



BMJ Open Study protocol for a phase II, double-blind, randomised controlled trial of cannabidiol (CBD) compared with placebo for reduction of brain neuroinflammation in adults with chronic low back pain

Chelsea K Pike,^{1,2} Minhae Kim,² Kristina Schnitzer,^{1,3} Nathaniel Mercaldo,^{4,5} Robert Edwards,⁶ Vitaly Napadow,^{2,7} Yi Zhang,⁸ Erin Janas Morrissey ², Zeynab Alshelh,^{2,5} A Eden Evins,^{1,3} Marco L Loggia,^{2,5,8} Jodi M Gilman ^{1,2,3}

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For numbered affiliations see end of article.

Correspondence to

Dr Jodi M Gilman;
jgilman1@mgh.harvard.edu

ABSTRACT

Introduction Chronic pain is a debilitating medical problem that is difficult to treat. Neuroinflammatory pathways have emerged as a potential therapeutic target, as preclinical studies have demonstrated that glial cells and neuroglial interactions play a role in the establishment and maintenance of pain. Recently, we used positron emission tomography (PET) to demonstrate increased levels of 18 kDa translocator protein (TSPO) binding, a marker of glial activation, in patients with chronic low back pain (cLBP). Cannabidiol (CBD) is a glial inhibitor in animal models, but studies have not assessed whether CBD reduces neuroinflammation in humans. The principal aim of this trial is to evaluate whether CBD, compared with placebo, affects neuroinflammation, as measured by TSPO levels.

Methods and analysis This is a double-blind, randomised, placebo-controlled, phase II clinical trial. Eighty adults (aged 18–75) with cLBP for >6 months will be randomised to either an FDA-approved CBD medication (Epidiolex) or matching placebo for 4 weeks using a dose-escalation design. All participants will undergo integrated PET/MRI at baseline and after 4 weeks of treatment to evaluate neuroinflammation using [¹¹C]PBR28, a second-generation radioligand for TSPO. Our primary hypothesis is that participants randomised to CBD will demonstrate larger reductions in thalamic [¹¹C]PBR28 signal compared with those receiving placebo. We will also assess the effect of CBD on (1) [¹¹C]PBR28 signal from limbic regions, which our prior work has linked to depressive symptoms and (2) striatal activation in response to a reward task. Additionally, we will evaluate self-report measures of cLBP intensity and bothersomeness, depression and quality of life at baseline and 4 weeks.

Ethics and dissemination This protocol is approved by the Massachusetts General Brigham Human Research Committee (protocol number: 2021P002617) and FDA (IND number: 143861) and registered with ClinicalTrials.gov. Results will be published in peer-reviewed journals and presented at conferences.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ To our knowledge, this is among the largest double-blind, randomised, placebo-controlled clinical trials to evaluate a pain intervention using positron emission tomography.
- ⇒ This is the first trial to assess whether cannabidiol (CBD) may reduce neuroinflammation and pain symptoms in chronic low back pain patients.
- ⇒ This study will advance knowledge on mechanisms of action of CBD that may aid in treatment of other conditions and test whether neuroinflammation is a promising therapeutic target for pain.
- ⇒ The length of study drug administration is 4 weeks, which will limit our ability to assess potential long-term therapeutic effects of CBD.
- ⇒ Chronic low back pain is a broad category, encompassing mechanistically different etiologies, which could limit the ability to identify a specific mechanism of action of CBD.

Trial registration number NCT05066308; ClinicalTrials.gov.

INTRODUCTION

Chronic pain affects an estimated 50 to 100 million individuals in the USA^{1 2} and is among the most debilitating medical conditions with profound physical, emotional and economic costs.³ Available treatment options including interventional techniques⁴ and non-opioid pain medications such as non-steroidal anti-inflammatory drugs⁵ are often ineffective.⁶ Until recently, efforts to improve pain care led to increased use of opioids, contributing to an epidemic of opioid use disorder and opioid overdose deaths.^{7–9} In

this setting of high public health need, there is a strong interest in discovering alternative therapeutic targets for chronic pain.

Animal studies have demonstrated that glial cells, as well as neuroglial interactions, play a key role in the establishment and maintenance of pain.^{10–15} In animal models of pain,^{16–18} activated glial cells^{10 19–36} initiate a series of cellular responses including increased expression of receptors and surface markers^{11 37} and production of inflammatory mediators^{10 38} that further sensitise pain pathways³⁹ in a ‘pain-produces-pain’ loop. Importantly, agents that disrupt glial function inhibit or attenuate various behavioural markers of pain hypersensitivity (eg, thermal and mechanical hyperalgesia).^{35 36 40 41}

Recently, our group used positron emission tomography (PET) to demonstrate the presence of increased levels of the 18 kDa translocator protein (TSPO), a marker of glial activation,^{16 42–50} in the brains⁵¹ and spinal cords⁵² of patients with chronic low back pain (cLBP) compared with controls. These TSPO signal elevations were consistently observed, particularly in the thalamus, in our original study⁵¹ and were later replicated in an independent cLBP cohort.⁵³ We therefore consider this signal as a potential marker of ‘pain-related’ neuroinflammation in cLBP. These observations, along with results from studies showing brain TSPO signal elevation in fibromyalgia, Gulf War Illness, migraine and others,^{54–57} suggest a role of neuroinflammation across these conditions and present a potential therapeutic target for pain disorders.

The endocannabinoid system plays a key role in regulation of pain sensation.^{58 59} Thus, cannabidiol (CBD), a non-intoxicating compound in the cannabis plant, could potentially be effective for treating pain. CBD is thought to be a weak inverse agonist of both cannabinoid 1 (CB1) and cannabinoid 2 (CB2) receptors⁵⁸ as well as an allosteric modulator of other receptors related to pain.⁶⁰ Both cannabinoid CB1 (found at presynaptic sites throughout the peripheral and central nervous systems) and CB2 (found principally on immune cells) receptors are being evaluated as potential therapeutic targets for pain disorders.^{61 62} Because CBD can behave as a CB2 receptor inverse agonist, this may account for its anti-inflammatory properties.⁶³

Animal models have identified a role for both CB1 and CB2 receptor activation in reducing neuropathic and inflammatory pain,⁵⁸ and several preclinical studies have suggested that systemic administration of cannabinoid receptor ligands produces analgesia in acute and chronic pain models.⁵⁹ In animals, CBD induces analgesic^{64–66} and antidepressant^{67 68} effects via a complex pathway that includes the inhibition of proinflammatory pathways in glial cells.⁶⁹

Although some preclinical studies provide evidence for the effectiveness of CBD for pain, results from clinical studies have been inconsistent. A recent report from our group found no significant effect of cannabis on pain,⁷⁰ supporting conclusions from a Cochrane review, which concluded that there was no strong evidence

for the effectiveness of cannabis-derived products for chronic pain.⁷¹ However, the National Academies of Sciences, Engineering and Medicine reported that there was substantial evidence that cannabis was effective in treating chronic pain.⁷² Such inconsistencies may be partially explained by heterogeneity in methods across studies (with some lacking a placebo control), by the fact that meta-analyses often combine results from studies using various combinations and doses of cannabinoids^{73 74} (eg, varying THC (tetrahydrocannabinol)/CBD potencies), and by combining studies addressing different kinds of pain. Perhaps more problematic is the fact that many commercial CBD products available are of unknown quality and contain variable doses of the active ingredient.⁷⁵ In the current study, we will use Epidiolex, the first and only FDA-approved drug containing a known and consistent dose of purified CBD. Thus, the current study will assess whether an FDA-approved CBD formulation, in a known dose, compared with placebo, reduces neuroinflammation in patients with cLBP. Such reduction may be the result of a direct effect of CBD on CB receptors expressed in glia, as mentioned above. However, given the emerging evidence of an effect of CBD on voltage-gated sodium channels in primary nociceptors in the mouse,⁷⁶ CBD may work by normalising aberrant neural activity and, therefore, reduce *neurogenic* neuroinflammation.⁷⁷

This study will also assess the role of CBD on neuroinflammation with respect to depressive symptoms. Comorbid depression and chronic pain are common, with approximately 40% of patients with cLBP also exhibiting negative affect, including depressive symptoms.^{78–81} Depression has been associated with neurobiological changes, including neurotransmitter deficits, endocrine disturbances and impaired neural adaptation and plasticity,^{82 83} and neuroinflammation may be implicated in these abnormalities.⁸⁴ Those with depression who commit suicide have shown dramatically increased microglial activation.⁸⁵ Indeed, cLBP patients who also have comorbid depression demonstrate, in addition to thalamic TSPO signal elevations observed irrespectively of depression status, TSPO signal elevations in limbic regions, which are proportional to scores on the Beck Depression Inventory.⁸⁶ Meta-analyses have shown that mechanistically diverse anti-inflammatory agents may be effective treatments for depression.^{87–89} Preliminary evidence suggests that CBD promotes antidepressant effects in animal models,^{67 68} however, randomised clinical trials of CBD for treatment of depression have not been conducted. Therefore, a secondary objective of the study is to assess whether CBD compared with placebo reduces depressive symptomatology and depression-related neuroinflammation in patients with cLBP.

Healthcare providers are increasingly interacting with patients who are interested in using CBD for various pain disorders, with little evidence available for therapeutic guidance. Results from this study will provide critical information regarding the potential utility of CBD for

cLBP and its involvement in mechanistic pathways of neuroinflammation.

METHODS AND ANALYSIS

The full protocol is included as supplementary information (see online supplemental file 1).

Study design

This is a phase II, double-blind, randomised, placebo-controlled 4-week clinical trial with a 6-week follow-up assessment. The principal goals of this trial are to assess the effects of CBD on neuroinflammation, pain and depressive symptomatology, in participants with cLBP. Neuroinflammation will be quantified with PET/MRI scans using [¹¹C]PBR28, a second-generation ligand for TSPO. Participants will continue their usual pain care regimen during the study. This trial is being conducted at Massachusetts General Hospital in the USA. The study is currently in progress; the first participant was enrolled in January 2022, and the last participant is expected to be enrolled in 2026.

Participants

We will recruit a total of 80 cLBP patients aged 18–75 through clinical research databases, physician referrals, clinical programs associated with the healthcare systems and community advertising. Participants must have a diagnosis of cLBP for at least 6 months and must report worst daily pain of at least a 4 on a 0–10 scale of pain intensity during a typical day, and pain present for at least 3–4 days during a typical week. Participants will be genotyped for the Ala147Thr TSPO polymorphism (rs6971) using blood or saliva. Approximately 10% of humans show low binding to the PET radioligand used in this study, [¹¹C]PBR28⁹⁰; the rs6971 polymorphism allows for the identification of low, mixed or high affinity binders.^{91 92} In this study, only high or mixed-affinity binders will be considered eligible. Any ongoing pain treatment (pharmacologic or behavioral) must be stable for 4 weeks prior to randomisation.

Exclusion criteria include: abnormal liver function test results, contraindications to PET/MRI scanning, unresolved neurological or major medical illness, use of medications deemed to have unsafe interactions with Epidiolex, use of marijuana in the previous 2 weeks or regular recreational drug use in the previous 3 months. See [table 1](#) for the full list of inclusion and exclusion criteria.

Participant enrollment

Participants will undergo a telephone screen or complete an online screening survey. Those who are likely to be eligible based on their responses will be scheduled for a screening visit where study procedures will be explained and informed consent will be obtained (see online supplemental file 2 for a copy of the consent form). Eligibility

assessments will be conducted during the screening visit, listed in [table 2](#).

Investigational product

Participants will be randomised to receive Epidiolex or placebo, both provided by Jazz Pharmaceuticals. Epidiolex is FDA approved for the treatment of certain forms of epilepsy. It is a 100 mg/mL purified oral solution dissolved in sesame oil and anhydrous ethanol with sucralose and strawberry flavouring. The drug is formulated from extracts prepared from *Cannabis sativa* L. plants that have a defined chemical profile and contain consistent levels of CBD as the principal phytocannabinoid. Extracts from these plants are processed to yield pure (>95%) CBD that typically contains less than 0.5% THC.

Participants will follow a dose escalation schedule based on Epidiolex package insert recommendations, with 2.5 mg/kg taken orally two times per day in week 1, 5 mg/kg two times per day in week 2, 7.5 mg/kg two times per day in week 3 and 10 mg/kg two times per day in week 4. If participants report significant adverse events (AEs) (eg, tiredness, dizziness, not tolerating the drug well, significant weight change) during the second, third or fourth week of taking the study drug, the study physician will decrease the dose of study drug to the previous week's dose.

Randomisation and treatment allocation

Eligible participants will be enrolled by study staff and randomised to receive either CBD or placebo. Stratified simple random sampling, based on age (>50 vs ≤50) and sex (male vs female), will be performed. Randomisation sheets have been developed by the study biostatistician and will be used by a study pharmacist to assign treatments. The MGH Clinical Trials pharmacy will handle the blinding of study medication, and all members of the study clinical staff and study participants will be blinded to treatment assignment.

Study procedure

See [figure 1](#) for the study schema and [table 2](#) for the schedule of assessments to be performed at each visit. Following randomisation, participants will be scheduled for a baseline PET/MRI scan. At this visit, participants will receive CBD or placebo, which they will be instructed to take daily for 4 weeks. Participants will be reminded to follow their study drug dose escalation at a weekly phone check-in. The post-treatment scan will take place at the end of week 4. Questionnaires assessing pain, depression, sleep and other constructs (see [table 2](#)) will be collected at baseline and week 4. AEs will be assessed at baseline and weeks 1, 2, 3, 4 and 6 (2 weeks after the discontinuation of the study drug) and expected improvement from treatment will be assessed at baseline and weeks 1, 2 and 3. In the case of scans scheduled more than 4 weeks apart, the participant will be instructed to start taking the study drug exactly 4 weeks before the post-treatment scan.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	<ol style="list-style-type: none"> 1. Age ≥ 18 and ≤ 75 2. The ability to give written, informed consent 3. Fluency in English 4. Diagnosis of chronic low back pain, ongoing for at least 6 months prior to enrollment 5. Average worst daily pain of at least 4, on a 0–10 scale of pain intensity, present for at least 50% of days during a typical week 6. On a stable pain treatment (pharmacologic or behavioural) for the previous 4 weeks 7. High or mixed affinity binding identified by rs6971 polymorphism
Exclusion criteria	<ol style="list-style-type: none"> 1. Outpatient surgery within 2 weeks and inpatient surgery within 1 month from the time of scanning (this timeframe may be extended if not fully recovered from surgery) 2. Elevated baseline transaminase (ALT and AST) levels above 3 times the upper limit of normal (ULN), accompanied by elevations in bilirubin above 2 times the ULN 3. Any interventional pain procedures within 6 weeks prior to scanning procedure or at any point during study enrollment 4. Surgical intervention or introduction/change in opioid regimen at any point during study enrollment 5. Contraindications to fMRI scanning and PET scanning (including presence of a cardiac pacemaker or pacemaker wires, metallic particles in the body, vascular clips in the head or previous neurosurgery, prosthetic heart valves, claustrophobia) 6. Implanted spinal cord stimulator (SCS) for pain treatment 7. Any history of neurological illness or major medical illness, unless clearly resolved without long-term consequences 8. Current or past history of major psychiatric illness (PTSD, depression, and anxiety are exclusion criteria <u>only</u> if the conditions were so severe as to require hospitalisation in the past year) 9. Harmful alcohol drinking as indicated by an AUDIT score ≥ 16 10. Pregnancy or breast feeding 11. History of head trauma requiring hospitalisation 12. Major cardiac event within the past 10 years 13. Regular use of recreational drugs in the past 3 months 14. Any cannabis use, medical or recreational, in the past 2 weeks, including ingestible CBD products 15. A clinically significant abnormality on a physical exam (eg, peripheral edema) 16. Use of immunosuppressive medications, such as prednisone or TNF medications within 2 weeks of the visit 17. Current bacterial or viral infection likely affecting the central nervous system 18. Epilepsy or any prescription of an anti-epileptic drug 19. Use of the medications valproate and clobazam, which may increase risk of hepatic AEs 20. Safety concerns related to use of any of the following medications will be discussed on an individualised basis with a physician: <ol style="list-style-type: none"> – Strong and moderate inhibitors of CYP3A4 and CYP2C19 (eg, diltiazem, erythromycin, fluoxetine) – Sensitive and moderately sensitive substrates of CYP2C19, CYP1A2, CYP2B6, CYP2C8, CYP2C9, UGT1A9 and UGT2B7 (eg, omeprazole, bupropion, morphine, lamotrigine) 21. CNS depressants including antipsychotics, benzodiazepines (except for alprazolam, clonazepam, and lorazepam, which have low binding affinity to TSPO^{100–104}), and non-benzodiazepine sleep aids that have a known reaction with CBD 22. Use of opioids ≥ 30 mg morphine equivalents on average per month 23. Active suicidal ideation, suicide attempt or an aborted attempt within the last 5 years, or engagement in non-suicidal self-injurious behaviour within the last year 24. Allergy to sesame oil, and any other ingredients of Epidiolex 25. Any other contraindications to CBD administration noted by the study physician 26. Any significant change in drug use and pain treatment between screening visits 27. In the opinion of the investigators, unable to safely participate in this study and/or provide reliable data (eg, unable to reliably rate pain, unlikely to remain still during the imaging procedures)

AEs, adverse events; AUDIT, Alcohol Use Disorders Identification Test; CBD, cannabidiol; CNS, Central Nervous System; PET, positron emission tomography; PTSD, Post-Traumatic Stress Disorder; TNF, Tumor Necrosis Factor; TSPO, translocator protein.

Blood samples will be collected at baseline and week 4, to be assayed for CBD and its metabolites.

PET/MRI scans

On the scan day, participants will complete screening checklists for PET/MRI to determine whether they have any contraindications for the test. A urine drug test will also be performed, and female participants of child-bearing potential will have blood drawn to perform a serum pregnancy test.

At the beginning of the scan sessions, an intravenous catheter will be placed in the participant's antecubital

vein of the left or right arm. Blood will be drawn to assess quantitative levels of cannabinoids, including CBD and THC. An arterial line will be placed in a radial artery with local anaesthesia if the participant has consented to this (optional) procedure and has no contraindications. The arterial line will be placed in the arm contralateral to the intravenous line that is used for the [¹¹C]PBR28 radiotracer injection and will enable blood sampling at various times during the imaging study for at most 160 mL of blood. The collected arterial blood will be used to compute metabolite-corrected arterial input function for

Table 2 Schedule of assessments

	Assessment	Screen	Baseline scan	Week 1	Week 2	Week 3	Post-Tx scan (Week 4)	Week 6
Eligibility and safety assessments	Consent form	x						
	Characterisation of pain	x						
	Physical examination	x						
	Medical history	x						
	Concomitant medications	x	x					
	Adverse events		x	x	x	x	x	x
	C-SSRS (suicidality)	x	x		x		x	x
	Urine drug test (10-Panel)	x	x				x	
	Urine pregnancy test	x						
	Serum pregnancy test		x				x	
	Liver function tests	x					x	
Primary outcome	[¹¹ C]PBR28 Signal in Thalamus		x				x	
Secondary outcomes	[¹¹ C]PBR28 Signal in Limbic Regions (pgACC, aMCC)		x				x	
	'Worst Pain' item of BPI-SF (0–10 scale)	<i>Daily survey ratings from ~2 weeks before scan 1 until Week 6</i>						
	Pain Bothersomeness Ratings (0–10 scale)	<i>Daily survey ratings from ~2 weeks before scan 1 until Week 6</i>						
	BDI-II	x	x				x	x
	PGIC						x	
Exploratory outcomes	Reward Task (MID)		x				x	
	BPI-SF	x	x				x	x
	PCS		x		x		x	x
	PainDETECT		x				x	
	ODI		x				x	
	ACR Fibromyalgia Survey		x		x		x	
	Depression Ratings (0–10 scale)	<i>Daily survey ratings from ~2 weeks before scan 1 until week 6</i>						
	PROMIS-29		x				x	
	PSQI	x	x				x	
	SymptomMapper		x				x	

BDI-II, Beck Depression Inventory; BPI-SF, Brief Pain Inventory-Short Form; MID, Monetary Incentive Delay Task; ODI, Oswestry Disability Index; PCS, Pain Catastrophizing Scale; PGIC, Patient Global Impression of Change; PROMIS-29, Patient Reported Outcomes Measurement Information System-29; PSQI, Pittsburgh Sleep Quality Index.

kinetic modelling analyses. Brain PET/MRI data will be acquired for approximately 90 min postinjection. Between 90 min and 110 min post-injection, we may acquire spinal cord data from the thoracic and upper lumbar spine and evaluate the signal from the most caudal segments of the spinal cord, as this region also demonstrated neuroinflammation in our prior study of patients with lumbar radiculopathy.⁵²

Our primary metric for brain [¹¹C]PBR28 signal quantification will be standardised uptake value ratio (SUVR), using the whole brain as a normalising factor (as described in prior work^{51 53 93}). In patients with arterial blood data available, we will compute distribution volume

(V_T) and ratio of distribution volume, which will be used as secondary outcome measures and to support the use of SUVR as an outcome metric. For spinal cord analyses, signal will be quantified by normalising the signal from the lowest 1–2 spinal segments present in the field of view for most/all of our participants (eg, T11-L1) with that of the uppermost 2–3 segments (eg, T7-T9) as in Albrecht *et al.*⁵²

In addition to PET scans, other neuroimaging measures (Diffusion Tensor Imaging, Blood Oxygenation Level Dependent (BOLD) resting-state functional connectivity, ¹H-magnetic resonance spectroscopy (MRS), and arterial spin labelling (ASL)) measures will be collected. We will also collect fMRI measures during a reward task (Monetary

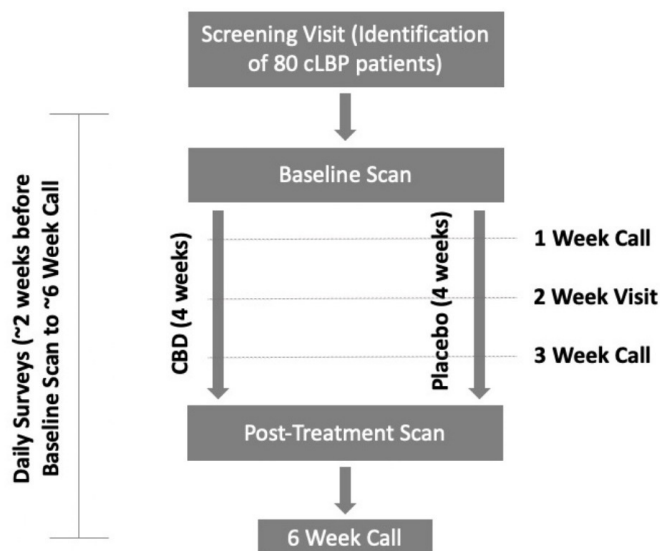


Figure 1 Study schema. CBD, cannabidiol; cLBP, chronic low back pain.

Incentive Delay Task⁹⁴). We have previously used this task to demonstrate striatal hypofunction, linked to depressive symptoms and anhedonia, in patients with cLBP.⁹⁵

Daily surveys

Beginning 2 weeks before the first scan to week 6, participants will complete online daily surveys assessing various domains, including their clinical pain ratings (as measured by the ‘worst pain’ item of the Brief Pain Inventory-Short Form, BPI-SF⁹³), pain bothersomeness ratings and depression ratings, each on a 0–10 scale. Participants will be asked to confirm daily medication adherence and will be asked about use of additional medications for pain management.

Data management

Data will be collected and entered by study staff into a REDCap database,⁹⁶ which has been designed and completed by the study team. Data obtained during assessments administered by study staff will be entered by study staff. Following each visit, data will be checked by the data manager and/or research coordinator to ensure data quality and completeness. All PET/MRI scans will undergo standard quality control to look for imaging artifacts. For instance, any participant whose scan shows excessive head movement (eg, between-frame motion that cannot be easily corrected in post-processing) or issues with attenuation correction that cannot be remediated via post-processing will be excluded from final analyses. Daily survey data will be included for participants responding to at least half of the daily surveys, including at least four of the seven daily surveys during the fourth week of study drug administration.

Statistical plan

A generalised linear mixed-effects model (GLMM) will be used to quantify the association between thalamic [¹¹C]PBR28 PET signal, treatment assignment at randomisation

(CBD, placebo; intent-to-treat) and time (baseline, week 4). The unadjusted model will only regress PET signal onto treatment and time indicators as well as their interaction. An adjusted model will also be constructed that independently accounts for potentially confounding variables (eg, age, depression severity, sex). Data dependencies will be accounted for using either random intercept or line (intercept and slope) parameterisations. To fully specify our GLMMs, we will initially consider the Gaussian family (identity link). Since PET signal is a strictly positive quantity, we will also consider the binomial family with the cumulative logit link. A residual analysis will be performed to assess modelling assumptions and guide our choice in determining the final model.

Our primary object of inference will be the treatment by time interaction, which reflects the absolute difference in the rates of change in PET signal between treatment groups (Gaussian family) or the relative change in odds of having a higher PET signal between treatment groups (binomial family) when holding all other covariates fixed. Linear combinations of parameter estimates will also be computed to summarise secondary objects of interest, including cross-sectional treatment comparisons (baseline: CBD vs control; week 4: CBD vs control) and treatment-specific temporal comparisons (CBD: week 4 vs baseline; control: week 4 vs baseline).

This analysis plan will be repeated using a per-protocol definition of treatment in which we omit subjects who did not reliably take the study medication. Additional secondary and exploratory analyses (box 1) will follow a similar analysis plan as described above. For these non-primary analyses, we will account for multiple comparisons by computing both unadjusted p values and false discovery rate adjusted p values.⁹⁷ Since we are randomising the treatment groups, confounding variables should be balanced between the groups—and, thus, we do not plan to adjust for confounding variables. However, if we do find that despite randomisation, there are imbalances between groups, we will adjust for potential confounding variables using directed acyclic graphs to determine which confounders may be an issue, and will control for these variables.

OUTCOME MEASURES

Power justification

Primary outcome. Using a linear mixed-effects model, we estimate the power to detect a temporal (week 4—baseline) rate of change in thalamic [¹¹C]PBR28 PET signal between CBD and control subjects when recruiting 40 subjects per treatment group. We assume: (1) the SD of the [¹¹C]PBR28 PET signal measures are 0.05,⁹⁸ (2) the correlation between repeated measurements ranges between 0.3 and 0.8 and (3) the attrition rate ranges between 5% and 15% and the type-I error is 0.05. If the within-subject correlation is 0.3, and the attrition rate for both treatment groups is 10%, then we will have 80% and 90%, power to detect mean differences in [¹¹C]PBR28

Box 1 Outcome measures

Primary outcome measure

1. Translocator protein (TSPO) signal from the thalamus (as measured with [¹¹C]PBR28 PET).

Secondary outcome measures

1. Daily clinical pain ratings (as measured by the 'worst pain' item of the Brief Pain Inventory-Short Form (BPI-SF) assessed in daily surveys).
2. TSPO signal from limbic regions (pregenual anterior cingulate cortex (pgACC) and anterior midcingulate cortex (aMCC); as measured with [¹¹C]PBR28 PET).
3. Daily pain bothersomeness ratings (daily survey).
4. Depressive symptoms (Beck Depression Inventory, BDI-II¹⁰⁵)*.
5. Quality of life (Patient Global Impression of Change*; assessed at post-treatment scan only).
6. Correlation between reductions in TSPO signal from the thalamus (as measured with [¹¹C]PBR28 PET) and reductions in clinical pain ratings.
7. Correlation between reductions in TSPO signal from limbic regions (as measured with [¹¹C]PBR28 PET) and reductions in depressive symptoms (as measured by BDI-II).

Exploratory outcome measures

1. Pain severity and interference (BPI-SF)*.
2. Pain catastrophising (Pain Catastrophizing Scale¹⁰⁶)*.
3. Neuropathic pain (PainDETECT¹⁰⁷)*.
4. Disability related to low back pain (Oswestry Disability Index¹⁰⁸)*.
5. Widespread pain and fibromyalgia symptom severity (American College of Rheumatology's fibromyalgia survey¹⁰⁹)*.
6. Daily depression ratings (daily survey).
7. Widespreadness of pain sensation (SymptomMapper app¹¹⁰).
8. Health-related quality of life (Patient Reported Outcomes Measurement Information System–29¹¹¹)*.
9. Sleep quality (Pittsburgh Sleep Quality Index¹¹²)*.
10. Spinal cord TSPO signal (as measured with [¹¹C]PBR28 PET).
11. Striatal activation to a reward task (Monetary Incentive Delay Task⁹⁴).
12. Other neuroimaging measures (Diffusion Tensor Imaging, Blood Oxygenation Level Dependent (BOLD) resting-state functional connectivity, ¹H-magnetic resonance spectroscopy to measure brain metabolites and ASL).

*Total score of these measures will be used in analyses.

PET signal measures of at least 0.039 and 0.045, respectively (table 3).

Missing data

All attempts will be made to minimise missing data, but, if present, we plan to multiply impute all missing imaging and behavioral data and make inferences using combined estimates of the fixed effects and their covariance matrices.⁹⁹ As a sensitivity analysis, we will repeat each analysis on the subset of subjects with complete imaging or behavioral data.

Adverse events

From the baseline scan to week 6, research coordinators will ask participants on a weekly basis to report any AEs (eg, tiredness, decreased appetite, diarrhoea), and, together with the study physicians and

principal investigators, will assess the severity of the events and whether the event is related to their participation in the study. A serious AE is an event that is deemed life threatening, requires hospitalisation, causes permanent damage or requires medical intervention to prevent permanent damage or results in death. Reporting and handling of AEs will be in accordance with Institutional Review Board regulations and good clinical practice guidelines.

Unblinding

All members of the trial team and patients are blinded to the trial drug throughout the trial. Unblinding will only occur if a participant experiences an AE for which the clinical management of the AE will be facilitated by the unblinding of the participant's treatment allocation. All recruited participants will be given contact details for the trial team, including emergency contact available 24 hours a day, 7 days per week.

Data and safety monitoring

A Data Safety Monitoring Board (DSMB) has been established for this study, consisting of a statistician, a pain expert and a psychiatrist (see online supplemental file 3 for DSMB Charter). The DSMB members have no competing interests and will ensure the safe use of the study drug throughout the project. The DSMB will also monitor the occurrence of all AEs on a quarterly basis. To perform this function, the DSMB will have independent access as necessary to the study drug code, indicating on which date the subject received CBD or placebo. The DSMB will review all unanticipated problems involving risk to participants or others, serious AEs. The DSMB will comment on the outcomes of the event and, in the case of a serious AE, determine the relationship to participation in the study.

Interim analyses will be performed on study data only when requested by the DSMB to assess the safety and efficacy of the ongoing study. The results of these analyses will be made available to the Institutional Review Board and the National Institute on Drug Abuse in accordance with annual reporting requirements or sooner if necessary.

Early termination of the trial

The DSMB will monitor the occurrence of all AEs on a quarterly basis to ensure that their rate and severity are acceptable within the overall risk/benefit ratio of the study.

Withdrawal from the study

Participation in this study is voluntary and individuals may choose to stop participation at any time. Participants will be told at consent to inform study staff if they wish to stop taking the study drug at any point, and reasons for withdrawal will be documented. Those who choose to stop taking the study drug will be asked to continue to follow the schedule of visits if they are willing. The study physician may also withdraw a participant from the study

Table 3 Detectable mean differences in rates of SUVR change between treatment groups as a function of within subject correlation, attrition, sample size and power

Within subject correlation	Attrition, %	Sample size	Detectable mean difference	
			Power=0.80	Power=0.90
0.3	0	80(40/40)	0.037	0.042
0.3	5	76(38/38)	0.038	0.044
0.3	10	72(36/36)	0.039	0.045
0.3	15	68(34/34)	0.040	0.047
0.5	0	80(40/40)	0.031	0.036
0.5	5	76(38/38)	0.032	0.037
0.5	10	72(36/36)	0.033	0.038
0.5	15	68(34/34)	0.034	0.039
0.8	0	80(40/40)	0.020	0.023
0.8	5	76(38/38)	0.020	0.024
0.8	10	72(36/36)	0.021	0.024
0.8	15	68(34/34)	0.021	0.025

without their permission if they cannot follow the study plan, or for medical reasons such as side effects from the study drug.

Confidentiality

Study staff will adhere to the confidentiality requirements set by the Massachusetts General Brigham Human Research Committee. Data on computers will be password protected, and all paper records are secured in a locked office. Any samples that are stored will be labeled with a code; no names or other identifying information will be on these samples.

Patient and public involvement

Neither patients nor the public were involved in the development, design and conduct of this study. Results of the study will be shared with the public through conference presentations and publications in peer-reviewed journals.

ETHICS AND DISSEMINATION

This protocol is approved by the Massachusetts General Brigham Human Research Committee (Protocol Number: 2021P002617) and the United States Food and Drug Administration (IND number: 143861). Informed consent will be obtained from all participants by a physician, nurse practitioner or the principal investigator. Important protocol modifications will be submitted to the Human Research Committee for approval and then communicated to participants. Findings from this trial will be presented in peer-reviewed journals and at national conferences. Data will be deidentified in all cases.

Author affiliations

¹Department of Psychiatry, Massachusetts General Hospital, Boston, Massachusetts, USA

²Massachusetts General Hospital Department of Radiology, Athinoula A. Martinos Center for Biomedical Imaging, Charlestown, Massachusetts, USA

³Department of Psychiatry, Harvard Medical School, Boston, Massachusetts, USA

⁴Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts, USA

⁵Department of Radiology, Harvard Medical School, Boston, Massachusetts, USA

⁶Department of Anesthesiology, Brigham and Women's Hospital, Boston, Massachusetts, USA

⁷Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Charlestown, Massachusetts, USA

⁸Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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ORCID iDs

Erin Janas Morrissey <http://orcid.org/0000-0002-8491-4963>

Jodi M Gilman <http://orcid.org/0000-0001-5180-6694>

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