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Extended Plasma Cannabinoid Excretion in Chronic Frequent Cannabis Smokers During Sustained Abstinence and Correlation with Psychomotor Performance

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Abstract

Cannabis smoking increases motor vehicle accident risk. Empirically defined cannabinoid detection windows are important to drugged driving legislation. Our aims were to establish plasma cannabinoid detection windows in frequent cannabis smokers and to determine if residual cannabinoid concentrations were correlated with psychomotor performance. Twenty-eight male chronic frequent cannabis smokers resided on a secure research unit for up to 33 days with daily blood collection. Plasma specimens were analyzed for ⁹-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH) by gas chromatography-mass spectrometry. Critical tracking and divided attention tasks were administered at baseline (after overnight stay to ensure lack of acute intoxication) and after 1, 2 and 3 weeks cannabis abstinence. Twenty-seven of 28 participants were THC-positive at admission (median 4.2 µg/L). THC concentrations significantly decreased 24 h after admission, but were still 2 µg/L in 16 of 28 participants 48 h after admission. THC was detected in 3 of 5 specimens on day 30. The last positive 11-OH-THC specimen was 15 days after admission. THCCOOH was measureable in 4 of 5 participants after 30 days of abstinence. Years of prior cannabis use significantly correlated with THC concentrations on admission, and days 7 and 14. Tracking error, evaluated by the Divided Attention Task, was the only evaluated psychomotor assessment significantly correlated with cannabinoid concentrations at baseline and day 8 (11-OH-THC only). Median THC was 0.3 µg/L

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in 5 chronic frequent cannabis smokers' plasma samples after 30 days of sustained abstinence. Tracking error significantly correlated with cannabinoid baseline concentrations.

Graphical Abstract

We monitored plasma cannabinoids and psychomotor performance in frequent cannabis smokers during abstinence and established plasma cannabinoid detection windows in frequent cannabis smokers. 11-hydroxy-THC (11-OH-THC) was detected up to 15 days after admission. Psychomotor performance correlated with THC concentrations at baseline.

Keywords

Cannabinoid; ⁹-tetrahydrocannabinol; cannabis; chronic; abstinence

INTRODUCTION

According to the 2014 World Drug Report from the United Nations Office of Drug Control, cannabis remains the most widely used illicit substance, with an estimated 177.3 million (3.8%) of the world's population aged 15-64 smoking in the preceding year [1]. In 2013-2014, the National Roadside Survey found that 12.6% of nighttime drivers were cannabinoid-positive in blood or oral fluid [2], a 48% increase from the 2007 survey [3]. In Washington State in 2014, 44% of surveyed drivers who smoked cannabis in the past year admitted they smoked within two hours of driving [4].

Several cannabis effects on driving reviews demonstrated that cannabis smoking was associated with poor driving performance and approximately doubles the risk of involvement in a MVA [6-8]. This serious public health concern prompted many states to adopt or consider zero-tolerance or *per se* laws regarding the presence of cannabinoids in biological specimens. In fact, recent recreational cannabis legalization in the State of Washington coincided with implementation of a 5 µg/L ⁹-tetrahydrocannabinol (THC) blood *per se* limit [9]. Other states' laws enforce 1 or 2 µg/L blood THC as indicative of impaired driving. Therefore, empirically determined cannabinoid detection windows are important to drugged driving legislation.

THC's window of detection varies based on THC concentration in the cigarette, and on the frequency and chronicity of cannabis smoking. Mean plasma THC detection windows (limit of quantification 0.5 µg/L) were identified in occasional cannabis smokers as 3-12 and 6-27

h following controlled paced smoking of a 1.75 or 3.55% THC cigarette (15.8 or 33.8 mg THC), respectively [10]. After *ad libitum* smoking of a 6.8% THC cigarette (54 mg THC) for 10 min, median (range) plasma THC detection windows (LOQ 0.5 µg/L) for occasional and frequent smokers were 4 (1-10.5) and >30 h, respectively [11]. THC concentrations decrease rapidly after the end of smoking due to distribution throughout the body, hepatic metabolism, and excretion. Quantifiable THC in blood or plasma of occasional cannabis smokers indicated recent cannabis exposure within 6 to 8 h [10].

When frequent cannabis smoking occurs over an extended timeframe, THC accumulates in adipose tissue, creating a large cannabinoid body burden or drug depot [12-15]. Cannabinoid excretion in chronic frequent cannabis smokers is prolonged by THC's slow diffusion from adipose tissue back into the bloodstream [15]. Additionally, postmortem studies in humans [16] and animals [17] observed extended THC detection in brain compared to blood.

THC is the primary centrally-acting cannabis component and the analyte most frequently referenced when analyzing blood or plasma cannabinoids. THC is rapidly metabolized to equipotent 11-hydroxy-THC (11-OH-THC) and inactive 11-nor-9-carboxy-THC (THCCOOH) metabolites. THC and metabolites also form polar glucuronide conjugates to facilitate excretion during Phase II metabolism [18-22]. A recent NIDA study showed that THC and THCCOOH were measureable for at least 30 days in blood [23] and THC, 11-OH-THC and THCCOOH at least 24 days in urine [24] of chronic frequent cannabis smokers after initiating continuously monitored cannabis abstinence. Although blood [23] and oral fluid [25] data were previously published from this National Institute on Drug Abuse (NIDA) study, plasma data also are critical for interpretation of cannabinoid concentrations in clinical and forensic cases.

Most published literature and legislation involves blood cannabinoids. Blood-to-plasma (B/P) cannabinoid ratios of 0.37-0.76 were previously described [26-29]. These ratios may be applied as a conversion factor for estimation, but due to ratio variation, plasma cannabinoid data provide more accurate interpretive value in cases involving plasma cannabinoids.

Currently, Australia and 11 European Union (EU) countries, including Sweden and France, have zero-tolerance *per se* laws that make it illegal for a person to operate a motor vehicle with any detectable THC and/or a metabolite present in their blood and/or oral fluid [23, 30-31]. In the US, 17 states currently have *per se* laws that make it illegal for a person to operate a motor vehicle with detectable THC and/or THCCOOH in blood and/or urine [32-34]. Of those 17 states, 10 enforce a strict zero-tolerance threshold, while 4 have blood THC cut-offs ranging from 1-5 µg/L [33]. Additionally, 23 states and Washington, D.C. decriminalized cannabis for medical use [35], but many did not change their impaired driving laws [32].

The aim of this study was to establish plasma cannabinoid detection windows for chronic frequent cannabis smokers and to determine if plasma concentrations were correlated with psychomotor performance in critical tracking and divided attention tasks. We monitored cannabinoid concentrations in plasma collected every 24 h from 28 chronic frequent cannabis smokers residing on a closed research unit to establish detection windows during

continuously observed abstinence for up to 33 consecutive days. While cannabinoid interpretation remains a complex subject, these results document prolonged plasma THC excretion in chronic frequent cannabis smokers and advocate for the use of multiple cannabinoids to improve result interpretation.

MATERIALS AND METHODS

Participants

Healthy, adult male cannabis-smoking volunteers, 18-65 years old were psychologically and medically evaluated for participation in a positron emission tomography (PET) study examining whether CB₁ receptor density was altered by chronic frequent cannabis smoking and after multiple weeks of sustained observed abstinence [36]. Participants were offered participation in this study if they met the following inclusion criteria (1) self-reported cannabis smoking for at least one year, (2) heavy cannabis smoking as defined by typical smoking pattern of 5 or more days per week over the last 6 months prior to admission, and a positive urine cannabinoid test within 90 days of admission. Participants were excluded if they met any of the following criteria (1) history or presence of a clinically significant medical, neurological or developmental disorder, (2) Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) axis I diagnosis other than cannabis, nicotine, or caffeine abuse or dependence, (3) history of head trauma with loss of consciousness lasting more than 10 min, (4) metallic foreign bodies (for the PET scanning study) or (5) if the participant was planning to or actively participating in drug abuse treatment.

The NIH Institutional Review Boards for NIDA and the National Institute of Mental Health approved the protocol. All participants provided voluntary written informed consent. Participants resided on the closed, secure Johns Hopkins Behavioral Pharmacology Research Unit for up to 33 days under 24 h staff monitoring to prevent use of unauthorized substances. On entry, participants and their belongings were searched for illegal drugs and no visitors were permitted. There were no dietary or physical activity restrictions. The trial is registered on www.clinicaltrials.gov (identification number NCT00816439).

Specimen Collection and Analysis

Blood specimens were collected in sodium heparin Vacutainer® (BD, Franklin Lakes, NJ, USA) tubes from peripheral venous catheters once daily in the morning. Blood samples were kept on ice, centrifuged (4000g for 10 min at 4°C), and plasma separated within 2 h. Venous catheters were left in place up to 72 h. Plasma specimens were stored in polypropylene cryotubes at -20°C until analysis.

Plasma specimens were analyzed with a previously published analytical method [37]. Briefly, 2 mL cold acetonitrile was added to 1 mL plasma aliquots to precipitate protein. Samples were centrifuged and supernatant decanted into 3 mL sodium acetate buffer (pH 4.0). Cannabinoids were isolated and concentrated with Clean Screen® ZSTHC020 solid phase extraction columns (UCT, Inc., Bristol, PA, USA) and were derivatized with 25 µL N,O-bis(trimethylsilyl)trifluoroacetamide and 1% trimethylchlorosilane (Regis Technologies, Inc., Morton Grove, IL, USA) at 70°C for 30 min. Two-dimensional gas chromatography

mass spectrometry with cryofocusing in electron impact selected-ion monitoring mode was employed to quantify derivatized cannabinoids. Low calibration curves were linear with $r^2 > 0.996$ from 0.25–25 $\mu\text{g/L}$ for THC and THCCOOH and 0.5–25 $\mu\text{g/L}$ for 11-OH-THC. Analytes quantifying $>25 \mu\text{g/L}$ were reprocessed on high calibration curves from 25–100 $\mu\text{g/L}$. Quality control samples were analyzed with each analytical run at 0.75, 2, 20, 30, 60 and 90 $\mu\text{g/L}$ for all analytes. Intra-day imprecision was 11.9% (% relative standard deviation), inter-batch imprecision was 7.3% (% relative standard deviation) and bias was within $\pm 11.8\%$ of target for all analytes.

Psychomotor Tests

Psychomotor tests for measuring attention and motor performance included the CTT (Critical Tracking Task) and DAT (Divided Attention Task) administered on days 1 or 2 (baseline), day 8, day 14, 15 or 16, and day 21, 22 or 23 as described in Bosker et al. [38]. Participants spent the previous night on the closed research unit to ensure lack of acute cannabis intoxication for baseline measurements. All subjects received extensive training on the psychomotor tests (at least 20 repetitions) until stable performance was achieved (less than 10% variance in 5 consecutive measurements) prior to baseline testing. CTT measures the participant's ability to control a displayed error signal in a 1st order compensatory tracking task [38]. Error appears as a horizontal deviation of the cursor from midpoint on a horizontal, linear scale. Compensatory joystick movements null the error and occur with a progressively higher frequency until the subject is unable to correct the deviation. The frequency at which control loss occurs is λ_c (the critical frequency). DAT assesses the ability to divide attention between two simultaneous tasks [38]. The primary task requires use of a joystick to continuously null the horizontal movement of a cursor from the center of a display as in CTT. The dependent measure of this task was control losses or the number of time a participant could not keep the cursor within the predefined range. As a subtask, tracking error was measured as the absolute distance in mm between the cursor's position and the center. The secondary task involved monitoring changing numbers in the four corners of the display. The requirement was to react as rapidly as possible by lifting the foot off a pedal every time a target number appeared in a corner. The average reaction time to target and percentages hit were recorded as dependent measures.

Statistical Analyses

Statistical evaluations were conducted with SPSS version 22.0, GraphPad Prism version 5.02 and Microsoft Excel 2010 for Windows. Body mass index (BMI) was calculated by $\text{BMI} = 703 \times [\text{weight (lb)} / (\text{height (in)})^2]$. If analytes were not detected, a zero was reported for descriptive statistical analyses. Median and range included non-detectable cannabinoid concentrations. Data were not normally distributed; thus, nonparametric statistical comparisons were conducted with Wilcoxon Signed Ranks tests and correlations performed with linear regression [39]. Correlations between cannabinoid concentrations and years of cannabis use were only performed on admission and days 7, 14, 21 and 28. Associations between task performance and cannabinoid concentrations were assessed by means of Pearson-r correlations.

Kaplan-Meier survival analyses^[40] were conducted with THC, 11-OH-THC and THCCOOH last detection times. If participants left the study prior to achieving 5 consecutive or non-consecutive negative THC or 2 negative 11-OH-THC results, their data were censored. One participant with negative cannabinoid results throughout the study was not included in the survival analysis. Statistical comparisons of survival curves were conducted with Log Rank tests. Two-tailed $P < 0.05$ were considered statistically significant for all statistical analyses.

RESULTS

Twenty-eight male chronic frequent cannabis smokers with a mean $\pm$ SD age of 27.4 $\pm$ 6.6 years (range: 19-43) reported smoking 10.6 $\pm$ 6.3 joints per day (range: 1-30) starting age 14.6 $\pm$ 3.2 years (range: 6-22) for a lifetime cannabis use duration of 10.6 $\pm$ 5.8 years (range: 4-28) (Table 1). Two participants were underweight (BMI 18.5), 14 were normal weight (BMI 18.6-24.9), 10 were overweight (BMI 25.0-29.9) and 2 were obese (BMI 30.0).

Participants abstained from cannabis smoking throughout the study and resided on the secure unit for at least 1 (n=24), 2 (n=20), 3 (n=13), or 4 (n=10) weeks, with the longest residence 33 days (n=1). Participants voluntarily withdrew from the study for family reasons or because they no longer desired to remain on the closed research unit, as indicated in the decreasing n seen in Table 2. On day 1, blood was not collected from 6 subjects for a variety of reasons including inaccessible peripheral vein, refusal to have blood drawn, or nursing error. On days 26 and 27, one subject refused blood draws, but accepted on day 28. From day 27 forward, an additional subject withdrew from the study. Thus, there were 10, 9, and 10 participants on days 26, 27, and 28, respectively.

THC descriptive statistics for 33 days of abstinence are presented in Table 2. THC was detected on admission $>$ LOQ (0.25 μ g/L) in all but one participant's plasma (96.4%; Figure 1), with a median (range) 4.2 μ g/L THC (not detected [ND]-30.9 μ g/L); 82.1% exceeded 2 μ g/L. THC concentrations significantly decreased ($P < 0.001$) 24 h after admission. On day 7, THC detection rate was 87.5%, with 29.2% of participants' plasma THC concentrations $\geq$ 2 μ g/L. One participant had plasma THC $\geq$ 2 μ g/L for 18 consecutive days. THC was detected in 3 of 5 specimens (0.3-1.3 μ g/L) on day 30, the last day before 4 participants were discharged.

11-OH-THC was never detected in plasma without concurrent THC. 11-OH-THC median (range) concentration was 1.7 μ g/L (ND-6.1) on admission, with 89.3% of specimens positive at the LOQ of 0.5 μ g/L (Table 2 and Figure 1) and 42.9% $\geq$ 2 μ g/L. At admission, 11-OH-THC and THC concentrations were significantly correlated ($r = 0.918$, $P < 0.001$). 11-OH-THC decreased ($P < 0.001$) faster than THC in the 24 h period after admission; however, THC and 11-OH-THC concentrations remained significantly correlated ($r = 0.664$, $P < 0.001$) over this period. 11-OH-THC was detected $\geq$ 1.0 μ g/L up to 3 days after abstinence initiation. No participants' 11-OH-THC concentrations exceeded 2 μ g/L 24 h after admission, and only 2 (7.0%) were greater than 1 μ g/L on days 2 and 3. 25.0% of specimens had $\geq$ 0.5 μ g/L 11-OH-THC for the first 7 days of abstinence. 11-OH-THC was quantifiable up to 15 days after admission in one subject.

THCCOOH was present in all specimens on admission, with a 56.7 µg/L median (range 3.1-196.1 µg/L; Table 2). THCCOOH and THC concentrations were significantly correlated at admission ($r=0.495$, $P=0.007$), as were THCCOOH and 11-OH-THC concentrations ($r=0.555$, $P=0.002$). Median THCCOOH concentrations significantly decreased ($P<0.001$) by day 1, with improved THCCOOH concentration correlations with THC ($r=0.649$, $P=0.001$) and 11-OH-THC ($r=0.618$, $P=0.002$) concentrations thereafter. All plasma specimens were positive for THCCOOH up to 10 days after admission, including specimens from one participant that never had detectable THC or 11-OH-THC. Four of 5 participants were THCCOOH positive (1.0-5.3 µg/L) after 30 days of abstinence; the one participant monitored on day 33 was also THCCOOH positive (1.2 µg/L).

Many participants had negative specimens interspersed with positive specimens for THC and 11-OH-THC; this was less common for THCCOOH. Median detection windows could not be determined for THC or THCCOOH, as THC and THCCOOH detection probability did not reach 50% by day 30 (Figure 2). Median 11-OH-THC detection was 24 h (95% confidence interval 0.0-2.6 days). All survival curve functions were statistically significantly different from each other when compared using Log Rank tests (THC vs. 11-OH-THC, $P<0.0001$; THC vs. THCCOOH, $P=0.035$; 11-OH-THC vs. THCCOOH, $P<0.0001$).

Median 11-OH-THC/THC ratios were 0.4 ($n=27$; range 0.0-1.2) on admission, decreasing significantly ($P<0.001$) to 0.2 ($n=21$; range 0.0-0.5) 24 h later, and decreasing further ($P=0.033$) to 0.0 ($n=25$; range 0.0-0.3) by day 2. On admission, median THCCOOH/THC was 10.6 ($n=27$; range 0.8-34.7), decreasing to 8.8 ($n=21$; $P=0.170$; range 3.9-55.2) on day 1, 5.5 ($n=21$; $P=0.001$; range 1.7-21.7) on day 7, 5.0 ($n=16$; $P=0.887$; range 2.6-9.8) on day 14, 4.4 ($n=10$; $P=0.878$; range 1.9-9.8) on day 21 and 4.1 ($n=6$; $P=0.027$; range 1.6-6.3) on day 28.

Years of prior cannabis use significantly correlated with THC concentrations on admission ($r=0.677$, $P<0.001$), day 7 ($r=0.602$, $P=0.002$) and day 14 ($r=0.571$, $P=0.009$), with only a trend on day 21 ($r=0.500$, $P=0.082$) (Figure 3a-e), most likely due to the low number of subjects still participating ($n=13$). 11-OH-THC was significantly correlated with years of use on admission ($r=0.551$, $P=0.002$) and day 7 ($r=0.482$, $P=0.017$), while THCCOOH was only significantly correlated on day 7 ($r=0.486$, $P=0.016$) and day 28 ($r=0.663$, $P=0.037$). No significant relationships were observed between BMI or cannabis smoking frequency and cannabinoid concentrations on admission, or on days 1, 7, 14, 21, or 28.

Tracking Error (TE) was correlated with THC ($r=0.456$, $P=0.050$), 11-OH-THC ($r=0.633$, $P=0.004$), and THCCOOH ($r=0.479$, $P=0.038$) concentrations at baseline, as shown in Table 3. Tracking error also was correlated with 11-OH-THC ($r=0.542$, $P=0.020$) on day 8. No other outcome measures from the DAT or CTT demonstrated any significant correlations with cannabinoid concentrations.

DISCUSSION

The results of this study argue against the utility of detectable THC or 11-OH-THC in the plasma of chronic frequent cannabis smokers as a reliable marker for recent cannabis use.

Our results show that plasma THC concentrations were still detectable (LOQ 0.25 µg/L) in 87.5% of participants on day 7 of abstinence and in 3 of 5 remaining participants on day 30. These results are consistent with previous reports by NIDA [41-42] and others [43], and recent data from NIDA quantifying THC in whole blood for up to 30 days 0.25 µg/L in chronic frequent cannabis smokers [23]. For the first time of which we are aware, we demonstrate THC in plasma up to 3 days at 5.0 µg/L, 18 consecutive days at 2.0 µg/L and up to 30 days 0.25 µg/L after abstinence initiation in this population. Plasma 11-OH-THC was previously reported 0.5 µg/L up to 3 days after abstinence initiation [41]. We now report 11-OH-THC 0.5 µg/L after 15 days of abstinence (in one participant, with a single negative specimen on day 11). 11-OH-THC concentrations never exceeded 2.0 µg/L beyond 24 h, which indicated that this may be a possible cutoff for recent (within 24 h) cannabis use. In the current study, four of five participants monitored through day 30 were THCCOOH positive (5.3 µg/L), with similar detection rates as whole blood THCCOOH 0.25 µg/L in the same cohort [23]. Pharmacokinetic differences between sexes could not be evaluated because all participants were males, as specifically recruited for PET imaging. However, previously we found female chronic frequent cannabis smokers to have longer urinary [44] and whole blood [42] THC detection times than males.

Metabolite-to-parent ratios vary based on THC administration route and time after smoking. In this study, the highest ratios were observed on admission. Median 11-OH-THC/THC ratios were low, as expected after smoked cannabis [10]. Additionally, we found ten-fold higher THCCOOH concentrations compared to those of THC on admission; declining to five-fold higher by day 9, with relative consistency through day 30. As previously suggested [41], THCCOOH concentrations during the first few days of abstinence reflect recent cannabis smoking and residual THC release from tissues. As abstinence continues, residual THC release and subsequent hepatic metabolism may be the primary THCCOOH contributor.

Years of lifetime cannabis use and cognitive impairment were positively correlated in a prior study [45]. In the current study, we observed moderate correlations between plasma THC concentrations on admission, day 7, and day 14 with lifetime cannabis use (years). 11-OH-THC concentrations also were moderately correlated with cannabis smoking duration on admission and day 7. In our previous seven day abstinence study in a separate cohort of chronic cannabis smokers, plasma THCCOOH concentrations on abstinence days 1-3 were significantly correlated with duration of cannabis use [41].

Persistent cognitive decrements are observed in chronic cannabis smokers abstinent for multiple weeks. We previously suggested a potential link between residual cognitive impairment in chronic frequent smokers and THC in blood [42]; others documented THC concentrations in brain when THC was no longer quantifiable in blood [16]. Neurocognitive deficits in attention and concentration [46-47], decision-making, concept formation and planning were reported after multiple weeks of cannabis abstinence [48]. Increased inhibition and impulsivity in chronic cannabis smokers compared to controls were reported by all but one study [49]. Earlier studies reported no significant effects in verbal fluency [50-51], while a later study [52] found significant effects in early onset cannabis smokers (began smoking prior to 17 years) compared to controls.

There are several limitations for the current study. Approximately half of participants withdrew from the study by day 21 for multiple reasons described above, including possible cannabis withdrawal discomfort. This reduced statistical power in analyses for later time points. Data analyses depended on self-report for cannabis smoking frequency (although baseline data supported frequent cannabis use), age of first use and lifetime cannabis use. Lastly, the population was predominantly African American (92.9%), but differences in cannabinoid pharmacokinetics are not known to be different between races. These limitations do not influence the primary study finding that THC and 11-OH-THC are not appropriate markers of recent use in plasma from chronic frequent cannabis smokers.

A defined cannabinoid concentration or *per se* limit for impairment is controversial and forensic toxicologists often disagree on an exact indicator of recent cannabis exposure. Recent meta-analyses suggest that cannabis use is significantly associated with increased crash risk [7, 53]. Culpability studies suggest that motor vehicle drivers with quantifiable THC in blood are 2.7 times (95% CI 1.0-7.0) more likely to be responsible for an accident than drivers without THC and up to 6.6 times (95% CI 1.5-28.0) more likely when whole blood THC was >5 µg/L (approximately 10 µg/L plasma) [54]. With a 10 µg/L plasma THC cutoff, only 4 of 28 participants met this criteria at admission, and all were <10 within 24 h after admission. Others suggested 7-10 µg/L serum impairment limits based on a meta-analysis of experimental data [55]. "Limits of impairment" also were determined in serum (between 2 and 5 µg/L THC) based on laboratory psychomotor evaluations [56]. However, it is not clear that these cutoffs identify impairment in chronic frequent cannabis smokers, who may develop partial tolerance to the acute impairing effects of cannabis. Ramaekers et al. [57] suggested that chronic cannabis smokers were less impaired than occasional smokers following cannabis intake on some psychomotor tasks. Those occasional smokers' tracking, divided attention, and motor impulse control tasks were impaired, while chronic smokers only displayed decreased motor impulse control. Previously published data from this study indicated that the chronic frequent cannabis smoking cohort had significantly impaired performance in CTT and DAT compared to controls [38]. Performance never recovered to the level of the control group, even after three weeks of abstinence. Although, we initially observed correlations between THC plasma concentrations and tracking error in the DAT, we did not observe statistically significant correlations at later time points. Psychomotor tracking impairment, though present, may not be correlated with specific residual plasma THC concentrations beyond 1-2 days after last cannabis exposure. However, as the number of participants residing on the unit decreased over the duration of the study, the resultant lower n may not have provided sufficient power for detecting a statistically significant correlation between impairment and specific THC concentrations. Psychomotor impairment remains an important public health question because 91% of frequent cannabis smokers surveyed admitted to driving under the influence of cannabis approximately 94 times per year [57].

CONCLUSIONS

We present here the first investigation of which we are aware of plasma cannabinoid concentrations in chronic cannabis smokers for up to 33 days of sustained, monitored abstinence. Clearly, detection of cannabinoids at these limits of quantification may not

represent recent cannabis intake; however, residual THC in plasma weeks after last smoking may be associated with impairment in this population. Such residual impairment may limit appropriate operation of a motor vehicle or mechanical equipment, resulting in injury and/or criminal litigation, although partial tolerance may develop to some impairing effects. Additional research is clearly needed to define driving impairment in chronic frequent cannabis smokers. These data should be considered in future accident and driving under the influence of drugs investigations and in clinical research and treatment in chronic frequent cannabis smokers.

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Figure 1.

Free ⁹-Tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC) and 11-nor-9-carboxy-THC (THCCOOH) detection rates (%) at limits of quantification throughout 30 days of monitored abstinence.

Figure 2.

Kaplan-Meier survival functions for free Δ^9 -tetrahydrocannabinol (THC; n=27), 11-hydroxy THC (11-OH-THC; n=25) and 11-nor-9-carboxy-THC (THCCOOH; n=27) detection times at limits of quantification^a during abstinence.

^aLimits of quantification of 0.25 $\mu\text{g/L}$ for free THC and THCCOOH and 0.5 $\mu\text{g/L}$ for free 11-OH-THC

Figure 3.

⁹-Tetrahydrocannabinol (THC) plasma concentration and years of cannabis exposure correlation at a) admission (n=28), b) day 7 (n=24), c) day 14 (n=20), d) day 21 (n=13) and e) day 28 (n=10). 95% confidence intervals are dashed lines surrounding the linear regression line.

Table 1

Demographic characteristics and self-reported cannabis use of 28 adult male chronic cannabis smokers.

Participant	Age (years)	Race ^a	BMI (kg/m ²) ^b	Cannabis smoking frequency (joints/day)	Age of 1st use	Lifetime cannabis use (years)
A	33	AA	22.4	6	6	13
B	25	AA	27.3	6	16	7
C	38	AA	25.8	18	21	15
D	19	AA	25.1	12	14	4
E	43	AA	25.8	4	13	28
F	29	AA	19.0	18	14	14
G	29	AA	21.6	12	14	10
H	27	AA	24.4	15	16	10
I	26	C	20.2	5	16	10
J	24	AA	19.7	18	18	5
K	22	AA	25.2	6	12	6
L	29	AA	23.8	9	14	15
M	36	C	16.4	1	22	10
N	30	AA	30.3	18	14	17
O	29	AA	29.3	9	11	17
P	25	AA	32.8	12	17	7
Q	24	AA	26.4	18	13	10
R	25	AA	27.7	6	15	10
S	21	AA	18.3	30	11	9
T	40	AA	26.1	6	18	22
U	25	AA	25.8	6	13	4
V	25	AA	19.9	12	17	5
W	38	AA	23.0	3	17	17
X	20	AA	21.8	9	13	6
Y	21	AA	21.5	6	14	5
Z	21	AA	21.5	15	13	8
2A	21	AA	22.0	9	12	6
2B	21	AA+C	24.4	8	14	7
mean	27.4		23.8	10.6	14.6	10.6
SD	6.6		3.8	6.3	3.2	5.8
median	25.0		24.1	9.0	14.0	10.0

^a AA: African American; C: Caucasian^b BMI- body mass index

Table 2

9-Tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH) positive plasma specimens (n) at specified cutoffs, median and concentration ranges (µg/L) over 33 days of cannabis abstinence in 28 chronic cannabis smokers with limits of quantification of 0.25 µg/L for free THC and THCCOOH and 0.5 µg/L for free 11-OH-THC.

Day	THC					11-OH-THC					THCCOOH				
	n	n	n	n	n	Median (µg/L)	Range (µg/L)	n	n	n	Median (µg/L)	Range (µg/L)	n	n	n
Adm	28	27	25	23	23	4.2	ND-30.9	25	12	12	1.7	ND-6.1	28	26	26
1	22	21	19	15	15	2.7	ND-8.7	12	0	0	0.6	ND-1.7	22	21	21
2	28	25	21	16	16	2.3	ND-5.7	10	0	0	ND	ND-1.5	28	25	25
3	28	27	22	14	14	2.0	ND-5.5	8	0	0	ND	ND-1.2	28	24	24
4	28	26	21	12	12	1.8	ND-4.4	8	0	0	ND	ND-0.9	28	22	22
5	26	24	18	11	11	1.6	ND-5.1	7	0	0	ND	ND-1.0	26	21	21
6	25	21	17	8	8	1.4	ND-3.9	7	0	0	ND	ND-0.9	25	20	20
7	24	21	15	7	7	1.2	ND-3.8	6	0	0	ND	ND-0.8	24	16	16
8	23	18	12	7	7	1.1	ND-4.0	6	0	0	ND	ND-0.7	23	12	12
9	21	16	8	5	5	0.9	ND-3.7	4	0	0	ND	ND-0.7	21	8	8
10	21	16	9	2	2	0.9	ND-3.6	4	0	0	ND	ND-0.8	21	7	7
11	21	16	9	3	3	0.7	ND-2.3	4	0	0	ND	ND-0.6	20	6	6
12	20	16	9	2	2	0.9	ND-2.5	2	0	0	ND	ND-0.6	19	6	6
13	20	15	7	2	2	0.7	ND-2.3	2	0	0	ND	ND-0.6	19	8	8
14	20	16	5	1	1	0.7	ND-2.6	2	0	0	ND	ND-0.6	19	7	7
15	18	15	6	1	1	0.7	ND-2.8	1	0	0	ND	ND-0.6	17	4	4
16	17	14	6	1	1	0.6	ND-2.4	0	0	0	ND	ND	17	4	4
17	16	13	6	1	1	0.7	ND-2.0						16	4	4
18	15	12	4	1	1	0.6	ND-2.2						15	4	4
19	13	10	2	0	0	0.4	ND-1.2						13	1	1
20	14	10	2	1	1	0.5	ND-2.3						14	2	2
21	13	10	1	0	0	0.4	ND-1.8						13	2	2
22	13	10	1	0	0	0.4	ND-1.4						12	2	2
23	12	8	1	0	0	0.4	ND-1.6						11	2	2
24	11	6	1	0	0	0.3	ND-1.8						10	2	2

Day	THC					11-OH-THC					THCCOOH				
	n	n	n	n	n	n	n	n	n	n	n	n	n	n	n
	0.25	0.50	1	2	Range (µg/L)	Median (µg/L)	Range (µg/L)	Median (µg/L)	Range (µg/L)	Median (µg/L)	0.25	0.50	1	2	Range (µg/L)
25	11	7	1	0	0.3	ND-1.4					11	1	1	1.6	0.5-5.5
26	10	5	0	0	ND	ND-0.8					10	1	1	1.1	0.4-5.7
27	9	6	0	0	0.3	ND-0.6					9	0	0	1.3	0.3-5.0
28	10	6	1	0	0.3	ND-1.2					10	0	0	1.2	0.6-4.8
29	7	4	0	0	0.3	ND-0.4					7	0	0	1.1	0.4-3.1
30	5	3	1	0	0.3	ND-1.3					4	1	1	1.2	ND-5.3
31	1	0	0	0	ND	ND					0	0	0	ND	ND
32	1	0	0	0	ND	ND					1	0	0	N/A	1.8
33	1	0	0	0	ND	ND					1	0	0	N/A	1.2

n= number of specimens; ND= not detected; N/A= not available; n=1

Table 3

Summary of mean Divided Attention Task (DAT) and Critical Tracking Task (CTT) performance data and correlations to 9-Tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH) concentrations

Day	n	Performance (mean $\pm$ SD)	THC	11-OH-THC	THCCOOH
DAT: Tracking Error					
Baseline	19	19.15 $\pm$ 4.43	0.456 *	0.633 *	0.479 *
8	18	17.53 $\pm$ 5.13	0.051	0.542 *	-0.173
14-16	19	16.91 $\pm$ 5.14	0.039	0.008	-0.05
21-23	11	17.14 $\pm$ 6.18	-0.063	-	-0.196
CTT: Mean Lambda-c					
Baseline	19	2.79 $\pm$ 0.76	-0.056	-0.103	-0.075
8	18	3.07 $\pm$ 0.65	0.114	-0.152	0.211
14-16	19	3.11 $\pm$ 0.61	0.204	0.065	0.376
21-23	11	3.04 $\pm$ 0.90	0.408	-	0.65

* Correlation is significant at the 0.05 level (2-tailed)