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RESEARCH ARTICLE

Medicinal cannabis improves sleep in adults with insomnia: a randomised double-blind placebo-controlled crossover study

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Summary

Insomnia or difficulty falling and or staying asleep is experienced by up to 30% of the general population. This randomised crossover double-blind placebo-controlled 6-week trial aimed to assess the tolerability and effectiveness of the Entoura-10:15 medicinal cannabis oil on sleep in adults with insomnia. A total of 29 participants with self-reported clinical insomnia completed the crossover trial. Participants were randomly allocated to receive placebo or active oil containing 10 mg/ml tetrahydrocannabinol (THC) and 15 mg/ml cannabidiol (CBD) over 2-weeks titrated 0.2–1.5 ml/day, followed by a 1-week wash-out period before crossover. Tolerability was assessed by daily diary. Effectiveness was measured by saliva midnight melatonin levels, validated questionnaires, i.e., the Insomnia Severity Index, and the Fitbit activity/sleep wrist tracker. Entoura-10:15 medicinal cannabis oil was generally well tolerated, and was effective in improving sleep, whereby 60% of participants no longer classified as clinical insomniacs at the end of the 2-week intervention period. Midnight melatonin levels significantly improved in the active group by 30% compared to a 20% decline in the placebo group ($p = 0.035$). Medicinal cannabis oil improved both time and quality of sleep, in particular light sleep increased by 21 min/night compared to placebo ($p = 0.041$). The quality of sleep improved overall by up to 80% in the active group ($p_{Phase2} = 0.003$), including higher daily functioning ($p = 0.032$). Observed effects were more pronounced in Phase 2 due to the period effect and loss of blinding. Entoura-10:15 medicinal cannabis oil was well tolerated and effective in improving sleep in adults with insomnia.

KEYWORDS
circadian rhythm, insomnia, medicinal cannabis, melatonin, sleep

1 | INTRODUCTION

Insomnia is a disorder characterised by a difficulty to fall asleep or stay asleep, even if the opportunity presents itself, such as lying in bed awake. Insomnia is a common sleep problem affecting 10%–30% of adults and is shown to increase with age and presence of comorbidities (Bhaskar et al., 2016; Patel et al., 2018; SleepFoundation, 2021). Insomnia can have a significant impact on one's daily functioning, energy levels, concentration, mood, and physical well-being (SleepFoundation, 2021).

Medicinal cannabis known to be helpful in relieving pain has shown promise in alleviating sleep dysfunction, as summarised in a recent systematic review involving 41 clinical studies that investigated

the effect of medicinal cannabis on sleep as a secondary outcome measure (Kuhathasan et al., 2019).

The cannabis plant produces ~100 cannabinoids (CBs) and a further 400 non-CB chemicals. With the two main CBs with therapeutic benefits being delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) (Lafaye et al., 2017). Sleep laboratory studies suggest THC as having a sedative effect, and low-dose CBD an activating effect (Babson et al., 2017; Russo et al., 2007). However, higher doses of CBD exhibit more sedative effects, and as CBD is non-psychoactive in contrast to THC, a lower THC:CBD ratio (or higher CBD:THC ratio) is recommended to treat insomnia (Babson et al., 2017, Cannasouth_NZ, Carlini & Cunha, 1981).

The CBs interact with the endocannabinoid system, which consists of a series of neuromodulator lipids and receptors, e.g., CB_1 and CB_2 receptors, located throughout the brain, as well as the central and peripheral nervous system. Expression of CB_1 and CB_2 receptors is regulated in a circadian/diurnal light–dark cycle manner, whereby expression and effectiveness of CB intake is higher at night-time (Vaughn et al., 2010).

In the systematic review on the effect of cannabis on sleep (Kuhathasan et al., 2019), nearly half of the trials ($n = 18/41$) tested THC-only medicinal cannabis, with dosages between 2 to 25 mg/day, nine trials tested THC:CBD (mainly 1:1) combination products of medicinal cannabis, and 14 trials used various products including smoked cannabis (Kuhathasan et al., 2019). With three-quarters of the included trials reporting significant improvements in sleep, the review concluded that cannabis-derived compounds have anxiolytic and somnolent properties, with minimal side-effects, in contrast to many pharmaceutical sleep medications (Kuhathasan et al., 2019).

Encouraged by these promising results evident in trials with sleep as a secondary outcome measure, the review called for randomised placebo-controlled trials designed to investigate the effects of CBs on sleep as a primary outcome measure for sleep disorders.

We are aware of a recent Australian randomised double-blind placebo-controlled crossover study involving 24 participants that found that medicinal cannabis for 2 weeks was significantly effective in improving sleep (Walsh et al., 2021). The study tested a combination medicinal cannabis products and assessed sleep by the Insomnia Severity Index (ISI) as the primary outcome measure (Morin et al., 2011).

Most trials investigating the effect of cannabis on sleep relied on questionnaires, namely the ISI, Stanford Sleepiness Scale, Pittsburgh Sleepiness Scale, and Brief Fatigue Inventory (Buysse et al., 1989; Hoddes et al., 1972; Mendoza et al., 1999; Morin et al., 2011); however, more objective measures are needed.

In addition, midnight melatonin levels have been found to be a useful physiological tool to assess sleep quality objectively. Melatonin is synthesised in the pineal gland and enhanced by darkness and inhibited by light. Increased melatonin levels promote sleep by binding to melatonin receptors in the suprachiasmatic nucleus of the hypothalamus (Srinivasan et al., 2009; Tordjman et al., 2017).

A study by Riemann et al. (2002) assessing midnight melatonin levels in adults with insomnia compared to controls, demonstrated that melatonin levels were significantly lower in insomniacs compared to controls (insomniacs: mean [SD] 58 [20] pg/ml versus controls: mean [SD] 90 [20] pg/ml).

Furthermore, sleep duration and pattern can be assessed with an activity wrist monitor including a sleep-staging feature, that is, the Fitbit. The Fitbit introduced its sleep-staging feature in 2017, which has since been incorporated into a number of models, including the one used in this trial. The sleep-staging algorithm relies on a combined body movement, heart and respiratory rate, and its accuracy has been tested against polysomnography in a number of studies (Cook et al., 2019; de Zambotti et al., 2018; Haghayegh et al., 2019). A systematic review and meta-analysis considered the Fitbit wrist activity tracker with the sleep feature as a reliable alternative for assessing gross sleep pattern, while also being more practical than a sleep laboratory in our study setting (Haghayegh et al., 2019).

As there is currently a dearth of clinical randomised controlled trials investigating the effect of CBs on sleep as a primary outcome measure, our study aimed to fill this gap.

Our double-blind placebo-controlled 6-week crossover trial assessed the tolerability and effectiveness of a medicinal cannabis oil containing THC:CBD (10:15) on sleep in adults with insomnia, using a combination of subjective and objective measures, including questionnaires, the Fitbit sleep tracker, and – to our knowledge for the first time – midnight saliva melatonin levels.

2 | SUBJECTS AND METHODS

2.1 | Aims, objectives and hypotheses

This trial aimed to assess the tolerability and effectiveness of a medicinal cannabis oil on sleep in adults with insomnia. Effectiveness was primarily assessed by midnight melatonin levels and the ISI. This trial tested the null hypothesis whether medicinal cannabis taken daily for 2 weeks does not influence sleep.

2.2 | Trial design and participants

The randomised crossover double-blind placebo-controlled study of 6 weeks duration was conducted between May 2020 and May 2021 at the National Institute of Integrative Medicine (NIIM) in Melbourne, Australia. Participants were recruited through the NIIM website, newsletter, flyers, Facebook, and public lectures in Melbourne.

The study was approved by the National Health and Medical Research Council (NHMRC) endorsed NIIM Human Research Ethics Committee and acknowledged under Clinical Trial Notification by the Australian Therapeutic Goods Administration (TGA). Participating patients provided written informed consent. The study is registered on the Australian New Zealand Clinical Trial Registry (ACTRN12620000220965).

2.3 | Screening and inclusion criteria

Adults aged 25–75 years with self-reported clinical insomnia, defined as difficulty falling asleep, waking up often during the night, and/or

having trouble going back to sleep, were screened for eligibility using the validated ISI questionnaire (Morin et al., 2011).

The lower age limit of 25 years was set based on general medicinal cannabis prescribing principles, where it is recommended to apply a risk-based approach to the use of THC in developing brains. There is conflicting evidence available on the potential adverse effect on neurocognition and the structural function on the adolescent brain. As further studies are needed in this area it was decided to exclude children, adolescents, and young adults from the study (National Institute on Drug Abuse [NIDA], 2021).

The ISI consists of seven questions on a 5-point Likert scale, with a maximum score of 28. A point score of 15–28 is regarded as clinical insomnia, and a point score of 8–14 as subthreshold insomnia. For this trial, we included adults with self-reported clinical insomnia, who scored >14 points on the ISI.

We excluded adults diagnosed with cancer, unstable cardiac disease, psychotic disorder, schizophrenia, manic episode, seizure disorder, glaucoma, urinary retention, or pregnancy. Furthermore, shift-workers were not eligible, as well as those on antidepressants including tricyclic antidepressant, monoamine oxidase inhibitors, or benzodiazepines were also excluded.

Participants were required to avoid taking any other sleep remedies both natural and pharmaceuticals and were willing not to drive a vehicle during the 6 weeks of the study.

2.4 | Randomisation, allocation and blinding

Consenting eligible participants were randomly allocated to the active medicinal cannabis oil or placebo group using a computer-generated permuted random number table provided by an independent researcher not involved in recruitment and data collection. Allocation of active and placebo medication was reversed after crossover.

Active and placebo oils were packaged offsite in identical containers. Participants, as well as investigators, research assistants and the authorised prescribing doctor were blinded to the group allocation. Blinding success of patients was evaluated by questionnaires after each intervention phase in this crossover trial.

2.5 | Trial medication and procedure

The active cannabis oil contained a ratio of THC:CBD (1:1.5) in concentrations of 10 mg/ml of THC and 15 mg/ml of CBD formulated with medium chain triglycerides (MCT) and lesser amounts of other CBs and naturally occurring terpenes and peppermint flavour, supplied in a 50 ml bottle with a 0.2-ml scaled dropper (supplied by Entoura).

The placebo oil consisted of the MCT carrier oil with peppermint flavour to assist with blinding and was supplied in opaque identical bottles, with a 0.2-ml scaled dropper (supplied by Entoura).

The trial product met the 'Therapeutic Goods Standard for Medicinal Cannabis Order 2017, TGO93' (TGA, 2017).

Participants were randomly allocated to receive active or placebo oil over 2 weeks. In each intervention period, participants were instructed to take the trial oil in the evening with food, and to titrate up in 0.1 ml (1 mg THC/1.5 mg CBD) increments each day, starting with 0.2 ml on day 1 (2 mg THC/3 mg CBD), to a maximum of 1.5 ml (15 mg THC/22.5 mg CBD). Titration was halted if side-effects were greater than benefits.

This titration scheme, low starting dose and small incremental daily titration up to a maximum tolerable dose, was based on recommendation of clinical practice.

The medicinal cannabis was available to trial participants by prescription by an authorised prescribing doctor and dispensed by the Australian Medicinal Cannabis Service Pty Ltd, My Compounding Pharmacy, Australia. The authorised prescribing doctor monitored the tolerability, dosing, and compliance of trial medication of all trial participants with the assistance of the research team.

2.6 | Study timeline

The 6-week study consisted of a 1-week run-in period, a 2-week intervention period (Phase 1), followed by a 1-week wash-out period, and a second 2-week intervention period after crossover (Phase 2). Assessments were taken at four time-points: at the start and completion of each intervention phase.

Specifically, baseline-1 measurements were taken after the 1-week run-in period, and baseline-2 measurements were taken after the 1-week wash-out period, respectively.

2.7 | Assessments

Primary outcome measures included saliva midnight melatonin levels, and insomnia symptoms as assessed by the ISI questionnaire (Morin et al., 2011).

Secondary outcome measures included assessment of sleep patterns using a Fitbit wrist activity/sleep tracker continuously throughout the 6-week trial period. Sleep quality and quality of life were assessed by a series of validated questionnaires, administered before and after each intervention period, as outlined above.

2.7.1 | Melatonin

We used the 'Sleep Profile Saliva Kit' by the NutriPATH, Australia (Test Code 1009), to assess midnight melatonin and cortisol levels. Participants were instructed to collect their midnight saliva between 12:00 a.m. and 2:00 a.m. (around midnight before falling asleep) at each of the four assessment time-points, and then send to the external test laboratory as per instructions.

2.7.2 | Questionnaires

The ISI is a validated questionnaire, assessing global insomnia symptoms on a seven-question 5-point Likert scale. The ISI was used as a screening

tool for eligibility and was administered four times throughout the trial, at baseline, after intervention Phase 1, after wash-out, and after intervention Phase 2. Participants were asked to reflect on either the past 2 weeks for assessments at baseline and each intervention period, or the past week for assessment of the 1-week wash-out phase.

The first three questions on the seven question ISI focus on the type of insomnia problem, that is difficulty falling asleep, staying asleep, and/or waking up too early, with scores from '0 = no problem' to '4 = very severe problem'. For additional information and to improve practicality and reduce subjective interpretation, we added further definitions to the ISI scores for these questions as follows:

For question 1 'difficulty falling asleep', we defined the score from '0=no problem' to '0 = no-problem = <15 min', '1 = mild = 15 min', '2 = moderate = 30 min', '3 = severe = 30 min–1 h', '4 = very severe = >1 h'.

For question 2 'difficulty staying asleep', we defined the score '0 = no problem'; '1 = mild = waking up once during the night', '2 = moderate = waking up twice during the night', '3 = severe = waking up three times during the night', '4 = very severe = waking up more than three times during the night'.

For question 3 'problems waking up too early', we defined the score by hours of sleep in total, with scores of '0 = no problem = ~8 h sleep in total', '1 = mild = <7 h sleep in total', '2 = moderate = <6 h', '3=severe = <5 h', '4 = very severe = <4 h'.

The remaining four questions focused on sleep satisfaction and were used in its original form. Appendix S1 shows the modified ISI.

The Stanford Sleepiness Scale (Hoddes et al., 1972) assesses the level of sleepiness during the day on a scale from 1 to 7, whereby higher scores are related to a higher degree of sleepiness. The total sleepiness score was calculated as the sum of all sleepiness levels × hours, with a maximum score of 84.

The Pittsburgh Sleep Quality Index (Buysse et al., 1989) consists of 10 questions on a 4-point Likert scale (maximum score of 30), assessing the reason behind poor quality of sleep in the last 2 weeks, such as needing to go to the bathroom, or feeling cold, whereby higher scores are associated with greater frequency. Generally, a higher score is associated with poorer quality of sleep.

The Brief Fatigue Inventory (Mendoza et al., 1999) consists of a series of nine questions on a 10-point Likert scale (maximum score of 90), assessing the level of fatigue and its interference with daily activities and functioning. The higher the score the greater the fatigue and its interference.

The Bond-Lader Mood Scale (Bond & Lader, 1974) assesses mood in a series of 17 opposing adjectives at each end of the scale, e.g., alert to drowsy, or happy to sad. The original assessment tool used a visual analogue scale, which we modified to a 10-point Likert scale for practicality.

2.7.3 | Fitbit wrist activity/sleep tracker (FitBit, 2020)

The Fitbit Inspire HR wrist activity tracker with sleep staging was fitted at the start of the trial and was worn continuously throughout the 6-week study period. Night-time sleep pattern associated with heart rate was monitored automatically on the device, uploaded daily to the participant's mobile phone application, and could be connected to an online program, which was accessible to the research team. Sleep pattern included total sleep time, and time (min) in sleep stages of light, deep sleep and rapid eye movement (REM). Weekly average sleep time/night was calculated for comparative analysis. (FitBit, 2020).

2.8 | Tolerability, side effects, titration, and compliance

During the intervention phases, participants were instructed to keep a daily titration and side-effect diary, in which to enter daily dose of trial medication, and any side-effects. Listed side-effects comprised of fatigue, sedation, vertigo, nausea, vomiting, fever, change in appetite, dry mouth, diarrhoea, or other. Any side-effects associated with withdrawal were assessed at the end of the 1-week wash-out period, and 1 week after completion of the study.

2.9 | Blinding

Blinding success was assessed at the end of each intervention phase, whereby participants were asked whether they thought to have been on the active agent or placebo, or whether they were unsure.

2.10 | Sample size

A sample size of 30 participants (15 in each group; per intervention period) was calculated based on the following assumptions:

(a) To detect a difference of 32 pg/ml (SD = 20) in melatonin levels at night-time between the active treatment ($n = 15$) and control ($n = 15$) with >90% power and 95% confidence;

(b) To detect a difference of ISI score of 7 (SD = 5; maximum of 28 points), between the active treatment ($n = 15$) and control ($n = 15$) with >90% power and 95% confidence;

(c) To account for 20% drop-out or non-attendance at all appointments.

2.11 | Statistical analysis

Analyses were performed using IBM Statistical Package for the Social Sciences (SPSS), version 26. Statistical significance was set at $p < 0.05$. 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. Effectiveness of wash-out or presence of carry-over effects from intervention Phase 1 to Phase 2 were assessed by comparison of each participant's baseline measures 2 versus 1.

Descriptive analyses were 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 cross-over trial, we combined data of intervention periods 1 and 2 (Phase 1 + 2) and also analysed each phase individually in secondary analysis. Differences between the groups at the end of each intervention period (Phase) compared to its baseline were analysed by Student's *t* test and factorial repeated-measures analysis of variance for continuous variables and chi-square for categorical variables.

Secondary analysis by intervention period/phase provided insight into whether treatment order may have influenced the outcome.

3 | RESULTS

3.1 | Participants

A total of 76 Caucasian adults with sleep problems were screened for eligibility, 34 fulfilled the inclusion criteria, and were randomly allocated to the active or placebo group for the first intervention phase before crossover. Three of the 34 eligible patients changed their mind regarding participation, resulting in a total of 31 eligible participants to be enrolled. One participant in the active group withdrew during the first intervention phase due to non-serious side-effects, and one participant was lost to follow-up, resulting in a total of 29 participants who completed the trial (Figure 1).

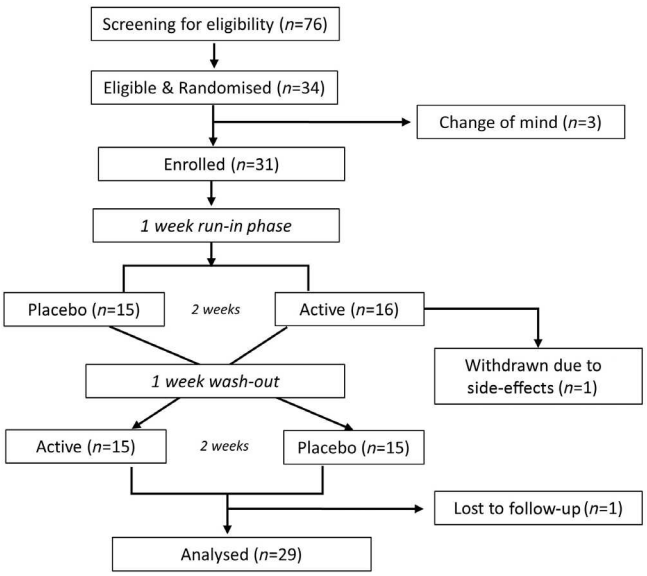

FIGURE 1 Study flow chart

Baseline characteristics included age, gender, body mass index (BMI), and smoking habits. Our trial attracted proportionally more females (76%) than males, with an average age of 47 years, and an average BMI of 25 kg/m^2. None of the participants smoked (Table 1).

The crossover design of the trial allows differences of participant characteristics between the groups in intervention Phase 1 to be controlled for, as each participant acts as their own control.

3.2 | Safety/side-effects

During cannabis oil dosing, four (14%) participants had no side-effects, and 24 (83%) reported non-serious side-effects possibly related to the active medication, such as dry mouth (52%), diarrhoea (27%), nausea (24%), and vertigo (17%). Importantly, all non-serious side-effects other than dry mouth were transient and experienced only on 1 or 2 non-consecutive days (Table 2).

About half of the participants in the active group titrated to the maximum dose of 1.5 ml over 2 weeks, while 20% stopped titration at 0.4–0.6 ml, due to side-effects such as vertigo or dizziness on higher doses. Other side-effects, such as diarrhoea, were transient at various titration levels and may have been triggered by other non-trial related factors (Table 2).

In the active group, more serious adverse effects were reported by two participants, which were resolved overnight after lowering the dose. These included one case of acute onset tachycardia on a dose of 1.4 ml during night 13, which was resolved on day 14 when taking a dose of 0.4 ml, with this participant being sensitive to cannabis oil and reporting an improvement in quality of sleep quality on lower doses.

A second participant reported extreme dizziness on a dose of 0.8 ml, which was resolved when lowering the dose to 0.4 ml (Table 2).

In the placebo group, 67% of participants had no side-effects, while non-serious side-effects were reported by 33% of participants,

TABLE 1 Demographics

Demographic	All ($N = 29$)	Phase 1 active/placebo	Phase 2 (crossover) active/placebo
Age, years, mean (SD, range)	47 (14.3, 25–74)	46.9 (13.3)/48 (15.7)	48 (15.7)/46.9 (13.3)
Gender, male:female, *n*	7:22	1:14/6:8	6:8/1:14
male, *n* (%)	7 (24)	(7)/(43)	
female, *n* (%)	22 (76)	(93)/(57)	
Smoker, *n*	0		
BMI, kg/m^2, mean (SD) Normal, *n* (%) Overweight, *n* (%)	25.5 (5.3) 17 (59) 12 (41)	25.1 (4.8)/25.9 (6) 9 (60)/8 (57) 6 (40)/6 (43)	25.9 (6)/25.1 (4.8)

including dry mouth (10%), diarrhoea (5%), nausea (7%), tingling of tongue and lips (7%), and headache (3%) (Table 2).

No withdrawal effects were reported.

At the conclusion of the trial, all but one participant (96%) found the cannabis oil an acceptable treatment for insomnia, with the majority of participants ($n = 24$, 79%) requesting an ongoing prescription of the active medicinal cannabis oil, including the participant who had tachycardia on a high dose.

Five out of the six participants, who chose not to continue with the cannabis oil, stated other reasons than side-effects for discontinuation of treatment, such as restrictions to work and driving a vehicle.

TABLE 2 Titration and side-effects

	Active group ($n = 29$), *n* (%)	Placebo, *n* (%)
(a) Titration (maximum), ml		
0.4–0.6	6 (20)	0
0.8	3 (10)	1 (3)
1–1.2	4 (14)	3 (10)
1.5 as per protocol	16 (55)	25 (87)
(b) Side-effects		
None	4 (14)	20 (67)
Dry mouth/xerostomia	15 (52)	4 (10)
Vertigo/dizziness	5 (17)	0
Nausea	7 (24)	3 (7)
Diarrhoea	8 (27)	2 (5)
Tachycardia	1 (3)	0
Tingling of tongue and lips	0	2 (7)
Headache	0	1 (3)

3.3 | Primary outcome measures

3.3.1 | Melatonin

Higher levels of melatonin at midnight are associated with better sleep. At baselines, half of the participants in the active and half in the placebo group had melatonin levels within the normal range (10–40 pg/ml), while half of the participants in each group had low levels (<10 pg/ml). Observed differences in mean melatonin levels at baseline were not significantly different between the groups (Table 3).

Analysis of midnight melatonin levels revealed a significant difference between the groups ($n_{active/placebo} = 29/29$), whereby mean melatonin levels in the active group increased by 30% (mean change [SD] 3.9 [13.6] pg/ml), while levels decreased in the placebo group by 20% (mean change [SD] −4.3 [13.9] pg/ml) during the 2-week trial period (mean difference [SE] 8.2 [3.8] pg/ml; $p = 0.035$; Table 3, Figure 2).

Additionally, subgroup analyses revealed significant differences between the active and placebo groups in: (a) the subgroup of participants with normal melatonin levels at baseline ($n_{active/placebo} = 16/13$; mean difference [SE] 15.0 [6.4] pg/ml, $p = 0.028$); and (b) in the second Phase 2 of the trial ($n_{active/placebo} = 13/16$; mean difference [SE] 12.0 [5.5] pg/ml; $p = 0.04$; Table 3, Figure 3).

3.3.2 | Insomnia categories and the ISI

Severity of insomnia was assessed by the ISI, where higher scores are associated with greater severity of insomnia symptoms.

At enrolment 27 of 29 (93%) participants reported moderate-to-severe clinical insomnia (ISI ≥14 points), and only two participants (one in each group: active/placebo = one/one) just fell short of classifying in this category with an ISI of 13 points at enrolment (baseline 1; Table 4).

TABLE 3 Melatonin measures

	Melatonin, pg/ml	Group	*N* (%)	Baseline Mean (SD)	2 weeks Mean (SD)	Within group Mean change (SD)	Active versus placebo between groups Mean difference (SE)	*p*
All		Active	29	11.8 (7.4)	15.2 (15.0)	3.9 (13.6)		
		Placebo	29	15.0 (13.6)	11.6 (9.0)	−4.3 (13.9)	8.2 (3.8)	**0.035**
Subgroup	Normal (10-40)	Active	16 (55)	16.6 (6.5)	22.9 (16.8)	6.8 (17.9)		
		Placebo	13 (45)	19.5 (8.8)	11.3 (10.1)	−8.2 (15.4)	15.0 (6.4)	**0.028**
	Low (<10)	Active	14 (48)	5.64 (2.5)	6.3 (4.1)	0.5 (3.9)		
		Placebo	15 (51)	5.4 (2.3)	9.2 (4.4)	3.3 (5.1)	−2.8 (1.9)	ns
Subgroup	Phase 1	Active	16	10.9 (7.7)	11.3 (9.3)	0.4 (10.5)		
		Placebo	13	18.0 (16.8)	13.8 (12.2)	−6.5 (16.8)	−6.9 (5.2)	ns
	Phase 2	Active	13	12.8 (7.2)	21.5 (20.3)	9.5 (16.5)		
		Placebo	16	11.6 (9.6)	9.7 (5.1)	−2.5 (11.3)	12.0 (5.5)	**0.04**

Abbreviations: ns, not significant; SD, standard deviation; SE, standard error.

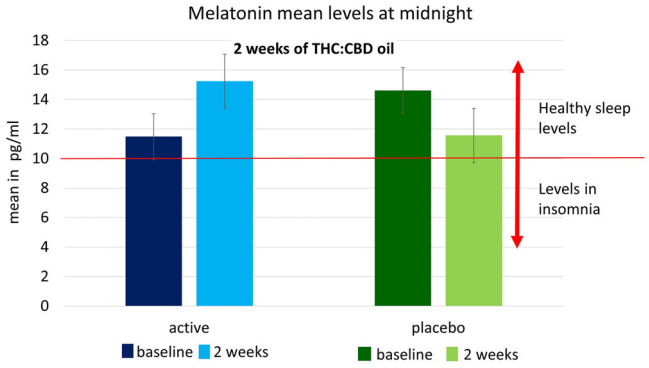

FIGURE 2 Midnight melatonin levels before and after the 2-week intervention. Dark blue = active baseline, light blue = active 2 weeks, dark green = placebo baseline, light green = placebo 2 weeks; red line = threshold level, melatonin <10 pg/ml is considered deficient and associated with insomnia. CBD, cannabidiol; THC, delta-9-tetrahydrocannabinol

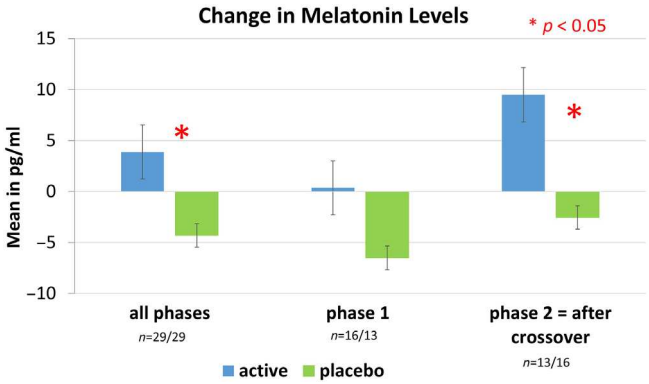

FIGURE 3 Change in melatonin levels overall and by phase. Blue bars (active), green bars (placebo); all phases = Phase 1 + Phase 2

When combining data of both phases, 79%–89% of the participants in the active or placebo groups reported moderate-to-severe clinical insomnia at baseline, while at the end of the trial, 65% of participants no longer classified as clinical insomniacs, which was clinically and statistically significant (4 × 4 chi-square: $p = 0.007$). The improvement was more pronounced in Phase 2 ($p = 0.004$), compared to Phase 1 (not significant; Table 4, Figure 4).

Insomnia symptoms significantly improved over 2 weeks in the active group compared to the placebo group, evident by a greater reduction in total scores on the ISI (Phase 2 mean difference [SE] −5.0 [1.4], $p = 0.002$; borderline significance for both phases; Table 5, Figure 5).

Further analysis of the ISI revealed a trend towards greater sleep improvement in the active group, including falling asleep sooner, waking up less often during the night, and sleeping longer (data not shown).

In addition, the active group was more satisfied with their sleep (borderline significance $p = 0.08$), less distressed, and significantly more satisfied with their daily functioning (improved by 80%; $p = 0.032$), which was also more noticeable by others (Figure 5).

No order-of-treatment effects or carry-over effects were evident, as baseline data for both intervention periods were comparable in primary and secondary outcome measures, without significant differences within and between groups.

3.4 | Secondary outcome measures

3.4.1 | Sleep pattern by Fitbit wrist activity tracker

Sleep pattern assessed by sleep length in minutes and sleep stage (deep, light, REM) was measured by a Fitbit Inspire HR wrist activity tracker with sleep staging. The mean sleep length of each stage/night was assessed weekly, whereby the baseline weeks (week 0) were

TABLE 4 Category of insomnia by Insomnia Sleep Index (ISI)

			Category of insomnia, *n* (%)			
Phase	**Time point**	**Group**	**0 = none**	**1 = subthreshold**	**2 = moderate clinical**	**3 = severe clinical**
All phases	Baseline	Active	0	6 (20)	16 (55)	7 (24)
	2 weeks	Active	5 (17)	14 (48)	6 (21)	4 (14)
	Baseline	Placebo	0	3 (10)	19 (65)	7 (24)
	2 weeks	Placebo	2 (8)	7 (27)	13 (50)	4 (15)
Phase 1	Baseline	Active	0	1 (6)	8 (50)	6 (38)
	2 weeks	Active	0	7 (44)	5 (31)	4 (25)
	Baseline	Placebo	0	1 (7)	10 (71)	3 (21)
	2 weeks	Placebo	2 (14)	2 (14)	5 (36)	3 (21)
Phase 2	Baseline	Active	0	5 (36)	8 (57)	1 (7)
	2 weeks	Active	5 (36)	7 (50)	1 (7)	0
	Baseline	Placebo	0	2 (13)	9 (56)	4 (25)
	2 weeks	Placebo	0	5 (31)	8 (50)	1 (6)

Note: ISI score 0–7 = no clinical insomnia; ISI score 8–14 = subthreshold insomnia; ISI score 15–21 = moderate clinical insomnia; ISI score 22–28 = severe clinical insomnia.

calculated during run-in and wash-out periods, and end measures were taken during the second week of the intervention (week 2). The change in sleep pattern was calculated as the difference between week 2 and week 0 in minutes.

Total sleep improved in the active group, with an average of 30 min/night longer sleep compared to baseline, while sleep time was only 9 min longer per night in the placebo group after 2 weeks of the intervention.

Light sleep improved significantly in the active group, with 21 min longer light sleep per night than at baseline, compared to the placebo group, who had 0.2 min longer light sleep per night after the intervention ($p = 0.04$).

A trend of longer REM sleep was observed in the active group compared to placebo, although not statistically significant (Table 6, Figure 6).

3.4.2 | Sleep quality

We assessed sleep quality by questionnaire, including the Stanford Sleepiness Scale, Pittsburgh Sleepiness Scale, and Brief Fatigue Inventory. Sleep quality and quality of life changed in both groups, albeit differences between the groups were not statistically significant (Table 7).

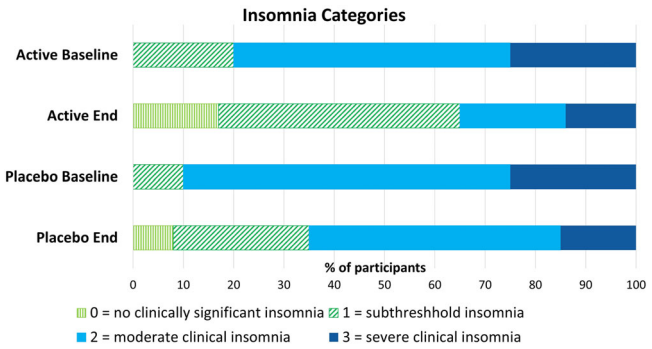

FIGURE 4 Insomnia categories before and after intervention by group. Categories in bar graph: 0 = no clinical insomnia (striped light green), 1 = sub-threshold insomnia (striped dark green), 2 = moderate clinical insomnia (solid light blue), 3 = severe clinical insomnia (solid dark blue). Insomnia categories are based on the Insomnia Severity Index score. We enrolled primarily adults with clinical insomnia (groups 2 and 3). In all, 60% of participants were no longer classified as clinical insomniacs at the end of the trial

3.4.3 | Mood

The Bond-Lader Mood Scale questionnaire revealed that both group's mood tended to improve over time, with the active group feeling significantly more clear-headed ($p = 0.039$) and tranquil ($p = 0.006$) compared to the placebo group after 2 weeks.

3.4.4 | Cortisol levels

No significant differences within group and between groups were observed (data not shown).

3.4.5 | Tolerability

Entoura 10:15 medicinal cannabis oil was generally well tolerated when titrated up by 0.1 ml daily from 0.2 ml to a maximum of 1.5 ml

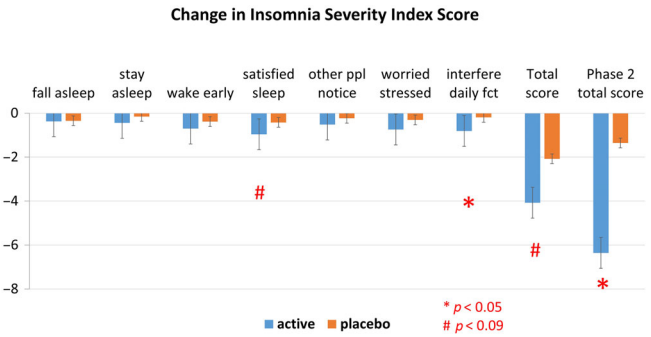

FIGURE 5 Change in severity of insomnia and daily functioning assessed by the Insomnia Severity Index score. Blue bars (baseline), orange bars (2 weeks); statistically significant *$p < 0.05$; borderline significant #$p < 0.09$. fct, functioning; ppl, people

TABLE 5 Change in Insomnia Sleep Index (ISI) score over 2-week intervention period

	TS score	Group	N	Baseline Mean (SD)	2 weeks Mean (SD)	Within group Mean change (SD)	Active versus placebo between groups	
							Mean difference (SE)	p
All		Active	29	17.5 (6.1)	13.2 (6.3)	−4.1 (5.6)		
		Placebo	29	19.0 (4.6)	17.1 (5.5)	−2.1 (5.0)	−2.0 (1.5)	**0.09**
Subgroup	Phase 1	Active	16	20.3 (4.2)	16.8 (4.7)	−2.5 (6.1)		
		Placebo	14	19.1 (4.6)	16.5 (7.1)	−2.9 (6.6)	0.4 (2.4)	ns
	Phase 2	Active	12	15.2 (6.0)	8.8 (5.0)	−6.4 (1.6)		
		Placebo	16	18.9 (4.7)	17.6 (4.0)	−1.4 (3.1)	−5.0 (1.4)	**0.002**

Abbreviations: ns, not significant; SD, standard deviation; SE, standard error; TS, total sleep.

TABLE 6 Sleep pattern by FitBit wrist activity tracker

	Variable, min/night	Group	N	Baseline Mean (SD)	2 weeks Mean (SD	Within group Mean change (SD	Active versus placebo between groups Mean difference (SE	p
All	Total sleep	Active	29	386 (74)	413 (68)	30 (44)		
		Placebo	29	401 (56)	410 (57)	9 (50)	21.1 (12.7)	ns
	Light sleep	Active	29	251 (42)	270 (37)	21 (38)		
		Placebo	29	257 (32)	256 (35)	0.2 (33)	20.6 (9.8)	**0.04**
	REM	Active	29	83 (22)	88 (23)	7.5 (18)		
		Placebo	29	86 (20.7)	88 (20)	3.0 (17)	4.5 (4.8)	ns
	Deep sleep	Active	29	62 (19)	60 (20)	0.7 (13)		
		Placebo	29	62 (18)	63 (16)	3 (8)	−2.1 (3.0)	ns

Abbreviations: ns, not significant; REM, rapid eye movement; SD, standard deviation; SE, standard error.

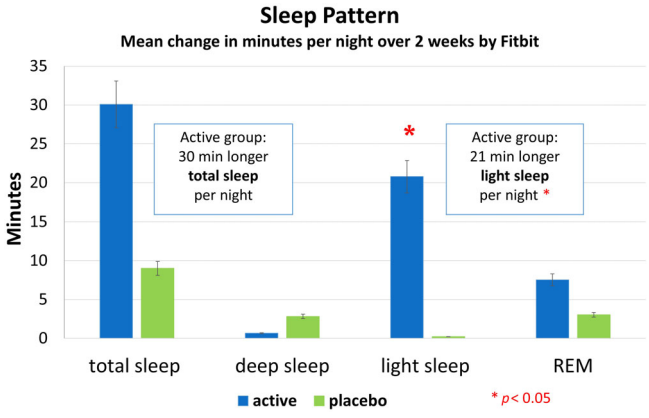

FIGURE 6 Change in sleep pattern over time. Length in min/night and by sleep stage (total, deep, light, rapid eye movement [REM]) assessed by Fitbit wrist activity tracker. Blue bars (active), green bars (placebo). Light sleep significantly improved by 21 min/night in the active group

(15 mg THC/22.5 mg CBD). While half of the participants (55%) reported improvements in sleep with increasing dose to the maximum dose without side-effects, the other half of the participants with higher sensitivity reported less side-effects and better sleep on a lower dose; with 20% of participants dosing up to a maximum of 0.4–0.6 ml (4–6 mg THC/6–9 mg CBD), and 25% to a maximum of 0.8–1.2 ml (8–12 mg THC/12–18 mg CBD).

3.4.6 | Blinding

In Phase 1, blinding was successful, with 40%–50% of the participants in both groups guessing incorrectly or being unsure whether they received the active or the placebo oil.

In Phase 2, after crossover, maintenance of blinding was not achieved, as expected in a crossover trial with CBs (Casarett, 2018), with only three participant (20%) guessing incorrectly or being unsure about their treatment (Table 8).

4 | DISCUSSION

Our trial suggests Entoura 10:15 medicinal cannabis oil to be effective in improving sleep in adults with insomnia within a 2-week intervention period.

Entoura 10:15 medicinal cannabis oil was found to be effective in improving sleep quality and duration, melatonin levels, quality of life, and mood. Midnight melatonin levels significantly improved by 30% in the active group compared to a decrease of 20% in the placebo group ($p = 0.035$). Sleep quality assessed by the ISI improved significantly in the active group compared to placebo ($p = 0.003$, Phase 2), resulting in higher satisfaction and daily functioning in the active group by up to 80% ($p = 0.032$). Sleep duration measured by the Fitbit wrist activity tracker improved in the active group, with significance of longer 'light sleep' by 21 min/night compared to placebo ($p = 0.04$). Furthermore, the active group felt significantly more clear-headed ($p = 0.04$) and more tranquil ($p = 0.006$) after the intervention compared to the placebo group.

Entoura 10:15 medicinal cannabis oil was generally well tolerated, with half of the participants tolerating the prescribed maximum dose of 15 mg THC/22.5 mg CBD, while 20% reported benefits without side-effects on a lower dose of 4–6 mg THC/6–9 mg CBD.

All side-effects, other than dry mouth, such as vertigo and nausea were transient and alleviated at a lower dose. Dry mouth is a common side-effect of cannabis intake, as salivary secretion is inhibited by activation of CB receptors in the submandibular glands (Prestifilippo et al., 2006; Prestifilippo et al., 2009).

At conclusion of the trial, all but one participant (96%) found the cannabis oil an acceptable treatment for insomnia, at their personal tolerable dose, with the majority of participants (79%) requesting an ongoing prescription, including a participant who experienced tachycardia on a high dose. A small number opted not to continue, as the THC containing medicinal cannabis oil was not practical due to restriction around driving.

Our study's findings are in line with a systematic review of 41 studies looking at the effect of cannabis on sleep as a secondary outcome measure, whereby cannabis was found to improve sleep

TABLE 7 Sleep quality by questionnaire

Questionnaire score	Group	*N*	Baseline Mean (SD)	2 weeks Mean (SD)	Within group Mean change (SD)	Active versus placebo between groups Mean difference (SE); *p*	Comment
Stanford Sleepiness Scale	Active	29	61.5 (30.4)	59.5 (35.2)	−6.7 (32.1)		The higher the score the better the sleep (max score = 84). The total score was lower after the intervention in both groups; however, the placebo group trended towards greater loss of sleep quality than the active group (ns).
	Placebo	29	62.1 (40.9)	45.4 (20.7)	−16.7 (36.5)		
Pittsburgh Sleepiness Scale	Active	29	19.1 (5.6)	15.1 (5.9)	−3.5 (6.2)		The lower the score, the better the sleep (max score = 30). Trend towards better sleep quality in both groups (ns).
	Placebo	29	19.2 (5.6)	16.3 (6.7)	−2.7 (6.5)	−0.06 (1.6); ns	
Brief Fatigue Inventory	Active	29	47.1 (16.9)	41.8 (23.6)	−5.8 (19.9)		The higher the score, the greater the fatigue, and the worse interference with quality of life (max score = 90). Trend for improvement in both groups (ns).
	Placebo	29	49.8 (18.2)	42.7 (20.1)	−8.5 (16.8)	2.7 (5.3); ns	

Abbreviations: ns, not significant; SD, standard deviation; SE, standard error.

TABLE 8 Blinding

	Phase 1 – Intervention			Phase 2 – Intervention after crossover		
	Active *N* = 16 *N* (%)	Placebo *N* = 14 *N* (%)	*p*	Active *N* = 13 *N* (%)	Placebo *N* = 16 *N* (%)	*p*
Correct	8 (50)	9 (69)	ns	12 (92)	13 (81)	ns
Incorrect	5 (31)	2 (15)	ns	0 (0)	1 (6)	ns
Unsure	3 (18)	2 (15)	ns	1 (8)	2 (13)	ns

Abbreviation: ns, not significant.

(Kuhathasan et al., 2019). Our findings are also in agreement with a recent similar randomised crossover trial investigating the effect of cannabis (maximum dose: 20 mg THC + 2 mg cannabinol + 1 mg CBD/ml) on sleep as primary outcome measure, whereby medicinal cannabis oil was found to be effective in improving insomnia symptoms and sleep quality after a 2-week trial period in adults with chronic insomnia (Walsh et al., 2021).

Our trial's finding of a significant longer 'light sleep stage' is consistent with the findings in animal studies, whereby CBs have been shown to shorten sleep latency, that is falling asleep more quickly, and therefore lengthening the early phases of the lighter stages of non-REM sleep (Mondino et al., 2019).

A strength of our study was the inclusion of the objective physiological measures in the form of midnight melatonin levels, which strengthened the findings of the subjective self-reported ISI questionnaire.

Our findings of increasing melatonin levels in response to CB ingestion are in line with the literature. A small (eight participants) controlled clinical study conducted in the 1980s that investigated the effect of smoking a 1 g cigarette with 1% of THC on melatonin levels found a significant rise in melatonin after ingestion of THC; with melatonin levels rising four-fold after 20 min, 30-fold after 60 min, and 40-fold after 120 min (Lissoni et al., 1986).

In addition, cell culture studies using rat pineal gland cells found that CBs attenuate melatonin biosynthesis through noradrenaline induction in a dose-dependent matter (Koch et al., 2006).

The melatonin levels, measured in our study at four time-points, at baseline and completion of each intervention phase before and after crossover, also allowed objective comparison of individual baseline levels, and confirmed adequate duration of the wash-out period.

Our study encountered some limitations. The onset of the global Severe Acute Respiratory Syndrome 2019 caused by Corona-Virus-2 (COVID-19) pandemic in March 2020, the increasing restrictions and repeated and lengthy lockdowns in Melbourne, Victoria, Australia during our study conducted between May 2020 and May 2021, hampered recruitment, challenged data collection, caused distress and anxiety, and likely confounded sleep (Berger & Reupert, 2020). Stress may have influenced participants' sleep differently in intervention Phase 1 compared to Phase 2.

In addition, the period effect and subsequent loss of blinding in period Phase 2 would have contributed to the outcome, as knowledge of treatment due to direct comparison would have directly influenced sleep.

5 | CONCLUSIONS

In summary, our short-term trial suggests Entoura 10:15 medicinal cannabis oil, containing THC:CBD 10:15 and lesser amounts of other CBs and naturally occurring terpenes, to be well tolerated and effective in significantly improving sleep quality and duration, midnight melatonin levels, quality of life, and mood within 2-weeks in adults with insomnia.

To our knowledge, our trial is the first to include midnight melatonin levels to assess the effect of medicinal cannabis oil on sleep quality in adults with insomnia, which provided a useful objective outcome measure to be included in any future trials assessing the effectiveness of medicinal cannabis on sleep.

Future research is warranted to assess the effectiveness and tolerability of alternative medicinal cannabis formulas without THC (CBD only), as these might be more acceptable and practical, if found to be effective and tolerable.

Furthermore, long-term studies are needed to assess whether chronic medicinal cannabis intake can restore natural circadian rhythm without the need for ongoing cannabis intake.

AUTHOR CONTRIBUTIONS

Karin Ried and Avni Sali conceptualised the study. Karin Ried acquired funding and oversaw data collection by Tasnuva Tamanna and Sonja Matthews. Karin Ried undertook data analysis and prepared the manuscript with contributions from the co-authors. All authors approved the final version.

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CONFLICT OF INTEREST

None of the authors have potential conflicts of interest to be disclosed.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The study was carried out in accordance with the recommendations of the NHMRC registered Human Research Ethics Committee (HREC) with written informed consent from all subjects in accordance with the Declaration of Helsinki. The protocol was approved by the NIIM HREC.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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