D'Souza et al 1999).

Neurobiology of the Behavioral and Cognitive Effects Induced by Δ-9-THC

The psychotropic effects of Δ-9-THC are mediated by partial agonist effects at CB-1 receptors (CB-1R), where it has modest affinity (K_i = 35–80 nmol) and low intrinsic activity (Compton et al 1992; Gerard et al 1991; Howlett et al 2002; Matsuda et al 1990).

CB-1 receptors are distributed with high density in the cerebral cortex, particularly frontal regions, basal ganglia, hippocampus, anterior cingulate cortex, and cerebellum (Egertova and Elphick 2000; Egertova et al 1998; Elphick and Egertova 2001; Glass et al 1997; Herkenham et al 1990, 1991), brain regions that are relevant to both the known effects of cannabinoids and also regions that have been implicated in the putative neural circuitry of psychosis. The primary effect of cannabinoids is the modulation of neurotransmitter release through activation of presynaptic CB-1Rs (reviewed in Freund et al 2003; Pertwee 1999).

Behavioral, biochemical, and electrophysiologic data demonstrate the involvement of dopaminergic systems in some of the actions of cannabinoids. Cannabinoids increase the activity and expression of tyrosine hydroxylase (Bonnin et al 1996; Hernandez et al 1997; Mallet 1996). Delta-9-tetrahydrocannabinol increases dopamine (DA) synthesis (Bloom and Dewey 1978; Maitre et al 1980; Rodriguez de Fonseca et al 1990) and inhibits DA uptake (Banerjee et al 1975; Hershkowitz and Szechtman 1979; Johnson et al 1976; Poddar and Dewey 1980; Sakurai-Yamashita et al 1989). Relevant to these data, a decrease in the DA transporter (DAT) that was observed in the caudate of schizophrenia patients negative for cannabis use was not observed in schizophrenia patients who used cannabis antemortem (Dean et al 2003); the investigators suggested that Δ-9-THC might reverse the decreases in DAT-associated schizophrenia. CB-1 receptor activation increases mesolimbic DA activity (Chen et al 1990, 1991; French 1997; French et al 1997; Melis et al 2000; Pistis et al 2002; Tanda et al 1997). Furthermore, CB-1 receptor agonists induce cfos in the nucleus accumbens (Miyamoto et al 1996) and A10 dopaminergic neurons within the ventral tegmentum (Patel and Hillard 2003), and these effects are blocked by DA D2 receptor antagonists (Miyamoto et al 1996) and CB-1R antagonists (Patel and Hillard 2003; Porcella et al 1998). Additionally, CB-1R activation by inhibiting γ-aminobutyric acid (GABA)ergic neurotransmission in the ventral tegmental area could increase the firing rate of dopaminergic neurons projecting from the ventral tegmental area, leading to an increase in DA in the nucleus accumbens (Szabo et al 2002). The effect of cannabinoids on increasing mesolimbic dopaminergic activity might provide one explanation for the increase in positive psychotic symptoms induced by Δ-9-THC. Altered DA function in schizophrenia (Abi-Dargham 2004) might make schizophrenia patients more vulnerable to the psychotomimetic effects of Δ-9-THC.

Interactions of CB-1R and GABAergic systems in the hippocampus provide another potential explanation for the psychotomimetic effects of Δ-9-THC. CB-1 receptors are localized presynaptically on hippocampal GABAergic interneurons (Irving et al 2000) and specifically on cholecystokinin-expressing basket cells (Katona et al 1999; Marsicano and Lutz 1999; Tsou et al 1999). These basket cells form dense axon terminal plexuses on the perisomatic regions of pyramidal neurons and are believed to play an important role in orchestrating pyramidal cell synchrony in the γ (40-Hz) frequency range (Hoffman and Lupica 2000; Traub et al 1996; Wang and Buzsaki 1996; Whittington et al 1995). Oscillations in the γ range have been implicated in the "binding" of features that are detected by sensory cortices into unified perceived objects, and in lower level processes, such as the phase coding of neuronal activity. In addition, coupling of neocortical and hippocampal γ oscillations might be able to bind representations associated with currently perceived and retrieved information (reviewed in Wilson and Nicoll 2002). Activation of CB-1Rs located on GABAergic hippocampal neurons reduces GABA release (Freund et al 2003; Katona et al 1999; Sullivan 1999). This would disrupt the synchronization of pyramidal cell activity (Hajos et al 2000; Hoffman and Lupica 2000; Wilson and Nicoll 2002). The latter would interfere with memory consolidation and associative functions and normal gating mechanisms, eventually leading to psychotic symptoms. Schizophrenia patients who have been reported to have abnormalities in γ band synchronization (Kwon et al 1999; Spencer et al 2003) might therefore, be more sensitive to Δ-9-THC effects.

CB-1 receptor activation disrupts hippocampal long-term potentiation and long-term depression, inhibits hippocampal glutamate release, and inhibits septohippocampal acetylcholine release (reviewed in D'Souza et al 2004). These hippocampal effects could explain some of the cognitive effects of cannabinoids, and because schizophrenia patients have evidence of altered hippocampal function (Weinberger 1999), this might explain their enhanced vulnerability to the amnestic effects of Δ-9-THC.

Finally, the effects of CB-1R activation in the prefrontal cortex (PFC) might provide a mechanism for the cognitive deficits and negative symptoms induced by Δ-9-THC. Imaging studies demonstrate that cannabis use is associated with decreased perfusion in the PFC (Amen and Waugh 1998; Lundqvist et al 2001). The activity of pyramidal neurons, the major efferents of the PFC, is regulated by complex interactions between dopaminergic and GABAergic neurons. The

PFC has a high density of CB-1Rs, and cannabinoids have been shown to modulate neuronal inputs impinging on PFC neurons (Herkenham et al 1991; Tsou et al 1998). By suppressing GABAergic and dopaminergic inhibitory neurotransmission, CB-1R activation might lead to nonspecific activation of the PFC, which in turn might disrupt normal signal processing and result in poor integration of transcortical inputs (Pistis et al 2001; Yang et al 1999). CB-1 receptor activation might also exacerbate the effects of the decreased mesocortical dopaminergic transmission and reduced D1 receptor density reported in schizophrenia (Abi-Dargham et al 2002; Okubo et al 1997a, 1997b), which would worsen working memory deficits and negative symptoms. Because schizophrenia patients have altered PFC function (Knable and Weinberger 1997), this might make them more vulnerable to the effects of Δ-9-THC on the PFC.

In summary, there are several possible mechanisms by which Δ-9-THC might increase the positive, negative, and cognitive symptoms of schizophrenia. Clearly, further work is necessary to elucidate the precise mechanism of the behavioral and cognitive effects of cannabinoids in schizophrenia.

Endocrine Effects Induced by Δ-9-THC

Consistent with the literature, Δ-9-THC increased serum cortisol levels. Delta-9-tetrahydrocannabinol increases adrenocorticotropic hormone and cortisol levels through CB-1R activation within the paraventricular nuclei and either directly or indirectly (through other neurotransmitters) modulates corticotropin-releasing hormone secretion (reviewed in Murphy et al 1998). Delta-9-tetrahydrocannabinol at 5 mg increased prolactin levels, whereas 2.5 mg had no effect. Delta-9-tetrahydrocannabinol produces an early and brief increase, followed by predominantly inhibitory effects on prolactin release (reviewed in Murphy et al 1998). The former might not be mediated by CB-1Rs because the CB-1R antagonist SR141716A does not antagonize these effects (Fernandez-Ruiz et al 1997). The predominantly inhibitory effect on prolactin release is mediated by CB-1R activation of tuberoinfundibular dopaminergic neurons (Rodriguez de Fonseca et al 1992). The biphasic effects on prolactin release might also depend on the hormone milieu, and because all the subjects were receiving DA D2 receptor antagonists, which increase prolactin levels, this might account for the lack of an inhibitory effect seen in this study.

Subjective Effects and Implications for Cannabis Use/Misuse

The lack of statistically significant euphoric effects of Δ-9-THC was unexpected. The substantial variability in response and the significant placebo effect observed could explain these findings. Alternatively, either schizophrenia or treatment with antipsychotics might explain the blunted euphoric effect of Δ-9-THC. Of note is that CB-1R agonists induce cfos, a marker of increased neuronal excitation, in the nucleus accumbens and that this effect is reduced by DA antagonists (Miyamoto et al 1996). One possible implication of the blunted euphoric effects of Δ-9-THC is that antipsychotic-treated schizophrenia patients might need to use greater amounts of cannabis to achieve a "high," which in turn would carry the risk of greater negative effects.

Delta-9-tetrahydrocannabinol effects on increasing extrapyramidal symptoms are consistent with the known involvement of CB-1R function in basal ganglia–related movement disorders (reviewed in Romero et al 2002).

There were no "beneficial" effects of Δ-9-THC on any of the outcome measures. Rather, the results of this study are consistent with several studies suggesting that cannabis has a negative influence on the expression and course of schizophrenia (Brunette et al 1997; Caspari 1999; Dervaux et al 2003; Green et al 2004; Linszen et al 1994; Liraud and Verdoux 2000, 2002; Negrete and Knapp 1986; Negrete et al 1986; Potvin et al 2003; Van Mastrigt et al 2004). The results of the study, however, do not provide an explanation as to why schizophrenia patients use cannabis, as the self-medication hypothesis suggests. Several issues need to be considered in interpreting the findings of this study and then generalizing the study results to the problem of cannabis misuse by schizophrenia patients. First, the study excluded cannabis-abusing subjects who might arguably derive "benefit/s" from cannabis. Second, cannabis is more than just Δ-9-THC. Cannabis is a composite of several (up to 80) cannabinoid compounds, terpenoids, and flavonoids that might modulate Δ-9-THC (Hollister 1988) effects and have "entourage" effects (Mechoulam and Ben-Shabat 1999; Russo and McPartland 2003). Cannabidiol (CBD), a major component of cannabis, has been shown to be a very-low-affinity, weak antagonist of CB-1R (Petitet et al 1998). Cannabidiol and Δ-9-THC might have pharmacokinetic and pharmacodynamic interactions. Thus, CBD might offset some Δ-9-THC effects by its anxiolytic effects (Guimaraes et al 1994; Zuardi et al 1982) and antipsychotic-like effects (Zuardi et al 1991, 1995) and might block the conversion of Δ-9-THC to the more psychoactive 11-hydroxy-THC (Bornheim et al 1995). The CBD content of cannabis varies greatly, however, and some samples of cannabis have been reported to be devoid of CBD (Pitts et al 1992). Third, the rate and IV route of administration of Δ-9-THC, the highly selected sample, the laboratory environment, and the fact that subjects did not have control over the drug titration do not reflect recreational cannabis use. Fourth, at lower doses, Δ-9-THC might have some "beneficial" effects that might not have been detected in this study. Fifth, the scales used might not have been sensitive to the "beneficial" effects of Δ-9-THC.

Implications for Psychotic Disorders

The magnitude of Δ-9-THC-induced changes in positive symptoms was similar to those seen in studies with amphetamine (Laruelle et al 1995) and ketamine (Lahti et al 1995a, 1995b; Malhotra et al 1997). Delta-9-tetrahydrocannabinol effects in schizophrenia subjects were more similar to ketamine effects (Lahti et al 1995a, 1995b; Malhotra et al 1997) than to stimulants, which increase only positive symptoms, reduce negative symptoms, and might even improve aspects of cognitive functioning (reviewed in Lieberman et al 1987). The exacerbation in symptoms despite treatment with DA antagonists raises the possibility that dopaminergic systems might not play a significant role in the symptom exacerbating effects of Δ-9-THC.

The findings from this pharmacologic study, taken collectively with data from postmortem (Dean et al 2001; Zavitsanou et al 2004), epidemiologic (Andreasson et al 1987, 1988; Arseneault et al 2002; McGuire et al 1995; Zammit et al 2002), neurochemical (Leweke et al 1999), and genetic (Ujike et al 2002) studies, warrant investigation of whether cannabinoid receptor system dysfunction contributes to the pathophysiology of schizophrenia. Finally, the finding that schizophrenia patients showed enhanced sensitivity to some of the cognitive

and perhaps behavioral effects of Δ-9-THC warrants exploration of CB-1Rs as a target for developing drugs to treat the cognitive deficits associated with schizophrenia. SR141617A, a CB-1R antagonist/inverse agonist, although not shown to be effective as a stand-alone treatment for positive and negative symptoms of schizophrenia (Meltzer et al 2004), was not studied for possible cognitive enhancing effects in schizophrenia patients. The availability of a wide range of ligands acting on the endocannabinoid system now make it possible to further study a possible role for CB-1R function in the pathophysiology and treatment of schizophrenia.

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