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

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3 **Study protocol for a phase II, double-blind, randomized controlled trial of cannabidiol**
4 **(CBD) compared to placebo for reduction of brain neuroinflammation in adults with**
5 **chronic low back pain**
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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 neuro-glial interactions play a role in the establishment and maintenance of pain. Recently, we used positron emission tomography (PET) to demonstrate increased levels of 18kDa 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 to placebo, affects neuroinflammation, as measured by TSPO levels.

Methods and analysis: This is a double-blind, randomized, placebo-controlled, phase II clinical trial. Eighty adults (aged 18-75) with cLBP for > 6 months will be randomized 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/magnetic resonance imaging (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 randomized to CBD will demonstrate larger reductions in thalamic [¹¹C]PBR28 signal compared to 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 low back pain 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 U.S. Food and Drug Administration (IND Number: 143861) and registered with ClinicalTrials.gov (NCT04827992). Results will be published in peer-reviewed journals and presented at conferences.

Registration details: ClinicalTrials.gov (NCT05066308)

Strengths and limitations of this study:

- To our knowledge, this is among the largest double-blind, randomized, placebo-controlled clinical trials to evaluate a pain intervention using PET.
- This is the first trial to assess whether 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.

INTRODUCTION

Chronic pain affects an estimated 50 to 100 million individuals in the United States[1, 2] and is among the most debilitating medical conditions with profound physical, emotional, and economic costs.[3] Available treatment options including interventional techniques[4] and non-opioid pain medications such as non-steroidal anti-inflammatory drugs[5] 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 neuro-glial 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 sensitize pain pathways[39] in a “pain-produces-pain” loop. Importantly, agents that disrupt glial function inhibit or attenuate various behavioral markers of pain hypersensitivity (e.g., 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 18kDa translocator protein (TSPO), a marker of glial activation,[16, 42-50] in the brains[51] and spinal cords[52] of patients with chronic low back pain (cLBP) compared to controls. These TSPO signal elevations were consistently observed, particularly in the thalamus, in our original study[51] 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) receptors,[58] 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 pre-clinical 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 pro-inflammatory 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

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3 Medicine reported that there was substantial evidence that cannabis was effective in treating
4 chronic pain.[72] Such inconsistencies may be partially explained by heterogeneity in methods
5 across studies (with some lacking a placebo control), by the fact that meta-analyses often
6 combine results from studies using various combinations and doses of cannabinoids[73, 74] (e.g.,
7 varying THC/CBD potencies), and by combining studies addressing different kinds of pain.
8 Perhaps more problematic is the fact that many commercial CBD products available are of
9 unknown quality and contain variable doses of the active ingredient.[75] In the current study, we
10 will use Epidiolex, the first and only FDA-approved drug containing a known and consistent
11 dose of purified CBD. Thus, the current study will assess whether an FDA-approved CBD
12 formulation, in a known dose, compared to placebo, reduces neuroinflammation in patients with
13 cLBP.
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16 This study will also assess the role of CBD on neuroinflammation with respect to
17 depressive symptoms. Comorbid depression and chronic pain is common, with approximately
18 40% of cLBP patients also exhibiting negative affect, including depressive symptoms.[76-79]
19 Depression has been associated with neurobiological changes, including neurotransmitter
20 deficits, endocrine disturbances, and impaired neural adaptation and plasticity,[80, 81] and
21 neuroinflammation may be implicated in these abnormalities.[82] Those with depression who
22 commit suicide have shown dramatically increased microglial activation.[83] Indeed, cLBP
23 patients who also have comorbid depression demonstrate, in addition to thalamic TSPO signal
24 elevations observed irrespectively of depression status, also TSPO signal elevations in limbic
25 regions, which are proportional to the scores on the Beck Depression Inventory.[84] Meta-
26 analyses have shown that mechanistically diverse anti-inflammatory agents may be effective
27 treatments for depression.[85-87] Preliminary evidence suggests that CBD promotes
28 antidepressant effects in animal models,[67, 68] however randomized clinical trials of CBD for
29 treatment of depression have not been conducted. Therefore, a secondary objective of the study
30 is to assess whether CBD compared to placebo reduces depressive symptomatology and
31 depression-related neuroinflammation in patients with cLBP.
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34 Healthcare providers are increasingly interacting with patients who are interested in using
35 CBD for various pain disorders, with little evidence available for therapeutic guidance. Results
36 from this study will provide critical information regarding the potential utility of CBD for cLBP
37 and its involvement in mechanistic pathways of neuroinflammation.
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40 **METHODS AND ANALYSIS**

41 The full protocol is included as supplementary information (see Supplementary File 1).
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44 **Study design**

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

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We will recruit a total of 80 cLBP patients aged 18 to 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 six 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]PBR28[88]; the rs6971 polymorphism allows for the identification of low, mixed or high affinity binders.[89, 90] In this study, only high or mixed-affinity binders will be considered eligible. Any ongoing pain treatment (pharmacologic or behavioral) must be stable for four weeks prior to randomization.

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 two weeks, or regular recreational drug use in the previous three months. See Table 1 for the full list of inclusion and exclusion criteria.

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	<ol style="list-style-type: none"> 1. Age \geq 18 and \leq 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 behavioral) for the previous four 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 hospitalization 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 hospitalization
 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 (e.g., peripheral edema)
 16. Use of immunosuppressive medications, such as prednisone, 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 individualized basis with a physician:
 - Strong and moderate inhibitors of CYP3A4 and CYP2C19 (e.g., diltiazem, erythromycin, fluoxetine)
 - Sensitive and moderately sensitive substrates of CYP2C19, CYP1A2, CYP2B6, CYP2C8, CYP2C9, UGT1A9, and UGT2B7 (e.g., omeprazole, bupropion, morphine, lamotrigine)
 21. CNS depressants including antipsychotics, benzodiazepines (except for alprazolam, clonazepam, and lorazepam, which have low binding affinity to TSPO[91-95]), 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 behavior 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 (e.g., unable to reliably rate pain, unlikely to remain still during the imaging procedures)
-

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

Supplementary File 2 for a copy of the consent form). Eligibility assessments will be conducted during the screening visit, listed in Table 2.

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						
	Characterization 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

Investigational product

Participants will be randomized 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 flavoring. 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 twice daily in week one, 5 mg/kg twice daily in week two, 7.5 mg/kg twice daily in week three, and 10 mg/kg twice daily in week four. If participants report significant adverse events (e.g., 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.

Randomization and treatment allocation

Eligible participants will be enrolled by study staff and randomized to receive either CBD or placebo. Stratified simple random sampling, based on age (>50 vs. ≤50) and sex (male vs. female), will be performed. Randomization sheets have been developed by the study biostatistician and will be used by a study pharmacist to assign treatments. The MGH Clinical Trial 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 randomization, 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 four 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. Adverse events will be assessed at baseline and weeks 1, 2, 3, 4, and 6 (two 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. 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 childbearing 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

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2
3 levels of cannabinoids, including CBD and THC. An arterial line will be placed in a radial artery
4 with local anesthesia if the participant has consented to this (optional) procedure and has no
5 contraindications. The arterial line will be placed in the arm contralateral to the intravenous line
6 that is used for the [¹¹C]PBR28 radiotracer injection, and will enable blood sampling at various
7 times during the imaging study for at most 160 mL of blood. The collected arterial blood will be
8 used to compute metabolite-corrected arterial input function for kinetic modeling analyses. Brain
9 PET/MRI data will be acquired for approximately 90 min post-injection. Between 90- and 110-
10 min post-injection, we may acquire spinal cord data from the thoracic and upper lumbar spine
11 and evaluate the signal from the most caudal segments of the spinal cord, as this region also
12 demonstrated neuroinflammation in our prior study of patients with lumbar radiculopathy.[52]

13
14 Our primary metric for brain [¹¹C]PBR28 signal quantification will be standardized
15 uptake value ratio (SUVR), using the whole brain as a normalizing factor (as described in prior
16 work[51, 53, 96]). In patients with arterial blood data available, we will compute distribution
17 volume (V_T) and ratio of distribution volume (DVR), which will be used as secondary outcome
18 measures and to support the use of SUVR as an outcome metric. For spinal cord analyses, signal
19 will be quantified by normalizing the signal from the lowest 1-2 spinal segments present in the
20 field of view for most/all of our participants (e.g., T11-L1) with that of the uppermost 2-3
21 segments (e.g., T7-T9) as in Albrecht et al.[52]

22
23 In addition to PET scans, other neuroimaging measures (Diffusion Tensor Imaging (DTI),
24 BOLD resting-state functional connectivity, ¹H-magnetic resonance spectroscopy (MRS), and
25 arterial spin labelling (ASL)) measures will be collected. We will also collect fMRI measures
26 during a reward task (Monetary Incentive Delay Task, MID[97]). We have previously used this
27 task to demonstrate striatal hypofunction, linked to depressive symptoms and anhedonia, in
28 cLBP patients.[98]

31 32 **Daily surveys**

33 Beginning two weeks before the first scan to week 6, participants will complete online
34 daily surveys assessing various domains, including their clinical pain ratings (as measured by the
35 “worst pain” item of the Brief Pain Inventory – Short Form, BPI-SF[96]), pain bothersomeness
36 ratings, and depression ratings, each on a 0-10 scale. Participants will be asked to confirm daily
37 medication adherence and will be asked about use of additional medications for pain
38 management.
39
40

41 **Outcome measures**

42 **Box 1. Outcome measures**

43 **Primary outcome measure**

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

45 46 **Secondary outcome measures**

- 47 1. Daily clinical pain ratings (as measured by the “worst pain” item of the BPI-SF
48 assessed in daily surveys)
- 49 2. TSPO signal from limbic regions (pregenual anterior cingulate cortex (pgACC) and
50 anterior midcingulate cortex (aMCC); as measured with [¹¹C]PBR28 PET)
- 51 3. Daily pain bothersomeness ratings (daily survey)
- 52 4. Depressive symptoms (Beck Depression Inventory, BDI-II[99])*

5. Quality of life (Patient Global Impression of Change*; assessed at post-treatment scan only)

Exploratory outcome measures

1. Pain severity and interference (BPI-SF)*
2. Pain catastrophizing (Pain Catastrophizing Scale, PCS[100])*
3. Neuropathic pain (PainDETECT[101])*
4. Disability related to low back pain (Oswestry Disability Index, ODI[102])*
5. Widespread pain and fibromyalgia symptom severity (American College of Rheumatology's fibromyalgia survey[103])*
6. Daily depression ratings (daily survey)
7. Widespreadness of pain sensation (SymptomMapper app[104])
8. Health-related quality of life (Patient Reported Outcomes Measurement Information System – 29, PROMIS-29[105])*
9. Sleep quality (Pittsburgh Sleep Quality Index, PSQI[106])*
10. Spinal cord TSPO signal (as measured with [¹¹C]PBR28 PET)
11. Striatal activation to a reward task (Monetary Incentive Delay Task, MID[97])
12. Other neuroimaging measures (Diffusion Tensor Imaging (DTI), BOLD resting-state functional connectivity, ¹H-magnetic resonance spectroscopy (MRS) to measure brain metabolites, and arterial spin labelling (ASL))

*Total score of these measures will be used in analyses

Data management

Data will be collected and entered by study staff into a REDCap database,[107] 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 (e.g., between-frame motion that cannot be easily corrected in post-processing) or issues with attenuation correction that cannot be remediated via postprocessing 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 generalized linear mixed-effects model (GLMM) will be used to quantify the association between thalamic [¹¹C]PBR28 PET signal, treatment assignment at randomization (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 (e.g., age, depression severity, sex). Data dependencies will be accounted for using either random intercept or line (intercept and slope) parametrizations. 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 modeling 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 summarize 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.[108]

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 standard deviations of the [¹¹C]PBR28 PET signal measures are 0.05,[109] (2) the correlation between repeated measurements ranges between 0.3 to 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 PET signal measures of at least 0.039 and 0.045, respectively (Table 3).

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

Missing data

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3 All attempts will be made to minimize missing data, but if present, we plan to multiply
4 impute all missing imaging and behavioral data and make inferences using combined estimates
5 of the fixed effects and their covariance matrices.[110] As a sensitivity analysis, we will repeat
6 each analysis on the subset of subjects with complete imaging or behavioral data.
7

8 9 **Adverse events**

10 From the baseline scan to week 6, research coordinators will ask participants on a weekly
11 basis to report any adverse events (AEs; e.g., tiredness, decreased appetite, diarrhea), and,
12 together with the study physicians and principal investigators, will assess the severity of the
13 events and whether the event is related to their participation in the study. A serious adverse event
14 (SAE) is an event that is deemed life-threatening, requires hospitalization, causes permanent
15 damage or requires medical intervention to prevent permanent damage, or results in death.
16 Reporting and handling of adverse events will be in accordance with Institutional Review Board
17 regulations and good clinical practice guidelines.
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20 21 **Unblinding**

22 All members of the trial team and patients are blinded to the trial drug throughout the
23 trial. Unblinding will only occur if a participant experiences an AE for which the clinical
24 management of the AE will be facilitated by the unblinding of the participant's treatment
25 allocation. All recruited participants will be given contact details for the trial team including
26 emergency contact 24 hours a day, 7 days per week.
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28 29 **Data and safety monitoring**

30 A Data Safety Monitoring Board (DSMB) has been established for this study, consisting
31 of a statistician, a pain expert, and a psychiatrist (see Supplementary File 3 for DSMB Charter).
32 The DSMB members have no competing interests and will ensure the safe use of the study drug
33 throughout the project. The DSMB will also monitor the occurrence of all adverse events on a
34 quarterly basis. To perform this function, the DSMB will have independent access as necessary
35 to the study drug code, indicating on which date the subject received CBD or placebo. The
36 DSMB will review all unanticipated problems involving risk to participants or others, serious
37 adverse events. The DSMB will comment on the outcomes of the event and, in the case of a
38 serious adverse event, determine the relationship to participation in the study.
39

40 Interim analyses will be performed on study data only when requested by the DSMB to
41 assess the safety and efficacy of the ongoing study. The results of these analyses will be made
42 available to the IRB and NIDA in accordance with annual reporting requirements or sooner if
43 necessary.
44

45 46 **Early termination of the trial**

47 The DSMB will monitor the occurrence of all adverse events on a quarterly basis to
48 ensure that their rate and severity are acceptable within the overall risk/benefit ratio of the study.
49

50 51 **Withdrawal from the study**

52 Participation in this study is voluntary and individuals may choose to stop participation at
53 any time. Participants will be told at consent to inform study staff if they wish to stop taking the
54 study drug at any point, and reasons for withdrawal will be documented. Those who choose to
55 stop taking the study drug will be asked to continue to follow the schedule of visits if they are
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3 willing. The study physician may also withdraw a participant from the study without their
4 permission if they cannot follow the study plan, or for medical reasons such as side effects from
5 the study drug.
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7 **Confidentiality**

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

15 Neither patients nor the public were involved in the development, design, and conduct of
16 this study. Results of the study will be shared with the public through conference presentations
17 and publications in peer-reviewed journals.
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20 **ETHICS AND DISSEMINATION**

21 This protocol is approved by the Massachusetts General Brigham Human Research
22 Committee (Protocol Number: 2021P002617) and the United States Food and Drug
23 Administration (IND Number: 143861). Informed consent will be obtained from all participants
24 by a physician, nurse practitioner, or the principal investigator. Important protocol modifications
25 will be submitted to the Human Research Committee for approval and then communicated to
26 participants. Findings from this trial will be presented in peer-reviewed journals and at national
27 conferences. Data will be deidentified in all cases.
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3 **Authors' contributions:** JMG and MLL developed and designed the trial and obtained funding
4 for the trial. CKP and MK wrote the first draft of this manuscript. JMG, MLL, KS, RE, VN, YZ,
5 ZA, AEE, CKP, and MK assisted with the study design. NM designed the statistical aspects of
6 this protocol. All were involved in the revision of the manuscript. All authors approved the final
7 version to be submitted.
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11 **Funding statement:** This work is supported by NIH grant number 1R01DA053316-01. The NIH
12 has not had nor will have any role in the design of the study, the collection, management,
13 analysis, and interpretation of data, the writing of manuscripts, or the decision to submit the
14 report for publication.
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18 **Competing interests statement:** The study drug was donated by Jazz Pharmaceuticals. Dr.
19 Loggia consulted for Shionogi in 2018. Dr. Evins reported receiving grants from Charles River
20 Analytics and nonfinancial support from Pfizer as well as serving as the chair of the data
21 monitoring board of Karuna Pharmaceuticals outside the submitted work. Dr. Napadow consults
22 for Cala Health, Inc. and Click Therapeutics, Inc. All other authors declare that they have no
23 competing interests.
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27 **Data sharing statement:** All data, code, and materials used in the analyses can be provided by
28 Jodi Gilman and Marco Loggia and Massachusetts General Hospital pending scientific review
29 and a completed data use agreement/material transfer agreement beginning one year after
30 publication of the results. Requests for all materials should be submitted to Jodi Gilman at
31 jgilman1@mgh.harvard.edu.
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35 **Ethics approval:** Massachusetts General Brigham IRB Protocol Number 2021P002617.
36 Protocol version 6.0 (dated March 16, 2022) is currently in use.
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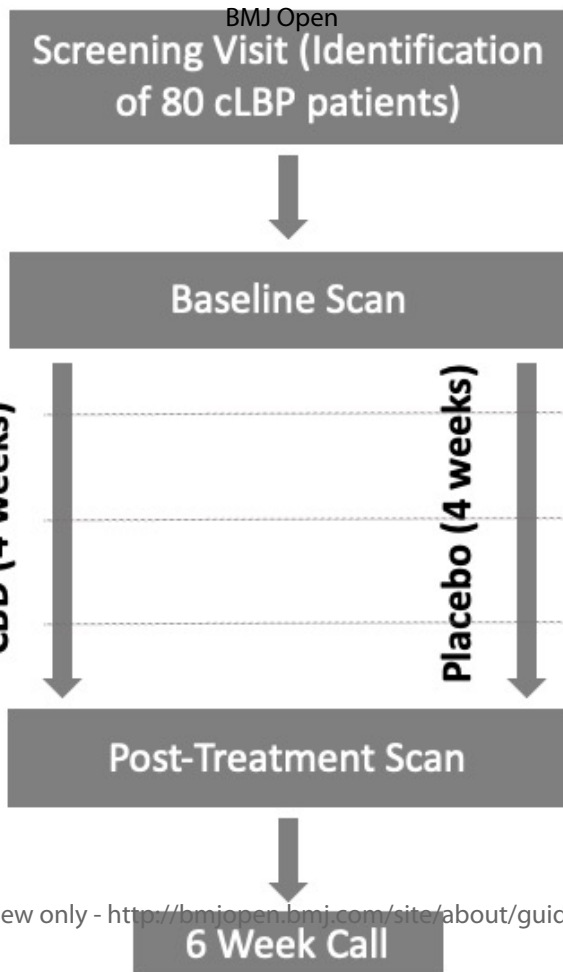
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Figure Legends
Figure 1. Study schema

For peer review only

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Daily Surveys (~2 weeks before
Baseline Scan to ~6 Week Call



CBD (4 weeks)

Placebo (4 weeks)

1 Week Call
2 Week Visit
3 Week Call

Institutional Review Board Intervention/Interaction Detailed Protocol

Principal Investigator: Jodi Gilman, PhD

Project Title: Evaluation of Cannabidiol (CBD) for Reduction of Brain Neuroinflammation

Version Date: 3/16/2022

For Intervention/Interaction studies, submit a Detailed Protocol that includes the following sections. If information in a particular section is not applicable, omit and include the other relevant information.

1. Background and Significance

Millions of individuals suffer from chronic pain

Chronic pain is defined as pain without apparent biological value that has persisted beyond the normal tissue healing time (usually taken to be 3 or 6 months^{1,2}). Chronic pain is a widespread public health issue³, and its prevalence is enormous. The weighted mean prevalence of chronic pain in the general population has been estimated by some at 35.5%, or 105 million, in the United States⁴. Not only does chronic pain affect both physical and mental functioning, thus compromising quality of life; it is also associated with astronomical costs. In addition to the direct costs of treating pain—including health care for diagnosis and treatment, drugs, therapies, and other medical expenses—chronic pain results in lost work time and reduced productivity^{5,6}. Past estimates of the annual cost of chronic pain in the United States, including healthcare expenses, lost income and productivity, were close to \$100 billion⁷.

Treatment for chronic pain is unsatisfactory

Despite the enormity of the phenomenon, clinical needs for chronic pain are largely unmet. The treatment of choice for the largest majority (as many as 90%⁸) of patients seeking chronic pain management is based on opioid analgesics. However, the evidence supporting long-term effectiveness of opioid drugs in relieving pain and improving functional status is weak⁹. For instance, despite the widespread use of opioids for palliative care, more than half of all hospitalized patients experience pain in the last days of their lives, and 50-75% of cancer patients die in moderate to severe pain¹⁰.

The current opioid-based pharmacological approaches to treat chronic pain are not only ineffective, but they generally have multiple unpleasant side effects, including constipation, pruritus, respiratory depression, nausea, vomiting, hyperalgesia, dizziness, sedation⁹, as well as abuse and dependence^{8,11,12}. Taken together, the unsatisfactory treatment efficacy and the occurrence of significant side effects, clearly stress the importance of achieving a deeper

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understanding of the pathophysiological mechanisms underlying chronic pain, in order to eventually identify viable treatment options alternative to ones currently available.

Microglia and pain

One of the reasons for the poor efficacy of the treatment options currently available for chronic pain might be that these are primarily aimed at suppressing neuronal activity within nociceptive pathways of the nervous system. However, it is now increasingly clear that neurons are far from being the only players that drive the establishment and/or maintenance of clinical pain symptoms. Rather, evidence from animal studies now suggests a central role of glial cells in the nervous system, including microglia^{13,14}.

Microglia are a subpopulation of macrophages that rapidly activate in response to a variety of pathological conditions¹⁵, including persistent pain¹⁶⁻²³. Microglial activation (MA) is characterized by a stereotypic pattern of cellular responses, including specific morphological changes, proliferation, increased or de-novo expression of cell surface markers or receptors, and migration to the site of injury²⁴. MA generally represents an adaptive homeostatic defense response which enables the destruction of invading micro-organisms, the removal of potentially deleterious debris as well the promotion of tissue repair. However, animal studies have now showed that the uncontrolled activation of microglial cells under pathological pain conditions induces the release of substances that can sensitize pain pathways, such as proinflammatory cytokines, complement components, and others²⁵. While evidence of pain-related MA was originally observed in the spinal cord, more recently it was also discovered at the level of the brain, including in the rostral ventromedial medulla^{20,26}, the trigeminal nuclear complex^{19,27}, and the ventral posterolateral nucleus of the thalamus^{28,29}.

While most of the evidence on the occurrence of pain-related glial responses in the central nervous system comes from animal studies, a few important observations indicate that similar phenomena should occur also in humans¹³. First, immunohistochemical markers of microglial and astroglial activation have been detected in the spinal cord of a patient with chronic regional pain syndrome in a postmortem study³⁰. Furthermore, an increase in the concentration of the glial marker s-100 β was reported in the cerebrospinal fluid of patients with lumbar disc herniation and in the serum of children with recurrent headaches^{31,32}. Finally, a positron emission tomography (PET) study has revealed that human subjects with neuropathic pain secondary to peripheral nerve damage express increased thalamic binding for [¹¹C](R)-PK11195³³, an in vivo marker of microglial cell activation^{34,35}.

Recently, Co-PI Dr. Marco Loggia has also shown that patients with chronic low back pain (cLBP) have increased brain levels of the 18kDa translocator protein (TSPO), a marker of glial activation³⁶. In addition, preliminary data collected from a different cohort of patients with cLBP and sciatica suggest an increase in spinal cord TSPO levels. Together, these results suggest that human chronic pain conditions are likely to be associated with a glial reaction, both in the spinal cord, as well as in the brain.

Cannabidiol and pain

There is a growing body of evidence to suggest that cannabinoids are beneficial for a range of clinical conditions, including pain, inflammation, epilepsy, and sleep disorders³⁷. A large body of

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preclinical and clinical research indicates that the cannabinoid system modulates a broad range of physiological processes and behaviors including, but not limited to, pain, mood, appetite, neuronal activity, memory, immunity, and cell development. The endocannabinoid system's contribution to the regulation of such a variety of processes makes phytocannabinoid pharmacological modulation a promising therapeutic strategy³⁸.

The primary cannabinoids found in the cannabis plant include delta-9 -tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN), with THC being the primary psychoactive compound. The second most abundant compound in the plant is CBD, which is minimally psychoactive³⁹. Cannabinoid receptor type 1 (CB1) and type 2 (CB2) belong to a family of seven transmembrane Guanosine Binding Protein-Coupled Receptors, and are widely expressed and distinguished by their specific functions, localization and signaling mechanisms. The psychotropic effects of cannabis are principally mediated by CB1, which is widely distributed throughout the brain, while CB2 is considered the peripheral cannabinoid receptor, found mainly in immune cells, as well as in chondrocytes, osteocytes and fibroblasts. Agonists targeting CB2 receptors have been proposed as therapies for the treatment or management of a range of painful conditions, including acute pain, chronic inflammatory pain, and neuropathic pain⁴⁰. In a preclinical model, researchers showed that stimulation of CB2 suppresses microglial activation⁴¹.

In the current study, we will test whether CBD is a glial inhibitor in patients with chronic lower back pain (cLBP) with and without mild-to-moderate depression. CBD was recently FDA-approved as a liquid formulation (see EPIDIOLEX package insert) for epilepsy for children ages 2 and up as well as adults, demonstrating significant reductions in total seizure frequency with minimal side effects. It is unclear whether cannabidiol reduces glial activation in humans. We will study 80 patients diagnosed with chronic low back pain (pain duration > 6 months) longitudinally before and after 4 weeks of treatment with cannabidiol or placebo. Endpoints will be pain scores as well as brain levels of the 18kDa translocator protein (TSPO), a marker of glial activation³⁶.

2. Specific Aims and Objectives

Primary Aim: Assess whether CBD compared to placebo reduces pain-related neuroinflammation in patients with cLBP.

Hypothesis 1: Patients in the CBD arm will demonstrate significantly larger treatment-related reductions in thalamic [¹¹C]PBR28 PET signal, compared to patients in the placebo arm.

Hypothesis 2: In the CBD arm, reductions in thalamic [¹¹C]PBR28 PET signal will be directly proportional to reductions in clinical pain ratings.

Aim 2: Assess whether CBD compared to placebo reduces depression-related neuroinflammation in cLBP patients.

Hypothesis 1: Patients in the CBD arm will demonstrate significantly larger treatment-related reductions in limbic (pgACC, aMCC) [¹¹C]PBR28 PET signal, compared to

patients in the placebo arm.

Hypothesis 2: In the CBD arm, reductions in pgACC/aMCC [^{11}C]PBR28 PET signal will be directly proportional to reductions in depressive symptoms, as measured using the Beck Depression Inventory-II (BDI-II).

Aim 3 (Exploratory): Assess the effect of CBD on functional reward brain circuitry.

Hypothesis 1: Patients in the CBD arm will demonstrate significantly larger treatment-related increases in striatal responses to the anticipation and consumption of rewards/losses in the Monetary Incentive Delay task, compared to patients in the placebo arm. This will be indicative of a possible normalization of striatal function⁴², which we have previously found to be dampened in cLBP (and other pain conditions).⁴³

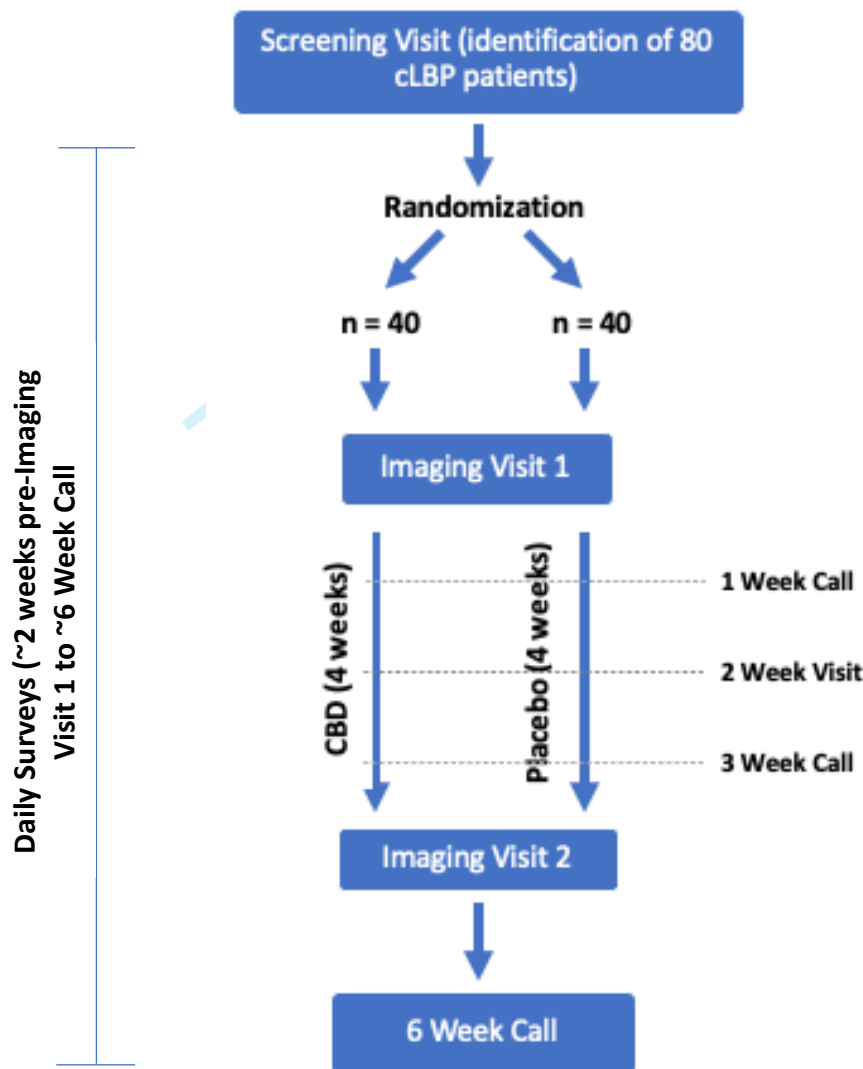
Hypothesis 2: In the CBD arm, increases in striatal activation will be proportional to increases in behavioral facilitation (i.e., slowing of reaction times during loss or rewards trials, indicative of an increase in sensitivity to incentives) and to reductions in depressive symptoms.

3. General Description of Study Design

We will conduct a 4-week randomized, double-blind, 2-arm mechanistic trial that assesses the effects of CBD vs. placebo in 80 patients with cLBP, using PET/MRI scans. Subjects will be randomized to receive either CBD ($n = 40$) or placebo ($n = 40$). Following randomization, subjects will participate in their first imaging visit, during which they will undergo a simultaneous PET/MRI scan and fill out questionnaires assessing their pain and other psychological constructs. At this visit, subjects will receive CBD or placebo, which they will be instructed to take daily for the 4 weeks prior to the date of their second scan. After 2 weeks of taking CBD or placebo, participants will undergo a follow-up appointment with a study clinician. We will also call participants at the end of the first and third weeks of taking CBD or placebo. Then, as soon as possible after the end of the 4-week drug trial period, all subjects will be scanned again and will complete several questionnaires (including some or all of those administered on the first imaging visit) to determine if any changes occurred since they entered the trial. Additionally, from about 2 weeks prior to the first scan and for 2 weeks after discontinuation of CBD or placebo, subjects will be sent a daily survey to assess the effect of the medication on their pain, mental health, sleep quality, fatigue, and other measures. Finally, we will conduct a follow-up call 2 weeks after the discontinuation of CBD or placebo.

Study Schema:

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4. Subject Selection

We plan to identify 80 patients with chronic low back pain (cLBP; i.e., with a pain duration longer than 6 months), who will complete the study. In order to achieve the final sample size of 80 study completers, we will consent up to a total of 150 participants, in order to account for screen fails and attrition. As millions of people in the United States live with chronic low back pain⁴, we believe that our recruitment goal will be attainable.

We are not planning to enroll subjects from at-risk populations (e.g., children and minors, cognitively impaired persons, prisoners). Written informed consent form will be obtained in all cases.

Inclusion Criteria:

1. Age ≥ 18 and ≤ 75 ;

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2. The ability to give written, informed consent;
3. Fluency in English;
4. Average worst daily pain of at least 4 on a 0-10 scale of pain intensity, during a typical day. Pain needs to be present for at least 50% of days during a typical week;
5. On a stable pain treatment (pharmacological or otherwise) for the previous four weeks;
6. Diagnosis of chronic low back pain, ongoing for at least 6 months prior to enrollment.

Exclusion Criteria:

1. Outpatient surgery within 2 weeks and inpatient surgery within 1 month of the time of scanning (this timeframe may be extended if they are not fully recovered from the 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 only if the conditions were so severe as to require hospitalization 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 hospitalization;
12. Major cardiac event within the past 10 years;
13. Regular use of recreational drugs in the past 3 months;
14. Any marijuana use, medical or recreational, in the past 2 weeks;
15. An abnormal physical exam (e.g., peripheral edema);
16. Use of immunosuppressive medications, such as prednisone, 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 individualized basis with a physician:
 - Strong and moderate CYP3A4 inhibitors including boceprevir, cobicistat, conivaptan, danoprevir, elvitegravir, ritonavir, indinavir, itraconazole, ketoconazole, lopinavir, paritaprevir and ombitasvir and/or dasabuvir, posaconazole, saquinavir and telaprevir, tipranavir, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir, troleandomycin, voriconazole, aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone,

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- erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, disulfiram, and verapamil;
- Strong and moderate inhibitors of CYP2C19 including fluoxetine and ticlopidine;
 - Sensitive and moderately sensitive substrates of CYP2C19 including clobazam, lansoprazole, omeprazole, S-mephenytoin, and rabeprazole;
 - Sensitive and moderately sensitive substrates of CYP1A2 including alosetron, duloxetine, ramelteon, tasimelteon, theophylline, tizanidine, pirfenidone, and ramosetron;
 - Sensitive and moderately sensitive substrates of CYP2B6 including bupropion and efavirenz;
 - Sensitive and moderately sensitive substrates of CYP2C8 including repaglinide, montelukast, pioglitazone, and rosiglitazone;
 - Sensitive and moderately sensitive substrates of CYP2C9 including tolbutamide, celecoxib, glimepiride, and warfarin;
 - Sensitive and moderately sensitive substrates of UGT1A9 including diflunisal, propofol, and fenofibrate;
 - Sensitive and moderately sensitive substrates of UGT2B7 including, gemfibrozil, lamotrigine, and morphine;
21. CNS depressants including all antipsychotics, benzodiazepines (except for alprazolam, clonazepam, and lorazepam, which have low binding affinity to TSPO⁴⁴⁻⁴⁸), and non-benzodiazepine sleep aids that have a known unsafe reaction with CBD;
 22. Use of opioids \geq 30 mg morphine equivalents on average per month;
 23. Actively suicidal, history of suicide attempt or an aborted attempt within the last 5 years, or engagement in non-suicidal self-injurious behavior 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 from screening visit;
 27. In the opinion of the investigators, unable to safely participate in this study and/or provide reliable data (e.g., unable to reliably rate pain; unlikely to remain still during the imaging procedures, etc).

Local Recruitment Procedures:

Subjects will be recruited on an ongoing basis by trained study staff. We will identify potential subjects through advertising by flyers and printed announcements posted within as well as outside of our Partners community. In addition, email, web, and bulletin board announcements posted in the community will be used. To recruit subjects, we will also use multiple research databases such as the Partners' RSVP for Health system, Partners Clinical Trials, Rally, EPIC, RPDR, and ResearchMatch, a database of research volunteers developed by Vanderbilt University and approved for use by the PHRC. We will run queries on EPIC and RPDR through MGB to find subjects with chronic low back pain, meeting the eligibility criteria for this research study. Subjects identified through these mechanisms will receive a recruitment letter via Patient Gateway or in the mail from study staff. The letter will not be sent to those who have opted out of receiving research invitations. Other methods that advertise the study to the greater community will be used, including social media posts, posting flyers on community billboards in the Greater Boston area, emails to physicians and family medicine centers, and advertisements in newspapers. All advertisements will briefly describe the study and invite subjects to call if they

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are interested. Newspaper advertisements in particular have been shown to be an effective strategy for recruiting minority populations⁴⁹. Additionally, participants will be offered parking vouchers for each on-site study visit in order to ease financial burden of attendance.

5. Subject Enrollment

Telephone Pre-Screening:

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All subjects will undergo a telephone pre-screening that will distinguish the majority of potentially eligible subjects from those not meeting eligibility criteria. This will consist of a brief discussion of the research study, as well as confirming a potential participant's understanding of the basic study procedures and interest in participation. To determine whether he/she may meet eligibility criteria, we will ask for information including current medications, gender, age, pregnancy status, substance use, and history of psychiatric conditions. Those who are likely to be eligible will be scheduled for an in-person screening visit. Note that in addition to using office phones, any calls made to participants for phone-screening or other reasons throughout the entire study may also be placed using Doximity Dialer, an MGB-approved platform. Also note that participants who express interest in the study may be asked to complete a REDCap survey containing questions from the phone screen, instead of completing the screen via phone call.

Procedures for Obtaining Informed Consent:

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During the in-person screening visit, potential participants will be fully informed of the purpose and activities involved in the research study. Written informed consent will be obtained prior to initiating any of the study procedures. One copy of the signed consent form will be given to the patient and one will be kept in the study files for documentation. No time limits will be imposed on the informed consent process. Participants will be permitted to take as much time as they desire to engage in the informed consent process; any and all of their questions will be answered. It is anticipated that obtaining written informed consent will take approximately 15-25 minutes, on average. Comprehension of the consent information will be assessed via solicitation of answers to questions throughout the process. If comprehension appears to be limited, participants will be actively queried to determine whether they need further explanation.

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In order to comply with public health efforts to address COVID-19, virtual visits may be conducted as necessary. Virtual visits will be conducted via MGB approved platforms (i.e., video calls over Zoom and phone conferences via Cisco Jabber) and will mirror in-person visits with the identical personnel present on the call. All questionnaires typically collected during the in-person screening visit may be collected during the remote screening visit, as they are largely already completed on secure online platforms (i.e., REDCap). All screening visit study procedures may be performed during the remote screening visit, with the exception of the urine drug test, blood draw, and physical exam, and any other assessments that cannot be performed remotely, which will be performed at the first in-person visit (i.e., first imaging visit) or at an extra, separate visit prior to the first imaging visit.

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At the start of the virtual screening visit, informed consent will be obtained remotely. This will be done via electronic consent (e.g., Partners REDCap e-consent, Adobe Sign), or a remote consent process where the participant will be asked to sign the consent form and return it by email or mail. In either case, the consent discussion will occur identically to an in-person visit,

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but instead held over phone call or video conference. Following the informed consent process, a copy of the signed consent document will be provided to the patient (electronically if e-consent was used). In the case of e-consent, consent will be documented on Partners REDCap or Adobe Sign. These are equivalent to written consent and are FDA compliant. As is with in-person consent, we will obtain and document informed consent before the participant is enrolled and any study procedures begin. Note that we may also use e-consent even for in-person screening visits.

Either a physician investigator or non-physician investigator will obtain informed consent in all cases. Note that the only non-physician investigators who will be allowed to obtain informed consent are Dr. Jodi Gilman (the IND holder) and nurse practitioner study staff members.

Treatment Assignment and Randomization:

Following the screening visit, participants who meet inclusion criteria, pass exclusion criteria, and provide their signed consent will be randomized in a 1:1 ratio to receive either CBD ($n = 40$) or placebo ($n = 40$). Randomization will be performed by stratifying subjects by age (>50 vs. ≤ 50) and sex (male vs. female). Each subject will be assigned a randomization number via a computerized random number generator. The Clinical Trials Pharmacy will maintain the specific subjects' treatment assignments (CBD or placebo) for later identification. Patients and study staff will be blinded to CBD or placebo assignment.

6. Study Procedures

Individuals who express interest in participating in the study will undergo a telephone screening to assess eligibility. If they are likely to be eligible, they will be scheduled for an in-person screening visit, during which a consent procedure will be conducted and a baseline assessment of questionnaires, interviews, and laboratory assessments will be conducted. Those who meet all eligibility criteria will be randomized to the CBD or placebo group. Then, subjects will be scheduled for their first imaging visit, during which they will undergo a simultaneous PET/MRI scan. At this visit, subjects will receive CBD or placebo, which they will be instructed to take daily for the 4 weeks prior to the date of their second scan. Note that, in cases where the screening visit and the first imaging visit are more than three months apart, eligibility criteria will be re-assessed.

Table of Study Procedures:

Domain	Measure	Source	Screen	Scan I (Pre-Treatment)	1 Week Call	2 Week Visit	3 Week Call	Scan II (Post-Treatment)	6 Week Call
Demographics	Custom (PhenX-based)	Participant	x						
General Health	Physical Examination	Physician/ NP/Nurse	x						
	Medical History	Physician/ NP/Nurse	x						
	Family History	CRC	x						
	Psychological Interview (MINI)	CRC	x						
	Characterization of Pain	Physician/ NP/Nurse	x						

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	Concomitant Medications	Physician/ NP/Nurse	x	x					
	Weekly Medication Questions	CRC			x	x	x	x	x
Genetics	Oragene (CGR-500)	CRC	x						
Adverse Events	Adverse Event Record	CRC, reviewed by Physician		x	x	x	x	x	x
Depression, Psychological Functioning, Sleep	BDI-II	Participant	x	x				x	x
	BAI ^a	Participant	x						
	PROMIS-29	Participant		x				x	
	C-SSRS	Clinician	x	x		x		x	x
	CHRT ^a	Participant	x						
	MID	Done in PET/MRI scanner			x				x
Pain	PSQI	Participant	x	x				x	
	BPI-SF	Participant	x	x				x	x
	ACR FM survey	Participant		x		x		x	
	PCS	Participant		x		x		x	x
	PainDETECT	Participant		x				x	
	Oswestry	Participant		x				x	
	Symptom- Mapper	Participant		x				x	
	Daily Survey	Participant	<i>Daily from ~2 Weeks before Scan 1 until 6-Week Call</i>						
Substance Use	TLFB (MJ, EtOH, nicotine, other substances)	CRC	x						
	AUDIT ^a	Participant	x						
	CUDIT-R ^a	Participant	x						
	FTND ^a	Participant	x						
	ECDI ^a	Participant	x						
Expectancy	Next Visit/Call	Participant		x	x	x	x		
	Final Visit	Participant		x					
Quality of Life	Patient Global Impression of Change (PGIC)	Participant						x	
IQ	WRAT5	CRC	x						
Delay Discounting	MCQ ^a	Participant	x						
Impulsivity	UPPS-P ^a	Participant	x						
ADHD	ASRS ^a	Participant	x						
COVID-19	EPII ^a	Participant	x						
	COVID-19 History ^a	Participant	x						
	Vaccination Questionnaire	Participant		x					
Urine Test	Urine Drug Test	CRC	x	x				x	
	Urine Pregnancy Test	CRC	x						
Blood Test	Liver function tests	Nurse / Physician / trained study staff	x					x	
	Whole Blood DNA (Genotype	Nurse / Physician /	x	x				x	

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	& PBMC & iPSC)	trained study staff							
	Serum Pregnancy Test (if applicable)	PET Tech/Nurse		x				x	
	Serum extraction (Cytokine panel)	Nurse / Physician		x				x	
	Arterial line (optional)	Anesthesia-trained clinician		x				x	
	COVID antibody	Nurse / Physician		x				x	
	CBD/THC Metabolites in plasma	CRC		x				x	

^a Indicates a measure that may be completed by the participant at home, following the screening visit.

Study Drug:

Epidiolex, an agent within the anti-epileptic drug class, will be used. Epidiolex, Greenwich Biosciences Inc.'s CBD formulation, is a 100 mg/mL purified oral solution, dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring. 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% (w/w) THC. Cannabidiol is the active ingredient in Epidiolex; inactive ingredients include dehydrated alcohol, sesame seed oil, strawberry flavor, and sucralose. Of note, CBD has no psychoactive properties. The empirical formula of Epidiolex is C₂₁H₃₀O₂ and its molecular weight is 314.46. The structure of CBD is provided in the figure below.

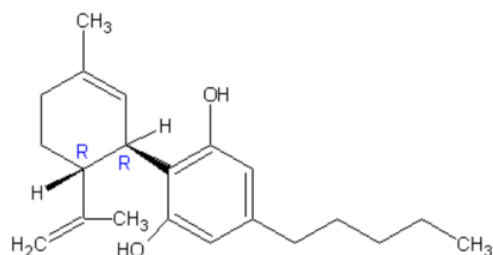


Figure 1. Cannabidiol Structure

Dose and Exposure:

Either EPIDIOLEX[®] or placebo will be dispensed by the Research Pharmacy at Massachusetts General Hospital. The recommended starting dosage is 2.5mg/kg taken twice daily. Participants will follow a titration schedule, with 2.5mg/kg taken orally twice daily in week 1, 5mg/kg twice daily in week 2, 7.5mg/kg twice daily in week 3, and 10mg/kg twice daily in week 4. Subjects will increase to 10mg/kg twice daily on the first day of the final week of the study (week 4) and take Epidiolex at this dose for the remainder of this final week. If participants report AEs (tiredness, dizziness, not tolerating the medication well) during the second, third, or fourth week of taking the study drug, the physician will decrease the dose to the previous week's dose. Participants will be treated for 4 weeks in total.

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The 4-week duration of CBD or placebo administration is proposed because in the current study, we are investigating an endophenotype of pain- neuroinflammation- which may be detectable before verbal reports of pain reduction, which is notoriously noisy and susceptible to placebo effects. This study will inform us of whether 4 weeks is enough to detect changes in TSPO binding that may precede reports of pain reduction.

Screening Visit:

Subjects eligible to participate will be recruited to participate in an approximately 3-hour characterization session. In this session, we will obtain a signed consent form from the subjects, explain the procedures involved in the experiment, and administer some or all of the following validated assessments. We will also collect detailed contact information (address, social security number, medical record number) and demographics, collect a saliva sample for genetic testing, assess medical and family history, and perform a physical examination, and assess concomitant medications. Finally, we will collect a blood sample and a urine sample. Computer-based rating scales and questionnaires will be completed on a laptop. Assessments will be performed by fully trained study staff members such as post-doctoral research fellows and Clinical Research Coordinators, under the supervision of and periodic monitoring by the Principal Investigator (PI).

During the informed consent procedure, participants will be informed about other treatment alternatives for chronic low back pain they can pursue (e.g., medications, transcutaneous nerve stimulation, physical exercise and stretching) in lieu of participation in this clinical trial.

Many of these assessments are already in use in one or more IRB approved protocols (e.g., 2011P002311). Note that participants may complete some of the following questionnaires at home after the screening visit if time does not allow for their completion during the screening visit.

History and physical examination: An MD, NP, or nurse will also collect medical history and perform a formal physical examination, including the recording of vital signs (heart rate, blood pressure, and body temperature). If these assessments are done by a nurse or NP, a physician will review them prior to prescribing the study drug.

*Beck Depression Inventory-II (BDI-II)*⁵⁰: The 21-item BDI-II has shown good reliability and validity for assessing depression in chronic pain patients⁵¹.

Brief Pain Inventory – Short Form (BPI-SF): The BPI is a 15-item questionnaire assessing pain location, and 0–10 ratings of pain intensity, relief, quality, pain-related quality of life, and function. It has been validated in cancer and noncancer pain conditions⁵².

*Timeline Followback (TLFB)*⁵³: The TLFB uses memory aids to trigger recall of substance use. It will be used to measure participants' use of cannabis, tobacco, alcohol, and other substances in the previous 90 days.

*Mini International Neuropsychiatric Interview (MINI)*⁵⁴: The MINI 7.0.2 is a structured diagnostic interview used to assess DSM-5 psychiatric disorders. It will be administered by trained study staff.

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5 *Wide Range Achievement Test, 5th Edition (WRAT5), Word Reading*⁵⁵: The word reading subset
6 of the WRAT5 will be used to assess speech and dictation.
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8 *Monetary Choice Questionnaire (MCQ)*⁵⁶: The MCQ presents participants with 27 questions,
9 each of which asks them to choose between smaller, immediate rewards, and larger, delayed
10 rewards. Participants' patterns of answers are able to provide an estimate of their delay
11 discounting rate.
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14 *Short UPPS-P Impulsive Behavior Scale*⁵⁷: The 20-item Short UPPS-P assesses five components
15 of impulsivity, including sensation seeking, lack of premeditation, lack of perseverance, negative
16 urgency, and positive urgency. Scores on many of these factors have been shown to relate to
17 risky behaviors.
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20 *Beck Anxiety Inventory (BAI)*⁵⁸: The 21-item BAI assess the frequency of anxiety symptoms,
21 including both cognitive and somatic symptoms.
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23 *Alcohol Use Disorders Identification Test (AUDIT)*⁵⁹: The AUDIT is a 10-item questionnaire
24 used to screen for harmful alcohol consumption. It assesses drinking frequency and problems
25 related to alcohol use. The scale ranges from 0 – 40; a score of 8 or higher is an indicator of
26 harmful alcohol consumption.
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29 *Cannabis Use Disorders Identification Test – Revised (CUDIT-R)*⁶⁰: The CUDIT-R is an 8-item
30 questionnaire that screens for problematic cannabis use in the past six months. It assesses
31 problems related to cannabis use, dependence, and use frequency. The scale ranges from 0 – 32;
32 a score of 13 or higher is indicative of possible cannabis use disorder.
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35 *Fagerstrom Test for Nicotine Dependence (FTND)*⁶¹: The 6-item FTND assesses nicotine
36 dependence. It measures amount of cigarette use, dependence on cigarettes, and compulsion to
37 use. The scale ranges from 0 – 10, with a higher score indicating greater dependence.
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40 *Electronic Cigarette Dependence Index (ECDI)*⁶²: The 10-item ECDI assesses dependence on
41 electronic cigarettes. The scale ranges from 0 – 20, with scores 13 and higher indicating high
42 dependence.
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44 *ADHD Self-Report Scale (ASRS)*⁶³: The 6-item screener scale of the ASRS will be used to assess
45 participants' ADHD symptoms, including both inattentive symptoms and hyperactive-impulsive
46 symptoms, during the past 6 months.
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49 *Concise Health Risk Tracking Self-Report form (CHRT-SR)*⁶⁴: The 12-item CHRT-SR assesses
50 active suicidal ideation and behavior, perceived lack of social support, and hopelessness. The
51 scale ranges from 0 – 48, with a higher score indicating greater suicidal thoughts and
52 propensity⁶⁵.
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55 *Pittsburgh Sleep Quality Index (PSQI)*⁶⁶: The PSQI is a 19-item questionnaire that assesses sleep
56 quality and patterns during the previous month. The scale ranges from 0 - 21, with a higher score
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indicating less healthy sleep quality.

*Epidemic-Pandemic Impacts Inventory (EPII)*⁶⁷: The EPII will be used to assess how the COVID-19 pandemic has impacted participants' lives, including impacts on work, home, and social life, as well as impact on emotional and physical health. It includes 92 items.

Suicidal Ideation: The Columbia-Suicide Severity Rating Scale (C-SSRS)⁶⁸ will be used for prospective suicidality assessment. C-SSRS is a tool used to assess the lifetime suicidality of a participant and to track suicidal events through the treatment. The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality. The scale will be administered by study staff at the screening visit, baseline, two-week visit, four-week visit, and six-week call. The C-SSRS "Screening/Baseline" will be collected at Screening and Baseline and the C-SSRS "since last visit" will be collected at subsequent visits. Participants who answer "yes" to any suicidal behavior questions or to suicidal ideation questions 4 or 5 on the C-SSRS during the study should be referred for appropriate psychiatric care. If there is more than a 30% increase in symptoms of anxiety or depression, this will be immediately reported to the PI, who will consult with study clinicians. Clinicians will then determine, with the participant, whether it is in their best interest to continue the medication. The decision to discontinue the participant from the study will be made by the PI in conjunction with clinical Co-Investigators.

Safety monitoring: As participant suicidality and depression is monitored throughout the study with the C-SSRS and BDI-II questionnaires, any new or worsening expression of suicidal ideation or Answers of "Yes" to questions 4 or 5 on C-SSRS throughout the study will be evaluation by a licensed clinician member of study staff. The Standard Operation Procedure will be reviewed. To summarize, if any risk for self-harm or suicidality is identified at any visit, the research coordinators will immediately report this to study clinicians, who will determine whether a safety assessment is needed. If a clinician is needed to perform a safety assessment, study staff will record the date, clinician initials, and comments related to the suicidality assessment in the REDCap C-SSRS module. Following the initial suspicion or identification of self-harm and/or suicidality, a study clinician will follow up with the participant on the current nature of their situation, querying about any new ideation, intent, and/or plan since the last visit. These clinicians, along with the PI will then determine whether a participant can safely continue the study. If the clinicians determine that the participant cannot safely continue the study, the participant will be discontinued, and will be provided with a list of resources for follow-up care.

Demographics: Demographic information, including age, sex, gender, sexual orientation, education level, income, race, height, language, employment status, marital status, and residence, as well as information about the participant's caregivers during childhood, will be collected.

DNA Collection, Saliva (optional): DNA samples will be collected using Oragene (OGR-500) saliva kits. Participants may be asked to provide a second sample if a re-collect is recommended after DNA extraction (i.e., there is very little DNA in the sample). Participants are not required to provide another sample if they do not wish to do so. Once extracted samples will be transferred to long term storage until genotyping. Samples will be stored with a unique participant ID.

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Family history: The family history subsection of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)⁶⁹ will be used to assess family history of psychiatric treatment, including treatment for depression, mania, anxiety, ADHD, schizophrenia, and substance use, as well as history of suicide.

Concomitant medications: Any prescription medications or over-the-counter drugs being taken by the participant at the time of the screening visit will be assessed, and dose and frequency will be recorded.

Blood tests: a trained member of the study staff will draw venous blood (up to 10 ml) from all subjects in order to have them genotyped for the Ala147Thr TSPO polymorphism in the *TSPO* gene (rs6971) (unless this genotype information is already available), and to check liver enzyme values. Additionally, during screening for eligibility, we will conduct routine chemistry and LFT/GGT. We will obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment with CBD.

While [¹¹C]PBR28 has the advantage of binding to the TSPO protein with a higher ratio of specific-to-nonspecific binding than [¹¹C](R)PK11195⁷⁰, it also presents a potential limitation, in that about 10% of human subjects show no binding to PBR28⁷¹ (whereas [¹¹C](R)-PK11195 has never been associated with non-binding⁷²). A recent study has demonstrated that the rs6971 polymorphism predicts PBR28 binding affinity in human platelets⁷³. Since the low-affinity binder phenotype is consistent across all tissues within the same subject⁷², testing for the Ala147Thr polymorphism has been suggested to predict low affinity for [¹¹C]PBR28 in all organs, including the brain. High or Mixed affinity binders (Ala/Ala or Ala/Thr) will be considered eligible, whereas the Low affinity binders (Thr/Thr) will be considered ineligible to continue in the research study. The MGH lab responsible for genotyping typically runs the genotyping assay only twice per month, requiring that we normally schedule screening and scanning visits approximately two weeks apart.

We may also use saliva instead of blood to genotype subjects for the Ala147Thr TSPO polymorphism. Saliva genotyping may be done prior to the in-person screening visit to eliminate low affinity binders, thus saving subjects the burden of having to travel to and attend the screening visit only to find they are not eligible for the study. Verbal consent will be obtained and documented if patient-subjects agree to this saliva collection, and subjects will be asked if they wish to receive a copy of the Privacy Notice and documentation linking them to the research study. Both forms will be provided upon request. Saliva collection kits with a pre-assigned study ID and a pre-paid return mailing supply will be mailed out to applicable subjects. Eligible subjects will be scheduled for an in-person visit. If subjects are ineligible for the study based on the saliva genotyping results, they will be compensated for providing the saliva sample.

An additional 10 mL of venous blood will be collected and stored for future investigations on the roles of genetic, molecular, and cellular factors in pain disorders. This will include the future possibility to generate induced pluripotent stem cells (iPSCs) from peripheral blood mononuclear cells⁷⁴⁻⁷⁶ to assess in-vitro alterations in patient-derived neural or glial cells^{77,78}.

Urine drug test: We will also perform a urine test to screen for use of opioids and illicit drugs

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(including amphetamine, barbiturates, cocaine, marijuana, etc.). The urine drug screen will be performed during the screening visit. A rapid urine drug screening that utilizes monoclonal antibodies to detect elevated levels of specific drugs in urine, will be used for this purpose. Results will be read five minutes after the test was started.

Urine pregnancy test: Urine will be collected at screening for a pregnancy test in female participants of childbearing age.

COVID-19 History: Participants will complete a short questionnaire that asks about COVID-19, including whether they have ever been exposed, experienced symptoms, and/or tested positive. Those reporting a positive test will be asked about how severe the course of illness was, including whether they were hospitalized. All participants will be asked about vaccination status.

Note that we may also do a brief MRI test scan with participants on the day of their screening visit, or on a different day, to ensure that they are a suitable candidate for scanning.

PET/MRI Visits:

Participants eligible to continue into the study based on the screening visit and genotype analyses will be asked to participate in a first PET/MRI visit.

Prior to each scan session, subjects will complete screening checklists for MRI and PET. These checklists will ask the patients whether they have any contraindications for MRI or PET scanning. Female participants of childbearing age will be asked to have ~3mL of their blood drawn in order to perform a serum pregnancy test on the day of the scan (blood will be sent to the core lab for super stat testing). They will also be asked about the date of their last menstrual cycle. In addition, a urine drug test will be repeated on the day of each PET/MRI visit.

At the beginning of the scan session, an intravenous catheter will be placed in the participant's antecubital vein of the left or right arm, prior to going to the scanning area. Up to 15mL of blood will be drawn to assess the levels of various substances in the blood, such as the proinflammatory cytokines IL-6 and TNF-alpha. Blood will be collected in various vials (e.g., purple top K3EDTA).

Blood may also be drawn for SARS-CoV-2 antibody serology testing, and the presence of antibodies will be used to explore the possible effects of prior exposure to the coronavirus on neuroinflammation, in exploratory analyses. Up to 10 ml of blood will be drawn for this purpose. This testing will be performed through a third party vendor or through the MGH core lab.

Following procedures identical to those adopted in other PET studies (including using [¹¹C]PBR28) from our center (e.g., 2015P001594, 2013P001297, 2011P001546, 2011P002311, 2016P001009, etc), an arterial line will be placed in a radial artery with local anesthesia (20 or 18 gauge cannula, 2-5 ml of lidocaine 1% intradermal and subcutaneous) using sterile techniques, if the participant has consented to this procedure. The placement of an arterial line will be presented as optional to the participants, and we will ask for the participants' consent each time. The arterial line will not be placed if the participant has any contraindications to arterial line placement, such as Raynaud syndrome, bleeding disorder, or use of anticoagulants

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such as Coumadin, Plavix or Lovenox. The arterial line will be placed in the arm contralateral to the intravenous line that is used for the [¹¹C]PBR28 radiotracer injection. The arterial line will enable blood sampling (1mL to 12mL) 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 kinetic modeling analyses (see Data Acquisition and Analyses). The catheter will be placed by an individual with anesthesia training (i.e., board-certified anesthesiologist, fully licensed anesthesia resident, or a certified registered nurse anesthetist), monitored throughout and accessed by an experienced research nurse. The catheter will be discontinued at the end of the study by a physician, a nurse practitioner, certified registered nurse anesthetist, or registered nurse. We will have all RNs who do this sign a form attesting that discontinuing the catheter and associated post-procedure monitoring is within the scope of their work and clinical privileges.

Subjects will be instructed to remain still, with eyes open, for the total duration of the scans, except when prompted to engage in various tasks (e.g., rate pain, perform the Monetary Incentive Delay task, etc.).

During the scan visit, subjects will be asked to complete the *BPI-SF*, *BDI-II*, *C-SSRS*, and *PSQI*, which were also assessed at the screening visit. We will again assess concomitant medications. Additionally, subjects will complete some or all of the following validated assessments. Any questionnaire may be sent home with participants to complete if there is not time to complete them during the scan visit.

*Patient Reported Outcomes Measurement Information System (PROMIS-29) questionnaire*⁷⁹: The PROMIS-29 is a 29-item self-report measure assessing physical, mental, and social health.

*PainDETECT*⁸⁰: The PainDETECT is a screening questionnaire used to estimate the likelihood of a neuropathic component in chronic pain.

*The Pain Catastrophizing Scale (PCS)*⁸¹: It is a 13-item self-report scale which measures pain-related Rumination, Magnification and Helplessness.

*Oswestry Disability Index (ODI)*⁸²: The ODI is an extensively used 10-item scale to describe the level of disability in patients with chronic low back pain and will be used to characterize the study population.

SymptomMapper: The SymptomMapper app is a digital tablet-based application used to localize areas where patients are experiencing pain. In the app, the patient picks a pain descriptor, i.e., burning or shooting, notes the severity of that descriptor, and then marks where on the body that descriptor is felt. All data are stored de-identified and securely onto local drives.

*Fibromyalgia Survey*⁸³: The American College of Rheumatology's fibromyalgia survey will be used to assess widespread pain and fibromyalgia symptom severity. The widespread pain subscale ranges from 0 - 19, with a higher score indicating more widespread pain. The fibromyalgia symptom severity subscale ranges from 0 - 12, with a higher score indicating more severe symptoms.

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Treatment Expectancy: Expectancy of symptom improvement will be assessed using three statements that ask about how participants expect to feel at the end of treatment (at their last visit), as well as 3 statements about how they expect to feel at their next study visit or call. These statements will assess expected pain intensity, pain bothersomeness, and depression, and will each be scored on a 0 – 10 scale, with a higher score indicating worse symptoms.

Adverse events: Any untoward or unfavorable medical occurrence participants have experienced will be assessed, whether or not the occurrences are considered related to their participation in the research.

Vaccination Questionnaire: The date of administration and manufacturer of each COVID-19 vaccine dose the participants have received will be assessed using a brief questionnaire. Additionally, participants will be asked whether they have received any other vaccinations in the past 14 days to capture a potential acute immune response.

During the scan, participants will be asked to complete the *Monetary Incentive Delay (MID) task*. The MID task features balanced incentive delivery and analytic strategies designed to identify activity specific to anticipation or consumption of incentives. In the reward condition, successful trials are associated with monetary gains whereas unsuccessful trials lead to no change. In the loss condition, successful trials are associated with no change whereas unsuccessful trials are associated with monetary penalties.

At the end of the scan, for those participants who received an a-line, an experienced nurse or MD will remove the catheter. These subjects will be kept under observation for a minimum of 30 minutes.

The total duration of each scanning visit will be approximately 4 hours (and up to 6 hours) (~45min for preparation, ~30min for a-line placement, if applicable, ~120 min for scanning procedures, ~20-30min optional spinal scan after completion of the brain scan, and ~60min for filling out questionnaires and observation after removal of arterial line, plus an additional ~90min to perform pregnancy test in women of childbearing age). In case of equipment failure (e.g., failure in radiosynthesis) delays of > 2 hours may be possible. In this case, we will ask the participant if he or she feels comfortable with staying longer than anticipated, or will prefer reschedule to another date.

Depending on the patients' level of discomfort and time constraints, we may occasionally shorten and simplify the scan visits. For instance, if the participant would feel too uncomfortable to lay down in the scanner for the full ~2:00 hours of scanning, we may administer the radioligand in the injection room and then scan the participant between ~45 and 90 minutes post-injection. If the participant cannot remain for the full 6-hour scan visit, it will be acceptable to forego the arterial line placement. Eliminating this procedure will save the time needed for the placement and the ~30 minutes of observation needed after the removal of the a-line (from these scans we will derive metrics that do not depend on arterial sampling, such as standardized uptake value ratio (SUVR)).

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The imaging visit, including all the procedures described above, will be repeated a second time after a 4-week trial of CBD or placebo. Blood drawn at the second imaging visit will also be tested to check liver enzyme values. Also, up to 4 additional mL of blood will be drawn, and the blood plasma samples will be sent to collaborators at Clinical Research and Development facilities Department of Anesthesiology, at the University of Colorado Anschutz Medical Campus. These blood plasma samples will be analyzed for quantitative levels of cannabinoids, including CBD and THC. All analyses will be carried out following standard operation procedures, which are based on all applicable CAP, CLSI, ICH, OECD and FDA guidelines. All samples will be fully de-identified, and will not contain any identifiers that could be used to link the specimens or data to individual subjects.

Parts of the PET/MRI visits may be conducted virtually, as necessary.

Follow-up Visits/Calls:

1-Week Call. Patients will have a phone call 1 week after their first scan with a study team member. In this call, adverse events, treatment expectancy, and medication use will be assessed and participants will be reminded to increase medication dose.

2-Week Visit. Patients will undergo a follow-up appointment at Week 2 with a trained study staff member, where health, other medication use, and adverse events will be assessed, and patients will complete questionnaires and will be reminded to increase medication dose. Treatment expectancy will also be assessed. Participant may receive a ride to and from the study visit if requested. Some or all of this visit may also be conducted virtually as necessary. If there are any adverse events or issues reported during this visit, we will refer the participant to a study clinician who will get back to them.

3-Week Call. Patients will have a phone call during Week 3 with a study team member. In this call, adverse events, treatment expectancy, and medication use will be assessed and participants will be reminded to increase medication dose.

4-Week Visit. Patients will undergo a second follow-up appointment immediately after the four-week treatment period with a study clinician, where we will assess back pain, general health, adverse events, and medication use. Portions of this visit may be conducted virtually, if necessary. On the same day or as close as possible depending on scheduling, patients will be re-scanned, using identical protocols, to evaluate the hypothesis that CBD reduces glial activation. We will also repeat the questionnaires administered during the first imaging visit to assess any changes in subjective pain. We will take a small sample of blood for a follow-up liver function test. Participant may receive a ride to and from the study visit if requested.

6-Week Call. We will conduct a follow-up call 2 weeks after the discontinuation of the study medication. In this call, we will assess back pain, general health, adverse events, and medication use.

Daily Surveys:

For about 2 weeks before Scan 1 to the 6-week call, we will ask participants to complete brief daily surveys assess various domains, including their levels of pain, depression, anxiety, fatigue,

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and sleep quality on various scales (e.g., 0-10). We will also ask participants whether they have taken the study medication that day, and whether they have taken any other medications to manage their pain.

Drug Administration Protocol:

Following the behavioral visit, subjects will receive CBD or placebo. Please see “Dose and Exposure” section above for dosing and titration schedule. Participants will be treated for 4 weeks in total. Chronic CBD dosing up to 1500 mg/day has been reported to be tolerated well without AEs⁸⁴⁻⁸⁷; minor AEs were reported after CBD use in children with epilepsy being treated with multiple other medications in doses up to 25mg/kg twice daily^{88,89}. Accordingly, we believe an upper limit of 10mg/kg twice daily orally is reasonable and safe.

Continuation of medication (e.g., NSAIDS) will be permitted on the condition that patients will be on a stable dose for at least 1 month before the baseline PET/MRI scan.

The Research Pharmacy at Massachusetts General Hospital will prepare the CBD and placebo. The bottle will contain 100mg/mL of CBD or placebo. It will also have a small ID label with a batch number printed on it. The label will explain the storage conditions, the shelf life, and the in-use shelf life. Each container will be labeled with a unique number that will be recorded by study staff at the time of administration. As soon as possible after the 4-week CBD or placebo period, patients will be re-scanned and/or re-evaluated clinically to evaluate the hypothesis that CBD compared to placebo reduces glial activation and pain/depressive symptoms. Participants will be instructed to take CBD or placebo with food, rather than in a fasted state, and not to take CBD or placebo concurrently with alcohol. Participants will be instructed to return any unused CBD or placebo at the second PET/MRI visit.

GWAS Genotyping:

The Broad Institute will perform genotyping (array-based) of subject DNA samples and subsequent in-depth analysis of the data, which will allow us to detect alterations in the genome including point mutations, small insertions and deletions, chromosomal copy number alterations, and translocations. These experiments are intended to help identify candidate genes involved in the pathophysiology of neurological and psychological diseases. The molecular information generated from these samples will not be returned to subjects at any time.

Data from this study may result in communications in journals or at scientific meetings. Subjects will not be identified in those communications. To facilitate research, the genetic information generated may upon publication be deposited in protected databases (such as dbGAP) available only to bona fide researchers with specific scientific questions who promise to not try to identify individuals. The data will be sent to these banks in a coded manner and again will not contain any traditionally used identifier such as name, address, phone number, or social security number. Although we cannot predict how genetic information will be used in the future, there are many safeguards in place and we do not think that there will be further risks to patients' privacy and confidentiality by sharing such information with these banks.

The Broad Institute will not be involved in subject ascertainment. Prior to transfer of bio-specimen aliquots to the Broad Institute, samples will be re-encoded at the collaborators

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institutions. No identifying patient information will be shared with Broad scientists at any time. Some limited clinical data will be obtained from collaborators. Again, all subject identifying information will remain with the collaborators and only de-identified clinical data will be shared with the Broad Institute.

Platforms for Data Collection:

Questionnaires Collected via Research Electronic Data Capture (REDCap): Surveys will be administered via REDCap, a HIPAA compliant, web-based application hosted by Partners HealthCare designed to support data capture for research studies⁹⁰, at in-person visits (or virtual if required per COVID-19 restrictions).

Data will be stored automatically and securely on a SQL Server, accessed over industry standard TLS 256 bit RSA encryption during data transfers. Data is routinely backed up locally onto a redundancy server and stored in a separate database. Long term storage on Partners servers occurs nightly and allows for incremental backup over multiple systems. Therefore, should one drive be physically damaged, there will be multiples within the chain to replace it. Both data servers are stored within PHS IS corporate firewall, in a secure, key access facility with password-protected computers. Only vetted PHS security officials will have access to physical machines storing study data. Since data are stored on a protected server, a compromise of any individual computer at a research facility will not lead to a breach of the secure database. Individual computers designated for data capture do not store participants' identifying information or study data.

Return of Research Results:

Participants should not expect to get information about the results of the study or the results of their individual participation in the study.

Incidental Findings:

In the unlikely event that evidence of physical or psychological disorder is found, with the individual's permission, the information will be shared with his or her primary care physician who can direct care as needed.

Outcomes:

Primary Outcomes:

1. Changes in neuroinflammation in the thalamus: We will test for the presence of a significant treatment effect in the brain [¹¹C]PBR28 signal in the thalamus, in order to test whether patients in the CBD arm will demonstrate significantly larger treatment-related reductions in neuroinflammation, compared to patients in the placebo arm.
 - a. Time Frame: Change from Baseline to Week 4.

Secondary Outcomes:

1. Changes in neuroinflammation in limbic regions: We will test for the presence of a significant treatment effect in the brain [¹¹C]PBR28 in limbic regions (pgACC, aMCC), in order to test whether patients in the CBD arm will demonstrate significantly larger treatment-related reductions in neuroinflammation, compared to patients in the placebo arm.

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- a. [Time Frame: Change from Baseline to Week 4]
2. Correlation Between Reductions in Thalamic [¹¹C]PBR28 PET Signal and Reductions in Clinical Pain Ratings: We will test whether reductions in thalamic [¹¹C]PBR28 PET signal correlate with reductions in clinical pain ratings, as assessed by the "worst pain" item of the Brief Pain Inventory - Short Form. The "worst pain" item's scale ranges from 0 - 10, with a higher score indicating worse pain intensity.
 - a. [Time Frame: Change from Baseline to Week 4]
3. Correlation Between Reductions in Limbic [¹¹C]PBR28 PET Signal and Reductions in Depressive Symptoms: We will test whether reductions in pgACC/aMCC [¹¹C]PBR28 PET signal (as measured by Standardized Uptake Value Ratio) correlate with reductions in depressive symptoms, as measured by the Beck Depression Inventory-II. The Beck Depression Inventory-II scale ranges from 0 - 63, with a higher score indicating greater depression.
 - a. [Time Frame: Change from Baseline to Week 4]
4. Change in Clinical Pain Ratings: The "worst pain" item of the Brief Pain Inventory - Short Form will be used daily to assess pain intensity. The scale ranges from 0 - 10, with a higher score indicating worse pain intensity.
 - a. Time Frame: We will examine change from average score during the 7 days prior to treatment (Baseline) to average score during the final week of treatment.
5. Change in Pain Bothersomeness: Pain bothersomeness will be assessed daily on a scale from 0 - 10, with a higher score indicating greater bothersomeness.
 - a. Time Frame: We will examine change from average score during the 7 days prior to treatment (Baseline) to average score during the final week of treatment.
6. Change in Depressive Symptoms: The Beck Depression Inventory-II will be used to assess symptoms of depression. The scale ranges from 0 - 63, with a higher score indicating greater depression.
 - a. Time Frame: Change from Baseline to Week 4.
7. Patient Global Impression of Change: The Patient Global Impression of Change scale will be used to assess participants' perceptions about their global improvement related to their low back pain. The scale ranges from 0 - 7, with a higher score indicating greater overall improvement.
 - a. Time Frame: Week 4

Study Termination Criteria:

Participants will be terminated from this study if there are any significant safety concerns (e.g., actively suicidal), failure to comply with study procedures, or if the opinion of the principal investigator, can no longer safely participate. In addition, subjects will be informed that if they feel uncomfortable with the study, they can choose to terminate the study at any time. They will be informed that their refusal to participate in the study or choosing to terminate it at some point will have no effect on care and treatment received by them at MGH now or in

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future. We will also discontinue EPIDIOLEX or placebo in any patients with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN.

If a participant decides to stop participating in the study before the planned end of the study, we will ask that they continue to follow the schedule of visits. If they are unable or unwilling to return to the MGH Charlestown Navy Yard campus for visits, we will ask if we can call them for phone interviews instead of study visits.

Study Compensation:

Subjects will be paid by check at the completion of the study for their participation.

We will pay up to \$770. Payments will be as follows:

- \$75 for the initial screening visit
- Up to \$76 for completing daily surveys (\$1 per survey completed)
 - Bonus \$25 if they complete 90% of surveys
- \$200 for each PET/MRI scanning visit
- \$25 for each blood test to exclude pregnancy (for females of childbearing age)
- \$50 for each arterial line placement
- Participants will be able to earn up to an additional \$17-\$22 during each Monetary Incentive Delay task

If during the imaging visit(s) we cannot inject the subject with the radioligand (e.g., due to a failure in radiosynthesis, or to issues with the scanner) and we HAVE NOT yet placed the arterial line, he/she will receive \$50. If we cannot inject the subject with the radioligand, and we HAVE already placed the arterial line, he/she will receive \$100.

If the subject will need to stop the scan early for any reason, he/she will still receive \$50 for his/her time. Additionally, parking fees will be covered as needed.

Subjects excluded per the genotyping results of a mailed-out saliva test will receive \$15.

7. Risks and Discomforts

All subjects will undergo a telephone or email pre-screening to attempt to distinguish potential subjects from those not meeting eligibility criteria. Likely candidates will undergo a characterization and training session, which will include a clinical screening procedure. This procedure will involve answering questions about subjects' medical history recording of medical history review and answering questions about their medical situation including liver disease, kidney disease, blood disorders, heart disease, alcohol and opioid use, high blood pressure, asthma, and other respiratory disorders.

Subjects will be instructed to complete the questionnaires to the best of their ability but will have the option to leave any question(s) blank. In the unlikely event that evidence of physical or psychological disorder is found, with the individual's permission, the information will be shared with his or her primary care physician who can direct care as needed.

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PET/MRI Procedure: The U.S. Food and Drug Administration (FDA) recently gave the first regulatory clearance of a hybrid PET/MRI scanner in the U.S. Additionally, FDA considers investigations of MRI software and hardware operating within FDA specific parameters as non-significant risk device studies. All studies will adhere to these FDA approved safety levels for the Siemens system. These safety parameters include static magnetic field, time varying magnetic fields (dB/dt), specific absorption rate (SAR), and acoustic noise levels. Subjects will be informed about minimal risks of routine high magnetic field and non-ionizing RF radiation involved in MR imaging.

Subjects will also be informed about the PET procedure and the minor risks associated with exposure to radiation. Subjects will also be informed about small space within the magnet and noises made by switching gradients. Subjects will be informed that if they feel uncomfortable with the study, they can choose to terminate the study at any time. They will be informed that their refusal to participate in the study or choosing to terminate it at some point will have no effect on care and treatment received by them at MGH now or in future. The subjects will be informed that their personal information will be protected as per the HIPAA guidelines.

Intravenous catheter: An intravenous catheter will be placed for this study. The subject will feel a slight pinprick, similar to a bee sting, and may feel some discomfort and have some bruising or bleeding at the site where the needle goes in. Depending on the length of time the catheter is in place, a bruise may last for a day or so. Rarely an infection may occur at this site. If infection does occur, it will be treated.

Optional arterial line: An intra-arterial catheter will be placed by an individual with anesthesia training (i.e., board-certified anesthesiologist, fully licensed anesthesia resident, a certified registered nurse anesthetist), on the arm opposite to the radio-ligand injection line, for blood draws during the PET study. Local infection, swelling, and redness could occur at the sites of line placement, as well as temporary loss of pulse at the wrist. This area may have a bruise or feel uncomfortable for 2-3 days after the catheter is removed. The risks associated with having blood drawn include: bruising, local discomfort, or infection at the site of the needle puncture. Rarely an infection may occur at this site, and if an infection does occur, it will be treated. Inserting an arterial line (A-line) can hurt more than having a regular IV or having blood drawn with a needle. We will place the A-line under local anesthesia (i.e., lidocaine), which may cause an allergic reaction. Even if we numb the wrist area first, the insertion may still hurt. Once the A-line is in place, it usually does not hurt. About 24 hours after the beginning of the imaging procedures, we will give the subject a phone call to determine whether he or she is experiencing study related issues.

The subject may experience pain, bleeding, swelling or redness at the wrist, short loss of pulse at the wrist if blood flow in the artery is briefly stopped, damage to the artery wall or nearby nerves, or catheter breaking or falling out. There have been reports of decreased blood flow to the hand, which resulted in the need for surgery. This is very rare and has not been reported when catheters have been in place for only a few hours for research. Additionally, the insertion or removal of the A-line might cause temporary dizziness, nausea or fainting. After the anesthesiologist, anesthesia resident, certified nurse anesthetist, or registered nurse removes the

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catheter and has held pressure for several minutes, we'll ask the subject to stay for 30 minutes (up to 60 minutes based on clinical opinion of NP or registered nurse) so we can monitor him/her in order to assess the occurrence of any adverse event. Dr. Loggia will file a report on Insight within the timeframe stipulated by the IRB (5 working days/7 days) should any adverse event occur. The subject may have a bruise or feel tenderness for 2-3 days around the area where the catheter was placed. We will instruct the subject to avoid lifting anything heavier than a small bag of flour for a day. We will instruct the subject to call us if bleeding occurs after the subject leaves (rare), and/or if the wrist area is painful or red or swollen. About 24 hours after the beginning of the imaging procedures, we will give the subject a phone call to determine whether he or she is experiencing study related issues.

Radiation exposure: The radiation exposure in this study will be small and there is no evidence that it represents a major health risk. If subjects have participated in other research studies in the past 12 months that have involved radiation exposure, they will be asked to inform the investigators or study staff (by writing initials on the consent form verifying that they have not been exposed to other radiation in the past 12 months). If it is determined that their prior radiation exposure exceeds our current guidelines, they may not be allowed to participate in this study.

We will use [¹¹C]PBR28 produced by the cyclotron/radiochemistry/radiopharmacy facility at the A. A. Martinos Center for Biomedical Imaging. The Martinos Center has studied several hundreds of people with this radioligand and have had no clinically detectable effects or side effects. Given the use of [¹¹C]PBR28 in a small clinical trial, we have obtained an IND from the FDA.

The IV injection will be administered by a licensed nuclear medicine technologist. Should there be an adverse event, Dr. Gilman will be responsible for communicating with the IRB within the stipulated time frame.

Imaging will be stopped should any untoward reaction be observed during the imaging session or if the participant so requests for whatever reason. Some subjects find it unpleasant or feel anxious when confined in the enclosed space of the scanner. If this happens, the study will be aborted. Patients will be required to use earplugs to decrease the noise perceived while in the scanner.

Saliva Genotyping: Although we cannot predict how genetic information will be used in the future, there are many safeguards in place and we do not think that there will be further risks to patients' privacy and confidentiality by sharing such information with these banks.

In addition, steps will be taken to protect confidentiality of genetic data as outlined:

1. All MGH study staff are trained to make confidentiality the first priority.
2. No genetic research data will be entered into the medical record.
3. The results of the genetic analyses will not be shared with participants, their family members or unauthorized third parties.
4. Genetic data are encoded using coded identifiers. These codes, rather than personal identifiers, are used in any analytic datasets. The code key linking coded identifiers to

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personal identifiers are kept in an access-restricted, password protected electronic file and are not shared with the genetics laboratories.

5. Consent forms are stored in locked cabinets apart from demographic and diagnostic data.
6. Samples and genetic data stored in the laboratory will be identified only by the code numbers and laboratory personnel will not have access to personal identifiers.
7. The most serious risk would be identification of individuals in the publicly shared database. To prevent this, computerized data files provided to other investigators will not include any of the HIPPA-defined personal identifiers. Published material will not identify subjects.

EPIDIOLEX (CBD): CBD is an FDA-approved medication used to treat epilepsy. According to the FDA briefing document on Epidiolex, dated 04/19/2018, treatment-emergent AEs in controlled trials for Lennox-Gastaut and Dravet syndromes included decreased appetite, diarrhea, irritability, somnolence, fatigue, aggression, pneumonia, rash, and hepatic symptoms, and in a very small number of patients, an increase in suicidal thoughts. Of note, AE related to hepatic function were likely due to the interaction between CBD and anti-epileptic drugs; prescription of an anti-epileptic drug is an exclusionary criterion for this proposed study. Further, CBD may produce pharmacokinetic interaction effects when taken with opioids^{91,92}. Any subjects who at baseline had elevated AST/ALT levels but still met the eligibility criteria for the study will undergo a follow-up liver function tests at 2 weeks. In addition, we will perform a liver function test in subjects who at any time point during the study develop clinical signs or symptoms suggestive of hepatic dysfunction.

Given the use of EPIDIOLEX in a small clinical trial, we have obtained an IND from the FDA.

Questionnaires: Minimal risks associated with completing questionnaires are subject fatigue and the possibility of minor psychological distress associated with answering sensitive questions regarding psychological functioning. Subjects will be instructed to complete the questionnaires to the best of their ability, but will have the option to leave any question(s) blank. In the unlikely event that evidence of physical or psychological disorder is found, with the individual's permission, the information will be shared with his or her primary care physician who can direct care as needed.

Confidentiality: As detailed, the investigators are quite careful regarding the protection of confidentiality, and multiple procedures are in place to reduce the likelihood of a breach of confidentiality. However, there is a small risk that information about subjects could become known to people outside of this study, and this risk is identified in the informed consent form.

The key investigators will meet quarterly to discuss any potential adverse event and side effects. We will involve the MGH Human Research Committee and Radiation Safety Committee if any additional potential risks arise. Adverse events and unanticipated problems involving risks to subjects or others will be reported to the PHRC in accordance with PHRC adverse event and unanticipated problems reporting guidelines, as well as FDA when appropriate.

8. Benefits

Potential benefits to participating individuals:

It is unlikely that individual subjects will benefit from taking part in this study. While this study is powered to possibly observe a statistically significant reduction in pain due to CBD, it is unclear whether the effect will be clinically meaningful.

Potential benefits to society:

Findings from these studies will help advance our understanding of the pathophysiology of pain disorders. In particular, this project will assess the role of microglia in the establishment and/or maintenance of chronic pain, and how this may be affected by CBD. As such, we envision that in the future the information obtained from the proposed research will enhance the diagnosis and management of a variety of chronic pain conditions.

9. Statistical Analysis

Data Acquisition

PET. [¹¹C]PBR28 binding will be measured on Siemens Biograph mMR, a whole-body 3T PET/MRI scanner, or a Siemens Tim Trio with a head-only PET insert. An intravenous catheter will be then placed in participants' antecubital vein to inject the radioligand. [¹¹C]PBR28 will be synthesized in-house using a procedure modified from the literature.⁹³ Up to 15 mCi of [¹¹C]PBR28 will be injected intravenously as a slow bolus over a 30s period.⁹⁴ In the first 90 minutes, PET/MRI data will be collected from the brain. Between 90- and 110-minutes post-injection the field of view may be repositioned to the thoracic and upper lumbar spine, so that spinal cord data can be acquired. Of note, while our primary PET imaging outcomes are brain-related (thalamic signal for "pain-related neuroinflammation" and pgACC/aMCC signal for "depression-related neuroinflammation"), we will also evaluate, in exploratory analyses in a subset of our participants (depending on the participant's availability or other factors), the signal from the most caudal segments of the spinal cord, as this regions also demonstrated neuroinflammation in our prior study of patients with lumbar radiculopathy.⁹⁵

For the brain data, motion correction will be applied using MRI-derived motion estimates for each individual frame.⁹⁶ For the spinal cord data, frame-by-frame motion correction will be implemented using the Spinal Cord Toolbox.⁹⁷ The head attenuation map (μ -map) will be obtained using a recently implemented MR-based attenuation correction method.⁹⁸ The μ -map for the spinal data will be collected using the Dixon-VIBE sequence and using in-house developed software to additionally segment the bone.⁹⁵

[¹¹C]PBR28 brain uptake will be measured voxelwise as Standardized Uptake Values ratio (SUVr), Volume of distribution (V_T), V_T ratio (DVR) and/or other commonly adopted metrics. In humans, SUV ratio (SUVr) estimation of [¹¹C]PBR28 binding has been used to reliably distinguish healthy volunteers from patients with Alzheimer's disease⁹⁹ as well in our own studies with chronic low back pain³⁶, and amyotrophic lateral sclerosis¹⁰⁰. Additionally, human and animal studies indicate SUV/SUVr estimates are less variable compared to blood-derived methods^{99,101}. These results suggest that SUVr estimation of [¹¹C]PBR28 binding could be a viable surrogate for arterial blood methods, and perhaps more sensitive to between group

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differences. However, V_T and other more quantitative metrics will be computed as well. As an intensity normalization factor we will use the whole-brain signal or a localized pseudoreference region (e.g., the occipital cortex) for the brain data, and the lowest 1-2 spinal cord segments present in the field of view for most/all of our participants (e.g., T11-L1) for the spinal signal. Brain SUVR will be spatially normalized to the Montreal Neurological Institute (MNI) space using nonlinear registration (FNIRT, from the FSL suite; www.fmrib.ox.ac.uk/fsl¹⁰²). Spatially-normalized SUVR images will be then spatially smoothed (full width at half maximum=8mm) to improve signal-to-noise ratio. Spinal cord SUVR will be normalized to MNI-Poly-AMU template¹⁰³ using the Spinal Cord Toolbox.

MRI. During the acquisition of brain PET data, several runs of BOLD fMRI data will be collected using whole brain T2*-weighted gradient echo BOLD EPI pulse sequence (TR/TE =2sec/30ms, flip angle=90°, voxel size=3.1x3.1x3mm, number of slices=37), for the purposes of evaluating striatal function using the MID task, performing MR-based motion-correction of PET data¹³⁶, as well as for additional exploratory analyses. In addition, a high resolution structural volume (e.g., multi-echo MPRAGE pulse; TR/TE1/TE2/TE3/T4=2530/1.64/3.5/5.36/7.22 ms, flip angle=7°, voxel size=1mm isotropic) will be collected for anatomical localization as well as attenuation correction.¹⁵⁵ For the spinal cord data, axial and coronal T1 (e.g., TR/TE=0.565s/13 ms; flip angle=120°; slice thickness=2mm; number of slices – 14) and T2 (e.g., TR/TE=3.38s/109 ms; flip angle=150°; slice thickness=2mm; # slices – 30) weighted images will be collected for anatomical localization and ROI definition purposes.⁷

Data Analyses

A generalized linear mixed-effects model (GLMM) will be used to quantify the association between thalamic [¹¹C]PBR28 PET signal, treatment assignment at randomization (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 (e.g., age, depression severity, sex). Data dependencies will be accounted for using either random intercept or line (intercept and slope) parametrizations. 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 modeling 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 summarize 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

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analyses 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.

Genotyping:

GWAS Genotyping: The Broad Institute will perform genotyping (array-based) of subject DNA samples and subsequent in-depth analysis of the data, which will allow us to detect alterations in the genome including point mutations, small insertions and deletions, chromosomal copy number alterations, and translocations. These experiments are intended to help identify candidate genes involved in the physiopathology of neurological and psychological diseases. The molecular information generated from these samples will not be returned to subjects at any time.

Data from this study may result in communications in journals or at scientific meetings. Subjects will not be identified in those communications. To facilitate research, the genetic information generated may upon publication be deposited in protected databases (such as dbGAP) available only to bona fide researchers with specific scientific questions who promise to not try to identify individuals. The data will be sent to these banks in a coded manner and again will not contain any traditionally used identifier such as name, address, phone number, or social security number. Although we cannot predict how genetic information will be used in the future, there are many safeguards in place and we do not think that there will be further risks to patients' privacy and confidentiality by sharing such information with these banks.

The Broad Institute will not be involved in subject ascertainment. Prior to transfer of bio-specimen aliquots to the Broad Institute, samples will be re-encoded at the collaborators institutions. No identifying patient information will be shared with Broad scientists at any time. Some limited clinical data will be obtained from collaborators. Again, all subject identifying information will remain with the collaborators and only de-identified clinical data will be shared with the Broad Institute.

Consideration of sex as a biological variable:

In addition to the aforementioned analyses, the effect of sex will be evaluated using ANOVAs, because animal research suggests the presence of a possible sexual dimorphism in the role of glia in pain (as pain hypersensitivity may be microglial-dependent only in males¹⁰⁴). The effect of menstrual cycle status will also be evaluated by comparing women in early follicular (day 2-7 after onset of menses) and midluteal (day 20-25 after onset of menses), based on self-report¹⁰⁵.

Effect of coronavirus on neuroinflammation:

Finally, in addition to the aforementioned analyses, the effect of prior exposure to coronavirus (as detected by the presence of antibodies to SARS-CoV-2) will be evaluated in both ROI and voxelwise analyses, in exploratory analyses. Identifying participants who are positive to the antibodies might allow us to test the exploratory hypothesis that prior exposure to the coronavirus can lead to neuroinflammation even without having experienced overt acute COVID-19 symptoms.

Power Analysis:

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Primary Aim: Using a linear mixed-effects model, we estimate the power to detect a temporal (week 4 – baseline) rate of change in thalamic [^{11}C]PBR28 PET signal between CBD and control subjects when recruiting 40 subjects per treatment group. We assume: (1) the standard deviations of the [^{11}C]PBR28 PET signal measures are 0.05,[106] (2) the correlation between repeated measurements ranges between 0.3 to 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 [^{11}C]PBR28 PET signal measures of at least 0.039 and 0.045, respectively.

10. Monitoring and Quality Assurance

There will be a DSMB for this study (see attached DSMB Charter). The proposed study will be monitored for safety, with monthly staff meetings reviewing adverse events and treatment outcomes and directly reporting any adverse events. The PI will also routinely monitor and assure the validity and integrity of collected data, adherence to the IRB-approved protocol, and recordkeeping. The trained staff members who carry out the procedures will also carefully monitor the study throughout its duration. The team will evaluate the progress of the study, verify that the rights and well-being of the subjects are protected, verify that the reported study data are accurate, complete and verifiable from source documents, and the conduct of the study is in compliance with the approved protocol and amendments. Outcome monitoring and adverse events will all be reported through appropriate channels of the Human Studies Committee as well to the FDA when appropriate.

If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, right upper quadrant abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), we will promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with EPIDIOLEX or placebo, as appropriate. We will discontinue EPIDIOLEX or placebo in any patients with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN. Our physician monitoring group (Drs. Mao, Zhang, Schnitzer, and Evins) will consider stopping the study if back pain becomes significantly worse in 3 or more patients. If serum liver enzyme concentrations are significantly elevated (with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN) in 2 or more patients, which will be considered serious adverse events, the study will be stopped. In addition, if two or more patients experience any serious adverse event, the study will be stopped.

The Siemens PET/MRI scanners have a built-in self-monitoring system that automatically shuts off if parameters exceed safe levels. For backup protection NMR technicians constantly monitor the subjects' physiological signs and the quality of the raw data.

Quality assurance of the scanner's performance is obtained by a daily quality assurance protocol. More extensive quality assurance protocols are performed monthly under the commercial service contract with Siemens Medical Systems. The daily quality assurance protocol consists of an image Signal-to-Noise measurement in a phantom and a stability run which checks the image-to-image variation in image intensity over 600 images using a standard echoplanar imaging sequence with a head-sized phantom. The images are analyzed by the technologist to provide

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data on SNR (as an absolute, unitless number) and stability expressed as the peak-to-peak variation in the mean of a 15x15 pixel region of interest (ROI) in the center of the phantom expressed as a percentage of the mean of the ROI. Runs are performed at each of 3 TR values (300ms, 800ms, 1300ms). The time course of the means is also reviewed to check for periodicities (the TR values are chosen so as not to be multiples of one another). If the peak-to-peak variation is greater than 0.5% of the mean value, the Siemens Medical System service engineer is called. In addition to these daily quality assurance tests, the Siemens Medical System service engineer performs quality assurance tests once a month. These tests include a SNR test, a small sample stability test, a gradient stability test, a gradient eddy current test, a shim test, an image uniformity test, and an RF stability test.

11. Privacy and Confidentiality

- Study procedures will be conducted in a private setting
- Only data and/or specimens necessary for the conduct of the study will be collected
- Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- All electronic communication with participants will comply with Mass General Brigham secure communication policies
- Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- Additional privacy and/or confidentiality protections

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Intervention/Interaction Detailed Protocol

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Protocol Title: Evaluation of Cannabidiol (CBD) for Reduction of Brain Neuroinflammation

Principal Investigator: Jodi Gilman, PhD

Site Principal Investigator:

Description of Subject Population: Adults with Chronic Low Back Pain

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

Key Information

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. Your decision won't change the medical care you get within Mass General Brigham now or in the future.

The following key information is to help you decide whether or not to take part in this research study. We have included more details about the research in the Detailed Information section that follows the key information.

Why is this research study being done?

In this research study we want to learn more about whether cannabidiol (CBD) reduces activation of glial cells, which are the immune cells of the nervous system. Cannabidiol is a naturally occurring compound found in cannabis plant, and is considered to be a safe, non-addictive substance. We are looking to find out whether CBD may reduce symptoms of low back pain.



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How long will you take part in this research study?

If you decide to join this research study, it will take you about 8-10 weeks to complete the study. During this time, we will ask you to make 2 imaging visits to MGH Charlestown Navy Yard campus and 2 office visits to 101 Merrimac Street. There will also be three follow up phone calls.

What will happen if you take part in this research study?

If you decide to join this research study, the following things will happen. First, you will come to MGH for an approximately 3-hour screening visit, which will include a blood test, a urine test, and a physical exam. Depending on the results of the initial screening visit, you might be eligible to participate in up to 2 imaging visits. As part of the study, we are using a machine which combines Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) into one device. The MRI part of it uses a powerful magnet to make a picture of the body, while the PET part of it makes pictures by using special dyes with a small dose of radioactivity attached to them that “light up” inside the body.

To study the effect of CBD, you will be asked to take either a medication called EPIDIOLEX or placebo for the 4 weeks prior to the date of your second imaging visit. EPIDIOLEX is a liquid formulation of CBD. A study doctor will talk to you about how much EPIDIOLEX to take.

Why might you choose to take part in this study?

We cannot promise any benefits to you from taking part in this research study. However, possible benefits may include a reduction in pain while taking the drug. Others with chronic back pain may benefit in the future from what we learn in this study.

Why might you choose NOT to take part in this study?

Taking part in this research study has some risks and requirements that you should consider carefully.

Important risks and possible discomforts to know about include sleepiness, decreased appetite, diarrhea, lack of energy, and risks of PET/MRI scans (radiation exposure). CBD may cause an increase in suicidal thoughts or actions in a very small number of people. It is possible that patients taking EPIDIOLEX may test positive on a cannabis drug screen. If this happens, we will tell the laboratory staff that you are involved in a research study using Epidiolex.



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A detailed description of side effects, risks, and possible discomforts can be found later in this consent form in the section called “What are the risks and possible discomforts from being in this research study?”

Other things to consider are the time commitment of 4 visits, and requirements to travel to MGH.

What other treatments or procedures are available for your condition?

Other treatments or procedures that are available to treat chronic low back pain include:

- Medications (e.g., non-steroidal anti-inflammatory drugs, opiates, muscle relaxants)
- Transcutaneous electrical nerve stimulation
- Physical exercise and stretching
- Epidural steroid injection
- Physical therapy
- Back surgeries
- Acupuncture

If you have questions or concerns about this research study, whom can you call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Jodi Gilman, PhD is the person in charge of this research study. You can call her at 617-643-7293 Monday-Friday from 9am to 5pm with questions about this research study. If you have any medical questions related to the study you can call Dr. Kristina Schnitzer at 617-726-2000, and ask for pager #27399 (24/7, for emergencies).

If you have questions about the scheduling of appointments or study visits, call our study staff:
 Chelsea Pike: (617)724-0382 ckpik@mg.harvard.edu

If you want to speak with someone **not** directly involved in this research study, please contact the Mass General Brigham IRB. You can call them at 857-282-1900.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research
- Any pressure to take part in, or to continue in the research study



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Detailed Information

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Why is this research study being done?

We are doing this research study to find out if cannabidiol (CBD) reduces activation of glial cells, which are the immune cells of the nervous system, compared to placebo. We are also looking to find out whether CBD may reduce symptoms of low back pain.

CBD (in the form of EPIDIOLEX) is a prescription medicine that is approved by the U.S. Food and Drug Administration (FDA) to treat seizures associated with Lennox-Gastaut syndrome or Dravet syndrome (rare forms of childhood epilepsy) in people 2 years of age and older. CBD is not approved by the FDA to treat chronic low back pain and it is not known whether it is effective for chronic back pain. We are asking you to take part in this study because you have chronic low back pain lasting at least 6 months.

This research study will compare CBD to placebo. The placebo looks exactly like CBD, but contains no CBD. During this study you may get a placebo instead of CBD. Placebos are used in research studies to see if the results are due to the medication or due to other reasons. If you decide to participate in this study, you will have a 50% chance of receiving active study medication and 50% chance of receiving placebo. That means 1 out of 2 people will receive only placebo during the study. Neither you nor study staff will know if you have received active medication or placebo until after the study is over, however study staff can get this information quickly if needed.

Who will take part in this research?

We are asking you to take part in this research study because you are an adult with chronic low back pain. About 80 people will take part in this research study at Massachusetts General Hospital. The National Institutes of Health is paying for this research study to be done.

What will happen in this research study?

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures.



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Screening Visit

The Screening Visit will take place at our 101 Merrimac Street office and will last about 3 hours. At this visit, we will do some tests and procedures to see if you qualify to take part in this research study. The study staff will review the results of these tests and procedures.

At this visit, we will:

- Ask you questions or have you complete questionnaires about your health (past and present), including mental and emotional health.
- Ask you to fill out questionnaires about your pain.
- Do a physical examination.
- Ask you about current medications you are taking.
- Ask you to fill out a form with information about your age, sex, race, marital status, and employment status.
- Draw about 2 tablespoons of blood to assess liver function and radiotracer binding affinity. Low affinity for the radiotracer known as [¹¹C]PBR28 disqualifies the subject for the research study. You may provide a saliva sample instead of a blood sample to assess radiotracer binding if you wish.
- Collect a urine sample to test for certain drugs. The results of the urine drug test will not become part of your medical record. These test results will, however, remain part of your study record.
- Collect a urine sample to test for pregnancy if you are a female who is able to become pregnant. Pregnant women cannot take part in this research study.
- With your permission, we may collect a saliva sample for other genetic research.

Study staff will also need to access your medical record in order to verify a pain diagnosis and any other medications.

This visit may also be held at the MGH Charlestown Navy Yard campus instead of our 101 Merrimac Street office, depending on your circumstances. Note that we may do a brief MRI test scan with you on the day of your screening visit, or on a different day, to ensure that you are a suitable candidate for scanning.

PET/MRI Visits

All the eligible participants will complete two PET/MRI scan visits. The PET/MRI visits will take place at MGH Charlestown Navy Yard campus. Each PET/MRI visit will last



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approximately 4 hours (and up to 6 hours). We will ask you to avoid strenuous exercise for 24 hours before the PET/MRI scan.

Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) are tests that allow us to take images of your brain and spinal cord. MRI uses a powerful magnet to make images of the body, while PET uses something called a radiotracer, that binds to the specific cells we are interested in viewing and causes them to “light up” so the scanner can detect them.

Before the PET/MRI scan, we will:

- Ask you some questions about your recent health and have you fill out some questionnaires to make sure it is safe for you to have a PET/MRI scan.
- Draw about 1 teaspoon of blood to test for pregnancy if you are a female who is able to become pregnant. Pregnant women cannot take part in this research study.
- Measure your weight.
- Collect a urine sample to test for certain drugs.
- Draw about 1 teaspoon of blood to test for the presence of cannabinoids (including CBD and THC) in the blood.
- Draw about 2 teaspoons of your blood to test for COVID-19 antibodies (to see if you have been infected by the SARS-CoV-2 virus and an immune response to it is still present in your body).

If you still qualify, we will ask you to take off anything that contains metal and change into hospital approved clothing. Then we will:

- Place an IV catheter (a thin, flexible plastic tube with a needle attached) into a vein in your arm. The IV catheter will be used to inject the radiotracer known as [¹¹C]PBR28 into your body, as well as draw about 2 tablespoons of blood to assess the function of various organs, body systems, cells, molecules, and genes in pain disorders.

We would like your permission to place an arterial line (“A-line”) into an artery in your wrist to draw blood samples throughout the scan, if the doctor or nurse practitioner has deemed it safe for us to do so. However, this procedure is optional for all subjects who qualify and you will still be able to participate in the study, even if you do not allow us to collect arterial blood. The collection of arterial blood allows us to measure how the radiotracer moves through your body, and we can use that information to get more accurate PET images.

PET/MRI Scans



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You will lie still in the PET/MRI scanner for about 2 hours. The scanner is a tunnel. You will lie on your back on a narrow table that will slide you into the tunnel. In order to help hold your head still, we may place foam pillows under and around your head.

The top and sides of the tunnel will be close to your face and body, which can make some people uncomfortable. If you have ever experienced a fear of enclosed spaces (claustrophobia), please tell the study staff.

The scanner makes loud banging and beeping noises taking images, so we will give you earplugs to protect your ears.

First, we will take some pictures of your brain and/or whole body. Then we will inject the radiotracer into the IV catheter in your vein and take more images. You will not feel the radiotracer in your body and it will quickly leave your body through your urine. The Martinos Center has completed hundreds of PET/MRI scans in a number of patient populations and healthy volunteers using [11C]PBR28. There have been no side effects associated with the administration of this radiotracer. This dye will travel through your blood stream, so the PET/MRI scanner can see how the different parts of your brain and/or whole body are working.

Before, during and after the scans, you may be asked to express various behavioral ratings, including pain intensity, unpleasantness and anxiety.

After the brain scan is complete, we may collect additional 20 minutes of data from your spinal cord. This spinal cord imaging is optional, and will only be done if you are still comfortable in the scanner.

After the scan is complete, you will sit up slowly and we will remove your catheter. After the removal of the arterial line we will observe you for 30 minutes. After this period of observation, you are free to leave.

Somebody from the study staff will call you the day following each scan to check on you. Of course, you can contact us at any time if you have questions (see contact information under "If I have questions or concerns about this research study, whom can I call?").

Taking the Study Drug

You will receive a bottle containing either CBD or a placebo at the first PET/MRI Visit to take home with you. You will be instructed to begin taking it four weeks prior to the scheduled date of your second PET/MRI Visit. A study doctor will tell you how much to take. You will take CBD or placebo for 4 weeks in total, and your dose will increase each week. When you start the study drug, we will ask you to take 2.5mg/kg twice daily. Each week, a member of the study



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team will remind you to increase the dose for the following week (week 2 dose = 5mg/kg twice daily; week 3 dose = 7.5mg/kg twice daily; week 4 final dose = 10mg/kg twice daily). At the end of the second week, a study physician will meet with you (by phone or in person) to assess tolerability. If you are not tolerating the study drug well (whether during the second week, or during the third or fourth week of taking the study drug), the physician will decrease your dose to the previous week’s dose. The study physician may also discontinue the study drug if you do not tolerate it well.

CBD should be taken consistently with respect to meals and should not be taken in a fasted state. In addition, CBD should not be taken with concurrent alcohol use. It is important for you to follow our instructions about how to take the study drug.

Daily Surveys

You will be asked to fill out a daily survey for about 2 weeks before your first scan, for 4 weeks while you are taking CBD or placebo, and for 2 weeks after the discontinuation of CBD or placebo. You will be sent a survey to complete by the end of each day. This survey will be sent to you each day via email or text message and you will have until 11:59pm each night to complete the survey. The survey will take less than 5 minutes to complete and will ask you about your low back pain symptoms, mental health, sleep quality, fatigue, whether you have been taking the study drug, and whether you have taken any other medications to manage your pain.

Please let the study staff know if you do not have internet access and we can arrange to call you to administer the survey.

Follow-up Visits and Calls

1-Week Call. You will have a phone call 1 week after your first scan visit. In this call, we will assess adverse events, treatment expectancy, and medication use. We will also remind you to increase your study drug dose.

2-Week Visit. You will have a follow-up appointment during Week 2 with a study staff member at 101 Merrimac Street. We will check on your health, remind you to increase your study drug dose, ask about other medication use, and ask you to complete some questionnaires. We may also take a small sample of blood for a follow-up liver function test. As you will be taking Epidiolex or placebo daily at the time of this visit, we will ask you whether you can drive to the visit; if you cannot because the study drug makes you drowsy, we will arrange transportation. Note that this visit may also be held at the MGH Charlestown Navy Yard campus, depending on your circumstances.



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3-Week Call. You will have a phone call during Week 3 to assess adverse events, treatment expectancy, and medication use. We will also remind you to increase your study drug dose.

4-Week Visit. You will have a second follow-up appointment immediately after the four-week treatment period, where we will assess back pain, general health, adverse events, and medication use. On the same day or as close as possible depending on scheduling, you will be re-scanned. We will also repeat the questionnaires administered during the baseline visit to assess any changes in subjective pain or general health. We will also take a small sample of blood for a follow-up liver function test. Again, we will ask you whether you can drive to the visit; if you cannot because the study drug makes you drowsy, we will arrange transportation.

6-Week Call. You will have a follow-up phone call 2 weeks after the discontinuation of the study drug. In this call, we will assess back pain, general health, adverse events, and medication use.

Stopping the Study Early

If you wish to stop taking the study drug, you should tell the principal investigator of this study, Dr. Jodi Gilman.

If you decide to stop participating in the study for any reason before the planned end of the study, we will ask that you continue to follow the schedule of visits. If you are unable or unwilling to return to the MGH Charlestown Navy Yard campus for visits, we will ask if we can call you for phone interviews instead of study visits.

Also, the study doctor may take you out of the study without your permission. This may happen because:

- The study team thinks you cannot follow the study plan.
- Your health is in question.
- You are experiencing side effects from the study drug.
- The study doctor thinks it is best for you to stop taking the study drug.
- We stop doing the study for other reasons.

Sending Study Information to Research Collaborators Outside Mass General Brigham

Blood Plasma Shipments

We will collect blood samples at the screening visit and the two PET/MRI visits, which will be tested for COVID-19 antibodies and pregnancy (in females). A small quantity (about 1 teaspoon)



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of blood plasma from your sample may be shipped to researchers working with us at a University of Colorado lab who can quantify cannabinoids (including CBD and THC) in the blood.

We will label all your study materials with a code number instead of your name. No names or important numbers that could be used to identify you, like hospital medical record number or social security number, will be kept on samples. Only MGH study staff will keep the link between your subject number and your name on a computer protected by a personal password.

Optional (not required) Saliva Samples for Genetic Testing

While collection of a blood or saliva sample to test for radiotracer binding affinity is required, the collection of a saliva sample for other genetic research at the screening visit is optional (not required). You can still take part in the main study even if you don't want to take part in the additional genetic study. Giving a DNA sample involves filling 1-2 small plastic containers with your saliva. This will be done at your first visit and should take less than 5 minutes. Usually researchers study just a few areas of genetic code that are linked to a disease or condition. Instead, we may perform a whole genome analysis on your DNA sample. In whole genome analyses, all or most of the genes are looked at and used by researchers to study links to substance use and mental health. These whole genome analyses will be conducted by investigators at the Broad Institute. Samples shared with investigators at the Broad Institute will be labeled with a code number and not with your name or other identifying information. Research using whole genome information is important for the study of virtually all diseases and conditions. Therefore, the anonymized samples will provide study data for researchers working on any disease.

It is not intended to provide important genetic information about your health. We have no plan to return any research results to you or your doctor. The results of the genetic testing will not be placed in your medical record. Your consenting to take part in this additional genetic study is voluntary, and you may decide to withdraw from the study at any time or decide not to join the study. If you change your mind and want to withdraw your saliva sample from further genetic research you can do so at any time by contacting Dr. Gilman (617-643-7293; jgilman1@mgh.harvard.edu). Any information obtained from the sample will also be withdrawn except to the extent to which the information has already been used in analyses. All information and samples obtained for this study will be assigned a code number. No names or important numbers that could be used to identify you, like hospital medical record number or social security number, will be kept on samples. Only MGH study staff will keep the link between your subject number and your name on a computer protected by a personal password.

Would you like to provide a saliva sample to be used for genetic testing as described above?
 Please mark your choice below.



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[] YES [] NO Initials _____

In order to allow researchers to share test results, the National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that analyze data and collect the results of whole genome studies. These banks may also analyze and store DNA samples, as well. These central banks will store your genetic information and samples and give them to other researchers to do more studies. We do not think that there will be further risks to your privacy and confidentiality by sharing your samples and whole genome information with these banks. However, we cannot predict how genetic information will be used in the future. The samples and data will be sent with only your code number attached. Your name or other directly identifiable information will not be given to central banks. There are many safeguards in place to protect your information and samples while they are stored in repositories and used for research.

How may we use and share your samples and health information for other research?

At the completion of this research study, we would like to store and be able to use and share your identifiable samples and health information with researchers at Mass General Brigham for other research related to pain disorders. If we share your samples and/or health information with other researchers outside of Mass General Brigham, we will label the samples and information with a code instead of your name or other directly identifying information. The key to the code connects your name or other identifiers to your sample and/or information. We will keep the code in a password protected computer.

Because these samples and/or health information are identifiable, we are asking your permission to store, use and share them for other research. You can still take part in the research study whether or not you give permission for the storage, use, and sharing of the samples and health information for other research.

Do you agree to let us store and use your samples and health information for other research related to pain disorders?

[] YES [] NO Initials _____

Will you get the results of this research study?



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You and your doctor should not expect to get information about the results of the research study or the results of your individual participation in the research study. The researchers involved in this study will study samples and information from many people. It could take many years before anyone knows whether the results have any meaning. There is a small chance that researchers could find out something from the study that might be important to your health. If this happens, we may contact you to find out if you would like to learn more. However, even if we find something important to your health, we cannot guarantee that you will be contacted.

What are the risks and possible discomforts from being in this research study?

Risks of Taking EPIDIOLEX

Taking **EPIDIOLEX** may cause you to have one or more of the side effects listed below.

Common side effects:

- Increase in liver enzymes: As part of the study, we will collect blood to check your liver before you start taking EPIDIOLEX and after one month of treatment. In some cases, EPIDIOLEX treatment may need to be stopped. If you had elevated liver enzymes at baseline but still met the eligibility criteria for the study, we may ask you to undergo a follow-up liver function tests at 2 weeks. In addition, we will perform a liver function test on anyone who develops clinical signs or symptoms suggestive of hepatic dysfunction.
- Sleepiness: EPIDIOLEX may cause you to feel sleepy, which may get better over time. Do not drive, operate heavy machinery, or do other dangerous activities until you know how EPIDIOLEX affects you. Other medicines (e.g., clobazam) or alcohol may increase sleepiness.
- Decreased appetite
- Diarrhea
- Lack of energy
- Insomnia
- Poor quality sleep
- Infections

Rare side effects:

- Suicidal thoughts or actions: EPIDIOLEX may cause suicidal thoughts or actions in a very small number of people, about 1 in 500. Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you: thoughts about suicide or dying, attempt to commit suicide, new or worse depression, new or worse anxiety, feeling agitated or restless, panic attacks, trouble sleeping, new or worse



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irritability, acting aggressive, being angry, or violent, acting on dangerous impulses, an extreme increase in activity and talking (mania), other unusual changes in behavior or mood. We will assess suicidality, depression, and anxiety throughout the study. If you report any new or worsening expression of suicidal ideation and or/emergent depression, you may be asked to speak with a licensed clinician. These clinicians, along with the PI will then determine whether you can safely continue the study. If the clinicians determine that you cannot safely continue the study, your participation in the study will be discontinued, and you will be provided with a list of resources for follow-up care.

- Allergic reactions: As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious, and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are having an allergic reaction, call the study doctor right away. If you are having trouble breathing, call 911 immediately.
- Positive drug screen for cannabis: It is possible that patients taking EPIDIOLEX may test positive on a cannabis drug screen.
- There may be other risks of EPIDIOLEX that are currently unknown at this time.

Risks of Taking EPIDIOLEX with Other Medications

Do not take medications that impact specific CYP450 enzymes, including some CNS depressants, while you are in the study. This includes:

- All antipsychotics
- Benzodiazepines (except for alprazolam, clonazepam, and lorazepam)
- Non-benzodiazepine sleep aid use will be reviewed by the study physician to determine safety

Taking these drugs and **EPIDIOLEX** together may cause serious side effects. All medications, including but not limited to those mentioned, must be discussed with the study physician.

Additionally, for your safety during this study, call your study doctor BEFORE you take any:

- New medications prescribed by your own doctor
- Other medications sold over-the-counter without a prescription
- Dietary or herbal supplements

Risks of Radiation Exposure

As a result of your participation in this study, you will be exposed to radiation from two PET scans of your brain and/or spinal cord. Please note that this radiation is not necessary for your medical care and is for research purposes only. The maximum amount of radiation to which you could be exposed to in this study is approximately 7.4 milliSieverts (mSv). A mSv is a



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unit of radiation dose. This amount of radiation is about the same as you would normally get in 2.4 years from natural background sources from the earth and the sky.

Scientists disagree on whether radiation doses at these low levels are harmful. Possible side effects that could occur at doses associated with this study include:

- A slight increase in the risk of developing cancer later in life

Since the effects of radiation can add up over time, it is important that you tell the study doctors about your past clinical imaging and research-related radiation exposure. If you have taken part in other research studies in the past 12 months that have involved radiation exposure, please tell us. If it appears that your earlier radiation exposure is more than our current guidelines, it is possible that you will not be allowed to take part in this study.

Have you participated in other research studies (not including this study) involving radiation exposure within the last 12 months?

YES NO **Initials** _____

Risks to an Embryo or Fetus, or to a Breastfeeding Infant

The effect of radiation exposure or the use of CBD (EPIDIOLEX) on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this study if they are:

- Pregnant or trying to become pregnant
- Breastfeeding

If you are a menopausal woman and have not had a menstrual period for the past 12 months or more, you will not need to have a pregnancy test. Also, if you have had any well-documented method of surgical sterilization, you will not need to have a pregnancy test. Methods of surgical sterilization include having had a hysterectomy (removal of the uterus), bilateral oophorectomy (removal of both ovaries), a tubal ligation (having your tubes tied), and transvaginal occlusion (plugging the opening of the tubes with a coil). All other female subjects must have a negative pregnancy test before starting the study drug and before having the PET/MRI scan.

If you miss a period, or think you might be pregnant during the study, you must tell the study doctor immediately. If you become pregnant, you must stop taking the study drug and stop taking part in the study.

There may be other risks and side effects of the PET/MRI scan that are not known at this time.



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Risks of MRIs

MRIs use powerful magnets to make images. There are no known radiation risks associated with MRI. However, you should not have an MRI if:

- You have certain medical metal implants, such as surgical clips or pacemakers
- You are pregnant or suspect you are pregnant

All credit cards and other items with magnetic strips should also be kept out of the MRI room. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow tube. The MRI makes loud banging noises as it takes images. Earplugs can be used to reduce the noises. The MRI can be stopped at any time at your request.

Other possible risks include:

- Localized warming of your skin and the underlying tissue during normal routine MRI use
- You should immediately inform us if you experience discomfort due to warming and the procedure will be stopped

Risks of IV Catheter and Blood Draw

Drawing blood or placing the IV catheter into a vein in your arm may cause the following in the area where we take blood samples from or place the IV catheter:

- Pain
- Discomfort
- Bruising
- Bleeding
- Swelling
- Redness

You may have a bruise or feel painful or uncomfortable for 2-3 days after. Rarely, an infection may occur, which can be treated.

Risks of Optional Arterial Line (A-line)

Inserting an A-line can hurt more than having a regular IV catheter or having blood drawn with a needle. If you agree to this procedure, we will numb your wrist area first, but it may still hurt when we place the A-line into your wrist. Once the A-line is in place, it usually does not hurt.

Having an arterial line placed may cause:



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- Pain, bleeding, swelling, or redness at the wrist. Rarely (less than 1 in 100), an infection may occur, which can be treated.
- Short loss of pulse at the wrist, if blood flow in the artery is briefly stopped (for example, because of a clot or spasm of the artery).
- Damage to the artery wall or nearby nerves.
- Catheter breaking or falling out.

Rare side effects:

- There have been reports of decreased blood flow to the hand that resulted in the need for surgery. This is very rare and has not been reported when catheters have been in place for only a few hours for research.

After we remove the catheter:

- We will ask you to stay for at least 30 min so that we can check that the site is healing properly.
- You may have a bruise or feel tenderness for 2-3 days around the area where the arterial line was placed.
- You should avoid lifting anything heavier than a small bag of flour for a day following the scan.

Call us if:

- Bleeding occurs after you leave (rare). Apply pressure to the site and go to the Emergency Department.
- The wrist area is painful, red, or swollen.

Do you allow us to collect arterial blood during the scan(s)? You can change your mind at any time.

YES NO **Initials** _____

Risks of Numbing Drug (Lidocaine)

The anesthesiologist will use lidocaine to numb your wrist area prior to placing the A-line. Risks of lidocaine include:

- Dizziness
- Nausea
- Drowsiness
- Ringing in the ears
- Numbness



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- Allergic reaction. An allergic reaction to lidocaine was observed in a very limited number of cases.

Risks of COVID-19 Antibody Testing

As part of the study, we wish to determine whether or not you have been exposed to COVID-19. We do this using an antibody serology test which involves taking up to 10 ml of blood (about 2 teaspoons) and sending it to an internal or third-party laboratory that provides testing services. Your test results will be communicated to you. Your results may become part of your MGH medical records. A positive test does not mean that you have an active COVID-19 infection, only that you have been exposed at some point in the past.

Risks of Genetic Testing

Genetic information that results from this study does not have medical or treatment importance at this time. However, there is a risk that information about taking part in a genetic study may influence insurance companies of employers regarding your health. To further safeguard your privacy, genetic information obtained in this study will not be placed in your medical record. Taking part in a genetic study may also have a negative impact on family or other relationships. If you do not share information about taking part in this study, you will reduce this risk. We may perform Genome wide association studies (GWAS) with this data. GWAS are hypothesis free methods to identify associations between genetic regions (loci) and traits (including diseases).

Risks of Questionnaires

We will ask you questions about your emotional or mental health (psychological questions). Some of these questions may make you uncomfortable. You are allowed to skip any question you do not want to answer, but it could mean being excluded by the study (depending on how necessary the particular answer is).

Incidental Findings

We are doing the PET/MRI scan in this study to answer research questions, not as part of your medical care. The information from this study will not usually become part of your hospital record. This PET/MRI scan is not the same as the one that your doctor would order. It may or may not show problems that would be found on a standard MRI or PET scan. This type of scan is considered experimental.

If we do see something that looks like a medical problem, we will ask a radiologist (a doctor who specializes in test results of this sort) to review the results. If the radiologist thinks that you may



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have a medical problem, we will tell you and help you get follow-up care. If the radiologist thinks that you may have a medical problem, but it turns out that you don't, we may have caused you to worry needlessly about your health.

Medical Information

We will make a notation in your medical record that you are a part of this study. There is a small risk that your confidential medical information could be revealed or discovered by mistake. The results of this research study won't be placed in your medical records. In addition, your samples and information will be coded and the key to the code will be kept in a separate, locked file. We won't share or publish any information that will identify you.

What are the possible benefits from being in this research study?

You may not benefit from taking part in this study. If you receive CBD (EPIDIOLEX), it is possible that your low back pain will improve while you are taking it. However, because EPIDIOLEX is not FDA-approved to treat low back pain, your doctor cannot prescribe it after you finish the study.

Others with low back pain may benefit in the future from what we learn in this study. We hope the information obtained from this study will help scientists discover a potential mechanism of action for CBD.

What other treatments or procedures are available for your condition?

You do not have to take part in this research study to be treated for low back pain. Other treatments or procedures that are available to treat low back pain include:

- Medications (e.g., non-steroidal anti-inflammatory drugs, opiates, muscle relaxants)
- Transcutaneous electrical nerve stimulation
- Physical exercise and stretching
- Epidural steroid injection
- Physical therapy
- Back surgeries
- Acupuncture

Talk with the study doctor if you have questions about any of these treatments or procedures.



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Can you still get medical care within Mass General Brigham if you don't take part in this research study, or if you stop taking part?

Yes. Your decision won't change the medical care you get within Mass General Brigham now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should you do if you want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will you be paid to take part in this research study?

We will pay you up to \$770 for the following:

- \$75 for the initial screening visit
Up to \$76 for completing daily surveys (\$1 per survey completed)
o Bonus \$25 if you complete 90% of surveys
\$200 for each PET/MRI scanning session
\$25 for each blood test to exclude pregnancy (if you are a female of childbearing age)
\$50 for each arterial line placement
Up to \$44 which you can earn from a task you will complete in the PET/MRI scanner

If, for some reason, we cannot inject you with the dye during the imaging visit(s) and we have not yet placed the arterial line, you will receive \$50. If we cannot inject you with the dye and we have already placed the arterial line, you will receive \$100. If you have to stop the scan early for any reason, we will pay you \$50 for the imaging visit(s). We will also reimburse you for your parking in the hospital garage during study visits.



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We may use your samples and information to develop a new product or medical test to be sold. The Sponsor, hospital, and researchers may benefit if this happens. There are no plans to pay you if your samples or information are used for this purpose.

What will you have to pay for if you take part in this research study?

Study funds will pay for certain study-related items and services. We may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs. You will also be responsible for paying for transportation to and from study visits, although we will validate parking in the hospital garage during study visits. It is important to note that if you do receive any benefit from the CBD treatment, and decide to continue treatment with CBD after your study participation is over, you and your insurance company will be responsible for the cost of the CBD.

What happens if you are injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the beginning of this consent form.

If you take part in this research study, how will we protect your privacy?



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Federal law requires Mass General Brigham to protect the privacy of health information and related information that identifies you. We refer to this information as "identifiable information."

In this study, we may collect identifiable information about you from:

- Past, present, and future medical records
• Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable information and why:

- Mass General Brigham researchers and staff involved in this study
• The sponsor(s) of the study, and people or groups it hires to help perform this research or to audit the research
• Other researchers and medical centers that are part of this study
• The Mass General Brigham ethics board or an ethics board outside Mass General Brigham that oversees the research
• A group that oversees the data (study information) and safety of this study
• Non-research staff within Mass General Brigham who need identifiable information to do their jobs, such as for treatment, payment (billing), or hospital operations (such as assessing the quality of care or research)
• People or groups that we hire to do certain work for us, such as data storage companies, accreditors, insurers, and lawyers
• Federal agencies (such as the U.S. Department of Health and Human Services (DHHS) and agencies within DHHS like the Food and Drug Administration, the National Institutes of Health, and the Office for Human Research Protections), state agencies, and foreign government bodies that oversee, evaluate, and audit research, which may include inspection of your records
• Public health and safety authorities, if we learn information that could mean harm to you or others (such as to make required reports about communicable diseases or about child or elder abuse)
• Other researchers within or outside Mass General Brigham, for use in other research as allowed by law.

Certificate of Confidentiality

A federal Certificate of Confidentiality (Certificate) has been issued for this research to add special protection for information and specimens that may identify you. With a Certificate,



Subject Identification

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unless you give permission (such as in this form) and except as described above, the researchers are not allowed to share your identifiable information or identifiable specimens, including for a court order or subpoena.

Certain information from the research will be put into your medical record and will not be covered by the Certificate. This includes records of medical tests or procedures done at the hospitals and clinics, and information that treating health care providers may need to care for you. Please ask your study doctor if you have any questions about what information will be included in your medical record. Other researchers receiving your identifiable information or specimens are expected to comply with the privacy protections of the Certificate. The Certificate does not stop you from voluntarily releasing information about yourself or your participation in this study.

Even with these measures to protect your privacy, once your identifiable information is shared outside Mass General Brigham, we cannot control all the ways that others use or share it and cannot promise that it will remain completely private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your identifiable information. Your permission to use and share your identifiable information does not expire.

The results of this research may be published in a medical book or journal, or used to teach others. However, your name or other identifiable information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your identifiable information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your identifiable information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others, and such information may continue to be used for certain purposes, such as to comply with the law or maintain the reliability of the study.



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You have the right to see and get a copy of your identifiable information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
I have had the opportunity to ask questions.
I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my identifiable information to be used and shared as described above.

Subject Date Time (optional)

Signature of Study Doctor or Person Obtaining Consent:

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
I have answered all questions about this research study to the best of my ability.

Study Doctor or Person Obtaining Consent Date Time (optional)

Consent Form Version Date: 2/17/2022

DSMB Charter

Investigation of Cannabidiol for Reduction of NeuroInflammation in Chronic Back Pain

1R01DA053316-01

Dr. Jodi Gilman and Dr. Marco Loggia

NIH

A. Safety monitoring

An independent Data and Safety Monitoring Board (DSMB) will be appointed for this study, to assess the safety of the study by determining whether there is an unacceptable level of risk due to study procedures and whether an increased number of adverse events occur.

The DSMB will be established to analyze interim results to assess the safety of the trial at regular intervals for the duration of the study by determining whether an increased number of adverse events occur among study participants receiving drug compared to participants receiving placebo.

The board will include a statistician, a pain expert, and a psychiatrist. Each member of the DSMB will not otherwise be associated with the trial. Safety data will be reviewed by the Data and Safety Monitoring Board Data every 6 months after the recruitment period begins. The DSMB will receive summary reports on recruitment, retention and description of all adverse events and review them at each biannual DSMB meeting. The DSMB will receive all communication with the IRB. Subject information provided to the board will be identified only with study IDs to protect the confidentiality of subjects. The DSMB will assess interim results to determine whether the active drug treatment is associated with substantial risk, including higher rate of adverse outcomes when compared with the placebo group.

B. Outcomes monitoring

A DSMB Report written by the chair and approved by all members will be issued to the IRB after every DSMB meeting. The report will include, but may not be limited to, a synopsis of the trials, their progress to date, characteristics of participants enrolled, retention and disposition of study participants, quality assurance issues, regulatory issues, and reports of AEs and SAEs.

DSMB Role	Name and Title	Affiliation/ Institution	Contact Details	Summary of Expertise
DSMB Chair and Statistician	Bettina Hoepfner, PhD	MGH, Harvard Medical School	bhoepfner@mgh.harvard.edu	Statistician
DSMB Pain Expert	Jianren Mao, MD	MGH	jmao@mgh.harvard.edu	Pain physician

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DSMB Psychiatrist	Esther Blessing, MD, PhD	NYU Grossman School of Medicine	esther.blessing@nyulangone.org	CBD, psychiatric disorders
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Trial investigators will not be members of the DSMB.

For peer review only



STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Included throughout the paper
Protocol version	3	Date and version identifier	14
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 14
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10 (and see Item 21a for data safety monitoring board)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4

1			
2		6b	Explanation for choice of comparators
3			4
4	Objectives	7	Specific objectives or hypotheses
5			4
6	Trial design	8	Description of trial design including type of trial (eg,
7			parallel group, crossover, factorial, single group),
8			allocation ratio, and framework (eg, superiority,
9			equivalence, noninferiority, exploratory)
10			4, 8
11			
12	Methods: Participants, interventions, and outcomes		
13			
14	Study setting	9	Description of study settings (eg, community clinic,
15			academic hospital) and list of countries where data will
16			be collected. Reference to where list of study sites can
17			be obtained
18			
19	Eligibility	10	Inclusion and exclusion criteria for participants. If
20	criteria		applicable, eligibility criteria for study centres and
21			individuals who will perform the interventions (eg,
22			surgeons, psychotherapists)
23			
24			5-6, Table 1
25	Interventions	11a	Interventions for each group with sufficient detail to
26			allow replication, including how and when they will be
27			administered
28			
29			6-9, Table 2
30		11b	Criteria for discontinuing or modifying allocated
31			interventions for a given trial participant (eg, drug dose
32			change in response to harms, participant request, or
33			improving/worsening disease)
34			
35			8, 12
36		11c	Strategies to improve adherence to intervention
37			protocols, and any procedures for monitoring adherence
38			(eg, drug tablet return, laboratory tests)
39			
40			8, 9
41		11d	Relevant concomitant care and interventions that are
42			permitted or prohibited during the trial
43			
44	Outcomes	12	Primary, secondary, and other outcomes, including the
45			specific measurement variable (eg, systolic blood
46			pressure), analysis metric (eg, change from baseline,
47			final value, time to event), method of aggregation (eg,
48			median, proportion), and time point for each outcome.
49			Explanation of the clinical relevance of chosen efficacy
50			and harm outcomes is strongly recommended
51			
52			Table 1
53	Participant	13	Time schedule of enrolment, interventions (including
54	timeline		any run-ins and washouts), assessments, and visits for
55			participants. A schematic diagram is highly
56			recommended (see Figure)
57			
58			4, Table 2,
59			Figure 1
60			(schema)

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-10, Table 2
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1				
2		18b	Plans to promote participant retention and complete	11-12
3			follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate	
5			from intervention protocols	
6				
7	Data	19	Plans for data entry, coding, security, and storage,	10
8	management		including any related processes to promote data quality	
9			(eg, double data entry; range checks for data values).	
10			Reference to where details of data management	
11			procedures can be found, if not in the protocol	
12				
13				
14	Statistical	20a	Statistical methods for analysing primary and secondary	10-11
15	methods		outcomes. Reference to where other details of the	
16			statistical analysis plan can be found, if not in the	
17			protocol	
18				
19				
20		20b	Methods for any additional analyses (eg, subgroup and	11
21			adjusted analyses)	
22				
23		20c	Definition of analysis population relating to protocol non-	11-12
24			adherence (eg, as randomised analysis), and any	
25			statistical methods to handle missing data (eg, multiple	
26			imputation)	
27				
28				
29	Methods: Monitoring			
30				
31	Data	21a	Composition of data monitoring committee (DMC);	12
32	monitoring		summary of its role and reporting structure; statement of	
33			whether it is independent from the sponsor and	
34			competing interests; and reference to where further	
35			details about its charter can be found, if not in the	
36			protocol. Alternatively, an explanation of why a DMC is	
37			not needed	
38				
39				
40		21b	Description of any interim analyses and stopping	12
41			guidelines, including who will have access to these	
42			interim results and make the final decision to terminate	
43			the trial	
44				
45				
46	Harms	22	Plans for collecting, assessing, reporting, and managing	11
47			solicited and spontaneously reported adverse events	
48			and other unintended effects of trial interventions or trial	
49			conduct	
50				
51				
52	Auditing	23	Frequency and procedures for auditing trial conduct, if	N/A
53			any, and whether the process will be independent from	
54			investigators and the sponsor	
55				
56				
57	Ethics and dissemination			
58				
59				
60				

1				
2	Research	24	Plans for seeking research ethics	13
3	ethics		committee/institutional review board (REC/IRB)	
4	approval		approval	
5				
6	Protocol	25	Plans for communicating important protocol	13
7	amendments		modifications (eg, changes to eligibility criteria,	
8			outcomes, analyses) to relevant parties (eg,	
9			investigators, REC/IRBs, trial participants, trial	
10			registries, journals, regulators)	
11				
12				
13	Consent or	26a	Who will obtain informed consent or assent from	13
14	assent		potential trial participants or authorised surrogates, and	
15			how (see Item 32)	
16				
17				
18		26b	Additional consent provisions for collection and use of	Supplementa
19			participant data and biological specimens in ancillary	ry file 2
20			studies, if applicable	(Consent
21				Form)
22				
23	Confidentialit	27	How personal information about potential and enrolled	13
24	y		participants will be collected, shared, and maintained in	
25			order to protect confidentiality before, during, and after	
26			the trial	
27				
28				
29	Declaration	28	Financial and other competing interests for principal	14
30	of interests		investigators for the overall trial and each study site	
31				
32	Access to	29	Statement of who will have access to the final trial	14
33	data		dataset, and disclosure of contractual agreements that	
34			limit such access for investigators	
35				
36				
37	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and	N/A
38	post-trial		for compensation to those who suffer harm from trial	
39	care		participation	
40				
41	Disseminatio	31a	Plans for investigators and sponsor to communicate trial	2, 13, 14
42	n policy		results to participants, healthcare professionals, the	
43			public, and other relevant groups (eg, via publication,	
44			reporting in results databases, or other data sharing	
45			arrangements), including any publication restrictions	
46				
47				
48		31b	Authorship eligibility guidelines and any intended use of	N/A
49			professional writers	
50				
51		31c	Plans, if any, for granting public access to the full	14
52			protocol, participant-level dataset, and statistical code	
53				
54				
55	Appendices			
56				
57				
58				
59				
60				

1				
2	Informed	32	Model consent form and other related documentation	Supplementa
3	consent		given to participants and authorised surrogates	ry file 2
4	materials			(Consent
5				Form)
6				
7	Biological	33	Plans for collection, laboratory evaluation, and storage	Supplementa
8	specimens		of biological specimens for genetic or molecular	ry file 2
9			analysis in the current trial and for future use in ancillary	(Consent
10			studies, if applicable	Form)
11				
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*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

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

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3 **Study protocol for a phase II, double-blind, randomized controlled trial of cannabidiol**
4 **(CBD) compared to placebo for reduction of brain neuroinflammation in adults with**
5 **chronic low back pain**
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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 neuro-glial interactions play a role in the establishment and maintenance of pain. Recently, we used positron emission tomography (PET) to demonstrate increased levels of 18kDa 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 to placebo, affects neuroinflammation, as measured by TSPO levels.

Methods and analysis: This is a double-blind, randomized, placebo-controlled, phase II clinical trial. Eighty adults (aged 18-75) with cLBP for >6 months will be randomized 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/magnetic resonance imaging (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 randomized to CBD will demonstrate larger reductions in thalamic [¹¹C]PBR28 signal compared to 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 (NCT04827992). 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, randomized, placebo-controlled clinical trials to evaluate a pain intervention using PET.
- This is the first trial to assess whether 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.

INTRODUCTION

Chronic pain affects an estimated 50 to 100 million individuals in the United States[1, 2] and is among the most debilitating medical conditions with profound physical, emotional, and economic costs.[3] Available treatment options including interventional techniques[4] and non-opioid pain medications such as non-steroidal anti-inflammatory drugs[5] 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 neuro-glial 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 sensitize pain pathways[39] in a “pain-produces-pain” loop. Importantly, agents that disrupt glial function inhibit or attenuate various behavioral markers of pain hypersensitivity (e.g., 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 18kDa translocator protein (TSPO), a marker of glial activation,[16, 42-50] in the brains[51] and spinal cords[52] of patients with chronic low back pain (cLBP) compared to controls. These TSPO signal elevations were consistently observed, particularly in the thalamus, in our original study[51] 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) receptors,[58] 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 pre-clinical 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 pro-inflammatory 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

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

19 This study will also assess the role of CBD on neuroinflammation with respect to
20 depressive symptoms. Comorbid depression and chronic pain is common, with approximately
21 40% of cLBP patients also exhibiting negative affect, including depressive symptoms.[78-81]
22 Depression has been associated with neurobiological changes, including neurotransmitter
23 deficits, endocrine disturbances, and impaired neural adaptation and plasticity,[82, 83] and
24 neuroinflammation may be implicated in these abnormalities.[84] Those with depression who
25 commit suicide have shown dramatically increased microglial activation.[85] Indeed, cLBP
26 patients who also have comorbid depression demonstrate, in addition to thalamic TSPO signal
27 elevations observed irrespectively of depression status, also TSPO signal elevations in limbic
28 regions, which are proportional to the scores on the Beck Depression Inventory.[86] Meta-
29 analyses have shown that mechanistically diverse anti-inflammatory agents may be effective
30 treatments for depression.[87-89] Preliminary evidence suggests that CBD promotes
31 antidepressant effects in animal models,[67, 68] however randomized clinical trials of CBD for
32 treatment of depression have not been conducted. Therefore, a secondary objective of the study
33 is to assess whether CBD compared to placebo reduces depressive symptomatology and
34 depression-related neuroinflammation in patients with cLBP.

38 Healthcare providers are increasingly interacting with patients who are interested in using
39 CBD for various pain disorders, with little evidence available for therapeutic guidance. Results
40 from this study will provide critical information regarding the potential utility of CBD for cLBP
41 and its involvement in mechanistic pathways of neuroinflammation.

43 METHODS AND ANALYSIS

44 The full protocol is included as supplementary information (see Supplementary File 1).

47 Study design

48 This is a phase II, double-blind, randomized, placebo-controlled 4-week clinical trial with
49 a 6-week follow-up assessment. The principal goals of this trial are to assess the effects of CBD
50 on neuroinflammation, pain and depressive symptomatology, in participants with cLBP.
51 Neuroinflammation will be quantified with PET/MRI scans using [¹¹C]PBR28, a second
52 generation ligand for TSPO. Participants will continue their usual pain care regimen during the
53 study. This trial is being conducted at Massachusetts General Hospital in the United States. The
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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 to 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 six 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]PBR28[90]; 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 four weeks prior to randomization.

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 two weeks, or regular recreational drug use in the previous three months. See Table 1 for the full list of inclusion and exclusion criteria.

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	<ol style="list-style-type: none"> 1. Age \geq 18 and \leq 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 behavioral) for the previous four 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 only if the conditions were so severe as to require hospitalization 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 hospitalization
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 (e.g., peripheral edema)
16. Use of immunosuppressive medications, such as prednisone, 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 individualized basis with a physician:
 - Strong and moderate inhibitors of CYP3A4 and CYP2C19 (e.g., diltiazem, erythromycin, fluoxetine)
 - Sensitive and moderately sensitive substrates of CYP2C19, CYP1A2, CYP2B6, CYP2C8, CYP2C9, UGT1A9, and UGT2B7 (e.g., omeprazole, bupropion, morphine, lamotrigine)
21. CNS depressants including antipsychotics, benzodiazepines (except for alprazolam, clonazepam, and lorazepam, which have low binding affinity to TSPO[93-97]), 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 behavior 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 (e.g., unable to reliably rate pain, unlikely to remain still during the imaging procedures)

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 Supplementary File 2 for a copy of the consent form). Eligibility assessments will be conducted during the screening visit, listed in Table 2.

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						
	Characterization 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

Investigational product

Participants will be randomized 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 flavoring. 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 twice daily in week one, 5 mg/kg twice daily in week two, 7.5 mg/kg twice daily in week three, and 10 mg/kg twice daily in week four. If participants report significant adverse events (e.g., 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.

Randomization and treatment allocation

Eligible participants will be enrolled by study staff and randomized to receive either CBD or placebo. Stratified simple random sampling, based on age (>50 vs. ≤50) and sex (male vs. female), will be performed. Randomization sheets have been developed by the study biostatistician and will be used by a study pharmacist to assign treatments. The MGH Clinical Trial 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 randomization, 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 four 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. Adverse events will be assessed at baseline and weeks 1, 2, 3, 4, and 6 (two 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. 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

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3 performed, and female participants of childbearing potential will have blood drawn to perform a
4 serum pregnancy test.

5
6 At the beginning of the scan sessions, an intravenous catheter will be placed in the
7 participant's antecubital vein of the left or right arm. Blood will be drawn to assess quantitative
8 levels of cannabinoids, including CBD and THC. An arterial line will be placed in a radial artery
9 with local anesthesia if the participant has consented to this (optional) procedure and has no
10 contraindications. The arterial line will be placed in the arm contralateral to the intravenous line
11 that is used for the [¹¹C]PBR28 radiotracer injection, and will enable blood sampling at various
12 times during the imaging study for at most 160 mL of blood. The collected arterial blood will be
13 used to compute metabolite-corrected arterial input function for kinetic modeling analyses. Brain
14 PET/MRI data will be acquired for approximately 90 min post-injection. Between 90- and 110-
15 min post-injection, we may acquire spinal cord data from the thoracic and upper lumbar spine
16 and evaluate the signal from the most caudal segments of the spinal cord, as this region also
17 demonstrated neuroinflammation in our prior study of patients with lumbar radiculopathy.[52]

18
19 Our primary metric for brain [¹¹C]PBR28 signal quantification will be standardized
20 uptake value ratio (SUVR), using the whole brain as a normalizing factor (as described in prior
21 work[51, 53, 98]). In patients with arterial blood data available, we will compute distribution
22 volume (V_T) and ratio of distribution volume (DVR), which will be used as secondary outcome
23 measures and to support the use of SUVR as an outcome metric. For spinal cord analyses, signal
24 will be quantified by normalizing the signal from the lowest 1-2 spinal segments present in the
25 field of view for most/all of our participants (e.g., T11-L1) with that of the uppermost 2-3
26 segments (e.g., T7-T9) as in Albrecht et al.[52]

27
28 In addition to PET scans, other neuroimaging measures (Diffusion Tensor Imaging (DTI),
29 BOLD resting-state functional connectivity, ¹H-magnetic resonance spectroscopy (MRS), and
30 arterial spin labelling (ASL)) measures will be collected. We will also collect fMRI measures
31 during a reward task (Monetary Incentive Delay Task, MID[99]). We have previously used this
32 task to demonstrate striatal hypofunction, linked to depressive symptoms and anhedonia, in
33 cLBP patients.[100]

34 35 36 37 **Daily surveys**

38 Beginning two weeks before the first scan to week 6, participants will complete online
39 daily surveys assessing various domains, including their clinical pain ratings (as measured by the
40 "worst pain" item of the Brief Pain Inventory – Short Form, BPI-SF[98]), pain bothersomeness
41 ratings, and depression ratings, each on a 0-10 scale. Participants will be asked to confirm daily
42 medication adherence and will be asked about use of additional medications for pain
43 management.
44

45 46 47 **Data management**

48 Data will be collected and entered by study staff into a REDCap database,[101] which
49 has been designed and completed by the study team. Data obtained during assessments
50 administered by study staff will be entered by study staff. Following each visit, data will be
51 checked by the data manager and/or research coordinator to ensure data quality and
52 completeness. All PET/MRI scans will undergo standard quality control to look for imaging
53 artifacts. For instance, any participant whose scan shows excessive head movement (e.g.,
54 between-frame motion that cannot be easily corrected in post-processing) or issues with
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attenuation correction that cannot be remediated via postprocessing 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 generalized linear mixed-effects model (GLMM) will be used to quantify the association between thalamic [¹¹C]PBR28 PET signal, treatment assignment at randomization (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 (e.g., age, depression severity, sex). Data dependencies will be accounted for using either random intercept or line (intercept and slope) parametrizations. 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 modeling 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 summarize 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.[102]

Outcome measures

Box 1. Outcome measures

Primary outcome measure

1. 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 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-II[103])*
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 catastrophizing (Pain Catastrophizing Scale, PCS[104])*
3. Neuropathic pain (PainDETECT[105])*
4. Disability related to low back pain (Oswestry Disability Index, ODI[106])*
5. Widespread pain and fibromyalgia symptom severity (American College of Rheumatology's fibromyalgia survey[107])*
6. Daily depression ratings (daily survey)
7. Widespreadness of pain sensation (SymptomMapper app[108])
8. Health-related quality of life (Patient Reported Outcomes Measurement Information System – 29, PROMIS-29[109])*
9. Sleep quality (Pittsburgh Sleep Quality Index, PSQI[110])*
10. Spinal cord TSPO signal (as measured with [¹¹C]PBR28 PET)
11. Striatal activation to a reward task (Monetary Incentive Delay Task, MID[99])
12. Other neuroimaging measures (Diffusion Tensor Imaging (DTI), BOLD resting-state functional connectivity, ¹H-magnetic resonance spectroscopy (MRS) to measure brain metabolites, and arterial spin labelling (ASL))

*Total score of these measures will be used in analyses

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 standard deviations of the [¹¹C]PBR28 PET signal measures are 0.05,[111] (2) the correlation between repeated measurements ranges between 0.3 to 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 PET signal measures of at least 0.039 and 0.045, respectively (Table 3).

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

Missing data

All attempts will be made to minimize 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.[112] 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 adverse events (AEs; e.g., tiredness, decreased appetite, diarrhea), 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 adverse event (SAE) is an event that is deemed life-threatening, requires hospitalization, causes permanent damage or requires medical intervention to prevent permanent damage, or results in death. Reporting and handling of adverse events 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 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 Supplementary 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 adverse events 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 adverse events. The DSMB will comment on the outcomes of the event and, in the case of a serious adverse event, 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 IRB and NIDA in accordance with annual reporting requirements or sooner if necessary.

Early termination of the trial

The DSMB will monitor the occurrence of all adverse events 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 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.

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3 **Authors' contributions:** JMG and MLL developed and designed the trial and obtained funding
4 for the trial. CKP and MK wrote the first draft of this manuscript. JMG, MLL, KS, RE, VN, YZ,
5 ZA, AEE, CKP, and MK assisted with the study design. NM designed the statistical aspects of
6 this protocol. JMG, MLL, CKP, MK, KS, NM, RE, VN, YZ, EJM, ZA, and AEE were involved
7 in the revision of the manuscript. All authors approved the final version to be submitted.
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12 has not had nor will have any role in the design of the study, the collection, management,
13 analysis, and interpretation of data, the writing of manuscripts, or the decision to submit the
14 report for publication.
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18 **Competing interests statement:** The study drug was donated by Jazz Pharmaceuticals. Dr.
19 Loggia consulted for Shionogi in 2018. Dr. Evins reported receiving grants from Charles River
20 Analytics and nonfinancial support from Pfizer as well as serving as the chair of the data
21 monitoring board of Karuna Pharmaceuticals outside the submitted work. Dr. Napadow consults
22 for Cala Health, Inc. and Click Therapeutics, Inc. All other authors declare that they have no
23 competing interests.
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27 **Data sharing statement:** All data, code, and materials used in the analyses can be provided by
28 Jodi Gilman and Marco Loggia and Massachusetts General Hospital pending scientific review
29 and a completed data use agreement/material transfer agreement beginning one year after
30 publication of the results. Requests for all materials should be submitted to Jodi Gilman at
31 jgilman1@mgh.harvard.edu or Marco Loggia at marco.loggia@mgh.harvard.edu.
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35 **Ethics approval:** Massachusetts General Brigham IRB Protocol Number 2021P002617.
36 Protocol version 6.0 (dated March 16, 2022) is currently in use.
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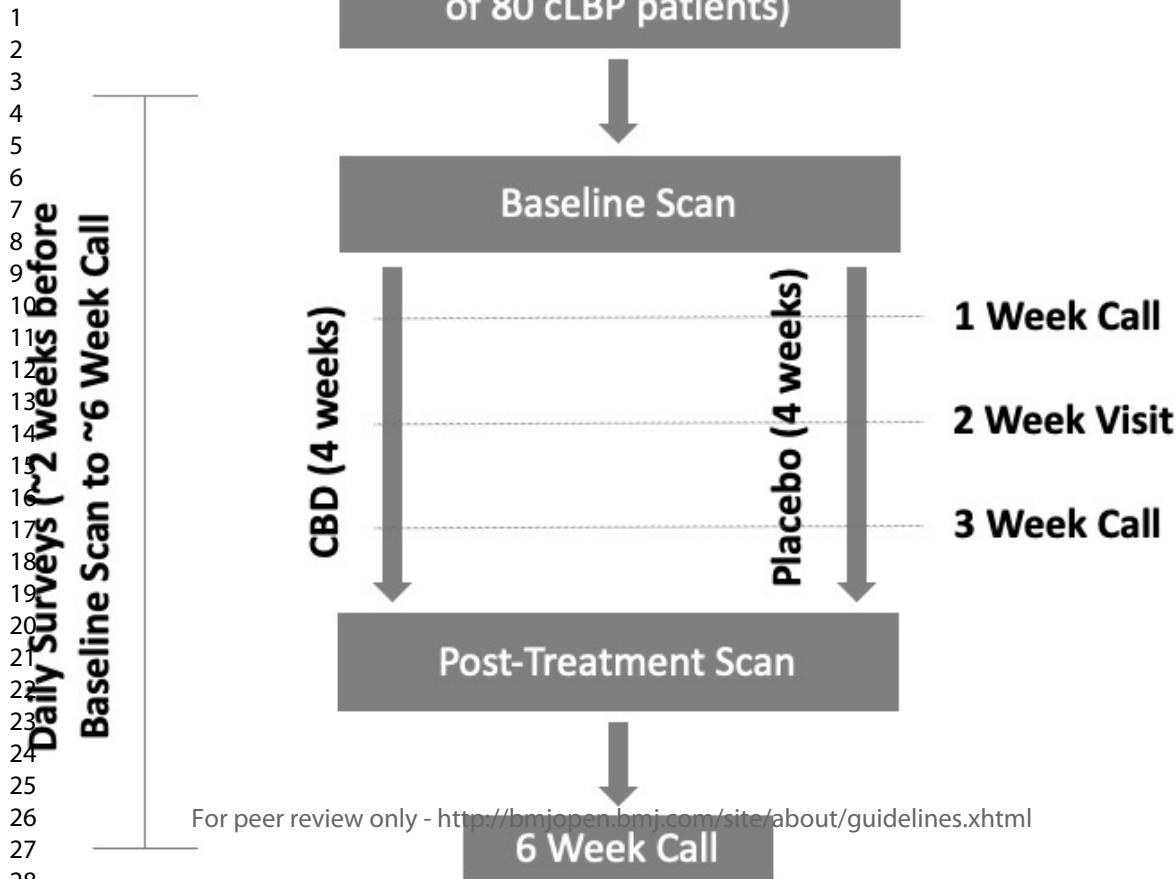
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Figure Legends
Figure 1. Study schema

For peer review only



Institutional Review Board Intervention/Interaction Detailed Protocol

Principal Investigator: Jodi Gilman, PhD

Project Title: Evaluation of Cannabidiol (CBD) for Reduction of Brain Neuroinflammation

Version Date: 3/16/2022

For Intervention/Interaction studies, submit a Detailed Protocol that includes the following sections. If information in a particular section is not applicable, omit and include the other relevant information.

1. Background and Significance

Millions of individuals suffer from chronic pain

Chronic pain is defined as pain without apparent biological value that has persisted beyond the normal tissue healing time (usually taken to be 3 or 6 months^{1,2}). Chronic pain is a widespread public health issue³, and its prevalence is enormous. The weighted mean prevalence of chronic pain in the general population has been estimated by some at 35.5%, or 105 million, in the United States⁴. Not only does chronic pain affect both physical and mental functioning, thus compromising quality of life; it is also associated with astronomical costs. In addition to the direct costs of treating pain—including health care for diagnosis and treatment, drugs, therapies, and other medical expenses—chronic pain results in lost work time and reduced productivity^{5,6}. Past estimates of the annual cost of chronic pain in the United States, including healthcare expenses, lost income and productivity, were close to \$100 billion⁷.

Treatment for chronic pain is unsatisfactory

Despite the enormity of the phenomenon, clinical needs for chronic pain are largely unmet. The treatment of choice for the largest majority (as many as 90%⁸) of patients seeking chronic pain management is based on opioid analgesics. However, the evidence supporting long-term effectiveness of opioid drugs in relieving pain and improving functional status is weak⁹. For instance, despite the widespread use of opioids for palliative care, more than half of all hospitalized patients experience pain in the last days of their lives, and 50-75% of cancer patients die in moderate to severe pain¹⁰.

The current opioid-based pharmacological approaches to treat chronic pain are not only ineffective, but they generally have multiple unpleasant side effects, including constipation, pruritus, respiratory depression, nausea, vomiting, hyperalgesia, dizziness, sedation⁹, as well as abuse and dependence^{8,11,12}. Taken together, the unsatisfactory treatment efficacy and the occurrence of significant side effects, clearly stress the importance of achieving a deeper

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understanding of the pathophysiological mechanisms underlying chronic pain, in order to eventually identify viable treatment options alternative to ones currently available.

Microglia and pain

One of the reasons for the poor efficacy of the treatment options currently available for chronic pain might be that these are primarily aimed at suppressing neuronal activity within nociceptive pathways of the nervous system. However, it is now increasingly clear that neurons are far from being the only players that drive the establishment and/or maintenance of clinical pain symptoms. Rather, evidence from animal studies now suggests a central role of glial cells in the nervous system, including microglia^{13,14}.

Microglia are a subpopulation of macrophages that rapidly activate in response to a variety of pathological conditions¹⁵, including persistent pain¹⁶⁻²³. Microglial activation (MA) is characterized by a stereotypic pattern of cellular responses, including specific morphological changes, proliferation, increased or de-novo expression of cell surface markers or receptors, and migration to the site of injury²⁴. MA generally represents an adaptive homeostatic defense response which enables the destruction of invading micro-organisms, the removal of potentially deleterious debris as well the promotion of tissue repair. However, animal studies have now showed that the uncontrolled activation of microglial cells under pathological pain conditions induces the release of substances that can sensitize pain pathways, such as proinflammatory cytokines, complement components, and others²⁵. While evidence of pain-related MA was originally observed in the spinal cord, more recently it was also discovered at the level of the brain, including in the rostral ventromedial medulla^{20,26}, the trigeminal nuclear complex^{19,27}, and the ventral posterolateral nucleus of the thalamus^{28,29}.

While most of the evidence on the occurrence of pain-related glial responses in the central nervous system comes from animal studies, a few important observations indicate that similar phenomena should occur also in humans¹³. First, immunohistochemical markers of microglial and astroglial activation have been detected in the spinal cord of a patient with chronic regional pain syndrome in a postmortem study³⁰. Furthermore, an increase in the concentration of the glial marker s-100 β was reported in the cerebrospinal fluid of patients with lumbar disc herniation and in the serum of children with recurrent headaches^{31,32}. Finally, a positron emission tomography (PET) study has revealed that human subjects with neuropathic pain secondary to peripheral nerve damage express increased thalamic binding for [¹¹C](R)-PK11195³³, an in vivo marker of microglial cell activation^{34,35}.

Recently, Co-PI Dr. Marco Loggia has also shown that patients with chronic low back pain (cLBP) have increased brain levels of the 18kDa translocator protein (TSPO), a marker of glial activation³⁶. In addition, preliminary data collected from a different cohort of patients with cLBP and sciatica suggest an increase in spinal cord TSPO levels. Together, these results suggest that human chronic pain conditions are likely to be associated with a glial reaction, both in the spinal cord, as well as in the brain.

Cannabidiol and pain

There is a growing body of evidence to suggest that cannabinoids are beneficial for a range of clinical conditions, including pain, inflammation, epilepsy, and sleep disorders³⁷. A large body of

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preclinical and clinical research indicates that the cannabinoid system modulates a broad range of physiological processes and behaviors including, but not limited to, pain, mood, appetite, neuronal activity, memory, immunity, and cell development. The endocannabinoid system's contribution to the regulation of such a variety of processes makes phytocannabinoid pharmacological modulation a promising therapeutic strategy³⁸.

The primary cannabinoids found in the cannabis plant include delta-9 -tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN), with THC being the primary psychoactive compound. The second most abundant compound in the plant is CBD, which is minimally psychoactive³⁹. Cannabinoid receptor type 1 (CB1) and type 2 (CB2) belong to a family of seven transmembrane Guanosine Binding Protein-Coupled Receptors, and are widely expressed and distinguished by their specific functions, localization and signaling mechanisms. The psychotropic effects of cannabis are principally mediated by CB1, which is widely distributed throughout the brain, while CB2 is considered the peripheral cannabinoid receptor, found mainly in immune cells, as well as in chondrocytes, osteocytes and fibroblasts. Agonists targeting CB2 receptors have been proposed as therapies for the treatment or management of a range of painful conditions, including acute pain, chronic inflammatory pain, and neuropathic pain⁴⁰. In a preclinical model, researchers showed that stimulation of CB2 suppresses microglial activation⁴¹.

In the current study, we will test whether CBD is a glial inhibitor in patients with chronic lower back pain (cLBP) with and without mild-to-moderate depression. CBD was recently FDA-approved as a liquid formulation (see EPIDIOLEX package insert) for epilepsy for children ages 2 and up as well as adults, demonstrating significant reductions in total seizure frequency with minimal side effects. It is unclear whether cannabidiol reduces glial activation in humans. We will study 80 patients diagnosed with chronic low back pain (pain duration > 6 months) longitudinally before and after 4 weeks of treatment with cannabidiol or placebo. Endpoints will be pain scores as well as brain levels of the 18kDa translocator protein (TSPO), a marker of glial activation³⁶.

2. Specific Aims and Objectives

Primary Aim: Assess whether CBD compared to placebo reduces pain-related neuroinflammation in patients with cLBP.

Hypothesis 1: Patients in the CBD arm will demonstrate significantly larger treatment-related reductions in thalamic [¹¹C]PBR28 PET signal, compared to patients in the placebo arm.

Hypothesis 2: In the CBD arm, reductions in thalamic [¹¹C]PBR28 PET signal will be directly proportional to reductions in clinical pain ratings.

Aim 2: Assess whether CBD compared to placebo reduces depression-related neuroinflammation in cLBP patients.

Hypothesis 1: Patients in the CBD arm will demonstrate significantly larger treatment-related reductions in limbic (pgACC, aMCC) [¹¹C]PBR28 PET signal, compared to

patients in the placebo arm.

Hypothesis 2: In the CBD arm, reductions in pgACC/aMCC [¹¹C]PBR28 PET signal will be directly proportional to reductions in depressive symptoms, as measured using the Beck Depression Inventory-II (BDI-II).

Aim 3 (Exploratory): Assess the effect of CBD on functional reward brain circuitry.

Hypothesis 1: Patients in the CBD arm will demonstrate significantly larger treatment-related increases in striatal responses to the anticipation and consumption of rewards/losses in the Monetary Incentive Delay task, compared to patients in the placebo arm. This will be indicative of a possible normalization of striatal function⁴², which we have previously found to be dampened in cLBP (and other pain conditions).⁴³

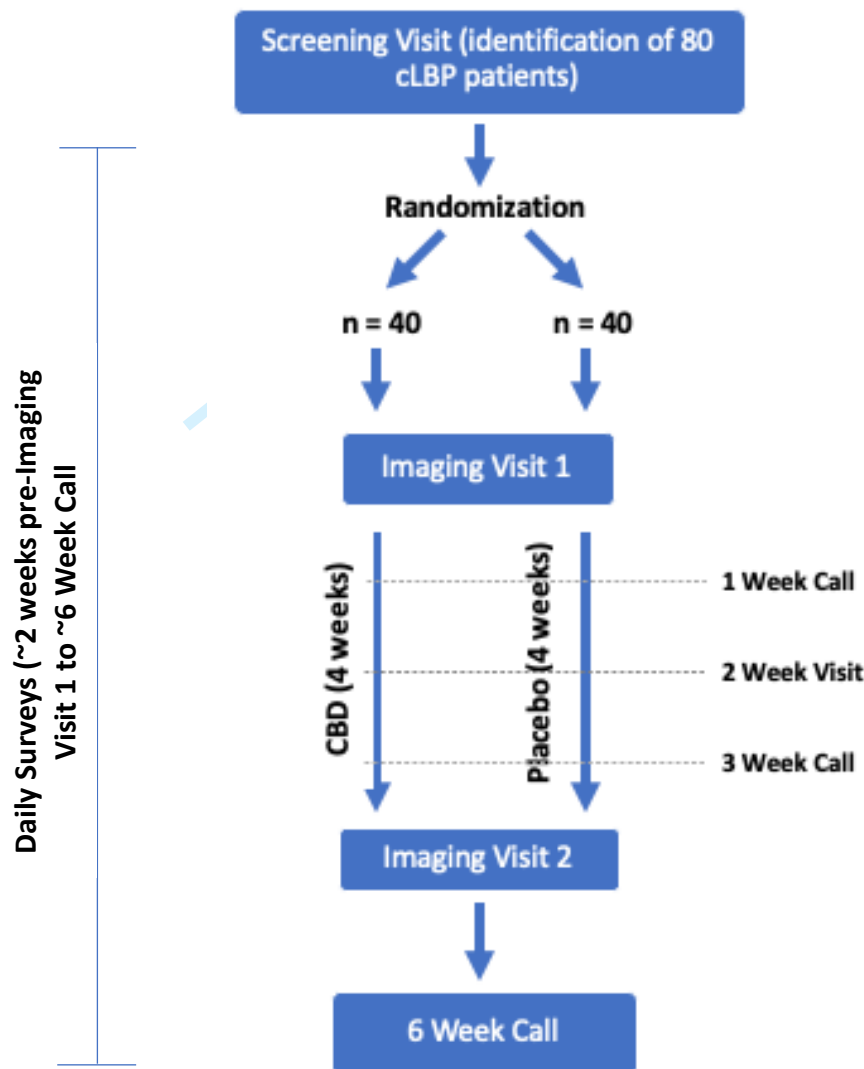
Hypothesis 2: In the CBD arm, increases in striatal activation will be proportional to increases in behavioral facilitation (i.e., slowing of reaction times during loss or rewards trials, indicative of an increase in sensitivity to incentives) and to reductions in depressive symptoms.

3. General Description of Study Design

We will conduct a 4-week randomized, double-blind, 2-arm mechanistic trial that assesses the effects of CBD vs. placebo in 80 patients with cLBP, using PET/MRI scans. Subjects will be randomized to receive either CBD ($n = 40$) or placebo ($n = 40$). Following randomization, subjects will participate in their first imaging visit, during which they will undergo a simultaneous PET/MRI scan and fill out questionnaires assessing their pain and other psychological constructs. At this visit, subjects will receive CBD or placebo, which they will be instructed to take daily for the 4 weeks prior to the date of their second scan. After 2 weeks of taking CBD or placebo, participants will undergo a follow-up appointment with a study clinician. We will also call participants at the end of the first and third weeks of taking CBD or placebo. Then, as soon as possible after the end of the 4-week drug trial period, all subjects will be scanned again and will complete several questionnaires (including some or all of those administered on the first imaging visit) to determine if any changes occurred since they entered the trial. Additionally, from about 2 weeks prior to the first scan and for 2 weeks after discontinuation of CBD or placebo, subjects will be sent a daily survey to assess the effect of the medication on their pain, mental health, sleep quality, fatigue, and other measures. Finally, we will conduct a follow-up call 2 weeks after the discontinuation of CBD or placebo.

Study Schema:

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4. Subject Selection

We plan to identify 80 patients with chronic low back pain (cLBP; i.e., with a pain duration longer than 6 months), who will complete the study. In order to achieve the final sample size of 80 study completers, we will consent up to a total of 150 participants, in order to account for screen fails and attrition. As millions of people in the United States live with chronic low back pain⁴, we believe that our recruitment goal will be attainable.

We are not planning to enroll subjects from at-risk populations (e.g., children and minors, cognitively impaired persons, prisoners). Written informed consent form will be obtained in all cases.

Inclusion Criteria:

1. Age ≥ 18 and ≤ 75 ;

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2. The ability to give written, informed consent;
3. Fluency in English;
4. Average worst daily pain of at least 4 on a 0-10 scale of pain intensity, during a typical day. Pain needs to be present for at least 50% of days during a typical week;
5. On a stable pain treatment (pharmacological or otherwise) for the previous four weeks;
6. Diagnosis of chronic low back pain, ongoing for at least 6 months prior to enrollment.

Exclusion Criteria:

1. Outpatient surgery within 2 weeks and inpatient surgery within 1 month of the time of scanning (this timeframe may be extended if they are not fully recovered from the 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 only if the conditions were so severe as to require hospitalization 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 hospitalization;
12. Major cardiac event within the past 10 years;
13. Regular use of recreational drugs in the past 3 months;
14. Any marijuana use, medical or recreational, in the past 2 weeks;
15. An abnormal physical exam (e.g., peripheral edema);
16. Use of immunosuppressive medications, such as prednisone, 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 individualized basis with a physician:
 - Strong and moderate CYP3A4 inhibitors including boceprevir, cobicistat, conivaptan, danoprevir, elvitegravir, ritonavir, indinavir, itraconazole, ketoconazole, lopinavir, paritaprevir and ombitasvir and/or dasabuvir, posaconazole, saquinavir and telaprevir, tipranavir, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir, troleandomycin, voriconazole, aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone,

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- erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, disulfiram, and verapamil;
- Strong and moderate inhibitors of CYP2C19 including fluoxetine and ticlopidine;
 - Sensitive and moderately sensitive substrates of CYP2C19 including clobazam, lansoprazole, omeprazole, S-mephenytoin, and rabeprazole;
 - Sensitive and moderately sensitive substrates of CYP1A2 including alosetron, duloxetine, ramelteon, tasimelteon, theophylline, tizanidine, pirfenidone, and ramosetron;
 - Sensitive and moderately sensitive substrates of CYP2B6 including bupropion and efavirenz;
 - Sensitive and moderately sensitive substrates of CYP2C8 including repaglinide, montelukast, pioglitazone, and rosiglitazone;
 - Sensitive and moderately sensitive substrates of CYP2C9 including tolbutamide, celecoxib, glimepiride, and warfarin;
 - Sensitive and moderately sensitive substrates of UGT1A9 including diflunisal, propofol, and fenofibrate;
 - Sensitive and moderately sensitive substrates of UGT2B7 including, gemfibrozil, lamotrigine, and morphine;
21. CNS depressants including all antipsychotics, benzodiazepines (except for alprazolam, clonazepam, and lorazepam, which have low binding affinity to TSPO⁴⁴⁻⁴⁸), and non-benzodiazepine sleep aids that have a known unsafe reaction with CBD;
 22. Use of opioids \geq 30 mg morphine equivalents on average per month;
 23. Actively suicidal, history of suicide attempt or an aborted attempt within the last 5 years, or engagement in non-suicidal self-injurious behavior 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 from screening visit;
 27. In the opinion of the investigators, unable to safely participate in this study and/or provide reliable data (e.g., unable to reliably rate pain; unlikely to remain still during the imaging procedures, etc).

Local Recruitment Procedures:

Subjects will be recruited on an ongoing basis by trained study staff. We will identify potential subjects through advertising by flyers and printed announcements posted within as well as outside of our Partners community. In addition, email, web, and bulletin board announcements posted in the community will be used. To recruit subjects, we will also use multiple research databases such as the Partners' RSVP for Health system, Partners Clinical Trials, Rally, EPIC, RPDR, and ResearchMatch, a database of research volunteers developed by Vanderbilt University and approved for use by the PHRC. We will run queries on EPIC and RPDR through MGB to find subjects with chronic low back pain, meeting the eligibility criteria for this research study. Subjects identified through these mechanisms will receive a recruitment letter via Patient Gateway or in the mail from study staff. The letter will not be sent to those who have opted out of receiving research invitations. Other methods that advertise the study to the greater community will be used, including social media posts, posting flyers on community billboards in the Greater Boston area, emails to physicians and family medicine centers, and advertisements in newspapers. All advertisements will briefly describe the study and invite subjects to call if they

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are interested. Newspaper advertisements in particular have been shown to be an effective strategy for recruiting minority populations⁴⁹. Additionally, participants will be offered parking vouchers for each on-site study visit in order to ease financial burden of attendance.

5. Subject Enrollment

Telephone Pre-Screening:

All subjects will undergo a telephone pre-screening that will distinguish the majority of potentially eligible subjects from those not meeting eligibility criteria. This will consist of a brief discussion of the research study, as well as confirming a potential participant's understanding of the basic study procedures and interest in participation. To determine whether he/she may meet eligibility criteria, we will ask for information including current medications, gender, age, pregnancy status, substance use, and history of psychiatric conditions. Those who are likely to be eligible will be scheduled for an in-person screening visit. Note that in addition to using office phones, any calls made to participants for phone-screening or other reasons throughout the entire study may also be placed using Doximity Dialer, an MGB-approved platform. Also note that participants who express interest in the study may be asked to complete a REDCap survey containing questions from the phone screen, instead of completing the screen via phone call.

Procedures for Obtaining Informed Consent:

During the in-person screening visit, potential participants will be fully informed of the purpose and activities involved in the research study. Written informed consent will be obtained prior to initiating any of the study procedures. One copy of the signed consent form will be given to the patient and one will be kept in the study files for documentation. No time limits will be imposed on the informed consent process. Participants will be permitted to take as much time as they desire to engage in the informed consent process; any and all of their questions will be answered. It is anticipated that obtaining written informed consent will take approximately 15-25 minutes, on average. Comprehension of the consent information will be assessed via solicitation of answers to questions throughout the process. If comprehension appears to be limited, participants will be actively queried to determine whether they need further explanation.

In order to comply with public health efforts to address COVID-19, virtual visits may be conducted as necessary. Virtual visits will be conducted via MGB approved platforms (i.e., video calls over Zoom and phone conferences via Cisco Jabber) and will mirror in-person visits with the identical personnel present on the call. All questionnaires typically collected during the in-person screening visit may be collected during the remote screening visit, as they are largely already completed on secure online platforms (i.e., REDCap). All screening visit study procedures may be performed during the remote screening visit, with the exception of the urine drug test, blood draw, and physical exam, and any other assessments that cannot be performed remotely, which will be performed at the first in-person visit (i.e., first imaging visit) or at an extra, separate visit prior to the first imaging visit.

At the start of the virtual screening visit, informed consent will be obtained remotely. This will be done via electronic consent (e.g., Partners REDCap e-consent, Adobe Sign), or a remote consent process where the participant will be asked to sign the consent form and return it by email or mail. In either case, the consent discussion will occur identically to an in-person visit,

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but instead held over phone call or video conference. Following the informed consent process, a copy of the signed consent document will be provided to the patient (electronically if e-consent was used). In the case of e-consent, consent will be documented on Partners REDCap or Adobe Sign. These are equivalent to written consent and are FDA compliant. As is with in-person consent, we will obtain and document informed consent before the participant is enrolled and any study procedures begin. Note that we may also use e-consent even for in-person screening visits.

Either a physician investigator or non-physician investigator will obtain informed consent in all cases. Note that the only non-physician investigators who will be allowed to obtain informed consent are Dr. Jodi Gilman (the IND holder) and nurse practitioner study staff members.

Treatment Assignment and Randomization:

Following the screening visit, participants who meet inclusion criteria, pass exclusion criteria, and provide their signed consent will be randomized in a 1:1 ratio to receive either CBD ($n = 40$) or placebo ($n = 40$). Randomization will be performed by stratifying subjects by age (>50 vs. ≤ 50) and sex (male vs. female). Each subject will be assigned a randomization number via a computerized random number generator. The Clinical Trials Pharmacy will maintain the specific subjects' treatment assignments (CBD or placebo) for later identification. Patients and study staff will be blinded to CBD or placebo assignment.

6. Study Procedures

Individuals who express interest in participating in the study will undergo a telephone screening to assess eligibility. If they are likely to be eligible, they will be scheduled for an in-person screening visit, during which a consent procedure will be conducted and a baseline assessment of questionnaires, interviews, and laboratory assessments will be conducted. Those who meet all eligibility criteria will be randomized to the CBD or placebo group. Then, subjects will be scheduled for their first imaging visit, during which they will undergo a simultaneous PET/MRI scan. At this visit, subjects will receive CBD or placebo, which they will be instructed to take daily for the 4 weeks prior to the date of their second scan. Note that, in cases where the screening visit and the first imaging visit are more than three months apart, eligibility criteria will be re-assessed.

Table of Study Procedures:

Domain	Measure	Source	Screen	Scan I (Pre-Treatment)	1 Week Call	2 Week Visit	3 Week Call	Scan II (Post-Treatment)	6 Week Call
Demographics	Custom (PhenX-based)	Participant	x						
General Health	Physical Examination	Physician/ NP/Nurse	x						
	Medical History	Physician/ NP/Nurse	x						
	Family History	CRC	x						
	Psychological Interview (MINI)	CRC	x						
	Characterization of Pain	Physician/ NP/Nurse	x						

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	Concomitant Medications	Physician/ NP/Nurse	x	x					
	Weekly Medication Questions	CRC			x	x	x	x	x
Genetics	Oragene (CGR-500)	CRC	x						
Adverse Events	Adverse Event Record	CRC, reviewed by Physician		x	x	x	x	x	x
Depression, Psychological Functioning, Sleep	BDI-II	Participant	x	x				x	x
	BAI ^a	Participant	x						
	PROMIS-29	Participant		x				x	
	C-SSRS	Clinician	x	x		x		x	x
	CHRT ^a	Participant	x						
	MID	Done in PET/MRI scanner			x				x
Pain	PSQI	Participant	x	x				x	
	BPI-SF	Participant	x	x				x	x
	ACR FM survey	Participant		x		x		x	
	PCS	Participant		x		x		x	x
	PainDETECT	Participant		x				x	
	Oswestry	Participant		x				x	
	Symptom- Mapper	Participant		x				x	
	Daily Survey	Participant	<i>Daily from ~2 Weeks before Scan 1 until 6-Week Call</i>						
Substance Use	TLFB (MJ, EtOH, nicotine, other substances)	CRC	x						
	AUDIT ^a	Participant	x						
	CUDIT-R ^a	Participant	x						
	FTND ^a	Participant	x						
	ECDI ^a	Participant	x						
Expectancy	Next Visit/Call	Participant		x	x	x	x		
	Final Visit	Participant		x					
Quality of Life	Patient Global Impression of Change (PGIC)	Participant						x	
IQ	WRAT5	CRC	x						
Delay Discounting	MCQ ^a	Participant	x						
Impulsivity	UPPS-P ^a	Participant	x						
ADHD	ASRS ^a	Participant	x						
COVID-19	EPII ^a	Participant	x						
	COVID-19 History ^a	Participant	x						
	Vaccination Questionnaire	Participant		x					
Urine Test	Urine Drug Test	CRC	x	x				x	
	Urine Pregnancy Test	CRC	x						
Blood Test	Liver function tests	Nurse / Physician / trained study staff	x					x	
	Whole Blood DNA (Genotype	Nurse / Physician /	x	x				x	

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	& PBMC & iPSC)	trained study staff							
	Serum Pregnancy Test (if applicable)	PET Tech/Nurse		x					x
	Serum extraction (Cytokine panel)	Nurse / Physician		x					x
	Arterial line (optional)	Anesthesia-trained clinician		x					x
	COVID antibody	Nurse / Physician		x					x
	CBD/THC Metabolites in plasma	CRC		x					x

^a Indicates a measure that may be completed by the participant at home, following the screening visit.

Study Drug:

Epidiolex, an agent within the anti-epileptic drug class, will be used. Epidiolex, Greenwich Biosciences Inc.'s CBD formulation, is a 100 mg/mL purified oral solution, dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring. 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% (w/w) THC. Cannabidiol is the active ingredient in Epidiolex; inactive ingredients include dehydrated alcohol, sesame seed oil, strawberry flavor, and sucralose. Of note, CBD has no psychoactive properties. The empirical formula of Epidiolex is $C_{21}H_{30}O_2$ and its molecular weight is 314.46. The structure of CBD is provided in the figure below.

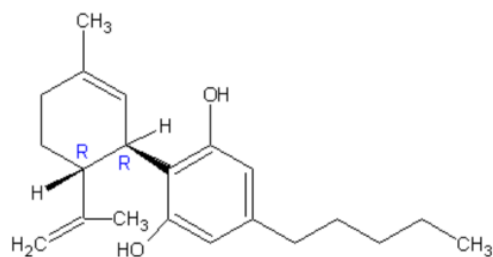


Figure 1. Cannabidiol Structure

Dose and Exposure:

Either EPIDIOLEX[®] or placebo will be dispensed by the Research Pharmacy at Massachusetts General Hospital. The recommended starting dosage is 2.5mg/kg taken twice daily. Participants will follow a titration schedule, with 2.5mg/kg taken orally twice daily in week 1, 5mg/kg twice daily in week 2, 7.5mg/kg twice daily in week 3, and 10mg/kg twice daily in week 4. Subjects will increase to 10mg/kg twice daily on the first day of the final week of the study (week 4) and take Epidiolex at this dose for the remainder of this final week. If participants report AEs (tiredness, dizziness, not tolerating the medication well) during the second, third, or fourth week of taking the study drug, the physician will decrease the dose to the previous week's dose. Participants will be treated for 4 weeks in total.

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The 4-week duration of CBD or placebo administration is proposed because in the current study, we are investigating an endophenotype of pain- neuroinflammation- which may be detectable before verbal reports of pain reduction, which is notoriously noisy and susceptible to placebo effects. This study will inform us of whether 4 weeks is enough to detect changes in TSPO binding that may precede reports of pain reduction.

Screening Visit:

Subjects eligible to participate will be recruited to participate in an approximately 3-hour characterization session. In this session, we will obtain a signed consent form from the subjects, explain the procedures involved in the experiment, and administer some or all of the following validated assessments. We will also collect detailed contact information (address, social security number, medical record number) and demographics, collect a saliva sample for genetic testing, assess medical and family history, and perform a physical examination, and assess concomitant medications. Finally, we will collect a blood sample and a urine sample. Computer-based rating scales and questionnaires will be completed on a laptop. Assessments will be performed by fully trained study staff members such as post-doctoral research fellows and Clinical Research Coordinators, under the supervision of and periodic monitoring by the Principal Investigator (PI).

During the informed consent procedure, participants will be informed about other treatment alternatives for chronic low back pain they can pursue (e.g., medications, transcutaneous nerve stimulation, physical exercise and stretching) in lieu of participation in this clinical trial.

Many of these assessments are already in use in one or more IRB approved protocols (e.g., 2011P002311). Note that participants may complete some of the following questionnaires at home after the screening visit if time does not allow for their completion during the screening visit.

History and physical examination: An MD, NP, or nurse will also collect medical history and perform a formal physical examination, including the recording of vital signs (heart rate, blood pressure, and body temperature). If these assessments are done by a nurse or NP, a physician will review them prior to prescribing the study drug.

*Beck Depression Inventory-II (BDI-II)*⁵⁰: The 21-item BDI-II has shown good reliability and validity for assessing depression in chronic pain patients⁵¹.

Brief Pain Inventory – Short Form (BPI-SF): The BPI is a 15-item questionnaire assessing pain location, and 0–10 ratings of pain intensity, relief, quality, pain-related quality of life, and function. It has been validated in cancer and noncancer pain conditions⁵².

*Timeline Followback (TLFB)*⁵³: The TLFB uses memory aids to trigger recall of substance use. It will be used to measure participants' use of cannabis, tobacco, alcohol, and other substances in the previous 90 days.

*Mini International Neuropsychiatric Interview (MINI)*⁵⁴: The MINI 7.0.2 is a structured diagnostic interview used to assess DSM-5 psychiatric disorders. It will be administered by trained study staff.

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5 *Wide Range Achievement Test, 5th Edition (WRAT5), Word Reading*⁵⁵: The word reading subset
6 of the WRAT5 will be used to assess speech and dictation.
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8 *Monetary Choice Questionnaire (MCQ)*⁵⁶: The MCQ presents participants with 27 questions,
9 each of which asks them to choose between smaller, immediate rewards, and larger, delayed
10 rewards. Participants' patterns of answers are able to provide an estimate of their delay
11 discounting rate.
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14 *Short UPPS-P Impulsive Behavior Scale*⁵⁷: The 20-item Short UPPS-P assesses five components
15 of impulsivity, including sensation seeking, lack of premeditation, lack of perseverance, negative
16 urgency, and positive urgency. Scores on many of these factors have been shown to relate to
17 risky behaviors.
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20 *Beck Anxiety Inventory (BAI)*⁵⁸: The 21-item BAI assess the frequency of anxiety symptoms,
21 including both cognitive and somatic symptoms.
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23 *Alcohol Use Disorders Identification Test (AUDIT)*⁵⁹: The AUDIT is a 10-item questionnaire
24 used to screen for harmful alcohol consumption. It assesses drinking frequency and problems
25 related to alcohol use. The scale ranges from 0 – 40; a score of 8 or higher is an indicator of
26 harmful alcohol consumption.
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29 *Cannabis Use Disorders Identification Test – Revised (CUDIT-R)*⁶⁰: The CUDIT-R is an 8-item
30 questionnaire that screens for problematic cannabis use in the past six months. It assesses
31 problems related to cannabis use, dependence, and use frequency. The scale ranges from 0 – 32;
32 a score of 13 or higher is indicative of possible cannabis use disorder.
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35 *Fagerstrom Test for Nicotine Dependence (FTND)*⁶¹: The 6-item FTND assesses nicotine
36 dependence. It measures amount of cigarette use, dependence on cigarettes, and compulsion to
37 use. The scale ranges from 0 – 10, with a higher score indicating greater dependence.
38

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40 *Electronic Cigarette Dependence Index (ECDI)*⁶²: The 10-item ECDI assesses dependence on
41 electronic cigarettes. The scale ranges from 0 – 20, with scores 13 and higher indicating high
42 dependence.
43

44 *ADHD Self-Report Scale (ASRS)*⁶³: The 6-item screener scale of the ASRS will be used to assess
45 participants' ADHD symptoms, including both inattentive symptoms and hyperactive-impulsive
46 symptoms, during the past 6 months.
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49 *Concise Health Risk Tracking Self-Report form (CHRT-SR)*⁶⁴: The 12-item CHRT-SR assesses
50 active suicidal ideation and behavior, perceived lack of social support, and hopelessness. The
51 scale ranges from 0 – 48, with a higher score indicating greater suicidal thoughts and
52 propensity⁶⁵.
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55 *Pittsburgh Sleep Quality Index (PSQI)*⁶⁶: The PSQI is a 19-item questionnaire that assesses sleep
56 quality and patterns during the previous month. The scale ranges from 0 - 21, with a higher score
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indicating less healthy sleep quality.

*Epidemic-Pandemic Impacts Inventory (EPII)*⁶⁷: The EPII will be used to assess how the COVID-19 pandemic has impacted participants' lives, including impacts on work, home, and social life, as well as impact on emotional and physical health. It includes 92 items.

Suicidal Ideation: The Columbia-Suicide Severity Rating Scale (C-SSRS)⁶⁸ will be used for prospective suicidality assessment. C-SSRS is a tool used to assess the lifetime suicidality of a participant and to track suicidal events through the treatment. The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality. The scale will be administered by study staff at the screening visit, baseline, two-week visit, four-week visit, and six-week call. The C-SSRS "Screening/Baseline" will be collected at Screening and Baseline and the C-SSRS "since last visit" will be collected at subsequent visits. Participants who answer "yes" to any suicidal behavior questions or to suicidal ideation questions 4 or 5 on the C-SSRS during the study should be referred for appropriate psychiatric care. If there is more than a 30% increase in symptoms of anxiety or depression, this will be immediately reported to the PI, who will consult with study clinicians. Clinicians will then determine, with the participant, whether it is in their best interest to continue the medication. The decision to discontinue the participant from the study will be made by the PI in conjunction with clinical Co-Investigators.

Safety monitoring: As participant suicidality and depression is monitored throughout the study with the C-SSRS and BDI-II questionnaires, any new or worsening expression of suicidal ideation or Answers of "Yes" to questions 4 or 5 on C-SSRS throughout the study will be evaluation by a licensed clinician member of study staff. The Standard Operation Procedure will be reviewed. To summarize, if any risk for self-harm or suicidality is identified at any visit, the research coordinators will immediately report this to study clinicians, who will determine whether a safety assessment is needed. If a clinician is needed to perform a safety assessment, study staff will record the date, clinician initials, and comments related to the suicidality assessment in the REDCap C-SSRS module. Following the initial suspicion or identification of self-harm and/or suicidality, a study clinician will follow up with the participant on the current nature of their situation, querying about any new ideation, intent, and/or plan since the last visit. These clinicians, along with the PI will then determine whether a participant can safely continue the study. If the clinicians determine that the participant cannot safely continue the study, the participant will be discontinued, and will be provided with a list of resources for follow-up care.

Demographics: Demographic information, including age, sex, gender, sexual orientation, education level, income, race, height, language, employment status, marital status, and residence, as well as information about the participant's caregivers during childhood, will be collected.

DNA Collection, Saliva (optional): DNA samples will be collected using Oragene (OGR-500) saliva kits. Participants may be asked to provide a second sample if a re-collect is recommended after DNA extraction (i.e., there is very little DNA in the sample). Participants are not required to provide another sample if they do not wish to do so. Once extracted samples will be transferred to long term storage until genotyping. Samples will be stored with a unique participant ID.

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Family history: The family history subsection of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)⁶⁹ will be used to assess family history of psychiatric treatment, including treatment for depression, mania, anxiety, ADHD, schizophrenia, and substance use, as well as history of suicide.

Concomitant medications: Any prescription medications or over-the-counter drugs being taken by the participant at the time of the screening visit will be assessed, and dose and frequency will be recorded.

Blood tests: a trained member of the study staff will draw venous blood (up to 10 ml) from all subjects in order to have them genotyped for the Ala147Thr TSPO polymorphism in the *TSPO* gene (rs6971) (unless this genotype information is already available), and to check liver enzyme values. Additionally, during screening for eligibility, we will conduct routine chemistry and LFT/GGT. We will obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment with CBD.

While [¹¹C]PBR28 has the advantage of binding to the TSPO protein with a higher ratio of specific-to-nonspecific binding than [¹¹C](R)PK11195⁷⁰, it also presents a potential limitation, in that about 10% of human subjects show no binding to PBR28⁷¹ (whereas [¹¹C](R)-PK11195 has never been associated with non-binding⁷²). A recent study has demonstrated that the rs6971 polymorphism predicts PBR28 binding affinity in human platelets⁷³. Since the low-affinity binder phenotype is consistent across all tissues within the same subject⁷², testing for the Ala147Thr polymorphism has been suggested to predict low affinity for [¹¹C]PBR28 in all organs, including the brain. High or Mixed affinity binders (Ala/Ala or Ala/Thr) will be considered eligible, whereas the Low affinity binders (Thr/Thr) will be considered ineligible to continue in the research study. The MGH lab responsible for genotyping typically runs the genotyping assay only twice per month, requiring that we normally schedule screening and scanning visits approximately two weeks apart.

We may also use saliva instead of blood to genotype subjects for the Ala147Thr TSPO polymorphism. Saliva genotyping may be done prior to the in-person screening visit to eliminate low affinity binders, thus saving subjects the burden of having to travel to and attend the screening visit only to find they are not eligible for the study. Verbal consent will be obtained and documented if patient-subjects agree to this saliva collection, and subjects will be asked if they wish to receive a copy of the Privacy Notice and documentation linking them to the research study. Both forms will be provided upon request. Saliva collection kits with a pre-assigned study ID and a pre-paid return mailing supply will be mailed out to applicable subjects. Eligible subjects will be scheduled for an in-person visit. If subjects are ineligible for the study based on the saliva genotyping results, they will be compensated for providing the saliva sample.

An additional 10 mL of venous blood will be collected and stored for future investigations on the roles of genetic, molecular, and cellular factors in pain disorders. This will include the future possibility to generate induced pluripotent stem cells (iPSCs) from peripheral blood mononuclear cells⁷⁴⁻⁷⁶ to assess in-vitro alterations in patient-derived neural or glial cells^{77,78}.

Urine drug test: We will also perform a urine test to screen for use of opioids and illicit drugs

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(including amphetamine, barbiturates, cocaine, marijuana, etc.). The urine drug screen will be performed during the screening visit. A rapid urine drug screening that utilizes monoclonal antibodies to detect elevated levels of specific drugs in urine, will be used for this purpose. Results will be read five minutes after the test was started.

Urine pregnancy test: Urine will be collected at screening for a pregnancy test in female participants of childbearing age.

COVID-19 History: Participants will complete a short questionnaire that asks about COVID-19, including whether they have ever been exposed, experienced symptoms, and/or tested positive. Those reporting a positive test will be asked about how severe the course of illness was, including whether they were hospitalized. All participants will be asked about vaccination status.

Note that we may also do a brief MRI test scan with participants on the day of their screening visit, or on a different day, to ensure that they are a suitable candidate for scanning.

PET/MRI Visits:

Participants eligible to continue into the study based on the screening visit and genotype analyses will be asked to participate in a first PET/MRI visit.

Prior to each scan session, subjects will complete screening checklists for MRI and PET. These checklists will ask the patients whether they have any contraindications for MRI or PET scanning. Female participants of childbearing age will be asked to have ~3mL of their blood drawn in order to perform a serum pregnancy test on the day of the scan (blood will be sent to the core lab for super stat testing). They will also be asked about the date of their last menstrual cycle. In addition, a urine drug test will be repeated on the day of each PET/MRI visit.

At the beginning of the scan session, an intravenous catheter will be placed in the participant's antecubital vein of the left or right arm, prior to going to the scanning area. Up to 15mL of blood will be drawn to assess the levels of various substances in the blood, such as the proinflammatory cytokines IL-6 and TNF-alpha. Blood will be collected in various vials (e.g., purple top K3EDTA).

Blood may also be drawn for SARS-CoV-2 antibody serology testing, and the presence of antibodies will be used to explore the possible effects of prior exposure to the coronavirus on neuroinflammation, in exploratory analyses. Up to 10 ml of blood will be drawn for this purpose. This testing will be performed through a third party vendor or through the MGH core lab.

Following procedures identical to those adopted in other PET studies (including using [¹¹C]PBR28) from our center (e.g., 2015P001594, 2013P001297, 2011P001546, 2011P002311, 2016P001009, etc), an arterial line will be placed in a radial artery with local anesthesia (20 or 18 gauge cannula, 2-5 ml of lidocaine 1% intradermal and subcutaneous) using sterile techniques, if the participant has consented to this procedure. The placement of an arterial line will be presented as optional to the participants, and we will ask for the participants' consent each time. The arterial line will not be placed if the participant has any contraindications to arterial line placement, such as Raynaud syndrome, bleeding disorder, or use of anticoagulants

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such as Coumadin, Plavix or Lovenox. The arterial line will be placed in the arm contralateral to the intravenous line that is used for the [¹¹C]PBR28 radiotracer injection. The arterial line will enable blood sampling (1mL to 12mL) 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 kinetic modeling analyses (see Data Acquisition and Analyses). The catheter will be placed by an individual with anesthesia training (i.e., board-certified anesthesiologist, fully licensed anesthesia resident, or a certified registered nurse anesthetist), monitored throughout and accessed by an experienced research nurse. The catheter will be discontinued at the end of the study by a physician, a nurse practitioner, certified registered nurse anesthetist, or registered nurse. We will have all RNs who do this sign a form attesting that discontinuing the catheter and associated post-procedure monitoring is within the scope of their work and clinical privileges.

Subjects will be instructed to remain still, with eyes open, for the total duration of the scans, except when prompted to engage in various tasks (e.g., rate pain, perform the Monetary Incentive Delay task, etc.).

During the scan visit, subjects will be asked to complete the *BPI-SF*, *BDI-II*, *C-SSRS*, and *PSQI*, which were also assessed at the screening visit. We will again assess concomitant medications. Additionally, subjects will complete some or all of the following validated assessments. Any questionnaire may be sent home with participants to complete if there is not time to complete them during the scan visit.

*Patient Reported Outcomes Measurement Information System (PROMIS-29) questionnaire*⁷⁹: The PROMIS-29 is a 29-item self-report measure assessing physical, mental, and social health.

*PainDETECT*⁸⁰: The PainDETECT is a screening questionnaire used to estimate the likelihood of a neuropathic component in chronic pain.

*The Pain Catastrophizing Scale (PCS)*⁸¹: It is a 13-item self-report scale which measures pain-related Rumination, Magnification and Helplessness.

*Oswestry Disability Index (ODI)*⁸²: The ODI is an extensively used 10-item scale to describe the level of disability in patients with chronic low back pain and will be used to characterize the study population.

SymptomMapper: The SymptomMapper app is a digital tablet-based application used to localize areas where patients are experiencing pain. In the app, the patient picks a pain descriptor, i.e., burning or shooting, notes the severity of that descriptor, and then marks where on the body that descriptor is felt. All data are stored de-identified and securely onto local drives.

*Fibromyalgia Survey*⁸³: The American College of Rheumatology's fibromyalgia survey will be used to assess widespread pain and fibromyalgia symptom severity. The widespread pain subscale ranges from 0 - 19, with a higher score indicating more widespread pain. The fibromyalgia symptom severity subscale ranges from 0 - 12, with a higher score indicating more severe symptoms.

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Treatment Expectancy: Expectancy of symptom improvement will be assessed using three statements that ask about how participants expect to feel at the end of treatment (at their last visit), as well as 3 statements about how they expect to feel at their next study visit or call. These statements will assess expected pain intensity, pain bothersomeness, and depression, and will each be scored on a 0 – 10 scale, with a higher score indicating worse symptoms.

Adverse events: Any untoward or unfavorable medical occurrence participants have experienced will be assessed, whether or not the occurrences are considered related to their participation in the research.

Vaccination Questionnaire: The date of administration and manufacturer of each COVID-19 vaccine dose the participants have received will be assessed using a brief questionnaire. Additionally, participants will be asked whether they have received any other vaccinations in the past 14 days to capture a potential acute immune response.

During the scan, participants will be asked to complete the *Monetary Incentive Delay (MID) task*. The MID task features balanced incentive delivery and analytic strategies designed to identify activity specific to anticipation or consumption of incentives. In the reward condition, successful trials are associated with monetary gains whereas unsuccessful trials lead to no change. In the loss condition, successful trials are associated with no change whereas unsuccessful trials are associated with monetary penalties.

At the end of the scan, for those participants who received an a-line, an experienced nurse or MD will remove the catheter. These subjects will be kept under observation for a minimum of 30 minutes.

The total duration of each scanning visit will be approximately 4 hours (and up to 6 hours) (~45min for preparation, ~30min for a-line placement, if applicable, ~120 min for scanning procedures, ~20-30min optional spinal scan after completion of the brain scan, and ~60min for filling out questionnaires and observation after removal of arterial line, plus an additional ~90min to perform pregnancy test in women of childbearing age). In case of equipment failure (e.g., failure in radiosynthesis) delays of > 2 hours may be possible. In this case, we will ask the participant if he or she feels comfortable with staying longer than anticipated, or will prefer reschedule to another date.

Depending on the patients' level of discomfort and time constraints, we may occasionally shorten and simplify the scan visits. For instance, if the participant would feel too uncomfortable to lay down in the scanner for the full ~2:00 hours of scanning, we may administer the radioligand in the injection room and then scan the participant between ~45 and 90 minutes post-injection. If the participant cannot remain for the full 6-hour scan visit, it will be acceptable to forego the arterial line placement. Eliminating this procedure will save the time needed for the placement and the ~30 minutes of observation needed after the removal of the a-line (from these scans we will derive metrics that do not depend on arterial sampling, such as standardized uptake value ratio (SUVR)).

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The imaging visit, including all the procedures described above, will be repeated a second time after a 4-week trial of CBD or placebo. Blood drawn at the second imaging visit will also be tested to check liver enzyme values. Also, up to 4 additional mL of blood will be drawn, and the blood plasma samples will be sent to collaborators at Clinical Research and Development facilities Department of Anesthesiology, at the University of Colorado Anschutz Medical Campus. These blood plasma samples will be analyzed for quantitative levels of cannabinoids, including CBD and THC. All analyses will be carried out following standard operation procedures, which are based on all applicable CAP, CLSI, ICH, OECD and FDA guidelines. All samples will be fully de-identified, and will not contain any identifiers that could be used to link the specimens or data to individual subjects.

Parts of the PET/MRI visits may be conducted virtually, as necessary.

Follow-up Visits/Calls:

1-Week Call. Patients will have a phone call 1 week after their first scan with a study team member. In this call, adverse events, treatment expectancy, and medication use will be assessed and participants will be reminded to increase medication dose.

2-Week Visit. Patients will undergo a follow-up appointment at Week 2 with a trained study staff member, where health, other medication use, and adverse events will be assessed, and patients will complete questionnaires and will be reminded to increase medication dose. Treatment expectancy will also be assessed. Participant may receive a ride to and from the study visit if requested. Some or all of this visit may also be conducted virtually as necessary. If there are any adverse events or issues reported during this visit, we will refer the participant to a study clinician who will get back to them.

3-Week Call. Patients will have a phone call during Week 3 with a study team member. In this call, adverse events, treatment expectancy, and medication use will be assessed and participants will be reminded to increase medication dose.

4-Week Visit. Patients will undergo a second follow-up appointment immediately after the four-week treatment period with a study clinician, where we will assess back pain, general health, adverse events, and medication use. Portions of this visit may be conducted virtually, if necessary. On the same day or as close as possible depending on scheduling, patients will be re-scanned, using identical protocols, to evaluate the hypothesis that CBD reduces glial activation. We will also repeat the questionnaires administered during the first imaging visit to assess any changes in subjective pain. We will take a small sample of blood for a follow-up liver function test. Participant may receive a ride to and from the study visit if requested.

6-Week Call. We will conduct a follow-up call 2 weeks after the discontinuation of the study medication. In this call, we will assess back pain, general health, adverse events, and medication use.

Daily Surveys:

From about 2 weeks before Scan 1 to the 6-week call, we will ask participants to complete brief daily surveys assess various domains, including their levels of pain, depression, anxiety, fatigue,

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and sleep quality on various scales (e.g., 0-10). We will also ask participants whether they have taken the study medication that day, and whether they have taken any other medications to manage their pain.

Drug Administration Protocol:

Following the behavioral visit, subjects will receive CBD or placebo. Please see “Dose and Exposure” section above for dosing and titration schedule. Participants will be treated for 4 weeks in total. Chronic CBD dosing up to 1500 mg/day has been reported to be tolerated well without AEs⁸⁴⁻⁸⁷; minor AEs were reported after CBD use in children with epilepsy being treated with multiple other medications in doses up to 25mg/kg twice daily^{88,89}. Accordingly, we believe an upper limit of 10mg/kg twice daily orally is reasonable and safe.

Continuation of medication (e.g., NSAIDS) will be permitted on the condition that patients will be on a stable dose for at least 1 month before the baseline PET/MRI scan.

The Research Pharmacy at Massachusetts General Hospital will prepare the CBD and placebo. The bottle will contain 100mg/mL of CBD or placebo. It will also have a small ID label with a batch number printed on it. The label will explain the storage conditions, the shelf life, and the in-use shelf life. Each container will be labeled with a unique number that will be recorded by study staff at the time of administration. As soon as possible after the 4-week CBD or placebo period, patients will be re-scanned and/or re-evaluated clinically to evaluate the hypothesis that CBD compared to placebo reduces glial activation and pain/depressive symptoms. Participants will be instructed to take CBD or placebo with food, rather than in a fasted state, and not to take CBD or placebo concurrently with alcohol. Participants will be instructed to return any unused CBD or placebo at the second PET/MRI visit.

GWAS Genotyping:

The Broad Institute will perform genotyping (array-based) of subject DNA samples and subsequent in-depth analysis of the data, which will allow us to detect alterations in the genome including point mutations, small insertions and deletions, chromosomal copy number alterations, and translocations. These experiments are intended to help identify candidate genes involved in the pathophysiology of neurological and psychological diseases. The molecular information generated from these samples will not be returned to subjects at any time.

Data from this study may result in communications in journals or at scientific meetings. Subjects will not be identified in those communications. To facilitate research, the genetic information generated may upon publication be deposited in protected databases (such as dbGAP) available only to bona fide researchers with specific scientific questions who promise to not try to identify individuals. The data will be sent to these banks in a coded manner and again will not contain any traditionally used identifier such as name, address, phone number, or social security number. Although we cannot predict how genetic information will be used in the future, there are many safeguards in place and we do not think that there will be further risks to patients' privacy and confidentiality by sharing such information with these banks.

The Broad Institute will not be involved in subject ascertainment. Prior to transfer of bio-specimen aliquots to the Broad Institute, samples will be re-encoded at the collaborators

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institutions. No identifying patient information will be shared with Broad scientists at any time. Some limited clinical data will be obtained from collaborators. Again, all subject identifying information will remain with the collaborators and only de-identified clinical data will be shared with the Broad Institute.

Platforms for Data Collection:

Questionnaires Collected via Research Electronic Data Capture (REDCap): Surveys will be administered via REDCap, a HIPAA compliant, web-based application hosted by Partners HealthCare designed to support data capture for research studies⁹⁰, at in-person visits (or virtual if required per COVID-19 restrictions).

Data will be stored automatically and securely on a SQL Server, accessed over industry standard TLS 256 bit RSA encryption during data transfers. Data is routinely backed up locally onto a redundancy server and stored in a separate database. Long term storage on Partners servers occurs nightly and allows for incremental backup over multiple systems. Therefore, should one drive be physically damaged, there will be multiples within the chain to replace it. Both data servers are stored within PHS IS corporate firewall, in a secure, key access facility with password-protected computers. Only vetted PHS security officials will have access to physical machines storing study data. Since data are stored on a protected server, a compromise of any individual computer at a research facility will not lead to a breach of the secure database. Individual computers designated for data capture do not store participants' identifying information or study data.

Return of Research Results:

Participants should not expect to get information about the results of the study or the results of their individual participation in the study.

Incidental Findings:

In the unlikely event that evidence of physical or psychological disorder is found, with the individual's permission, the information will be shared with his or her primary care physician who can direct care as needed.

Outcomes:

Primary Outcomes:

1. Changes in neuroinflammation in the thalamus: We will test for the presence of a significant treatment effect in the brain [¹¹C]PBR28 signal in the thalamus, in order to test whether patients in the CBD arm will demonstrate significantly larger treatment-related reductions in neuroinflammation, compared to patients in the placebo arm.
 - a. Time Frame: Change from Baseline to Week 4.

Secondary Outcomes:

1. Changes in neuroinflammation in limbic regions: We will test for the presence of a significant treatment effect in the brain [¹¹C]PBR28 in limbic regions (pgACC, aMCC), in order to test whether patients in the CBD arm will demonstrate significantly larger treatment-related reductions in neuroinflammation, compared to patients in the placebo arm.

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- a. [Time Frame: Change from Baseline to Week 4]
2. Correlation Between Reductions in Thalamic [¹¹C]PBR28 PET Signal and Reductions in Clinical Pain Ratings: We will test whether reductions in thalamic [¹¹C]PBR28 PET signal correlate with reductions in clinical pain ratings, as assessed by the "worst pain" item of the Brief Pain Inventory - Short Form. The "worst pain" item's scale ranges from 0 - 10, with a higher score indicating worse pain intensity.
 - a. [Time Frame: Change from Baseline to Week 4]
3. Correlation Between Reductions in Limbic [¹¹C]PBR28 PET Signal and Reductions in Depressive Symptoms: We will test whether reductions in pgACC/aMCC [¹¹C]PBR28 PET signal (as measured by Standardized Uptake Value Ratio) correlate with reductions in depressive symptoms, as measured by the Beck Depression Inventory-II. The Beck Depression Inventory-II scale ranges from 0 - 63, with a higher score indicating greater depression.
 - a. [Time Frame: Change from Baseline to Week 4]
4. Change in Clinical Pain Ratings: The "worst pain" item of the Brief Pain Inventory - Short Form will be used daily to assess pain intensity. The scale ranges from 0 - 10, with a higher score indicating worse pain intensity.
 - a. Time Frame: We will examine change from average score during the 7 days prior to treatment (Baseline) to average score during the final week of treatment.
5. Change in Pain Bothersomeness: Pain bothersomeness will be assessed daily on a scale from 0 - 10, with a higher score indicating greater bothersomeness.
 - a. Time Frame: We will examine change from average score during the 7 days prior to treatment (Baseline) to average score during the final week of treatment.
6. Change in Depressive Symptoms: The Beck Depression Inventory-II will be used to assess symptoms of depression. The scale ranges from 0 - 63, with a higher score indicating greater depression.
 - a. Time Frame: Change from Baseline to Week 4.
7. Patient Global Impression of Change: The Patient Global Impression of Change scale will be used to assess participants' perceptions about their global improvement related to their low back pain. The scale ranges from 0 - 7, with a higher score indicating greater overall improvement.
 - a. Time Frame: Week 4

Study Termination Criteria:

Participants will be terminated from this study if there are any significant safety concerns (e.g., actively suicidal), failure to comply with study procedures, or if the opinion of the principal investigator, can no longer safely participate. In addition, subjects will be informed that if they feel uncomfortable with the study, they can choose to terminate the study at any time. They will be informed that their refusal to participate in the study or choosing to terminate it at some point will have no effect on care and treatment received by them at MGH now or in

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future. We will also discontinue EPIDIOLEX or placebo in any patients with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN.

If a participant decides to stop participating in the study before the planned end of the study, we will ask that they continue to follow the schedule of visits. If they are unable or unwilling to return to the MGH Charlestown Navy Yard campus for visits, we will ask if we can call them for phone interviews instead of study visits.

Study Compensation:

Subjects will be paid by check at the completion of the study for their participation.

We will pay up to \$770. Payments will be as follows:

- \$75 for the initial screening visit
- Up to \$76 for completing daily surveys (\$1 per survey completed)
 - Bonus \$25 if they complete 90% of surveys
- \$200 for each PET/MRI scanning visit
- \$25 for each blood test to exclude pregnancy (for females of childbearing age)
- \$50 for each arterial line placement
- Participants will be able to earn up to an additional \$17-\$22 during each Monetary Incentive Delay task

If during the imaging visit(s) we cannot inject the subject with the radioligand (e.g., due to a failure in radiosynthesis, or to issues with the scanner) and we HAVE NOT yet placed the arterial line, he/she will receive \$50. If we cannot inject the subject with the radioligand, and we HAVE already placed the arterial line, he/she will receive \$100.

If the subject will need to stop the scan early for any reason, he/she will still receive \$50 for his/her time. Additionally, parking fees will be covered as needed.

Subjects excluded per the genotyping results of a mailed-out saliva test will receive \$15.

7. Risks and Discomforts

All subjects will undergo a telephone or email pre-screening to attempt to distinguish potential subjects from those not meeting eligibility criteria. Likely candidates will undergo a characterization and training session, which will include a clinical screening procedure. This procedure will involve answering questions about subjects' medical history recording of medical history review and answering questions about their medical situation including liver disease, kidney disease, blood disorders, heart disease, alcohol and opioid use, high blood pressure, asthma, and other respiratory disorders.

Subjects will be instructed to complete the questionnaires to the best of their ability but will have the option to leave any question(s) blank. In the unlikely event that evidence of physical or psychological disorder is found, with the individual's permission, the information will be shared with his or her primary care physician who can direct care as needed.

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PET/MRI Procedure: The U.S. Food and Drug Administration (FDA) recently gave the first regulatory clearance of a hybrid PET/MRI scanner in the U.S. Additionally, FDA considers investigations of MRI software and hardware operating within FDA specific parameters as non-significant risk device studies. All studies will adhere to these FDA approved safety levels for the Siemens system. These safety parameters include static magnetic field, time varying magnetic fields (dB/dt), specific absorption rate (SAR), and acoustic noise levels. Subjects will be informed about minimal risks of routine high magnetic field and non-ionizing RF radiation involved in MR imaging.

Subjects will also be informed about the PET procedure and the minor risks associated with exposure to radiation. Subjects will also be informed about small space within the magnet and noises made by switching gradients. Subjects will be informed that if they feel uncomfortable with the study, they can choose to terminate the study at any time. They will be informed that their refusal to participate in the study or choosing to terminate it at some point will have no effect on care and treatment received by them at MGH now or in future. The subjects will be informed that their personal information will be protected as per the HIPAA guidelines.

Intravenous catheter: An intravenous catheter will be placed for this study. The subject will feel a slight pinprick, similar to a bee sting, and may feel some discomfort and have some bruising or bleeding at the site where the needle goes in. Depending on the length of time the catheter is in place, a bruise may last for a day or so. Rarely an infection may occur at this site. If infection does occur, it will be treated.

Optional arterial line: An intra-arterial catheter will be placed by an individual with anesthesia training (i.e., board-certified anesthesiologist, fully licensed anesthesia resident, a certified registered nurse anesthetist), on the arm opposite to the radio-ligand injection line, for blood draws during the PET study. Local infection, swelling, and redness could occur at the sites of line placement, as well as temporary loss of pulse at the wrist. This area may have a bruise or feel uncomfortable for 2-3 days after the catheter is removed. The risks associated with having blood drawn include: bruising, local discomfort, or infection at the site of the needle puncture. Rarely an infection may occur at this site, and if an infection does occur, it will be treated. Inserting an arterial line (A-line) can hurt more than having a regular IV or having blood drawn with a needle. We will place the A-line under local anesthesia (i.e., lidocaine), which may cause an allergic reaction. Even if we numb the wrist area first, the insertion may still hurt. Once the A-line is in place, it usually does not hurt. About 24 hours after the beginning of the imaging procedures, we will give the subject a phone call to determine whether he or she is experiencing study related issues.

The subject may experience pain, bleeding, swelling or redness at the wrist, short loss of pulse at the wrist if blood flow in the artery is briefly stopped, damage to the artery wall or nearby nerves, or catheter breaking or falling out. There have been reports of decreased blood flow to the hand, which resulted in the need for surgery. This is very rare and has not been reported when catheters have been in place for only a few hours for research. Additionally, the insertion or removal of the A-line might cause temporary dizziness, nausea or fainting. After the anesthesiologist, anesthesia resident, certified nurse anesthetist, or registered nurse removes the

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catheter and has held pressure for several minutes, we'll ask the subject to stay for 30 minutes (up to 60 minutes based on clinical opinion of NP or registered nurse) so we can monitor him/her in order to assess the occurrence of any adverse event. Dr. Loggia will file a report on Insight within the timeframe stipulated by the IRB (5 working days/7 days) should any adverse event occur. The subject may have a bruise or feel tenderness for 2-3 days around the area where the catheter was placed. We will instruct the subject to avoid lifting anything heavier than a small bag of flour for a day. We will instruct the subject to call us if bleeding occurs after the subject leaves (rare), and/or if the wrist area is painful or red or swollen. About 24 hours after the beginning of the imaging procedures, we will give the subject a phone call to determine whether he or she is experiencing study related issues.

Radiation exposure: The radiation exposure in this study will be small and there is no evidence that it represents a major health risk. If subjects have participated in other research studies in the past 12 months that have involved radiation exposure, they will be asked to inform the investigators or study staff (by writing initials on the consent form verifying that they have not been exposed to other radiation in the past 12 months). If it is determined that their prior radiation exposure exceeds our current guidelines, they may not be allowed to participate in this study.

We will use [¹¹C]PBR28 produced by the cyclotron/radiochemistry/radiopharmacy facility at the A. A. Martinos Center for Biomedical Imaging. The Martinos Center has studied several hundreds of people with this radioligand and have had no clinically detectable effects or side effects. Given the use of [¹¹C]PBR28 in a small clinical trial, we have obtained an IND from the FDA.

The IV injection will be administered by a licensed nuclear medicine technologist. Should there be an adverse event, Dr. Gilman will be responsible for communicating with the IRB within the stipulated time frame.

Imaging will be stopped should any untoward reaction be observed during the imaging session or if the participant so requests for whatever reason. Some subjects find it unpleasant or feel anxious when confined in the enclosed space of the scanner. If this happens, the study will be aborted. Patients will be required to use earplugs to decrease the noise perceived while in the scanner.

Saliva Genotyping: Although we cannot predict how genetic information will be used in the future, there are many safeguards in place and we do not think that there will be further risks to patients' privacy and confidentiality by sharing such information with these banks.

In addition, steps will be taken to protect confidentiality of genetic data as outlined:

1. All MGH study staff are trained to make confidentiality the first priority.
2. No genetic research data will be entered into the medical record.
3. The results of the genetic analyses will not be shared with participants, their family members or unauthorized third parties.
4. Genetic data are encoded using coded identifiers. These codes, rather than personal identifiers, are used in any analytic datasets. The code key linking coded identifiers to

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personal identifiers are kept in an access-restricted, password protected electronic file and are not shared with the genetics laboratories.

5. Consent forms are stored in locked cabinets apart from demographic and diagnostic data.
6. Samples and genetic data stored in the laboratory will be identified only by the code numbers and laboratory personnel will not have access to personal identifiers.
7. The most serious risk would be identification of individuals in the publicly shared database. To prevent this, computerized data files provided to other investigators will not include any of the HIPPA-defined personal identifiers. Published material will not identify subjects.

EPIDIOLEX (CBD): CBD is an FDA-approved medication used to treat epilepsy. According to the FDA briefing document on Epidiolex, dated 04/19/2018, treatment-emergent AEs in controlled trials for Lennox-Gastaut and Dravet syndromes included decreased appetite, diarrhea, irritability, somnolence, fatigue, aggression, pneumonia, rash, and hepatic symptoms, and in a very small number of patients, an increase in suicidal thoughts. Of note, AE related to hepatic function were likely due to the interaction between CBD and anti-epileptic drugs; prescription of an anti-epileptic drug is an exclusionary criterion for this proposed study. Further, CBD may produce pharmacokinetic interaction effects when taken with opioids^{91,92}. Any subjects who at baseline had elevated AST/ALT levels but still met the eligibility criteria for the study will undergo a follow-up liver function tests at 2 weeks. In addition, we will perform a liver function test in subjects who at any time point during the study develop clinical signs or symptoms suggestive of hepatic dysfunction.

Given the use of EPIDIOLEX in a small clinical trial, we have obtained an IND from the FDA.

Questionnaires: Minimal risks associated with completing questionnaires are subject fatigue and the possibility of minor psychological distress associated with answering sensitive questions regarding psychological functioning. Subjects will be instructed to complete the questionnaires to the best of their ability, but will have the option to leave any question(s) blank. In the unlikely event that evidence of physical or psychological disorder is found, with the individual's permission, the information will be shared with his or her primary care physician who can direct care as needed.

Confidentiality: As detailed, the investigators are quite careful regarding the protection of confidentiality, and multiple procedures are in place to reduce the likelihood of a breach of confidentiality. However, there is a small risk that information about subjects could become known to people outside of this study, and this risk is identified in the informed consent form.

The key investigators will meet quarterly to discuss any potential adverse event and side effects. We will involve the MGH Human Research Committee and Radiation Safety Committee if any additional potential risks arise. Adverse events and unanticipated problems involving risks to subjects or others will be reported to the PHRC in accordance with PHRC adverse event and unanticipated problems reporting guidelines, as well as FDA when appropriate.

8. Benefits

Potential benefits to participating individuals:

It is unlikely that individual subjects will benefit from taking part in this study. While this study is powered to possibly observe a statistically significant reduction in pain due to CBD, it is unclear whether the effect will be clinically meaningful.

Potential benefits to society:

Findings from these studies will help advance our understanding of the pathophysiology of pain disorders. In particular, this project will assess the role of microglia in the establishment and/or maintenance of chronic pain, and how this may be affected by CBD. As such, we envision that in the future the information obtained from the proposed research will enhance the diagnosis and management of a variety of chronic pain conditions.

9. Statistical Analysis

Data Acquisition

PET. [¹¹C]PBR28 binding will be measured on Siemens Biograph mMR, a whole-body 3T PET/MRI scanner, or a Siemens Tim Trio with a head-only PET insert. An intravenous catheter will be then placed in participants' antecubital vein to inject the radioligand. [¹¹C]PBR28 will be synthesized in-house using a procedure modified from the literature.⁹³ Up to 15 mCi of [¹¹C]PBR28 will be injected intravenously as a slow bolus over a 30s period.⁹⁴ In the first 90 minutes, PET/MRI data will be collected from the brain. Between 90- and 110-minutes post-injection the field of view may be repositioned to the thoracic and upper lumbar spine, so that spinal cord data can be acquired. Of note, while our primary PET imaging outcomes are brain-related (thalamic signal for "pain-related neuroinflammation" and pgACC/aMCC signal for "depression-related neuroinflammation"), we will also evaluate, in exploratory analyses in a subset of our participants (depending on the participant's availability or other factors), the signal from the most caudal segments of the spinal cord, as this regions also demonstrated neuroinflammation in our prior study of patients with lumbar radiculopathy.⁹⁵

For the brain data, motion correction will be applied using MRI-derived motion estimates for each individual frame.⁹⁶ For the spinal cord data, frame-by-frame motion correction will be implemented using the Spinal Cord Toolbox.⁹⁷ The head attenuation map (μ -map) will be obtained using a recently implemented MR-based attenuation correction method.⁹⁸ The μ -map for the spinal data will be collected using the Dixon-VIBE sequence and using in-house developed software to additionally segment the bone.⁹⁵

[¹¹C]PBR28 brain uptake will be measured voxelwise as Standardized Uptake Values ratio (SUVr), Volume of distribution (V_T), V_T ratio (DVR) and/or other commonly adopted metrics. In humans, SUV ratio (SUVr) estimation of [¹¹C]PBR28 binding has been used to reliably distinguish healthy volunteers from patients with Alzheimer's disease⁹⁹ as well in our own studies with chronic low back pain³⁶, and amyotrophic lateral sclerosis¹⁰⁰. Additionally, human and animal studies indicate SUV/SUVr estimates are less variable compared to blood-derived methods^{99,101}. These results suggest that SUVr estimation of [¹¹C]PBR28 binding could be a viable surrogate for arterial blood methods, and perhaps more sensitive to between group

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differences. However, V_T and other more quantitative metrics will be computed as well. As an intensity normalization factor we will use the whole-brain signal or a localized pseudoreference region (e.g., the occipital cortex) for the brain data, and the lowest 1-2 spinal cord segments present in the field of view for most/all of our participants (e.g., T11-L1) for the spinal signal. Brain SUVR will be spatially normalized to the Montreal Neurological Institute (MNI) space using nonlinear registration (FNIRT, from the FSL suite; www.fmrib.ox.ac.uk/fsl¹⁰²). Spatially-normalized SUVR images will be then spatially smoothed (full width at half maximum=8mm) to improve signal-to-noise ratio. Spinal cord SUVR will be normalized to MNI-Poly-AMU template¹⁰³ using the Spinal Cord Toolbox.

MRI. During the acquisition of brain PET data, several runs of BOLD fMRI data will be collected using whole brain T2*-weighted gradient echo BOLD EPI pulse sequence (TR/TE =2sec/30ms, flip angle=90°, voxel size=3.1x3.1x3mm, number of slices=37), for the purposes of evaluating striatal function using the MID task, performing MR-based motion-correction of PET data¹³⁶, as well as for additional exploratory analyses. In addition, a high resolution structural volume (e.g., multi-echo MPRAGE pulse; TR/TE1/TE2/TE3/T4=2530/1.64/3.5/5.36/7.22 ms, flip angle=7°, voxel size=1mm isotropic) will be collected for anatomical localization as well as attenuation correction.¹⁵⁵ For the spinal cord data, axial and coronal T1 (e.g., TR/TE=0.565s/13 ms; flip angle=120°; slice thickness=2mm; number of slices – 14) and T2 (e.g., TR/TE=3.38s/109 ms; flip angle=150°; slice thickness=2mm; # slices – 30) weighted images will be collected for anatomical localization and ROI definition purposes.⁷

Data Analyses

A generalized linear mixed-effects model (GLMM) will be used to quantify the association between thalamic [¹¹C]PBR28 PET signal, treatment assignment at randomization (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 (e.g., age, depression severity, sex). Data dependencies will be accounted for using either random intercept or line (intercept and slope) parametrizations. 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 modeling 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 summarize 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

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analyses 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.

Genotyping:

GWAS Genotyping: The Broad Institute will perform genotyping (array-based) of subject DNA samples and subsequent in-depth analysis of the data, which will allow us to detect alterations in the genome including point mutations, small insertions and deletions, chromosomal copy number alterations, and translocations. These experiments are intended to help identify candidate genes involved in the physiopathology of neurological and psychological diseases. The molecular information generated from these samples will not be returned to subjects at any time.

Data from this study may result in communications in journals or at scientific meetings. Subjects will not be identified in those communications. To facilitate research, the genetic information generated may upon publication be deposited in protected databases (such as dbGAP) available only to bona fide researchers with specific scientific questions who promise to not try to identify individuals. The data will be sent to these banks in a coded manner and again will not contain any traditionally used identifier such as name, address, phone number, or social security number. Although we cannot predict how genetic information will be used in the future, there are many safeguards in place and we do not think that there will be further risks to patients' privacy and confidentiality by sharing such information with these banks.

The Broad Institute will not be involved in subject ascertainment. Prior to transfer of bio-specimen aliquots to the Broad Institute, samples will be re-encoded at the collaborators institutions. No identifying patient information will be shared with Broad scientists at any time. Some limited clinical data will be obtained from collaborators. Again, all subject identifying information will remain with the collaborators and only de-identified clinical data will be shared with the Broad Institute.

Consideration of sex as a biological variable:

In addition to the aforementioned analyses, the effect of sex will be evaluated using ANOVAs, because animal research suggests the presence of a possible sexual dimorphism in the role of glia in pain (as pain hypersensitivity may be microglial-dependent only in males¹⁰⁴). The effect of menstrual cycle status will also be evaluated by comparing women in early follicular (day 2-7 after onset of menses) and midluteal (day 20-25 after onset of menses), based on self-report¹⁰⁵.

Effect of coronavirus on neuroinflammation:

Finally, in addition to the aforementioned analyses, the effect of prior exposure to coronavirus (as detected by the presence of antibodies to SARS-CoV-2) will be evaluated in both ROI and voxelwise analyses, in exploratory analyses. Identifying participants who are positive to the antibodies might allow us to test the exploratory hypothesis that prior exposure to the coronavirus can lead to neuroinflammation even without having experienced overt acute COVID-19 symptoms.

Power Analysis:

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Primary Aim: Using a linear mixed-effects model, we estimate the power to detect a temporal (week 4 – baseline) rate of change in thalamic [^{11}C]PBR28 PET signal between CBD and control subjects when recruiting 40 subjects per treatment group. We assume: (1) the standard deviations of the [^{11}C]PBR28 PET signal measures are 0.05,[106] (2) the correlation between repeated measurements ranges between 0.3 to 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 [^{11}C]PBR28 PET signal measures of at least 0.039 and 0.045, respectively.

10. Monitoring and Quality Assurance

There will be a DSMB for this study (see attached DSMB Charter). The proposed study will be monitored for safety, with monthly staff meetings reviewing adverse events and treatment outcomes and directly reporting any adverse events. The PI will also routinely monitor and assure the validity and integrity of collected data, adherence to the IRB-approved protocol, and recordkeeping. The trained staff members who carry out the procedures will also carefully monitor the study throughout its duration. The team will evaluate the progress of the study, verify that the rights and well-being of the subjects are protected, verify that the reported study data are accurate, complete and verifiable from source documents, and the conduct of the study is in compliance with the approved protocol and amendments. Outcome monitoring and adverse events will all be reported through appropriate channels of the Human Studies Committee as well to the FDA when appropriate.

If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, right upper quadrant abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), we will promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with EPIDIOLEX or placebo, as appropriate. We will discontinue EPIDIOLEX or placebo in any patients with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN. Our physician monitoring group (Drs. Mao, Zhang, Schnitzer, and Evins) will consider stopping the study if back pain becomes significantly worse in 3 or more patients. If serum liver enzyme concentrations are significantly elevated (with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN) in 2 or more patients, which will be considered serious adverse events, the study will be stopped. In addition, if two or more patients experience any serious adverse event, the study will be stopped.

The Siemens PET/MRI scanners have a built-in self-monitoring system that automatically shuts off if parameters exceed safe levels. For backup protection NMR technicians constantly monitor the subjects' physiological signs and the quality of the raw data.

Quality assurance of the scanner's performance is obtained by a daily quality assurance protocol. More extensive quality assurance protocols are performed monthly under the commercial service contract with Siemens Medical Systems. The daily quality assurance protocol consists of an image Signal-to-Noise measurement in a phantom and a stability run which checks the image-to-image variation in image intensity over 600 images using a standard echoplanar imaging sequence with a head-sized phantom. The images are analyzed by the technologist to provide

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data on SNR (as an absolute, unitless number) and stability expressed as the peak-to-peak variation in the mean of a 15x15 pixel region of interest (ROI) in the center of the phantom expressed as a percentage of the mean of the ROI. Runs are performed at each of 3 TR values (300ms, 800ms, 1300ms). The time course of the means is also reviewed to check for periodicities (the TR values are chosen so as not to be multiples of one another). If the peak-to-peak variation is greater than 0.5% of the mean value, the Siemens Medical System service engineer is called. In addition to these daily quality assurance tests, the Siemens Medical System service engineer performs quality assurance tests once a month. These tests include a SNR test, a small sample stability test, a gradient stability test, a gradient eddy current test, a shim test, an image uniformity test, and an RF stability test.

11. Privacy and Confidentiality

- Study procedures will be conducted in a private setting
- Only data and/or specimens necessary for the conduct of the study will be collected
- Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- All electronic communication with participants will comply with Mass General Brigham secure communication policies
- Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- Additional privacy and/or confidentiality protections

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Subject Identification

Research Consent Form
Certificate of Confidentiality Template
Version Date: February 2021

Protocol Title: Evaluation of Cannabidiol (CBD) for Reduction of Brain Neuroinflammation

Principal Investigator: Jodi Gilman, PhD

Site Principal Investigator:

Description of Subject Population: Adults with Chronic Low Back Pain

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

Key Information

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. Your decision won't change the medical care you get within Mass General Brigham now or in the future.

The following key information is to help you decide whether or not to take part in this research study. We have included more details about the research in the Detailed Information section that follows the key information.

Why is this research study being done?

In this research study we want to learn more about whether cannabidiol (CBD) reduces activation of glial cells, which are the immune cells of the nervous system. Cannabidiol is a naturally occurring compound found in cannabis plant, and is considered to be a safe, non-addictive substance. We are looking to find out whether CBD may reduce symptoms of low back pain.



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How long will you take part in this research study?

If you decide to join this research study, it will take you about 8-10 weeks to complete the study. During this time, we will ask you to make 2 imaging visits to MGH Charlestown Navy Yard campus and 2 office visits to 101 Merrimac Street. There will also be three follow up phone calls.

What will happen if you take part in this research study?

If you decide to join this research study, the following things will happen. First, you will come to MGH for an approximately 3-hour screening visit, which will include a blood test, a urine test, and a physical exam. Depending on the results of the initial screening visit, you might be eligible to participate in up to 2 imaging visits. As part of the study, we are using a machine which combines Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) into one device. The MRI part of it uses a powerful magnet to make a picture of the body, while the PET part of it makes pictures by using special dyes with a small dose of radioactivity attached to them that “light up” inside the body.

To study the effect of CBD, you will be asked to take either a medication called EPIDIOLEX or placebo for the 4 weeks prior to the date of your second imaging visit. EPIDIOLEX is a liquid formulation of CBD. A study doctor will talk to you about how much EPIDIOLEX to take.

Why might you choose to take part in this study?

We cannot promise any benefits to you from taking part in this research study. However, possible benefits may include a reduction in pain while taking the drug. Others with chronic back pain may benefit in the future from what we learn in this study.

Why might you choose NOT to take part in this study?

Taking part in this research study has some risks and requirements that you should consider carefully.

Important risks and possible discomforts to know about include sleepiness, decreased appetite, diarrhea, lack of energy, and risks of PET/MRI scans (radiation exposure). CBD may cause an increase in suicidal thoughts or actions in a very small number of people. It is possible that patients taking EPIDIOLEX may test positive on a cannabis drug screen. If this happens, we will tell the laboratory staff that you are involved in a research study using Epidiolex.



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A detailed description of side effects, risks, and possible discomforts can be found later in this consent form in the section called “What are the risks and possible discomforts from being in this research study?”

Other things to consider are the time commitment of 4 visits, and requirements to travel to MGH.

What other treatments or procedures are available for your condition?

Other treatments or procedures that are available to treat chronic low back pain include:

- Medications (e.g., non-steroidal anti-inflammatory drugs, opiates, muscle relaxants)
- Transcutaneous electrical nerve stimulation
- Physical exercise and stretching
- Epidural steroid injection
- Physical therapy
- Back surgeries
- Acupuncture

If you have questions or concerns about this research study, whom can you call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Jodi Gilman, PhD is the person in charge of this research study. You can call her at 617-643-7293 Monday-Friday from 9am to 5pm with questions about this research study. If you have any medical questions related to the study you can call Dr. Kristina Schnitzer at 617-726-2000, and ask for pager #27399 (24/7, for emergencies).

If you have questions about the scheduling of appointments or study visits, call our study staff:
 Chelsea Pike: (617)724-0382 ckpik@mg.harvard.edu

If you want to speak with someone **not** directly involved in this research study, please contact the Mass General Brigham IRB. You can call them at 857-282-1900.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research
- Any pressure to take part in, or to continue in the research study



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Detailed Information

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Why is this research study being done?

We are doing this research study to find out if cannabidiol (CBD) reduces activation of glial cells, which are the immune cells of the nervous system, compared to placebo. We are also looking to find out whether CBD may reduce symptoms of low back pain.

CBD (in the form of EPIDIOLEX) is a prescription medicine that is approved by the U.S. Food and Drug Administration (FDA) to treat seizures associated with Lennox-Gastaut syndrome or Dravet syndrome (rare forms of childhood epilepsy) in people 2 years of age and older. CBD is not approved by the FDA to treat chronic low back pain and it is not known whether it is effective for chronic back pain. We are asking you to take part in this study because you have chronic low back pain lasting at least 6 months.

This research study will compare CBD to placebo. The placebo looks exactly like CBD, but contains no CBD. During this study you may get a placebo instead of CBD. Placebos are used in research studies to see if the results are due to the medication or due to other reasons. If you decide to participate in this study, you will have a 50% chance of receiving active study medication and 50% chance of receiving placebo. That means 1 out of 2 people will receive only placebo during the study. Neither you nor study staff will know if you have received active medication or placebo until after the study is over, however study staff can get this information quickly if needed.

Who will take part in this research?

We are asking you to take part in this research study because you are an adult with chronic low back pain. About 80 people will take part in this research study at Massachusetts General Hospital. The National Institutes of Health is paying for this research study to be done.

What will happen in this research study?

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures.



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Screening Visit

The Screening Visit will take place at our 101 Merrimac Street office and will last about 3 hours. At this visit, we will do some tests and procedures to see if you qualify to take part in this research study. The study staff will review the results of these tests and procedures.

At this visit, we will:

- Ask you questions or have you complete questionnaires about your health (past and present), including mental and emotional health.
- Ask you to fill out questionnaires about your pain.
- Do a physical examination.
- Ask you about current medications you are taking.
- Ask you to fill out a form with information about your age, sex, race, marital status, and employment status.
- Draw about 2 tablespoons of blood to assess liver function and radiotracer binding affinity. Low affinity for the radiotracer known as [¹¹C]PBR28 disqualifies the subject for the research study. You may provide a saliva sample instead of a blood sample to assess radiotracer binding if you wish.
- Collect a urine sample to test for certain drugs. The results of the urine drug test will not become part of your medical record. These test results will, however, remain part of your study record.
- Collect a urine sample to test for pregnancy if you are a female who is able to become pregnant. Pregnant women cannot take part in this research study.
- With your permission, we may collect a saliva sample for other genetic research.

Study staff will also need to access your medical record in order to verify a pain diagnosis and any other medications.

This visit may also be held at the MGH Charlestown Navy Yard campus instead of our 101 Merrimac Street office, depending on your circumstances. Note that we may do a brief MRI test scan with you on the day of your screening visit, or on a different day, to ensure that you are a suitable candidate for scanning.

PET/MRI Visits

All the eligible participants will complete two PET/MRI scan visits. The PET/MRI visits will take place at MGH Charlestown Navy Yard campus. Each PET/MRI visit will last



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approximately 4 hours (and up to 6 hours). We will ask you to avoid strenuous exercise for 24 hours before the PET/MRI scan.

Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) are tests that allow us to take images of your brain and spinal cord. MRI uses a powerful magnet to make images of the body, while PET uses something called a radiotracer, that binds to the specific cells we are interested in viewing and causes them to “light up” so the scanner can detect them.

Before the PET/MRI scan, we will:

- Ask you some questions about your recent health and have you fill out some questionnaires to make sure it is safe for you to have a PET/MRI scan.
- Draw about 1 teaspoon of blood to test for pregnancy if you are a female who is able to become pregnant. Pregnant women cannot take part in this research study.
- Measure your weight.
- Collect a urine sample to test for certain drugs.
- Draw about 1 teaspoon of blood to test for the presence of cannabinoids (including CBD and THC) in the blood.
- Draw about 2 teaspoons of your blood to test for COVID-19 antibodies (to see if you have been infected by the SARS-CoV-2 virus and an immune response to it is still present in your body).

If you still qualify, we will ask you to take off anything that contains metal and change into hospital approved clothing. Then we will:

- Place an IV catheter (a thin, flexible plastic tube with a needle attached) into a vein in your arm. The IV catheter will be used to inject the radiotracer known as [¹¹C]PBR28 into your body, as well as draw about 2 tablespoons of blood to assess the function of various organs, body systems, cells, molecules, and genes in pain disorders.

We would like your permission to place an arterial line (“A-line”) into an artery in your wrist to draw blood samples throughout the scan, if the doctor or nurse practitioner has deemed it safe for us to do so. However, this procedure is optional for all subjects who qualify and you will still be able to participate in the study, even if you do not allow us to collect arterial blood. The collection of arterial blood allows us to measure how the radiotracer moves through your body, and we can use that information to get more accurate PET images.

PET/MRI Scans



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You will lie still in the PET/MRI scanner for about 2 hours. The scanner is a tunnel. You will lie on your back on a narrow table that will slide you into the tunnel. In order to help hold your head still, we may place foam pillows under and around your head.

The top and sides of the tunnel will be close to your face and body, which can make some people uncomfortable. If you have ever experienced a fear of enclosed spaces (claustrophobia), please tell the study staff.

The scanner makes loud banging and beeping noises taking images, so we will give you earplugs to protect your ears.

First, we will take some pictures of your brain and/or whole body. Then we will inject the radiotracer into the IV catheter in your vein and take more images. You will not feel the radiotracer in your body and it will quickly leave your body through your urine. The Martinos Center has completed hundreds of PET/MRI scans in a number of patient populations and healthy volunteers using [11C]PBR28. There have been no side effects associated with the administration of this radiotracer. This dye will travel through your blood stream, so the PET/MRI scanner can see how the different parts of your brain and/or whole body are working.

Before, during and after the scans, you may be asked to express various behavioral ratings, including pain intensity, unpleasantness and anxiety.

After the brain scan is complete, we may collect additional 20 minutes of data from your spinal cord. This spinal cord imaging is optional, and will only be done if you are still comfortable in the scanner.

After the scan is complete, you will sit up slowly and we will remove your catheter. After the removal of the arterial line we will observe you for 30 minutes. After this period of observation, you are free to leave.

Somebody from the study staff will call you the day following each scan to check on you. Of course, you can contact us at any time if you have questions (see contact information under "If I have questions or concerns about this research study, whom can I call?").

Taking the Study Drug

You will receive a bottle containing either CBD or a placebo at the first PET/MRI Visit to take home with you. You will be instructed to begin taking it four weeks prior to the scheduled date of your second PET/MRI Visit. A study doctor will tell you how much to take. You will take CBD or placebo for 4 weeks in total, and your dose will increase each week. When you start the study drug, we will ask you to take 2.5mg/kg twice daily. Each week, a member of the study



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team will remind you to increase the dose for the following week (week 2 dose = 5mg/kg twice daily; week 3 dose = 7.5mg/kg twice daily; week 4 final dose = 10mg/kg twice daily). At the end of the second week, a study physician will meet with you (by phone or in person) to assess tolerability. If you are not tolerating the study drug well (whether during the second week, or during the third or fourth week of taking the study drug), the physician will decrease your dose to the previous week’s dose. The study physician may also discontinue the study drug if you do not tolerate it well.

CBD should be taken consistently with respect to meals and should not be taken in a fasted state. In addition, CBD should not be taken with concurrent alcohol use. It is important for you to follow our instructions about how to take the study drug.

Daily Surveys

You will be asked to fill out a daily survey for about 2 weeks before your first scan, for 4 weeks while you are taking CBD or placebo, and for 2 weeks after the discontinuation of CBD or placebo. You will be sent a survey to complete by the end of each day. This survey will be sent to you each day via email or text message and you will have until 11:59pm each night to complete the survey. The survey will take less than 5 minutes to complete and will ask you about your low back pain symptoms, mental health, sleep quality, fatigue, whether you have been taking the study drug, and whether you have taken any other medications to manage your pain.

Please let the study staff know if you do not have internet access and we can arrange to call you to administer the survey.

Follow-up Visits and Calls

1-Week Call. You will have a phone call 1 week after your first scan visit. In this call, we will assess adverse events, treatment expectancy, and medication use. We will also remind you to increase your study drug dose.

2-Week Visit. You will have a follow-up appointment during Week 2 with a study staff member at 101 Merrimac Street. We will check on your health, remind you to increase your study drug dose, ask about other medication use, and ask you to complete some questionnaires. We may also take a small sample of blood for a follow-up liver function test. As you will be taking Epidiolex or placebo daily at the time of this visit, we will ask you whether you can drive to the visit; if you cannot because the study drug makes you drowsy, we will arrange transportation. Note that this visit may also be held at the MGH Charlestown Navy Yard campus, depending on your circumstances.



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3-Week Call. You will have a phone call during Week 3 to assess adverse events, treatment expectancy, and medication use. We will also remind you to increase your study drug dose.

4-Week Visit. You will have a second follow-up appointment immediately after the four-week treatment period, where we will assess back pain, general health, adverse events, and medication use. On the same day or as close as possible depending on scheduling, you will be re-scanned. We will also repeat the questionnaires administered during the baseline visit to assess any changes in subjective pain or general health. We will also take a small sample of blood for a follow-up liver function test. Again, we will ask you whether you can drive to the visit; if you cannot because the study drug makes you drowsy, we will arrange transportation.

6-Week Call. You will have a follow-up phone call 2 weeks after the discontinuation of the study drug. In this call, we will assess back pain, general health, adverse events, and medication use.

Stopping the Study Early

If you wish to stop taking the study drug, you should tell the principal investigator of this study, Dr. Jodi Gilman.

If you decide to stop participating in the study for any reason before the planned end of the study, we will ask that you continue to follow the schedule of visits. If you are unable or unwilling to return to the MGH Charlestown Navy Yard campus for visits, we will ask if we can call you for phone interviews instead of study visits.

Also, the study doctor may take you out of the study without your permission. This may happen because:

- The study team thinks you cannot follow the study plan.
- Your health is in question.
- You are experiencing side effects from the study drug.
- The study doctor thinks it is best for you to stop taking the study drug.
- We stop doing the study for other reasons.

Sending Study Information to Research Collaborators Outside Mass General Brigham

Blood Plasma Shipments

We will collect blood samples at the screening visit and the two PET/MRI visits, which will be tested for COVID-19 antibodies and pregnancy (in females). A small quantity (about 1 teaspoon)



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of blood plasma from your sample may be shipped to researchers working with us at a University of Colorado lab who can quantify cannabinoids (including CBD and THC) in the blood.

We will label all your study materials with a code number instead of your name. No names or important numbers that could be used to identify you, like hospital medical record number or social security number, will be kept on samples. Only MGH study staff will keep the link between your subject number and your name on a computer protected by a personal password.

Optional (not required) Saliva Samples for Genetic Testing

While collection of a blood or saliva sample to test for radiotracer binding affinity is required, the collection of a saliva sample for other genetic research at the screening visit is optional (not required). You can still take part in the main study even if you don't want to take part in the additional genetic study. Giving a DNA sample involves filling 1-2 small plastic containers with your saliva. This will be done at your first visit and should take less than 5 minutes. Usually researchers study just a few areas of genetic code that are linked to a disease or condition. Instead, we may perform a whole genome analysis on your DNA sample. In whole genome analyses, all or most of the genes are looked at and used by researchers to study links to substance use and mental health. These whole genome analyses will be conducted by investigators at the Broad Institute. Samples shared with investigators at the Broad Institute will be labeled with a code number and not with your name or other identifying information. Research using whole genome information is important for the study of virtually all diseases and conditions. Therefore, the anonymized samples will provide study data for researchers working on any disease.

It is not intended to provide important genetic information about your health. We have no plan to return any research results to you or your doctor. The results of the genetic testing will not be placed in your medical record. Your consenting to take part in this additional genetic study is voluntary, and you may decide to withdraw from the study at any time or decide not to join the study. If you change your mind and want to withdraw your saliva sample from further genetic research you can do so at any time by contacting Dr. Gilman (617-643-7293; jgilman1@mgh.harvard.edu). Any information obtained from the sample will also be withdrawn except to the extent to which the information has already been used in analyses. All information and samples obtained for this study will be assigned a code number. No names or important numbers that could be used to identify you, like hospital medical record number or social security number, will be kept on samples. Only MGH study staff will keep the link between your subject number and your name on a computer protected by a personal password.

Would you like to provide a saliva sample to be used for genetic testing as described above?
 Please mark your choice below.



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[] YES [] NO Initials _____

In order to allow researchers to share test results, the National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that analyze data and collect the results of whole genome studies. These banks may also analyze and store DNA samples, as well. These central banks will store your genetic information and samples and give them to other researchers to do more studies. We do not think that there will be further risks to your privacy and confidentiality by sharing your samples and whole genome information with these banks. However, we cannot predict how genetic information will be used in the future. The samples and data will be sent with only your code number attached. Your name or other directly identifiable information will not be given to central banks. There are many safeguards in place to protect your information and samples while they are stored in repositories and used for research.

How may we use and share your samples and health information for other research?

At the completion of this research study, we would like to store and be able to use and share your identifiable samples and health information with researchers at Mass General Brigham for other research related to pain disorders. If we share your samples and/or health information with other researchers outside of Mass General Brigham, we will label the samples and information with a code instead of your name or other directly identifying information. The key to the code connects your name or other identifiers to your sample and/or information. We will keep the code in a password protected computer.

Because these samples and/or health information are identifiable, we are asking your permission to store, use and share them for other research. You can still take part in the research study whether or not you give permission for the storage, use, and sharing of the samples and health information for other research.

Do you agree to let us store and use your samples and health information for other research related to pain disorders?

[] YES [] NO Initials _____

Will you get the results of this research study?



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You and your doctor should not expect to get information about the results of the research study or the results of your individual participation in the research study. The researchers involved in this study will study samples and information from many people. It could take many years before anyone knows whether the results have any meaning. There is a small chance that researchers could find out something from the study that might be important to your health. If this happens, we may contact you to find out if you would like to learn more. However, even if we find something important to your health, we cannot guarantee that you will be contacted.

What are the risks and possible discomforts from being in this research study?

Risks of Taking EPIDIOLEX

Taking **EPIDIOLEX** may cause you to have one or more of the side effects listed below.

Common side effects:

- Increase in liver enzymes: As part of the study, we will collect blood to check your liver before you start taking EPIDIOLEX and after one month of treatment. In some cases, EPIDIOLEX treatment may need to be stopped. If you had elevated liver enzymes at baseline but still met the eligibility criteria for the study, we may ask you to undergo a follow-up liver function tests at 2 weeks. In addition, we will perform a liver function test on anyone who develops clinical signs or symptoms suggestive of hepatic dysfunction.
- Sleepiness: EPIDIOLEX may cause you to feel sleepy, which may get better over time. Do not drive, operate heavy machinery, or do other dangerous activities until you know how EPIDIOLEX affects you. Other medicines (e.g., clobazam) or alcohol may increase sleepiness.
- Decreased appetite
- Diarrhea
- Lack of energy
- Insomnia
- Poor quality sleep
- Infections

Rare side effects:

- Suicidal thoughts or actions: EPIDIOLEX may cause suicidal thoughts or actions in a very small number of people, about 1 in 500. Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you: thoughts about suicide or dying, attempt to commit suicide, new or worse depression, new or worse anxiety, feeling agitated or restless, panic attacks, trouble sleeping, new or worse



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irritability, acting aggressive, being angry, or violent, acting on dangerous impulses, an extreme increase in activity and talking (mania), other unusual changes in behavior or mood. We will assess suicidality, depression, and anxiety throughout the study. If you report any new or worsening expression of suicidal ideation and or/emergent depression, you may be asked to speak with a licensed clinician. These clinicians, along with the PI will then determine whether you can safely continue the study. If the clinicians determine that you cannot safely continue the study, your participation in the study will be discontinued, and you will be provided with a list of resources for follow-up care.

- Allergic reactions: As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious, and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are having an allergic reaction, call the study doctor right away. If you are having trouble breathing, call 911 immediately.
Positive drug screen for cannabis: It is possible that patients taking EPIDIOLEX may test positive on a cannabis drug screen.
There may be other risks of EPIDIOLEX that are currently unknown at this time.

Risks of Taking EPIDIOLEX with Other Medications

Do not take medications that impact specific CYP450 enzymes, including some CNS depressants, while you are in the study. This includes:

- All antipsychotics
Benzodiazepines (except for alprazolam, clonazepam, and lorazepam)
Non-benzodiazepine sleep aid use will be reviewed by the study physician to determine safety

Taking these drugs and EPIDIOLEX together may cause serious side effects. All medications, including but not limited to those mentioned, must be discussed with the study physician.

Additionally, for your safety during this study, call your study doctor BEFORE you take any:

- New medications prescribed by your own doctor
Other medications sold over-the-counter without a prescription
Dietary or herbal supplements

Risks of Radiation Exposure

As a result of your participation in this study, you will be exposed to radiation from two PET scans of your brain and/or spinal cord. Please note that this radiation is not necessary for your medical care and is for research purposes only. The maximum amount of radiation to which you could be exposed to in this study is approximately 7.4 milliSieverts (mSv). A mSv is a



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unit of radiation dose. This amount of radiation is about the same as you would normally get in 2.4 years from natural background sources from the earth and the sky.

Scientists disagree on whether radiation doses at these low levels are harmful. Possible side effects that could occur at doses associated with this study include:

- A slight increase in the risk of developing cancer later in life

Since the effects of radiation can add up over time, it is important that you tell the study doctors about your past clinical imaging and research-related radiation exposure. If you have taken part in other research studies in the past 12 months that have involved radiation exposure, please tell us. If it appears that your earlier radiation exposure is more than our current guidelines, it is possible that you will not be allowed to take part in this study.

Have you participated in other research studies (not including this study) involving radiation exposure within the last 12 months?

YES NO **Initials** _____

Risks to an Embryo or Fetus, or to a Breastfeeding Infant

The effect of radiation exposure or the use of CBD (EPIDIOLEX) on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this study if they are:

- Pregnant or trying to become pregnant
- Breastfeeding

If you are a menopausal woman and have not had a menstrual period for the past 12 months or more, you will not need to have a pregnancy test. Also, if you have had any well-documented method of surgical sterilization, you will not need to have a pregnancy test. Methods of surgical sterilization include having had a hysterectomy (removal of the uterus), bilateral oophorectomy (removal of both ovaries), a tubal ligation (having your tubes tied), and transvaginal occlusion (plugging the opening of the tubes with a coil). All other female subjects must have a negative pregnancy test before starting the study drug and before having the PET/MRI scan.

If you miss a period, or think you might be pregnant during the study, you must tell the study doctor immediately. If you become pregnant, you must stop taking the study drug and stop taking part in the study.

There may be other risks and side effects of the PET/MRI scan that are not known at this time.



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Risks of MRIs

MRIs use powerful magnets to make images. There are no known radiation risks associated with MRI. However, you should not have an MRI if:

- You have certain medical metal implants, such as surgical clips or pacemakers
You are pregnant or suspect you are pregnant

All credit cards and other items with magnetic strips should also be kept out of the MRI room. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow tube. The MRI makes loud banging noises as it takes images. Earplugs can be used to reduce the noises. The MRI can be stopped at any time at your request.

Other possible risks include:

- Localized warming of your skin and the underlying tissue during normal routine MRI use
You should immediately inform us if you experience discomfort due to warming and the procedure will be stopped

Risks of IV Catheter and Blood Draw

Drawing blood or placing the IV catheter into a vein in your arm may cause the following in the area where we take blood samples from or place the IV catheter:

- Pain
Discomfort
Bruising
Bleeding
Swelling
Redness

You may have a bruise or feel painful or uncomfortable for 2-3 days after. Rarely, an infection may occur, which can be treated.

Risks of Optional Arterial Line (A-line)

Inserting an A-line can hurt more than having a regular IV catheter or having blood drawn with a needle. If you agree to this procedure, we will numb your wrist area first, but it may still hurt when we place the A-line into your wrist. Once the A-line is in place, it usually does not hurt.

Having an arterial line placed may cause:



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- Pain, bleeding, swelling, or redness at the wrist. Rarely (less than 1 in 100), an infection may occur, which can be treated.
- Short loss of pulse at the wrist, if blood flow in the artery is briefly stopped (for example, because of a clot or spasm of the artery).
- Damage to the artery wall or nearby nerves.
- Catheter breaking or falling out.

Rare side effects:

- There have been reports of decreased blood flow to the hand that resulted in the need for surgery. This is very rare and has not been reported when catheters have been in place for only a few hours for research.

After we remove the catheter:

- We will ask you to stay for at least 30 min so that we can check that the site is healing properly.
- You may have a bruise or feel tenderness for 2-3 days around the area where the arterial line was placed.
- You should avoid lifting anything heavier than a small bag of flour for a day following the scan.

Call us if:

- Bleeding occurs after you leave (rare). Apply pressure to the site and go to the Emergency Department.
- The wrist area is painful, red, or swollen.

Do you allow us to collect arterial blood during the scan(s)? You can change your mind at any time.

YES NO **Initials** _____

Risks of Numbing Drug (Lidocaine)

The anesthesiologist will use lidocaine to numb your wrist area prior to placing the A-line. Risks of lidocaine include:

- Dizziness
- Nausea
- Drowsiness
- Ringing in the ears
- Numbness



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- Allergic reaction. An allergic reaction to lidocaine was observed in a very limited number of cases.

Risks of COVID-19 Antibody Testing

As part of the study, we wish to determine whether or not you have been exposed to COVID-19. We do this using an antibody serology test which involves taking up to 10 ml of blood (about 2 teaspoons) and sending it to an internal or third-party laboratory that provides testing services. Your test results will be communicated to you. Your results may become part of your MGH medical records. A positive test does not mean that you have an active COVID-19 infection, only that you have been exposed at some point in the past.

Risks of Genetic Testing

Genetic information that results from this study does not have medical or treatment importance at this time. However, there is a risk that information about taking part in a genetic study may influence insurance companies of employers regarding your health. To further safeguard your privacy, genetic information obtained in this study will not be placed in your medical record. Taking part in a genetic study may also have a negative impact on family or other relationships. If you do not share information about taking part in this study, you will reduce this risk. We may perform Genome wide association studies (GWAS) with this data. GWAS are hypothesis free methods to identify associations between genetic regions (loci) and traits (including diseases).

Risks of Questionnaires

We will ask you questions about your emotional or mental health (psychological questions). Some of these questions may make you uncomfortable. You are allowed to skip any question you do not want to answer, but it could mean being excluded by the study (depending on how necessary the particular answer is).

Incidental Findings

We are doing the PET/MRI scan in this study to answer research questions, not as part of your medical care. The information from this study will not usually become part of your hospital record. This PET/MRI scan is not the same as the one that your doctor would order. It may or may not show problems that would be found on a standard MRI or PET scan. This type of scan is considered experimental.

If we do see something that looks like a medical problem, we will ask a radiologist (a doctor who specializes in test results of this sort) to review the results. If the radiologist thinks that you may



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have a medical problem, we will tell you and help you get follow-up care. If the radiologist thinks that you may have a medical problem, but it turns out that you don't, we may have caused you to worry needlessly about your health.

Medical Information

We will make a notation in your medical record that you are a part of this study. There is a small risk that your confidential medical information could be revealed or discovered by mistake. The results of this research study won't be placed in your medical records. In addition, your samples and information will be coded and the key to the code will be kept in a separate, locked file. We won't share or publish any information that will identify you.

What are the possible benefits from being in this research study?

You may not benefit from taking part in this study. If you receive CBD (EPIDIOLEX), it is possible that your low back pain will improve while you are taking it. However, because EPIDIOLEX is not FDA-approved to treat low back pain, your doctor cannot prescribe it after you finish the study.

Others with low back pain may benefit in the future from what we learn in this study. We hope the information obtained from this study will help scientists discover a potential mechanism of action for CBD.

What other treatments or procedures are available for your condition?

You do not have to take part in this research study to be treated for low back pain. Other treatments or procedures that are available to treat low back pain include:

- Medications (e.g., non-steroidal anti-inflammatory drugs, opiates, muscle relaxants)
- Transcutaneous electrical nerve stimulation
- Physical exercise and stretching
- Epidural steroid injection
- Physical therapy
- Back surgeries
- Acupuncture

Talk with the study doctor if you have questions about any of these treatments or procedures.



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Can you still get medical care within Mass General Brigham if you don't take part in this research study, or if you stop taking part?

Yes. Your decision won't change the medical care you get within Mass General Brigham now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should you do if you want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will you be paid to take part in this research study?

We will pay you up to \$770 for the following:

- \$75 for the initial screening visit
Up to \$76 for completing daily surveys (\$1 per survey completed)
o Bonus \$25 if you complete 90% of surveys
\$200 for each PET/MRI scanning session
\$25 for each blood test to exclude pregnancy (if you are a female of childbearing age)
\$50 for each arterial line placement
Up to \$44 which you can earn from a task you will complete in the PET/MRI scanner

If, for some reason, we cannot inject you with the dye during the imaging visit(s) and we have not yet placed the arterial line, you will receive \$50. If we cannot inject you with the dye and we have already placed the arterial line, you will receive \$100. If you have to stop the scan early for any reason, we will pay you \$50 for the imaging visit(s). We will also reimburse you for your parking in the hospital garage during study visits.



Subject Identification

Research Consent Form
Certificate of Confidentiality Template
Version Date: February 2021

We may use your samples and information to develop a new product or medical test to be sold. The Sponsor, hospital, and researchers may benefit if this happens. There are no plans to pay you if your samples or information are used for this purpose.

What will you have to pay for if you take part in this research study?

Study funds will pay for certain study-related items and services. We may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs. You will also be responsible for paying for transportation to and from study visits, although we will validate parking in the hospital garage during study visits. It is important to note that if you do receive any benefit from the CBD treatment, and decide to continue treatment with CBD after your study participation is over, you and your insurance company will be responsible for the cost of the CBD.

What happens if you are injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the beginning of this consent form.

If you take part in this research study, how will we protect your privacy?



Subject Identification

Research Consent Form
Certificate of Confidentiality Template
Version Date: February 2021

Federal law requires Mass General Brigham to protect the privacy of health information and related information that identifies you. We refer to this information as "identifiable information."

In this study, we may collect identifiable information about you from:

- Past, present, and future medical records
• Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable information and why:

- Mass General Brigham researchers and staff involved in this study
• The sponsor(s) of the study, and people or groups it hires to help perform this research or to audit the research
• Other researchers and medical centers that are part of this study
• The Mass General Brigham ethics board or an ethics board outside Mass General Brigham that oversees the research
• A group that oversees the data (study information) and safety of this study
• Non-research staff within Mass General Brigham who need identifiable information to do their jobs, such as for treatment, payment (billing), or hospital operations (such as assessing the quality of care or research)
• People or groups that we hire to do certain work for us, such as data storage companies, accreditors, insurers, and lawyers
• Federal agencies (such as the U.S. Department of Health and Human Services (DHHS) and agencies within DHHS like the Food and Drug Administration, the National Institutes of Health, and the Office for Human Research Protections), state agencies, and foreign government bodies that oversee, evaluate, and audit research, which may include inspection of your records
• Public health and safety authorities, if we learn information that could mean harm to you or others (such as to make required reports about communicable diseases or about child or elder abuse)
• Other researchers within or outside Mass General Brigham, for use in other research as allowed by law.

Certificate of Confidentiality

A federal Certificate of Confidentiality (Certificate) has been issued for this research to add special protection for information and specimens that may identify you. With a Certificate,



Subject Identification

Research Consent Form
Certificate of Confidentiality Template
Version Date: February 2021

unless you give permission (such as in this form) and except as described above, the researchers are not allowed to share your identifiable information or identifiable specimens, including for a court order or subpoena.

Certain information from the research will be put into your medical record and will not be covered by the Certificate. This includes records of medical tests or procedures done at the hospitals and clinics, and information that treating health care providers may need to care for you. Please ask your study doctor if you have any questions about what information will be included in your medical record. Other researchers receiving your identifiable information or specimens are expected to comply with the privacy protections of the Certificate. The Certificate does not stop you from voluntarily releasing information about yourself or your participation in this study.

Even with these measures to protect your privacy, once your identifiable information is shared outside Mass General Brigham, we cannot control all the ways that others use or share it and cannot promise that it will remain completely private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your identifiable information. Your permission to use and share your identifiable information does not expire.

The results of this research may be published in a medical book or journal, or used to teach others. However, your name or other identifiable information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your identifiable information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your identifiable information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others, and such information may continue to be used for certain purposes, such as to comply with the law or maintain the reliability of the study.



Subject Identification

Research Consent Form
Certificate of Confidentiality Template
Version Date: February 2021

You have the right to see and get a copy of your identifiable information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
I have had the opportunity to ask questions.
I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my identifiable information to be used and shared as described above.

Subject Date Time (optional)

Signature of Study Doctor or Person Obtaining Consent:

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
I have answered all questions about this research study to the best of my ability.

Study Doctor or Person Obtaining Consent Date Time (optional)

Consent Form Version Date: 2/17/2022

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2
3 DSMB Charter

4 Investigation of Cannabidiol for Reduction of NeuroInflammation in Chronic Back Pain
5 1R01DA053316-01

6 Dr. Jodi Gilman and Dr. Marco Loggia
7 NIH
8
9

10 **A. Safety monitoring**

11
12 An independent Data and Safety Monitoring Board (DSMB) will be appointed for this study, to
13 assess the safety of the study by determining whether there is an unacceptable level of risk due to
14 study procedures and whether an increased number of adverse events occur.

15
16 The DSMB will be established to analyze interim results to assess the safety of the trial at regular
17 intervals for the duration of the study by determining whether an increased number of adverse
18 events occur among study participants receiving drug compared to participants
19 receiving placebo.
20

21
22 The board will include a statistician, a pain expert, and a psychiatrist. Each member of the
23 DSMB will not otherwise be associated with the trial. Safety data will be reviewed by the Data
24 and Safety Monitoring Board Data every 6 months after the recruitment period begins. The
25 DSMB will receive summary reports on recruitment, retention and description of all adverse
26 events and review them at each biannual DSMB meeting. The DSMB will receive all
27 communication with the IRB. Subject information provided to the board will be identified only
28 with study IDs to protect the confidentiality of subjects. The DSMB will assess interim results to
29 determine whether the active drug treatment is associated with substantial risk, including higher
30 rate of adverse outcomes when compared with the placebo group.
31
32

33 **B. Outcomes monitoring**

34
35 A DSMB Report written by the chair and approved by all members will be issued to
36 the IRB after every DSMB meeting. The report will include, but may not be limited to, a
37 synopsis of the trials, their progress to date, characteristics of participants enrolled, retention and
38 disposition of study participants, quality assurance issues, regulatory issues, and reports of AEs
39 and SAEs.
40
41

DSMB Role	Name and Title	Affiliation/ Institution	Contact Details	Summary of Expertise
DSMB Chair and Statistician	Bettina Hoepfner, PhD	MGH, Harvard Medical School	bhoepfner@mgh.harvard.edu	Statistician
DSMB Pain Expert	Jianren Mao, MD	MGH	jmao@mgh.harvard.edu	Pain physician

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DSMB Psychiatrist	Esther Blessing, MD, PhD	NYU Grossman School of Medicine	esther.blessing@nyulangone.org	CBD, psychiatric disorders
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Trial investigators will not be members of the DSMB.

For peer review only



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Included throughout the paper
Protocol version	3	Date and version identifier	14
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 14
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10 (and see Item 21a for data safety monitoring board)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4

1			
2		6b	Explanation for choice of comparators
3			4
4	Objectives	7	Specific objectives or hypotheses
5			4
6	Trial design	8	Description of trial design including type of trial (eg,
7			parallel group, crossover, factorial, single group),
8			allocation ratio, and framework (eg, superiority,
9			equivalence, noninferiority, exploratory)
10			4, 8
11			
12	Methods: Participants, interventions, and outcomes		
13			
14	Study setting	9	Description of study settings (eg, community clinic,
15			academic hospital) and list of countries where data will
16			be collected. Reference to where list of study sites can
17			be obtained
18			
19	Eligibility	10	Inclusion and exclusion criteria for participants. If
20	criteria		applicable, eligibility criteria for study centres and
21			individuals who will perform the interventions (eg,
22			surgeons, psychotherapists)
23			
24			5-6, Table 1
25	Interventions	11a	Interventions for each group with sufficient detail to
26			allow replication, including how and when they will be
27			administered
28			
29			6-9, Table 2
30		11b	Criteria for discontinuing or modifying allocated
31			interventions for a given trial participant (eg, drug dose
32			change in response to harms, participant request, or
33			improving/worsening disease)
34			
35			8, 12
36		11c	Strategies to improve adherence to intervention
37			protocols, and any procedures for monitoring adherence
38			(eg, drug tablet return, laboratory tests)
39			
40			8, 9
41		11d	Relevant concomitant care and interventions that are
42			permitted or prohibited during the trial
43			
44	Outcomes	12	Primary, secondary, and other outcomes, including the
45			specific measurement variable (eg, systolic blood
46			pressure), analysis metric (eg, change from baseline,
47			final value, time to event), method of aggregation (eg,
48			median, proportion), and time point for each outcome.
49			Explanation of the clinical relevance of chosen efficacy
50			and harm outcomes is strongly recommended
51			
52			Table 1
53	Participant	13	Time schedule of enrolment, interventions (including
54	timeline		any run-ins and washouts), assessments, and visits for
55			participants. A schematic diagram is highly
56			recommended (see Figure)
57			
58			4, Table 2,
59			Figure 1
60			(schema)

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-10, Table 2
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2		18b	Plans to promote participant retention and complete	11-12
3			follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate	
5			from intervention protocols	
6				
7	Data	19	Plans for data entry, coding, security, and storage,	10
8	management		including any related processes to promote data quality	
9			(eg, double data entry; range checks for data values).	
10			Reference to where details of data management	
11			procedures can be found, if not in the protocol	
12				
13				
14	Statistical	20a	Statistical methods for analysing primary and secondary	10-11
15	methods		outcomes. Reference to where other details of the	
16			statistical analysis plan can be found, if not in the	
17			protocol	
18				
19				
20		20b	Methods for any additional analyses (eg, subgroup and	11
21			adjusted analyses)	
22				
23		20c	Definition of analysis population relating to protocol non-	11-12
24			adherence (eg, as randomised analysis), and any	
25			statistical methods to handle missing data (eg, multiple	
26			imputation)	
27				
28				
29	Methods: Monitoring			
30				
31	Data	21a	Composition of data monitoring committee (DMC);	12
32	monitoring		summary of its role and reporting structure; statement of	
33			whether it is independent from the sponsor and	
34			competing interests; and reference to where further	
35			details about its charter can be found, if not in the	
36			protocol. Alternatively, an explanation of why a DMC is	
37			not needed	
38				
39				
40		21b	Description of any interim analyses and stopping	12
41			guidelines, including who will have access to these	
42			interim results and make the final decision to terminate	
43			the trial	
44				
45				
46	Harms	22	Plans for collecting, assessing, reporting, and managing	11
47			solicited and spontaneously reported adverse events	
48			and other unintended effects of trial interventions or trial	
49			conduct	
50				
51				
52	Auditing	23	Frequency and procedures for auditing trial conduct, if	N/A
53			any, and whether the process will be independent from	
54			investigators and the sponsor	
55				
56				
57	Ethics and dissemination			
58				
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60				

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2	Research	24	Plans for seeking research ethics	13
3	ethics		committee/institutional review board (REC/IRB)	
4	approval		approval	
5				
6	Protocol	25	Plans for communicating important protocol	13
7	amendments		modifications (eg, changes to eligibility criteria,	
8			outcomes, analyses) to relevant parties (eg,	
9			investigators, REC/IRBs, trial participants, trial	
10			registries, journals, regulators)	
11				
12				
13	Consent or	26a	Who will obtain informed consent or assent from	13
14	assent		potential trial participants or authorised surrogates, and	
15			how (see Item 32)	
16				
17				
18		26b	Additional consent provisions for collection and use of	Supplementa
19			participant data and biological specimens in ancillary	ry file 2
20			studies, if applicable	(Consent
21				Form)
22				
23	Confidentialit	27	How personal information about potential and enrolled	13
24	y		participants will be collected, shared, and maintained in	
25			order to protect confidentiality before, during, and after	
26			the trial	
27				
28				
29	Declaration	28	Financial and other competing interests for principal	14
30	of interests		investigators for the overall trial and each study site	
31				
32	Access to	29	Statement of who will have access to the final trial	14
33	data		dataset, and disclosure of contractual agreements that	
34			limit such access for investigators	
35				
36				
37	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and	N/A
38	post-trial		for compensation to those who suffer harm from trial	
39	care		participation	
40				
41	Disseminatio	31a	Plans for investigators and sponsor to communicate trial	2, 13, 14
42	n policy		results to participants, healthcare professionals, the	
43			public, and other relevant groups (eg, via publication,	
44			reporting in results databases, or other data sharing	
45			arrangements), including any publication restrictions	
46				
47				
48		31b	Authorship eligibility guidelines and any intended use of	N/A
49			professional writers	
50				
51		31c	Plans, if any, for granting public access to the full	14
52			protocol, participant-level dataset, and statistical code	
53				
54				
55	Appendices			
56				
57				
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2	Informed	32	Model consent form and other related documentation	Supplementa
3	consent		given to participants and authorised surrogates	ry file 2
4	materials			(Consent
5				Form)
6				
7	Biological	33	Plans for collection, laboratory evaluation, and storage	Supplementa
8	specimens		of biological specimens for genetic or molecular	ry file 2
9			analysis in the current trial and for future use in ancillary	(Consent
10			studies, if applicable	Form)
11				
12				

13 *It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013
 14 Explanation & Elaboration for important clarification on the items. Amendments to the
 15 protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT
 16 Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)"
 17 license.
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BMJ Open

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

Journal:	<i>BMJ Open</i>
Manuscript ID	bmjopen-2022-063613.R2
Article Type:	Protocol
Date Submitted by the Author:	02-Sep-2022
Complete List of Authors:	<p>Pike, Chelsea ; Massachusetts General Hospital Department of Psychiatry; Athinoula A Martinos Center for Biomedical Imaging Kim, Minhae; Athinoula A Martinos Center for Biomedical Imaging Schnitzer, Kristina ; Massachusetts General Hospital Department of Psychiatry; Harvard Medical School Mercaldo, Nathaniel; Harvard Medical School; Massachusetts General Hospital Department of Radiology Edwards, Robert; Brigham and Women's Hospital, Anesthesiology Napadow, Vitaly; Athinoula A Martinos Center for Biomedical Imaging; Spaulding Rehabilitation Hospital, Department of Physical Medicine and Rehabilitation Zhang, Yi; Massachusetts General Hospital Department of Anesthesia Critical Care and Pain Medicine Morrissey, Erin; Athinoula A Martinos Center for Biomedical Imaging Alshelh, Zeynab; Athinoula A Martinos Center for Biomedical Imaging; Harvard Medical School Evins, Anne; Massachusetts General Hospital Department of Psychiatry; Harvard Medical School Loggia, Marco; Athinoula A Martinos Center for Biomedical Imaging; Harvard Medical School Gilman, Jodi; Massachusetts General Hospital Department of Psychiatry, Psychiatry</p>
Primary Subject Heading:	Radiology and imaging
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	Back pain < ORTHOPAEDIC & TRAUMA SURGERY, Magnetic resonance imaging < RADIOLOGY & IMAGING, Clinical trials < THERAPEUTICS, PAIN MANAGEMENT, NEUROPHYSIOLOGY

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Manuscripts

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3 **Study protocol for a phase II, double-blind, randomized controlled trial of cannabidiol**
4 **(CBD) compared to placebo for reduction of brain neuroinflammation in adults with**
5 **chronic low back pain**
6
7

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33 Word Count: 3,585
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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 neuro-glial interactions play a role in the establishment and maintenance of pain. Recently, we used positron emission tomography (PET) to demonstrate increased levels of 18kDa 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 to placebo, affects neuroinflammation, as measured by TSPO levels.

Methods and analysis: This is a double-blind, randomized, placebo-controlled, phase II clinical trial. Eighty adults (aged 18-75) with cLBP for >6 months will be randomized 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/magnetic resonance imaging (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 randomized to CBD will demonstrate larger reductions in thalamic [¹¹C]PBR28 signal compared to 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 (NCT04827992). 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, randomized, placebo-controlled clinical trials to evaluate a pain intervention using PET.
- This is the first trial to assess whether 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.

INTRODUCTION

Chronic pain affects an estimated 50 to 100 million individuals in the United States[1, 2] and is among the most debilitating medical conditions with profound physical, emotional, and economic costs.[3] Available treatment options including interventional techniques[4] and non-opioid pain medications such as non-steroidal anti-inflammatory drugs[5] 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 neuro-glial 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 sensitize pain pathways[39] in a “pain-produces-pain” loop. Importantly, agents that disrupt glial function inhibit or attenuate various behavioral markers of pain hypersensitivity (e.g., 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 18kDa translocator protein (TSPO), a marker of glial activation,[16, 42-50] in the brains[51] and spinal cords[52] of patients with chronic low back pain (cLBP) compared to controls. These TSPO signal elevations were consistently observed, particularly in the thalamus, in our original study[51] 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) receptors,[58] 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 pre-clinical 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 pro-inflammatory 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

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

19 This study will also assess the role of CBD on neuroinflammation with respect to
20 depressive symptoms. Comorbid depression and chronic pain is common, with approximately
21 40% of cLBP patients also exhibiting negative affect, including depressive symptoms.[78-81]
22 Depression has been associated with neurobiological changes, including neurotransmitter
23 deficits, endocrine disturbances, and impaired neural adaptation and plasticity,[82, 83] and
24 neuroinflammation may be implicated in these abnormalities.[84] Those with depression who
25 commit suicide have shown dramatically increased microglial activation.[85] Indeed, cLBP
26 patients who also have comorbid depression demonstrate, in addition to thalamic TSPO signal
27 elevations observed irrespectively of depression status, also TSPO signal elevations in limbic
28 regions, which are proportional to the scores on the Beck Depression Inventory.[86] Meta-
29 analyses have shown that mechanistically diverse anti-inflammatory agents may be effective
30 treatments for depression.[87-89] Preliminary evidence suggests that CBD promotes
31 antidepressant effects in animal models,[67, 68] however randomized clinical trials of CBD for
32 treatment of depression have not been conducted. Therefore, a secondary objective of the study
33 is to assess whether CBD compared to placebo reduces depressive symptomatology and
34 depression-related neuroinflammation in patients with cLBP.

38 Healthcare providers are increasingly interacting with patients who are interested in using
39 CBD for various pain disorders, with little evidence available for therapeutic guidance. Results
40 from this study will provide critical information regarding the potential utility of CBD for cLBP
41 and its involvement in mechanistic pathways of neuroinflammation.

43 METHODS AND ANALYSIS

44 The full protocol is included as supplementary information (see Supplementary File 1).

47 Study design

48 This is a phase II, double-blind, randomized, placebo-controlled 4-week clinical trial with
49 a 6-week follow-up assessment. The principal goals of this trial are to assess the effects of CBD
50 on neuroinflammation, pain and depressive symptomatology, in participants with cLBP.
51 Neuroinflammation will be quantified with PET/MRI scans using [¹¹C]PBR28, a second
52 generation ligand for TSPO. Participants will continue their usual pain care regimen during the
53 study. This trial is being conducted at Massachusetts General Hospital in the United States. The
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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 to 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 six 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]PBR28[90]; 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 four weeks prior to randomization.

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 two weeks, or regular recreational drug use in the previous three months. See Table 1 for the full list of inclusion and exclusion criteria.

Table 1. Inclusion and exclusion criteria

Inclusion Criteria	<ol style="list-style-type: none"> 1. Age \geq 18 and \leq 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 behavioral) for the previous four 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 only if the conditions were so severe as to require hospitalization 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 hospitalization
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 (e.g., peripheral edema)
16. Use of immunosuppressive medications, such as prednisone, 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 individualized basis with a physician:
 - Strong and moderate inhibitors of CYP3A4 and CYP2C19 (e.g., diltiazem, erythromycin, fluoxetine)
 - Sensitive and moderately sensitive substrates of CYP2C19, CYP1A2, CYP2B6, CYP2C8, CYP2C9, UGT1A9, and UGT2B7 (e.g., omeprazole, bupropion, morphine, lamotrigine)
21. CNS depressants including antipsychotics, benzodiazepines (except for alprazolam, clonazepam, and lorazepam, which have low binding affinity to TSPO[93-97]), 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 behavior 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 (e.g., unable to reliably rate pain, unlikely to remain still during the imaging procedures)

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 Supplementary File 2 for a copy of the consent form). Eligibility assessments will be conducted during the screening visit, listed in Table 2.

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						
	Characterization 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

Investigational product

Participants will be randomized 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 flavoring. 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 twice daily in week one, 5 mg/kg twice daily in week two, 7.5 mg/kg twice daily in week three, and 10 mg/kg twice daily in week four. If participants report significant adverse events (e.g., 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.

Randomization and treatment allocation

Eligible participants will be enrolled by study staff and randomized to receive either CBD or placebo. Stratified simple random sampling, based on age (>50 vs. ≤50) and sex (male vs. female), will be performed. Randomization sheets have been developed by the study biostatistician and will be used by a study pharmacist to assign treatments. The MGH Clinical Trial 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 randomization, 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 four 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. Adverse events will be assessed at baseline and weeks 1, 2, 3, 4, and 6 (two 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. 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

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3 performed, and female participants of childbearing potential will have blood drawn to perform a
4 serum pregnancy test.

5
6 At the beginning of the scan sessions, an intravenous catheter will be placed in the
7 participant's antecubital vein of the left or right arm. Blood will be drawn to assess quantitative
8 levels of cannabinoids, including CBD and THC. An arterial line will be placed in a radial artery
9 with local anesthesia if the participant has consented to this (optional) procedure and has no
10 contraindications. The arterial line will be placed in the arm contralateral to the intravenous line
11 that is used for the [¹¹C]PBR28 radiotracer injection, and will enable blood sampling at various
12 times during the imaging study for at most 160 mL of blood. The collected arterial blood will be
13 used to compute metabolite-corrected arterial input function for kinetic modeling analyses. Brain
14 PET/MRI data will be acquired for approximately 90 min post-injection. Between 90- and 110-
15 min post-injection, we may acquire spinal cord data from the thoracic and upper lumbar spine
16 and evaluate the signal from the most caudal segments of the spinal cord, as this region also
17 demonstrated neuroinflammation in our prior study of patients with lumbar radiculopathy.[52]

18
19 Our primary metric for brain [¹¹C]PBR28 signal quantification will be standardized
20 uptake value ratio (SUVR), using the whole brain as a normalizing factor (as described in prior
21 work[51, 53, 98]). In patients with arterial blood data available, we will compute distribution
22 volume (V_T) and ratio of distribution volume (DVR), which will be used as secondary outcome
23 measures and to support the use of SUVR as an outcome metric. For spinal cord analyses, signal
24 will be quantified by normalizing the signal from the lowest 1-2 spinal segments present in the
25 field of view for most/all of our participants (e.g., T11-L1) with that of the uppermost 2-3
26 segments (e.g., T7-T9) as in Albrecht et al.[52]

27
28 In addition to PET scans, other neuroimaging measures (Diffusion Tensor Imaging (DTI),
29 BOLD resting-state functional connectivity, ¹H-magnetic resonance spectroscopy (MRS), and
30 arterial spin labelling (ASL)) measures will be collected. We will also collect fMRI measures
31 during a reward task (Monetary Incentive Delay Task, MID[99]). We have previously used this
32 task to demonstrate striatal hypofunction, linked to depressive symptoms and anhedonia, in
33 cLBP patients.[100]

34 35 36 37 **Daily surveys**

38 Beginning two weeks before the first scan to week 6, participants will complete online
39 daily surveys assessing various domains, including their clinical pain ratings (as measured by the
40 "worst pain" item of the Brief Pain Inventory – Short Form, BPI-SF[98]), pain bothersomeness
41 ratings, and depression ratings, each on a 0-10 scale. Participants will be asked to confirm daily
42 medication adherence and will be asked about use of additional medications for pain
43 management.
44

45 46 **Data management**

47 Data will be collected and entered by study staff into a REDCap database,[101] which
48 has been designed and completed by the study team. Data obtained during assessments
49 administered by study staff will be entered by study staff. Following each visit, data will be
50 checked by the data manager and/or research coordinator to ensure data quality and
51 completeness. All PET/MRI scans will undergo standard quality control to look for imaging
52 artifacts. For instance, any participant whose scan shows excessive head movement (e.g.,
53 between-frame motion that cannot be easily corrected in post-processing) or issues with
54 attenuation correction that cannot be remediated via postprocessing will be excluded from final
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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 generalized linear mixed-effects model (GLMM) will be used to quantify the association between thalamic [¹¹C]PBR28 PET signal, treatment assignment at randomization (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 (e.g., age, depression severity, sex). Data dependencies will be accounted for using either random intercept or line (intercept and slope) parametrizations. 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 modeling 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 summarize 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.[102] Since we are randomizing 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 randomization, there are imbalances between groups, we will adjust for potential confounding variables using directed acyclic graphs (DAGs) to determine which confounders may be an issue, and will control for these variables.

Outcome measures

Box 1. Outcome measures

Primary outcome measure

1. 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 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-II[103])*
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 catastrophizing (Pain Catastrophizing Scale, PCS[104])*
3. Neuropathic pain (PainDETECT[105])*
4. Disability related to low back pain (Oswestry Disability Index, ODI[106])*
5. Widespread pain and fibromyalgia symptom severity (American College of Rheumatology's fibromyalgia survey[107])*
6. Daily depression ratings (daily survey)
7. Widespreadness of pain sensation (SymptomMapper app[108])
8. Health-related quality of life (Patient Reported Outcomes Measurement Information System – 29, PROMIS-29[109])*
9. Sleep quality (Pittsburgh Sleep Quality Index, PSQI[110])*
10. Spinal cord TSPO signal (as measured with [¹¹C]PBR28 PET)
11. Striatal activation to a reward task (Monetary Incentive Delay Task, MID[99])
12. Other neuroimaging measures (Diffusion Tensor Imaging (DTI), BOLD resting-state functional connectivity, ¹H-magnetic resonance spectroscopy (MRS) to measure brain metabolites, and arterial spin labelling (ASL))

*Total score of these measures will be used in analyses

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 standard deviations of the [¹¹C]PBR28 PET signal measures are 0.05,[111] (2) the correlation between repeated measurements ranges between 0.3 to 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 PET signal measures of at least 0.039 and 0.045, respectively (Table 3).

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

Missing data

All attempts will be made to minimize 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.[112] 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 adverse events (AEs; e.g., tiredness, decreased appetite, diarrhea), 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 adverse event (SAE) is an event that is deemed life-threatening, requires hospitalization, causes permanent damage or requires medical intervention to prevent permanent damage, or results in death. Reporting and handling of adverse events 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 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 Supplementary 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 adverse events 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 adverse events. The DSMB will comment on the outcomes of the event and, in the case of a serious adverse event, determine the relationship to participation in the study.

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3 Interim analyses will be performed on study data only when requested by the DSMB to
4 assess the safety and efficacy of the ongoing study. The results of these analyses will be made
5 available to the IRB and NIDA in accordance with annual reporting requirements or sooner if
6 necessary.
7

8 9 **Early termination of the trial**

10 The DSMB will monitor the occurrence of all adverse events on a quarterly basis to
11 ensure that their rate and severity are acceptable within the overall risk/benefit ratio of the study.
12

13 14 **Withdrawal from the study**

15 Participation in this study is voluntary and individuals may choose to stop participation at
16 any time. Participants will be told at consent to inform study staff if they wish to stop taking the
17 study drug at any point, and reasons for withdrawal will be documented. Those who choose to
18 stop taking the study drug will be asked to continue to follow the schedule of visits if they are
19 willing. The study physician may also withdraw a participant from the study without their
20 permission if they cannot follow the study plan, or for medical reasons such as side effects from
21 the study drug.
22

23 24 **Confidentiality**

25 Study staff will adhere to the confidentiality requirements set by the Massachusetts
26 General Brigham Human Research Committee. Data on computers will be password-protected,
27 and all paper records are secured in a locked office. Any samples that are stored will be labeled
28 with a code; no names or other identifying information will be on these samples.
29

30 31 **Patient and public involvement**

32 Neither patients nor the public were involved in the development, design, and conduct of
33 this study. Results of the study will be shared with the public through conference presentations
34 and publications in peer-reviewed journals.
35

36 37 **ETHICS AND DISSEMINATION**

38 This protocol is approved by the Massachusetts General Brigham Human Research
39 Committee (Protocol Number: 2021P002617) and the United States Food and Drug
40 Administration (IND Number: 143861). Informed consent will be obtained from all participants
41 by a physician, nurse practitioner, or the principal investigator. Important protocol modifications
42 will be submitted to the Human Research Committee for approval and then communicated to
43 participants. Findings from this trial will be presented in peer-reviewed journals and at national
44 conferences. Data will be deidentified in all cases.
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3 **Authors' contributions:** JMG and ML developed and designed the trial and obtained funding
4 for the trial. CKP and MK wrote the first draft of this manuscript. JMG, ML, KS, RE, VN, YZ,
5 ZA, AEE, CKP, and MK assisted with the study design. NM designed the statistical aspects of
6 this protocol. JMG, ML, CKP, MK, KS, NM, RE, VN, YZ, EJM, ZA, and AEE were involved in
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8
9

10
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21 monitoring board of Karuna Pharmaceuticals outside the submitted work. Dr. Napadow consults
22 for Cala Health, Inc. and Click Therapeutics, Inc. All other authors declare that they have no
23 competing interests.
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27 **Data sharing statement:** All data, code, and materials used in the analyses can be provided by
28 Jodi Gilman and Marco Loggia and Massachusetts General Hospital pending scientific review
29 and a completed data use agreement/material transfer agreement beginning one year after
30 publication of the results. Requests for all materials should be submitted to Jodi Gilman at
31 jgilman1@mgh.harvard.edu or Marco Loggia at marco.loggia@mgh.harvard.edu.
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35 **Ethics approval:** Massachusetts General Brigham IRB Protocol Number 2021P002617.
36 Protocol version 6.0 (dated March 16, 2022) is currently in use.
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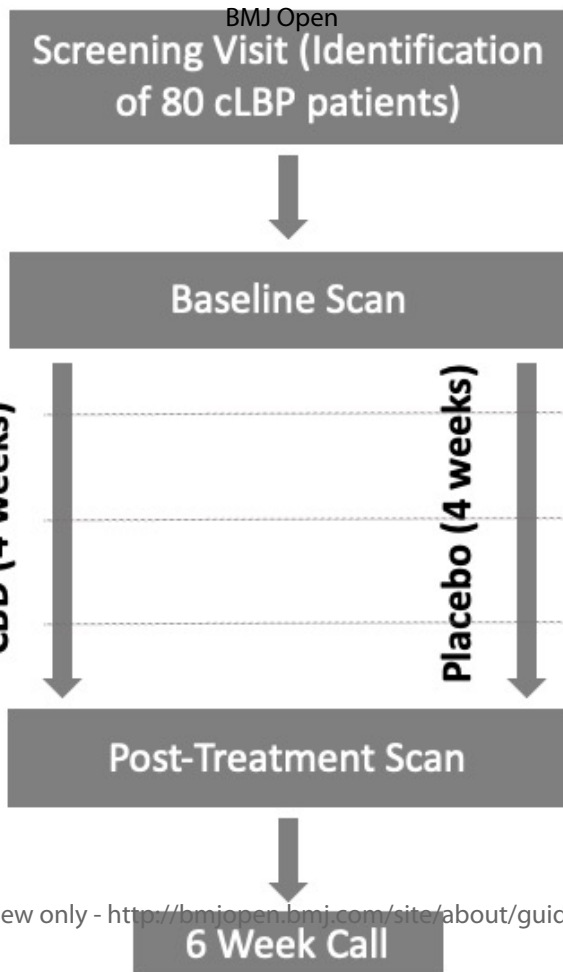
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Figure Legends
Figure 1. Study schema

For peer review only

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**Daily Surveys (~2 weeks before
Baseline Scan to ~6 Week Call**



CBD (4 weeks)

Placebo (4 weeks)

1 Week Call

2 Week Visit

3 Week Call

Institutional Review Board Intervention/Interaction Detailed Protocol

Principal Investigator: Jodi Gilman, PhD

Project Title: Evaluation of Cannabidiol (CBD) for Reduction of Brain Neuroinflammation

Version Date: 3/16/2022

For Intervention/Interaction studies, submit a Detailed Protocol that includes the following sections. If information in a particular section is not applicable, omit and include the other relevant information.

1. Background and Significance

Millions of individuals suffer from chronic pain

Chronic pain is defined as pain without apparent biological value that has persisted beyond the normal tissue healing time (usually taken to be 3 or 6 months^{1,2}). Chronic pain is a widespread public health issue³, and its prevalence is enormous. The weighted mean prevalence of chronic pain in the general population has been estimated by some at 35.5%, or 105 million, in the United States⁴. Not only does chronic pain affect both physical and mental functioning, thus compromising quality of life; it is also associated with astronomical costs. In addition to the direct costs of treating pain—including health care for diagnosis and treatment, drugs, therapies, and other medical expenses—chronic pain results in lost work time and reduced productivity^{5,6}. Past estimates of the annual cost of chronic pain in the United States, including healthcare expenses, lost income and productivity, were close to \$100 billion⁷.

Treatment for chronic pain is unsatisfactory

Despite the enormity of the phenomenon, clinical needs for chronic pain are largely unmet. The treatment of choice for the largest majority (as many as 90%⁸) of patients seeking chronic pain management is based on opioid analgesics. However, the evidence supporting long-term effectiveness of opioid drugs in relieving pain and improving functional status is weak⁹. For instance, despite the widespread use of opioids for palliative care, more than half of all hospitalized patients experience pain in the last days of their lives, and 50-75% of cancer patients die in moderate to severe pain¹⁰.

The current opioid-based pharmacological approaches to treat chronic pain are not only ineffective, but they generally have multiple unpleasant side effects, including constipation, pruritus, respiratory depression, nausea, vomiting, hyperalgesia, dizziness, sedation⁹, as well as abuse and dependence^{8,11,12}. Taken together, the unsatisfactory treatment efficacy and the occurrence of significant side effects, clearly stress the importance of achieving a deeper

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understanding of the pathophysiological mechanisms underlying chronic pain, in order to eventually identify viable treatment options alternative to ones currently available.

Microglia and pain

One of the reasons for the poor efficacy of the treatment options currently available for chronic pain might be that these are primarily aimed at suppressing neuronal activity within nociceptive pathways of the nervous system. However, it is now increasingly clear that neurons are far from being the only players that drive the establishment and/or maintenance of clinical pain symptoms. Rather, evidence from animal studies now suggests a central role of glial cells in the nervous system, including microglia^{13,14}.

Microglia are a subpopulation of macrophages that rapidly activate in response to a variety of pathological conditions¹⁵, including persistent pain¹⁶⁻²³. Microglial activation (MA) is characterized by a stereotypic pattern of cellular responses, including specific morphological changes, proliferation, increased or de-novo expression of cell surface markers or receptors, and migration to the site of injury²⁴. MA generally represents an adaptive homeostatic defense response which enables the destruction of invading micro-organisms, the removal of potentially deleterious debris as well the promotion of tissue repair. However, animal studies have now showed that the uncontrolled activation of microglial cells under pathological pain conditions induces the release of substances that can sensitize pain pathways, such as proinflammatory cytokines, complement components, and others²⁵. While evidence of pain-related MA was originally observed in the spinal cord, more recently it was also discovered at the level of the brain, including in the rostral ventromedial medulla^{20,26}, the trigeminal nuclear complex^{19,27}, and the ventral posterolateral nucleus of the thalamus^{28,29}.

While most of the evidence on the occurrence of pain-related glial responses in the central nervous system comes from animal studies, a few important observations indicate that similar phenomena should occur also in humans¹³. First, immunohistochemical markers of microglial and astroglial activation have been detected in the spinal cord of a patient with chronic regional pain syndrome in a postmortem study³⁰. Furthermore, an increase in the concentration of the glial marker s-100 β was reported in the cerebrospinal fluid of patients with lumbar disc herniation and in the serum of children with recurrent headaches^{31,32}. Finally, a positron emission tomography (PET) study has revealed that human subjects with neuropathic pain secondary to peripheral nerve damage express increased thalamic binding for [¹¹C](R)-PK11195³³, an in vivo marker of microglial cell activation^{34,35}.

Recently, Co-PI Dr. Marco Loggia has also shown that patients with chronic low back pain (cLBP) have increased brain levels of the 18kDa translocator protein (TSPO), a marker of glial activation³⁶. In addition, preliminary data collected from a different cohort of patients with cLBP and sciatica suggest an increase in spinal cord TSPO levels. Together, these results suggest that human chronic pain conditions are likely to be associated with a glial reaction, both in the spinal cord, as well as in the brain.

Cannabidiol and pain

There is a growing body of evidence to suggest that cannabinoids are beneficial for a range of clinical conditions, including pain, inflammation, epilepsy, and sleep disorders³⁷. A large body of

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preclinical and clinical research indicates that the cannabinoid system modulates a broad range of physiological processes and behaviors including, but not limited to, pain, mood, appetite, neuronal activity, memory, immunity, and cell development. The endocannabinoid system's contribution to the regulation of such a variety of processes makes phytocannabinoid pharmacological modulation a promising therapeutic strategy³⁸.

The primary cannabinoids found in the cannabis plant include delta-9 -tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN), with THC being the primary psychoactive compound. The second most abundant compound in the plant is CBD, which is minimally psychoactive³⁹. Cannabinoid receptor type 1 (CB1) and type 2 (CB2) belong to a family of seven transmembrane Guanosine Binding Protein-Coupled Receptors, and are widely expressed and distinguished by their specific functions, localization and signaling mechanisms. The psychotropic effects of cannabis are principally mediated by CB1, which is widely distributed throughout the brain, while CB2 is considered the peripheral cannabinoid receptor, found mainly in immune cells, as well as in chondrocytes, osteocytes and fibroblasts. Agonists targeting CB2 receptors have been proposed as therapies for the treatment or management of a range of painful conditions, including acute pain, chronic inflammatory pain, and neuropathic pain⁴⁰. In a preclinical model, researchers showed that stimulation of CB2 suppresses microglial activation⁴¹.

In the current study, we will test whether CBD is a glial inhibitor in patients with chronic lower back pain (cLBP) with and without mild-to-moderate depression. CBD was recently FDA-approved as a liquid formulation (see EPIDIOLEX package insert) for epilepsy for children ages 2 and up as well as adults, demonstrating significant reductions in total seizure frequency with minimal side effects. It is unclear whether cannabidiol reduces glial activation in humans. We will study 80 patients diagnosed with chronic low back pain (pain duration > 6 months) longitudinally before and after 4 weeks of treatment with cannabidiol or placebo. Endpoints will be pain scores as well as brain levels of the 18kDa translocator protein (TSPO), a marker of glial activation³⁶.

2. Specific Aims and Objectives

Primary Aim: Assess whether CBD compared to placebo reduces pain-related neuroinflammation in patients with cLBP.

Hypothesis 1: Patients in the CBD arm will demonstrate significantly larger treatment-related reductions in thalamic [¹¹C]PBR28 PET signal, compared to patients in the placebo arm.

Hypothesis 2: In the CBD arm, reductions in thalamic [¹¹C]PBR28 PET signal will be directly proportional to reductions in clinical pain ratings.

Aim 2: Assess whether CBD compared to placebo reduces depression-related neuroinflammation in cLBP patients.

Hypothesis 1: Patients in the CBD arm will demonstrate significantly larger treatment-related reductions in limbic (pgACC, aMCC) [¹¹C]PBR28 PET signal, compared to

patients in the placebo arm.

Hypothesis 2: In the CBD arm, reductions in pgACC/aMCC [¹¹C]PBR28 PET signal will be directly proportional to reductions in depressive symptoms, as measured using the Beck Depression Inventory-II (BDI-II).

Aim 3 (Exploratory): Assess the effect of CBD on functional reward brain circuitry.

Hypothesis 1: Patients in the CBD arm will demonstrate significantly larger treatment-related increases in striatal responses to the anticipation and consumption of rewards/losses in the Monetary Incentive Delay task, compared to patients in the placebo arm. This will be indicative of a possible normalization of striatal function⁴², which we have previously found to be dampened in cLBP (and other pain conditions).⁴³

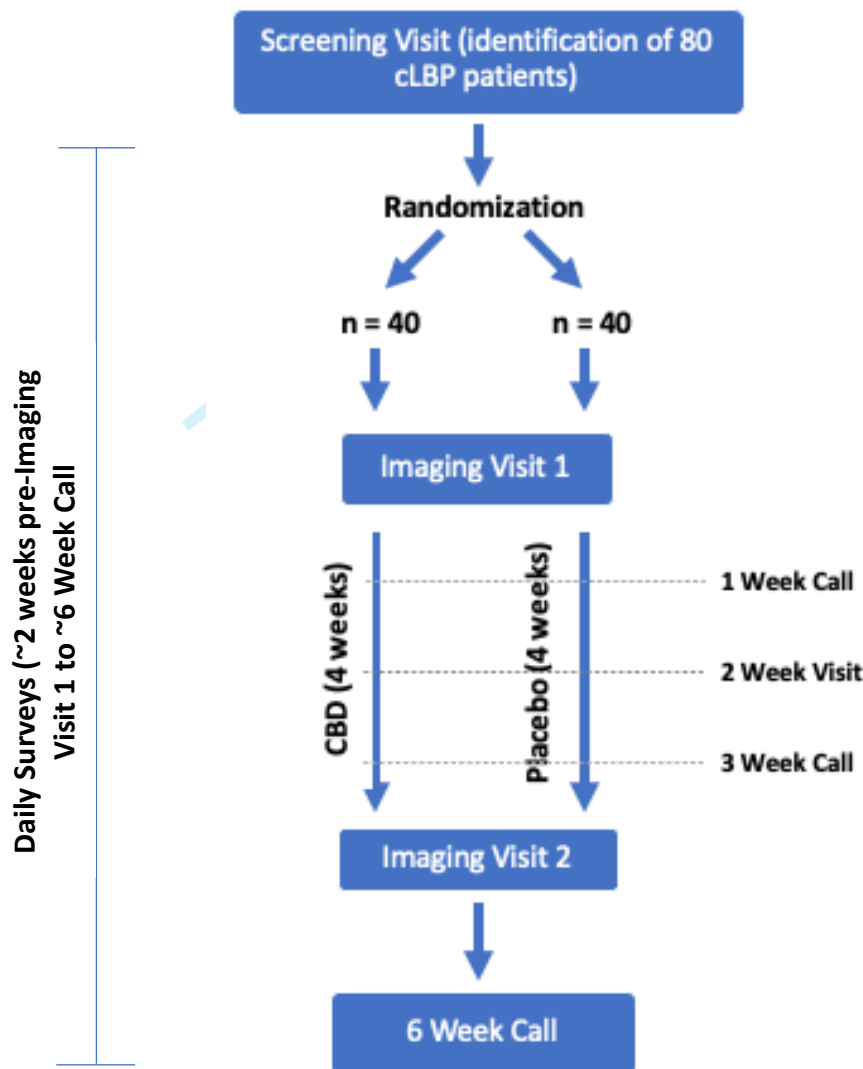
Hypothesis 2: In the CBD arm, increases in striatal activation will be proportional to increases in behavioral facilitation (i.e., slowing of reaction times during loss or rewards trials, indicative of an increase in sensitivity to incentives) and to reductions in depressive symptoms.

3. General Description of Study Design

We will conduct a 4-week randomized, double-blind, 2-arm mechanistic trial that assesses the effects of CBD vs. placebo in 80 patients with cLBP, using PET/MRI scans. Subjects will be randomized to receive either CBD ($n = 40$) or placebo ($n = 40$). Following randomization, subjects will participate in their first imaging visit, during which they will undergo a simultaneous PET/MRI scan and fill out questionnaires assessing their pain and other psychological constructs. At this visit, subjects will receive CBD or placebo, which they will be instructed to take daily for the 4 weeks prior to the date of their second scan. After 2 weeks of taking CBD or placebo, participants will undergo a follow-up appointment with a study clinician. We will also call participants at the end of the first and third weeks of taking CBD or placebo. Then, as soon as possible after the end of the 4-week drug trial period, all subjects will be scanned again and will complete several questionnaires (including some or all of those administered on the first imaging visit) to determine if any changes occurred since they entered the trial. Additionally, from about 2 weeks prior to the first scan and for 2 weeks after discontinuation of CBD or placebo, subjects will be sent a daily survey to assess the effect of the medication on their pain, mental health, sleep quality, fatigue, and other measures. Finally, we will conduct a follow-up call 2 weeks after the discontinuation of CBD or placebo.

Study Schema:

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4. Subject Selection

We plan to identify 80 patients with chronic low back pain (cLBP; i.e., with a pain duration longer than 6 months), who will complete the study. In order to achieve the final sample size of 80 study completers, we will consent up to a total of 150 participants, in order to account for screen fails and attrition. As millions of people in the United States live with chronic low back pain⁴, we believe that our recruitment goal will be attainable.

We are not planning to enroll subjects from at-risk populations (e.g., children and minors, cognitively impaired persons, prisoners). Written informed consent form will be obtained in all cases.

Inclusion Criteria:

1. Age ≥ 18 and ≤ 75 ;

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2. The ability to give written, informed consent;
3. Fluency in English;
4. Average worst daily pain of at least 4 on a 0-10 scale of pain intensity, during a typical day. Pain needs to be present for at least 50% of days during a typical week;
5. On a stable pain treatment (pharmacological or otherwise) for the previous four weeks;
6. Diagnosis of chronic low back pain, ongoing for at least 6 months prior to enrollment.

Exclusion Criteria:

1. Outpatient surgery within 2 weeks and inpatient surgery within 1 month of the time of scanning (this timeframe may be extended if they are not fully recovered from the 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 only if the conditions were so severe as to require hospitalization 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 hospitalization;
12. Major cardiac event within the past 10 years;
13. Regular use of recreational drugs in the past 3 months;
14. Any marijuana use, medical or recreational, in the past 2 weeks;
15. An abnormal physical exam (e.g., peripheral edema);
16. Use of immunosuppressive medications, such as prednisone, 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 individualized basis with a physician:
 - o Strong and moderate CYP3A4 inhibitors including boceprevir, cobicistat, conivaptan, danoprevir, elvitegravir, ritonavir, indinavir, itraconazole, ketoconazole, lopinavir, paritaprevir and ombitasvir and/or dasabuvir, posaconazole, saquinavir and telaprevir, tipranavir, clarithromycin, diltiazem, idelalisib, nefazodone, nelfinavir, troleandomycin, voriconazole, aprepitant, cimetidine, ciprofloxacin, clotrimazole, crizotinib, cyclosporine, dronedarone,

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- erythromycin, fluconazole, fluvoxamine, imatinib, tofisopam, disulfiram, and verapamil;
- Strong and moderate inhibitors of CYP2C19 including fluoxetine and ticlopidine;
 - Sensitive and moderately sensitive substrates of CYP2C19 including clobazam, lansoprazole, omeprazole, S-mephenytoin, and rabeprazole;
 - Sensitive and moderately sensitive substrates of CYP1A2 including alosetron, duloxetine, ramelteon, tasimelteon, theophylline, tizanidine, pirfenidone, and ramosetron;
 - Sensitive and moderately sensitive substrates of CYP2B6 including bupropion and efavirenz;
 - Sensitive and moderately sensitive substrates of CYP2C8 including repaglinide, montelukast, pioglitazone, and rosiglitazone;
 - Sensitive and moderately sensitive substrates of CYP2C9 including tolbutamide, celecoxib, glimepiride, and warfarin;
 - Sensitive and moderately sensitive substrates of UGT1A9 including diflunisal, propofol, and fenofibrate;
 - Sensitive and moderately sensitive substrates of UGT2B7 including, gemfibrozil, lamotrigine, and morphine;
21. CNS depressants including all antipsychotics, benzodiazepines (except for alprazolam, clonazepam, and lorazepam, which have low binding affinity to TSPO⁴⁴⁻⁴⁸), and non-benzodiazepine sleep aids that have a known unsafe reaction with CBD;
 22. Use of opioids \geq 30 mg morphine equivalents on average per month;
 23. Actively suicidal, history of suicide attempt or an aborted attempt within the last 5 years, or engagement in non-suicidal self-injurious behavior 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 from screening visit;
 27. In the opinion of the investigators, unable to safely participate in this study and/or provide reliable data (e.g., unable to reliably rate pain; unlikely to remain still during the imaging procedures, etc).

Local Recruitment Procedures:

Subjects will be recruited on an ongoing basis by trained study staff. We will identify potential subjects through advertising by flyers and printed announcements posted within as well as outside of our Partners community. In addition, email, web, and bulletin board announcements posted in the community will be used. To recruit subjects, we will also use multiple research databases such as the Partners' RSVP for Health system, Partners Clinical Trials, Rally, EPIC, RPDR, and ResearchMatch, a database of research volunteers developed by Vanderbilt University and approved for use by the PHRC. We will run queries on EPIC and RPDR through MGB to find subjects with chronic low back pain, meeting the eligibility criteria for this research study. Subjects identified through these mechanisms will receive a recruitment letter via Patient Gateway or in the mail from study staff. The letter will not be sent to those who have opted out of receiving research invitations. Other methods that advertise the study to the greater community will be used, including social media posts, posting flyers on community billboards in the Greater Boston area, emails to physicians and family medicine centers, and advertisements in newspapers. All advertisements will briefly describe the study and invite subjects to call if they

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are interested. Newspaper advertisements in particular have been shown to be an effective strategy for recruiting minority populations⁴⁹. Additionally, participants will be offered parking vouchers for each on-site study visit in order to ease financial burden of attendance.

5. Subject Enrollment

Telephone Pre-Screening:

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All subjects will undergo a telephone pre-screening that will distinguish the majority of potentially eligible subjects from those not meeting eligibility criteria. This will consist of a brief discussion of the research study, as well as confirming a potential participant's understanding of the basic study procedures and interest in participation. To determine whether he/she may meet eligibility criteria, we will ask for information including current medications, gender, age, pregnancy status, substance use, and history of psychiatric conditions. Those who are likely to be eligible will be scheduled for an in-person screening visit. Note that in addition to using office phones, any calls made to participants for phone-screening or other reasons throughout the entire study may also be placed using Doximity Dialer, an MGB-approved platform. Also note that participants who express interest in the study may be asked to complete a REDCap survey containing questions from the phone screen, instead of completing the screen via phone call.

Procedures for Obtaining Informed Consent:

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During the in-person screening visit, potential participants will be fully informed of the purpose and activities involved in the research study. Written informed consent will be obtained prior to initiating any of the study procedures. One copy of the signed consent form will be given to the patient and one will be kept in the study files for documentation. No time limits will be imposed on the informed consent process. Participants will be permitted to take as much time as they desire to engage in the informed consent process; any and all of their questions will be answered. It is anticipated that obtaining written informed consent will take approximately 15-25 minutes, on average. Comprehension of the consent information will be assessed via solicitation of answers to questions throughout the process. If comprehension appears to be limited, participants will be actively queried to determine whether they need further explanation.

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In order to comply with public health efforts to address COVID-19, virtual visits may be conducted as necessary. Virtual visits will be conducted via MGB approved platforms (i.e., video calls over Zoom and phone conferences via Cisco Jabber) and will mirror in-person visits with the identical personnel present on the call. All questionnaires typically collected during the in-person screening visit may be collected during the remote screening visit, as they are largely already completed on secure online platforms (i.e., REDCap). All screening visit study procedures may be performed during the remote screening visit, with the exception of the urine drug test, blood draw, and physical exam, and any other assessments that cannot be performed remotely, which will be performed at the first in-person visit (i.e., first imaging visit) or at an extra, separate visit prior to the first imaging visit.

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At the start of the virtual screening visit, informed consent will be obtained remotely. This will be done via electronic consent (e.g., Partners REDCap e-consent, Adobe Sign), or a remote consent process where the participant will be asked to sign the consent form and return it by email or mail. In either case, the consent discussion will occur identically to an in-person visit,

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but instead held over phone call or video conference. Following the informed consent process, a copy of the signed consent document will be provided to the patient (electronically if e-consent was used). In the case of e-consent, consent will be documented on Partners REDCap or Adobe Sign. These are equivalent to written consent and are FDA compliant. As is with in-person consent, we will obtain and document informed consent before the participant is enrolled and any study procedures begin. Note that we may also use e-consent even for in-person screening visits.

Either a physician investigator or non-physician investigator will obtain informed consent in all cases. Note that the only non-physician investigators who will be allowed to obtain informed consent are Dr. Jodi Gilman (the IND holder) and nurse practitioner study staff members.

Treatment Assignment and Randomization:

Following the screening visit, participants who meet inclusion criteria, pass exclusion criteria, and provide their signed consent will be randomized in a 1:1 ratio to receive either CBD ($n = 40$) or placebo ($n = 40$). Randomization will be performed by stratifying subjects by age (>50 vs. ≤ 50) and sex (male vs. female). Each subject will be assigned a randomization number via a computerized random number generator. The Clinical Trials Pharmacy will maintain the specific subjects' treatment assignments (CBD or placebo) for later identification. Patients and study staff will be blinded to CBD or placebo assignment.

6. Study Procedures

Individuals who express interest in participating in the study will undergo a telephone screening to assess eligibility. If they are likely to be eligible, they will be scheduled for an in-person screening visit, during which a consent procedure will be conducted and a baseline assessment of questionnaires, interviews, and laboratory assessments will be conducted. Those who meet all eligibility criteria will be randomized to the CBD or placebo group. Then, subjects will be scheduled for their first imaging visit, during which they will undergo a simultaneous PET/MRI scan. At this visit, subjects will receive CBD or placebo, which they will be instructed to take daily for the 4 weeks prior to the date of their second scan. Note that, in cases where the screening visit and the first imaging visit are more than three months apart, eligibility criteria will be re-assessed.

Table of Study Procedures:

Domain	Measure	Source	Screen	Scan I (Pre-Treatment)	1 Week Call	2 Week Visit	3 Week Call	Scan II (Post-Treatment)	6 Week Call
Demographics	Custom (PhenX-based)	Participant	x						
General Health	Physical Examination	Physician/ NP/Nurse	x						
	Medical History	Physician/ NP/Nurse	x						
	Family History	CRC	x						
	Psychological Interview (MINI)	CRC	x						
	Characterization of Pain	Physician/ NP/Nurse	x						

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	Concomitant Medications	Physician/ NP/Nurse	x	x					
	Weekly Medication Questions	CRC			x	x	x	x	x
Genetics	Oragene (CGR-500)	CRC	x						
Adverse Events	Adverse Event Record	CRC, reviewed by Physician		x	x	x	x	x	x
Depression, Psychological Functioning, Sleep	BDI-II	Participant	x	x				x	x
	BAI ^a	Participant	x						
	PROMIS-29	Participant		x				x	
	C-SSRS	Clinician	x	x		x		x	x
	CHRT ^a	Participant	x						
	MID	Done in PET/MRI scanner			x				x
Pain	PSQI	Participant	x	x				x	
	BPI-SF	Participant	x	x				x	x
	ACR FM survey	Participant		x		x		x	
	PCS	Participant		x		x		x	x
	PainDETECT	Participant		x				x	
	Oswestry	Participant		x				x	
	Symptom- Mapper	Participant		x				x	
	Daily Survey	Participant	<i>Daily from ~2 Weeks before Scan 1 until 6-Week Call</i>						
Substance Use	TLFB (MJ, EtOH, nicotine, other substances)	CRC	x						
	AUDIT ^a	Participant	x						
	CUDIT-R ^a	Participant	x						
	FTND ^a	Participant	x						
	ECDI ^a	Participant	x						
Expectancy	Next Visit/Call	Participant		x	x	x	x		
	Final Visit	Participant		x					
Quality of Life	Patient Global Impression of Change (PGIC)	Participant						x	
IQ	WRAT5	CRC	x						
Delay Discounting	MCQ ^a	Participant	x						
Impulsivity	UPPS-P ^a	Participant	x						
ADHD	ASRS ^a	Participant	x						
COVID-19	EPII ^a	Participant	x						
	COVID-19 History ^a	Participant	x						
	Vaccination Questionnaire	Participant		x					
Urine Test	Urine Drug Test	CRC	x	x				x	
	Urine Pregnancy Test	CRC	x						
Blood Test	Liver function tests	Nurse / Physician / trained study staff	x					x	
	Whole Blood DNA (Genotype	Nurse / Physician /	x	x				x	

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	& PBMC & iPSC)	trained study staff							
	Serum Pregnancy Test (if applicable)	PET Tech/Nurse		x				x	
	Serum extraction (Cytokine panel)	Nurse / Physician		x				x	
	Arterial line (optional)	Anesthesia-trained clinician		x				x	
	COVID antibody	Nurse / Physician		x				x	
	CBD/THC Metabolites in plasma	CRC		x				x	

^a Indicates a measure that may be completed by the participant at home, following the screening visit.

Study Drug:

Epidiolex, an agent within the anti-epileptic drug class, will be used. Epidiolex, Greenwich Biosciences Inc.'s CBD formulation, is a 100 mg/mL purified oral solution, dissolved in the excipients sesame oil and anhydrous ethanol with added sweetener (sucralose) and strawberry flavoring. 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% (w/w) THC. Cannabidiol is the active ingredient in Epidiolex; inactive ingredients include dehydrated alcohol, sesame seed oil, strawberry flavor, and sucralose. Of note, CBD has no psychoactive properties. The empirical formula of Epidiolex is C₂₁H₃₀O₂ and its molecular weight is 314.46. The structure of CBD is provided in the figure below.

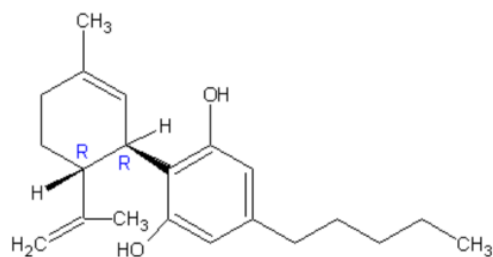


Figure 1. Cannabidiol Structure

Dose and Exposure:

Either EPIDIOLEX[®] or placebo will be dispensed by the Research Pharmacy at Massachusetts General Hospital. The recommended starting dosage is 2.5mg/kg taken twice daily. Participants will follow a titration schedule, with 2.5mg/kg taken orally twice daily in week 1, 5mg/kg twice daily in week 2, 7.5mg/kg twice daily in week 3, and 10mg/kg twice daily in week 4. Subjects will increase to 10mg/kg twice daily on the first day of the final week of the study (week 4) and take Epidiolex at this dose for the remainder of this final week. If participants report AEs (tiredness, dizziness, not tolerating the medication well) during the second, third, or fourth week of taking the study drug, the physician will decrease the dose to the previous week's dose. Participants will be treated for 4 weeks in total.

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The 4-week duration of CBD or placebo administration is proposed because in the current study, we are investigating an endophenotype of pain- neuroinflammation- which may be detectable before verbal reports of pain reduction, which is notoriously noisy and susceptible to placebo effects. This study will inform us of whether 4 weeks is enough to detect changes in TSPO binding that may precede reports of pain reduction.

Screening Visit:

Subjects eligible to participate will be recruited to participate in an approximately 3-hour characterization session. In this session, we will obtain a signed consent form from the subjects, explain the procedures involved in the experiment, and administer some or all of the following validated assessments. We will also collect detailed contact information (address, social security number, medical record number) and demographics, collect a saliva sample for genetic testing, assess medical and family history, and perform a physical examination, and assess concomitant medications. Finally, we will collect a blood sample and a urine sample. Computer-based rating scales and questionnaires will be completed on a laptop. Assessments will be performed by fully trained study staff members such as post-doctoral research fellows and Clinical Research Coordinators, under the supervision of and periodic monitoring by the Principal Investigator (PI).

During the informed consent procedure, participants will be informed about other treatment alternatives for chronic low back pain they can pursue (e.g., medications, transcutaneous nerve stimulation, physical exercise and stretching) in lieu of participation in this clinical trial.

Many of these assessments are already in use in one or more IRB approved protocols (e.g., 2011P002311). Note that participants may complete some of the following questionnaires at home after the screening visit if time does not allow for their completion during the screening visit.

History and physical examination: An MD, NP, or nurse will also collect medical history and perform a formal physical examination, including the recording of vital signs (heart rate, blood pressure, and body temperature). If these assessments are done by a nurse or NP, a physician will review them prior to prescribing the study drug.

*Beck Depression Inventory-II (BDI-II)*⁵⁰: The 21-item BDI-II has shown good reliability and validity for assessing depression in chronic pain patients⁵¹.

Brief Pain Inventory – Short Form (BPI-SF): The BPI is a 15-item questionnaire assessing pain location, and 0–10 ratings of pain intensity, relief, quality, pain-related quality of life, and function. It has been validated in cancer and noncancer pain conditions⁵².

*Timeline Followback (TLFB)*⁵³: The TLFB uses memory aids to trigger recall of substance use. It will be used to measure participants' use of cannabis, tobacco, alcohol, and other substances in the previous 90 days.

*Mini International Neuropsychiatric Interview (MINI)*⁵⁴: The MINI 7.0.2 is a structured diagnostic interview used to assess DSM-5 psychiatric disorders. It will be administered by trained study staff.

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5 *Wide Range Achievement Test, 5th Edition (WRAT5), Word Reading*⁵⁵: The word reading subset
6 of the WRAT5 will be used to assess speech and dictation.
7

8 *Monetary Choice Questionnaire (MCQ)*⁵⁶: The MCQ presents participants with 27 questions,
9 each of which asks them to choose between smaller, immediate rewards, and larger, delayed
10 rewards. Participants' patterns of answers are able to provide an estimate of their delay
11 discounting rate.
12

13
14 *Short UPPS-P Impulsive Behavior Scale*⁵⁷: The 20-item Short UPPS-P assesses five components
15 of impulsivity, including sensation seeking, lack of premeditation, lack of perseverance, negative
16 urgency, and positive urgency. Scores on many of these factors have been shown to relate to
17 risky behaviors.
18

19
20 *Beck Anxiety Inventory (BAI)*⁵⁸: The 21-item BAI assess the frequency of anxiety symptoms,
21 including both cognitive and somatic symptoms.
22

23 *Alcohol Use Disorders Identification Test (AUDIT)*⁵⁹: The AUDIT is a 10-item questionnaire
24 used to screen for harmful alcohol consumption. It assesses drinking frequency and problems
25 related to alcohol use. The scale ranges from 0 – 40; a score of 8 or higher is an indicator of
26 harmful alcohol consumption.
27

28
29 *Cannabis Use Disorders Identification Test – Revised (CUDIT-R)*⁶⁰: The CUDIT-R is an 8-item
30 questionnaire that screens for problematic cannabis use in the past six months. It assesses
31 problems related to cannabis use, dependence, and use frequency. The scale ranges from 0 – 32;
32 a score of 13 or higher is indicative of possible cannabis use disorder.
33

34
35 *Fagerstrom Test for Nicotine Dependence (FTND)*⁶¹: The 6-item FTND assesses nicotine
36 dependence. It measures amount of cigarette use, dependence on cigarettes, and compulsion to
37 use. The scale ranges from 0 – 10, with a higher score indicating greater dependence.
38

39
40 *Electronic Cigarette Dependence Index (ECDI)*⁶²: The 10-item ECDI assesses dependence on
41 electronic cigarettes. The scale ranges from 0 – 20, with scores 13 and higher indicating high
42 dependence.
43

44 *ADHD Self-Report Scale (ASRS)*⁶³: The 6-item screener scale of the ASRS will be used to assess
45 participants' ADHD symptoms, including both inattentive symptoms and hyperactive-impulsive
46 symptoms, during the past 6 months.
47

48
49 *Concise Health Risk Tracking Self-Report form (CHRT-SR)*⁶⁴: The 12-item CHRT-SR assesses
50 active suicidal ideation and behavior, perceived lack of social support, and hopelessness. The
51 scale ranges from 0 – 48, with a higher score indicating greater suicidal thoughts and
52 propensity⁶⁵.
53

54
55 *Pittsburgh Sleep Quality Index (PSQI)*⁶⁶: The PSQI is a 19-item questionnaire that assesses sleep
56 quality and patterns during the previous month. The scale ranges from 0 - 21, with a higher score
57
58

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indicating less healthy sleep quality.

*Epidemic-Pandemic Impacts Inventory (EPII)*⁶⁷: The EPII will be used to assess how the COVID-19 pandemic has impacted participants' lives, including impacts on work, home, and social life, as well as impact on emotional and physical health. It includes 92 items.

Suicidal Ideation: The Columbia-Suicide Severity Rating Scale (C-SSRS)⁶⁸ will be used for prospective suicidality assessment. C-SSRS is a tool used to assess the lifetime suicidality of a participant and to track suicidal events through the treatment. The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality. The scale will be administered by study staff at the screening visit, baseline, two-week visit, four-week visit, and six-week call. The C-SSRS "Screening/Baseline" will be collected at Screening and Baseline and the C-SSRS "since last visit" will be collected at subsequent visits. Participants who answer "yes" to any suicidal behavior questions or to suicidal ideation questions 4 or 5 on the C-SSRS during the study should be referred for appropriate psychiatric care. If there is more than a 30% increase in symptoms of anxiety or depression, this will be immediately reported to the PI, who will consult with study clinicians. Clinicians will then determine, with the participant, whether it is in their best interest to continue the medication. The decision to discontinue the participant from the study will be made by the PI in conjunction with clinical Co-Investigators.

Safety monitoring: As participant suicidality and depression is monitored throughout the study with the C-SSRS and BDI-II questionnaires, any new or worsening expression of suicidal ideation or Answers of "Yes" to questions 4 or 5 on C-SSRS throughout the study will be evaluation by a licensed clinician member of study staff. The Standard Operation Procedure will be reviewed. To summarize, if any risk for self-harm or suicidality is identified at any visit, the research coordinators will immediately report this to study clinicians, who will determine whether a safety assessment is needed. If a clinician is needed to perform a safety assessment, study staff will record the date, clinician initials, and comments related to the suicidality assessment in the REDCap C-SSRS module. Following the initial suspicion or identification of self-harm and/or suicidality, a study clinician will follow up with the participant on the current nature of their situation, querying about any new ideation, intent, and/or plan since the last visit. These clinicians, along with the PI will then determine whether a participant can safely continue the study. If the clinicians determine that the participant cannot safely continue the study, the participant will be discontinued, and will be provided with a list of resources for follow-up care.

Demographics: Demographic information, including age, sex, gender, sexual orientation, education level, income, race, height, language, employment status, marital status, and residence, as well as information about the participant's caregivers during childhood, will be collected.

DNA Collection, Saliva (optional): DNA samples will be collected using Oragene (OGR-500) saliva kits. Participants may be asked to provide a second sample if a re-collect is recommended after DNA extraction (i.e., there is very little DNA in the sample). Participants are not required to provide another sample if they do not wish to do so. Once extracted samples will be transferred to long term storage until genotyping. Samples will be stored with a unique participant ID.

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Family history: The family history subsection of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)⁶⁹ will be used to assess family history of psychiatric treatment, including treatment for depression, mania, anxiety, ADHD, schizophrenia, and substance use, as well as history of suicide.

Concomitant medications: Any prescription medications or over-the-counter drugs being taken by the participant at the time of the screening visit will be assessed, and dose and frequency will be recorded.

Blood tests: a trained member of the study staff will draw venous blood (up to 10 ml) from all subjects in order to have them genotyped for the Ala147Thr TSPO polymorphism in the *TSPO* gene (rs6971) (unless this genotype information is already available), and to check liver enzyme values. Additionally, during screening for eligibility, we will conduct routine chemistry and LFT/GGT. We will obtain serum transaminases (ALT and AST) and total bilirubin levels in all patients prior to starting treatment with CBD.

While [¹¹C]PBR28 has the advantage of binding to the TSPO protein with a higher ratio of specific-to-nonspecific binding than [¹¹C](R)PK11195⁷⁰, it also presents a potential limitation, in that about 10% of human subjects show no binding to PBR28⁷¹ (whereas [¹¹C](R)-PK11195 has never been associated with non-binding⁷²). A recent study has demonstrated that the rs6971 polymorphism predicts PBR28 binding affinity in human platelets⁷³. Since the low-affinity binder phenotype is consistent across all tissues within the same subject⁷², testing for the Ala147Thr polymorphism has been suggested to predict low affinity for [¹¹C]PBR28 in all organs, including the brain. High or Mixed affinity binders (Ala/Ala or Ala/Thr) will be considered eligible, whereas the Low affinity binders (Thr/Thr) will be considered ineligible to continue in the research study. The MGH lab responsible for genotyping typically runs the genotyping assay only twice per month, requiring that we normally schedule screening and scanning visits approximately two weeks apart.

We may also use saliva instead of blood to genotype subjects for the Ala147Thr TSPO polymorphism. Saliva genotyping may be done prior to the in-person screening visit to eliminate low affinity binders, thus saving subjects the burden of having to travel to and attend the screening visit only to find they are not eligible for the study. Verbal consent will be obtained and documented if patient-subjects agree to this saliva collection, and subjects will be asked if they wish to receive a copy of the Privacy Notice and documentation linking them to the research study. Both forms will be provided upon request. Saliva collection kits with a pre-assigned study ID and a pre-paid return mailing supply will be mailed out to applicable subjects. Eligible subjects will be scheduled for an in-person visit. If subjects are ineligible for the study based on the saliva genotyping results, they will be compensated for providing the saliva sample.

An additional 10 mL of venous blood will be collected and stored for future investigations on the roles of genetic, molecular, and cellular factors in pain disorders. This will include the future possibility to generate induced pluripotent stem cells (iPSCs) from peripheral blood mononuclear cells⁷⁴⁻⁷⁶ to assess in-vitro alterations in patient-derived neural or glial cells^{77,78}.

Urine drug test: We will also perform a urine test to screen for use of opioids and illicit drugs

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(including amphetamine, barbiturates, cocaine, marijuana, etc.). The urine drug screen will be performed during the screening visit. A rapid urine drug screening that utilizes monoclonal antibodies to detect elevated levels of specific drugs in urine, will be used for this purpose. Results will be read five minutes after the test was started.

Urine pregnancy test: Urine will be collected at screening for a pregnancy test in female participants of childbearing age.

COVID-19 History: Participants will complete a short questionnaire that asks about COVID-19, including whether they have ever been exposed, experienced symptoms, and/or tested positive. Those reporting a positive test will be asked about how severe the course of illness was, including whether they were hospitalized. All participants will be asked about vaccination status.

Note that we may also do a brief MRI test scan with participants on the day of their screening visit, or on a different day, to ensure that they are a suitable candidate for scanning.

PET/MRI Visits:

Participants eligible to continue into the study based on the screening visit and genotype analyses will be asked to participate in a first PET/MRI visit.

Prior to each scan session, subjects will complete screening checklists for MRI and PET. These checklists will ask the patients whether they have any contraindications for MRI or PET scanning. Female participants of childbearing age will be asked to have ~3mL of their blood drawn in order to perform a serum pregnancy test on the day of the scan (blood will be sent to the core lab for super stat testing). They will also be asked about the date of their last menstrual cycle. In addition, a urine drug test will be repeated on the day of each PET/MRI visit.

At the beginning of the scan session, an intravenous catheter will be placed in the participant's antecubital vein of the left or right arm, prior to going to the scanning area. Up to 15mL of blood will be drawn to assess the levels of various substances in the blood, such as the proinflammatory cytokines IL-6 and TNF-alpha. Blood will be collected in various vials (e.g., purple top K3EDTA).

Blood may also be drawn for SARS-CoV-2 antibody serology testing, and the presence of antibodies will be used to explore the possible effects of prior exposure to the coronavirus on neuroinflammation, in exploratory analyses. Up to 10 ml of blood will be drawn for this purpose. This testing will be performed through a third party vendor or through the MGH core lab.

Following procedures identical to those adopted in other PET studies (including using [¹¹C]PBR28) from our center (e.g., 2015P001594, 2013P001297, 2011P001546, 2011P002311, 2016P001009, etc), an arterial line will be placed in a radial artery with local anesthesia (20 or 18 gauge cannula, 2-5 ml of lidocaine 1% intradermal and subcutaneous) using sterile techniques, if the participant has consented to this procedure. The placement of an arterial line will be presented as optional to the participants, and we will ask for the participants' consent each time. The arterial line will not be placed if the participant has any contraindications to arterial line placement, such as Raynaud syndrome, bleeding disorder, or use of anticoagulants

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such as Coumadin, Plavix or Lovenox. The arterial line will be placed in the arm contralateral to the intravenous line that is used for the [¹¹C]PBR28 radiotracer injection. The arterial line will enable blood sampling (1mL to 12mL) 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 kinetic modeling analyses (see Data Acquisition and Analyses). The catheter will be placed by an individual with anesthesia training (i.e., board-certified anesthesiologist, fully licensed anesthesia resident, or a certified registered nurse anesthetist), monitored throughout and accessed by an experienced research nurse. The catheter will be discontinued at the end of the study by a physician, a nurse practitioner, certified registered nurse anesthetist, or registered nurse. We will have all RNs who do this sign a form attesting that discontinuing the catheter and associated post-procedure monitoring is within the scope of their work and clinical privileges.

Subjects will be instructed to remain still, with eyes open, for the total duration of the scans, except when prompted to engage in various tasks (e.g., rate pain, perform the Monetary Incentive Delay task, etc.).

During the scan visit, subjects will be asked to complete the *BPI-SF*, *BDI-II*, *C-SSRS*, and *PSQI*, which were also assessed at the screening visit. We will again assess concomitant medications. Additionally, subjects will complete some or all of the following validated assessments. Any questionnaire may be sent home with participants to complete if there is not time to complete them during the scan visit.

*Patient Reported Outcomes Measurement Information System (PROMIS-29) questionnaire*⁷⁹: The PROMIS-29 is a 29-item self-report measure assessing physical, mental, and social health.

*PainDETECT*⁸⁰: The PainDETECT is a screening questionnaire used to estimate the likelihood of a neuropathic component in chronic pain.

*The Pain Catastrophizing Scale (PCS)*⁸¹: It is a 13-item self-report scale which measures pain-related Rumination, Magnification and Helplessness.

*Oswestry Disability Index (ODI)*⁸²: The ODI is an extensively used 10-item scale to describe the level of disability in patients with chronic low back pain and will be used to characterize the study population.

SymptomMapper: The SymptomMapper app is a digital tablet-based application used to localize areas where patients are experiencing pain. In the app, the patient picks a pain descriptor, i.e., burning or shooting, notes the severity of that descriptor, and then marks where on the body that descriptor is felt. All data are stored de-identified and securely onto local drives.

*Fibromyalgia Survey*⁸³: The American College of Rheumatology's fibromyalgia survey will be used to assess widespread pain and fibromyalgia symptom severity. The widespread pain subscale ranges from 0 - 19, with a higher score indicating more widespread pain. The fibromyalgia symptom severity subscale ranges from 0 - 12, with a higher score indicating more severe symptoms.

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Treatment Expectancy: Expectancy of symptom improvement will be assessed using three statements that ask about how participants expect to feel at the end of treatment (at their last visit), as well as 3 statements about how they expect to feel at their next study visit or call. These statements will assess expected pain intensity, pain bothersomeness, and depression, and will each be scored on a 0 – 10 scale, with a higher score indicating worse symptoms.

Adverse events: Any untoward or unfavorable medical occurrence participants have experienced will be assessed, whether or not the occurrences are considered related to their participation in the research.

Vaccination Questionnaire: The date of administration and manufacturer of each COVID-19 vaccine dose the participants have received will be assessed using a brief questionnaire. Additionally, participants will be asked whether they have received any other vaccinations in the past 14 days to capture a potential acute immune response.

During the scan, participants will be asked to complete the *Monetary Incentive Delay (MID) task*. The MID task features balanced incentive delivery and analytic strategies designed to identify activity specific to anticipation or consumption of incentives. In the reward condition, successful trials are associated with monetary gains whereas unsuccessful trials lead to no change. In the loss condition, successful trials are associated with no change whereas unsuccessful trials are associated with monetary penalties.

At the end of the scan, for those participants who received an a-line, an experienced nurse or MD will remove the catheter. These subjects will be kept under observation for a minimum of 30 minutes.

The total duration of each scanning visit will be approximately 4 hours (and up to 6 hours) (~45min for preparation, ~30min for a-line placement, if applicable, ~120 min for scanning procedures, ~20-30min optional spinal scan after completion of the brain scan, and ~60min for filling out questionnaires and observation after removal of arterial line, plus an additional ~90min to perform pregnancy test in women of childbearing age). In case of equipment failure (e.g., failure in radiosynthesis) delays of > 2 hours may be possible. In this case, we will ask the participant if he or she feels comfortable with staying longer than anticipated, or will prefer reschedule to another date.

Depending on the patients' level of discomfort and time constraints, we may occasionally shorten and simplify the scan visits. For instance, if the participant would feel too uncomfortable to lay down in the scanner for the full ~2:00 hours of scanning, we may administer the radioligand in the injection room and then scan the participant between ~45 and 90 minutes post-injection. If the participant cannot remain for the full 6-hour scan visit, it will be acceptable to forego the arterial line placement. Eliminating this procedure will save the time needed for the placement and the ~30 minutes of observation needed after the removal of the a-line (from these scans we will derive metrics that do not depend on arterial sampling, such as standardized uptake value ratio (SUVR)).

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The imaging visit, including all the procedures described above, will be repeated a second time after a 4-week trial of CBD or placebo. Blood drawn at the second imaging visit will also be tested to check liver enzyme values. Also, up to 4 additional mL of blood will be drawn, and the blood plasma samples will be sent to collaborators at Clinical Research and Development facilities Department of Anesthesiology, at the University of Colorado Anschutz Medical Campus. These blood plasma samples will be analyzed for quantitative levels of cannabinoids, including CBD and THC. All analyses will be carried out following standard operation procedures, which are based on all applicable CAP, CLSI, ICH, OECD and FDA guidelines. All samples will be fully de-identified, and will not contain any identifiers that could be used to link the specimens or data to individual subjects.

Parts of the PET/MRI visits may be conducted virtually, as necessary.

Follow-up Visits/Calls:

1-Week Call. Patients will have a phone call 1 week after their first scan with a study team member. In this call, adverse events, treatment expectancy, and medication use will be assessed and participants will be reminded to increase medication dose.

2-Week Visit. Patients will undergo a follow-up appointment at Week 2 with a trained study staff member, where health, other medication use, and adverse events will be assessed, and patients will complete questionnaires and will be reminded to increase medication dose. Treatment expectancy will also be assessed. Participant may receive a ride to and from the study visit if requested. Some or all of this visit may also be conducted virtually as necessary. If there are any adverse events or issues reported during this visit, we will refer the participant to a study clinician who will get back to them.

3-Week Call. Patients will have a phone call during Week 3 with a study team member. In this call, adverse events, treatment expectancy, and medication use will be assessed and participants will be reminded to increase medication dose.

4-Week Visit. Patients will undergo a second follow-up appointment immediately after the four-week treatment period with a study clinician, where we will assess back pain, general health, adverse events, and medication use. Portions of this visit may be conducted virtually, if necessary. On the same day or as close as possible depending on scheduling, patients will be re-scanned, using identical protocols, to evaluate the hypothesis that CBD reduces glial activation. We will also repeat the questionnaires administered during the first imaging visit to assess any changes in subjective pain. We will take a small sample of blood for a follow-up liver function test. Participant may receive a ride to and from the study visit if requested.

6-Week Call. We will conduct a follow-up call 2 weeks after the discontinuation of the study medication. In this call, we will assess back pain, general health, adverse events, and medication use.

Daily Surveys:

From about 2 weeks before Scan 1 to the 6-week call, we will ask participants to complete brief daily surveys assess various domains, including their levels of pain, depression, anxiety, fatigue,

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and sleep quality on various scales (e.g., 0-10). We will also ask participants whether they have taken the study medication that day, and whether they have taken any other medications to manage their pain.

Drug Administration Protocol:

Following the behavioral visit, subjects will receive CBD or placebo. Please see “Dose and Exposure” section above for dosing and titration schedule. Participants will be treated for 4 weeks in total. Chronic CBD dosing up to 1500 mg/day has been reported to be tolerated well without AEs⁸⁴⁻⁸⁷; minor AEs were reported after CBD use in children with epilepsy being treated with multiple other medications in doses up to 25mg/kg twice daily^{88,89}. Accordingly, we believe an upper limit of 10mg/kg twice daily orally is reasonable and safe.

Continuation of medication (e.g., NSAIDS) will be permitted on the condition that patients will be on a stable dose for at least 1 month before the baseline PET/MRI scan.

The Research Pharmacy at Massachusetts General Hospital will prepare the CBD and placebo. The bottle will contain 100mg/mL of CBD or placebo. It will also have a small ID label with a batch number printed on it. The label will explain the storage conditions, the shelf life, and the in-use shelf life. Each container will be labeled with a unique number that will be recorded by study staff at the time of administration. As soon as possible after the 4-week CBD or placebo period, patients will be re-scanned and/or re-evaluated clinically to evaluate the hypothesis that CBD compared to placebo reduces glial activation and pain/depressive symptoms. Participants will be instructed to take CBD or placebo with food, rather than in a fasted state, and not to take CBD or placebo concurrently with alcohol. Participants will be instructed to return any unused CBD or placebo at the second PET/MRI visit.

GWAS Genotyping:

The Broad Institute will perform genotyping (array-based) of subject DNA samples and subsequent in-depth analysis of the data, which will allow us to detect alterations in the genome including point mutations, small insertions and deletions, chromosomal copy number alterations, and translocations. These experiments are intended to help identify candidate genes involved in the pathophysiology of neurological and psychological diseases. The molecular information generated from these samples will not be returned to subjects at any time.

Data from this study may result in communications in journals or at scientific meetings. Subjects will not be identified in those communications. To facilitate research, the genetic information generated may upon publication be deposited in protected databases (such as dbGAP) available only to bona fide researchers with specific scientific questions who promise to not try to identify individuals. The data will be sent to these banks in a coded manner and again will not contain any traditionally used identifier such as name, address, phone number, or social security number. Although we cannot predict how genetic information will be used in the future, there are many safeguards in place and we do not think that there will be further risks to patients' privacy and confidentiality by sharing such information with these banks.

The Broad Institute will not be involved in subject ascertainment. Prior to transfer of bio-specimen aliquots to the Broad Institute, samples will be re-encoded at the collaborators

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institutions. No identifying patient information will be shared with Broad scientists at any time. Some limited clinical data will be obtained from collaborators. Again, all subject identifying information will remain with the collaborators and only de-identified clinical data will be shared with the Broad Institute.

Platforms for Data Collection:

Questionnaires Collected via Research Electronic Data Capture (REDCap): Surveys will be administered via REDCap, a HIPAA compliant, web-based application hosted by Partners HealthCare designed to support data capture for research studies⁹⁰, at in-person visits (or virtual if required per COVID-19 restrictions).

Data will be stored automatically and securely on a SQL Server, accessed over industry standard TLS 256 bit RSA encryption during data transfers. Data is routinely backed up locally onto a redundancy server and stored in a separate database. Long term storage on Partners servers occurs nightly and allows for incremental backup over multiple systems. Therefore, should one drive be physically damaged, there will be multiples within the chain to replace it. Both data servers are stored within PHS IS corporate firewall, in a secure, key access facility with password-protected computers. Only vetted PHS security officials will have access to physical machines storing study data. Since data are stored on a protected server, a compromise of any individual computer at a research facility will not lead to a breach of the secure database. Individual computers designated for data capture do not store participants' identifying information or study data.

Return of Research Results:

Participants should not expect to get information about the results of the study or the results of their individual participation in the study.

Incidental Findings:

In the unlikely event that evidence of physical or psychological disorder is found, with the individual's permission, the information will be shared with his or her primary care physician who can direct care as needed.

Outcomes:

Primary Outcomes:

1. Changes in neuroinflammation in the thalamus: We will test for the presence of a significant treatment effect in the brain [¹¹C]PBR28 signal in the thalamus, in order to test whether patients in the CBD arm will demonstrate significantly larger treatment-related reductions in neuroinflammation, compared to patients in the placebo arm.
 - a. Time Frame: Change from Baseline to Week 4.

Secondary Outcomes:

1. Changes in neuroinflammation in limbic regions: We will test for the presence of a significant treatment effect in the brain [¹¹C]PBR28 in limbic regions (pgACC, aMCC), in order to test whether patients in the CBD arm will demonstrate significantly larger treatment-related reductions in neuroinflammation, compared to patients in the placebo arm.

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- a. [Time Frame: Change from Baseline to Week 4]
2. Correlation Between Reductions in Thalamic [¹¹C]PBR28 PET Signal and Reductions in Clinical Pain Ratings: We will test whether reductions in thalamic [¹¹C]PBR28 PET signal correlate with reductions in clinical pain ratings, as assessed by the "worst pain" item of the Brief Pain Inventory - Short Form. The "worst pain" item's scale ranges from 0 - 10, with a higher score indicating worse pain intensity.
 - a. [Time Frame: Change from Baseline to Week 4]
3. Correlation Between Reductions in Limbic [¹¹C]PBR28 PET Signal and Reductions in Depressive Symptoms: We will test whether reductions in pgACC/aMCC [¹¹C]PBR28 PET signal (as measured by Standardized Uptake Value Ratio) correlate with reductions in depressive symptoms, as measured by the Beck Depression Inventory-II. The Beck Depression Inventory-II scale ranges from 0 - 63, with a higher score indicating greater depression.
 - a. [Time Frame: Change from Baseline to Week 4]
4. Change in Clinical Pain Ratings: The "worst pain" item of the Brief Pain Inventory - Short Form will be used daily to assess pain intensity. The scale ranges from 0 - 10, with a higher score indicating worse pain intensity.
 - a. Time Frame: We will examine change from average score during the 7 days prior to treatment (Baseline) to average score during the final week of treatment.
5. Change in Pain Bothersomeness: Pain bothersomeness will be assessed daily on a scale from 0 - 10, with a higher score indicating greater bothersomeness.
 - a. Time Frame: We will examine change from average score during the 7 days prior to treatment (Baseline) to average score during the final week of treatment.
6. Change in Depressive Symptoms: The Beck Depression Inventory-II will be used to assess symptoms of depression. The scale ranges from 0 - 63, with a higher score indicating greater depression.
 - a. Time Frame: Change from Baseline to Week 4.
7. Patient Global Impression of Change: The Patient Global Impression of Change scale will be used to assess participants' perceptions about their global improvement related to their low back pain. The scale ranges from 0 - 7, with a higher score indicating greater overall improvement.
 - a. Time Frame: Week 4

Study Termination Criteria:

Participants will be terminated from this study if there are any significant safety concerns (e.g., actively suicidal), failure to comply with study procedures, or if the opinion of the principal investigator, can no longer safely participate. In addition, subjects will be informed that if they feel uncomfortable with the study, they can choose to terminate the study at any time. They will be informed that their refusal to participate in the study or choosing to terminate it at some point will have no effect on care and treatment received by them at MGH now or in

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future. We will also discontinue EPIDIOLEX or placebo in any patients with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN.

If a participant decides to stop participating in the study before the planned end of the study, we will ask that they continue to follow the schedule of visits. If they are unable or unwilling to return to the MGH Charlestown Navy Yard campus for visits, we will ask if we can call them for phone interviews instead of study visits.

Study Compensation:

Subjects will be paid by check at the completion of the study for their participation.

We will pay up to \$770. Payments will be as follows:

- \$75 for the initial screening visit
- Up to \$76 for completing daily surveys (\$1 per survey completed)
 - Bonus \$25 if they complete 90% of surveys
- \$200 for each PET/MRI scanning visit
- \$25 for each blood test to exclude pregnancy (for females of childbearing age)
- \$50 for each arterial line placement
- Participants will be able to earn up to an additional \$17-\$22 during each Monetary Incentive Delay task

If during the imaging visit(s) we cannot inject the subject with the radioligand (e.g., due to a failure in radiosynthesis, or to issues with the scanner) and we HAVE NOT yet placed the arterial line, he/she will receive \$50. If we cannot inject the subject with the radioligand, and we HAVE already placed the arterial line, he/she will receive \$100.

If the subject will need to stop the scan early for any reason, he/she will still receive \$50 for his/her time. Additionally, parking fees will be covered as needed.

Subjects excluded per the genotyping results of a mailed-out saliva test will receive \$15.

7. Risks and Discomforts

All subjects will undergo a telephone or email pre-screening to attempt to distinguish potential subjects from those not meeting eligibility criteria. Likely candidates will undergo a characterization and training session, which will include a clinical screening procedure. This procedure will involve answering questions about subjects' medical history recording of medical history review and answering questions about their medical situation including liver disease, kidney disease, blood disorders, heart disease, alcohol and opioid use, high blood pressure, asthma, and other respiratory disorders.

Subjects will be instructed to complete the questionnaires to the best of their ability but will have the option to leave any question(s) blank. In the unlikely event that evidence of physical or psychological disorder is found, with the individual's permission, the information will be shared with his or her primary care physician who can direct care as needed.

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PET/MRI Procedure: The U.S. Food and Drug Administration (FDA) recently gave the first regulatory clearance of a hybrid PET/MRI scanner in the U.S. Additionally, FDA considers investigations of MRI software and hardware operating within FDA specific parameters as non-significant risk device studies. All studies will adhere to these FDA approved safety levels for the Siemens system. These safety parameters include static magnetic field, time varying magnetic fields (dB/dt), specific absorption rate (SAR), and acoustic noise levels. Subjects will be informed about minimal risks of routine high magnetic field and non-ionizing RF radiation involved in MR imaging.

Subjects will also be informed about the PET procedure and the minor risks associated with exposure to radiation. Subjects will also be informed about small space within the magnet and noises made by switching gradients. Subjects will be informed that if they feel uncomfortable with the study, they can choose to terminate the study at any time. They will be informed that their refusal to participate in the study or choosing to terminate it at some point will have no effect on care and treatment received by them at MGH now or in future. The subjects will be informed that their personal information will be protected as per the HIPAA guidelines.

Intravenous catheter: An intravenous catheter will be placed for this study. The subject will feel a slight pinprick, similar to a bee sting, and may feel some discomfort and have some bruising or bleeding at the site where the needle goes in. Depending on the length of time the catheter is in place, a bruise may last for a day or so. Rarely an infection may occur at this site. If infection does occur, it will be treated.

Optional arterial line: An intra-arterial catheter will be placed by an individual with anesthesia training (i.e., board-certified anesthesiologist, fully licensed anesthesia resident, a certified registered nurse anesthetist), on the arm opposite to the radio-ligand injection line, for blood draws during the PET study. Local infection, swelling, and redness could occur at the sites of line placement, as well as temporary loss of pulse at the wrist. This area may have a bruise or feel uncomfortable for 2-3 days after the catheter is removed. The risks associated with having blood drawn include: bruising, local discomfort, or infection at the site of the needle puncture. Rarely an infection may occur at this site, and if an infection does occur, it will be treated. Inserting an arterial line (A-line) can hurt more than having a regular IV or having blood drawn with a needle. We will place the A-line under local anesthesia (i.e., lidocaine), which may cause an allergic reaction. Even if we numb the wrist area first, the insertion may still hurt. Once the A-line is in place, it usually does not hurt. About 24 hours after the beginning of the imaging procedures, we will give the subject a phone call to determine whether he or she is experiencing study related issues.

The subject may experience pain, bleeding, swelling or redness at the wrist, short loss of pulse at the wrist if blood flow in the artery is briefly stopped, damage to the artery wall or nearby nerves, or catheter breaking or falling out. There have been reports of decreased blood flow to the hand, which resulted in the need for surgery. This is very rare and has not been reported when catheters have been in place for only a few hours for research. Additionally, the insertion or removal of the A-line might cause temporary dizziness, nausea or fainting. After the anesthesiologist, anesthesia resident, certified nurse anesthetist, or registered nurse removes the

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catheter and has held pressure for several minutes, we'll ask the subject to stay for 30 minutes (up to 60 minutes based on clinical opinion of NP or registered nurse) so we can monitor him/her in order to assess the occurrence of any adverse event. Dr. Loggia will file a report on Insight within the timeframe stipulated by the IRB (5 working days/7 days) should any adverse event occur. The subject may have a bruise or feel tenderness for 2-3 days around the area where the catheter was placed. We will instruct the subject to avoid lifting anything heavier than a small bag of flour for a day. We will instruct the subject to call us if bleeding occurs after the subject leaves (rare), and/or if the wrist area is painful or red or swollen. About 24 hours after the beginning of the imaging procedures, we will give the subject a phone call to determine whether he or she is experiencing study related issues.

Radiation exposure: The radiation exposure in this study will be small and there is no evidence that it represents a major health risk. If subjects have participated in other research studies in the past 12 months that have involved radiation exposure, they will be asked to inform the investigators or study staff (by writing initials on the consent form verifying that they have not been exposed to other radiation in the past 12 months). If it is determined that their prior radiation exposure exceeds our current guidelines, they may not be allowed to participate in this study.

We will use [¹¹C]PBR28 produced by the cyclotron/radiochemistry/radiopharmacy facility at the A. A. Martinos Center for Biomedical Imaging. The Martinos Center has studied several hundreds of people with this radioligand and have had no clinically detectable effects or side effects. Given the use of [¹¹C]PBR28 in a small clinical trial, we have obtained an IND from the FDA.

The IV injection will be administered by a licensed nuclear medicine technologist. Should there be an adverse event, Dr. Gilman will be responsible for communicating with the IRB within the stipulated time frame.

Imaging will be stopped should any untoward reaction be observed during the imaging session or if the participant so requests for whatever reason. Some subjects find it unpleasant or feel anxious when confined in the enclosed space of the scanner. If this happens, the study will be aborted. Patients will be required to use earplugs to decrease the noise perceived while in the scanner.

Saliva Genotyping: Although we cannot predict how genetic information will be used in the future, there are many safeguards in place and we do not think that there will be further risks to patients' privacy and confidentiality by sharing such information with these banks.

In addition, steps will be taken to protect confidentiality of genetic data as outlined:

1. All MGH study staff are trained to make confidentiality the first priority.
2. No genetic research data will be entered into the medical record.
3. The results of the genetic analyses will not be shared with participants, their family members or unauthorized third parties.
4. Genetic data are encoded using coded identifiers. These codes, rather than personal identifiers, are used in any analytic datasets. The code key linking coded identifiers to

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personal identifiers are kept in an access-restricted, password protected electronic file and are not shared with the genetics laboratories.

5. Consent forms are stored in locked cabinets apart from demographic and diagnostic data.
6. Samples and genetic data stored in the laboratory will be identified only by the code numbers and laboratory personnel will not have access to personal identifiers.
7. The most serious risk would be identification of individuals in the publicly shared database. To prevent this, computerized data files provided to other investigators will not include any of the HIPPA-defined personal identifiers. Published material will not identify subjects.

EPIDIOLEX (CBD): CBD is an FDA-approved medication used to treat epilepsy. According to the FDA briefing document on Epidiolex, dated 04/19/2018, treatment-emergent AEs in controlled trials for Lennox-Gastaut and Dravet syndromes included decreased appetite, diarrhea, irritability, somnolence, fatigue, aggression, pneumonia, rash, and hepatic symptoms, and in a very small number of patients, an increase in suicidal thoughts. Of note, AE related to hepatic function were likely due to the interaction between CBD and anti-epileptic drugs; prescription of an anti-epileptic drug is an exclusionary criterion for this proposed study. Further, CBD may produce pharmacokinetic interaction effects when taken with opioids^{91,92}. Any subjects who at baseline had elevated AST/ALT levels but still met the eligibility criteria for the study will undergo a follow-up liver function tests at 2 weeks. In addition, we will perform a liver function test in subjects who at any time point during the study develop clinical signs or symptoms suggestive of hepatic dysfunction.

Given the use of EPIDIOLEX in a small clinical trial, we have obtained an IND from the FDA.

Questionnaires: Minimal risks associated with completing questionnaires are subject fatigue and the possibility of minor psychological distress associated with answering sensitive questions regarding psychological functioning. Subjects will be instructed to complete the questionnaires to the best of their ability, but will have the option to leave any question(s) blank. In the unlikely event that evidence of physical or psychological disorder is found, with the individual's permission, the information will be shared with his or her primary care physician who can direct care as needed.

Confidentiality: As detailed, the investigators are quite careful regarding the protection of confidentiality, and multiple procedures are in place to reduce the likelihood of a breach of confidentiality. However, there is a small risk that information about subjects could become known to people outside of this study, and this risk is identified in the informed consent form.

The key investigators will meet quarterly to discuss any potential adverse event and side effects. We will involve the MGH Human Research Committee and Radiation Safety Committee if any additional potential risks arise. Adverse events and unanticipated problems involving risks to subjects or others will be reported to the PHRC in accordance with PHRC adverse event and unanticipated problems reporting guidelines, as well as FDA when appropriate.

8. Benefits

Potential benefits to participating individuals:

It is unlikely that individual subjects will benefit from taking part in this study. While this study is powered to possibly observe a statistically significant reduction in pain due to CBD, it is unclear whether the effect will be clinically meaningful.

Potential benefits to society:

Findings from these studies will help advance our understanding of the pathophysiology of pain disorders. In particular, this project will assess the role of microglia in the establishment and/or maintenance of chronic pain, and how this may be affected by CBD. As such, we envision that in the future the information obtained from the proposed research will enhance the diagnosis and management of a variety of chronic pain conditions.

9. Statistical Analysis

Data Acquisition

PET. [¹¹C]PBR28 binding will be measured on Siemens Biograph mMR, a whole-body 3T PET/MRI scanner, or a Siemens Tim Trio with a head-only PET insert. An intravenous catheter will be then placed in participants' antecubital vein to inject the radioligand. [¹¹C]PBR28 will be synthesized in-house using a procedure modified from the literature.⁹³ Up to 15 mCi of [¹¹C]PBR28 will be injected intravenously as a slow bolus over a 30s period.⁹⁴ In the first 90 minutes, PET/MRI data will be collected from the brain. Between 90- and 110-minutes post-injection the field of view may be repositioned to the thoracic and upper lumbar spine, so that spinal cord data can be acquired. Of note, while our primary PET imaging outcomes are brain-related (thalamic signal for "pain-related neuroinflammation" and pgACC/aMCC signal for "depression-related neuroinflammation"), we will also evaluate, in exploratory analyses in a subset of our participants (depending on the participant's availability or other factors), the signal from the most caudal segments of the spinal cord, as this regions also demonstrated neuroinflammation in our prior study of patients with lumbar radiculopathy.⁹⁵

For the brain data, motion correction will be applied using MRI-derived motion estimates for each individual frame.⁹⁶ For the spinal cord data, frame-by-frame motion correction will be implemented using the Spinal Cord Toolbox.⁹⁷ The head attenuation map (μ -map) will be obtained using a recently implemented MR-based attenuation correction method.⁹⁸ The μ -map for the spinal data will be collected using the Dixon-VIBE sequence and using in-house developed software to additionally segment the bone.⁹⁵

[¹¹C]PBR28 brain uptake will be measured voxelwise as Standardized Uptake Values ratio (SUVr), Volume of distribution (V_T), V_T ratio (DVR) and/or other commonly adopted metrics. In humans, SUV ratio (SUVr) estimation of [¹¹C]PBR28 binding has been used to reliably distinguish healthy volunteers from patients with Alzheimer's disease⁹⁹ as well in our own studies with chronic low back pain³⁶, and amyotrophic lateral sclerosis¹⁰⁰. Additionally, human and animal studies indicate SUV/SUVr estimates are less variable compared to blood-derived methods^{99,101}. These results suggest that SUVr estimation of [¹¹C]PBR28 binding could be a viable surrogate for arterial blood methods, and perhaps more sensitive to between group

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differences. However, V_T and other more quantitative metrics will be computed as well. As an intensity normalization factor we will use the whole-brain signal or a localized pseudoreference region (e.g., the occipital cortex) for the brain data, and the lowest 1-2 spinal cord segments present in the field of view for most/all of our participants (e.g., T11-L1) for the spinal signal. Brain SUVR will be spatially normalized to the Montreal Neurological Institute (MNI) space using nonlinear registration (FNIRT, from the FSL suite; www.fmrib.ox.ac.uk/fsl¹⁰²). Spatially-normalized SUVR images will be then spatially smoothed (full width at half maximum=8mm) to improve signal-to-noise ratio. Spinal cord SUVR will be normalized to MNI-Poly-AMU template¹⁰³ using the Spinal Cord Toolbox.

MRI. During the acquisition of brain PET data, several runs of BOLD fMRI data will be collected using whole brain T2*-weighted gradient echo BOLD EPI pulse sequence (TR/TE =2sec/30ms, flip angle=90°, voxel size=3.1x3.1x3mm, number of slices=37), for the purposes of evaluating striatal function using the MID task, performing MR-based motion-correction of PET data¹³⁶, as well as for additional exploratory analyses. In addition, a high resolution structural volume (e.g., multi-echo MPRAGE pulse; TR/TE1/TE2/TE3/T4=2530/1.64/3.5/5.36/7.22 ms, flip angle=7°, voxel size=1mm isotropic) will be collected for anatomical localization as well as attenuation correction.¹⁵⁵ For the spinal cord data, axial and coronal T1 (e.g., TR/TE=0.565s/13 ms; flip angle=120°; slice thickness=2mm; number of slices – 14) and T2 (e.g., TR/TE=3.38s/109 ms; flip angle=150°; slice thickness=2mm; # slices – 30) weighted images will be collected for anatomical localization and ROI definition purposes.⁷

Data Analyses

A generalized linear mixed-effects model (GLMM) will be used to quantify the association between thalamic [¹¹C]PBR28 PET signal, treatment assignment at randomization (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 (e.g., age, depression severity, sex). Data dependencies will be accounted for using either random intercept or line (intercept and slope) parametrizations. 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 modeling 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 summarize 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

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analyses 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.

Genotyping:

GWAS Genotyping: The Broad Institute will perform genotyping (array-based) of subject DNA samples and subsequent in-depth analysis of the data, which will allow us to detect alterations in the genome including point mutations, small insertions and deletions, chromosomal copy number alterations, and translocations. These experiments are intended to help identify candidate genes involved in the physiopathology of neurological and psychological diseases. The molecular information generated from these samples will not be returned to subjects at any time.

Data from this study may result in communications in journals or at scientific meetings. Subjects will not be identified in those communications. To facilitate research, the genetic information generated may upon publication be deposited in protected databases (such as dbGAP) available only to bona fide researchers with specific scientific questions who promise to not try to identify individuals. The data will be sent to these banks in a coded manner and again will not contain any traditionally used identifier such as name, address, phone number, or social security number. Although we cannot predict how genetic information will be used in the future, there are many safeguards in place and we do not think that there will be further risks to patients' privacy and confidentiality by sharing such information with these banks.

The Broad Institute will not be involved in subject ascertainment. Prior to transfer of bio-specimen aliquots to the Broad Institute, samples will be re-encoded at the collaborators institutions. No identifying patient information will be shared with Broad scientists at any time. Some limited clinical data will be obtained from collaborators. Again, all subject identifying information will remain with the collaborators and only de-identified clinical data will be shared with the Broad Institute.

Consideration of sex as a biological variable:

In addition to the aforementioned analyses, the effect of sex will be evaluated using ANOVAs, because animal research suggests the presence of a possible sexual dimorphism in the role of glia in pain (as pain hypersensitivity may be microglial-dependent only in males¹⁰⁴). The effect of menstrual cycle status will also be evaluated by comparing women in early follicular (day 2-7 after onset of menses) and midluteal (day 20-25 after onset of menses), based on self-report¹⁰⁵.

Effect of coronavirus on neuroinflammation:

Finally, in addition to the aforementioned analyses, the effect of prior exposure to coronavirus (as detected by the presence of antibodies to SARS-CoV-2) will be evaluated in both ROI and voxelwise analyses, in exploratory analyses. Identifying participants who are positive to the antibodies might allow us to test the exploratory hypothesis that prior exposure to the coronavirus can lead to neuroinflammation even without having experienced overt acute COVID-19 symptoms.

Power Analysis:

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Primary Aim: Using a linear mixed-effects model, we estimate the power to detect a temporal (week 4 – baseline) rate of change in thalamic [^{11}C]PBR28 PET signal between CBD and control subjects when recruiting 40 subjects per treatment group. We assume: (1) the standard deviations of the [^{11}C]PBR28 PET signal measures are 0.05,[106] (2) the correlation between repeated measurements ranges between 0.3 to 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 [^{11}C]PBR28 PET signal measures of at least 0.039 and 0.045, respectively.

10. Monitoring and Quality Assurance

There will be a DSMB for this study (see attached DSMB Charter). The proposed study will be monitored for safety, with monthly staff meetings reviewing adverse events and treatment outcomes and directly reporting any adverse events. The PI will also routinely monitor and assure the validity and integrity of collected data, adherence to the IRB-approved protocol, and recordkeeping. The trained staff members who carry out the procedures will also carefully monitor the study throughout its duration. The team will evaluate the progress of the study, verify that the rights and well-being of the subjects are protected, verify that the reported study data are accurate, complete and verifiable from source documents, and the conduct of the study is in compliance with the approved protocol and amendments. Outcome monitoring and adverse events will all be reported through appropriate channels of the Human Studies Committee as well to the FDA when appropriate.

If a patient develops clinical signs or symptoms suggestive of hepatic dysfunction (e.g., unexplained nausea, vomiting, right upper quadrant abdominal pain, fatigue, anorexia, or jaundice and/or dark urine), we will promptly measure serum transaminases and total bilirubin and interrupt or discontinue treatment with EPIDIOLEX or placebo, as appropriate. We will discontinue EPIDIOLEX or placebo in any patients with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN. Our physician monitoring group (Drs. Mao, Zhang, Schnitzer, and Evins) will consider stopping the study if back pain becomes significantly worse in 3 or more patients. If serum liver enzyme concentrations are significantly elevated (with elevations of transaminase levels greater than 3 times the ULN and bilirubin levels greater than 2 times the ULN) in 2 or more patients, which will be considered serious adverse events, the study will be stopped. In addition, if two or more patients experience any serious adverse event, the study will be stopped.

The Siemens PET/MRI scanners have a built-in self-monitoring system that automatically shuts off if parameters exceed safe levels. For backup protection NMR technicians constantly monitor the subjects' physiological signs and the quality of the raw data.

Quality assurance of the scanner's performance is obtained by a daily quality assurance protocol. More extensive quality assurance protocols are performed monthly under the commercial service contract with Siemens Medical Systems. The daily quality assurance protocol consists of an image Signal-to-Noise measurement in a phantom and a stability run which checks the image-to-image variation in image intensity over 600 images using a standard echoplanar imaging sequence with a head-sized phantom. The images are analyzed by the technologist to provide

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data on SNR (as an absolute, unitless number) and stability expressed as the peak-to-peak variation in the mean of a 15x15 pixel region of interest (ROI) in the center of the phantom expressed as a percentage of the mean of the ROI. Runs are performed at each of 3 TR values (300ms, 800ms, 1300ms). The time course of the means is also reviewed to check for periodicities (the TR values are chosen so as not to be multiples of one another). If the peak-to-peak variation is greater than 0.5% of the mean value, the Siemens Medical System service engineer is called. In addition to these daily quality assurance tests, the Siemens Medical System service engineer performs quality assurance tests once a month. These tests include a SNR test, a small sample stability test, a gradient stability test, a gradient eddy current test, a shim test, an image uniformity test, and an RF stability test.

11. Privacy and Confidentiality

- Study procedures will be conducted in a private setting
- Only data and/or specimens necessary for the conduct of the study will be collected
- Data collected (paper and/or electronic) will be maintained in a secure location with appropriate protections such as password protection, encryption, physical security measures (locked files/areas)
- Specimens collected will be maintained in a secure location with appropriate protections (e.g. locked storage spaces, laboratory areas)
- Data and specimens will only be shared with individuals who are members of the IRB-approved research team or approved for sharing as described in this IRB protocol
- Data and/or specimens requiring transportation from one location or electronic space to another will be transported only in a secure manner (e.g. encrypted files, password protection, using chain-of-custody procedures, etc.)
- All electronic communication with participants will comply with Mass General Brigham secure communication policies
- Identifiers will be coded or removed as soon as feasible and access to files linking identifiers with coded data or specimens will be limited to the minimal necessary members of the research team required to conduct the research
- All staff are trained on and will follow the Mass General Brigham policies and procedures for maintaining appropriate confidentiality of research data and specimens
- The PI will ensure that all staff implement and follow any Research Information Service Office (RISO) requirements for this research
- Additional privacy and/or confidentiality protections

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Subject Identification

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Protocol Title: Evaluation of Cannabidiol (CBD) for Reduction of Brain Neuroinflammation

Principal Investigator: Jodi Gilman, PhD

Site Principal Investigator:

Description of Subject Population: Adults with Chronic Low Back Pain

About this consent form

Please read this form carefully. It tells you important information about a research study. A member of our research team will also talk to you about taking part in this research study. People who agree to take part in research studies are called "subjects." This term will be used throughout this consent form.

If you decide to take part in this research study, you must sign this form to show that you want to take part. We will give you a signed copy of this form to keep.

Key Information

Taking part in this research study is up to you. You can decide not to take part. If you decide to take part now, you can change your mind and drop out later. Your decision won't change the medical care you get within Mass General Brigham now or in the future.

The following key information is to help you decide whether or not to take part in this research study. We have included more details about the research in the Detailed Information section that follows the key information.

Why is this research study being done?

In this research study we want to learn more about whether cannabidiol (CBD) reduces activation of glial cells, which are the immune cells of the nervous system. Cannabidiol is a naturally occurring compound found in cannabis plant, and is considered to be a safe, non-addictive substance. We are looking to find out whether CBD may reduce symptoms of low back pain.



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How long will you take part in this research study?

If you decide to join this research study, it will take you about 8-10 weeks to complete the study. During this time, we will ask you to make 2 imaging visits to MGH Charlestown Navy Yard campus and 2 office visits to 101 Merrimac Street. There will also be three follow up phone calls.

What will happen if you take part in this research study?

If you decide to join this research study, the following things will happen. First, you will come to MGH for an approximately 3-hour screening visit, which will include a blood test, a urine test, and a physical exam. Depending on the results of the initial screening visit, you might be eligible to participate in up to 2 imaging visits. As part of the study, we are using a machine which combines Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) into one device. The MRI part of it uses a powerful magnet to make a picture of the body, while the PET part of it makes pictures by using special dyes with a small dose of radioactivity attached to them that “light up” inside the body.

To study the effect of CBD, you will be asked to take either a medication called EPIDIOLEX or placebo for the 4 weeks prior to the date of your second imaging visit. EPIDIOLEX is a liquid formulation of CBD. A study doctor will talk to you about how much EPIDIOLEX to take.

Why might you choose to take part in this study?

We cannot promise any benefits to you from taking part in this research study. However, possible benefits may include a reduction in pain while taking the drug. Others with chronic back pain may benefit in the future from what we learn in this study.

Why might you choose NOT to take part in this study?

Taking part in this research study has some risks and requirements that you should consider carefully.

Important risks and possible discomforts to know about include sleepiness, decreased appetite, diarrhea, lack of energy, and risks of PET/MRI scans (radiation exposure). CBD may cause an increase in suicidal thoughts or actions in a very small number of people. It is possible that patients taking EPIDIOLEX may test positive on a cannabis drug screen. If this happens, we will tell the laboratory staff that you are involved in a research study using Epidiolex.



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A detailed description of side effects, risks, and possible discomforts can be found later in this consent form in the section called “What are the risks and possible discomforts from being in this research study?”

Other things to consider are the time commitment of 4 visits, and requirements to travel to MGH.

What other treatments or procedures are available for your condition?

Other treatments or procedures that are available to treat chronic low back pain include:

- Medications (e.g., non-steroidal anti-inflammatory drugs, opiates, muscle relaxants)
- Transcutaneous electrical nerve stimulation
- Physical exercise and stretching
- Epidural steroid injection
- Physical therapy
- Back surgeries
- Acupuncture

If you have questions or concerns about this research study, whom can you call?

You can call us with your questions or concerns. Our telephone numbers are listed below. Ask questions as often as you want.

Jodi Gilman, PhD is the person in charge of this research study. You can call her at 617-643-7293 Monday-Friday from 9am to 5pm with questions about this research study. If you have any medical questions related to the study you can call Dr. Kristina Schnitzer at 617-726-2000, and ask for pager #27399 (24/7, for emergencies).

If you have questions about the scheduling of appointments or study visits, call our study staff:
 Chelsea Pike: (617)724-0382 ckpik@mg.harvard.edu

If you want to speak with someone **not** directly involved in this research study, please contact the Mass General Brigham IRB. You can call them at 857-282-1900.

You can talk to them about:

- Your rights as a research subject
- Your concerns about the research
- A complaint about the research
- Any pressure to take part in, or to continue in the research study



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Detailed Information

A description of this clinical trial will be available on <http://www.ClinicalTrials.gov>, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

Why is this research study being done?

We are doing this research study to find out if cannabidiol (CBD) reduces activation of glial cells, which are the immune cells of the nervous system, compared to placebo. We are also looking to find out whether CBD may reduce symptoms of low back pain.

CBD (in the form of EPIDIOLEX) is a prescription medicine that is approved by the U.S. Food and Drug Administration (FDA) to treat seizures associated with Lennox-Gastaut syndrome or Dravet syndrome (rare forms of childhood epilepsy) in people 2 years of age and older. CBD is not approved by the FDA to treat chronic low back pain and it is not known whether it is effective for chronic back pain. We are asking you to take part in this study because you have chronic low back pain lasting at least 6 months.

This research study will compare CBD to placebo. The placebo looks exactly like CBD, but contains no CBD. During this study you may get a placebo instead of CBD. Placebos are used in research studies to see if the results are due to the medication or due to other reasons. If you decide to participate in this study, you will have a 50% chance of receiving active study medication and 50% chance of receiving placebo. That means 1 out of 2 people will receive only placebo during the study. Neither you nor study staff will know if you have received active medication or placebo until after the study is over, however study staff can get this information quickly if needed.

Who will take part in this research?

We are asking you to take part in this research study because you are an adult with chronic low back pain. About 80 people will take part in this research study at Massachusetts General Hospital. The National Institutes of Health is paying for this research study to be done.

What will happen in this research study?

If you choose to take part in this study, we will ask you to sign this consent form before we do any study procedures.



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Screening Visit

The Screening Visit will take place at our 101 Merrimac Street office and will last about 3 hours. At this visit, we will do some tests and procedures to see if you qualify to take part in this research study. The study staff will review the results of these tests and procedures.

At this visit, we will:

- Ask you questions or have you complete questionnaires about your health (past and present), including mental and emotional health.
- Ask you to fill out questionnaires about your pain.
- Do a physical examination.
- Ask you about current medications you are taking.
- Ask you to fill out a form with information about your age, sex, race, marital status, and employment status.
- Draw about 2 tablespoons of blood to assess liver function and radiotracer binding affinity. Low affinity for the radiotracer known as [¹¹C]PBR28 disqualifies the subject for the research study. You may provide a saliva sample instead of a blood sample to assess radiotracer binding if you wish.
- Collect a urine sample to test for certain drugs. The results of the urine drug test will not become part of your medical record. These test results will, however, remain part of your study record.
- Collect a urine sample to test for pregnancy if you are a female who is able to become pregnant. Pregnant women cannot take part in this research study.
- With your permission, we may collect a saliva sample for other genetic research.

Study staff will also need to access your medical record in order to verify a pain diagnosis and any other medications.

This visit may also be held at the MGH Charlestown Navy Yard campus instead of our 101 Merrimac Street office, depending on your circumstances. Note that we may do a brief MRI test scan with you on the day of your screening visit, or on a different day, to ensure that you are a suitable candidate for scanning.

PET/MRI Visits

All the eligible participants will complete two PET/MRI scan visits. The PET/MRI visits will take place at MGH Charlestown Navy Yard campus. Each PET/MRI visit will last



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approximately 4 hours (and up to 6 hours). We will ask you to avoid strenuous exercise for 24 hours before the PET/MRI scan.

Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) are tests that allow us to take images of your brain and spinal cord. MRI uses a powerful magnet to make images of the body, while PET uses something called a radiotracer, that binds to the specific cells we are interested in viewing and causes them to “light up” so the scanner can detect them.

Before the PET/MRI scan, we will:

- Ask you some questions about your recent health and have you fill out some questionnaires to make sure it is safe for you to have a PET/MRI scan.
- Draw about 1 teaspoon of blood to test for pregnancy if you are a female who is able to become pregnant. Pregnant women cannot take part in this research study.
- Measure your weight.
- Collect a urine sample to test for certain drugs.
- Draw about 1 teaspoon of blood to test for the presence of cannabinoids (including CBD and THC) in the blood.
- Draw about 2 teaspoons of your blood to test for COVID-19 antibodies (to see if you have been infected by the SARS-CoV-2 virus and an immune response to it is still present in your body).

If you still qualify, we will ask you to take off anything that contains metal and change into hospital approved clothing. Then we will:

- Place an IV catheter (a thin, flexible plastic tube with a needle attached) into a vein in your arm. The IV catheter will be used to inject the radiotracer known as [¹¹C]PBR28 into your body, as well as draw about 2 tablespoons of blood to assess the function of various organs, body systems, cells, molecules, and genes in pain disorders.

We would like your permission to place an arterial line (“A-line”) into an artery in your wrist to draw blood samples throughout the scan, if the doctor or nurse practitioner has deemed it safe for us to do so. However, this procedure is optional for all subjects who qualify and you will still be able to participate in the study, even if you do not allow us to collect arterial blood. The collection of arterial blood allows us to measure how the radiotracer moves through your body, and we can use that information to get more accurate PET images.

PET/MRI Scans



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You will lie still in the PET/MRI scanner for about 2 hours. The scanner is a tunnel. You will lie on your back on a narrow table that will slide you into the tunnel. In order to help hold your head still, we may place foam pillows under and around your head.

The top and sides of the tunnel will be close to your face and body, which can make some people uncomfortable. If you have ever experienced a fear of enclosed spaces (claustrophobia), please tell the study staff.

The scanner makes loud banging and beeping noises taking images, so we will give you earplugs to protect your ears.

First, we will take some pictures of your brain and/or whole body. Then we will inject the radiotracer into the IV catheter in your vein and take more images. You will not feel the radiotracer in your body and it will quickly leave your body through your urine. The Martinos Center has completed hundreds of PET/MRI scans in a number of patient populations and healthy volunteers using [11C]PBR28. There have been no side effects associated with the administration of this radiotracer. This dye will travel through your blood stream, so the PET/MRI scanner can see how the different parts of your brain and/or whole body are working.

Before, during and after the scans, you may be asked to express various behavioral ratings, including pain intensity, unpleasantness and anxiety.

After the brain scan is complete, we may collect additional 20 minutes of data from your spinal cord. This spinal cord imaging is optional, and will only be done if you are still comfortable in the scanner.

After the scan is complete, you will sit up slowly and we will remove your catheter. After the removal of the arterial line we will observe you for 30 minutes. After this period of observation, you are free to leave.

Somebody from the study staff will call you the day following each scan to check on you. Of course, you can contact us at any time if you have questions (see contact information under "If I have questions or concerns about this research study, whom can I call?").

Taking the Study Drug

You will receive a bottle containing either CBD or a placebo at the first PET/MRI Visit to take home with you. You will be instructed to begin taking it four weeks prior to the scheduled date of your second PET/MRI Visit. A study doctor will tell you how much to take. You will take CBD or placebo for 4 weeks in total, and your dose will increase each week. When you start the study drug, we will ask you to take 2.5mg/kg twice daily. Each week, a member of the study



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team will remind you to increase the dose for the following week (week 2 dose = 5mg/kg twice daily; week 3 dose = 7.5mg/kg twice daily; week 4 final dose = 10mg/kg twice daily). At the end of the second week, a study physician will meet with you (by phone or in person) to assess tolerability. If you are not tolerating the study drug well (whether during the second week, or during the third or fourth week of taking the study drug), the physician will decrease your dose to the previous week’s dose. The study physician may also discontinue the study drug if you do not tolerate it well.

CBD should be taken consistently with respect to meals and should not be taken in a fasted state. In addition, CBD should not be taken with concurrent alcohol use. It is important for you to follow our instructions about how to take the study drug.

Daily Surveys

You will be asked to fill out a daily survey for about 2 weeks before your first scan, for 4 weeks while you are taking CBD or placebo, and for 2 weeks after the discontinuation of CBD or placebo. You will be sent a survey to complete by the end of each day. This survey will be sent to you each day via email or text message and you will have until 11:59pm each night to complete the survey. The survey will take less than 5 minutes to complete and will ask you about your low back pain symptoms, mental health, sleep quality, fatigue, whether you have been taking the study drug, and whether you have taken any other medications to manage your pain.

Please let the study staff know if you do not have internet access and we can arrange to call you to administer the survey.

Follow-up Visits and Calls

1-Week Call. You will have a phone call 1 week after your first scan visit. In this call, we will assess adverse events, treatment expectancy, and medication use. We will also remind you to increase your study drug dose.

2-Week Visit. You will have a follow-up appointment during Week 2 with a study staff member at 101 Merrimac Street. We will check on your health, remind you to increase your study drug dose, ask about other medication use, and ask you to complete some questionnaires. We may also take a small sample of blood for a follow-up liver function test. As you will be taking Epidiolex or placebo daily at the time of this visit, we will ask you whether you can drive to the visit; if you cannot because the study drug makes you drowsy, we will arrange transportation. Note that this visit may also be held at the MGH Charlestown Navy Yard campus, depending on your circumstances.



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3-Week Call. You will have a phone call during Week 3 to assess adverse events, treatment expectancy, and medication use. We will also remind you to increase your study drug dose.

4-Week Visit. You will have a second follow-up appointment immediately after the four-week treatment period, where we will assess back pain, general health, adverse events, and medication use. On the same day or as close as possible depending on scheduling, you will be re-scanned. We will also repeat the questionnaires administered during the baseline visit to assess any changes in subjective pain or general health. We will also take a small sample of blood for a follow-up liver function test. Again, we will ask you whether you can drive to the visit; if you cannot because the study drug makes you drowsy, we will arrange transportation.

6-Week Call. You will have a follow-up phone call 2 weeks after the discontinuation of the study drug. In this call, we will assess back pain, general health, adverse events, and medication use.

Stopping the Study Early

If you wish to stop taking the study drug, you should tell the principal investigator of this study, Dr. Jodi Gilman.

If you decide to stop participating in the study for any reason before the planned end of the study, we will ask that you continue to follow the schedule of visits. If you are unable or unwilling to return to the MGH Charlestown Navy Yard campus for visits, we will ask if we can call you for phone interviews instead of study visits.

Also, the study doctor may take you out of the study without your permission. This may happen because:

- The study team thinks you cannot follow the study plan.
- Your health is in question.
- You are experiencing side effects from the study drug.
- The study doctor thinks it is best for you to stop taking the study drug.
- We stop doing the study for other reasons.

Sending Study Information to Research Collaborators Outside Mass General Brigham

Blood Plasma Shipments

We will collect blood samples at the screening visit and the two PET/MRI visits, which will be tested for COVID-19 antibodies and pregnancy (in females). A small quantity (about 1 teaspoon)



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of blood plasma from your sample may be shipped to researchers working with us at a University of Colorado lab who can quantify cannabinoids (including CBD and THC) in the blood.

We will label all your study materials with a code number instead of your name. No names or important numbers that could be used to identify you, like hospital medical record number or social security number, will be kept on samples. Only MGH study staff will keep the link between your subject number and your name on a computer protected by a personal password.

Optional (not required) Saliva Samples for Genetic Testing

While collection of a blood or saliva sample to test for radiotracer binding affinity is required, the collection of a saliva sample for other genetic research at the screening visit is optional (not required). You can still take part in the main study even if you don't want to take part in the additional genetic study. Giving a DNA sample involves filling 1-2 small plastic containers with your saliva. This will be done at your first visit and should take less than 5 minutes. Usually researchers study just a few areas of genetic code that are linked to a disease or condition. Instead, we may perform a whole genome analysis on your DNA sample. In whole genome analyses, all or most of the genes are looked at and used by researchers to study links to substance use and mental health. These whole genome analyses will be conducted by investigators at the Broad Institute. Samples shared with investigators at the Broad Institute will be labeled with a code number and not with your name or other identifying information. Research using whole genome information is important for the study of virtually all diseases and conditions. Therefore, the anonymized samples will provide study data for researchers working on any disease.

It is not intended to provide important genetic information about your health. We have no plan to return any research results to you or your doctor. The results of the genetic testing will not be placed in your medical record. Your consenting to take part in this additional genetic study is voluntary, and you may decide to withdraw from the study at any time or decide not to join the study. If you change your mind and want to withdraw your saliva sample from further genetic research you can do so at any time by contacting Dr. Gilman (617-643-7293; jgilman1@mgh.harvard.edu). Any information obtained from the sample will also be withdrawn except to the extent to which the information has already been used in analyses. All information and samples obtained for this study will be assigned a code number. No names or important numbers that could be used to identify you, like hospital medical record number or social security number, will be kept on samples. Only MGH study staff will keep the link between your subject number and your name on a computer protected by a personal password.

Would you like to provide a saliva sample to be used for genetic testing as described above?
 Please mark your choice below.



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[] YES [] NO Initials _____

In order to allow researchers to share test results, the National Institutes of Health (NIH) and other central repositories have developed special data (information) banks that analyze data and collect the results of whole genome studies. These banks may also analyze and store DNA samples, as well. These central banks will store your genetic information and samples and give them to other researchers to do more studies. We do not think that there will be further risks to your privacy and confidentiality by sharing your samples and whole genome information with these banks. However, we cannot predict how genetic information will be used in the future. The samples and data will be sent with only your code number attached. Your name or other directly identifiable information will not be given to central banks. There are many safeguards in place to protect your information and samples while they are stored in repositories and used for research.

How may we use and share your samples and health information for other research?

At the completion of this research study, we would like to store and be able to use and share your identifiable samples and health information with researchers at Mass General Brigham for other research related to pain disorders. If we share your samples and/or health information with other researchers outside of Mass General Brigham, we will label the samples and information with a code instead of your name or other directly identifying information. The key to the code connects your name or other identifiers to your sample and/or information. We will keep the code in a password protected computer.

Because these samples and/or health information are identifiable, we are asking your permission to store, use and share them for other research. You can still take part in the research study whether or not you give permission for the storage, use, and sharing of the samples and health information for other research.

Do you agree to let us store and use your samples and health information for other research related to pain disorders?

[] YES [] NO Initials _____

Will you get the results of this research study?



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You and your doctor should not expect to get information about the results of the research study or the results of your individual participation in the research study. The researchers involved in this study will study samples and information from many people. It could take many years before anyone knows whether the results have any meaning. There is a small chance that researchers could find out something from the study that might be important to your health. If this happens, we may contact you to find out if you would like to learn more. However, even if we find something important to your health, we cannot guarantee that you will be contacted.

What are the risks and possible discomforts from being in this research study?

Risks of Taking EPIDIOLEX

Taking **EPIDIOLEX** may cause you to have one or more of the side effects listed below.

Common side effects:

- Increase in liver enzymes: As part of the study, we will collect blood to check your liver before you start taking EPIDIOLEX and after one month of treatment. In some cases, EPIDIOLEX treatment may need to be stopped. If you had elevated liver enzymes at baseline but still met the eligibility criteria for the study, we may ask you to undergo a follow-up liver function tests at 2 weeks. In addition, we will perform a liver function test on anyone who develops clinical signs or symptoms suggestive of hepatic dysfunction.
- Sleepiness: EPIDIOLEX may cause you to feel sleepy, which may get better over time. Do not drive, operate heavy machinery, or do other dangerous activities until you know how EPIDIOLEX affects you. Other medicines (e.g., clobazam) or alcohol may increase sleepiness.
- Decreased appetite
- Diarrhea
- Lack of energy
- Insomnia
- Poor quality sleep
- Infections

Rare side effects:

- Suicidal thoughts or actions: EPIDIOLEX may cause suicidal thoughts or actions in a very small number of people, about 1 in 500. Call a healthcare provider right away if you have any of these symptoms, especially if they are new, worse, or worry you: thoughts about suicide or dying, attempt to commit suicide, new or worse depression, new or worse anxiety, feeling agitated or restless, panic attacks, trouble sleeping, new or worse



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irritability, acting aggressive, being angry, or violent, acting on dangerous impulses, an extreme increase in activity and talking (mania), other unusual changes in behavior or mood. We will assess suicidality, depression, and anxiety throughout the study. If you report any new or worsening expression of suicidal ideation and or/emergent depression, you may be asked to speak with a licensed clinician. These clinicians, along with the PI will then determine whether you can safely continue the study. If the clinicians determine that you cannot safely continue the study, your participation in the study will be discontinued, and you will be provided with a list of resources for follow-up care.

- Allergic reactions: As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious, and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or trouble breathing. If you think you are having an allergic reaction, call the study doctor right away. If you are having trouble breathing, call 911 immediately.
- Positive drug screen for cannabis: It is possible that patients taking EPIDIOLEX may test positive on a cannabis drug screen.
- There may be other risks of EPIDIOLEX that are currently unknown at this time.

Risks of Taking EPIDIOLEX with Other Medications

Do not take medications that impact specific CYP450 enzymes, including some CNS depressants, while you are in the study. This includes:

- All antipsychotics
- Benzodiazepines (except for alprazolam, clonazepam, and lorazepam)
- Non-benzodiazepine sleep aid use will be reviewed by the study physician to determine safety

Taking these drugs and **EPIDIOLEX** together may cause serious side effects. All medications, including but not limited to those mentioned, must be discussed with the study physician.

Additionally, for your safety during this study, call your study doctor BEFORE you take any:

- New medications prescribed by your own doctor
- Other medications sold over-the-counter without a prescription
- Dietary or herbal supplements

Risks of Radiation Exposure

As a result of your participation in this study, you will be exposed to radiation from two PET scans of your brain and/or spinal cord. Please note that this radiation is not necessary for your medical care and is for research purposes only. The maximum amount of radiation to which you could be exposed to in this study is approximately 7.4 milliSieverts (mSv). A mSv is a



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unit of radiation dose. This amount of radiation is about the same as you would normally get in 2.4 years from natural background sources from the earth and the sky.

Scientists disagree on whether radiation doses at these low levels are harmful. Possible side effects that could occur at doses associated with this study include:

- A slight increase in the risk of developing cancer later in life

Since the effects of radiation can add up over time, it is important that you tell the study doctors about your past clinical imaging and research-related radiation exposure. If you have taken part in other research studies in the past 12 months that have involved radiation exposure, please tell us. If it appears that your earlier radiation exposure is more than our current guidelines, it is possible that you will not be allowed to take part in this study.

Have you participated in other research studies (not including this study) involving radiation exposure within the last 12 months?

YES NO **Initials** _____

Risks to an Embryo or Fetus, or to a Breastfeeding Infant

The effect of radiation exposure or the use of CBD (EPIDIOLEX) on an embryo or fetus (developing baby still in the womb), or on a breastfeeding infant, is unknown and may be harmful. Because of these unknown risks, women cannot take part in this study if they are:

- Pregnant or trying to become pregnant
- Breastfeeding

If you are a menopausal woman and have not had a menstrual period for the past 12 months or more, you will not need to have a pregnancy test. Also, if you have had any well-documented method of surgical sterilization, you will not need to have a pregnancy test. Methods of surgical sterilization include having had a hysterectomy (removal of the uterus), bilateral oophorectomy (removal of both ovaries), a tubal ligation (having your tubes tied), and transvaginal occlusion (plugging the opening of the tubes with a coil). All other female subjects must have a negative pregnancy test before starting the study drug and before having the PET/MRI scan.

If you miss a period, or think you might be pregnant during the study, you must tell the study doctor immediately. If you become pregnant, you must stop taking the study drug and stop taking part in the study.

There may be other risks and side effects of the PET/MRI scan that are not known at this time.



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Risks of MRIs

MRIs use powerful magnets to make images. There are no known radiation risks associated with MRI. However, you should not have an MRI if:

- You have certain medical metal implants, such as surgical clips or pacemakers
You are pregnant or suspect you are pregnant

All credit cards and other items with magnetic strips should also be kept out of the MRI room. People who feel uncomfortable in confined spaces (claustrophobia) may feel uncomfortable in the narrow tube. The MRI makes loud banging noises as it takes images. Earplugs can be used to reduce the noises. The MRI can be stopped at any time at your request.

Other possible risks include:

- Localized warming of your skin and the underlying tissue during normal routine MRI use
You should immediately inform us if you experience discomfort due to warming and the procedure will be stopped

Risks of IV Catheter and Blood Draw

Drawing blood or placing the IV catheter into a vein in your arm may cause the following in the area where we take blood samples from or place the IV catheter:

- Pain
Discomfort
Bruising
Bleeding
Swelling
Redness

You may have a bruise or feel painful or uncomfortable for 2-3 days after. Rarely, an infection may occur, which can be treated.

Risks of Optional Arterial Line (A-line)

Inserting an A-line can hurt more than having a regular IV catheter or having blood drawn with a needle. If you agree to this procedure, we will numb your wrist area first, but it may still hurt when we place the A-line into your wrist. Once the A-line is in place, it usually does not hurt.

Having an arterial line placed may cause:



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- Pain, bleeding, swelling, or redness at the wrist. Rarely (less than 1 in 100), an infection may occur, which can be treated.
- Short loss of pulse at the wrist, if blood flow in the artery is briefly stopped (for example, because of a clot or spasm of the artery).
- Damage to the artery wall or nearby nerves.
- Catheter breaking or falling out.

Rare side effects:

- There have been reports of decreased blood flow to the hand that resulted in the need for surgery. This is very rare and has not been reported when catheters have been in place for only a few hours for research.

After we remove the catheter:

- We will ask you to stay for at least 30 min so that we can check that the site is healing properly.
- You may have a bruise or feel tenderness for 2-3 days around the area where the arterial line was placed.
- You should avoid lifting anything heavier than a small bag of flour for a day following the scan.

Call us if:

- Bleeding occurs after you leave (rare). Apply pressure to the site and go to the Emergency Department.
- The wrist area is painful, red, or swollen.

Do you allow us to collect arterial blood during the scan(s)? You can change your mind at any time.

YES NO **Initials** _____

Risks of Numbing Drug (Lidocaine)

The anesthesiologist will use lidocaine to numb your wrist area prior to placing the A-line. Risks of lidocaine include:

- Dizziness
- Nausea
- Drowsiness
- Ringing in the ears
- Numbness



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- Allergic reaction. An allergic reaction to lidocaine was observed in a very limited number of cases.

Risks of COVID-19 Antibody Testing

As part of the study, we wish to determine whether or not you have been exposed to COVID-19. We do this using an antibody serology test which involves taking up to 10 ml of blood (about 2 teaspoons) and sending it to an internal or third-party laboratory that provides testing services. Your test results will be communicated to you. Your results may become part of your MGH medical records. A positive test does not mean that you have an active COVID-19 infection, only that you have been exposed at some point in the past.

Risks of Genetic Testing

Genetic information that results from this study does not have medical or treatment importance at this time. However, there is a risk that information about taking part in a genetic study may influence insurance companies of employers regarding your health. To further safeguard your privacy, genetic information obtained in this study will not be placed in your medical record. Taking part in a genetic study may also have a negative impact on family or other relationships. If you do not share information about taking part in this study, you will reduce this risk. We may perform Genome wide association studies (GWAS) with this data. GWAS are hypothesis free methods to identify associations between genetic regions (loci) and traits (including diseases).

Risks of Questionnaires

We will ask you questions about your emotional or mental health (psychological questions). Some of these questions may make you uncomfortable. You are allowed to skip any question you do not want to answer, but it could mean being excluded by the study (depending on how necessary the particular answer is).

Incidental Findings

We are doing the PET/MRI scan in this study to answer research questions, not as part of your medical care. The information from this study will not usually become part of your hospital record. This PET/MRI scan is not the same as the one that your doctor would order. It may or may not show problems that would be found on a standard MRI or PET scan. This type of scan is considered experimental.

If we do see something that looks like a medical problem, we will ask a radiologist (a doctor who specializes in test results of this sort) to review the results. If the radiologist thinks that you may



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have a medical problem, we will tell you and help you get follow-up care. If the radiologist thinks that you may have a medical problem, but it turns out that you don't, we may have caused you to worry needlessly about your health.

Medical Information

We will make a notation in your medical record that you are a part of this study. There is a small risk that your confidential medical information could be revealed or discovered by mistake. The results of this research study won't be placed in your medical records. In addition, your samples and information will be coded and the key to the code will be kept in a separate, locked file. We won't share or publish any information that will identify you.

What are the possible benefits from being in this research study?

You may not benefit from taking part in this study. If you receive CBD (EPIDIOLEX), it is possible that your low back pain will improve while you are taking it. However, because EPIDIOLEX is not FDA-approved to treat low back pain, your doctor cannot prescribe it after you finish the study.

Others with low back pain may benefit in the future from what we learn in this study. We hope the information obtained from this study will help scientists discover a potential mechanism of action for CBD.

What other treatments or procedures are available for your condition?

You do not have to take part in this research study to be treated for low back pain. Other treatments or procedures that are available to treat low back pain include:

- Medications (e.g., non-steroidal anti-inflammatory drugs, opiates, muscle relaxants)
- Transcutaneous electrical nerve stimulation
- Physical exercise and stretching
- Epidural steroid injection
- Physical therapy
- Back surgeries
- Acupuncture

Talk with the study doctor if you have questions about any of these treatments or procedures.



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Can you still get medical care within Mass General Brigham if you don't take part in this research study, or if you stop taking part?

Yes. Your decision won't change the medical care you get within Mass General Brigham now or in the future. There will be no penalty, and you won't lose any benefits you receive now or have a right to receive.

We will tell you if we learn new information that could make you change your mind about taking part in this research study.

What should you do if you want to stop taking part in the study?

If you take part in this research study, and want to drop out, you should tell us. We will make sure that you stop the study safely. We will also talk to you about follow-up care, if needed.

Also, it is possible that we will have to ask you to drop out of the study before you finish it. If this happens, we will tell you why. We will also help arrange other care for you, if needed.

Will you be paid to take part in this research study?

We will pay you up to \$770 for the following:

- \$75 for the initial screening visit
Up to \$76 for completing daily surveys (\$1 per survey completed)
o Bonus \$25 if you complete 90% of surveys
\$200 for each PET/MRI scanning session
\$25 for each blood test to exclude pregnancy (if you are a female of childbearing age)
\$50 for each arterial line placement
Up to \$44 which you can earn from a task you will complete in the PET/MRI scanner

If, for some reason, we cannot inject you with the dye during the imaging visit(s) and we have not yet placed the arterial line, you will receive \$50. If we cannot inject you with the dye and we have already placed the arterial line, you will receive \$100. If you have to stop the scan early for any reason, we will pay you \$50 for the imaging visit(s). We will also reimburse you for your parking in the hospital garage during study visits.



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We may use your samples and information to develop a new product or medical test to be sold. The Sponsor, hospital, and researchers may benefit if this happens. There are no plans to pay you if your samples or information are used for this purpose.

What will you have to pay for if you take part in this research study?

Study funds will pay for certain study-related items and services. We may bill your health insurer for, among other things, routine items and services you would have received even if you did not take part in the research. You will be responsible for payment of any deductibles and co-payments required by your insurer for this routine care or other billed care. If you have any questions about costs to you that may result from taking part in the research, please speak with the study doctors and study staff. If necessary, we will arrange for you to speak with someone in Patient Financial Services about these costs. You will also be responsible for paying for transportation to and from study visits, although we will validate parking in the hospital garage during study visits. It is important to note that if you do receive any benefit from the CBD treatment, and decide to continue treatment with CBD after your study participation is over, you and your insurance company will be responsible for the cost of the CBD.

What happens if you are injured as a result of taking part in this research study?

We will offer you the care needed to treat any injury that directly results from taking part in this research study. We reserve the right to bill your insurance company or other third parties, if appropriate, for the care you get for the injury. We will try to have these costs paid for, but you may be responsible for some of them. For example, if the care is billed to your insurer, you will be responsible for payment of any deductibles and co-payments required by your insurer.

Injuries sometimes happen in research even when no one is at fault. There are no plans to pay you or give you other compensation for an injury, should one occur. However, you are not giving up any of your legal rights by signing this form.

If you think you have been injured or have experienced a medical problem as a result of taking part in this research study, tell the person in charge of this study as soon as possible. The researcher's name and phone number are listed in the beginning of this consent form.

If you take part in this research study, how will we protect your privacy?



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Federal law requires Mass General Brigham to protect the privacy of health information and related information that identifies you. We refer to this information as "identifiable information."

In this study, we may collect identifiable information about you from:

- Past, present, and future medical records
• Research procedures, including research office visits, tests, interviews, and questionnaires

Who may see, use, and share your identifiable information and why:

- Mass General Brigham researchers and staff involved in this study
• The sponsor(s) of the study, and people or groups it hires to help perform this research or to audit the research
• Other researchers and medical centers that are part of this study
• The Mass General Brigham ethics board or an ethics board outside Mass General Brigham that oversees the research
• A group that oversees the data (study information) and safety of this study
• Non-research staff within Mass General Brigham who need identifiable information to do their jobs, such as for treatment, payment (billing), or hospital operations (such as assessing the quality of care or research)
• People or groups that we hire to do certain work for us, such as data storage companies, accreditors, insurers, and lawyers
• Federal agencies (such as the U.S. Department of Health and Human Services (DHHS) and agencies within DHHS like the Food and Drug Administration, the National Institutes of Health, and the Office for Human Research Protections), state agencies, and foreign government bodies that oversee, evaluate, and audit research, which may include inspection of your records
• Public health and safety authorities, if we learn information that could mean harm to you or others (such as to make required reports about communicable diseases or about child or elder abuse)
• Other researchers within or outside Mass General Brigham, for use in other research as allowed by law.

Certificate of Confidentiality

A federal Certificate of Confidentiality (Certificate) has been issued for this research to add special protection for information and specimens that may identify you. With a Certificate,



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unless you give permission (such as in this form) and except as described above, the researchers are not allowed to share your identifiable information or identifiable specimens, including for a court order or subpoena.

Certain information from the research will be put into your medical record and will not be covered by the Certificate. This includes records of medical tests or procedures done at the hospitals and clinics, and information that treating health care providers may need to care for you. Please ask your study doctor if you have any questions about what information will be included in your medical record. Other researchers receiving your identifiable information or specimens are expected to comply with the privacy protections of the Certificate. The Certificate does not stop you from voluntarily releasing information about yourself or your participation in this study.

Even with these measures to protect your privacy, once your identifiable information is shared outside Mass General Brigham, we cannot control all the ways that others use or share it and cannot promise that it will remain completely private.

Because research is an ongoing process, we cannot give you an exact date when we will either destroy or stop using or sharing your identifiable information. Your permission to use and share your identifiable information does not expire.

The results of this research may be published in a medical book or journal, or used to teach others. However, your name or other identifiable information **will not** be used for these purposes without your specific permission.

Your Privacy Rights

You have the right **not** to sign this form that allows us to use and share your identifiable information for research; however, if you don't sign it, you can't take part in this research study.

You have the right to withdraw your permission for us to use or share your identifiable information for this research study. If you want to withdraw your permission, you must notify the person in charge of this research study in writing. Once permission is withdrawn, you cannot continue to take part in the study.

If you withdraw your permission, we will not be able to take back information that has already been used or shared with others, and such information may continue to be used for certain purposes, such as to comply with the law or maintain the reliability of the study.



Research Consent Form
Certificate of Confidentiality Template
Version Date: February 2021

Subject Identification

You have the right to see and get a copy of your identifiable information that is used or shared for treatment or for payment. To ask for this information, please contact the person in charge of this research study. You may only get such information after the research is finished.

Informed Consent and Authorization

Statement of Person Giving Informed Consent and Authorization

- I have read this consent form.
- This research study has been explained to me, including risks and possible benefits (if any), other possible treatments or procedures, and other important things about the study.
- I have had the opportunity to ask questions.
- I understand the information given to me.

Signature of Subject:

I give my consent to take part in this research study and agree to allow my identifiable information to be used and shared as described above.

Subject

Date

Time (optional)

Signature of Study Doctor or Person Obtaining Consent:

Statement of Study Doctor or Person Obtaining Consent

- I have explained the research to the study subject.
- I have answered all questions about this research study to the best of my ability.

Study Doctor or Person Obtaining Consent

Date

Time (optional)

Consent Form Version Date: 2/17/2022

1
2
3 DSMB Charter

4 Investigation of Cannabidiol for Reduction of NeuroInflammation in Chronic Back Pain
5 1R01DA053316-01

6 Dr. Jodi Gilman and Dr. Marco Loggia
7 NIH
8
9

10 **A. Safety monitoring**

11
12 An independent Data and Safety Monitoring Board (DSMB) will be appointed for this study, to
13 assess the safety of the study by determining whether there is an unacceptable level of risk due to
14 study procedures and whether an increased number of adverse events occur.

15
16 The DSMB will be established to analyze interim results to assess the safety of the trial at regular
17 intervals for the duration of the study by determining whether an increased number of adverse
18 events occur among study participants receiving drug compared to participants
19 receiving placebo.
20

21
22 The board will include a statistician, a pain expert, and a psychiatrist. Each member of the
23 DSMB will not otherwise be associated with the trial. Safety data will be reviewed by the Data
24 and Safety Monitoring Board Data every 6 months after the recruitment period begins. The
25 DSMB will receive summary reports on recruitment, retention and description of all adverse
26 events and review them at each biannual DSMB meeting. The DSMB will receive all
27 communication with the IRB. Subject information provided to the board will be identified only
28 with study IDs to protect the confidentiality of subjects. The DSMB will assess interim results to
29 determine whether the active drug treatment is associated with substantial risk, including higher
30 rate of adverse outcomes when compared with the placebo group.
31
32

33 **B. Outcomes monitoring**

34
35 A DSMB Report written by the chair and approved by all members will be issued to
36 the IRB after every DSMB meeting. The report will include, but may not be limited to, a
37 synopsis of the trials, their progress to date, characteristics of participants enrolled, retention and
38 disposition of study participants, quality assurance issues, regulatory issues, and reports of AEs
39 and SAEs.
40
41

42 DSMB Role	43 Name and Title	44 Affiliation/ Institution	45 Contact Details	46 Summary of Expertise
47 DSMB Chair and Statistician	48 Bettina Hoepfner, PhD	49 MGH, Harvard Medical School	50 bhoepfner@mgh.harvard.edu	51 Statistician
52 DSMB Pain Expert	53 Jianren Mao, MD	54 MGH	55 jmao@mgh.harvard.edu	56 Pain physician

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DSMB Psychiatrist	Esther Blessing, MD, PhD	NYU Grossman School of Medicine	esther.blessing@nyulangone.org	CBD, psychiatric disorders
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Trial investigators will not be members of the DSMB.

For peer review only



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page #
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	Included throughout the paper
Protocol version	3	Date and version identifier	14
Funding	4	Sources and types of financial, material, and other support	14
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1, 14
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	14
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	10 (and see Item 21a for data safety monitoring board)
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4

1			
2		6b	Explanation for choice of comparators
3			4
4	Objectives	7	Specific objectives or hypotheses
5			4
6	Trial design	8	Description of trial design including type of trial (eg,
7			parallel group, crossover, factorial, single group),
8			allocation ratio, and framework (eg, superiority,
9			equivalence, noninferiority, exploratory)
10			4, 8
11			
12	Methods: Participants, interventions, and outcomes		
13			
14	Study setting	9	Description of study settings (eg, community clinic,
15			academic hospital) and list of countries where data will
16			be collected. Reference to where list of study sites can
17			be obtained
18			
19	Eligibility	10	Inclusion and exclusion criteria for participants. If
20	criteria		applicable, eligibility criteria for study centres and
21			individuals who will perform the interventions (eg,
22			surgeons, psychotherapists)
23			
24			5-6, Table 1
25	Interventions	11a	Interventions for each group with sufficient detail to
26			allow replication, including how and when they will be
27			administered
28			
29			6-9, Table 2
30		11b	Criteria for discontinuing or modifying allocated
31			interventions for a given trial participant (eg, drug dose
32			change in response to harms, participant request, or
33			improving/worsening disease)
34			
35			8, 12
36		11c	Strategies to improve adherence to intervention
37			protocols, and any procedures for monitoring adherence
38			(eg, drug tablet return, laboratory tests)
39			
40			8, 9
41		11d	Relevant concomitant care and interventions that are
42			permitted or prohibited during the trial
43			
44	Outcomes	12	Primary, secondary, and other outcomes, including the
45			specific measurement variable (eg, systolic blood
46			pressure), analysis metric (eg, change from baseline,
47			final value, time to event), method of aggregation (eg,
48			median, proportion), and time point for each outcome.
49			Explanation of the clinical relevance of chosen efficacy
50			and harm outcomes is strongly recommended
51			
52			Table 1
53	Participant	13	Time schedule of enrolment, interventions (including
54	timeline		any run-ins and washouts), assessments, and visits for
55			participants. A schematic diagram is highly
56			recommended (see Figure)
57			
58			4, Table 2,
59			Figure 1
60			(schema)

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	5

Methods: Assignment of interventions (for controlled trials)

Allocation:

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	12

Methods: Data collection, management, and analysis

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6-10, Table 2
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1				
2		18b	Plans to promote participant retention and complete	11-12
3			follow-up, including list of any outcome data to be	
4			collected for participants who discontinue or deviate	
5			from intervention protocols	
6				
7	Data	19	Plans for data entry, coding, security, and storage,	10
8	management		including any related processes to promote data quality	
9			(eg, double data entry; range checks for data values).	
10			Reference to where details of data management	
11			procedures can be found, if not in the protocol	
12				
13				
14	Statistical	20a	Statistical methods for analysing primary and secondary	10-11
15	methods		outcomes. Reference to where other details of the	
16			statistical analysis plan can be found, if not in the	
17			protocol	
18				
19				
20		20b	Methods for any additional analyses (eg, subgroup and	11
21			adjusted analyses)	
22				
23		20c	Definition of analysis population relating to protocol non-	11-12
24			adherence (eg, as randomised analysis), and any	
25			statistical methods to handle missing data (eg, multiple	
26			imputation)	
27				
28				
29	Methods: Monitoring			
30				
31	Data	21a	Composition of data monitoring committee (DMC);	12
32	monitoring		summary of its role and reporting structure; statement of	
33			whether it is independent from the sponsor and	
34			competing interests; and reference to where further	
35			details about its charter can be found, if not in the	
36			protocol. Alternatively, an explanation of why a DMC is	
37			not needed	
38				
39				
40		21b	Description of any interim analyses and stopping	12
41			guidelines, including who will have access to these	
42			interim results and make the final decision to terminate	
43			the trial	
44				
45				
46	Harms	22	Plans for collecting, assessing, reporting, and managing	11
47			solicited and spontaneously reported adverse events	
48			and other unintended effects of trial interventions or trial	
49			conduct	
50				
51				
52	Auditing	23	Frequency and procedures for auditing trial conduct, if	N/A
53			any, and whether the process will be independent from	
54			investigators and the sponsor	
55				
56				
57	Ethics and dissemination			
58				
59				
60				

1				
2	Research	24	Plans for seeking research ethics	13
3	ethics		committee/institutional review board (REC/IRB)	
4	approval		approval	
5				
6	Protocol	25	Plans for communicating important protocol	13
7	amendments		modifications (eg, changes to eligibility criteria,	
8			outcomes, analyses) to relevant parties (eg,	
9			investigators, REC/IRBs, trial participants, trial	
10			registries, journals, regulators)	
11				
12				
13	Consent or	26a	Who will obtain informed consent or assent from	13
14	assent		potential trial participants or authorised surrogates, and	
15			how (see Item 32)	
16				
17				
18		26b	Additional consent provisions for collection and use of	Supplementa
19			participant data and biological specimens in ancillary	ry file 2
20			studies, if applicable	(Consent
21				Form)
22				
23	Confidentialit	27	How personal information about potential and enrolled	13
24	y		participants will be collected, shared, and maintained in	
25			order to protect confidentiality before, during, and after	
26			the trial	
27				
28				
29	Declaration	28	Financial and other competing interests for principal	14
30	of interests		investigators for the overall trial and each study site	
31				
32	Access to	29	Statement of who will have access to the final trial	14
33	data		dataset, and disclosure of contractual agreements that	
34			limit such access for investigators	
35				
36				
37	Ancillary and	30	Provisions, if any, for ancillary and post-trial care, and	N/A
38	post-trial		for compensation to those who suffer harm from trial	
39	care		participation	
40				
41	Disseminatio	31a	Plans for investigators and sponsor to communicate trial	2, 13, 14
42	n policy		results to participants, healthcare professionals, the	
43			public, and other relevant groups (eg, via publication,	
44			reporting in results databases, or other data sharing	
45			arrangements), including any publication restrictions	
46				
47				
48		31b	Authorship eligibility guidelines and any intended use of	N/A
49			professional writers	
50				
51		31c	Plans, if any, for granting public access to the full	14
52			protocol, participant-level dataset, and statistical code	
53				
54				
55	Appendices			
56				
57				
58				
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1				
2	Informed	32	Model consent form and other related documentation	Supplementa
3	consent		given to participants and authorised surrogates	ry file 2
4	materials			(Consent
5				Form)
6				
7	Biological	33	Plans for collection, laboratory evaluation, and storage	Supplementa
8	specimens		of biological specimens for genetic or molecular	ry file 2
9			analysis in the current trial and for future use in ancillary	(Consent
10			studies, if applicable	Form)
11				
12				

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.