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Cannabidiol treatment in hand osteoarthritis and psoriatic arthritis: a randomized, double-blind placebo-controlled trial

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Abstract

Cannabidiol (CBD) is increasingly used as analgesic medication even though the recent International Association for the Study of Pain presidential task force on cannabis and cannabinoid analgesia found a lack of trials examining CBD for pain management. The present trial examines CBD as add on analgesic therapy in patients with hand osteoarthritis or psoriatic arthritis experiencing moderate pain intensity despite therapy. Using a randomized double-blind, placebo-controlled design, patients received synthetic CBD 20-30mg or placebo daily for 12 weeks. Primary outcome was pain intensity during the last 24 hours (0-100mm); safety outcomes were percentage of patients experiencing adverse events and a characterization of serious adverse events. Explorative outcomes included change in Pittsburgh Sleep Quality Index (PSQI), Hospital Anxiety

and Depression Scale (HADS), Pain Catastrophizing Scale (PCS) and Health Assessment Questionnaire (HAQ-DI).

One hundred and thirty-six patients were randomized 129 were included in the primary analysis. Between group difference in pain intensity at 12 weeks was 0.23mm (95%CI -9.41 to 9.90; p = 0.96). 22% patients receiving CBD and 21% receiving placebo experienced a reduction in pain intensity of more than 30mm. We found neither clinically nor statistically significant effect of CBD for pain intensity in patients with hand osteoarthritis and psoriatic arthritis when compared to placebo. Additionally, no statistically significant effects were found on sleep quality, depression, anxiety, or pain catastrophizing scores.

Keywords: cannabidiol; joint pain; Psoriatic arthritis; Hand Osteoarthritis; Medical Cannabis

1. Introduction

Chronic musculoskeletal pain conditions are a major global burden and rank among the top 11 conditions out of 328 diseases[46] adding to the global burden of pain[6].

Medical cannabis has been suggested as a modulator of joint pain due to possible anti-inflammatory and analgesic properties of phytocannabinoids as shown in animal studies[18,40]. Yet, a systematic review of randomised controlled trials conducted in 2020 by the International Association for the Study of Pain (IASP) presidential task force on cannabis and cannabinoid analgesia found sparse evidence of a beneficial effect in the trials performed to date[19]. This lead to the conclusion that

cannabinoids, based on the current available evidence, could not be recommended for pain management[36].

One notable observation by the IASP Task Force was the lack of high-quality trials examining the analgesic properties of Cannabidiol (CBD) without the addition of Delta-9-Δ-tetrahydrocannabinol (THC)[30].

The mechanisms of action of CBD have not been fully elucidated. CBD could mediate its effects by acting as an antagonist of the 5-HT1A[20,25,48] receptor, an agonist of the Transient receptor potential vanilloid family[33] causing desensitization in a similar fashion to capsaicin and as an Adenosine A2A receptor agonist[35]. CBD is generally well tolerated in clinical trials[43] and considered nonintoxicating[29] though sedation can occur at higher doses[41]. However long-term effects and safety of cannabinoid treatments have not been studied [21].

In a recent metanalysis of 17 pre-clinical trials with different pain models a small yet significant effect was found for CBD standardised mean difference of 1.12 (95% CI 0.84 to 1.40)[40] with greatest effect seen in neuropathic pain models (nerve injury, chemotherapy, and diabetes) and conflicting results in inflammatory pain models (formalin, Freund's adjuvant, and Carrageenan) and osteoarthritis[18].

Van de donk et al. performed a randomized controlled crossover trial[15] exploring the effects of a single dose of cannabis medication (18.8mg CBD, less than 1 mg THC) in patients with fibromyalgia but this combination had no effect on pressure pain threshold or patient reported pain. Similar, Bebee et al. performed a randomized controlled trial[2] exploring the effects of a single dose 400mg CBD in patients admitted to the emergency department for acute low back pain and found no effect on pain intensity two hours after administration when compared with a placebo. Yet despite a paucity of clinical evidence, CBD is currently used for pain conditions as is evident from a

web-based survey of CBD users from 2018 which showed that 62% of respondents reported using CBD for medical conditions with chronic pain and arthritis/joint pain as the main reasons[12].

Thus, at present CBD is being introduced as medicine worldwide with a lack of evidence for effect. This necessitates investigation of CBD including dosing regimens, treatment efficacy in different pain conditions in high quality studies as recently suggested[21].

The aim of this single-centre randomized double-blind placebo-controlled trial was to investigate the analgesic effect and safety of 12-weeks administration of synthetic CBD as an add-on treatment to conventional pain management in patients with hand-osteoarthritis (Hand-OA) and psoriatic arthritis (PsA).

2. Methods

2.1 Design

The trial (NordCAN) was designed as a single-centre, double-blind, randomized and placebo-controlled trial conducted at the Rheumatological Research Unit at the Department of Rheumatology, Aalborg University Hospital, Denmark. The trial was approved by The Danish Human Ethics Committee (N-20170074), the Danish Medicines Agency (2017091784) and the Danish Data Protection Agency (2017-245). The NordCAN project was registered on clinical trials.gov (NTC03693833) and in the European Clinical Trials database (2017-003574-13). The trial was continually monitored by the Good Clinical Practice (GCP) Unit of Aalborg University Hospital, externally audited by the Danish Medicine Agency, and was conducted in accordance with the Helsinki declaration, GCP and Danish regulatory requirements.

2.2 Patients and participants

Patients with PsA or Hand-OA were included between November 2018 and September 2020 after obtaining written informed consent. Inclusion criteria were: Fulfilling the 2006 Classification Criteria for Psoriatic Arthritis (CASPAR)[44] or the 1990 American College of Rheumatology (ACR) criteria[1], pain intensity during the last 24 hours measured by visual analogue scale (VAS) ≥ 30/100 mm at inclusion, age ≥ 18 years and an ability and willingness to give written informed consent and to meet the requirements of the trial protocol. Exclusion criteria included: Concurrent diagnosis of chronic regional pain syndrome or neuropathy, other known disease where exacerbations needed to be treated with systemic corticosteroids (i.e., certain types of inflammatory bowel disease) or patients who have received systemic corticosteroid treatment during the last 3 months, concurrent diagnosis of other inflammatory joint diseases e.g., rheumatoid arthritis or ankylosing spondylitis and patients with gout were excluded if their disease had not been in remission for more than 6 months. Concurrent active malignant disease, planned major surgery during the intervention period or recent major surgery, current or planned pregnancy during the trial period, known allergy or contraindication to CBD treatment, previous addictive behaviour defined as abuse of cannabis, opioids or other recreational or pharmaceutical drugs, severely decreased liver function, kidney function or known chronic heart failure, history of epilepsy or severe cramps were also exclusion criteria.

2.3 Intervention

The active synthetic CBD 10 mg tablet and placebo tablet (containing the same ingredients except CBD) were produced by Glostrup Pharmacy (Glostrup, Denmark).

Patients initially received either oral CBD 10 mg or a placebo tablet once daily with the dose increased to 10 mg twice daily after two weeks. Patients were contacted by the investigator after

four weeks and those not experiencing pain reduction of more than 20 mm on the VAS had their dose increased to 10 mg thrice daily until the end of treatment period. Patients were advised to take the trial medication together with meals to ensure optimal uptake[4] and were also encouraged to keep their usual analgesic regimen. Change in disease modifying anti-rheumatic drug regimen in patients with PsA led to discontinuation from the trial.

2.4 Randomisation procedure and allocation concealment

The randomisation sequence was computer generated by a trial pharmacist from Glostrup Pharmacy, who had no clinical involvement in the trial. Patients who met the eligibility criteria were randomized to receive either CBD or placebo in predefined blocks of 8, 16 and 24. Stratification was based on disease (PsA or Hand-OA) and allocation was concealed from patients and investigators.

2.5 Outcomes measures

The primary outcome was the difference between groups in the change of patient reported pain intensity during the last 24 hours on visual analogue scale (VAS) after 12 weeks of treatment (ΔVAS-pain). This was assessed using a paper based 100 mm VAS accompanied with the text "How much pain have you experienced in the most symptomatic joint during the last 24 hours", with 0 signifying no pain and 100 signifying worst pain imaginable.

Safety outcomes included percentage of patients experiencing adverse events (AE) and a characterization of serious adverse events (SAE).

Explorative outcomes included assessment of anxiety and depression quantified using the Hospital Anxiety and Depression Scale (HADS)[50] providing a score of 0 to 21 for each domain where higher scores equal greater involvement of either anxiety or depression.

Subjective assessment of sleep quality was evaluated using the Pittsburgh Sleep Quality Index (PSQI). Scored ranging from 0 to 21 where 21 indicates severe difficulties in all sleep related areas[8].

Pain-specific catastrophizing was quantified using the Pain catastrophizing scale (PCS) scored from 0 to 52 with 52 indicating the highest levels of catastrophizing[42]. Disability was assessed using the Health Assessment Questionnaire Disability Index (HAQ-DI)[45] scale ranging from 0 to 3 with 3 indicating maximal disability. Pre-treatment expectancy was quantified using the Stanford expectation of treatment scale (SETS)[49] quantifying both positive and negative expectations of treatment on a scale from 0 to 21 were 21 indicates maximal positive or negative expectation.

2.6 Clinical laboratory tests

Blood samples were collected as part of routine laboratory tests performed on patients. Analysis panel included c-reactive protein (CRP), creatinine, and alanine aminotransferase (ALAT).

2.7 Power and sample size considerations

Sample size calculation was performed with the following assumptions: alpha = 0.05, power = 80 % and standard deviations for pain intensity for Hand-OA and PsA at 30 mm. Detecting a difference of 15 mm in a two sample, two tailed t-test would require a sample of 65 patients in each group.

2.8 Statistical analysis

Baseline variables were described for all participants with means and standard deviations (SDs) for or medians and interquartile ranges (IQR's) for continuous variables according to sample distribution. Discrete variables were reported with count and percentages.
Normality of the variable's sample distribution was assessed visually by Q-Q plot.

The efficacy analysis was based on the data from the full-analysis set, that is, the intention-to-treat (ITT) population—including all participants who were randomised, assessed at baseline, and received at least one dose of trial medication.
The safety analysis includes all patients who were randomly assigned to a trial group and have had exposure to the trial drug or placebo.
Sensitivity analysis included stratification based on disease (PsA or Hand-OA). Furthermore, post-hoc analyses were done; A between group comparison of the number of patients achieving more than 30 mm reduction in pain intensity, 30 % reduction in pain intensity, 50% reduction in pain intensity and number needed to treat.

Difference in continuous outcomes between groups were compared using an independent two-sided t-test for normal distributed variables and bootstrap t-test with 10000 replicates for continuous non-normally distributed variables[16]. Additionally, confidence intervals were created using bootstrap for non-normal distributed variables. Discrete variables were compared using a Chi^2 test.
Differences were considered significant with a p-value of < 0.05.

All data management and analyses were carried out using R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1 Subjects

One-hundred-and-fifty-two patients were screened, and 136 patients (59 with PsA and 77 with hand-OA) were randomized to either CBD or placebo. Two participants in the CBD group withdrew due to personal reasons. Two participants in the placebo group withdrew due to side effects: One with gastrointestinal distress and one with an allergic reaction. Two participants in the placebo group underwent surgery unrelated to the trial and withdrew. One participant had rheumatoid arthritis which was misdiagnosed as Hand-OA (Figure 1). For baseline demographics see Table 1. Few patients used opioids as concomitant analgesic medication in both groups 2.8% in the CBD group vs. 3.0% in the placebo group ($p > 0.99$). For concomitant analgesic medicine see Table 2.

When asked which intervention they received, a greater number in the placebo group guessed correctly compared to the CBD group (61 % vs 22 %). The number of patients receiving 20mg at the end of the study was 17 (25%) in the CBD group vs 17 (27.9 %) in the placebo group ($p = 0.866$).

Figure 1: CONSORT diagram

Table 1. Summary of characteristics for patients

Table 2. Concomitant analgesic medicine

3.2 Primary outcome

No statistically significant differences in pain intensity were found between the CBD group and placebo group at 12 weeks for the intention to treat analysis with a mean difference of 0.23 mm (95%CI -9.41 to 9.90; p = 0.96) on a 0-100 mm scale. A statistically significant reduction from baseline in pain intensity was found for both CBD 11.68 mm (95%CI 5.33 to 18.0; p< 0.001) and placebo 11.45 mm (95%CI 0.51 to 1.78; p = 0.001).

A sensitivity analysis based on disease showed similarly effect of CBD for the PsA group (between group difference of 4.48 with 95%CI -17.44 to 8.49; p= 0.49) and Hand-OA 2.94 (95%CI -10.03 to 15.92; p = 0.65).

Fifteen patients (22 %) in the CBD group experienced a reduction in pain intensity of more than 30mm versus 13 patients (21 %) in the placebo group (p > 0.99).

Reduction of pain intensity of more than 30 % was experienced by 27 (40 %) and 24(40 %) in the CBD group and placebo group respectively (p > 0.99). Reduction of more than 50% was experienced by 17 (25 %) and 16 (27 %) in the CBD group and placebo group respectively (p = 0.99).

3.3 Explorative outcomes

The CBD group demonstrated a significant decrease from baseline in the HAQ of 0.13 (95%CI 0.04 to 0.22; p < 0.01) and decrease PCS score of 3.55 (95%CI 1.90 to 5.34 p < 0.001) while the placebo group experienced a reduction in PCS score of 2.48 (95%CI 0.20 to 4.76; p = 0.03). However, no significant group differences between the two groups were found in any of the explorative outcomes (see table 3).

Table 3. Outcomes after 12 weeks

3.4 Adverse events

A total of four SAEs were reported during the 12-week trial period. In the CBD group one participant was diagnosed with ductal carcinoma and one participant with lipotymia requiring observation in the emergency department. In the placebo group one patient experienced an acute shoulder fracture and one patient required observation in the emergency department due to malignant hypertension. None of the SAE's were deemed adverse drug reactions by the trial group. A total of 59 patients (33 in the CBD group, 26 in the placebo group) experienced a total of 119 AEs. Patients in the CBD group experienced more AEs related to the ear-nose-throat region with 8 events vs 0 in the placebo group and AEs related to the skin with 3 events in the CBD group vs 0 in the placebo group (See table 4).

Table 4: Serious adverse events and adverse events

4. Discussion

To our knowledge this trial is the first randomised placebo-controlled trial investigating the effect of pure CBD as an add-on analgesic therapy in patients with joint disease. The main finding was that 12 weeks of CBD treatment did not demonstrate significant clinical analgesic effects in patients with Hand-OA or PsA and pain of at least moderate intensity.

Sensitivity analysis based on number of patients experiencing a reduction of ≥ 30 mm pain intensity

and number of patients experiencing a reduction of pain intensity of ≥ 30 % or ≥ 50 % gave similar results.

These findings are similar to two recent RCT's examining the short term (2 hour follow-up) analgesic effects of a single dose of CBD, were no significant difference between placebo was seen[2,14].

Our results contradict two small previous trials[13,47] investigating CBD as an analgesic therapy. However, in both studies the patients were treated with a mix of CBD and THC (up to 50 %). In a randomized controlled trial, Wade et al., 2003 studied the effect of a CBD rich cannabis extract on pain intensity in 12 patients with painful neurological disorders and a statistically significant decrease in pain intensity in the CBD group compared to placebo, but they did not disclose the amount of THC in the extract and patients were allowed to use THC rich rescue medication. An uncontrolled trial assessed seven patients with kidney transplant receiving 300 mg CBD and reported an analgesic effect in four out of seven patients[13]. The authors did not explain how pain was quantified and the CBD solution used had a CBD to THC ratio of 30:1 which resulted in a THC dose of 10mg which could be intoxicating with psychotropic side effects[28].

4.1 Explorative outcomes

Poor sleep quality, anxiety and depression have previously been linked to clinical pain intensity outcomes[26]. Although CBD is used as a sleep aid the evidence for this claim is currently lacking. The present trial found no difference in PSQI scores comparing the placebo and CBD groups. This is in line with a previous case series of 72 patients (1/3 complained of sleep disorder) were

treatment with 25 mg – 150 mg CBD daily did not improve PSQI scores after 3 months of treatment[39].

Results from preclinical trials suggests that CBD could have antidepressant properties but only a single clinical trial has included a depression score in patients without neurological disease or cannabis abuse disorder and found no difference between CBD and placebo[24]. In this trial we used the HADS to identify signs of depression or anxiety. Patients had low median depression scores at baseline (median 2; IQR 1 , 5) and CBD treatment did not reduce the HADS depression score.

CBD has been extensively examined as an anxiolytic drug[34] and most studies are single dose trials performed during a speaking performance. These show inconsistent efficacy in terms of dose and time of effect[3,27,51]. As with HADS depression patients in the present study had low median anxiety scores at baseline (CBD; 5 IQR 2 , 7 and Placebo 5 IQR 2 , 8) and CBD treatment did not reduce the HADS anxiety score.

Bjelland et al. found the optimal cut-off values to detect psychiatric morbidity cases to be >7 for anxiety and >9 for depression both of which are above the upper limit of baseline IQR values in the CBD group[5]. Further trials with patients with comorbid anxiety and or depression are needed to determine if an anxiolytic or anti-depressive effect exists.

4.2 Adverse events and side effects

In this trial two patients in the CBD group experienced serious adverse events. One patient experienced an episode of lipotymia which was deemed due to an underlying medical condition and one patient was diagnosed with a ductal carcinoma in situ after a few weeks of treatment and hence this was most likely not related to the treatment. Except for one possible case in the placebo group, no participants experienced any obvious allergic reactions. A review of serious adverse events in 18

randomised trials testing pure CBD found the occurrences of SAE's to be low. The highest proportion of SAE's occurred in epilepsy trials with concomitant use of different anti-epileptic drugs and CBD doses greater than 300 mg daily[38]. A review of adverse events in 13 randomised trials found greater odds of decreased appetite, diarrea, sedation and somnolence in participants treated with CBD. When excluding studies with patients with epilepsy only diarrea was found to be a significant side effect with OR 2.61 (1.07 to 4.64) the mean dose in non-epilepsy studies were 900 mg/day[10].

4.3 Pain intensity measurement

Patients of rheumatology outpatient clinics in Denmark register pain intensity at each visit in the nation-wide DANBIO register via the 100mm VAS during the last 24 hours. This was chosen as the primary outcome since patients and clinicians are accustomed with this measure and since our group have consistently used VAS during the last 24 hours in our studies of osteoarthritis[31,32].

4.4 Limitations

Due to lack of trials investigating optimal CBD doses for an analgesic effect, we choose a pragmatic dose of 20-30 mg daily based on recommendations from patient surveys and used similar trials [7,9,23]. This dose could prove insufficient to produce the plasma concentrations required to activate relevant receptors involved in inflammation and nociception[9]. CBD dosage regimes used in trials regarding neurological disease often surpass 1000 mg daily but with a significant number of side-effects[10]. Future high quality double-blind, randomized and placebo-controlled trials are needed to further explore the possible analgesic properties of higher doses of CBD. Furthermore, patients were encouraged to adhere to their usual analgesic regimen during the trial but were not required to keep a diary of daily analgesic use or use of the trial intervention. We found no

association between CBD and serious adverse events, but this trial was insufficiently powered to detect rare adverse events.

We investigated synthetic CBD in a “single ingredient” setting allowing for examination of CBD without the presence of other cannabinoids (including THC), terpenes and flavonoids as these could, in theory modify the therapeutic effect of CBD. This phenomenon has been dubbed the “entourage effect”, which is a proposed synergistic effect [37] between different components of the cannabis plant, but evidence supporting this effect is conflicting[17,22] and clinical trials examining the entourage effect are currently lacking [11]. Still, generalisability of our results with regards to other cannabidiol formulations should be done with consideration.

Strengths of the present trial was the randomized, double blind, placebo-controlled design and the large number of participants which is in accordance with recommendations by the IASP[21].

Conclusion

This is the first large, randomized placebo-controlled trial examining the effect of CBD on pain intensity in patients with chronic pain of at least moderate intensity. The current trial found neither clinically nor statistically significant effect of 20-30 mg/daily CBD for 12 weeks on pain intensity in patients with hand osteoarthritis and psoriatic arthritis when compared to placebo. Additionally, no statistically significant effects were found on sleep quality, signs of depression, anxiety or pain catastrophizing when comparing CBD to placebo. Studies investigating higher doses of CBD and assessing different pain disorders are needed.

Contributors

JV was the primary contributor to the conception and design of the protocol and JV is responsible for drafting of the manuscript. SK, KKP, LD, KSD and LAN contributed to the conception and design of the trial.

SK, KKP, LD, KSD and LAN have all contributed substantially during manuscript revision and approved of the final draft.

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Conflicts of interest statement

All authors report nothing to declare.

Data availability statement

Data is available upon reasonable request from the corresponding author.

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Supplemental video content

A video abstract associated with this article can be found at http://links.lww.com/PAIN/B480.

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Figure 1: CONSORT diagram

Abbreviations: CBD, Cannabidiol

Table 1. Baseline parameters		
	CBD	Placebo
N	70	66
Age, years median [IQR]	62.00 [56.25 to 68.00]	61.50 [53.00 to 70.75]
Women, n (%)	42 (60.0)	46 (70.0)
BMI, (kg/m2) median [IQR]	26.99 [23.86 to 31.16]	26.25 [23.03 to 29.72]
Pack-years, median [IQR]	1 [0 to 15]	0 [0 to 16.50]
PsA, n (%)	31 (44)	28 (42)
Hand-OA, n (%)	39 (56)	38 (58)
Pain VAS mm, median [IQR]	52.00 [40.50, 70.70]	61.00 [43.20, 73.50]
HAQ-DI, median [IQR]	0.62 [0.25, 0.88]	0.88 [0.50, 1.50]
HADS depression, median [IQR]	2 [1, 4]	2.50 [1, 5]
HADS anxiety, median [IQR]	5 [2, 7]	5 [2, 8]
PSQI, median [IQR]	7.00 [5.00, 11.00]	10.00 [6.00, 12.00]
PCS, median [IQR]	16.00 [11.00, 21.00]	15.00 [11.00, 24.75]
Pre-treatment expectancy (SETS)		
Positive expectancy score [IQR]	17.00 [14.25, 18.00]	16.00 [14.00, 19.00]

Negative expectancy score [IQR]	11.00 [9.00, 13.75]	10.00 [8.00, 12.00]
Previous CBD use n (%)	10 (14)	15 (23)
Serology		
CRP mg/l, median [IQR]	2.20 [0.90, 4.90]	2.90 [1.30, 4.30]
Alanine aminotransferase U/l, median [IQR]	22.00 [18.00, 30.00]	25.00 [18.00 to 32.00]
Creatinine, mean umol/l, (SD)	70.16 (13.87)	70.25 (16.71)

Abbreviations: CBD, Cannabidiol; IQR, Interquartile range; BMI, Body mass index; PsA, Psoriatic arthritis; Hand-OA, Hand osteoarthritis; VAS, Visual analogue scale; HAQ-DI, Health assessment questionnaire disability index; PSQI, Pittsburgh sleep quality index; HADS, Hospital anxiety and depression scale; PCS, Pain catastrophizing scale; SETS, Stanford expectations of treatment scale; CRP, C-reactive protein.

Table 2. Concomitant analgesic medicine

	CBD	Placebo
N	70	66
Paracetamol, n (%)	55 (78.6)	47 (71.2)
NSAIDs, n (%)	28 (40.0)	27 (40.9)
Anti-epileptics, n (%)	5 (7.1)	11 (16.7)
Codeine, n (%)	3 (4.3)	2 (3.0)
Tramadol, n (%)	5 (7.1)	8 (12.1)
Opioids, n (%)	2 (2.8)	2 (3,0)
None, n (%)	12 (17.1)	8 (12.1)

Abbreviations: CBD, Cannabidiol; NSAID, Nonsteroidal anti-inflammatory drug

Table 3. Outcomes after 12 weeks				
	CBD	Placebo		
	Change	Change	Between-Group Difference	P Value
Primary outcome				
Pain VAS, mm	11.68 (5.33 to 18.0) †	11.45 (5.01 to 18.15) †	0.23 (-9.41 to 9.90)	0.96
Explorative outcomes				
HAQ-DI	0.13 (0.04 to 0.22) *†	0.10 (-0.02 to 0.21) *	0,03 (-0.11 to 0.18) *	0.65
PSQI	0.13(-0.7 to 0.83) *	0.84(-0.28 to 1.96) *	- 0.71 (-1.99 to 0.55) *	0.27
HADS-Depression	0 (-0.59 to 0.57) *	0.04 (-0.42 to 0.52) *	- 0.04 (-0.79 to 0.70) *	0.92
HADS-Anxiety	0.07 (-0.63 to 0.69) *	0.59 (-0.16 to 1.35) *	- 0.69 (-0.41 to 2.75) *	0.14
PCS	3.55 (1.90 to 5.34) *†	2.48 (0.20 to 4.76) *†	1.07 (-1.73 to 3.88) *	0.46

* Means and confidence intervals calculated using bootstrapped t-test

† $p < 0.05$

Abbreviations: CBD, Cannabidiol; HAQ-DI, Health assessment questionnaire disability index; VAS, Visual analogue scale; PSQI, Pittsburgh sleep quality index; HADS, Hospital anxiety and depression scale; PCS, Pain catastrophizing scale.

Table 4: Serious adverse events and adverse events		
	CBD, No. (%)	Placebo, No. (%)

	N= 58	N= 61
Serious Adverse Events		
Overall	2	2
Deaths	0	0
Adverse Events		
Musculoskeletal	11(19)	11(18)
Lower gastrointestinal	2(4)	9(15)
Mood	4(7)	3(5)
Urogenital	0(0)	5(8)
Upper gastrointestinal	6(10)	10(16)
Airways	7(12)	6(10)
Ear-Nose-Throat	8(14)	0(0)
Dermal	3(5)	0(0)
Cardiovascular	4(7)	4(7)
Other	13(22)	13(21)

Abbreviations: CBD, Cannabidiol