Published in final edited form as:
Neuropsychopharmacology. 2008 September ; 33(10): 2505–2516. doi:10.1038/sj.npp.1301643.

Blunted Psychotomimetic and Amnestic Effects of Δ-9-Tetrahydrocannabinol in Frequent Users of Cannabis

Deepak Cyril D'Souza, MD[1,2,3], **Mohini Ranganathan, MD**[1,3], **Gabriel Braley, BA**[1,3], **Ralitza Gueorguieva, PhD**[2,4], **Zoran Zimolo, MD, PhD**[1,3], **Thomas Cooper, MA**[5], **Edward Perry, MD**[1,3], and **John Krystal, MD**[1,2,3]

[1]Schizophrenia Biological Research Center, VA Connecticut Healthcare System, West Haven, CT

[2]Abraham Ribicoff Research Facilities, Connecticut Mental Health Center, New Haven, CT

[3]Department of Psychiatry, Yale University School of Medicine, New Haven, CT

[4]Division of Biostatistics, Department of Epidemiology and Public Health, Yale University, New Haven CT

[5]Department of Psychiatry, Columbia University, College of Physicians and Surgeons, New York, New York and the Nathan Kline Institute, Orangeburg New York

Abstract

BACKGROUND—Cannabis is one of the most widely used illicit substances and there is growing interest in the association between cannabis use and psychosis. Delta-9-Tetrahydrocannabinol (Δ-9-THC) the principal active ingredient of cannabis has been shown to induce psychotomimetic and amnestic effects in healthy individuals. Whether people who frequently use cannabis are either protected from or are tolerant to these effects of Δ-9-THC has not been established.

METHODS—In a 3-day, double-blind, randomized, placebo-controlled study, the dose-related effects of 0, 2.5 and 5 mg intravenous Δ-9-THC were studied in 30 frequent users of cannabis and compared to 22 historical healthy controls.

RESULTS—Δ-9-THC 1) produced transient psychotomimetic effects and perceptual alterations; 2) impaired memory and attention; 3) increased subjective effects of "high"; 4) produced tachycardia and 5) increased serum cortisol in both groups. However, relative to controls, frequent users showed blunted responses to the psychotomimetic, perceptual altering, cognitive impairing, anxiogenic, and cortisol increasing effects of Δ-9-THC but not to its euphoric effects. Frequent users also had lower prolactin levels.

CONCLUSIONS—These data suggest that frequent users of cannabis are either inherently blunted in their response to, and/or develop tolerance to the psychotomimetic, perceptual altering, amnestic, endocrine and other effects of cannabinoids.

Keywords

Cannabis; cannabinoids; delta-9-tetrahydrocannabinol; tolerance; abuse; cognition; memory

Corresponding Author: D. C. D'Souza, MD Address: Psychiatry Service, 116A, VA Connecticut Healthcare System, 950 Campbell Avenue, West Haven, CT 06516 Telephone: (203) 932-5711 × 2594 Fax: (203) 937-4860 deepak.dsouza@yale.edu.

DECLARATION OF INTEREST: There are no direct or indirect conflicts of interest for any of the authors relevant to the subject of this manuscript.

INTRODUCTION

Cannabis is one of the most widely used illicit substances and recent evidence suggests an increase in the prevalence of cannabis use, abuse and dependence (Compton et al. 2004; SAMHSA 2004; Stinson et al. 2006). There is considerable interest in the association between cannabis and psychosis (D'Souza 2007; Hall et al. 2004; Henquet et al. 2005; Leweke et al. 2004; Verdoux & Tournier 2004; Weiser & Noy 2005). A growing number of studies suggest that the acute administration of cannabinoids including delta-9-tetrahydrocannabinol (Δ-9-THC), nabilone and cannabis induces a broad range of transient symptoms, behaviors and cognitive deficits in healthy individuals that resemble some aspects of endogenous psychoses (D'Souza 2007; D'Souza et al. 2004; Henquet et al. 2006a; Leweke et al. 2004; Leweke et al. 2000; Leweke et al. 1999). But whether individuals who frequently use cannabis also experience such effects has not been clearly established.

While tolerance to some of the effects of cannabinoids has been reported (Green et al. 2003; Lichtman & Martin 2005) whether tolerance develops to the psychotomimetic effects of cannabinoids is not clear. Alternatively, individuals who frequently use cannabis may be "protected" from its psychotomimetic and other undesirable effects, similar to individuals at high risk for alcoholism (Schuckit 1985a; Schuckit 2000; Schuckit et al. 2004).

Finally, the experimental data on cannabinoid effects is mainly based on studies of individuals with substantial exposure to cannabis. Thus, if cannabis exposure is associated with the development of tolerance or if individuals who use/abuse cannabis are protected from some of its undesirable effects, then the existing experimental literature may likely underestimate the effects of cannabinoids in cannabis naïve or less experienced individuals.

METHODS

It was hypothesized that individuals who currently use cannabis frequently, heretofore referred to as frequent users, were differentially sensitive to the psychotomimetic, amnestic, perceptual altering and endocrine effects of Δ-9-THC. This randomized, double-blind, placebo-controlled study was conducted between 1998 and 2004 at the Neurobiological Studies Unit (VA Connecticut Healthcare System [VACHS], West Haven, CT) and the Abraham Ribicoff Research Facilities (Connecticut Mental Health Center, New Haven, CT). Subjects were recruited by advertisements and by word of mouth, and were paid for their participation. The study was approved by the Protocol Review Committee of the Department of Psychiatry, Yale University School of Medicine (YUSM) and the Institutional Review Boards of both VACHS and YUSM, and was carried out in accordance with the Helsinki Declaration of 1975. Subjects were informed about the potential for adverse effects of Δ-9-THC including psychosis, anxiety, and panic.

Subjects

Current frequent users of cannabis and healthy controls were studied in parallel. Current frequent users were defined as having 1) a positive urine toxicological test for cannabis at screening, and 2) at least 10 exposures to cannabis within the past month as quantified by a time line follow back approach (Sobell & Sobell 1992). These subjects also met criteria for current DSM-IV cannabis abuse disorder while none of the controls did. Controls were required to have 1) a negative urine toxicological test at screening, 2) no exposure to cannabis in the past week and 3) no more than 1 exposure to cannabis in the past month. Data in healthy controls have been reported elsewhere (D'Souza et al. 2004).

After obtaining written informed consent, subjects (18-55 years) underwent a structured psychiatric interview for DSM-IIIR or IV (First et al. 2002) and were carefully screened for

any DSM Axis I or Axis II lifetime psychiatric or substance use disorder (except for cannabis in the case of frequent users) and family history of major Axis I disorder. All subjects were asked to estimate their lifetime cannabis exposure (# times), heaviest exposure and last exposure to cannabis. Subjects were excluded for recent abuse (3 months) or dependence (1 year) to alcohol or any substances, other than nicotine in both groups. Cannabis-naïve individuals were excluded to minimize any risk of promoting future cannabis use/abuse. The history provided by subjects was confirmed by a telephone interview conducted with an individual (spouse or family member) identified by the subject prior to screening. A general physical and neurological examination, EKG and laboratory tests (serum electrolytes, liver function tests, complete blood count with differential and urine toxicology) were also conducted. Both groups were instructed to refrain from alcohol, illicit drugs or prescription drugs not approved by the research team for 2 weeks before the study and throughout study participation. Frequent users were permitted to use cannabis until 24 hours prior to each test day, to minimize cannabis withdrawal.

Subjects completed 3 test days during which they received [Δ-9-THC] (2.5 or 5 mg), or vehicle by intravenous (i.v.) route in a randomized, counterbalanced order under double-blind conditions (Table 1) (D'Souza et al. 2004). Staff and both groups of subjects received identical information without reference to any hypothesized group differences.

Drugs

The preparation, formulation and storage of Δ-9-THC solution are reported elsewhere (D'Souza et al. 2004). For the control condition, an equivalent volume (≈ 2 ml) of ethanol (vehicle) was used which was undetectable in multiple post-injection samples. As reviewed elsewhere (D'Souza et al. 2004), the i.v route of administration, while not socially relevant, was chosen to standardize the delivery of Δ-9-THC. Subjects were administered Δ-9-THC, a point that should be noted in interpreting the results. Cannabis consists of several compounds that may modulate Δ-9-THC effects (Hollister 1988) and have "entourage" effects (Mechoulam & Ben-Shabat 1999; Russo & McPartland 2003). For example, cannabidiol (CBD) may offset some Δ-9-THC effects by its anxiolytic effects (Guimaraes et al. 1994; Zuardi et al. 1982), antipsychotic-like effects (Zuardi et al. 1995; Zuardi et al. 1991), and may block the conversion of Δ-9-THC to the more psychoactive 11-hydroxy-THC (Bornheim et al. 1995). A recent clinical trial showed that stand alone cannabidiol was as effective as the gold standard antipsychotic Amisulpiride in the treatment of acutely ill schizophrenic patients (Leweke, 2007). In contrast, Wachtel et al., have shown that the psychoactive effects of cannabis in healthy volunteers are due *primarily* to Δ-9-THC (Wachtel et al. 2002). Nevertheless, to reduce any potentially confounding effects of other cannabinoids present in herbal cannabis, only Δ-9-THC, was administered in this study.

Test Days

Test days were separated by at least 1 week (>3 times the elimination half life of Δ-9-THC) to minimize carryover effects. Subjects fasted overnight, reported to the test facility around 8 a.m., and were provided a standard breakfast. Urine toxicology was conducted on the morning of each test day to rule out recent illicit drug use. A positive urine drug screen resulted in exclusion from the study except when positive for cannabis in the frequent user group. A positive urine pregnancy test also resulted in exclusion. In-study safety procedures are described elsewhere (D'Souza et al. 2004).

Outcome Measures

Intelligence Quotient (I.Q.) was measured using the Slosson IQ scale (Slosson 1963). The behavioral and cognitive outcome measures (Table 1) which were selected with a focus on psychosis, are described in detail elsewhere (D'Souza et al. 2004). Positive, negative and

general symptoms associated with schizophrenia were assessed using relevant subscales of the Positive and Negative Syndrome Scale for Schizophrenia (PANSS) (Kay et al. 1989), perceptual alterations were measured using the Clinician Administered Dissociative Symptoms Scale (CADSS) (Bremner et al. 1998) and feeling states ("high", "calm and relaxed" and "anxiety") associated with cannabis intoxication were measured using a self-reported visual analog scale (Haertzen 1965; Haertzen 1966). The same research coordinators rated all 3 test days for each subject. Interrater reliability sessions were conducted every 1-2 months and for example, Intraclass Correlation Coefficient for the PANSS were consistently greater than 0.85.

A cognitive test battery in a fixed sequence was initiated 30 minutes after Δ-9-THC administration. Unlike other measures, the cognitive battery was administered only once per test day. Verbal learning and immediate and delayed recall were measured using equivalent versions of the Hopkins Verbal Learning Test (HVLT) (Brandt 1991; Bylsma et al. 1991). Vigilance and distractibility to visual stimuli were measured using a continuous performance task (CPT) (Gordon 1986) in which subjects attended to numbers presented sequentially on a screen. Subjects were instructed to push a button to signal when a '9' was preceded by a '1'. 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. Heart rate was measured continuously using a pulse oximeter. However, heart rate data was recorded for analysis as an outcome measure only at predetermined timepoints.

Blood was sampled from the i.v. line from the arm opposite to the one used for administering study drug (D'Souza et al 2004) for Δ-9-THC, its primary inactive metabolite 11-nor-Δ-9-THC-9-COOH (THC-COOH), prolactin and cortisol. Δ-9-THC and THC-COOH were only assayed from samples taken on the active Δ-9-THC test days. Endocrine measures were collected to provide biological indices of possible baseline and Δ-9-THC induced group differences. Immediately after collection, blood samples were placed on ice, centrifuged and the extracted plasma was alliquoted into vials for storage at −70° C until assayed. Prolactin and cortisol assays were run in duplicate pairs using antibody radioimmunoassay.

A field sobriety test was conducted at the end of each test day. The study was amended to include prospective safety assessments at 1, 3 and 6 months after the last test session to query cannabis use or the emergence of any new medical or psychiatric symptoms.

Statistical analyses

All statistical analyses were performed in SAS Version 8.2. Baseline differences and changes from baseline were assessed in separate models. Unlike in parallel randomized controlled trials where randomization balances measured and unmeasured covariates, in this study baseline differences were expected but not of primary interest. Hence, while each measure was compared at baseline to detect baseline differences since the focus of the analysis was to detect group difference in response to Δ-9-THC, the *change* from baseline was of primary interest. Normal probability plots and Kolmogorov-Smirnov test statistics showed non-normality and positive skewness of the distributions of the score changes. The absence of variance during the placebo Δ-9-THC (vehicle) administration and the highly skewed responses during the Δ-9-THC conditions necessitated the use of a nonparametric approach for repeated measures data (Brunner 2002). An additional advantage of this statistical approach is that it analyzes all available data on each subject including data collected on subjects who dropped out. The data were first rank-transformed and then PROC MIXED was used to fit mixed effects models with unconstrained variance-covariance structure on the ranked data. P-values for the tests of the within-subject effects were adjusted

as described by Brunner et al. (2002). PANSS scores, VAS scores, CADSS clinician and CADSS subject ratings were analyzed using a nonparametric mixed model with dose (placebo, 2.5 mg, 5 mg) and time (P10, P80, P200) as within-subject factors and group (abuser, non-abuser) as a between-subject factor. Verbal memory (HVLT) and measures of sustained attention (CPT) were analyzed using a nonparametric mixed model with dose (placebo, 2.5 mg, 5 mg) as a within-subject factor and group as a between-subject factor. Δ-9-THC levels were analyzed in the same way restricting the dose levels to 2.5 mg and 5 mg since the main interest of this analysis was to rule out pharmacokinetic differences between groups on the active Δ-9-THC conditions. Age and IQ were included as covariates in the analysis. Contrasts were used to explain significant interactions and main effects. The overall alpha level for each hypothesis was fixed at 0.05. Bonferroni correction was applied within but not across hypotheses. For example, for delayed recall (HVLT), a cut-off alpha level of 0.05/3 = 0.0167 was used to declare effects significant for each subscale.

RESULTS

Frequent users (n=30) and healthy control subjects (n=22) were not significantly different for age, education, socioeconomic status or smoking status (table 2). However, frequent users (119 ± 15) had significantly lower (p =0.045) I.Q scores than controls (130 ± 19), which was used as a covariate in the analysis. There were no significant group differences in dropout rates (p =0.64 Fishers exact test).

Relative to controls, frequent users had significantly greater recent (past month) cannabis exposure and lifetime exposure to cannabis (table 3). Further, all the frequent users reported having used cannabis sometime within 72 hours prior to each test day, but not within the 24 hours preceding each test day. In contrast, controls reported not having used cannabis in the week prior to each test day.

Perceptual Alterations (CADSS)

CADSS Clinician-rated Perceptual alterations (Figure 1)—There were no significant group differences at baseline. Δ-9-THC transiently increased clinician rated perceptual alterations scores as previously reported (D'Souza et al. 2004). However, frequent users had smaller Δ-9-THC induced increases in CADSS-C scores [group effect (ANOVA Type Statistic [ATS] =7.54, df=1, p = 0.006), group by time (ATS=7.44, df=1.89, p = 0.001), group by dose (ATS=2.76, df=1.18, p=0.069) and group by dose by time (ATS=4.79, df=3.45, p = 0.001)]. Post-hoc analyses for dose and time revealed that relative to controls, frequent users had blunted increases in perceptual alterations at 80 minutes for both 2.5 mg (ATS=5.21,df=1,p=0.02) and 5 mg (ATS=13.47,df=1,p=0.0002) Δ-9-THC doses.

CADSS Self-rated Perceptual alterations—At baseline, frequent users reported small (mean=0.82, SD=1.58) but significantly higher scores than controls (mean=0.2, SD=0.85) (ATS=6.64, df=1, p = 0.01). Δ-9-THC transiently increased self-rated perceptual alterations scores in both groups, but frequent users had smaller increases relative to controls [group effect (ATS=18.55, df=1, p < .0001) and group by time interaction (ATS=7.13, df=1.86, p = 0.001)]. Post hoc comparisons for dose and time revealed that relative to controls, frequent users reported blunted increases in perceptual alterations both at 10 (ATS=15.72, df=1, p<. 0001) and 80 minutes (ATS=19.23, df=1, p<.0001).

Psychotomimetic Effects

Total PANSS (Figure 1)—There were no baseline group differences. Δ-9-THC transiently increased PANSS total scores in both groups but frequent users had smaller

increases relative to controls (group × dose × time ATS=4.34, df=3.58, p=0.0025; group by time ATS=9.34, df=1.88, p=0.0001; dose by time ATS=15.34, df=3.58, p<0.0001). Post-hoc comparisons for time and dose revealed that the difference between abusers and controls was significant both for the 2.5 mg dose at 10 minutes (ATS=6.84,df=1,p=0.0089) and 80 minutes (ATS=5.20,df=1,p=0.023), and the 5 mg dose at the 10 minutes (ATS=5.76,df=1,p=0.016) and 80 minutes (ATS=13.66,df=1,p=0.0002).

Self-reported Feeling States Associated with the Cannabis Response Visual Analog Scale (VAS) "high" (Figure 2): There were no significant group differences at baseline. As expected Δ-9-THC transiently increased VAS "high" scores in both groups. While the group × dose × time interaction trended towards significance (ATS=2.48, df=2.88, p = 0.06), there were no significant group (ATS=0.00, df=1, p = 0.98), group by dose (ATS=0.4, df=1.93, p = 0.66) or group by time (ATS=0.49, df=1.8, p = 0.60) effects.

Visual Analog Scale (VAS) "anxiety" (Figure 2): There were no significant group differences at baseline. Δ-9-THC transiently increased VAS anxiety scores in controls greater than in frequent users. The group (ATS=4.04, df=1, p = 0.05) and group by dose (ATS=5.44, df=1.87, p=0.005) effects were significant while the group by time (ATS=3.06, df=1.52, p = 0.06) and group by dose by time (ATS=2.13, df=3.32, p = 0.09) interactions showed weak trends towards significance. It is unclear why anxiety scores increased at the 200 minute timepoint in both groups.

Visual Analog Scale (VAS) "calm & relaxed": Consistent with the above, Δ-9-THC transiently decreased VAS "calm and relaxed" scores (dose × time: ATS=2.42, df=3.72, p=0.05) in both groups. However, there were no group (ATS=5.47, df=1, p = 0.7), group by dose (ATS=2.31, df=1.89, p = 0.1) or group by dose by time (ATS=0.33, df=3.72, p = 0.84) effects.

Learning And Recall (Hopkins Verbal Learning Task)

Immediate Recall (Figure 3): Controls recalled more words on the placebo test day than frequent users (ATS=4.58, df=1, p=0.03) suggesting baseline differences. As expected Δ-9-THC impaired immediate recall in both groups. There was a significant group by dose interaction (ATS=4.06, df=1, p=0.03) with frequent users performing worse at baseline (placebo condition), yet showing smaller Δ-9-THC induced recall impairments than controls.

Delayed Free Recall (Figure 3): Δ-9-THC impaired delayed recall in both groups (ATS=5.97, df=1.87, p =0.003). While there was no significant group effect (ATS=0.37, df=1, p =0.5), there was a significant group × dose interaction effect (ATS= 4.29, df= 1.87, p= 0.02). Thus, only in controls did Δ-9-THC impair recall in a linear dose-dependent fashion (ATS = 15.72, df= 1, p <0.0001). Interestingly, frequent users had higher delayed free recall on 2.5 mg dose Δ-9-THC (9.54 ± 1.79) relative to placebo (8.89 ± 1.76).

Delayed Cued Recall: While there was a group × dose interaction on cued recall (ATS = 3.48, df = 1.89, p = 0.03), this effect did not survive Bonferroni correction.

Delayed Recognition Recall: Δ-9-THC did not impair recognition recall. Finally, Δ-9-THC increased the number of intrusions (ATS=4.48, df=1.84, p =0.013) and false positive responses (ATS=9.04, df=1.96, p=0.0001), but there were no group differences.

Attention

Vigilance: Δ-9-THC increased omission (dose ATS=4.11, df=1.92, p=0.02) and commission (dose ATS=3.04, df=1.98, p=0.05) errors in both groups on the vigilance task. There was a

significant group by dose interaction such that the difference between 5 mg and placebo dose was significant in frequent users (ATS=10.77, df=1, p=0.002 for omissions and ATS=6.91, df=1, p=0.01 for commissions) but not in controls.

Distractibility: Δ-9-THC increased omission errors only in controls (ATS = 7.86, df = 1, p = 0.01 for 5 mg vs. placebo comparison and ATS=10.41, p=0.002 for 5 mg vs. 2.5 mg comparison) without increasing commission errors.

Heart Rate—Δ-9-THC increased heart rate in a dose dependent manner [dose: F (1,427) =65.5, P<.0001] and dose × time [F (8,427) =21.1, P<.0001] without any significant group differences.

Plasma Δ-9-THC and 11-nor-Δ-9-THC-9-COOH (THC-COOH) levels—Plasma Δ-9-THC levels increased in a dose dependent manner (dose: ATS=7.70, df=1.43, p=0.002) and peaked at +10 minutes (82 [± 87] ng/dl for the 2.5 mg dose, and 119 [± 166] ng/dl for the 5 mg dose). There was significant individual variability in Δ-9-THC levels. However, there were no significant group differences (ATS=0.82, df=1, p=0.36) or group by dose interactive effects on plasma Δ-9-THC levels (ATS=0.29, df=1.43, p = 0.67).

As expected, relative to controls, frequent users had higher baseline plasma levels of THC-COOH the principal inactive metabolite of Δ-9-THC (ATS=105.56, df=1, p<0.0001). However, there were no significant group by dose interactive effects on plasma THC-COOH levels (ATS=1.14, df=1.53, p=0.52).

Plasma Cortisol and Prolactin—Δ-9-THC increased plasma cortisol levels in both groups [dose by time F (6,356) = 5.64, p<0.0001] however, frequent users had smaller increases relative to controls [group F (1,356) = 4.86, p=0.028; group × dose F (6,356) = 2.5, p=0.08; group × time F (6,356) = 4.6, p=0.0036; group × dose × time F (6,356) = 0.6, p=0.7) (figure 4). Post-hoc analyses revealed that controls had higher cortisol levels at the +80 [F (6,356) =7.99, p = 0.005] and +140 [F (6,356) =11.75, p = 0.0007] minute timepoints. While Δ-9-THC had no significant effects on plasma prolactin levels (dose by time: ns) in either group, frequent users had lower plasma prolactin levels (group F [1,347] = 15.31, p=0.0001) (figure 4).

DISCUSSION

This is the first report to our knowledge comparing the behavioral, subjective, cognitive, physiological and endocrine effects of intravenous Δ-9-THC in frequent users of cannabis and controls.

In summary, frequent users showed blunted perceptual alterations (CADSS), psychotomimetic effects (PANSS), "anxiety" (VAS), recall impairments, distractibility and increases in plasma cortisol induced by Δ-9-THC. Frequent users also had lower baseline prolactin levels. Overall, the magnitude of the group differences in Δ-9-THC effects ranged in effect sizes of 0.38 for psychotomimetic effects (PANSS) to 0.78 for anxiety (VAS). These group differences cannot be explained by pharmacokinetic differences since there were no group differences in plasma Δ-9-THC or Δ-9-THCCOOH levels. In contrast to the above, frequent users were no different from controls in their response to Δ-9-THC induced feeling states of "high" and "calm and relaxed" (VAS). Similarly, there were no group differences in the tachycardiac effects of Δ-9-THC.

Feeling "high", "calm and relaxed", mellow, and creative are characterized as "desirable" or positive effects of cannabis while paranoia, hallucinations, anxiety, perceptual alterations

and memory impairments are characterized as "undesirable" or "negative" effects. Taken collectively, frequent users showed blunted responses to some of the "undesirable" effects of Δ-9-THC but not to its "desirable" effects. These group differences in Δ-9-THC effects raise the possibilities that frequent users develop tolerance to the negative effects of Δ-9-THC and/or are "protected" from these effects.

Tolerance

There is considerable preclinical evidence demonstrating tolerance to most of the pharmacological effects of cannabinoids reviewed in(Gonzalez et al. 2005; Lichtman & Martin 2005). However, the evidence supporting tolerance in humans is limited. Self-report (Anthony & Trinkoff 1989), experimental (Jones et al. 1976; Jones et al. 1981) and direct observational (Haney et al. 1999a; Haney et al. 1999b) studies in humans suggest that with heavy and prolonged exposure to cannabis tolerance develops to some of its subjective and physiological effects reviewed in(Lichtman & Martin 2005). But whether tolerance develops to the psychotomimetic and amnestic effects of cannabinoids has not been systematically studied. In light of the current focus on the association between cannabis and psychosis, this would be important. One interpretation of the current results is that frequent cannabis use is associated with the development of tolerance to the psychotomimetic effects of Δ-9-THC.

Animal studies have shed light on the mechanisms of cannabinoid tolerance with increasing detail. For example, behavioral tolerance has been correlated with changes in brain glucose utilization before and after repeated dosing with cannabinoids (Freedland et al. 2002), with normalization i.e. tolerance, of cerebral glucose utilization following chronic exposure (Whitlow et al. 2003). The mechanisms underlying tolerance to cannabinoids include the downregulation and desensitization of receptors. Down regulation is believed to be due to receptor internalization (Romero et al. 1997), the rate and magnitude of which has been shown to vary by region (Breivogel et al. 1999; Romero et al. 1998). In the current study, frequent users showed blunted responses to the amnestic but not to the euphoric effects of Δ-9-THC, which are believed to be mediated by different regions: the hippocampus and basal ganglia, respectively. Region specific differences in CB1 receptor density are believed to determine the magnitude of receptor downregulation (Martin et al. 2004; Romero et al. 1998; Sim-Selley 2003). For example, the basal ganglia has a higher density of CB1 receptors relative to the hippocampus or cerebellum, yet down regulation occurs more rapidly in the hippocampus and cerebellum compared to basal ganglia. This may provide a possible explanation for the differential blunting of Δ-9-THC effects observed in this study. Similarly, the desensitization of receptors due to changes in downstream second messenger cascade including G protein coupling may also vary by region (Martin et al. 2004).

The group differences in Δ-9-THC-induced subjective, behavioral and cognitive effects were complemented by endocrine group differences. This is the first report that we are aware of demonstrating Δ-9-THC induced blunted cortisol release and lower prolactin levels in frequent cannabis users as compared to healthy controls. Cannabinoids increase ACTH and cortisol release via CB-1R activation in the hypothalamus pituitary (HPA) axis (Pagotto et al. 2006). The blunted Δ-9-THC induced cortisol release in frequent users of cannabis is consistent with the animal literature (Murphy et al. 1998a). The latter is thought to reflect tolerance secondary to a downregulation of CB-1R in the HPA axis. The absence of group differences in baseline cortisol levels may be explained by the lack of very early morning (< 6 a.m.) sampling.

Cannabinoids produce a predominantly late inhibitory effect on prolactin release (Harclerode 1984; Murphy et al. 1998b; Pagotto et al. 2006) which is mediated by CB-1R activation of tuberoinfundibular DA neurons (Rodriguez De Fonseca et al. 1992). Δ-9-THC failed to reduce prolactin release; this may be explained by the short sampling duration.

However, consistent with preclinical evidence that chronic exposure to cannabinoids leads to a long lasting suppression of prolactin release (de Miguel et al. 1998) frequent users of cannabis had significantly lower prolactin levels compared to controls.

Frequent users had equivalent "high," "calm and relaxed" feelings and tachycardia induced by Δ-9-THC. Perhaps, as discussed earlier, tolerance to the various effects of Δ-9-THC develops at different rates. Alternatively, frequent users of cannabis may be innately "protected" from some of the negative effects of cannabis.

Innate Differences

Several recent studies provide examples of how innate differences may account for some of the variance in the response to cannabis and also the risk for cannabis use disorders. Higher concordance in the subjective response to cannabis in monozygotic vs. dizygotic twins (Lyons et al. 1997), identification of specific CB1 receptor haplotypes that contribute to the risk of developing cannabis dependence symptoms (Hopfer et al. 2006b), and recent evidence of linkage for cannabis dependence on chromosome 3q21 and 9q34 (Hopfer et al. 2006a) suggest genetic influences on the cannabis response. Finally, recent evidence suggests that a single nucleotide polymorphism of the Catechol-methyl-transferase (COMT) gene may influence vulnerability to the psychotomimetic effects of cannabis (Caspi et al. 2005; Henquet et al. 2006b). While admittedly speculative, innate differences may contribute to the blunted "negative" effects of Δ-9-THC in frequent users.

Another interpretation to the study results is that frequent users who arguably are more experienced with the "negative" effects of cannabis may discount these effects more than infrequent users i.e., the controls in this study. Several findings in this study would not support the above hypothesis. First, the group differences were selective; there were no group differences on other self-report measures (e.g., VAS "high" and "calm & relaxed"). Second, as discussed in the results section, frequent users reported *greater* baseline (preΔ-9-THC) perceptual alterations. Finally, there were group differences in Δ-9-THC effects on performance based (e.g., memory) and endocrine measures which are less likely to be influenced by subjective effects.

Group Differences in Baseline and Δ-9-THC induced recall deficits

Relative to controls, frequent users had significantly worse baseline (placebo condition) immediate, delayed and cued recall (Figure 3). Whether these baseline differences reflect long term or residual effects of cannabis, or innate differences is unclear. Importantly however, despite having lower I.Q. scores and worse recall at baseline (placebo condition), frequent users had blunted Δ-9-THC induced immediate recall impairment relative to controls. Another intriguing finding of this study is that frequent users had *better* delayed recall under the influence of 2.5 mg Δ-9-THC, relative to the placebo condition (Figure 3). This pattern of effects is consistent with unpublished observations in ongoing studies at our center (D'Souza et al., in review) and may represent a distinct response of frequent users to low doses of Δ-9-THC. Perhaps state (Δ-9-THC)-dependent learning or the reversal of withdrawal might explain the better performance under 2.5 mg Δ-9-THC dose in frequent users. The latter is unlikely given the absence of any baseline symptoms suggestive of withdrawal e.g., nervousness, anxiety, irritability, restlessness [reviewed in](Budney et al. 2004) and the exclusion of cannabis dependence.

Implications for cannabis related psychosis

Individuals without any psychotic disorder, family history of psychosis or other Axis 1 disorder who frequently use cannabis may be innately protected and/or develop tolerance to the psychotomimetic and amnestic effects of Δ-9-THC. However, these data may not be

relevant to individuals who have a risk for psychosis or have an established psychotic disorder.

The findings are relevant to a growing literature suggesting an association between cannabis exposure and the risk of developing a psychotic disorder. Thus, studies of individuals with significant cannabis exposure may find a lower risk for psychotic disorders since as our data suggest these individuals either develop tolerance to or are inherently less vulnerable to the psychotomimetic effects of cannabis. Further, in association studies it may be possible that beyond a certain, albeit unspecified, magnitude of cannabis exposure, the likelihood of finding an increased risk of psychosis may actually decrease.

Implications for cannabis addiction

Individuals at risk for nicotine and alcohol addiction have blunted sensitivity to the "negative" effects, but heightened sensitivity to the "positive" effects of these drugs (Conrod et al. 2001; Eissenberg & Balster 2000; Newlin & Thomson 1990; Pollock 1992; Schuckit 1985b; Schuckit 1994; Schuckit et al. 1991a; Schuckit et al. 1991b; Schuckit et al. 1996). Similarly, positive reactions to early cannabis use are associated with an increased risk of later cannabis dependence (Fergusson et al. 2003b). In this study, while frequent users showed blunted responses to the "negative" or "undesirable" effects of Δ-9-THC, they were no different from controls in their response to Δ-9-THC induced "high". The findings of this study may provide an explanation as to why some individuals may be more likely to use cannabis frequently (Fergusson et al. 2003a; Lyons et al. 1997).

Limitations

Perhaps a more balanced battery of assessments that included more measures of "positive" effects may not have shown this profile of group differences predominantly in "undesirable" effects of cannabinoids. Further, since expectancy to drug effects was not measured or manipulated it is unknown whether expectancy may have contributed to the results. However, given that participation was voluntary and that both groups had experience with cannabis, albeit to different degrees, it is unlikely that subjects had strong negative expectancy to drug effects. Finally, as discussed elsewhere (D'Souza et al. 2004), the intravenous route, the speed of drug administration and the subjects not being able to "titrate" the dose or rate of administration is different from recreational cannabis use or the substantial literature on studies with smoked and oral Δ-9-THC administration. Nevertheless, the experimental controls in the current study address some of the confounding factors associated with naturalistic studies or studies with oral/smoked THC (D'Souza et al. 2004). Finally, this study was not designed to discriminate the contributions of tolerance and innate differences to the group differences observed.

In summary, there are differences in the psychotomimetic, amnestic, endocrine and subjective effects of Δ-9-THC between frequent users of cannabis and healthy controls. These differences may have implications for cannabis related psychosis and addiction. The precise neurobiology of these differences remains unclear and warrants further investigation.

Acknowledgments

The authors wish to thank Dr. George Kottayil (Unimed Pharmaceuticals, Inc.) for providing Δ-9-THC. The authors acknowledge the critical clinical research contributions of the Biological Studies Unit, VA Connecticut Healthcare System including Elizabeth O'Donell, R.N; Angelina Genovese, R.N; Sonah Yoo, RPh; Robert Sturwold, RPh, and Mr. Willie Ford. This study was supported by National Institute of Drug Abuse (DA12382-01) to DCD in addition to indirect support from the 1) Department of Veterans Affairs (Schizophrenia Biological Research Center, Alcohol Research Center, National Center for PTSD [John Krystal]), 2) National Institute of Mental Health (MH61019-02 to DCD).

Abbreviations

Δ-9-THC	(delta-9-tetrahydrocannabinol)
CB	(Cannabinoid)

REFERENCES

Anthony JC, Trinkoff AM. United States epidemiologic data on drug use and abuse: how are they relevant to testing abuse liability of drugs? NIDA Res Monogr. 1989; 92:241–66. [PubMed: 2512496]

Bornheim LM, Kim KY, Li J, Perotti BY, Benet LZ. Effect of cannabidiol pretreatment on the kinetics of tetrahydrocannabinol metabolites in mouse brain. Drug Metabolism & Disposition. 1995; 23:825–31. [PubMed: 7493549]

Brandt J. The Hopkins Verbal Learning Test. Development of a New Memory Test with 6 Equivalent Forms. The Clinical Neuropsychologist. 1991; 5:125–142.

Breivogel CS, Childers SR, Deadwyler SA, Hampson RE, Vogt LJ, Sim-Selley LJ. Chronic delta9-tetrahydrocannabinol treatment produces a time-dependent loss of cannabinoid receptors and cannabinoid receptor-activated G proteins in rat brain. J Neurochem. 1999; 73:2447–59. [PubMed: 10582605]

Bremner JD, Krystal JH, Putnam FW, Southwick SM, Marmar C, Charney DS, Mazure CM. Measurement of dissociative states with the Clinician-Administered Dissociative States Scale (CADSS). Journal of Traumatic Stress. 1998; 11:125–36. [PubMed: 9479681]

Brunner, E.; Domhof, S.; Langer, F. Nonparametric analysis of longitudinal data in factorial experiments. John Wiley and Sons; New York, NY: 2002.

Budney AJ, Hughes JR, Moore BA, Vandrey R. Review of the validity and significance of cannabis withdrawal syndrome. Am J Psychiatry. 2004; 161:1967–77. [PubMed: 15514394]

Bylsma FW, Rebok GW, Brandt J. Long-term retention of implicit learning in Huntington's disease. Neuropsychologia. 1991; 29:1213–21. [PubMed: 1838794]

Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H, Taylor A, Arseneault L, Williams B, Braithwaite A, Poulton R, Craig IW. Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene × environment interaction. Biol Psychiatry. 2005; 57:1117–27. [PubMed: 15866551]

Compton WM, Grant BF, Colliver JD, Glantz MD, Stinson FS. Prevalence of marijuana use disorders in the United States: 1991-1992 and 2001-2002. Jama. 2004; 291:2114–21. [PubMed: 15126440]

Conrod PJ, Peterson JB, Pihl RO. Reliability and validity of alcohol-induced heart rate increase as a measure of sensitivity to the stimulant properties of alcohol. Psychopharmacology (Berl). 2001; 157:20–30. [PubMed: 11512039]

D'Souza DC. Cannabinoids and psychosis. Int Rev Neurobiol. 2007; 78:289–326. [PubMed: 17349865]

D'Souza DC, Perry E, MacDougall L, Ammerman Y, Cooper T, Wu YT, Braley G, Gueorguieva R, Krystal JH. The psychotomimetic effects of intravenous delta-9-tetrahydrocannabinol in healthy individuals: implications for psychosis. Neuropsychopharmacology. 2004; 29:1558–72. [PubMed: 15173844]

de Miguel R, Romero J, Munoz RM, Garcia-Gil L, Gonzalez S, Villanua MA, Makriyannis A, Ramos JA, Fernandez-Ruiz JJ. Effects of cannabinoids on prolactin and gonadotrophin secretion: involvement of changes in hypothalamic gamma-aminobutyric acid (GABA) inputs. Biochem Pharmacol. 1998; 56:1331–8. [PubMed: 9825732]

Eissenberg T, Balster RL. Initial tobacco use episodes in children and adolescents: current knowledge, future directions. Drug Alcohol Depend. 2000; 59(Suppl 1):S41–60. [PubMed: 10773437]

Fergusson DM, Horwood LJ, Lynskey MT, Madden PA. Early reactions to cannabis predict later dependence. Arch Gen Psychiatry. 2003a; 60:1033–9. [PubMed: 14557149]

Fergusson DM, Horwood LJ, Swain-Campbell NR. Cannabis dependence and psychotic symptoms in young people. Psychol Med. 2003b; 33:15–21. [PubMed: 12537032]

First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV-TR Axis I Disorders- Non-patient Edition. American Psychiatric Association; Washington,DC.: 2002.

Freedland CS, Whitlow CT, Miller MD, Porrino LJ. Dose-dependent effects of Delta9-tetrahydrocannabinol on rates of local cerebral glucose utilization in rat. Synapse. 2002; 45:134–42. [PubMed: 12112406]

Gonzalez S, Cebeira M, Fernandez-Ruiz J. Cannabinoid tolerance and dependence: a review of studies in laboratory animals. Pharmacol Biochem Behav. 2005; 81:300–18. [PubMed: 15919107]

Gordon M. Microprocessor-based assessment of attention deficit disorders (ADD). Psychopharmacology Bulletin. 1986; 22:288–90. [PubMed: 3523580]

Green B, Kavanagh D, Young R. Being stoned: a review of self-reported cannabis effects. Drug Alcohol Rev. 2003; 22:453–60. [PubMed: 14660135]

Guimaraes FS, de Aguiar JC, Mechoulam R, Breuer A. Anxiolytic effect of cannabidiol derivatives in the elevated plus-maze. General Pharmacology. 1994; 25:161–4. [PubMed: 7913072]

Haertzen CA. Addiction Research Center Inventory (ARCI): development of a general drug estimation scale. Journal of Nervous & Mental Disease. 1965; 141:300–7. [PubMed: 5846592]

Haertzen CA. Development of scales based on patterns of drug effects, using the addiction Research Center Inventory (ARCI). Psychological Reports. 1966; 18:163–94. [PubMed: 5908477]

Hall W, Degenhardt L, Teesson M. Cannabis use and psychotic disorders: an update. Drug Alcohol Rev. 2004; 23:433–43. [PubMed: 15763748]

Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following oral THC administration to humans. Psychopharmacology. 1999a; 141:385–94. [PubMed: 10090646]

Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following smoked marijuana in humans. Psychopharmacology (Berl). 1999b; 141:395–404. [PubMed: 10090647]

Harclerode, J. Endocrine Effects of Marijuana in the Male: Preclinical Studies. Braude, MC.; Ludford, JP., editors. National Institute on Drug Abuse 5600 Fishers Lane Rockville; Maryland 20857, Rockville: 1984. p. 45-114.NIDA Research Monograph Series

Henquet C, Murray R, Linszen D, van Os J. The environment and schizophrenia: the role of cannabis use. Schizophr Bull. 2005; 31:608–12. [PubMed: 15976013]

Henquet C, Rosa A, Krabbendam L, Papiol S, Fananas L, Drukker M, Ramaekers JG, van Os J. An experimental study of catechol-o-methyltransferase Val158Met moderation of delta-9-tetrahydrocannabinol-induced effects on psychosis and cognition. Neuropsychopharmacology. 2006a; 31:2748–57. [PubMed: 16936704]

Henquet C, Rosa A, Krabbendam L, Papiol S, Fananas L, Drukker M, Ramaekers JG, van Os J. An Experimental Study of Catechol-O-Methyltransferase Val(158)Met Moderation of Delta-9-Tetrahydrocannabinol-Induced Effects on Psychosis and Cognition. Neuropsychopharmacology. 2006b

Hollister LE. Cannabis--1988. Acta Psychiatr Scand Suppl. 1988; 345:108–18. [PubMed: 2852450]

Hopfer CJ, Lessem JM, Hartman CA, Stallings MC, Cherny SS, Corley RP, Hewitt JK, Krauter KS, Mikulich-Gilbertson SK, Rhee SH, Smolen A, Young SE, Crowley TJ. A genome-wide scan for loci influencing adolescent cannabis dependence symptoms: Evidence for linkage on chromosomes 3 and 9. Drug Alcohol Depend. 2006a

Hopfer CJ, Young SE, Purcell S, Crowley TJ, Stallings MC, Corley RP, Rhee SH, Smolen A, Krauter K, Hewitt JK, Ehringer MA. Cannabis receptor haplotype associated with fewer cannabis dependence symptoms in adolescents. Am J Med Genet B Neuropsychiatr Genet. 2006b

Jones RT, Benowitz N, Bachman J. Clinical studies of cannabis tolerance and dependence. Annals of the New York Academy of Sciences. 1976; 282:221–39. [PubMed: 798533]

Jones RT, Benowitz NL, Herning RI. Clinical relevance of cannabis tolerance and dependence. Journal of Clinical Pharmacology. 1981; 21:143S–152S. [PubMed: 6271820]

Kay SR, Opler LA, Lindenmayer JP. The Positive and Negative Syndrome Scale (PANSS): rationale and standardisation. British Journal of Psychiatry - Supplementum. 1989:59–67.

Leweke FM, Gerth CW, Klosterkotter J. Cannabis-associated psychosis: current status of research. CNS Drugs. 2004; 18:895–910. [PubMed: 15521792]

Leweke FM, Schneider U, Radwan M, Schmidt E, Emrich HM. Different effects of nabilone and cannabidiol on binocular depth inversion in Man. Pharmacol Biochem Behav. 2000; 66:175–81. [PubMed: 10837858]

Leweke FM, Schneider U, Thies M, Munte TF, Emrich HM. Effects of synthetic delta9-tetrahydrocannabinol on binocular depth inversion of natural and artificial objects in man. Psychopharmacology (Berl). 1999; 142:230–5. [PubMed: 10208314]

Lichtman AH, Martin BR. Cannabinoid tolerance and dependence. Handb Exp Pharmacol. 2005:691–717. [PubMed: 16596793]

Lyons MJ, Toomey R, Meyer JM, Green AI, Eisen SA, Goldberg J, True WR, Tsuang MT. How do genes influence marijuana use? The role of subjective effects. Addiction. 1997; 92:409–17. [PubMed: 9177062]

Martin BR, Sim-Selley LJ, Selley DE. Signaling pathways involved in the development of cannabinoid tolerance. Trends Pharmacol Sci. 2004; 25:325–30. [PubMed: 15165748]

Mechoulam R, Ben-Shabat S. From gan-zi-gun-nu to anandamide and 2-arachidonoylglycerol: the ongoing story of cannabis. Natural Product Reports. 1999; 16:131–43. [PubMed: 10331283]

Murphy LL, Munoz RM, Adrian BA, Villanua MA. Function of cannabinoid receptors in the neuroendocrine regulation of hormone secretion. Neurobiol Dis. 1998a; 5:432–46. [PubMed: 9974176]

Murphy LL, Munoz RM, Adrian BA, Villanua MA. Function of cannabinoid receptors in the neuroendocrine regulation of hormone secretion. Neurobiology of Disease. 1998b; 5:432–46. [PubMed: 9974176]

Newlin DB, Thomson JB. Alcohol challenge with sons of alcoholics: a critical review and analysis. Psychol Bull. 1990; 108:383–402. [PubMed: 2270234]

Pagotto U, Marsicano G, Cota D, Lutz B, Pasquali R. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. Endocr Rev. 2006; 27:73–100. [PubMed: 16306385]

Pollock VE. Meta-analysis of subjective sensitivity to alcohol in sons of alcoholics. Am J Psychiatry. 1992; 149:1534–8. [PubMed: 1415821]

Rodriguez De Fonseca F, Fernandez-Ruiz JJ, Murphy LL, Cebeira M, Steger RW, Bartke A, Ramos JA. Acute effects of delta-9-tetrahydrocannabinol on dopaminergic activity in several rat brain areas. Pharmacology, Biochemistry & Behavior. 1992; 42:269–75.

Romero J, Berrendero F, Manzanares J, Perez A, Corchero J, Fuentes JA, Fernandez-Ruiz JJ, Ramos JA. Time-course of the cannabinoid receptor down-regulation in the adult rat brain caused by repeated exposure to delta9-tetrahydrocannabinol. Synapse. 1998; 30:298–308. [PubMed: 9776133]

Romero J, Garcia-Palomero E, Castro JG, Garcia-Gil L, Ramos JA, Fernandez-Ruiz JJ. Effects of chronic exposure to delta9-tetrahydrocannabinol on cannabinoid receptor binding and mRNA levels in several rat brain regions. Brain Res Mol Brain Res. 1997; 46:100–8. [PubMed: 9191083]

Russo EB, McPartland JM. Cannabis is more than simply delta(9)-tetrahydrocannabinol.[comment]. Psychopharmacology. 2003; 165:431–2. author reply 433-4. [PubMed: 12491031]

SAMHSA. Results from the 2003 National Survey on Drug Use and Health: National Findings. Substance Abuse and Mental Health Services Administration; Rockville, MD.: 2004.

Schuckit MA. Behavioral effects of alcohol in sons of alcoholics. Recent Dev Alcohol. 1985a; 3:11–9. [PubMed: 3975448]

Schuckit MA. Ethanol-induced changes in body sway in men at high alcoholism risk. Arch Gen Psychiatry. 1985b; 42:375–379. [PubMed: 3977555]

Schuckit MA. Low level of response to alcohol as a predictor of future alcoholism. American Journal of Psychiatry. 1994; 151:184–9. [PubMed: 8296886]

Schuckit MA. Genetics of the risk for alcoholism. Am J Addict. 2000; 9:103–12. [PubMed: 10934572]

Schuckit MA, Duthie LA, Mahler HI, Irwin M, Monteiro MG. Subjective feelings and changes in body sway following diazepam in sons of alcoholics and control subjects. J Stud Alcohol. 1991a; 52:601–8. [PubMed: 1758188]

Schuckit MA, Greenblatt D, Gold E, Irwin M. Reactions to ethanol and diazepam in healthy young men. J Stud Alcohol. 1991b; 52:180–7. [PubMed: 2016879]

Schuckit MA, Smith TL, Anderson KG, Brown SA. Testing the level of response to alcohol: social information processing model of alcoholism risk--a 20-year prospective study. Alcohol Clin Exp Res. 2004; 28:1881–9. [PubMed: 15608605]

Schuckit MA, Tsuang JW, Anthenelli RM, Tipp JE, Nurnberger JI Jr. Alcohol challenges in young men from alcoholic pedigrees and control families: a report from the COGA project. J Stud Alcohol. 1996; 57:368–77. [PubMed: 8776678]

Sim-Selley LJ. Regulation of cannabinoid CB1 receptors in the central nervous system by chronic cannabinoids. Crit Rev Neurobiol. 2003; 15:91–119. [PubMed: 14977366]

Slosson, RL. Slosson Intelligence Test (SIT) for Children and Adults. Slosson Educational Publications; East Aurora, NY: 1963.

Sobell, LC.; Sobell, MB. Timeline Follow-Back: A technique for assessing self-reported alcohol consumption. Measuring Alcohol Consumption. Litten, AR.; Totowa, J., editors. The Humana Press; NJ: 1992.

Stinson FS, Ruan WJ, Pickering R, Grant BF. Cannabis use disorders in the USA: prevalence, correlates and co-morbidity. Psychol Med. 2006; 36:1447–60. [PubMed: 16854249]

Verdoux H, Tournier M. Cannabis use and risk of psychosis: an etiological link? Epidemiologia e Psichiatria Sociale. 2004; 13:113–9. [PubMed: 15298320]

Wachtel SR, ElSohly MA, Ross SA, Ambre J, de Wit H. Comparison of the subjective effects of Delta(9)-tetrahydrocannabinol and marijuana in humans. Psychopharmacology (Berl). 2002; 161:331–9. [PubMed: 12073159]

Weiser M, Noy S. Interpreting the association between cannabis use and increased risk for schizophrenia. Dialogues Clin Neurosci. 2005; 7:81–5. [PubMed: 16060598]

Whitlow CT, Freedland CS, Porrino LJ. Functional consequences of the repeated administration of Delta9-tetrahydrocannabinol in the rat. Drug Alcohol Depend. 2003; 71:169–77. [PubMed: 12927655]

Zuardi AW, Morais SL, Guimaraes FS, Mechoulam R. Antipsychotic effect of cannabidiol [letter]. Journal of Clinical Psychiatry. 1995; 56:485–6. [PubMed: 7559378]

Zuardi AW, Rodrigues JA, Cunha JM. Effects of cannabidiol in animal models predictive of antipsychotic activity. Psychopharmacology. 1991; 104:260–4. [PubMed: 1678894]

Zuardi, AW.; Shirakawa, I.; Finkelfarb, E.; Karniol, IG. Action of cannabidiol on the anxiety and other efects produced by delta 9-THC in normal subjects.

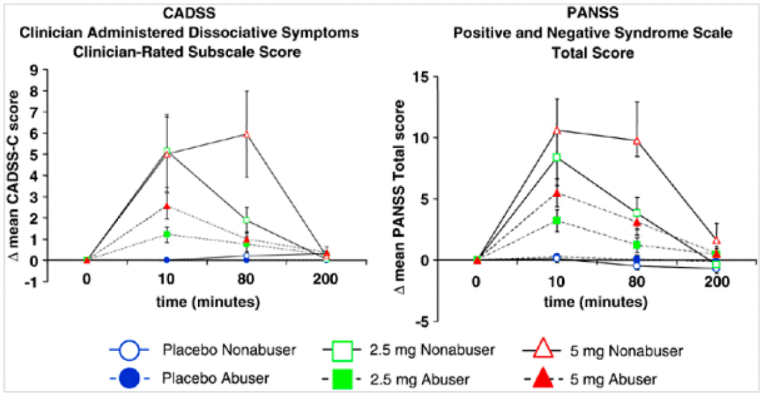

Figure 1. Psychotomimetic & Perceptual Alterations Effects

Perceptual Alterations measured by the Clinician and Subject Rated subscales of the Clinician Administered Dissociative Symptoms Scale (T bars indicate S.E.M.s). Frequent users had smaller Δ-9-THC induced increases in CADSS-Clinician Subscale Scores scores and PANSS Total scores relative to controls.

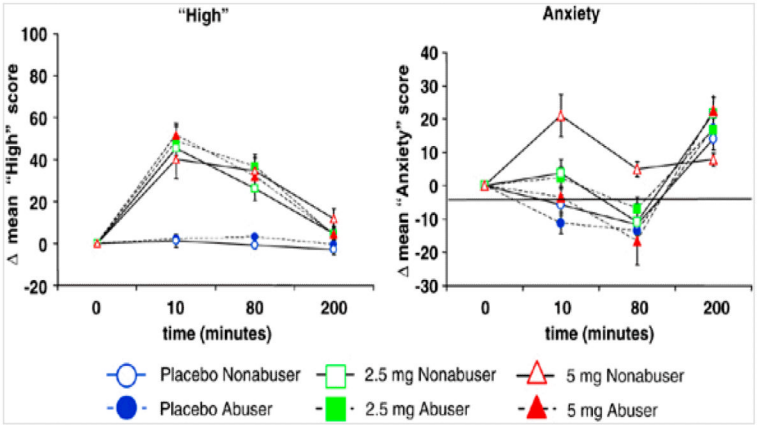

Figure 2. Subjective Effects (VAS: Visual Analog Scale)

Subjective symptoms of 'high' and anxiety measured on the Visual Analog Scale (T bars indicate SEMs). 'high': Δ-9-THC transiently increased scores on VAS 'high': equivalently in both groups. 'anxiety': Δ-9-THC transiently increased VAS 'anxiety' scores but to a lower extent in frequent users compared to controls.

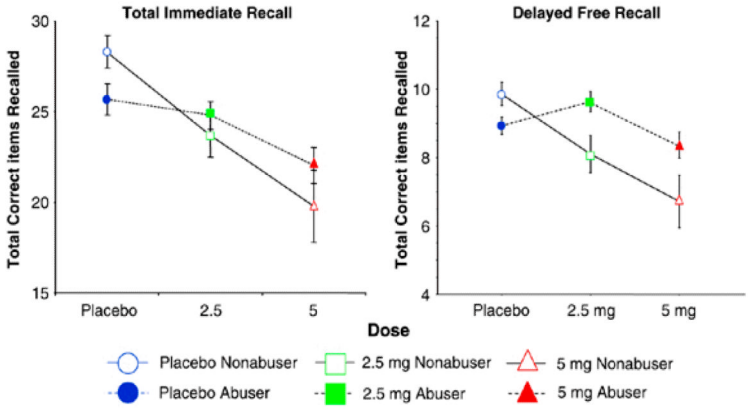

Figure 3. Learning and Recall (Hopkins Verbal Learning Task)

Immediate and Delayed verbal recall measured by the Hopkins Verbal Learning Task (T bars indicate SEMs). **Immediate recall:** frequent users performed worse at baseline, but had smaller Δ-9-THC-induced impairments than controls. **Delayed recall:** Δ-9-THC impaired delayed recall in both groups. Only in frequent users, recall was worse on placebo than the low dose.

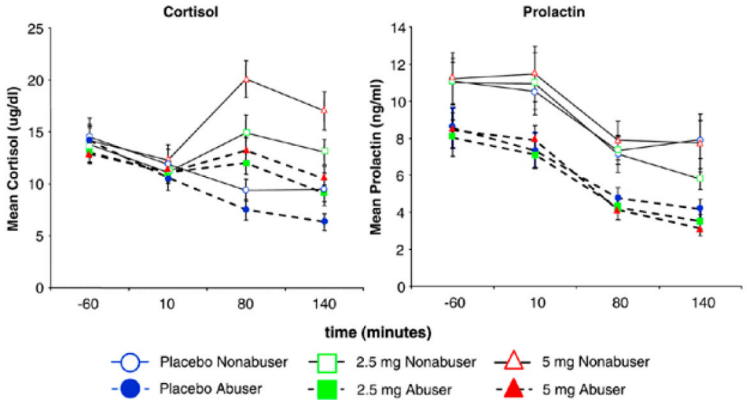

Figure 4. Plasma Cortisol and Prolactin

Plasma cortisol and prolactin levels (T bars indicate SEMs). Frequent users showed reduced Δ-9-THC-induced increases in plasma cortisol and lower overall prolactin levels.

Table 1

Schedule of Testing

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," and "anxiety"
	Blood sampling: Δ-9-THC and THC-COOH
	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," and "anxiety"
	Blood sampling: Δ-9-THC and THC-COOH
+30	Learning (immediate recall): HVLT
+45	Distractibility and vigilance: Gordon Box
+60	Delayed Free, cued, and recognition recall: HVLT
+80	Behavioral assessments: PANSS CADSS VAS for "high," "calm and relaxed," and "anxiety"
	Blood sampling: Δ-9-THC and THC-COOH
+140	Blood sampling: Δ-9-THC and THC-COOH
+200	Behavioral assessments: PANSS CADSS VAS for "high," "calm and relaxed," and "anxiety"
	Blood sampling: Δ-9-THC and THC-COOH
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; Δ-9-THC: Δ-9-tetrahydrocannibinol; THC-COOH: 11-nor-Δ-9-THC-9-COOH; HVLT: Hopkins Verbal Learning Test.

Table 2

Subject Demographics

		Controls		Frequent Users	
		Mean (S.D)		**Mean (S.D)**	
Total n		22 (14 males, 8 females)		30 (21 males, 9 females)	
Age (years)		29 * (11.6)		24.8 * (5.5)	
Education (years)		16.3 (1.9)		15.4 (1.3)	
Handedness		Right	18	Right	25
		Left	4	Left	5
Race		Caucasian	15	Caucasian	24
		Indian	1	Native American	1
		African American	6	African American	3
		Hispanic	0	Hispanic	2
Weight		174.7 (46.4)		165.7 (31.2)	
I.Q		130 (19)		119 ** (15)	
Completers	3 test days	15		17	
	2 test days	5		9	
	1 test day	2		4	

* No subjects below the age of 18 years were studied.

** p = 0.045

Table 3

Cannabis Use History

Urine Toxicology Positive for Cannabis		
	Controls [N (%)]	**Frequent Users [N (%)]**
# of subjects	0 (0)	30 (100%)
Past Month Mean Cannabis Exposure		
	Controls	**Frequent Users**
# of exposures	0.16 (±0.01)	21.5 (±9)
Last exposure to cannabis		
Time	**Controls [N (%)]**	**Frequent Users [N (%)]**
Past week	0 (0%)	25 (83%)
1 week-1 month	4 (18%)	5 (17%)
1-6 months	6 (27%)	0 (0%)
6months-1 yr	1 (5%)	0 (0%)
1-5 years	4 (18%)	0 (0%)
5-10 years	3 (14%)	0 (0%)
>10 years	4 (18%)	0 (0%)
Heaviest Ever Cannabis Exposure		
Frequency	**Controls [N (%)]**	**Frequent Users [N (%)]**
7 times/week (daily)	0	16 (53)
1-6 times/week	0	14 (46)
1-3 times/month	0	0
1-11/year	22 (100)	0
Less than once per year	0	0
Lifetime Cannabis Exposure		
# of exposures	**Controls [N (%)]**	**Frequent Users [N (%)]**
Less than 5 times	7 (32)	0
5-10 times	0	0
11-20 times	3 (14)	0
21-50 times	2 (9)	0
51-100 times	4 (18)	1 (3)
>100 times	6 (27)	29 (97)