



Assessing cognitive behavioral therapy for insomnia in individuals with cannabis use disorder utilizing actigraphy and serum biomarkers: A pilot study^{☆, ☆ ☆}



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ABSTRACT

Objective/background: This pilot study aims to assess the effect of Cognitive Behavioral Therapy for insomnia (CBTi) in individuals with cannabis use disorder and insomnia. It also aims to investigate the effect of CBTi on levels of serum inflammatory markers in relation to insomnia symptoms.

Methods/patients: Individuals with cannabis use disorder and insomnia symptoms were recruited over 18 months. Data collected included demographics, self-reported sleep parameters, and cannabis use. Blood samples were drawn to measure IL-2, IL-6, CRP, and cortisol. Participants completed the Insomnia Severity Index questionnaire (ISI) and the Patient Health Questionnaire-4 (PHQ-4), and they were provided with an actigraphy (wrist) device for 1 week before CBTi and a subsequent week after completing the 4 CBTi sessions.

Results: Nineteen participants were enrolled in the study. The mean ISI score decreased from moderately severe insomnia at baseline to no clinically significant insomnia after CBTi with a sustained decrease at 3- and 6-months follow-up. Actigraphy showed a significant decrease in sleep onset latency (SOL) after CBTi. Three months after CBTi, 80% of participants reported a decrease in their cannabis use. There was also a significant and sustained decrease in mean PHQ-4 scores after CBTi. Although only trending towards significance, the levels of three out of four biomarkers (IL-2, IL-6, CRP) were decreased 6 months after CBTi.

Conclusions: CBTi is effective as a short- and long-term treatment of insomnia and comorbid anxiety/depression in individuals who regularly use cannabis. A potential added benefit is a reduction in cannabis consumption and inflammatory serum biomarkers.

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1. Introduction

Sleep disturbances are common in individuals who use cannabis, with poor sleep quality being the most common

complaint in this population [1–3]. Research suggests a bidirectional relationship between disturbed sleep and cannabis use [4]. While many individuals use cannabis as a remedy for insomnia [5], studies have shown that chronic cannabis use is associated with negative self-reported effects on sleep [6]. Early onset of regular cannabis use was found to be associated with increased rates of insomnia [7], with some studies suggesting a rate of insomnia of around one in five in regular cannabis users as compared to one in ten in non-users [8].

Evidence about the effects of cannabis on sleep is mixed [8–10]. A study by Conroy et al. showed that individuals who use cannabis daily had more sleep disturbances as compared to non-daily users

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Abbreviations

ACTH	Adrenocorticotrophic hormone
CBT	Cognitive Behavioral Therapy
CBTi	Cognitive Behavioral Therapy for Insomnia
CRP	C-Reactive Protein
DBAS	Dysfunctional Beliefs and Attitudes about Sleep
ELISA	Enzyme-Linked Immunosorbent Assay
IL-2	Interleukin-2
IL-6	Interleukin-6
IRB	Institutional Review Board
ISI	Insomnia Severity Index
PHQ-4	Patient Health Questionnaire-4
PSG	Polysomnography
SE	Sleep Efficiency
SOL	Sleep Onset Latency
TIB	Time in Bed
TST	Total Sleep Time
WASO	Wake-After-Sleep-Onset

[8]. This suggests that intermittent cannabis use may not increase sleep disturbances [8] and may confer a therapeutic effect when used for a short period [11]. The sleep-enhancing effects of cannabis are however reduced in chronic users compared to naïve or casual users [12–14], since chronic use leads to habituation to the substance's sleep-promoting properties [11]. Cannabis users may find themselves stuck in a vicious cycle of seeking cannabis to improve their sleep, building tolerance to its effects, and consequently increasing their use [11]. Moreover, negative effects on sleep tend to be more prominent during the discontinuation of cannabis, even among individuals exposed to low doses [6]. In a study conducted by Pacek et al. on frequent heavy cannabis users, around half of the participants noted sleep disturbances during periods of abstinence from cannabis [5].

Insomnia is the most common sleep disorder in cannabis users [15]. It is characterized by nocturnal symptoms (difficulties initiating and/or maintaining sleep, or non-restorative sleep) and daytime symptoms (impairment in functioning due to fatigue and lethargy) [16]. Polysomnography (PSG) and actigraphy studies are objective tools to evaluate insomnia by assessing sleep and wake times [17]. Insomnia has also been associated with higher levels of adrenocorticotrophic hormone (ACTH) and cortisol, and its severity has been found to be directly proportional to the levels of cortisol and C-reactive protein (CRP) elevation [18].

Misconceptions and dysfunctional attitudes toward sleep promote insomnia and pave the way for negative emotional responses that in turn impair sleep [19]. Cognitive-behavioral therapy (CBT) is a type of psychotherapy that helps patients identify, challenge, and change negative or unhealthy thought patterns that contribute to negative emotions [19,20]. CBT has been adapted to treat insomnia and is known as cognitive behavioral therapy for insomnia (CBTi) which aims to correct sleep-related disruptive behaviors and restructure maladaptive cognitions that reinforce them [19,21–25]. In order to do so, CBTi encompasses different behavioral components: 1) stimulus control which identifies and tackles bedroom/bedtime conditions that prevent sleep, 2) sleep hygiene which addresses lifestyle habits that impair sleep, 3) sleep restriction which is temporarily used to regain normal sleep drive, and 4) relaxation and other stress reduction techniques which alleviate sleep-related stressors [26]. CBTi is currently recommended as first-line treatment for insomnia [27]. It has demonstrated both short- and long-term efficacy with sustained improvement seen for

6–24 months post-treatment [26]; unlike pharmacological treatment which research has shown that its effect on insomnia is limited to the duration of the pharmacological treatment [28]. CBTi has also been utilized in a special high-risk population, including individuals with alcohol use disorders [29]. Recurrent cannabis users who received CBTi scored higher on the Dysfunctional Beliefs and Attitudes about Sleep (DBAS) scale as compared to healthy adults [5], suggesting that CBTi may be especially useful in challenging such attitudes and beliefs in individuals who use cannabis.

This study aims to use CBTi in individuals with cannabis use disorder and insomnia and to assess its effects on insomnia; self-reported and objective data were collected to evaluate the response to CBTi. It also aims to quantify the severity of insomnia before and after CBTi with actigraphy data and by examining the levels of Interleukin-2 (IL-2), Interleukin-6 (IL-6), cortisol, and CRP before and after the intervention. A secondary aim is to investigate whether CBTi results in a reduction in cannabis use in this population. Follow-up was conducted at 1 month, 3 months, and 6 months.

2. Methods

2.1. Participants and recruitment procedure

This is a pilot study that received approval from the Institutional Review Board (IRB) at our institution (IRB ID: BIO-2017-0471). The authors aimed to recruit participants with cannabis use disorder attending the outpatient clinic at the Psychiatry Department at our institution. A power analysis using an estimated prevalence of insomnia of 25% among patients with cannabis use disorder yielded a margin of error of 10 if 60 patients were recruited.

Participants were recruited over a span of 18 months (June 2018 to January 2020). Patients who presented for treatment of cannabis use disorder and had a complaint of insomnia were asked by the psychiatrist treating them if they were willing to participate in the study. In case of agreement, they were referred to the research fellow and informed consent was obtained. Patients under 18 years of age, those with a known sleep disorder other than insomnia (sleep apnea, narcolepsy, or restless leg syndrome), history of neurological disease including epilepsy/seizures and traumatic brain injury, and concurrent substance use disorder other than cannabis (alcohol, opioids, etc.) were excluded. Recruitment was curtailed due to the COVID-19 pandemic in line with our institutional and public health directives. A total of 19 participants were included in the study; 4 participants were lost to follow-up after CBTi, reducing the sample to 15 participants after CBTi and at 3- and 6-months follow-up.

2.2. Data collected

2.2.1. Demographics

Demographics including past medical history, psychiatric history, history of sleep disorders, current psychotropic drug use, over-the-counter sleep medications, nicotine, and caffeine use were collected.

2.2.2. Self-reported sleep parameters

Self-reported sleep parameters included data about sleep habits, such as napping and self-reported sleep duration. Participants completed the Insomnia Severity Index (ISI) questionnaire. The ISI is a 7-item validated questionnaire, with each item scored from 0 to 4 in order of symptom severity. It is validated in the Arabic speakers [30]. A total score greater than 15 suggests clinically significant insomnia with moderate severity whereas a score greater than 22 suggests severe insomnia [31]. The ISI questionnaire was re-administered after CBTi and at 3-months and 6-months follow-up.

2.2.3. Actigraphy parameters

The Actiwatch Spectrum 2 (Actiwatch Spectrum, Philips, OR) is an accelerometer device placed on the participant's wrist and used to monitor their sleep activity. It is a valid tool in detecting insomnia and studying sleep parameters by integrating movement frequency and intensity into a single measurement as well as detecting the levels of incoming light and storing its data [32–35]. Activity and light data are then imported to the Philips Actiware 6 software on the computer which generates an estimated sleep/wake pattern illustrated by an actogram representing the days of recording and a “clinician's report” which summarizes the calculated sleep parameters. The average Total Sleep Time (TST, sum of all sleep intervals between sleep onset and sleep end), the average Time in Bed (TIB, time between lights being turned off and sleep ending), the Sleep Onset Latency (SOL, interval between lights being turned off and sleep starting), the average Wake-After-Sleep-Onset (WASO, sum of all wake intervals between sleep onset and sleep end) and Sleep Efficiency (SE, the ratio of TST to TIB multiplied by 100) are among the parameters typically assessed [36]. Participants were provided with an Actiwatch for one week prior to starting CBTi and were instructed to mark the time upon which they get into or out of bed by pressing the Actiwatch. After two weeks, at the end of the fourth session of CBTi, the Actiwatch was used again for one week. One out of the 19 initial participants reported an operational issue with their Actiwatch, therefore we included pre-CBTi sleep parameters for 18 participants. The actogram was interpreted and scored by the same two members of our team, a board-certified sleep specialist and the senior research fellow both trained in actigraphy.

2.2.4. Cannabis use

The amount and frequency of cannabis use were collected. Self-reported cannabis use was also recorded before the intervention as well as at 3- and 6-months follow-up. Participants were also asked at every follow-up if they thought their change in sleep had an impact on their cannabis use.

2.2.5. Patient Health Questionnaire-4 (PHQ-4)

The Patient Health Questionnaire-4 (PHQ-4) is a brief screening instrument for mood and anxiety [37], and is validated in Arabic [38]. It consists of 4 questions scored from 0 to 3 in order of symptom severity, with the first 2 questions assessing for anxiety and the last 2 for depression. A total score of at least 3 on every 2 sub-questions respectively suggests anxiety and/or depression. A total score of at least 9 on the 4 questions suggests severe anxiety and depression. The PHQ-4 was administered to participants at baseline and then re-administered after CBTi and at 3- and 6-months follow-up.

2.2.6. Biomarkers

Three blood samples (3–5 ml each) were taken from each participant; before CBTi, after CBTi, and at 6 months. The blood samples were collected between 10:30 a.m. and 5:30 p.m. and were separated into 2 tubes. The first tube was sent to the chemistry laboratory at our institution for measurement of cortisol and CRP. The second tube was separated immediately by centrifugation and the serum was frozen at -80°C until assayed. An enzyme-linked immunosorbent assay (ELISA) was used to quantify serum levels of IL-2 and IL-6 according to the manufacturer's instructions (Sigma-Aldrich, USA). We selected these four biomarkers since they have been found to play a significant role in the pathophysiology of inflammation in insomnia [39–41].

2.3. Intervention

CBTi is typically delivered over a range of four to eight weekly or biweekly sessions lasting 30–60 min each [42]. In this study, four structured/manualized CBTi sessions were administered to participants after establishing their diagnosis of insomnia. CBTi consists of a systematic approach to insomnia and has been clinically proven to improve sleep. The first session introduced the participant to the entire program and taught them methods to control different stimuli before going to sleep, as well as controlling the sleep experience itself [19,43]. The second session consisted of reviewing the strategies adopted in the first session, discussing factors shared by most people experiencing insomnia, setting realistic expectations for a healthy sleeping habit, and learning relaxation techniques during bedtime [19,43]. The third session consisted of feedback regarding the techniques adopted in the first two sessions, reinforcing sleep/wake times, and teaching participants how to create a personalized sleep-wake schedule [19,43]. The fourth and final session ensured that the participant fully understood the reasons behind their insomnia as well as the techniques needed to maintain a healthy sleeping pattern [19,43]. The participant was also taught to monitor their sleep pattern, recognize problems that might interfere with it, and step in to prevent any potential problems from interfering with their sleep pattern. Finally, the participant was prepared for a possible insomnia relapse and the need for follow-up. The four sessions were delivered in person in a brief course of two sessions per week over two consecutive weeks. We decided on an accelerated shorter course of CBTi to minimize participant dropout (if the course was perceived as lengthy) and to potentially demonstrate that shorter CBTi versions are feasible. The CBTi session were all delivered by two psychologists trained and experienced in CBTi.

2.4. Statistical analysis

Statistical analysis was conducted via SPSS version 26. The significant value of all statistical tests was set at $P \leq 0.05$. Descriptive statistical analysis was first conducted to assess the demographics of participants and the prevalence of insomnia, depression, and anxiety among the sample. Then, mixed models' analysis was conducted to compare ISI, PHQ-4 and biomarkers means at different follow-ups. Given the relatively small sample size, non-parametric tests were used to compare means of sleep parameters before and after CBTi. Scatter plots of relevant results are available as supplementary material.

3. Results

3.1. Demographics

A total of 19 participants were recruited and completed the baseline assessment. Participants were predominantly males (84.2%), young adults, and presenting with a chief complaint of insomnia (79%) (Table 1). All participants were cannabis users, with slightly more than half of them reporting the use of synthetic cannabis (52.6%). About half of the participants reported using over-the-counter sleep medications (42.1%) (Table 1). Detailed information about the characteristics of participants is available in Table 1.

3.2. Self-reported sleep parameters

Prior to CBTi, the mean ISI score for all participants was 15.5, corresponding to clinically significant insomnia of moderate severity (Fig. 1). There was a statistically significant decrease in ISI

Table 1
Baseline demographics (N = 19).

	N (%)
Sex	
Male	16 (84.2)
Female	3 (15.8)
Age	
< 30 years old	9 (47.4)
≥ 30 years old	10 (52.6)
Relationship Status	
Single	15 (78.9)
Married	4 (21.1)
Employment Status	
Student	3 (15.8)
Employed	12 (63.2)
Unemployed	4 (21)
<i>*values of variables below represent participants who endorsed them</i>	
Chief complaint of insomnia	15 (79)
Use of synthetic cannabis	10 (52.6)
Nicotine use	16 (84.2)
Caffeine use	13 (68.4)
Psychiatric history	14 (73.7)
Sleep disorders history	3 (15.8)
Over-the-counter sleep medications	8 (42.1)
Medical history	6 (31.6)

score after CBTi to a mean of 9.9, corresponding to subthreshold insomnia. At 3- and 6-months follow-up, the mean ISI score was 5.3 and 6.7, respectively, both corresponding to no clinically significant insomnia ($P = 0.000$) (Fig. 1). The percentage of participants that reported receiving at least 7 h of sleep per night increased from 52.6% before CBTi to 73.3% and 80% at 3- and 6-months follow-up, respectively (Table 2). In addition, the percentage of participants who reported taking daytime naps decreased from 31.6% before CBTi to 20% at 3 months follow-up. Overall, 80% of participants reported sleep satisfaction after 3 months, with this percentage decreasing to 66.7% at 6 months (Table 2).

3.3. Actigraphy sleep parameters

There was a statistically significant decrease in SOL from 28.6 min before CBTi to 22 min post-CBTi ($P = 0.023$). An increase in sleep efficiency (SE) was noted from 82.2% before CBTi to 83.9% post-CBTi ($P = 0.078$). A decrease in WASO from 39.6 before CBTi to 37.5 times post-CBTi ($P = 0.975$) was noted and TST increased from 6.9 h before CBTi to 7.2 h post-CBTi; however, these findings were not statistically significant ($P = 0.570$) (Table 3).

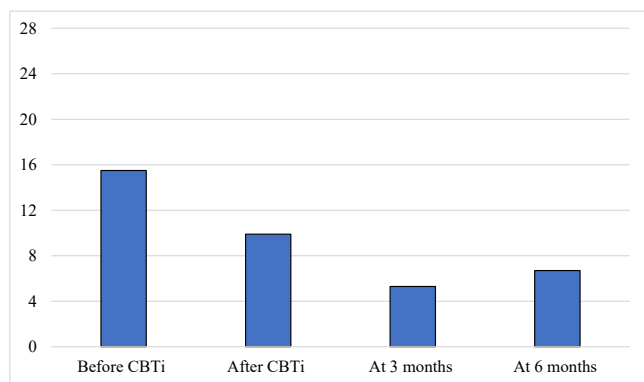


Fig. 1. Mean insomnia severity index (ISI) score of participants. P -value = 0.000 generated using repeated measures in mixed model analysis. N = 19 before CBTi and N = 15 after CBTi and at 3 and 6 months.

Table 2
Self-reported sleep parameters (N (%)).

	Before CBTi	At 3 months	At 6 months
Self-reported sleep			
<7 h	9 (47.4)	4 (26.7)	3 (20)
≥ 7 h	10 (52.6)	11 (73.3)	12 (80)
<i>*values of variables below represent participants who endorsed them</i>			
Naps	6 (31.6)	3 (20)	5 (38.5)
Sleep satisfaction		12 (80)	10 (66.7)
Total N	19	15	15

3.4. Cannabis use

Improvement in cannabis use was assessed at 3- and 6-months follow-up. After 3 months, 80% of participants reported a decrease in their cannabis use compared to baseline. Half (53.3%) of participants maintained their reduction in cannabis use at 6-months follow-up while 26.7% relapsed into prior patterns of use (Fig. 2). At 6-months follow-up, 66% of participants reported a decrease in their cannabis use compared to baseline: 53.3% had improved after 3 months and maintained their improvement while 13.3% reported further improvement in their use (Fig. 2). Almost half of participants (46.6%) reported that they believed that their sleep improvement helped them reduce their cannabis use on both 3- and 6-months follow-up.

3.5. Patient Health Questionnaire-4 scores

The mean total PHQ-4 score pre-CBTi was 7.9, suggesting moderate anxiety and depression symptoms in participants. This score significantly decreased to 4.8 post-CBTi, 4.2 at 3-months follow-up, and 4.1 at 6-months follow-up ($P = 0.000$) (Fig. 3). The mean score for anxiety was 4.6 before CBTi and significantly decreased to 2.8, 2.6, and 2.4 post-CBTi, at 3 months, and at 6 months, respectively ($P = 0.000$) (Fig. 3). The mean score for depression also decreased from 3.3 pre-CBTi to 2, 1.6, and 1.7 post-CBTi, at 3 months, and 6 months respectively ($P = 0.007$) (Fig. 3).

3.6. Biomarkers levels

The mean IL-2 level increased from 86 pg/ml pre-CBTi to 94.1 pg/ml post-CBTi before dropping to 30.9 pg/ml at 6-months follow-up (normal IL-2 range: 11–24 pg/mL) ($P = 0.130$) (Fig. 4a). Similarly, the mean IL-6 level increased from 282.3 before CBTi to 282.7 after CBTi before decreasing to 186.9 at 6-months follow-up (normal IL-6 range: 0.7–3.5 pg/ml) ($P = 0.108$) (Fig. 4a). In addition, the mean CRP level increased from 2.1 before CBTi to 2.2 after CBTi before decreasing to 2 at 6-months follow-up (normal CRP values: <2.5 mg/L) ($P = 0.843$) (Fig. 4b). On the other hand, the mean cortisol level transiently decreased from 9.36 before CBTi to 9 after CBTi before increasing again to 9.4 at 6-months follow-up (normal cortisol range: 5–25 µg/dL before noon and 0–10 µg/dL afternoon) ($P = 0.935$) (Fig. 4b).

4. Discussion

The main purpose of this study was to examine the effects of CBTi on insomnia in patients with cannabis use disorder. It also aims to investigate the effect of CBTi on levels of serum inflammatory markers in relation to insomnia symptoms. A secondary aim was to examine if CBTi results in a reduction in cannabis use in these individuals.

All participants were regular cannabis users with a mean ISI score of 15.5 and most (57.9%) had moderate-to-severe insomnia. This

Table 3
Actigraphy sleep parameters.

	Before CBTi			After CBTi			P-value ^a
	Mean (SD)	Median	IQR	Mean (SD)	Median	IQR	
Time in bed (hours)	8.4 (1.25)	8.5	2.5	8.7 (1.36)	8.9	2	0.496
Total sleep time (hours)	6.9 (0.98)	6.4	1.81	7.2 (1.22)	7.4	1.8	0.57
Sleep onset latency (minutes)	28.6	24.6	25.5	22	15.4	21.2	0.023
Sleep efficiency (%)	82.2	82.6	4.8	83.9	83.9	6.2	0.078
Wake after sleep onset (times)	39.6	38.2	15.4	37.5	36	16.5	0.975
Awake time (minutes)	50.7	48.6	20.5	52.5	50	10	0.46
Total N	18			15			

^a P-values were generated using McNemar's test.

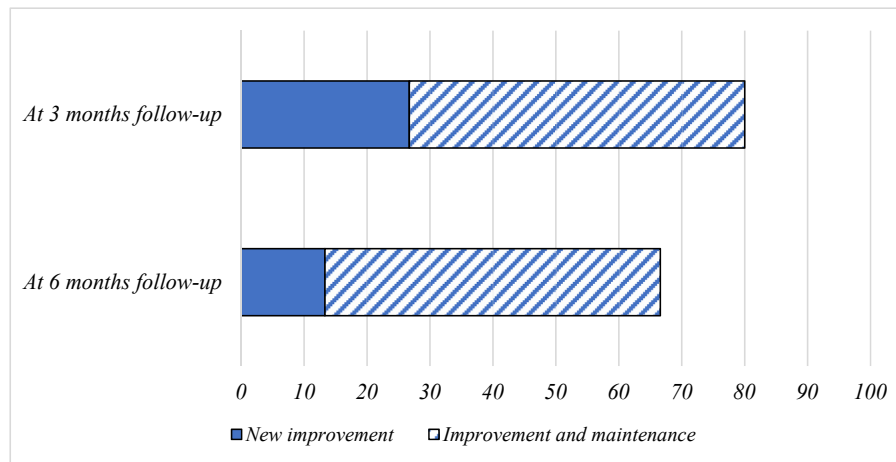


Fig. 2. Participants who reduced their cannabis use (%).
N = 15 at 3 and 6 months.

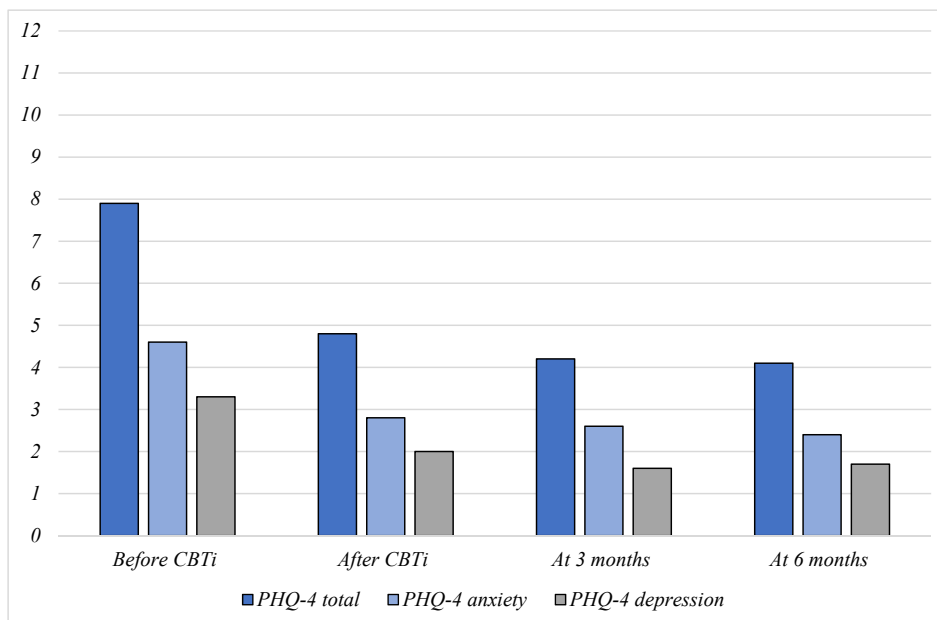


Fig. 3. Mean PHQ-4 total, anxiety and depression scores of participants.
P-values <0.05 generated using repeated measures in mixed model analysis.
N = 19 before CBTi and N = 15 after CBTi and at 3 and 6 months.

prevalence is almost five times higher than the estimated prevalence of insomnia in the generation population (10–15%) [44]. This observation is also consistent with a previous study where young adults with frequent cannabis use had significantly higher rates of

clinical insomnia as compared to non-users [8]. In addition, almost half of the participants (52.6%) were not receiving the normal 7–9 h range of sleep. This is in agreement with the findings of a recent study showing that individuals who use cannabis were significantly

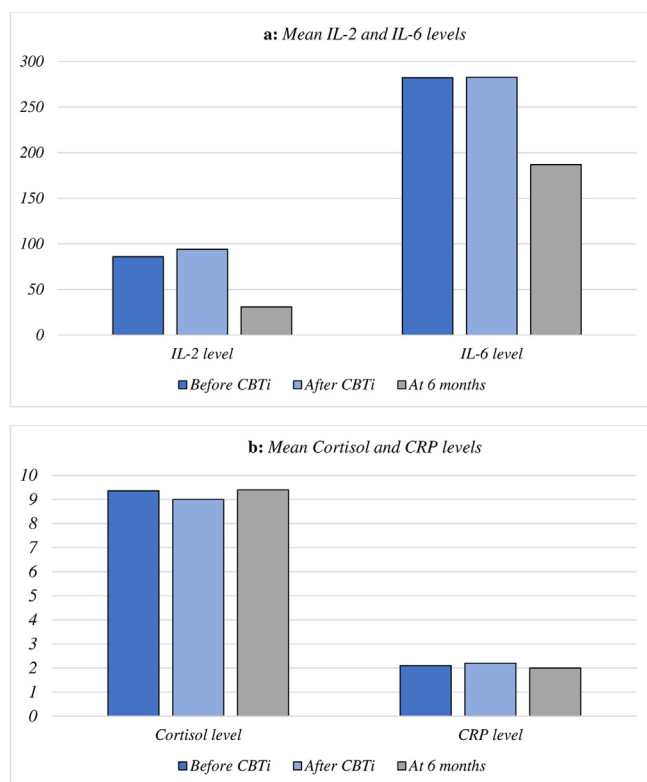


Fig. 4. Mean biomarkers levels of participants. N = 19 before CBTi and N = 15 at 3 and 6 months.

more likely than non-users to get less than 6 h of sleep a night [9]. These findings suggest a bidirectional relationship between these two entities, where insomnia symptoms tend to be significantly associated with both hazardous cannabis use (OR = 1.02, $P = 0.05$) and cannabis use disorder (OR = 1.04, $P < 0.01$) [4].

After undergoing CBTi, only 13.3% of participants remained in the moderate-to-severe insomnia range on the ISI. This improvement is similar to the results of the study by Davidson et al. where ISI scores in the moderate-to-severe range decreased from 87% to 12% following CBTi applied to a general primary care setting [45]. Moreover, the maintained decrease in ISI score and increase in the percentage of participants who reported receiving at least 7 h a night at 3- and 6-months follow-up supports the evidence that CBTi is effective in the treatment of insomnia in this population group. A similar study in individuals with alcohol use disorder showed consistent results, with CBTi significantly improving insomnia with a sustained improvement for up to 6 months post-intervention [29].

The most significant improvement in sleep parameters recorded by actigraphy was the decrease in SOL. This is clinically relevant since the most common subtypes of insomnia include SOL-insomnia [46]. Additionally, although not statistically significant, TST, WASO, and SE improved after CBTi. These objective improvements confirm recent findings of a meta-analysis showing consistent improvements in SOL, WASO, and SE after CBTi [47]. The meta-analysis, however, showed a reduction in TST following CBTi; this decrease was hypothesized to reflect an initial reduction in sleep time driven by sleep restriction therapy taught in CBTi [47]. In addition, our results show that actigraphy was able to record changes in sleep patterns before and after CBTi. This suggests that actigraphy may provide a better assessment of insomnia as compared to polysomnography which was found to be limited in showing deviation from normal values in patients with insomnia

and to sometimes fail to capture self-reported awakenings [17].

Cannabis use decreased in the short term. This trend was maintained on follow-up. Significantly, 46.6% of participants attributed this to the improvement in their sleep. As previously described, a bidirectional relationship between cannabis use and insomnia has been established in the literature [4]. In this study, by treating insomnia using CBTi, cannabis consumption may have trended down in those who use cannabis to self-medicate. One could also hypothesize that CBTi might facilitate the management of cannabis withdrawal symptoms, typically manifesting as sleep disturbances and triggering a relapse [11]. A similar study in veterans with cannabis use disorder showed that CBTi implemented via mobile application was effective in not only improving self-reported sleep efficiency but also decreasing cannabis use [48]. Another study using Brief Behavioral Treatment for Insomnia (BBTI) also resulted in a significant reduction in self-reported insomnia symptoms and cannabis-related problems in trauma-exposed young adults [49]. In individuals with alcohol use disorder CBTi did not have an effect on alcohol use [29,50]. This could partially be attributed to the significant attrition rates in the available studies [29,50], but it could also suggest that the effect of CBTi on relapse prevention might be substance-specific.

Our participants had elevated anxiety and depression scores at baseline, as per PHQ-4 scores. Poor sleep is recognized as a factor in the development of anxiety and depressive symptoms [51]. The observed decrease in anxiety scores post-CBTi is consistent with the previously demonstrated effect of CBTi on anxiety comorbid with insomnia [52]. Similarly, the decrease in depression scores post-CBTi highlights the potential of CBTi in treating concomitant depression [53]. It is hypothesized that the improvement in insomnia post-CBTi may improve depressive symptoms [53].

Participants had elevated mean IL-2 and IL-6 levels at baseline, due to insomnia being a pro-inflammatory condition [18]. Although only trending towards significance, these levels dropped at 6-months follow-up. Mean CRP level was and remained within the normal range throughout the study, with a modest drop at 6-months follow-up. As for cortisol, the mean level was consistently within the normal range and only transiently decreased post-CBTi. Inconsistency in the timing of blood sampling could have affected cortisol levels. A more comprehensive sampling in a larger pool of participants, including other inflammatory markers such as ACTH [18], would overcome this limitation in future studies.

At the time of the 6-months follow-up, our population was going through very challenging times due to the unfortunate serious events that affected the country (Lebanon). The fact that the participants maintained improvement in insomnia, mood, and anxiety during these difficult times further supports the efficacy of CBTi on both sleep and mental health.

This study has several limitations. First, it is a pilot study with a small sample size, which poses a limit on the level of evidence and reduces the power of the statistical analysis. The sample consisted of patients presenting to the clinic seeking help for insomnia and/or cannabis use, conferring a selection bias. CBTi was administered as four sessions over two weeks while a standard course is usually spread over a longer period of one to two months in order to provide adequate time for trial, identification of barriers, and subsequent problem-solving to maximize compliance. The administration of a brief version of CBTi and the choice of selected biomarkers and the inconsistency of timing of blood sampling may have prevented the observation of clear trends in the evolution of biomarker levels. The PHQ-4 used in our study, is another limitation since it is a screening rather than a diagnostic tool which can help the investigators infer that the participant maybe depressed and refer them to further investigation. The brevity and ease of administration of the PHQ-4 was a factor in adopting it for this

study. In follow-up larger studies we will consider using a more robust questionnaire for mood and anxiety.

The study did not account for some variables that might have affected the observed results, including: actigraphy interpretation bias, the effects of the COVID-19 pandemic on mental health outcomes, and the occurrence of a severe economic/political crisis in Lebanon and the catastrophic August 2020 Beirut port explosion. In follow-up studies, building on these findings and expertise gained, we aim to recruit a larger sample size and more consistently assess biomarkers and potentially add a control group. Incorporating drug testing (urine toxicology) will also help objectively evaluate cannabis use patterns.

5. Conclusions

This study demonstrates that CBTi can be effective in the treatment of insomnia in individuals who regularly use cannabis. Potentially, this intervention may be helpful in decreasing cannabis use and improving symptoms of anxiety and depression. These benefits were observed on both short- and long-term follow-up. CBTi is a safe, effective, and economically feasible intervention; implementing it in specialized clinical settings or primary care settings would be cost-effective and feasible. A more in-depth study, over a longer period, with the use of a time- and attention-matched control is recommended as the next step in studying this phenomenon.

Availability of data and material

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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CRediT authorship contribution statement

Luna Geagea: Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. **Pia Maria Ghanimé:** Data curation, Formal analysis, Project administration, Writing – original draft, Writing – review & editing. **Samer El Hayek:** Formal analysis, Investigation, Writing – review & editing. **Firas Kobeissy:** Funding acquisition, Methodology, Supervision, Writing – original draft. **Hani Tamim:** Formal analysis, Funding acquisition, Methodology, Supervision, Visualization, Writing – review & editing. **Martine Elbejjani:** Formal analysis, Funding acquisition, Investigation, Methodology, Validation, Visualization. **Farid Talih:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.sleep.2022.09.017>.

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