

Novel Formulation of THC and CBN in a Repeat-Action Tablet Improves Objective and Subjective Measurements of Sleep

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ABSTRACT

BACKGROUND: The use of cannabis to improve sleep quality and treat sleep-related disorders has received increased attention due to the expanded legalization of cannabis for medical use in 36 states and Washington DC. Data on the effects of delta-9-tetrahydrocannabinol (THC), in combination with cannabidiol (CBD), on sleep is preliminary; however, preclinical research indicates that CBD may prolong sleep and be particularly effective when combined with other cannabinoids.

OBJECTIVE: The aim of this study was to evaluate the effect of a repeat-action tablet containing 10 mg THC and 5 mg CBD on sleep quality, sleep duration, and awakenings in participants (medical cannabis users). The effect of the combination tablet was evaluated using objectively measured and self-reported data.

METHODS: A sleep-tracking device (SleepScore Max) was used to measure objective sleep. Self-report questionnaires were administered to measure perceived sleep quality. The validated, at-home sleep-tracking system uses a patented technology to unobtrusively and objectively track an individual's gross and micro-movements.

RESULTS: Objective data demonstrated that the 35 participants who completed the study slept an average of 6 hours and 29 minutes per night before starting on the repeat-action tablets. During the combination tablet-use period, participants slept an average of 20 minutes longer (ie, 6 hours and 49 minutes; $P < 0.001$; 5% improvement). There was a 22% increase in reported feelings of restfulness upon awakening ($P < 0.0001$), with an average rating of 53.32 (on a 100-point sleep quality scale) before product use to 65.21 during product use. Additionally, there was an 18% increase in reported overall sleep quality ($P < 0.0001$), with an average rating of 57.36 (on a 100-point sleep quality scale) before product use to 67.90 during product use.

CONCLUSION: This validation study found that a repeat-action tablet formulation of THC and CBD was associated with improved sleep quality in a sample of 35 participants who were medical cannabis users. Findings were obtained using both a validated sleep-tracking system to measure objective sleep and self-reported data obtained from questionnaires.

Introduction

The cultivation and use of the cannabis plant for its medicinal and industrial benefits date back to ancient times. The use of cannabis to improve sleep and to treat sleep disorders has received increased attention in light of the current legalization of cannabis for medical use in 36 states and Washington DC.¹ Recent studies indicate that individuals using cannabis in general expect it to decrease their sleep-related issues and reduce their need for sleep medications.^{2,3} Participants in a study by Altman and colleagues reported that using cannabis helped them fall asleep about 15 minutes faster and sleep for about 2 hours longer.² Further research, however, is needed to understand the objective and perceived effects of cannabinoids on sleep. Delta-9-tetrahydrocannabinol (THC) is one of the most widely studied cannabinoids, but its effects on sleep are not yet well understood.^{4,5} An early study by Cousens and DiMascio found that THC decreased one's time to fall asleep (measured objectively) but led to a "hangover" aftereffect (ie, continued "high" feeling) the following day.⁶ However, Chait et al. found that THC was not associated with hangover effects.⁷ Other early studies suggested that THC might reduce the duration of rapid eye movement (REM) and increase the duration of deep sleep.^{7,8}

Recent research has benefited from a more sophisticated understanding of THC and sleep relative to earlier eras. Nonetheless, the optimal concentration, dosage, timing, and route of administration of cannabis for sleep remain unknown.⁵ Given these complexities and others, laboratory studies do not reflect people's naturalistic experiences of cannabis use and sleep.⁸

For the purposes of this study, we aimed to quantify and categorize the sleep-wake cycle into the following 4 phases: light sleep, deep sleep, REM, and wakefulness.

Methods

Participants

Curio Wellness, LLC, recruited medical cannabis patients (certified by the Maryland Medical Cannabis Commission) who reported having trouble staying asleep. Eligible participants were asked to visit the Curio Wellness dispensary in person on 2 occasions. During the first visit, participants reviewed and signed informed consent forms, picked up the SleepScore Max device, downloaded the research version of the SleepScore Max companion app, and reviewed the study instructions. At the second visit, participants were given cannabis repeat-action tablets containing 10 mg THC and 5 mg cannabidiol (CBN), along with study instructions.

Forty-one individuals met all eligibility criteria and 35 completed the study. Before the study, all participants signed an informed consent form, explaining potential

risks and benefits as well as other information about the voluntary study. Participants were given a \$100 gift card upon completion of the study and were provided with a SleepScore Max sleep-tracking device, a validated noncontact at-home monitoring system designed to measure the user's sleep.

Objective sleep data were collected using the sleep-tracking system, which includes a noncontact monitor designed to unobtrusively and objectively measure participants' sleep at home. The system provides standard annotated 30-second epoch sleep-stage data and commonly used sleep metrics, including time to fall asleep (sleep-onset latency), number of awakenings, start and end of sleep sessions, and total sleep time. These sleep measurements have been validated multiple times, demonstrating good performance compared with polysomnography, which is considered the gold standard technique for measuring sleep objectively.⁹⁻¹¹ The technology can be compared with ultra-low-energy radar. The sensitivity of the sensor and the performance of the signal processing algorithms allow the detection of gross body movement and full respiration patterns by measuring the micro-motion of the chest cavity.

The sleep-tracking system provided 3 types of sleep scores: SleepScore, BodyScore, and MindScore. These scores are normalized to 100-point sleep quality scales that are based on proprietary algorithms and use scientific averages for a user's age and sex.¹² SleepScore is defined by 6 sleep parameters (total sleep duration, time to fall asleep, time in light sleep, time in deep sleep, time in REM, and number of awakenings throughout the night) and can be regarded as a general sleep quality scale.

Study Design

A non-counterbalanced, pre-post study design was used. Although we preferred to use a placebo-controlled trial, we were not able to do so based on the state of Maryland's labeling requirements for medical cannabis products. Instead, to create a baseline for comparison, we established a pre-product sleep-performance period using the sleep-tracking technology. Both quantitative and qualitative self-report data and objective sleep data were collected. During the first visit, participants reviewed and signed informed consent forms, picked up the sleep-tracking device (Figure 1), downloaded the research version of the companion app, and reviewed the study instructions. The product was tested in the participant's home, which provided insight into the effectiveness of the product under real-life conditions and yielded more ecologically valid results. An overview of the timeline is displayed in Figure 2.

Each repeat-action tablet contained 15 mg of cannabinoids (10 mg THC and 5 mg CBN). These specific

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FIGURE 1. SleepScore Max app, a validated noncontact at-home monitoring system designed to measure the user’s sleep.

concentrations are commercially available to medical cannabis users in Maryland and were chosen for the current study based on previous research conducted by Curio Wellness. The product is designed to release the first half of the dose immediately after oral administration, and the remaining half released 2 to 3 hours later.

Participants used the research version of the sleep-tracking companion app, a slimmed-down version of the publicly available app; it is a dedicated sleep-recording device and is available to researchers upon request. The sleep recorder tracks sleep in the same way as the publicly available app; however, it does not display sleep data and does not offer consumer features such as a sleep guide or smart alarm; rather, it simply acts as a sleep tracker.

To assess participant compliance with sleep tracking, compliance to repeat-action dosage during the product-use period, and to measure their perceived sleep quality (eg, “How long did you feel it took to fall asleep last night?”), daily questionnaires were electronically sent each morning via Survey Monkey. These brief daily questionnaires were

sent during the entire 6-week study, both before and during product use.

Results

Of the 41 participants who were recruited into the study, 1 did not register a sleep-tracking system account and 2 withdrew from the study. One of the participants cited a preexisting medical condition as the reason for withdrawing from the study; the other participant withdrew due to technological difficulties with the app (he declined troubleshooting support). Among the participants who remained in the study, 3 did not provide complete data. Therefore, due to missing data, the objective sleep analyses included 35 participants. Likewise, due to missing survey data, the perceived sleep analyses included self-report data from 35 participants.

Demographics

Demographic data are presented in Table 1. The average participant was 47 years of age (range, 22–69 years); 57% were women; 77% described their race as white; and 54% were married. The majority of patients (57%) were employed full time, and 63% were college graduates (held undergraduate or graduate degrees). Annual household income ranged from <\$20,000 (3%) to ≥\$100,000 (40%). The 35 participants who consistently tracked their sleep did so for 69% of all nights in the study. There were 594 nights of tracked sleep before test product use and 426 nights during which participants used the test product and tracked their sleep (58% compliance rate for both activities during product use).

At the beginning of the study, the most common medical conditions for which participants reported taking cannabis were sleep/insomnia (69%), pain (40%), and generalized anxiety disorder (29%). (All reasons cited for cannabis use are listed in Figure 3.) Sleep concerns noted by participants during the weeks before initiating combination THC/CBN repeat-action tablets are shown in Figure 4. The most common concerns cited were waking up too often during

Study week	Pre-product use (baseline)			Product in use			Post-product use
	-1	-2	-3	1	2	3	
SleepScore Max measurement	→			→			
Product use				→			
Brief daily questionnaire	→			→			
Sleep experience questionnaire			X	X		X	X

FIGURE 2. Study timeline.

TABLE 1. Objective Sleep Analyses Sleep Score: Baseline Treatment Effect vs Baseline*

	Observed		Estimated	
	Pretest period (baseline)	Product use	Constant	β
SleepScore (0–100)	78.98	80.21	79.04	1.232
BodyScore (0–100)	76.50	76.66	76.50	0.081
MindScore (0–100)	78.18	79.87	78.26	1.479
Total sleep time (min)	388.91	408.96	389.30	20.719
Sleep-onset latency (min)	21.58	24.94	21.58	2.655
Number of awakenings	4.78	4.94	4.78	0.214
Wake after sleep onset (min)	43.43	44.36	43.57	1.506
Time in bed (min)	460.35	482.22	460.66	22.917
Sleep efficiency	84.26	83.76	84.22	–0.396
Sleep maintenance	84.43	84.41	84.40	–0.154
Light (min)	240.49	256.36	240.75	17.003
REM (min)	76.58	79.74	76.79	2.474
Deep (min)	71.84	72.86	71.76	1.170
% Light sleep	55	56	55	0.983
% REM sleep	18	17	18	–0.276
% Deep sleep	17	17	17	–0.610
% Wake after sleep onset	10	10	10	–0.106

REM, rapid eye movement.

*For the pretest and the product-use period, a single average was calculated using the average nights across participants (listed under the “Observed” column). The “Estimated” column lists the outcomes of the multilevel regression analyses. Regression model was as follows: $Sleep_{measure_i} = Const0_i + B \cdot TestPeriod_i$; the test period was coded as “0” for observations that occurred during nights when participants were not using the repeat-action dosage, and “1” for nights when participants tracked their sleep and reported using the repeat-action dosage. Nights during the product-use period in which participants did not have objective data or did not report using the repeat-action dosage were not included in the analyses.

the night (83%); not feeling well rested upon awakening in the morning (74%); and taking too long to fall asleep at night and waking up too early in the morning (26%). The fact that the participants’ concerns about being able to stay asleep during the night outweighed their concerns about being able to fall asleep confirmed that those recruited were an appropriate match for the product being tested.

Additionally, when participants were asked whether medical cannabis made them feel sleepy; 89% replied “yes” and 11% replied “no.” Participants reported using a variety of forms of cannabis in the past to help with sleep, the most common of which was cannabis flower (49%; Figure 5).

Results of the objective sleep analyses are shown in Table 1. These results revealed that the measurements

indicative of staying asleep did not change. The effects of the combination THC/CBN repeat-action tablets for wake after sleep onset, number of awakenings, sleep efficiency, and sleep maintenance were not significant, and there was no significant change in time to fall asleep. However, participants’ average length of time in bed increased by 22minutes ($P < 0.001$; 5% improvement), leading to a healthier amount of sleep. Objective sleep and multilevel regression results comparing nights before product use to nights during product use for 35 participants (N=1020 nights) are presented in Table 1.

Analyses of the daily self-report data suggest that the repeat-action dosage helped participants experience better sleep. Overall sleep quality of the participants increased

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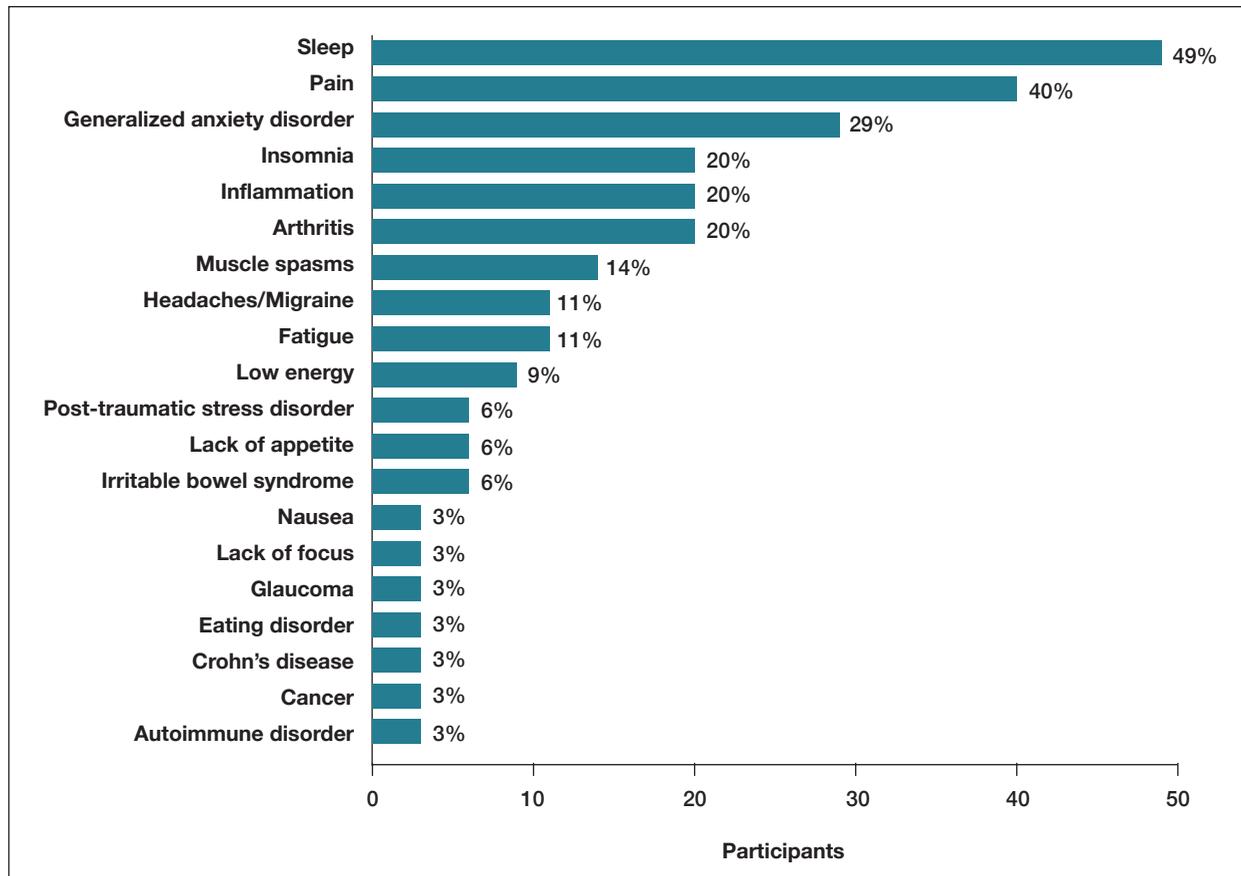


FIGURE 3. Medical conditions for which cannabis was used. Up to 3 conditions could be selected by each participant.

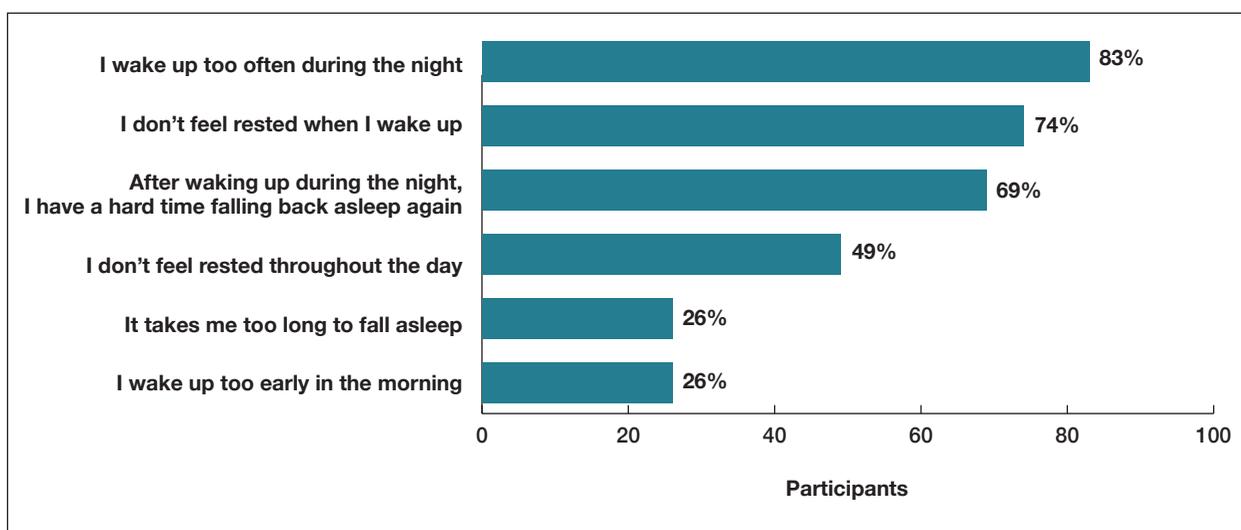


FIGURE 4. Sleep concerns before using the repeat-action dosage form.*

*Percentages do not total 100 because multiple answers were allowed.

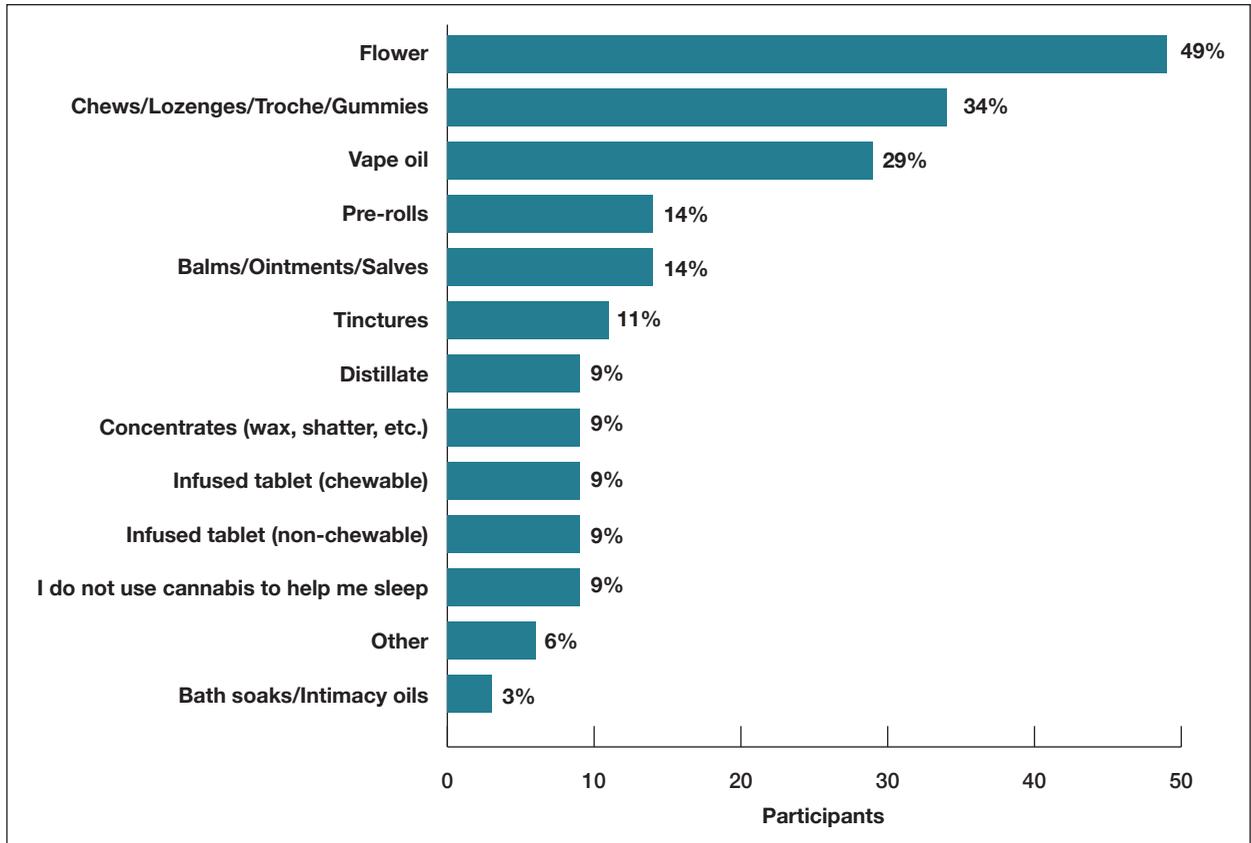


FIGURE 5. Forms of cannabis being used to help with sleep before the product use period.*

*Percentages do not total 100 because multiple answers were allowed.

18% ($P < 0.0001$); sleep quality ratings increased from an average of 57.36 before product use to 67.90 during product use (Table 2).

From a user-experience perspective, response to the repeat-action tablets were positive overall. Due to Maryland's labeling requirements for medical cannabis products, a placebo-controlled trial was not possible for this study.

Study Limitations

When interpreting the study results, it must be considered that the timing of this study unexpectedly coincided with the COVID-19 pandemic. Given that the study design did not include a control group, the extent to which the effects of repeat-action dosage of cannabis on sleep vs health and lifestyle changes associated with the COVID-19 pandemic cannot be fully known. Data collection occurred from February 24, 2020 to April 5, 2020. Maryland's stay-at-home directive was not ordered until March 30, 2020, but closures of nonessential businesses, schools, and other restrictions were in place earlier.¹³ The increase in

total sleep time found in the current study sample is in line with national data from March 16 to April 3, 2020, showing that, on average, people in the United States spent more time in bed and slept longer during COVID-19 restrictions than pre-pandemic.¹⁴

Legality of Cannabinol

Products containing CBN are legal in 36 states under current medical cannabis laws. Some states have different laws regarding the extraction, sale, and use of CBN products, so clinicians should first double-check their respective state's legislation and regulations.

Conclusion

Our study used a validated sleep-tracking technology and self-reported patient data. Tablets were administered as a repeat-action dosage form: Half of the doses released immediately after oral administration, and the remaining half released 2 to 3 hours later. This study found that an oral product containing a combination of THC and CBN

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TABLE 2. Self-Report Daily Questionnaire and Multilevel Regression Results Comparing Nights Before Product Use to Nights During Product Use for 35 Patients (N=1236 Nights)*

	Observed		Estimated		
	Pretest period	Product use	Constant	β	P-value
Bedtime sleepiness (0–100)	65.71	67.02	65.74	1.293	0.103
Time to fall asleep (min)	24.58	24.25	24.37	0.059	0.482
No. of awakenings	2.87	2.33	2.86	-0.531	<0.0001
No. of times out of bed	1.21	0.95	1.21	-0.256	<0.0001
Well-rested in the morning (0–100)	53.32	65.21	53.38	11.922	<0.0001
Sleep quality (0–100)	57.36	67.90	57.43	10.59	<0.0001

*For the pretest and the product-use period, a single average was calculated using the average nights across participants (listed under "Observed" in the Table).

was directly associated with both improved objective and perceived sleep quality and duration in a sample of patients taking medical cannabis. However, there were no significant changes in the objective sleep measurements specific to remaining sleep, despite the participant-perceived improvements, including reports of longer time in bed and total sleep time records. The sensitivity of the self-report tools used in this study are subjected to the typical responder bias limitations observed in similar studies. Participants in the study evaluated the tablet favorably overall, and they experienced sleep improvements while taking the product. Given the timing of the study period, we cannot rule out that the observed effects were partly due to the COVID-19 pandemic.

Disclosure

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