

Cannabidiol treatment for symptomatic knee osteoarthritis: a randomized, placebo- controlled, cross-over pilot-feasibility trial

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Abstract

Background

Many Americans are using cannabis-related products like cannabidiol (CBD) for reducing pain-related symptoms associated with knee osteoarthritis (KOA). There is an extremely large consumer base for CBD-related products which is expanding exponentially; and therefore, scientific investigation is necessary. Our primary objective was to examine the feasibility of our recruitment, retention, and blinding methods, and the tests and measures used to obtain precision estimates. Our secondary objectives were to confirm the safety and tolerability of the drug product, and to calculate variance parameters and effect sizes to make preliminary estimates of efficacy.

Methods

Randomized, double-blind, placebo-controlled, cross-over trial. Study duration: 10 weeks. Study drug: CBD oil or placebo (oil no CBD) allocated randomly 1:1 and dosed 50mg TID (150mg/d). Primary outcome: Feasibility estimates (accrual rates, data completeness, blinding, and tests and measures). Secondary outcomes: Safety/tolerability; and preliminary efficacy (change from baseline scores for pain severity/interference, disability, and psychological well-being).

Results

3 men (25%) and 9 women (75%) with symptomatic KOA completed the trial. Expected sample size/% screen failures: 15 (40%). 75% of participants reported side effects; top 3: difficulty sleeping, fatigue, and diarrhea. No serious adverse reactions were reported. Recruitment and retention rates were lower than expected [62 screenings, 32% randomly allocated to treatment order; 40% lost to follow-up, 12 included in final analysis], data completeness exceeded expectations [34 missing data points (0.05%)], blinding method was flawed [58.3% were aware of the treatment order, 41.7% said they were uncertain]. Precision estimates demonstrated change from baseline reductions in pain-related symptoms and disability, with generally larger effect sizes and tighter 95% confidence intervals for the CBD condition compared to placebo.

Conclusions

CBD was safe to use and well tolerated by participants. Both treatment conditions demonstrated change from baseline reductions in pain-related symptoms, disability and psychological distress. In order to demonstrate clinical efficacy, we hypothesize that large sample sizes will be necessary in future trials to offset the strong placebo responses for our outcome measures.

Clinical trial number NCT06414473, registered on April 24, 2024.

INTRODUCTION

Osteoarthritis (OA) is a disease that affects millions of Americans and is the leading cause of persistent pain and physical disability in the older adult population (Hunter and Bierma-Zeinstra 2019). Knee osteoarthritis (KOA) is the most common joint disease and a major cause of functional limitation and pain in adults (Bricca et al. 2019, Tanaka et al. 2015). Damage to articular cartilage creates a cascade of pathophysiological events that lead to inflammation, tissue degeneration, swelling and in many cases articular neuropathy (Goldring 2012). Inflammatory mediators released into the joint cavity sensitize free nerve endings (A δ and C-fibers) resulting in hyperalgesia and nociceptive pain (Philpott et al. 2017). Pain is the primary symptom of KOA, and the main reason people seek medical treatment (He et al. 2025). Joint stiffness and limited mobility in these individuals make simple everyday tasks extremely difficult to complete (Neogi 2013, Clynes et al. 2019). Behavioral modifications such as a sedentary lifestyle are a common consequence of chronic pain and disability (Gu et al. 2026), and oftentimes progress to other problems such as impaired sleep, obesity, and feelings of helplessness and depression (Senba and Kami 2017).

Although pharmacologic treatments for KOA such as nonsteroidal anti-inflammatory drugs (NSAIDs) and opioid-based medications may help in the short-term with reducing pain-related symptoms, they are known to have mild to severe side effects along with the potential for long-term dependency (Cao et al. 2020, Goncalves et al. 2022). In contrast to NSAIDs, cannabidiol (CBD), which has also shown anti-inflammatory and anti-nociceptive properties, and has been found to be safe and well tolerated, suggesting its potential utility in human health conditions (Iffland and Grotenhermen 2017, Li et al. 2021). Therefore, CBD may be complementary to, and a replacement for traditional pharmacological treatments for KOA (Reiman et al. 2017, Cunningham et al. 2020).

Unlike Delta^{8,9}-tetrahydrocannabinol ($\Delta^{8,9}$ -THC), the principal psychoactive compound of cannabis, CBD has a low affinity for cannabinoid receptors CB₁ and CB₂, encoded by CNR₁ and CNR₂ genes respectively, as well as several G-protein coupled receptors (Mechoulam et al. 2007, Pertwee 2008, Ryberg et al. 2007, Laun et al. 2018). *In vitro* evidence indicates that CBD could work synergistically with the endocannabinoid system (eCS) in modulating pain by regulating concentrations of eCS ligands in the central and peripheral nervous system (Corroon and Felice 2019). Since these ligands are elevated during periods of physical stress within the body and are known to activate CB₂ receptors peripherally, it is postulated that the eCS functions as a closed-loop feedback system designed to modulate an immune response (Schuelert and McDougall 2011). *In vivo* studies using rodent models of OA induction were able to show that CBD administered systemically (intraperitoneally) and orally was effective in modulating degenerative responses after induced arthritis in a dose-dependent manner (Malfait et al. 2000, Verrico et al. 2008). Hammell et al. (2016) in a preclinical animal model studied the effects of topically applied CBD using a transdermal route of administration and found that it significantly reduced pain behavior, cytokine concentrations, synovial membrane thickening, joint swelling, and leukocyte infiltration. In addition, the effects were found to be dose-dependent with the lower to moderate doses showing the most effectiveness. The results in human clinical populations are equivocal and despite the popularity and anecdotal benefits of CBD, there remains a lack of comprehensive clinical data to support

its safety and efficacy in managing pain for individuals with symptomatic KOA (Mojoli et al. 2025, Pramhas et al. 2023). CBD is available OTC in many states across the USA, and there is an extremely large consumer base for CBD-related products (Cheng 2023). This base will be expanding exponentially over the course of this decade; and therefore, scientific investigation into its safety and therapeutic potential is necessary (Cannabidiol 2025, U.S. Food & Drug Administration 2025).

Our primary objective was to examine the feasibility of our recruitment, retention, and blinding methods, and the tests and measures used to obtain precision estimates. Our secondary objectives were to confirm the safety and tolerability of the drug product, and to calculate variance parameters and effect sizes to make preliminary estimates of efficacy.

METHODS

Study Design

This pilot feasibility clinical trial was authorized by the U.S. Food & Drug Administration (IND #147985) and registered with ClinicalTrials.gov (NCT06414473). Institutional Review Board approval (IRB202301136; University of Florida, Gainesville, FL, USA) and participant consent was obtained prior to study enrollment. Our study design and intervention procedures were planned and implemented in accordance with the current Osteoarthritis Research Society International (OARSI) recommendations for the design, conduct, and reporting of clinical trials for knee osteoarthritis (McAlindon et al. 2015). A randomized, double-blind, placebo-controlled, two-arm, cross-over study design was used to investigate the therapeutic benefits of a hemp-derived CBD extract compared to placebo-control in participants with KOA.

Study Participants

Volunteers between 40 and 75 years of age with an established clinical diagnosis of KOA were eligible to participate. To be included in the study, participants must report having moderate to severe knee pain ($\geq 4/10$) with physical activity in one or both knees within the past 2 weeks (Dworkin et al. 2010). Participants were instructed to stop taking any prescribed (e.g., opioids) or OTC (e.g., NSAIDs or Tylenol) pain medications for their knee pain prior to their scheduled participation.

Candidates were excluded if they: (1) were pregnant (urine pregnancy test) or lactating, (2) currently used cannabis (THC and/or CBD), (3) had any prior or ongoing medical condition that, in the investigators' opinion, could adversely affect the safety of the participant (e.g., severe hypertension $\geq 180/120$ mmHg), (4) had any major surgery within 3 months prior to recruitment or planned orthopedic surgery for any time during this study which would interfere with the ability to report pain or quality of life outcome measures, (5) had any exposure to another investigational drug within 3 months prior to screening, (6) had a BMI ≥ 45 ; (7) currently use enzyme-modifying drugs, including strong inhibitors or strong inducers of cytochrome P enzymes, (8) had a history of: a) seizure disorder or traumatic brain injury, b) liver or kidney disease, and c) cardiovascular diseases.

Intervention

The hemp-derived CBD was extracted by Socati Montana, LLC (5840 Expressway, Missoula, MT 59808), and shipped to SunFlora, Inc. (411 19th Street South, St. Petersburg, FL 33712) where it was formulated into oil-based tinctures. The investigational product (SunMed™ Hemp Supplement) is a full spectrum CBD-rich formulation (~10%) containing very low levels of THC (<0.3%), along with all naturally occurring minor cannabinoids, terpenes, and essential oils from the plant extract. Flavoring agents were added to ensure palatability. The tincture solution was provided in a 30mL bottle (3000mg CBD; concentration = 100mg/mL) with a syringe dropper (1 full drop = 100mg CBD). A medium chain triglyceride-based mixing agent blended with coconut oil was used as the placebo-control (0mg CBD). The investigational products for the entire study period were packaged and numbered by SunFlora, Inc.; and delivered to the principal investigator prior to the initiation of the study.

Participant Flow

Interested candidates responded to advertisements posted around the University of Florida (UF) campus and UF Health medical facilities in the local Gainesville area. Candidates were contacted by a study team member for a phone screen to determine if he/she met the entry criteria. If the candidate met the entry criteria and verbally agreed to participate the candidate was scheduled for an on-site laboratory visit. Participants were required to complete a 7-day washout period for any analgesic medications (prescribed or OTC) they were currently taking and were permitted to continue taking other prescribed medication as long as they were on a stable dose for at least 3 months.

Randomization

Prior to participant enrollment, a randomization sequence was generated in Microsoft Excel (Microsoft Corp., Redmond, WA, USA) using the *RAND* function to link participant identification numbers to blinded treatment codes. The randomization list was created by a study team member not involved in data collection, was not accessible to personnel involved in outcome assessment, and was not altered throughout the study. Random allocation to treatment order was performed on a 1:1 basis (CBD/placebo or placebo/CBD), with stratification applied for age (40-50 yrs., 50-60 yrs., >60 yrs.) and biological sex (male, female). All participants and study personnel were blinded to treatment order assignments throughout the study.

Experimental Procedures

On-site study visits were scheduled at baseline and 30-day follow-up for each treatment arm. Participants provided written informed consent and agreed to comply with the study protocol at the initial baseline visit. After consent, socio-demographic (age, sex, race/ethnicity, education, income), anthropometric (height, weight), and health (vitals) data was collected (**Table 1**).

Participants were instructed to administer the drug (CBD or placebo-control) under the tongue (0.5cc or ~½ dropper = 50mg), thrice daily (TID), 5 hours apart (morning, afternoon, and evening) with food at the

prescribed daily dosage of 150mg/day for 30 days. Prescription for daily dosage was recommended by the manufacturer (SunFlora, Inc.). A 2-week (14-day) wash-out period between treatment arms was required to ensure that the drug was cleared from the participant's system. Participants completed a urine test prior to beginning each arm of the trial to screen for the presence of THC, and women of childbearing potential were screened with urine pregnancy tests at baseline visits of each treatment arm (Figure 1).

Study Outcomes

Feasibility outcomes examined our recruitment and retention (accrual), loss to follow-up, and data completeness rates, and precision of our data collection and blinding methods. For each participant there was a total of 57 data points collected over the 4 on-site visits (684 total data points for 12 participants). *A priori* thresholds for the feasibility outcomes were: (1) accrual rate ≥ 5 participants per month, (2) loss to follow-up $\leq 20\%$, (3) data completeness $\geq 90\%$, and (4) blinding efficacy (goal was to have $\geq 50\%$ of the participants to answer c) as uncertain). We established our own thresholds for some metrics and used published studies for others (Teresi et al. 2022). For example, given the demographics in our recruitment area, we expected that there would be just over one person per week who would be eligible and want to participate. In contrast, a retention rate of 80% was chosen based on recommendations about bias within results at $>20\%$ loss to followup (Dettori 2011).

Recruitment, enrollment and retention numbers were tracked and recorded by a research assistant. Numbers were analyzed for feasibility: recruitment (number of participants who contacted investigators and the methods through which potential participants became aware of the study), enrollment (goal was ≥ 5 eligible participants enrolled per month), accrual/retention rates (goal was $\geq 80\%$ participant follow-up rate), and data completeness (goal was $\leq 10\%$ missing data) (Watson et al. 2022).

At final follow-up, participants were asked which treatment order they believed to have been assigned, with participants providing 1 of 3 possible standard answers: a) CBD/placebo, b) placebo/CBD, or c) uncertain. This information was collected to evaluate the effectiveness of our blinding method.

Safety and tolerability of the drug product was evaluated by monitoring the presence, frequency and severity of side effects. Safety and tolerability were assessed using a modified version of the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE[®]) (Dueck et al. 2015). The PRO-CTCAE[®] is a multi-symptom checklist developed by the National Cancer Institute to capture side effects in clinical trial participants. The [survey](#) included 15 total side effects evaluating the symptom attributes of presence/absence, frequency, and severity. Participants completed the survey at the end of each week of the trial using a Qualtrics survey. If the side effect was reported within the first 2 weeks of the intervention it was considered to be during the early period of the intervention, and if the side effect was reported within the last 2 weeks of the intervention it was considered to be during the late period of the intervention. The responses provided a clinical picture of product safety and tolerability for both treatment arms of the intervention.

Preliminary efficacy outcomes calculated the change from baseline to follow-up (30 days) for pain severity/interference, disability, and psychological well-being. Participants rated their level of knee pain severity (worst, least and average) and interference using a visual analog scale (VAS). The VAS consisted of a 100mm horizontal line with 0 (no pain or does not interfere) on the left pole and 100 (pain as bad as you can imagine or completely interferes) on the right pole and participants placed a slash on the line that best represented their level of pain or how much pain interfered with aspects of their daily life (work, mood, general activity, sleep) in or during the past 24 hours. (Mendoza et al. 2006).

Movement-evoked Pain (MEP) was assessed using a standard stair climbing test (Ronai and Gallo 2020). Participants ascended (up) and descended (down) a flight of 10 stairs. After the stair climbing test, the participant was asked to rate their level of knee pain while performing the test using the VAS.

Disability ratings were measured using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Collins et al. 2011). The WOMAC is a self-report questionnaire that is used to assess the severity of symptoms related to hip and knee OA. The questionnaire contains 24 items divided into 3 subscales that address pain (5), stiffness (2), and functional limitations (17). The test questions are scored on a hierarchical grading scale of 0-4 with symptoms rated as 0 = none, 1 = mild, 2 = moderate, 3 = severe, and 4 = extreme. The scores from each subscale are summed and the scores range from 0-20 for pain, 0-8 for stiffness, and 0-68 for functional limitations. The higher the score the more severe the symptoms. The questionnaire has been used widely in clinical trials and has been found to be valid, reliable, and responsive to clinical changes in symptoms (Collins et al. 2011).

Participants completed two self-report questionnaires to identify their level of psychological well-being during the study. The Pain Anxiety Symptom Scale (PASS-20) is a 20 item, 5-point rating scale that assesses 4 theoretically distinct components of pain-related anxiety including cognitive anxiety, fear of pain, escape/avoidance behavior, and physiological anxiety (Abrams et al. 2007). The Pain Catastrophizing Scale (PCS) is a 13-item, 5-point rating scale used to assess different thoughts that may be associated with experiencing pain (Sullivan et al. 1995).

Data Management & Analytic Plan

Consistent with guidance regarding pilot studies, we did not perform a sample size analysis, nor were inferential statistics completed (Kunselman 2024). Trial data was collected and managed using REDCap electronic data capture tools hosted at UF (Harris et al. 2009). Continuous variables were expressed as mean $\pm$ standard deviation ($\pm$ SD) or as median $\pm$ interquartile range (IQR), 95% 95% CI, upper and lower limits, and effect size depending on data distribution as determined by the Shapiro-Wilk normality test. Categorical variables were presented as proportions: absolute (n) and relative frequencies (%). All data analyses were performed using R programming language (v4.5.2 R Foundation, Vienna, Austria).

Distributional analysis was performed for each measurement-based outcome that detected a treatment effect (pain/interference, disability, and psychological distress). The analysis included participants who had usable values under both conditions to serve as a complete case; no imputation was performed in

the data analyses. The within-subject difference was tested for normality using Shapiro-Wilk. If Shapiro-Wilk displayed $P < 0.05$ it was classified as non-normal, resulting in the use of median ($\pm$ IQR) values and a Wilcoxon signed-ranked sum test (two-sided $\alpha=0.05$). If $P \geq 0.05$ then mean ($\pm$ SD) values were reported.

RESULTS

Feasibility Outcomes

Recruitment lasted from 7/17/2024–5/4/2025, treatments and data collection were performed from 8/7/2024–6/18/2025. Sixty-two individuals completed the phone screen to determine if they met entry criteria for the study. Thirty-four people did not meet eligibility criteria. Seven people met eligibility but did not attend the first visit to be enrolled. One eligible participant elected not to enroll, giving no reason. Twenty (32%) candidates agreed to participate and were randomly allocated to a treatment order. Eight (40%) participants were lost to follow-up with twelve participants included in the final analysis (Fig. 2). The most common reasons for loss to follow up were taking sleep medication and scheduling conflicts.

We counted 34 missing data points (0.05%) from two participants. One participant was not able to attend the follow-up visit for the CBD arm of the trial due to illness resulting in a total of 14 data points missing. Another participant had data missing from multiple visits that resulted in a total of 20 data points missing. In this case, the data points were not saved correctly by the data input tablet.

When the participants were asked whether they were given the CBD product first or last or if they were uncertain, 7 (of the 12) participants (58.3%) were aware of the treatment order while the other 5 participants (41.7%) said they were not certain which order of product they were provided.

Table 1
Sociodemographic data of participants

Characteristics	Value
N	12
Age (years, Mean $\pm$ SD)	57.3 $\pm$ 11
Sex, n (%)	
Women	9 (75%)
Men	3 (25%)
BMI (kg/m ² , Mean $\pm$ SD)	37.2 $\pm$ 10.5
Race, n (%)	
White/Caucasian	9 (75%)
Black/African American	3 (25%)
Ethnicity, n (%)	
Not Hispanic or Latino	11 (92%)
Did not answer	1 (8.3%)
Education Level, n (%)	
High School/GED	3 (25%)
Technical Certification	1 (8.3%)
Associate Degree	1 (8.3%)
Undergraduate Degree	2 (17%)
Graduate Degree	4 (33%)
Did not answer	1 (8.3%)
Annual Income, n (%)	
Less than 10,000	3 (25%)
10,000–50,000	6 (50%)
50,000-100,000	2 (17%)
More than 150,000	1 (8.3%)

Safety/Tolerability Outcomes

Side effects were common with nine out of the 12 participants (75%) reporting at least 1 side effect during the course of the study. Of the 9 participants that reported side effects, 7 (78%) reported them

during both active and placebo phases of the study. Most side effects were reported during the early (10/15 for CBD; 8/15 placebo (PLA)), late (5/15 for CBD; 7/15 PLA) or both early/late (2/15 for CBD; 1/15 PLA) periods of the intervention phase. Difficulty sleeping was the most common side effect reported for both phases (8 CBD/8 PLA), followed by fatigue/tiredness (8 CBD/7 PLA), diarrhea (6 CBD/6 PLA), and dizziness (5 CBD/5 PLA). On a rating scale of 0 (none, never or not at all) to 4 (very severe, almost constantly or very much), most reported side effects were rated 1 (mild, rarely, or a little bit) or 2 (moderate, occasionally, or somewhat) (**Table 2**).

Table 2: Side effects reported during the clinical trial

Side Effect	CBD # (%) N=12	Placebo # (%) N=12
Difficulty Sleeping	8 (67)	8 (67)
Fatigue/Tiredness	8 (67)	7 (58)
Diarrhea	6 (50)	6 (50)
Dizziness	5 (42)	5 (42)
Abdominal Pain	3 (25)	5 (42)
Blurry Vision	3 (25)	4 (33)
Decreased Appetite	4 (33)	3 (25)
Mouth/Throat Soreness	4 (33)	2 (17)
Nausea	2 (17)	3 (25)
Shortness of Breath	2 (17)	3 (25)
Heart Palpitations	3 (25)	2 (17)
Skin Rash	3 (25)	2 (17)
Skin Itch	2 (17)	3 (25)
Tinnitus	3 (25)	1 (8.3)
Vomiting	1 (8.3)	2 (17)

Precision Estimation Outcomes

Shapiro-Wilk testing observed non-normal data distributions; therefore, precision estimates were summarized using the median $\pm$ IQR, 95% CI, and effect sizes via a Wilcoxon signed-rank test. Inspection of the within-subjects' difference scores revealed stronger estimations (95% CI, effect sizes) for the CBD treatment condition compared to the placebo control condition for pain severity (average, least, and movement-evoked), pain interference (normal work, relationships, enjoyment of life, and sleep), disability (WOMAC index) and psychological well-being (PASS-20) (**Table 3**).

Table 3

Estimated marginal medians $\pm$ interquartile ranges (IQR) and 95% confidence intervals (CI) with upper/lower limits, and effect size (ES) for preliminary efficacy outcomes

Outcome	CBD (N = 11) (Median $\pm$ IQR)	95% CI	ES	Placebo (N = 12) (Median $\pm$ IQR)	95% CI	ES
Pain Severity:						
Worst	-14.0 (-31.5 to -8.0)	[-28.0, 1.0]	0.71	-15.0 (-29.5 to 5.3)	[-38.0, -3.0]	0.86
Average	-11.0 (-20.8 to -4.5)	[-38.0, -7.0]	0.91	-13.0 (-29.5 to 6.0)	[-31.0, 5.5]	0.67
Least	-5.0 (-22.0 to 7.0)	[-25.0, 8.0]	0.44	-9.0 (-28.5 to 15.0)	[-35.0, 17.0]	0.18
Movement-evoked	-19.0 (-26.5 to -12.0)	[-27.0, -8.0]	0.82	-5.5 (-18.0 to 6.5)	[-19.0, 7.0]	0.45
Pain Interference:						
General Activity	-27.0 (-41.5 to -10.0)	[-42.0, -6.0]	0.89	-21.5 (-35.0 to -12.0)	[-35.0, -10.0]	0.87
Mood	-15.0 (-35.5 to 5.0)	[-36.0, 8.0]	0.64	-21.5 (-24.8 to -6.8)	[25.5, -4.5]	0.86
Walking Ability	-13.0 (-36.0 to -7.0)	[-40.0, -6.0]	1.00	-19.5 (-24.3 to -9.3)	[-25.5, -8.5]	1.00
Normal Work	-8.0 (-28.0 to -2.5)	[-32.0, -2.0]	0.79	-14.5 (-34.8 to 2.5)	[-39.5, 3.0]	0.59
Relationships	-12.0 (-30.0 to -1.0)	[-40.0, 1.0]	0.73	4.5 (-18.0 to 12.8)	[-19.0, 14.5]	0.03
Enjoyment of Life	-27.0 (-40.5 to -12.0)	[-41.0, -11.0]	1.00	-26.5 (-44.0 to -1.0)	[-46.0, -1.0]	0.85
Sleep	-36.0 (-41.5 to -21.0)	[-42.0, -18.0]	1.00	-18.0 (-50.8 to 0)	[-51.5, 0.0]	0.96
WOMAC	-11.5 (-13.5 to -5.7)	[-14.6, -4.2]	0.88	-1.04 (-15.9 to 3.9)	[-18.2, 4.7]	0.30
PCS	-8.0 (-12.3 to -1.0)	[-13.0, 0.0]	0.67	-7.0 (-8.0 to -3.0)	[-8.0, -2.0]	0.71
PASS-20	-14.0 (-21.0 to -8.8)	[-22.0, -7.5]	0.93	-1.0 $\pm$ (-11.5 to 9.0)	[-12.0, 10.0]	0.20
Western Ontario & McMaster's University Arthritis Index (WOMAC); Pain Catastrophizing Scale (PCS); Pain Anxiety Symptom Scale – 20 (PASS-20)						

DISCUSSION

Overall, the investigational drug product was found to be safe and well-tolerated by the participants. Side effects did occur in our trial with 75% of participants reporting at least 1 side effect during the course of the study. Of the 75% that reported side effects, more than half reported side effects during both treatment conditions of the trial.

Most side effects were reported during the early phase (first 2 weeks) of the intervention period. Difficulty sleeping was the most common side effect reported for both treatment conditions, followed by fatigue/tiredness, diarrhea, and dizziness. Most published research indicates that cannabis improves sleep behavior, however the findings of a recently published report suggests that cannabinoids, particularly THC, may acutely influence sleep, primarily by suppressing REM sleep, without noticeable next-day impairment (Suraev et al. 2026). A scoping review published in the Journal of Clinical Sleep Medicine reported that while 21% of studies have shown improvements in sleep with cannabis products, 48% reported worsening sleep, 14% reported mixed results, and 17% showed no impact at all. Open-label trials of cannabis have shown no improvement in sleep quality over three months. Large epidemiological studies of patients reporting regular use of cannabis for medical reasons have shown that cannabis products are associated with increased middle-of-the-night awakenings, and regular cannabis users report substantially increased or decreased total sleep duration as compared to non-users.

Even though the side effects appear to be treatment-emergent (e.g., diarrhea) they were not deemed to be associated with the administration of the drug (CBD), but rather we suspected it was with elements of the oil-based tincture. Overall, most reported side effects were rated as mild and resolved quickly. No side effects reported were serious. Our safety and tolerability findings are consistent with those of other studies using oral CBD as a treatment for pain-related symptoms (Iffland and Grotenhermen 2017, Li et al. 2021).

Our recruitment efforts lasted approximately 10 months, and data showed that 68% of respondents did not meet eligibility criteria. Patients frequently fail to qualify for clinical trials of OA because of strict inclusion/exclusion criteria as well as having other medical comorbidities (Huang et al. 2018). Although 68% of our respondents did not meet eligibility criteria, our exclusion criteria were standard among KOA trials using cannabinoids as an intervention. Because OA is typically a chronic, long-term condition, disease-modifying OA drug trials can span anywhere from 1 to 5 years, leading to high attrition rates over the course of the study.

Of the 32% of participants that agreed to be enrolled in the trial and were randomized to a treatment order, 40% were lost to follow-up and did not complete the trial. The loss to follow-up rate was higher than we expected; however, OA trials have notably poor enrollment and accrual rates (Kadam et al. 2016, Banerjee et al. 2009). Studies show that the mean recruitment rate across OA trials is roughly 63% with 85% of clinical trials failing to reach their enrollment targets within their planned timelines, and up to 19% are terminated prematurely due to slow or insufficient recruitment (Huang et al. 2018).

All participant dropouts in the current trial occurred during the first phase of the trial (before cross-over). The most common reasons why participants were lost to follow-up were related to errors on the part of the study team, and malfunctions with data collection instruments; and not with participant noncompliance.

Accrual in pain and OA trials averages roughly 3 to 5 participants per month, per trial site (Watson et al. 2022). Because of slow accrual, the enrollment phase frequently takes much longer than initial projections and drop-out or attrition rates hover around 25% to 30% (Watson et al. 2022). This was evident in our trial with recruitment lasting 10 months and our final sample size was 12 participants. This translates to an accrual rate of approximately 1–2 participants per month which is well below our projected threshold of 5 per month. In addition, 40% of participants were lost to follow-up, which was also above our projected threshold of 20% loss.

Our data completeness exceeded our goal of $\leq 10\%$ missing data. We had a total of 34 missing data points from two participants (0.05%). One participant was not able to attend the follow-up visit for the CBD arm of the trial due to illness resulting in a total of 14 data points missing. Another participant had data missing from multiple visits that resulted in a total of 20 data points missing.

Our trial was conducted through an academic research laboratory not attached to a health science center; that is, participants needed to travel specifically to our site to participate rather than be enrolled and tested 'in situ' at a healthcare facility. This may account for the lower-than-expected enrollment. Location and site capabilities are reported to have a significant impact on the recruitment rate of OA clinical trials. OA clinical trials that recruited from hospitals were likely to have a recruitment rate above 80% when compared to those that recruited from community sources (Watson et al. 2022). A pragmatic approach for future clinical trials would be to closely associate our research lab with a health science facility that specializes in conducting clinical trials. A facility of this type would have the experience and expertise in recruiting and retaining study patients, which would likely improve our participant recruitment and retention rates.

Our blinding methods were not as effective as we hypothesized. Since we used a cross-over design the participants were required to ingest both the CBD and the placebo product in a randomized order. Over half (58.3%) of the participants were aware of the order they were provided the investigational product due to the smell, sight, and the taste of the product. Participants commented that the CBD product smelled more floral, had a darker consistency, and a stronger taste than the placebo product. Future trials might consider an encapsulated gel product, which will more efficiently mask those qualities that an oil-based sublingual tincture could not.

Our estimates of precision for each treatment condition (CBD or placebo) demonstrated reductions in pain-related symptoms and disability, with generally larger effect sizes and tighter 95% confidence intervals for the CBD condition compared to placebo, especially for movement-evoked pain (MEP), disability (as scored by the WOMAC index), and pain-related fear and anxiety (as scored by the PASS-20).

Movement-evoked pain (MEP), assessed by the stair-climb test in our KOA trial, demonstrated a median reduction of 19 VAS points from baseline to follow up when using CBD compared to only a 5.5-point reduction while on placebo. Stratford and Kennedy (2006) had expressed performance-based tasks such as climbing stairs to provide valuable information beyond self-report for patients with KOA. Several studies have used stair climb protocols to increase mechanical load demand on the knee joint to more closely observe if pain can be manipulated from an intervention (Mizner et al. 2005). The degree of directional improvement may hold clinical relevance as MEP is a widely sought after metric of interest regarding pain constructs in osteoarthritic populations. Contrary to resting pain, MEP demonstrates the pain experienced while carrying out physical tasks, resulting in a strong association in movement pattern alterations, disability and overall reduced quality of life (QoL) for people suffering from KOA (Wideman et al. 2019, Rice et al. 2018, Bennell and Hinman 2011). Srikandarakh and Gilron (2011) report that MEP may provide more ecological validity rather than static pain measurements as it better reflects symptomatic burden that is experienced during daily living activities such as walking, moving up and down stairs, etc. They further expressed that MEP should be a metric monitored separately from resting pain in chronic pain research due to its relationship with functional impairment. Collectively, these studies support the clinical relevance of using the stair-climb test as an outcome in future trials.

Similar to MEP, our pain interference and psychological distress effect size estimates were larger while taking CBD compared to placebo especially in the areas of walking ability, enjoyment of life, sleep and pain-related anxiety suggesting that the drug may have contributed to broader pain-related QoL circumstances. This was evident in the self-reported pain interference outcomes for sleep which showed a median reduction of 36 VAS points from baseline to follow up when using CBD compared to only an 18-point reduction while on placebo. Pain is a multidimensional construct which can extend beyond severity alone as it extends to physical, emotional and social impairment (Bennell and Hinman 2011). Other studies have emphasized that reductions found in pain interference are highly meaningful as patients believe that it more directly captures the impact of daily living and overall well-being (Turk et al. 2003, Dworkin et al. 2005). As a consequence, pain interference may not be reflective of just pharmacologic effects, but may also include enhanced expectation, symptom awareness, and contextual effects that are associated with participation in a repeated therapeutic clinical trial design. While acknowledging pain interference's inherent sensitivity to psychological behavioral and environmental covariates, the CBD's inability to outperform the placebo should not be seen as an absence of symptomatic benefit.

The noticeable improvements in our outcomes for both treatment conditions reinforce the recurring observation of strong placebo responsiveness especially in self-report chronic pain and interference scores. These observations are notable as placebo analgesic/anti-nociceptive responses in chronic pain drug trials have been found to be robust (Bannuru et al. 2015). Finniss et al. (2010) describes how placebo analgesia is capable of producing genuine reductions in pain severity perception by serving as a biologically measurable phenomenon involving conditioning, expectation, and contextual therapeutic effect. The estimated improvements in outcomes that were found in both of our treatment conditions

may demonstrate a complex interaction between pharmacologic effects, symptom monitoring, and expectation bias that is associated in repeated oral dosing intervention procedures.

A key limitation to our study design was the recruiting and retention plan, which we would not consider for a larger study. Performing the study through our research laboratory limited our ability to effectively recruit, enroll and retain participants. Affiliation with a health science center would likely help improve our recruitment and enrollment rates.

We had a large group of measures to examine safety and feasibility of conducting a clinical trial of CBD in patients with KOA. In addition, we tested use of a battery of outcomes across levels of impairments, function and disability. Despite this, we identified areas that would have provided additional information for planning future trials. For example, physical activity and sleep quality were not comprehensively captured with our proposed measures and methods. For future KOA clinical trials, we do recommend the inclusion of performance-based assessments such as the stair climbing test to capture the full scope of the symptomatic response.

Additionally, our oil-based investigational product limited our ability to mask the product effectively, which likely contributed to the lack of blinding of participants. Loss of blinding may have influenced participant responses. Future trials should consider an alternative to the oil-based solution for the investigational product.

CONCLUSIONS

CBD, administered sublingually, was safe to use and well tolerated by participants. Our estimates of precision demonstrated positive change from baseline effects for both CBD and placebo control. Efficacy and feasibility estimates favor CBD when compared to placebo, although both treatment conditions demonstrated reductions in pain-related symptoms, disability and psychological distress. In order to demonstrate clinical efficacy, large sample sizes will be necessary in future trials to offset the strong placebo responses for our outcome measures.

Abbreviations

CBD	cannabidiol
eCS	endocannabinoid system
THC	tetrahydrocannabinol
VAS	visual analog scale
MEP	movement-evoked pain
NSAIDs	non-steroidal anti-inflammatory drugs

IND	investigational new drug
OTC	over the counter
OA	osteoarthritis
PCS	pain catastrophizing scale
PASS-20	pain anxiety symptom scale – 20
SMRL	sports medicine research laboratory
OSV	on-site visit
TID	thrice per day
REDCap	Research Electronic Data Capture
GPRs	G protein-coupled receptors
CB	cannabinoid
CNR	cannabinoid receptor
IQR	interquartile range
MCT	medium-chain triglyceride
Mg	milligram
mL	milliliter
mm	millimeter
Kg	kilogram
KOA	knee osteoarthritis
WOMAC	Western Ontario and McMaster’s University Osteoarthritis Index
Q-aire	Questionnaire
BMI	body mass index

Declarations

Ethics approval and consent to participate

Institutional Review Board approval and participant written informed consent was obtained prior to study enrollment. All methods were performed according to the Declaration of Helsinki, Good Clinical Practice Guidelines (HE641619), and regulations.

Consent for publication

The work is not under consideration for publication elsewhere, and the authors consent to publication and grant the Publisher's exclusive license for full copyright.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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The study was supported by the University of Florida (UF). UF was not involved in the study design, collection, analysis and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication. We (University of Florida) purchased the investigational product (CBD or placebo) from SunFlora, Inc. and a representative of the company (Anthony Ferrari, PhD, CSO) informed the PI which product was the CBD, and which was the placebo formulation. Other than that, SunFlora, Inc. was not involved in any aspect of the study.

Authors' contributions

JWS contributed to the conception and design of the study, acquisition and analysis of data, and final draft and approval of the work; JAB contributed to the acquisition, analysis, and interpretation of data, and final draft and approval of the work; MDB contributed to the conception and design of the study, acquisition and interpretation of data, and final draft and approval of the work; JWS contributed to the conception and design of the study, interpretation of data, and final draft and approval of the work; PAB contributed to the conception and design of the study, acquisition, analysis, and interpretation of data, and final draft and approval of the work. All authors approve of the submitted version.

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Figures

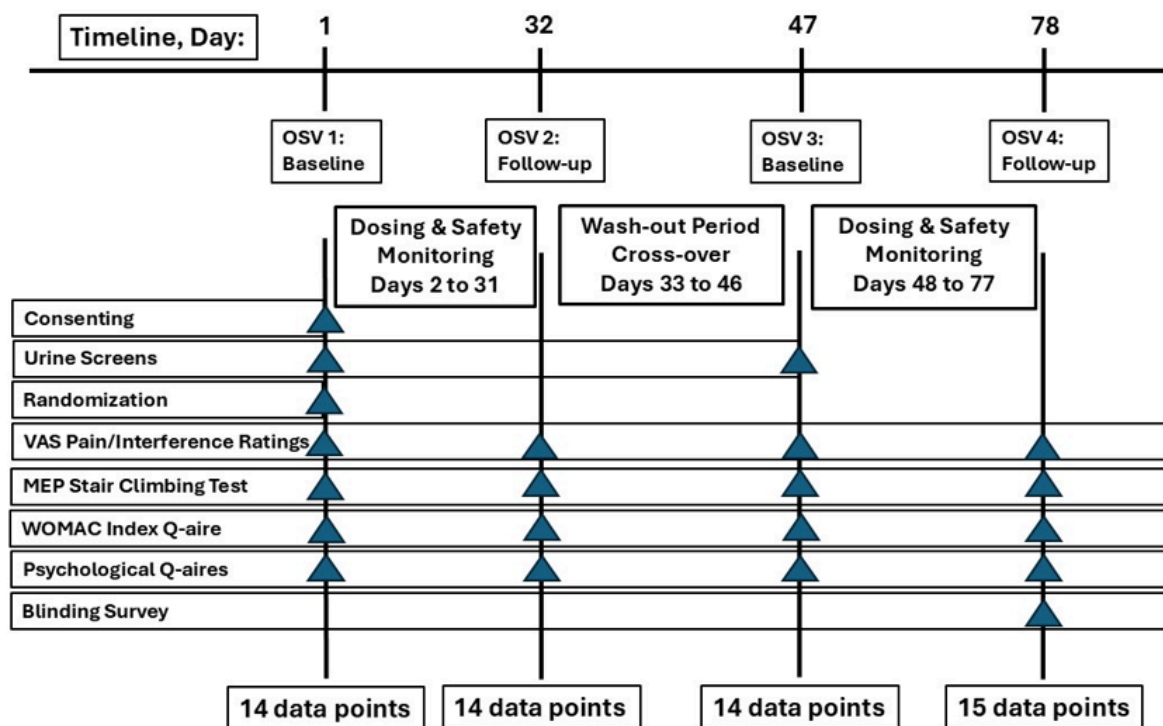


Figure 1

Timeline and Experimental Procedures. OSV – on-site visit; VAS – visual analog scale; MEP – movement-evoked pain; WOMAC – Western Ontario and McMaster’s University Arthritis Index; Q-aire – questionnaire. For all 4 OSVs, there was a total of 57 data points collected per participant (684 total data points for 12 participants).

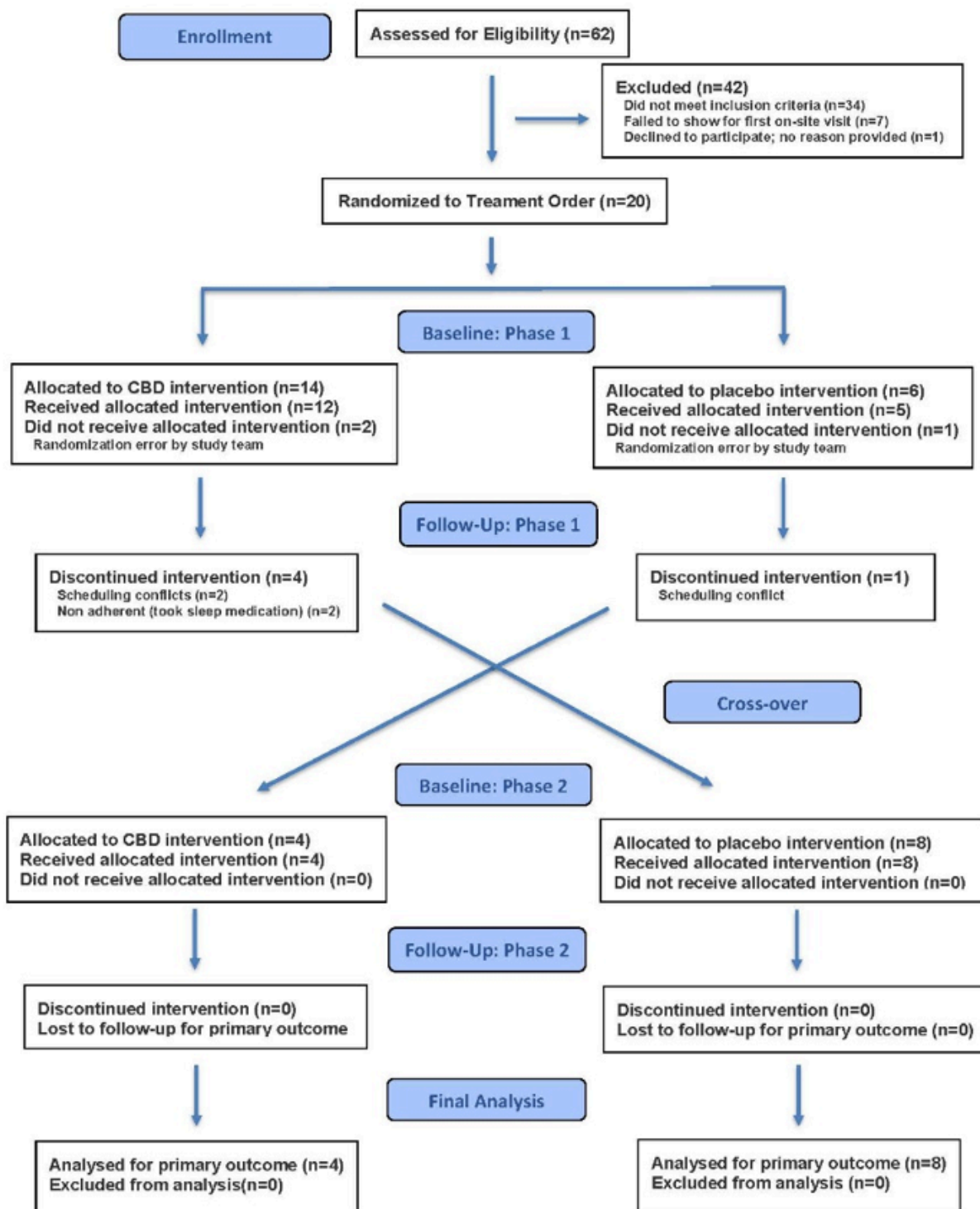


Figure 2

CONSORT Flow diagram

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