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Cannabis Withdrawal in Chronic, Frequent Cannabis Smokers during Sustained Abstinence within a Closed Residential Environment

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Abstract

Objectives—Chronic, frequent cannabis smokers may experience residual and offset effects, withdrawal, and craving when abstaining from the drug. We characterized the prevalence, duration, and intensity of these effects in chronic frequent cannabis smokers during abstinence on a closed research unit.

Methods—Non-treatment-seeking participants (N=29 on admission, 66% and 34% remaining after 2 and 4 weeks) provided subjective effects data. A battery of 5 instruments was computer-administered daily to measure psychological, sensory, and physical symptoms associated with cannabinoid intoxication and withdrawal. Plasma and oral fluid specimens were concurrently collected and analyzed for cannabinoids. Outcome variables were evaluated as change from admission (Day 0) with regression models.

Results—Most abstinence effects, including irritability and anxiety were greatest on Days 0–3 and decreased thereafter. Cannabis craving significantly decreased over time, whereas decreased appetite began to normalize on Day 4. Strange dreams and difficulty getting to sleep increased over time, suggesting intrinsic sleep problems in chronic cannabis smokers. Symptoms likely induced by residual drug effects were at maximum intensity on admission and positively correlated with plasma and oral fluid cannabinoid concentrations on admission but not afterward; these symptoms showed overall prevalence higher than cannabis withdrawal symptoms.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Conclusions—The combined influence of residual/offset drug effects, withdrawal and craving was observed in chronic cannabis smokers during monitored abstinence. Abstinence symptoms were generally more intense in the initial phase, implying importance of early intervention in cannabis quit attempts. Sleep disturbance persisting for an extended period suggests that hypnotic medications could be beneficial in treating cannabis dependence.

Introduction

Cannabis use disorders are a significant global public health problem.[1] In 2011, 4.2 million Americans aged 12 years or older met diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders, fourth edition [DSM-IV]) for cannabis dependence or abuse.[2]

Cannabis withdrawal is an important component of cannabis dependence. In the US, 34% of frequent cannabis smokers who never abused other substances reported experiencing ≥3 cannabis withdrawal symptoms.[3] Moreover, 65–70% of cannabis smokers reported relief of abstinence effects as a factor in their relapse to cannabis intake,[4–5] suggesting that withdrawal symptoms can serve as negative reinforcement for relapse and, thereby, hinder quit attempts. Physical and psychological distress from cannabis withdrawal (e.g., sleep disturbance, anxiety, appetite loss) were reported as associated with severity of cannabis dependence and relapse.[6] Thus, better characterizing cannabis withdrawal may improve treatment. Because the symptom profile, time course, and severity of withdrawal may differ depending on environment,[7] it is important to evaluate inpatient cannabis abstinence effects. The effects could be less severe than those in outpatient settings due to lack of environmental stimuli associated with cannabis smoking.[8]

Early descriptive inpatient studies evaluated up to 28 days of abstinence, but did not define the time course of withdrawal symptoms.[9–10] A more recent 4-day inpatient study found peak symptom intensity generally on the fourth day,[11] while a 10-day study found peak intensity at admission.[12] However, there has been limited attempt to distinguish cannabis withdrawal phenomena from residual drug effects and drug offset effects (i.e., unmasking of pre-existing characteristics suppressed by cannabis intake that may not return to baseline level, such as irritability or disturbed sleep) that may also be experienced by individuals abstaining from cannabis use.[13–14] An additional confound in inpatient studies is the effect of residing in an unfamiliar inpatient environment, e.g., anxiety and disturbed sleep.[15]

Biological drug testing can provide objective evidence of cannabis intake, particularly valuable in the field of cannabis use disorders treatment. Oral fluid (OF) or saliva is a promising alternative matrix for drug monitoring in clinical and forensic programs. OF testing offers non-invasive sample collection under direct observation. Our recent studies demonstrated that plasma and OF tests can identify recent cannabis exposure, particularly with identification of THC-glucuronide, or minor cannabinoids [e.g., cannabidiol (CBD) and cannabinol (CBN)].[16–18]

In the present study, we characterized the time course of cannabis withdrawal in non-treatment-seeking chronic cannabis smokers residing on a closed research unit. Data were collected for up to 30 days, with concurrent measurement of plasma and OF cannabinoid

concentrations. We hypothesized that significant positive or negative associations between cannabinoid concentrations and symptoms would allow distinction between cannabis withdrawal and residual drug or drug offset effects. This enhanced and extended evaluation of cannabis abstinence effects is especially timely given that the DSM-5 proposal for a cannabis withdrawal syndrome will increase recognition of this condition.

Materials and Methods

Participants

Male cannabis smokers, ages 18–65 years, were recruited to participate in a positron emission tomography (PET) imaging study evaluating cannabinoid CB_1 receptor density in brain; 2 PET scans were administered, one on Day 1 and one after approximately 4 weeks of abstinence.[19] Participants were required to be physically and psychologically healthy. Additional inclusion criteria were cannabis smoking for at least one year and ≥5 days per week for the last six months, and a positive urine result for cannabinoids on admission. Exclusion criteria were history of any clinically significant medical or psychiatric illness, ingestion of psychoactive medication within the preceding 28 days, history of head trauma with unconsciousness >10 min, recent radiation exposure, average of >6 alcoholic drinks per day four times per week in the prior month, current physical dependence on any substance other than cannabis, nicotine, or caffeine, and interest in or participation in drug abuse treatment within 60 days preceding study entry. The National Institute of Mental Health Institutional Review Board approved the study. Participants provided written informed consent, were compensated, and resided on the Johns Hopkins Behavioral Pharmacology Research Unit (BPRU) under continuous medical supervision to ensure cannabis abstinence. Participants were searched for drugs upon admission and were not allowed to leave the unit or receive visitors, but could use cellular phones. Alcohol and illicit drugs were prohibited. Tobacco smoking was allowed *ad libitum* in designated areas and was not directly monitored. BPRU is designed to accommodate prolonged residential stays, with television, internet access, video games, and an outdoor recreational area. There were no physical activity restrictions. Participants ate meals self-selected from the hospital cafeteria menu.

Assessment of Abstinence Effects

Cannabis abstinence symptoms were evaluated daily between 9 and 11am via a battery of 5 instruments: 1) Eleven 100-mm visual-analogue scales (VAS) anchored with “not at all” at the left end and “extremely” at the right end, assessed “good drug effect,” “high,” “stoned, “stimulated,” “sedated,” “anxious,” “depressed,” “irritable,” “restless,” “craving for marijuana,” and “angry/aggressive.” 2) Thirty-seven 5-point Likert scales (Likert) measured sensory and physical symptoms associated with cannabinoid intoxication and withdrawal,[20–21] including “difficulty concentrating,” “altered sense of time,” “slowed or slurred speech,” “body feels sluggish or heavy,” “feel hungry,” “feel thirsty,” “shakiness/ tremulousness,” “nausea,” “headache,” “palpitations,” “upset stomach,” “dizzy,” and “dry mouth or throat,” “shaky/tremulous,” “decreased appetite,” “diarrhea/loose stools,” “nauseous,” “sweating,” “hiccups,” “decreased sexual arousal,” “stuffy nose,” “strange or vivid dreams,” “hot flashes,” chills,” “increased appetite,” “fatigue/tiredness,” “yawning,” “increased sexual arousal,” “muscle aches or pains,” “heaviness in limbs,” “noises seem

louder than usual," "talkative," "stomach pain," "mellow," "clumsy," "muscle spasms," and "blurred vision." Responses were scored as 0 = none, 1 = slight, 2 = mild, 3 = moderate, or 4 = severe. 3) St. Mary's Hospital Sleep Questionnaire (SMHSQ) contains 14 items assessing participants' previous night's sleep duration and quality;[22] 4) Marijuana Craving Questionnaire (MCQ) consisted of 12 items measuring compulsivity, emotionality, expectancy, and purposefulness associated with cannabis craving.[23] Participants selected one option along each line between 1 = strongly disagree and 7 = strongly agree, regarding positively worded statements on cannabis craving; and 5) Symptom Checklist-90 revised (SCL-90R) consisted of 90 items assessing common physical and psychological symptoms. It generated 9 subscales measuring somatization, obsessive-compulsive behavior, feelings of inadequacy or inferiority, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism.[24] Several subscales evaluated cannabis withdrawal symptoms (e.g., hostility, depression, anxiety). Responses were 0 = not at all, 1 = a little bit, 2 = moderately, 3 = quite a bit, or 4 = extremely. Administration of SCL-90R utilized the SCL-90-R® Q Local™ Scoring and Reporting Software, version 2.5.7 (Pearson Inc., Ontario, Canada). Order of questionnaire administration was consistent throughout the study.

Biological Specimen Collection and Analysis

Following subjective measures, venous blood was collected in heparinized tubes and placed on ice until centrifugation within 2 h to separate plasma. OF was collected with the Quantisal™ collection device (Immunalysis Inc., Pomona, CA). Plasma and OF specimens were stored at −20°C until analysis. Δ^9-tetrahydrocannabinol (THC), 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH) in plasma and THC, CBD, CBN, and THCCOOH in OF were quantified according to previously published, validated two-dimensional gas chromatography mass spectrometry methods.[25–26] Limits of quantification (LOQ) in plasma were 0.125 ng/mL (THC and THCCOOH) and 0.25 ng/mL (11-OH-THC); OF LOQs were 0.5 ng/mL (THC and CBD), 1 ng/mL (CBN), and 7.5 pg/mL (THCCOOH).

Statistical Analysis

Statistics were determined with SAS version 9.2 (SAS Institute, Cary, NC). Changes in ratings over time were evaluated with repeated measures mixed linear regression; outcome variables were converted to "change from admission," determined as (score on each study day – score on admission) to normalize data distributions. Admission was Day 0. Length of stay (LOS) was included in all regression models as a covariate to evaluate changes over time in abstinence effects after adjusting for duration of stay. Rating changes over time were not evaluated for Likert scale and SCL-90R items with overall occurrence frequency <5%. Post-hoc comparisons between Days 1 and 2–30 utilized Dunnett-Hsu adjustment to control type I error. Associations between symptom ratings and plasma and OF cannabinoid concentrations employed the non-parametric Spearman's correlation coefficient (ρ) due to skewed data distributions. MCQ scores were arithmetic means of all 12 MCQ ratings.

A cannabis withdrawal syndrome was considered present if a participant had at least 3 of the following 7 symptoms: 1) irritability, anger, or aggression, 2) nervousness or anxiety, 3) sleep difficulty (e.g., insomnia, strange/vivid dreams), 4) decreased appetite or weight loss, 5) restlessness, 6) depression, and 7) at least one of the following physical symptoms:

stomach pain, shakiness/tremors, sweating, chills, or headache. This mirrors Criterion B of the proposed DSM-5 syndrome (www.dsm5.org).[27] Two levels of symptom intensity were evaluated: any symptoms reported (i.e., any rating ≥1) and symptoms of at least moderate intensity (VAS ≥30 mm, based on VAS ≥30 equivalent to moderate pain intensity).[28] The latter evaluation was chosen to reflect Criterion C of the proposed DSM-5 syndrome, i.e., that withdrawal symptoms cause clinically significant distress or impairment.

Two types of analyses assessed the internal validity of participants' responses (Supplemental Material 1). First, answer consistency to each member of 9 pairs of items was evaluated by 2x2 contingency tables after conversion to dichotomous variables (present, absent). Second, associations between each member of 14 pairs of items scored on ordinal or continuous scales were evaluated with the Spearman's ρ. This internal validity analysis utilized data from Day 2 (after 48 h on the research unit) to minimize the influence of anxiety resulting from admission to an unfamiliar residential environment and yet include all participants. All results with 2-tailed P <0.05 were considered significant.

Results

Participants

Thirty male chronic cannabis smokers resided on the closed research unit for 2–33 days. Data from Days 31–33 (1 participant) were not included in the analysis. One participant's data were excluded from all analyses because of high ratings on mutually exclusive pairs of variables (data not shown), resulting in a final sample size of 29. Participants remaining on the closed research unit after 1 week were 79%, 2 weeks 66%, 3 weeks 45%, and 4 weeks 34%; median and mean LOS were 18 days. Reasons for early withdrawal included family emergencies, homesickness, job offers, and discharge for behavioral issues and protocol noncompliance. No participant withdrew because of self-reported symptomatic discomfort. One to four participants resided on the BPRU at any one time. Participants' demographic characteristics and self-reported drug use histories are reported in Table 1. Participants had normal psychological ratings (SCL-90R) at screening (Table 1) and throughout the study (data not shown).

Psychological or Sensory Symptoms

After controlling for LOS, craving for cannabis decreased significantly over time as measured by means of the MCQ total scores (F=5.38, P=0.021), while VAS craving showed no significant change (Figure 1; Table 2). Anxiety and irritability (VAS) decreased significantly over time (Figure 1, Table 2), with no significant difference between Day 1 and subsequent days (all P's >0.05). Anger/aggression, depression, and restlessness (all VAS; Table 2) showed no time-dependent changes.

Subjective effects reflecting possible residual effects of cannabis (rather than withdrawal) were always greatest on admission. "High," "stimulated,""mellow," "dry mouth/throat," "feel hungry," and "feel thirsty" ratings all decreased significantly over time (Figures 1–2; Table 2). Other ratings did not change significantly (Table 2). "Feel hungry," "mellow," "high," and "stimulated" ratings became significantly different from Day 1 on Days 3–5,

whereas “feel thirsty” and “dry mouth/throat” were not significantly different until Day 8 (Table 2). Severity of symptoms was generally mild to moderate.

Physical Symptoms

A few sleep variables increased significantly over time (e.g., strange/vivid dreams, difficulty getting to sleep, and depth of sleep), while frequency of waking decreased significantly (Table 2). Depth of sleep ratings were significantly higher starting on Day 4 compared to Day 1 (Table 2). There were no significant time-dependent changes in other sleep variables, including sleep latency and nighttime sleep duration. Decreased appetite declined significantly over time, starting on Day 4 (Figure 2, Table 2). The prevalence of other physical symptoms was too low to evaluate changes over time (Table 2). As with psychological/sensory symptoms, severity of physical symptoms was typically mild to moderate.

Cannabis Withdrawal Syndrome

Applying a cutoff to include any reported symptoms [≥1 for VAS items, ≥1 (slight) for Likert items, and ≥2 (some) for the SMHSQ “difficulty getting off to sleep” item], 11 (38%) participants met DSM-5 surrogate diagnostic criteria for cannabis withdrawal syndrome on admission, increasing to 16 (55%), 11 (38%), and 15 (56%) on Days 1–3, respectively. During Days 4–30, 20–50% participants met these criteria. Applying a stricter cutoff (symptoms with at least moderate intensity [≥30 for VAS items and ≥3 (moderate or a lot) for Likert or SMHSQ items]), 3 (10%) participants met the diagnostic criteria on admission, and 1 or 2 participants intermittently met the criteria on Days 1–2, 12–13, and 15–16.

Association of Cannabis Abstinence Effects with Plasma and OF Cannabinoid Concentrations

On admission, expected residual drug effects were positively correlated with plasma THC and 11-OH-THC and OF THC: plasma THC vs. “high” (ρ=0.42, P=0.023); plasma 11-OH-THC vs. “high” (ρ=0.40, P=0.033), “hungry” (ρ=0.42, P=0.024), “dry mouth” (ρ=0.38, P=0.042), and “thirsty” (ρ=0.41, P=0.026); and OF THC vs. “high” (ρ=0.42, P=0.025). Expected withdrawal effects, “difficulty getting off to sleeping” and “anxious,” were negatively correlated with plasma THC (ρ=−0.40, P=0.032) and OF CBN (ρ=−0.40, P=0.033), respectively. After admission through Day 30, there were no clinically significant correlations between plasma and OF cannabinoid concentrations and cannabis abstinence effects.

Median plasma THC gradually decreased from 4.1 ng/mL on admission to 2.7, 1.2, and 0.7 ng/mL on Days 1, 7, and 14, respectively. Sixty-nine percent of plasma specimens after Day 14 were THC-positive (all concentrations ≤2.8 ng/mL). Plasma 11-OH-THC, OF THC, and OF CBN declined more rapidly, with medians <LOQ on Days 2, 1, and admission, respectively. One or 2 participants were occasionally positive for plasma 11-OH-THC on Days 12–19 and for OF THC on Days 4–28, with concentrations ≤3 ng/mL. OF CBN was not detected after admission.

No clinically significant correlations were found between cannabis abstinence effects on admission and participants' cannabis use history (age at first use, amount smoked per day, and lifetime years of use) (data not shown).

Discussion

Symptoms frequently reported on admission (dry mouth and feeling high, mellow, stimulated, hungry, and thirsty) probably reflect residual drug intoxication because: 1) they are typical of cannabis intoxication,[29] rather than withdrawal, 2) were positively correlated with plasma and OF cannabinoid concentrations on admission but not on later days, and 3) significantly decreased over time (Table 2). The findings suggest that plasma and OF cannabinoid tests can be alternative monitoring tools to evaluate residual drug effects, in place of the urine testing commonly employed in cannabis abstinence studies.[13–14] However, it should be noted that the relationship between subjective effects and OF THC/CBN concentrations is temporal rather than causal, because the primary source of those parent cannabinoids in OF is oral cavity contamination from drug-laden cannabis smoke.[17]

Symptoms related to residual cannabis effects were more prevalent in our Likert scales, while symptoms related to cannabis withdrawal occurred more frequently in our VAS (Table 2). The results reflect that cannabis withdrawal symptoms are primarily psychological.[7] Our Likert scales mainly measured sensory and physical symptoms whereas our VAS assessed psychological effects.

While 20–56% of participants met Criterion B of the proposed DSM-5 diagnostic criteria for cannabis withdrawal syndrome, ≤10% met the criteria with at least moderate intensity. Anxiety was greatest on admission and decreased thereafter, (Figure 1), a time course similar to that observed in a prior 10-day inpatient study.[12] Irritability also decreased over time, with evidence of longer duration; mean ratings were highest on Day 2, although post-hoc analysis showed no significant difference among days, likely due to adjusted alpha error thresholds with multiple comparisons (Figure 1). Conversely, in outpatient studies, anxiety and irritability increased from baseline for 12–27 days, peaking within 9 days.[13–14] Decreased appetite similarly had a shorter duration compared to an outpatient setting (3 vs. 12 days).[14] During inpatient abstinence after 4 days of smoked cannabis administration, anxiety and irritability peaked on the fourth (last) day of abstinence; decreased food intake also persisted for 4 days.[11]

Cannabis craving significantly decreased from admission, with large inter-subject variability (Figure 1). Prior inpatient[12] and outpatient[30] studies also found substantial individual variability in craving intensity. On the other hand, some underlying participant characteristic such as motivation for study participation or susceptibility to distress in a closed environment could have affected both craving and length of stay. As with other studies,[8, 12, 14, 30] craving for cannabis showed the highest intensity and prevalence among all psychological withdrawal symptoms (Table 2).

These time course and intensity differences suggest that cannabis withdrawal phenomena could vary depending on the environment in which abstinence occurs. Indeed, the overall withdrawal profile in this study most closely resembled that of a prior inpatient study with abstinence conditions similar to ours (closed setting with no experimental cannabis smoking period prior to abstinence initiation).[12] Undergoing abstinence in a closed research unit devoid of cannabis-associated stimuli could have contributed to the shorter duration and lower prevalence of withdrawal effects compared to outpatient studies.[13–14] Higher cessation rates from opiates[31] and alcohol use[32] also were observed in inpatient compared to outpatient conditions in which withdrawal symptoms were one of the main reasons for relapse. When inpatient abstinence was followed by cannabis smoking on a research unit,[9, 11] a higher intensity of withdrawal symptoms could have been observed due to associations between the research environment and cannabis use. In 2 inpatient studies,[9, 33] cannabis withdrawal symptoms were observed after cannabis smoking for 21 and 28 days, but not during the pre-smoking abstinence period.

Strange/vivid dreams and difficulty getting off to sleep increased over time. This is similar to a 45-day outpatient study, in which strange dreams peaked on Day 9 and did not return to baseline, while sleep difficulty lasted for 12 days.[14] High prevalence of sleep dysfunction also occurred among dependent cannabis smokers during 2-weeks of abstinence.[34] Alternatively, results could reflect drug offset effects in which participants' pre-existing sleep problems are unmasked by cessation of cannabis use. While difficulty getting off to sleep showed significant increase over time, sleep latency did not. This could be due to differences between actual time to fall asleep and participants' perception of sleep latency.

This study has several limitations. First, it lacks precise information on the interval since participants' last cannabis smoking, which limits the ability to attribute observed symptoms to withdrawal effects vs. residual drug effects and possibly underestimates effect duration. However, 26 (90%) participants last smoked cannabis within 48 h of admission, based on self-report at admission and/or OF cannabinoid concentrations applied to previously published cutoff criteria.[17] Furthermore, on admission, all participants were positive for THCCOOH (data not shown) and all but 1 participant (who reported smoking only 1 joint daily) was THC-positive in plasma. All participants also reported 5–7 day/week smoking at the time of screening (Table 1), making it likely that all had smoked within 48 h of admission. Second, residing in a closed, unfamiliar environment and living under a standardized schedule could have influenced the effects reported by our participants. Third, sample size decreased over time. While LOS was controlled for in statistical analyses, the findings should be interpreted cautiously due to potentially confounding factors (e.g., possible early dropout related to withdrawal severity). Fourth, tobacco smoking could have influenced abstinence symptom severity. Frequency of tobacco use over time was not monitored; however, average daily amount of money spent on cigarettes during the study was comparable to the amount spent prior to study admission (Table 1). Finally, external validity is limited because the study population included only healthy adult, predominantly African-American males without any significant psychiatric, medical, or substance abuse co-morbidity. Because the history and severity of cannabis withdrawal correlates positively with psychiatric symptom severity,[3, 30] our psychologically healthy participants may provide an underestimate of the overall prevalence and severity of cannabis withdrawal.

In conclusion, the present study comprehensively investigated possible cannabis withdrawal symptoms, residual cannabis effects, and drug offset effects for 2–30 days of monitored abstinence in a closed residential setting. Our findings provide important data for developing and managing inpatient dependence treatment for chronic, frequent cannabis smokers. Symptoms were generally more intense around admission, suggesting the need for early intervention to avoid drop out. Most effects with significant time-dependent changes had ratings lower than at admission within 4 days. However, sleep disturbance may persist for an extended period, suggesting that medications to improve sleep could be a valuable adjunct in treating cannabis dependence.[35] We also reported that plasma and OF cannabinoid concentrations were significantly correlated with some residual cannabis effects and withdrawal symptoms on admission but not on later days. Plasma and OF cannabinoid testing may serve as a valuable tool to monitor residual drug effects and/or to identify recent smoking exposure.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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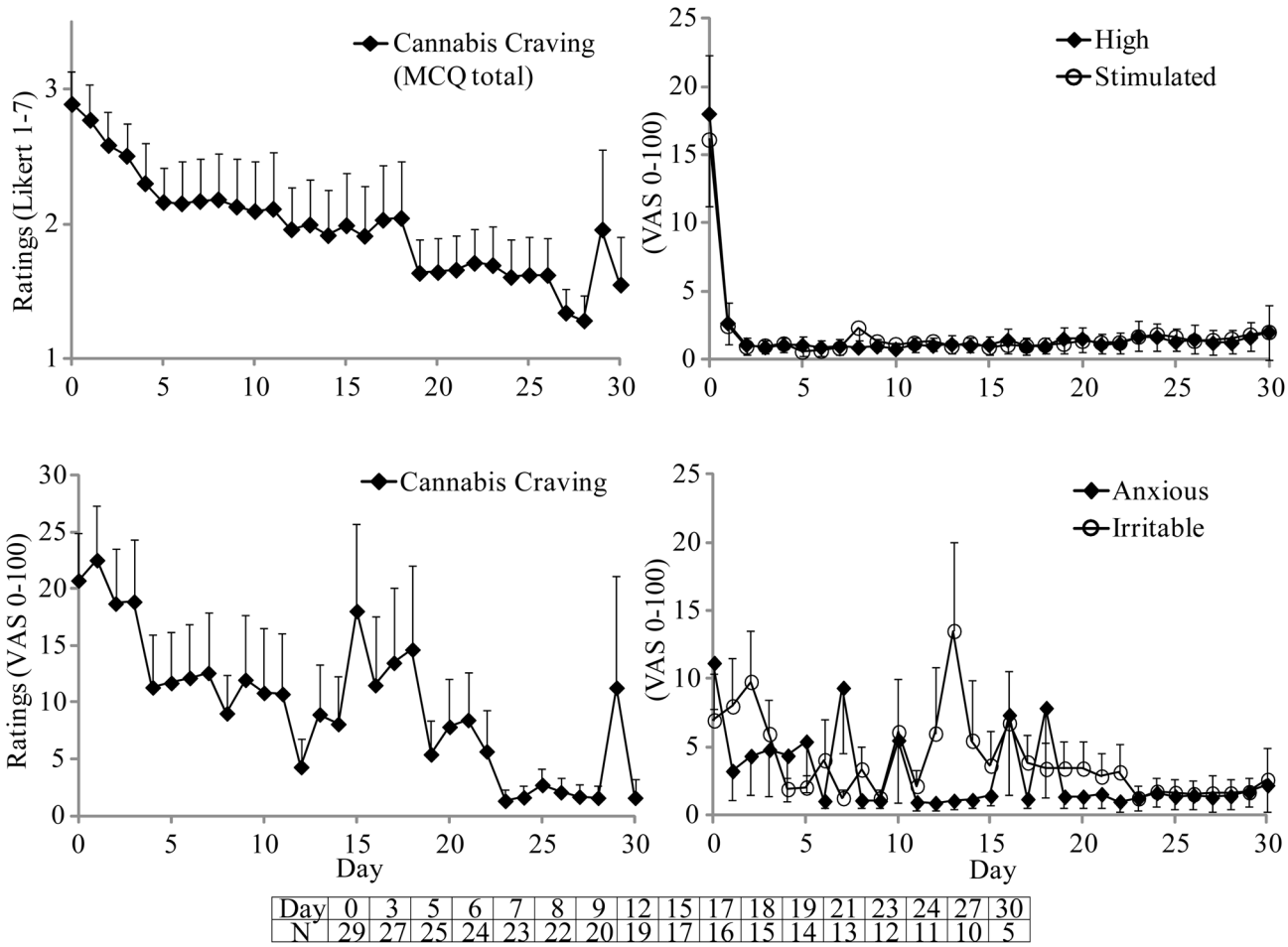

Day	0	3	5	6	7	8	9	12	15	17	18	19	21	23	24	27	30
N	29	27	25	24	23	22	20	19	17	16	15	14	13	12	11	10	5

Figure 1.

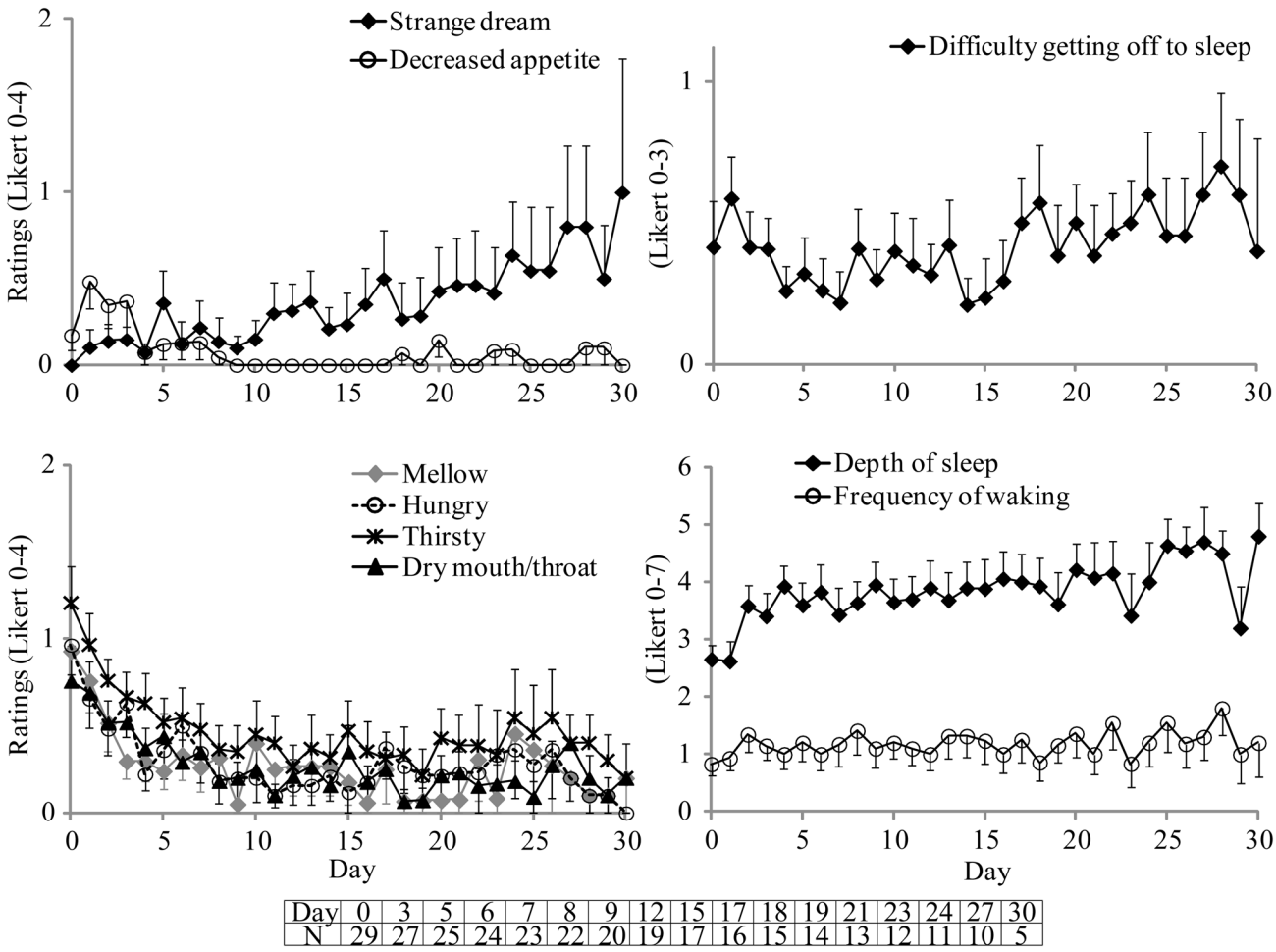

Figure 2.

Table 1

Demographic characteristics, self-reported drug use history, and admission Δ^9-tetrahydrocannabinol (THC) concentrations in plasma and oral fluid of 29 chronic cannabis smokers

Age, years	28.5 ± 7.8 (19–52)
Race, % African American	86.2
Age at 1st cannabis smoking, years	14.6 ± 3.1 (6–22)
Amount of cannabis smoking, joints/day	9.9 ± 6.3 (1–30)
Days cannabis-smoked in past 14 days	13.3 ± 1.0 (10–14)
Duration of cannabis smoking, years	11.6 ± 7.6 (4–38)
Current cannabis dependence (DSM-IV)	79.3
Oral fluid THC on admission, ng/mL	26.7 ± 41.4 (0–205)
% positive	86.2
Plasma THC on admission, ng/mL	5.4 ± 5.7 (0–31)
% positive	96.6
Tobacco smokers, %	82.8
Amount spent on tobacco prior to study[a], US $/day	2.1–2.6 ± 2.0–2.5 (0–11.3)
Amount spent on tobacco per study day[b], US $	2.3 ± 3.1 (0–14.5)
Days of alcohol use to intoxication in past 30 days	2.6 ± 3.7 (0–15)
Substance of choice, % cannabis	93.1
Amount spent on drugs in past 30 days, US $	387.4 ± 424.6 (40–2000)
Treatment for drug abuse, % participants ever treated	6.9

Symptom Checklist-90 Revised	Raw score	T-score[b]
Somatization	0.18 ± 0.20	46 ± 9
Obsessive-compulsive	0.38 ± 0.35	52 ± 8
Interpersonal sensitivity	0.20 ± 0.24	49 ± 8
Depression	0.36 ± 0.40	52 ± 11
Anxiety	0.13 ± 0.20	47 ± 8
Hostility	0.24 ± 0.31	49 ± 9
Phobic anxiety	0.04 ± 0.11	49 ± 6
Paranoid ideation	0.48 ± 0.48	53 ± 10
Psychoticism	0.17 ± 0.23	53 ± 9

Values are mean ± standard deviation (range) unless otherwise specified

Data collected during the participant screening process 13–171 days (mean 50 days) prior to study admission unless otherwise specified

[a] Calculated value based on self-reported mean number of tobacco cigarettes smoked daily [7.0 ± 6.8 (0–30)], cost of 1 cigarette pack ($6–7.5), and 20 cigarettes per pack

[b] total amount spent on tobacco during the study divided by number of days spent on the research unit

[c] based on adult, non-patient normative values

Table 2

Frequency and severity of cannabis abstinence symptoms reported by 29 adult chronic cannabis smokers during 2–30 days of monitored abstinence[a].

	Symptoms	Prevalence (%) Total[b] (Moderate-Severe[c])	Change over time[d] F (P)	Direction[e]	Days different from Day 1[f]	Proposed DSM-5[g]
Likert	Feel thirsty	35.9 (2.9)	14.62 (0.0001)	↓	8, 12, 17–19, 23	
	Dry mouth/throat	25.6 (0.5)	21.54 (<0.0001)	↓	8, 11, 18, 19, 25, 29	
	Feel hungry	23.8 (3.1)	18.96 (<0.0001)	↓	4, 8, 11–16, 19, 21, 22	
	Mellow	20.3 (3.1)	23.98 (<0.0001)	↓	3–9, 11–23, 25–29	
	Increased appetite	18.0 (2.0)	0.13 (0.72)			
	Increased sexual arousal	15.2 (5.1)	0.03 (0.87)			
	Strange/vivid dreams	14.3 (4.9)	11.59 (0.0007)	↑	None	√
	Yawning	13.1 (0.4)	1.20 (0.27)			
	Fatigue/tiredness	12.3 (0.5)	0.10 (0.76)			
	Talkative	11.3 (0.0)	1.07 (0.30)			
	Feel sluggish/heavy	10.0 (0.5)	2.01 (0.16)			
	Decreased appetite	7.4 (0.5)	12.35 (0.0005)	↓	4–19, 21, 22, 25–27	√
	Muscle aches/pains	6.7 (0.2)	0.22 (0.64)			
	Sweating	4.0 (0.2)				√
	Headache	3.4 (0.4)				√
	Chills	2.5 (0.0)				√
	Stomach pain	1.6 (0.0)				√
	Shakiness/tremulousness	0.5 (0.0)				√
VAS	Craving for marijuana	48.8 (6.2)	1.13 (0.29)			
	Irritable	36.8 (2.2)	4.77 (0.03)	↓	None	√
	Restless	26.8 (2.4)	1.91 (0.17)			√
	Angry/aggressive	36.3 (1.3)	1.18 (0.28)			√
	Depressed	31.0 (0.2)	0.20 (0.66)			√
	Anxious	28.7 (2.2)	8.35 (0.004)	↓	None	√
	High	27.0 (0.7)	5.89 (0.016)	↓	3, 6–15, 17, 18	
	Stimulated	27.0 (0.9)	5.48 (0.020)	↓	5–7, 13, 15–19	
	Good drug effect	25.6 (1.1)	1.92 (0.17)			

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	Symptoms	Prevalence (%) Total[b] (Moderate-Severe[c])	Change over time[d] F (P)	Direction[e]	Days different from Day 1[f]	Proposed DSM-5[g]
	Sedated	25.4 (0.2)	2.93 (0.087)			
	Stoned	24.7 (0.4)	0.36 (0.55)			
SMHSQ	Depth of sleep		15.85 (<0.0001)	↑	4, 6, 8–12, 14–18, 20–22, 25–28	
	Frequency of waking		6.94 (0.0087)	↓	None	
	Sleep quality		0.79 (0.37)			
	Morning drowsiness		0.44 (0.51)			
	Sleep satisfaction		0.05 (0.82)			
	Early waking		3.14 (0.077)			
	Difficulty getting off to sleep		7.29 (0.0072)	↑	None	
	Hours of sleep		1.59 (0.21)			
	Sleep latency		0.51 (0.47)			

Symptoms assessed on 5-point Likert scales: 0 = none, 1 = slight, 2 = mild, 3 = moderate, 4 = severe, on 100-mm visual analogue scales (VAS) anchored with “not at all” (0) at the left end and “extremely” (100) at the right end, and scales described in the St. Mary’s Hospital Sleep questionnaire (SMHSQ)[23]; only symptoms that had at least 5% prevalence and/or included in the DSM-5 proposed criteria for cannabis withdrawal[28] are shown

[a] Number of participants decreased over time; see Figure 1 data table for the sample size on each day

[b] number of responses with severity ratings ≥1 (Likert or VAS)

[c] number of responses with severity ratings ≥3 (Likert) or ≥50 (VAS)

[d] evaluated with repeated measures mixed linear regression as difference from admission scores after adjusting for duration of stay

[e] ↓ and ↑ denote significant decrease and increase over time, respectively

[f] evaluated with post hoc analysis after the Dunnett-Hsu adjustment

[g] √ denotes symptoms included in the proposed DSM-5 diagnostic criteria for cannabis withdrawal syndrome (www.dsm5.org)