Around-the-Clock Oral THC Effects on Sleep in Male Chronic Daily Cannabis Smokers

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Abstract

Background and Objectives— 9-tetrahydrocannabinol (THC) promotes sleep in animals; clinical use of THC is associated with somnolence. Human laboratory studies of oral THC have not shown consistent effects on sleep. We prospectively evaluated self-reported sleep parameters during controlled oral THC administration to research volunteers.

Methods—Thirteen male chronic daily cannabis smokers (mean ± SD age 24.6± 3.7 years, self-reported smoking frequency of 5.5 ± 5.9 (range 1–24) joint-equivalents daily at study entry) were administered oral THC doses (20 mg) around-the-clock for 7 days (40–120 mg daily) starting the afternoon after admission. The St. Mary's Hospital Sleep Questionnaire was completed every morning. Plasma THC and 11-OH-THC (active metabolite) concentrations were measured in venous blood samples collected every evening. Changes in sleep characteristics over time and associations between sleep characteristics and plasma cannabinoid concentrations were evaluated with repeated measures mixed linear regression.

Results—Higher evening THC and 11-OH-THC concentrations were significantly associated with shorter sleep latency, less difficulty falling asleep, and more daytime sleep the following day. In contrast, the duration of calculated and self-reported nighttime sleep decreased slightly (3.54 and 5.34 minutes per night, respectively) but significantly during the study.

Conclusions—These findings suggest that tolerance to the somnolent effects of THC may have occurred, but results should be considered preliminary due to design limitations.

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Scientific Significance—Somnolence from oral THC may dissipate with chronic, high-dose use. This has implications for patients who may take chronic oral THC for medicinal purposes, including cannabis dependence treatment.

INTRODUCTION

Cannabis, the most widely used illegal drug,[1] generally promotes sleep by activating cannabinoid CB1 receptors.[2,3] This also is true of its primary psychoactive constituent, 9-tetrahydrocannabinol (THC), whose oral formulation is approved for medical use in many countries. The approved product labeling for synthetic THC (dronabinol, Marinol® Untimed Pharmaceuticals, Marietta, GA) includes somnolence as a common side effect, reported in up to 10% of patients in clinical trials. However, human laboratory studies involving controlled administration of oral THC have not shown consistent effects on nighttime sleep latency or duration with single 1.5–30 mg doses,[4,5] 20–40 mg daily for up to 14 days,[4,6,7] or 210 mg daily for 16 days.[8] Interpretation is limited by small sample sizes (2–10 subjects per study) and heterogeneity in degree of cannabis use at the time of study.[3] We are not aware of any prior study that evaluated the relationship between sleep characteristics and plasma cannabinoid concentrations.

As part of a larger study on human cannabis withdrawal[9] (registered as NCT01041170 at www.clinicaltrials.gov), we had the opportunity to evaluate effects on nighttime sleep of around-the-clock oral THC (increasing from 40 to 120 mg daily) for 7 days in 13 male chronic daily cannabis smokers. Furthermore, we examined the correlation of sleep effects with evening plasma cannabinoid concentrations.

METHODS

Participants

The study was approved by the institutional review boards of the National Institute on Drug Abuse (NIDA) Intramural Research Program, the University of Maryland School of Medicine, and the Maryland Department of Health and Mental Hygiene. All participants provided written informed consent when not acutely intoxicated or in withdrawal. Inclusion criteria were 18–45 years old, smoked cannabis for the prior 1 year and averaging daily use for at least 3 months prior to admission, cannabis use within 24 hours of admission, urine specimen positive for cannabinoids in the 30 days prior to study entry, normal cardiac function, and IQ 85 (based on the Wechsler Abbreviated Scale of Intelligence). Exclusion criteria consisted of past or present clinically significant medical disease that might interfere with safe study participation; history of psychosis or any current DSM-IV axis I disorder (other than cannabis, caffeine, or nicotine dependence, or simple phobia); current physical dependence on substances other than cannabis, nicotine, or caffeine; history of clinically significant adverse events associated with cannabis intoxication or withdrawal, for example, psychosis;6 alcohol drinks/day4 times/week in the month prior to study entry; sesame oil allergy; or current interest or participation in drug abuse treatment.

Participants were admitted to a secure research unit the evening before Day 1, 17.5–21 hours before their first oral THC dose. The unit had 24-hour staffing, ensuring that subjects had no

access to drugs except those provided in the study. Fourteen participants enrolled in the study; 13 completed.

Oral THC Administration

An escalating dose design was utilized. Oral synthetic THC (dronabinol, Marinol®) was administered in 20 mg capsules with increasing frequency (every 4–8 hours) for total daily doses as follows: 40 mg on Day 1; 100 mg on Days 2–4; and 120 mg on Days 5 and 6. All dosing occurred between 06:00 and 24:00, except for a 02:00 dose on Day 3. The first dose was administered on Day 1 at 15:00, 17.5–21 hours after admission to the research unit. This regimen standardized cannabis tolerance across participants while minimizing adverse events previously reported with 30 mg THC doses.[10]

Assessments

Sleep—Participants' sleep characteristics prior to admission to the research unit were assessed with the Johns Hopkins Sleep Center Sleep History Questionnaire (SHQ) (92 six- or seven-point Liker scale items)[11] and the Boringness–Eveningness Questionnaire (MEQ) (6 clock time items and 13 four-point Liker scale items)[12] completed within one week of admission. This data provided baseline sleep characteristics prior to THC dosing.

After admission, subjects completed every morning (08:00–10:15) the St. Mary's Hospital Sleep Questionnaire,[13] a 14-item instrument assessing duration and quality of the previous night's sleep. This questionnaire has previously been employed in outpatient[14] studies of cannabis smokers.

In addition, the subjective feeling of "sedated" was assessed with a 100 mm Visual Analogue Scale (VAS) every night at 20:00 (as part of a larger battery of 11 VAS evaluating symptoms of cannabis intoxication and withdrawal).[9] The VAS was anchored at the left with "not at all" and at the right with "most ever." The VAS score was the number of mm the participant marked to the right of the left anchor point.

Pharmacokinetics—Peripheral blood was collected periodically through an indwelling venous catheter for quantification of THC and its pharmacologically active metabolite 11-hydroxy-THC (11-OH-THC). Specimens were collected in heparinised tubes, stored on ice no more than 2 hours prior to centrifugation, and separated plasma stored refrigerated at 4°C until analysis by two-dimensional gas chromatography mass spectrometry with cryofocusing (2D-GCMS),[15] with a limit of quantification of 0.25 ng/ml for THC and 0.5 ng/ml for 11-OH-THC. Specimens were collected the evening of admission and thrice daily (08:00 or 10:00, 20:00 or 20:30, and 22:00 or 22:30) on Days 1–8. Plasma cannabinoid concentrations in six of these participants were previously reported.[16]

Statistical Methods

Comparisons between variables employed *t* tests. Associations between pairs of variables were evaluated with Pearson correlation coefficients. Changes in sleep characteristics over time and the associations between sleep and participant characteristics were evaluated with repeated measures mixed linear regression, which allowed inclusion of data from the three

non-completers. Participant baseline characteristics of age, years of regular cannabis use, and joints smoked per day were used as static covariates; study day, feeling sedated the night before, and plasma cannabinoid concentrations as time-varying covariates. Separate regression models were fit for each sleep variable, using an unstructured covariance structure and random intercept. Regression coefficients are reported as mean ± SE. A *p*-value <0.05 was considered statistically significant. All analyses were conducted with SAS version 9.2 (SAS Institute, Cary, NC).

RESULTS

Participants

Fourteen participants enrolled in the larger study[9]: one was discharged prior to receiving any medication because the study was terminated, one withdrew after 1 day of oral THC dosing for personal reasons, two were discharged on the fourth day of dosing (one due to premature ventricular contractions and one due to psychological reactions to THC), and 10 completed 8 days of dosing. All 13 participants (13 male, 10 African American, 2 Caucasian, 1 mixed race, mean ± SD age 24.6 ± 3.7 years) who received THC are included in this analysis. These participants first smoked cannabis at 14.0 ± 2.4 years of age and began regular (at least weekly) smoking at age 15.6 ± 3.7 years. All but one participant reported at least 1,000 lifetime cannabis uses; eight reported at least 5,000 uses. All participants smoked cannabis joints and/or blunts (cannabis wrapped in tobacco leaves); five also had smoked hashish in the past. Seven participants reported lifetime experience with cannabis tolerance (needing to smoke more to get the same effect); five of these seven also reported experiencing cannabis withdrawal. At the time of study entry, participants averaged 5.5 ± 5.9 (median = 3, range 1–24) joints daily. All participants self-reported cannabis smoking in the 24 hours prior to admission; all had a positive cannabinoid urine test upon admission.

All 13 participants were lifetime cigarette smokers; 9 were daily smokers at the time of study entry, averaging 17.9 ± 18.8 (median = 10, range 2–50) cigarettes daily. The remaining 4 participants abstained from tobacco smoking for 4 and 6 months, and 8 and 10 years prior to admission. All participants were lifetime alcohol drinkers, although two abstained for 1 month prior to study entry. The 11 current drinkers averaged 12.1 ± 10.9 (median = 12, range 0.25–32) standard drinks per week over the 3 months prior to study screening. Two participants reported current oral amphetamines intake, averaging two pills each week. There was no other current illicit drug use.

Pre-admission Sleep Characteristics

Ten participants reported no sleep problems prior to admission. Three reported one sleep problem each: one prolonged sleep latency (1 hour), one disturbed sleep ("tossing and turning"), and one early morning awakening. The majority of participants (10 of 13) reported good to very good sleep quality on the SQI. Four participants reported "almost always" smoking cannabis to help sleep; eight others reported "sometimes" smoking cannabis for this purpose. In contrast, only four participants "rarely" ingested alcohol to help sleep and two "rarely" took sleeping pills. No participant reported ever taking other

medication to help sleep. Quantitative pre-admission sleep characteristics are listed in Table 1.

Internal Validity of St. Mary's Hospital Sleep Questionnaire Data

In-bed time was earlier than fall-asleep time for all participants on all days. Get-out-of-bed time was later than wake-up time on all except two questionnaires. Calculated hours of nighttime sleep (time woke up ± time fell asleep) did not differ significantly from self-reported duration of sleep: mean difference $.03 \pm .6$ hours ($t = .5$, $p = .61$), median and modal values both zero. Similarly, calculated sleep latency (time fell asleep – time got into bed) did not differ significantly from self-reported how long to fall asleep: mean difference $.063 \pm .33$ hours ($t = 1.9$, $p = .06$), median and modal values both zero.

Conceptually related sleep variables were significantly associated in the expected directions. Difficulty falling asleep was positively associated with sleep latency, that is, participants reporting greater difficulty falling asleep also reported longer duration of time to fall asleep ($.52 \pm .13$, $p = .0002$). Duration of nighttime sleep was positively associated with both depth of sleep ($.22 \pm .085$, $p = .012$) and quality of sleep ($.39 \pm .090$, $p < .0001$). Number of nighttime awakenings was negatively associated with both depth of sleep ($-.49 \pm .12$, $p < .0001$) and quality of sleep ($-.71 \pm .12$, $p < .0001$).

First Night Sleep Characteristics

Participants spent a mean (±SD) of 7.1 ± 1.3 hours in bed and 5.9 ± 1.3 hours asleep their first night on the research unit, prior to receiving any oral THC. Their sleep latency was 1.0 ± 0.7 hours and they reported 1.6 ± 1.9 nighttime awakenings. Almost one-third (30.8%) reported little or no difficulty falling asleep (23.1% reported a lot or extreme difficulty), less than one-quarter (23.1%) reported less than average depth of sleep, 84.6% reported good sleep quality, and a majority (61.6%) reported being completely alert (less than a third [30.8%] reported any drowsiness) the next morning (ie, morning of Day 1).

First night sleep characteristics (assessed by the St. Mary's Hospital Sleep Questionnaire) were not generally similar to participant's self-reported typical pre-admission sleep characteristics (assessed by the SQI). Correlations between first night and typical pre-admission hours in bed, sleep duration, sleep quality, and next morning alertness were generally low and not significant ($-.17$, $p = .57$; $.27$, $p = .37$; $-.17$, $p = .59$; and $-.52$, $p = .07$, respectively). In particular, hours in bed and sleep duration were shorter on Day 1 than pre-admission, while ratings of sleep quality were higher (Table 1).

Changes in Sleep Characteristics with Oral THC Dosing

The first THC doses, administered the afternoon of Day 1 (20 mg each at 15:00 and 20:00), after at least 17.5 hours of abstinence, had no acute effect on sleep parameters compared to the first night on the research unit, before THC administration (ie, comparing Day 2 vs. Day 1 values, Table 1). There were small but statistically significant decreases in both calculated hours asleep (mean 3.54 fewer minutes per night; $-.059 \pm .026$, $p = .025$) and self-reported hours of nighttime sleep (mean 5.34 fewer minutes per night; $-.089 \pm .031$, $p = .005$) over

the 7 nights of the study. None of the other eight sleep variables showed any significant change over the 7 days of oral THC dosing (Table 1).

Association of Sleep Characteristics with Plasma Cannabinoid Concentrations and Subject Baseline Characteristics

Higher evening plasma concentrations of THC, its active metabolite 11-OH-THC, and THC + 11-OH-THC, were significantly associated with shorter sleep latency ($-.0091 \pm .0045$, p = .046; $-.022 \pm .0091$, p = .015; and $-.0069 \pm .0031$, p = .028, respectively) and lower self-rated difficulty falling asleep ($-.015 \pm .0064$, p = .023; $-.028 \pm .013$, p = .035; and $-.010 \pm .0044$, p = .023, respectively). Evening plasma concentrations of THC and THC + 11-OH-THC also predicted more hours of daytime sleep the following day ($.019 \pm .0075$, p = .011; and $.013 \pm .0052$, p = .017, respectively). There were no other significant bivariate associations.

Duration of regular cannabis smoking was positively associated with hours spent in bed and morning alertness upon waking. For every additional year that a participant had used cannabis regularly, they spent .08 hours longer in bed ($.081 \pm .040$, p = .046) and reported .35 units greater morning alertness ($.35 \pm .17$, p = .043). African American participants were associated with fewer hours of daytime sleep ($-1.55 \pm .24$, $p < .0001$). Intensity of self-reported sedation in the evening was positively associated with number of awakenings that night ($.029 \pm .012$, p = .014).

DISCUSSION

This study showed the feasibility of assessing sleep characteristics in adult chronic daily cannabis smokers exposed to around-the-clock dosing with oral THC for 7 days on a secure residential research unit. The study found no acute effect of THC on sleep characteristics the second night on the research unit (after at least 17.5 hours of abstinence). This finding is consistent with previous single-dose human laboratory studies with 1.5–30 mg THC,[4,5,17] but not with animal studies[2] or clinical reports of somnolence associated with oral THC (dronabinol) use. It is possible that any sleep-promoting effect of the initial oral THC doses (40 mg) was counteracted, and thereby masked, in our study (and in prior human laboratory studies) by the sleep disturbance engendered by admission to an unfamiliar environment (the research unit).[18] Such a novelty-induced transient insomnia would also explain the dissimilarity between participants' self-reported typical pre-admission sleep characteristics and their sleep characteristics on the first night on the research unit. This issue could be addressed in future studies by administering THC only after subjects had spent sufficient time in the research environment to ensure complete adaptation.

Around-the-clock THC dosing was associated with a small (about 5 minutes per night) but statistically significant decrease in overall hours of nighttime sleep during the 7 dosing days. This suggests the possible development of tolerance to any somnolent effect of THC. However, higher evening plasma concentrations of both THC and its active metabolite 11-OH-THC were associated with shorter sleep latency and less self-rated difficulty falling asleep that night, and THC alone and in combination with 11-OH-THC was associated with more hours of daytime sleep the following day, suggesting that cannabinoids maintained

some of their sleep-promoting properties throughout the study. This is consistent with participants' reported pre-admission intake of cannabis as a sleep aid. The mechanisms contributing to the balance between the acute somnolent effect of cannabinoids and development of tolerance to this effect with around-the-clock dosing for 7 days remain unclear. A modest worsening of sleep characteristics with chronic oral THC dosing may not have been detected in prior human laboratory studies because of small sample sizes. We are aware of three such studies administering oral THC for at least 6 days: one had two subjects,[6] one three,[4] and one seven subjects.[8]

The findings of this study should be considered preliminary because of design limitations. First, all data was collected by participant self-report, rather than staff observation or polysomnography. However, the major data collection instrument employed, the St. Mary's Hospital Sleep Questionnaire, is widely utilized in clinical research,[19] and has been used in studies of cannabis smokers.[14] Furthermore, the high degree of consistency on several internal validity checks suggests that participants were providing valid data. Even if there were some inaccuracies in the sleep data, one would have to assume a varying bias over time to completely invalidate the within-subject findings of this study. Second, there was no THC placebo group. Thus, it remains possible that stronger than observed somnolent effects of higher evening plasma cannabinoid concentrations were masked by other non-pharmacological factors in the research setting. Third, THC dosing began while participants were likely in early acute cannabis withdrawal and data collection began the first night on the research unit. Thus, the observed findings could have been influenced by both cannabis withdrawal and acclimation to sleeping in a new environment.

CONCLUSIONS

This study, with a sample size almost double that of previously published human laboratory studies, observed only modest sleep-enhancing effects of around-the-clock dosing with oral THC (40–120 mg daily) for 7 days in 13 male daily cannabis smokers. The effects of such THC dosing on sleep were limited to shorter sleep latency and less difficulty falling asleep associated with higher evening plasma cannabinoid concentrations. The overall amount of nighttime sleep decreased slightly during the study, suggesting that tolerance to the somnolent effects of THC may have occurred. These findings are largely inconsistent with reports of somnolent side-effects with clinical oral THC therapy, but should be considered preliminary because of design limitations. Larger studies with objective sleep measures (eg, polysomnography) in subjects acclimated to the research environment before exposure to THC are warranted.

Acknowledgments

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TABLE 1

Sleep characteristics of 13 male chronic daily cannabis smokers taking around-the-clock oral THC

	Pre-admission	Day 1 (N = 13)	Day 2 (N = 13)	Day 3 (N = 12)	Day 4 (N = 12)	Day 5 (N = 12)	Day 6 (N = 10)	Day 7 (N = 10)	Day 8 (N = 10)
Duration in bed (hour)	8.5 ± 1.6	7.1 ± 1.3	6.8 ± 0.8	7.0 ± 0.4	6.6 ± 0.8	6.9 ± 0.6	6.6 ± 0.8	6.8 ± 0.7	6.8 ± 0.7
Sleep latency (hour)		1.0 ± 0.7	0.8 ± 0.8	0.4 ± 0.3	0.6 ± 0.3	0.6 ± 0.4	0.8 ± 0.7	0.7 ± 0.3	1.0 ± 0.9
Difficulty falling asleep		2.1 ± 1.0	1.5 ± 0.5	1.2 ± 0.4	2.0 ± 1.7	1.8 ± 1.1	1.4 ± 0.5	1.5 ± 0.7	2.1 ± 1.5
Duration of nighttime sleep (hour)	6.8 ± 1.7	6.2 ± 1.0	5.8 ± 1.5	6.3 ± 0.7	6.2 ± 0.7	6.1 ± 0.6	5.8 ± 0.3	5.9 ± 0.9	5.7 ± 0.7
Duration of daytime sleep (hour)		0.5 ± 1.2	0.2 ± 0.6	1.3 ± 1.7	1.1 ± 1.4	0.8 ± 1.6	0.7 ± 1.2	0.5 ± 0.6	0.7 ± 0.9
Depth of sleep		3.9 ± 1.3	3.5 ± 1.1	4.5 ± 0.9	4.3 ± 0.9	4.6 ± 0.9	4.2 ± 1.2	4.7 ± 0.8	4.5 ± 0.8
Quality of sleep	2.5 ± 1.2	4.3 ± 1.3	3.9 ± 1.1	4.5 ± 0.5	4.3 ± 0.8	4.2 ± 0.8	4.2 ± 0.8	4.2 ± 1.1	4.3 ± 0.5
Nighttime awakenings (#)		1.6 ± 1.9	2.0 ± 2.0	1.2 ± 0.6	1.4 ± 1.6	1.2 ± 0.7	1.4 ± 1.3	1.6 ± 1.3	1.3 ± 1.4
Post-awakening duration in bed (AM)		0.2 ± 0.5	0.1 ± 0.2	0.1 ± 0.1	0.03 ± 0.3	0.2 ± 0.3	0.2 ± 0.1	0.3 ± 0.2	0.2 ± 0.2
Alertness (AM)	2.9 ± 0.5	3.1 ± 1.8	7.1 ± 10.2	3.2 ± 1.5	5.7 ± 5.7	2.9 ± 1.8	3.7 ± 0.9	3.5 ± 1.8	8.9 ± 16.2

Participants were admitted to the closed research unit the evening of Day 0 and received around-the-clock oral THC dosing starting 15:00 on Day 1. The St. Mary's Hospital Sleep Questionnaire was administered each morning. Pre-admission sleep characteristics are based on the Sleep Quality Index and Morningness–Eveningness Questionnaire completed within one week of admission. Data are presented as mean ± standard deviation.