

**Evaluation of Medical Cannabis and Prescription Opioid Taper Support for
Reduction of Pain and Opioid Dose in Patients with Chronic, Non-Cancer Pain**

NCT04827992

Study Protocol Document Date: November 3, 2025

Statistical Analysis Plan Document Date: October 31, 2025

MGH INSTITUTIONAL REVIEW BOARD DETAILED PROTOCOL

DETAILED PROTOCOL: Evaluation of Medical Cannabis and Prescription Opioid Taper Support for Reduction of Pain and Opioid Dose in Patients with Chronic Non-Cancer Pain

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Version Date: November 3, 2025

I. BACKGROUND AND SIGNIFICANCE

Approximately 50 million adults in the United States suffer from chronic non-cancer pain (CNCP), a debilitating medical condition that is among the most complex to manage [1]. Though nearly 90% of those with CNCP are treated with chronic opioid therapy (COT) [2], the evidence supporting effectiveness of chronic opioid analgesics to improve pain and functioning is weak.[3] Further, use of COT for CNCP has contributed to an epidemic of opioid use disorder (OUD) [2, 4, 5]. In 2016, more than 80,000 individuals died from an opioid overdose in the US [4, 5]. Moreover, in pain clinics, those treated for CNCP have opioid misuse and OUD prevalence of 8-16% and 2-14% respectively [6, 7]. Opioid misuse and OUD significantly increases mortality risk [6, 8] in a dose related manner. The 2016 CDC Guideline for Prescribing Opioids for Chronic Pain [9] recommended several strategies to mitigate these risks of using COT for chronic pain, including 1) prescribing the lowest effective dose, and avoiding escalations of dose above 90 MME/day, and 2) tapering opioids when the risks exceed the benefits. The limited available evidence about outcomes of PO tapering suggests that pain and functioning often improve and do not worsen with opioid dose reduction [10, 11]. Though converging evidence has led to a consensus that COT dose reduction generally improves pain, function, and quality of life in those with CNCP [10], and also reduces risk of OUD and opioid overdose deaths, optimal strategies for reducing opioid dose in real-world settings are largely unknown [12].

The cannabinoid CB1 and CB2 receptors of the endocannabinoid system modulate pain-processing pathways [13, 14]. CB2 receptor agonists indirectly stimulate opioid receptors located in primary afferent pathways [15], and therefore, in addition to their direct analgesic effects that are independent of opioid receptor activation, it has been hypothesized that cannabinoids may work synergistically with opioid analgesics to reduce pain. Initial pre-clinical studies have been promising, as animal models have identified a role for CB1 receptor activation in reducing neuropathic, visceral, and inflammatory pain [16], and several pre-clinical studies have suggested that systemic use of cannabinoid receptor ligands produces analgesia in acute and chronic pain models [17]. A meta-analysis of 19 pre-clinical studies (with acute-dosing paradigms) demonstrated that combining a cannabinoid with an opioid produced a synergistic analgesic effect, better than each individual drug alone [18]. Human laboratory studies also indicated that cannabidiol (CBD), a constituent of medical marijuana (MM), may reduce craving for opioids in those with OUD [19, 20].

As of May 2020, MM has been legalized in 33 states and Washington, D.C. CB began to be conceptualized as a 'substitute' for opioids following a report that states with legal MM had lower-than-expected opioid overdose (OOD) mortality rates from 1999 to 2010 [21]. Without further evidence for efficacy, MM was approved by several states as a treatment for OUD [22]. A reanalysis of the state level data, with longer duration of data collection (through 2017), reported the opposite result; rather than a 21% lower than expected OOD rate, the new analysis with more data showed states with MM had a 23% increased rate of OOD [23]. Further, a recent 4-year, longitudinal study of CNCP patients found that MM use among those on opioids neither improved patient outcomes nor exerted an opioid-sparing effect (an effect whereby co-administration of MM with opioids would enable opioid dose reduction without loss of analgesic efficacy) [24]. In contrast, a report of a single-site retrospective cohort study claimed that among 180 patients with chronic low back pain on COT, half stopped all opioid medications and a further 31% reduced their opioid dose after starting MM [25]. Despite limited and controversial evidence for MM efficacy on COT [26], chronic pain is the most common reason that individuals seek MM cards [27], many adults with CNCP are trying MM to try to improve their pain and functioning and to reduce opioid doses and are asking clinicians for guidance.

Rationale behind the proposed research, and potential benefits to patients and/or society

There are no published reports of randomized trials of cannabis (CB) or MM effectiveness for reducing opioid dose. Findings from clinical trials on the effectiveness of cannabinoids for chronic pain

are inconsistent and most studies have serious limitations, such as lack of control conditions. A 2018 Cochrane review[26] examined 16 studies involving 1750 individuals and concluded that “there is a lack of good evidence that any cannabis-derived product works for any chronic neuropathic pain.” This review included studies of oromucosal spray with a plant-derived combination of tetrahydrocannabinol (THC) and cannabidiol (CBD; 10 studies), a synthetic cannabinoid mimicking THC (nabilone; 2 studies), inhaled herbal cannabis (2 studies), and plant-derived THC (dronabinol; 2 studies). A 2017 review by the Department of Veterans Affairs similarly concluded that there was insufficient evidence of the efficacy of cannabis for populations with chronic pain (though they determined that evidence suggested cannabis may alleviate neuropathic pain) [28]. Yet, a 2017 report from the National Academies of Sciences, Engineering and Medicine (NASEM) concluded that there was “conclusive or substantial evidence” that cannabis is effective in treating chronic pain, though this report did not separate different types of pain in this analysis [29]. The most consistent evidence for the effectiveness of cannabis is for neuropathic pain [30-33], though this clearly needs further study.

Healthcare providers are increasingly confronted with patients who are interested in using cannabis to treat various disorders, especially CNCP, and evidence-based studies do not exist to offer guidance regarding risks of addiction, basic use behavior, or side effect profiles of MM. In contrast to medicines that undergo FDA review, MM lacks basic information about safety, efficacy, and adverse effects. Evidence to support the effectiveness of CB for chronic pain is controversial [34], and evidence for CB to treat OUD, or even to promote successful opioid tapering, is virtually non-existent [24]. Moreover, data is lacking on whether those who use CB for chronic conditions develop similar rates of addiction to those who use cannabis for recreational purposes. The most recent US national data reports that 3 out of 10 cannabis users develop CUD, and 23% of these are symptomatically severe (≥ 6 CUD criteria) [35]. Cannabis users also develop physical dependence on the drug, reporting tolerance to many of the effects of THC [36, 37]. Thus, controlled trial data is critically needed to evaluate opioid sparing claims in this population, and to assess impact of adding CB to COT on pain, symptoms of OUD, other SUD, cognition, and other outcomes that are critical to this decision-making.

This will be the first randomized, pragmatic trial to test whether CB use by adults on high-dose COT for CNCP is associated with reduced opioid dose and improved pain severity when added to a behavioral intervention. Results will provide critical information to patients and providers about potential benefits, as well as unintended consequences, of using CB to treat chronic pain, a practice that is widely publicized as effective and low risk. This study will provide data to help patients and providers weigh risks and benefits of CB and make more informed treatment decisions.

II. SPECIFIC AIMS

The goal of this proposal is to assess whether cannabis, when added to a 24-week behavioral prescription opioid taper support (POTS) program that has been shown to support safe opioid dose reduction without worsening of pain, reduces opioid dose and improves pain intensity and interference in adults on COT for CNCP, more so than POTS alone (without the addition of CB).

Aim 1: Evaluate whether adults with CNCP on COT assigned to CB+POTS, compared with those assigned to WL+POTS, have greater reduction in opioid dose (prescription monitoring program verified MME/day), and/or greater improvement in pain intensity and interference (PEG Scores) from baseline to 24 weeks (*co-primary outcomes*). These outcomes will be assessed via Prescription Monitoring Program data and daily diaries.

Aim 2: Evaluate whether participants assigned to CB+POTS, compared with those assigned to WL+POTS, have improved quality of life (Q-LES-Q-SF), depression (PROMIS-29), and anxiety (PROMIS-29); and reductions in self-reported opioid dose (MME/day).

Aim 3: Evaluate whether those assigned to CB+POTS develop symptoms of CUD over the 24-week intervention, as well as at the 12-month time point. This will be assessed by the DSM-5 Cannabis Use Disorder Checklist. We also plan to evaluate whether those assigned to CB+POTS have a reduced number of OUD symptoms (DSM-5 OUD Checklist) at 24 weeks compared to the WLC.

This is a multi-site trial. Cambridge Health Alliance (CHA) and Maine Medical Center (MMC) will be engaged in conducting the same study procedures as MGH and will rely on the oversight of the MGB IRB.

III. SUBJECT SELECTION

Inclusion Criteria:

1. Men and women aged 18-75, inclusive.
2. Endorsing > 6 months of CNCP
3. On stable prescription opioid doses of ≥ 25 MME/day for >90 days, verified by the Prescription Monitoring Program.
4. Either no prior use or current light cannabis use (weekly or less in the past 12 months).
5. Plans to use medical cannabis for pain to control pain and/or reduce opioid dose.
6. Competent and willing to provide written informed consent in English.
7. Potential participants of childbearing potential must not be pregnant at enrollment. They will be asked to self-report pregnancy status and the start date of their most recent menstrual period and agree to use effective contraception: abstinence; hormonal contraception; intra-uterine device, sterilization; or double barrier contraception, during the study.

Exclusion Criteria:

1. Current cannabis use (including inhaled or ingested CBD products) of greater than weekly on average in the past 12 months, assessed via self-report (no more than 10 times in the last 90 days).
2. Current cannabis use disorder; moderate to severe substance use disorder for any substance (e.g., alcohol, cocaine, stimulant) by structured interview, EXCEPT nicotine and opioids (OUD).
3. Current uncontrolled major medical illness, such as cancer, cardiovascular disease, sickle cell disease, symptomatic hypothyroidism/hyperthyroidism or severe respiratory compromise.
4. Use of non-prescribed opioids, by self-report.
5. Dose change or initiation of medications with significant analgesic effects (e.g., tricyclic antidepressants, SSRIs, gabapentin, NSAIDs) in the past 4 weeks.
6. Concomitant medications will be discussed at each visit, and any medications that may interact with cannabinoids (e.g., warfarin) will be discussed with a study clinician prior to enrollment or continued participation.
7. Actively suicidal and/or suicide attempt or psychiatric hospitalization in past year, or current suicidal ideation with specific plan or intent.
8. History of intellectual disability (e.g., Down's syndrome) or other severe developmental disorder or IQ < 70.
9. Current diagnosis of delirium, dementia, amnesia, or another cognitive disorder; current diagnosis of bipolar II disorder; lifetime diagnosis of bipolar I disorder, schizophrenia spectrum or other psychotic disorder.
10. Surgery within the past month or planned during the next 6 months.
11. Pregnant or trying to get pregnant or breastfeeding.
12. In the opinion of the investigator or study physicians, not able to complete study procedures or safely participate in this study.

Source of subjects and recruitment methods

Participants will be recruited through community advertising, accessing a cross-section of the population in Greater Boston, as well as advertising and physician referral from local MGH clinics, the MGB Healthcare network, the Cambridge Health Alliance healthcare system, and the Maine Medical Center healthcare system. We will also use multiple research databases such as the RSVP for Health system, MGB Clinical Trials, Rally, the Research Patient Data Registry (RPDR), EPIC, and Research Match, a database of research volunteers developed by Vanderbilt University and approved for use by the MGB IRB. We will run queries on EPIC and RPDR to find subjects with chronic pain on stable prescription opioid doses of ≥ 25 MME/day for >90 days, meeting the eligibility criteria for this research study. Subjects identified through these mechanisms will receive a recruitment letter via Patient Gateway or by mail from study staff. The letter will not be sent to those who have opted out of

receiving research invitations. Study staff will also use existing patient registries and lists to show primary care providers lists of their patients on chronic opioid therapy, with a nudge to mention the study to patients in person or by letter. Other methods that advertise the study to the greater community will be used, including social media posts, posting flyers on billboards in the community or in community health centers, emails to physicians and community health centers, and newspaper advertisements. We will also work with a recruiting platform, BuildClinical, to advertise on social media platforms. All advertisements will be IRB approved and will target people who are interested in obtaining CB who endorse >6 months of chronic non-cancer pain (CNCP), are on stable prescription opioid doses of ≥ 25 MME/day for >90 days and have no prior use or current light cannabis use (monthly or less in the past 12 months). Potential participants will complete a telephone screen for eligibility.

IV. SUBJECT ENROLLMENT

Study staff will conduct telephone screening in response to a potential participant inquiry. A telephone screening will distinguish most potentially eligible subjects from those not meeting eligibility criteria. Telephone screening will consist of a brief discussion of the research study, confirming a potential participant's understanding of the basic study procedures, interest in participation and whether he/she meets eligibility criteria and includes asking for current medications, gender, age, pregnancy status, and history of psychiatric conditions including substance use disorders. Those not eligible for the experiment based on the phone screen will be informed that they do not qualify for entry into this particular study. 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.

All individuals who expressed interest in participating in the study and are potentially eligible based on the telephone screen will be scheduled for an in-person or remote enrollment visit to sign consent and complete eligibility screening procedures.

Procedures for obtaining informed consent

MGH staff will schedule potentially eligible participants for a screening visit. The informed consent form will be sent to the participant prior to the screening visit to allow for time to review. During the enrollment visit, the usual discussion of procedure, risks, side effects, confidentiality, voluntary participation, and right to refuse participation without prejudice will be explained to participants by a trained member of the study staff prior to administering any study procedures. All participants will be given the opportunity to ask questions to a doctoral-level member of the study staff during the consent process. Participants must be capable of understanding the nature of this study, its potential risks, discomforts, and benefits before signing consent. Contact information of key MGH study staff will be provided to participants, they will be encouraged to ask any questions or concerns they may have about the study. All participants will be provided with a copy of their signed consent forms.

To comply with public health efforts to address COVID-19 and to expand access to diverse populations, 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).

If the screening visit is conducted virtually, informed consent will be obtained remotely. This will be done via electronic consent using an IRB approved-platform (e.g., MGB REDCap e-consent, Adobe eSign), or a remote consent process where the participant will be asked to sign the consent form and return back by email or mail. In either case, the consent discussion will occur identically to an in-person visit, but instead held over phone call or video conference. At the time of such visit, informed consent will be obtained by a trained member of the study staff with investigator back-up. All participants will be given the opportunity to ask questions to a doctoral-level member of study staff or

an Investigator during the consent process. 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 MGB REDCap and through a Note to File for each subject for which it was obtained remotely. The e-consent template being utilized is equivalent to written consent and is IRB-approved. As is with in-person consent, the study team will obtain and document informed consent before the participant is enrolled and any study procedures begin.

Treatment assignment, and randomization

Eligible participants will be randomly assigned in blocks of 3-6, to CB+POTS or WL+POTS. If we find that more patients drop out in the WL+POTS group, we will randomize, in blocks of 6, 1:2 CB+POTS: WL+POTS to achieve our goal of 100 patients completed in each arm by the end of the trial.

Randomization will be computer generated. Assessments will be conducted by study staff blind to the study intervention.

V. STUDY PROCEDURES

Participants who express interest in participating in the study will undergo a telephone screen to assess eligibility. If eligible, they will be scheduled for a screening (enrollment) visit, during which a consent procedure will be conducted with the study staff with a PhD-level investigator available for questions.

Enrolled participants will be scheduled for a baseline study visit (V1, week 0), during which a baseline assessment of questionnaires, cognitive testing, and interviews will be conducted. Following completion of the first intervention session (S1, Week 1), participants will be randomly assigned to either the CB+POTS group or the WLC+POTS group. Participants assigned to CB+POTS will be able to use dispensary cannabis products without delay. All participants will be scheduled for a weekly POTS behavioral intervention group.

Participants will be scheduled for repeat study visits at approximately 4, 8, 12, 16, 20, and 24 weeks. At each study visit, participants will be asked to complete questionnaires, interviews, cognitive tests (V7, Week 24) and qualitative urine testing (V2, V4, V7). Our primary endpoint is the 24-week assessment.

A follow-up visit is scheduled at approximately 52 weeks and will assess further long-term changes in our outcomes of interest.

Some or all of the study visits may be conducted virtually using an IRB-approved platform (i.e., Zoom, Cisco Jabber).

a. Study visits and parameters to be measured

Screening Visit (V0):

After a participant has met basic eligibility criteria over the phone, they will be scheduled for an enrollment visit where potential participants will be consented to the study based on procedures previously described under Procedures for Obtaining Informed Consent. After Informed Consent is obtained, the following procedures will take place to determine the subject's eligibility:

- i. Interviews: Medical history and assessment of current medical conditions, concomitant medications, substance use history, MINI Neuropsychiatric Interview, DSM-5 OUD Checklist, DSM-5 CUD Checklist
- ii. Assessments/Questionnaires: Contact information, demographics, family medical history (KSADS), Brief Pain Inventory- Short Form,
- iii. WTAR Reading Ability Test (IQ)

Study staff approved to use the Prescription Monitoring Program (PMP) (study physicians and their delegates) will use the PMP to document statewide prescriptions for opioid medications and

other medications monitored by the PMP doses and verify the subject's prescription opioid dose for eligibility ($\geq 25\text{MME}$ for at least 90 days). Study staff will use the electronic medical record to document concomitant medications prescribed by caregivers in the MGB, CHA, and MMC systems of care to improve the accuracy of and augment self-report of concomitant medications.

As part of study procedures, participants will be asked to share their participation in the study with their treatment team(s) and provide contact information for their prescribing physician to the study team. Study staff will contact the provider(s) primarily responsible for the participant's opioid prescribing at the time of enrollment to inform them of the participant's participation in the study, and again each time a new dose is agreed upon by the participant and the study team. Decisions regarding opioid dose adjustment are subject to approval by the prescribing physician.

Participants who give permission to receive text messages from the study staff will receive appointment reminders via text one week and one day before upcoming appointments.

Baseline visit to week 24:

Study visits will take place approximately at study weeks 0 (baseline), 4, 8, 12, 16, 20, and 24. Data collection at these visits will include: self-administered assessments, clinician-administered assessments, and a urine drug test. See time and events table. Assessments will use standard, validated measures, selected for consistency with the PhenX Toolkit [38], the IMMPACT recommendations for chronic pain trials [39], and the NIH Research Standards for Chronic Low Back Pain [40], many of these items and scales are also PROMIS measures [41, 42]. Using these measures will improve data harmonization and the ability to interpret our findings in the context of other rigorous pain trials. Data collection at study visits will also include covariates including sociodemographic information and clinical characteristics comprising pain type/location and duration on opioids (baseline) as well as current opioid dose and non-opioid pain medications or treatments (all study visits).

Follow up study visit (week 52):

At this long-term follow up visit, data collection will include self-administered assessments such as the PROMIS-29, BPI, PEG Scale, SPS-10, and Readiness Ruler, as well as clinician-administered assessments including the timeline follow back (one month, cannabis only), DSM OUD Checklist, DSM CUD Checklist, and adverse events. Current prescription opioid dose will be verified with PMP data.

Obtaining CB: Participants can obtain CB at medical dispensaries or recreational shops.

Participants can use any type of CB they chose; study staff will assess brands, amount used (days per week, times per day), method of use (smoke/consume), apparatus (bong/bowl/pipe, vaporizer, joint, blunt, edibles, dabs/wax, spliff, other), and potency of THC/CBD and other cannabinoids, if known. Participants will be responsible for the cost of the CB.

Time and Events Table

Measure	Instrument	Visit 0 Screen	Visit 1 Week 0	Visit 2 Week 4	Visit 3 Week 8	Visit 4 Week 12	Visit 5 Week 16	Visit 6 Week 20	Visit 7 Week 24	Week 52
Demographics	Custom (PhenX-based)	x								

Medical History	Custom (MedDRA, Review of Symptoms)	x								
Family History	Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS)	x								
Quality of Life	Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q SF)		x	x	x	x	x	x	x	
	Patient Global Impression of Change		x			x			x	
Social Support	10-Item Social Provisions Scale (SPS-10)		x						x	X
Pain	Brief Pain Inventory Short Form (BPI)	x	x	x	x	x	x	x	x	x
Depression, Anxiety, Sleep	PROMIS-29		x	x	x	x	x	x	x	X
Cognitive Functioning	California Verbal Learning Test (CVLT)-3		x						x	
	Weschler Adult Intelligence Scale (WAIS)-IV		x						x	
IQ	WTAR	x								
Cannabis Use Disorder	DSM-5 CUD Checklist	x	x			x			x	x
Opioid Misuse	Current Opioid Misuse Measure		x	x	x	x	x	x	x	
Opioid Problems	Prescribed Opioid Difficulties Scale		x	x	x	x	x	x	x	
Opioid Withdrawal Scale	Clinical Opioid Withdrawal Scale		x	x	x	x	x	x	x	
	Short Opiate Withdrawal Scale		x	x	x	x	x	x	x	
Substance use	Urine drug test (THC)			x		x			x	
	Substance Use History (Custom)	x								

Opioid Use Disorder (OUD)	DSM-5 OUD Checklist	x	x	x	x	x	x	x	x	x
Pain Impact	Pain Self-Efficacy Questionnaire		x	x	x	x	x	x	x	
Pain Catastrophizing	Pain Catastrophizing Scale		x	x	x	x	x	x	x	
Distress	Distress Tolerance Scale		x			x			x	
Pleasure	Snaith-Hamilton Pleasure Scale		x			x			x	
Psychiatric Disorders	Neuropsychiatric Interview	x								
Delusions/ Psychotic Experiences	Peters Delusion Inventory (PDI)		x						x	
Suicidality and Risk Taking	CHRT		x	x	x	x	x	x	x	
Experience(s) of Trauma	Brief Trauma Questionnaire			x						
Frequency of substance use	TLFB (CB, EtOH, nicotine, other drugs)	x	x	x	x	x	x	x	x	X (Cannabis only)
Cannabis Use	Cannabis Use Disorder Identification Test (CUDIT)		x						x	
Marijuana Expectancies	Medical Marijuana Effects Expectancy Questionnaire		x						x	
Medical Marijuana Use	Canadian Cannabis Survey (Medical Use Only)								x	
Program Evaluation	POTS Program Evaluation								x	
Adverse events (AEs)	Adverse Event Record		x	x	x	x	x	x	x	x
Metabolites in Urine (only CB +POTS group)	Cannabis metabolites								x	
Concomitant Medication Changes	Concomitant Medication Record	x	x	x	x	x	x	x	x	
Opioid Dose (self-report)	MME/day (daily)	x	x	x	x	x	x	x	x	
Opioid Dose (PMP-verified)	MME/day	X	X	X	X	X	X	X	X	X
Pain Intensity and Interference	PEG (Pain, Enjoyment, General Activity) Scale (Range 0-30; daily)	x	x	x	x	x	x	x	x	X
CB use	CB Use Frequency (daily)	x	x	x	x	x	x	x	x	

Readiness to Change	Readiness Ruler		x	x	x	x	x	x	x	X
Group Dynamics	Group Climate Questionnaire								x	

b. Drugs to be used N/A

c. Devices to be used: N/A

d. Interventions

Prescription Opioid Taper Support (POTS), a manualized behavioral prescription opioid taper support intervention developed by consultant, Dr. Judy Turner [11], will be offered weekly to all participants to support behavioral self-management of pain and structured, voluntary taper of COT dose. POTS has been validated for use in person, by phone, and videoconference. We plan to deliver sessions via videoconference or in-person. Sessions will be led by a trained clinician. There is no cost to subjects or their insurance for these sessions. With participant consent, POTS sessions will be video recorded to assess treatment fidelity.

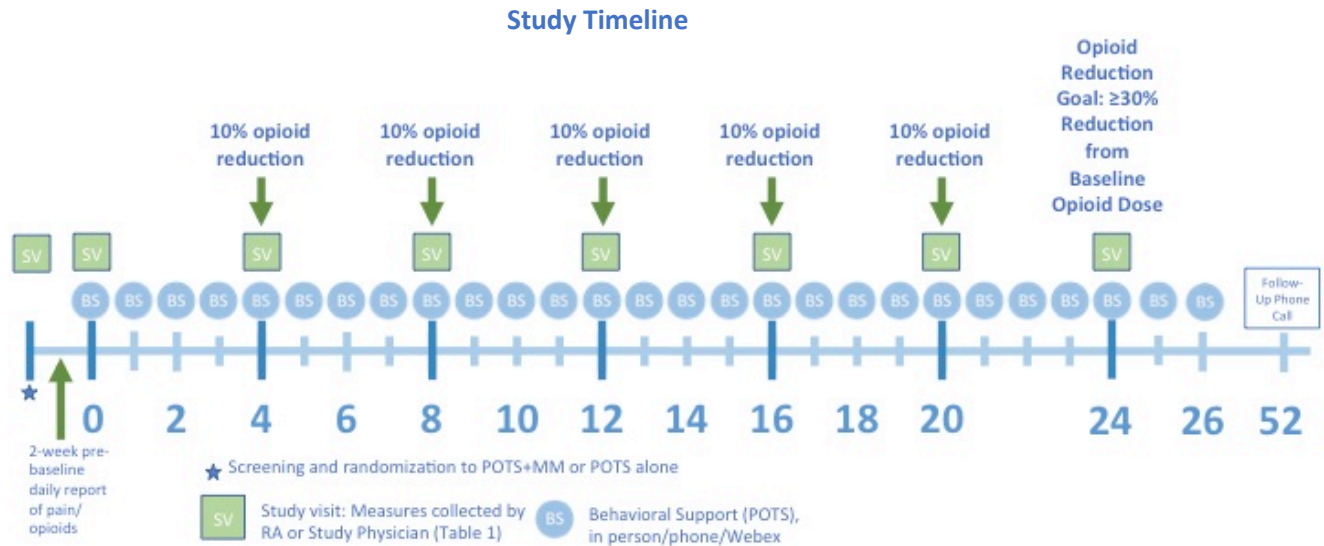
POTS sessions will be focused on individualized problem solving for behavioral self-management of pain and pros and cons of COT dose taper. During the 5 POTS sessions in study weeks 4-20 that coincide with the monthly study visits, study clinicians will work with participants to reduce opioid dose in increments of approximately 10% of the baseline opioid dose.

At the first intervention session (following consent, enrollment, and baseline study visit) participants will be introduced to the process of opioid tapering. They will participate in a discussion of topics including:

- 1) describing their history of pain and benefits and difficulties with opioid therapy,
- 2) education on the health risks of high dose COT, and
- 3) identifying barriers that they may perceive to tapering opioid dose and strategies to overcome them.

Participants will be encouraged but not required to taper their opioid dose. At visits at (approximately) weeks 4, 8, 12, 16, 20, if the patient agrees, an opioid dose reduction as close to 10% of opioid dose at study start as is practical will be initiated, as reported by consultants Drs. Mark Sullivan and Judy Turner [11]. Participants can choose at any of these 5 visits to not decrease their opioid dose or to decrease their opioid dose by any amount agreed upon with their study clinician. The study clinician will not recommend an increase in opioid dose over their baseline dose. All participants, whether or not they increase their opioid dose, will be encouraged to remain in the study and attend both POTS and monthly study visits and follow up visits, so their outcome data can be collected, and will be incentivized to do so.

Two POTS sessions will be conducted in weeks 25-26 to facilitate and coordinate return of care to the primary care physician, and the clinician will consult on adjunctive therapy that may be beneficial for pain control and maintenance of opioid dose achieved in the trial or continuation of dose taper. POTS sessions will not be focused on CB; clinicians will be instructed to neither encourage nor discourage CB use as they work to optimize behavioral pain management strategies. This is natural for this intervention, as its focus is on non-pharmacological approaches to pain and opioid dose taper.



e. Data to be collected

Dosing Diaries. We will collect data every day for approximately 26 weeks (plus approximately a 2-week pre-baseline period to establish levels of pain and symptoms) using a REDCap daily survey. The link will be sent via text message. Participants will be asked to enter a four-digit code prior to completing the survey to protect privacy, and participants will have the opportunity to opt out of receiving text messages. Participants will be asked to keep a daily log of (1) opioid dose (MME/day), (2) pain intensity and interference, which will be assessed with the PEG scale (3) CB use, and (4) ratings of sleep quality, mood, and general health. To encourage daily reporting, participants will receive daily micro-reimbursements for reporting opioid/ CB use in their dosing diaries, including no use. At the screening visit, we will teach participants to use the diaries and participants will be asked to begin completing the daily survey 2-weeks prior to their baseline visit.

Urine Testing. At study visits 2, 4, and 7, participants will provide a urine sample, which will be qualitatively screened for THC. The urine sample will be used to verify that those assigned to the WL+POTS condition are not using cannabis. In addition, participants in the CB +POTS group will provide a urine sample which will be sent to the Pharmacy and Therapeutics Committee at the University of Colorado School of Medicine for a quantitative metabolite assay that will measure cannabis metabolites. Metabolites will be assessed at week 24.

For remote visits, participants will be asked to consent to shipping their urine samples to study staff for analysis of cannabinoid metabolites. Participants who consent will receive urine sample kits by mail after their screening visit, and prior to any subsequent remote visits. We developed SOPs for safe at home collection and mailing of biological specimens, a procedure that was piloted during the closure of MGH clinical research facilities from March-June 2020. For shipments back to the Center for Addiction Medicine office (V7), participants will be instructed to leave the packaged sample at the location where their mail is picked up at their home before the scheduled pickup time. Study staff will schedule a UPS or FedEx pickup for overnight shipping from the participant's home to the Center for Addiction Medicine office.

Quality of Life Enjoyment and Satisfaction Questionnaire - Short Form (Q-LES-Q-SF) [43] is a 16-item self-administered questionnaire that captures life satisfaction over the past week. It will assess an individual's perceived general physical and mental health and has been shown to be both a reliable measure of self-reported health and a powerful predictor of mortality and morbidity. It will be administered at all study visits.

Patient Global Impression of Change is a 7-point scale recommended by IMMPACT [39], to assess patient satisfaction with treatment at Weeks 0, 12, and 24.

Brief Pain Inventory (BPI)[44] interference subscale score (0 to 10) will assess pain impact (pain-related function) over the past week and is sensitive to change [45]. It will be administered at all study visits and the 52-week follow up call.

PROMIS-29 (v2.0)[42] is a well-validated measure recommended for use in chronic pain trials by both IMMPACT and the NIH Research Standards for Chronic Low Back Pain [39-42]. Three subscales will be administered at all study visits. The depression subscale assesses self-reported negative mood (sadness, guilt), views of self (self-criticism, worthlessness), and social cognition (loneliness, interpersonal alienation), as well as decreased positive affect and engagement (loss of interest, meaning, and purpose). The anxiety subscale assesses self-reported fear (fearfulness, panic), anxious misery (worry, dread), hyperarousal (tension, nervousness, restlessness), and somatic symptoms related to arousal (racing heart, dizziness). The sleep disturbance subscale assesses sleep quality.

California Verbal Learning Test (CVLT)-3 is a comprehensive assessment of learning and memory for older adolescents and adults. The CVLT is considered to be the most sensitive measure of episodic verbal learning and includes standardized scores across a variety of demographic measures. The CVLT-3 includes both standard and alternate forms, one of which will be administered at baseline (V1) and the other will be administered at 24 weeks (V7).

Weschler Adult Intelligence Scale (WAIS)-IV is a measure of cognitive ability for which normative data is available. We will measure working memory using the Digit Span Task. It will be administered at baseline (V1) and 24 weeks (V7).

DSM-5 Cannabis Use Disorder Checklist [47] will evaluate for symptoms of CUD. It will be administered at screening, weeks 0, 12, and 24, and 52-week call.

Timeline follow-back (TLFB) [48] will assess opioids, cannabis, alcohol, nicotine, and other illicit substance use and will be completed at all screening and all study visits. A one-month timeline follow-back for cannabis only will be administered at the 52-week call.

The DSM-5 Opiate Use Disorder Checklist [47] will evaluate for diagnosis and symptoms of OUD will be administered at screening, all study visits, and 52-week call.

The Current Opioid Misuse Measure (COMM) [49] is a brief patient self-assessment that assesses aberrant behaviors associated with misuse of opioid medications will be administered at each study visit

The Prescribed Opioid Difficulties Scale (PODS) [50] will assess common difficulties that patients ascribe to chronic opioid therapy, such as opioid control concerns and psychosocial problems will be administered at each study visit

The Clinical Opioid Withdrawal Scale (COWS) [51] will assess opioid withdrawal symptoms and will be administered at each study visit

The Short Opiate Withdrawal Scale (SOWS) will assess self-reported opioid withdrawal symptoms and will be administered at each study visit.

The Pain Self-Efficacy Questionnaire [52] will be collected at all study visits.

The Pain Catastrophizing Scale (PCS) [53] will be collected at all study visits.

Weschler Test of Adult Reading (WTAR) is a measure to predict full-scale IQ with a range of 0-40.

Concise Health Risk Tracking Self-Report form (CHRT-SR)[54]: The 12-item CHRT-SR assesses active suicidal ideation and behavior, perceived lack of social support, and hopelessness. The scale ranges from 0 – 48, with a higher score indicating greater suicidal thoughts and propensity.

Social Provisions Scale – 10 (SPS-10)[55]: The 10-item SPS-10 assesses social support. It measures six social needs, including guidance, reliable alliance, reassurance of worth, attachment, and social integration. The scale ranges from 10 – 40, with a higher score indicating greater social support.

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.

Family history: The family history subsection of the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) [56] 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.

Distress Tolerance Scale (DTS) will assess perceived capacity to endure distress.

Snaith Hamilton Pleasure Scale (SHAPS) will assess anhedonia and ability to experience pleasure.

Mini International Neuropsychiatric Interview (MINI) [57]: 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.

Peters Delusion Inventory Test (PDI) [58] is a 21-item measure that will assess delusions as well as distress, preoccupation, and conviction.

Medical History: We will assess medical history at screening visit to help determine study eligibility.

Concomitant Medications. We will assess changes to dose, frequency, and use of all concomitant medications at screening and all study visits.

Pregnancy status. Pregnancy status for participants of childbearing potential will be confirmed by participant self-report and documentation of the start date of last menstrual cycle in medical history at V0.

Adverse events. Adverse events from cannabis (e.g., paranoia, anxiety), fatal or non-fatal overdose events, along with all other AEs (accidents, falls) will be assessed at all study visits and the 52-week call.

Readiness Ruler: We will assess stage of change and motivation to reduce opioid dose at all study visits and the 52-week call.

PEG (Pain, Enjoyment, General Activity) Scale [59]: The PEG will be used to assess pain intensity and interference. The scale ranges from 0-30, with a lower score indicating lesser pain intensity and interference.

Brief Trauma Questionnaire (BTQ) [60]: The BTQ assesses 10 traumatic events: (1) combat, (2) serious car accident, (3) major natural or technological disaster, (4) life-threatening illness, (5) physical punishment as child, (6) physical assault, (7) unwanted sexual contact, (8) other situation in which respondent was seriously injured or feared being seriously injured or killed, (9) violent death of close friend or family member, and (10) witnessing a situation in which someone was seriously injured or killed or in which respondent feared someone might be seriously injured or killed.

Cannabis Use Disorders Identification Test – Revised (CUDIT-R)[61]: The CUDIT-R is an 8-item questionnaire that screens for problematic cannabis use in the past six months. It assesses problems related to cannabis use, dependence, and use frequency. The scale ranges from 0 – 32; a score of 13 or higher is indicative of possible cannabis use disorder.

Medical Marijuana Effects Expectancy Questionnaire (MMEEQ): The MMEEQ evaluates medical marijuana expectancies and was developed by Dr. Gilman for use in a randomized clinical trial of the effect of medical marijuana card ownership in adults on symptoms of pain, insomnia, anxiety, and depression. This questionnaire is the first longitudinally validated measure of medical marijuana expectancies. The MMEEQ will be administered at V1 and V7.

Program Evaluation Survey: A POTS program evaluation survey will be administered at V7. This survey will assess frequency of use and perceived helpfulness of pain management techniques covered in the behavioral intervention.

The Canadian Cannabis Survey 2020 (CCS): This survey aims to gather information about use of cannabis for medical purposes and the reasons for this use, including information on patterns of use, quantities used, sources and prices, and issues of public safety such as impaired driving.

Group Climate Questionnaire [62]: A 12-item measure completed by group facilitators to assess group psychotherapy dynamics. This measure contains 3 sub scales including overall group engagement, conflict, and avoidance of responsibilities. This will be completed following completion of the group intervention at V7/Week 24.

Early Termination

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.

Study compensation

Participants will be paid by check up to \$1150 for completing all study procedures. Remuneration will be \$40 for all of the 8 study visits, \$30 for the follow up phone call, up to \$540 for attending the POTS sessions at \$20 per session, and up to \$280 for daily diary completion from pre-baseline through Week 24, at up to \$10 per week (e.g., \$1 for each day, and a \$3 bonus for completing 7 out of 7 days to incentivize for completeness). Participants will also be paid up to \$5 per study visit for travel costs and can also receive parking validation for parking at MGH garages during study visit.

Week#	visit	
-2	Screening	\$40
0	Baseline	\$40
4	In person/zoom	\$40
8	In person/zoom	\$40
12	In person/zoom	\$40
16	In person/zoom	\$40
20	In person/zoom	\$40
24	In person/zoom	\$40
52	Phone call/Zoom	\$30
	Dosing Diaries (28 weeks x \$10/week)	\$280

	POTS sessions (26 sessions x \$20/session ; Zoom)	\$520
Total		\$1150

VI. BIOSTATISTICAL ANALYSIS

- Specific data variables being collected for the study (e.g., data collection sheets).
- Study endpoints.
- Statistical methods.
- Power analysis (e.g., sample size, evaluable subjects, etc.).

Statistical Design and Power:

Aim 1: co-primary outcomes:

- The summed score (ranging from 0 to 30) of the 3-item Pain Enjoyment General Activity (PEG) scale [70] where higher scores indicate greater pain severity and/or interference.
 - The PEG scores will be collected daily via self-report through a smartphone app from the baseline assessment to the end of the 24-week period (i.e., up to 168 observations per participant). All post-baseline daily observations for PEG scores through the week 24 visit will be analyzed.
- Prescription monitoring program (PMP) verified opioid dose, in median daily morphine milligram equivalents (MME), defined over the “monthly” (30-day) interval preceding the final (week 24) study visit.
 - The observed median daily MME will be defined over each interval, as well as each interval between study visits, and 30 days after week 24 (totalling 8 intervals pre-baseline, between visits, and after week 24).
 - The observed median may be subject to artifacts in the PMP daily dose that arise commonly due to overlapping prescriptions or to filling prescriptions several days early or late. Therefore, an independent review will be conducted separately by two qualified clinicians who are blind to group assignment, to evaluate the 8 monthly intervals of PMP-reported daily MME in order to correct the MME for artifacts. These clinicians will independently verify the median daily prescribed MME for each month prior and following the baseline and week 24, resulting in 8 measurements. If the separate reviews by the clinicians are in consensus that a MME value other than the observed median dose should be used, the dose will be adjusted in analyses accordingly. If reviewers do not agree, they will discuss and try to reach a consensus. If no consensus can be reached, opioid dose will be defined as the observed median of the daily MME reported by the PMP over the specified 30-day intervals. We will compute inter-rater reliability scores for the clinical reviews and document all dose adjustments from the PMP dose.
 - We expect long periods of stable opioid doses over the 6-month trial. Therefore, our primary analysis will assess differences in prescribed dose over the 30-day interval preceding the visit at week 24 of the study (i.e., opioid dose over month 7 of the study), while accounting for dose in the interval prior to the baseline visit.
 - PMP-based opioid doses will serve as the dose for primary analysis. Self reported dose will be analyzed as a secondary outcome. It is hoped that the PMP dose will capture change in prescriptions and more stable long-term dose reduction than daily self reported dose.

Statistical model

We will analyze both outcomes using a linear regression model. For the PEG score, coefficients and standard errors for the linear model will be obtained using a linear mixed effects model with random intercepts for each therapy group and subject to account for the nested hierarchical structure. If there are issues with model convergence due to the inclusion of two sets of random intercepts, then the models will instead be fit using only random intercepts for subject.

For the PMP verified opioid dose, a linear mixed effects model with random intercepts for each therapy group will be specified, and again if there are issues with model convergence due to the random intercepts then a model without random effects will be fit. The specification of covariates and confirmatory estimate of interest for each outcome is described below.

The p-value for the primary contrast will be computed via a t-test using the coefficient estimate and model-based standard error. The primary contrast testing for a constant effect of CB above and beyond POTS will be deemed statistically significant for $p < 0.025$, thereby ensuring an overall family-wise error rate of 5% despite two primary outcomes.

For each outcome, the key confirmatory effect of interest will be...

PEG scores: The model will include the following covariates: (a) a restricted cubic spline specification for change over days since baseline (with two spline knots placed at recommended data quantiles); (b) A participant's average PEG score over all measurements taken before and at the baseline visit; (c) A participant's median prescription opioid dose (MME) in the interval preceding the baseline visit; and the confirmatory effect of interest, (d) a dummy-coded contrast between WL+POTS (the referent, coded as 0) and CB+POTS (coded as 1), testing whether a constant effect of CB exists, averaged over all time points. In other words, we specify an additive model, adjusting for baseline levels and with main effects for a) the impact of CB and b) change over time, but no treatment by time interaction.

Opioid dose: The model will include the following covariates: (a) a participant's median prescription opioid dose (MME) in the interval preceding the baseline visit; (b) A participant's average PEG score over all measurements taken before and at the baseline visit; and the confirmatory effect of interest, (c) a dummy-coded contrast between WL+POTS (the referent, coded as 0) and CB+POTS (coded as 1), testing whether there is a significant difference in opioid dose at week 24 for WL+POTS versus CB+POTS, holding baseline dose constant (and adjusting for the other listed covariate(s)).

Intent-to-treat analysis

We understand that there may be some contamination between groups (e.g., some patients in the WL+POTS group may use CB, and some patients in the CB+POTS group may decide not to use CB). As this is a pragmatic trial, our primary analysis will be an intent-to-treat analysis, in which all participants will be analyzed by group (CB vs WL+POTS). This intent-to-treat analysis will *be representative of real-world, ecologically valid outcomes*, in which a clinician would recommend CB to a patient, and then the patient would come to a decision about whether CB was helpful, and act accordingly. Therefore, this type of analysis, designed for pragmatic trials such as this, will help inform real-world clinical decision-making. However, we do acknowledge that this intent-to-treat analysis cannot answer the question of whether CB has a biological effect on pain and/or opioid use.

In addition, for the week 24 PMP outcome we will conduct a per-protocol analysis to address the risk of bias by indication (e.g., patients in the WL+POTS group who are suffering worse pain may be more likely to use CB). We will compare those who used CB regularly (weekly or more) vs those who did not use (verified by negative urine screens and no self-reported use) using a marginal structural modeling approach to correct for "confounding by indication" by weighting data by the inverse probability of being in the CB or non-user group.

Sensitivity analyses

For the PMP outcome, we will perform a sensitivity analysis estimating the difference in mean of the monthly median opioid dose at week 24 using a linear mixed effects model fit to all post-baseline data points, with random intercepts for each therapy group and subject to account for the nested hierarchical structure. If there are issues with model convergence due to the inclusion of two sets of random intercepts, then the models will instead be fit using only random intercepts for subject. This model will be fit using the following covariates: (a) a restricted cubic spline specification for change over days since baseline; (b) A participant's average PEG score over all measurements taken before and at the baseline

visit; (c) A participant's median prescription opioid dose (MME) in the interval preceding the baseline visit; (d) a dummy-coded contrast between WL+POTS (the referent, coded as 0) and CB+POTS (coded as 1), and (e) treatment by time interaction terms. From this model, the difference in adjusted mean of the monthly median opioid dose at week 24 between CB+POTS and WL+POTS will be estimated and a Wald hypothesis test will be performed.

In addition, for each primary outcome we will conduct a minimum of 2 sensitivity analyses.

1. We will examine if the direction and significance of the primary contrast between CB+POTS and WL+POTS is robust to the inclusion of additional covariates, specifically age (in years), biological sex (male versus female), number of baseline OUD symptoms.
2. We will examine if the direction and significance the primary contrast between CB+POTS and WL+POTS is sensitive to our treatment of missing data, by fitting the statistical model to the observed data only.

Note it may be necessary to include additional sensitivity analyses to address unanticipated developments during the course of the study.

Secondary analysis

As a secondary analysis, we will extend the additive model for PEG scores by fitting a model including a treatment by time interaction (i.e., the product of the contrast between CB+POTS and WL+POTS and the time trend). We will conduct an analysis of variance comparing the simpler additive model to the more complex interaction model. This test will be included in the Benjamini-Hochberg false discovery rate correction applied to the analyses of secondary outcomes, and if the associated Wald test is significant at $p < 0.05$, this will indicate the presence of a treatment by time interaction.

Missing Data:

We will address missingness using multiple imputation via chained equations (MICE), performed separately in each study group. However, participants who have fewer than 14 days (two weeks) of non-missing data will be excluded from the analysis (i.e., participants with less than 8.3% of the total number of possible observations will be excluded).

The following predictors will be used in all imputation models for all outcomes:

- A participant's age in years;
- A participant's biological sex (male versus female);
- A participant's median prescription opioid dose (MME) in the interval preceding the baseline visit;
- Number of baseline opioid use disorder (OUD) symptoms;
- A participant's average PEG score over all measurements taken before and at the baseline visit;
- Time specified as a restricted cubic spline

If additional variables are determined prior to data analysis to be predictive of missingness, they will also be included.

For PEG data, post-baseline daily scores will be imputed in a "long" format using a mixed effects imputation model.

For PMP opioid dose, the interval medians will be imputed as separate variables in a "wide" format.

Missing outcome data will be imputed 40 times, and analyses will be run using complete and imputed data for each imputation iteration, and results will be pooled according to Rubin's rule.

Clinical significance

Examination of PEG scores and opioid doses means that a combination of clinical outcomes is possible (see Table 1), which will indicate whether *CB is helpful* (e.g. decreases opioid doses and/or PEG scores), *CB is harmful* (e.g. increases opioid dose and/or PEG scores), or that *CB has no clear effect on opioid dose/PEG scores (no notable changes, or increases one outcome and decreases another)*. In the third condition, an exploratory analysis will evaluate costs/benefits of CB to the individual patient, measured via the proposed secondary outcomes.

Table 1: Decision table for each possible outcome

Decision	PEG scores at 6 months compared to Baseline	Opioid dose at 6 months compared to Baseline	Meaning
CB is beneficial	CB+POTS < WL+POTS	CB+POTS < WL+POTS	CB reduces PEG score AND decreases opioid dose
	CB+POTS < WL+POTS	ns	CB reduces PEG score and does not affect opioid dose
	ns	CB < WL+POTS	CB does not affect PEG score but decreases opioid dose
CB is harmful	CB+POTS > WL+POTS	CB+POTS > WL+POTS	CB increases PEG score and increases opioid dose
	CB+POTS > WL+POTS	ns	CB increases PEG score and does not affect opioid dose
	ns	CB+POTS > WL+POTS	CB does not affect PEG score and increases opioid dose
Individual costs/benefits should be evaluated	ns	ns	CB does not affect PEG score or opioid dose
	CB+POTS < WL+POTS	CB+POTS > WL+POTS	CB decreases PEG score but increases opioid dose
	CB+POTS > WL+POTS	CB+POTS < WL+POTS	CB increases PEG score but decreases opioid dose

Secondary outcomes:

1. The summed score (ranging from 14 to 70) of the 14-item Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF), where lower scores indicate greater dissatisfaction with life.
2. The T-score (mean of 50 and SD of 10) of the 8-item Depression subscale of the PROMIS-29, where higher scores indicate a greater degree of depression.
3. The T-score (mean of 50 and SD of 10) of the 7-item Anxiety subscale of the PROMIS-29, where higher scores indicate a greater degree of anxiety.
4. The number of symptoms (ranging from 0 to 11) for Opioid Use Disorder (OUD), based on the DSM-5 Opioid Use Disorder Checklist.
5. The number of symptoms (ranging from 0 to 11) for Cannabis Use Disorder (CUD), based on the DSM-5 Cannabis Use Disorder Checklist.
6. Self-reported opioid dose in MME units collected daily via self-report through a smartphone app.

The secondary outcomes will be collected monthly during in-person study visits over the 24-week period (i.e., up to 7 observations per participant), except for CUD symptoms which are collected at weeks 0, 12, and 24 and self-reported opioid dose which is collected daily.

Secondary Outcomes: Statistical model

For each secondary outcome, we will use the same linear regression model, design matrix, and linear mixed effects modeling method as proposed for the primary outcome of PEG score with main effects specification for the treatment and each covariate, and a restricted cubic spline specification of time. Due to CUD symptoms only being measured at two post-baseline time points, time will be specified as a binary indicator (week 24 vs. week 12). In each model, the primary contrast testing for a constant effect of CB above and beyond POTS will be deemed statistically significant for $p < 0.05$ following an adjustment across all secondary outcomes using the Benjamini-Hochberg method, thereby ensuring a false-discovery rate of 5% despite multiple comparisons over nine secondary outcomes.

Secondary Outcomes: Missing data

Separately for each secondary outcome, we will use the same approach (multiple imputation via chained equations in a wide format) as specified for the PMP outcome, with the same set of additional covariates.

Secondary Outcomes: Sensitivity analyses

At a minimum, the 2 sensitivity analyses proposed for both primary outcomes will also be run for each secondary outcome. Again, note it may be necessary to include additional sensitivity analyses to address unanticipated developments during the course of the study.

Power analyses:

Given the slower-than-anticipated recruitment, we have conducted a sample size re-estimation for this trial. We have revised our power and expectations and concluded that with $n=120$ (50 completed per group assuming 20% attrition), at 80% power, we will be able to detect a **28% improvement in PEG scores and/or a 20% decrease in opioid dose**, which are likely to be clinically significant. While final analyses will rely linear regressions robust to clustering and heteroscedasticity, because the key contrast of interest is the mean difference between CB+POTS and WL+POTS, power can be approximated via standard methods for independent samples t-tests.

PEG scores: Power curve estimates were based on preliminary data, 3205 daily pain scores (a component of PEG scores) reported by 46 participants in the previous CB study over a period of 84 days (roughly 3 months). The mean (6.3) and standard deviation (3.1) for pain scores in the first two weeks was used to compute percent reduction. For 60 participants per group, we would have 80% power to detect a minimum percent reduction of 25% in PEG scores for the CB+POTS group above and beyond that for the WL+POTS group. With only 50 participants per group, we would have 80% power to detect a minimum percent reduction of 28% in PEG scores for the CB+POTS group above and beyond that for the WL+POTS group. Research suggests that current chronic pain treatments can result in an approximately 30% reduction in an individual's pain scores [1], and that a 30% reduction in pain can significantly improve function and quality of life [2].

Opioid dose: Power curve estimates were based on opioid dose data for the 145 PEG score patients extracted from Massachusetts General Hospital's 2017 records. We used the mean (88) and standard deviation (32) in morphine milligram equivalents (MME) for compute percent reduction. For 60 participants per group, we would have 80% power to detect a minimum percent reduction of 19% in opioid dose for the CB+POTS group above and beyond that for the WL+POTS group. With only 50 participants per group, we would have 80% power to detect a minimum percent reduction of 20% in opioid dose for the CB+POTS group above and beyond that for the WL+POTS group.

Our original power analysis stated that $n = 250$ (100 participants completed in each group assuming 20% attrition) would be needed to achieve an 80% power to detect an 18% improvement in pain (PEG) scores and/or a 13% decrease in opioid dose.

- *PEG scores:* Power curve estimates were based on preliminary data, 3205 daily pain scores (a component of PEG scores) reported by 46 participants in the previous CB study over a period of 84 days (roughly 3 months). The mean (6.3) and standard deviation (3.1) for pain scores in the first two weeks was used to compute percent reduction. For 125 participants per group, we would have 80% power to detect a minimum percent reduction of 18% in PEG scores for the CB+POTS group above and beyond that for the WL+POTS group. Even with only 100 participants per group, we would have 80% power to detect a minimum percent reduction of 20% in PEG scores for the CB+POTS group above and beyond that for the WL+POTS group.
- *Opioid dose:* Power curve estimates were based on opioid dose data for the 145 PEG score patients extracted from Massachusetts General Hospital's 2017 records. We used the mean (88) and standard deviation (32) in morphine milligram equivalents (MME) for compute percent reduction. For 125 participants per group, we would have 80% power to detect a minimum percent reduction of 13% in opioid dose for the CB+POTS group above and beyond that for the WL+POTS group. Even with only 100 participants per group, we would have 80% power to detect a minimum percent reduction of 20% in opioid dose for the CB+POTS group above and beyond that for the WL+POTS group.

VII. RISKS AND DISCOMFORTS

Potential risks in the study are considered minimal and include:

1. **Discomfort related to completing questionnaires** about sensitive information such as psychiatric health and illicit substance use: any distress will be minimized by assuring participants that they can refuse to answer any question that they do not feel comfortable addressing and that they may withdraw from the study at any time without penalty. During this clinical trial, we will notify officials, as mandated by law, if a participant reports intention to harm him/herself or others, or reports child abuse or abuse of an elder. In the event a participant were to report a need or interest in treatment for substance dependence, psychiatric disorder, or distress, an appropriate referral to resources will be provided. If there are any concerns about a subject in need of clinical attention, the site PI will be made aware of the issue immediately and determine appropriate steps. The PI and/or medically trained co-investigators will assess the needs of the subject and offer the subject either prompt treatment or medical referral, whichever is appropriate for the situation. There is a licensed clinician at each site 40 hours per week.

2. **Breach of confidentiality and/or privacy:** Protecting the confidentiality and integrity of our research participants is a top priority for this and all MGH-based research projects. Any breach is unlikely because all information will be identified with a numeric code only and stored on password-protected servers. Only study staff will have access to this database. All staff will be fully trained in relevant ethical principles and procedures, including confidentiality. All assessment and treatment procedures will be closely supervised by the PI. Electronic data capture will also be safeguarded. Data will be collected using REDCap (Research Electronic Data Capture) tools hosted by MGB HealthCare. REDCap is a secure, web-based application designed to support data capture for research studies, and which is fully compliant with HIPAA-Security guidelines. REDCap data collection projects rely on a thorough study-specific data dictionary defined in an iterative self-documenting process by all members of the research team with planning assistance from MGB HealthCare Research Computing, Enterprise Research Infrastructure & Services (ERIS) group. Self-report questionnaires will be administered via REDCap

minimizing the risk of confidentiality breaches. Both REDCap and REDCap Survey systems provide secure, HIPAA compliant, web-based applications.

Confidentiality will be maintained by numerically coding all data, by removing identifying information, and by keeping all data in locked file drawers in locked offices. Any data files in electronic format will be housed in our network server at the Center for Addiction Medicine at MGH and will be password protected in encrypted devices so that only authorized project personnel have access to them. Individually identifiable information about human subjects will be accessible only to research staff. All study staff will be trained in protection of privacy of research participants and will be CITI certified. Information about study participants will not leave the institution in any form that would identify individual subjects. Data will be transmitted with subjects identified only by code.

Limits of Confidentiality on Clinical Information (Emergency Protocol): While we are committed to maintaining confidentiality to the extent to which we are able, confidentiality is limited when there is a deemed imminent risk to oneself or others or reports of child and elder abuse. Study staff will inform participants during the consent process that in emergency situations (in which an individual is at immediate risk for harm) we will release information about the participant. Specifically, if a participant tells any member of study staff that he/she has intent and/or a plan to cause harm to self or others, study staff will start the Center Emergency protocol that includes a psychiatric evaluation by a licensed mental health professional and even calling 911. If the participant says that he/she has recurrent thoughts about harming him/herself or someone else but does not have intent or plan to do so, study staff will ask participant permission to notify appropriate medical or counseling personnel, including the guidance counselor or therapist. If study staff learns about mood concerns or problematic substance use, study staff will provide the participant with referral resources for follow-up consultation and care. The PI has prepared a comprehensive list of local and national resources for this purpose.

3. Discomfort/adverse events with opioids: While it is expected that opioid withdrawal symptoms will be extremely rare, we will assess opioid withdrawal symptoms in all participants throughout the study. At in person visits, opioid withdrawal will be assessed. Study participants will also rate their craving for opioids in the past week on the Short Opiate Withdrawal Scale (SOWS), a 10-item questionnaire developed to evaluate opioid withdrawal symptom severity. If there are any concerns about a subject in need of clinical attention, the MPIs and study physicians will be made aware of the issue immediately and will determine appropriate steps. The PIs and medically trained co-investigators will assess the needs of the subject and offer the subject either prompt treatment or medical referral, whichever is appropriate for the situation. Further, we will collect extensive safety and tolerability data, including opioid withdrawal symptoms, that will be reviewed by the DSMB and revisions to procedures will be instituted if indicated.

While opioid overdose is not expected, as participants will not be increasing their opioid dose as part of this study, the study team has the following plan in place to manage potential opioid overdose. We expect that all participants will have naloxone since they are on COT. During the first POTS group session, naloxone will be discussed, and group leaders will recommend that all participants obtain a naloxone kit. In the state of MA, the Department of Public Health has issued a statewide standing order that allows retail pharmacies to dispense naloxone without a prescription. If participants decline to obtain naloxone, we will schedule a one-on-one meeting to explore their concerns and explain the benefits of having a naloxone kit.

4. Discomfort/adverse events with CB use: Cannabis is associated with reversible effects on appetite, mood, cognition, memory, and perception. At low to moderate doses, THC can produce behavioral intoxication and physiological changes (feeling intoxicated, high, euphoric, dizzy, giddy, tired and lightheaded; increased heart rate, and slowed reaction time). Participants may experience changes in behavioral, symptoms, or cognition that they find disturbing or troubling if they do escalate cannabis use. Some participants will experience adverse events including increased anxiety, paranoia, sleeping difficulties, or temporary psychosis. Some studies have found associations between cannabis use and suicidal thoughts. Some participants may develop cannabis use disorders as a result of using CB. Though study participants will choose what type and how much cannabis to use and when, we will recommend that participants do not use certain types of marijuana products (e.g., waxes, shatter) that are more likely to lead to dependence. Long-term effects of CB are still unknown. Other potential adverse

events from using CB are risk of psychosis and worsening depression. Vaping has been linked to cases of serious lung injury, some resulting in death. While the exact cause is still not confirmed, the CDC recommends that people not use vapes. Symptoms of vaping-related lung injury include rapid onset of coughing, breathing difficulties, weight loss, nausea and vomiting, and diarrhea. These will all be important outcome measures of this study, which will be carefully measured and assessed at each study visit. Subjects will be encouraged to report adverse events at any time by calling study staff. Study staff who will be interacting with subjects are clinically trained and able to assess need for medical or professional intervention and will ensure prompt treatment or medical referral for any participant requiring medical or professional intervention during the study. If there are any concerns about a subject in need of clinical attention, the MPIs and Site PIs will be made aware of the issue immediately to determine appropriate steps. The MPIs and medically trained co-investigators will assess the needs of the subject and offer the subject either prompt treatment or medical referral, whichever is appropriate for the situation. There is a licensed clinician at each site 40 hours per week, and other MGH resources can be used as necessary. Further, CB -related AEs will be reviewed by the DSMB and revisions to procedures will be instituted if indicated.

Serious adverse events are not expected. Any SAEs that do occur will be reported by the principal investigator to the MGH IRB according to current MGH IRB Adverse Event Reporting Policy (version dated: October 1, 2021). All adverse events (if not unexpected and related/possibly related) will be reported in writing to the MGH Institutional Review Board at a yearly Continuing Review.

5. Legal/Social Risk from using CB: There are few legal risks to the participants associated with these paradigms. Cannabis use is for medical and recreational use is legal in Massachusetts and Maine. There is no legal risk to self-report of regular cannabis use. Socially, some subjects may be embarrassed if others found out that they were using CB. Therefore, we will protect privacy and confidentiality of all participants.

Confidentiality of Drug Tests: The results of the qualitative and quantitative drug testing will be confidential. When submitting requisition forms to the Pharmacy and Therapeutics Committee at the University of Colorado School of Medicine, only the assigned identifying code will be included, there will be no information on the forms that non-study staff could associate with a specific participant. The only individuals who will have knowledge of the results of these tests are research staff directly working on the project. Information will be stored in a secure computer database that uses participant codes (rather than names) as identifiers.

6. Randomization in clinical trials: Participants will be assigned to an intervention by chance. The intervention to which a participant is assigned may prove to be less effective than the alternate intervention.

VIII. POTENTIAL BENEFITS

a. Potential benefits to participating individuals:

Participants may find that POTS and medical cannabis are helpful for opioid tapering, and may experience associated benefits. Participants may also find that talking about cannabis and opioid use increases their awareness of any issues related to drug use. Any participant who asks about treatment will be provided information regarding local drug treatment programs. Participants may experience pain reduction or reduce their opioid dose. Further, millions of individuals have CNCP that is very often debilitating and complex, and clinicians have few strategies to meet the complex medical needs of this patient group. This study could potentially benefit other patients with CNCP. Thus, the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.

b. Potential benefits to society:

CB use has now been sanctioned by several states as a treatment for both chronic pain and for OUD with very little evidence of effectiveness for either indication. Thus, the proposed study will answer a timely and critically important public health controversy over whether CB use is beneficial or harmful in this population, information that will be critically important to patients, healthcare providers, and policymakers. The proposed project will fill a critical gap in our knowledge, at a critical time when

cannabis is being legalized for 'medical' use with little known about effects of CB on target symptoms such as pain, addictions, or neurocognition.

IX. MONITORING AND QUALITY ASSURANCE

a. Independent monitoring of source data:

All data management will be conducted in the offices of the PI at the MGH Center for Addiction Medicine (CAM) in Boston. Study data will be collected and managed using REDCap, a secure, HIPAA-compliant web application designed to support data capture for research studies. Data are stored on a secure server, and the database is protected by nightly backup to MGH servers. Data in REDCap are encrypted, access to the database requires authentication, and every interaction with the data is logged, creating an audit trail.

A study database will be designed by the PI and data manager. This database will be maintained by the PI, data manager, and research coordinators. Data entry will be performed by IRB-approved study staff trained in human subjects research. Participants will receive instruction on completing REDCap surveys. Prior to starting use of the daily survey, participants will be instructed on how to set up the application that it can confirm their identity and will practice learning how to use it and entering data.

Physical copies of any study documents will be stored in locked cabinets at the Center for Addiction Medicine offices. Access to this office requires authentication (photo ID badge with access privileges). All data will be stored safely for at least 7 years after study completion.

The data manager will review data entry on a periodic basis to ensure data quality. Study staff will be trained in the study protocol and supervised by senior staff to maintain protocol adherence. Either PIs or other members of study staff will review a proportion of data entry after initial entry by other study staff for completeness. Data quality tools included in REDCap will be utilized to identify incorrect data types, out of range data and outliers. The PI will meet weekly with all study staff to review the details of data acquisition and analysis as well as any minor problems. If necessary, retraining of study staff will be conducted.

b. Safety and Outcomes Monitoring: Data and Safety Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be appointed for this study, to assess safety of this clinical trial by determining whether there is an unacceptable level of risk due to CB and whether an increased number of adverse events occur in the CB +POTS group compared with the WLC+POTS group.

The DSMB will be made up of one psychiatrist, one statistician, and one addiction neuroscientist. The psychiatrist will serve as the Chair of the DSMB. Each member of the DSMB will not otherwise be associated with the trial and the study investigators will not be members of the DSMB.

DSM Report: The study biostatistical team will prepare reports to the DSMB. Safety information for this study will be reported to the DSMB in a blinded manner, however; if unblinded data is requested by the DSMB, it will be made available to them. A statistical penalty will not be assessed for the ongoing unblinded review of safety by the DSMB. Subject information provided to the board will be identified only with study IDs to protect the confidentiality of subjects.

The DSMB report will include the following: brief description of progress, enrollment updates, retention and disposition of participants (active, completed, withdrawn, etc.), adverse events (AEs) and serious adverse events (SAEs), quality assurance issues, and regulatory issues. It is considered necessary for the purposes of monitoring the safety of the study that the DSMB review not only AEs and SAEs, but other data that may reflect differences in safety and efficacy between treatment groups. This includes, but is not limited to, treatment retention rates, reasons for drop-out, and clinical outcomes.

Frequency of Monitoring: Safety data will be reviewed by the study team in weekly project management meetings, and reviewed by the DSMB every 6 months, at which time they will conduct a blind analysis of safety and efficacy data. Investigators will monitor overall progress, subject accrual, adverse events, and subject safety.

Reporting DSMB Minutes to IRB and NIDA: A DSMB report written by the chair and approved by all members will be issued to the MGH IRB and the NIDA Project Officer after each DSMB meeting. The DSMB report will be made available to NIDA in accordance with annual reporting requirements.

c. Adverse event reporting guidelines

Study staff, including PIs, co-investigators, research coordinators, and data managers, will review study progress, including adverse events, at a weekly project management meeting.

All adverse events volunteered, observed, or solicited will be recorded in the AE CRF from the time the subject signs the informed consent up to and including the last visit (week 52). AEs will be assessed for each subject at every visit. All adverse events will be recorded and will include the dates of occurrence; severity; assessment of relationship to study procedures; expectedness; countermeasure(s), including specific drug therapy or interventional treatments used in countermeasure; and outcome.

Women of childbearing potential who are pregnant at the time of enrollment will not be eligible to participate in this study. To be eligible, all women of childbearing potential will agree to use effective contraception throughout the duration of the study. Changes in pregnancy status will be monitored through systematic collection of adverse events at study visits, in which subjects are asked about any significant changes to their mental or physical health. If an enrolled subject reported pregnancy during the trial, they would not be allowed to continue participating in the study without a protocol exception approved by the IRB in advance.

Reporting Adverse Events (AEs): The principal investigator will report all adverse events experienced by the study subjects in accordance with MGB IRB guidelines. Adverse events will be reviewed by the PI, who will complete an adverse event report form and submit this to the IRB upon annual review.

Adverse events will also be reported by the principal investigator to the NIDA Program Officer as outlined in the Data Safety and Monitoring Plan. Per the revised DSMP (dated 9/13/2024), significant changes to the protocol and/or DSMP will be submitted to the NIDA PO for approval prior to implementation.

In case of unexpected, related adverse events or any unanticipated problem involving risks to subjects or others (UPIRTSO), the principal investigator will report the adverse event through Insight within 5 business days (or 7 calendar days) of the date the investigator first became aware of the problem. An annual report will be submitted to the IRB of the progress of the trial. This will include individual study information and information on safety reports from the previous year.

X. DATA AND RESEARCH MATERIAL SHARING

Sending Data/Materials to Research Collaborators outside Mass General Brigham

De-identified data will be shared with academic/scientific collaborators at Duke University (PI: Rubenstein). Data for approximately 80 participants will be shared. Data will include demographics, substance use assessments, and daily survey data. Analyses will be conducted to evaluate the effect of nicotine use status on opioid dose reduction in adults with chronic, non-cancer pain. Data will be de-identified and coded. The coded key will not be shared with anyone outside of MGB. Data will be shared using MGB Dropbox for Business. A data use agreement will be executed through Research Management before any data is shared.

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**Evaluation of Medical Cannabis and Prescription Opioid Taper Support for Reduction of Pain and
Opioid Dose in Patients with Chronic, Non-Cancer Pain**

NCT04827992

Version 3.4

First version: 12/20/2021

Latest version: 10/31/2025

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Glossary

Abbreviation	Term
APA	American Psychological Association
CNCP	Chronic non-cancer pain
CUD	Cannabis use disorder
GEE	Generalized estimating equations
CB	Cannabis
MME	Morphine milligram equivalents
OD	Opioid use disorder
PMP	Prescription monitoring program
POTS	Prescription opioid tapering support
WL	Waitlist

Design

The study will examine the efficacy of the addition of cannabis (CB) to prescription opioid tapering support (POTS) to help reduce pain and opioid use for patients with chronic non-cancer pain (CNCP). The study will contrast participants randomized to a 24-week period of either (1) receiving both POTS and CB post-baseline (**CB+POTS**) versus (2) receiving POTS post-baseline while wait-listed for receiving CB (**WL+POTS**).

The study aims to enroll up to 250 participants, adults aged 18 to 75 with CNCP endorsing >6 months of pain (neuropathic, nociceptive, or centralized pain) on stable prescription opioid doses of ≥ 25 MME/day for >90 days. Participants will be randomized in a 1:1 ratio at the therapy-group level (Therapy groups will consist of up to 6 participants, and all participants in a group will be randomized to the same condition to avoid cross-contamination). Therefore, it is expected that the CB+POTS and WL+POTS groups will each have up to 125 participants.

Analytic approach

Primary outcomes

Our co-primary outcomes will be...

1. The summed score (ranging from 0 to 30) of the 3-item Pain Enjoyment General Activity (PEG) scale (Krebs et al., 2009), where higher scores indicate greater pain severity and/or interference.
 - The PEG scores will be collected daily via self-report through a smartphone app from the baseline assessment to the end of the 24-week period (i.e., up to 168 observations per participant). All post-baseline daily observations for PEG scores through the week 24 visit will be analyzed.
2. Prescription monitoring program (PMP) verified opioid dose, in median daily morphine milligram equivalents (MME), defined over the “monthly” (30-day) interval preceding the final (week 24) study visit.
 - The observed median daily MME will be defined over each interval, as well as each interval between study visits, and 30 days after week 24 (totalling 8 intervals pre-baseline, between visits, and after week 24).
 - The observed median may be subject to artifacts in the PMP daily dose that arise commonly due to overlapping prescriptions or to filling prescriptions several days early or late. Therefore, an independent review will be conducted separately by two qualified clinicians who are blind to group assignment, to evaluate the 8 monthly intervals of PMP-reported daily MME in order to correct the MME for artifacts. These clinicians will independently verify the median daily prescribed MME for each month prior and following the baseline and week 24, resulting in 8 measurements. If the separate reviews by the clinicians are in consensus that a MME value other than the observed median dose should be used, the dose will be adjusted in analyses accordingly. If reviewers do not agree, they will discuss and try to reach a consensus. If no consensus can be reached, opioid dose will be defined as the observed median of the daily MME reported by the PMP over the specified 30-day intervals. We will compute inter-rater reliability scores for the clinical reviews and document all dose adjustments from the PMP dose.
 - We expect long periods of stable opioid doses over the 6-month trial. Therefore, our primary analysis will assess differences in prescribed dose over the 30-day interval preceding the visit at week 24 of the study (i.e., opioid dose over month 7 of the study), while accounting for dose in the interval prior to the baseline visit.
 - PMP-based opioid doses will serve as the dose for primary analysis. Self reported dose will be analyzed as a secondary outcome. It is hoped that the PMP dose will capture change in prescriptions and more stable long-term dose reduction than daily self reported dose.

Statistical model

We will analyze both outcomes using a linear regression model.

For the PEG score, coefficients and standard errors for the linear model will be obtained using a linear mixed effects model with random intercepts for each therapy group and subject to account for the nested hierarchical structure. If there are issues with model convergence due to the inclusion of two sets of random intercepts, then the models will instead be fit using only random intercepts for subject.

For the PMP verified opioid dose, a linear mixed effects model with random intercepts for each therapy group will be specified, and again if there are issues with model convergence due to the random intercepts then a model without random effects will be fit. The specification of covariates and confirmatory estimate of interest for each outcome is described below.

The p-value for each primary contrast will be computed via a t-test using the coefficient estimate and model-based standard error. The primary contrast testing for an effect of CB above and beyond POTS will be deemed statistically significant for $p < 0.025$, thereby ensuring an overall family-wise error rate of 5% despite two primary outcomes.

For each outcome, the model specification and key confirmatory effect of interest will be...

PEG scores: The model will include the following covariates: (a) a restricted cubic spline specification for change over days since baseline (with two spline knots placed at recommended data quantiles); (b) A participant's average PEG score over all measurements taken before and at the baseline visit; (c) A participant's median prescription opioid dose (MME) in the interval preceding the baseline visit; and the confirmatory effect of interest, (d) a dummy-coded contrast between WL+POTS (the referent, coded as 0) and CB+POTS (coded as 1), testing whether a constant effect of CB exists, averaged over all time points. In other words, we specify an additive model, adjusting for baseline levels and with main effects for a) the impact of CB and b) change over time, but no treatment by time interaction.

Opioid dose: The model will include the following covariates: (a) a participant's median prescription opioid dose (MME) in the interval preceding the baseline visit; (b) A participant's average PEG score over all measurements taken before and at the baseline visit; and the confirmatory effect of interest, (c) a dummy-coded contrast between WL+POTS (the referent, coded as 0) and CB+POTS (coded as 1), testing whether there is a significant difference in opioid dose at week 24 for WL+POTS versus CB+POTS, holding baseline dose constant (and adjusting for the other listed covariate(s)).

Missing data

We will address missingness using multiple imputation via chained equations (MICE), performed separately in each study group. However, participants who have fewer than 14 days (two weeks) of non-missing data will be excluded from the analysis (i.e., participants with less than 8.3% of the total number of possible observations will be excluded).

The following predictors will be used in all imputation models for all outcomes:

- A participant's age in years;
- A participant's biological sex (male versus female);
- A participant's median prescription opioid dose (MME) in the interval preceding the baseline visit;
- Number of baseline opioid use disorder (OUD) symptoms;
- A participant's average PEG score over all measurements taken before and at the baseline visit;
- Time specified as a restricted cubic spline

If additional variables are determined prior to data analysis to be predictive of missingness, they will also be included.

For PEG data, post-baseline daily scores will be imputed in a "long" format using a mixed effects imputation model.

For PMP opioid dose, the interval medians will be imputed as separate variables in a "wide" format.

Missing outcome data will be imputed 40 times, and analyses will be run using complete and imputed data for each imputation iteration, and results will be pooled according to Rubin's rule.

Intent-to-treat analysis

We understand that there may be some contamination between groups (e.g., some patients in the WL+POTS group may use CB, and some patients in the CB+POTS group may decide not to use CB). As this is a pragmatic trial, our primary analysis will be an intent-to-treat analysis, in which all participants will be analyzed by group (CB vs WL+POTS). This intent-to-treat analysis will *be representative of real-world, ecologically valid outcomes*, in which a clinician would recommend CB to a patient, and then the patient would come to a decision about whether CB was helpful, and act accordingly. Therefore, this type of analysis, designed for pragmatic trials such as this, will help inform real-world clinical decision-making. However, we do acknowledge that this intent-to-treat analysis cannot answer the question of whether CB has a biological effect on pain and/or opioid use.

In addition, for the week 24 PMP outcome we will conduct a per-protocol analysis to address the risk of bias by indication (e.g., patients in the WL+POTS group who are suffering worse pain may be more likely to use CB). We will compare those who used CB regularly (weekly or more) vs those who did not use (verified by negative

urine screens and no self-reported use) using a marginal structural modeling approach to correct for “confounding by indication” by weighting data by the inverse probability of being in the CB or non-user group.

Secondary analysis

As a secondary analysis, we will extend the additive model for PEG scores by fitting a model including a treatment by time interaction (i.e., the product of the contrast between CB+POTS and WL+POTS and the time trend). We will conduct an analysis of variance comparing the simpler additive model to the more complex interaction model. This test will be included in the Benjamini-Hochberg false discovery rate correction applied to the analyses of secondary outcomes, and if the associated Wald test is significant at $p < 0.05$, this will indicate the presence of a treatment by time interaction.

Sensitivity analyses

For the PMP outcome, we will perform a sensitivity analysis estimating the difference in mean of the monthly median opioid dose at week 24 using a linear mixed effects model fit to all post-baseline data points, with random intercepts for each therapy group and subject to account for the nested hierarchical structure. If there are issues with model convergence due to the inclusion of two sets of random intercepts, then the models will instead be fit using only random intercepts for subject. This model will be fit using the following covariates: (a) a restricted cubic spline specification for change over days since baseline; (b) A participant’s average PEG score over all measurements taken before and at the baseline visit; (c) A participant’s median prescription opioid dose (MME) in the interval preceding the baseline visit; (d) a dummy-coded contrast between WL+POTS (the referent, coded as 0) and CB+POTS (coded as 1), and (e) treatment by time interaction terms. From this model, the difference in adjusted mean of the monthly median opioid dose at week 24 between CB+POTS and WL+POTS will be estimated and a Wald hypothesis test will be performed.

In addition, for each primary outcome we will conduct a minimum of 2 sensitivity analyses.

1. We will examine if the direction and significance of the primary contrast between CB+POTS and WL+POTS is robust to the inclusion of additional covariates, specifically age (in years), biological sex (male versus female), number of baseline OUD symptoms.
2. We will examine if the direction and significance the primary contrast between CB+POTS and WL+POTS is sensitive to our treatment of missing data, by fitting the statistical model to the observed data only.

Note it may be necessary to include additional sensitivity analyses to address unanticipated developments during the course of the study.

Clinical significance

Examination of PEG scores and opioid doses means that a combination of clinical outcomes is possible (see Table 1), which will indicate whether *CB is helpful* (e.g. decreases opioid doses and/or PEG scores), *CB is harmful* (e.g. increases opioid dose and/or PEG scores), or that *CB has no clear effect on opioid dose/PEG scores (no notable changes, or increases one outcome and decreases another)*. In the third condition, an exploratory analysis will evaluate costs/benefits of CB to the individual patient, measured via the proposed secondary outcomes.

Table 1: Decision table for each possible outcome

Decision	PEG scores at 6 months compared to Baseline	Opioid dose at 6 months compared to Baseline	Meaning
CB is beneficial	CB+POTS < WL+POTS	CB+POTS < WL+POTS	CB reduces PEG score AND decreases opioid dose
	CB+POTS < WL+POTS	ns	CB reduces PEG score and does not affect opioid dose
	ns	CB < WL+POTS	CB does not affect PEG score but decreases opioid dose
CB is harmful	CB+POTS > WL+POTS	CB+POTS > WL+POTS	CB increases PEG score and increases opioid dose
	CB+POTS > WL+POTS	ns	CB increases PEG score and does not affect opioid dose
	ns	CB+POTS > WL+POTS	CB does not affect PEG score and increases opioid dose
Individual costs/benefits should be evaluated	ns	ns	CB does not affect PEG score or opioid dose
	CB+POTS < WL+POTS	CB+POTS > WL+POTS	CB decreases PEG score but increases opioid dose
	CB+POTS > WL+POTS	CB+POTS < WL+POTS	CB increases PEG score but decreases opioid dose

Secondary Outcomes

Our secondary outcomes will be...

1. The summed score (ranging from 14 to 70) of the 14-item Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q-SF; Schechter, Endicott, & Nee, 2007), where lower scores indicate greater dissatisfaction with life.
2. The T-score (mean of 50 and SD of 10) of the 8-item Depression subscale of the PROMIS-29 (Cella et al., 2010), where higher scores indicate a greater degree of depression.

3. The T-score (mean of 50 and SD of 10) of the 7-item Anxiety subscale of the PROMIS-29 (Cella et al., 2010), where higher scores indicate a greater degree of anxiety.
4. The number of symptoms (ranging from 0 to 11) for Opioid Use Disorder (OUD), based on the DSM-5 Opioid Use Disorder Checklist (American Psychiatric Association [APA], 2013).
5. The number of symptoms (ranging from 0 to 11) for Cannabis Use Disorder (CUD), based on the DSM-5 Cannabis Use Disorder Checklist (APA, 2013).
6. Self-reported opioid dose in MME units collected daily via self-report through a smartphone app.

The secondary outcomes will be collected monthly during in-person study visits over the 24-week period (i.e., up to 7 observations per participant), except for CUD symptoms which are collected at weeks 0, 12, and 24, and self-reported opioid dose which is collected daily.

Statistical model

For each secondary outcome, we will use the same linear regression model, design matrix, and linear mixed effects modeling method as proposed for the primary outcome of PEG score with main effects specification for the treatment and each covariate, and a restricted cubic spline specification of time. Due to CUD symptoms only being measured at two post-baseline time points, time will be specified as a binary indicator (week 24 vs. week 12). In each model, the primary contrast testing for a constant effect of CB above and beyond POTS will be deemed statistically significant for $p < 0.05$ following an adjustment across all secondary outcomes using the Benjamini-Hochberg method, thereby ensuring a false-discovery rate of 5% despite multiple comparisons over nine secondary outcomes.

Missing data

Separately for each secondary outcome, we will use the same approach (multiple imputation via chained equations in a wide format) as specified for the PMP outcome, with the same set of additional covariates.

Sensitivity analyses

At a minimum, the 2 sensitivity analyses proposed for both primary outcomes will also be run for each secondary outcome. Again, note it may be necessary to include additional sensitivity analyses to address unanticipated developments during the course of the study.

Power

Our original power analysis stated that $n=250$ (100 participants completed in each group assuming 20% attrition) would be needed to achieve an 80% power to detect an 18% improvement in pain (PEG) scores and/or a 13% decrease in opioid dose.

- *PEG scores*: Power curve estimates were based on preliminary data, 3205 daily pain scores (a component of PEG scores) reported by 46 participants in the previous CB study over a period of 84 days (roughly 3 months). The mean (6.3) and standard deviation (3.1) for pain scores in the first two weeks was used to compute percent reduction. For 125 participants per group, we would have 80% power to detect a minimum percent reduction of 18% in PEG scores for the CB+POTS group above and beyond that for the WL+POTS group. Even with only 100 participants per group, we would have 80% power to detect a minimum percent reduction of 20% in PEG scores for the CB+POTS group above and beyond that for the WL+POTS group.
- *Opioid dose*: Power curve estimates were based on opioid dose data for the 145 PEG score patients extracted from Massachusetts General Hospital's 2017 records. We used the mean (88) and standard deviation (32) in morphine milligram equivalents (MME) for compute percent reduction. For 125 participants per group, we would have 80% power to detect a minimum percent reduction of 13% in opioid dose for the CB+POTS group above and beyond that for the WL+POTS group. Even with only 100 participants per group, we would have 80% power to detect a minimum percent reduction of 20% in opioid dose for the CB+POTS group above and beyond that for the WL+POTS group.

Given the slower-than-anticipated recruitment, we conducted a power re-estimation for this trial, and revised expectations to conclude that with $n=120$ (50 completed per group assuming 20% attrition), at 80% power, we will be able to detect a **28% improvement in PEG scores and/or a 20% decrease in opioid dose**, which are likely to be clinically significant. While final analyses will rely on linear regression and mixed effects to address correlated outcomes, because the key contrast of interest can be expressed as differences in mean between CB+POTS and WL+POTS, power can be approximated via standard methods for independent two-sample t-tests.

- *PEG scores*: Power curve estimates were based on preliminary data, 3205 daily pain scores (a component of PEG scores) reported by 46 participants in the previous CB study over a period of 84 days (roughly 3 months). The mean (6.3) and standard deviation (3.1) for pain scores in the first two weeks was used to compute percent reduction. For 60 participants per group, we would have 80% power to detect a minimum percent reduction of 25% in PEG scores for the CB+POTS group above and beyond that for the WL+POTS group. With only 50 participants per group, we would have 80% power to detect a minimum percent reduction of 28% in PEG scores for the CB+POTS group above and beyond that for the WL+POTS group. Research suggests that current chronic pain treatments can

result in an approximately 30% reduction in an individual's pain scores [1], and that a 30% reduction in pain can significantly improve function and quality of life [2].

- *Opioid dose*: Power curve estimates were based on opioid dose data for the 145 PEG score patients extracted from Massachusetts General Hospital's 2017 records. We used the mean (88) and standard deviation (32) in morphine milligram equivalents (MME) for compute percent reduction. For 60 participants per group, we would have 80% power to detect a minimum percent reduction of 19% in opioid dose for the CB+POTS group above and beyond that for the WL+POTS group. With only 50 participants per group, we would have 80% power to detect a minimum percent reduction of 20% in opioid dose for the CB+POTS group above and beyond that for the WL+POTS group.

Software

All analyses will be done using the statistical software R (version 4.1.1; R Core Team, 2021) and integrated development environment RStudio (version 2020.9.0.351; RStudio Team, 2021). Data will be prepared using the R packages 'dplyr' (version 1.0.7; Wickham, François, Henry, & Müller, 2021) and 'tidyr' (version 1.1.4; Wickham, 2021). Models will be fit using the R package 'geepack' (version 1.3-2; Højsgaard, Halekoh, & Yan, 2006). Missing data will be imputed using the R package 'mice' (version 3.13.0; Van Buuren & Groothuis-Oudshoorn, 2011). Reproducible code and de-identified data will be organized using the R package 'targets' (version 0.8.1; Landau, 2021) and Gitlab (version 14.6.7; Gitlab Team, 2022).

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