ORIGINAL ARTICLE

Efficacy and Safety of Cannabidiol Oil on Chronic Insomnia: The First Randomized, Double-Blind, Placebo-Controlled, Crossover, Pilot Study in Thailand

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Objective: Cannabidiol (CBD) is a non-intoxicating extract from Cannabis sativa. The advantages of CBD on sleep-wake cycle and insomnia remain sparse. The present study investigated the impact of a continuous four-week sublingual CBD intake on sleep indicators.

Materials and Methods: The present study was a randomized, double-blind, placebo-controlled, crossover pilot study involving 45 chronic insomnia patients. The participants were administered medium-chain triglycerides oil soluble cannabidiol (MCT-CBD) using 1 mg/kg/dose, sublingually for four weeks, then two weeks of washout period, and a subsequent four-week placebo phase. Sleep architecture with N1, N2, N3, and rapid eye movement (REM), sleep quality (PSQI), daytime sleepiness (ESS), and quality of life were investigated.

Results: Polysomnography (PSG) revealed that the total sleep time (TST), sleep onset latency (SOL), wake time after sleep onset (WASO), and arousal index were significantly improved compared to the patients who were taking placebo, while sleep structure remained unaltered. Additionally, actigraphy showed a substantial improvement in TST, sleep efficiency (SE), and SOL. The results of PSQI, ESS, and EQ-5D-5L were statistically significant and better than placebo ($p<0.05$).

Conclusion: Continuously sublingual CBD treatment could improve sleep duration, sleep maintenance, sleep induction, quality of life, and daytime sleepiness without altering the sleep architecture in patients with chronic insomnia. No evidence of serious side-effects was found.

Keywords: Hemp; CBD; Cannabidiol; Cannabis; Insomnia; Sleep

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Good quality sleep is crucial for normal body functions[1]. However, a common sleep disorder known as insomnia is prevalent in about 10% to 30% of the global population, and even high between 30% to 60% among the elderly with half having a persistent problem lasting more than a month[2]. Of importance, sleeping disorders have resulted in work productivity loss, and treatment costs of about US$ 4,093 million annually throughout the globe[3]. Psychiatric education on sleep hygiene and treatment with sleep aids or drugs such as benzodiazepines helps patients fall asleep faster, reduce waking up in the middle of the night, or reduce anxiety[4]. However, the drug often causes side effects and may disturb sleep architecture, increase sleep fragmentation, and result in non-restorative sleep[5].

Cannabis, the products derived from Cannabis sativa contains 100 different cannabinoids along with cannabidiol (CBD)[6]. CBD engages with various molecular targets that play pivotal roles in sleep regulation and insomnia. CBD interacts with CB1 and CB2 receptors within the endocannabinoid system (ECS), influencing neurotransmitter release and potentially inducing sleep through the activation of CB1 receptors. Additionally, CBD has been reported as an antagonist for an unidentified receptor, displaying affinity for the CB1 receptor, which is associated with sleep induction[7]. Biochemical studies reveal that CBD inhibits the enzyme fatty acid amide hydrolase (FAAH), leading to an increase in the concentration of anandamide (AEA), a major endogenous cannabinoid associated with mood and stress regulation[8]. Furthermore, CBD's interaction with serotonin receptors (5-HT1A) suggests a potential role in modulating mood and sleep-wake

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cycles[8]. Lastly, CBD interacts with gamma-aminobutyric acid (GABA) receptors, the primary inhibitory neurotransmitters, promoting relaxation and potentially alleviating insomnia-related factors[8]. These multifaceted interactions highlight CBD's promising role in addressing insomnia and enhancing sleep quality.

Previous efficacy trials showed it had a dose-dependent effect on alertness and relaxation, so that mild sedation could decrease time in rapid eye movement (REM) sleep and increased total sleep time (TST) and slow wave sleep[9]. A study suggested that moderate to high doses of CBD may be effective for insomnia and REM sleep behavior disorder treatment[10]. Publications recommended the benefits of CBD on sleep and sleep disorders[11-13]. Recommended therapeutic dose for epilepsy or other neurological disease is available in guidelines, but the standard dose for sleep disorders is not mentioned[14,15]. This has been the main issue considering the rapidly growing use of cannabinoid and cannabinoid products in older populations[16]. Safe CBD dosage has been used between 16 to 1,000 mg per time[17]. CBD had been investigated to confirm pre-clinical beneficial effects on sleep, until subjective effects in humans. However, a randomized controlled trial was still lacking. Therefore, the authors performed this phase-II clinical trial aimed to study the efficacy of CBD and determine an appropriate dose together with any possible short-term complications.

Materials and Methods

A randomized, double-blind, placebo-controlled, crossover study was conducted in cannabis clinics at Suranaree University of Technology Hospital. It is a 250-bed tertiary care hospital in the Nakhon Ratchasima Province of Thailand. The present study was conducted between September 2021 and April 2023.

In the first phase of treatment, 45 patients were randomly allocated into two groups, 1) medium-chain triglycerides oil soluble cannabidiol (MCT-CBD) period followed by placebo period, as control group, and 2) a placebo period, as control group, followed by the MCT-CBD period. The treatment was continued for four weeks separated by a two-week washout period, to study the efficacy of MCT-CBD compared to placebo. The half-life of CBD was reported between 1.4 and 10.9 hours after the oro-mucosal route[18], ensuring the crossover protocol did not interfere with the treatment effect tested. The patients were subjected to two doses of CBD, 10 mg in the morning and 1 mg/kg/dose at bedtime.

The second phase of treatment studied the adverse side effects and 12-weeks sleep quality assessment, with same dosage as the first phase, a low dose of CBD of 10 mg in the morning and 1 mg/kg/dose before bedtime. The treatment was continued for another 12 weeks. The volunteers were monitored at the clinic one month after the cessation of treatment. This project had been registered retrospectively in the Thai clinical trials registry (TCTR20230417005). The study flow is shown in Figure 1.

Study criteria

Adults aged 18 to 60 years with chronic insomnia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), Insomnia Severity Index (ISI) score greater than 15, thus, moderate-to-severe clinical insomnia, and insomnia more than three times a week for more than three months were enrolled in the present study[19]. On the other hand, a person with duty hours in a shift, a medical condition such as chronic pain, or medications that cause insomnia, severe sleep apnea defined as apnea hypopnoea index (AHI) of greater than 30 and oxygen desaturation index (ODI) of greater than 10 or sleep-related movement disorder depending on the outcome of polysomnography (PSG), advanced or delayed sleep-wake phase disorder based on actigraphy, any treatment for insomnia including cognitive behavioral therapy (CBT) and central nervous system-acting drugs within three months before screening, or at the discretion of the physician were excluded. Likewise, a person with international travel of greater than two time zones within the past one month, use of drugs that may affect cannabinoid elimination such as inhibitors/inducers of the CYP450 pathway, disorders of the heart and blood vessels, pregnancy or breastfeeding, history of psychiatric disorder in the past 12 months except for mild symptoms of depression or anxiety according to the DSM-5, or at the discretion of the physician, history of suicide attempts or suicidal thoughts, history of drug or alcohol abuse/dependence in the past two years, an allergic reaction to cannabis and cannabis extracts, marijuana use within the past three months, excessive daily caffeine use based on the physician's opinion or inability to abstain from caffeine use for more than 24 hours before the overnight sleep test, cannot abstain alcohol for 24 hours or more before each sleep test, medical conditions that cause one to leave bed frequently such as frequent urination during the night, a state that required a marijuana

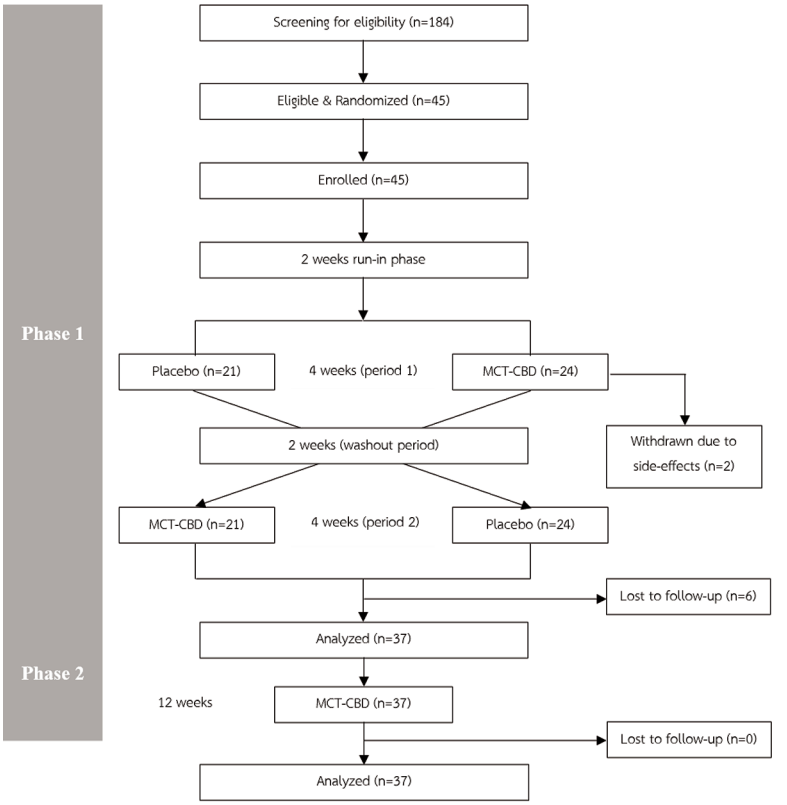

Figure 1. Cannaree Sleep Trial 01 - Study flow diagram.

inspection such as a workplace inspection, or a court order, and abnormal liver or kidney function were also excluded[19]. Patients were free to withdraw from the study at any time or if they had serious adverse problems after the treatment.

Methods for assessing sleep quality

Sleep quality was assessed using PSG and actigraphy, especially TST, sleep efficiency (SE), sleep onset latency (SOL), number of awakenings (NAW), and wake time after sleep onset (WASO) were investigated. Pittsburgh sleep quality index (PSQI)-Thai version[20], Epworth sleepiness scale (ESS), and quality-of-life questionnaire (EQ-5D-5L) were also applied in the present study. Level 1 PSG or type 1 PSG was done overnight in the sleep lab of Suranaree University of Technology Hospital. A level 1 PSG was used to help to diagnose various sleep disorders. A Level 1 PSG recorded electroencephalogram (EEG), electro-oculogram (EOG), electro-myogram (EMG), and electrocardiogram (ECG) as patients slept. A wrist-worn device, ActiGraph Xiaomi Mi Band 5 was used to record sleep quality at home[21]. All patients were informed to wear it at least 12 hours a day, starting before going to bed and getting out of bed.

Treatment and other interventions

MCT-CBD used in the present study was coded as CNR-SL-01 by the Thai Government Pharmaceutical Organization (GPO, Bangkok, Thailand)[22]. Hemp, adhering to good agricultural practices (GAP), was cultivated on GPO farms located in the provinces of Chonburi and Prathumthani. The extraction and manufacturing processes were conducted at the GPO factory situated in the provinces of Pathum Thani, following good manufacturing practices (GMP). The concentration of a solution was 100 mg/mL of CBD in olive oil with less than 1 to 20 on the THC to CBD ratio[22]. The taste and odor of MCT-CBD were mild with a brown color. Olive oil flavored and colored to resemble the MCT-CBD was used as a placebo. The treatment was sublingual when the patients kept MCT-CBD or placebo drops under the tongue for one to two minutes and then swallowed. Food or drink was permitted only after five to ten minutes of the treatments. All participants were instructed how to take medicine by pharmacists

and then prescribed as charge. The morning CBD dose, 10 mg, justified by a previous study showed that 15 mg of CBD administered to young adults increased wakefulness[23]. Meanwhile, 1 mg/kg/dose of bedtime dose was justified according to Australian Guidelines: safety of low dose CBD[15].

Procedures

The study project was detailed, and objectives were explained to the insomnia patients through a phone call and requested their participation. Once agreed, an initial assessment was done through an online questionnaire. The participants were screened and diagnosed within a month of enrollment to rule out sleep disorders other than insomnia. The severity and impact of insomnia were assessed using PSQI upon measuring sleep quality and sleep behavior. Data on demographic variables such as age, gender, race or ethnicity, education, employment, household income, and family size including medical conditions such as hypertension, diabetes mellitus, and body mass index (BMI) with greater than 30 were collected. Moreover, all participants were checked for a history of cannabis intake, and cannabis use disorder was screened according to ICD-10 criteria. A standard 12-lead ECG was performed to check for abnormalities in the cardiovascular system. The participants were then instructed to write a sleep diary and taught to use a sleep tracker to record their sleep and wake times for a week before a sleep test. All participants were informed to go to bed at about 10 pm regularly, improving daily routine according to sleep hygiene[24].

Sample size calculation

The sample size and statistical analyses for this pilot study, which explored the sublingual administration of CBD, had been meticulously designed. Given the absence of prior clinical studies employing CBD via the sublingual route, the research protocol was tailored to assess the preliminary safety and efficacy of short-term repeated doses of CBD in volunteers with primary insomnia. Employing a straightforward 2-way crossover design, an independent t-test will be utilized to compare CNR-SL-01 against a placebo, aiming to detect an effect size of 0.67 with 80% power at an alpha level of 0.05 (two-tailed)[19]. The collected data would undergo mixed-effects analysis to determine significant differences in the treatment modalities. A significance level of 0.05 will be considered for the primary outcome evaluation.

Ethical approval

The present study was approved by the Institutional Review Board (EC-64-94) of Suranaree University of Technology, filed in the Thai Clinical Trials Registry (TCTR20230417005), and complied with the Declaration of Helsinki. The participants provided written informed consent before the study.

Data analysis

Statistical analysis was performed according to the plan analysis, the first per-protocol (PP) analysis, and the main analysis using the intention to treat (ITT) principle. Data were collected at four time points, the start and end of intervention Phase 1, and the start and end of intervention Phase 2. The crossover design allowed controlling for potential confounding factors by reducing variability between participants. The effectiveness of wash-out or presence of carry-over effects from intervention Phase 1 to Phase 2 was assessed by comparison of each participant's baseline measures 2 versus Descriptive analyses conducted at each baseline 1 and 2, data were assessed for normality. Any carry-over effects were adjusted for in covariate analysis. For the main analysis in this crossover trial, the authors combined data from intervention periods 1 and 2 and analyzed each phase individually in a secondary analysis. Differences between the groups at the end of each period compared to its baseline were analyzed by Student's t-test and factorial repeated-measures analysis of variance for continuous variables. Secondary analysis by intervention period/phase provided insight into whether treatment order may have influenced the outcome, and the findings were considered statistically significant at $p=0.05$. Statistical analyses were performed using IBM SPSS Statistics, version 29.0 (IBM Corp., Armonk, NY, USA).

Results

Of the 184 patients who underwent sleep screening, 45 met the enrollment criteria and were randomized into the MCT-CBD group with 24 participants and placebo group with 21 participants. Thirty-five participants completed the study, seven participants dropped out while on MCT-CBD and three while on placebo due to various reasons. The reasons for dropping out of the study were voluntary revocation and protocol violations. The mean age of the patients was 45.06±11.67 years, ranging from 22 to 60 years. Most patients were female at 66.67%. Table 1 shows the baseline PSG data between the groups. The average dose of MCT-CBD that the

Table 1. Baseline characteristics of the participants

Variables	Frequency/durations
Sex; n (%)	
Male	15 (33.33)
Female	30 (66.67)
BMI; mean±SD	23.64±4.76
Age; mean±SD	45.06±11.67
PSG-TST (min:sec); mean±SD	
Group A	343:23±63:26
Group B	317:00±79:42
PSG-SE (min:sec); mean±SD	
Group A	74:23±12:12
Group B	71:05±18:25
PSG-SOL (min:sec); mean±SD	
Group A	46:30±43.62
Group B	50:43±43:43
PSG-WASO (min:sec); mean±SD	
Group A	19:87±10:42
Group B	2:15±1:97

BMI=body mass index; PSG=polysomnography; TST=total sleep time; SE=sleep efficiency; SOL=sleep onset latency; WASO=wake time after sleep; SD=standard deviation

patient received during treatment was about 50 to 60 mg per day according to the recommended dosage in the protocol, which was 1 mg/kg/dose MCT-CBD. In group 2, placebo-CBD, three of the patients reported using rescue medication (lorazepam) for five to seven days on a placebo period during the first phase of the study.

The mean PSG-TST change after MCT-CBD treatment compared to the baseline was 56.83±63.45 and 65.08±66.40 in ITT and PP analysis, respectively. These differences in the scores were statistically significant. The mean difference between the groups in ITT and PP analysis was 57.23±14.48 and 65.26±15.51, respectively. The mean PSG-SE difference before and after MCT-CBD treatment in ITT analysis was 4.52±11.84 and 11.68±12.15 in other analyses. These scores were statistically significant. In addition, the mean PSG-SE change in patients before and after the placebo was 5.71±12.64 (ITT) and 6.64±14.20 (PP). The difference was statistically significant. When comparing the PSG-SE difference between the placebo group and the MCT-CBD group, it was statistically significant as shown in Table 2.

Table 3 shows that the mean PSG-SOL change after MCT-CBD treatment in patients compared to baseline was –20.12±31.0 and –23.08±34.75 in ITT and PP analysis, respectively. The scores were statistically significant. Likewise, the mean PSG-SOL difference before and after the placebo in the patients was 6.09±36.01 (ITT) and 7.39±41.82 (PP). The mean PSG-SOL difference between the two groups in ITT and PP analysis were 26.21±9.38 and 30.48±12.26, respectively. The difference was statistically significant ($p<0.01$).

The mean PSG-WASO change in the study patients before and after MCT-CBD treatment compared to baseline was –18.52±30.30 and –23.62±33.44 in ITT and PP analysis, respectively. These differences in the scores were statistically significant, and the mean difference between the groups in ITT and PP analysis were 20.94±9.96 and 25.33±11.17, respectively. The mean PSG-NAW difference after MCT-CBD treatment in PP analysis compared to the initial score was –6.9±15.41, which was significantly different including the mean difference between the two study groups (7.5±2.78, $p=0.009$). The arousal index was significantly different in both analyses when a comparison was

Table 2. Sleep duration (PSG-TST and PSG-SE)

Analysis	Variables	Group	n	Baseline mean±SD	2 weeks mean±SD	Mean change (within group)	CBD versus placebo group		
							Mean difference (±S.E.)	95% CI	p-value
ITT	PSG-TST	Placebo	35	324.42±68.23	324.02±60.06	–0.40±58.49	57.23±14.48	28.33 to 86.13	<0.01
		CBD	35		381.25±61.10	56.83±63.45*			
PP	PSG-TST	Placebo	26	332.13±73.15	331.95±62.87	–0.18±68.17	65.26±15.51	34.09 to 96.42	<0.01
		CBD	26		397.21±48.01	65.08±66.40*			
ITT	PSG-SE	Placebo	35	71.45±14.10	77.17±13.22	5.71±12.64*	4.52±2.90	–1.28 to 10.32	0.12
		CBD	35		81.69±11.01	4.52±11.84*			
PP	PSG-SE	Placebo	26	72.88±15.40	79.53±13.71	6.64±14.20*	5.05±3.13	–1.25 to 11.34	0.11
		CBD	26		84.57±8.24	11.68±12.15*			

ITT=intention to treat analysis; PP=per-protocol analysis; PSG=polysomnography; TST=total sleep time; SE=sleep efficiency; CBD=cannabidiol; SD=standard deviation; S.E.=standard error; CI=confidence interval

* Significant

Table 3. Sleep duration (PSG-SOL)

Analysis	Variables	Group	n	Baseline mean±SD	2 weeks mean±SD	Mean change (within group)	CBD versus placebo group		
							Mean difference (±S.E.)	95% CI	p-value
ITT	PSG-SOL	Placebo	35	49.34±39.08	55.44±44.98	6.09±36.01	26.21±9.38	6.88 to 45.55	<0.01
		Active	35		29.22±32.54	−20.12±31.0*			
PP	PSG-SOL	Placebo	26	48.62±44.43	56.01±51.49	7.39±41.82	30.48±12.26	5.84 to 55.11	0.01
		Active	26		25.53±35.50	−23.08±34.75*			

ITT=intention to treat analysis; PP=per-protocol analysis; PSG=polysomnography; SOL=sleep onset latency; CBD=cannabidiol; SD=standard deviation; S.E.=standard error; CI=confidence interval

* Significant

Table 4. PSG-WASO, PSG-NAW, and arousal index

Analysis	Variables	Group	n	Baseline mean±SD	2 weeks mean±SD	Mean change (within group)	CBD versus placebo group		
							Mean difference (±S.E.)	95% CI	p-value
ITT	PSG-WASO	Placebo	35	64.29±36.48	66.17±49.07	2.41±43.51	20.94±9.96	0.50 to 40.29	0.04
		Active	35		45.77±32.72	−18.52±30.30*			
PP	PSG-WASO	Placebo	26	62.16±36.51	63.87±50.30	1.71±48.69	25.33±11.17	2.88 to 47.77	0.02
		Active	26		38.54±26.78	−23.62±33.44*			
ITT	PSG-NAW	Placebo	35	2.58±1.88	3.09±1.98	0.51±1.22*	1.14±0.44	0.26 to 2.01	0.01
		Active	35		1.95±1.69	−0.62-1.64*			
PP	PSG-NAW	Placebo	26	2.52±1.76	3.17±1.92	0.64±1.40*	1.42±0.45	0.48 to 2.34	0.003
		Active	26		1.75±1.34	−0.76±1.88*			
ITT	Arousal index	Placebo	35	17.77±10.96	18.22±10.06	0.45±6.34	4.92±10.48	−16.01 to 25.84	0.64
		Active	35		23.14±61.20	5.37±62.21			
PP	Arousal index	Placebo	26	18.26±11.96	18.84±10.93	0.57±7.32	7.5±2.78	1.90 to 13.09	0.009
		Active	26		11.34±9.06	−6.9±15.41*			

ITT=intention to treat analysis; PP=per-protocol analysis; PSG=polysomnography; WASO=wake time after sleep; NAW=number of awakenings; CBD=cannabidiol; SD=standard deviation; S.E.=standard error; CI=confidence interval

* Significant

made within or between the groups (Table 4). The sleep architecture indices for N1, N2, N3, and REM, were statistically insignificant in the study when compared between the CBD and placebo groups.

Sleep outcomes from actigraphy revealed that ACT-TST, ACT-SE, and ACT-SOL were significantly different within and between the placebo and MCT-CBD groups. The mean intra-group difference of ACT-TST was 58.48±15.82 and 60.91±14.06 in ITT and PP analysis, respectively. Likewise, the mean intra-group difference of ACT-SE was 10.78±2.51 in ITT and 12.12±2.16 in PP analysis. The mean ACT-SOL between the groups was 45.83±12.74 in ITT and 53.90±14.65 in PP analysis (Table 5).

The measure of sleep effectiveness using the Sleep Quality Questionnaire is listed in Table 6. The mean change in PSQI was statistically decreased after MCT-CBD treatment compared to the baseline score. Moreover, the mean difference between the two groups was 6.52±0.68 and 7.28±0.64 in ITT and PP, respectively. The ESS in both the placebo and MCT-CBD groups were significantly decreased compared to the baseline scores. The mean ESS difference between the two groups was 4.15±1.03 and 4.19±1.19 in ITT and PP, respectively.

The quality of life was significantly higher in MCT-CBD-receiving patients compared to placebo (0.69±0.30 vs 0.28±0.30, p<0.01).

Adverse events from MCT-CBD treatment were reported in 10 participants (22.2%). Nine participants (15%) reported adverse effects in the first month of treatment and the rest in the second month. Two subjects withdrew from the study due to adverse events. The most frequently reported adverse events were anorexia in three subjects (5%), and nausea/vomiting in two patients (3.3%). However, there were no serious adverse side effects. After 4-weeks of MCT-CBD use, thirty-three subjects (73%) had difficulty sleeping after its discontinuation. These subjects were followed up at a medical cannabis clinic within two weeks and were transferred to the psychiatric department for continued appropriate treatment. No significant change in liver and kidney function markers and CBC was recorded.

Table 5. Sleep duration from actigraphy

Analysis	Variables	Group	n	Baseline mean±SD	2 weeks mean±SD	Mean change (within group)	CBD versus placebo group		
							Mean difference (±S.E.)	95% CI	p-value
ITT	Total sleep time	Placebo	45	340.22±64.92	347.17±81.56	6.95±47.73	58.48±15.82	27.02 to 89.94	<0.01
		Active	45		405.66±68.0	65.44±61.51*			
PP	Total sleep time	Placebo	37	354.97±58.62	366.40±73.03	11.43±49.70	60.91±14.06	32.88 to 88.895	<0.01
		Active	37		427.32±44.56	72.35±62.33*			
ITT	Sleep efficacy	Placebo	45	71.72±10.14	76.32±12.62	4.59±9.23*	10.78±2.51	5.79 to 15.77	<0.01
		Active	45		87.10±11.14	15.38±10.31*			
PP	Sleep efficacy	Placebo	37	72.85±9.55	78.49±11.70	5.63±9.85*	12.12±2.16	7.80 to 16.43	<0.01
		Active	37		90.61±6.02	17.75±9.38*			
ITT	Sleep induction	Placebo	45	95.77±59.78	96.06±72.27	0.29±56.13	45.83±12.74	20.52 to 71.15	<0.01
		Active	45		50.22±45.62	45.54±10.11*			
PP	Sleep induction	Placebo	37	99.15±62.42	99.15±77.48	0.02±62.00	53.90±14.65	24.67 to 83.12	<0.01
		Active	37		45.25±44.14	53.90±71.94*			

ITT=intention to treat analysis; PP=per-protocol analysis; CBD=cannabidiol; SD=standard deviation; S.E.=standard error; CI=confidence interval
* Significant

Table 6. Sleep effectiveness from the Sleep Quality Questionnaire

Analysis	Variables	Group	n	Baseline mean±SD	2 weeks mean±SD	Mean change (within group)	CBD versus placebo group		
							Mean difference (±S.E.)	95% CI	p-value
ITT	PSQI	Placebo	45	13.76±2.63	13.43±2.46	−0.32±1.85	6.52±0.68	5.14 to 7.89	<0.01
		Active	45		6.91±3.92	−6.84±4.11*			
PP	PSQI	Placebo	37	13.97±2.45	13.60±2.30	−0.36±1.96	7.28±0.64	5.97 to 8.60	<0.01
		Active	37		6.31±3.27	−7.65±3.82*			
ITT	ESS	Placebo	45	12.6±4.95	10.77±5.23	−1.82±4.80*	4.15±1.03	2.09 to 6.20	<0.01
		Active	45		6.62±4.55	−5.97±5.61*			
PP	ESS	Placebo	37	12.89±5.12	10.40±5.49	−2.48±5.18*	4.19±1.19	1.80 to 6.57	<0.01
		Active	37		6.21±4.79	−6.67±5.64*			

ITT=intention to treat analysis; PP=per-protocol analysis; PSQI=Pittsburgh sleep quality index; ESS=Epworth sleepiness scale; CBD=cannabidiol; SD=standard deviation; S.E.=standard error; CI=confidence interval
* Significant

Discussion

The present study investigated the efficacy of CBD treatment through the sublingual route to treat chronic insomnia in adults and found a longer sleep duration (PSG-TST, ACT-TST), faster asleep (PSG-SOL, ACT-SOL), decreased waking times after falling asleep (PSG-Arousal Index), and time to wake after falling asleep (PSG-WASO) than placebo. Moreover, improved PSQI and quality-of-life, and decreased daytime sleepiness were revealed. The patients did not experience any adverse side effects upon 12-week CBD treatment. These findings could aid in understanding the effects of CBD on the sleep cycle with the possibility of better treatment for insomnia. These findings could aid in understanding the effects of CBD on the sleep cycle with the possibility for insomnia.

The potential mechanisms through which CBD could address chronic insomnia are diverse, encompassing the modulation of factors related to sleep regulation and beta-amyloid (Aβ) accumulation. Prior studies have consistently demonstrated a connection between elevated cerebrospinal fluid (CSF) Aβ levels and insomnia[25], particularly associated with traits such as poor sleep quality[26]. Sleep disruptions, including insomnia, have been linked to increased Aβ accumulation[27]. Research indicates that longer sleep duration is associated with reduced amyloid levels, suggesting that interventions promoting extended sleep may contribute to lowering Aβ accumulation and potentially delaying cognitive dysfunction onset[27]. CBD plays a pivotal role by restoring the functionality of key proteins involved in mitigating Aβ plaque accumulation[28]. Furthermore, CBD's anti-inflammatory effects are noteworthy[8], as chronic inflammation is tied to heightened Aβ

production[29]. This reduction in inflammation by CBD may indirectly downregulate Aβ production[28]. Considering its impact on sleep-related traits and factors contributing to Aβ accumulation, CBD emerges as a potential adjuvant treatment for chronic insomnia. The multifaceted effects of CBD, including its modulation of sleep patterns and its influence on serotonin receptors (5-HT1A)[8] and GABA receptors[8], position it as a promising candidate for managing chronic insomnia by improving mood and sleep quality through these varied pathways.

Although Food and Drug Administration (FDA)-approved CBD is unavailable in some countries due to the legal and marketing issues at the current time, access to medical cannabis is on a gradual increase globally and may become the substitute for expensive sleeping pills in the future[30]. In addition, users of sleeping pills are becoming more aware of the long-term use of sleeping pills, benzodiazepines, increases the risk of dementia[31], causing these patients to look for alternatives to help with sleep. One study found that participants decreased their dosage of sleeping pills when treated with medical marijuana[32].

PSG has been rarely applied to the study of testing of CBD on sleep efficacy, except for the study on sleeping pills[33]. Previously, preclinical and clinical studies have concluded that CBD may contribute to sleep cycle improvement and not affect sleep architecture such that Monti found that a single high dose CBD helped rats fall asleep faster[34]. In addition, Carlini et al. and Cunha et al. have reported that short-term CBD administration improves sleep quality[35,36]. The protocol in the present study[19] had a longer period using CBD effects on sleep than the previously mentioned study[34-36]. The mean half-life for sublingual CBD in the multiple-dose study was 68.4 hours or 2.85 days[37]. Concerning the carryover effect, the present study had an adequate washout period of more than 5 half-lives[24] for CBD to be eliminated, or two weeks. To the author's knowledge, no studies addressed the effects of continuously sublingual CBD on sleep disorders via reliable instruments like type 1 PSG.

Chagas et al. in 2013 found that CBD prolongs TST in rats[38]. Sleep duration is extremely critical, and the National Sleep Foundation recommends that adults should have a TST of more than 6.5 hours per day[39]. Therefore, an ideal sleeping pill should be able to extend the TST[5]. However, no studies have previously reported the TST and SE of CBD in humans. In the present study, CBD improved the TST and SE consistent across both instruments, PSG and actigraphy. Sleep induction is the amount of time taken for transition from wakefulness to sleep usually starting from turning off the lights to sleep not more than 30 minutes. SOL is an important measure of individual sleep quality[40]. Saper et al. described the phenomenon of SOL with a flip-flop mechanism, which is caused by changes in internal physiology and the external environment. The transition from waking to complete sleep occurs abruptly with a similar duration of sleep latency[41]. However, the effectiveness of CBD on SOL either in animals or humans using PSG and actigraphy has not been reported. Although 2-week CBD failed to correct sleep problems in a recent study compared to placebo[42], sublingual CBD with optimal dose and longer duration may help to get faster sleep.

In the present study, MCT-CBD-treated subjects had better PSG-WASO and arousal index than the placebo. Therefore, CBD may contribute to improved sleep maintenance, which is the continuation of good sleep. Increasing this value will result in better sleep quality as well[41]. Sleep architecture refers to how sleep patterns change between the different stages of sleep, including non-rapid eye movement (NREM) and REM including deep sleep and waking changes sleep architecture changes resulting in sleep problems[43]. Medication or disease can also cause changes in sleep architecture[40]. A good sleeping pill should not affect sleep architecture[43]. After four weeks of CBD in the present trial, no significant changes in sleep architecture were observed in both light and deep sleep. This corroborates earlier study by Linares et al. that studied the effect of CBD on a sleep program using PSG[44]. Since early data on the effects of CBD on sleep architecture are limited, the present study stresses that CBD can be useful for the short-term treatment of chronic insomnia.

Daytime sleepiness is a result of past quality and sufficiency of sleep. Daytime sleepiness is likely to increase in patients with sleep deprivation[45]. In the present study, subjects were designed to receive CBD two doses, morning with 10 mg and before sleep with 1 mg/kg/dose. The morning dosing was because of a study by Nicholson et al. that found that CBD extract doses below 15 mg reduced daytime sleepiness[46]. The drug was given before bedtime in the present study to enhance sleep efficacy. Daytime sleepiness can be measured with the ESS questionnaire. The present study found that the CBD extract reduced daytime sleepiness.

Sleep quality is an important indicator in sleep disorder[41]. However, few studies have reported the

effects of CBD on PSQI. Improvements in the PSQI from the first four weeks of treatment were observed in the study subjects. The PSQI variables were found to be consistent with PSG and actigraphy measurements, and the sleep quality continued to improve during the three months of CBD intake. Next, studies have found that CBD improves the quality of life in various disease[47]. Further adding to the facts, as measured by the EQ-5D-5L questionnaire, the insomnia patients in the present study had a better quality of life after using CBD for three months. This is consistent with the study of Chagas et al. who reported an increased quality of life in subjects with Parkinson's disease upon CBD treatment[48].

The present study investigated the short-term effects of CBD intake. Gastrointestinal adverse events were most common among participants in the present study, but the symptoms were temporary and disappeared without need of hospitalization. Like the present study, a study has reported that CBD extract increases the incidence of adverse events, but the effects can be tolerated well with no severe effects[49]. In a preceding investigation, individuals who had been consistently administered CBD for a duration of two weeks did not exhibit any indications of a physical withdrawal syndrome upon the sudden cessation of CBD[50]. Thus, the current study revealed that CBD is safe.

The present study has limitations. First, the study had less ethnic diversity, only Thai volunteers. Second, this was a single-center study such that the number of patients might not be sufficient to truly describe the adverse event and the reliability of results to the fullest. Third, administration of MCT-CBD under the tongue may have had different bioavailability, and droplet size via self-administration may have affected the blood levels of the drug, and the effectiveness of sleep accordingly. Fourth, the study did not assess long-term follow-up, beyond one month after cessation of CBD. And last, the potential impact of confounding factors, particularly the frequency of exercise, should be acknowledged in the context of the present project. Insufficient consideration of exercise habits among participants may introduce a confounding element that could influence the outcomes related to insomnia.

Conclusion

CBD was effective in the treatment of chronic insomnia in the present study. Its sublingual intake increased sleep duration and sleep induction, reduced sleep maintenance, did not change sleep architecture, decreased daytime sleepiness, and improved quality of life. CBD was safe with no serious adverse effects when continuously used for 12 weeks.

What is already known on this topic?

CBD had been investigated to confirm pre-clinical beneficial effects on sleep, but not on humans. A randomized controlled trial on sublingual CBD extract was lacking.

What does this study add?

This phase-II clinical trial aimed to study the efficacy of sublingual CBD and determine an appropriate continuous dose together with any possible short-term complications.

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Conflicts of interest

The authors declare no conflict of interest.

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